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Indoloxypropanolamine analogues as 5-HT$_{1A}$ receptor antagonists

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Abstract—Analogues of pindolol, 1-(1H-indol-4-yloxy)-3-isopropylamino-propan-2-ol, were synthesized and evaluated as 5-HT$_{1A}$ receptor antagonists. The structural features required for optimal binding to the 5-HT1A receptor are as follows: *S*-2-propanol linker, 4-indoloxy substituent, and a large lipophilic cyclic amine substituent.
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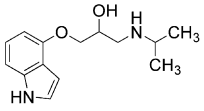
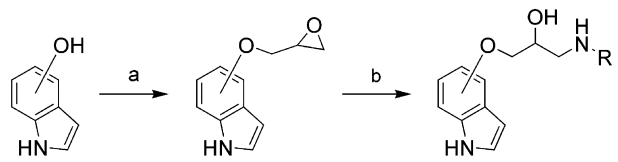
Fluoxetine (Prozac®) has been a breakthrough therapy in the fight against depression. In spite of this, depression continues to be a prevalent disease and is predicted to be the second leading cause of illness-induced disability in the world by 2020.[1] The SSRIs exert their pharmacological action (elevation of synaptic serotonin levels) in hours[2] but require prolonged administration before significant clinical improvement occurs.[3] One proposal for this delay is that these elevated serotonin levels cause a negative feedback at the presynaptic 5-HT$_{1A}$ autoreceptors. This delayed onset of action could be overcome by antagonizing the action of 5-HT at the presynaptic 5-HT$_{1A}$ autoreceptors.[4]



Pindolol

The indoloxypropanolamine β-adrenoceptor antagonist pindolol is also a 5-HT$_{1A}$ receptor ligand. Pindolol antagonizes several actions mediated by central 5-HT$_{1A}$ receptors such as hypothermia[5] and hormone secretion.[6] Pindolol has been reported to enhance and accelerate the clinical effects of antidepressant drugs in several placebo-controlled clinical trials.[7] Pindolol has also been reported to be a partial agonist at 5-HT$_{1A}$ receptors. While other medicinal chemistry studies[8] have been performed on pindolol, our goal was to alter the pindolol structure in such a way as to maximize both the 5-HT$_{1A}$ receptor affinity and antagonist function. Herein we describe the effect of the following five types of structural change on activity: chain length, position of attachment of the indole ring, role of the hydroxyl group, alkylation of the C-2 position, and modification of the alkyl amine. The compounds were studied as racemates and enantiomers of the most interesting compounds were prepared to evaluate the importance of stereochemistry. We report the synthesis, 5-HT$_{1A}$ receptor binding affinities, and the intrinsic efficacy at the 5-HT$_{1A}$ receptor. No attempt was made to modify the β-adrenergic affinity of these compounds.

The regioisomeric 4- and 5-substituted 1-(1H-indolyloxy)-3-(alkylamino)-2-propanols were prepared according to Scheme 1. The 4-hydroxyindole **1** and 5-hydroxyindole **2** were alkylated with epichlorohydrin[9] to give the intermediate epoxides, **3** and **4**. The epoxide ring was opened with the appropriate amine to give the indoloxypropanolamines (**5a**–**e**, **6a**,**b**).



Scheme 1. Reagents and conditions: (a) 5 N NaOH, epichlorohydrin, 60 °C, 1 h (**3** (4-isomer), 68% and **4** (5-isomer), 83%); (b) RNH$_2$, MeOH, reflux (**5a**, R = cyclohexyl, 79%; **5b**, R = 1-adamantyl, 63%; **5c**, R = cyclopentyl, 34%; **5d**, R = cycloheptyl, 37%; **5e**, R = 3-pentyl, 77%; **6a**, R = cyclohexyl, 82%; **6b**, R = 1-adamantyl, 76%).

Keywords: 5-HT1A antagonist; Serotonin; Pindolol.
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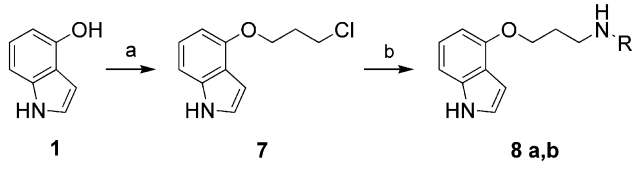
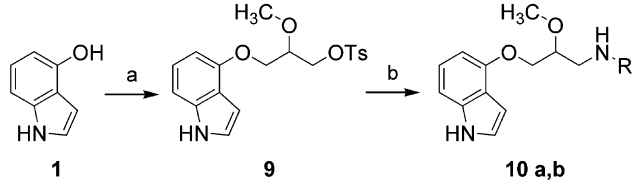
The 1-(1H-indol-4-yloxy)-3-(alkylamino) propanes were prepared according to Scheme 2. The 4-hydroxyindole **1** was alkylated with 3-chloro-1-propanol under Mitsunobu conditions to give the intermediate chloride **7**. The chloride was displaced with the appropriate amine to give the indoloxypropanamines **8a**,**b**.

The 1-(1H-indol-4-yloxy)-2-methoxy-3-(alkylamino) propanes were prepared according to Scheme 3. Dimethyl methoxymalonate was reduced with LAH to give 2-methoxy-1,3-propanediol in 54% yield and the hydroxyl groups were converted to the tosylates to give 2-methoxy-1,3-diol bis(4-methylbenzenesulfonate) in 97% yield. The hydroxyindole **1** was alkylated with 2-methoxy-1,3-diol bis(4-methylbenzenesulfonate) to give the intermediate tosylate **9**. The tosylate was displaced with the appropriate amine to give the indoloxymethoxypropanamines **10a**,**b**.

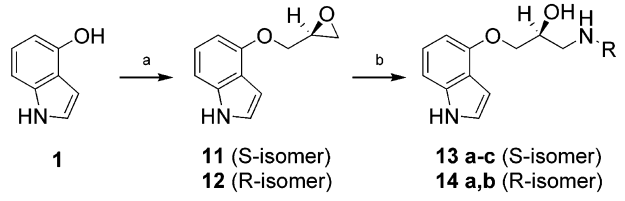
The (*S*)- and (*R*)-1-(1H-indol-4-yloxy)-3-(alkylamino)-2-propanols were prepared according to Scheme 4 (stereochemistry in Scheme 4 is depicted for the *S* enantiomer). The 4-hydroxyindole **1** was alkylated with (2*S*)-(+)-glycidyl 3-nitrobenzene sulfonate or (2*R*)-(−)-glycidyl 3-nitrobenzene sulfonate to give their respective intermediate epoxides, **11** and **12**.[10] The epoxide ring was opened with the appropriate amine to give the indoloxypropanolamines (**13a**–**c** and **14a**,**b**).



Scheme 2. Reagents and conditions: (a) diethyl azodicarboxylate, PPh_3, $Cl(CH_2)_3OH$, THF, 57%; (b) RNH_2, Na_2CO_3, DMF, 100 °C, (R = cyclohexyl, 43% and R = cyclopentyl, 28%).



Scheme 3. Reagents and conditions: (a) NaH, 2-methoxypropane-1,3-diol bis(4-methylbenzenesulfonate), DMF, 91%; (b) RNH_2, DMF, 85 °C (R = cyclohexyl, 47%; R = 1-adamantyl, 54%).



Scheme 4. Reagents and conditions: (a) NaH, (2*S*)-(+)-glycidyl 3-nitrobenzene sulfonate or (2*R*)-(−)-glycidyl 3-nitrobenzene sulfonate, DMF, *S*-isomer 88%; (b) RNH_2, MeOH, reflux (**13a**, R = cyclohexyl, 63%; **13b**, R = 1-adamantyl, 70%).

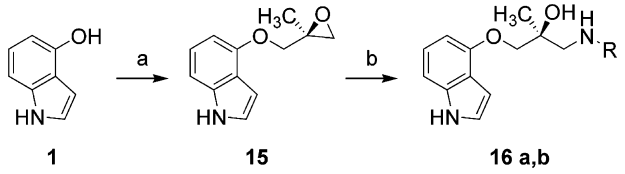
The (*S*)-1-(1H-indol-4-yloxy)-2-methyl-3-(alkylamino)-2-propanols were prepared according to Scheme 5. (2*S*)-(+)-methylglycidyl-3-nitrobenzene sulfonate was prepared from (2*R*)-methylglycidol. The 4-hydroxyindole **1** was alkylated with (2*S*)-(+)-methylglycidyl 3-nitrobenzene sulfonate to give the intermediate epoxide **15**.[10] The epoxide ring was opened with the appropriate amine to give the indoloxypropanolamines **16a**,**b**.

The 4-(alkylamino)-1-(1H-indol-4-yloxy)-3-butanols were prepared according to Scheme 6. The 4-hydroxyindole **1** was alkylated with 1,2-epoxy-4-butanol under Mitsunobu conditions to give the intermediate epoxide **17**. The epoxide ring was opened with the appropriate amine to give the indoloxybutanolamines **18a**–**c**.

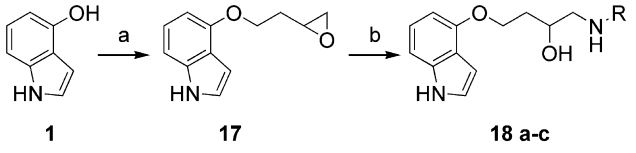
The 1-(1H-indol-4-yloxy)-4-(alkylamino)-2-butanols were prepared according to Scheme 7. The 4-hydroxyindole **1** was alkylated with 1,4-dichloro-2-butanol to give the intermediate chloride **19**. The chloride was displaced with the appropriate amine to give the indoloxybutanolamines **20a**,**b**.

The 5-HT_{1A} receptor binding assays and the [^{35}S]GTPγS binding assays were performed according to Rasmussen et al.[11]

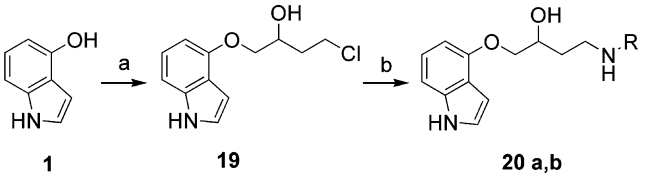
The importance of the amine substituent in modulation of 5-HT_{1A} receptor affinity can be readily seen in Table 1. Increasing the size of the substituent from isopropyl



Scheme 5. Reagents and conditions: (a) NaH, (2*S*)-(+)-methylglycidyl 3-nitrobenzene sulfonate, DMF, 45%; (b) RNH_2, MeOH, reflux (R = cyclohexyl, 85% and R = 1-adamantyl, 92%).



Scheme 6. Reagents and conditions: (a) diethyl azodicarboxylate, PPh_3, 1,2-epoxy-4-butanol, THF, 27%; (b) RNH_2, MeOH, reflux (R = cyclohexyl, 77%; R = 1-adamantyl, 75%; R = isopropyl, 12%).



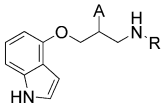
Scheme 7. Reagents and conditions: (a) KOH, 1,4-dichloro-2-butanol, H_2O, 65 °C, 38%; (b) RNH_2, IPA, reflux (R = cyclohexyl, 90% and R = 1-adamantyl, 49%).

(pindolol = 22.4 nM) to the 3-pentyl (**5e** = 28.6 nM) maintained 5-HT_{1A} receptor affinity. But amine substitution with a carbocyclic ring system (**5a** = 3.58 nM, **5b** = 9.29 nM, **5c** = 10.6 nM, and **5d** = 6.82 nM) gave a marked increase in binding affinity for the 5-HT_{1A} receptor. With this information the cyclohexyl and 1-adamantyl amine substituents became the focus of the subsequent SAR.

The hydroxyl group is important for potent 5-HT_{1A} receptor affinity. Removal of the hydroxyl group (Table 1, **8a** = 78 nM and **8b** = 94 nM) diminished 5-HT_{1A} receptor affinity 8 to 21-fold and alkylation of the hydroxyl group (Table 1, **10a** = 40.6 nM and **10b** = 32 nM) resulted in a 3 to 10-fold loss in affinity. This suggests that both the hydrogen bond donor and acceptor properties of the hydroxyl group are important, although the steric bulk of the methoxy group may attenuate the 5-HT_{1A} affinity. These modifications also decrease 5-HT_{1A} receptor antagonist activity.

The role of the stereochemical configuration of the hydroxyl group was explored. The affinity of the *S* isomers (Table 2, **13a** = 1.33 nM and **13b** = 3.8 nM) was superior to the *R* isomers (Table 2, **14a** = 26.1 nM and **14b** = 18.3 nM) and to the racemates (Table 1, **5a** = 3.58 nM and **5b** = 9.29 nM). The *S* isomers were substituted with a methyl group at the 2 position creating a quaternary center (**16a** and **16b**). This steric bulk led to a significant loss in receptor affinity. All these compounds showed a similar low degree of partial agonist activity.

Table 1. 5-HT_{1A} binding affinities and functional data of hydroxyl group modifications



Compound	A	R	5-HT_{1A} K_i[a] (nM)	Inhibition of 5-HT-stimulated GTPγS binding	
				K_i[b] (nM)	E_{min}[c] (%)
Pindolol	OH	Isopropyl	22.4 ± 3.8	81.1 ± 9.88	9.76 ± 1.37
5a	OH	Cyclohexyl	3.58 ± 0.25	9.83 ± 1.83	9.88 ± 0.68
5b	OH	1-Adamantyl	9.29 ± 1.53	7.84 ± 0.76	6.56 ± 0.83
5c	OH	Cyclopentyl	10.6 ± 2.9	35.5 ± 3.77	11.8 ± 1.08
5d	OH	Cycloheptyl	6.82 ± 0.59	11.3 ± 0.63	8.90 ± 1.41
5e	OH	3-Pentyl	28.6 ± 6.1	49.8 ± 3.19	4.74 ± 0.72
8a	H	Cyclohexyl	78.4 ± 8.7	nd[d]	31.3 ± 1.5[e]
8b	H	Cyclopentyl	94.3 ± 15.7	233 ± 28.7	24.8 ± 0.22
10a	OCH_3	Cyclohexyl	40.6 ± 9.6	nd[d]	36.2 ± 2.1[e]
10b	OCH_3	1-Adamantyl	32.0 ± 5.8	nd[d]	28.9 ± 1.1[e]

[a] Affinities were determined in vitro by radioligand binding using cell lines expressing the human 5-HT_{1A} receptor. Each value is means ± SEM of at least three determinations.

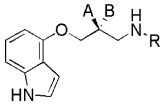
[b] K_i calculated from the inhibition of 300 nM 5-HT mediated stimulation of [^{35}S]GTPγS binding in mouse LM(tk$^-$) cells expressing the human 5-HT_{1A} receptor.

[c] Degree of maximal inhibition of 300 nM 5-HT mediated stimulation of [^{35}S]GTPγS binding expressed as % of the stimulation produced by 10 μM 5-HT.

[d] K_i not determined.

[e] Degree of inhibition of 300 nM 5-HT mediated stimulation of [^{35}S]GTPγS binding at 10 μM, the maximal concentration of compound that could be accurately tested. Data expressed as % of the stimulation produced by 10 μM 5-HT.

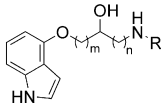
Table 2. 5-HT_{1A} binding affinities and functional data of hydroxyl group stereochemistry and C2 substitution



Compound	A	B	R	5-HT_{1A} K_i[a] (nM)	Inhibition of 5-HT-stimulated GTPγS binding	
					K_i[b] (nM)	E_{min}[c] (%)
13a	OH	H	Cyclohexyl	1.33 ± 0.14	6.68 ± 1.05	7.52 ± 0.36
13b	OH	H	1-Adamantyl	3.89 ± 0.58	4.65 ± 0.57	6.38 ± 0.64
13c	OH	H	2-Adamantyl	11.2 ± 0.2	24.0 ± 3.45	8.75 ± 1.75
14a	H	OH	Cyclohexyl	26.1 ± 1.6	50.8 ± 4.94	8.87 ± 1.48
14b	H	OH	1-Adamantyl	18.3 ± 4.9	29.9 ± 5.91	3.15 ± 0.68
16a	OH	CH_3	Cyclohexyl	1450 ± 300	nt	nt
16b	OH	CH_3	1-Adamantyl	868 ± 75	nt	nt

See Table 1 legend (nt, not tested).

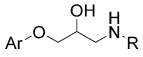
Table 3. 5-HT_{1A} binding affinities and functional data of chain length modification



Compound	*m*	*n*	R	5-HT_{1A} K_i[a] (nM)	5-HT_{1A} EC_{50}[f] (nM)	5-HT_{1A} E_{max}[g] (%)
18a	2	1	Isopropyl	1772 ± 396	nt	nt
18b	2	1	Cyclohexyl	872 ± 6	nt	nt
18c	2	1	1-Adamantyl	551 ± 97	nt	nt
20a	1	2	Cyclohexyl	125 ± 14	394 ± 16	45.6 ± 1.3
20b	1	2	1-Adamantyl	76.1 ± 8.0	854 ± 110	51.8 ± 1.1

See Table 1 legend (nt, not tested).
[f] EC_{50} for stimulation of [^{35}S] GTPγS binding in mouse LM(tk$^-$) cells expressing the human 5-HT_{1A} receptor.
[g] Maximum stimulation of [^{35}S] GTPγS binding expressed relative to the maximal effect of 5-HT.

Table 4. 5-HT_{1A} binding affinities of the positional isomers of indole



Compound	Ar	R	5-HT_{1A} K_i[a] (nM)
5a	4-Indole	Cyclohexyl	3.58 ± 0.25
5b	4-Indole	1-Adamantyl	9.29 ± 1.53
6a	5-Indole	Cyclohexyl	>3000
6b	5-Indole	1-Adamantyl	833 ± 30

See Table 1 legend.

Table 5. Blockade of 8-OH-DPAT-induced increase in rat serum corticosterone concentrations by compound **13a**

Treatment	Corticosterone, ng/ml	Percent antagonism
Vehicle	33.6 ± 2.4	—
8-OH-DPAT alone	398.4 ± 13.4	—
13a + 8-OH-DPAT		
0.03 mg/kg, sc	350.4 ± 15.4	13
0.1 mg/kg, sc	304.8 ± 46.1	26*
0.3 mg/kg, sc	206.0 ± 60.6	53*
1.0 mg/kg, sc	62.4 ± 9.6	92*

Male Sprague–Dawley rats were administered compound **13a** subcutaneously (sc) 15 min prior to 0.3 mg/kg, sc 8-OH-DPAT, and rats were sacrificed 1 h after 8-OH-DPAT. Serum corticosterone levels were measured using H-corticosterone kits (ICN Biomedicals, Costa Mesa, CA) according to kit instructions. Means and standard errors for five rats per group are shown.
* $P \leqslant 0.05$.

Table 6. β_1 and β_2 receptor binding affinities of selective compounds

Compound	β_1, K_i[a] (nM)	β_2, K_i[a] (nM)
Pindolol	0.52	0.40
13a	2.37	3.75
13b	7.92	6.63

[a] Affinities were determined in vitro by radioligand binding using cell lines expressing the human β receptors. Each value is the mean of two determinations with a 95% confidence interval.

The effect of the chain length on receptor affinity was investigated. A methylene unit was inserted on either the indoloxy side of the 2-propanol chain to give the 3-butanol analogues or on the amine side of the 2-propanol chain to give the 2-butanol analogues. The 3-butanol derivatives (Table 3, **18a** = 1772 nM, **18b** = 872 nM, and **18c** = 551 nM) and 2-butanol derivatives (Table 3, **20a** = 124.7 nM and **20b** = 76.1 nM) suffered a significant loss in affinity for the 5-HT_{1A} receptor. An increase in agonist efficacy was observed in the 2-butanol derivatives.

The 4-indole substituent was replaced with the 5-indole substituent. The 5-indole derivatives (Table 4, **6a** = >5000 nM and **6b** = 833 nM) were poor ligands at the 5-HT_{1A} receptor.

We have shown that the optimal structural features for potent 5-HT_{1A} receptor affinity are the 4-indole substituent, the 2-propanol linker, the *S* configuration of the hydroxyl group, and larger, lipophilic substituent on the amine. Compounds **13a** and **13b** represent these requirements. Compounds **13a** and **13b** show a low degree of partial agonist efficacy, E_{min} = 7.52% and 6.38%, respectively.

Compound **13a**, upon further in vivo evaluation, blocked the 8-OH DPAT-induced increase in rat serum corticosterone concentrations with an ED_{50} = 2.5 mg/kg, sc (Table 5).[12]

Profiling of compounds **13a** and **13b** at the human β_1 and β_2 receptors[13] showed comparable receptor affinity to pindolol (Table 6).

In conclusion, we have developed compound **13a**, which is a potent antagonist at the 5-HT_{1A} receptor. This compound is not a candidate for further development because of its affinity for the β_1 and β_2 receptors. This platform is an appropriate starting place to develop a compound which is devoid of β affinity but retains the $5HT_{1A}$ affinity and antagonism.

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