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3-(4-Piperidinyl)- and 3-(8-Aza-bicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indoles as Bioavailable h5-HT_{2A} Antagonists

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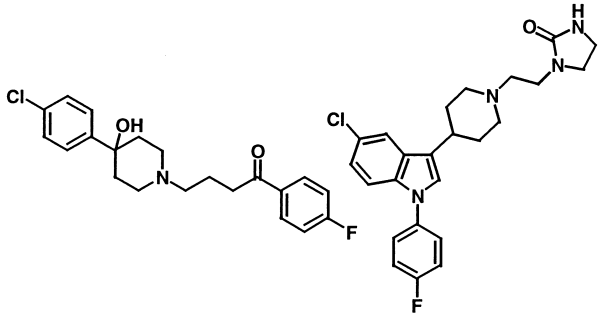
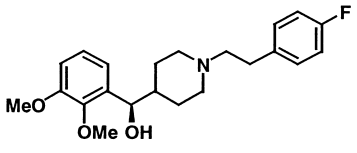
Abstract—A series of 3-(4-piperidinyl)- and 3-(8-aza-bicyclo[3.2.l]oct-3-yl)-2-phenyl-1*H*-indoles have been prepared and evaluated as ligands for the h5-HT_{2A} receptor. 3-(8-Phenethyl-8-aza-bicyclo[3.2.l]oct-3-yI)-2-phenyl-1*H*-indole is a high-affinity (1.2 nM), selective (>800 fold over h5-HT_{2C} and hD_2 receptors) antagonist at the h5-HT_{2A} receptor with oral bioavailability in rats.

Since the introduction of chlorpromazine, the treatment of psychoses with neuroleptic drugs has become well established. It is widely accepted that schizophrenia is related to excessive dopaminergic activity in the CNS and the typical antipsychotic haloperidol **1** acts by blocking central D_2 receptors.[1]

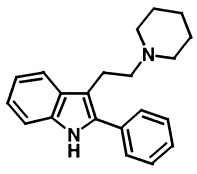


1 Haloperidol

2 Sertindole



3 MDL-100907



4

Although this compound is effective for the treatment of the positive symptoms of schizophrenia, it is ineffective against negative symptoms. Dopamine D_2 blockade is also associated with the occurrence of extrapyramidal side effects (EPS), observed with these compounds. Atypical antipsychotics such as sertindole **2** show a greater efficacy in the treatment of the negative symptoms of schizophrenia, and a reduced liability for EPS.[1,2] This atypical nature is regarded as a consequence of their preferential activity through the h5-HT_2 rather than the hD_2 receptor. Until recently, there were no selective 5-HT_{2A} antagonists, but MDL-100907 **3** has recently been disclosed as a very selective 5-HT_{2A} antagonist in phase III clinical trial for schizophrenia.[3] Our studies with a series of 2-phenyl tryptamine derivatives[4] indicated that it is possible to obtain compounds in this series that display good affinity and selectivity for the h5-HT_{2A} receptor over h5-HT_{2C} and hD_2 receptors, as exemplified by the piperidine derivative **4** (Table 1). It is not entirely clear what the effect in schizophrenia of binding to h5-HT_{2C} receptors may be, so if it were to be an undesired effect this may represent a useful result. This compound, however, suffered from a poor pharmacokinetic profile, with an oral bioavailability in rats of less than 5%. As a continuation of our study of 2-phenyl tryptamine derivatives, we sought to investigate the amine moiety of **4** in order to improve its affinity and pharmacokinetic parameters. In this letter, we describe the synthesis and receptor binding affinities of compounds where the tryptamine side chain has been constrained within a ring.

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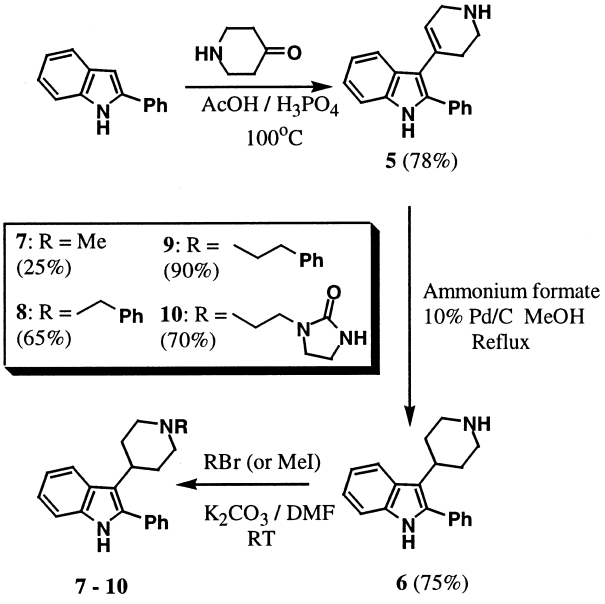
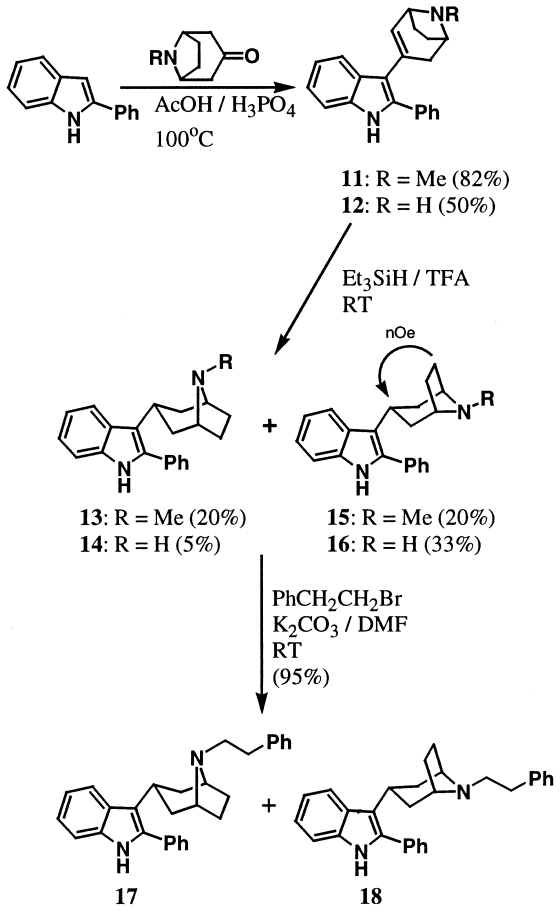
The piperidinyl derivatives **6–10** were prepared from 2-phenyl indole in three steps as described in Scheme 1. Reaction of 4-piperidone with the indole under acidic conditions,[5] followed by reduction of the tetrahydropyridine **5** gave the piperidine **6**. This could be alkylated with the appropriate alkyl halide to give compounds **7–10**.



Scheme 1.



Scheme 2.

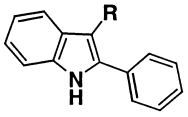
The 8-aza-bicyclo derivatives **13–18** were synthesised as shown in Scheme 2. Condensation of 2-phenyl indole with tropanone or nortropanone under acidic reaction conditions gave **11** and **12** in 82 and 50% yields, respectively. Attempted reduction of the double bonds in **11** or **12** using either transfer hydrogenation or under increased pressure of hydrogen proved troublesome, extended reaction times being required for product formation. Reduction with triethylsilane and trifluoroacetic acid afforded the desired amines as a mixture of isomers in the ratio of 1:1 and 6:1 for the NMe and NH case, respectively, that were separable by flash chromatography to give **13–16**. The structures were confirmed by ^{1}H NMR NOE experiments. Alkylation of **14** and **16** with phenethyl bromide then gave **17** and **18**.

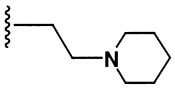
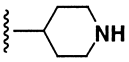
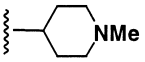
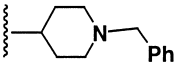
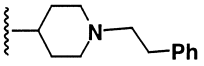
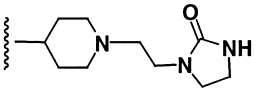
Constraining the tryptamine side chain into the piperidyl ring in compounds **6**, **7** gave some loss in h5-HT_{2A} affinity compared to **4** (Table 1). Encouragingly, however, this compound did retain some selectivity over h5-HT_{2C} and hD_2 receptors. Alkylation on the amine nitrogen with a benzyl moiety gave **8**, which exhibited a further loss in h5-HT_{2A} affinity. This drop in binding may be due to the reduction in the p*K*a of the basic nitrogen.

The imidazolidinone **10** shows binding affinity comparable to the methyl analogue **7**, and had a slightly improved selectivity profile. In pharmacokinetic studies, this compound had oral bioavailability in rats and dogs of 40 and 33%, respectively. A substantial improvement in affinity and selectivity was seen with the phenethyl compound **9**, displaying subnanomolar h5-HT_{2A} affinity, very good selectivity and an oral bioavailability of 12% in rats. In rat liver microsomes, compound **4** was metabolised at the indole 6-position and the *para*-position of the 2-phenyl ring. Compound **9** was also metabolised at the *para*-position of the 2-phenyl ring, and at the *para*-position of the phenethyl benzene ring.

In order to investigate the role of the amine nitrogen in the possible recognition process for P450 enzymes, we decided to increase the bulk around the basic nitrogen atom by construction of the aza-bicyclo ring system typified by **14**. This showed an improved binding affinity at h5-HT_{2A} receptors compared to **6** (Table 2) and a much higher hD_2 selectivity as a result of this improved affinity. For the methyl analogues **13** and **15**, there is little difference between the profiles of the two isomers. However, in the phenethyl analogues the isomer **17** retains high h5-HT_{2A} affinity and displays a better selectivity window over h5-HT_{2C} and hD_2 receptors

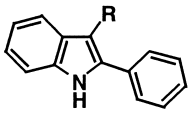
Table 1. Piperidines[a]

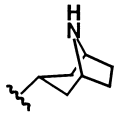
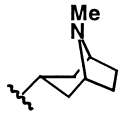
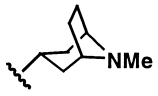
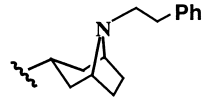
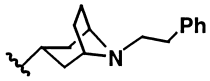


No.	R	K_i (nM) h5-HT_{2A}[c]	Selectivity[b] h5-HT_{2C}[d]	Selectivity[b] hD_2[e]
4		2.7	100	330
6		12.1	30	130
7		7.8	30	205
8		28	30	2
9		0.5	160	690
10		7.3	160	250

[a]Binding affinities are quoted as K_i values and are the geometric mean of at least two experiments.
[b]Ratio of the K_i (nM) values h5-HT_{2C}/h5-HT_{2A}, and hD_2/h5-HT_{2A}.
[c]Displacement of [^{3}H]-ketanserin from CHO cells stably expressing h5-HT_{2A} receptors.[6]
[d]Displacement of [^{3}H]-mesulergine from Chinese hamster ovary (CHO) cells stably expressing h5-HT_{2C} receptors.[7]
[e]Displacement of [^{3}H]-spiperone from CHO cells stably expressing hD_2 receptors.[8]

Table 2. Azabicycles[a]



No.	R	K_i (nM) h5-HT_{2A}[c]	Selectivity[b] h5-HT_{2C}[d]	Selectivity[b] hD_2[e]
14		1.8	200	1055
13		1.1	70	1190
15		1.5	45	960
17		1.2	860	1080
18		2.6	60	170

[a]Binding affinities are quoted as K_i values and are the geometric mean of at least two experiments.
[b]Ratio of the K_i (nM) values h5-HT_{2C}/h5-HT_{2A}, and hD_2/h5-HT_{2A}.
[c]Displacement of [^{3}H]-ketanserin from CHO cells stably expressing h5-HT_{2A} receptors.[6]
[d]Displacement of [^{3}H]-mesulergine from Chinese hamster ovary (CHO) cells stably expressing h5-HT_{2C} receptors.[7]
[e]Displacement of [^{3}H]-spiperone from CHO cells stably expressing hD_2 receptors.[8]

than **18**. Compound **17** also demonstrated oral bioavailability in rat of 18%.

In summary, by constraining the tryptamine side chain into a piperidine ring, we were able to retain moderate h5-HT_{2A} affinity relative to the initial 2-phenyl tryptamine lead **4**. Adding a phenethyl side chain gave **9** with an improvement in affinity, and this compound shows an oral bioavailability in rats of 12%. Inclusion of an azabicyclo ring system gave **17**, which retains good affinity and excellent selectivity over h5-HT_{2C} and hD_2 receptors, with an oral bioavailability in rat of 18%. Compounds **9** and **17** are antagonists at the h5-HT_{2A} receptor: in h5-HT_{2A} CHO cells, 1 μM of each alone had no effect, but antagonised the 5-HT (1 μM) mediated accumulation of inositol phosphates.[6,7]

Acknowledgements

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Referencess

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