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5-HT$_4$ RECEPTOR ANTAGONISTS : OXAZOLO, OXAZINO AND OXAZEPINO[3,2-a]INDOLE DERIVATIVES

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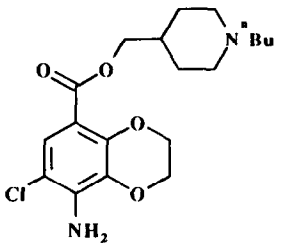
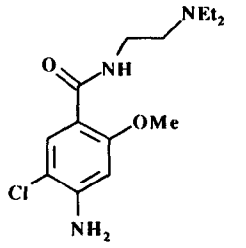
Abstract: The identification of oxazolo, oxazino and oxazepino[3,2-a]indoles as new structural classes of highly potent 5-HT$_4$ receptor antagonists is described. Compounds (4) (5) and (6) are among the most potent 5-HT$_4$ receptor antagonists reported to date.

5-HT$_4$ receptor mediated responses have been reported in several tissues and several species[1] but it is only recently that potent and selective antagonists for this receptor have been identified [2,3]. Among these was the benzodioxan ester SB 204070 (1)[2] which was derived originally from a 4-piperidinylmethyl ester analogue of the 5-HT$_4$ receptor partial agonist metoclopramide (2) by incorporation of the oxygen of the 2-methoxy substituent within a 6-membered ring [4]. SB 204070 was identified using structure activity relationships determined from a functional model of the receptor in the guinea-pig isolated distal colon[5] and was hitherto the most potent and selective 5-HT$_4$ receptor antagonist reported.



1 SB 204070

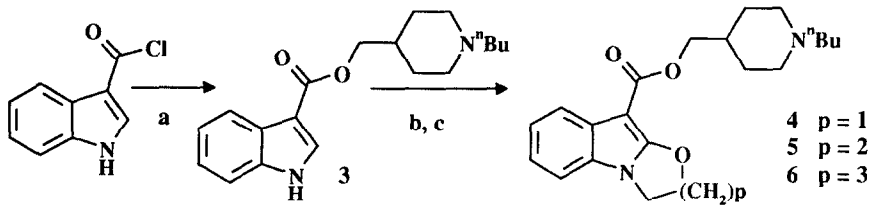


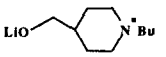
2 metoclopramide

We now report the identification of the novel oxazolo, oxazino and oxazepino[3,2-a]indole derivatives (4 - 6) as highly potent 5-HT$_4$ receptor antagonists. These compounds belong to a new structural class previously unreported as antagonists for this receptor. Compounds (4-6) were prepared from the indole ester (3)[6] by the method shown in the scheme and full experimental details are described elsewhere[7].

The ability of these compounds to block the 5-HT$_4$ receptor mediated effects of 5-HT was assessed in the guinea-pig distal colon longitudinal muscle myenteric plexus preparation (LMMP)[5] and the results expressed as pIC$_{50}$ values (the negative logarithm of the concentration of test compound required to reduce the response evoked by the EC$_{50}$ concentration of 5-HT by 50%) (Table). The compounds were also evaluated for their ability to inhibit the binding of the previously reported[8] 5-HT$_4$ receptor radioligand [^{125}I] SB 207710 to piglet hippocampal membranes and the results expressed as pK$_i$ values (Table).

Scheme.



Reagents: (a) THF,  (b) NCS, $BrCH_2(CH_2)_pOH$, $CHCl_3$ (c) K_2CO_3, Me_2CO

Yields (b,c) 4=35%, 5=39%, 6=31%

Table.

Compound	Guinea-pig distal colon LMMP pIC_{50} [mean±sem] (n)	Affinity at piglet hippocampal $5HT_4$ receptors pK_i (n)
1	10.1 ± 0.7 (5)	9.9 ± 0.1 (3)
3	9.3 ± 0.2 (3)	8.6, 8.8 (2)
4	10.0 ± 0.2 (3)	10.1, 10.4 (2)
5	10.6 ± 0.2 (6)	10.2, 10.1 (2)
6	9.8 ± 0.1 (3)	9.7, 9.7 (2)

In the guinea-pig distal colon, these novel oxazolo, oxazino and oxazepino[3,2-a]indole derivatives (4-6) were highly potent 5-HT_4 receptor antagonists and this was also demonstrated by their ability to inhibit the binding of the 5-HT_4 receptor radioligand [^{125}I] SB 207710 to piglet hippocampal membranes. They show comparable potency to SB 204070 and as such they are useful new tools for characterising this receptor.

References and Notes

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