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Indazole and Indoline as Aromatic Bioisosteres in the Imidazole Class of Serotonin 5-HT_3 Receptor Antagonists

J. Bermudez, F.D. King* and G.J. Sanger.

SmithKline Beecham Pharmaceuticals, The Pinnacles, Harlow, Essex, CM19 5AD, UK.

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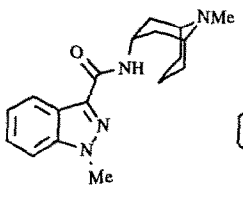
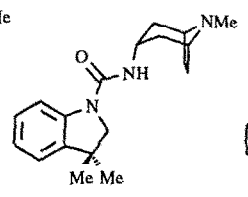
Abstract: The synthesis and 5-HT_3 receptor antagonist activity of imidazole derivatives of 3-keto-indazoles, and 3,3-dimethylindolin-1-yl and o-methoxyphenyl amides is described. Results demonstrate that indazole and indoline are effective bioisosteres in the imidazole class of 5-HT_3 receptor antagonists.

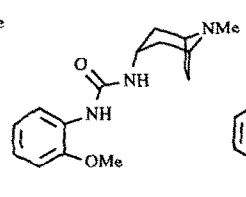
In previous communications we have described the synthesis and 5-HT_3 receptor antagonist properties of azabicycles linked via either an ester or amide to an indazole,[1] as in granisetron, **1**, an indoline,[2] such as BRL 46470, **2**, and ortho-alkoxyphenyl ureas,[3] for example BRL 44687, **3**. A second class of 5-HT_3 receptor antagonists are the imidazolylketones as exemplified by ondansetron **4**.[4] To date all compounds decribed from this latter class of 5-HT_3 receptor antagonists have contained an indole aromatic nucleus. The present communication describes the synthesis and 5-HT_3 receptor antagonist activity of compounds which retain an imidazole, but which contain the alternative aromatic nuclei of **1**, **2** and **3**.



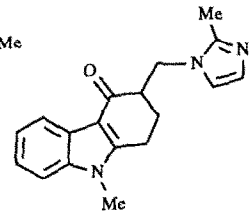
granisetron **1**



BRL 46470 **2**



BRL 44687 **3**

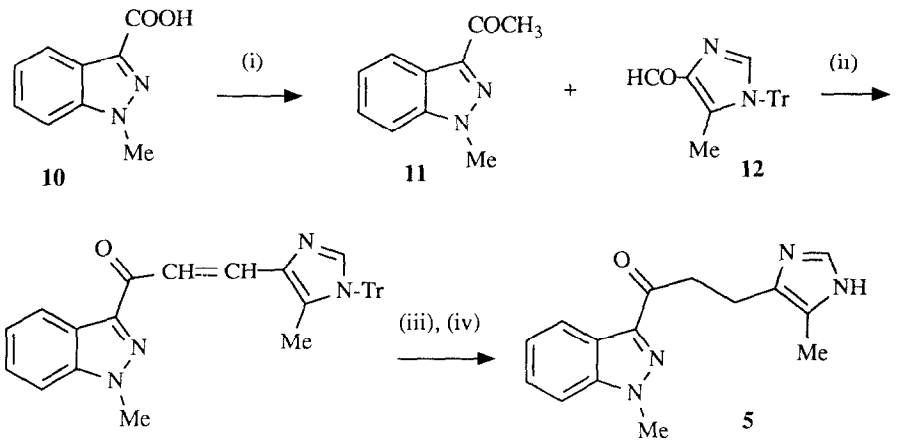


ondansetron **4**

The indazolylketone **5**[5] was prepared from 1-methylindazole-3-carboxylic acid **10**[6] in an overall yield of 10% (not optimised) by reaction with methyllithium to give the 3-acetyl compound **11**. Condensation with the trityl-protected imidazolylaldehyde **12**[7] followed by catalytic hydrogenation and acid hydrolysis to complete the deprotection of the imidazole gave the desired product **5** (Scheme I).

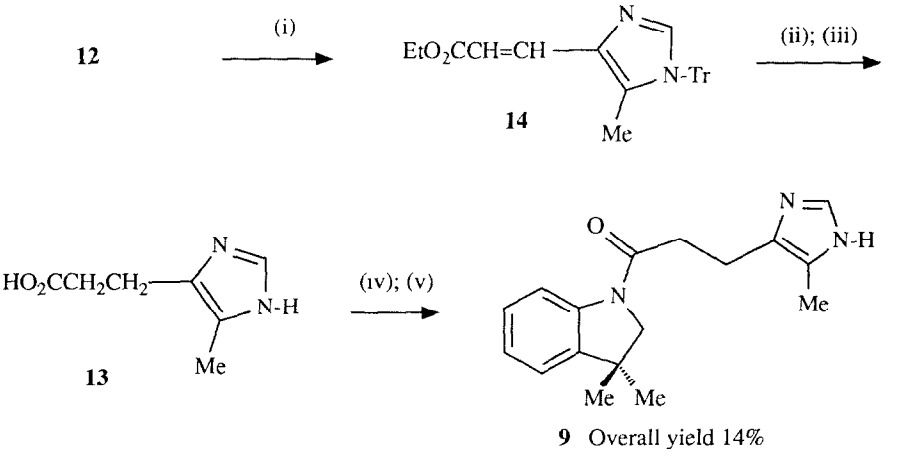
The amides of o-methoxyaniline **6** and 3,3-dimethylindoline, **8** were prepared from 3-(4-imidazolyl)propionic acid.[8] The 3-(5-methyl-4-imidazolyl)propionic acid **13** for the 5-methyl analogues **7** and **9** was also prepared from **12** by Wadsworth-Emmons[9] conversion to the unsaturated ester, **14**, followed by reduction and hydrolysis (Scheme II). Coupling to

Scheme I: Synthesis of **5**.



(i) MeLi; (ii) KOBu-t; (iii) H_2/Pd/C; (iv) HOAc; Tr = Ph_3C-

Scheme II: Synthesis of **9**



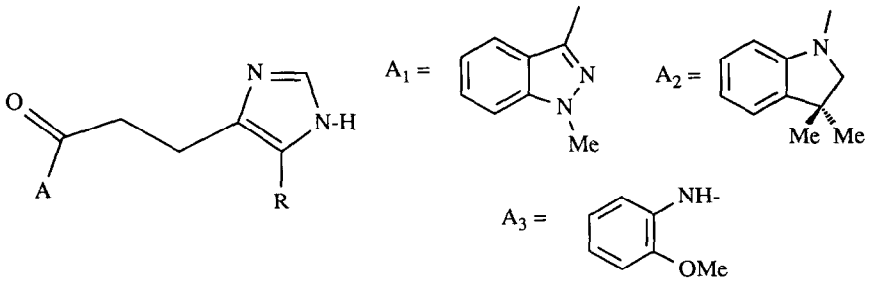
9 Overall yield 14%

(i) $(EtO)_2POCH_2CO_2Et$/KOBu-t; (ii) H_2/Pd/C; (iii) HCl; (iv) $SOCl_2$; (v) amine

the amines was carried out by activation of the acids using thionyl chloride.

The 5-HT_3 receptor antagonist potency of **5** - **9** was assessed by their ability to antagonise the

TABLE: Structure and 5-HT_3 receptor antagonist potencies of compounds **5** - **9**.



Compound No.	Structure A	R	Antagonism of B-J Reflex* ID_{50} µg/kg iv (± SEM)	n**
1	granisetron		0.66 ± 0.15	9
2	BRL 46470		0.67 ± 0.13	8
3	BRL 44687		2.5 ± 0.7	7
4	ondansetron		3.6 ± 1.1	4
5	A_1	Me	3.1 ± 0.6	6
6	A_2	H	4.2 ± 2.0	3
7	A_2	Me	2.2 ± 0.9	4
8	A_3	H	35 ± 18	5
9	A_3	Me	20 ± 6	5

* Inhibition of bradycardia induced by a sub-maximal dose of 5-HT in the rat [1]

**n = no. of rats

5-HT induced reflex bradycardia, the Bezold-Jarisch reflex, in the rat[1] and the results are presented in the Table. Also included for comparison are the results for **1** - **4**. All the compounds **5** - **9** showed 5-HT_3 receptor antagonist activity but of a lower order of potency than the equivalent granatane (**5** vs **1**) or tropane (**6,7** vs **2**; **8,9** vs **3**) by a factor of between 3 (for **7**) and 14 (for **8**). Although the introduction of the 5-methyl group into the imidazole (compounds **7**, **9**) only resulted in a non-significant trend towards an increase in potency, a greater consistency between tests was noted. An increase in potency associated with a 5-methyl substituent has been seen in related imidazole-containing 5-HT_3 receptor antagonists.[10]

Consistently the most potent compound was the 3,3-dimethylindoline, **7** BRL 49231, whose pharmacological properties were further investigated. An iv duration of action study in the rat showed that the time (mean and standard error of the mean) required to achieve a 50% recovery of the Bezold-Jarisch reflex for **7** given at a dose of 6µg/kg was 66 ± 17 min (91 ± 3% maximum inhibition recorded 5 min after dosing; n = 4). By comparison, the values for 6 µg/kg iv of the more potent **1** and the less potent **4** were 46 ± 5 min (88 ± 2% maximum inhibition; n = 9) and 14 ± 5 min (68 ± 11% maximum inhibition; n = 5) respectively. In

guinea-pig isolated ileum, **7** antagonised the 5-HT_3 receptor mediated effects of 5-HT with a pA_2 of 8.1 ± 0.2, and in radioligand binding studies in rat brain[11] **7** displaced ^{1}H-**1** with a pK_i of 9.3. The compound was highly selective for the 5-HT_3 receptor, showing either no detectable activity or binding at 5-HT_{1A}, 5-HT_{1C}, 5-HT_{1D}, 5-HT_2 or 5-HT_4 receptors. The compound did have weak affinity (pK_i 6.2) at α_2 adrenoceptors in rat brain. The anti-emetic activity was demonstrated in the ferret against total body X-irradiation-induced emesis. **7**, at a dose of 0.5 mg/kg po, both significantly reduced the number of episodes of emesis (1.3 ± 0.8; mean ± standard error of the mean; n = 4) and the latency period to the first episode (90.5 ± 27.8 min) when compared with controls (12.4 ± 2.4 and 21.4 ± 1.4 min respectively). The number of emetic episodes observed with 0.01 mg/kg po was 7.7 ± 0.7 (latency 22.5 ± 2.6) indicative of a dose-dependency of action. This efficacy and potency was comparable with that observed for granisetron in this test model.[12]

In conclusion we have demonstrated that the indazole and the indoline aromatic nuclei can be used as bioisosteric replacements for indole in the imidazolyl-containing class of 5-HT_3 receptor antagonists related to ondansetron.

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