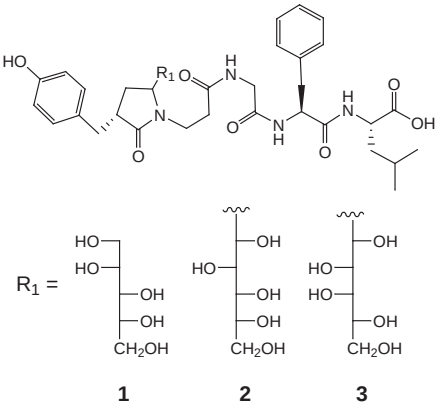
Monitor: molecules and profiles

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.

Hexose-related imidazolidinones

The reducing sugars, such as glucose, can react nonenzymatically with proteins, glycoproteins, lipids and nucleic acids to produce diverse carbohydrate adducts known as advanced glycation end products (AGEs). AGEs arise from a succession of chemical steps that begin with spontaneous addition of reducing sugars to amino groups forming reversible Schiff bases. Initially, these adducts rearrange to form keto-sugars, or Amadori products, but over time, further reactions occur such as dehydrations, rearrangements, fragmentation and the formation of highly reactive carbonyl compounds. These compounds continue to react with free amino groups, resulting in cross-linking of molecules. This complex reaction, known as the Maillard reaction, contributes to pathophysiological changes associated with diabetes and ageing processes.

Using the sugar-peptide model systems, Horvat, Š. and coworkers have recently gained a better insight into the mechanisms and products of the Maillard reaction by demonstrating that, in addition to the Amadori rearrangement, an alternative pathway of glycation is possible yielding imidazolidinones (**1–3**) from initially formed hexose-peptide



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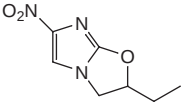
adducts [*Chem. Commun.* (1998) 1663–1664]. The imidazolidinones (**1–3**) are obtained by intramolecular rearrangement of 6-O-peptidyl monosaccharide esters. Hydrolysis of the ester bond led to the corresponding chiral imidazolidinones of D-mannose (**1**), D-glucose (**2**) or D-galactose (**3**). These compounds are useful in understanding the details of the mechanism of nonenzymatic glycation *in vivo*.

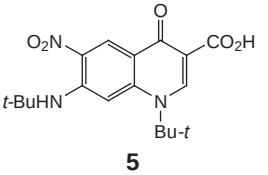
Antimycobacterial agents

Although nitroheterocycles have been widely studied as potential agents for the treatment of bacterial, fungal and protozoal infections, there are limited reports on the antimycobacterial activity of these types of compounds. 2-Ethyl-2,3-dihydro-6-nitroimidazo[2,1-b]oxazole (**4**) was previously shown to have potent *in vitro* and *in vivo* antimycobacterial activity, but has subsequently been found to be mutagenic.



4

Artico, M. and coworkers have recently reported the synthesis and evaluation of a novel range of nitroquinolones as potential antimycobacterial agents [*Bioorg. Med. Chem. Lett.* (1999) 9, 1651–1656]. The compounds were evaluated against both Gram-positive and Gram-negative bacteria and against various mycobacteria. 1-*t*-Butyl-7-*t*-butylamino-6-nitro-1,4-dihydro-4-quinolone-3-carboxylic acid (**5**) proved to be more potent *in vitro* against *Streptococcus* and *Staphylococcus* than ofloxacin and ciprofloxacin. This 6-nitroquinolone was also shown to be effective against



5

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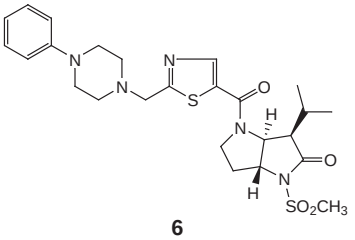
Mycobacterium tuberculosis and other atypical mycobacteria.

Leukocyte elastase and macrophage metalloelastase inhibitors

The destruction of the alveolar walls by leukocytes as part of the inflammatory process in the lung has been long associated with the development of pulmonary emphysema particularly in smokers. The destruction of the alveolar cell walls has been traditionally associated with the degradation of the fibrous protein elastin by human leukocyte elastase. However, recent evidence has suggested that tissue macrophages might play a role in this process as these cells have a greater lifetime in the tissue, and macrophage metalloelastases have been shown to be more effective at degrading elastin than leukocyte elastase. Inhibitors of both these enzymes could therefore have a role in the treatment of pulmonary emphysema.

The therapeutic potential of leukocyte elastase and macrophage metalloelastase inhibitors in this field has been reviewed in an extensive article by Skiles, J.W. and Jeng, A.Y. [*Expert Opin. Ther. Pat.* (1999) 9, 869–895]. This review describes the array of compounds described in the conventional and patent literature over recent years that have been shown to be effective inhibitors of both these enzymes. Some of the most interesting compounds highlighted by this review are those leukocyte elastase inhibitors, such as (**6**), recently patented by Glaxo Group Ltd. Some of these agents have been shown to have an effective oral dose of less than 10 mg kg^{-1} and provide a duration of action of at least six hours in an *in vivo* hamster assay.



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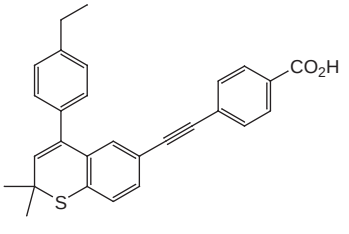
High-affinity retinoic acid receptor-antagonists

Recent retinoid research has demonstrated the importance of these molecules in the control of normal cellular processes. Retinoids function as modulators of gene transcription both in embryogenesis and in the subsequent maintenance of cellular functions such as proliferation and differentiation. There are two known retinoid receptors, the retinoic acid receptors and the retinoid X-receptors. The natural ligands for these receptors differ in their geometric isomeric forms with all-*trans* retinoic acid being the endogenous ligand for the retinoic acid receptors and the 9-*cis*-retinoic acid the proposed endogenous ligand for the retinoid X-receptors.

Retinoic acid receptor-antagonists have potential uses in the prevention of retinoid-induced toxicity caused by systemic retinoid treatment such as Accutane™. As part of a programme of research into the development of novel retinoid receptor ligands, workers at Allergan Inc. (Irvine, CA, USA) have synthesized and evaluated a range of novel retinoic acid receptor antagonists [*Bioorg. Med. Chem.* (1999) 7, 1321–1338]. Binding, transcriptional and *in vivo* assays have identified the 2,2-dimethylthiochromene analogue (**7**) as a potential antidote for the treatment of retinoid-induced activity. This compound is presently in preclinical development as a topical agent for the treatment and prevention of mucocutaneous toxicity caused by systemic retinoids.



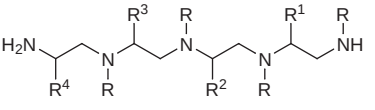
7

Combinatorial chemistry

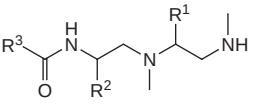
Novel antitumour agents

A new strategy has been described that combines the combinatorial synthesis of several libraries and the testing of these compounds against 60 different cell-based antitumour screens at the National Cancer Institute (Bethesda, MD, USA) [Appel, J.R. *et al.* (1999) *Mol. Divers.* 4, 91–102]. Five different combinatorial libraries consisting of peptides, peptidomimetics, polyamines or small molecules were initially prepared and tested against three representative cell lines to identify the most active library types. Following this investigation, the search was narrowed down to two libraries based on *N*-perbenzylated pentamine structures (**1**) and *N*-acylated permethylated triamines (**2**).

The libraries were prepared on solid support using the 'tea-bag' method for simultaneous multiple synthesis. The



1 R = benzyl



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mixtures were generated by using a range of building blocks in proportions previously shown to yield equimolar ratios of products. The *N*-perbenzylated pentamines were constructed from a total of 52 building blocks, giving a final library size of 7,311,616 compounds. The *N*-acylated permethylated triamines also used 52 monomers to give a library size of 454,272 compounds. In each case, the synthetic route employed a borane reduction to reduce peptide intermediates to polyamines.

Active compounds were tested in mice to determine the maximum tolerated dose, followed by screening against

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