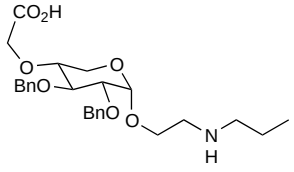
Combinatorial chemistry

Carbohydrate-based peptidomimetics

Dysfunction of integrin-mediated adhesion is often related to cancer metastasis, angiogenesis and osteoporosis. The most biologically relevant $\alpha_{IIb}\beta_3$ and $\alpha_V\beta_3$ integrins recognize the short Arg-Gly-Asp (RGD) peptidin sequence exhibited by their protein ligands, fibronectin, vitronectin and other proteins of the extracellular matrix. A major problem with inhibition of adhesion is to achieve this with selectivity of a protein *vis-à-vis* with a particular integrin. This selectivity is thought to be related to a bioactive conformation of the RGD sequence and could be specific for its receptor. Chapleur and coworkers have designed novel selective RGD mimics based on chiral scaffolds using a combination of computer-aided design and a solution-phase combinatorial approach for compound synthesis[1]. A library of 126 mimetics of the RGD sequence based on the D-xylose sugar scaffold was synthesized in solution as mixtures of 14. These mixtures were then tested by estimating the adhesion of S180 sarcoma cells, which express only the $\alpha_V\beta_3$ integrin, on a substrate of fibronectin or vitronectin in the presence of the compounds, and compared with the effect of the RGDS peptide as reference on the same cells. Active mixtures identified were iteratively deconvoluted, followed by resynthesis of individual compounds to determine activity. One of the most potent compounds discovered was **(i)**, which gave a percentage inhibition of approximately 45% in this assay, which was identical to the RGDS peptide. This library has been successful in identifying compounds with moderate activity as antagonists of the $\alpha_V\beta_3$ integrin, and could be useful in the future for the construction of other biologically relevant libraries of peptidomimetics, and also in the design of synthetic receptors using parallel synthesis.



(i)

1 Chapleur, Y. *et al.* (2001) Design, synthesis and preliminary biological evaluation of a focused combinatorial library of stereodiverse carbohydrate-scaffold-based peptidomimetics. *Bioorg. Med. Chem. Lett.* 9, 511–523

Neuropeptide FF antagonists

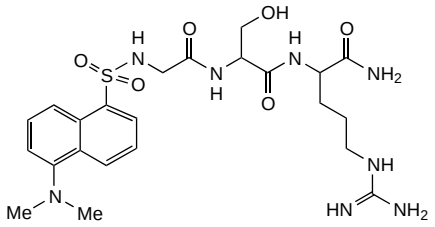
Opiate tolerance, dependence and abuse represent major medical and social problems. Neuropeptide FF (Phe-Leu-Phe-Gln-Pro-Gln-Arg-Phe-NH_2), together with the related mammalian neuropeptides NPAF and the N-terminally extended compound **(ii)**, have been identified as a high affinity endogenous ligand for a novel neuropeptide Y-like human orphan G-protein-coupled receptor, HLWAR77. Neuropeptide FF is an anti-opioid and has been implicated in pain modulation, morphine tolerance and morphine abstinence. Antagonists of **(ii)**, besides their importance as pharmacological agents helpful in defining the physiological and pharmacological role of the endogenous neuropeptide, could enable the management of withdrawal symptoms that adversely affect the treatment of opiate abuse. Prokai and coworkers are searching for novel antagonists of **(ii)** that show improved potency and also retain the ability to cross the blood–brain barrier (BBB) (Ref. 2). A library of 741 compounds was synthesized in mixtures of 19 on a Rink amide-methoxybenzyl-hydrazine (MBHA) resin (AnaSpec, San Jose, CA, USA). Screening of these mixtures in a rat spinal-cord membrane preparation for displacement of [^{125}I]YLFQPQRF-NH_2 **(iii)** gave several active mixtures. Mixtures containing glycine (G), lysine (L) and glutamine (Q) showed the highest increase in the percentage displacement of **(iii)** upon screening. Following deconvolution of

Phe-Leu-Phe-Gln-Pro-Gln-Arg-Phe-NH-Ala-Gln-Ser

(ii)

[^{125}I] Tyr-Leu-Phe-Gln-Pro-Gln-Arg-Phe-NH_2

(iii)



(iv)

the active mixtures, one of the most active compounds obtained was **(iv)**, which gave a measured K_i value in the radioligand-binding assay of 1.4 ± 0.5 μM. This work has provided moderately potent antagonists of **(ii)**, which are able to cross the BBB, and thus lays the foundation for the design of more potent inhibitors in the future.

2 Prokai, L. *et al.* (2001) Combinatorial lead optimization of a neuropeptide FF antagonist. *J. Med. Chem.* 44, 1623–1626

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Profile

Glycine transporter GlyT-2 blockers: potential pain-relief and anti-spastic drugs

The amino acid glycine is a major neurotransmitter, active in both excitatory and inhibitory synapses in the brain and the spinal cord. The inhibitory actions of glycine are mediated by a strychnine-sensitive glycine receptor, which is a glycine-gated chloride ion channel. Opening of the chloride ion channel following binding of glycine to its receptor results in membrane hyperpolarization,

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