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1-(1-Naphthyl)piperazine as a novel template for 5-HT$_6$ serotonin receptor ligands

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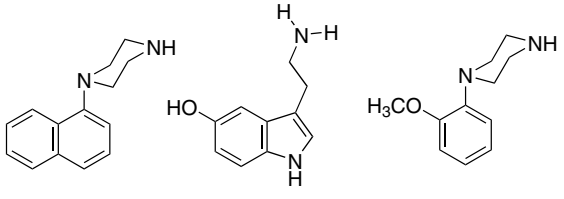
Abstract—4-Sulfonyl analogs of 1-(1-naphthyl)piperazine bind at human 5-HT$_6$ receptors and represent a novel class of human 5-HT$_6$ receptor ligands.

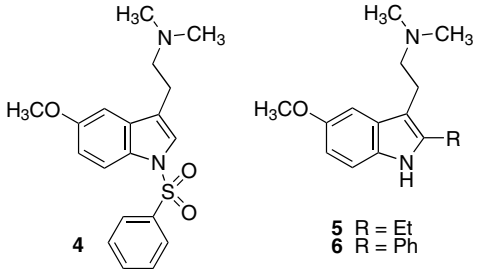
1-(1-Naphthyl)piperazine (1-NP; **1a**), like serotonin (5-hydroxytryptamine, 5-HT, **2**) itself, is a fairly promiscuous serotonergic ligand that binds in a nonselective manner at multiple populations of serotonin (5-HT) receptors; we have suggested that 1-NP is a general tryptamine-mimic.[1] Consistent with this notion, we have found that 1-NP (**1a**, K_i = 120 nM) binds to human 5-HT$_6$ (*h*5-HT$_6$) 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-methoxyphenylpiperazine **3** (K_i = 1.200 nM),[2] indicating that its bicyclic nature might contribute to binding.

5-HT$_6$ Serotonin receptors represent one of the seven major types of 5-HT receptors (5-HT$_1$–5-HT$_7$).[3–7] This receptor population was identified about 10 years ago and within the past few years several selective ligands have been reported (reviewed[6–9]). 5-HT$_6$ receptors are of interest due to their possible involvement in depression, psychosis, cognition, and appetite.[6–9]

We identified MS-245 (**4**) as one of the first 5-HT$_6$ antagonists and have studied its structure–affinity relationships.[10] For example, the 5-methoxy group of MS-245 (**4**) can be replaced by hydrogen with little impact on affinity; Russell and Dias[11] have reported similar findings. Although the presence of the sulfonyl moiety is optimal, a methylene group in its place causes only a modest decrease in affinity[12] 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 *h*5-HT$_6$ receptors with relatively high affinity.[13]

The present investigation was focused not so much on developing novel 5-HT$_6$ ligands as it was on testing





Keyword: 5-HT$_6$ Serotonin receptors.
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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_6 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 *h*5-HT_6 receptors.

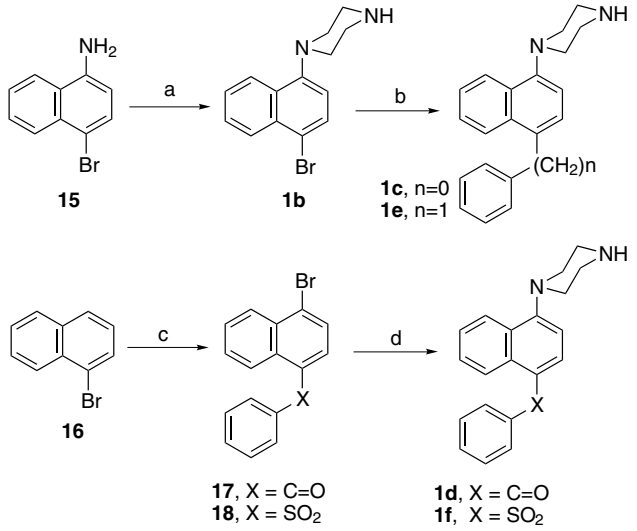
Results and discussion

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).

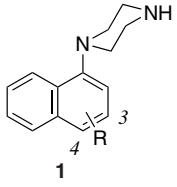
Compounds **1d** and **f** were prepared in a common manner (Scheme 1). Reaction of **16** with PhCOCl or $PhSO_2Cl$ in the presence of $AlCl_3$ afforded **17** and **18**; subsequent coupling with piperazine provided the desired targets. Compound **1g** was prepared from *N*-Boc-protected **1b** by treatment with BuLi and 4-nitrobenzenesulfonyl chloride, deprotection of the product with trifluoroacetic acid, and $SnCl_2$ reduction of the nitro group.

The 3-substituted naphthylpiperazines were obtained from the protected naphthalene diol **20**,[14] which was prepared in four steps from commercially available diol **19** (Scheme 2). Using a Suzuki-type coupling reaction, 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.[15] 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.



Scheme 1. Reagents: (a) $HN(CH_2CH_2Cl)_2$, NEt_3; (b) $PdCl_2$(dppf), Ph or Bn 9-BBN, dioxane; (c) PhCOCl or $PhSO_2Cl$, $AlCl_3$; (d) piperazine, NaOBu-*t*, $PdCl_2[P(o\text{-tol})_3]_2$.

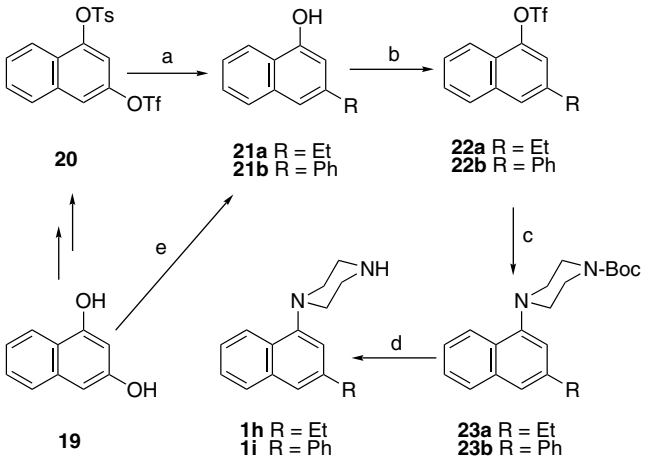
Table 1. Physicochemical and *h*5-HT_6 serotonin receptor binding properties of arylpiperazines and related derivatives



1

	R	Overall yield, %	Melting point, °C	Recrystallization solvent	Empirical formula[a]	*h*5-HT_6 K_i, nM (±SEM)[b]
1a	H	—	—	—	—	120 (±20)
1b	4-Br	45	208–209	MeOH	$C_{14}H_{15}BrN_2 \cdot C_2H_2O_4$	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_2O	$C_{21}H_{20}N_2O \cdot C_2H_2O_4$[e]	57 (±10)
1e	4-CH_2Ph	37	210–211	MeOH	$C_{20}H_{20}N_2 \cdot C_2H_2O_4$[d]	35 (±9)
1f	4-SO_2Ph	38	201–203	MeOH/Et_2O	$C_{20}H_{20}N_2O_2S \cdot C_2H_2O_4$	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_2O	$C_{16}H_{20}N_2 \cdot HCl$	21 (±2)
1i	3-Ph	15	252–254	MeOH/Et_2O	$C_{20}H_{20}N_2 \cdot HCl$[f]	9.3 (±1.3)
8	—	64	200–202[c]	2-PrOH	$C_{16}H_{13}NO_2S$	34 (±4)
9	—	18	185–186	EtOAc	$C_{16}H_{13}NO_3S \cdot HCl$	63 (±11)

[a] All compounds analyzed within 0.4% of theory for C, H, and N; $C_2H_2O_4$ = oxalate salt. Compound **1a**, as its HCl salt, was available from previous investigations.
[b] K_i values were determined in triplicate.[21]
[c] Lit.[23] mp 203–205 °C.
[d] Crystallized with 0.1 mol H_2O.
[e] Crystallized with 0.5 mol H_2O.
[f] Crystallized with 0.25 mol H_2O.



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, $AlCl_3$.

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 $SnCl_2$.

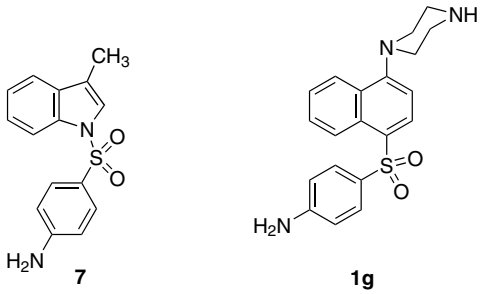
Pharmacology

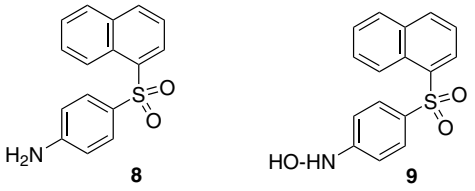
MS-245 (**4**; K_i = 2.1 nM)[10] binds with high affinity to *h*5-HT_6 receptors. Replacement of the benzenesulfonyl moiety with a phenyl group (K_i = 33 nM) or benzoyl group (K_i = 18 nM) results in about 10- to 15-fold decreased affinity; the corresponding benzyl analog (K_i = 6.5 nM) binds with only 3-fold decreased affinity.[12] In the present investigation, the benzenesulfonyl analog of **1** (**1f**; K_i = 3.8 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 nM), benzoyl group (**1d**; K_i = 57 nM), or benzyl group (**1e**, K_i = 35 nM) resulted in lower-affinity compounds. As with the benzenesulfonyltryptamine series, the sulfonyl group seems optimal for *h*5-HT_6 serotonin receptor affinity.

Compounds **1h** (K_i = 21 nM) and **1i** (K_i = 9.3 nM) are the 1-(1-naphthyl)piperazine analogs of tryptamines **5** and **6** (K_i = 16 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 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_6 affinity.[16] For example, compound **7** (K_i = 12 nM),[16] 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 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 nM) that binds to 5-HT_6 receptors, albeit with about 10-fold reduced affinity relative to **1f**. Hydroxylamine **9** (K_i = 63 nM) was isolated as a byproduct in the synthesis of **8**; compound **9** is the first hydroxylamine shown to bind to 5-HT_6 receptors.



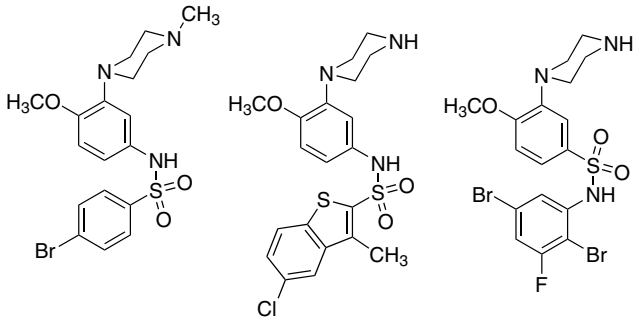


Tryptamine **4**, MS-245, is a 5-HT_6 antagonist.[10] The functional activity of compound **1f** at *h*5-HT_6 receptors was examined (i.e., 5-HT-stimulated adenylate cyclase; data not shown) and showed that **1f** also is a 5-HT_6 antagonist (**1f** $pA_2 = 7.5 \pm 0.2$).

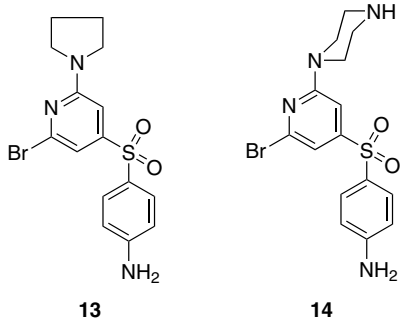
Given the lack of strict structural correspondence between an indole ring and a naphthyl ring, the results support the general notion that those structural features tolerated by, or that enhance, the 5-HT_6 serotonin receptor affinity of the tryptamine nucleus are also tolerated by or enhance the affinity 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[2,10,12]) 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_6 receptors with low affinity.[2] However, the arylpiperazine derivatives described here are not the first to demonstrate significant affinity for 5-HT_6 receptors. Incorporation of specific arylsulfonamide moieties dramatically enhances the affinity of **3**

[i.e., **10**; K_i = 5 nM and **11** (SB-271046); K_i = 1 nM].[17] Furthermore, 'reverse' sulfonamides such as **12** (SB-357134; K_i = 3 nM)[18] also bind to 5-HT_6 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 *h*5-HT_6 serotonin receptors, and that compound **1f**, like MS-245 (**4**), is a 5-HT_6 antagonist. However, unlike the sulfonamide MS-245 (**4**), **1f** is a sulfone. Several other sulfones have been recently shown to bind to 5-HT_6 receptors;[19,20] compounds **13** (K_i ca. 1 nM)[19] and especially **14** (K_i ca. 0.1 nM)[19] 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_6 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 *h*5-HT_6 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.

Acknowledgments

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References and notes

1. Glennon, R. A.; Westkaemper, R.; Bartyzel, P. In *Serotonin Receptor Subtypes*; Peroutka, S., Ed.; Wiley-Liss: NY, 1991; pp 19–64.
2. Glennon, R. A.; Bondarev, M.; Roth, B. L. *Med. Chem. Res.* **1999**, *9*, 108.
3. Hoyer, D.; Hannon, J. P.; Martin, G. R. *Pharmacol. Biochem. Behav.* **2002**, *71*, 533.
4. Kroeze, W. K.; Kristiansen, K.; Roth, B. L. *Curr. Top. Med. Chem.* **2002**, *2*, 507.
5. Humphrey, P. P. A.; Hartig, P. R.; Hoyer, D. *Trends Pharmacol. Sci.* **1993**, *14*, 233.
6. Roth, B. L.; Hanizavareh, S. M.; Blum, A. E. *Psychopharmacology (Berl.)* **2004**, *174*, 17.
7. Woolley, M. L.; Marsden, C. A.; Fone, K. C. F. *Curr. Drug Top.* **2004**, *3*, 59.
8. Slassi, A.; Isaac, M.; O'Brien, A. *Expert Opin. Ther. Patents* **2002**, *12*, 513.
9. Glennon, R. A. *J. Med. Chem.* **2003**, *46*, 2795.
10. Tsai, Y.; Dukat, M.; Slassi, A.; MacLean, N.; Demchyshyn, L.; Savage, J. E.; Roth, B. L.; Hufesein, S.; Lee, M.; Glennon, R. A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2295.
11. Russell, M. G. N.; Dias, R. *Curr. Top. Med. Chem.* **2002**, *2*, 643.
12. Lee, M.; Rangisetty, J. B.; Dukat, M.; Slassi, A.; MacLean, N.; Lee, D. K. H.; Glennon, R. A. *Med. Chem. Res.* **2000**, *10*, 230.
13. Glennon, R. A.; Lee, M.; Rangisetty, J. B.; Dukat, M.; Roth, B. L.; Savage, J. E.; McBride, A.; Rauser, L.; Hufesien, L.; Lee, D. K. H. *J. Med. Chem.* **2000**, *43*, 1011.
14. Ye, B.; Burke, T. R., Jr. *Tetrahedron* **1996**, *52*, 9963.
15. Koltunov, K. Y.; Repinskaya, I. B.; Shakirov, M. M. *Russ. J. Org. Chem.* **1994**, *30*, 88.
16. Pullagurla, M.; Setola, V.; Roth, B. L.; Glennon, R. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3355.
17. Bromidge, S. M.; Brown, A. M.; Clarke, S. E.; Dodgson, K.; Gager, T.; Grassam, H. L.; Jeffrey, P. M.; Joiner, G. F.; King, F. D.; Middlemiss, D. N.; Moss, S. F.; Newman, H.; Riley, G.; Routledge, C.; Wyman, P. *J. Med. Chem.* **1999**, *42*, 202.
18. Bromidge, S. M.; Clarke, S. E.; Gager, T.; Griffith, K.; Jeffrey, P.; Jennings, A. J.; Joiner, G. F.; King, F. D.; Lovell, P. J.; Moss, S. F.; Newman, H.; Riley, G.; Rogers, D.; Routledge, C.; Serafinowska, H.; Smith, D. R. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 55.
19. Riemer, C.; Borroni, E.; Levit-Trafit, B.; Martin, J. R.; Poli, S.; Porter, R. H.; Bos, M. *J. Med. Chem.* **2003**, *46*, 1273.
20. Wu, Y.-J.; He, H.; Hu, S.; Huang, Y.; Scola, P. M.; Grant-Young, K.; Bertekap, R. L.; Wu, D.; Gao, Q.; Li, Y.; Klakouski, C.; Westphal, R. S. *J. Med. Chem.* **2003**, *46*, 4834.
21. The *h*5-HT_6 radioligand binding assay was performed as previously described.[22] In brief, *h*5-HT_6 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 $MgCl_2$, 0.1 mM EDTA, pH = 7.40) with [^{3}H]LSD (1 nM final concentration) using 10 μM 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.

22. Kohen, R.; Metcalf, M. A.; Khan, N.; Druck, T.; Huebner, K.; Lachowicz, J. E.; Meltzer, H. Y.; Sibley, D. R.; Roth, B. L.; Hamblin, M. W. *J. Neurochem.* **1996**, *66*, 47.
23. Gilbert, E. E. *Synth. Commun.* **1971**, 372.