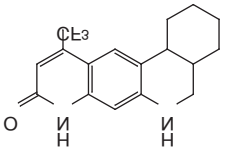
### Nonsteroidal androgen receptor agonists

The androgens testosterone and dihydrotestosterone are important in male sexual and musculo-skeletal development. However, as the oral bioavailability of these compounds is poor, androgen deficiency is normally treated using transdermal patches or intramuscular injection. A recent paper from Ligand Pharmaceuticals Inc. (San Diego, CA, USA) describes the synthesis and evaluation of a series of androgen receptor agonists based on 4-alkyl-, 4,4-dialkyl- and 3,4-dialkyl-1,2,3,4-tetrahydro-8-pyridono[5,6-*g*]quinoline [Higuchi, R.I. *et al.* (1999) *Bioorg. Med. Chem. Lett.* 9, 1340–1355]. A number of compounds, exemplified by (**9**), were found to be as effective as agonists as dihydrotestosterone in both competitive receptor binding and androgen receptor cotransfection assays.



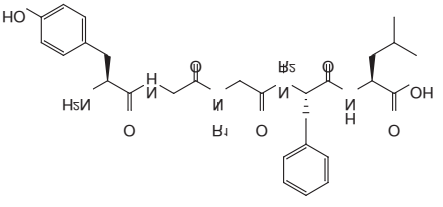
**9**

## Profiles

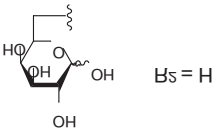
### Sugar-based peptidomimetics

The opioid receptors, μ, δ and κ, and their subtypes, are involved in the control of various aspects of the perception of pain, pleasure and mood as well as the regulation of immune function. The development of selective opioid receptor ligands offers the potential for improving clinical treatments involving these systems. In the search for potent opioid ligands, the two endogenous opioid peptides, Leu- and Met-enkephalin (H-Tyr-Gly-Gly-Phe-Leu/Met-OH) make an ideal template and many selective and conformationally restricted analogues of those peptides have been prepared.

In the course of such studies, Horvat, Š. and coworkers [*J. Chem. Soc. Perkin Trans.* 1 (1998) 1789–1795] produced novel types of sugar-based peptidomimetics (**10,11**) related to the pentapeptide Leu-enkephalin, in which $Gly^2$ (**10**), or both $Gly^2$ and $Gly^3$ residues (**11**), were replaced by an *N*-alkylated glycine residue bearing a 6-deoxy-D-galactose moiety. The synthesis of the mono- and the bis-glycated pentapeptide were performed in a stepwise manner in solution by employing *N*-glycated glycine as the building block. The incorporated carbohydrate element in (**10,11**) offers applications in molecular recognition studies and might serve as a point of attachment (through the unsubstituted anomeric centre) for amino groups of proteins and other biologically active amines.

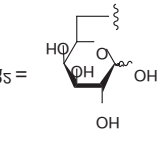


**10** $R_1$ =



$R_2$ = H

**11** $R_1 = R_2$ =



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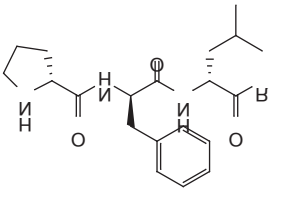
## Combinatorial chemistry

### A new fibrinogen receptor motif

The Arg-Gly-Asp tripeptide motif is well known to bind to the platelet gpIIbIIIa fibrinogen receptor and has been the basis for the design of a large number of novel non-peptidic inhibitors. Using combinatorial chemistry, a novel motif of unnatural amino acids has been discovered [Thorpe, D.S. *et al.* (1999) *Biochem. Biophys. Res. Commun.* 256, 537–541].

Having demonstrated that a bead-based library of pentapeptides of the structure Tyr-X-X-Asp-Val (where X is 1 of 19 L-amino acids) could be used to reveal the Arg-Gly-Asp motif through the staining of beads containing active sequences, the project moved on to explore unnatural peptide sequences. Using 18 D-amino acids plus glycine to generate an on-bead library of pentapeptides, the motif D-Pro(D-Phe/D-Tyr)D-Leu (**1**) was identified. The most active compound detected had an $IC_{50}$ value of 14 μM.



**1**

Intriguingly, these compounds lacked the carboxylic acid of the Arg-Gly-Asp sequence that is presumed to bind calcium, and molecular modelling was employed to suggest a mode of molecular recognition. A reversed binding mechanism was noted, which is often observed with D-amino acid mimetics, and the model also proposed that π-electrons substituted for the carboxylic acid of Arg-Gly-Asp. This library discovery offers a number of new opportunities for the design and synthesis of novel integrin inhibitors.

### Novel screening methodology

A novel screening method for combinatorial libraries has been employed in the detection of pentapeptides that bind weakly to tryptophan [Sugimoto N. *et al.* (1999) *J. Chem. Soc. Chem. Commun.* 677–678]. This new method

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