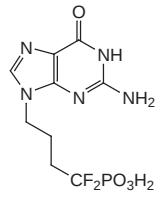
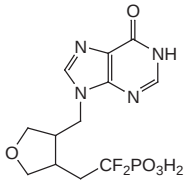
nucleoside phosphorylase inhibitor reported so far is 9-(5,5′-difluoro-5′-phosphonopentyl)guanine (**iv**).



iv



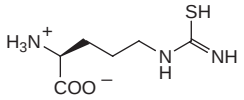
v

A recent paper by Yokomatsu, T. and coworkers has described the synthesis of conformationally constrained *cis*- and *trans*-analogues of this compound (**v**) (Ref. 3). Both analogues are potent inhibitors of purine nucleoside phosphorylase isolated from *Cellulomonas* sp. with IC_{50} values of 35 and 37 nM, respectively. However, the *cis*-isomer is a more potent inhibitor of human erythrocyte purine nucleoside phosphorylase (IC_{50} = 88 nM) than either the *trans*-isomer (IC_{50} = 320 nM) or compound (**iv**) (IC_{50} = 380 nM).

3 Yokomatsu, T. *et al.* (1999) Synthesis and biological evaluation of 1,1-difluoro-2-(tetrahydro-3-furanyl)ethylphosphonic acids possessing a N9-purinylmethyl functional group at the ring. A new class of inhibitors for purine nucleoside phosphorylases. *Bioorg. Med. Chem. Lett.* 9, 2833–2836

Nitric oxide synthase inhibitor

Nitric oxide is an important chemical messenger mediating many effects associated with maintaining cardiovascular homeostasis in different tissues. The agent is produced biosynthetically from L-arginine by nitric oxide synthase (NOS). There are two types of NOS isoforms, the constitutive calcium/calmodulin-dependent type (cNOS), which can be further divided into the neuronal form (nNOS) and the endothelial form (eNOS), and the inducible calcium/calmodulin-independent type (iNOS). Tissue- and isoform-selective NOS inhibitors offer the potential to develop agents for the specific treatment of many nitric oxide-mediated conditions. A recent paper from Ulhaq, S. and coworkers describes an investigation into the structure–activity relationships of L-thiocitrulline (**vi**), a known potent inhibitor of several nitric oxide synthase isoforms[4].



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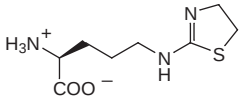


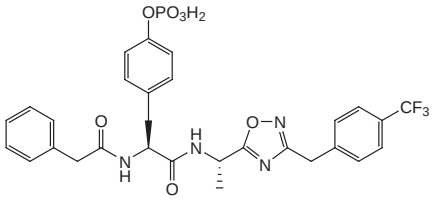
vii

These studies have led to the identification of N^{δ}-(4,5-dihydrothiazol-2-yl)ornithine (**vii**) as a potent inhibitor of rat iNOS (IC_{50} = 8.1 μM) and nNOS (IC_{50} = 4.3 μM), and cNOS derived from a human tumour xenograft (IC_{50} = 1.3 μM). The group is presently investigating the development of tissue-specific prodrugs to enhance the site-specific delivery of this agent.

4 Ulhaq, S. *et al.* (1999) Heterocyclic analogues of L-citrulline as inhibitors of the isoforms of nitric oxide synthase (NOS) and identification of N^{δ}-(4,5-dihydrothiazol-2-yl)ornithine as a potent inhibitor. *Bioorg. Med. Chem.* 7, 1787–1796

Tyrosine kinase ZAP-70 inhibitors

The protein tyrosine kinase ZAP-70 has an important role in T-cell function *in vivo* in knockout mice and in humans with disrupted ZAP-70. In both instances, the absence of T-cell function caused by suppression of the enzyme compromises the immune response. This enzyme might, therefore, be a useful therapeutic target for the development of novel immune suppressants. The enzyme consists of two tandem SH2 domains of approximately 100 amino acids, which preferentially bind to specific tyrosine-phosphorylated proteins. Workers from ARIAD Pharmaceuticals (Cambridge, MA, USA) have recently reported the discovery of a series of 1,2,4-oxadiazole analogues, exemplified by (**viii**), as potent and selective SH2-related inhibitors of this enzyme[5]. This group of compounds has a high selectivity for ZAP-70 over the closely related tyrosine kinase SYK and other SH2-containing peptides such as SRC and GRB2. Gel-shift studies indicate that these compounds interact with the C-terminal of the ZAP-70 SH2. The group is presently using these compounds as leads for the development of ZAP-70 inhibitors for cellular studies.



viii

5 Vu, C.B. *et al.* (1999) Discovery of potent and selective SH2 inhibitors of the tyrosine kinase ZAP-70. *J. Med. Chem.* 42, 4088–4098

Combinatorial chemistry

Melanocortin-1 receptor agonists

The melanocortin peptides that include the α-, β-, γ-melanocyte-stimulating hormones (MSH) and adrenocorticotrophin (ACTH) all possess a His-Phe-Arg-Trp epitope known as the 'message' sequence. These peptides are responsible for a range of physiological actions including skin pigmentation, energy

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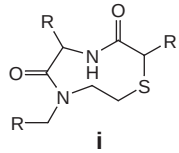
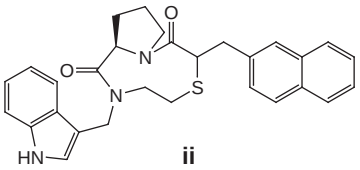
homeostasis and adrenocortical steroidogenesis. Five melanocortin receptors have been identified to date, with the melanocortin-1 receptor (MC1R) being involved in skin pigmentation. As the bioactive conformation of the MSH peptides is based on a peptide β-turn, a recent study has focused on the synthesis of a library of small molecules based upon this structural feature[1].

Solid-phase synthesis was used to produce 951 compounds (**i**) using sidechains based on structures known to be important for receptor recognition and activation. The compounds were evaluated for their ability to activate the MC1R subtype when tested at 10 μM in a colorimetric bioassay.

Of the compounds prepared, two were chosen for resynthesis, purification and characterization. One of these (**ii**) had an EC_{50} value of 42.5 μM for the mouse MC1R subtype, whilst eliciting no agonist response at the mouse MC3R or MC4R subtypes. This provides a starting point for further studies of non-peptide heterocyclic agonists.



i

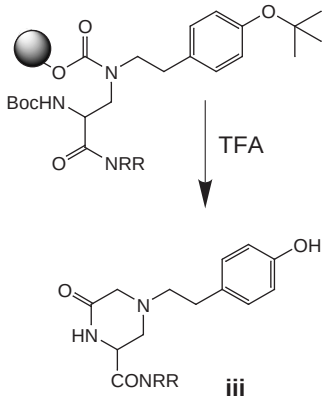


ii

1 Haskell-Luevano, C. *et al.* (1999) Compounds that activate the mouse melanocortin-1 receptor identified by screening a small molecule library based upon the β-turn. *J. Med. Chem.* 42, 4380–4387

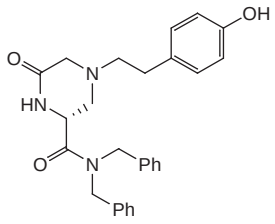
Enkephalin mimetics

The solid-phase synthesis of several piperazinone-containing Leu-enkephalin mimetics has been described in a recent paper[2]. The preparation of eight analogues followed a synthetic route that commenced with the acylation of Wang resin with bromoacetyl bromide. The piperazinone heterocycle was constructed such that acid-catalyzed cyclization of the ring in the final step also released the product (**iii**) from the solid support, leaving no trace of the resin attachment point.



iii

Screening of the compounds for affinity at the μ and δ opioid receptors showed that compound (**iv**) had an affinity of 400 nM for the μ receptor. This study paves the way for the synthesis of larger combinatorial libraries of non-peptide enkephalin analogues.

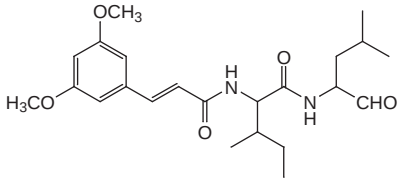


iv

2 Shreder, K. *et al.* (1999) Solid phase organic synthesis of piperazinone containing enkephalin mimetics: A readily derivatized, traceless scaffold. *J. Comb. Chem.* 1, 383–387

β-Amyloid inhibitors

Alzheimer's disease is characterized by the formation of amyloid plaques in brain tissue. These plaques contain a 39–43 amino acid peptide called β-amyloid (Aβ), which is produced by proteolytic processing of the β-amyloid precursor protein (βAPP). The pathways by which the processing occurs have not been fully elucidated, although the existence of a family of enzymes called secretases has been proposed. As both β- and γ-secretase are required for the formation of Aβ, these enzymes are good targets for therapeutic intervention. Indeed, aldehydic inhibitors of γ-secretase have already been identified.



v

To find more potent inhibitors of Aβ formation, a combinatorial library approach to discovering potent inhibitors of γ-secretase has been undertaken[3]. The solid-phase combinatorial synthesis of mixtures of ten related peptide aldehydes was successfully achieved using reduction of a Weinreb amide intermediate to generate the aldehyde function. Following screening and deconvolution, the most active aldehyde (**v**), was discovered to inhibit Aβ formation with an IC_{50} value of 9.6 μM.

3 Higaki, J.N. *et al.* (1999) A combinatorial approach to the identification of dipeptide aldehyde inhibitors of β-amyloid production. *J. Med. Chem.* 42, 3889–3898

Nick Terrett
Discovery Chemistry
Pfizer Central Research
Sandwich, Kent
UK CT13 9NJ
fax: +44 1304 655419
e-mail:
nick_terrett@sandwich.pfizer.com