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# 1-(1-Naphthyl)piperazine as a novel template for 5-HT<sub>6</sub> serotonin receptor ligands

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Abstract—4-Sulfonyl analogs of 1-(1-naphthyl)piperazine bind at human 5-HT<sub>6</sub> receptors and represent a novel class of human 5-HT<sub>6</sub> receptor ligands. © 2005 Elsevier Ltd. All rights reserved.

1-(1-Naphthyl)piperazine (1-NP; **1a**), like serotonin (5-hydroxytryptamine, 5-HT, **2**) itself, is a fairly promiscuous serotonergic ligand that binds in a nonselective manner at multiple populations of serotonin (5-HT) receptors; we have suggested that 1-NP is a general tryptamine-mimic.<sup>1</sup> Consistent with this notion, we have found that 1-NP (**1a**,  $K_i = 120$  nM) binds to human 5-HT<sub>6</sub> (h5-HT<sub>6</sub>) serotonin receptors with an affinity comparable to that of 5-HT ( $K_i = 100$  nM), and with 10-fold higher affinity than the monocyclic 2-methoxyphenyl-piperazine **3** ( $K_i = 1.200$  nM),<sup>2</sup> indicating that its bicyclic nature might contribute to binding.

5-HT<sub>6</sub> Serotonin receptors represent one of the seven major types of 5-HT receptors  $(5-HT_1-5-HT_7)$ .<sup>3–7</sup> This receptor population was identified about 10 years ago and within the past few years several selective ligands have been reported (reviewed<sup>6–9</sup>). 5-HT<sub>6</sub> receptors are of interest due to their possible involvement in depression, psychosis, cognition, and appetite.<sup>6–9</sup>

We identified MS-245 (4) as one of the first 5-HT<sub>6</sub> antagonists and have studied its structure–affinity relationships.<sup>10</sup> For example, the 5-methoxy group of MS-245 (4) can be replaced by hydrogen with little impact on affinity; Russell and Dias<sup>11</sup> have reported similar

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findings. Although the presence of the sulfonyl moiety is optimal, a methylene group in its place causes only a modest decrease in affinity<sup>12</sup> without altering antagonist action. We have also shown that the tryptaminergic ligands 2-ethyl-5-methoxy-N,N-dimethyltryptamine (5;  $K_i = 16$  nM) and 2-phenyl-5-methoxy-N,N-dimethyltryptamine (6;  $K_i = 20$  nM) bind to h5-HT<sub>6</sub> receptors with relatively high affinity.<sup>13</sup>

The present investigation was focused not so much on developing novel 5-HT<sub>6</sub> ligands as it was on testing



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the hypothesis that 1-NP (1a) is a tryptamine-mimic at these receptors. Toward this end, we prepared analogs of 1a bearing tryptaminergic substituents either known to be tolerated, or that impart enhanced 5-HT<sub>6</sub> receptor affinity. Specifically, we prepared 1-(1-naphthyl)piperazine analogs of several previously characterized MS-245 (4) derivatives and of compounds 5 and 6, and then measured their affinity at h5-HT<sub>6</sub> receptors.

### **Results and discussion**

## Synthesis

Piperazine intermediate **1b** was obtained by treatment of **15** with bis(2-chloroethylamine) in the presence of triethylamine (Scheme 1). Reaction of **1b** with phenyl or benzyl 9-BBN in the presence of  $PdCl_2(dppf)$  afforded **1c** and **e**, respectively, (Table 1).

Compounds 1d and f were prepared in a common manner (Scheme 1). Reaction of 16 with PhCOCl or PhSO<sub>2</sub>Cl in the presence of AlCl<sub>3</sub> afforded 17 and 18; subsequent coupling with piperazine provided the desired targets. Compound 1g was prepared from *N*-Boc-protected 1b by treatment with BuLi and 4-nitrobenzenesulfonyl chloride, deprotection of the product with trifluoroacetic acid, and SnCl<sub>2</sub> reduction of the nitro group.

The 3-substituted naphthylpiperazines were obtained from the protected naphthalene diol **20**,<sup>14</sup> which was prepared in four steps from commercially available diol **19** (Scheme 2). Using a Suzuki-type coupling reaction,



Scheme 1. Reagents: (a) HN(CH<sub>2</sub>CH<sub>2</sub>Cl)<sub>2</sub>, NEt<sub>3</sub>; (b) PdCl<sub>2</sub>(dppf), Ph or Bn 9-BBN, dioxane; (c) PhCOCl or PhSO<sub>2</sub>Cl, AlCl<sub>3</sub>; (d) piperazine, NaOBu-*t*, PdCl<sub>2</sub>[P(*o*-tol)<sub>3</sub>]<sub>2</sub>.

compound **20** was converted to **21b**, and **21b** was converted to triflate **22b**. Compound **22b** was allowed to react with *N*-Boc-protected piperazine using BINAP,  $Cs_2CO_3$ , and 18-crown-6 in toluene with  $Pd_2dba_3$  as catalyst. Deprotection of **23b** afforded **1i**. Compound **21b** could also be obtained directly from **19** as previously reported.<sup>15</sup> Compound **1h** was obtained by a similar sequence of reactions using a Stille reaction by first converting **20** to its corresponding ethyl derivative **21a** by reaction with  $Et_4Sn/PdCl_2(PPh_3)_2$  and LiCl in DMF.

Table 1. Physicochemical and h5-HT<sub>6</sub> serotonin receptor binding properties of arylpiperazines and related derivatives

# N-N-N-

	R	Overall yield, %	Melting point, °C	Recrystallization solvent	Empirical formula <sup>a</sup>	$h5$ -HT <sub>6</sub> $K_i$ , nM (±SEM) <sup>b</sup>
1a	Н	_	_	_	_	120 (±20)
1b	4-Br	45	208-209	MeOH	$C_{14}H_{15}BrN_2 C_2H_2O_4$	54 (±7)
1c	4-Ph	51	207-208	MeOH	$C_{20}H_{20}N_2 \cdot C_2H_2O_4^{d}$	190 (±90)
1d	4-C(=O)Ph	39	171-172	MeOH/Et <sub>2</sub> O	$C_{21}H_{20}N_2O \cdot C_2H_2O_4^{e}$	57 (±10)
1e	4-CH <sub>2</sub> Ph	37	210-211	MeOH	$C_{20}H_{20}N_2 \cdot C_2H_2O_4^{\ d}$	35 (±9)
1f	4-SO <sub>2</sub> Ph	38	201-203	MeOH/Et <sub>2</sub> O	$C_{20}H_{20}N_2O_2S \cdot C_2H_2O_4$	3.8 (±0.8)
1g	$4-SO_2C_6H_4NH_2-p$	5	197–199	MeOH	$C_{20}H_{21}N_3O_2S \cdot 2.75HCl$	0.9 (±0.3)
1h	3-Et	16	244-246	MeOH/Et <sub>2</sub> O	C16H20N2·HCl	21 (±2)
1i	3-Ph	15	252–254	MeOH/Et <sub>2</sub> O	C <sub>20</sub> H <sub>20</sub> N <sub>2</sub> ·HCl <sup>f</sup>	9.3 (±1.3)
8		64	$200-202^{\circ}$	2-PrOH	$C_{16}H_{13}NO_2S$	34 (±4)
9		18	185–186	EtOAc	C <sub>16</sub> H <sub>13</sub> NO <sub>3</sub> S·HCl	63 (±11)

<sup>a</sup> All compounds analyzed within 0.4% of theory for C, H, and N; C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> = oxalate salt. Compound **1a**, as its HCl salt, was available from previous investigations.

<sup>b</sup>  $K_i$  values were determined in triplicate.<sup>21</sup>

<sup>c</sup> Lit.<sup>23</sup> mp 203–205 °C.

<sup>d</sup> Crystallized with 0.1 mol H<sub>2</sub>O.

<sup>e</sup> Crystallized with 0.5 mol H<sub>2</sub>O.

<sup>f</sup>Crystallized with 0.25 mol H<sub>2</sub>O.



Scheme 2. Reagents: (a)  $Et_4Sn$ ,  $PdCl_2(PPh_3)_2$ , LiCl, DMF; or  $PhB(OH)_2$ ,  $Na_2CO_3$ ,  $Pd(PPh_3)_4$ , THF; (b)  $(CF_3SO_2)_2O$ ,  $Et_3N$ ,  $CH_2Cl_2$ ; (c) *N*-Boc-piperazine, BINAP,  $Cs_2CO_3$ , 18-crown-6,  $Pd_2dba_3$ , toluene; (d) HCl, EtOH; (e) benzene, AlCl<sub>3</sub>.

Compound **8** was obtained following hydrolysis of the product obtained by heating naphthalene, trifluoroacetic acid, and trifluoroacetic anhydride with sulfanilic acid. Hydroxylamine **9** was isolated in an attempt to obtain **8** from 1-bromonaphthalene by reaction with BuLi and 4-nitrobenzenesulfonyl chloride followed by reduction of the product with SnCl<sub>2</sub>.

### Pharmacology

MS-245 (4;  $K_i = 2.1 \text{ nM}$ )<sup>10</sup> binds with high affinity to h5-HT<sub>6</sub> receptors. Replacement of the benzenesulfonyl moiety with a phenyl group ( $K_i = 33 \text{ nM}$ ) or benzoyl group ( $K_i = 18 \text{ nM}$ ) results in about 10- to 15-fold decreased affinity; the corresponding benzyl analog ( $K_i = 6.5 \text{ nM}$ ) binds with only 3-fold decreased affinity.<sup>12</sup> In the present investigation, the benzenesulfonyl analog of **1** (**1f**;  $K_i = 3.8 \text{ nM}$ ; Table 1) displayed an affinity comparable to that of MS-245 (**4**). Replacement of the benzenesulfonyl moiety by a phenyl group (**1c**;  $K_i = 190 \text{ nM}$ ), benzoyl group (**1d**;  $K_i = 57 \text{ nM}$ ), or benzyl group (**1e**,  $K_i = 35 \text{ nM}$ ) resulted in lower-affinity compounds. As with the benzenesulfonyltryptamine series, the sulfonyl group seems optimal for h5-HT<sub>6</sub> serotonin receptor affinity.

Compounds **1h** ( $K_i = 21 \text{ nM}$ ) and **1i** ( $K_i = 9.3 \text{ nM}$ ) are the 1-(1-naphthyl)piperazine analogs of tryptamines **5** and **6** ( $K_i = 16 \text{ nM}$  and 20 nM, respectively). As in the tryptamine series, an ethyl or phenyl substituent results in enhanced affinity relative to the parent compound 1-NP (**1a**;  $K_i = 120 \text{ nM}$ ).

We have previously demonstrated (i) that the methoxy substituent of **4** does not contribute to binding, (ii) that a 4'-amino substituent is tolerated, and (iii) that an intact tryptamine moiety is not essential for 5-HT<sub>6</sub> affinity.<sup>16</sup> For example, compound 7 ( $K_i = 12 \text{ nM}$ ),<sup>16</sup> which lacks the tryptamine amine moiety, binds with only about 6-fold reduced affinity relative to **4**.

To further test possible binding similarities between the naphthylpiperazines and the tryptamines, we prepared compounds **1g** and **8**. The 4'-amine analog **1g** ( $K_i = 0.9 \text{ nM}$ ) was found to bind with high affinity. Furthermore, as with the tryptamines, removal of the 'side chain' (i.e., the piperazine moiety) in the benzenesulfonylnaphthylpiperazine series, also resulted in a compound (i.e., **8**;  $K_i = 34 \text{ nM}$ ) that binds to 5-HT<sub>6</sub> receptors, albeit with about 10-fold reduced affinity relative to **1f**. Hydroxylamine **9** ( $K_i = 63 \text{ nM}$ ) was isolated as a byproduct in the synthesis of **8**; compound **9** is the first hydroxylamine shown to bind to 5-HT<sub>6</sub> receptors.



Tryptamine 4, MS-245, is a 5-HT<sub>6</sub> antagonist.<sup>10</sup> The functional activity of compound **1f** at h5-HT<sub>6</sub> receptors was examined (i.e., 5-HT-stimulated adenylate cyclase; data not shown) and showed that **1f** also is a 5-HT<sub>6</sub> antagonist (**1f**  $pA_2 = 7.5 \pm 0.2$ ).

Given the lack of strict structural correspondence between an indole ring and a naphthyl ring, the results support the general notion that those structural features tolerated by, or that enhance, the 5-HT<sub>6</sub> serotonin receptor affinity of the tryptamine nucleus are also tolerated by or enhance the affinity of the corresponding 1-(1-naphthyl)piperazines. In fact, for eight compounds where such comparisons could be made (i.e., compounds **1a,c-1i**, and their corresponding tryptamine derivatives— $K_i$  values for which have been previously published<sup>2,10,12</sup>) there was a significant correlation between their  $pK_i$  values (r = 0.856) supporting the idea that parallel structural modification in the two series results in parallel shifts in receptor affinity.

Initially, it was found that simple arylpiperazines, such as **3**, bind to 5-HT<sub>6</sub> receptors with low affinity.<sup>2</sup> However, the arylpiperazine derivatives described here are not the first to demonstrate significant affinity for 5-HT<sub>6</sub> receptors. Incorporation of specific arylsulfonamide moieties dramatically enhances the affinity of **3** 

[i.e., 10;  $K_i = 5 \text{ nM}$  and 11 (SB-271046);  $K_i = 1 \text{ nM}$ ].<sup>17</sup> Furthermore, 'reverse' sulfonamides such as 12 (SB-357134;  $K_i = 3 \text{ nM}$ )<sup>18</sup> also bind to 5-HT<sub>6</sub> receptors with relatively high affinity. These findings indicate that the orientation of the sulfonamide portion of these molecules might not be a critical determinant of binding.



In the present investigation it was found that certain 1-(1-naphthyl)piperazine analogs of tryptamine bind to h5-HT<sub>6</sub> serotonin receptors, and that compound **1f**, like MS-245 (**4**), is a 5-HT<sub>6</sub> antagonist. However, unlike the sulfonamide MS-245 (**4**), **1f** is a sulfone. Several other sulfones have been recently shown to bind to 5-HT<sub>6</sub> receptors;<sup>19,20</sup> compounds **13** ( $K_i$  ca. 1 nM)<sup>19</sup> and especially **14** ( $K_i$  ca. 0.1 nM)<sup>19</sup> are particularly relevant to the present work. Nevertheless, whereas **14** is the sulfone of a 3-substituted arylpiperazine, compounds **1f** and **g** are sulfones of 4-substituted arylpiperazines.



The general conclusion drawn from these studies is that 1-NP (1a) represents a suitable template for the further development of 5-HT<sub>6</sub> serotonin receptor ligands, and upon incorporation of appropriate substituents (e.g., 1f,g), can result in compounds with high affinity for the receptor. The findings also present additional evidence for the high-affinity binding of sulfones to h5-HT<sub>6</sub> serotonin receptors, and demonstrate that arylpiperazines can bear the sulfone moiety at the ring 4-position as opposed to arylpiperazine compounds such as 14, which bear a sulfonyl moiety at the arylpiperazine 3-position. Additional studies with such compounds are now in progress.

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### **References and notes**

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- 21. The h5-HT<sub>6</sub> radioligand binding assay was performed as previously described.<sup>22</sup> In brief, h5-HT<sub>6</sub> cDNA was transiently expressed in HEK-293 cells using Fugene6 according to the manufacturer's recommendations. After 24 h transfection the medium was replaced; 24 h later, medium containing dialyzed serum (to remove 5-HT) was added. At 75 h after transfection, cells were harvested by scraping and centrifugation. Cells were then washed by

centrifugation and resuspension once in phosphate buffered saline (PBS; pH = 7.40) and then frozen as tight pellets at -80 °C until use. Binding assays were performed at room temperature for 90 min in binding buffer (50 mM Tris-Cl, 10 mM MgCl<sub>2</sub>, 0.1 mM EDTA, pH = 7.40) with [<sup>3</sup>H]LSD (1 nM final concentration) using 10  $\mu$ M clozapine for non-specific binding. Concentrations of unlabeled test agent (1–10,000 nM) were used for  $K_i$  determinations with  $K_i$  values calculated using the program LIGAND. Specific binding represented 80–90% of total binding.  $K_i$  values are the result of triplicate determinations.

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