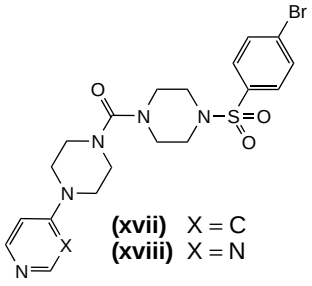
Compound **(xvi)** was prepared, and the *R*-isomer, shown, was found to be 10-fold more potent than its isomer and compound **(xv)**. The absolute configuration was determined by total synthesis from *R*(+) lactic acid. Compound **(xvi)** also exhibited a dose-dependent inhibition of fructose accumulation in diabetic rat sciatic nerve [ED_{50} = 1.6 mg kg^{-1}, compared to 14 mg kg^{-1} for compound **(xv)**]. However, the half-life of these compounds is short because of the *N*-demethylation of the sulfonamide. The reported large-scale synthesis of compound **(xvi)** will facilitate the discovery of sorbitol dehydrogenase inhibitors with a longer serum half-life.

10 Myalari, B.L. (2001) Sorbitol dehydrogenase inhibitors (SDIs): a new potent, enantiomeric SDI, 4-[2-1*R*-hydroxy-ethyl)-pyrimidin-4-yl]-piperazine-1-sulfonic acid dimethylamide. *J. Med. Chem.* 44, 2695–2700

Consideration of pK_a in the identification of new agents to lower cholesterol

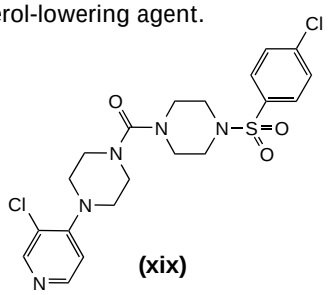
Considerable success in the treatment of cardiovascular disease has been achieved through the lowering of plasma cholesterol levels using HMG-CoA reductase inhibitors, also known as statins.

This success has focused attention on identifying inhibitors of later steps in the biosynthetic pathway to cholesterol, including 2,3-oxidosqualene lanosterol synthase (OSC). A group at AstraZenca (Macclesfield, UK) have previously described *N*-pyridyl and *N*-pyrimidinyl piperidines, **(xvii)** and **(xviii)**, respectively, as potent inhibitors of microsomal OSC from both human and rat [11]. The compounds demonstrated a similar reduction in cholesterol biosynthesis to the statin drug, simvastatin, in the rat. However, at higher oral doses the pyridyl derivative was found to cause a reduction of food intake of 64% (50 mg kg^{-1}), whereas the pyrimidinyl derivative only gave a 17% (100 mg kg^{-1}) reduction in food intake. Thus, the pyridine would not be permitted to enter clinical development because safety testing at higher doses would be precluded.



(xvii) X = C
(xviii) X = N

The mechanism for the effect on feeding behaviour is unknown, and the group hypothesized that the pK_a values of the terminal pyridine and pyrimidine might be important [12]. The pK_a for the pyridine is 9.2 and for the pyrimidine is 6.1. The group thus set out to lower the pK_a of the pyridine ring. One approach was to replace the electron-donating nitrogen of the piperidine with a carbon. A second approach was halogenation of the 3-position of the pyridine to give, for example, the chloro-derivative **(xix)**, which has a reduced pK_a of 5.8, is a potent inhibitor of microsomal OSC (87% at 100 nM) and exhibited good reduction of cholesterol biosynthesis via oral administration in the rat (ED_{80} = 1.4 mg kg^{-1}). The compound induced an improved feeding profile (14% reduction in feeding at 100 mg kg^{-1}) and is a development candidate as a novel cholesterol-lowering agent.



(xix)

11 Brown, G.R. (2000) A novel series of 4-piperidinopyridine and 4-piperidinopyrimidine inhibitors of 2,3-oxidosqualene cyclase-lanosterol synthase. *J. Med. Chem.* 43, 4964–4972

12 Brown, G.R. (2001) Novel 4-piperidinopyridine inhibitors of oxidosqualene cyclase-lanosterol synthase derived by consideration of inhibitor pK_a. *Bioorg. Med. Chem.* 11, 2213–2216

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Drug Delivery

Preparation of an experimental animal model by use of a drug delivery system

The pharmaceutical industry relies heavily on experimental animal models of disease states. These animal models are used to assay the potential effectiveness of new drug candidates. However, some diseases prove extremely difficult for which to develop appropriate models. One such disease is chronic hyperendotoxemia, a complication of Gram-negative bacterial infection, which can develop after trauma or surgery. Research aimed at the development of a treatment for chronic hyperendotoxemia has been hampered by the lack of a good animal model. Considerable research has been conducted to develop an appropriate model but, to date, a convenient, reproducible preparation of such a model has not been accomplished.

Lipopolysaccharide (LPS) is involved in the immune cascade and can induce a state of chronic hyperendotoxemia in animal models, but controlling the amount of LPS has proven to be difficult. Small doses of LPS cannot prevent Gram-negative sepsis, whereas overdose results in septic shock and multi-organ failure. To date, the application of an appropriate dosage form of LPS to induce chronic hyperendotoxemia has not been achieved. The controlled release of LPS could provide a suitable animal model.

 1359-6446/02/$ – see front matter PII: S1359-6446(02)02084-0

Kakinoki and coworkers recently reported the application of a drug delivery system (DDS) to the preparation of an animal model [1]. A DDS consisting of a non-biodegradable, biocompatible polymer and LPS was prepared and investigated for both its *in vitro* release characteristics and its application *in vivo* to produce an animal model of chronic hyperendotoxemia. It was found that an appropriate LPS-DDS provided controlled release of LPS *in vivo* and the observed effects on the animal correlated well to clinical observations of chronic hyperendotoxemia.

The LPS-DDS was prepared from 2-hydroxyethylmethacrylate (HEMA) and a crosslinking agent chosen from diethyleneglycoldimethacrylate (2G) or two different MWs of polyethyleneglycoldimethacrylate (4G, 9G). HEMA and crosslinking agents 2G, 4G or 9G were mixed in molar ratios of 1:3, 1:1 and 3:1, respectively, and stirred. A catalytic amount of 1-hydroxycyclohexylphenylketone was added as an initiator, and 30 mg of LPS per gram of mixture was uniformly dispersed. The mixture was polymerized in a test tube under UV irradiation and the resultant polymer was cut into 515 mg tablets, each measuring 8.0 × 9.0 mm. Tablets without LPS were prepared as controls.

In the *in vitro* experiments, LPS-DDS tablets were immersed in 100 ml physiological saline. A 1 ml aliquot of the solution was periodically removed and the concentration of LPS determined by spectrophotometry at 257.6 nm. The accumulated amount of LPS released decreased with increasing amounts of HEMA in the LPS-DDS and also increased according to the type of crosslinking agent, in the order 2G<4G<9G. In most formulations of LPS-DDS, the rate of LPS release consisted of a rapid initial phase, followed by a slow linear phase and, finally, a plateau. However, in the HEMA:4G 1:3 and 1:1 formulations, the decrease in release rate was relatively small after an initial 'burst'. The LPS release rate of the HEMA:4G 1:3 formulation showed an almost constant release rate after the initial burst. This constant release rate is desirable for the application to an animal model of chronic hyperendotoxemia.

Rats (48-week old Wistar) were implanted with four LPS-DDS tablets in the abdominal cavity, and measurements of LPS blood concentration, body weight, diet intake, hair appearance and activity were observed. Three different formulations of LPS-DDS were tested *in vivo*; HEMA:4G 1:3 LPS-DDS (group A), HEMA:4G 1:1 LPS-DDS (group B), and HEMA:4G 1:3 DDS as a control. The LPS concentration in the blood remained almost constant at a high level of over 200 pg ml^{-1} in group A for three days. By contrast, the blood LPS concentration level peaked at 12 h following implantation in group B, and then dropped. As expected, LPS blood concentration in the control group remained at an almost constant, normal level.

In both groups A and B, body weight and dietary intake dropped considerably in the first 24 h after implantation, then gradually returned to almost normal over several days. Rat hair remained erect for 72 h in group A and for 48 h in group B. Rat activity in both groups A and B was less than that in the control group. All the observed effects resulting from LPS-DDS implantation are similar to clinical observation of chronic hyperendotoxemia. The successful approach could lend itself to other instances where the controlled release of a chemical or biological agent can induce a disease state in a small animal, thereby also providing an animal model for other diseases.

1 Kakinoki, S. *et al.* (2001) The preparation of the chronic hyperendotoxemia experimental animal model by means of a drug delivery system *J. Control. Release* 75, 167–172

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