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Non-Peptide $\alpha_v\beta_3$ Antagonists. Part 4: Potent and Orally Bioavailable Chain-Shortened RGD Mimetics

Paul J. Coleman,[a,*] Ben C. Askew,[a,†] John H. Hutchinson,[a] David B. Whitman,[a] James J. Perkins,[a] George D. Hartman,[a] Gideon A. Rodan,[b] Chih-Tai Leu,[b] Thomayant Prueksaritanont,[c] Carmen Fernandez-Metzler,[c] Kara M. Merkle,[c] Robert Lynch,[d] Joseph J. Lynch,[d] Sevgi B. Rodan[b] and Mark E. Duggan[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[b]*Department of Bone Biology and Osteoporosis Research, Merck Research Laboratories, West Point, PA 19486, USA*
[c]*Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, USA*
[d]*Department of Pharmacology, Merck Research Laboratories, West Point, PA 19486, USA*

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Abstract—Potent non-peptidic $\alpha_v\beta_3$ antagonists have been prepared where deletion of an amide bond from an earlier series of linear RGD-mimetics provides a novel series of chain-shortened $\alpha_v\beta_3$ antagonists with significantly improved oral pharmacokinetics. These chain-shortened $\alpha_v\beta_3$ antagonists represent structurally novel integrin inhibitors. © 2002 Published by Elsevier Science Ltd.

Osteoporosis is a disease of the skeleton associated with diminishing bone mass and an increased risk of debilitating fractures.[1] In most instances, osteoporosis arises from an imbalance between the activities of bone-resorbing osteoclast cells and bone-depositing osteoblast cells.[2] In post-menopausal women, estrogen depletion results in increased bone resorption due to the enhanced activity and number of osteoclasts. Osteoclasts mediate bone resorption by initial attachment to the bone surface followed by secretion of matrix-degrading proteinases. Attachment of osteoclasts to bone involves binding of the highly expressed integrin $\alpha_v\beta_3$ to an RGD (arg-gly-asp) tripeptide sequence found in extracellular matrix proteins.[3] The integrin, $\alpha_v\beta_3$, is thought to be involved in not only cellular adhesion of osteoclasts to the bone surface but also in regulating their migration along the bone surface. Antagonists that block the binding of RGD expressing proteins to $\alpha_v\beta_3$ inhibit bone resorption in rodent models and offer a potential therapy for the prevention and treatment of osteoporosis.[4]

Previously, several reports from this laboratory have detailed the design and synthesis of novel, high affinity non-peptidic RGD mimetics as $\alpha_v\beta_3$ antagonists.[5] Replacement of the guanidine moiety of arginine with a tetrahydro[1,8]naphthyridine (THN) provides integrin selectivity for $\alpha_v\beta_3$ versus the fibrinogen receptor $\alpha_{IIb}\beta_3$ (**2**, Fig. 1). Further enhancements in binding affinity were realized by replacement of aspartic acid with a 3-aryl β-amino acid and inclusion of a pyrrolidinone central constraint.[5] Although receptor antagonists from this class bound to human $\alpha_v\beta_3$ with sub-nanomolar affinity, the oral pharmacokinetic profiles for these zwitterionic moieties were generally poor. For example, full-length antagonist **2** when dosed orally to dogs is poorly bioavailable (10%) and rapidly cleared (Cl = 20 mL/min/kg) from plasma. Herein, we describe a chain-length truncation of these full-length $\alpha_v\beta_3$ antagonists (represented by **2**) to give a new class of chain-shortened analogues with significantly improved pharmacokinetics.

The synthesis of the $\alpha_v\beta_3$ antagonists described in this paper involved the coupling of 3-aryl-β-aminoesters[6] to the tetrahydro[1,8]naphthyridine pentanoic acid **5b** (Scheme 1). The preparation of carboxylic acid **5b** began with commercially available 5-acetylvaleric acid **3a**. Fisher esterification of **3a** gave ketoester **3b** in quantitative yield. Friedlander condensation of ketoester **3b** with 2-amino-3-formylpyridine gave a mixture of two naphthyridine isomers **4a** and **4b** (ratio 3:1). Although separation of naphthyridine regioisomers was feasible by flash chromatography, separation after naphthyridine

*Corresponding author. Tel.: +1-215-652-4618; fax: +1-215-652-7310; e-mail: paul_coleman@merck.com
†Current address: Amgen, Inc., Thousand Oaks, CA 91320, USA.

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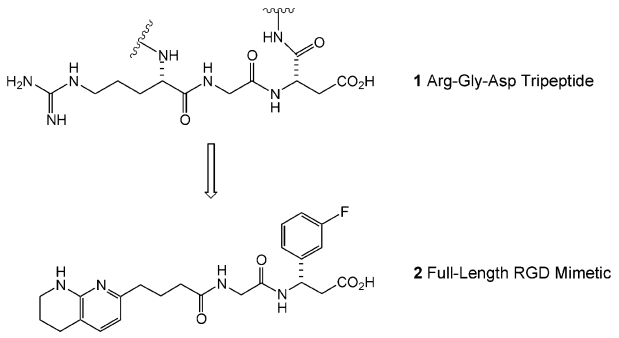
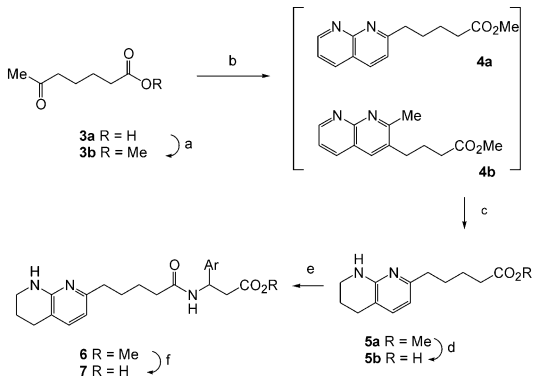


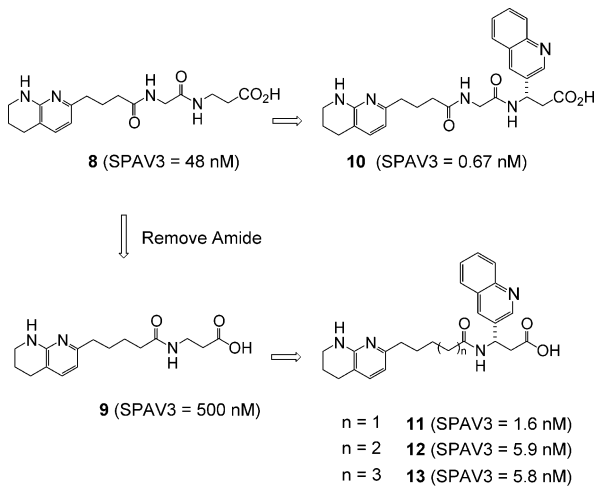
Figure 1. Evolution of full-length RGD mimetic.



Scheme 1. Synthesis of $\alpha_v\beta_3$ antagonists. Reagents and conditions: (a) MeOH, $ClCH_2CH_2Cl$, H_2SO_4; (b) 2-amino-3-formylpyridine, proline, EtOH; (c) PtO_2, H_2 (1 atm), 34% (three steps); (d) LiOH, EtOH, 79%; (e) 3-aryl-β-aminoester, EDC, HOBt, morpholine; (f) LiOH, EtOH.

reduction proved to be more facile. Catalytic hydrogenation of naphthyridines **4a** and **4b** was achieved in a smooth fashion with platinum oxide to give the desired tetrahydronapthyridine **5a**. Saponification gave the intermediate acid **5b**. Carboxylic acid **5b** was transformed to receptor antagonists **7** by standard carbodiimide coupling to 3-aryl-β-aminoesters followed by ester hydrolysis.

The $\alpha_v\beta_3$ antagonists prepared in this study were tested for their ability to inhibit the in vitro binding of a high affinity radioligand to human $\alpha_v\beta_3$ immobilized on scintillation proximity beads (SPAV3).[7] Selectivity for the vitronectin receptor ($\alpha_v\beta_3$), versus the fibrinogen receptor ($\alpha_{IIb}\beta_3$) was determined by measuring inhibition of the rate of ADP-stimulated platelet aggregation.[8] Full-length receptor antagonists typified by **8** (Scheme 2) have a linear backbone that spans ten atoms between the terminal carboxylic acid and tetrahydro[1,8]naphthyridine (THN). In an effort to probe the effects of amide deletion and chain length alterations within this series of RGD mimetics, analogue **9** which lacks the central asp-gly amide was prepared and evaluated. The *chain-shortened* antagonist **9** which has a chain-length of eight atoms between the carboxylic acid and THN terminus, has an IC_{50} in the SPAV3 assay that is approximately 10-fold less potent than the corresponding full-length analogue **8**. This result prompted us to incorporate a potency enhancing 3-quinolinyl substituent which imparted significant potency in our



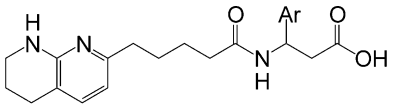
Scheme 2. Chain-shortened RGD mimetics.

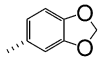
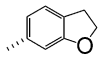
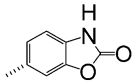
receptor binding assay to the full-length analogues **10** and the chain-shortened counterparts **11**. Although the potency of **11** is modestly compromised in comparison to **10**, the chain-shortened analogue **11** exhibits an excellent pharmacokinetic profile when dosed orally to dogs with good bioavailability (F = 65%), low clearance (Cl = 5.8 mL/min/kg), and moderate plasma half-life ($T_{1/2}$ = 2.4 h). In contrast, our earlier series of full-length analogues generally had much poorer pharmacokinetics (F ~ 10%; Cl > 20 mL/min/kg). Chain-length was further investigated in this amide-deleted series by increasing the chain-length of **11** by one methylene unit (**12**; SPAV3 = 5.9 nM) and by two methylene units (**13**; SPAV3 = 5.8 nM).[9] From this study, we concluded that the chain-shortened **11**, with eight atoms separating the THN N-terminus and carboxylic acid, possessed a potency-optimized chain length in the amide-deleted series.

From previous studies, we discovered that 3-aryl moieties have significant potential to affect receptor binding affinity and to modify physicochemical properties of the derived antagonists.[5] Indeed, replacement of the 3-quinolinyl substituent in **11** with either benzodioxole **14** or 6-dihydrobenzofuranyl **15** yielded potent chain-shortened antagonists with reduced lipophilicity (Table 1). The 5-pyrimidinyl substituent **17** provided a less potent analogue with increased hydrophilicity. The benzoxazolidone **18** is an appreciably less potent $\alpha_v\beta_3$ antagonist with an IC_{50} in the SPAV3 assay of 13 nM. None of these $\alpha_v\beta_3$ antagonists had significant activity in our platelet aggregation assays.

Pharmacokinetic evaluations of these $\alpha_v\beta_3$ antagonists were made following their oral and iv administration to dogs (Table 1). Compared to the quinoline lead **11**, the dihydrobenzofuran analogue **15** displayed a significantly improved oral profile. Within this series of compounds, it was evident that plasma clearance and oral bioavailability were closely related to measured Log P. Indeed, the more polar benzoxazolidone antagonist **18** and 5-pyrimidinyl **17** suffer decreased bioavailability and higher clearance relative to **11** and **14**. From this series, dihydrobenzofuran **15** represents

Table 1. Aryl substitution on chain-shortened backbone: potency and dog pharmacokinetics[a]



Entry	Ar	SPAV3 (IC_{50}, nM)	Plaggin (IC_{50}, nM)	F (%)	CI (mL/min/kg)	$T_{1/2}$ (h)	Log P
11		1.6	4440 nM	65	5.8	2.4	0.76
14		1.5	> 10 μM	94	1.2	2.4	0.47
15		3.0	> 10 μM	99	1.2	2.5	0.53
16		23.0	> 10 μM	81	2.0	5.5	0.29
17		3.3	> 10 μM	10	26	2.4	−1.21
18		13.1	> 10 μM	25	37	1.2	−0.24

[a]Compounds were dosed at 1 mpk po and 0.2 mpk iv to dogs ($n = 2$).

an optimal compound in terms of receptor potency, pharmacokinetics, and physicochemical properties.

In summary, this series of chain-shortened $\alpha_v\beta_3$ antagonists provides high affinity, integrin-selective ligands with good pharmacokinetics in dogs. This finding represents the first demonstration that the molecular framework of $\alpha_v\beta_3$ RGD mimetics can be dramatically modified by the removal of two atoms between the carboxylic acid and guanidine surrogate while preserving integrin affinity and selectivity.[10,11] Deletion of the arg-gly amide from these tripeptide mimetics provides antagonists with lower plasma clearance and improved bioavailability. In keeping with our observations of full-length antagonists, 3-aryl substituents provide a significant enhancement in receptor affinity. Additionally, the 3-aryl substituent is capable of modifying lipophilicity of the derived antagonists. Within this series of chain-shortened antagonists, measured Log P correlates with lower plasma clearance. Further studies on these structurally novel chain-shortened $\alpha_v\beta_3$ antagonists will be reported in due course.

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