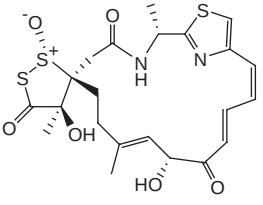
Monitor: molecules and profiles

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.

Antitumour activity of thioester derivatives of leinamycin

Leinamycin (**1**) is an antitumour antibiotic, previously isolated from a culture of the *Streptomyces* species. *In vitro,* this agent has been shown to cause single-strand cutting of plasmid DNA in the presence of thiol co-factors.



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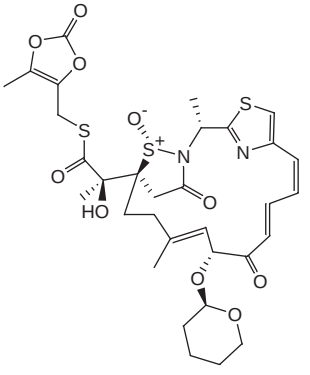
A recent communication from a Japanese group has described the synthesis of novel, stable thioester derivatives of leinamycin, which demonstrates nanomolar *in vitro* antiproliferative activity and effective *in vivo* antitumour activity [Kanda, Y. *et al.* (1999) *J. Med. Chem.* 42, 1330–1332]. These compounds possess a unique 3-isothiazolidinone-1-oxide promoiety, which might allow the conversion of these compounds into active dithiolanone derivatives in biological media. Compound (**2**) was shown to have potent antitumour activity against a wide variety of human tumour xenografts and has been selected for further evaluation as a potential antitumour agent.



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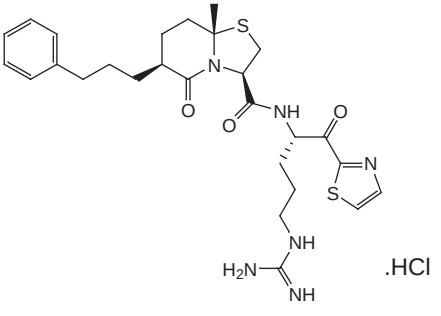
Thrombin inhibitors

Thrombin is a key enzyme in converting fibrinogen to fibrin in thrombus formation. This enzyme also activates a range of other coagulation factors including factor V, VIII, XI and XIII. Thrombus formation is involved in a variety of medical conditions including pulmonary embolism, and myocardial and cerebral infarctions. This has led to substantial research into thrombin inhibitors that can be used for both the prevention and the treatment of such thrombotic disorders. The tripeptide D-Phe-Pro-Arg is known to inhibit thrombin formation by directly binding to the enzyme's catalytic site. A recent paper from BioChem Therapeutic Inc. (Quebec, Canada) describes the synthesis and evaluation of bicyclic lactams as potential peptidomimetic thrombin inhibitors [Bachand, B., DiMaio, J. and Siddiqui, M.A. (1999) *Bioorg. Med. Chem. Lett.* 9, 913–918]. Structure–activity studies have demonstrated that compounds having a phenylpropyl-group in the P3 pharmacophore site were the most active, with compound (**3**) having an affinity of 2 nM. These peptidomimetic inhibitors also offer the advantages of enhanced metabolic and protolytic stability and therefore the potential for oral delivery.



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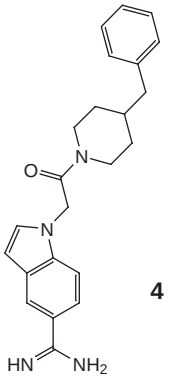
Another recent paper from DuPont Pharmaceuticals (Wilmington, DE, USA) describes the design and synthesis of several series of non-peptide 5,6-fused heterocyclic thrombin inhibitors [Dominguez, C. *et al.* (1999) *Bioorg. Med. Chem. Lett.* 9, 925–930]. The group compared the potency and selectivity of a range of amidinobenzimidazoles, amidinoindazoles, 3-amidinoindoles and 5-amidinoindoles. The 5-amidinoindoles were shown to be the most potent and selective of the series investigated, with XU817 (**4**) (K_i = 18 nM) being shown to be efficacious against venous thrombosis in a rat vena cava thrombosis model.



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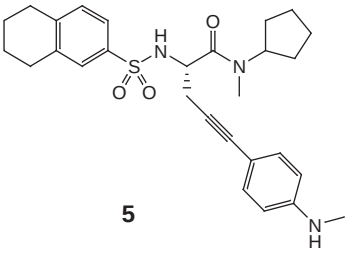
Another group has reported the synthesis and evaluation of thrombin inhibitors based on a propargylglycine template, as part of a programme to develop thrombin inhibitors with improved oral bioavailability. The group synthesized a series of novel arylsulfonylpropargylglycinamide derivatives, exemplified by (**5**), focussing on the structure–activity of the acetylenic terminus. Selected compounds were found to have nanomolar K_i values and good selectivity for thrombin over other serine proteases. Pharmacokinetic evaluation of (**5**) has demonstrated that this compound had good oral bioavailability in rats.

Workers from Novartis Horsham Research Centre (Horsham, UK) have reported the discovery of a different series of compounds that have an enhanced oral bioavailability [Ambler, J. *et al.* (1999) *Bioorg. Med. Chem. Lett.* 9, 1103–1108]. These compounds were identified as part of a programme to replace the strongly basic guanidine in the P1 pharmacophore with a substituent that would exploit the lipophilicity of the S1 pocket in the thrombin catalytic site. The most active of these compounds (**6**) was a potent, selective inhibitor of thrombin with 12% oral bioavailability on administration to rats at 10 mg kg^{-1}.



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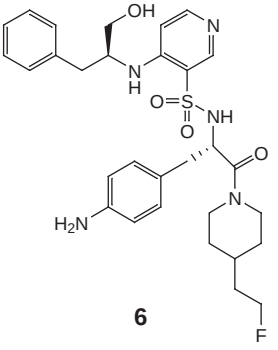
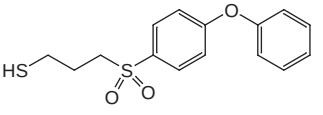


6

Novel MMP inhibitors

The matrix metalloproteinases (MMPs) are an important group of zinc-dependent enzymes involved in the remodelling of the extracellular matrix. It has been suggested that specific MMP inhibitors may have a role in the treatment of osteoarthritis by preventing the degradation and loss of cartilage. Data supporting this hypothesis has been reported in animal models of osteoarthritis using broad-spectrum MMP inhibitors. The MMPs are subclassified according to which matrix components they degrade and there is clearly an advantage in developing MMP inhibitors that will target the specific MMPs associated with such disease states.

Freskos, J.N. and coworkers have recently reported the identification of a series of γ-sulfone thiols that preferentially inhibit MMP-8 and MMP-13 over MMP-1 [*Bioorg. Med. Chem. Lett.* (1999) 9, 943–948]. Compound (**7**) was the most potent of these compounds (IC_{50}: MMP-13 = 0.5 nM; MMP-1 = 1500 nM; MMP-3 = 500 nM; MMP-8 = 4 nM) and is presently undergoing evaluation in animal models of osteoarthritis.



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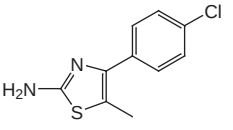
IL-6 secretion inhibitor

The cytokine, interleukin-6 (IL-6), plays an important role in the regulation of inflammatory and immune responses by inducing the proliferation and differentiation of B- and T-cells to antibody-producing cells and cytotoxic cells, respectively, and through the regulation of acute-phase proteins in the liver. It has been suggested that IL-6 might be involved in disease states such as postmenopausal osteoporosis and certain immune diseases. The screening of a series of 4-phenylthiazole derivatives as inhibitors of parathyroid hormone-stimulated IL-6 induction in osteoblastic MC3T3-E1 cells has recently led to the identification of 2-amino-4-(4-chlorophenyl)-5-methylthiazole (**8**) [Yamaguchi, K. *et al.* (1999) *Bioorg. Med. Chem. Lett.* 9, 957–960]. Further studies have also shown that this compound significantly suppresses bone-weight loss in the ovariectomized mouse model of osteoporosis.



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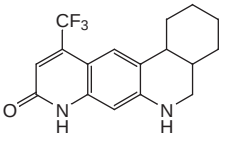
Nonsteroidal androgen receptor agonists

The androgens testosterone and dihydrotestosterone are important in male sexual and musculo-skeletal development. However, as the oral bioavailability of these compounds is poor, androgen deficiency is normally treated using transdermal patches or intramuscular injection. A recent paper from Ligand Pharmaceuticals Inc. (San Diego, CA, USA) describes the synthesis and evaluation of a series of androgen receptor agonists based on 4-alkyl-, 4,4-dialkyl- and 3,4-dialkyl-1,2,3,4-tetrahydro-8-pyridono[5,6-*g*]quinoline [Higuchi, R.I. *et al.* (1999) *Bioorg. Med. Chem. Lett.* 9, 1340–1355]. A number of compounds, exemplified by (**9**), were found to be as effective as agonists as dihydrotestosterone in both competitive receptor binding and androgen receptor cotransfection assays.



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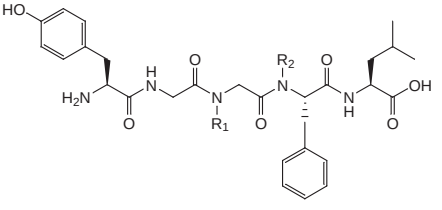
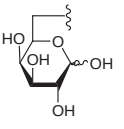
Profiles

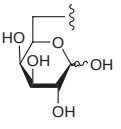
Sugar-based peptidomimetics

The opioid receptors, μ, δ and κ, and their subtypes, are involved in the control of various aspects of the perception of pain, pleasure and mood as well as the regulation of immune function. The development of selective opioid receptor ligands offers the potential for improving clinical treatments involving these systems. In the search for potent opioid ligands, the two endogenous opioid peptides, Leu- and Met-enkephalin (H-Tyr-Gly-Gly-Phe-Leu/Met-OH) make an ideal template and many selective and conformationally restricted analogues of those peptides have been prepared.

In the course of such studies, Horvat, Š. and coworkers [*J. Chem. Soc. Perkin Trans.* 1 (1998) 1789–1795] produced novel types of sugar-based peptidomimetics (**10,11**) related to the pentapeptide Leu-enkephalin, in which Gly^2 (**10**), or both Gly^2 and Gly^3 residues (**11**), were replaced by an *N*-alkylated glycine residue bearing a 6-deoxy-D-galactose moiety. The synthesis of the mono- and the bis-glycated pentapeptide were performed in a stepwise manner in solution by employing *N*-glycated glycine as the building block. The incorporated carbohydrate element in (**10,11**) offers applications in molecular recognition studies and might serve as a point of attachment (through the unsubstituted anomeric centre) for amino groups of proteins and other biologically active amines.



10 R_1 =  R_2 = H

11 $R_1 = R_2$ = 

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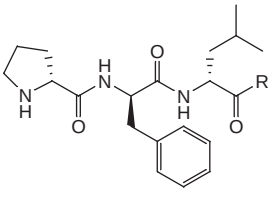
Combinatorial chemistry

A new fibrinogen receptor motif

The Arg-Gly-Asp tripeptide motif is well known to bind to the platelet gpIIbIIIa fibrinogen receptor and has been the basis for the design of a large number of novel non-peptidic inhibitors. Using combinatorial chemistry, a novel motif of unnatural amino acids has been discovered [Thorpe, D.S. *et al.* (1999) *Biochem. Biophys. Res. Commun.* 256, 537–541].

Having demonstrated that a bead-based library of pentapeptides of the structure Tyr-X-X-Asp-Val (where X is 1 of 19 L-amino acids) could be used to reveal the Arg-Gly-Asp motif through the staining of beads containing active sequences, the project moved on to explore unnatural peptide sequences. Using 18 D-amino acids plus glycine to generate an on-bead library of pentapeptides, the motif D-Pro(D-Phe/D-Tyr)D-Leu (**1**) was identified. The most active compound detected had an IC_{50} value of 14 μM.



1

Intriguingly, these compounds lacked the carboxylic acid of the Arg-Gly-Asp sequence that is presumed to bind calcium, and molecular modelling was employed to suggest a mode of molecular recognition. A reversed binding mechanism was noted, which is often observed with D-amino acid mimetics, and the model also proposed that π-electrons substituted for the carboxylic acid of Arg-Gly-Asp. This library discovery offers a number of new opportunities for the design and synthesis of novel integrin inhibitors.

Novel screening methodology

A novel screening method for combinatorial libraries has been employed in the detection of pentapeptides that bind weakly to tryptophan [Sugimoto N. *et al.* (1999) *J. Chem. Soc. Chem. Commun.* 677–678]. This new method

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