HHS Public Access

Author manuscript

Curr Top Med Chem. Author manuscript; available in PMC 2018 March 06.

Published in final edited form as:

Curr Top Med Chem. 2010 ; 10(5): 579–595.

The Medicinal Chemistry of 5-HT$_6$ Receptor Ligands with a Focus on Arylsulfonyltryptamine Analogs

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Abstract

Arylsulfonyl analogs of aminopyrimidines (e.g. Ro 04-6790; **2**), aminopyridines (e.g. Ro 63-0563; **3**), 1-phenylpiperazines (e.g. SB-271046; **4**), and tryptamines (e.g. MS-245; **5**) were described as the first examples of selective 5-HT$_6$ receptor antagonists only ten years ago. Today, hundreds of compounds of seemingly diverse structure have been reported. The early antagonists featured an arylsulfonyl group leading to the widespread assumption that an arylsulfonyl moiety might be critical for binding and antagonist action. With respect to the arylsulfonyltryptamines, it seems that neither the "*arylsulfonyl*" nor the "*tryptamine*" portion of these compounds is essential for binding or for antagonist action, and some such derivatives even display agonist action. The present review describes many of the currently available 5-HT$_6$ receptor ligands and, unlike prior reviews, provides a narrative of the thinking (where possible) that led to their design, synthesis, and evaluation. The arylsulfonyltryptamines are also used as the structural basis of attempts to relate various structure-types to one another to afford a better understanding of the overall structural requirements for 5-HT$_6$ receptor binding.

5-HT$_6$ serotonin (i.e., 5-hydroxytryptamine; **1**) receptors, one of seven members (5-HT$_1$ – 5-HT$_7$) of the serotonin receptor family, were first identified in the early 1990s. These transmembrane-spanning G-protein coupled receptors are positively coupled to an adenylate cyclase second messenger system. It was only a decade ago that 5-HT$_6$-selective agents were unknown. Today, literally hundreds of examples have been reported. Many of the now-available agents were developed on the basis of the structures of the first few examples that were described. Rather than being a comprehensive review of the literature, the intent of this article is to provide some historical background, and to focus on some of the more recent medicinal chemistry findings and how they might have been influenced, directly or indirectly, by the initial discovery of N_1-arylsulfonyltryptamines, or at least how some of these structures might be structurally interrelated. Several reviews are available on the pharmacology and medicinal chemistry associated with 5-HT$_6$ receptors and their ligands

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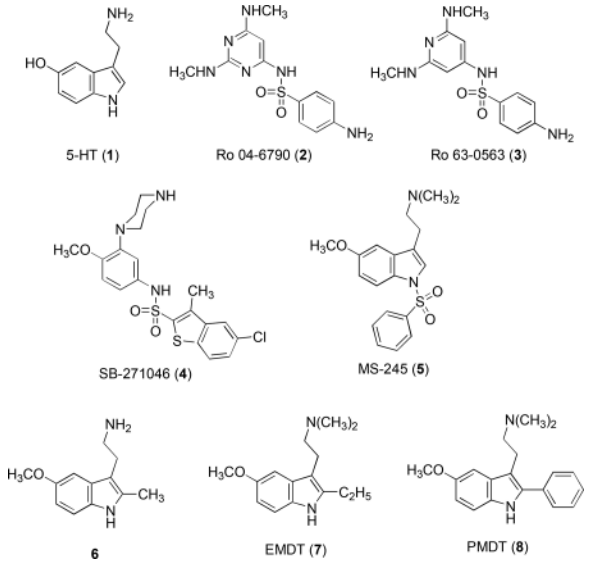
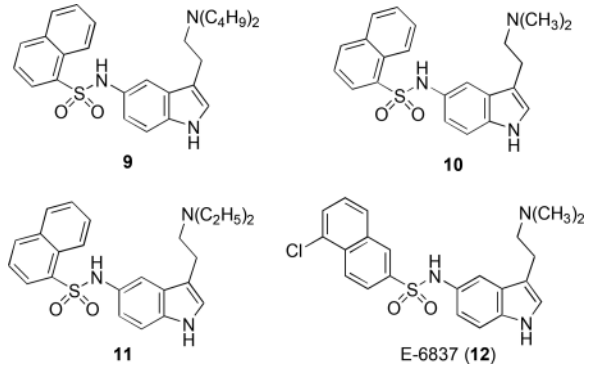
[1–5], and a compilation of 5-HT_6 receptor agents currently undergoing clinical development has been published [6a]. 5-HT_6 receptors have been implicated as playing possible roles in, for example, schizophrenia, depression, obesity, memory and cognitive function, epilepsy, and drug abuse. As agents are identified, they are evaluated in preclinical assays that might support their effectiveness for the treatment of such disorders. For more detailed information on the pharmacology of these compounds, the interested reader is referred to the primary literature cited below, or to the review articles [i.e., 1–5, 6a] cited above.

The first examples of 5-HT_6 receptor antagonists were serendipitous discoveries having their roots in random screening [reviewed: 2]. Interesting and curious is that, although they represented independent discoveries, Ro 04-6790 (**2**; K_i = 47 nM) and its *des*-aza analog Ro 63-0563 (**3**; K_i = 12 nM), SB-271046 (**4**; K_i = 1.3 nM), and MS-245 (**5**; K_i = 2.1 nM) all possessed a sulfonamide moiety [2]. Indeed, the majority of 5-HT_6 receptor antagonists still possess a sulfonyl-related feature. In contrast, the first 5-HT_6 receptor agonist, EMDT (**7**), was designed based on the finding that 5-HT_6 receptors tolerate a small alkyl group at the tryptamine 2-position whereas many other serotonin receptors do not [2]. 5-HT_3 serotonin receptors are an exception; for example, 2-methyl-5-HT has long been used as a “selective” 5-HT_3 receptor agonist. However, once it was realized that 2-methyl-5-HT binds with much higher affinity at 5-HT_6 receptors than at 5-HT_3 receptors (K_i values *ca.* 45 nM and 1,200 nM, respectively) [2], and that 5-HT_3 receptors do not readily accommodate a methoxy substituent at the 5-position of the tryptamine nucleus, it was apparent that 2-substituted 5-methoxytrptamines should be investigated. 5-Methoxy-2-methyltryptamine (**6**) was shown to bind at 5-HT_6 receptors with little to no affinity (i.e., K_i >10,000 nM) for 5-HT_3 receptors [2]. Studies aimed at increasing the lipophilicity and metabolic stability of this compound eventually resulted in EMDT (**7**; K_i = 16 nM) [7]. A related analog examined in the course of these studies was PMDT (**8**; also referred to in the literature as BGC20-761 on occasion); unexpectedly, PMDT (K_i = 20 nM) was demonstrated to be a 5-HT_6 receptor antagonist [7]. Hence, shortly after the discovery of **2–5**, there was evidence that a sulfonamide moiety was not required for binding at 5-HT_6 receptors or for 5-HT_6 receptor antagonist action. An indirect consequence of these studies was that pharmacological actions once ascribed to a 5-HT_3 receptor mechanism on the basis that they were produced by 2-methyl-5-HT, an agent now recognized as a 5-HT_3/5-HT_6 receptor agonist, were (and are still) in need of re-examination [8].

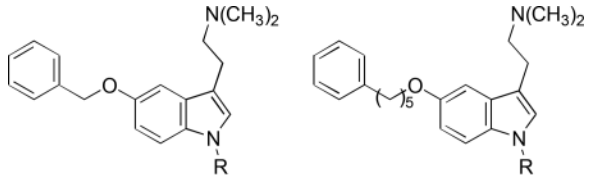


A rather remarkable finding was made by researchers of Esteve in 2005 [5, 9, 10]. By incorporating a sulfonamide moiety at the tryptamine 5-position, the resulting compounds (total of >50) displayed a range of functional activities at 5-HT_6 receptors. For example, compound **9** (K_i = 7.2 nM) is 5-HT_6 receptor antagonist, compound **10** (K_i = 0.8 nM) is a partial agonist, and compound **11** (K_i = 3.5 nM) is a full agonist [5]. E-6837 (**12**; K_i = 0.2 nM) was initially reported to be an antagonist, but was subsequently found to be a 5-HT_6 receptor partial agonist in in vitro assays and a full agonist at a constitutively active 5-HT_6 receptor [5, 10].



The vast majority of investigations of 5-HT_6 receptor pharmacology have employed Ro 04-6790 (**2**), Ro 63-0563 (**3**), SB-271046 (**4**), and their immediate structural descendants and/or radiolabeled analogs. However, there is a considerable literature on arylsulfonyltryptamines, such as MS-245 (**5**) and related compounds, that has not been previously reviewed. The general purpose of this review is to describe the impact that tryptamine derivatives such as MS-245 (**5**), EMDT (**7**), and PMDT (**8**) have had on 5-HT_6 receptor research, to examine how various 5-HT_6 receptor ligands might be structurally interrelated, and to attempt to synthesize concepts that might be useful for subsequent ligand design.

The N_1-benzenesulfonyltryptamine MS-245 (**5**) was independently reported by two different investigative groups at nearly the same time – by an academic group in 2000 [11] and by Merck in 2001 [12]. Both groups conducted structure-affinity relationship (SAFIR) studies, but the Merck group conducted more extensive pharmacological evaluations [12, 13]. Initial structure-affinity studies focused primarily on the benzenesulfonyl portion, tryptamine 5-position substituents, and terminal amine substituents; the results were in general agreement in that a variety of substituents was tolerated on the benzenesulfonyl group or that it could be replaced by a 1- or 2-naphthyl group, that an indolic 5-methoxy group was generally optimal, and that small terminal amine substituents were preferred [11–13]. Since that time, numerous structure-activity studies have been conducted on N_1-arylsulfonyltryptamines and many novel agents have been developed. Noteworthy is that an aryl group is required, but that an intact tryptamine nucleus is not. Introduction of an N_1-arylsulfonyl group to a simple tryptamine parent, depending upon the particular tryptamine, can enhance affinity by at least 10- to upwards of 100-fold [14]. There are, however, some curious exceptions. For example, introduction of the N_1-benzenesulfonyl moiety did not enhance the affinity of **13** (K_i = 18 nM) or **15** (K_i = 6.3 nM) (K_i = 14 nM and 17 nM for **14** and **16**, respectively) [14]. Perhaps tryptamine analogs with large or bulky 5-position substituents bind differently than compounds such as MS-245 (**5**), or bind in a manner similar to **9–12**.



13: R = H
14: R = SO_2Ph

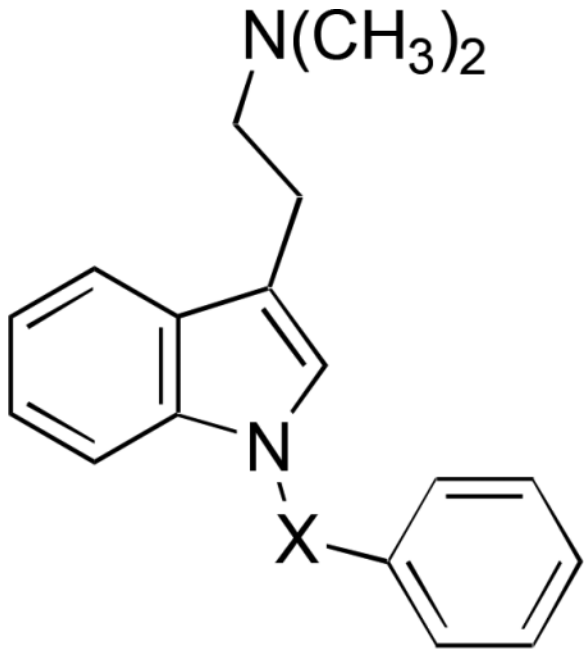
15: R = H
16: R = SO_2Ph

What follows is a discussion of the influence on 5-HT_6 receptor binding of structural modification of arylsulfonyltryptamines in as systematic a manner as possible.

Sulfonyl moiety

A variety of N_1-aryl- or N_1-heteroarylsulfonyl groups, and aryl- or heteroarylsulfonyl substituents, is tolerated. Indeed, manipulation of the arylsulfonyl moiety can alter affinity over a broad range and can also alter functional activity from antagonist to agonist action as will be described. It was demonstrated some time ago that N_1-benzyltryptamines bind at 5-HT_6 receptors [14], but only a few examples were examined. For example, **17** (K_i = 6 nM) binds with an affinity comparable to its benzenesulfonyl counterpart **18** (K_i = 4.1 nM) [2]. This raised a question about the necessity of a sulfonyl group for binding at 5-HT_6 receptors. A more recent study found that although N_1-benzyltryptamines bind, they typically do so with lower affinity than their corresponding N_1-benzenesulfonyl analogs, and that parallel structural changes within the two series (i.e., N_1-benzyltryptamines and N_1-benzenesulfonyltryptamines) did not result in parallel shifts in receptor affinity [15]. On this basis, it was speculated that the N_1-benzyl and N_1-benzenesulfonyl series might be binding in a dissimilar manner. This is noteworthy when attempting to explain the binding of these agents (e.g. docking studies using graphics receptor models): does the sulfonyl group (i.e.,

do the sulfonyl oxygen atoms) of benzenesulfonyltryptamines interact with a specific receptor feature? A more direct test was to examine sulfenamide **19** which lacked the two oxygen functions of **18**; compound **19** (K_i = 90 nM) displayed 20-fold reduced affinity relative to **18** suggesting that one, if not both, oxygen atoms of **18** contribute to the binding of the N_1-benzenesulfonyltryptamines [16]. The results are supported by current graphics models of 5-HT_6 receptors, and docking studies with 5-HT_6 receptor agonists and antagonists [16] (e.g. see Figure 1).

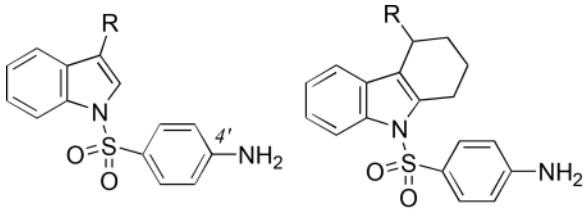


17: X = CH_2
18: X = SO_2
19: X = S

Terminal amine and side chain

Being a tryptamine analog, like serotonin (**1**) itself, it was assumed that the terminal amine and the aminoethyl chain would be required for binding. It was found that small alkylamine substituents were generally tolerated, but that larger substituents typically resulted in decreased 5-HT_6 receptor affinity [11–14]. The presence of the amine itself was assumed to be essential. This was especially true when it was considered that this amine most likely interacts with the 5-HT_6 receptor TM3 aspartate moiety (i.e., the aspartate residue in the third transmembrane helix of 5-HT_6 receptors) [16]. However, shortening the chain of **18** to its corresponding gramine counterpart (**20**; K_i = 3.1 nM) did not adversely impact affinity, and **20** retained 5-HT_6 receptor antagonist action [17]. The results were wholly unexpected. Table 1 shows a comparison of several additional tryptamine and gramine analogs and, with the exception of **25**, chain shortening had little effect on 5-HT_6 receptor affinity.

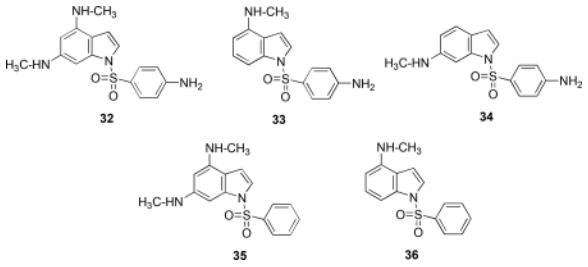
So, a tryptamine is not required for binding. This led to another question: is the terminal amine itself required for binding? The hypothesis might be tested by removing the terminal amine; because removal of the amine would result in a water insoluble compound, it was necessary to locate a distant region of the molecule where an amine could be introduced to facilitate the preparation of a water-soluble salt. Compounds **28** and **29** (K_i = 12 and 10 nM, respectively) were found to bind with high affinity at 5-HT_6 receptors [e.g. see: 19]. Similar results were obtained with **30** and **31** (K_i = 2.0 and 29 nM, respectively).



28: R = CH_3
29: R = H

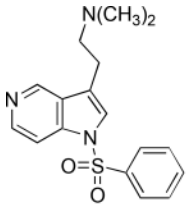
30: R = $CH_2N(CH_3)_2$
31: R = H

At this point, structures such as **29** were beginning to take on some structural resemblance to Ro 04-6790 (**2**) and Ro 63-0563 (**3**) and it was considered that they might possibly represent conformationally constrained analogs of these ligands. Ro 04-6790 (**2**) and Ro 63-0563 (**3**) possess five or four, respectively, basic nitrogen atoms and it is not known with certainty which one(s) is (are) crucial for binding [e.g. see: 20]. An investigation was undertaken whereby methylamino groups were added to the structure of **29** [19]. The results were inconclusive. That is, although the tri-amine **32** (K_i = 1.9 nM) displayed higher affinity than **29** (K_i = 10 nM) or di-amines **33**, **34**, and **35** (K_i = 21, 7.0, and 26 nM, respectively) [19], the range of affinities was very narrow making it impossible to determine which amine might be more important than another for binding. Of interest, though, was the finding that no particular amine, including the benzenesulfonyl amine (i.e., see **35**), seemed essential for binding. But, this, too, was less than clear because **36** (K_i = 217 nM) displayed much lower affinity than **33** [21]. On the basis of superimposition studies, it was speculated that in some cases where a 4'-amino group is present the 4'-amino arylsulfonylindoles might bind "upside-down" relative to the arylsulfonyltryptamines [21]. That is, in the absence of the tryptamine side chain, the 4'-amino group might utilize the same amine binding site, presumably the TM3 aspartate, as the terminal amine of the arylsulfonyltryptamine analogs.



In comparison with Ro 63-0563 (**3**), to determine if the pyridine ring nitrogen atom is contributory to binding, several 5-azaindoles were examined. Compound **37** (K_i = 84 nM) displayed reduced affinity relative to **18** (K_i = 4.1 nM), as did **38** (K_i = 41 nM) relative to **28**

(K_i = 12 nM) [22]. Nevertheless, these compounds possessed affinities similar to those of **2** and **3**.



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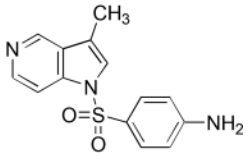
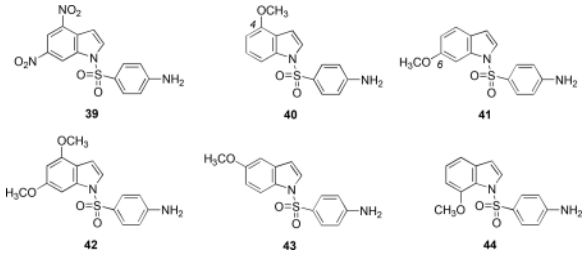
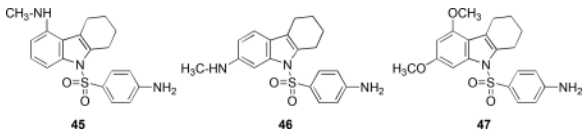


38

Interestingly, the di-nitro counterpart of **32** (i.e., **39**, K_i *ca.* 1,000 nM) displayed low affinity for 5-HT_6 receptors suggesting that the methylamine groups of **32** might be making an electronic contribution to binding [19]. Accordingly, several analogs were prepared that possessed electron-donating methoxy groups; in each case, the methoxy compounds (i.e., **40**, **41**, **42**; K_i = 3.3, 1.8, and 0.8 nM, respectively) displayed higher affinity than their corresponding methylamine analogs [23]. The affinity of **42** was 15 times higher than that of Ro 63-0563 (**3**), and nearly 60 times that of Ro 04-6790 (**2**). Introduction of a 5-methoxy or 7-methoxy group (**43** and **44**, K_i = 22 and 53 nM, respectively), examined simply to complete the series, did not have this affinity-enhancing effect [21].

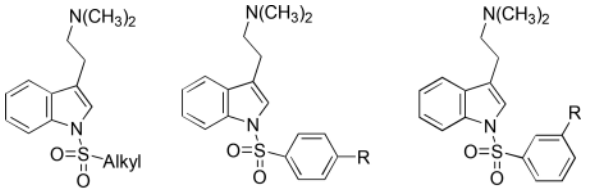


Introduction of a 4’-amino group was generally tolerated for the interaction of benzenesulfonyltryptamines and benzenesulfonylindoles at 5-HT_6 receptors and often resulted in several-fold enhanced affinity [e.g. 17]. Similar results were seen with the “tricyclic tryptamines”; for example conversion of the *des*-4’-amino analog of **30** (structure not shown, K_i = 1.5 nM) to its 4’-amino counterpart **30** (K_i = 2.0 nM) was tolerated [24]. But, the “tricyclic indoles” seemed to behave differently than the simpler indoles. For example, rather than showing enhanced affinity, methylamino analogs **45** (K_i = 165 nM) and **46** (K_i = 205 nM), and the dimethoxy analog **47** (K_i = 200 nM), as compared with **33**, **34**, and **42**, respectively, displayed lower affinity than **31** (K_i = 29 nM); this led to the suggestion that tricyclic indoles (i.e., tetrahydrocarbazoles) might bind differently than the other compounds previously examined [21].



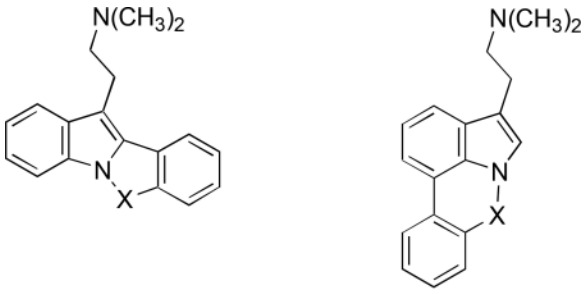
Arylsulfonyl moiety

A wide variety of N_1-arylsulfonyl (e.g. substituted phenyl, 1-naphthyl, 2-naphthyl, various heteroaryl) groups has been examined [5, 11] and an entire review could be written on this topic alone. However, replacement of the N_1-arylsulfonyl group by an N_1-alkylsulfonyl or branched alkylsulfonyl group (i.e. **48**) resulted in low-affinity compounds [15]. This likely excludes a simple hydrophobic-type of interaction between the aryl group and the receptor. Also, aryl substituents can have a very dramatic influence on affinity. For example, translocation and extension of the 4'-position amine substituent was investigated. Compound **49** (K_i = 0.8 nM) [17], the 4'-amino counterpart of **18** (K_i = 4.1 nM), binds with 5-fold enhanced affinity. Moving the amino group to the 3'-position (**50**, K_i = 2.1 nM) was tolerated; but, insertion of a methylene group between the amine and the aromatic ring (i.e., **51**, K_i = 2,360 nM; **52**, K_i = 960 nM) reduced affinity considerably [18].



48 **49**: R = -NH_2 **51**: R = -CH_2NH_2 **50**: R = -NH_2 **52**: R = -CH_2NH_2

Of interest was the preferred conformation of the arylsulfonyl moiety upon binding to the receptor. To address this question, several conformationally-constrained analogs were examined. Compound **53** was of particular interest because it represented a hybrid of **18** and the general structure of the 5-HT_6 antagonist PMDT (**8**) (see **57** below). That both **53** (K_i = 143 nM and **54** (K_i = 4,500 nM) bind with lower affinity than **18** (K_i = 4.1 nM) led to speculation that neither of these structures represented a preferred binding conformation for the arylsulfonyl group and that a more gauche conformation was probably optimal [25]. Alternatively, the constrained structure also imposed conformational restrictions on the 2-phenyl group of PMDT-like compounds that might be less than optimal. Somewhat similar results were obtained with constrained analogs of **17** (i.e., **55** and **56**; K_i = 60 and 3,770 nM, respectively) [21].



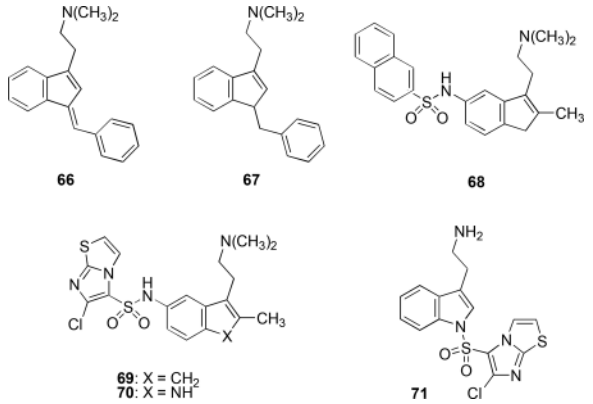
53: X = SO_2 **55**: R = CH_2 **54**: X = SO_2 **56**: R = CH_2

This led to another question. The 2-phenyl compound PMDT (**8**) and the N_1-benzenesulfonyl compound **18** are 5-HT_6 receptor antagonists. Can the receptor tolerate both substituents at the same time? Indeed, as shown in Table 2, introduction of the N_1-benzenesulfonyl substituent resulted in enhanced affinity in the presence of a 2-phenyl group. In light of this new information, had it been available at the time, it might have been unreasonable to expect that **53** should bind with high affinity.

Indole ring

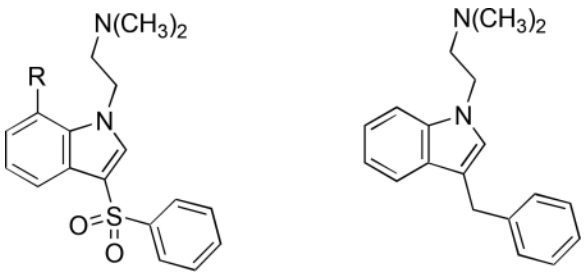
Early questions addressed the necessity or importance of an intact indole nucleus. Obviously, the binding of compounds such as Ro 04-6790 (**2**), Ro 63-0563 (**3**) and SB-271046 (**4**) indicated that an indole ring is not required for 5-HT_6 receptor binding. Because of the uncertainty of how arylsulfonyltryptamines or arylsulfonylindoles bind relative to **2–4**, it was not yet appropriate to extrapolate between indole-containing and indole-lacking structures. So, the question became: is the presence of the indole nitrogen atom a prerequisite for the binding of tryptamine (or indole-related) analogs at 5-HT_6 receptors?

Indene **66** (K_i = 57 nM), lacking an indolic N_1 nitrogen atom, displayed 10-fold lower affinity than **17** (K_i = 6 nM); but, the reduced affinity of **66** might be explained by the conformational restraint imposed on the “benzyl” group by the benzylidene moiety [26]. The reduced analog of **66** (i.e., **67**, K_i = 3 nM) displayed an affinity comparable to **17** indicating that the indole nitrogen atom was not required for binding [26]. Taking advantage of this observation, a series of 5-substituted indene analogs was recently examined [27]. Compounds **68** (K_i = 50.6 nM) was found to be an agonist, as was **69** (E-15136; K_i = 4.5 nM) [28]. A particularly nice comparison is the structural relationship between **69** and the agonist **70** (E-6801; K_i = 2.2 nM) [28]. Of note is that WAY-181187 (**71**, K_i = 2 nM), which bears the same arylsulfonyl group as **69** and **70**, but at the indole 1-position, has been reported to be a potent, selective, and orally available 5-HT_6 receptor agonist [29].



The necessity of the indole nitrogen atom could also be assessed by an examination of isotryptamines wherein the nitrogen atom has been effectively moved from the tryptamine “1-position” to the “3-position”. Compounds **72** (K_i = 20 nM) and **73** (K_i = 22 nM) bind at

5-HT_6 receptors, and the latter is an antagonist [30]. Likewise, the benzyl analog **74** (K_i = 32 nM) also binds [26].



72: R = H
73: R = OCH_3

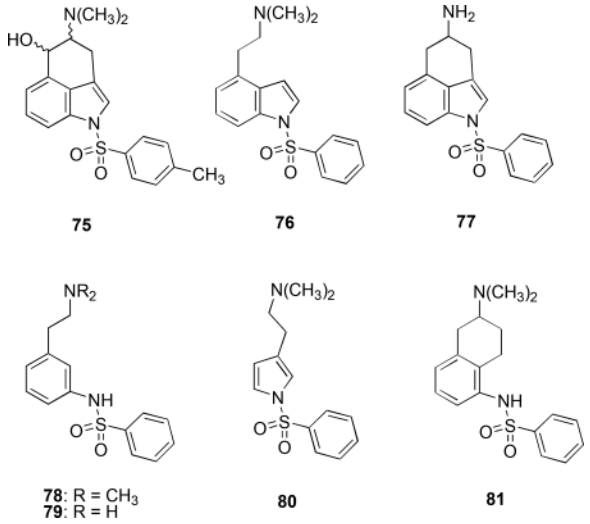
74

From these studies, it might be concluded that the presence of an indolic nitrogen atom, at the "ring 1-position", is not a prerequisite for binding. Additional studies will be described below.

Side chain conformation

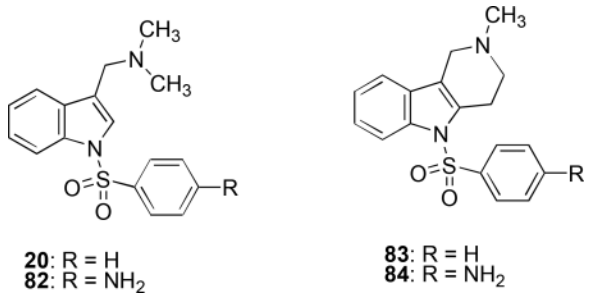
Lysergic acid diethylamide (K_i *ca.* 1 nM), although non-selective, binds with high affinity at 5-HT_6 receptors suggesting that tryptamines might adopt an ergoline-like conformation upon binding [31]. Merck investigators demonstrated that the benz[*cd*]indole **75** (K_i = 7.2 nM) binds at 5-HT_6 receptors; they also demonstrated that the *N*,*N*-dimethylaminoethyl chain of **18** could be moved from the indole 3-position to the 4-position (**76**, K_i = 1.5 nM) [12]. Although **75** possessed a benzylic hydroxyl group, a 4'-methyl group, and the stereochemistry of **75** was undefined (except that the hydroxyl and amine groups were trans to one another) – making it difficult to formulate structure-affinity comparisons – consideration of the results from **75** together with those from **76** provided some insight about the conformation of the side chain necessary for binding. A structurally simpler benz[*cd*]indole was later prepared and the racemate displayed high affinity (i.e., racemic **77**, K_i = 1.6 nM); **(-)-77** (K_i = 0.7 nM) displayed 5-fold higher affinity than **(+)-77** (K_i = 3.4 nM) [18].

The indole nucleus of **18** (K_i = 4.1 nM) was "bisected" to **78** (K_i = 52 nM) and **80** (K_i = 15 nM) with each bearing the *N*,*N*-dimethylaminoethyl chain (*viz*: **5** and **76**). The primary amine **79** (K_i = 21 nM) displayed twice the affinity of **78** [32]. Furthermore, the flexible chain of **78** was constrained to aminotetralin **81**. There was little difference in the affinities of *R*-**(+)-81** (K_i = 49 nM) and *S*-**(-)-81** (K_i = 90 nM) [16], and their affinities were comparable to that of **78**. This argues that an ergoline-type conformation is important; but, it also argues (due to the higher affinity of **76** and **77**), that an intact indolic nucleus, although perhaps not required, might be optimal for high affinity.

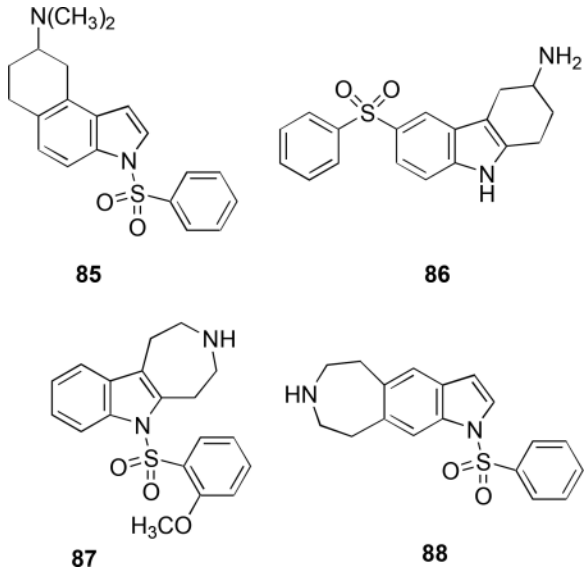


75 76 77 78: R = CH_3 79: R = H 80 81

Consistent with the above findings, conformationally constrained analogs of gramines **20** (K_i = 3.1 nM) and **82** (K_i = 6.9 nM) [17], which constrain the side chain in a “non-ergoline” type of conformation (i.e., **83** and **84**; K_i = 155 and 140 nM, respectively) displayed substantially reduced affinity [18]. Taken together, the results indicated that ergoline-type conformations of arylsulfonyltryptamines are probably optimal (but: see below), and that stereochemistry about the ergoline 4-position is playing a role (but a minimal role) in binding. In addition, the results supplement the above argument that while an intact indole, or the presence of an indolic nitrogen atom, is not an absolute requirement for binding, the presence of both might be optimal.



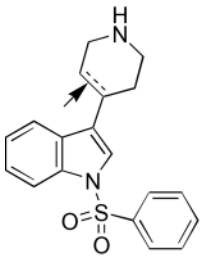
In their review, Holenz et al. [5] provided binding data on a variety of conformationally constrained tryptamines or tryptamine-related agents (examples include racemic **85** and **86**; K_i = 1 nM and 58 nM, respectively). Wyeth has recently described a series of azepinoindoles (e.g. **87**; K_i = 19 nM) [33], as has GlaxoSmithKline (i.e., **88**; functional K_i in a cAMP accumulation assay = 1.6 nM) [34]. These revelations, coupled with the binding of gramines (see Table 1), benzenesulfonylindoles such as **32**, **42**, Esteve compounds such as **7**, as well as others (see below), give reason for pause when attempting to envision how these agents bind at 5-HT_6 receptors. They also create problems in QSAR and molecular modeling studies where assumptions are made on how to superimpose indolic nuclei. Is an ergoline-like conformation really that important? Or, is it just one of several possible tryptamine conformations accepted by 5-HT_6 receptors?



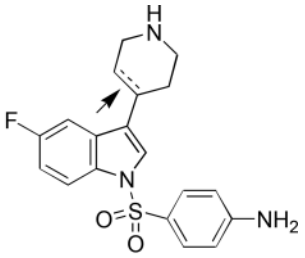
Side chain modifications

During the past 25 or so years of serotonin receptor research, medicinal chemists have found that the “tryptamine core” of serotonin often can be replaced with other structurally related moieties that, sometimes, results in interesting and subtype-selective agents. Hence, it was logical that some of these “cores” be examined in the 5-HT_6 field; this strategy is especially attractive when it is realized that incorporation of an N_1-arylsulfonyl moiety typically renders agents selective for 5-HT_6 (sometimes 5-HT_7) receptors (indeed, there is increased focus on comparing 5-HT_6 *versus* 5-HT_7 receptor affinity for novel agents that are being developed). Such studies, which might identify new compounds, and new “cores”, are well worth the effort. An example already discussed is the isotryptamines (initially identified in studies with 5-HT_{1A} receptors). There are several other core structures that have been exploited and, actually, some novel cores have been identified.

Wyeth found that piperidinoindole analogs of **18** (K_i = 4.1 nM) bind with high affinity at 5-HT_6 receptors (**89**, K_i = 2 nM; **90**, K_i = 12 nM). However, distinction in 5-HT_6 receptor affinity between the saturated (i.e., single bond) and unsaturated (i.e., double bond) series was lost upon introduction of a 4’-amino group (**91**, K_i = 1 nM; **92**, K_i = 2 nM); furthermore, all analogs behaved as 5-HT_6 receptor antagonists, but the presence of a 4’-amino group resulted in enhanced antagonist potency in functional assays [35].

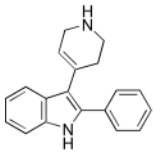


89: double bond
90: single bond

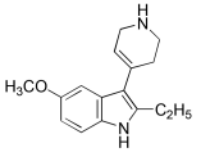


91: double bond
92: single bond

High-throughput screening by Merck led to the discovery of the antagonist **93** (IC_{50} = 2 nM) [36]. By analogy to the structures of the antagonist PMDT (**8**) and the agonist EMDT (**7**), the investigators speculated that **94** would be an agonist. This was found to be the case (**94**, IC_{50} = 90 nM); furthermore, structure-activity studies allowed the identification of an even higher-affinity, more selective agonist (**95**, IC_{50} = 7.4 nM) [36] with structural similarity to **6**. Bearing a piperidine ring substituent, analogs **96** (K_i values ranging from 1 to 24 nM) were identified as 5-HT_6 receptor antagonists [9], as was the ester LY-483518 (also known as SGS518, **97**; K_i = 1.3 nM) [5].



93



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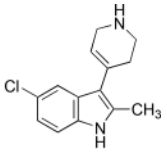

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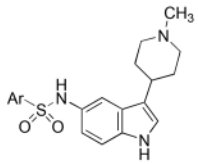

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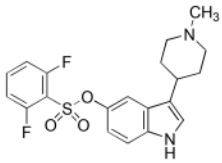
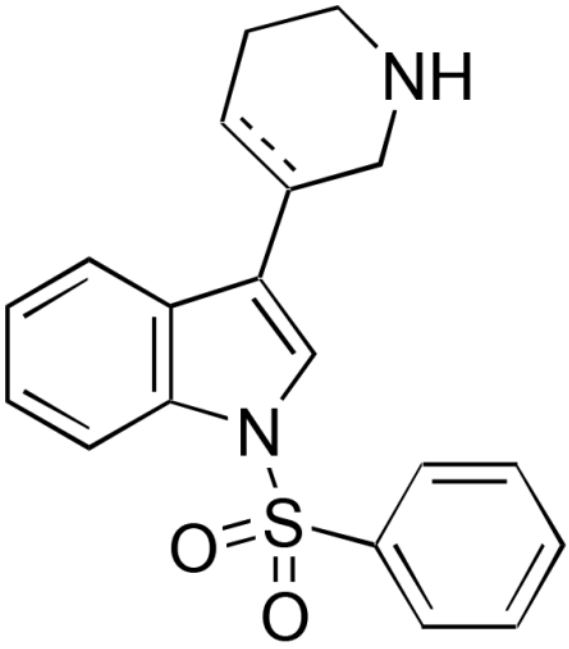


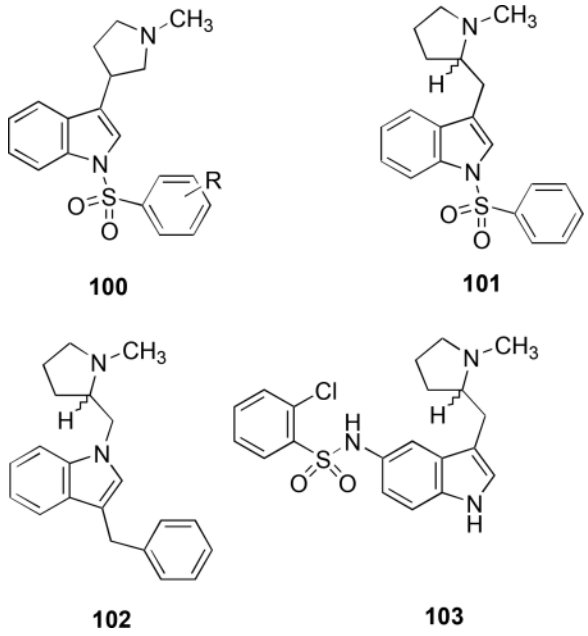
97

Moving the position of the piperidine nitrogen atom of **89**/**90** also resulted in some interesting compounds. Compound **98** (K_i = 4.6 nM) was found to bind with high affinity; but, when the double bond was reduced (**99**; racemate K_i = 2 nM), this created two optical isomers. The two enantiomers of the reduced compound (i.e., **99**) were separated and one (K_i = 3 nM) lacked agonist activity whereas the other (K_i = 1 nM) was a full agonist. Here is an example of where stereochemistry controlled functional activity [37].



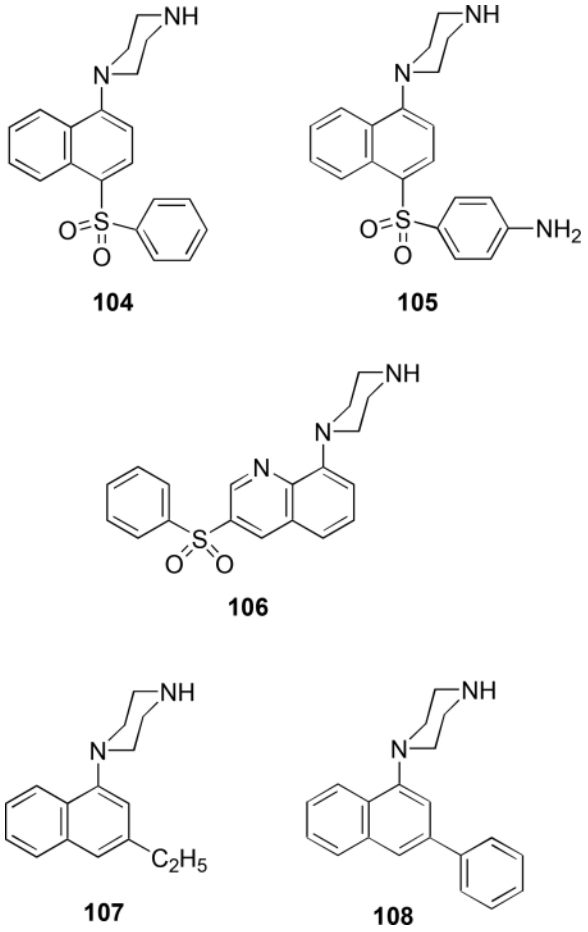
98: double bond
99: single bond

Contraction of the six-membered ring of **99** to a pyrrolidine ring resulted in a series of high-affinity antagonists (**100**; K_i values ranging from 1 to 15 nM depending on the identity of the aryl substituent) [36]. Allelix Pharmaceuticals identified **101**; they reported in the patent literature [38] that the *R*-isomer of this compound was a 5-HT_6 receptor antagonist with very high affinity (K_i <10 nM) without disclosing its physicochemical characteristics, or describing it's opposite enantiomer. Subsequently, Abate et al. [39] reported that the fully characterized ***R*-(+)-101** (K_i = 0.3 nM) binds with 5-fold higher higher affinity than its ***S*-(+)-101** isomer (K_i = 1.7 nM) [39]. Qualitatively similar binding results were obtained with the 3-benzylisotryptamine **102**; that is, ***R*-(-)-102** (K_i = 0.9 nM) displayed a higher affinity than ***S*-(+)-102** (K_i = 29 nM) [39]. Wyeth reported K_i values of 8.0 and 5.0 nM, respectively, for the two **101** isomers, but found that the lower-affinity ***R*-(+)-101** was the more effective of the two as an antagonist [37]. Interestingly, whereas ***S*-103** functioned as an antagonist, its *R*-enantiomer was an agonist [40]. Overall, stereoselectivity did not seem to be a controlling factor (i.e., stereoselectivity might play a role, but does not seem to be a major determinant) for binding, but can play a role in functional potency.



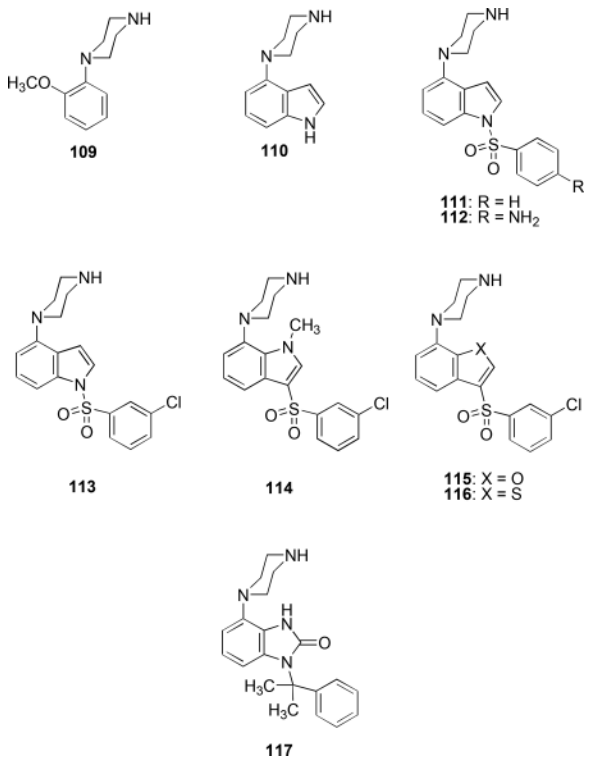
Other core modifications

Depending upon substituents that are present in the molecule, 1-naphthylpiperazines bind at a number of different populations of 5-HT receptors but are, generally, non-selective ligands. In other words, the naphthylpiperazine core is a rather “neutral” core and, by itself, does not confer any selectivity. Because it had been demonstrated by several investigators, for other series of 5-HT_6 receptor ligands, that the arylsulfonamide could be replaced by an aryl sulfone, compound **104** (K_i = 3.8 nM) was prepared and found to bind with high affinity [41]. Its 4’-amino counterpart **105** (K_i = 0.9 nM) displayed somewhat enhanced affinity [41]. The azanaphthyl compound (i.e., the 3-substituted 8-aminoquinoline) SB-742457 (**106**; K_i *ca.* 0.2 nM) is a 5-HT_6 receptor antagonist [4].The binding of the naphthylpiperazine counterparts of EMDT (**7**) and PMDT (**8**), that is **107** and **108** (K_i = 21 nM and 9.3 nM, respectively) [41], supported the contention that the 1-naphthylpiperazine core might be useful for development of novel 5-HT_6 receptor ligands, and further supports the idea that neither an indole nucleus, indole nitrogen atom, nor tryptamine side chain is required for binding.

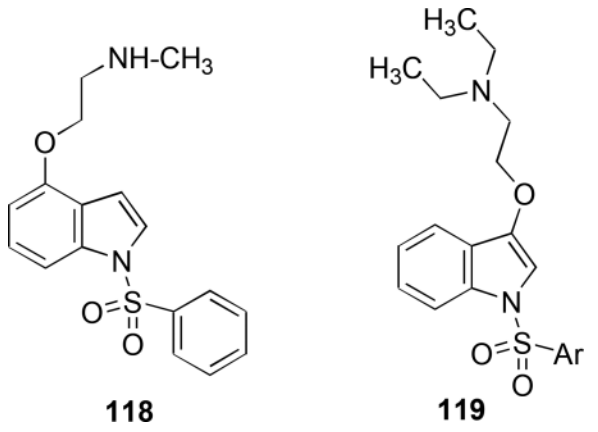


Although 1-(2-methoxyphenyl)piperazine (**109**; K_i = 1,200 nM) binds with low affinity at 5-HT_6 receptors [31], introduction of the appropriate arylsulfonamide results in high-affinity compounds, (e.g. SB-271046; **4**). Given the rotational flexibility about the aryl-piperazine bond found in the naphthylpiperazines, 4-(1-piperazino)indoles might represent yet another template for 5-HT_6 receptor ligands. Indeed, piperazinoindoles could conceivably represent a conformationally constrained form of phenylpiperazines such as SB-271046 (**4**) much in the same manner that compounds such as **32** might represent conformationally constrained analogs of Ro 04-6790 (**2**) and Ro 63-0563 (**3**) as discussed above. Accordingly, several piperazinoindoles were prepared and evaluated. The N_1-unsubstituted piperazinoindole **110** (K_i = 2,700 nM) displayed very low affinity [19]. However, incorporation of an N_1-benzenesulfonyl moiety resulted in a dramatic enhancement of affinity (**111**; K_i = 1.0 nM) [19]. Moreover, although known that introduction of an N_1-arylsulfonamide can enhance affinity, this is one of the largest enhancements observed to date. Further incorporation of a 4'-amino group led to a slight increase in 5-HT_6 receptor affinity (**112**; K_i = 0.4 nM) [19]. Compound **111** was also independently reported by GlaxoSmithKline, who designed the compound using the same conformational-constraint strategy, to bind with high affinity (K_i *ca.* 0.3 nM), and further identified **113** (K_i *ca.* 3 nM) as a selective, brain-penetrant 5-HT_6 receptor antagonist [42]. Again showing the utility of the isotryptamine core, **114** (K_i *ca.* 3 nM) displayed an affinity comparable to that of **113**, and the *N*-methyl group of **114** could

be replaced by either an oxygen or a sulfur atom (**115** and **116**; K_i *ca.* 1 nM and 0.5 nM, respectively) [42]. Roche has patented a related benzimidazolone (**117**; K_i *ca.* 0.3 nM) [6a].

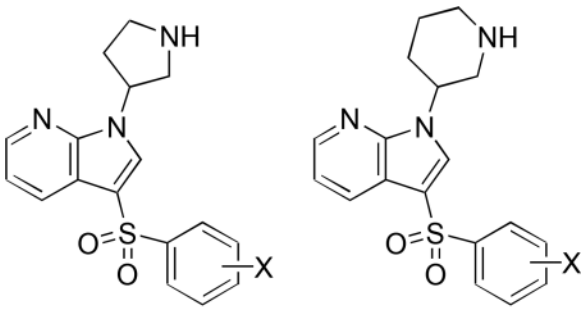


Investigators at Wyeth replaced the piperazine moiety of SB-271046 (**4**)-related agents with an aminoethoxy group to identify a novel series of indolic 5-HT_6 receptor antagonists including **118** (K_i = 1 nM) [43]. A series of related compounds was prepared where the aminoethoxy group was located at the indole 3-position (i.e., **119**) [44]; unfortunately, no binding data were reported.



Other indole-related cores include 5-azatryptamines (e.g. **37**), 5-azaindoles (e.g. **38**) [22], and 7-azaindoles [45]. For example, the 7-azaindole **120** (K_i = 1.3 nM) was found to be a 5-

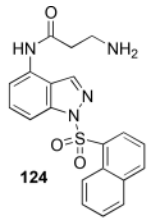
HT_6 receptor partial agonist whereas **121** (K_i = 4.3 nM) was an antagonist; also, **122** (K_i = 2.0 nM) was an antagonist whereas **123** (K_i = 2.4 nM) was a partial agonist [45].



120: X = 3-Br
121: X = 4-Br

122: X = 2-F
123: X = 3-F

Indazoles might be viewed as representing yet another class of “azaindoles”, and compound **124** (K_i = 7.9 nM) [46] bears some structural resemblance to **118**. Although moving the side chain to the ring 5-position decreased affinity by about 6-fold, the 6-substituted compound displayed enhanced affinity (**125**; K_i = 0.5 nM). Other modifications included cyclization of the side chain to **126** (K_i = 2.3 nM) and **127** (K_i = 1.3 nM) [46].



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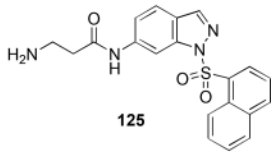

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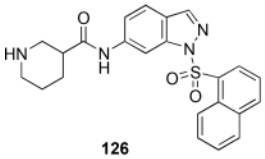

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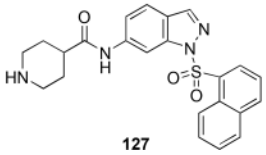
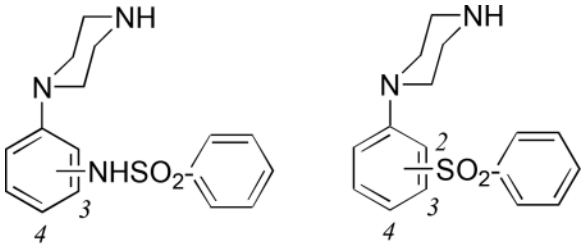


127

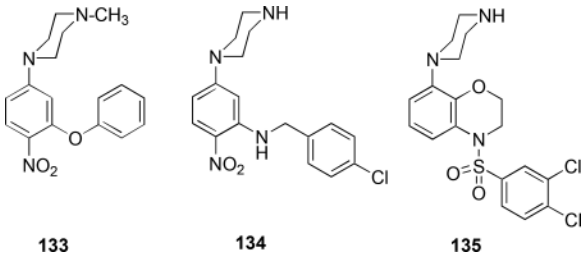
As already discussed, the bicyclic indole ring is not required for binding at 5-HT_6 receptors. In fact, various monocyclic arylamines (e.g. **2**, **3**) display affinity for this population of receptors. Monocyclic analogs of **104** have been examined. The 4-substituted sulfonamide **128** (K_i = 85 nM) displayed lower affinity than **104**, but the sulfonamide was also tolerated at the 3-position (**129**; K_i = 62 nM) [32]. Unexpectedly, it was found that conversion of **128** to its corresponding sulfone (i.e., **130**; K_i = 6.9 nM) resulted in enhanced affinity, and in an affinity approximating that of **104** [32]. The 3-substituted sulfone displayed even higher affinity (**131**; K_i = 1.2 nM) [32]. Showing that this is not a nonspecific effect, the 2-substituted compound did not bind as well (**132**; K_i = 4,000 nM) [32].



128: 4-
129: 3-

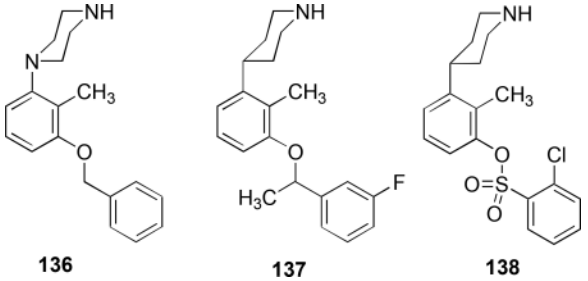
130: 4-
131: 3-
132: 2-

Esteve screened a large virtual library of compounds and identified a set of 2000 compounds that might bind at 5-HT$_6$ receptors; further refinement of the model identified 235 compounds of interest. This screening led to several monocyclic arypiperazines such as **133** and **134** [47]. Compound **133** (K_i = 27 nM) behaved as a partial agonist whereas **134** (K_i = 8 nM) was an agonist [47]. Noteworthy is that these compounds do not possess a sulfonamide or sulfone moiety. Roche has also examined arylpiperazines as conformationally constrained analogs of SB-271046 (**4**). A series of dihydrobenzoxazines was prepared and evaluated, structure-affinity relationships were examined, and the highest-affinity ligand identified was the antagonist **135** (K_i *ca.* 0.1 nM) [48].



133 **134** **135**

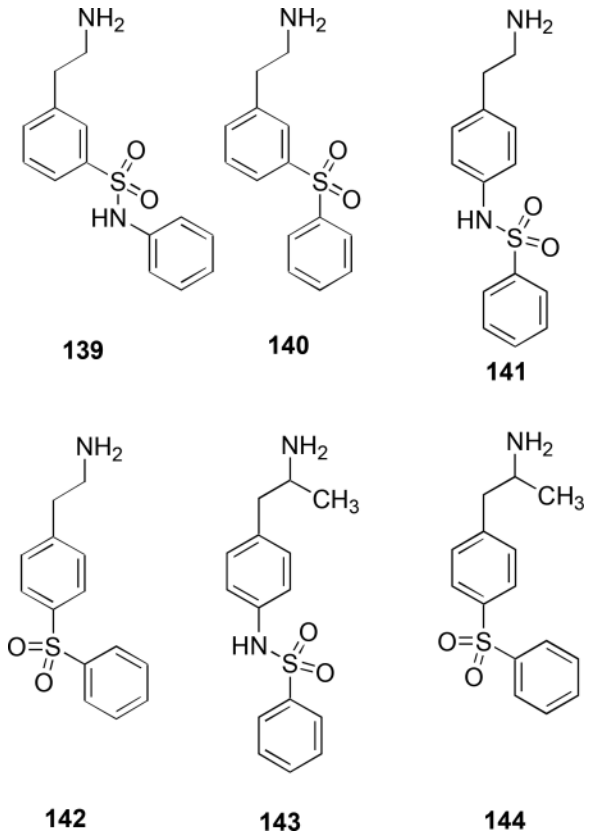
Investigators at Pfizer identified phenylpiperazine **136** (K_i = 1.3 nM) by high-throughput screening; the structure was modified to phenylpiperidine **137** (K_i = 6.9 and 39.8 nM for *S*-**137** and *R*-**137**, respectively) that showed a better ADME and selectivity profile [49]. Several sulfonates such as **138** (K_i = 5.9 nM) were also examined [49].



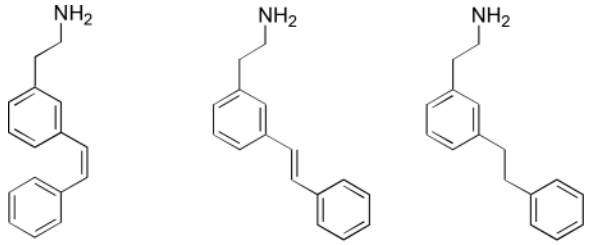
136 **137** **138**

Phenylethylamines have been used as 1-(phenyl)piperazine mimics. Indeed, it was discussed above that certain phenylethylamines (e.g. **78** and **79**; K_i = 52 nM and 21 nM, respectively) bind at 5-HT$_6$ receptors [32]. The “reverse sulfonamide” of **78** (i.e., **139**; K_i = 70 nM) as well as its sulfone counterpart **140** (K_i = 50 nM) retained the affinity of **78** [32]. By analogy

to results obtained with **104**, several 4-substituted phenylethylamines were examined. Sulfonamide **141** (K_i = 38 nM) displayed an affinity comparable to **79**, but less than that of **104**; sulfone **142** (K_i = 37 nM) possessed similar affinity [32]. An α-methyl group was incorporated into **141** to assess the effect of stereochemistry; the *R*- and *S*-isomers of **143** (K_i = 34 nM and 100 nM, respectively) again showed that stereochemistry about this position plays a minimal role in binding [21] and the results were consistent with those obtained with the isomers of aminotetralin **81**. Similar results were obtained with sulfone **144** (K_i = 73 nM and 177 nM for the *R*- and *S*-isomers, respectively) [18].

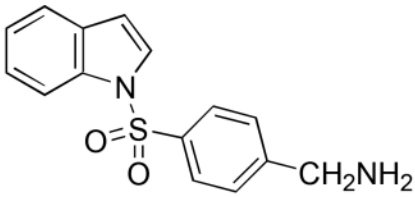


In order to determine if it was simply the presence of the aryl group of the 3-position substituent of **139** that was responsible for 5-HT_6 receptor affinity, several simplified analogs possessing a spacer in place of the sulfonamide were evaluated. The low affinities of **145**, **146**, and **147** (K_i = 930 nM, 173 nM, and 630 nM, respectively) indicate that the sulfonyl portion of **139** contributes to binding [18].



145 **146** **147**

As described earlier, insertion of a methylene group between the 4'-amine and aryl ring of 4'-benzenesulfonyltryptamines resulted in decreased affinity (e.g. compare the nearly 3,000-fold difference in affinity between **49** and **51**). However, this same molecular modification of 4'-arylsulfonylindole **29** (K_i = 10 nM) had little effect on affinity (i.e. **148**, K_i = 25 nM), once again suggesting that some arylsulfonyltryptamines and arylsulfonylindoles might bind differently. Further homologation of the chain in **148** to **149** (K_i = 2.5 nM) resulted in enhanced affinity [18]. Compound **149** now contains a phenylethylamine, leading to the suggestion that **149** might bind in an orientation similar to that of other phenylethylamine analogs (e.g. as shown by **149b**). Compound **150** (K_i = 59 nM) is the "reverse sulfonamide" of **141** (K_i = 38 nM). Hence, **149** might be viewed as a conformationally constrained analog of **141**.



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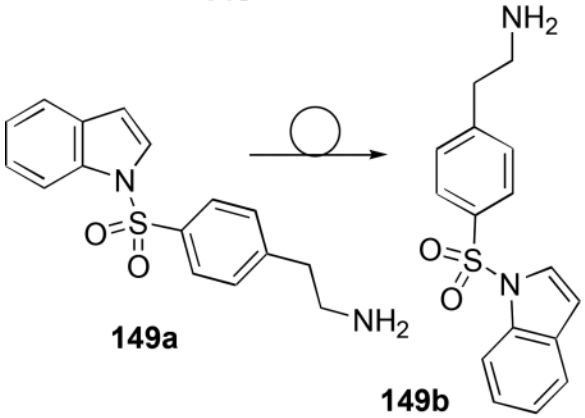
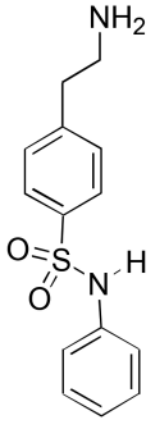
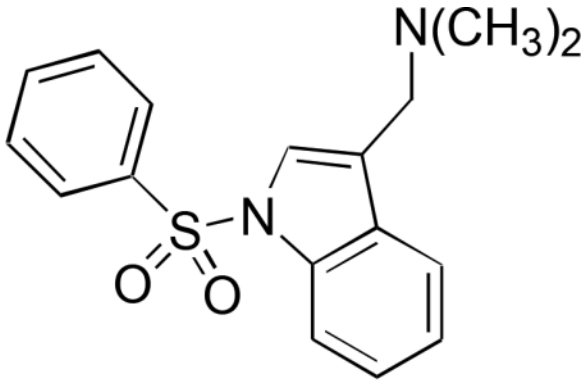


149a **149b**



150

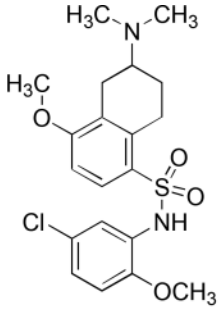
While on the topic of phenylethylamines, gramines might be viewed as a partially conformationally constrained phenylethylamine; that is, the benzenesulfonylgramines might conceivably interact with 5-HT_6 receptors in an orientation (e.g. see **151**) where the N_1-arylsulfonyl moiety mimics the 5-position arylsulfonyl portion of compounds such as **7**-**9**. If this is the case, there might be no correspondence between the affinities of a series of substituted benzenesulfonylgramine and benzenesulfonyltryptamines. However, the binding data in Table 1 tend to argue against this.



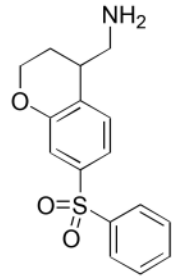
151

Compound **152** (K_i = 1.7 nM) is a reverse sulfonamide with an aminotetralin core whereas **153** (K_i *ca.* 0.7 nM) is a partially conformationally constrained phenylethylamine; both have been patented [6]. Despite lacking an ergoline-type conformation, compound **154** (K_i *ca.* 25 nM) possessed an affinity similar to that of **142** and **143** [50]. Nevertheless, increasing the size of the 6-membered ring afforded **155** (K_i *ca.* 1 nM) that displayed enhanced affinity [50].

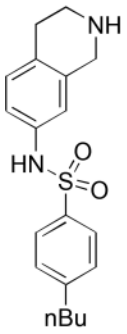
Wyeth has described a series of benzoxazoles as 5-HT_6 receptor antagonists (e.g. **156**; K_i = 7.1 nM) [51]. Might these represent conformationally constrained analogs of **140**; is the intact piperazine moiety required for binding? These are questions that will need to be answered.



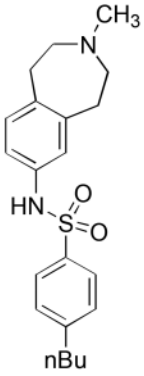
152



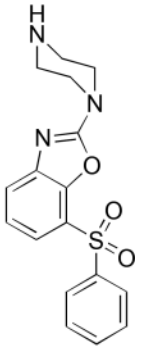
153



154

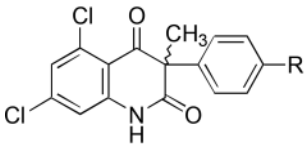


155

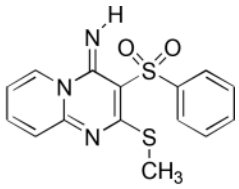


156

All this having been said, novel 5-HT_6 receptor ligands continue to be developed with non-indolic cores that are seemingly unrelated to those described above. For example, quinolinedione **157** where R = H (K_i = 54.7 nM) was identified by high-throughput screening as a novel 5-HT_6 receptor antagonist [52]. Introduction of a *p*-hydroxyl group (i.e., **157**, R = OH; K_i = 12.3 nM) resulted in a higher-affinity compound [52]. Remarkable is that these compounds, unlike all the others described herein, lack a basic nitrogen atom. On the other hand, **158** (IC_{50} = 4 nM), identified on the basis of virtual screening, was shown several years ago to be a 5-HT_6 receptor antagonist [53]; its structural resemblance to **157** might offer some clues to how these agents bind.



157



158

QSAR and molecular modeling studies

In the early days of 5-HT_6 receptor research, it was assumed that introduction of an N_1-arylsulfonyl substituent converted a simple tryptamine from a 5-HT_6 receptor agonist to a 5-HT_6 receptor antagonist. This is now known to be a false assumption; it is true that many N_1-arylsulfonyltryptamines (see above discussion) display actions as antagonists; however, some behave as partial agonists, and yet others as full agonists. 5-HT_6 receptor agonists and

antagonists might bind differently [16]. But, the question remains: do tryptamine-derived antagonists bind more like the tryptamine agonists or like non-tryptamine antagonists?

Various QSAR and molecular modeling studies have been reported [e.g. 16, 20, 54–57], and they have advanced our understanding of what structural features might be important for binding and how they might interact with amino acid residues of 5-HT_6 receptor graphics models. Nevertheless, such studies may be in need of constant revision as new compounds are identified that challenge established concepts.

Summary

This review has attempted to address the impact, direct or indirect, that N_1-arylsulfonyltryptamines and N_1-arylsulfonylindoles have had on the identification and development of novel 5-HT_6 receptor ligands, and makes an attempt to show (often in retrospect) how the many currently available agents might be related to one another. The important issues of 5-HT_6 receptor selectivity, bioavailability, and pharmacokinetics were not addressed; indeed, it is generally more important, from our perspective, to understand how compounds bind at a receptor before tackling these issues, and information derived from structure-affinity and structure-activity studies can often aid in the design of agents with greater selectivity and bioavailability. Gratitude is owed to investigators at Esteve for providing exhaustive compilations [5, 6a] of the many structure-types found in the primary scientific and patent literature that bind at 5-HT_6 receptors. But, the present review (although acknowledging their reviews) differs in that it is (1) not as comprehensive; the present review attempts to show how various structure-types might be related to one another and, (2) where possible, to provide the thinking of those who were preparing these compounds. Where hypotheses were described, they are provided here. In many instances, the design approaches taken were quite rational. Often, no attempt was made to maximize affinity or activity within a given series; rather, specific questions were being addressed such as: what is a preferred conformation for binding; what is the necessity or contribution of a particular substituent to 5-HT_6 receptor affinity? There is certainly room to improve upon the affinity, selectivity, bioavailability, and pharmacokinetics of many of these compounds. Obviously, high-throughput screening and virtual screening methods have sometimes resulted in novel structure-types; docking of agents to graphics models of 5-HT_6 receptors and QSAR studies also have made contributions. Needless to say, a wide variety of 5-HT_6 receptor agonists, partial agonists, and antagonists have been developed during the past decade. It is still uncertain how all these compounds bind relative to one another. However, there are some intriguing clues that might eventually lead to a global model of interaction (or, perhaps, to more than one model – which seems more likely).

Arylsulfonyltryptamines as 5-HT_6 receptor ligands represent a serendipitous discovery [11, 12]. As it turns out, neither the “arylsulfonyl” nor the “tryptamine” portion of these compounds is essential for binding. However, their presence is often found to be optimal. The arylsulfonyl group can be replaced with a benzyl group, and the tryptamine moiety can be truncated to a gramine or even an indole. Even an intact indole nucleus is not required for binding. When present, a preferred conformation of the tryptamine aminoethyl side chain seems to be one that mimics the ergolines; but there are numerous exceptions. In fact, it is

difficult (if not impossible) to envision how the basic amines of some of the compounds can interact at a common locus if their indolic ring systems are strictly superimposed. Several studies pursued arylsulfonylindoles as possibly representing conformationally constrained analogs of Ro 04-6790 (**2**), Ro 63-0563 (**3**) and SB-271046 (**4**) – three of the first 5-HT_6 receptor antagonists reported. This led to the discovery of novel structure-types, and might explain a common mode of binding at 5-HT_6 serotonin receptors. In reverse fashion, the "bicyclic" tryptamines were bisected into monocyclic agents resembling **2–4** that, by and large, retained affinity. These were then further developed and exploited to identify new high-affinity ligands, and so that structures might be related back to the arylsulfonyltryptamines and **2-4**. Core structures previously used in 5-HT receptor research were exploited, and new core structures were identified. Novel structures were also identified by high-throughput screening. The world currently has available an enormous number of 5-HT_6 receptor ligands. Those interested in QSAR studies certainly have a wealth of data to draw upon. What remains is to fully understand the pharmacology of these agents.

Acknowledgments

Work conducted in the author's laboratory was supported, in part, by US Public Health Service grant MH 60599 and the A. D. Williams Fund. RK was supported by T32 grant DA 007027.

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18. This review presents some new data on previously unreported compounds. The compounds analyzed within 0.4% of theory for C, H, and N and spectral data are consistent with assigned structures. Human 5-HT_6 receptor binding assays were conducted as previously reported [16]. The particular salts utilized, their recrystallization solvents, and their melting points are provided. **For 21**: HCl, MeOH/Et_2O, 226–228 °C; **22**: HCl, MeOH/Et_2O, 208–210 °C; **23**: HCl, MeOH/Et_2O, 240–242 °C; **24**: HCl, MeOH/CH_2Cl_2, 254–255 °C **25**: oxalate, precipitated with Et_2O, 126 °C with decomposition; **26**: HCl, MeOH/Et_2O, 208–212 °C; **27**: HCl, MeOH/CH_2Cl_2, 215–216 °C; **50**: HCl, MeOH/Et_2O, 229–231 °C; **51**: HCl, MeOH/Et_2O, 242–243 °C; **52**: HCl, MeOH/Et_2O, 259–265 °C; **57**: oxalate, MeOH, 134–136 °C; **58**: oxalate, MeOH, 242–243 °C; **59**: oxalate, MeOH, 198–199 °C; **60**: oxalate, acetone, 189–190 °C; **61**: oxalate, acetone, 189–190 °C; **62**: oxalate, MeOH/Et2O, 175–176 °C; **63**: oxalate, acetone, 164–165 °C; **64**: oxalate, MeOH, 192–193 °C; **65**: oxalate, MeOH/Et_2O, 205–207 °C; (+)**-77**: HCl, iPrOH/Et_2O, 148–150 °C; **(−)-71**: tartrate, MeOH/Et_2O, 204–206 °C; **(+)-71**: tartrate, MeOH/Et_2O, 204–206 °C; **83**: HCl, MeOH/Et_2O, 263–265 °C; **84**: oxalate, MeOH/Et_2O, 150–152 °C; *R*-**(−)-144**: HCl, MeOH/Et_2O, 249–251 °C; *S*-**(+)-144**: HCl, MeOH/Et_2O, 252–253 °C; **145**: HCl, MeOH/Et_2O, 142–144 °C; **146**: HCl, MeOH/Et_2O, 270–272 °C; **147**: HCl, MeOH/Et_2O, 215–215 °C; **148**: HCl, MeOH/Et_2O, 228–230 °C; **149**: HCl, EtOH/Et_2O, 251–254 °C; **150**: HCl, MeOH/Et_2O, 268–271 °C.
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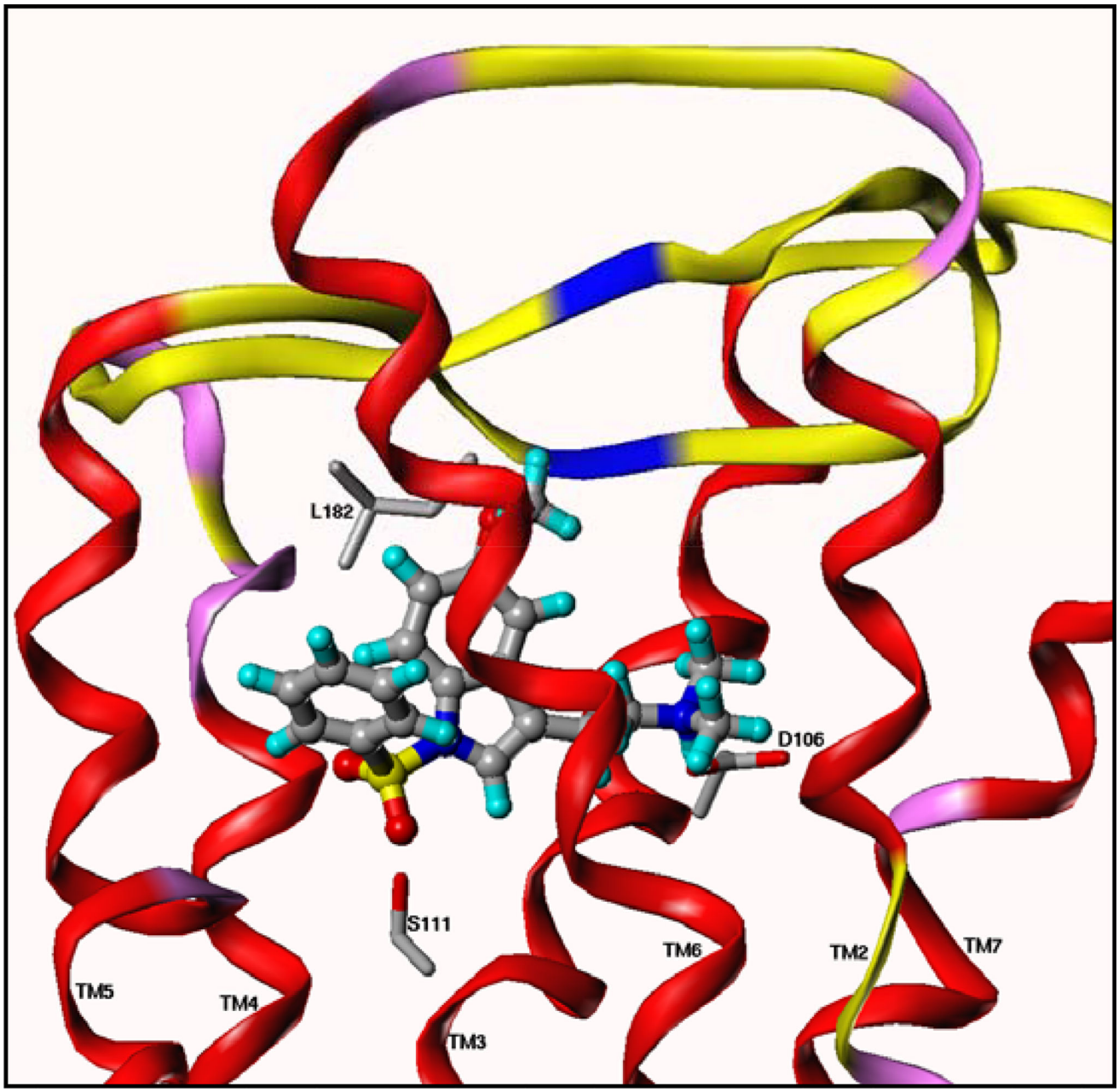


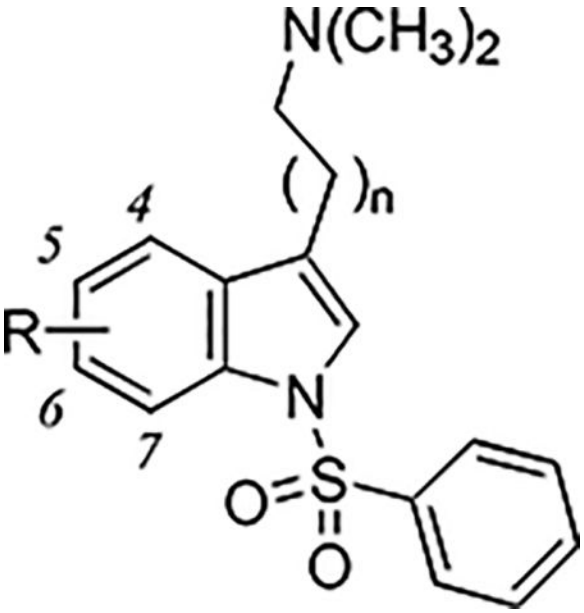
Figure 1.

A proposed binding mode of MS-245 (**5**) at the h5-HT_6 receptor looking through the extracellular side of the helical bundle. Transmembrane helix 5 (TM5), TM6, and TM7 are nearest the viewer. MS-245 is rendered as a ball-and-stick model and the heavy atoms of side chain residues whose heavy atoms fall within 3 Å of a ligand heavy atom are shown as capped sticks. The model was generated as previously reported [16] but represents a different view. Note that the terminal amine of MS-245 is within 2.7 Å of Asp106 (D106) whereas the sulfonyl oxygen atoms are within hydrogen bond distance to Ser111 (S111) on

TM3 and Thr-196 on TM4 (not shown in this view). Greater detail and discussion are available [16].

Table 1

Comparison of h5-HT_6 receptor affinities for several *N*,*N*-dimethyltryptamines (n = 1) and their corresponding gramine analogs (n = 0) [18].

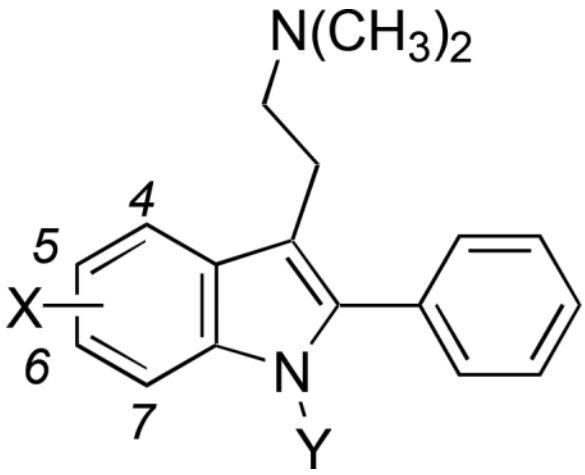


R		K_i, nM (±SEM)[a]		
		n = 1		n = 0
H	**18**	4.4	**20**	3.1
4-OCH_3	**21**	11 (±1)	**24**	13 (±2)
5-OCH_3	**5**	2.1	**25**	87 (±15)
6-OCH_3	**22**	15 (±1)	**26**	40 (±6)
7-OCH_3	**23**	140 (±15)	**27**	180 (±40)

[a]The assay was conducted (h5-HT_6 cDNA transiently expressed in HEK-293 cell) with [^{3}H]LSD as radioligand [16]. SEM not provided where data have been previously reported.

Table 2

Comparison of h5-HT_6 receptor affinities for several N_1-unsubstituted and N_1-benzenesulfonyl-substituted analogs of PMDT (**8**) [18].



		K_i, nM (±SEM)[a]		
X	**Y = H**		**Y = SO_2Ph**	
H	**57**	2.0 (±1)	**61**	1.3 (±0.1)
4-OCH_3	**58**	11 (±5)	**62**	4.6 (±1.1)
5-OCH_3	**8**	20	**63**	3.8 (±1.6)
6-OCH_3	**59**	65 (±15)	**64**	10 (±3)
7-OCH_3	**60**	110 (±45)	**65**	12 (±5)

[a]The assay was conducted (h5-HT_6 cDNA transiently expressed in HEK-293 cell) with [^{3}H]LSD as radioligand [16]. SEM not provided where data have been previously reported.