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Pyrrolo(iso)quinoline derivatives as 5-HT$_{2C}$ receptor agonists

David R. Adams, Jonathan M. Bentley, Karen R. Benwell, Michael J. Bickerdike, Corinna D. Bodkin, Ian A. Cliffe, Colin T. Dourish, Ashley R. George, Guy A. Kennett, Antony R. Knight, Craig S. Malcolm, Howard L. Mansell,* Anil Misra, Kathleen Quirk, Jonathan R. A. Roffey and Steven P. Vickers

Vernalis plc, Oakdene Court, 613 Reading Road, Winnersh, Wokingham, Berkshire RG41 5UA, UK

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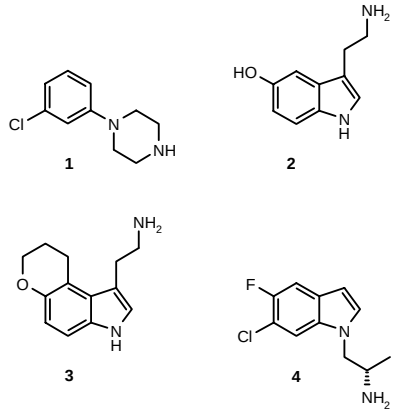
Abstract—A series of 1-(1-pyrrolo(iso)quinolinyl)-2-propylamines was synthesised and evaluated as 5-HT$_{2C}$ receptor agonists for the treatment of obesity. The general methods of synthesis of the precursor indoles are described. The functional efficacy and radioligand binding data for the compounds at 5-HT$_2$ receptor subtypes are reported. The analogue which showed the highest 5-HT$_{2C}$ binding affinity (**27**, 1.6 nM) was found to be successful in reducing food intake in rats.

The rising prevalence of obesity in the developed and developing world carries an enormous financial burden.[1] Obesity is a major risk factor in the development of such conditions as cancer, coronary artery disease, dyslipidaemia and hyperglycaemia. In the US, a recent survey has suggested that 64% of adults are either overweight or obese.[2]

The non-selective 5-HT$_{2C}$ receptor agonist *meta*-chlorophenylpiperazine (*m*CPP, **1**) reduces food intake and accelerates the appearance of the behavioural satiety sequence in rats.[3,4] It also decreases food intake in normal human volunteers[5] and obese subjects.[6] The anorectic action of *m*CPP is absent in mutant mice lacking the 5-HT$_{2C}$ receptor[7] and is attenuated by the selective 5-HT$_{2C}$ receptor antagonist SB-242084 in rats.[8]

The endogenous ligand 5-hydroxytryptamine (5-HT, **2**) is non-selective across 5-HT receptor subtypes. The conformationally restricted tryptamine **3** however is reported to show selectivity for 5-HT$_2$ receptors.[9] In addition to *m*CPP (**1**), the 1-(1-indolyl)-2-propylamine RO600175 (**4**) has been identified as a potent 5-HT$_{2C}$ receptor agonist and is selective for 5-HT$_{2C}$ and 5-HT$_{2B}$ receptors.[10] In the light of recent evidence[11] that 5-HT$_{2B}$ agonism might be associated with cardiac valvulopathy, the development of compounds having improved selectivity for 5-HT$_{2C}$ receptors over 5-HT$_{2B}$ receptors is considered a desirable objective.



In accordance with these literature leads, 1-(1-pyrrolo(iso)quinolinyl)-2-propylamines such as **27**–**39** (Schemes 2 and 3) were proposed as conformationally restricted targets for synthesis and evaluation as 5-HT$_{2C}$ receptor agonists. It was reasoned that these novel targets might retain the hydrogen bond accepting characteristics of the oxygen atoms of 5-HT (**2**) and the conformationally restricted tryptamine **3**, the steric properties of **3**, as well as the electronic properties of the isotryptamine **4**.

Keywords: Obesity; Serotonin; 5-HT$_{2C}$; Agonist.
* Corresponding author. Tel.: +44 1189 773133; fax: +44 1189 899300; e-mail: h.mansell@vernalis.com

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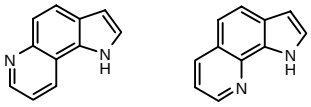
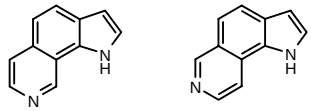
Accordingly, a discovery research programme was initiated to evaluate 1-(1-pyrrolo(iso)quinolinyl)-2-propylamines as novel 5-HT_{2C} receptor agonists for the treatment of obesity.[12]

In order to obtain a series of 1-(1-pyrrolo(iso)quinolinyl)-2-propylamines **27**–**39**, the synthesis of a selection of pyrrolo(iso)quinolines (**5**–**8** and **11**) was undertaken.



5 **6**

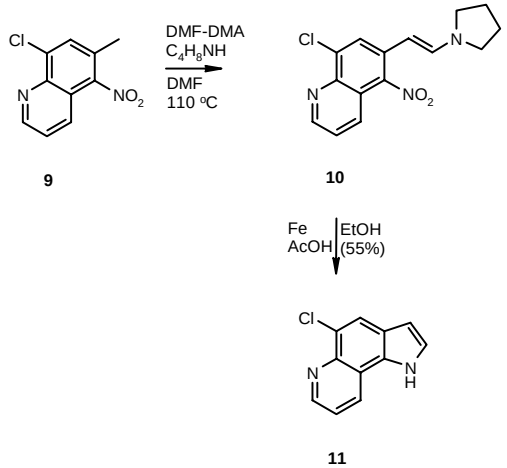


7 **8**

For example, 1*H*-pyrrolo[2,3-*f*]quinoline **5** was prepared by the Bartoli reaction of 5-nitroquinoline with excess vinylmagnesium bromide.[13] The 5-chloro analogue **11** of **5** was initially prepared in the same way in low yield from 8-chloro-5-nitroquinoline, the latter being made by nitration of 8-chloroquinoline.

5-Chloro-1*H*-pyrrolo[2,3-*f*]quinoline (**11**) was later prepared in a more efficient manner using the Leimgruber–Batcho reaction (Scheme 1).[14]

Accordingly 8-chloro-6-methyl-5-nitroquinoline (**9**)[15] was treated with *N*,*N*-dimethylformamide, dimethyl acetal and pyrrolidine to give the nitroenamine **10**, which underwent reductive cyclisation to give the chloroquinoline **11**. The Leimgruber–Batcho reaction was also applied in analogous fashion to 6-methyl-5-nitroquinoline to provide an improved synthesis of **5** (in 69% overall yield).[16] This procedure was additionally employed in the synthesis of 1*H*-pyrrolo[3,2-*h*]quinoline (**6**)[16–18] from 7-methyl-8-nitroquinoline, and in the synthesis of the pyrrolo(iso)quinolines **7**[19] and **8**[20,21] from the appropriately substituted methylnitroisoquinolines. The requisite methylnitroisoquinolines were obtained in quantitative yield by nitration of 7- and 6-methylisoquinoline using potassium nitrate in sulfuric acid.[22] The precursor methylisoquinolines[23] were prepared in two steps and in low yields from *m*- and *p*-tolualdehyde by a modified[24] Pomeranz–Fritsch reaction.[25] The mixture of 5- and 7-methylisoquinoline regioisomers obtained during the synthesis of **7** was separated by recrystallisation from heptane.



9 **10** **11**

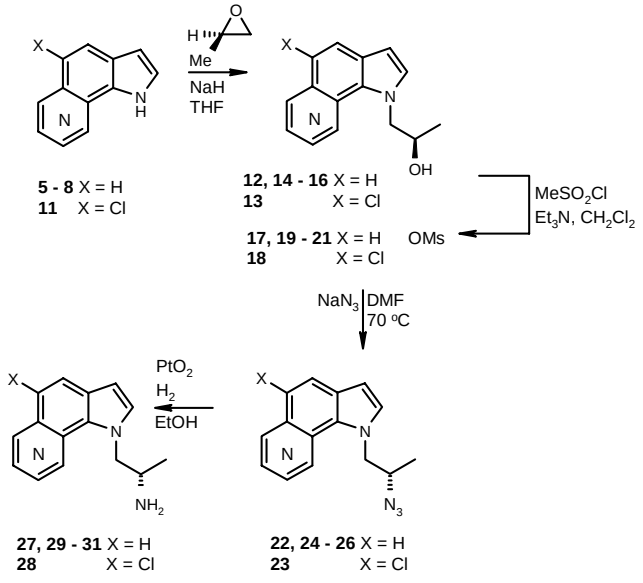
Scheme 1. Synthesis of 5-chloro-1*H*-pyrrolo[2,3-*f*]quinoline **11**.

The pyrrolo(iso)quinoline intermediates **5**–**8** and **11** were transformed to the target (*S*)-*N*-unsubstituted indole derivatives **27**–**31** as shown in Scheme 2.

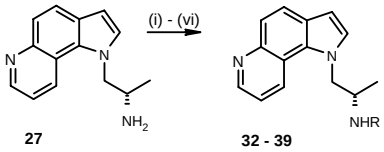
Thus, reaction of the pyrrolo(iso)quinolines **5**–**8**, **11** with sodium hydride and (*R*)-propylene oxide gave the (*R*)-alcohols **12**–**16**, which were converted via their methanesulfonate ester derivatives **17**–**21** to the (*S*)-azides **22**–**26**. Catalytic hydrogenation of **22**–**26** then gave the target primary amines **27**–**31**.[26]

Finally, in order to explore structure–activity relationships around the nitrogen atom of the 2-propylamine unit, a small series of *N*-alkyl derivatives were prepared from **27** using solution-phase parallel reductive amination reactions (Scheme 3).

This entailed imine formation, reduction with polymer supported borohydride, the use of polymer-supported



Scheme 2. Synthesis of (*S*)-1-(1-pyrrolo(iso)quinolinyl)-2-propylamines **27**–**31** (see Table 1).



27 **32 - 39**

Scheme 3. Synthesis of (*S*)-*N*-alkyl-1-(1-pyrrolo[2,3-*f*]quinolinyl)-2-propylamine derivatives **32**–**39** (see Table 1). Reagents: (i) RCHO, MeOH; (ii) PS–BH_4; (iii) PS–4-$BnOC_6H_4CHO$, CH_2Cl_2; (iv) filtration; (v) SCX-2, MeOH; (vi) NH_3, 2 M in MeOH.

Table 1. 5-HT_2 receptor subtype functional efficacy, potency and binding for **1**, **2**, **4** and 1-(1-pyrrolo(iso)quinolinyl)-2-propylamines **27**–**39**

Compound	Substituent(s)	Percentage relative efficacy (EC_{50}, nM)[a]			Binding affinity (nM)[a]		
		h5-HT_{2A}[b]	h5-HT_{2B}[b]	h5-HT_{2C}[b]	K_i h5-HT_{2A}[c]	K_i h5-HT_{2B}[d]	K_i h5-HT_{2C}[d]
1 (*m*CPP)		41% (75)	33% (>1000)	83% (26)	54	32	9
2 (5-HT)		98% (11)	101% (1.5)	99% (1.7)	14	12	6.9
4 (RO600175)		72% (131)	71% (4.3)	93% (18)	38	5.1	2.3
27 (VER-2692)	Pyrrolo[2,3-*f*]quinolinyl	88% (32)	65% (1.1)	99% (2.9)	31	12	1.6
28	5-Chloropyrrolo[2,3-*f*]quinolinyl	85% (36)	61% (2.1)	101% (6.9)	29	18	2.4
29	Pyrrolo[3,2-*h*]quinolinyl	41% (446)	60% (45)	39% (97)	229	115	27
30	Pyrrolo[3,2-*h*]isoquinolinyl	67% (473)	67% (62)	98% (73)	230	210	37
31	Pyrrolo[2,3-*f*]isoquinolinyl	63% (>1000)	70% (152)	93% (297)	1041	778	72
32	*N*-(2-Naphthyl)methyl	56% (222)	76% (27)	99% (52)	181	136	16
33	*N*-(3,4-Methylenedioxy)benzyl	69% (359)	71% (20)	98% (42)	398	138	16
34	*N*-(2-Chloro)benzyl	58% (638)	72% (44)	95% (74)	674	380	39
35	*N*-Benzyl	39% (>1000)	70% (97)	86% (200)	842	515	77
36	*N*-(Cyclohexyl)methyl	32% (>1000)	67% (128)	88% (348)	927	624	78
37	*N*-Allyl	54% (777)	70% (91)	92% (257)	1158	455	86
38	*N*-(2-Methoxy)benzyl	24% (>1000)	41% (462)	77% (551)	1568	883	168
39	*N*-(2-Methyl)benzyl	49% (>1000)	64% (128)	87% (219)	1681	739	171

[a] Relative efficacy, EC_{50} and K_i values are the mean of two determinations run at 11 different concentrations. Each experiment was carried out in triplicate. Standard errors were within ±20% of the mean.
[b] Efficacy relative to 10 μM 5-HT (100%).
[c] Displacement of [^{125}I]DOI.
[d] Displacement of [^{3}H]5-HT.

4-benzyloxybenzaldehyde as a scavenger resin for unreacted **27** and catch-release purification with SCX-2 cartridges. The *N*-allyl derivative **37** was made by alkylation with allyl bromide.

The target 2-propylamines **27**–**39** were screened for functional activity at recombinant human 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors expressed in CHO cells using a Fluorometric Imaging Plate Reader (FLIPR) (Table 1). The maximum fluorescent signal was measured and compared with the response produced by 10 μM 5-HT (defined as 100%).[27] The compounds were then compared in radioligand binding assays using recombinant human 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors expressed in mammalian cell lines.[28]

The 2-propylamines **27**–**39** were potent partial or full agonists at 5-HT_{2C} receptors. In binding studies, all of the compounds **27**–**39** had greater selectivity for 5-HT_{2C} receptors over 5-HT_{2B} receptors than RO600175 (**4**) (2.2-fold). Compounds **27**–**39** also had greater selectivity for 5-HT_{2C} receptors over both 5-HT_{2A} and 5-HT_{2B} receptors than *m*CPP (**1**) (6.0- and 3.6-fold, respectively). Compounds **27** and **28** also had higher binding affinities for 5-HT_{2C} receptors than both *m*CPP (**1**) and 5-HT (**2**). With the exception of compound **29**, compounds **27**–**39** showed a broadly similar percentage relative efficacy profile to RO600175 (**4**). Compounds **27**–**39** did, however, show less functional selectivity than **4** for 5-HT_{2B} receptors over 5-HT_{2C} receptors (EC_{50} ratios of 1.2- to 3.3-fold vs 4.2-fold). Finally, the *N*-alkyl analogues **32**–**39** retained the binding and functional selectivities of their precursor **27**, but the binding affinities and functional potencies were significantly reduced.

Selected compounds were tested for their ability to decrease food consumption in 23 h food-deprived rats using dexfenfluramine as a positive control.[29] Animals treated 3 mg/kg with either compound **27** or dexfenfluramine significantly reduced food intake 4 h after food presentation when compared to vehicle treated animals using the analysis of variance test and Dunnett's post hoc test. The anorectic effect of compound **27** was dose-dependently blocked by pre-treatment with the selective 5-HT_{2C} receptor antagonist SB-242084, indicating a 5-HT_{2C} receptor mediated effect.

In conclusion, a series of 1-(1-pyrrolo(iso)quinolinyl)-2-propylamines and selected *N*-alkyl derivatives has been synthesised and subjected to pharmacological evaluation. Compound **27** (VER-2692) was shown to be a potent 5-HT_{2C} receptor agonist and reduced feeding in rats. Thus, the 1-(1-pyrrolo(iso)quinolinyl)-2-propylamines **27**–**39** have potential for use in therapy as anti-obesity agents.

Acknowledgments

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