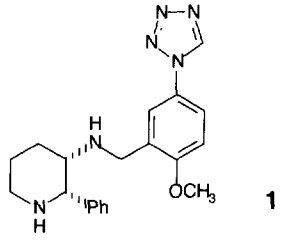
Monitor: molecules, synthesis and profiles

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.

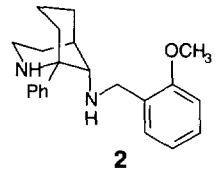
NK_1 receptor antagonists

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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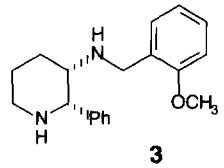

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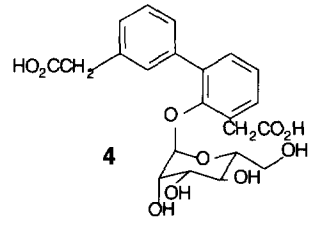
These compounds may have application in reducing chemotherapy-associated emesis in cancer patients and may also be useful in the treatment of migraine, pain and inflammation.

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.



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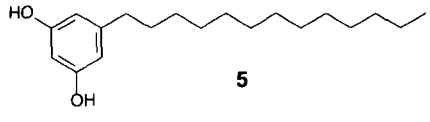
Compound **4** was found to be more potent than the sialyl Lewis^x oligosaccharide in an *in vitro* E-selectin/HL60 cell binding assay. An alternative approach has been adopted by Lin, C-H. and coworkers [*Bioorg. Med. Chem.* (1995) 3, 1625–1630] who have enzymatically prepared a sialyl Lewis^x dimer 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]



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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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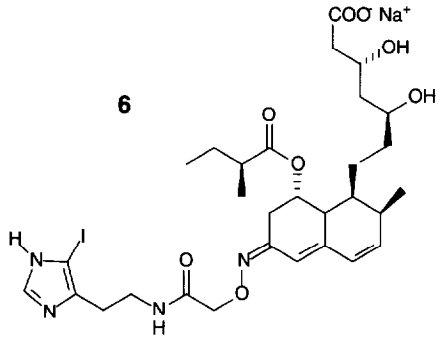
cholesterol and inhibitors of this enzyme therefore have potenial as antihypercholesteremic agents. Turabi, N. and coworkers [*Bioorg. Med. Chem.* (1995) 3, 1479–1484] report the synthesis and biological evaluation of a series of oxime ether analogs of pravastatin, a known potent antihypercholesteremic agent. Compound **6** was found to be several times more potent than pravastatin.



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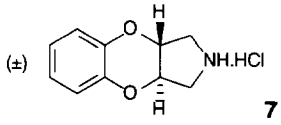
α_2-Adrenoceptor antagonists

Presynaptic α_2-adrenoceptors modulate the release of noradrenaline from nerve endings through a local feedback mechanism. α_2-Adrenoceptor antagonists should therefore increase synaptic concentrations of noradrenaline and the resultant postsynaptic stimulation of α- and β-adrenoceptors. Such agents may have clinical utility in the treatment of diabetes, depression and male sexual dysfunction. Kitchin, J. and coworkers [*Bioorg. Med. Chem.* (1995) 3, 1595–1603] report the synthesis and evaluation of a series of tetrahydrobenzodioxinopyrroles, such as **7**, as potent, selective α_2-adrenoceptor antagonists.



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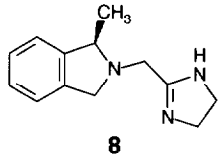

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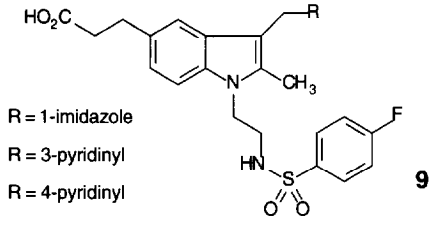
In the same journal, Beeley, L.J. and coworkers [*Bioorg. Med. Chem.* (1995) 3, 1693-1698] describe the chiral synthesis of *R*-(–)-2,3-dihydroisoindolylmethylimidazole (BRL 48962, **8**), a potent, selective α_{2A}-adrenoceptor antagonist, and the characterization of this compound using cloned human α-adrenoceptors.

These studies demonstrated that the compound was 30 times more selective for the α_{2A}-adrenoceptor subtype.

Thromboxane-modulating agents

The use of thromboxane A_2 (TxA_2) synthase inhibitors to prevent the vasoconstrictive and platelet aggregatory actions of TxA_2 have been of limited success because the biosynthetic precursor, prostaglandin H_2 (PGH_2), is also a potent TxA_2 receptor agonist. TxA_2 receptor antagonists offer an alternative because they block the action of both TxA_2 and PGH_2. However, such agents do not have the potential advantage of the TxA_2 synthase inhibitors, in that the accumulated PGH_2 may be utilized by PGI_2 synthase to produce the vasodilator and anti-aggregatory PGI_2. Dickenson, R.P., Dack, K.N. and Steele, J. [*Bioorg. Med. Chem. Lett.* (1995) 5, 3017–3022] have therefore designed a series of dual thromboxane synthase inhibitor/thromboxane receptor antagonists by combining the key structural features for each activity in a single molecule.

This approach has yielded a number



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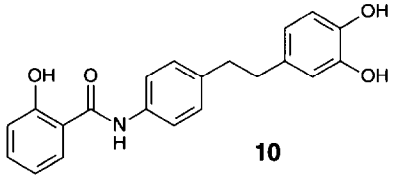
of indole-5-propanoic acid derivatives **9**, which are potent dual agents *in vitro*.

15-Lipoxygenase inhibitor

A mass screening of the Parke-Davis compound portfolio has identified **10** as a potent 15-lipoxygenase inhibitor [Tait, B.D. *et al. Bioorg. Med. Chem. Lett.* (1996) 6, 93–96].



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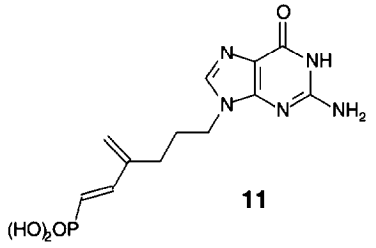
This compound will facilitate an investigation into the role of 15-lipoxygenase in atherosclerosis.

HIV-1 inhibitor

Navé J.F. and coworkers [*Bioorg. Med. Chem. Lett.* (1996) 6, 179–184] report the synthesis, phosphorylation by guanylate kinase, anti-HIV-1 and anti-herpes virus activity of two acyclic dienyl phosphonate derivatives of guanine.



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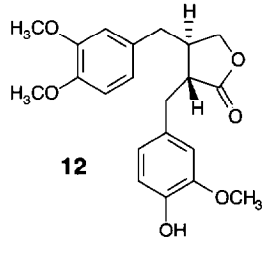
Compound **11** was found to be phosphorylated by guanylate kinase and to be a significant inhibitor of HIV-1 replication. This work illustrates the potential for utilizing the dienyl phosphonate as a substitute for the phosphate group employed in other acyclonucleotide analogues.

HIV-1 integrase inhibitor

Recent attention has been directed toward HIV-1 integrase as an alternative therapeutic target for anti-HIV therapy. This protein mediates the integration of the viral DNA into the host genome and is therefore essential for survival of the virus. Eich, E. and coworkers [*J. Med. Chem.* (1996) 39, 86–95] describe the selection of the lignanolide (–)-arcrigenin **12** as a lead structure for the development of inhibitors of HIV-1 integrase.



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Structure-activity studies utilizing natural, semisynthetic and synthetic lignands demonstrated that the biological activity is dependent on (i) the presence of the lactone moiety and the number and (ii) the arrangement of the phenolic hydroxyl groups on the molecule.