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Isoindolone derivatives, a new class of 5-HT$_{2C}$ antagonists: Synthesis and biological evaluation

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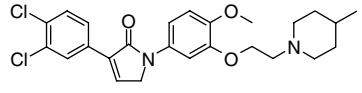
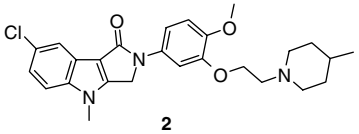
Abstract—Two independent approaches resulted in the identification of a series of isoindolone derivatives as potent and selective 5-HT$_{2C}$ antagonists. From a Medicinal Chemistry perspective this template was considered interesting as it allowed the incorporation of the carbon–carbon double bond of an earlier dihydropyrrolone series in an aromatic system within a comparatively simple and compact motif. Additionally an *in silico* screening approach of the corporate database using a 5-HT$_{2C}$ pharmacophore model resulted in the identification of a related structure containing this template. The strategy used to optimise potency at the target receptor and to improve the pharmacokinetic profile is described, resulting in molecules combining high potency with good selectivity and oral bioavailability.

Modulation of the 5-HT$_{2C}$ receptor is of significant interest to the area of neuropsychiatric disorders.[1] As a result of the long-standing interest of GSK in ligands for the 5-HT$_{2C}$ receptor classes based on several alternative templates were investigated and disclosed.[2] Recently, we reported two new series of compounds exemplified by **1**[3] and **2**[4] (Fig. 1). These classes combine potency at the 5-HT$_{2C}$ receptor with good selectivity and encouraging pharmacokinetic profiles. Herein we report the discovery and properties of a novel series of isoindolones combining potent and selective 5-HT$_{2C}$ inhibition with good bioavailability.

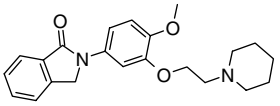
An important aspect of the rationale leading to the discovery of fused tricyclic 5-HT$_{2C}$ antagonists such as **2** was the incorporation of the dihydropyrrolone carbon–carbon double bond in an aromatic system. Rather than using an indole system as in **2**, phenyl fusion was considered as a further option to meet that goal. Accordingly, isoindolone **3** was synthesized as a prototype to investigate this modification, following a chemical approach similar to the one established for the indole series (Scheme 1). Gratifyingly, in spite of its reduced dimensions, **3** retained some affinity to the 5-HT$_{2C}$ receptor (pK_i = 7.3) with selectivity over the 5-HT$_{2A}$ and 5-HT$_{2B}$ subtypes (Table 1). The observed ca. 20-fold loss in potency for this new structural type with respect to the previous series might be explained by the fact that the fused phenyl ring of isoindolone **3** can only partially



1



2



3

Figure 1. Recently reported 5-HT$_{2C}$ antagonists (**1** and **2**) and prototype **3** of the isoindolone series.

Keywords: Serotonin receptors; 5-HT receptors; 5-HT$_{2C}$ receptor antagonists; Fused rings; Vinylic and aromatic double bonds; Antidepressant; Anxiolytic agent; *In silico* screening.
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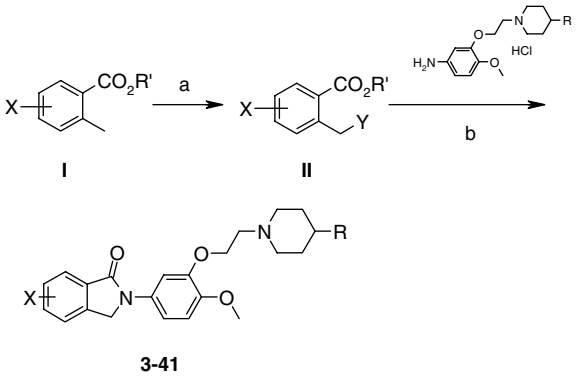


Scheme 1. Schematic synthetic approach to the isoindolone class. Reagents and conditions: (a) NBS or NCS (1.1 equiv; Y = Br or Cl), $(PhCOO)_2$ (0.05 equiv), CCl_4, reflux; (b) DMF, 120 °C (thermal heating) or 150 °C (microwave heating).

exploit a putative hydrophobic pocket occupied by the fused indole moiety of **2**.

Additional confirmation that the isoindolone template was suitable for further optimisation was obtained when an *in silico* screen of the corporate database was performed using a refined version of the pharmacophore model previously described.[3,6] Compound **4**, Figure 2, was identified as one of the most promising hits. Despite its suboptimal substitution pattern it displayed some affinity and selectivity for the target receptor.

Refinement of the pharmacophore model referred to above was carried out with the inclusion of further chemical classes in addition to those used in the previously published version,[3] selected from the historical collection as well as more recent templates (Fig. 3).[7] As reported before, all compounds included in the study were endowed with high affinity in a 5-HT_{2C} binding assay[2a] ($pK_i > 8.5$) and were at least 100-fold selective over 5-$HT_{2A/2B}$. In addition, they were assumed to bind at the 5-HT_{2C} receptors with a common binding mode, as suggested by SAR data around the selected molecules. Representative structures are shown in Figure 3.

All pharmacophore modelling work was performed with program Catalyst 4.6,[8] applying the protocol previously

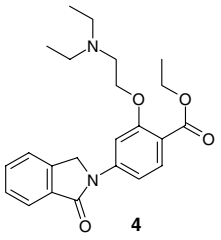


Figure 2. One of most interesting structures resulting from the 3D searches using the 5-HT_{2C} pharmacophore.

reported.[3] Among the different top scoring pharmacophore solutions generated by the program, the most satisfactory models were chosen according to quality of ligand conformations, RMS deviation of the ligand conformations to pharmacophore features, and common volumes.

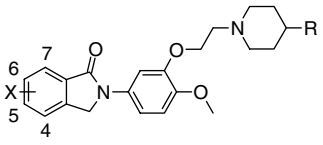
In Figure 4 the best pharmacophore model obtained is shown superimposed with some representative compounds included in the study.

As can be seen from Figure 4 the pharmacophore model consists of a positive ionisable group (red sphere) which is mapped by the basic nitrogen on the piperidine side chain of compound **7**, a H-bond acceptor (green spheres), mapped by the carbonyl oxygen on the cyclic urea moiety of compound **7**, and 3 hydrophobic groups (cyan spheres). This model is not significantly different from the one previously published[3] thus confirming its general validity.

Encouraged by the two converging pieces of information in support of this novel structural type we decided to probe ways to recover affinity at the 5-HT_{2C} receptor. Following the hypothesis of an only partially filled hydrophobic pocket we explored the pattern of substitution of the fused benzene ring, initially using a chlorine scan. Analogues **11**–**18** were obtained in analogy to the preparation of **3** (Scheme 1).

Gratifyingly, a clear trend emerged: when moving the chloro group around the phenyl ring a slight decrease in affinity for the 4-isomers **11** and **15** gradually turned into significantly increased potency for the 7-isomers

Table 1. Affinity at the 5-HT_2 receptors[5]



X	R = H			R = Me		
	Compound	pK_i 5-HT_{2C}	pK_i 5-$HT_{2A/B}$	Compound	pK_i 5-HT_{2C}	pK_i 5-$HT_{2A/B}$
H	**3**	7.3	<5.0/<5.8			
4-Cl	**11**	6.6	<5.1/<6.1	**15**	6.9	<5.8/6.7
5-Cl	**12**	7.3	<5.2/<5.0	**16**	7.6	<6.0/<6.0
6-Cl	**13**	7.8	<5.6/<5.8	**17**	7.7	6.1/<6.0
7-Cl	**14**	8.4	6.0/6.5	**18**	8.8	6.1/6.9

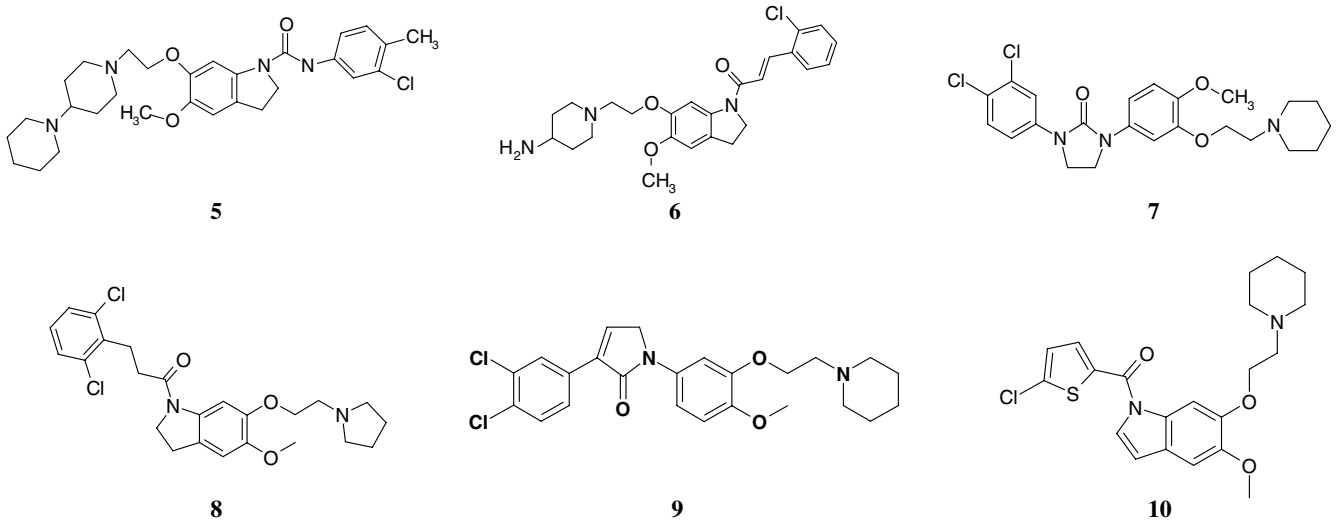


Figure 3. Representative compounds included in the pharmacophore modelling exercise.

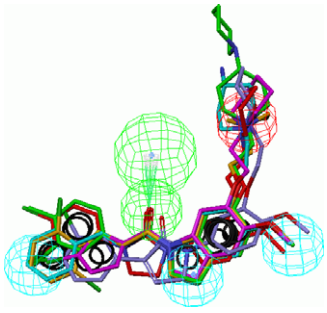
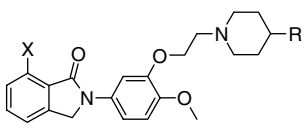


Figure 4. Pharmacophore model for the 5-HT_{2C} ligands. Colour coding of pharmacophoric features: green, H-bond acceptor; red, positive ionisable; cyan, hydrophobic.

14 and **18** (Table 1). All of the examples of increased potency also displayed good selectivity over the other 5-HT_2 receptor subtypes. As predicted from our original rationale further exploration of the optimal nature of the 7-substituent confirmed that lipophilic groups are preferred in this position. Thus, bromo-, methyl- or trifluoromethylsubstitution as in **20**–**22** resulted in compounds equipotent to the chloro analogue **18**. The smaller fluoro substituent in **19** or the cyano group in **23** resulted in reduced affinity. A methoxy substituent was found to be particularly disfavoured (compound **24**, Table 2).

Table 2. Affinity at the 5-HT_2 receptors[5]

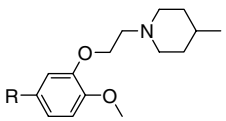


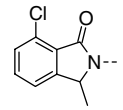
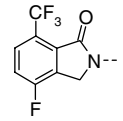
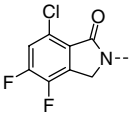
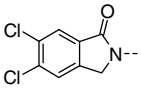
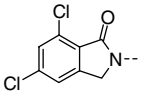
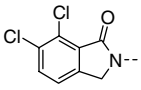
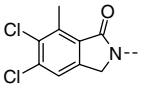
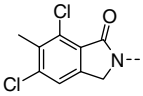
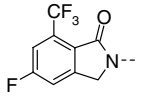
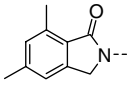
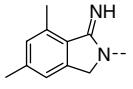
X	R	Compound	pK_i 5-HT_{2C}	pK_i 5-$HT_{2A/B}$
F	H	**19**	7.1	<5.0/<5.5
Br	Me	**20**	9.1	6.2/6.8
Me	Me	**21**	8.6	<5.2/6.7
CF_3	Me	**22**	8.8	6.2/6.3
CN	Me	**23**	8.0	<5.5/<6.1
OMe	H	**24**	6.7	<5.2/<5.1

The in vivo pharmacokinetic (PK) profile was determined in rat for **16**, **17** and **18**.[9] Again a clear trend emerged. While the 6- and 7-Cl isomers **17** and **18** were subject to rapid blood clearance (Clb = 53 and 57 mL/min/kg, respectively) and consequently showed low oral bioavailability, the 5-Cl substituent apparently protects **16** from metabolism (Clb = 31 mL/min/kg, bioavailability F_{po} 48%). Volume of distribution was found to be moderate (V_d = 5.8 L).[10] In order to achieve potency at the receptor level combined with good bioavailability it thus appeared likely that multiple substitution of the isoindolone system would be required.

Consequently, a range of more highly substituted examples, as well as examples carrying substituents in alternative positions of the isoindolone moiety were prepared and characterised (Table 3). Substitution of the isoindolone methylene group was explored by introduction of a methyl residue to give **25**. While this compound retained high affinity for the 5-HT_{2C} receptor no increase in metabolic stability was observed. Due to the detrimental effect on potency of chlorine in position 4 further substitution of this position was limited to fluorine. It was speculated that this smaller substituent might be more easily accommodated by the receptor binding pocket while still blocking a metabolically labile position. Indeed, examples **26** and **27** were found to be potent 5-HT_{2C} ligands. Unfortunately, **26** was cleared rapidly from the bloodstream, with the effect being exacerbated by a reduced volume of distribution. More encouragingly a number of compounds with substituents in position 5 in the presence of 6- and/or 7-substituents showed promising profiles. Of the dichloro analogues investigated the 5,6-dichloro derivative **28** showed particularly good metabolic stability. Introduction of an additional lipophilic substituent in position 7 was expected to further increase target potency and, by virtue of shielding the polar carbonyl moiety, increase oral bioavailability. Indeed we found that compound **31**, possessing a 7-methyl substituent, displayed an excellent overall profile. Importantly, considering the nature of the potential

Table 3. Affinity at the 5-HT_2 receptors[5] and PK parameters[9,10]



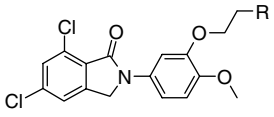
R=	Compound	pK_i 5-HT_{2C}	pK_i 5-$HT_{2A/B}$	Clb[a]	V_d[b]	F_{po} (%, rat)
	**25**	8.9	<5.9 / 6.7	53	8.2	nc
	**26**	8.2	<6.0/<6.0	48	1.9	4
	**27**	8.7	6.3/6.9			
	**28**	8.3	6.3/6.7	16	8.5	22
	**29**	8.8	6.4/6.7	50	5.8	nc
	**30**	9.0	6.3/7.0			
	**31**	8.6	6.4/7.0	16	6.8	43
	**32**	8.9	6.2/7.2	43	9.1	24
	**33**	9.4	6.6/6.6			
	**34**	8.5	5.9/6.5	59	7.8	10
	**35**	6.9	<5.4/<5.5			

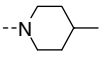
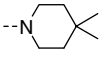
nc, no count.
[a] mL/min/kg, *iv*, rat.
[b] L/kg, *iv*, rat.

therapeutic applications, this includes very good brain permeability, as measured by a brain: blood plasma ratio of 3.6.[10] Methyl substituents in the more exposed positions 5 or 6 were found to be less useful due to rapid clearance of the resulting compounds from the bloodstream. Outstanding potency was observed for the 5-fluoro-7-trifluoromethyl analogue **33**. Unfortunately this material was obtained in insufficient quantity for further characterisation. Finally, replacing the amide moiety of **34** with an amidine (**35**) resulted in a pronounced decrease in affinity for the 5-HT_{2C} receptor (Table 3).

Using compound **29** as a baseline a small array varying the basic heterocycle was prepared. Homopiperidine (**40**) and morpholine (**41**) were investigated besides a number of alternative methylated piperidine derivatives. As can be seen from the results summarised in Table 4, methyl groups in positions 3 and 4 as well as ring enlargement were all well tolerated. Methylation α to the basic nitrogen however led to slightly reduced target affinities. In line with previous findings[3] 4-methyl piperidine was confirmed to be optimal amongst the set of basic groups explored while the more polar and less basic morpholine analogue **41** showed ca. 10-fold reduced affinity.

Table 4. Affinity at the 5-HT_2 receptors



R=	Compound	pK_i 5-HT_{2C}	pK_i 5-$HT_{2A/B}$
	**29**	8.8	6.4/6.7
	**36**	8.6	<5.9/6.9
	**37**	8.0	<5.4/<5.6
	**38**	8.2	6.5/6.9
	**39**	8.7	6.4/6.6
	**40**	8.6	6.2/6.7
	**41**	7.9	<5.1/<6.0

Examples from the compounds described herein were tested for agonist and antagonist properties at the human 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors.[11] 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 **11**: 6.0; **12**: 6.9; **13**: 7.2; **18**: 8.7; **20**: 9.3; **29**: 8.8).

In conclusion, discovery and optimisation of a series of ligands of the human 5-HT_{2C} receptor was described. This novel class of potent and selective 5-HT_{2C} antagonists is endowed with good developability characteristics. Compound **31** in particular showed a highly attractive combination of in vitro and in vivo parameters.

Acknowledgments

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5. 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,

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8. Catalyst 4.6, Accelrys Inc.
9. The research complied with national legislation and with company policy on the Care and Use of Animals and with related codes of practice.
10. 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.
11. Compounds were tested for agonist and antagonist properties at the human 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors using mobilisation of intracellular calcium as described in, and pK_b values determined according to, Jerman, J. C.; Brough, S. J.; Gager, T.; Wood, M.; Coldwell, M. C.; Smart, D.; Middlemiss, D.N. *Eur. J. Pharmacol.* **2001**, *414*, 23, with the exception that the receptors were expressed in HEK293 cells as described in Ref. 5.