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2-Aryl Tryptamines: Selective High-Affinity Antagonists for the h5-HT_{2A} Receptor

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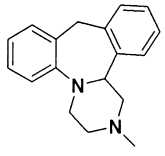
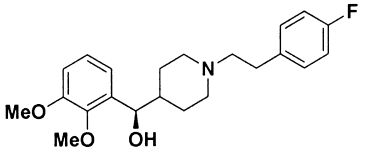
Abstract—A series of 2-aryl tryptamines have been identified as high-affinity h5-HT_{2A} antagonists. Structure–activity relationship studies have shown that h5-HT_{2A} affinity can be attained via modifications to the tryptamine side chain and that selectivity over h5-HT_{2C} and hD_2 receptors can be controlled by suitable C-2 aryl groups. © 2000 Elsevier Science Ltd. All rights reserved.

Historically, the pathophysiology of schizophrenia has involved the 'serotonin hypothesis',[1] based on the observation that LSD induces schizophrenia-like effects in man, and the 'dopamine hypothesis',[1] arising from the apparent effectiveness of typical antipsychotics in treating the core symptoms of the disease. Typical antipsychotic drugs are thought to act mainly by hD_2 receptor blockade which is believed to be associated with extrapyramidal side effects (EPS), such as tardive dyskinesia. With the introduction of atypical antipsychotics such as clozapine, which has greater affinity for h5-HT_{2A}, h5-HT_{2C}, h5-HT_6 and h5-HT_7 receptors than for hD_2 and shows a much lower incidence of EPS, the 'serotonin hypothesis' has gained ground in the understanding and treatment of schizophrenia. Since the development of more selective h5-HT_{2A} antagonists such as mianserin[2] **1** and the highly h5-HT_{2A} selective MDL 100907[3] **2**, currently in phase III clinical trials for chronic schizophrenia, attention has focused on the h5-HT_{2A} receptor as a therapeutic target.



1 Mianserin



2 MDL 100907

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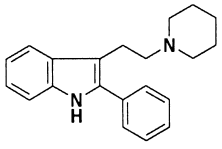
We recently reported the development of a novel solid-phase synthesis which led to the identification of the 2-phenyltryptamine derivative **3** as a high-affinity h5-HT_{2A} antagonist showing good selectivity over h5-HT_{2C} and hD_2 receptors.[4] Recent developments in the serotonin area have indicated that C-2 substituted tryptamines are tolerated at 5-HT receptors[5] and realising the potential of **3** we embarked on a program to rapidly explore the SAR of 2-phenyl tryptamines.



3

In order to facilitate the rapid development of SAR around **3**, we initially exploited the established solid-phase methodology. This approach is shown in Scheme 1. The resin bound intermediate **4** can be prepared easily from tryptophol in five steps at around 0.6–0.8 mmol/g.[4] Initial attempts to introduce the C-2 aryl function by coupling with a boronic acid derivative often resulted in incomplete conversion to the desired product and significant decreases in resin loading, the latter being attributed to the basic conditions required for this type of reaction. If, however, the coupling was based upon the reaction of an aryl stannane with **4**, the reaction was neutral and no decrease in loading was observed. Good conversion rates could be achieved with one or two couplings. Removal of the THP group from **5** afforded the resin bound alcohol; activation as the triflate and

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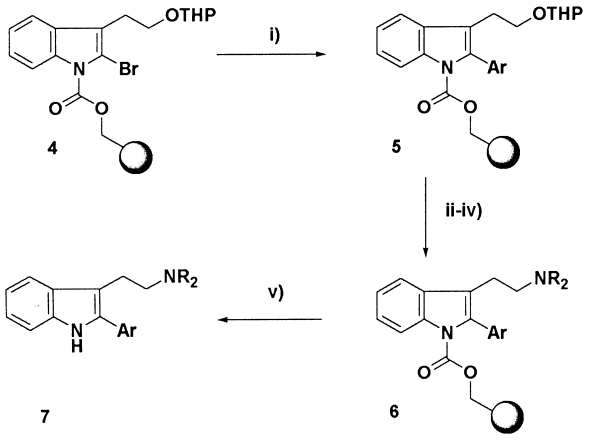
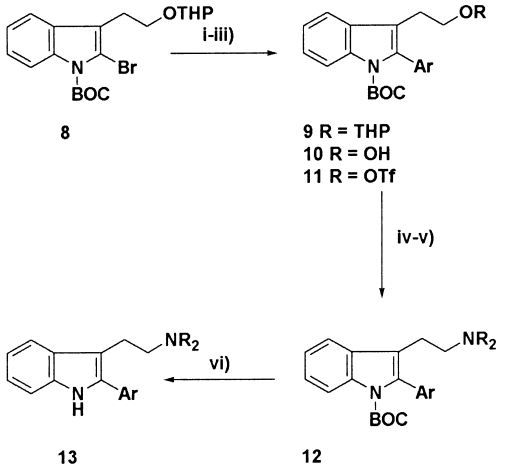
displacement with a nucleophilic amine then gave **6**. Finally, the products **7** were cleaved from the resin using hot acetic acid, and purified by ion exchange chromatography.[6]



Scheme 1. Reagents: (i) $Pd(PPh_3)_4$, $ArSnR_3$, THF, 70 °C; (ii) PPTS, 10% EtOH/DCE; (iii) Tf_2O, 2,6-Di′Butyl-4-methylpyridine; (iv) HNR_2 DCE; (v) AcOH, 110 °C.

In the cases where the introduction of the C-2 aryl group failed using the solid-phase route (Table 2, entries **29**–**32**), a second, solution-phase route was developed as shown in Scheme 2.



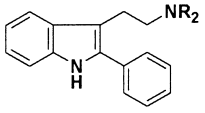
Scheme 2. Reagents: (i) $Pd(PPh_3)_4$, $ArB(OH)_2$, DMF, 2 N Na_2CO_3; (ii) PPTS, 10% EtOH/DCE; (iii) Tf_2O, 2,6-Di′Butyl-4-methylpyridine, DCE −78 °C; (iv) HNR_2, DCE; (v) PS-NCS, DCE; (vi) HCl, MeOH.

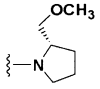
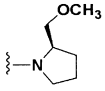
In contrast to the route shown in Scheme 1, introduction of the C-2 aryl group by coupling with a boronic acid was found to be satisfactory both in terms of yield and purity. Conversion of **8** to **9** was achieved via coupling with the appropriate boronic acid followed by deprotection to give the alcohol **10**. Activation of **10** was achieved by conversion to the triflate **11** at −78 °C followed by displacement with nucleophilic amines. Initial attempts to preform **11** in bulk and dispense in a parallel synthesis fashion failed. To overcome this, the triflation itself was carried out in a parallel fashion using 8 mL septum capped tubes as the reaction vessels. In a typical procedure, a solution of the appropriate tryptophol (0.042 mmol) and Et_3N (0.17 mmol) in 1,2-dichloroethane (1.0 mL) was dispensed into a 8 mL tube containing a flea stirrer. The tube was sealed under nitrogen with a septum top and cooled by placing in a suitable rack in a cold bath. Trifluoromethanesulfonic anhydride (0.06 mmol) was then dispensed to each tube using a repeating syringe.

After 30 min, the appropriate amine HNR_2 (100 μL of a 1.0 mmol solution in DCE) was added and the reaction allowed to warm to room temperature over 3 h. The crude products **12** were isolated following treatment with methylisothiocyanate polystyrene resin[10] to remove excess amine, filtration and solvent removal. Deprotection under acidic conditions followed by ion exchange chromatogaphy[6] gave the final products **13**.

Table 1 shows the initial SAR development in the tryptamine side chain. Ring contraction to either the pyrrolidine **14** or cyclobutane **15** analogues resulted in a

Table 1. Effect of amine variations on h5-HT_{2A} affinity and selectivity

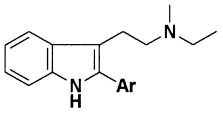


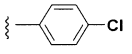
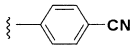
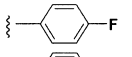
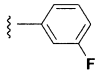
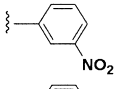
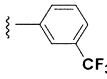
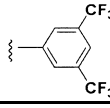
		K_i (nM)		
Example	NR_2	h5-HT_{2A}[a,b,c]	h5-HT_{2C}[d]	hD_2[e]
3		2.60	268	896
14		9	260	>1 μM
15		44	>1 μM	>1 μM
16		0.18	36	21
17		4.0	230	290
18		0.26	29	92
19		>3 μM	>3 μM	>3 μM
20		4.4	180	>1 μM
21		2.8	160	>1 μM
22		0.14	11	85

[a]All compounds antagonised PI accumulation stimulated by 1 μM 5HT in CHO cells expressing h5-HT_{2A} receptors.
[b]Binding affinities are quoted as K_i values and are the geometric mean of at least two experiments.
[c]Displacement of [^{3}H]-ketanserin from CHO cells expressing h5-HT_{2A} receptors.[7]
[d]Displacement of [^{3}H]-mesulergine from CHO cells expressing h5-HT_{2C} receptors.[8]
[e]Displacement of [^{3}H]-spiperone from CHO cells expressing hD_2 receptors.[9]

loss of h5-HT_{2A} affinity and overall selectivity. Replacement of the piperidine of **3** with both enantiomers of α-methyl piperidine (**16**, **17**) demonstrated that it was possible to achieve high h5-HT_{2A} affinity, albeit with somewhat reduced selectivity over hD_2, and that there was some of enantiodifferentiation in binding. High h5-HT_{2A} affinity and selectivity could be achieved with the side chain derived from (*S*)-2-(methoxymethyl)pyrrolidine **18**, the enantiomer of which, **19**, was completely inactive (cf. **17**). Surprisingly, it was the simple dialkylamines **20**, **21** and **22**, which had the best profiles, with **22** having 75 fold selectivity over h5-HT_{2C} and 600-fold selectivity over hD_2, whilst showing a 20-fold improvement in affinity over **3** at h5-HT_{2A}. Having optimized the tryptamine side chain, we turned our attention to the C-2 aryl group.

Table 2. Effect of aryl variations on h5-HT_{2A} affinity and selectivity



Example	Ar	K_i (nM) h5-HT_{2A}[a,b,c]	h5-HT_{2C}[d]	hD_2[e]
22		0.14	11	85
23		>1 μM	>1 μM	>1 μM
24		1.7	120	78
25		3.5	36	250
26		2.6	160	0.42
27		0.43	31	17
28		0.30	30	150
29		0.08	8.4	68
30		0.14	36	39
31		0.13	12	17
32		0.19	15	187

[a]All compounds antagonised PI accumulation stimulated by 1 μM 5HT in CHO cells expressing h5-HT_{2A} receptors.
[b]Binding affinities are quoted as K_i values and are the geometric mean of at least two experiments.
[c]Displacement of [^{3}H]-ketanserin from CHO cells expressing h5-HT_{2A} receptors.[7]
[d]Displacement of [^{3}H]-mesulergine from CHO cells expressing h5-HT_{2C} receptors.[8]
[e]Displacement of [^{3}H]-spiperone from CHO cells expressing hD_2 receptors.[9]

Using **22** as a baseline, it can be seen from the results in Table 2 that whilst replacement of the C-2 phenyl group of **22** with furan (**23**) is not tolerated, other changes in the nature of the C-2 aryl group had varying effects on h5-HT_{2A} affinity. Replacement of the C-2 phenyl group of **22** with thiophene **24** caused a decrease in h5-HT_{2A} affinity resulting in decreased selectivity over hD_2. Introduction of a 4-chloro substituent (**25**) resulted in a loss in h5-HT_{2A} affinity and decreased selectivity, whereas the 4-cyano analogue **26** shows significantly increased hD_2 affinity resulting in reversed selectivity. This indicates that the substitution pattern of the C-2 aryl function has a profound effect upon selectivity. As the fluoro isomers **27**, **28** and **29** possess subnanomolar h5-HT_{2A} affinity and generally excellent selectivity over h5-HT_{2C} and hD_2, the effect seen in **26** is not simply that of an electron deficient ring. It would also appear that substitution at the C-3 position of the aryl ring offers the best h5-HT_{2A} affinity/selectivity profile. Alternative electron withdrawing groups at this position, such as nitrophenyl (**30**) or trifluoromethyl (**31**) maintain h5-HT_{2A} affinity but have reduced selectivity over hD_2. However, excellent selectivity over hD_2 can be achieved by the introduction of a 3,5 bis(trifluoromethyl)phenyl group at C-2 (**32**).

In conclusion we have shown that 2-phenyl tryptamine can be used as a template for the design of high-affinity h5-HT_{2A} antagonists. Subnanomolar h5-HT_{2A} affinity and selectivity over h5-HT_{2C} and hD_2 can be achieved via the tryptamine side chain and modification of the C-2 aryl group.

References and Notes

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