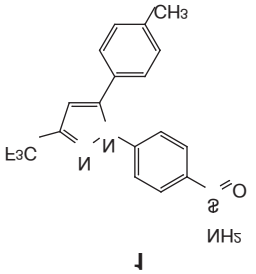
Monitor: molecules and profiles

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.

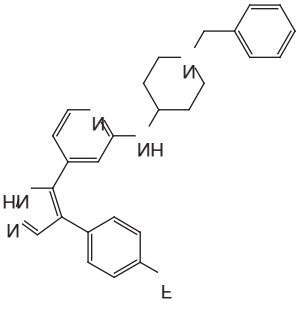
Novel structural classes of p38 kinase inhibitors

The serine–threonine p38 kinase, also known as MAP kinase or cytokine-suppressive anti-inflammatory drugs (CSAID)-binding protein (CSBP), regulates the production of cytokines and chemokines in response to various stimuli, such as stress, lipopolysaccharide, interleukin-1 and tumour necrosis factor. The kinase has been shown to be involved in various inflammatory disease states and is therefore a potential therapeutic target for the treatment of disorders such as rheumatoid arthritis.



1

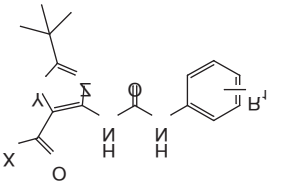
Two recent patents from workers at Bayer Corp. [WO9852558] and GD Searle & Co. [WO9852937] claim the use of structurally distinct p38 kinase inhibitors and these patents have been compared in a recent patent evaluation by Ashley Publishing Ltd [*Exp. Opin. Ther. Patents* (1999) 9, 477–480]. Searle's development of celecoxib (**1**), the selective inhibitor of inducible cyclooxygenase (COX-2), has led to an extensive evaluation of aryl-substituted pyrazole derivatives, including the aryl heteroarylpyrazole (**2**) described in this recent patent.



2

This compound was found to have an IC_{50} of 10 nM in an assay using PHAS-I substrate. The Bayer patent application describes the use of asymmetric bisarylurea derivatives exemplified by structure **3**. These compounds have been tested *in vitro* as inhibitors of recombinant human p38 kinase with the most potent of these compounds having IC_{50}s of 1 nM.

The patent evaluation also highlights the limitation presented by these compounds and concludes by indicating that we are likely to see additional patents filed in the future for improved compounds or modified templates.



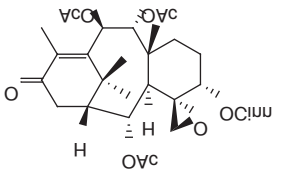
3

Modulation of multidrug resistance by taxinine derivatives

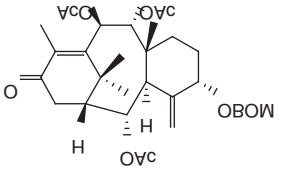
Multidrug resistance (MDR) to antitumour agents represents a significant challenge to effective chemotherapy. The P-glycoprotein efflux pump for hydrophobic antitumour drugs contributes significantly to the MDR of tumour cells. Studies have shown that compounds, such as verapamil, which bind to P-glycoprotein or compete directly for the efflux pump, can be used to increase the intracellular accumulation of antitumour drugs.

Monitor Editor: **Andrew W. Lloyd**, School of Pharmacy and Biomolecular Sciences, 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

 1359-6446/99/$ – see front matter PII: S1359-6446(99)01360-4



4



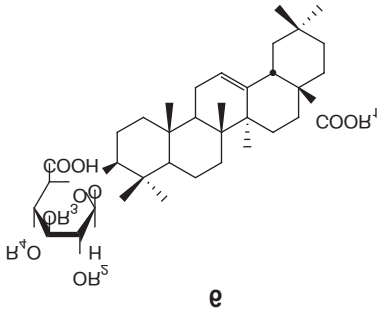
5

A recent paper from Hosoyama, H. and co-workers describes the synthesis and evaluation of taxinine derivatives as MDR modulators [*Bioorg. Med. Chem. Lett.* (1999) 9, 389–394]. This study led to the identification of two taxoids (**4** and **5**), which caused greater accumulation of vincristine in MDR tumour cells than verapamil and the identification of a further six compounds with activities comparable to verapamil. These studies suggest that these compounds are particularly effective modulators of MDR in tumour cells.

Controlling gastric emptying

Rapid gastric emptying in patients with diabetes mellitus results in an increased rate of food absorption and subsequently higher postprandial glucose levels. The control of gastric emptying is therefore important in the regulation of glucose homeostasis. Abnormalities in gastric emptying are common in diabetic patients and animal models, and other studies have indicated that obese individuals have faster gastric emptying rates than their corresponding healthy controls. Agents that regulate gastric emptying may therefore be useful in the prevention and treatment of diabetes and morbid obesity in patients with accelerated gastric emptying.

A recent paper from Matsuda, H. and co-workers has described the examination of the effects of various herbal



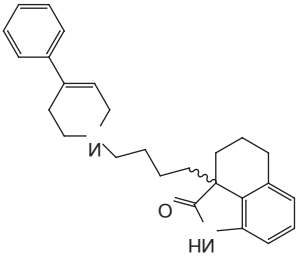
6

oleanic acid oligoglycosides on gastric emptying in non-nutrient meal- and nutrient meal-loaded mice [*Bioorg. Med. Chem.* (1999) 7, 323–327]. Several of the oleanic acid 3-*O*-monodessmosides (**6**) were found to have inhibitory effects on gastric emptying in mice following a 1.5% sodium carboxymethyl cellulose test meal, 40% glucose test meal, milk test meal or 60% ethanol test meal.

Tetrahydrobenzindoles as selective 5-HT$_7$ receptor antagonists

The 5-HT$_7$ receptor was recently identified through molecular cloning. The biological function of this receptor has yet to be fully elucidated. However, initial pharmacological studies indicate that the receptor may be involved in the vasodilation of blood vessels, and in the disruption of circadian rhythms occurring in jet lag, delayed sleep–wake disorder and non-24-h sleep–wake disorder. To improve the understanding of the role of this receptor, there is a need for selective ligands that may be used as pharmacological tools. A selective 5-HT$_7$ receptor antagonist (SB258719) was recently reported [Forbes, I.T. *et al.* (1998) *J. Med. Chem.* 41, 655–657] but, as yet, no selective agonists for the receptor are available.

A recent paper from Kikuchi, C. and co-workers has reported the synthesis and evaluation of a novel series of tetrahydrobenzindoles as potential 5-HT$_7$ receptor ligands [*J. Med. Chem.* (1999) 42, 533–535]. Many of these compounds were shown to have high

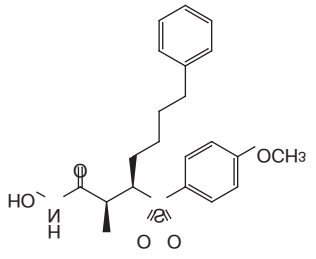


7

affinity and selectivity for the 5-HT$_7$ receptor. Compound **7** was found to be a highly potent ligand (pK_i = 8.67) with at least 47-fold selectivity for the 5-HT$_7$ receptor over the 5-HT$_2$ and other 5-HT receptor. An evaluation of 5-HT-induced stimulation of cyclic-AMP-(cAMP) accumulation in COS-7 cells expressing the 5-HT$_7$ receptor, confirmed **7** to be a 5-HT$_7$ receptor antagonist.

Dual inhibitors of phosphodiesterase type 4 and matrix metalloproteinases

Inhibition of the c-AMP-specific phosphodiesterase type 4 (PDE$_4$) in inflammatory and immune cell types causes elevation of intracellular levels of cAMP, resulting in a general suppression of proinflammatory cellular activity. PDE$_4$ inhibitors have been shown to be efficacious in both preclinical and clinical studies for diseases such as rheumatoid arthritis, multiple sclerosis and psoriasis. Similar results have been observed in clinical studies of matrix metalloproteinase (MMP) inhibitors. MMPs such as collagenase, stromelysin and gelatinase are involved in the degradation of the extracellular matrix. Although these enzymes normally play an important homeostatic role through the continual remodelling of the extracellular matrix under various pathological conditions, including those detailed above, these MMPs are often overexpressed, causing unnecessary damage to connective tissues and basement membranes. It may therefore be beneficial to modulate both the PDE$_4$ and MMP biological pathways.



8

A recent communication from workers at Rhône-Poulenc Rorer (Collegeville, PA, USA) describes the first compounds, exemplified by β-(arylsulfonyl)hydroamic acid **8**, which simultaneously inhibits both PDE_4 and the MMPs gelatinase, collagenase and stromelysin [Groneberg, R.D. *et al.* (1999) *J. Med. Chem.* 42, 541–544]. These compounds may be of use in the treatment of a wide range of inflammatory disorders.

Emerging therapeutic targets

Asthma treatments

The ultimate goal in the treatment of asthma is the development of orally active agents that will modify the underlying disease processes of asthma and reduce airway inflammation, hyperreactivity and bronchoconstriction. Current therapies tend to treat the symptoms of the disease rather than the disease processes, resulting in a polypharmacy approach to modern day asthma treatment. Although leukotrienes are important in the pathophysiology of asthma, the administration of leukotriene receptor antagonists alone fails to provide a single means of treating all of the symptoms of this multifaceted disease.

Recent research has provided a greater insight into the underlying mechanisms of asthma. This research indicates that asthma may be driven by dysregulation of T-lymphocyte function and a Th2-like (helper T2-lymphocyte) response. This dysregulation process may be controlled by the administration of specific immunomodulatory cytokines. Such an approach offers the potential advantage that the problems of generalized immunosuppression or hormonal dysregulation, which occur upon administration of steroids, may be avoided. However, given the pleiotropic effects of many cytokines, this may require specific delivery to the site of action.

A recent review by Cerasoli, F. discusses this potential use of immunomodulatory cytokines for the treatment of asthma and describes the application of regulated gene therapy as a means of delivering cytokines directly to the affected airway [*Emerging Therapeutic Targets* (1999) 3, 27–39]. The paper highlights the advantages of gene therapy for overcoming the problems normally associated with conventional cytokine therapy, such as poor oral bioavailability and expensive protein manufacture.

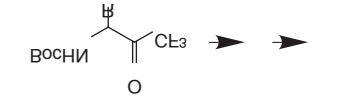
Another recent paper, from Levitt, R.C. and Nicolaides, N.C., highlights the important role that interleukin-9 plays in the pathogenesis of asthma [*Emerging Therapeutic Targets* (1999) 3, 41–51]. The paper also describes other approaches to suppressing the asthma-associated inflammatory cascade, including the use of immunoglobulin antagonists, adhesion molecule antagonists and cytokine antagonists. All of these therapeutic strategies have been shown in animal models to be effective in preventing or treating the underlying asthma-associated inflammation.

Andrew Lloyd

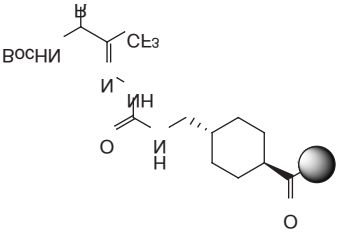
Combinatorial chemistry

Peptidyl trifluoromethyl ketones

Several serine proteases are attractive targets for pharmacological intervention. Consequently, there has been a concerted effort to find compounds that have an affinity for these enzymes, and the trifluoromethyl ketone group has been a key structural feature of substrate-based inhibitors of elastase, chymotrypsin and CMV protease. In order to accelerate the discovery of novel serine protease inhibitors, a solid-phase approach to the preparation of peptidic trifluoromethyl ketones has recently been disclosed [Poupart, M-A. *et al.* (1999) *J. Org. Chem.* 64, 1356–1361].



1



5

This approach relies on the use of a semicarbazone linker that can act as a reversible protecting group for the ketone. Various trifluoromethyl ketone synthons (**1**) were prepared and used to generate semicarbazides, which were in turn tethered to BHA polystyrene resin through an ester linkage (**2**). The linkage was stable under the conditions used to deprotect the amine and extend the peptide chain. At the end of the synthesis, the ketones could be regenerated from the resin by heating in aqueous HCl and acetic acid. Following semi-preparative HPLC, the desired products were isolated in 15–40% yields. The method has been used to prepare more than 100 trifluoromethyl ketones as potential HCMV protease inhibitors.

Tetanus toxin inhibitors

The bacterial protein, tetanus neurotoxin (TeNt) is a zinc endopeptidase that cleaves synaptobrevin selectively at the single peptide bond, Gln^{76}-Phe^{77}. As the substrate protein is an essential part of the neurotransmitter exocytosis apparatus, inhibition of the metallopeptidase would be a possible target for the treatment of tetanus. A recent study

1359-6446/99/$ – see front matter PII: S1359-6446(99)01362-8