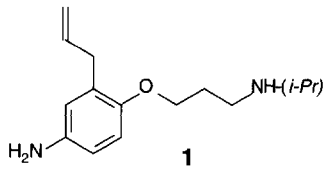
Monitor: molecules, synthesis and profiles

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.

Squalene synthase inhibitors

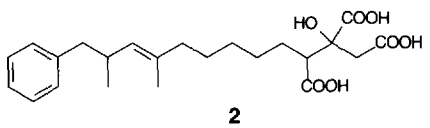
In the search for more effective hypocholesterolemic agents, compounds have been studied *in vitro* that block cholesterol biosynthesis by inhibition of squalene synthase. However, these compounds have been found to be toxic or to have poor oral bioavailability in animals. Brown, G.R. and coworkers [*J. Med. Chem.* (1995) 38, 4157–4160] describe a new series of squalene synthase inhibitors based on phenoxypropylamines such as **1**.



1

These compounds were shown to be highly potent *in vitro* inhibitors of squalene synthase and inhibited cholesterol biosynthesis on oral administration in rats.

Harris, G.H. and coworkers [*Bioorg. Med. Chem. Lett.* (1995) 5, 2403–2408] have reported the isolation, structure determination and squalene synthase activity of two alkyl citrates **2** and **3** obtained on large scale fermentation of MF5453 fungi.



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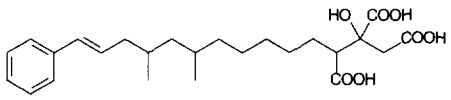

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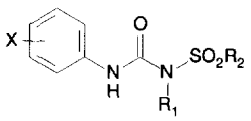
These compounds were found to be submicromolar inhibitors. of squalene synthase *in vitro*.

Acyl-CoA:cholesterol acyltransferase inhibitors

The inhibition of acyl-CoA:cholesterol acyltransferase (ACAT) represents an alternative approach to the treatment of hypercholesterolemia because ACAT appears to be important in the intestinal absorption of dietary cholesterol, secretion of very-low density lipoproteins by the liver and the synthesis and storage of cholesterol esters in the arterial wall. A recent study of the hypocholesterolemic activity of a range of sulphonylurea inhibitors **4** demonstrated that, although these compounds have limited *in vitro* ACAT inhibitory activity, some cause a marked reduction in serum cholesterol levels *in vivo* [Roth, B.D. *et al., Bioorg. Med. Chem. Lett.* (1995) 5, 2367–2370].



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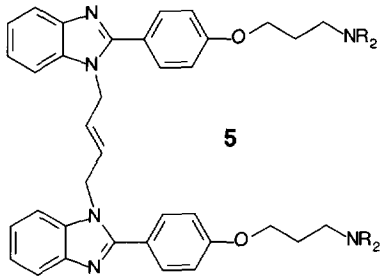
Dopamine D_3 -antagonists and partial agonists



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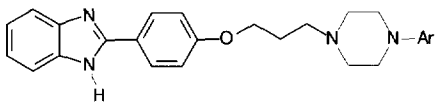

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Dopamine D_3 -antagonists may have applications as antipsychotic agents without neurological side-effects. Wright, J. and coworkers have described a novel series of dimeric 2-[4-(3-aminopropoxy)-phenyl]benzimidazole D_3 antagonists **5** [*Bioorg. Med. Chem. Lett.* (1995) 5, 2541–2546] and a series of 2-[4-[3-(4-aryl-1 piperazinyl)propoxy]phenyl]-benzimidazole D_3 partial agonists **6** [*Bioorg. Med. Chem. Lett.* (1995) 5, 2547–2550].

Although the antagonists have yet to be shown to be beneficial for the treatment of schizophrenia, these compounds will help further the future understanding of the role of D_3 -receptors.

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