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Communications to the Editor

Discovery of Potent Nonpeptide Vitronectin Receptor ($\alpha_V\beta_3$) Antagonists

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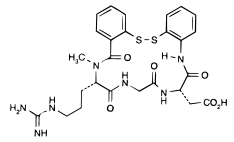
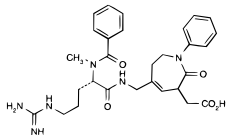
The vitronectin receptor ($\alpha_V\beta_3$) is a member of the integrin family of transmembrane heterodimeric glycoprotein complexes, which function in cell−cell and cell−substrate adhesion and communication.[1] The integrin $\alpha_V\beta_3$ is expressed on the surface of a variety of cell types, including osteoclasts, vascular smooth muscle cells, endothelial cells, and tumor cells, and has been shown to mediate several biologically relevant processes, including adhesion of osteoclasts to the bone matrix,[2] vascular smooth muscle cell migration,[3] and angiogenesis.[4] As a result, $\alpha_V\beta_3$ antagonists are expected to have utility in the treatment of osteoporosis, restenosis following balloon angioplasty, and diseases involving neovascularization, such as macular degeneration,[5] diabetic retinopathy,[5] and cancer.[4b,6]

The vitronectin receptor ($\alpha_V\beta_3$) is related to the platelet fibrinogen receptor ($\alpha_{IIb}\beta_3$) in that both integrins possess the β_3 subunit. Furthermore, both $\alpha_V\beta_3$ and $\alpha_{IIb}\beta_3$ are known to recognize the Arg-Gly-Asp (RGD) tripeptide sequence.[1] A number of groups have reported the discovery of potent nonpeptide $\alpha_{IIb}\beta_3$ antagonists based on mimetics of the RGD sequence.[7] In our previous investigations into RGD peptidomimetics, a detailed evaluation of cyclic RGD-containing peptides revealed that, in addition to the key Asp and Arg residues, a turn−extended-turn conformation for the RGD sequence was crucial for potent $\alpha_{IIb}\beta_3$ peptide antagonists.[8−10] Guided by these cyclic peptide studies, we designed small-molecule RGD mimetics based on the 1,4-benzodiazepine ring system which provided highly potent and selective $\alpha_{IIb}\beta_3$ antagonists.[11−14] In the present communication, we describe the application of a similar strategy to the identification of a series of potent and selective nonpeptide $\alpha_V\beta_3$ antagonists.

Table 1. Binding Activity of Constrained RGD Analogs

Entry	Structure	$\alpha_V\beta_3$ K_i (μM)	$\alpha_{IIb}\beta_3 K_i$ (μM)
1		0.0035 ± 0.0002	0.0028 ± 0.0001
2	cyclo(RGDfV)	0.010 ± 0.002	42 ± 3
3	cyclo(RGDSPG)	0.010 ± 0.001	75 ± 25
4		0.050 ± 0.003	0.11 ± 0.01

Our initial studies on $\alpha_V\beta_3$ antagonists focused on constrained RGD analogs, and identified several key compounds (Table 1). We found that the cyclic pentapeptide cyclo(RGDfV) (**2**), as reported by Kessler and co-workers,[15] had high affinity for $\alpha_V\beta_3$ and showed substantial selectivity for $\alpha_V\beta_3$ relative to $\alpha_{IIb}\beta_3$.[16,17] The reported conformation of the RGD sequence in **2**, based on ^{1}H NMR studies, invoked a turn in the Gly region. The cyclic hexapeptide cyclo(RGDSPG)[18] (**3**) showed similar affinity and selectivity and, by analogy to other cyclic hexapeptides,[8] could be expected to also adopt a conformation of the RGD sequence containing a turn in the Gly region. Since our previous studies had indicated that an extended conformation about Gly is optimal for $\alpha_{IIb}\beta_3$, the results suggested that selectivity for $\alpha_V\beta_3$ may be related to a conformation that contains a turn about Gly. Figure 1 depicts an overlay comparison of the cyclic peptide **1**, in which the RGD sequence

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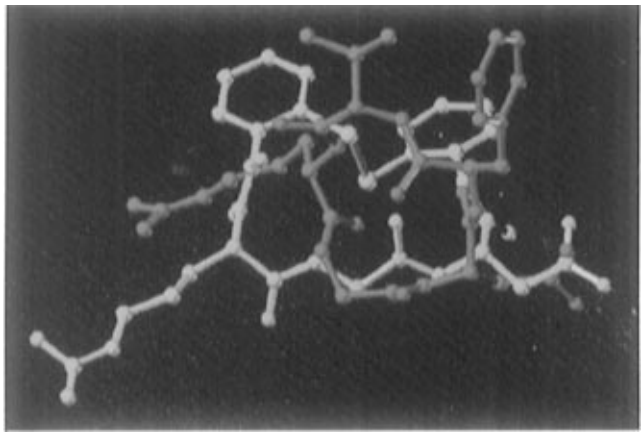


Figure 1. Overlay of cyclic peptides **1** (cyan) and **2** (magenta) revealing the difference in the distance between the Arg and Asp centers.

is in the turn−extended-turn conformation with the arginine side chain extended such that the guanidine group lines up with the cationic residues present in potent nonpeptide $\alpha_{IIb}\beta_3$ antagonists,[14] and the cyclic pentapeptide **2** in the conformation containing a turn in the Gly region derived from ^{1}H NMR studies. This comparison suggested that an important manifestation of the turn about Gly present in **2** is that the overall length for preferred binding to $\alpha_V\beta_3$ is shorter than for $\alpha_{IIb}\beta_3$ (Figure 1).[19]

Analysis of semipeptide **4**,[9] which contains a γ-turn mimetic about Asp, provided additional insight into structural features which might be tolerated by $\alpha_V\beta_3$. This compound has comparable affinity for both $\alpha_V\beta_3$ and $\alpha_{IIb}\beta_3$, suggesting that the γ-turn about Asp imposed by the seven-membered ring of **4** may be accommodated by $\alpha_V\beta_3$ as well as by $\alpha_{IIb}\beta_3$. Taken together, these data suggested that a conformation of the RGD sequence containing turns about both Gly and Asp, resulting in a reduced overall separation between the Arg and Asp centers, may be favorable for binding to $\alpha_V\beta_3$.

Since a γ-turn about Asp appeared to be tolerated by $\alpha_V\beta_3$, we felt that appropriate functionalization of our 1,4-benzodiazepine system, in which the seven-membered diazepine ring is a γ-turn mimetic, might afford potent and selective nonpeptide $\alpha_V\beta_3$ antagonists. Comparison of our 1,4-benzodiazepine nucleus with cyclic peptide **2** (Figure 2) suggested that attachment of an arginine mimetic to the 7-position of the 1,4-benzodiazepine nucleus would be optimal to mimic the turn about Gly. To quickly test this hypothesis, we screened our collection of 7-substituted 1,4-benzodiazepine-based RGD mimetics for binding to $\alpha_V\beta_3$ and identified two important leads **5** and **7** (Table 2).

The *m*-benzamidine derivative **5**[20] had submicromolar affinity for $\alpha_V\beta_3$ and low micromolar affinity for $\alpha_{IIb}\beta_3$. The corresponding *p*-benzamidine **6**, however, was a potent $\alpha_{IIb}\beta_3$ antagonist[8] and had much lower affinity for $\alpha_V\beta_3$. Since compound **5** is shorter than compound **6** in the distance from the carboxyl terminus to the amidine terminus, these results appeared to support our modeling hypothesis. The arylpiperazine derivative **7**, although clearly a potent and selective $\alpha_{IIb}\beta_3$ antagonist, also showed low micromolar affinity for $\alpha_V\beta_3$. We speculated, based on our modeling hypothesis, that the central anilino nitrogen was responsible for the $\alpha_V\beta_3$ activity, and the distal pyridyl nitrogen was responsible

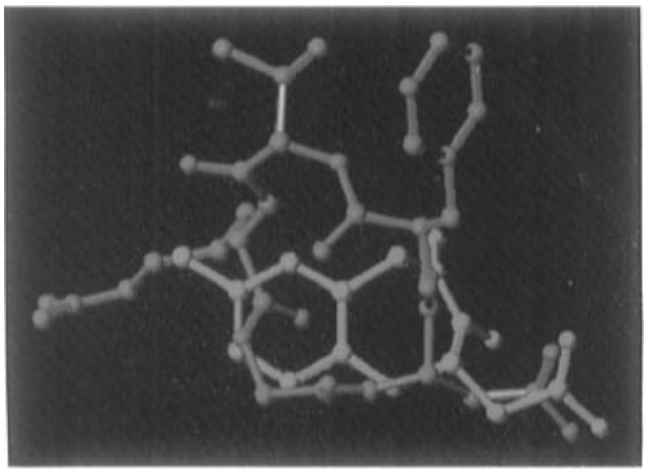
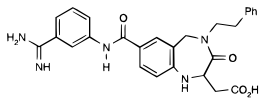
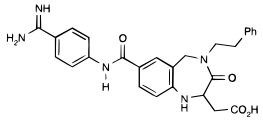
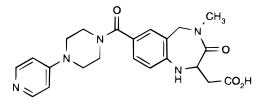
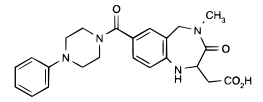


Figure 2. Overlay of the benzodiazepine nucleus (green) on the cyclic peptide **2** (magenta) indicating the 7-position as the optimal point of attachment for arginine mimetics.

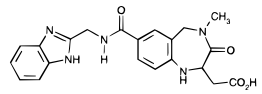
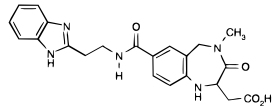
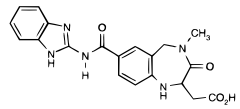
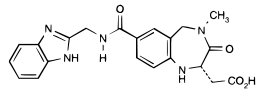
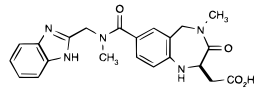
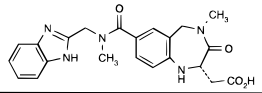
Table 2. Binding Activity of Small Molecule $\alpha_V\beta_3$ Antagonist Leads

Entry	Structure	$\alpha_V\beta_3$ K_i (μM)	$\alpha_{IIb}\beta_3$ K_i (μM)
5		0.51 ± 0.04	4.5 ± 0.3
6		56 ± 2	0.026 ± 0.002
7		1.0 ± 0.1	0.008 ± 0.001
8		9.2 ± 0.6	>100

for the $\alpha_{IIb}\beta_3$ activity. To test this hypothesis, we prepared derivative **8**, which lacks the pyridyl nitrogen. Compound **8** had $\alpha_V\beta_3$ affinity comparable to that of **7** but had drastically reduced affinity for $\alpha_{IIb}\beta_3$, providing additional evidence that the length required for optimal binding to $\alpha_V\beta_3$ is shorter than for $\alpha_{IIb}\beta_3$. These data also demonstrated that the 1,4-benzodiazepine system could be employed to generate nonpeptides selective for the vitronectin receptor.

Using the information gleaned from these preliminary studies, we evaluated a wide range of potential Arg mimetics in our 7-substituted 1,4-benzodiazepine series and identified the benzimidazole-containing derivative **9** as a potent and selective $\alpha_V\beta_3$ antagonist (Table 3). In this compound, the benzimidazole unit presumably functions as an Arg mimetic, although the exact nature of the interactions between the benzimidazole moiety and $\alpha_V\beta_3$ are not entirely clear at this time. Analogs of **9** which were one methylene unit longer (**10**) or one methylene unit shorter (**11**) were much less active, confirming that the overall length in **9** was optimized for interaction with $\alpha_V\beta_3$. Subsequently, we evaluated the resolved enantiomers of **9** and found the activity to reside almost exclusively in the (*S*)-enantiomer (**12**), the same as the natural configuration of Asp, supporting

Table 3. Binding Activity of Benzimidazole-Containing $\alpha_V\beta_3$ Antagonists

Entry	Structure	$\alpha_V\beta_3$ K_i (μM)	$\alpha_{IIb}\beta_3$ K_i (μM)
9		0.024 ± 0.002	30 ± 1
10		1.10 ± 0.05	>50
11		1.15 ± 0.04	>50
12		0.015 ± 0.001	52 ± 3
13		4.2 ± 0.3	>50
14		0.002 ± 0.0001	30 ± 2

the hypothesis that the 1,4-benzodiazepine acts as a Gly-Asp mimic. In our work on both peptide and nonpeptide $\alpha_{IIb}\beta_3$ antagonists, we had found that amide N-methylation resulted in an increase in activity.[12] Application of the same tactic in the present investigation afforded SB 223245 (**14**),[20] which had 2 nM affinity for $\alpha_V\beta_3$ and 30 μM affinity for $\alpha_{IIb}\beta_3$—greater than 10000-fold selectivity.

The discovery of **14** demonstrated that highly potent and selective nonpeptide $\alpha_V\beta_3$ antagonists could be designed by consideration of the conformations of constrained RGD peptides and peptidomimetics in an approach similar to that used in the identification of highly potent and selective nonpeptide $\alpha_{IIb}\beta_3$ antagonists. Further evaluation in functional assays has revealed that **14** is a potent inhibitor of both human osteoclast-mediated bone resorption[21] and vitronectin-induced haptotaxis of human endothelial cells,[22] showing the potential therapeutic utility of compounds in this series. This work has also revealed the remarkable versatility of the benzodiazepine nucleus as a Gly-Asp mimetic, as potent nonpeptide antagonists from the benzodiazepine series can be designed with selectivity for either $\alpha_{IIb}\beta_3$[14] or $\alpha_V\beta_3$ simply by altering the length and nature of the Arg mimetic.

Supporting Information Available: Characterization data (^{1}H NMR, MS, and elemental analyses) for compounds **5**−**14** (10 pages). Ordering information is given on any current masthead page.

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(16) Binding affinity for human $\alpha_V\beta_3$ was determined in a competitive binding assay employing [^{3}H]SK&F 107260 as the displaced ligand. The K_i values represent the means of values determined in two to three separate experiments. See: Wong, A.; Hwang, S. M.; McDevitt, P.; McNulty, D.; Stadel, J. M.; Johanson, K. Studies on $\alpha_V\beta_3$/Ligand Interactions Using a [^{3}H]-SK&F-107260 Binding Assay. *Mol. Pharmacol.* **1996**, *50*, 529−537.

(17) Binding affinity for human $\alpha_{IIb}\beta_3$ was determined in a competitive binding assay employing [^{3}H]SK&F 107260 as the displaced ligand. The K_i values represent the means of values determined in two to three separate experiments (see ref 10).

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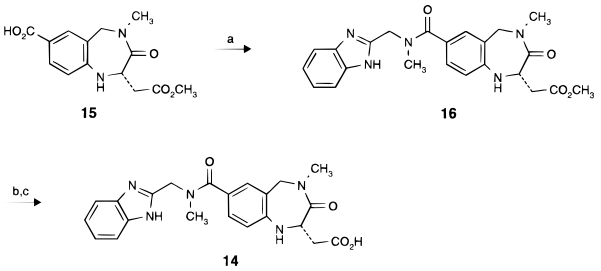
(19) For related studies on cyclic RGD peptides which come to a similar conclusion, see: (a) Pfaff, M.; Tangemann, K.; Müller, B.; Gurrath, M.; Müller, G.; Kessler, H.; Timpl, R.; Engel, J. Selective Recognition of Cyclic RGD peptides of NMR Defined Conformation by $\alpha_{IIb}\beta_3$, $\alpha_V\beta_3$, and $\alpha_5\beta_1$ Integrins. *J. Biol. Chem.* **1994**, *269*, 20233−20238. (b) Bach, A. C.; Espina, J. R.; Jackson, S. A.; Stouten, P. F. W.; Duke, J. L.; Mousa, S. A.; DeGrado, W. F. Type II′ to Type I β-Turn Swap Changes Specificity for Integrins. *J. Am. Chem. Soc.* **1996**, *118*, 293−294. (c) Burgess, K.; Lim, D.; Mousa, S. A. Synthesis and Solution Conformation of Cyclo[RGDRGD]: A Cyclic Peptide with Selectivity for the $\alpha_V\beta_3$ Receptor. *J. Med. Chem.* **1996**, *39*, 4520−4526.

(20) Compounds **5**−**14** were synthesized by coupling of the appropriate amine to the 1,4-benzodiazepine-7-carboxylic acid. The synthesis of **14** is shown as an example:



(a) 2-(methylaminomethyl)benzimidazole · TFA, DCC, (i-Pr)$_2$NEt, DMF (100%); (b) 2 N NaOH, MeOH; (c) HCl to pH 6.0 (71%).

The preparation of the starting material for this synthesis, methyl (*S*)-2,3,4,5-tetrahydro-7-carboxy-4-methyl-3-oxo-1*H*-1,4-benzodiazepine-2-acetic acid, has been reported. See: Miller, W. H.; Ku, T. W.; Ali, F. E.; Bondinell, W. E.; Calvo, R. R.; Davis, L. D.; Erhard, K. F.; Hall, L. B.; Huffman, W. F.; Keenan, R. M.; Kwon, C.; Newlander, K. A.; Ross, S. T.; Samanen, J. M.; Takata, D. T.; Yuan, C.-K. Enantiospecific Synthesis of SB 214857, a Potent, Orally Active, Nonpeptide Fibrinogen Receptor Antagonist. *Tetrahedron Lett.* **1995**, *36*, 9433−9436. The TFA salt of 2-[(methylamino)methyl]benzimidazole was prepared from Boc-sarcosine and 1,2-phenylenediamine by appropriate modification of the general procedure for the preparation of substituted benzimidazoles. See: Nestor, J. J.; Horner, B. L.; Ho, T. L.; Jones, G. H.; McRae, G. I.; Vickery, B. H. Synthesis of a Novel Class of Heteroaromatic Amino Acids and Their Use in the Preparation of Analogues of Luteinizing Hormone-Releasing Hormone. *J. Med. Chem.* **1984**, *27*, 320−325.

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(23) A preliminary account of this work was presented at the 211th American Chemical Society National Meeting, New Orleans, LA, March 24−28, 1996.

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