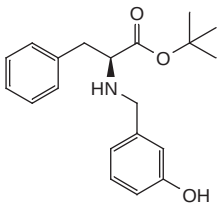
Monitor: molecules and profiles

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.

Molecules

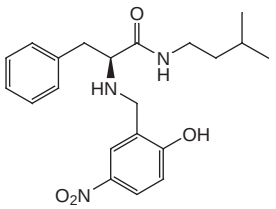
Leukocyte cell adhesion antagonists

The extravascular migration of leukocytes involves various receptor–ligand interactions mediated by selectins, integrins and chemokines. The overexpression of mucosal addressin cell adhesion molecule (MAdCAM) is known to be associated with increased infiltration of lymphocytes bearing the $\alpha_4\beta_7$ integrin in both murine and non-human primate models of inflammatory bowel disease. Workers from Millennium Pharmaceuticals (Cambridge, MA, USA) have previously identified (**i**) as an



(i)

inhibitor of MAdCAM-mediated lymphocyte adhesion. As an extension of this work, the group has recently reported the synthesis of a series of related phenylalanine-based inhibitors[1]. An evaluation of the inhibition of the adhesion of B-cell lymphoma RPMI 8866 cells to MAdCAM-coated microtitre plates identified (**ii**) as the most effective antagonist with an IC_{50} of 6 μM.

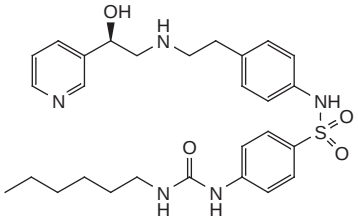


(ii)

1 Harriman, G.C. *et al.* (2000) Cell adhesion antagonists: synthesis and evaluation of a novel series of phenylalanine based inhibitors. *Bioorg. Med. Chem. Lett.* 10, 1497–1499

Potent β_3-adrenoceptor agonists as potential anti-obesity drugs

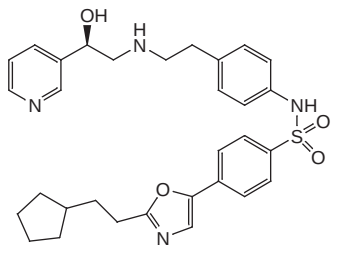
The discovery that the β_3 adrenoceptor regulates lipolysis and thermogenesis in brown adipose tissue has led to investigations by several groups into the use of β_3-adrenoceptor agonists as potential anti-obesity drugs. Workers from Merck Research Laboratories (Rahway, NJ, USA) have recently reported the identification of a series of 3-pyridylethanolamines, exemplified by (**iii**), as selective and highly potent β_3-adrenoceptor agonists[2,3]. Although these agents were shown to be effective at increasing lipolysis and energy



(iii)

expenditure in animals, they had poor oral bioavailability owing, in part, to extensive metabolism.

A recent paper from the same laboratories describes the substitution of the urea moiety on the aryl sulfonamides by oxazoles[4]. Several of these compounds were found to be potent, selective β_3-adrenoceptor agonists with excellent oral bioavailability in dogs. For example, (**iv**) had an EC_{50} of 14 nM, with a 340-fold and 160-fold selectivity over β_1 and β_2 adrenoceptors, respectively.



(iv)

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

 1359-6446/00/$ – see front matter ©2000 Elsevier Science Ltd. All rights reserved. PII: S1359-6446(00)01565-8

This compound had 38% oral bioavailability in dogs with a half-life of 5 h and was shown to evoke hyperglycerolemia when administered to dogs at 10 mg kg^{-1}. Furthermore, intravenous administration to monkeys also induced hyperglycerolemia (ED_{50} = 0.09 mg kg^{-1}) with no observed change in heart rate.

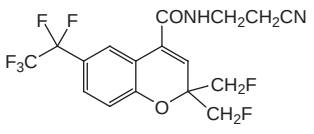
2 Parmee, E.R. *et al.* (1999) Human β_3 adrenergic receptor agonists containing cyclic ureidobenezenesulfonamides. *Bioorg. Med. Chem. Lett.* 9, 749–754

3 Naylor, E.M. *et al.* (1999) Human β_3 adrenergic receptor agonists containing imidazolidinone and imidazolone benezenesulfonamides. *Bioorg. Med. Chem. Lett.* 9, 755–758

4 Ok, H.O. *et al.* (2000) Substituted oxazole benzenesulfonamides as potent human β_3 adrenergic receptor agonists. *Bioorg. Med. Chem. Lett.* 10, 1531–1534

Novel potassium channel openers

It has been suggested that potassium channel openers would offer advantages over other antihypertensive drugs if the unwanted side effects associated with acute peripheral vasodilatation could be avoided. These side effects have been attributed to rapid elevations of the antihypertensive drugs in plasma levels after dosing. To overcome this problem, workers at Chugai Pharmaceutical Co. Ltd (Skizuoka, Japan) have been investigating the use of prodrugs that are converted to an active form after oral administration. As part of these studies, the group has identified *N*-(2-cyanoethyl)-2,2-bis(fluoromethyl)-6-pentafluoroethyl-2*H*-1-benzopyran-4-carboxamide (**v**) as a potent slow and



(v)

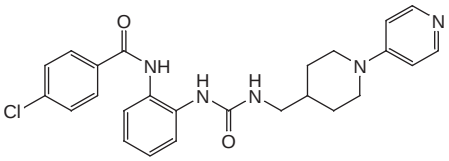
long-lasting hypertensive agent with reduced reflex tachycardia[5]. The onset of the hypotensive effect of this agent in hypertensive rats was gradual with a maximum response 6 h after dosing. At a dose of 0.1 mg kg^{-1}, the duration of action was >18 h. In addition, this agent offered benefits with respect to lipid metabolism. On administration for 2 weeks to hypertensive rat models, a significant and dose-dependent reduction in serum triglycerides to <70% of the control was observed with no effect on total cholesterol levels. This compound will be a useful lead candidate for the development of novel potassium channel opener-based antihypertensive agents.

5 Taka, N. *et al.* (2000) 6-Substituted 2,2-bis(fluoromethyl)-benzopyran-4-carboxamide K^1 channel openers. *Bioorg. Med. Chem.* 8, 1393–1405

Non-amidine-containing 1,2-dibenzamidobenzene inhibitors of human factor Xa

Human factor Xa is a trypsin-like serine protease that plays an important role in the coagulation of blood. Inhibitors of factor Xa offer potential as novel therapies for the treatment of thromboembolic disorders. Masters, J.J. and coworkers have recently reported the synthesis and evaluation of a novel series of non-amidine-containing 1,2-dibenzamidobenzene inhibitors of human factor Xa (Ref. 6).

The antithrombotic activity of (**vi**)



(vi)

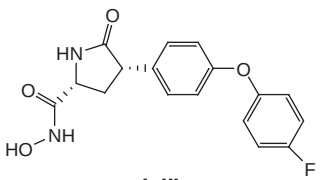
was comparable with that of the most potent amidine-based inhibitors *in vitro*. Intravenous administration to a rabbit arteriovenous shunt model *in vivo* also showed dose-dependent antithrombotic efficacy comparable to that observed for the potent amidine-based inhibitors. These potent and selective non-amidine-containing inhibitors of factor Xa will be useful tools for the further evaluation of the mechanism of competitive factor Xa inhibition as well as being potential lead compounds for the development of novel anticoagulants.

6 Masters, J.J. *et al.* (2000) Non-amidine-containing 1,2-dibenzamidobenzene inhibitors of human factor Xa with potent anticoagulant and antithrombotic activity. *J. Med. Chem.* 43, 2087–2092

Matrix metalloproteinase-13 inhibitor

Matrix metalloproteinase-13 (MMP-13) activity contributes to loss of cartilage in osteoarthritis. Inhibitors of this enzyme could therefore be useful in treating this disabilitating disease. Existing matrix MMP inhibitors are generally either substrate-like peptidomimetics or aryl sulfonamide-based hydroxamic acids. A recent paper from workers at Pfizer (Groton, CT, USA) describes the structure-based design and synthesis of novel, potent and selective MMP-13 inhibitors based on a pyrrolidinone ring scaffold[7].

The most potent of the compounds in the series is (**vii**), which has an IC_{50}



(vii)

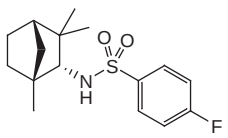
of 7 nM and at least tenfold selectivity for the MMP-13 over other matrix MMPs. Although this work has focussed on the development of matrix MMP-13 inhibitors, it is likely that further modifications of this structural template will yield potent and selective inhibitors of other MMPs.

7 Robinson, R.P. *et al.* (2000) Structure-based design and synthesis of a potent matrix metalloproteinase-13 inhibitor based on a pyrrolidinone scaffold. *J. Med. Chem.* 43, 2293–2296

Therapeutic agents for the treatment of Alzheimer's disease

The formation of insoluble plaques in the brain associated with Alzheimer's disease has been linked to the proteolytic processing of β-amyloid precursor protein. In particular, elevated levels of the relatively hydrophobic Aβ42 amyloid β peptide has been shown to be associated with early-onset familial Alzheimer's disease. The β-amyloid N-terminal residue cleavage is catalyzed by a recently characterized aspartic acid protease β-secretase. The β-amyloid C-terminal residue cleavage is catalyzed by a currently unknown protease(s) referred to as γ-secretase(s). The inhibition of these secretases would be expected to decrease the production of amyloid β peptides and thereby reduce the onset and progression of Alzheimer's disease.

A recent paper by workers at Amgen (Thousand Oaks, CA, USA) describes the identification of low-MW chemically stable fenchylamine sulfonamides as *in vitro* inhibitors of the γ-secretase proteolytic pathway[8]. The most potent compound was (**viii**), which inhibited



(viii)

the production of Aβ42 amyloid β peptide by 58% at 2.5 μM with an IC_{50} of 1.8 μM. These compounds will be useful leads for the development of inhibitors of the γ-secretase proteolytic degradation of β-amyloid precursor protein and small-molecule therapeutic agents for the treatment of Alzheimer's disease.

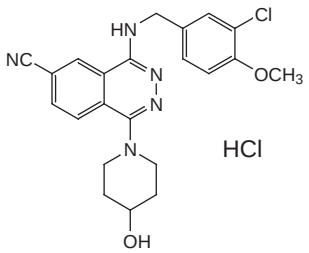
8 Rishton, G.M. *et al.* (2000) Fenchylamine sulfonamide inhibitors of amyloid β peptide production by γ-secretase proteolytic pathway: potential small-molecule therapeutic agents for the treatment of Alzheimer's disease. *J. Med. Chem.* 43, 2297–2299

Phosphodiesterase 5 inhibitor

Phosphodiesterase 5 (PDE5) is an isozyme of the cyclic nucleotide phosphodiesterase family that specifically hydrolyses cGMP. Recently, various potent PDE5 inhibitors have been reported to exert vasodilation, antihypertensive and penile erection-promoting effects.

A recent paper from Watanabe, N. and coworkers describes the synthesis of various 4-(3-chloro-4-methoxybenzyl)aminophthalazines as potential PDE5 inhibitors[9]. The vasorelaxation properties of these compounds was assessed using an isolated porcine coronary artery model in which the tissue was precontracted by treatment with prostaglandin F2α at 10 μM.

The most potent of these compounds was (**ix**), which had an IC_{50} of 560 pM



(ix)

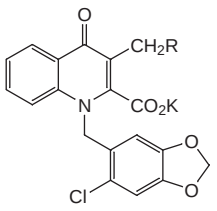
and >1700-fold selectivity for PDE5 over other PDE isozymes. This compound also had the most potent vasorelaxant action (EC_{50} = 13 nM) *in vitro* and reduced mean pulmonary arterial pressure by 29.9% on intravenous administration at 30 μg kg^{-1} to chronically hypoxic rats. Initial evaluations of oral bioavailability in rats has shown the compound to have an oral bioavailability of 19.5%, making this a useful compound for further biological evaluation.

9 Watanabe, N. *et al.* (2000) 4-(3-Chloro-4-methoxybenzyl)aminophthalazines: synthesis and inhibitory activity toward phosphodiesterase 5. *J. Med. Chem.* 43, 2523–2529

Endothelin A-receptor antagonists

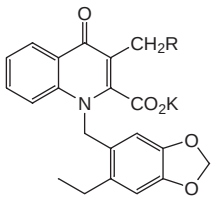
The endothelin A receptor (ET_A) is a G protein-coupled receptor that is selective for the endothelin 1 (ET-1) and ET-2 peptide ligands over ET-3. ET_A receptors are found on vascular smooth muscle cells where they mediate vasoconstriction and vascular smooth muscle cell proliferation. The other endothelin receptor, ET_B, is nonselective for the different endothelin peptides and mediates both vasoconstriction and vasodilatation depending on tissue location. Endothelin has been associated with several disease states including hypertension, acute renal failure, pulmonary hypertension, restenosis and stroke. Various selective and nonselective endothelin-receptor antagonists have been reported in recent years.

A recent paper from Haesslein, J-L. and coworkers has reported the design, synthesis and biological evaluation of a series of 2-carboxy quinolone compounds that act as selective antagonists for the ET_A receptor[10]. *In vivo* studies using the pithed rat assay indicated that compounds of type (**x**) and (**xi**)

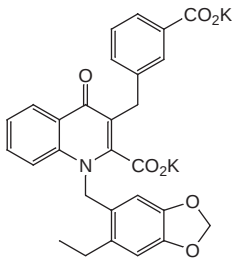


(x)

were effective ET_A-receptor antagonists. Optimization of these lead structures led to the identification of (**xii**). This compound had an ED_{50} of 0.1 mg kg^{-1}



(xi)



(xii)

in the pithed rat assay, a high receptor binding affinity of 690 pM for the ET_A receptor, and a >500-fold selectivity for ET_A over ET_B receptors. Furthermore, this compound was shown to be orally active against ET-1-induced death in mice (ED_{50} = 10 mg kg^{-1} administered orally).

10 Haesslein, J-L. *et al.* (2000) 1,3-Disubstituted -2-carboxy quinolones: highly potent and selective endothelin a receptor antagonists. *J. Med. Chem.* 10, 1487–1490

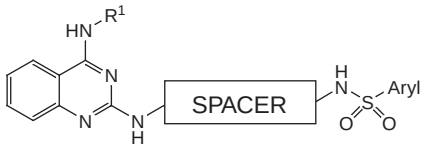
Andrew Lloyd

Combinatorial chemistry

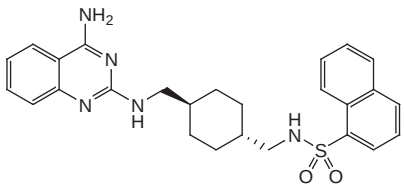
Neuropeptide Y-receptor antagonists

Neuropeptide Y (NPY) is the most abundant peptide in the mammalian brain, and at least six receptor subtypes have been characterized by pharmacological and molecular cloning techniques. It is highly conserved across species and is involved in several physiological responses and implicated in the pathophysiology of several disorders. Within the hypothalamus, NPY is intimately involved in the regulation of several aspects of neuroendocrine function and behaviour, in particular food intake.

Recently, the hypothetical 'feeding' NPY receptor Y_5 was cloned and expressed. Evidence was generated indicating that the Y_5 receptor is one of the primary mediators of NPY-induced feeding. A combinatorial approach using both solution- and solid-phase techniques was used to identify Y_5-subtype selective compounds[1]. A library of 500 individual compounds was prepared in solution, and a library of 360 individual compounds prepared on solid phase, both based on the motif (**i**).



(i)



(ii)

One of the most potent and selective compounds identified was (**ii**), which had a hY_5 IC_{50} of 2.9 nM, and possessed selectivity over the following subtypes: hY_1 (2886-fold), hY_2 (651-fold) and hY_4 (1979-fold). These libraries have enabled the identification of key pharmacophoric elements necessary for hY_5 selectivity, and have helped to elucidate the Y_5-subtype involvement in mediating food intake induced by NPY.

1 Rueeger, H. *et. al.* (2000) Design, synthesis and SAR of a series of 2-substituted 4-amino-quinazoline neuropeptide Y Y_5 receptor antagonists. *Bioorg. Med. Chem. Lett.* 10, 1175–1179

SH2-directed ligands of tyrosine kinase

Tyrosine-specific protein kinases are composed of two subfamilies: receptor tyrosine kinases, which are integral membrane proteins, and nonreceptor cytoplasmic counterparts. The former, on binding to specific extracellular ligands, forms aggregates and key tyrosine residues are subsequently phosphorylated. Cytoplasmic signalling proteins, including nonreceptor tyrosine kinases, bind to these phosphotyrosine (pTyr) residues through Src homology 2 (SH2) domains. This binding event triggers the activation of specific intracellular signalling pathways, ultimately leading to a cellular response in reaction to the extracellular stimulus.

SH2 domains play a crucial role in organising coherent signal transducing complexes that are essential for the appropriate cellular response to extracellular stimuli. Constitutively active signal transduction pathways have been identified in many disease states such as certain cancers and autoimmune diseases. Ligands that are able to disrupt these inappropriately hyperstimulated pathways, by blocking SH2 domain-dependant interactions, could ultimately find utility as therapeutic targets.

Ligands directed against the Lck SH2 domain could serve in various capacities, such as for the treatment of autoimmune diseases and T cell-based leukaemias and lymphomas. A combinatorial chemistry approach has been used to determine which residues of the tetrapeptide peptide ligand (**iii**) are

Ac–pTyr–Glu–Glu–Ile–NH_2

(iii)

crucial for binding to the SH2 domain[2]. One library of 84 individual compounds was synthesized on Tentagel S NH_2 resin and was used to determine whether the Glu–Glu residue of (**iii**) is essential for binding to the SH2 domain. This was used to guide the synthesis of a second library of 900 individual compounds, also synthesized on Tentagel S NH_2 resin, for the purpose of acquiring non-amino acid mimetics for the P+4 Ile moiety.

One of the most potent compounds prepared from this library was (**iv**),

 1359-6446/00/$ – see front matter ©2000 Elsevier Science Ltd. All rights reserved. PII: S1359-6446(00)01566-X