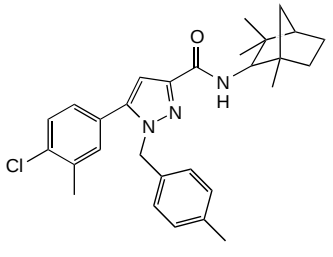
suppression following organ transplantation, and in AIDS patients. Several innovative cancer therapies target the immune system; a notable current drug candidate being the cytokine interleukin-2 (IL-2), which is also a potential therapeutic target for treating AIDS and other retroviral diseases.

It has recently been suggested that endogenously produced cannabinoids, such as anandamide (arachidonylethanolamide) and 2-arachidonylglycerol, might participate in immune modulation via specific type 2 cannabinoid receptors (CB_2) located on B and T cells [Kaminski, N.E., *Biochem. Pharmacol.* (1996) 52, 1133–1140]. Activation of such CB_2 receptors on lymphocytes has been associated with decreased cyclic AMP production, and an associated reduced expression of IL-2, by lymphocytes.

The cannabinoid receptors, therefore, represent logical therapeutic targets for modulating immune response in cancer and AIDS patients. However, type 1 cannabinoid receptors (CB_1) are ubiquitously expressed in brain neurons and glia, heart muscle cells and organ associated endothelium. In addition, endogenous cannabinoids seem to be implicated in many physiological functions including cognition and blood pressure. Thus, blocking the action of endogenous cannabinoids without causing major side-effects is not a simple task.

However, Sanofi Recherché (Montpellier, France), which has pioneered cannabinoid drug research, has recently reported the discovery of SR144528 (**1**), the first selective CB_2 cannabinoid antagonist [Rinaldi-Carmona M. *et al. J. Pharmacol. Exp. Ther.* (1998) 284, 644–650]. This recent study showed SR144528 to be a highly potent [K_d for the cloned human CB_2 = 0.6 nM] and selective CB_2 antagonists, being 700-fold less potent for the cloned human CB_1 receptor. Moreover, it did not seem to interact with other identified receptors or ion channels. In addition, SR144528 was shown to be orally active in mice [ED_{50} = 0.35 mg kg^{-1}], blocking the binding of the tritium-labelled synthetic cannabinoid [^{3}H]-CP55940 in mouse spleen, but not in brain membranes. No doubt, this new drug will be a very valuable tool for clarifying the role of the endogenous cannabinoids in controlling the immune system, and may soon emerge as a prototype drug for modulating immune function.



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Development of new cholesterol-lowering drugs

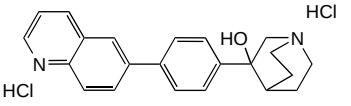
Cholesterol biosynthesis control

The inhibition of cholesterol biosynthesis constitutes an important approach to the reduction of LDL cholesterol, a key risk factor in coronary heart disease. The 'statins', a family of HMG-CoA reductase inhibitors, that are currently clinically used as cholesterol-lowering drugs, could in principle suppress all post-mevalonate biosynthetic pathways. Thus, the supplies of biologically important nonsteroidal isoprenoids (e.g. dolichol, ubiquinone, isopentenyl tRNA and prenylated proteins), which play important roles in regulation of normal cellular processes, would be compromised. Paradoxically, however, levels of HMG-CoA reductase tend to increase because of up-regulation of gene transcription and translation; clinically, this is counterbalanced by up-regulation of LDL-receptor levels leading to a net lowering of serum cholesterol. Nonetheless, selective inhibition of cholesterol biosynthesis is a desirable pharmaceutical goal, and enzyme inhibitors for three enzymes – squalene synthase (SS), squalene epoxidase (SE) and oxidosqualene cyclase (OSC), which are unique to cholesterol biogenesis – have been potential targets for the design of such therapeutic agents [Abe I. *et al. Natural Products Report* (1994) 11, 279–302].

Squalene synthase inhibitors

SS catalyzes the first committed step in the *de novo* biosynthesis of cholesterol – the reductive dimerization of farnesyl diphosphate with NADPH to form squalene at the final branch-point of the isoprenoid biosynthetic pathway. Several compounds designed as substrate analogues or high-energy intermediate analogues and novel classes of natural products that inhibit SS have been reported. Many of these compounds have been shown to be potent and effective cholesterol-lowering agents in animal models. However, they could induce a marked increase in HMG-CoA reductase activity, resulting in an accumulation of a toxic farnesol-derived dicarboxylic acid. This was also the case for the recently disclosed RPR107393 (**1**), an orally effective and extremely potent SS inhibitor from Rhône-Poulenc Rorer (IC_{50} = 0.6 nM for rat liver SS) [Amin, D. *et al. J. Pharmacol. Exp. Therap.* (1997) 281, 746–752].

By contrast, P3622 (**2**), a diethylaminoethoxystilbene derivative from



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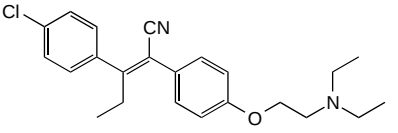

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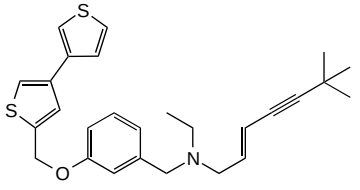
Pfizer (K_i = 0.7 μM for rat liver SS), did not increase HMG-CoA reductase activity in cultured human cells [Harwood, H.J. Jr *et al. Biochem. Pharmacol.* (1997) 53, 839–864]. There are as yet no reports of human clinical trials with SS inhibitors.

Squalene epoxidase inhibitors

SE is a non-cytochrome P450 enzyme that catalyzes the conversion of squalene to 2,3-oxidosqualene. In addition to oxygen, vertebrate SE requires FAD, NADPH, a supernatant protein factor and NADPH-cytochrome P450 reductase. The allylamine class of antifungal compounds are specific inhibitors of SE. Depending on their chemical structure, allylamine derivatives can be highly selective for either fungal or mammalian SEs. NB598 (**3**) was the first potent and specific inhibitor of mammalian SE developed by Banyu (K_i = 0.68 nM for human HepG2 SE); it is based on the structure of terbinafine – Sandoz's prototype allylamine antimycotic, which is known to selectively inhibit fungal SE [Horie, M. *et al. J. Biol. Chem.* (1990) 265, 18075–18078].



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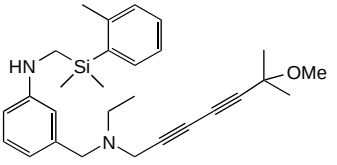
Oral administration of NB598 inhibits cholesterol synthesis more potently than L654969, an HMG-CoA reductase inhibitor, and causes intracellular accumulation of squalene. Moreover, NB598 treatment dramatically increases the LDL-receptor level in Hep G2 cells, without a concomitant elevation of HMG-CoA reductase activity. From these observations, NB598 is expected to be highly effective in the treatment of hypercholesterolaemia.

Recent extensive SAR studies have led to further development of several new inhibitors of SE with equivalent or improved *in vitro* and *in vivo* biological profiles, including an (aryloxy)methylsilane derivative (**4**) developed at Pierre Fabre (IC_{50} = 0.2 μM for HepG2 cells) [Gotteland, J-P. *et al. Bioorg. Med. Chem. Lett.* (1996) 6, 533–538]. However, to date, no compounds have been reported to have entered clinical trials. Preliminary observations from *in vivo* studies have led to the conclusion that NB598 showed some signs of dermatitis-like toxicity, presumably due to squalene accumulation in skin cells.



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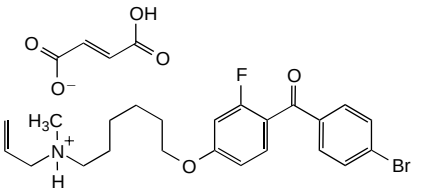
Oxidosqualene cyclase inhibitors

OSC catalyzes the conversion of 2,3-oxidosqualene to lanosterol, the first cyclic precursor of cholesterol. Partial inhibition of OSC is known to result in the accumulation of 2,3-oxidosqualene and 2,3:22,23-dioxidosqualene, which is further metabolized to 24,25-epoxycholesterol, a potent repressor of HMG-CoA reductase. Thus, OSC inhibitors could contribute, synergistically, to the overall inhibition of cholesterol biosynthesis, with little effect on the nonsteroidal isoprenoids. This makes the OSC a particularly attractive target enzyme for the design of cholesterol-lowering drugs.

Ro488071 (**5**) is an extremely potent and specific inhibitor of OSC (IC_{50} = 6.5 nM for human liver OSC) recently disclosed by Hoffmann-La Roche [Morand, O.H. *et al. J. Lipid Res.* (1997) 38, 373–390]. The two structurally-related compounds, BIBX79 (**6**) [Mark, M. *et al. J. Lipid Res.* (1996) 37, 148–158] and BIBB515 (**7**) [Eisele, B. *et al. J. Lipid Res.* (1997) 38, 564–575] from Karl Thomae/Boehringer Ingelheim, also showed potent inhibition of OSC (IC_{50} = 6 nM and 9 nM for human Hep G2 OSC, respectively), as well as oral bioavailability and *in vivo* activity. Ro488071 did not reduce coenzyme Q10 levels, and importantly did not show a compensatory increase in the activities of HMG-CoA reductase, SS and OSC; thus, a massive accumulation of potentially harmful intermediates is avoided. Although the molecular mechanism by which the OSC inhibition occurs is not well understood, these compounds are expected to be highly promising cholesterol-lowering drugs. OSC inhibitors are unique among the known inhibitors of cholesterol biosynthetic target enzymes, which do not allow for the production of oxysterols and the resulting synergistic inhibition of cholesterol biosynthesis. In this way, OSC inhibitors offer a novel and an attractive alternative approach to cholesterol-lowering agents.



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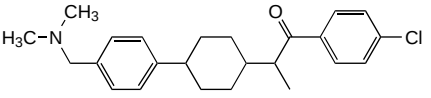

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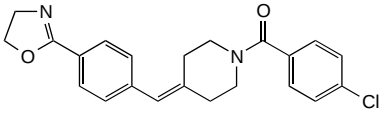

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