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AZAHETEROAROMATIC ETHERS AS CARBONYL BIOISOSTERES. SYNTHESIS AND EVALUATION OF A NOVEL CLASS OF 5-HT$_3$ RECEPTOR ANTAGONISTS

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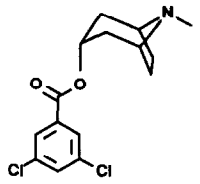
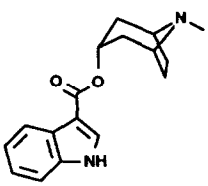
Abstract: *Quinolin-2-yl and benzothiazol-2-yl derivatives of 3-tropane and 3-quinuclidine are novel 5-HT$_3$ receptor antagonists. The heteroaromatic groups behave as bioisosteres of the carbonyl groups found in standard 5-HT$_3$ receptor antagonists.*

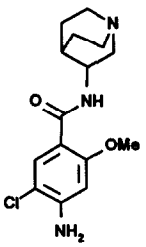
The 5-HT$_3$ receptor has been identified in the peripheral[1,2] and central[3,4] nervous systems. Antagonists of the 5-HT$_3$ receptor located in the area postrema[5] have shown clinical effectiveness in the relief of emesis induced by chemotherapy.[6-8] 5-HT$_3$ receptor antagonists have also been shown to modulate dopaminergic pathways in the mesolimbic system and may therefore be useful as antipsychotic or anxiolytic agents.[9,10] The identification in recent years of a number of potent and selective 5-HT$_3$ receptor antagonists has, through the application of computer-aided molecular modelling techniques, allowed certain features of the 5-HT$_3$ receptor to be unravelled and permitted the design of novel 5-HT$_3$ receptor antagonists. For instance, Hibert's six-point model led to the design of a specific keto-amino-indole derivative.[11] The use by Rosen and Rizzi of hydrogen-bond donor and hydrogen-bond acceptor probes produced a definition of the common areas of interaction between the 5-HT$_3$ receptor and different 5-HT$_3$ receptor antagonists.[12,13] Peroutka's simplistic steric model[14] ignores conformational energies.[15] We now report the development of a novel class of 5-HT$_3$ receptor antagonists in which the aryloxo substituent found in many 5-HT$_3$ receptor antagonists such as the aromatic carboxylates MDL-72222 **1** and ICS 205-930 **2**, the benzamide zacopride **3**, and the aryl ketone ondansetron **4** is replaced by bioisosteric azaheteroaromatic groups as in compounds **5-7**.



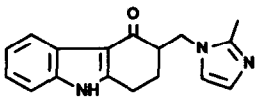
1, MDL-72222



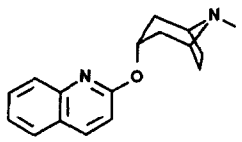
2, ICS 205-930



3, zacopride



4, ondansetron



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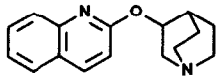

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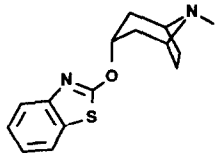

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The azaheteroaromatic ethers **5-7** were prepared by the reactions of chloro substituted heteroaromatic compounds with the sodium salts of tropine or quinuclidine (Scheme).[16]

$$R^1Cl + R^2ONa \longrightarrow R^1OR^2 + NaCl$$

where R^1 = azaheteroaromatic group;
and R^2 = *endo*-8-methyl-3-tropanyl or 3-quinuclidinyl group

Scheme

The Table gives the 5-HT_3 receptor binding affinities and potencies to antagonise 5-HT-induced bradycardia in the anaesthetised rat (the von Bezold-Jarisch reflex) for compounds **1-7**. Compound **7** had a particularly high affinity for the 5-HT_3 binding site *in vitro* and was a potent antagonist *in vivo*.

Table 5-HT_3 Activity

compd	*in vitro* receptor affinity [a]: [^{3}H]-zacopride displacement IC_{50}, nM (± S.E.M.) [b]	*in vivo* antagonist activity [c]: Inhibition of von Bezold-Jarisch reflex [d] mg/kg *i.v.* [e]
1	42.6 (± 5.1) [d]	0.1
2	2.3 (± 0.7)	0.01
3	2.2 (± 0.3)	0.01
4	7.1 (± 1.8) [d]	0.01
5	39.6 (± 2.2)	1 0
6	48.0 (± 19.4)	3.0
7	6.9 (± 3.6)	0.1

[a] The determination of 5-HT_3 receptor binding affinity was based upon the method of Barnes *et al* (ref. 17).
[b] Average of a minimum of three determinations.
[c] The measurement of the inhibition of the von Bezold-Jarisch reflex (a bradycardia produced by a bolus injection of 5-HT *in vivo*) in anaesthetised rats was based upon the method of Fozard *et al* (ref. 18).
[d] Average of a minimum of four determinations.
[e] Dose of antagonist giving >85% inhibition of the Bezold-Jarisch reflex.

Molecular modelling studies revealed that the global low energy conformations of **1-7** could be overlapped using a three-point fitting process. The low energy conformations were generated from a three dimensional rigid conformational search using SYBYL5.3 (by a process in which the torsion angles around the flexible bonds were changed at intervals of 10°, and the conformational energy was computed using electrostatic, H-bonding, and non-bonded interactions. The charges for computing the electrostatic energy were those derived from MOPAC[19]). From the conformations generated by the c-search module of SYBYL5.3, one hundred low energy conformations were selected for minimization using MOPAC from which the global minimum energy conformation was obtained for each molecule. The Figure shows the superposition of compounds **5-7** onto MDL-72222 **1** using the MAXIMIN MULTIFIT procedure within SYBYL5.3. This process entailed the fitting of the amine nitrogen atoms, the aromatic ring nitrogen atoms, and the ethereal oxygen atoms of compounds **5-7** onto the tropanyl nitrogen atom, the carbonyl oxygen atom, and the alkoxy oxygen atom of MDL-72222. The fitted structures were then further minimised using MOPAC. The difference in the energy of the conformations before and after fitting was less than 0.3 kcal mol^{-1} and the RMS difference between MDL-72222 and the fitted structures was less than 0.4. It appears therefore that all the fitted compounds can adopt a conformation very close to that of MDL-72222 without too much energy strain. The full analysis suggests that the aromatic nitrogen atoms of **5-7** can take part in a key hydrogen bond interaction with the 5-HT_3 receptor in a way similar to that reported for the carbonyl oxygen atoms of compounds **1-4**.[11-13]

Compounds **5-7** are bicyclic aromatic systems in which a benzene ring is fused onto a pyridine or thiazole ring. Monocyclic heteroaromatic systems in which the benzo fusion was absent were an order of magnitude less potent than compounds **5-7**. The poor activity of these compounds (*ie.* 2-pyridinyl, 2-pyrimidinyl, and 2-pyrazinyl derivatives) may have been a consequence of the loss of potentially favourable hydrophobic or π-stacking interactions between the benzene rings of compounds **5-7** and the 5-HT_3 receptor.

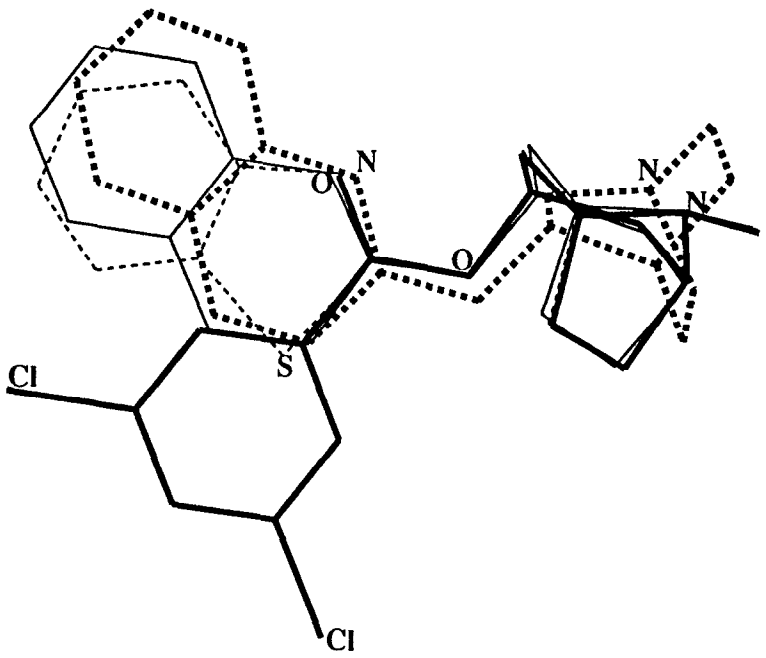

Figure. Superposition of MDL-72222 **1** and compounds **5-7**.
Only the carbon skeletons are displayed.
Line-styles : **1** ——— ; **5** ——— ; **6** ▪▪▪▪▪▪▪▪ ; **7** ---------

References and Notes

1. Gaddum, J. H.; Picarelli, Z. P. *Br. J. Pharmacol. Chemother.* **1957**, *12*, 323.
2. Richardson, B. P.; Engel, G.; Donatsch, P.; Stadler, P. A.; *Nature* **1985**, *316*, 126.
3. Kilpatrick, G. J.; Jones, B. J.; Tyers, M. B. *Nature* **1987**, *330*, 746.
4. Dumuis, A.; Bouhelal, R.; Sebben, M.; Bockaert, J. *Eur. J. Pharmacol.* **1988**, *146*, 187.
5. Higgins, G. A.; Kilpatrick, G. J.; Bunce, K. T.; Jones. B. J.; Tyers, M. B. *Br. J. Pharmacol.* **1989**, *97*, 247.
6. Cunningham, D.; Pople, A. Ford, H. T.; Hawthorne, J.; Gazet, J. C.; Challoner, T. *Lancet* **1987**, *I*, 1461.
7. Costall, B.; Domeney, A. M.; Gunning, S. J.; Naylor, R. J.; Tatersall, F. D.; Tyers, M. B. *Br. J. Pharmacol.* **1987**, *90*, 90P.
8. Smith, W. L.; Jackson, C. B.; Proakis, A. G.; Leonard, C. A.; Munson, H. R.; Alphine, R. S. *Proc. Am. Soc. Clin. Oncol.* **1986**, *5*, 1017.
9. Jones, B. J.; Costall, B.; Domeney, A. M.; Kelly, M. E.; Naylor, R. J.; Oakley, N. R.; Tyers, B. M. *Br. J. Pharmacol.* **1988**, *93*, 985.
10. Tricklebank, M. B. *Trends Pharmacol. Sci.* **1989**, *10*, 127.
11. Hibert, M. F.; Hoffmann, R.; Miller, R. C.; Carr, A. A. *J. Med. Chem.* **1990**, *33*, 1594.
12. Rizzi, J. P.; Nagel, A. A.; Rosen, T.; McLean, S.; Seeger, T. *J. Med. Chem.* **1990**, *33*, 2721.
13. Rosen, T.; Nagel, A. A.; and Rizzi, J. P. *Synlett.* **1991**, 213.
14. Schmidt, A. W.; Peroutka, S. J. *Mol. Pharmacol.* **1989**, *36*, 505.
15. King, F. D.; Dabbs, S.; Bermudez, J.; Sanger, G. J. *J. Med. Chem.* **1990**, *33*, 2942.
16. Preparation of ***endo*-3-(benzothiazol-2-yloxy)-8-methyl-8-azabicyclo[3. 2.1]octane (7) : General Method.** A stirred solution of tropine (6.1 g, 43.3 mmol) in dry dimethylsulphoxide (100 ml) was treated with sodium hydride, 50% dispersion in oil (2.3 g, *ca.* 48 mmol) under nitrogen. After 40 min, 2-chlorobenzothiazole (6.2 ml, 47.7 mmol) was added and, after 18 h, the mixture was poured into water (400 ml). The precipitate was filtered and recrystallised from ethyl acetate to give **7** (10.2 g, 86%) as yellow crystals. The solid was converted into the hydrochloride salt with ethereal hydrogen chloride and methanol. Recrystallisation from ethyl acetate-methanol gave the hydrochloride salt as colourless crystals (7.0 g, 52%). All compounds had satisfactory spectral and analytical data.
17. Barnes, N. M.; Costall, B.; Naylor, R. J. *J. Pharm. Pharmacol.* **1988**, *40*, 548.
18. Fozard, J. R.; Host, M. *Br. J. Pharmacol.* **1982**, *77*, 520P.
19. Stewart, J. J. P. *J. Computer Aided Molecular Design* **1990**, *4*, 1.