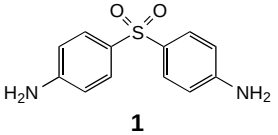
Monitor: molecules and profiles

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 antinephritic agent

The treatment of nephritis, inflammation of the kidney, is presently limited to the use of corticosteroids, such as prednisolone, and immunosuppressants, such as cyclophosphamide. As part of an attempt to identify safer antinephritic agents, a research group from Fujisawa Pharmaceutical Co. (Osaka, Japan) has previously demonstrated that dapsone (**1**), which is clinically used for the topical treatment of leprosy and dermatitis herpetiformis, is effective against graft-versus-host disease, which is considered an experimental model for human lupus nephritis. However, the systemic administration of dapsone is limited by its associated blood toxicity.



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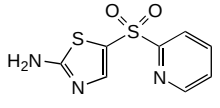

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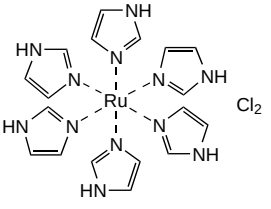
The group has now reported the synthesis of a series of dapsone-related 4-aminophenyl and 2-aminothiazolyl derivatives and the evaluation of their antinephritic activity and blood toxicity [Ogino, T. *et al. Bioorg. Med. Chem. Lett.* (1998) 8, 75–80]. 5-(2-Pyridylsulphonyl)-2-thiazolamine (**2**, FR115092) was found to have a similar potency and pharmacological profile to dapsone, when evaluated using two nephritis models, but without the associated blood toxicity and mutagenicity.

Novel immunosuppressants

Although immunosuppressants are widely used in the treatment of autoimmune diseases and the prevention of graft rejection following transplantation surgery, current therapy fails to address fully the issues of toxicity and efficacy. Bastos, C.M, Gordon, K.A. and Ocain, T.D. have undertaken a screening programme to identify novel compounds



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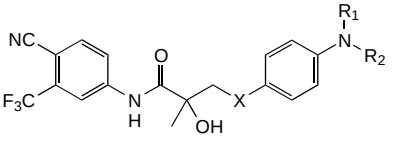
that inhibit T-cell proliferation *in vitro* at concentrations in the low nanomolar range [*Bioorg. Med. Chem. Lett.* (1998) 8, 147–150]. This has led to the identification of a potentially new therapeutic class of immunosuppressive agents based on ruthenium complexes. The most potent of these compounds (**3**) was shown to inhibit T-cell proliferation with an IC_{50} = 5 nM, which compares favourably with two existing immunosuppressants, cyclosporin A and rapamycin.

Nonsteroidal androgen receptor agonist

Androgen receptor antagonists have potential applications in male contraception and hormone replacement therapy. Kirkovsky, L. and coworkers have recently reported the synthesis of the enantiomers of a series of compounds (**4**) as structural analogues of bicalutamide, a known androgen antagonist [*ACS Meeting* (1998) 29 March – 2 April, Dallas, TX, USA, Abstr. Medi 055]. The *R*-isomers were found to have higher binding affinities to the androgen receptor than bicalutamide, and in transfection experiments using an androgen receptor expression vector and a



R_1 and R_2 = H, $COCH_3$, $COCH_2CH_3$ or $COCH_2Cl$

X = S or SO_2

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Monitor Editor: **Andrew W. Lloyd**, Department of Pharmacy, University of Brighton, Cockcroft Building, Moulsecoomb, Brighton, UK BN2 4GJ. tel: +44 1273 642049, fax: +44 1273 679333, e-mail: a.w.lloyd@brighton.ac.uk

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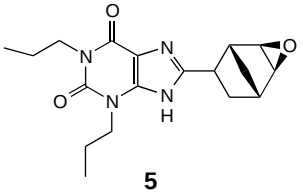
luciferase reporter vector containing androgen DNA response elements, the molecules were shown, unlike bicalutamide, to be full androgen receptor agonists. The authors believe that these molecules represent the first nonsteroidal full agonists of androgen receptors reported to date.

A_1 adenosine receptor antagonist

Selective A_1 adenosine receptor antagonists have potential use in the treatment of oedema associated with congestive heart failure. A paper by Petter, R.C. (Biogen, Cambridge, MA, USA) described the highly selective A_1 adenosine receptor antagonist BG9719 (**5**) at the recent *ACS Meeting* in Dallas, TX, USA (Abstr. Medi 094). This potent molecule (K_i = 0.5 nM) is 400, 2,000 and 9,000 times less active at A_{2B}, A_{2A} and A_3 receptor subtypes, respectively, than at the A_1 receptor subtype. The combined potency and selectivity of this compound suggests that it will inhibit proximal-tubule-mediated reabsorption and oppose vasoconstriction of the afferent arterioles in the kidney. Studies using saline-loaded normal rats have shown that BG9719 increases urine output and sodium excretion but does not affect potassium excretion. The drug is presently being evaluated in Phase II clinical trials.



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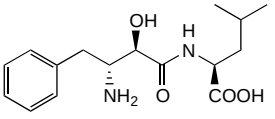
Potent nonpeptide aminopeptidase N inhibitors

Proteolytic degradation of the extracellular matrix is an important part of the process by which metastasizing tumour cells pass through connective tissue barriers. Aminopeptidase N is an exopeptidase that binds to membranes as an ecto-enzyme. Previous studies have shown that tumour cell invasion is inhibited by monoclonal antibodies to aminopeptidase N, and that bestatin (**6**), a potent inhibitor of aminopeptidase N, inhibits tumour invasion and matrix degradation *in vitro*. Bestatin has also been shown to inhibit metastasis of leukaemia and melanoma in mice.



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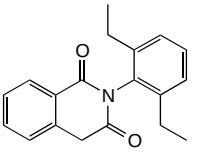
Like several other potent aminopeptidase N inhibitors, bestatin is a pseudodipeptide, which limits its clinical usage because of low bioavailability, proteolytic degradation, biliary excretion and short duration of action. Nonpeptidic analogues of these inhibitors may therefore be useful therapeutic agents.

Miyachi, H. and coworkers have described the discovery of *N*-phenyl cyclic imide derivatives as nonpeptide aminopeptidase N inhibitors [*J. Med. Chem.* (1998) 41, 263–265]. These compounds were shown to be specific inhibitors of aminopeptidase N, with some being more potent than bestatin and other naturally occurring aminopeptidase N inhibitors. The most potent of these molecules, for instance **7** (IC_{50} = 120 ng ml^{-1}), will be useful lead compounds for the future development of low molecular weight, nonpeptidic aminopeptidase N inhibitors for metastasis-preventing therapy.



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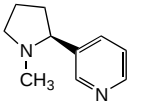
Neuronal nicotinic ACh receptor modulators

Neuronal nicotinic acetylcholine receptors (nAChRs) represent attractive targets for drug discovery [Holladay, M.W. *et al. J. Med. Chem.* (1997) 40, 4169–4194]. Studies in humans and animals have suggested beneficial effects of (*S*)-nicotine (**1**) for several disease states, including Alzheimer's disease, attention deficit hyperactivity disorder, Parkinson's disease, depression and schizophrenia. Moreover, epibatidine (**2**), an alkaloid from the skin of a South American frog, was recently shown to exhibit potent nAChR-mediated analgesic properties in rodents [Badio, B. *et al. Drug Dev. Res.* (1995) 36, 46–59]. Whereas side effects diminish the attractiveness of nicotine or epibatidine as therapeutic agents, the recognition that multiple subtypes of nAChRs exist raises the hope that new chemical entities will be discovered that differentiate beneficial from undesired effects.

The nAChRs are ion channels com-



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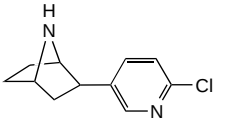

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prised of five subunits assembled around a central pore. It has been known for many years that the nAChRs mediating primary motor function in skeletal muscle and those mediating primary neurotransmission in autonomic ganglia are pharmacologically distinct. The existence of multiple subtypes in brain and other tissues has been implicated by the diverse pharmacology exhibited by various ligands. Moreover, numerous nAChR subunits have been identified that are not only differentially distributed in the CNS, but that can also assemble in various combinations in artificial expression systems to form functional ion channels with diverse pharmacological properties. Two of the major subtypes in brain (termed $\alpha4\beta2$ and $\alpha7$ based on their component subunits) have been pharmacologically characterized. While it is clear that neuronal nAChRs are involved in the release of various neurotransmitters, including acetylcholine, dopamine, serotonin, glutamate and

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