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Pyrrolo[3,2,1-*ij*]quinoline Derivatives, a 5-HT_{2c} Receptor Agonist with Selectivity over the 5-HT_{2a} Receptor: Potential Therapeutic Applications for Epilepsy and Obesity

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Abstract—A series of pyrrolo[3,2,1-*ij*]quinoline derivatives was synthesized, evaluated for their activity against the 5-HT_{2c} and 5-HT_{2a}, receptors and found to be agonists at 5-HT_{2c} with selectivity over 5-HT_{2a}. © 2000 Elsevier Science Ltd. All rights reserved.

5-Hydroxytryptamine (5-HT or serotonin), a key neurotransmitter of the peripheral and central nervous system (PNS and CNS), has been implicated in a variety of sensory, motor, and behavioral processes. The diverse effects of this neurotransmitter are related to the extensive projections of serotonergic neurons throughout the brain and the large number of distinct serotonin receptor subtypes. At least 14 distinct serotonin receptor subtypes are expressed in the mammalian CNS.[1] The contribution of these receptors to the action of serotonin has been difficult to ascertain owing to the paucity of selective pharmacological agents.

The 5-HT_2 subfamily of serotonin receptors is composed of three subtypes, the 5-HT_{2a}, 5-HT_{2b}, and 5-HT_{2c} receptors. All three receptors couple to the activation of the inositol phosphate and diacyl glycerol pathways via the G-protein, $G_{q/11}$.[1] Recently, other second messenger systems have been shown to be regulated by 5-HT_2 stimulation, including mitogen activated protein kinase (MAP-kinase).[2] The limited access to selective pharmacological tools amongst the 5-HT_2 subfamily of serotonin receptors has led to the use of gene targeting techniques to generate mouse lines that selectively lack functional receptor genes.[3] This strategy has been applied to the study of 5-HT_{2c} receptor function. 5-HT_{2c} receptors are expressed in many brain regions (the limbic structures, extrapyramidal motor pathways, hypothalamus, thalamus, and monoaminergic cell groups) and have been implicated in the regulation of food intake and anxiety.[4] For example, the non-selective 5-HT_{2c} receptor agonist, *m*-chlorophenylpiperazine **1** (*m*CPP), produces hypophagic and anxiogenic effects that were attenuated by 5-HT_{2c} receptor antagonists (Fig. 1).[5] Recently, the novel potent and preferential 5-HT_{2c} receptor agonist **2** has been shown to mediate the prototypical behavioral response of penile erection.[6] Although these studies implicated the 5-HT_{2c} receptors in the modulation of feeding and anxiety, elucidation of the functional roles of these receptors has been hindered by a limited availability of selective agents. In addition, such paucity of selective agents can be attributed to the fact that the 5-HT_{2c} receptors share substantial sequence homology with the 5-HT_{2a} receptor.

Through library screening along with synthetic chemistry, we have developed a class of human 5-HT_{2c} receptor agonists that have good to moderate selectivity over the human 5-HT_{2a}, receptor. This paper describes the synthesis, structure–activity relationship and in vitro pharmacology of a series of pyrrolo[3,2,l-*i*,*j*]quinoline derivatives. These selective compounds offer the possibility of a novel approach to the treatment of obesity and epilepsy.

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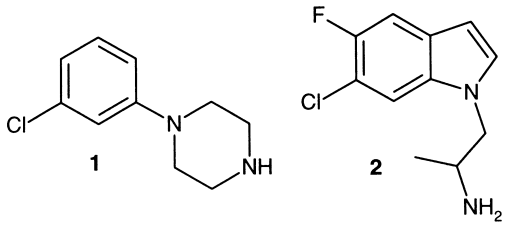


Figure 1. 5-HT_2 agonists.

Chemistry

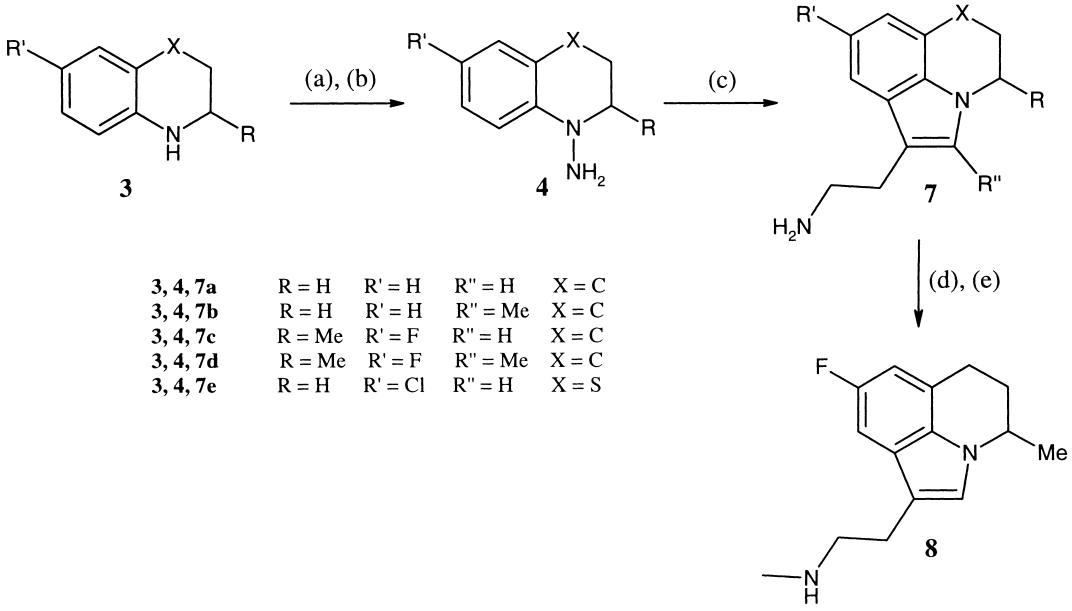
The pyrrolo[3,2,1-*ij*]quinolin-1-yl ethylamine derivatives,[7] **7a**–**e**, were synthesized as shown in Scheme 1. Nitrosation of the 1,2,3,4-tetrahydroquinolines **3** with $NaNO_2$ and H_2SO_4 at 0 °C, followed by reduction with $LiAlH_4$, afforded the corresponding 1-amino-1,2,3,4-tetrahydroquinoline **4**. Subsequent Fischer indole cyclization with either 4-chlorobutanal **5**, or 5-chloropentan-2-one **6**, in refluxing aqueous methanol (MeOH:H_2O = 9:1) gave the compounds **7a**–**e** in moderate to good yields. The *N*-methyl derivative **8** was synthesized from **7c** in two steps by treatment with $(Boc)_2O$ followed by reduction with $LiAIH_4$ (Scheme 1).

Pharmacological Testing

Compounds **7a**–**e** and **8** were evaluated in vitro for their 5-HT_{2c} and 5-HT_{2a} receptor binding affinity (Table 1). Membranes prepared from HEK-293 cells stably expressing the 5-HT_{2a} or 5-HT_{2c} receptor were incubated with ^{3}H-ketanserin (5-HT_{2a} receptor) or ^{3}H-mesulergine (5-HT_{2c} receptor) and increasing concentrations of test compounds. Estimated K_i values of each test compound were subsequently determined for both receptor subtypes. Functional agonist activity was determined by a fluorescence-based assay measuring intra-cellular calcium mobilization for both 5-HT_{2a} and 5-HT_{2c} receptor cell lines (Table 1).

Results and Discussion

The pyrrolo[3,2,l-*ij*]quinoline derivative **7a**, with a simple tricyclic core and an ethylamine side chain, was identified as a 5-HT_{2c} receptor ligand from library screening. This compound showed moderate 5-HT_{2c} receptor affinity (K_i = 41 nM) with a 19-fold selectivity over the 5-HT_{2a} receptor. In contrast, the 2-methyl



3, 4, 7a	R = H	R' = H	R" = H	X = C
3, 4, 7b	R = H	R' = H	R" = Me	X = C
3, 4, 7c	R = Me	R' = F	R" = H	X = C
3, 4, 7d	R = Me	R' = F	R" = Me	X = C
3, 4, 7e	R = H	R' = Cl	R" = H	X = S

Scheme 1. Reagents: (a) $NaNO_2$, H_2SO_4, 0–5 °C; (b) LIA1H_4, ether; (c) **5** or **6**, MeOH (aq), reflux; (d) $(Boc)_20$, NaOH; (e) $LiAlH_4$, THF.

Table 1. In vitro activity of pyrrolo[3,2, 1-*i*,*j*]quinolin- 1-yl ethylamines at the h5-HT_{2a} and h5-HT_{2c} receptors

Compound	Binding activity		Binding ratio	Functional activity (agonist)	
	5-HT_{2c} (K_i[a] nM)	5-HT_{2a} (K_i[a] nM)	5-HT_{2a}/5-HT_{2c}	5-HT_{2c} (EC_{50}, nM)	5-HT_{2a} (EC_{50}, nM)
7a	41	794	19.4	0.20[b]	145[b]
7b	225	676	3.0	9.0[b]	—
7c	18	2340	130	5.7[c]	269[b]
7d	194	954	4.9	41[c]	—
7e	47	631	13.4	0.23[b]	348[b]
8	33	1458	44	180[c]	>10,000[d]

[a]K_i values are given as the mean of at least two independent determinations performed in triplicate.
[b]Full agonist with no antagonist activity.
[c]Partial agonist only.
[d]Antagonist with 1.1 μM EC_{50}.

derivative **7b** showed lower 5-HF_{2c}, receptor affinity than **7a** with a significant loss of 5-HT_{2c}, receptor selectivity. Compound **7c** (R = Me, R′ = F, X = C) having an 8-fluoro substituent along with a 4-methyl group was found to be very potent and selective. The presence of two substituents in **7c** significantly increased both 5-HT_{2c}, receptor affinity (K_i = 18 nM) and 5-HT_{2a}/5-HT_{2c}, receptor selectivity (130-fold). However, as in the case of **7b**, the presence of a 2-methyl substituent in **7d** resulted in loss of both 5-HT_{2c}, receptor affinity (K_i = 194 nM) and selectivity (5-fold) compared to **7c**. The introduction of an *N*-methyl group onto the amino side chain (i.e., from **7c** to **8**) lead to a slight decrease in both 5-HT_{2c}, receptor affinity for **8** (K_i = 33 nM) and selectivity (44-fold). The substitution of a carbon atom for a heteroatom (i.e. C to S) in the quinoline ring system along with an 8-chloro substituent gave derivative **7e** (K_i = 47 nM, selectivity 13-fold). This compound did not show any improvement when compared to the lead compound **7a**.

Functional activity, determined by measuring intracellular calcium mobilization in HEK-293 cells expressing the 5-HT_{2c} and 5-HT_{2a} receptors, indicated that all compounds demonstrated agonist activity at the 5-HT_{2c} receptor. More interestingly, compounds **7a**, **7b** and **7e** were all found to be full agonists (EC_{50} of 0.20, 9.0 and 0.23 nM, respectively) with very good functional selectivity over the 5-HT_{2a}, receptor (Table 1).

In conclusion, the pyrrolo[3,2,1-*ij*]quinoline derivatives **7a**–**e** and **8** were all found to be agonists at the 5-HT_{2c} receptor in vitro. The derivatives **7c** and **7e** were potent and functionally selective ligands thus making them promising candidates for the prophylactic management of epilepsy and obesity. Moreover, compound **7c** was racemic with a chiral center at C-4, thus separation of the enantiomers may show that one enantiomer has a higher affinity at the 5-HT_{2c} receptor than its antipode. Efforts are currently under way to resolve these enantiomers.

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