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.

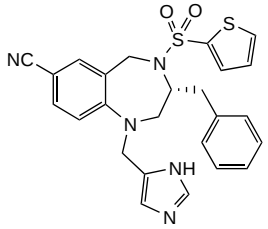
Monitor Editor: Debbie Tranter

Monitor Contributors:
David Barrett, *Fujisawa Pharmaceutical Company*
Steven Langston, *Millennium Pharmaceuticals*
Paul Edwards, *Pfizer*
Michael Walker, *Bristol-Myers Squibb*
Andrew Westwell, *Nottingham University*
John Weidner, *Emisphere*
Daniela Barlocco, *University of Milan*

Molecules

A potent farnesyltransferase inhibitor

The farnesylation of cytosolic Ras protein is the first key step in a cascade of events that ultimately result in the association of Ras with the cell membrane and initiation of normal cell signaling. Because abnormal cell signaling is related to mutation of *ras* genes, drugs that inhibit the farnesylation of Ras are potential anticancer agents. Inhibitors of farnesyltransferase (FT) have been the subject of intense interest in scientific research and several compounds have been advanced to human clinical trials. Recently, researchers at Bristol-Myers Squibb (New York, NY, USA) have identified the benzodiazepine derivative **(i)** as a novel, potent, nanomolar *in vitro* inhibitor that displays good oral *in vivo* efficacy in an HCT-116 human colon tumor model expressing mutated K-ras; this has been advanced to clinical trials[1].



(i)

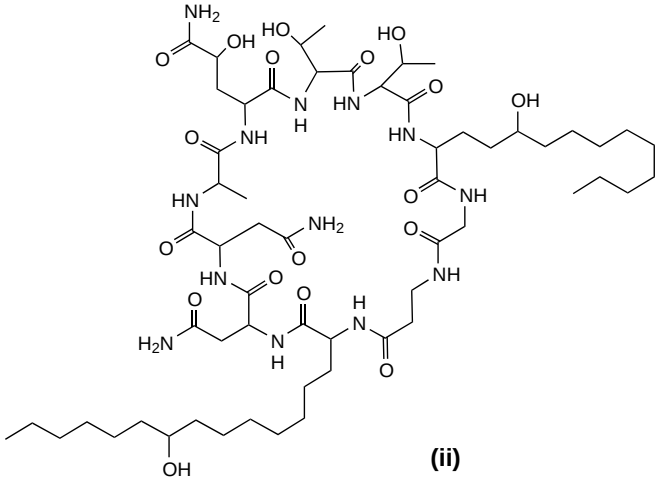
The identification of a tetrahydrobenzodiazepine scaffold bearing an imidazol-4-ylalkyl group at the 1-position as a lead compound, followed by optimization of *in vivo* activity by varying the substituents at other positions, led to improvements in potency, water solubility and selectivity compared with the related enzyme geranylgeranyl transferase 1 (GGT1). The optimized compound **(i)** displayed good *in vivo* efficacy in the HCT-116 model and an oral bioavailability of 56%.

1 Hunt, J.T. *et al.* (2000) Discovery of (*R*)-7-cyano-2,3,4,5-tetrahydro-1-(1*H*-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(2-thienylsulfonyl)-1*H*-1,4-benzodiazepine (BMS214662), a farnesyltransferase inhibitor with potent preclinical antitumor activity. *J. Med. Chem.* 43, 3587–3595

Novel 1,3-β-glucan synthase inhibitors

Several azole compounds and the polyene macrolide amphotericin B are the only approved drugs for the treatment of invasive fungal infections. However, new drugs are urgently required because of various limitations with these agents. The synthesis of fungal cell wall components is a potential target area for new drugs, and the fungal 1,3-β-glucan synthase complex is the target of two major classes of natural products: the papulacandins and the echinocandins. Several echinocandins are currently in clinical development as treatments for severe fungal infection. Recently, workers at Sankyo (Tokyo, Japan) have isolated a structurally novel series of lipopeptide natural products, arborcandins A–F, from the culture broth of a filamentous fungus. These were shown to inhibit the synthesis of 1,3-β-glucan, a key component of the cell wall of pathogenic fungi[2].

Arborcandin C **(ii)** demonstrated potent fungicidal activity against strains of *Candida albicans* and strong growth inhibition of *Aspergillus fumigatus*. This natural product was shown to be a



(ii)

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non-competitive inhibitor of the 1,3-β glucan synthase isolated from both types of fungal species, displaying IC_{50} values comparable to the echinocandin natural product pneumocandin Ao. Overall, these compounds appear to have potent *in vitro* antifungal activity, although not as potent as the echinocandins. This newly identified class of 1,3-β-glucan synthase inhibitors has expanded the range of known inhibitors of this enzyme and could be a lead for the development of new antifungal agents.

2 Ohyama, T. *et al.* (2000) Arborcandins A, B, C, D, E and F: novel 1,3-β-glucan synthase inhibitors: production and biological activity. *J. Antibiot.* 53, 1108–1116

Human mast cell tryptase inhibitors

Tryptase is one of the major secretory proteases produced by mast cells, which have an important role in the immune system. This protease is involved in the inflammatory response and, in particular, has been shown to have a role in the onset of asthma. Although the exact details of how tryptase functions within the immune system have not yet been fully elucidated, several potential mechanisms have been identified. Recently, a series of dibasic inhibitors of human tryptase have been identified[3,4], and the optimized compound **(iii)** advanced to Phase II clinical trials for the treatment of psoriasis and ulcerative colitis.

A *p*-xylylenediamine oligomer was initially identified as a potent inhibitor of tryptase with excellent selectivity over related proteases such as trypsin, thrombin and plasmin. Chemical optimization, focusing on improved metabolic stability and oral bioavailability, indicated a strict requirement for highly basic terminal groups, and a relative insensitivity of the central core scaffold with regard to overall potency. Compound **(iii)**, APC2059, demonstrated *in vivo* efficacy in a sheep model of allergic asthma after aerosol administration.

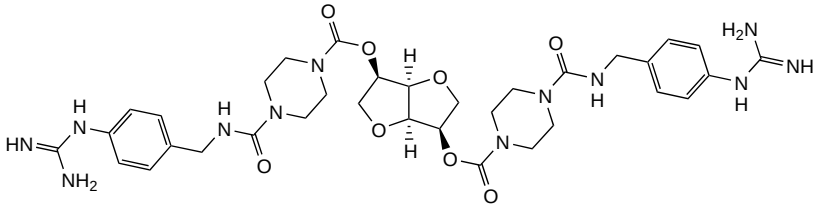
3 Rice, K.D. *et al.* (2000) Dibasic inhibitors of human mast cell tryptase. Part 1: synthesis and optimization of a novel class of inhibitors. *Bioorg. Med. Chem. Lett.* 10, 2357–2360

4 Rice, K.D. *et al.* (2000) Dibasic inhibitors of human mast cell tryptase. Part 2: structure–activity relationships and requirements for potent activity. *Bioorg. Med. Chem. Lett.* 10, 2361–2366

Selective inhibitors of glycogen synthase kinase-3

Glycogen synthase kinase-3 (GSK-3) is a serine-threonine protein kinase that is involved in many cell signaling pathways. Two forms of this kinase have been identified and it is known that elevated GSK-3 activity is a feature of several disease states, for example, non-insulin dependent diabetes mellitus (NIDDM). Selective inhibitors of this kinase, therefore, have potential as novel therapeutics.

Recently, workers at SmithKline Beecham (Welwyn, UK) have identified compounds **(iv)** and **(v)** as potent and selective inhibitors of GSK-3 (Ref. 5). Maleimides were identified as lead compounds by HTS against rabbit GSK-3α. Compounds **(iv)** and **(v)** were then identified and shown to be nanomolar *in vitro* inhibitors of both human GSK-3α and GSK-3β. Furthermore, these compounds did not significantly inhibit any of a series of 24 other protein kinases. Compounds (**iv**) and (**v**) increased glycogen synthesis in human liver cells by activating glycogen synthase, an enzyme inactivated by GSK-3-mediated phosphorylation.



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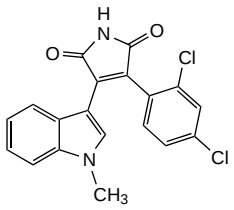

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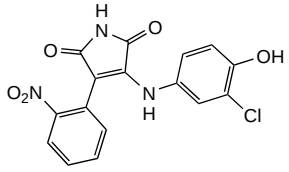


(v)

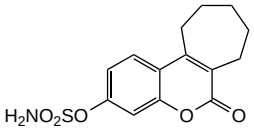
5 Coghlan, M.P. *et al.* (2000) Selective small-molecule inhibitors of glycogen synthase kinase-3 modulate glycogen metabolism and gene transcription. *Chem. Biol.* 7, 793–803

Novel steroid sulphatase inhibitors

Hormone-dependent breast cancer represents a significant proportion of all cases of breast cancer in post-menopausal women. Reduction of oestrogen levels by inhibition of aromatase, an enzyme that transforms androstenedione to oestrone, can be an effective means of disease management. Recently however, it has become clear that steroid sulphatase-mediated conversion of oestrone sulphate to oestrone now appears to be the main source of oestrogens in tumours, leading to treatment failure with aromatase inhibitors alone. Inhibition of the activity of steroid sulphatase is thus an attractive approach for improving the response of hormone-dependent breast tumours.

Recently, a series of steroid sulphatase inhibitors based on a non-steroidal coumarin sulphamate structure has been identified[6]. Earlier work with steroid-derived sulphamates led to potent inhibitors; however, the presence of a steroidal structure resulted in oestrogenic properties. The optimized compound in this new series **(vi)** was shown to be a potent irreversible inhibitor of steroid sulphatase and to possess oral activity. Most importantly, this compound was also shown to be non-oestrogenic

and is currently undergoing preclinical development.



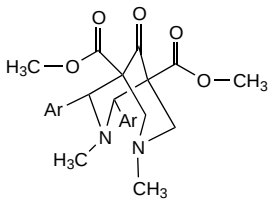
(vi)

6 Woo, L.L. *et al.* (2000) Potent active site-directed inhibition of steroid sulphatase by tricyclic coumarin-based sulphamates. *Chem. Biol.* 7, 773–791

3,7-Diazabicyclononane derivatives as opioid-receptor ligands

Pain is a complex and dynamic process involving multiple, inter-related neurotransmitter and neuromodulator systems in the spinal cord, in ascending and descending spinal pathways, and at supraspinal sites. Although several approaches have been shown to isolate new compounds that are able to effectively treat pain[7], the three major subtypes of the opioid receptors μ, δ and κ, are still primary targets. In particular, κ-agonists were initially thought to be devoid of the side effects of morphine. However, clinical trials showed the presence of dysphoria in several models[8]. This observation has led to the search for peripherally acting κ-agonists.

Researchers from the University of Würzburg (Würzberg, Germany) have previously identified the 2,4-di-2-pyridine-substituted-3,7-dimethyl-3,7-diaza-9-oxo-bicyclo[3.3.1]nonane-1,5-dicarboxylate **(vii)** as a selective κ-ligand that demonstrates strong antinociceptive activity[9]. More recently, they have reported[10] a series of compounds **(viii)**, that have substituted phenyl rings with different moieties at positions 2 and 4.



(vii) Ar = 2-pyridyl
(viii) Ar = substituted phenyl

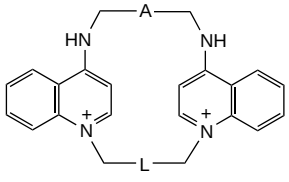
These new compounds have no affinity for the δ-receptor and show higher affinity for the κ-receptor over the μ-receptor. Compounds that have a *meta*-F (*m*.F) or *meta*-OH (*m*.OH) as well as a *para*-OCH_3 (*p*.OCH_3) on the phenyl rings were found to have a potency comparable with the model **(vii)**, (K_i = 0.015 μM on rat κ-opioid site). However, because of their poor solubility, several compounds could not be tested intravenously in the writhing test. In future, quaternization of the 7-nitrogen, which would direct the compound specifically to peripheral κ-opioid receptors, might aid the development of new peripheral κ-agonists.

7 Williams, M. *et al.* (1999) Emerging molecular approaches to pain therapy. *J. Med. Chem.* 42, 1481–1500
8 Kovaluk, E.A. *et al.* (1998) Novel molecular approaches to analgesia. *Annu. Rep. Med. Chem.* 33, 11–20
9 Holzgrabe, U. *et al.* (1994) Structurally novel group of ligands selective for κ-opioid receptors. *Regul. Pept.* 54, 27–28
10 Holzgrabe, U. *et al.* (2000) Synthesis and opioid receptor affinity of a series of 2,4-diaryl-substituted 3,7-diazabicyclononanones. *J. Med. Chem.* 43, 3746–3751

Non-peptidic blockers of apamin-sensitive Ca^{2+}-activated K^+ channels

Small conductance Ca^{2+}-activated K^+ (SK_{Ca}) channels occur in many cell types and have a variety of physiological roles. Apamin, a peptidic toxin from bee venom, potently blocks SK_{Ca} channels. However, alternative novel non-peptidic blockers are being sought that could have important therapeutic applications, such as increasing gastrointestinal motility. Moreover, SK_{Ca} channels are involved in the relaxation of blood vessels, and their aberrant expression causes several disorders in myotonic muscular dystrophy. The SK_{Ca} channels are also thought to be responsible for altered responses in the CNS.

Workers from University College London (London, UK) have previously identified a series of *bis*-quinolinium cyclophanes of the general type **(ix)**, as potent blockers of the SK_{Ca} channel[11]. In series **(ix),** A and/or L can be alkylene groups or moieties containing one or two aromatic rings. More recently, the group has reported[12] several *bis*-alkylene cyclophanes **(x)** (*n* = 3–10). These were able to block the SK_{Ca} channels at submicromolar concentrations. The highest activity was observed with the *n* = 5 compound and was significantly decreased in longer and shorter analogues. These results support the previously suggested hypothesis that the linkers do not interact with the channel in a direct way, but control the spatial arrangement of the molecule. In addition to being almost equipotent with apamin for blocking the SK_{Ca} channel in rat sympathetic neurons (IC_{50} = 2.7 ± 0.2 nM), the *n* = 5 compound was also shown to be highly selective for the channel, which makes it a useful tool for further studies.



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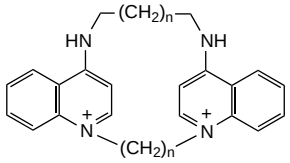

(x)

11 Ganellin, C.R. *et al.* (2000) Synthesis, molecular modelling and pharmacological testing of *bis*-quinolinium cyclophanes: potent, non-peptidic blockers of the apamin-sensitive Ca^{2+}-activated K^+ channel. *J. Med. Chem.* 43, 420–431
12 Ganellin, C.R. *et al.* (2000) *Bis*-quinolinium cyclophanes: 8,14-Diaza-1,7(1,4)-diquinolinacyclotetradecaphane (UCL1848), a highly potent and selective, non-peptidic blocker of the apamin-sensitive Ca^{2+}-activated K^+ channel. *J. Med. Chem.* 43, 3478–3481

David Barrett
Medicinal Chemistry Research Laboratories
Fujisawa Pharmaceutical Company
Osaka 532-8514, Japan
tel: +81 06 6390 1285
e-mail: david_barrett@po.fujisawa.co.jp

Daniela Barlocco
University of Milan
Viale Abruzzi, 42, 20131 Milano, Italy
tel: +39 02 29502223
e-mail: daniela.barlocco@unimi.it