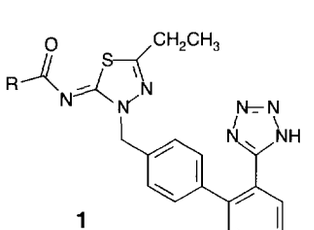
Monitor: molecules, synthesis and profiles

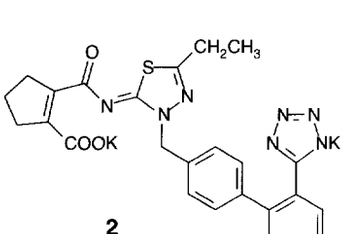
Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are three sections: *Molecules* summarizes the chemistry and the pharmacological significance and biological relevance of new molecules reported in the literature and on the conference scene; *Synthesis* outlines the latest advances in synthetic and separation techniques, approaches to the total synthesis of natural products of pharmaceutical relevance and the screening of new chemical entities; *Profiles* offers commentary on promising lines of research, emerging molecular targets, novel technology and legislative issues.

Orally active angiotensin II receptor antagonist

Inhibitors of the renin–angiotensin system are widely used in the treatment of hypertension and congestive heart failure. Recently, attention has been directed towards the use of angiotensin II receptor antagonists such as losartan. Hirata, T. and coworkers [*Bioorg. Med. Chem. Lett.* (1996) 6, 1469–1474] have described the synthesis and evaluation of a series of acyliminothiadiazoline derivatives **1** as a novel class of orally active angiotensin II receptor antagonists. Compound **2** was shown to exhibit the most potent activity in both *in vitro* and *in vivo* models. This compound was found to have good bioavailability in dogs and oral efficacy in hypertensive rats. On the basis of its pharmacological profile, it is now being progressed towards clinical evaluation.



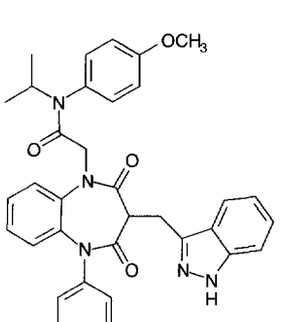
1



2

Novel satiety agent

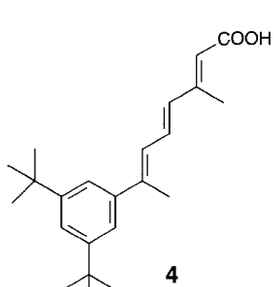
Workers at GlaxoWellcome (NC, USA) [Henke, B.R. *et al. J. Med. Chem.* (1996) 39, 2655–2658] have reported the synthesis and evaluation of a series of 3-(1*H*-indazol-3-ylmethyl)-1,5-benzodiazepines as orally active cholecystokinin-A (CCK_A) agonists. Indazole **3** was shown to bind selectively to the CCK_A receptor and to be orally active in the mouse-gallbladder-emptying assay. The group also discovered that this compound suppressed food intake on oral administration in a rat feeding model. This compound may therefore have therapeutic use as an orally active satiety agent for the treatment of obesity.



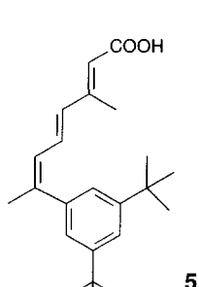
3

Novel antiproliferative retinoids

The ability of retinoids to control abnormal cellular processes through the intracellular retinoid receptors has led to their use for the treatment of particular cancers and dermatological diseases. Zhang, L. and coworkers [*J. Med. Chem.* (1996) 39, 2659–2663] have described



4



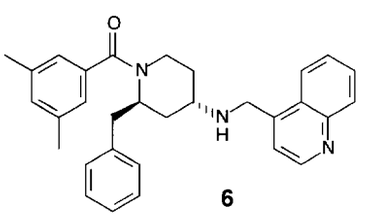
5

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

  1359-6446/96/$15.00. PII:S1359-6446(96)30083-4

the discovery of two novel retinoic-acid-receptor agonists, **4** and **5**, which have been shown to have potent activity in binding and cotransfection assays, and antiproliferative activity in human cervical carcinoma cells. Preliminary data on compound **4** suggest that this agent effectively inhibits the growth of human head and neck carcinomas in an *in vivo* xenograft mouse model. On the basis of these and other studies this compound has been selected as a possible clinical candidate for the treatment of a wide range of cancers.

Novel NK_1 antagonist

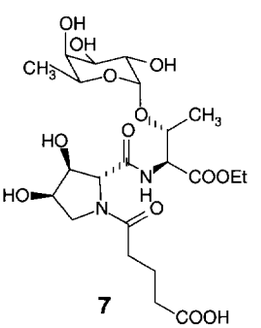


6

Ofner, S. and coworkers [*Bioorg. Med. Chem. Lett.* (1996) 6, 1629–1634] have described the synthesis and evaluation of a series of 2-benzyl-4-aminopiperidines as novel NK_1 antagonists for the potential treatment of the wide range of diseases with which substance P is now thought to be associated. In particular, compound **6** was found to be a potent and selective NK_1 receptor antagonist, and was shown to antagonize the CNS effect of substance P methyl ester on oral administration to gerbils.

Sialyl Lewis X mimetics

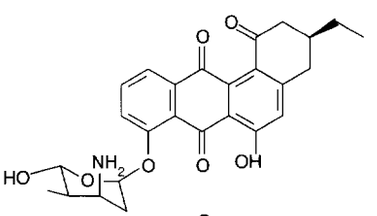
Although the E-selectin ligand sialyl Lewis X (SLe^x) saccharide can be manufactured on a large scale and is presently undergoing clinical trials as a new anti-inflammatory agent for the treatment of reperfusion injury and heart attack, it is unstable and orally inactive. Workers from the Scripps Research Institute (La Jolla, CA, USA) [Lin, C-C. *et al. J. Am. Chem. Soc.* (1996) 118, 6826–6840] have reported the synthesis and evaluation of several series of SLe^x mimetics, which were prepared using glycosyl phosphite methodology. The activities of the various fucopeptides were determined by assessing their ability to inhibit the binding of SLe^x-glycoconjugate to E-selectin. A number of these mimetics exhibited greater inhibitory binding activity against E-selectin than SLe^x (IC_{50} = 0.5 mM), with **7** being the most effective (IC_{50} = 0.05 mM).



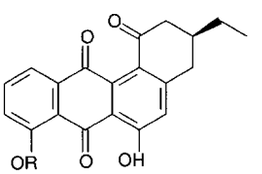
7

Brasiliquinones A–C

Tsuda and coworkers [*J. Chem. Soc., Perkin Trans. 1* (1996) 1773–1775] have described the isolation and structure elucidation of three new cytotoxic benz[*a*]anthraquinones, brasiliquinones A–C (**8–10**), from the actinomycete *Nocardia brasiliensis* IFM 0089. These compounds were found to be cytotoxic against various tumour cells *in vitro*, exhibited antibacterial activity against *Mycobacterium smegmatis*, *Micrococcus luteus*, *Staphylococcus aureus* and methacillin-resistant *Staphylococcus aureus* (MRSA), but showed no antifungal activity against *Aspergillus niger*. Brasiliquinone C was also found to inhibit epidermal growth factor receptor kinase and c-ErbB-2 kinase.



8



9 R = H
10 R = CH_3

About *Monitor*...

Monitor is a regular current awareness feature of *Drug Discovery Today*. Information is published in three separate sections: *Profiles*, *Molecules* and *Synthesis*.

Profiles offers commentary on promising lines of research, new technologies and progress in therapeutic areas. We welcome offers of contributions of 500–1,000 words for this series. Articles should provide an accurate summary of the essential facts together with an expert commentary to provide a perspective. Brief outlines of proposed *Profiles* articles should be directed to the *Monitor* Editor (see below). Articles for publication in *Monitor* are subject to peer-review and occasionally may be rejected or, as is more often the case, authors may be asked to revise their contribution. The *Monitor* Editor also reserves the right to edit articles after acceptance.

Molecules and *Synthesis* report on new bioactive compounds and the latest advances in synthetic and separation techniques. In order to ensure the currency of material published in these sections we welcome information on manuscripts recently accepted for publication in the primary literature.

All suggestions or queries relating to *Monitor* should be directed to: Dr Andrew W Lloyd, *Monitor* Editor, Department of Pharmacy, University of Brighton, Moulsecoomb, Brighton, UK BN2 4GJ. tel: +44 1273 642049, fax: +44 1273 679333, e-mail: a.w.lloyd@brighton.ac.uk.