A Novel (Benzodifuranyl)aminoalkane with Extremely Potent Activity at the 5-HT_{2A} Receptor[1]

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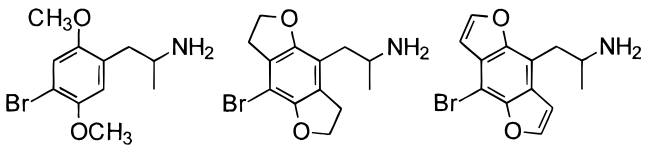
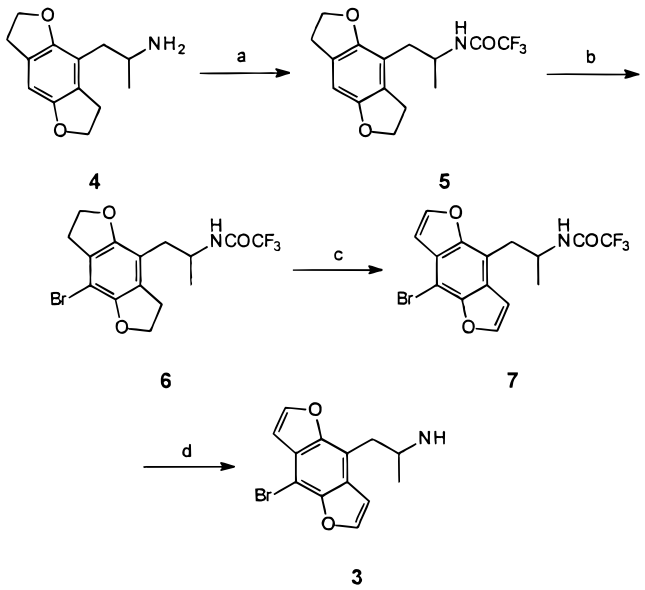
A major focus of our research for a number of years has been to understand the structure−activity relationship (SAR) of classical hallucinogens and their derivatives, the pharmacological action of which is believed to be mediated primarily by agonist activity at the serotonin 5-HT_{2A} receptor.[2,3] In particular we have sought to understand the relationship between the modes of binding of the hallucinogens containing an indole nucleus, including LSD and psilocybin, and those containing a benzene nucleus, such as mescaline and its potent structural analogue **1** (DOB).[4] In pursuing this goal, we recently reported the synthesis of the tetrahydrobenzodifuran **2** as a rigid analogue of DOB.[5] Rat behavioral data and human receptor binding data showed that **2** is more potent than **1**, a finding that was consistent with a binding site model first postulated by Westkaemper and Glennon,[6] in which two hydrogen-bond-donor residues in the receptor, possibly serine residues, lie on opposite sides of the molecule and form hydrogen bonds with the ether oxygen lone pairs. It was conjectured that the increase in activity of **2** relative to **1** is due to the fact that the lone pairs in **2** are fixed in an orientation favorable for forming such hydrogen bonds.



1 **2** **3**

It occurred to us that a protected precursor of **2** could be aromatized in one step, leading after deprotection to the fully aromatic benzodifuran **3**. We anticipated that this compound would provide valuable information about the electronic requirements for binding to 5-HT_2 receptor subtypes, since sterically it would be almost identical to **2** but electronically it would differ dramatically. Thus, **3** was synthesized and evaluated in a rat behavioral assay and in binding assays using rat and cloned human 5-HT_{2A} receptor preparations.

Scheme 1[a]



[a] (a) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 0 °C to rt, 2 h, 87%; (b) Br_2, HOAc, 15 °C to rt, 5 h, 71%; (c) DDQ, toluene, reflux, 10.5 h, 89%; (d) NaOH, H_2O, MeOH, rt, 12 h; 86% as the HCl salt.

Chemistry. Benzodifuran **3** was prepared as depicted in Scheme 1. The aminopropane **4**, available from our previous synthetic work,[5] was protected as the trifluoroacetamide **5**. Bromination with Br_2 gave **6**, which was then oxidized with dichlorodicyanobenzoquinone (DDQ) in toluene, yielding the aromatized derivative **7**. Deprotection produced the free amine that was neutralized with ethanolic HCl and precipitated from ether as fine white crystals of the hydrochloride salt of **3**.

Pharmacology. Compound **3** was evaluated in the two-lever drug discrimination assay in two groups of rats, each of which was trained to discriminate the effects of ip injections of saline from those of either LSD or DOI; the methods have been described previously.[5] Potencies were calculated as ED_{50} values with 95% confidence intervals.[7] In addition, **3** was assayed for its ability to displace the highly selective 5-HT_{2A} antagonist [^{3}H]MDL 100,907[8] from rat prefrontal cortex and to compete for the nonselective 5-HT_2 agonist [^{125}I]DOI at cloned human 5-HT_{2A} and 5-HT_{2C} receptors and for [^{3}H]-serotonin at cloned human 5-HT_{2B} receptors; the methods employed here have also been described previously.[5]

Results and Discussion. Compound **3** possessed a K_i of 0.23 ± 0.03 nM in competition with the 5-HT_{2A} antagonist [^{3}H]MDL 100,907 in rat cortical homogenates. It has an approximately 60-fold higher affinity than **2** (K_i = 14.8 ± 1.6 nM). In addition, its affinity for agonist-labeled members of the cloned human 5-HT_2 receptor family (Table 1) is at least 8-fold higher than that of **2**. The high potency of **3** is not limited to in vitro assays; in the rat drug discrimination assay (Table 2), **3** is 3 times more potent than **2** and indeed surpasses even LSD in potency by a small margin. Although we have not yet carried out studies that would indicate the

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Table 1. Radioreceptor Competition Assays in Cloned Human Receptors[a]

	K_i (nM)		
compd	5-HT_{2A} [^{125}I]DOI	5-HT_{2B} [^{3}H]serotonin	5-HT_{2C} [^{125}I]DOI
(−)-DOI	0.46 ± 0.12	42.7 (av n = 2)	1.82 ± 0.80
(±)-2[b]	0.48 ± 0.03	1.60 ± 0.25	0.30 ± 0.02
(±)-**3**	0.04 ± 0.01	0.19 ± 0.10	0.02 ± 0.01

[a] Each value is the mean ± SEM from three separate experiments, except as noted. [b] Values for compound **2** are from Monte et al.[5]

Table 2. Results of Drug Discrimination Studies in Rats

training drug	test drug	ED_{50} (nmol/kg)	95% CI[a] (nmol/kg)	n[b]
LSD	LSD	40	20−60	22
	2	61[c]	31−120	7−15
	3	22	14−35	16−19
DOI	DOI	300	200−470	12
	3	39	23−67	9−12

[a] Range of 95% confidence interval for ED_{50}. [b] Number of animals tested at each dose. [c] From ref 5.

relative efficacy of **3** at the 5-HT_{2A} receptor, full substitution in the drug discrimination assay in LSD-trained rats is correlated with full efficacy at that receptor.[9]

Thus, benzodifuran **3** is the most potent known ligand for the 5-HT_{2A} receptor. It is the first arylethylamine derivative to surpass LSD in potency in a behavioral assay and the first compound with LSD-like activity to have an aromatic nucleus other than benzene or indole. At the cloned human 5-HT_{2C} receptor, its affinity is double that at the 5-HT_{2A} receptor, making it also the most potent ligand yet reported for that site. Unfortunately, therefore, despite its very high potency, the compound maintains the lack of specificity that is characteristic of ligands such as **1** and **2**, reinforcing the belief that the agonist ligand recognition domains of the two receptor isoforms are extremely similar.

It should also be noted that **3** was synthesized here as the racemate. If, as previously observed for hallucinogenic phenethylamines,[10−13] the activity is found to reside primarily in the *R* enantiomer, it would be expected to exhibit approximately twice the potency of the racemic material.

The high activity of **3** has prompted investigations in these laboratories that are leading to new insights regarding the effects of nonsteric factors on affinity for 5-HT_2 receptor subtypes. A full report of our findings will be published in short order.

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Supporting Information Available: Synthetic procedures and characterization for all compounds as well as details of pharmacological procedures (7 pages). Ordering information is given on any current masthead page.

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