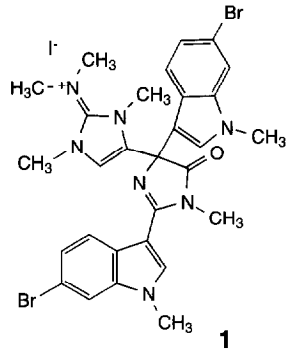
Monitor: molecules and profiles

Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and biological relevance of new molecules reported in the literature and on the conference scene; *Profiles* offers commentary on promising lines of research, emerging molecular targets, novel technology, advances in synthetic and separation techniques and legislative issues.

Cytotoxic nortopsentin D analogue

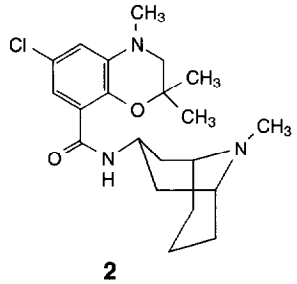
The nortopsentin family of imidazolediyl-bis(indole) alkaloids have previously been found to have inhibitory activity against both the human pathogenic yeast *Candida albicans* and P388 tumour cells [Sakemi, S. and Sun, H.H. *J. Org. Chem.* (1991) 56, 4304–4307]. Mancini, I. and coworkers [*Helv. Chim. Acta* (1996) 79, 2075–2082] have described the isolation of a further member of this family, nortopsentin D, from the deep-water axinellid sponge *Dragmacidon* sp. Although this compound was found to be inactive against KB tumour cells *in vitro*, a simple methylation of this compound gave **1**, which was found to be highly cytotoxic against KB cell lines (EC_{50} = 14 ng/ml). The role of permethylation of this compound on its cytotoxic effect is as yet not understood although the authors suggest that the amphiphylic nature of the **1** may be an important factor.



1

5-HT_3 receptor antagonists

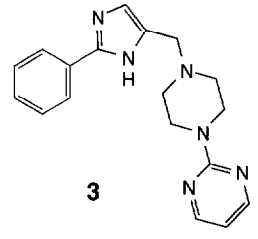
5-HT_3 receptor antagonists such as ondansetron, granisetron and azasetron are now commonly used for the treatment of chemotherapy- and radiation-induced emesis. The therapeutic uses of these compounds for the treatment of a range of other conditions including drug abuse, pain, migraine and dementia is also presently being investigated. Workers from Yoshitomi Pharmaceutical Industries Ltd (Fukuoka, Japan) have reported the synthesis, conformational analysis and structure–activity relationships of 3,4-dihydro-2*H*-1,4-benzoxazine-8-carboxamides as potential 5-HT_3 receptor antagonists [Kuroita, T. *et al. Chem. Pharm. Bull.* (1996) 44, 2061–2069]. 6-Chloro-3,4-dihydro-*N*-(9-methyl-9-azabicyclo-[3.3.1]non-3-yl)-2,2,4-trimethyl-2*H*-1,4-benzoxazine-8-carboxamide **2** was found to have the highest affinity for the 5-HT_3 receptor (K_i = 0.019 nM) and demonstrated long-lasting inhibition of 5-HT-induced bradycardia (Bezold–Jarisch reflex) in the rat.



2

Selective D_4 receptor antagonist

The D_4 receptor is believed to have an important role in the etiology of schizophrenia. A group from the Neurogen Corporation have recently reported the synthesis and evaluation of a series of 2-phenyl-4-(1-[piperazin-1-yl])methylimidazoles as potential D_4 antagonists [Thurkauf, A. *et al. J. Med. Chem.* (1997) 40, 1–3]. Compound **3** was found to be particularly interesting with highly selective and potent affinity for the D_4 receptor (K_i = 3.8 nM) over the D_2 and D_3 receptors. This compound was shown to have no significant binding to any other CNS and non-CNS receptor systems except for 5-HT_{1a} (K_i = 181 nM) and shown to have D_4 antagonistic properties in a biochemical assay. Behavioural testing for antipsychotic efficacy was conducted in a rat model and gave results consistent with those obtained for other antipsychotic drugs in this model. Other studies suggest that this compound will show minimal extrapyramidal side effects in man. On the basis of this promising pharmacological profile **3** has been selected as a clinical candidate for the treatment of schizophrenia.



3

Monitor Editor: **Andrew W. Lloyd**, Department of Pharmacy, University of Brighton, Cockcroft Building, Moulsecoomb, Brighton, UK BN2 4GJ. tel: +44 1273 642049, fax: +44 1273 679333, e-mail: a.w.lloyd@brighton.ac.uk

  1359-6446/97/$17.00. PII:S1359-6446(97)01031-3