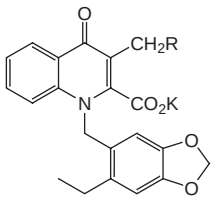
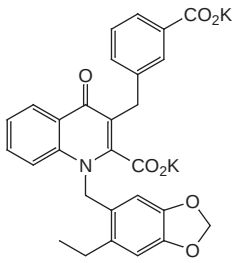


(xi)



(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

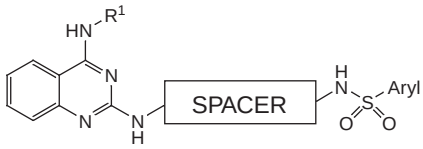
Andrew Lloyd

Combinatorial chemistry

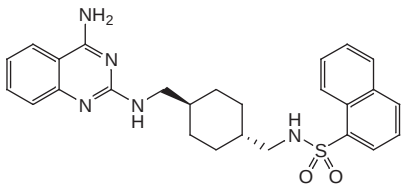
Neuropeptide Y-receptor antagonists

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**),

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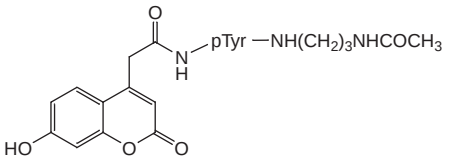

(iv)

which has an IC_{50} of 660 nM. This work demonstrated that three amino acid residues of the SH2 ligand (**iii**) can be replaced with non-amino acid substituents without loss of affinity. Future studies could utilize this knowledge in the design of ligands with higher affinity for SH2 domains than that displayed by conventional peptide ligands, thereby providing potential treatments for a variety of medical disorders.

2 Lee, T.R. and Lawrence, D.S. (2000) SH2-directed ligands of the Lck tyrosine kinase, *J. Med. Chem.* 43, 1173–1179

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Collaboration…

Orchid Biosciences (Princeton, NJ, USA) and **The SNP Consortium** (Chicago, IL, USA) have announced a collaboration in which Orchid will determine the allelic frequency of 60,000 single nucleotide polymorphism (SNP) markers in diverse populations. Collaborations will also be set up with two major academic institutions to conduct similar SNP analyses. Dale Pfost, Chairman and CEO of Orchid said, 'These types of studies are the cornerstone of the next phase of the genomics revolution, as the raw data of genetic variability is mined to identify, understand and address medically important differences among individuals.' Arthur Holden, Chairman and CEO of the Consortium said, 'Confirming the frequency of SNPs identified by the Consortium in diverse populations is a critically important step in the construction of a publicly available SNP map.'