Indoline derivatives as 5-HT\textsubscript{2C} receptor agonists


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\textsubscript{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\textsubscript{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.\textsuperscript{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.\textsuperscript{2}

The nonselective 5-HT\textsubscript{2C} receptor agonist \textit{meta}-chlorophenylpiperazine (\textit{mCPP}; \ref{1}) reduces food intake, accelerates the appearance of the behavioural satiety sequence in rats\textsuperscript{3,4} and decreases food intake in normal human volunteers\textsuperscript{5} and obese subjects.\textsuperscript{6} The anorectic action of \textit{mCPP} is absent in mutant mice lacking the 5-HT\textsubscript{2C} receptor,\textsuperscript{7} and is attenuated by the selective 5-HT\textsubscript{2C} receptor antagonist SB-242084 in rats.\textsuperscript{8}

Several chemical classes of 5-HT\textsubscript{2C} receptor agonists have been reported, notably \textit{mCPP} (\ref{1}) and the more potent 1-(1-indoly)-2-propylamine \textit{RO600175} (\ref{2}).\textsuperscript{9} Based on these literature leads, 1-(1-indolinyl)-2-propylamines were proposed as targets for synthesis and evaluation as 5-HT\textsubscript{2C} receptor agonists.

It was reasoned that the incorporation of the two basic nitrogen atoms from the piperazine ring of \textit{mCPP} (\ref{1}) into the indole structure of \textit{RO600175} (\ref{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\textsubscript{2C} receptor agonists for the treatment of obesity.\textsuperscript{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,

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.

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-1H-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 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

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.
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).

The indolines 48-58 were screened for functional activity at recombinant human 5-HT2A, 5-HT2B and 5-HT2C 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%).

The most efficacious compounds from the functional assay were then compared in radioligand binding at recombinant human 5-HT2A, 5-HT2B and 5-HT2C receptors expressed in mammalian cell lines.

In general indolines 48-58 were potent partial agonists at 5-HT2C receptors. In binding studies, compounds 48, 50, 51 and 55-58 had greater selectivity for 5-HT2C receptors over 5-HT2A (6.0-fold) and 5-HT2B (3.6-fold) receptors than mCPP (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-HT2B over 5-HT2C 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-HT2 subtypes (5-HT2C/2A: 12-fold; 5-HT2C/2B: 2.2-fold) but significantly lower binding affinities. However the 6-alkylthio analogues 50, 51, 55 and 56, and the furo and pyrano fused derivatives 57 and 58 had greater binding selectivity for 5-HT2C receptors over 5-HT2A receptors than both the 6-chloro-5-fluoro analogues 2 and 52.

Selected compounds were tested for their ability to decrease food intake. 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-HT2C receptors over non-5-HT2 receptor subtypes.

### Table 1. 5-HT2 receptor subtype functional efficacy, potency and binding for 5-HT, 1, 2 and 1-(1-indolinyl)-2-propylamines 48-58

<table>
<thead>
<tr>
<th>Compound</th>
<th>Substituent(s)</th>
<th>Percentage relative efficacy (EC50)</th>
<th>Binding affinity (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>h5-HT2A</td>
<td>h5-HT2B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>98% (11)</td>
<td>99% (1.7)</td>
</tr>
<tr>
<td>5-HT</td>
<td>[5-OH]</td>
<td>101% (1.5)</td>
<td>14</td>
</tr>
<tr>
<td>1 (mCPP)</td>
<td>[meta-Cl]</td>
<td>98% (1.4)</td>
<td>14</td>
</tr>
<tr>
<td>2 (RO600175)</td>
<td>[6-Cl-5-F]</td>
<td>98% (1.4)</td>
<td>14</td>
</tr>
<tr>
<td>48</td>
<td>6-Cl</td>
<td>98% (1.4)</td>
<td>14</td>
</tr>
<tr>
<td>49 (VER-3323)</td>
<td>6-Br</td>
<td>98% (1.4)</td>
<td>14</td>
</tr>
<tr>
<td>50</td>
<td>6-Br</td>
<td>98% (1.4)</td>
<td>14</td>
</tr>
<tr>
<td>51</td>
<td>6-EtS</td>
<td>98% (1.4)</td>
<td>14</td>
</tr>
<tr>
<td>52</td>
<td>6-EtS-5-F</td>
<td>98% (1.4)</td>
<td>14</td>
</tr>
<tr>
<td>53</td>
<td>5-F-6-6-I</td>
<td>98% (1.4)</td>
<td>14</td>
</tr>
<tr>
<td>54</td>
<td>5-F-6-6-F,C</td>
<td>98% (1.4)</td>
<td>14</td>
</tr>
<tr>
<td>55 (VER-5593)</td>
<td>5-F-6-MeS</td>
<td>98% (1.4)</td>
<td>14</td>
</tr>
<tr>
<td>56</td>
<td>6-EtS-5-F</td>
<td>98% (1.4)</td>
<td>14</td>
</tr>
<tr>
<td>57 (VER-5384)</td>
<td>2,3,7,8-Tetrahydro-1H-furo[2,3-g]</td>
<td>98% (1.4)</td>
<td>14</td>
</tr>
<tr>
<td>58</td>
<td>1,2,3,7,8,9-Hexahydropyrano[2,3-g]</td>
<td>98% (1.4)</td>
<td>14</td>
</tr>
</tbody>
</table>

Relative efficacy, EC50 and Kᵢ 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 [3H]5-HT.

c Displacement of [3H]DOI.
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-HT2C 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