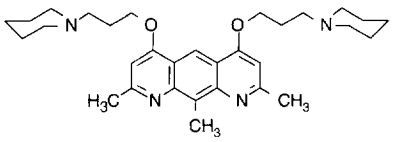
Monitor: molecules and profiles

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, 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, therapeutic advances, emerging molecular targets, novel technology, advances in synthetic and separation techniques and legislative issues.

Novel antimalarial

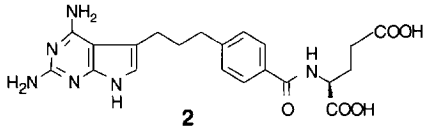
Chloroquine-resistant strains of *Plasmodium falciparum* present a serious problem in the treatment of malaria in various parts of the world. The lack of alternative therapeutic agents against such strains of *Plasmodium falciparum* has led Matias, C. and coworkers [*Heterocycles* (1996) 43, 1621–1632] to investigate the antimalarial activity of novel pyrido[3,2-*g*]quinoline derivatives. Series of 4,6-dialkoxy and 4,6-bis(alkylthio)pyrido[3,2-*g*]quinolines were prepared from 2,8,10-trimethylpyrido [3,2-*g*]quinoline-4,6-dione and their antimalarial activities were evaluated against the chloroquine-susceptible D6 and the chloroquine-resistant W2 *Plasmodium falciparum* clones. Compound **1** was found to be particularly effective against both strains (IC_{50} < 100 nM) and may offer potential as a future antimalarial drug.



1

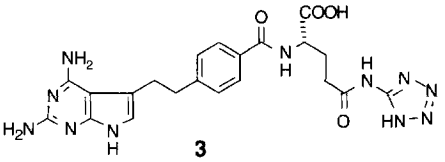
Non-glutamate type antifolates

The antifolate methotrexate has been widely used in the treatment of acute lymphocytic leukemia and choriocarcinoma over recent decades. However, a number of methotrexate-resistant tumours have been identified that have defects in methotrexate intracellular transport or polyglutamylation activity, which are essential for enzyme inhibition. A group from Takeda Chemical Industries Ltd have recently described a novel dihydrofolate reductase inhibitor *N*-{4-[3-(2,4-diamino-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)propyl] benzoyl}-L-glutamic acid (**2**, TNP351), which was shown to have potent antitumour activity against solid tumours *in vivo* [Akimoto, H. *et al. Proc. Am. Assoc. Cancer Res.* (1995) 54, 97–107].



2

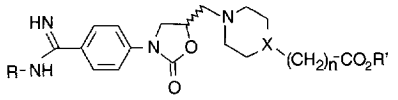
In a more recent paper this group reports the synthesis and antitumour activity of a series of N^5-substituted glutamine analogues of TNP351 [Itoh, F. *et al. Chem. Pharm. Bull.* (1996) 44, 1498–1509]. All the analogues were found to be more potent inhibitors of dihydrofolate reductase (DHFR) than TNP351, and selected compounds were found to be effective against methotrexate-resistant human CCRF-CEM cells in culture. The activities of a number of the glutamine analogues were examined *in vivo* against murine leukemia and solid tumours. The tetrazole analogue **3** was found to be effective against two types of methotrexate-resistant human CCRF-CEM cells and had the most potent activity *in vivo*. The potent activity of these compounds has been attributed to the combined effects of their potent inhibition of DHFR and their likely uptake *via* the reduced folate carrier-mediated transport system.



3

Bioavailable antithrombotic RGD mimetics

Antithrombotic peptidomimetic analogues of RGD have therapeutic utility in the treatment of a wide variety of pathological conditions including thrombosis, myocardial infarction and thrombotic stroke. Gante, J. and coworkers [*Bioorg. Med. Chem. Lett.* (1996) 6, 2425–2430] have described a new class of antithrombotic RGD mimetics based on a central oxazolidinonemethyl moiety, as illustrated by **4**, with good oral bioavailability and potency.



4

X = CH or N
n = 1 or 2

New azole antifungals

Miyauchi, H. and coworkers from Sumitomo Pharmaceutical Company (Osaka, Japan) have described the synthesis and antifungal properties of a series of azole derivatives containing an oxathiane ring [*Bioorg. Med. Chem. Lett.* (1996) 6, 2377–2380]. The 3,3-dimethyl derivatives, such as **5**, were shown to be particularly

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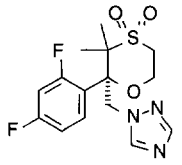
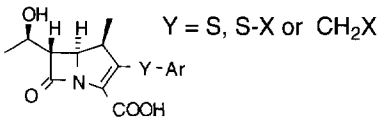
effective against murine systemic candidosis and and aspergillosis.



5

Antibacterial lipophilic carbapenems

The need for new antimicrobial agents to address the recent increased prevalence of antibiotic-resistant infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci (MRCNS) has led Arnould, J.C. and coworkers to investigate the use of lipophilic carbapenems [*Bioorg. Med. Chem. Lett.* (1996) 6, 2449–2454]. The broad-spectrum carbapenem antibiotics are used widely to treat serious infections, but lack efficacy against methicillin-resistant staphylococci and penicillin-resistant enterococci. Arnould, J.C. and coworkers prepared series of sulphur-linked and carbon-linked lipophilic carbapenems (**6**) and evaluated their antibacterial activity *in vitro* and *in vivo*. These compounds were found to exhibit good activity against Gram-positive strains that are resistant to existing carbapenems.



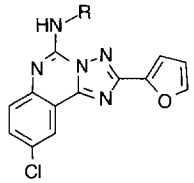
6

Novel linear polyene antibiotics

Sakuda, S. and coworkers from Osaka University (Osaka, Japan) have isolated two novel polyene antibiotics, linearmycin A and B from the mycelial extracts of a *Streptomyces* species. These compounds have long carbon chains of either 60 or 62 carbons with amino and carboxylic acid terminals and were found to possess antimicrobial activity against *Staphylococcus aureus, Escherichia coli, Saccharomyces cerevisiae, Candida albicans* and *Aspergillus niger*. Of particular interest is the fact that linearmycin is the first reported example of a simple linear polyene antibiotic with antifungal activity.

A_3 receptor ligands

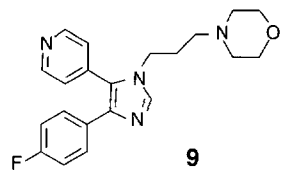
The A_3 adenosine receptor subtype has been shown to be involved in mediation of inflammation, hypotension and mast cell degranulation and may therefore be a useful therapeutic target for the treatment of a number of disease states including central inflammation and ischemia. Kim, Y-C., Ji, X-D. and Jacobson, K.A. [*J. Med. Chem.* (1996) 39, 4142–4148] report the high-affinity binding (K_i = 14 nM) of the adenosine antagonist 9-chloro-2-(2-furanyl) [1,2,4]triazolo[1,5-c]quinazolin-5-amine (**7**, CGS15943) to cloned human A_3 receptors, although the compound lacks affinity for the rat A_3 receptors. *N*-Acylation of this compound was found to increase affinity and selectivity for the human A_3-receptors with the 5-*N*-phenylacetyl derivative (**8**) being 470-fold more selective for the human A_3 receptor than the rat A_1 receptor (K_i = 0.65 nM).



7 R = H
8 R = $COCH_2Ph$

Cytokine suppressive drugs

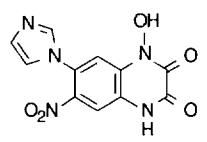
4-Aryl-5-pyridinylimidazoles have previously been shown to bind to the human homologue of murine protein kinase p38 and inhibit the biosynthesis of inflammatory cytokines. Such compounds have been termed CSAIDs and may be useful as an alternative to non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of inflammatory diseases such as arthritis. The use of NSAIDs is limited by their associated side-effects, and NSAIDs treat the symptoms of inflammation rather than the disease process. The advantage of CSAIDs is that they disrupt the signalling pathways initiated by inflammatory stimuli, thereby treating the underlying disease process leading to inflammation. Workers from SmithKline Beecham Pharmaceuticals (King of Prussia, PA, USA) have prepared series of 4-aryl-5-pyridinylimidazole derivatives, and investigated their binding to the target kinase, known as the CSAID binding protein (CSBP), and their inhibition of lipopolysaccharide-stimulated TNF production in mice [*J. Med. Chem.* (1996) 39, 3929–3937]. A number of compounds were shown to have strong affinity for the CSPB and showed potent inhibition of TNF biosynthesis. Compound **9**, which was shown to be a potent CSPB ligand and inhibitor of TNF biosynthesis while having minimal inhibitory effect on arachidonate metabolism, was evaluated for anti-arthritic activity in the AA rat model of arthritis. This compound was found to significantly reduce oedema and increase bone mineral density in this model, demonstrating that the modulation of inflammatory cytokine biosynthesis is effective in treating such inflammation without the need for direct inhibition of arachidonate metabolism.



9

Novel AMPA receptor antagonists

The α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) subtype of the excitatory amino acid (EAA) receptors has recently been shown to be involved in neurodegeneration after cerebral ischemia and AMPA antagonists were found to exhibit neuroprotective properties in model systems. Ohmori, J. and coworkers [*J. Med. Chem.* (1996) 39, 3971–3979] have described the synthesis and structure–activity relationships of a series of novel AMPA receptor antagonists. 1-Hydroxy-7-(1*H*-imidazol-1-yl)-6-nitro-2,3(1*H*,4*H*)-quinoxalinedione (**10**) was shown to have high affinity for the AMPA receptor (K_i = 21 nM) and a 100-fold selectivity for the AMPA receptor over the *N*-methyl-D-aspartate (NMDA) EAA receptor.



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