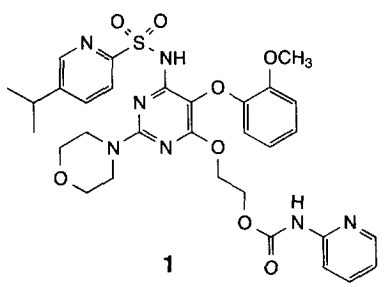
Monitor: molecules and profiles

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 two sections: *Molecules* summarizes the chemistry and the pharmacological significance and biological relevance of new molecules reported in the literature and on the conference scene; *Profiles* offers commentary on promising lines of research, emerging molecular targets, novel technology, advances in synthetic and separation techniques and legislative issues.

Endothelin receptor antagonist

Endothelin-1 is a potent and long-lasting vasoconstrictor which binds to G-protein-coupled receptors ET_A and ET_B. Workers from Hoffmann-La Roche Ltd (Basel, Switzerland) have reported the development of a potent orally active nonpeptide receptor antagonist (RO485695, **1**) by the incorporation of a pyridylcarbamoyl group and an isopropylpyridylsulphonamide substituent into the scaffold of Bosentan [Neidhart, W. *et al. Bioorg. Med. Chem. Lett.* (1997) 7, 2223–2228].

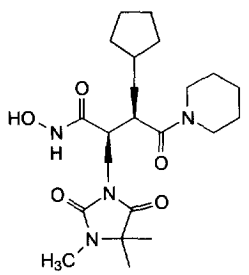


1

This compound has been shown to have affinity for both ET_A and ET_B receptors (IC_{50} = 0.3 nM and 5 nM respectively) and high functional antagonistic potency *in vitro*. The authors also report that compound **1** is orally active in dogs and rats (40–60% bioavailability) and has good *in vivo* activity in various preclinical animal models.

Collagenase inhibitor

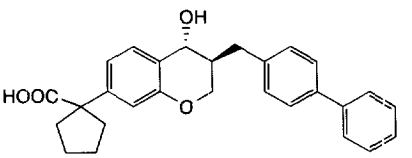
The matrix metalloproteinases (MMPs) are widely involved in extracellular matrix remodelling. The role of specific MMPs in the degradation of cartilage is of particular interest because inhibitors of these enzymes may be useful in the treatment of rheumatoid- and osteo-arthritis. The key step in the degradation of collagen is the cleavage of the triple helix collagen fibres by collagenase. Although a number of collagenase-specific inhibitors have been reported, their clinical development has been limited by poor solubility and bioavailability.



2

A group from Roche (Welwyn Garden City, UK) have recently described a series of novel MMP inhibitors that are potent, selective inhibitors of collagenase and have good solubility and oral bioavailability [Broadhurst, M.J. *et al. Bioorg. Med. Chem. Lett.* (1997) 7, 2299–2302]. Compound **2** has been selected specifically for development as a cartilage-protective agent for the treatment of these arthritic diseases.

Leukotriene B_4 receptor antagonists



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Leukotriene B_4 (LTB_4) is known to stimulate the synthesis and release of cytokines from various inflammatory cells and to act as a powerful chemoattractant for granulocytes. It has therefore been implicated as a mediator in a number of inflammatory diseases including rheumatoid arthritis, inflammatory bowel disease, psoriasis and asthma. Workers from Pfizer (Groton, CT, USA) have reported the optimization of LTB_4 receptor antagonism in a series of 7-chromanylacetic acid derivatives, which led to the identification of **3**. This compound possesses strong affinity (IC_{50} = 6.4 nM) for the LTB_4 receptor and inhibits human neutrophil chemotaxis [Reiter, A.A. *et al. Bioorg. Med. Chem. Lett.* (1997) 7, 2307–2312]. Although this

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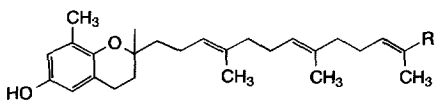
compound was subsequently selected for development, it was finally abandoned owing to issues associated with its long half-life.

New natural products

Antioxidants

Terashima, K. and coworkers [*Heterocycles* (1997) 45, 1559–1566] have described the isolation and spectroscopic identification of two new chromanols, garcinoic acid (**4**) and garcinal (**5**), from methanol extracts of the seeds of *Garcinia kola* collected in Nigeria.

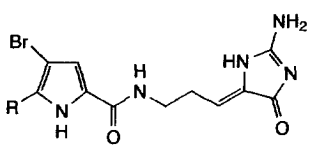
These agents were shown to be 1.5 times as strong as DL-α-tocopherol as antioxidants using the Umezawa method.



4 R = COOH
5 R = CHO

Antihistamines

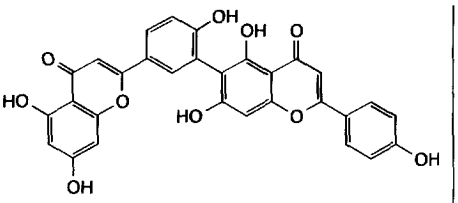
Cafieri, F. and coworkers [*Bioorg. Med. Chem. Lett.* (1997) 7, 2283–2288] have described the isolation and biological evaluation of a series of known bromopyrrole alkaloids and two related novel compounds, dispacamides C (**6**) and D (**7**), from four Caribbean *Agelas* sponges. All the bromopyrrole alkaloids were found to be weak non-competitive histamine antagonists in the guinea-pig ileum model.



6 R = Br
7 R = H

Hepatitis B inhibitor

Lim, Y-M. and coworkers [*Bioorg. Med. Chem. Lett.* (1997) 7, 2325–2328] have demonstrated that robustaflavone (**8**), a naturally occurring biflavanoid isolated from the seed kernel of



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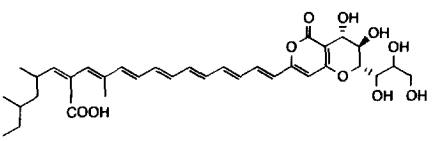
Rhus succedanea, is a potent *in vitro* inhibitor of hepatitis B (EC_{50} = 250 nM). Further studies indicate that this compound inhibits the hepatitis B virus' DNA polymerase.

HIV-1 inhibitors

Human immunodeficiency virus type 1 (HIV-1) encodes a transactivator protein of viral gene expression (Rev) that accumulates in the cell and binds to the Rev response element (RRE) on the viral messenger RNA sequence. This interaction regulates the accumulation of mRNAs in the cytoplasm of infected cells, which is essential for the synthesis of structural proteins and the replication of the virus. Specific inhibitors of the Rev/RRE interaction may therefore inhibit HIV replication. Shu, Y-Z. and coworkers [*Bioorg. Med. Chem. Lett.* (1997) 7, 2295–2298] have reported the isolation of orevactaene (**9**), a novel oxopolyene, from *Epicoccum nigram* WC47880 as an inhibitor of the Rev/RRE interaction (IC_{50} = 3.6 μM).



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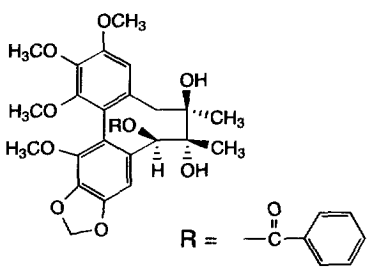
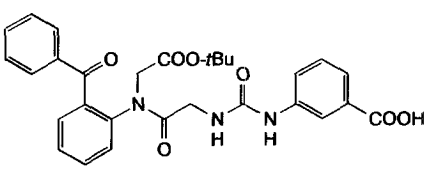


10

Another group have described the screening of lignans isolated from the stems of *Kadsura interior* for general anti-HIV activity [Chen, D-F. *et al. Bioorg. Med. Chem.* (1997) 5, 1715–1723]. Twelve lignans were isolated of which seven were found to have anti-HIV activity. Gomisin-G (**10**) was found to be the most active of these lignans with EC_{50} and therapeutic index of 6 ng/ml and 300 respectively.

CCK_B/gastrin antagonist

The CCK_B/gastrin receptor is responsible for gastrin-stimulated acid secretion in the stomach during feeding and for neurotransmission and modulation in the CNS. CCK_B/gastrin receptor antagonists may therefore offer an alternative pharmacological approach to the treatment of gastric ulceration. Hagishita, S. and coworkers [*Bioorg. Med. Chem.* (1997) 5, 1695–1714] have described the synthesis and evaluation of a novel series of CCK_B/gastrin receptor antagonists based on ureidomethylcarbamoylphenylketones. These studies have led to the identification of **11** as a potent, selective CCK_B/gastrin receptor antagonist *in vitro*. This compound was also shown to inhibit pentagastrin-induced gastric acid secretion in anaesthetized rats (ED_{50} = 14 μg/kg). The blood–brain barrier penetration of this compound was shown to be poor, thereby increasing the selectivity for the peripheral effects of gastrin antagonism *in vivo*.



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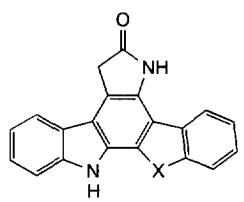
Novel immunostimulants

The increasing number of immunocompromised patients, such as those suffering from viral infections, cancer and autoimmune diseases, has led to a clinical need for therapeutic agents that will

enhance the immune response. Interferon-γ (IFN-γ) is a potent immune activator but has dose-related side effects that limit its effectiveness. It has been suggested previously that molecules that enhance the activity of IFN-γ might allow clinicians to prescribe lower doses of IFN-γ while retaining therapeutic efficacy. A group from Cephalon (West Chester, PA, USA) has reported a series of fused pyrrolo[2,3,*c*]carbazol-6-ones (**12**) that potentiate the IFN-γ induction of major histocompatability complex class II molecules in a human monocyte-derived cell line [Hudkins, R.L. *et al. J. Med. Chem.* (1997) 40, 2994–2996]. These compounds may provide an alternative approach, through the enhancement of the natural immune system, for the treatment of viral infections and cancer growth.



X = O, S, NH or CH_2

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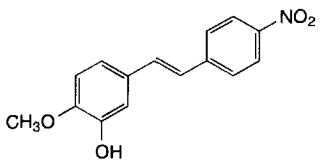
Combinatorial chemistry

Hydroxystilbene kinase inhibitor library

Protein kinases are attractive drug targets because protein phosphorylation catalysed by these enzymes is a key mechanism in signal transduction pathways. However, a major obstacle to the discovery of selective inhibitors is the considerable number of known protein kinases and the degree of homology between the family members. To overcome these difficulties, a combinatorial library of stilbenes has been tested against B cell cytoplasmic tyrosine kinases in the search for inhibitors of receptor-mediated phosphorylation [Bishop, A.C. *et al. Tetrahedron* (1997) 53, 11995–12004].

The assay was based on the use of an anti-phosphotyrosine that binds almost any phosphotyrosine-containing protein. Thus it was possible to examine the extent of phosphorylation of many different cellular tyrosine kinase substrates simultaneously using a protein blotting assay. The combinatorial library products, based on 3,4,3′,5′-tetrahydroxy-*trans*-stilbene, were individually tested against the B cell antigen receptor-initiated signalling cascade, and several compounds were found to disrupt kinase activity.

One compound in particular (**1**), when tested at 250 μM, inhibited the phosphorylation of four of the cellular proteins, thus revealing a modest level of enzyme selectivity and providing a potential starting point for further libraries of kinase inhibitors.



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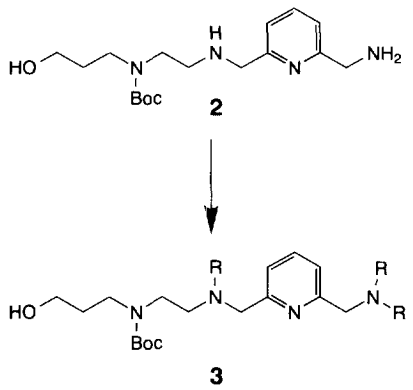
Antibacterial solution libraries

Solution methods for combinatorial chemistry are effective approaches to libraries when the route is a high-yielding one-step synthesis. Several libraries based on linear diaminopyridines have been prepared and screened for antibacterial activity [An, H. *et al. J. Org. Chem.* (1997) 62, 5156–5164]. Templates such as the diamine (**2**) were prepared using a cyclic nickel complex, and were then reacted in the library-forming step with equimolar amounts of six different benzylic bromides. Although there are three sites of derivatization, the symmetry of the primary amine led to a final library size of 126 components. The *tert*-butoxycarbonyl (Boc) protecting group in (**3**) could be removed to allow the formation of further sublibraries.

Testing the libraries as mixtures against *Streptococcus pyogenes* and *Escherichia coli* revealed several with



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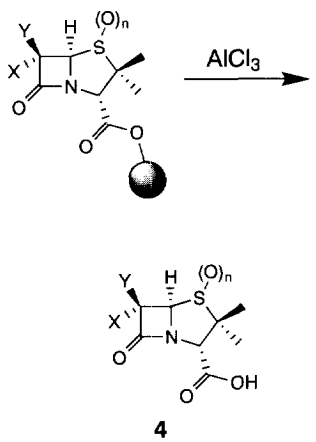
MIC values in the range of 1 to 5 μM. Some libraries also showed antifungal activity by inhibiting the growth of *Candida albicans*.

Synthesis of penicillins on solid phase

As the solid-phase preparations of pharmacologically significant molecules gain greater importance, methods to accommodate the synthesis of sensitive structures are rapidly being determined. The β-lactam structure, which occurs in penicillins and cephalosporins, is readily degraded under strongly acidic conditions, and thus the resin-cleavage conditions often used with Merrifield or Wang resins are unsuitable for its preparation. A recent paper discloses the development of an alternative cleavage method that avoids exposure of these labile molecules to acidic conditions [Mata, E.G. *Tetrahedron Lett.* (1997) 38, 6335–6338].



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