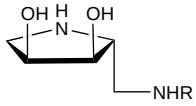
Aminomethylpyrrolidine derivatives as selective α-mannosidase inhibitors

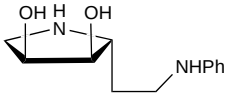
The quantitative distribution of complex carbohydrates on the surface of breast, colon and skin cancer cells is associated with disease prognosis. Thus, The specific inhibition of *N*-linked glycoprotein-processing α-mannosidases could provide a useful anticancer strategy[23]. Mannostatin A and B isolated from the soil microorganism *Streptoverticillum verticillus* and a synthetic analogue[24] are among the most potent inhibitors of α-mannosidases reported, to date. However, α-mannosidase inhibitors that are monosaccharide mimics, also inhibit other glycosidase types, in particular α-L-fucosidases[25]. It is, therefore, suggested that enzyme selectivity could be improved if the inhibitor could include some information of the glycosidic bond that is cleaved (e.g. α vs β) and of the aglycon itself. Such inhibitors could be represented by disaccharide mimics linked to monosaccharides through non-hydrolyzable linkages[26]; however, synthesis of such mimics proved to be lengthy. In addition, these compounds would not possess the essential requirements to become a drug, such as membrane permeability.

On this basis, Vogel and collaborators have recently reported on a series of (2*R*,3*R*,4*S*)-2-(substituted-amino)-methyl-3,4-dihydroxypyrrolidines (**xiv, a–k**)[27], which can mimic a transitional or intermediate structure of the hydrolytic process, and are potential novel inhibitors of α-mannosidases.



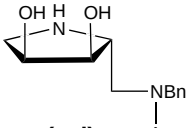
(xiv, a–k)

The compounds were tested for their activity towards 25 commercially available glycosidases. In agreement with the authors' hypothesis, which suggests that synthetic compounds could mimic a transitional or intermediate structure of the hydrolytic pathways, several compounds showed interesting properties. In particular, the most potent compound was derivative **i** (R = benzyl; K_i = 7.4 μM, competitive inhibition towards α-mannosidase purified from the plant, jack bean), which also showed the best selectivity towards α-mannosidases. It should be noted that **xv**, a structural isomer of **xiv** derivative **i** in which the amino moiety of the side chain is two-bonds apart from the pyrrolidine ring, is a much weaker α-mannosidase inhibitor (33% at 1 mM against α-mannosidase from jack bean) and is completely inactive towards the other glycosidases tested.



(xv)

This result highlights the importance of the (2*R*)-aminomethyl group of this series in a possible electrostatic interaction with a carboxylic group of the α-mannosidases. Further support for this hypothesis is given by the fact that the acetamide **(xvi)** is completely inactive.



(xvi)

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Combinatorial chemistry

Nucleoside phosphoramidates

Compounds with the phosphoramidate functionality have a range of biological activities, including acting as anticancer and cardioprotective agents. As phosphoric and carboxylic equivalents, phosphoramidates have been evaluated as analogues of nucleosides and oligonucleotides. Only a limited number of nucleoside phosphoramidates have been prepared and evaluated for antiviral activity.

A combinatorial approach was undertaken, employing screening of biologically relevant libraries for their ability to modulate biological pathways, with or without regard to specific molecular targets. This strategy is appropriate in the context of antiviral lead discovery, simultaneously identifying leads with the potential discovery of novel molecular targets[1]. A library of 600 single phosphoramidates was synthesized on solid phase. Antiviral evaluation of this library against hepatitis B virus in cell-based assays helped validate the biological relevance of the library with respect to its ability to cross cell membranes, its metabolic stability and its antiviral activity.

Several potent compounds were obtained from this library, but only preliminary activity data were presented for the library in this publication. Further lead optimization is in progress by

the authors to optimize the potency of this potential new class of nucleoside phosphoramidate compounds.

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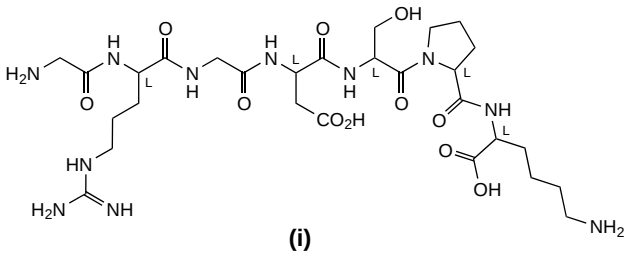
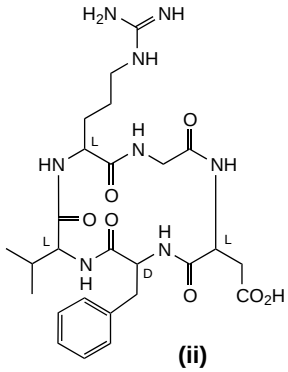
Non-peptide RGD mimetics

Integrins are a family of heterodimeric transmembrane cell-surface receptors that are involved in cell–cell and cell–matrix adhesion processes. More than 20 different integrin receptors have been identified consisting of various combinations of at least 17 α- and nine β-subunits. Previously, integrins of the β_3-subfamily have been the focus of drug discovery research, attention being focussed towards the platelet integrin $\alpha_{IIb}\beta_3$. More recently, the vitronectin receptor $\alpha_v\beta_3$, expressed on almost all cells originating from the mesenchyme, has received attention. This receptor represents a therapeutic target because of its important role in pathologies as diverse as osteoporosis, restenosis following angioplasty, acute renal failure, ocular diseases, tumour-induced angiogenesis and metastasis formation.

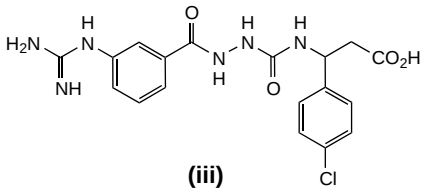
The tripeptide sequence RGD (Arg-Gly-Asp) is a common cell-recognition motif that is part of integrin binding ligands, such as fibronectin, fibrogen and vitronectin. The RGD sequence has been used as a lead for developing different integrin antagonists and, in particular recently, the development of selective nonpeptide $\alpha_v\beta_3$ integrin antagonists. Because of enhanced metabolic stability, bioavailability and biological absorption of aza-amino acid-containing peptides, the study of a library of low molecular weight RGD mimetics containing the aza-glycine has been undertaken[2]. A library of 37 single compounds was synthesized on a tritylchloridepolystyrol (TCP) resin (PepChem). Screening assays were performed by measuring the effect of RGD mimetics on the interaction between immobilized integrin-receptors and biotinylated soluble-ligands. The ability of RGD mimetics to inhibit the binding of vitronectin and fibrinogen to the isolated, immobilized $\alpha_v\beta_3$ and $\alpha_{IIb}\beta_3$ receptors was compared with that of the standard peptides GRGDSPK **(i)** and c(RGDfV) **(ii)**. One of the most active compounds obtained was **(iii)**, which gave an IC_{50} value of 0.1 nM against $\alpha_v\beta_3$ and >50,000-fold selectivity over the platelet receptor $\alpha_{IIb}\beta_3$. This work has provided potent and selective RGD mimetics with promising properties for further pharmacokinetic investigations.



(i)



(ii)



(iii)

2 Kessler, H. *et al.* (2001) Solid-phase synthesis of a nonpeptide RGD mimetic library: new selective $\alpha_v\beta_3$ integrin antagonists. *J. Med. Chem.* 44, 1938–1950

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