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Indoline derivatives as 5-HT$_{2C}$ receptor agonists

J. M. Bentley,* D. R. Adams, D. Bebbington, K. R. Benwell, M. J. Bickerdike, J. E. P. Davidson, C. E. Dawson, C. T. Dourish, M. A. J. Duncton, S. Gaur, A. R. George, P. R. Giles, R. J. Hamlyn, G. A. Kennett, A. R. Knight, C. S. Malcolm, H. L. Mansell, A. Misra, N. J. T. Monck, R. M. Pratt, K. Quirk, J. R. A. Roffey, S. P. Vickers and I. A. Cliffe

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

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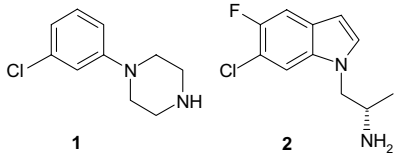
Abstract—A series of 1-(1-indolinyl)-2-propylamines was synthesised and evaluated as 5-HT$_{2C}$ receptor agonists for the treatment of obesity. The general methods of synthesis of the precursor indoles are described. The functional efficacy and radioligand binding data for all of the compounds at 5-HT$_2$ receptor subtypes are reported. A number of compounds were found to reduce food intake in rats after oral administration.

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 hypertension, hyperglycemia, dyslipidemia, coronary artery disease and cancer. In the US, a recent survey has suggested that 64% of adults are either overweight or obese.[2]

The nonselective 5-HT$_{2C}$ receptor agonist *meta*-chlorophenylpiperazine (*m*CPP; **1**) reduces food intake, accelerates the appearance of the behavioural satiety sequence in rats[3,4] and 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]

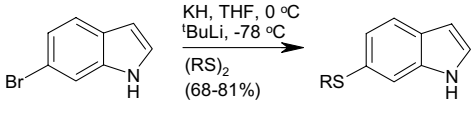
Several chemical classes of 5-HT$_{2C}$ receptor agonists have been reported, notably *m*CPP (**1**) and the more potent 1-(1-indolyl)-2-propylamine RO600175 (**2**).[9] Based on these literature leads, 1-(1-indolinyl)-2-propylamines were proposed as targets for synthesis and evaluation as 5-HT$_{2C}$ receptor agonists.



1 **2**

It was reasoned that the incorporation of the two basic nitrogen atoms from the piperazine ring of *m*CPP (**1**) into the indole structure of RO600175 (**2**) might produce new analogues with improved selectivity and oral potency. Accordingly a discovery research programme was initiated to investigate 1-(1-indolinyl)-2-propylamines as novel 5-HT$_{2C}$ receptor agonists for the treatment of obesity.[10,11]

In order to obtain a diverse array of 1-(1-indolinyl)-2-propylamines, a selection of indoles was prepared using several standard methods (Schemes 1–4). Thus,



4

5 R = Me
6 R = Et

Scheme 1. Synthesis of 6-alkylthioindoles **5** and **6**.

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* Corresponding author. Tel.: +44-(0)118-977-3133; fax: +44-(0)118-989-9300; e-mail: j.bentley@vernalis.com

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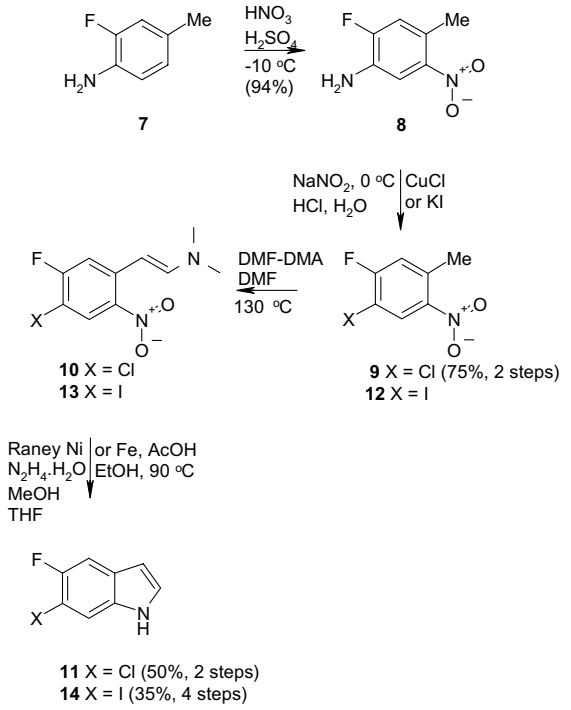
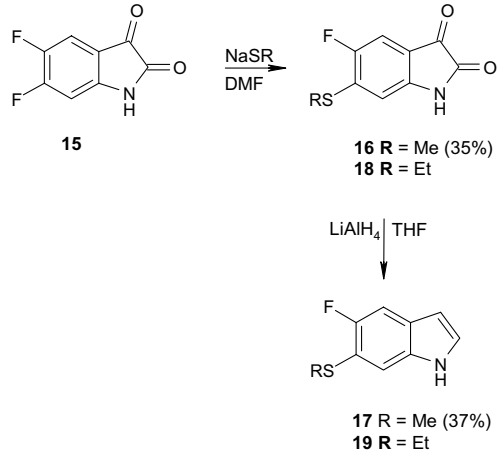


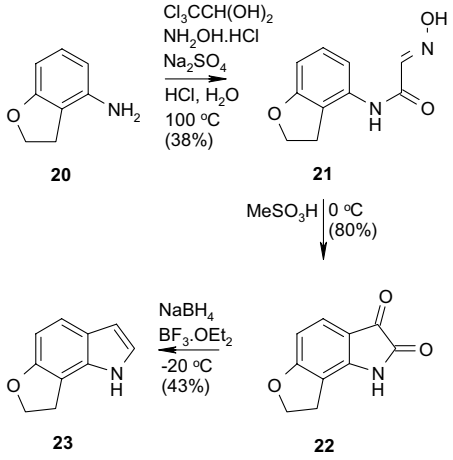
Scheme 2. Synthesis of 5-fluoro-6-haloindoles **11** and **14**.



Scheme 3. Synthesis of 6-alkylthio-5-fluoroindoles **17** and **19**.

6-methylthioindole (**5**) was prepared by metallation of 6-bromoindole (**4**) with potassium hydride and *tert*-butyllithium, followed by treatment with methyl disulfide (Scheme 1).[12] 6-Ethylthioindole (**6**) was also prepared using this approach. 6-Chloroindole (**3**) and 6-bromoindole (**4**) are commercially available.

A sequence involving the Leimgruber–Batcho reaction was employed to prepare 6-chloro-5-fluoroindole (**11**) from 2-fluoro-4-methylaniline (**7**) (Scheme 2).[13] Thus nitration of the aniline **7** gave the nitrotoluene **8**, which was treated with sodium nitrite and copper(I) chloride to give the chlorofluoronitrotoluene **9**. The nitrotoluene **9** reacted with *N*,*N*-dimethylformamide dimethyl acetal to give the nitroenamine **10**, which underwent reductive cyclisation with Raney nickel and hydrazine to yield **11**.

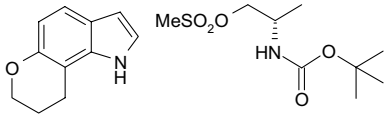


Scheme 4. Synthesis of 7,8-dihydro-1*H*-furo[2,3-*g*]indole (**23**).

The use of potassium iodide in the place of copper(I) chloride gave 5-fluoro-4-iodo-2-nitrotoluene (**12**), and this afforded a synthesis of 5-fluoro-6-iodoindole (**14**). The iodoenamine **13** was reductively cyclised using iron in acetic acid.

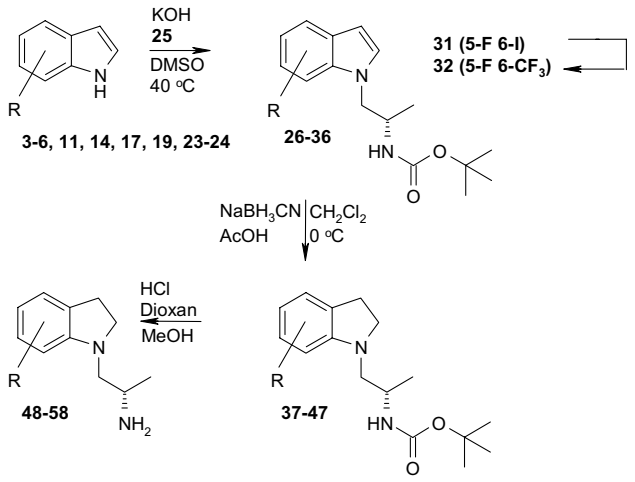
Reaction of 5,6-difluoroisatin (**15**)[14] with sodium thiomethoxide gave 5-fluoro-6-methylthioisatin (**16**), which was reduced with lithium aluminium hydride to give 5-fluoro-6-methylthioindole (**17**) (Scheme 3). In the same way, 6-ethylthio-5-fluoroindole (**19**) was prepared via 6-ethylthio-5-fluoroisatin (**18**) using sodium ethane–thiolate.

7,8-Dihydro-1*H*-furo[2,3-*g*]indole (**23**) and 1,7,8,9-tetrahydropyrano[2,3-*g*]indole (**24**) were both obtained from arenecarboxaldehyde precursors and methyl azidoacetate using the Hemetsberger indole synthesis.[15,16] In addition, a regiospecific synthesis of the furoindole **23** from 4-amino-2,3-dihydrobenzofuran (**20**) using chloral hydrate and hydroxylamine and via the α-isonitrosoacetanilide and isatin intermediates **21** and **22**, respectively, was also developed (Scheme 4).[17,18]



The target indolines **48**–**58** were then obtained from the indoles **3**–**6**, **11**, **14**, **17**, **19**, **23** and **24** as outlined in Scheme 5. Alkylation of the appropriate indole with (*S*)-*tert*-butyl [2-(1-methanesulfonyloxy)propyl]carbamate (**25**) produced the indole carbamates **26**–**31** and **33**–**36**.[19]

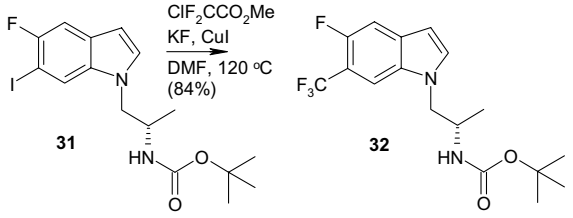
Reduction of **26**–**36** with sodium cyanoborohydride in acetic acid gave the indoline carbamates **37**–**47**, which were deprotected under acidic conditions to form the indolines **48**–**58**.



Scheme 5. Synthesis of 1-(1-indolinyl)-2-propylamines **48**–**58**.

The 5-fluoro-6-trifluoromethylindole **32** was obtained from **31** via reaction with methyl 2-chloro-2,2-difluoroacetate, copper(I) iodide and potassium fluoride (Scheme 6).[20]

The indolines **48**–**58** 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).[21] The maximum fluorescent signal was measured and compared with the response produced by 10 μM 5-HT (defined as 100%).[21]



Scheme 6. Synthesis of 5-fluoro-6-trifluoromethylindole **32**.

The most efficacious compounds from the functional assay were then compared in radioligand binding at recombinant human 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors expressed in mammalian cell lines.[22]

In general indolines **48**–**58** were potent partial agonists at 5-HT_{2C} receptors. In binding studies, compounds **48**, **50**, **51** and **55**–**58** had greater selectivity for 5-HT_{2C} receptors over 5-HT_{2A} (6.0-fold) and 5-HT_{2B} (3.6-fold) receptors than *m*CPP (**1**). Compounds **50**–**58** showed a broadly similar relative efficacy profile to RO600175 (**2**). However, compounds **50**–**58** did show less functional selectivity than **2** for 5-HT_{2B} over 5-HT_{2C} receptors (0.55–4.2-fold vs 4.2-fold). Compound **52**, containing the 6-chloro-5-fluoro substitution pattern of RO600175, showed similar binding selectivities to the dehydro variant **2** for the 5-HT_2 subtypes (5-$HT_{2C/2A}$: 12-fold; 5-$HT_{2C/2B}$: 2.2-fold) but significantly lower binding affinities. However the 6-alkylthio analogues **50**, **51**, **55** and **56**, and the furo and pyrano *g* fused derivatives **57** and **58** had greater binding selectivity for 5-HT_{2C} receptors over 5-HT_{2B} receptors than both the 6-chloro-5-fluoro analogues **2** and **52**.

Selected compounds were tested for their ability to decrease food intake.[23] 23-Hour, food-deprived rats were administered compounds **1**, **49**, **55** and **57** either subcutaneously (sc) or orally (po). Compounds **1**, **49**, **55** and **57** significantly reduced feeding in a dose-dependent manner with the minimal efficacious doses (MEDs) shown in Table 2. Compounds **49**, **55** and **57** showed >100-fold binding selectivity for 5-HT_{2C} receptors over non-5-HT_2 receptor subtypes.

Table 1. 5-HT_2 receptor subtype functional efficacy, potency and binding for 5-HT, **1**, **2** and 1-(1-indolinyl)-2-propylamines **48**–**58**

Compound	Substituent(s)	Percentage relative efficacy (EC_{50}, nM)[21]			Binding affinity (nM)[22]		
		[a]h5-HT_{2A}	[a]h5-HT_{2B}	[a]h5-HT_{2C}	[b]K_i h5-HT_{2A}	[c]K_i h5-HT_{2B}	[c]K_i h5-HT_{2C}
5-HT	[5-OH]	98% (11)	101% (1.5)	99% (1.7)	14	12	6.9
1 (*m*CPP)	[*meta*-Cl]	41% (75)	33% (>1 μM)	83% (26)	54	32	9
2 (RO600175)	[6-Cl-5-F]	72% (131)	71% (4.3)	93% (18)	38	5.1	2.3
48	6-Cl	55% (602)	76% (6.5)	91% (44)	364	54	13
49 (VER-3323)	6-Br	54% (719)	78% (11)	88% (44)	351	46	24
50	6-MeS	72% (164)	78% (10)	95% (26)	171	89	5.7
51	6-EtS	71% (378)	67% (72)	90% (40)	184	189	16
52	6-Cl-5-F	66% (367)	77% (7.3)	89% (31)	167	31	14
53	5-F-6-I	54% (432)	71% (22)	79% (64)	139	38	17
54	5-F-6-F_3C	45% (1063)	86% (49)	86% (130)	432	88	26
55 (VER-5593)	5-F-6-MeS	87% (76)	72% (4.1)	97% (6.7)	53	21	3.2
56	6-EtS-5-F	80% (181)	66% (31)	92% (21)	58	62	6.4
57 (VER-5384)	2,3,7,8-Tetrahydro-1*H*-furo[2,3-*g*]	81% (62)	74% (3.0)	98% (4.5)	112	49	8.7
58	1,2,3,7,8,9-Hexahydropyrano[2,3-*g*]	71% (125)	67% (36)	94% (28)	395	355	38

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.

[a] Efficacy relative to 10 μM 5-HT (100%).

[b] Displacement of [^{125}I]-DOI.

[c] Displacement of [^{3}H]-5-HT.

Table 2. 23-Hour food-deprived rat feeding test results for compounds **1**, **49**, **55** and **57**

Compound	Substituent(s)	MED (mg/kg)	
		Subcutaneously (sc)	Orally (po)
1 (*m*CPP)	[*meta*-Cl]	1	10
49 (VER-3323)	6-Br	3	30
55 (VER-5593)	5-F-6-MeS	0.3	3
57 (VER-5384)	2,3,7,8-Tetrahydro-1*H*-furo[2,3-*g*}	0.1	1

A variety of indoles have been synthesised and transformed into a novel series of 1-(1-indolinyl)-2-propylamines **48**–**58** by alkylation, reduction and nitrogen deprotection. Several analogues including **49** (VER-3323), **55** (VER-5593) and **57** (VER-5384) were shown to be potent 5-HT_{2C} receptor agonists and reduced feeding in rats following oral administration. Thus, the 1-(1-indolinyl)-2-propylamines **48**–**58** have potential for use in therapy as anti-obesity agents.

Acknowledgements

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References and notes

1. Carek, P. J.; Dickerson, L. M. *Drugs* **1999**, *57*, 883–904.
2. National Center for Health Statistics, US Centers for Disease Control and Prevention (http://www.cdc.gov/nchs/).
3. Kennett, G. A.; Curzon, G. *Psychopharmacology* **1988**, *96*, 93–100.
4. Kitchener, S. J.; Dourish, C. T. *Psychopharmacology* **1994**, *113*, 369–377.
5. Walsh, A. E. S.; Smith, K. A.; Oldman, A. D.; Williams, C.; Goodall, E. M.; Cowen, P. J. *Psychopharmacology* **1994**, *116*, 120–122.
6. Sargent, P. A.; Sharpley, A. L.; Williams, C.; Goodall, E. M.; Cowen, P. J. *Psychopharmacology* **1997**, *133*, 309–312.
7. Tecott, L. H.; Sun, L. M.; Akana, S. F.; Strack, A. M.; Lowenstein, D. H.; Dallman, M. F.; Julius, D. *Nature* **1995**, *374*, 542–546.
8. Kennett, G. A.; Wood, M. D.; Bright, F.; Trail, B.; Riley, G.; Holland, V.; Avenell, K. Y.; Stean, T.; Upton, N.; Bromidge, S.; Forbes, I. T.; Brown, A. M.; Middlemiss, D. N.; Blackburn, T. P. *Neuropharmacology* **1997**, *36*, 609–620.
9. Bös, M.; Jenck, F.; Martin, J. R.; Moreau, J.-L.; Sleight, A. J.; Wichmann, J.; Widmer, U. *J. Med. Chem.* **1997**, *40*, 2762–2769.
10. Adams, D. R.; Bentley, J. M.; Roffey, J. R. A.; Hamlyn, R. J.; Gaur, S.; Duncton, M. A. J.; Bebbington, D.; Monck, N. J.; Dawson, C. E.; Pratt, R. M.; George, A. R. Patent WO 0012475, 2000; *Chem. Abstr*. **2000**, *132*, 194289.
11. Roffey, J. R. A.; Davidson, J. E. P.; Mansell, H. L.; Hamlyn, R. J.; Adams, D. R. Patent WO 0112602, 2001; *Chem. Abstr*. **2001**, *134*, 193338.
12. Yang, Y.; Martin, A. R.; Nelson, D. L.; Regan, J. *Heterocycles* **1992**, *34*, 1169–1175.
13. Batcho, A. D.; Leimgruber, W. *Org. Synth.* **1985**, *63*, 214–225.
14. Bitha, P.; Lin, Y. I. U.S. Patent 4,833,270, 1989; *Chem. Abstr*. **1989**, *111*, 173772.
15. North, P. C.; Carter, M. C. Patent WO 9,517,405, 1995; *Chem. Abstr*. **1995**, *123*, 340087.
16. (a) Kim, P. T.; Guilard, R.; Renaut, P. *Can. J. Chem.* **1982**, *60*, 2093–2098; (b) Picart, F. European Patent 43752, 1982; *Chem. Abstr.* **1982**, *96*, 162678.
17. Marburg, S.; Tolman, R. L. *J. Heterocycl. Chem.* **1980**, *17*, 1333–1335.
18. Marvel, C. S.; Hiers, G. S. In *Organic Syntheses Collective Volumes*; Wiley: New York, 1941; Vol. 1, pp 327–330.
19. (a) Higashiura, K.; Morino, H.; Matsuura, H.; Toyomaki, Y.; Ienaga, K. *J. Chem. Soc., Perkin Trans. 1* **1989**, *8*, 1479–1481; (b) Rogers-Evans, M.; Soukup, M. Patent WO 9747598, 1997; *Chem. Abstr*. **1998**, *128*, 75296.
20. Su, D.; Duan, J.; Chen, Q. *Tetrahedron Lett.* **1991**, *32*, 7689–7690.
21. Porter, R. H. P.; Benwell, K. R.; Lamb, H.; Malcolm, C. S.; Allen, N. H.; Revell, D. F.; Adams, D. R.; Sheardown, M. J. *Br. J. Pharmacol.* **1999**, *128*, 13–20.
22. 5-HT_{2A}: McKenna, D. J.; Peroutka, S. J. *J. Neurosci.* **1989**, *9/10*, 3482–3490; 5-HT_{2B}: Schmuck, K.; Ullmer, C.; Engels, P.; Lubbert, H. *FEBS Lett.* **1994**, *342*, 85–90; 5-HT_{2C}: Hoyer, D.; Engel, G.; Kalkman, H. O. *Eur. J. Pharmacol.* **1985**, *118*, 13–23.
23. Vickers, S. P.; Dourish, C. T.; Kennett, G. A. *Neuropharmacology* **2001**, *41*, 200–209.