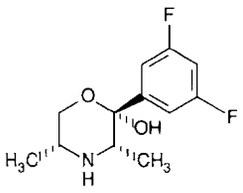
Monitor: molecules, synthesis and profiles

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.

Novel antidepressant agent

Kelley, J.L. and coworkers [*J. Med. Chem.* (1996) 39, 347–349] report a novel antidepressant agent, (2*S*,3*S*,5*R*)-2-(3,5-dimethyl)-2-morpholinol **1** that selectively inhibits norepinephrine uptake with much weaker effects on dopamine and serotonin uptake.



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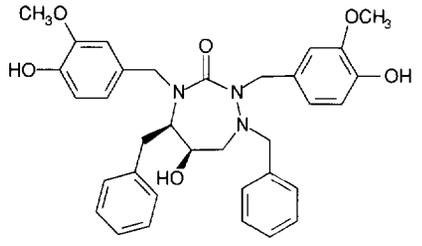
According to the authors, the pharmacological profile suggests that this compound will be active in humans and will not cause the cholinergic and cardiac depression effects that are associated with the use of tricyclic antidepressant agents.

HIV-1 protease inhibitor



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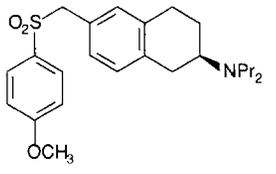
Sham, H.L. and coworkers [*J. Med. Chem.* (1996) 39, 392–397] describe a novel series of HIV-1 protease inhibitors based on azacyclic ureas. The most potent of these agents was **2**, which was found to possess high potency in both the HIV-1 protease inhibition assay and the *in vitro* MT-4 cell culture assay (K_i ~5 pM; EC_{50} = 2 nM).

Dopamine D_3 receptor antagonists

It has been suggested that agents which selectively bind to dopamine D_3 receptors may offer potential as effective antipsychotic agents without the extrapyramidal side-effects associated with typical D_2 antagonists. Murray, P.J. and coworkers [*Bioorg. Med. Chem. Lett.* (1996) 6, 403–408] describe the synthesis of novel 6-substituted 2-aminotetralins, based on (1*S*,2*R*)-5-methoxy-1-methyl-2-*N*,*N*-dipropylaminotetralin [(+)-UH-232] as a lead structure, which have high affinity for the dopamine D_3 receptor.



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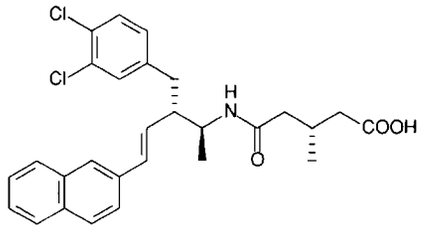
GR 218231, **3**, was found to be 400-fold more selective for the D_3 receptor than for the D_2 receptor and 10,000-fold more selective for the D_3 receptor than for the D_1 and D_4 receptors.

Orally active squalene synthase inhibitor

Squalene synthase inhibitors are ideal hypocholesterolemic agents because they do not inhibit the synthesis of ubiquinone, dolichol and isopentyl tRNA. A recent publication [Iwasawa, Y. *et al. Bioorg. Med. Chem. Lett.* (1996) 6, 463–466] describes the synthesis and cholesterol-lowering effect in dogs of a novel orally active inhibitor of squalene synthase (J 104123, **4**), which has been synthesized stereoselectively from methyl (*R*)-3-hydroxybutyrate.



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Antioxidant hypocholesterolemic agents

It has recently been suggested that LDL oxidation may be an important step in the development of atherogenesis. Gotteland, J-P. and coworkers [*Bioorg. Med. Chem. Lett.* (1996) 6, 533–538] describe the design and synthesis of a range of new (arylamino)methylsilane-

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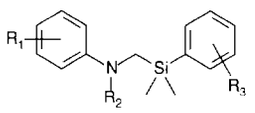
based hypocholesterolemic agents **5**, which have antioxidant properties. They also describe the synthesis and biological evaluation of **6**, which has antioxidant properties and inhibits the biosynthesis of cholesterol through inhibition of the enzyme squalene epoxidase.



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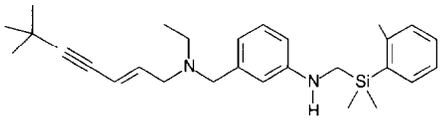
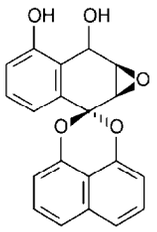


6

Novel fungal phospholipase D inhibitors

Chu, M. and coworkers [*Bioorg. Med. Chem. Lett.* (1996) 6, 579–584] describe the isolation of novel phospholipase D inhibitors **7** and **8** from the fermentation broth of an unidentified fungus collected from the dead leaves of *Ruercus virginana*. Both compounds exhibited *in vitro* inhibitory activity in a phospholipase assay with IC_{50} values of 24 and 19 μM respectively.



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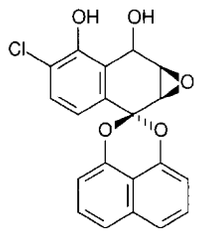

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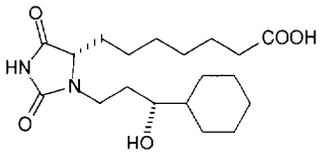
Selective PGD_2 receptor agonists

Prostaglandin D_2 (PGD_2) is a potent inhibitor of human platelet aggregation, and agonists at the PGD_2 receptor may be useful in preventing arterial thrombosis. Although the PGD_2 agonist **9** has been studied in human volunteers, the clinical use of this agent is limited by its short half-life and vasodepressor side-effects. Barraclough, P. and coworkers [*Bioorg. Med. Chem.* (1996) 4, 81–90] describe the use of **9** as a lead compound in the development of selective ligands as platelet-selective agonists.

These studies identified three bicyclic imidazolidinone analogues **10**, **11**, **12** which were potent inhibitors of human platelet aggregation and selective PGD_2 agonists in washed platelet and jugular vein isolated tissue assays.



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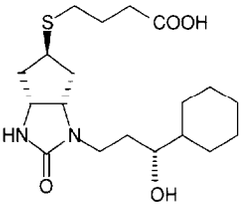

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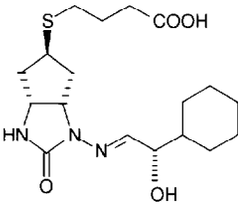

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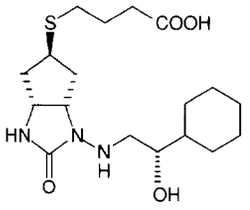
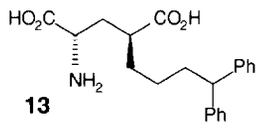


12

Metabotropic glutamate receptor antagonist

The study of the G protein-linked metabotropic glutamate receptors (mGluRs) has been hindered by a lack of potent and selective antagonists. These receptors are coupled to a range of secondary messengers through adenylate cyclase inhibition, phosphoinositide-specific phospholipase C activation and modulation of ion channels. Wermuth, C.G. and coworkers [*J. Med. Chem.* (1996) 39, 814–816] have identified (2*S*,4*S*)-2-amino-4-(4,4-diphenyl-but-1-yl)-pentane-1,5-dioic acid **13** as a potent, selective antagonist of the group-2 mGluRs, which are negatively coupled to adenylate cyclase without exerting any effect on the other subclasses of receptors.



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VanX inhibitors

Clinical vancomycin resistance represents a significant problem in the treatment of Gram-positive bacterial infection. It has been previously shown that VanX, a zinc-dependent dipeptidase, is essential for vancomycin resistance in *Enterococcus faecium* [Wu, Z., Wright, G. and Walsch, C. *Biochemistry* (1995) 3, 2455–2463]. An effective design of zinc peptidase inhibitors is to use a mercaptan moiety as a zinc-binding ligand. Wu, Z. and Walsch, C. [*J. Am. Chem. Soc.* (1996) 118, 1785–1786] describe an investigation into the use of dithiol compounds as potent, time-dependent inhibitors of VanX. Of the compounds evaluated, 2,3-dimercapto-1-propanesulphonic acid and 2,3-dimercapto-1-propanol were found to be the most potent. The authors suggest that the incorporation of the dithiol moiety into the natural VanX D-Ala-D-Ala substrate scaffold may yield a more potent and specific inhibitor of VanX, which could be used to overcome the vancomycin resistance of Gram-positive bacteria.