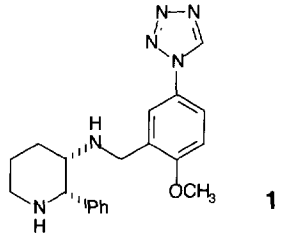
Monitor: molecules, synthesis and profiles

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 three sections: *Molecules* summarizes the chemistry and the pharmacological significance and biological relevance of new molecules reported in the literature and on the conference scene; *Synthesis* outlines the latest advances in synthetic and separation techniques, approaches to the total synthesis of natural products of pharmaceutical relevance and the screening of new chemical entities; *Profiles* offers commentary on promising lines of research, emerging molecular targets, novel technology and legislative issues.

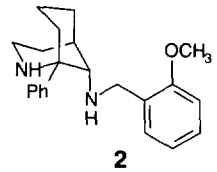
NK_1 receptor antagonists

Neurokinin NK_1 receptor antagonists may have therapeutic potential as antiemetic agents. Ward, P. and coworkers [*J. Med. Chem.* (1995) 38, 4985–4992] describe the discovery of an orally bioavailable NK_1 receptor antagonist **1** that has been shown to reduce radiation induced emesis in a ferret model.



1

This compound was found to have high potency and long duration of action when administered both orally and subcutaneously in this model and to have oral bioavailability in the dog. Another potent NK_1 receptor antagonist **2** has been reported by Cocker, J.D. and Davies, H.G. [*Bioorg. Med. Chem. Lett.* (1996) 6, 13–16]. This molecule is a bridged derivative of the substance P antagonist CP 99,994 **3**.



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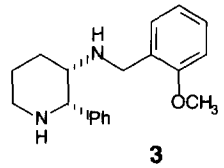
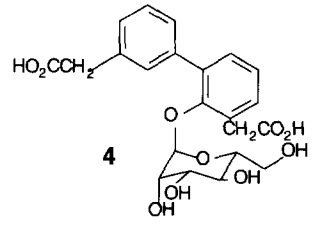


3

These compounds may have application in reducing chemotherapy-associated emesis in cancer patients and may also be useful in the treatment of migraine, pain and inflammation.

Selectin inhibitors

Selectins are carbohydrate-binding proteins that are expressed on the surface of cells in response to certain inflammatory mediators and facilitate the recruitment of leukocytes to injured areas within the body. Agents which block the initial binding of the inflammatory cells to the selectins may be of use in the treatment of several immune system-mediated disease states, such as diabetes, psoriasis, asthma and inflammatory bowel diseases. Kogan, T.P. and coworkers [*J. Med. Chem.* (1995) 38, 4976–4984] have rationally designed and synthesized a range of small, nonoligosaccharide selectin inhibitors based on (α-D-mannopyranosyloxy)biphenyl-substituted carboxylic acids.

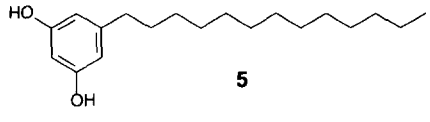


4

Compound **4** was found to be more potent than the sialyl Lewis^x oligosaccharide in an *in vitro* E-selectin/HL60 cell binding assay. An alternative approach has been adopted by Lin, C-H. and coworkers [*Bioorg. Med. Chem.* (1995) 3, 1625–1630] who have enzymatically prepared a sialyl Lewis^x dimer from an *N*-linked oligosaccharide prepared from egg yolk. The dimer was found to be as active as the monomer in an E-selectin-mediated cell adhesion assay. The authors suggest that improved inhibition may be possible by modifying the orientation and distance between the two monomeric sialyl Lewis^x units.

5-Alkylresorcinols

Five 5-alkylresorcinols, including **5**, which are able to catalyse the relaxation of supercoiled, covalently closed, circular φX174 DNA in the presence of Cu(II) and oxygen have been isolated from the roots, twigs and bark of *Hakea trifurcata* [Lytollis, W.L. *et al. J. Am. Chem. Soc.* (1995) 117, 12683–12690]



5

3-Hydroxy-3-methylglutaryl-CoA reductase inhibitors

3-Hydroxy-3-methylglutaryl-CoA reductase is a key enzyme in the biosynthesis of

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