

Synthesis of RGD Mimetic Peptides with Heterocyclic Residues

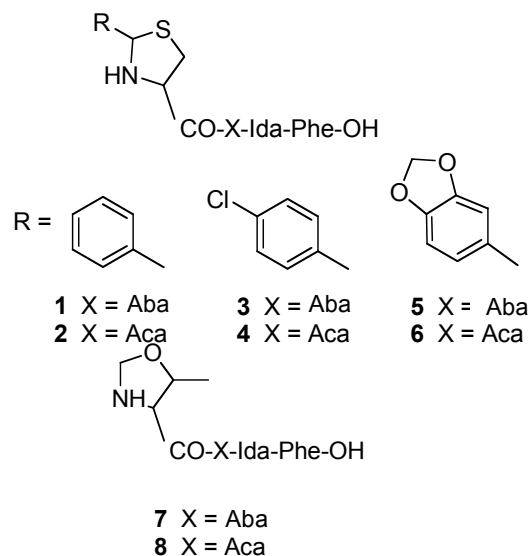
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Introduction

The integrin $\alpha_v\beta_3$, vitronectin receptor, is expressed in a number of cell types and has been shown to mediate adhesion of osteoclasts to bone matrix, vascular smooth muscle cell migration, and angiogenesis. Integrin $\alpha_v\beta_3$ also play a significant role in tumor growth, invasion and metastasis, and is a receptor for the extracellular matrix proteins with the exposed arginine-glycine-aspartic (RGD) tripeptide sequence, which has been shown to be a potent antagonists of the integrin $\alpha_v\beta_3$ and has excellent anti-angiogenic properties including its suppression of tumor growth in animal models. Therefore drug design based on the RGD structure may provide new treatments for diseases such as thrombosis, osteoporosis, and cancer.

In this paper, ten RGD mimic peptides were designed and synthesized by using unnatural building blocks as the surrogates for residue Arg, Gly and Asp, in order to search highly potent orally active integrin $\alpha_v\beta_3$ antagonists.



(1) thiazolino or oxazolino residue were used instead of the basic residue Arg;

(2) iminodiacetic acid (Ida) were coupled in place of the acidic residue Asp.

2、Backbone atypically cyclized peptides 9, 10

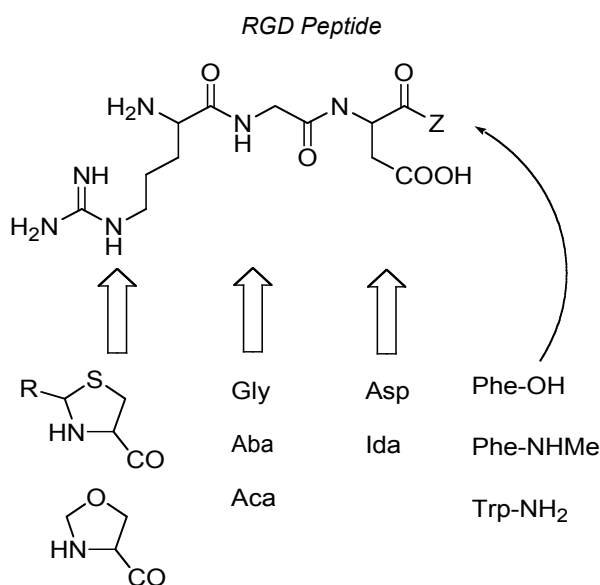
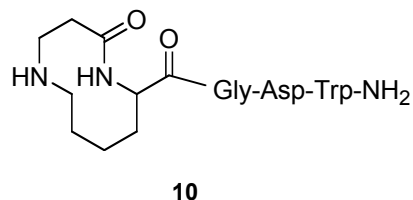
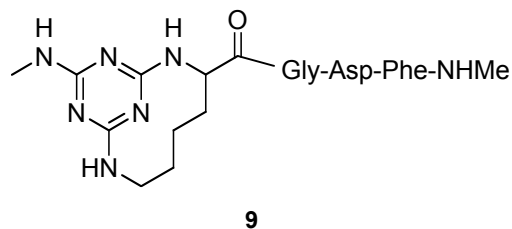


Fig. 1. Design of RGD Mimetic Peptides.

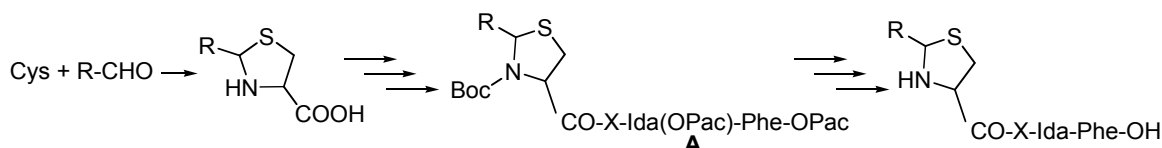
Results and Discussion

Two kinds of backbone structures were concerned in present products:

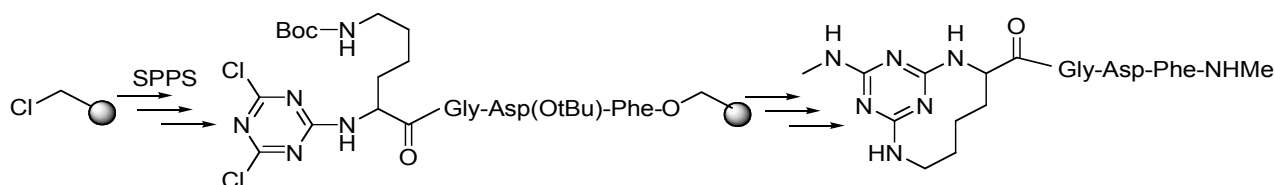
1、Linear RGD mimetics 1 ~ 8

Arg was substituted by a locally cyclized structure between α -amino and ω -amino groups of Lys with different bridge structures in 9 and 10.

Products 1 ~ 8 were prepared by classical solution procedure:



Scheme 1



Scheme 2

The key intermediates **A** were obtained via mixed anhydride approach with maximum protection strategy, and then reacted with thiazolidine or oxazolidine derivatives respectively via mixed anhydrides approach. After the removal of Pac and Boc groups eight targeting compounds **1** ~ **8** were obtained.

Two new scaffold atypically cyclized peptides **9**, **10** mimicking RGD sequence were first synthesized by solid phase procedure. In the related synthesis, the cyclization was facilitated by the pseudo-dilution effect from solid support. The locally constrained structure of product **9** was yielded via α -NH₂ of lysine reacting with one of active chlorine atoms of cyanuric chloride on Merrifield resin,

and the second Cl atom was substituted with the ω -NH₂ group of lysine residue. The 10-membered ring at *N*-terminal in products **10** was constructed in two steps: the α -NH₂ of lysine was acylated with β -bromopropyl via mixed anhydrides approach, then ω -NH₂ of lysine reaction with Br atom via intermolecular S_N reaction.

Ten modified RGD peptides were synthesized. All products were characterized by HPLC and MS analysis (Table 1).

It is valuable that the protocols related in the present paper would afford some feasible way to synthesize novel cyclo peptide derivatives.

Table 1. Physical and chemical properties of the heterocyclic residue containing and backbone atypically cyclized peptides **1** ~ **10**

Compd.	m.p. / \square	$[\alpha]_D^{20}$	Purity ^a / %	Total yield / %	MS ^b / m/z
1	102~105	-28.7	> 95	16.9	557.6 [M+H] ⁺
2	89~93	-30.5	> 95	21.1	585.4 [M+H] ⁺
3	182~185	-29.9	> 95	14.7	591.2 [M+H] ⁺
4	132~135	-23.7	> 95	22.0	619.4 [M+H] ⁺
5	127~129	-23.6	> 95	18.3	601.4 [M+H] ⁺
6	139~142	-27.3	> 95	23.1	629.4 [M+H] ⁺
7	119~123	-10.5	> 95	14.4	479.4 [M+H] ⁺
8	89~92	-25.2	> 95	17.8	507.5 [M+H] ⁺
9	147~149	-27.9	~80	72.4	585.7 [M+H] ⁺
10	128~130	-22.9	~85	76.3	558.2 [M+H] ⁺
11	126~128	+1.14	~80	62.8	608.2 [M+H] ⁺

^a by HPLC analysis

^b by FAB-MS or ESI-MS analysis

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