Monitor: molecules and profiles

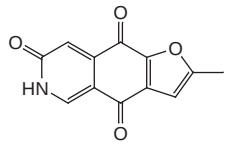
Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and 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.

Molecules

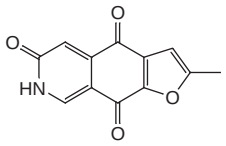
Quinonic derivatives active against *Toxoplasma gondii*

The *Toxoplasma gondii* parasite has been associated with both congenital and encephalitic toxoplasmosis. Congenital toxoplasmosis, caused as a result of maternal infection, can lead to abortion in the first three months or to neurological and ophthalmological problems if infection occurs later in pregnancy. Although drugs such as pyrimethamine are effective against the infection, it appears that the parasite forms cysts in cerebral tissue that are resistant to such agents. These cysts remain dormant in normal individuals but become reactivated in immunodeficient patients leading to encephalitic toxoplasmosis.

As part of a programme of work in search of drugs active against *T. gondii*, Nebois, P. and coworkers have prepared and evaluated furoisoquinolinetriones (**i**) and (**ii**) and various quinonic derivatives against the virulent RH strain of *T. gondii*[1]. In parasite growth inhibition studies in the human myelomonocytic

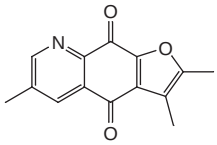


(i)



(ii)

cell line THP-1, the group identified the two benzofuran compounds (**i**) and (**iii**),



(iii)

which have activities similar to that of pyrimethamine with no associated cytotoxicity. The group intends to further evaluate these compounds *in vivo* using a murine model.

1 Nebois, P. *et al.* (2000) Quinonic derivatives active against a virulent strain of *Toxoplasma gondii*. Synthesis of 2-methylfuro[2,3-*g*]- and [3,2-*g*]isoquinolinetriones. *Bioorg. Med. Chem. Lett.* 10, 871–873

Dual cytokine regulators

The proinflammatory cytokine tumour necrosis factor α (TNFα) has been associated with the pathology of septic shock and a wide range of autoimmune diseases including rheumatoid arthritis, Crohn's disease and multiple sclerosis. The anti-TNFα chimera antibody has been used effectively for the treatment of several of these diseases and various low-MW compounds have been reported that inhibit TNFα production. Interleukin 10 (IL-10), an anti-inflammatory cytokine, also suppresses the production of TNFα and has been shown to be clinically effective in the treatment of steroid-resistant Crohn's disease and rheumatoid arthritis. Agents that regulate both TNFα and IL-10 might therefore have a synergistic effect in the treatment of TNFα-associated diseases.

Workers from Yoshitomi Pharmaceutical Industries (Saitama, Japan) have recently reported the synthesis and biological evaluation of a novel series of phenylpiperazine derivatives that both suppress TNFα production and enhance IL-10 production on oral administration[2].

A lead compound (**iv**) was initially identified from the screening of an anti-inflammatory compound library for agents that regulate both TNFα and IL-10 in lipopolysaccharide (LPS)-stimulated mice. Lead optimization of this compound led to the identification of compound (**v**) with potent and selective effects on the production of

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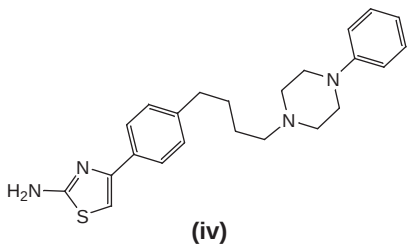

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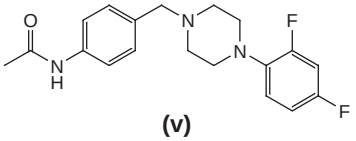
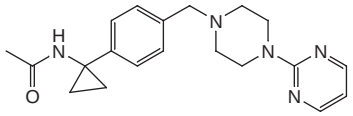


(v)

TNFα and IL-10. This compound was subsequently shown to dose-dependently protect mice against a lethal challenge of LPS, offering protection against shock death at 10 mg kg^{-1}. Furthermore, the compound has good oral bioavailability on administration to female mice at 30 mg kg^{-1}. This compound might therefore prove to be a useful drug candidate for the treatment of TNFα-associated diseases including septic shock.

A second paper by the same group showed that another series of compounds that suppress TNFα and augment IL-10 production might be effective as disease-modifying anti-rheumatic drugs[3]. The group synthesized a series of arylpiperazines for evaluation in a chronic inflammatory rat model based on the lead compound (**iv**), which possesses dual cytokine regulation *in vitro*. Structure optimization studies have subsequently led to the identification of compound (**vi**) as a potential drug candidate for the treatment of rheumatoid arthritis.



(vi)

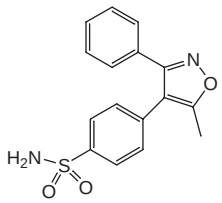
2 Hanano, T. *et al.* (2000) Novel phenylpiperazine derivatives as dual cytokine regulators with TNFα suppressing and IL-10 augmenting activity. *Bioorg. Med. Chem. Lett.* 10, 875–879

3 Hanano, T. *et al.* (2000) Novel DMARDs on the basis of a new concept of dual cytokine regulation, TNFα suppression and IL-10 augmentation activity. *Bioorg. Med. Chem. Lett.* 10, 881–884

Injectable COX-2 inhibitor: parecoxib sodium

Selective inhibitors of COX-2 are widely recognized as offering advantages over existing commercially available non-steroidal anti-inflammatory drugs (NSAIDs) through minimization of the side effects associated with COX-1 inhibition including gastric ulceration and bleeding. Few NSAIDs are administered parenterally for the treatment of pain and inflammation because of their limited aqueous solubility, and those taken orally can lead to severe side effects. The problem of poor aqueous solubility also limits the parenteral administration of the common diarylheterocycle-based COX-2 inhibitors.

In an attempt to overcome this problem, workers from Searle Research and Development (Skokie, IL, USA) have used a prodrug approach[4]. The group acylated the isoxazole sulfonamide COX-2 inhibitor (**vii**) with an anhydride to obtain the corresponding acylated sulfonamide, which was then converted to the corresponding sodium salt (**viii**) by treatment with sodium hydroxide.



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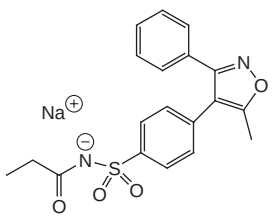


(viii)

This agent was shown to be efficacious in a therapeutic model of acute pain and offered advantages over the most potent analgesic NSAIDs ketorolac. The drug, named parecoxib sodium, is presently under clinical evaluation for the treatment of acute pain.

4 Talley, J.J. *et al.* (2000) *N*-[[(5-methyl-3-phenylisoxazol-4-yl)-phenyl]sulfonyl]-propanamide, sodium salt, parecoxib sodium: a potent and selective inhibitor of COX-2 for parenteral administration. *J. Med. Chem.* 43, 1661–1663

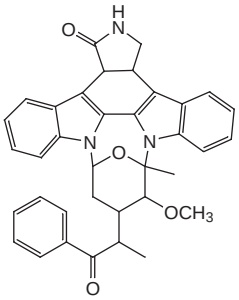
Ocular angiostatic agents

Although angiogenesis is important in the normal development of the eye, continued postnatal proliferation will result in a variety of ocular disorders that might result in blindness. There are several avascular tissues in the eye including the cornea, lens and vitreous that must remain optically transparent to enable the focussing of light onto the retina. Several diseases lead to vascularization of these tissues and there has been a considerable effort in recent years to develop novel approaches to inhibit the growth of such blood vessels.

Various fields have contributed to our understanding of the angiogenesis process including oncology and wound healing. This complex process involves the release of angiogenic factors leading to activation of receptor linked pathways that modulate the gene expression of control proteins and extracellular proteases. The extracellular proteases degrade the vascular endothelial cell basement membrane and extracellular matrix. Angiogenic factors also stimulate the migration of activated vascular endothelial cells to the site of angiogenesis where differentiation into new blood vessels occurs.

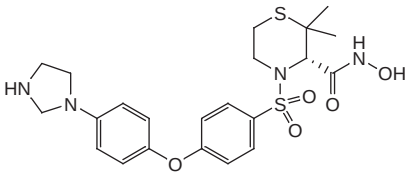
The numerous processes that might be targeted to control angiogenesis are highlighted in a recent review by Clark, A.F. and coworkers[5]. This describes the use of:

- Inhibitors of proangiogeneic growth factor stimulation such as the general signal transduction inhibitor, midostaurin (**ix**)



(ix)

- Antagonists of proangiogenic growth factors
- Matrix metalloproteinase inhibitors such as (**x**) presently under development for the treatment of age-related macular degeneration



(x)

- Inhibitors of vascular endothelial cell proliferation and migration.

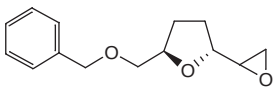
It is clear from the number of agents presently in clinical trials that the availability of new drugs to treat ocular angiogenesis will serve to provide opportunities to ensure the maintenance of vision of our ever increasing aged population. However, the delivery of an agent to a specific region of the eye at a therapeutic concentration will undoubtedly present a significant challenge.

5 Clark, A.F. *et al.* (2000) Ocular angiostatic agents. *Exp. Opin. Ther. Patents* 10, 427–448

Rationally designed anticancer drug

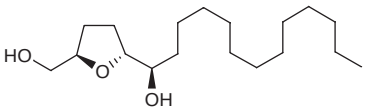
Microtubules, formed by self-association of αβ tubulin heterodimers, have an important role in mitotic spindle assembly and cell division. Drugs, such as taxol and vinc alkaloids, which bind to tubulin are effective anti-cancer agents.

Uckun, F.M. and coworkers have used computer-based molecular modeling to construct a three-dimensional model of tubulin using the recently resolved electron crystallographic structure of this molecule[6]. This led to the identification of a unique, previously unrecognized, drug binding cavity on the surface of tubulin. A structure search of the company's organic compound files led to the identification of the chiral tetrahdrofuran (THF) epoxide (**xi**) as a potential molecular template



(xi)

for the rational synthesis of novel anticancer agents. Computer-based structural optimization led to the identification of (**xii**), which provided



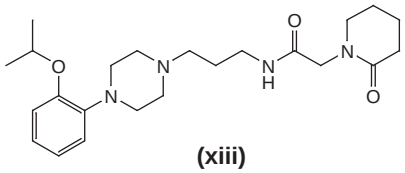
(xii)

improved binding to the tubulin binding cavity. Synthesis of this compound and subsequent evaluation of its anticancer activity against human cancer cell lines, using an MTT-based assay, confirmed the activity of this compound. Further structural optimization might provide useful therapeutic agents targeting this particular binding domain.

6 Uckun, F.M. *et al.* (2000) A rationally designed anticancer drug targeting a unique binding cavity of tubulin. *Bioorg. Med. Chem. Lett.* 10, 1015–1018

Selective α_1-adrenoceptor antagonists

The nonmalignant enlargement of the prostate (benign prostate hyperplasia) is a common occurrence in men caused by a combination of the enlargement of the prostate gland and increased smooth muscle tone of the bladder neck and prostate. The smooth muscle tone is regulated by α_1 adrenoceptors. Administration of α_1-receptor antagonists reduces the smooth muscle tone, alleviating the obstructive symptoms. Adrenoceptors are found throughout the body and are also involved in the regulation of blood pressure, nasal congestion and other processes. However, various subtypes have been identified in recent years and, in particular, the human prostatic smooth muscle is populated with primarily α_{1a} receptors. The development of subtype-selective receptor antagonists might therefore provide therapeutic drugs with reduced side effects to treat benign prostate hyperplasia.



(xiii)

Li, X. and coworkers have recently described the synthesis and evaluation of a novel series of arylpiperazines, exemplified by (**xiii**), as potential α_{1a}-receptor antagonists[7]. These compounds were found to be potent, selective antagonists with some having high affinities for membrane-bound α_{1a}-receptors (K_i <0.7 nM). These compounds might offer a potentially useful approach to the treatment of benign prostatic hyperplasia in the future.

7 Murray, L.X. *et al.* (2000) Novel arylpiperazines as selective α_1-adrenergic receptor antagonists. *Bioorg. Med. Chem. Lett.* 10, 1093–1096

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