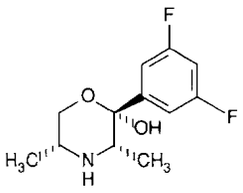
Monitor: molecules, synthesis and profiles

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

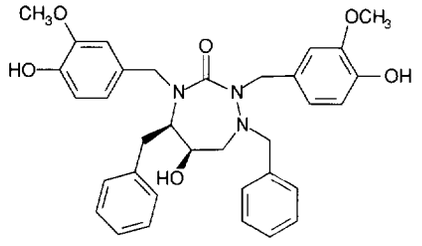
Kelley, J.L. and coworkers [*J. Med. Chem.* (1996) 39, 347–349] report a novel antidepressant agent, (2*S*,3*S*,5*R*)-2-(3,5-dimethyl)-2-morpholinol **1** that selectively inhibits norepinephrine uptake with much weaker effects on dopamine and serotonin uptake.



1

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

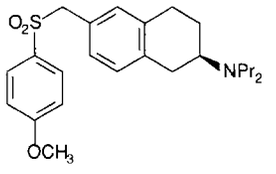


2

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.

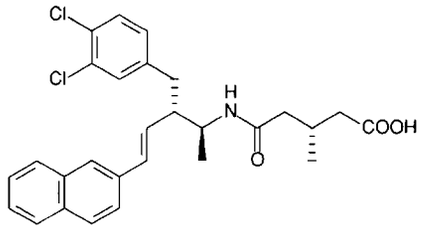


3

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.



4

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-

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

  1359-6446/96/$15.00. PII: S1359-6446(96)30048-2