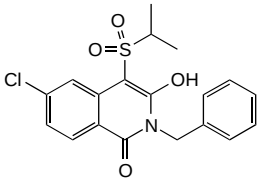
Monitor: molecules and profiles

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.

Novel COX-2 inhibitors

Recent evidence suggests that the gastrointestinal and renal toxicity observed on administration of nonsteroidal anti-inflammatory drugs (NSAID) may be attributed to inhibition of the COX-1 isoform of cyclooxygenase, whilst the anti-inflammatory action is associated with inhibition of the COX-2 isoforms. This implies that specific inhibitors of COX-2 would have a better therapeutic index. Various pharmaceutical companies have therefore recently focused on the identification of selective COX-2 inhibitors.



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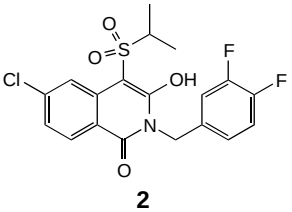

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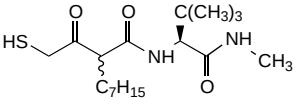
Lazer, E.S. and coworkers have recently reported the preparation of a series of 2-benzyl-4-sulphonyl-4*H*-isoquinoline-1,3-diones from which were identified several selective inhibitors of COX-2 in both microsomal and cellular assays [*Bioorg. Med. Chem. Lett.* (1998) 8, 1181–1186]. Compounds **1** and **2** were also shown to have anti-inflammatory activity in the carrageenan-induced paw oedema model when orally administered at 30 mg kg^{-1}.

Matrix metalloproteinase inhibitors

Matrix metalloproteinases (MMPs) are responsible for the remodelling of extracellular matrix throughout the body. Inhibitors of these enzymes have been been suggested as potential therapeutic agents for use in the treatment of various disease states including cancer, arthritis and auto-immunity. More recently it has been shown that MMPs may also have a role in the release of soluble cytokine receptors, growth factors and other cell mediators, suggesting that selective MMP inhibitors may have wider therapeutic applications than previously proposed.

Typically, MMP inhibitors include a ligand that binds to the zinc atom in the catalytic site and a peptidic moiety that binds to the particular peptide-specific binding site of the target MMP. A collaborative group comprised of workers from Affymax Research Institute (Santa Clara, CA, USA) and Wyeth-Ayerst Research (Princeton, NJ, USA; Pearl River, NY, USA) have recently described the synthesis of a novel series of MMP inhibitors incorporating a terminal α-mercaptoketone or α-mercaptoalcohol as a zinc binding ligand [Campbell, D.A. *et al. Bioorg. Med. Chem. Lett.* (1998) 8, 1157–1162]. From these compounds the group were able to identify compounds with nanomolar activity against collagenase-1 (MMP-1), stromelysin (MMP-3) and gelatinase-B (MMP-9), exemplified by compound **3** (IC_{50} = 15 nM, 16 nM and 0.3 nM for MMP-1, MMP-3 and MMP-9, respectively).



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A second paper from the same collaborative group describes a series of succinyl-based mercaptoketones and diasteromeric mercaptoalcohols, such as **4** and **5** [Levin, J.I. *et al. Bioorg. Med. Chem. Lett.* (1998) 8, 1163–1168]. A direct comparison of these compounds with the analogous malonyl-based compounds described in the first paper showed no difference in reactivity between the two series. A comparison of the activity of these compounds with the MMP inhibitor Ro319790 (**6**) in the same assays demonstrated that the appropriately substituted mercaptoalcohols and mercaptoketones have

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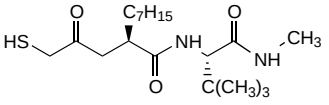
similar potency to the corresponding hydroxamic acid-based inhibitors against MMP-1 and may offer improved potency against MMP-3 and MMP-9.



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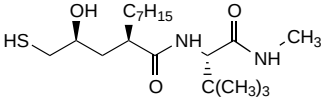

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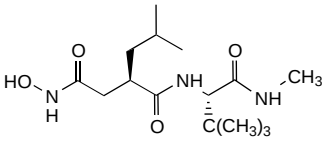

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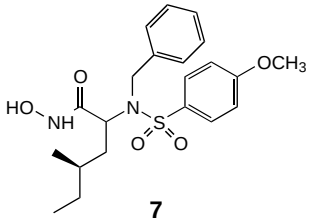
Macrophage metalloelastase inhibitor

The release of proteolytic enzymes by macrophages at sites of chronic inflammation can result in localized tissue damage. Recent evidence has suggested that macrophage metalloelastase (MME) may be involved in the pathogenesis of emphysema through the degradation of elastin in the lung alveolar wall. MME inhibitors may therefore be useful therapeutic agents for the treatment of such diseases. Workers from Novartis Pharmaceuticals (Summit, NJ, USA) have recently reported an investigation into the structural requirements of sulphonamide-based hydroxamic acids for the inhibition of MME [Jeng, A.Y., Chou, M. and Parker, D.T. *Bioorg. Med. Chem. Lett.* (1998) 8, 897–902]. These studies have led to the identification of series of potent inhibitors of MME, with the most potent, exemplified by **7**, having IC_{50} values of between 5 and 6 nM.



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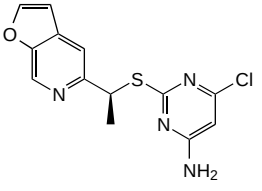
HIV-1 non-nucleoside reverse transcriptase inhibitor

Despite the recent success with triple combination therapy using nucleoside reverse transcriptase inhibitors in conjunction with protease inhibitors in the fight against HIV, the emergence of drug resistance is still a major concern. The rapid rates of viral replication and turnover offer the potential for the formation of quasi-species from which drug-resistant strains emerge during drug therapy. There is therefore still a need to develop new, more-potent compounds that will target these drug-resistant species. Workers at Pharmacia & Upjohn (Kalamazoo, MI, USA) have described the synthesis, and antiviral and preliminary pharmacokinetic evaluation of (−)-6-chloro-2-{[1-furo(2,3-c) pyridin-5-yl-ethyl]thio}-4-pyrimidinamine (PNU142721, **8**) as a potential broad-spectrum non-nucleoside reverse transcriptase inhibitor [Wishka, D.G *et al. J. Med. Chem.* (1998) 41, 1357–1360] This compound was found to offer a significantly improved antiviral profile over Pharmacia & Upjohn's existing marketed non-nucleoside reverse transcriptase inhibitor delavirdine, being 50-times more potent against a laboratory strain of wild-type HIV-1 and extremely potent against variant viruses selected for by other non-nucleoside reverse transcriptase inhibitors. The potent activity and favourable pharmacokinetic profile of this compound has led to its selection for further clinical development.



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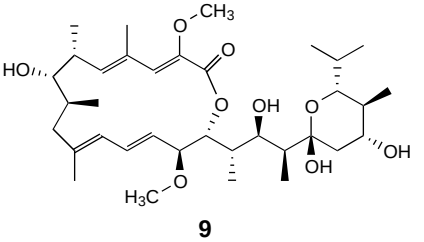
Bone resorption inhibitors

Postmenopausal osteoporosis is caused by an inbalance in the bone remodelling process where the rate bone resorption by osteoclasts exceeds that of bone regeneration by osteoblasts. Bone resorption requires the secretion of acid into the sealed microcompartment beneath the osteoclasts to dissolve the bone minerals and provide the necessary acidic environment required by matrix metallaproteinases that degrade the bone matrix. The localized acidic environment is maintained by the presence of vacuolar-type H^+-ATPases on the ruffled border of the osteoclast. These vacuolar-type H^+-ATPases are therefore a potential therapeutic targets for the inhibition of osteoclast activity in the treatment of osteoporosis.

Using the the specific vacuolar-type H^+-ATPase inhibitor bafilomycin A1 (**9**) as a template, Gagliardi, S. and coworkers have designed a new class of potent and selective inhibitors based on 5-(5,6-dichloro-2-indolyl)-2-methoxy-2,4-pentadienamides as osteoclast proton-pump inhibitors [*J. Med. Chem.* (1998) 41, 1568–1573]. These compounds, exemplified by **10**, were shown to be potent inhibitors of vacuolar-type H^+-ATPases in chicken osteoclast membranes and to inhibit bone resorption by human osteoclasts at low nanomolar concentrations *in vitro*.



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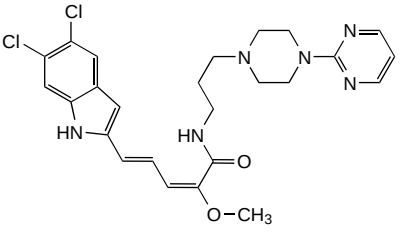

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