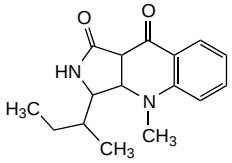


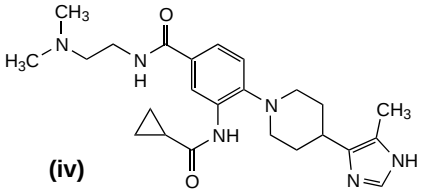
(iii)

4 Kakinuma, N. *et al.* (2000) Quinolactacins A, B and C: novel quinolone compounds from *Penicillium* sp. EPF-6. I. Taxonomy, production, isolation and biological properties. *J. Antibiot.* 53, 1247–1251

5 Takahashi, S. *et al.* (2000) Quinolactacins A, B and C: novel quinolone compounds from *Penicillium* sp. EPF-6. II. Physico-chemical properties and structure elucidation. *J. Antibiot.* 53, 1252–1256

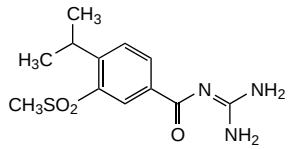
A novel sodium/hydrogen exchange inhibitor

The Na^{2+}/H^{+} exchanger regulates intracellular pH and is involved in cell injury resulting from ischaemia and reperfusion. Inhibitors of this exchanger are potentially attractive as cardioprotective agents for the treatment of ischaemia, because of their ability to prevent the accumulation of sodium and calcium ions. Recently, workers at Sanofi-Synthelabo (Cedex, France) identified compound **(iv)** as the first example of a new structural class of inhibitors of the NHE1 isoform of the ubiquitous Na^{2+}/H^{+} transporter[6].



(iv)

Cariporide **(v)** is a representative of the structurally distinct acylguanidine class of NHE1 inhibitors, whereas this newly identified compound **(iv)** is a novel imidazoylpiperidine. Biological activity was demonstrated by measuring the recovery of pH in NHE1- and NHE2-expressing CCL39-derived PS120-variant cells exposed to intracellular acid-load. Intracellular pH recovery was inhibited by **(iv)** with an IC_{50} value of 3.3 ± 1.3 nM for NHE1-expressing cells and an IC_{50} value of 2.3 ± 1.0 μM for NHE2-expressing cells. By contrast, cariporide showed respective IC_{50} values of 103 ± 28 nM (NHE1) and 73 ± 46 μM (NHE2).

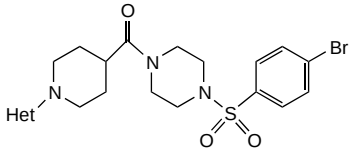


(v)

6 Lorrain, J. *et al.* (2000) Pharmacological profile of SL591227, a novel inhibitor of the sodium/hydrogen exchanger. *Br. J. Pharmacol.* 131, 1188–1194

Novel inhibitors of cholesterol biosynthesis

Successful therapy using the statin class of hypocholesterolemic agents has led to the search for other novel inhibitors of the cholesterol biosynthesis pathway. In particular, inhibitors of the squalene synthase (SQS) step have been considered. In addition to their work on SQS inhibitors, Brown and colleagues have recently investigated the inhibition of 2,3-oxidosqualene cyclase (OSC) and reported a series of 4-piperidinopyridine and 4-piperidinopyrimidine inhibitors of OSC **(vi)**[7].



Het = Pyridine, pyrimidine

(vi)

The compounds were tested orally in rats for inhibition of cholesterol biosynthesis. *In vivo* inhibition of OSC was confirmed by *in vitro* studies. Comparison of the two series indicated that the pyrimidine moiety afforded more potency to the compounds than the corresponding pyridino derivatives both *in vitro* and *in vivo*. The most interesting compounds were comparable with simvastatin, a clinically used hydroxymethylglutarylCoA (HMGCoA) reductase inhibitor. Because the pK_a values of the most interesting derivatives vary only slightly (pK_a = 6 and 7), the authors suggest that further novel OSC inhibitors might be found in either series by exploring a broader range of pK_a values (e.g. 5–9).

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

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Combinatorial chemistry

HIV-1 protease inhibitors

The HIV-1 protease is a member of the aspartic protease family of enzymes that produces essential structural and functional viral proteins by proteolytic processing of the *gag*- and *gag-pol* viral gene products. Protease inhibitors have shown clinical efficacy for the treatment of HIV-1 infection by reducing the plasma viral-load in infected individuals. However, rapid turnover of HIV-1 and the high frequency of mutations in the HIV genome eventually result in the selection of mutant strains and in the development of clinical resistance. Therefore, there is a requirement for the development of new HIV-1 protease inhibitors.

A solid-phase parallel synthesis approach was used for the generation of novel unsymmetrical protease inhibitors[1]. A small library of eight individual compounds was synthesized on 3,4-dihydro-2*H*-2-ylmethoxymethyl polystyrene solid-phase resin. The compounds were

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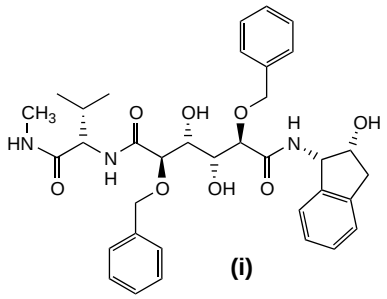
tested for the inhibition of HIV-1 protease and several potent compounds were identified. One of the most potent was **(i),** which possessed an EC_{50} value of 100 nM against HIV-1 protease. This work could, therefore, prove useful for the further optimization of antiviral activity for this class of compounds.



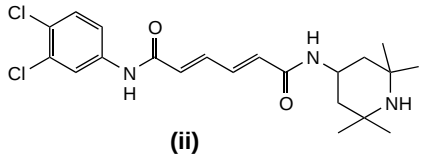
(i)

1 Oscarsson, K. *et al.* (2000) Solid-phase assisted synthesis of HIV-1 protease inhibitors. Expedient entry to unsymmetrical substitution of a C_2 symmetric template. *Can. J. Chem.* 78, 829–837

Bone resorption inhibitors

The osteoclast vacuolar-ATPase plays an essential role in bone resorption, and inhibition of this acid pump has been shown to inhibit bone resorption both *in vitro* and *in vivo*. Inhibitors of bone resorption are potentially useful for the treatment of osteoporosis, that is, the loss of bone.

A library of 806 individual compounds was synthesized on a Rink chloride solid-support[2]. The compounds were screened at 9 μM for their effect on vacuolar-ATPase-mediated proton transport in membrane vesicles derived from chicken medullary bone. One of the most potent compounds obtained was **(ii)**, which



(ii)

caused 51% inhibition. However, no clear SARs could be deduced from the compounds contained within this library, and further work will be necessary to establish the credentials of this class of diamides as potential bone resorption inhibitors.

2 Edvinsson, K.M. *et al.* (2000) Solid-phase synthesis of diamides as potential bone resorption inhibitors. *Bioorg. Med. Chem. Lett.* 10, 503–507

Antibiotics effective against vancomycin-resistant bacteria

Vancomycin, a member of the glycopeptide class of antibiotics, has been used clinically for the past 40 years to treat infections caused by gram-positive bacteria. Its renowned action against methicillin-resistant *Staphylococcus aureus* (MRSA) has made it a last-resort choice of therapy. However, the emergence of vancomycin-resistant *Enterococci* (VRE) and, more recently, vancomycin-intermediate susceptible *S. aureus* (VISA) is cause for concern, and has prompted renewed and vigorous efforts at developing modified vancomycin analogues with restored activity against VRE or VISA (Ref. 3).

The antibacterial activity of vancomycin arises from its ability to inhibit peptidoglycan biosynthesis within the bacterial cell wall. Specifically, vancomycin binds to the terminal Lys-D-Ala-D-Ala fragment of the growing peptidoglycan biosynthetic precursor via an intricate network of five hydrogen bonds, thereby inhibiting cell-wall growth and cross-linking. A library of 30 compounds was synthesized in solution using 'dynamic target-accelerated combinatorial synthesis' (TACS) of vancomycin dimers, which was used for the identification of ligands with the highest affinity for the D-Ala-D-Ala motif.

TACS is a process whereby building-blocks of a combinatorial library are allowed to assemble and react in the presence of a target. This synthetic approach should selectively deliver the product with the highest affinity for the target out of a virtual library of all possible reaction products. By this method, several compounds from this library were produced that possess potent activities against VRE and VISA that were either comparable with, or exceeding, the most active compounds known against these bacterial strains. The TACS concept has been shown to be a powerful technique for the generation of highly potent antibiotics that are active against VRE and VISA, and the acute need for new antibiotics dictates the further development of these compounds.

3 Nicolaou, K.C. *et al.* (2000) Target-accelerated combinatorial synthesis and discovery of highly potent antibiotics effective against vancomycin-resistant bacteria. *Angew. Chem., Int. Ed. Engl.* 39, 3823–3828

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