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INDAZOLE AS AN INDOLE BIOISOSTERE: 5-HT$_4$ RECEPTOR ANTAGONISM.

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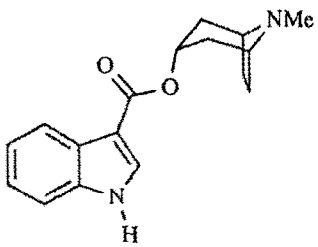
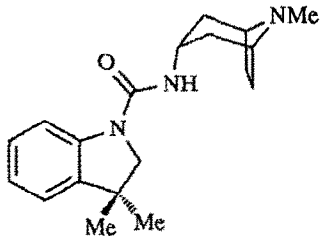
Abstract: A comparison of the potencies of ICS 205-930 (1), the indazoles (2)-(6) and the indoline (7) as 5-HT$_3$ and 5-HT$_4$ receptor antagonists is described. Although indazole is an effective indole bioisostere for both activities, the indoline is effective for 5-HT$_3$ only.

Serotonin - 5-HT$_4$ receptors have been identified in mouse embryo coliculli neurones,[1] guinea pig hippocampus,[2] the gastro-intestinal tract[3,4] and in both piglet[5] and human atrium.[6] In all cases the standard antagonist used to characterise the pharmacological response was the 5-HT$_3$ receptor antagonist ICS 205-930. In an earlier publication we reported the 5-HT$_3$ receptor antagonist activity of the indazole (6)[7] which was the first report of the successful use of indazole as a bioisosteric replacement for indole in the 5-HT area. In subsequent papers we reported the 5-HT$_3$ receptor antagonist activity of the indazoles (2)-(6) (Table) and showed that 5-HT$_3$ receptor antagonist activity was retained with indolines, as exemplified by BRL 46470 (7).[9]



(1) ICS 205-930

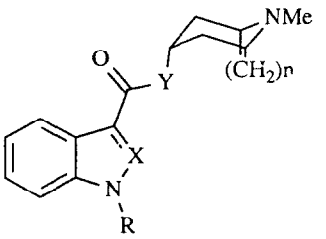


(7) BRL 46470

The present communication describes the results we have obtained from an investigation of indazoles (2)-(6) and (7) in our recently published model for the 5-HT$_4$ receptor in the piglet isolated atrium.[5] The structure and potency of compounds (2)-(6) in this model are shown in the Table.

The indazole (2), which is the closest analogue to (1), was marginally more potent as a 5-HT$_4$ receptor antagonist. This contrasts with its relatively lower potency as a 5-HT$_3$ receptor antagonist.[8] A marginal reduction in potency was observed with the amide (3), with a further reduction with the 1-methyl analogue (4). The indazolyl-granatanes (5) and (6) were more potent than their equivalent tropanes (3) and (4) respectively as 5-HT$_3$ receptor antagonists. However, for 5-HT$_4$ receptor antagonism, both the granatanes were much less potent than the tropanes. Compound (6) is

Table



Compound No.	R	X	Y	n	-log K_B**	ID_{50} μg/kg***
1	ICS 205-930				6.9	1.4
2	H	N	O	2	7.2	5.0
3	H	N	NH	2	6.8	1.5
4	Me	N	NH	2	6.5	1.4
5	H	N	NH	3	5.0	1.0
6*	Me	N	NH	3	Ia at 1μM	0.7

* granisetron; ** Piglet atrium model for 5-HT_4; *** Bezold-Jarisch for 5-HT_3 iv.[10]

granisetron, which has recently been marketed as an anti-emetic for use in cancer therapy. The lower potency of (6) in the piglet isolated atrium model demonstrates that it is a more selective 5-HT_3 receptor antagonist than ICS 205-930. In addition, we have reported that the indoline (7), BRL 46470, is a highly potent 5-HT_3 receptor antagonist (2x ICS 205-930).[11] In contrast (7) was 100x less potent than (1) as a 5-HT_4 receptor antagonist (-log K_B 4.9), thus again demonstrating an even greater selectivity for the 5-HT_3 receptor. Clearly, therefore, the structural characteristics for both the basic side chain and the aromatic nucleus which determine potency for 5-HT_3 receptor antagonism do not correlate with those required for 5-HT_4 receptor antagonism.

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