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5-HT_{2C} antagonists based on fused heterotricyclic templates: Design, synthesis and biological evaluation

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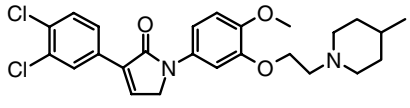
Abstract—Design, synthesis and properties of a new tricyclic series of selective 5-HT_{2C} receptor antagonists are reported. Conformational analysis of a 2-phenyl-dihydropyrrolone scaffold suggested that ring fusion, locking coplanarity between the rings of this moiety, might be tolerated by the 5-HT_{2C} receptor. An interesting effect of this is the change of the nature of the carbon–carbon double bond of the lactam ring from vinylic to aromatic. The changes were found to result in a favourable profile at both, receptor and in vivo level.

The central role of the serotonergic neurotransmitter system in controlling CNS function of importance in the pathology of depression and anxiety disorders is well established. The gold standard antidepressant treatments, the selective serotonin reuptake inhibitors (SSRIs) exert their efficacy with some lag time via this system by modulating synaptic serotonin (5-hydroxytryptamin, 5-HT) levels and thus effecting activity of the 5-HT receptor subtypes in a non-specific way. More selective action on 5-HT receptor subtypes may be expected to avoid some of the shortcomings of SSRIs, such as side effects and delayed onset of action.[1] In this context the 5-HT_{2C} receptor has been recognised as a target of potentially significant therapeutic interest. Thus, for example, 5-HT_{2C} receptor mediated responses are decreased as a result of chronic SSRI treatment suggesting that these receptors contribute to mediating the therapeutic effect.[2] Furthermore, the moderately selective 5-HT_{2C} agonist *meta*-chlorophenylpiperazine (mCPP) has anxiogenic properties, suggesting that 5-HT_{2C} antagonism would result in an anxiolytic effect,[3] as has indeed been demonstrated in animal models of anxiety.[4]

In a previous communication[5] we described a series of compounds exemplified by **1** (Fig. 1) which combine potency at the 5-HT_{2C} receptor with good selectivity for this target and a favourable profile in vivo.

Given the large interest in compounds such as **1**, we started to analyse conformational aspects of the template. Conformational analysis for the scaffold of **1** was carried out using program Macromodel within Maestro,[6] starting from a 3D structure generated with Corina.[7] One thousand steps of Low-Mode conformational search were carried out using the MMFFs force field in combination with the GB/SA hydration model. Energy minimisations were carried out using the truncated Newton conjugate gradient algorithm (500 steps, 0.005 convergence threshold). Minimised structures with energy higher than 50 kJ/mol above the global minimum were discarded. Redundant conformations were removed by heavy atom superimposition (max distance between atoms in equivalent structures <0.25 Å).



1

Figure 1. Structure of a previously described 5-HT_{2C} antagonist.

Keywords: Serotonin receptors; 5-HT_{2c} receptors; 5-HT_{2c} receptor antagonists; Fused rings; Vinylic and aromatic double bonds; Antidepressant; Anxiolytic agent.
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The thus obtained global minimum conformer shows a rather small dihedral angle between the lactam and the adjacent LHS phenyl ring (37°). We observed that a similar (coplanar) conformation could be locked by introducing cyclisation from the lactam beta position to the phenyl *ortho*-position by a ca. 1-atom bridge such as a substituted nitrogen atom. Taken together this suggested that, if the conformation most relevant for binding at the target receptor was similar to the minimum energy conformer, tricyclic indole derivatives such as **5** might be able to bind to the 5-HT_{2C} receptor (Fig. 2). We furthermore hypothesized that inclusion of the carbon–carbon double bond of the lactam in an aromatic ring, by profoundly changing the chemical nature of this fragment, could modulate the overall properties of the resulting compounds in a useful way.

To test this concept we prepared the tricyclic indole derivative **5** as a prototype of this new class of ligands. Radical halogenation of ethyl 1,2-dimethylindole-3-carboxylate **2** gave the 2-chloromethyl intermediate **3** with the indole 2- and 3-substituents already in the desired oxidation stages. Heating of compound **3** with aniline **4**[5] resulted in N-alkylation of the anilinic nitrogen. Cyclisation with condensation was subsequently achieved in the presence of trimethylaluminum to provide indolyl dihydropyrrolone **5** in moderate yield (Scheme 1).

We were pleased to find that compound **5** displayed potent affinity for the 5-HT_{2C} receptor ($pK_i = 8.2$) with selectivity over the 5-HT_{2A} ($pK_i = 6.3$) and 5-HT_{2B} ($pK_i = 6.7$) subtypes.[8] Encouraged by these results we decided to explore substitution of the indolyl phenyl ring, initially focussing on chloro substitution that had been found to be optimal in **1**. We adapted the elegant oxindole synthesis described by Gruda[9] to the synthesis of the required 2-alkyl indole 3-carboxylate intermediates, as recently also reported by Bunce and coworkers.[10] Thus, *ortho*-fluoronitrobenzene derivative **6** reacted smoothly with methyl acetylacetate (**7**) to give intermediate **8**. Reduction of the nitro group with iron

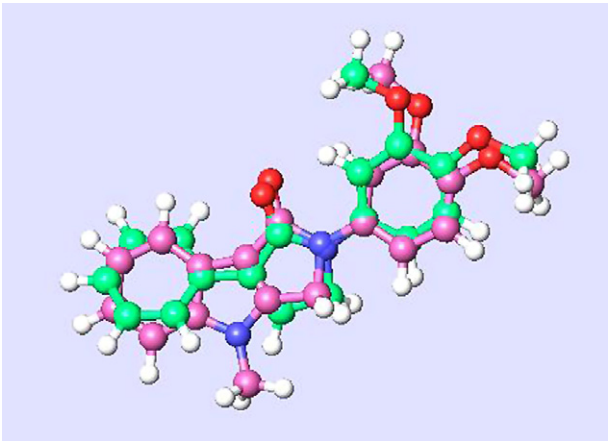
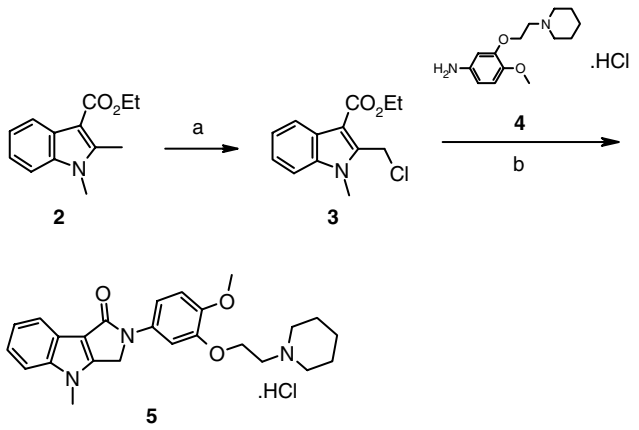


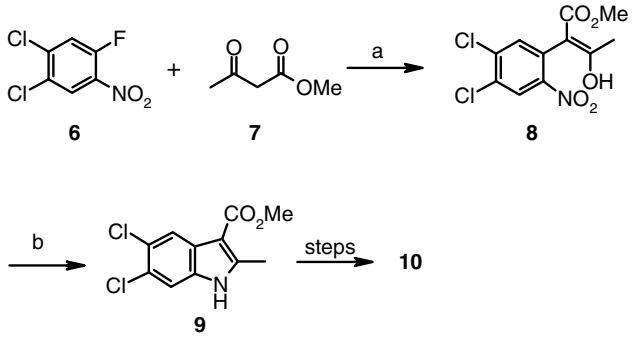
Figure 2. Molecular overlay of truncated forms of 1 and 5 showing high similarity in the spatial display of key features and a high degree of shape similarity (superimposition of topologically correspondent heavy atoms: RMSD = 0.51).



Scheme 1. Reagents and conditions: (a) NCS (1.1 equiv), $(PhCO_2)_2$ (0.05 equiv), CCl_4, reflux (94%); (b) DMF, dioxane, 2,6-lutidine, 95 °C (41%); then Me_3Al, DCM, 25 °C; then HCl, Et_2O, rt (87%).

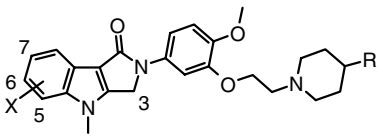
powder/ammonium chloride gave mainly the *N*-hydroxy indole derivative besides only minor amounts of **9**. This problem was overcome when $TiCl_3$ was employed as the reducing agent to give indole **9** in good yield (Scheme 2). N-Methylation, radical chlorination and condensation with aniline **4** as outlined in Scheme 1 gave the desired dichlorinated product **10**. It is interesting to note that *tert*-butyl ester analogues of intermediate **8**, prepared by arylation of acetyl acetate *tert*-butyl ester, were less suitable substrates for the final condensation reaction with aniline **4**.[11]

The route outlined in Scheme 2 allowed the preparation of a range of substituted indolyl dihydropyrrolone analogues. As we had previously demonstrated improved properties when a methyl substituent was introduced into the 4-position of the piperidine moiety[5] a number of examples with this modification were included. Results are summarised in Table 1. It becomes apparent that 6,7-dichloro substitution in compound **10** does not increase affinity at the 5-HT_{2C} receptor in this series. From the mono chloro substituted examples a slight preference can be seen for the 7-substituent in **12** which results in an increase in potency and better selectivity over the 5-HT_{2B} isoform. In the fluoro substituted



Scheme 2. Reagents and conditions: (a) **7** (2.1 equiv), NaH (2.1 equiv), DMF, 0 °C to rt (85%); (b) $TiCl_3$ in aq HCl, HOAc, dioxane, 90 °C (79%).

Table 1. Affinity results[8]



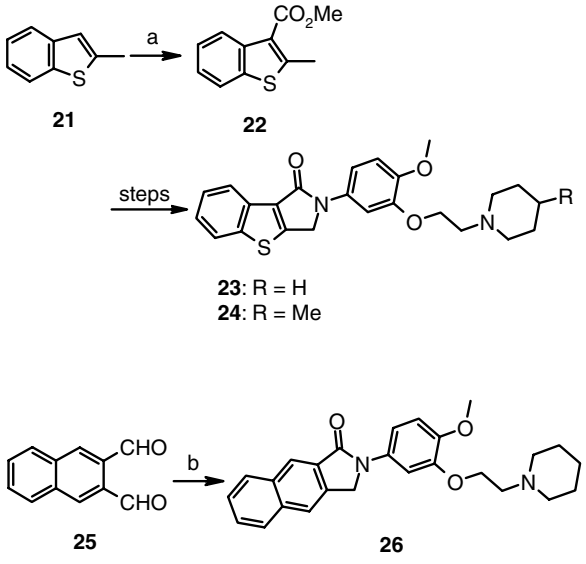
X	Compound	R = H		Compound	R = Me	
		pK_i 5-HT$_{2C}$	pK_i 5-HT$_{2A/B}$		pK_i 5-HT$_{2C}$	pK_i 5-HT$_{2A/B}$
6,7-Bis Cl	**10**	8.2	6.3/6.7	n.d.		
6-Cl	**11**	8.3	6.5/6.8	**15**	8.4	6.6/6.7
7-Cl	**12**	8.6	6.8/<6.0	**16**	8.5	6.9/7.4
5-F	n.d.			**17**	8.6	6.6/7.5
6-F	**13**	7.9	<5.0/<5.0	**18**	7.8	6.6/6.6
7-F	n.d.			**19**	8.6	6.8/7.2
7-OMe	**14**	7.5	6.0/6.1	n.d.		
3-Me	n.d.			**20**	8.3	<5.0/<5.2

n.d. = not done.

examples 6-substitution (e.g., compound **18**) is disfavoured, suggesting electronic effects may be of importance. In contrast, fluorination of the 5- or 7-position (**17** and **19**) results in examples with high 5-HT$_{2C}$ affinity, though at the expense of slightly reduced selectivity with respect to the 5-HT$_{2B}$ receptor. In this context it is noteworthy that introduction of a methyl group in the dihydropyrrolone moiety (**20**, racemic) results in significantly improved selectivity over both, 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors.

Substitution of the exposed indolyl phenyl ring was expected to have an influence on pharmacokinetic (PK) parameters. Indeed, in a standard rat iv/po crossover PK study[12] we found that while compound **5** had limited oral bioavailability and was rapidly cleared from the blood stream (F_{po} 15%, CLb 53 mL/min/g), the 7-Cl derivative **12** showed improved parameters (F_{po} 21%, CLb 39 mL/min/g).[13] A significant further improvement was achieved when moving to the 4-methyl piperidine series where compound **16** was found to have much improved metabolic stability correlating with improved oral bioavailability (F_{po} 44%, CLb 23 mL/min/g). Importantly, the compound furthermore demonstrated good brain permeability as expressed by a brain–blood plasma ratio of 1.0.[13]

We became interested in the importance of the indolyl fragment of the indolyl dihydropyrrolone moiety for potent and selective affinity to the 5-HT$_{2C}$ receptor. To investigate this aspect we prepared two additional scaffolds which maintain the dihydropyrrolone feature (Scheme 3). Replacement of the indolyl pyrrole with a thiophene resulted in fused benzothiophenes **23** and **24**. Fused naphthalene **26** was obtained directly from naphthalene dicarbaldehyde **25** and aniline **4**, albeit in low yield.[14] Both benzothiophene based examples showed potent and selective binding to the 5-HT$_{2C}$ receptor (**23**: pK_i 5-HT$_{2C/2A/2B}$ = 8.5/6.4/<6.2; **24**: pK_i 5-HT$_{2C/2A/2B}$ = 8.8/<6.1/6.7).[8] This suggests that similar binding modes may be accessible to a wider range of heterotricycles. Fused naphthalene **26** however was found to be of reduced affinity and selectivity, possibly



Scheme 3. Reagents and conditions: (a) 1—$(COCl)_2$, $AlCl_3$, 1,2-dichloroethane, 0 °C; then $(COCl)_2$, DCM, cat. DMF, 0 °C to rt; then MeOH, rt to 60 °C (19%); (b) **4**, DMF, HCl (0.2 equiv), 120 °C (5%).

due to its more linear shape, though the effect of different electronic properties may also be of importance.

Examples from this series were tested for agonist and antagonist properties at the human 5-HT$_{2A}$, 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors.[15] All compounds lacked agonist activity at concentrations up to 10 μM but blocked the effects of 5-HT (5-HT$_{2C}$ affinity estimates: pK_b **16**, 8.6; **18**, 7.5; **19**, 8.6; **24**, 8.7).

In conclusion we report design, synthesis and properties of a new series of tricyclic 5-HT$_{2C}$ selective antagonists. The newly introduced ring fusion, locking coplanarity between the rings of the 2-phenyl-dihydropyrrolone moiety, is apparently well tolerated by the 5-HT$_{2C}$ receptor. The concurrent change of the nature of the carbon–carbon double bond of the lactam ring (from vinylic to aromatic) is compatible with a favourable pro-

file at both, receptor and in vivo level. Within this series good systemic exposure in preclinical species is achievable after oral administration. Further progress in the development of 5-HT_{2C} antagonists will be published in a subsequent paper.

Acknowledgments

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8. pK_i data were determined using [^{3}H]-ketanserin, [^{3}H]-5-HT and [^{3}H]-mesulergine displacement, respectively, in HEK293 cells with stable expression of human 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors, in analogy to the procedure described in Wood, M. D.; Reavill, C.; Trail, B.; Wilson, A.; Stean, T.; Kennett, G. A.; Lightowler, S.; Blackburn, T. P.; Thomas, D.; Gager, D. L.; Riley, G.; Holland, V.; Bromidge, S. M.; Forbes, I. T.; Middlemiss, D. N. *Neuropharmacology* **2001**, *41*, 186.
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11. While N-alkylation of **4** proceeded without difficulty cyclisation of the resulting intermediate using $AlMe_3$ resulted in very low conversion yielding traces only of product. Also, a two-step protocol via the carboxylic acid (removing the *tert*-butyl group using trifluoroacetic acid) and subsequent acid activation (oxalyl chloride, then NEt_3; or EDCI) provided only low yields.
12. The research complied with national legislation and with company policy on the Care and Use of Animals and with related codes of practice.
13. For iv administration, the compound was dissolved in 25% (v/v) PEG400 aq containing 5% (v/v) DMSO at a concentration of 0.5 mg free base/mL and administered (2 mL/kg) as a bolus to male rats ($n = 3$) at a nominal dose level of 1 mg free base/kg. Brain penetration was evaluated at 1 h. For po administration, the compound was dissolved in Methocel 0.5% w/v containing 5% DMSO at a concentration of 0.6 mg free base/mL and administered (5 mL/kg) by gavage to male rats ($n = 3$) at a nominal dose level of 3 mg free base/kg.
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