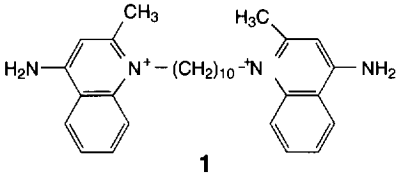
Monitor: molecules and profiles

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.

Selective SK_{Ca} blockers

It has been suggested that small conductance calcium-activated potassium (SK_{Ca}) channels may have a physiological role in myotonic muscular dystrophy. Dequalinium (**1**) has recently been shown to be a selective blocker of the SK_{Ca} channels [Castle, N.A. *et al. Eur. J. Pharmacol.* (1993) 235, 201–207). A group from UCL (London, UK) have now described the synthesis and evaluation of a series of dequalinium-related bis-quinolinium cyclophanes as potential blockers of SK_{Ca} channels [Rosa, J.C. *et al. Bioorg. Med. Chem. Lett.* (1997) 7, 7–10]. These compounds exhibited submicromolar activity when tested for inhibition of hyperpolarization (AHP) of rat sympathetic neurones.

UCL1530 (**2**) is of particular interest, because this agent showed greater selectivity for the rat sympathetic neuronal SK_{Ca} channels (IC_{50} = 80 nM) than for the SK_{Ca} channels in guinea pig hepatocytes. This supports the evidence for different SK_{Ca}-channel subtypes in different tissues and suggests that the bis-quinolinium cyclophanes may be useful for the pharmacological characterization of putative SK_{Ca}-channel subtypes.



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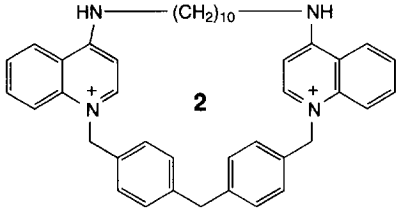
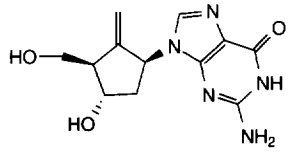


2

Hepatitis B antiviral

The hepatitis B virus is a major worldwide cause of chronic liver disease and subsequent cirrhosis and/or hepatocellular carcinoma. Although a number of agents, including lamivudine and famciclovir, are presently being evaluated in patients with chronic hepatitis B infections there is a constant need for new therapies for the treatment of infected individuals. Bisacchi, G.S. and coworkers [*Bioorg. Med. Chem. Lett.* (1997) 7, 127–132] have described the synthesis and *in vitro* evaluation of a novel carbocyclic analogue of 2′-deoxyguanosine (BMS200475, **3**) as an inhibitor of the hepatitis B virus. This agent was shown to be a selective, potent inhibitor of the hepatitis B virus (ED_{50} = 3 nM) with relatively limited cytotoxicity against a variety of other cell lines.



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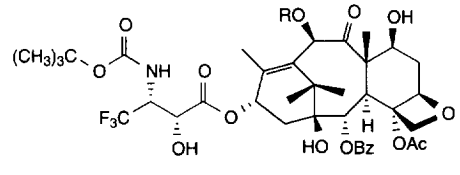
Novel 3′-trifluoromethyl taxoids

The approval of paclitaxel and docetaxel for use against various types of cancer, particularly breast and ovarian cancers, has led to major advances in the treatment of cancers against which conventional anticancer therapies have proved ineffective. However, the use of these agents often results in a number of undesirable side effects and the onset of multiple drug resistance (MDR). In an attempt to generate a second generation of taxoid anticancer agents with fewer side effects and enhanced activity against drug-resistant tumours, Ojima, I. and coworkers [*Bioorg. Med. Chem. Lett.* (1997) 7, 133–138] have synthesized a series of 3′-trifluoromethyl taxoids (**4**). These agents were found to have enhanced *in vitro* cytotoxicities against a range of human cancer cell lines compared with paclitaxel and docetaxel. In particular, these compounds were found to be active against the MCF7-R drug-resistant breast cancer cell line, indicating that these agents may be useful in the treatment of cancers following the onset of MDR.



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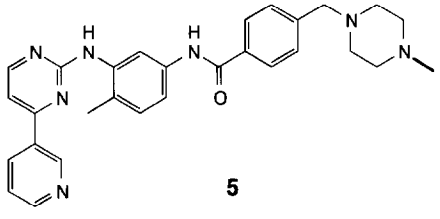
Abl-kinase inhibitors

The Bcr-Abl protein has previously been shown to induce leukaemia in mice and has therefore been implicated as the cause of chronic myelogenous leukaemia. The tyrosine protein kinase activity of the Bcr-Abl protein is known to be essential for cellular transformation and is therefore an ideal therapeutic target. Although a number of Bcr-Abl tyrosine protein kinase inhibitors have been identified, these compounds show either poor selectivity or low activity.

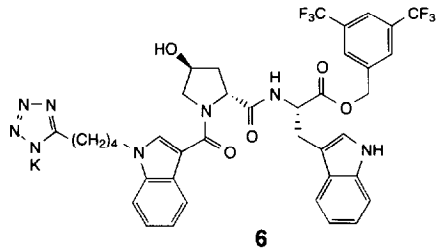
An oncology research group from Ciba Pharmaceuticals (Basel, Switzerland) has reported some preliminary findings on the synthesis and evaluation of a series of novel phenylaminopyrimidines as potential Bcr-Abl tyrosine protein kinase inhibitors [Zimmermann, J. *et al. Bioorg. Med. Chem. Lett.* (1997) 7, 187–192]. Compound **5** was shown to be a particularly selective, highly potent inhibitor of Abl tyrosine kinase activity *in vitro* and may represent a useful lead compound for the development of novel therapeutic agents for the treatment of Philadelphia chromosome-positive leukaemias.



5

NK_1 antagonist

Fauchère, J-L. and coworkers [*Bioorg. Med. Chem. Lett.* (1997) 7, 209–212] have described a novel, highly selective NK_1 receptor antagonist (S19752, **6**). This dipeptide is water soluble and highly potent in *in vitro* binding and bioassays (K_i = 2.4 nM) with potency and selectivity comparable with those obtained for the most active nonpeptide NK_1 antagonists. On aerosol administration, this agent was shown to be a potent and long-acting inhibitor of substance-P-induced airway bronchoconstriction in a guinea-pig model and may therefore have clinical application in the treatment of chronic inflammatory airway diseases.

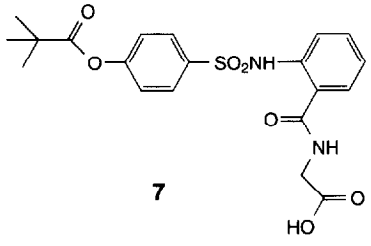


6

Human neutrophil elastase inhibitors

The serine protease human neutrophil elastase is normally released from neutrophils in response to inflammatory stimuli. Although the activity of human neutrophil elastase is normally modulated by the presence of endogenous α-1-proteinase inhibitors, excessive human neutrophil elastase activity may cause tissue damage and has been implicated in the development of emphysema. It has therefore been suggested that low-molecular-weight inhibitors of human neutrophil elastase may be useful in the treatment of such diseases.

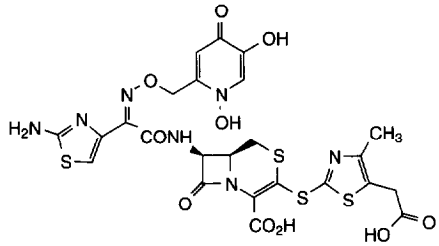
Workers from the Ono Pharmaceutical Company (Osaka, Japan) have recently identified a novel series of pivaloyloxybenzene derivatives as potent and selective inhibitors of this serine protease [Imaki, K. *et al. Bioorg. Med. Chem.* (1996) 4, 2115–2134]. In particular, the sulphonamide-containing analogue **7** was found to be active *in vivo* in the newly developed skin capillary permeability guinea pig model and may therefore be useful in the evaluating the roles of neutrophil elastase *in vivo*.



7

New antibacterial agents

Opportunistic infection by Gram-negative bacteria, such as *Pseudomonas aeruginosa, Serratia marcescens, Proteus vulgaris* and *Acinetobacter baumanii,* is an increasingly common problem in patients undergoing chemotherapy. Some of these organisms are becoming particularly resistant to most anti-infectives, leading to increased cases of bacterial pneumonia, meningitis and sepsis. Tsuji, K. and coworkers have described the synthesis and antimicrobial activity of a range of cephalosporins, 2-isocephems and 2-oxaisocephems with C-3′ catechol-containing (pyridinium-4-thio)methyl groups and 2-isocephems with C-7 catechol-related aromatics [*Bioorg. Med. Chem.* (1996) 4, 2135–2149]. These compounds were found to be highly active against Gram-negative bacteria, in particular *P. aeruginosa.*



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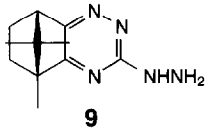
Compound **8** was found to be the most active compound of the series having potent *in vitro* activity against both *P. aeruginosa* and *A. baumanii* and *in vivo* activity against a clinical isolate of *P. aeruginosa.*

CNS stimulants

Nagai, S-I. and coworkers [*Heterocycles* (1997) 1, 117–120] have reported the synthesis and evaluation of camphor-1,2,4-triazines fused with 1,2,4-triazole, tetrazole and 1,2,4-triazine as potential CNS stimulants. Although **10** and **11** also showed some CNS activity in the mouse model, the most potent compound was the 1,2,4-benzotriazine **9**, from which the other compounds were prepared.



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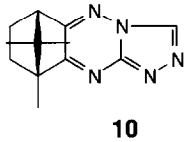

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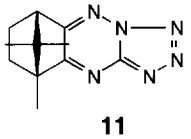


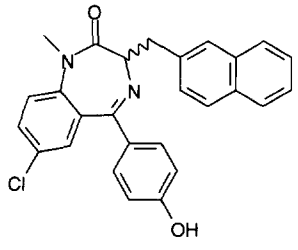
11

Combinatorial chemistry

Systemic lupus erythematosus inhibitors

Systemic lupus erythematosus (SLE) is an autoimmune disease that is characterized by the presence of plasma antibodies that bind single and double stranded DNA (ss and dsDNA). Some of these antibodies are pathogenic, in that they can mediate glomerulonephritis by binding to DNA adherent to the glomerular basement. A recent paper describes the discovery of non-nucleic acid inhibitors that block recognition of DNA by anti-DNA monoclonal antibodies [Ellman, J.A. *et al. J. Am. Chem. Soc.* (1996) 118, 10650–10651].

A combinatorial library of 1680 different 1,4-benzodiazepines was synthesized from three 2-aminobenzophenones, 35 amino acids and 16 alkylating agents using the Chiron Mimotopes multipin methodology. The products were screened by competition ELISA for the ability to prevent the DNA-binding monoclonal antibody, 11F8, from binding to ssDNA. From the binding data, it was clear that one particular aminobenzophenone, **1**, interacted specifically with the antibody as it was present in several of the most potent binding inhibitors giving 60% inhibition at 20 μM. Studies are under way to examine whether this activity *in vitro* translates to benefit in animal models of SLE.

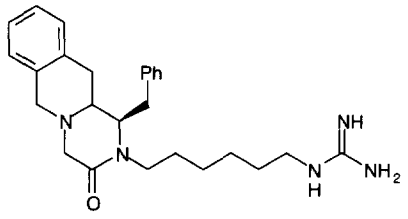


1

Bradykinin antagonists

Molecular modelling of peptide bradykinin antagonists has suggested that the 1,2,3,4-tetrasubstituted 1,4-piperazin-6-one structure is a reasonable mimic of the β-turn system. This has been used to design CP2055 (**2**), a 55 μM inhibitor of the cloned human BK2 receptor [Goodfellow, V.S. *et al. Mol. Diversity* (1996) 2, 97–102]. The success of this strategy has encouraged the group to investigate alternative piperazine structures synthesized as part of a combinatorial library. In particular, solid-phase synthesis of piperazinediones was achieved by routes that allowed the creation of novel and diverse amino acids on the solid-phase. Simultaneous cleavage and ring closure yielded piperazinediones, and reduction yielded highly substituted piperazines (**3**).

From a library of approximately 2,500 compounds several novel bradykinin antagonists were identified. One compound, CP2458 (structure not revealed), initially identified from a mixture of ten compounds by HPLC separation followed by MALDI-MS, was shown to have an IC_{50} value of 4.1 μM against the human receptor and an IC_{50} = 19 μM in a BK-stimulated human fibroblast calcium-flux functional assay. Parallel synthesis based on this lead has led to more potent antagonists that possess *in vivo* activity in a rat model of BK-induced hypotension.



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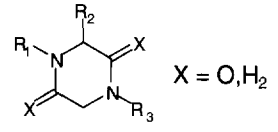
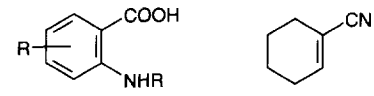


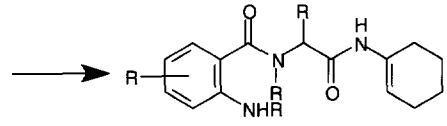
3

Rapid routes to 1,4-benzodiazepine-2,5-diones

1,4-Benzodiazepine-2,5-diones are an exceedingly important class of pharmacologically active molecules. Consequently, they have been the focus of several solid-phase combinatorial library approaches. A recent paper describes a novel solution synthesis of benzodiazepinediones that could readily lend itself to rapid parallel synthesis [Keating, T.A., and Armstrong, R.W., *J. Org. Chem.* (1996) 61, 8935–8939]. This synthesis uses an Ugi four-component reaction of a range of anthranilic acids with amines, aldehydes and a convertible isocyanide (1-isocyanocyclohexene) to generate the precursor α-acylaminoamide (**4**). The product was cyclized under acidic conditions to give the desired benzodiazepinediones (**5**).



+ amines and aldehydes



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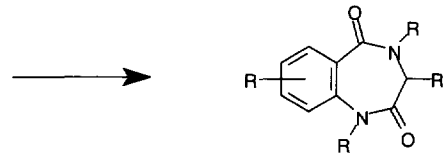

5

In addition to giving a wide range of benzodiazepinediones in good yields, because this approach is not dependent on available amino acids, a greater potential for molecular diversity is offered.

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Contributions to *Profiles*

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