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1-(Bicyclopiperazinyl)ethylindoles and 1-(Homopiperazinyl)ethyl-indoles as Highly Selective and Potent 5-HT$_7$ Receptor Ligands

Methvin B. Isaac,* Tao Xin, Anne O'Brien, David St-Martin, Angela Naismith, Neil MacLean, Julie Wilson, Lidia Demchyshyn, Ashok Tehim and Abdelmalik Slassi

NPS Pharmaceuticals Inc., 6850 Goreway Drive, Mississauga, ON, Canada L4V 1V7

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Abstract—A novel series of 1-(bicyclopiperazinyl)ethylindole and 1-(homopiperazinyl)ethyl-indole derivatives was synthesized and found to be potent and selective 5-HT$_7$ receptor ligands.

Serotonin (5-hydroxytriptamine, 5-HT) is a neurotransmitter that mediates a wide variety of sensory, motor, and cortical functions through multiple 5-HT receptor subtypes.[1] Recently, application of molecular cloning has led to the identification and isolation of the 5-HT$_7$ receptor subtype from four mammalian species: rat,[2] mouse,[3] guinea pig,[4] and human.[5] The human 5-HT$_7$ receptor (h5-HT$_7$) is a 445 amino acid protein with 39–53% sequence homology when compared to other 5-HT receptor subtypes. This receptor is positively coupled to adenylyl cyclase.[6]

The 5-HT$_7$ receptor is located centrally, in the thalamus, hypothalamus (particularly in the suprachiasmatic nucleus) and several limbic and cortical regions. Such a distribution of this receptor implicates it in the control of circadian rythyms.[3,7] The affinity of a number of antipsychotic agents for the 5-HT$_7$ receptor also suggests that this receptor may mediate the therapeutic actions of these compounds.[4] In addition, high levels of 5-HT$_7$ receptor mRNA have been found in human coronary arteries suggesting a possible role in the vasodilation of blood vessel.[8]

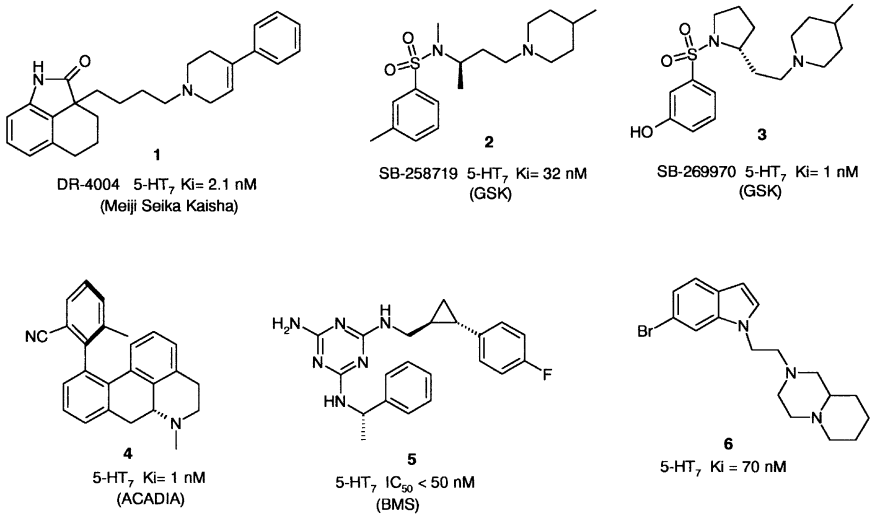

Figure 1. Selective 5-HT$_7$ receptor ligands.

*Corresponding author. Fax: +1-905-677-9595; E-mail: misaac@npsp.com

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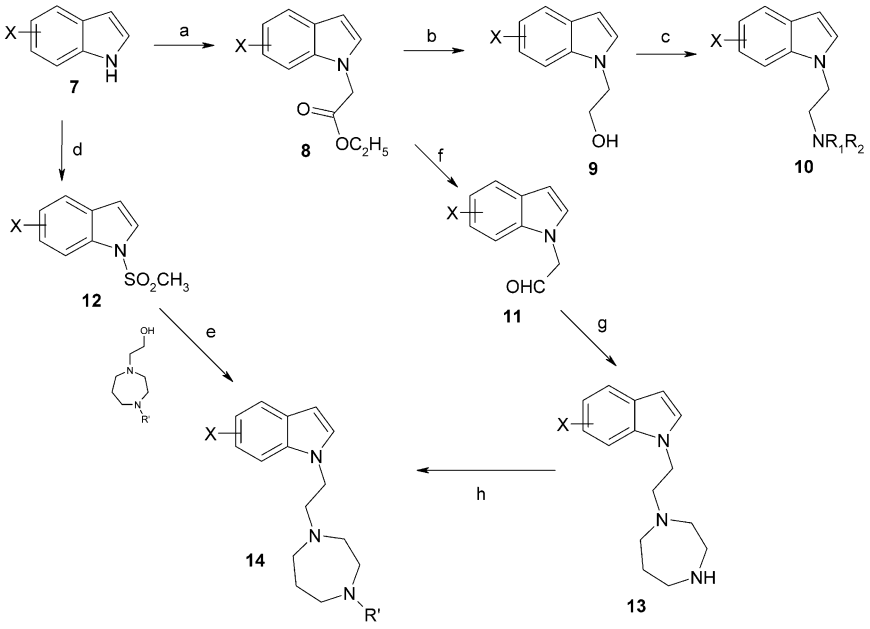


Scheme 1. Reagents and conditions: (a) NaH, DMF, $BrCH_2CO_2C_2H_5$, 0 °C; (b) 2 equiv DIBAL-H, THF, rt; (c) (i) MsCl, Et_3N, CH_2Cl_2, rt; (ii). HNR_1R_2, THF, 70 °C; (d) MsCl, NaH, DMF, 0 °C–rt; (e) NaH, K_2CO_3, toluene, 110 °C; (f) 1.5 equiv DIBAL-H, toluene, −78 °C; (g) $NaBH_3CN$, NaOAc, HOAc, homopiperazine, rt; (h) $NaBH_3CN$, NaOAc, HOAc, aldehydes or ketones.

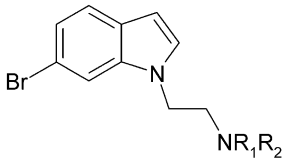
Whilst the 5-HT_7 receptor displays a unique pharmacology, only very recently has the identity of selective ligands been reported (**1**, **2**, **3**, **4**, and **5**).[9–13] Clearly, the 5-HT_7 receptor may be a valuable, novel therapeutic drug target and the development of potent and selective ligands is highly desirable. As part of our research program directed toward the design and synthesis of potent and selective 5-HT_{1D} receptor ligands, we serendipitously discovered that the intermediate **6** (Fig. 1) was a potent human 5-HT_7 receptor ligand ($K_i = 70$ nM). Compound **6** was identified as an initial lead and optimization was immediately pursued. We report here on the synthesis and structure–activity relationship (SAR) that led to a novel class of selective 5-HT_7 receptor ligands.

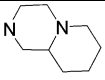
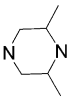
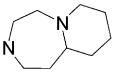
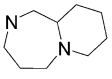
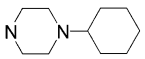
The synthesis of a series of aminoethylindoles of general structures **10** and **14** is shown in Scheme 1. *N*-Alkylation of the substituted indoles **7** with ethylbromoacetate afforded compound **8**. Subsequent reduction of the ester function with DIBAL-H gave the corresponding alcohol **9**. Treatment of **9** with methanesulphonylchloride followed by displacement with the various amines delivered compounds of general structure **10**.

Compounds of general structure **14** were synthesized by mesylation of the indole nitrogen followed by treatment with the aminoethylalcohol in the presence of sodium hydride, potassium carbonate in toluene giving the product of structure **14**. Alternatively, compound **14** was synthesized from the common and versatile intemediate **8** from partial reduction with DIBAL-H to aldehyde **11**, followed by reductive amination with homopiperazine to afford compound **13**. Further reductive amination of **13** with various aldehydes and ketones gave compounds of structure **14**.

The synthesized compounds were primarily evaluated for their binding affinities to the human 5-HT_7 receptor in vitro. The assay protocol entails the incubation of membranes, prepared from HEK293 cells expressing the human 5-HT_7 receptor, with ^{3}H-LSD and using clozapine, a typical 5-HT_7 receptor antagonist, as a standard.

Table 1. In vitro affinity of piperazinyl and homopiperazinyl ethyl indoles



Compd	NR_1R_2	5-HT_7 Binding[a]	Compd	NR_1R_2	5-HT_7 Binding[a]
15		61	**6**		78
16		52	**18**		72
17		26	**20**		71
19		93	**21**		99
22		36			

[a]Percent inhibition @1 μM.

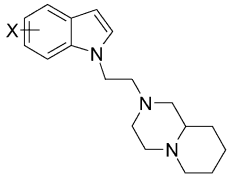
Various concentrations of the test compound were incubated with the radioligand (^{3}H-LSD) and the receptor affinity (K_i in nM, or μ% inhibition @ 1 uM) was determined.

Initially, we examined the various piperazinylethyl and homopiperazinylethyl indole analogues of **6** (**15**–**22**, Table 1) and found that the *N*-methylhomopiperazine **19** and 6,7-bicyclohomopiperazine **21** retained potency at the human 5-HT$_7$ receptor with K_is of 31 and 3 nM, respectively. The relatively high affinity of **6**, **19**, and **21** encouraged us to further examine the effect of the position of the bromo substituent on the indole ring system. By keeping the indole nitrogen substituent fixed as the *N*-methylhomopiperazinylethyl and 6,6-bicyclopiperazinylethyl groups, the various bromine substituted indole analogues were examined. It was found that the 5- and 6-bromosubstituted indoles were more potent than the corresponding 4- and 7-substituted indoles (Table 2). However, the 6-bromo-substituted indole derivatives (**6** and **19**) were generally shown to have higher 5-HT$_7$ receptor affinity than the corresponding 5-sustituted analogues (**11** and **14**, Table 2).

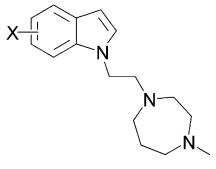
With the above information in hand, the nitrogen substituent was fixed as a *N*-methylhomopiperazinylethyl group and the steric and electronic effects of the substituents at the 6-position of the indole were thoroughly examined (**29**–**46**, Table 3). Replacement of the 6-bromo substituent of **19** with chlorine (**30**) resulted in a ligand with very similar 5-HT$_7$ receptor affinity, whereas the 6-fluoro-analogue **29** led to a 9-fold decrease in receptor affinity. However, hydrogen bond donors such as 6-hydroxyl (**31**) and 6-amino (**32**) groups were found to be detrimental to receptor activity. Interestingly, the 6-trifluoromethyl group (**34**) led to a slight increase in receptor affinity ($K_i = 23$ nM).

Some other substituents at the 6-position of the indole were also explored (**35**–**46**, Table 3) demonstrating the electronic and steric flexibility inherent in this novel 5-HT$_7$ pharmacophore. Nonetheless, the majority of substituents led to ligands with reduced affinity at the 5-HT$_7$ receptor compared to compound **19**.

Table 2. In vitro affinity of bromo substituted piperazinyl and homopiperazinylethylindoles



Compd	X	5-HT$_7$ binding	
23	4-Br	43%[a]	—
24	5-Br	65%[a]	158[b]
6	6-Br	78%[a]	70[b]
25	7-Br	13%[a]	—

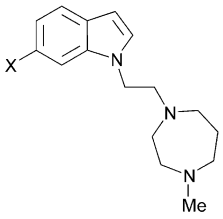


Compd	X	5-HT$_7$ binding	
26	4-Br	33%[a]	—
27	5-Br	65%[a]	88[b]
19	6-Br	93%[a]	31[b]
28	7-Br	18%[a]	—

[a]% Inhibition @ 1 μM.
[b]K_i, nM (see ref 14).

Removal of the *N*-methyl group from **19** gave ligand **47** with reduced receptor affinity (Table 4). However, introduction of various alkyl and cycloalkyl groups onto the nitrogen atom of the homopiperazine (**47**) afforded a series of 5-HT$_7$ ligands with enhanced receptor potency. For example, replacement of the methyl group of **19** with a cyclopropylmethyl and cyclopentyl

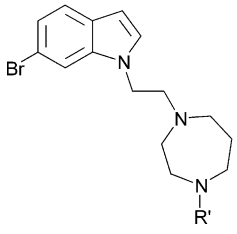
Table 3. In vitro affinity of 6-substituted *N*-methylhomopiperazinyl ethyl indoles



Compd	X	5-HT$_7$ binding	
29	F	60%[a]	288[b]
30	Cl	85%[a]	34[b]
19	Br	93%[a]	31[b]
31	NH_2	0%[a]	—
32	OH	28%[a]	—
33	H_2NCO	33%[a]	—
34	CF_3	89%[a]	23[b]
35	NO_2	72%[a]	139[b]
36	$PhCH_2O$	28%[a]	182[b]
37	CH_3O	50%[a]	1573[b]
38	CH_2=CH	79%[a]	109[b]
39	CH≡C	79%[a]	140[b]
40	CH_3	62%[a]	125[b]
41	CH_3CH_2	66%[a]	166[b]
42	*i*-Propyl	72%[a]	145[b]
43	*i*-Propenyl	72%[a]	70[b]
44	1-Hydoxy-*i*-propyl	6%[a]	—
45	3-Pyridyl	35%[a]	—
46	3-Thienyl	68%[a]	109[b]

[a]% inhibition @ 1 μM.
[b]K_i, nM (see ref 14).

Table 4. In vitro affinity of 6-bromo *N*-substituted homopiperazinylethylindoles



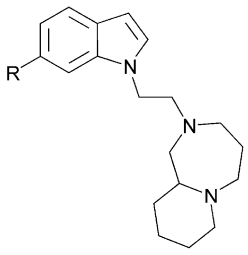
Compd	R′	5-HT$_7$ binding	
19	Methyl	93%[a]	31[b]
47	H	77%[a]	—
48	Isopropyl	92%[a]	14[b]
49	Isobutyl	95%[a]	37[b]
50	Neopentyl	70%[a]	163[b]
51	Cyclopropylmethyl	95%[a]	9[b]
52	Cyclopropyl	96%[a]	16[b]
53	Cyclopentyl	98%[a]	10[b]
54	Cyclohexyl	96%[a]	17[b]
55	Phenyl	18%[a]	—

[a]% inhibition @ 1 μM.
[b]K_i, nM (see ref 14).

Table 5. Receptor binding profile of compound **21**

Receptor	% Inhibition @ 1 μM	Receptor	% Inhibition @ 1 μM
5-HT_{1A}	1	5-HT_7	3[a]
5-HT_{1B}	0	$M_1 + M_2$	35
5-HT_{1D}	0	D1	2
5-HT_{1F}	0	D2	15
5-HT_{2A}	20	D3	27
5-HT_{2C}	26	D4	4
5-HT_6	4066[a]	D5	17

[a]K_i values in nM (see ref 14).



56 R = Cl, **57** R = CF_3

Figure 2. Potent 6,7-bicyclohomopiperazine analogues.

led to **51** and **53** with K_is 9 and 10 nM, respectively (Table 4). On the contrary, the corresponding *N*-neopentyl (**50**) and *N*-phenyl (**55**) analogue reduced 5-HT_7 receptor affinity.

The information gleaned from the *N*-methylhomopiperazinylethyl indole derivatives and the finding that 6,7-bicyclohomopiperazine **21** was very potent prompted us to synthesize and evaluate the affinity of the 6-chloro (**56**) and 6-trifluoromethyl (**57**) analogues of **21**. Both compound were found to be highly potent 5-HT_7 receptor ligands (**56**, $K_i = 10$ nM and **57**, $K_i = 7$ nM, respectively, Fig. 2).

For the most potent compound **21**[15] ($K_i = 3$ nM), the binding affinities at other serotonin receptors, dopamine receptors and muscarinic receptors were measured (Table 5). It can be seen that **21** possesses very good selectivity over the battery of receptors examined.

In conclusion, a novel series of potent and selective 5-HT_7 receptor ligands has been discovered. Compound **21** was the most potent in this series and has demonstrated good in vitro receptor selectivity, thus making it a valuable tool with which to further characterize the distribution and function of 5-HT_7 receptors in native tissue and to elucidate their potential role in disease states. Compound **21** will be further evaluated for its functional activity at this receptor.

References and Notes

1. Barnes, N.; Sharp, T. *Neuropharmacology* **1999**, *38*, 1083.
2. Plassat, J.; Amlaiky, N.; Hen, R. *Mol. Pharmacol.* **1993**, *44*, 229.
3. Lovenberg, T.; Baron, B.; De Lecea, L.; Miller, J.; Prosser, R.; Rea, M.; Foye, P.; Racke, M.; Slone, A.; Siegel, B.; Danielson, P.; Sutcliffe, J.; Erlander, M. *Neuron* **1993**, *11*, 449.
4. Tsou, A.; Kosaka, A.; Bach, C.; Zuppan, P.; Yee, C.; Tom, L. *J. Neurochem.* **1994**, *63*, 456.
5. Bard, J.; Zgombick, J.; Adham, N.; Vaysse, P.; Branchek, T.; Weinshank, R. *J. Biol. Chem.* **1993**, *268*, 23422.
6. Shen, Y.; Monsma, F.; Metcalfe, A.; Jose, P.; Hamblin, M.; Sibley, D. *J. Biol. Chem.* **1993**, *268*, 18200.
7. Ruat, M.; Traiffort, E.; Leurs, R.; Tarddivel-Lacombe, J.; Diaz, J.; Arrang, J.; Schwartz, J. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 8547.
8. Terron, J.; Falcon-Neri, A. *Br. J. Pharmacol.* **1999**, *127*, 609.
9. Linnanen, T.; Brisander, M.; Unelius, L.; Rosqvist, S.; Nordvall, G.; Hacksell, U.; Johansson, A. *J. Med. Chem.* **2001**, *44*, 1337.
10. Forbes, I.; Dabbs, S.; Duckworth, D.; Jennings, A.; King, F.; Lovell, P.; Brown, A.; Collin, L.; Hagan, J.; Middlemiss, D.; Riley, G.; Thomas, D.; Upton, N. *J. Med. Chem.* **1998**, *41*, 655.
11. Kikuchi, C.; Nagaso, H.; Hiranuma, T.; Koyama, M. *J. Med. Chem.* **1999**, *42*, 533.
12. Lovell, P.; Bromidge, S; Dabbs, S; Duckworth, D; Forbes, I.; Jennings, A; King, F.; Middlemiss, D.; Rahman, S.; Saunders, D.; Collin, L.; Hagan, J.; Riley, G.; Thomas, D. *J. Med. Chem.* **2000**, *43*, 342.
13. Poss, M.; Purandare, A.; Mattson, R.; Sun, L. (Bristol-Myers Squibb Co.) Patent WO-00185701, 2001.
14. K_i values in nM are given as the mean of at least two independent determinations performed in triplicate with less than 15% deviation.
15. ^{1}HNMR ($CDCl_3$) for compound **21** (a yellow oil): δ 7.51 (s, 1H), 7.46 (d, 1H), 7.18 (d, 1H), 7.13 (d, 1H), 6.46 (d,1H), 4.13 (t, 2H), 2.88 (t, 2H), 2.83–1.16 (m, 17H).