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8-Piperazinyl-2,3-dihydropyrrolo[3,2-*g*]isoquinolines: Potent, selective, orally bioavailable 5-HT_1 receptor ligands

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Abstract—The novel 8-piperazinyl-2,3-dihydropyrroloisoquinoline template was synthesized in nine steps. The template was *N*-substituted to give a series of compounds showing binding to human cloned 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors with pK_i's greater than 9 and selectivities up to 1000-fold against other serotonin, dopamine and adrenergic receptors. Several compounds were shown to possess weak partial agonist activity in cloned receptors, which translated to antagonism in in vitro studies.

Although the precise mechanism of antidepressant action remains poorly understood, many currently prescribed treatments for depression are believed to enhance neurotransmission by increasing extracellular levels of serotonin (5-hydroxytryptamine, 5-HT) in the brain.[1] Neuronal 5-HT release is modulated by presynaptic inhibitory 5-HT_1 autoreceptors. 5-HT_{1A} receptors are mainly somatodendritic, and cause a reduction in the rate of cell firing and 5-HT release when stimulated.[2] 5-HT_{1B} receptors are mainly located on cell terminals, where they mediate a reduction in the amount of 5-HT released on each firing event.[3] The role of terminal 5-HT_{1D} receptors is less clear, although there is recent evidence to suggest that they play a role in modulating extracellular brain 5-HT levels in guinea pig.[4] The combined activation of all three receptor subtypes by extracellular 5-HT thus has the potential to cause a decrease in the amount and frequency of 5-HT released into the synaptic cleft. Stimulation of these autoreceptors may be responsible for the delayed onset of action of most antidepressants which work wholly or partly by inhibiting 5-HT reuptake.[5] The two to four week onset time for these antidepressants is consistent with the time taken for these autoreceptors to desensitize in rats upon treatment with fluoxetine or citalopram.[6] Therefore, a drug which antagonizes all 5-HT_1 inhibitory autoreceptors simultaneously should acutely mimic their chronic desensitization, and thereby lead to an immediate and sustained increase in levels of synaptic 5-HT for each transmission event.[5] Such a drug could well provide a much needed rapidly acting antidepressant.

We have previously reported the in vitro pharmacology of SB-272183, the first selective 5-$HT_{1A/B/D}$ receptor antagonist.[7] In this paper we describe the synthesis

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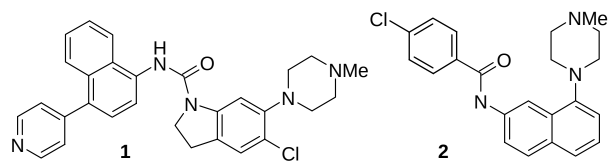
and pharmacology of a new series of highly potent and selective 5-$HT_{1A/B/D}$ receptor partial agonists/antagonists.

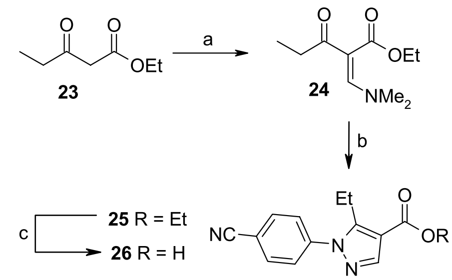
The novel dihydropyrrolo[3,2-*g*]isoquinoline template **10** was proposed from a pharmacophore alignment of the indoline SB-272183 (**1**) and a series of naphthylpiperazines,[8] e.g., **2**, with reported 5-HT_1 pK_i's > 6.2.



The synthesis is illustrated in Scheme 1. Indole-6-carboxylic acid (**3**) was converted to the *N*-monobenzylated indoline **4** by dibenzylation; reduction of the five-membered ring; and saponification of the ester, all under standard conditions.

To construct the pyridyl ring, a procedure related to the Pomeranz–Fritsch method was used via the intermediate 2,2-dimethoxyethyl amide **5**. Treatment of **5** with Brønsted acids (H_2SO_4, TFA or HCl) gave rise to a mixture of cyclized regioisomers, presumably by partially favouring *N*-protonation of the indoline leading to intramolecular delivery of the proton to the acetal, so that the reactive oxonium species is formed in proximity to the 7-position of the indoline. The use of boron trifluoride-diethyl etherate in refluxing THF gave a single regioisomer **6**, easily distinguished from the alternative regioisomer by the presence of two new singlets in the aromatic region of the ^{1}H NMR. This is consistent with selective boron complexation of the acetal oxygen atoms, leading to formation of the reactive oxonium intermediate in the less hindered region of the molecule, and favouring reaction at the 5-position of the indoline. Attempts to cyclize analogues of **5** with *N*-acyl protecting groups were not successful.

The hydroxy group of isoquinoline **6** was readily activated by triflation, and displaced by *N*-methyl piperazine. Debenzylation was effected by catalytic hydrogenation under strongly acidic conditions, giving the key intermediate **9**, which was coupled to form amides and ureas under standard conditions.



Scheme 2. Reagents and conditions: (a) DMFDMA, DMF, 120 °C, quant.; (b) 4-cyanophenyl hydrazine, EtOH, 97%; (c) NaOH aq, dioxane.

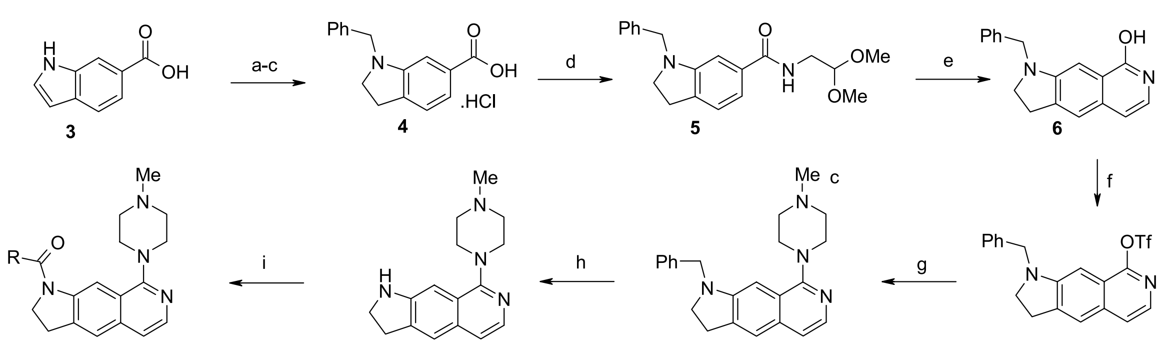
Analogues of the *N*-methyl piperazine moiety were introduced into intermediate triflate **7** and further derivatized using analogous procedures to those outlined in Scheme 1. The 4-cyanophenyl pyrazole carboxylic acid intermediate **26** used in the synthesis of **22** was prepared by combination of 4-cyanophenyl hydrazine with the dimethylaminomethylene oxopentanoate ester **24**[9] followed by saponification, as per Scheme 2.

Compounds were tested for their activity at 5-HT_1 receptors using standard binding assays with [^{3}H]5-HT or [^{3}H]8-OH-DPAT as the radioligand (Table 1). Substituted benzamides showed clear SAR with 4-substituents showing higher affinity than two or three isomers. Heterocycles were also tolerated in this position with some loss of potency, but this was restored with biaryl groups.

The *N*-methyl piperazinyl group proved relatively insensitive to steric modifications: removal of the methyl group (**31**) resulted in only a slight loss of potency, but a dramatic loss of selectivity against the β_2 adrenoreceptor (Table 2).

Increasing the size of the *N*-alkyl substituent caused the affinity to diminish incrementally (**32, 33**). The 3,5-dimethylpiperazine **34** showed somewhat reduced activity particularly at the 5-HT_{1A} receptor, but replacement of the *N*-methyl piperazine with either enantiomer of diazabicyclooctane was well tolerated (**35, 36**).

Compounds in this series showed a wide range of efficacies vs 5-HT for 5-HT_{1A} and 5-HT_{1B} receptor subtypes



Scheme 1. Reagents: (a) NaH, BnBr, NMP, 90%; (b) $NaBH_3CN$, AcOH, 96%; (c) aq NaOH, dioxane, quant.; (d) EDC, HOBT, DMF, 98%; (e) $BF_3{\cdot}OEt_2$, THF, 87%; (f) Tf_2O, pyridine, 63%; (g) *N*-methyl piperazine, 93%; (h) H_2/Pd/C, MeOH, HCl, 81%; (i) RCO_2H, DIC, HOBt, DMF.