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The Synthesis, and Dopamine D_2 and Serotonin 5-HT_3 Receptor Affinity of 3-Aza Analogues (Pyridyl) of 4-Amino-5-chloro-2-methoxybenzamides

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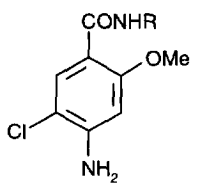
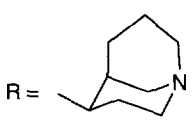
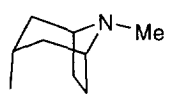
Abstract. The synthesis of potential metabolically blocked 3-aza analogues (pyridyl) of 4-amino-5-chloro-2-methoxybenzamides is described. Retention of dopamine D_2 and serotonin 5-HT_3 receptor affinity is observed.

The 4-amino-5-chloro-2-methoxybenzoyl moiety is common to a number of potent serotonin and dopamine modulators such as renzapride (**1**, BRL 24924)[1], BRL 24682 (**2**)[2] and BRL 25594 (**3**)[3]. Although this nucleus is present in the marketed compounds metoclopramide (**4**) and cisapride (**5**)[4], the 3 position is potentially open to metabolism to the polar 3-hydroxy or sulfated derivatives which could limit the duration of action of compounds containing this aromatic nucleus[5]. In an attempt to avoid this potential metabolism, we targeted compounds which contain the 3-aza nucleus for synthesis and pharmacological investigation. The first step was to show that these 3-aza analogues retained pharmacological activity and for our initial targets we chose to study the 3-aza analogue of (**2**), its granatane homologue, and the granatane homologue of (**3**).

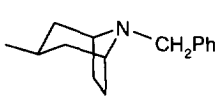




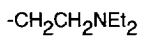
(1) renzapride



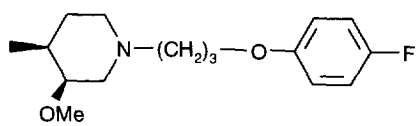
(2) BRL 24682



(3) BRL 25594



(4) metoclopramide

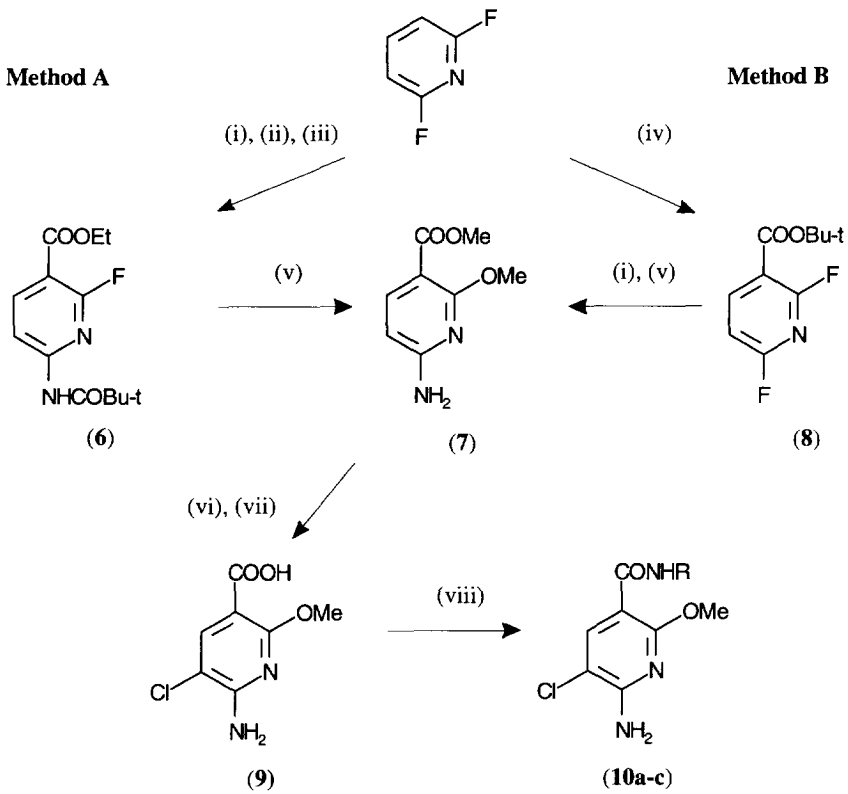


(5) cisapride

The 3-aza aromatic nucleus was prepared from 2,6-difluoropyridine by two methods as outlined in the Scheme[6]. In Method A, ortho-directed lithiation of 2-fluoro-6-pivaloylaminopyridine [prepared from 2,6-difluoropyridine by selective displacement of one F by NH_3 (sealed bomb, ~120°C, 6h) and acylation] followed by reaction with ethyl chloroformate gave a 1:1 mixture of regio-isomeric esters (78% yield) from which (**6**) was separated by column chromatography on silica, eluting with 40/60 petrol containing an increasing proportion of Et_2O up to 5%. Displacement of the F by methoxide with concomitant ester

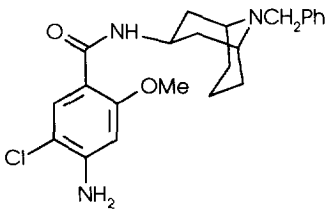
exchange and de-acylation gave the intermediate methyl ester (**7**). In Method B, the anion formed from ortho-lithiation of the difluoropyridine was so reactive that normal addition to ethyl chloroformate gave mainly the dipyridyl ketone. However, the use of di-tert-butyl dicarbonate[7] at -78°C for 30 min. gave a good yield of tert-butyl ester (**8**, 85%). Higher temperature or prolonged reaction time gave none of the desired product, an unidentified, more polar, product being obtained which was thought to be formed via an intramolecular displacement of the 2-F by the intermedate anion addition product[8]. Subsequent treatment of **8** with ammonia under mild conditions effected F displacement but again gave a 1:1 regio-isomeric mixture[9]. However, this time the desired ester was readily separable by fractional crystallisation (36% yield from **8**) and treatment with methoxide again gave the intermediate ester (**7**). This was readily converted to 2-amino-3-chloro-6-methoxypyridyl-5-carboxylic acid (**9**) required for conversion to the target amides (**10**). The required amides were prepared by acid activation with carbonyl diimidazole (CDI) and reaction with the appropriate amine.

Scheme:

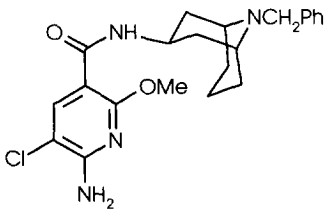


Reagents: (i) excess 0.88 NH_3/iPrOH in a bomb at 120°C for 6h; (ii) tBuCOCl/Et_3N/CH_2Cl_2; (iii) nBuLi/THF -78°C to r.t. for 2h then $ClCO_2Et$ at -78°C; (iv) LDA/THF -78°C 1h, then $(tBuOCO)_2O$ (exothermic) -78°C 30 min.; (v) tBuOK/MeOH; (vi) Cl_2/AcOH; (vii) KOH; (viii) CDI then H_2NR.

To investigate the possibility that this pyridyl nucleus can be a viable alternative to the normal benzamide for dopamine antagonism, the *exo*-N-benzyl-granatane, the ring expanded analogue of (**3**), was chosen as a representative basic side chain. The D_2 receptor binding affinities[10] of the granatane (**10a**) and the analogous benzamide, BRL 26175 are shown below.



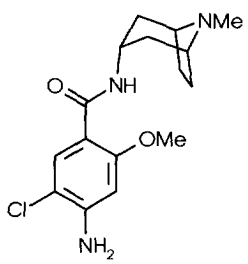
BRL 26175 pKi (dopamine D_2) 9.6



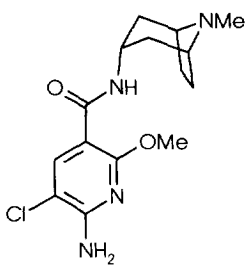
(**10a**) pKi (dopamine D_2) 8.9

Although (**10a**) is approximately 5 fold less potent than the benzamide BRL 26175, it does still retain high potency and therefore the 3-aza nucleus can be considered as a viable alternative aromatic for this class of dopamine receptor antagonists.

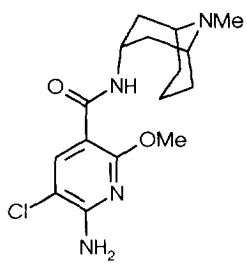
To investigate the possibility of the pyridyl nucleus being a viable alternative in the 5-HT_3 receptor antagonist area, both the *endo*-N-methyl -tropane and -granatane side chains were selected for investigation. Thus, the 5-HT_3 receptor binding affinities[11] of (**10b**) and (**10c**) are shown below. The affinity of the equivalent benzamide BRL 24682 is included for comparison.



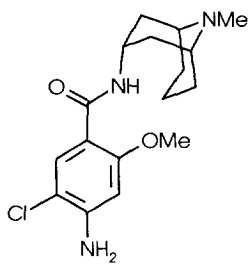
BRL 24682 pKi 9.5



(**10b**) pKi 8.8



(**10c**) pKi 9.4



BRL 26465

Similar to the results found in the dopamine area, a direct comparison of BRL 24682 and (**10b**) shows a five fold reduction in 5-HT_3 receptor affinity. However, by changing to the granatane homologue (**10c**) higher 5-HT_3 receptor affinity has been achieved. An identical increase in potency in changing from tropane to the granatane, BRL 26465, has previously been reported based on their ability to inhibit the Bezold-Jarisch reflex[12] (ID_{50} 0.4 μg/kg i.v. for BRL 26465 vs 0.8 μg/kg for BRL 24682).

In conclusion, this study has shown that the 2-amino-3-chloro-6-methoxypyrid-5-yl is a viable bioisostere for the 4-amino-5-chloro-2-methoxyphenyl aromatic nucleus for the benzamide class of dopamine D_2 and serotonin 5-HT_3 receptor antagonists and that these aza analogues are therefore suitable candidates for comparative oral bioavailability, duration of action and metabolism studies.

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