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Non-Peptide $\alpha_v\beta_3$ Antagonists. Part 5: Identification of Potent RGD Mimetics Incorporating 2-Aryl β-Amino Acids as Aspartic Acid Replacements

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Abstract—A series of novel, highly potent $\alpha_v\beta_3$ receptor antagonists with favorable pharmacokinetic profiles has been identified. In this series of antagonists, 2-aryl β-amino acids function as potent aspartic acid replacements.

Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass and associated with an increased risk of fractures.[1] In post-menopausal women, osteoporotic bone loss results from a net increase in the number and activity of bone-resorbing osteoclast cells. The integrin receptor $\alpha_v\beta_3$ is highly expressed in osteoclasts and plays a critical role in both the adhesion and migration of osteoclasts on the bone surface.[2] Antibodies to $\alpha_v\beta_3$, and more recently non-peptide RGD (arg-gly-asp) mimetics, have been reported to inhibit bone resorption in vitro and prevent bone loss in vivo.[3] Our laboratories have been active in the search for non-peptide $\alpha_v\beta_3$ antagonists that could be utilized as novel therapies in the prevention and treatment of osteoporosis.

In a previous communication,[4] we described a novel, potent class of 'chain-shortened' $\alpha_v\beta_3$ antagonists that display favorable pharmacokinetic profiles. We have also reported antagonists to the integrin receptor GPIIbIIIa (also known as $\alpha_{IIb}\beta_3$),[5] that also recognizes the RGD tripeptide sequence. A critical potency-enhancing feature identified in an earlier series of GPIIbIIIa antagonists[6] was the sulfonamide substitiuent alpha to the carboxylic acid terminus. Indeed, α-sulfonamyl $\alpha_v\beta_3$ antagonists were known to be potent inhibitors although oral pharmacokinetic profiles as a whole were poor.[7] We postulated that α-aryl substituted analogues might also function as potent $\alpha_v\beta_3$ antagonists, while maintaining similar physical properties and pharmacokinetic profiles to their β-aryl counterparts. We examined the 3-aryl versus 2-aryl substitution SAR in the chain-shortened series and in particular for substituted and cyclized tetrahydronaphthyridine analogues (Fig. 1).

Chemistry

The synthesis of specific 2-aryl β-amino esters and the final products are shown in Schemes 1–4. This chemistry

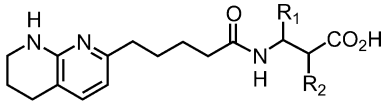

Figure 1. 2-Aryl versus 3-aryl substitution. For 2-aryl series, $R_1 = H$, $R_2 = aryl$; For 3-aryl series, $R_1 = aryl$, $R_2 = H$.

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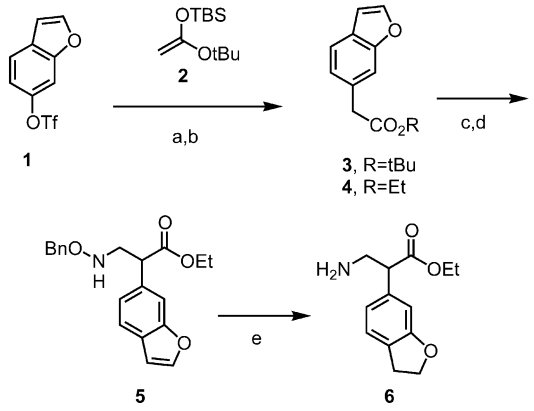
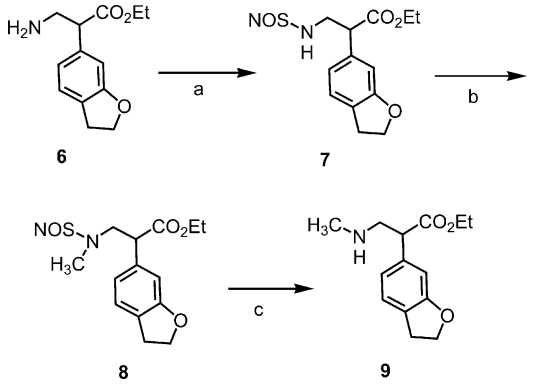


Scheme 1. (a) $Pd_2(dba)_3$, dppf, LiOAc; (b) HCl/EtOH; (c) LDA, TMS-Cl, THF; (d) CH_2NOBn, TMS-OTf (cat), CH_2Cl_2; (e) $Pd(OH)_2$, EtOH, H_2.

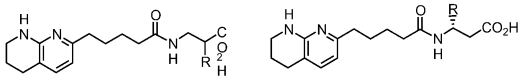


Scheme 2. (a) *p*-Nitrophenylsulfonyl chloride, aq $NaHCO_3$, CH_2Cl_2; (b) DIAD/DEAD, PPh_3, THF/MeOH; (c) mercaptoacetic acid, Et_3N, CH_2Cl_2.

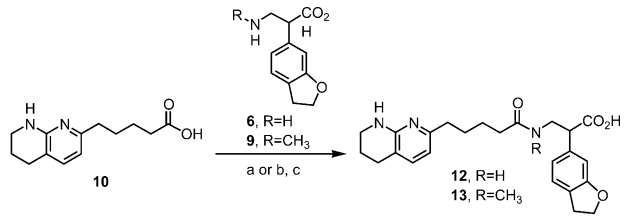
was applied to prepare the other 2-aryl analogues shown in Table 1.

The preferred route for synthesis of the 2-aryl β-amino esters utilized a Mannich-type addition of the lithio enolate of an aryl acetate to benzyloxime of formaldehyde (Scheme 1). Heck coupling of the aryl triflate[8] **1** with the silyl ketene acetal **2** derived from *tert*-butyl acetate provided the aryl acetate **3**. Transesterification of **3** was accomplished in ethanolic HCl to furnish **4**. Reaction of the silyl ketene acetal of **4** with the benzyloxyimine, in the presence of a catalytic amount of TMS-triflate, gave the benzyloxyamine **5** in good yield.[9] Hydrogenolysis/hydrogenation of **5** with palladium hydroxide in ethanol provided the desired 2-aryl β-amino ester **6** as a racemic mixture.

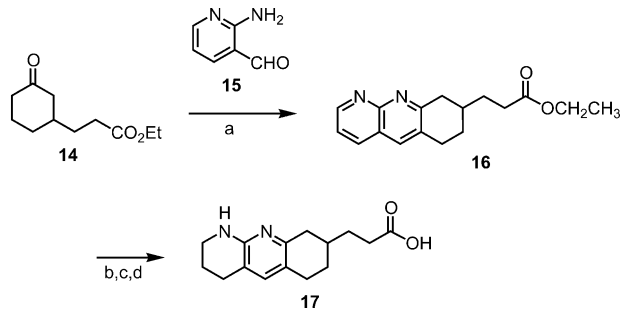
Table 1. SPAV3 binding data for 2-aryl versus 3-aryl analogues



R	Entry	SPAV, IC_{50} (nM)	Entry	SPAV3, IC_{50} (nM)
	**1-1A**	57.4	**1-1B**	84
	**1-2A**	10.9	**1-2B**	22.8
	**1-3A**	0.82	**1-3B**	1.07
	**1-4A**	1.01	**1-4B**	3.03



Scheme 3. (a) Where R = H, EDC, HOBT, Et_3N, DMF; (b) where R = CH_3, *N*,*N*,*N*′,*N*′-bis(tetramethylene)-chloroformamidinium hexafluorophosphate, CH_2Cl_2, DIPEA; (c) 1 N NaOH, MeOH/THF.



Scheme 4. (a) L-Proline, ethanol, reflux; (b) Pd/C, ethanol H_2, 1 atm; (c) chiral resolution: chiral OD column, 95% hexane, 5% 2-propanol, 0.1% diethylamine added, slower-moving enantiomer was isolated in 94% ee; (d) 1 N NaOH, THF/H_2O.

The *N*-methyl β-amino ester **9** was prepared as shown in Scheme 2. Sulfonylation of **6** followed by a Mitsunobu reaction with methanol yielded compound **8**. Desulfonylation of **8** with mercaptoacetic acid and triethylamine in methylene chloride provided the *N*-methyl β-amino ester **9**.

As described in Scheme 3, the β-amino ester **6** was coupled to the tetrahydronaphthyridinyl-pentanoic acid **10** using standard carbodiimide conditions, followed by saponification to provide **12**. The *N*-methyl β-amino ester **9** was coupled using PYCLU (*N*,*N*,*N*′,*N*′-bis(tetramethylene)-chloroformamidinium hexafluorophosphate) conditions, and also underwent saponification to yield the desired **13**.

The tetrahydronaphthyridinyl tricyclic side chain **17** was prepared as described in Scheme 4. The known cyclohexone propionic acid ethyl ester[10] **14** underwent a Friedländer condensation with 2-amino-3-formyl pyridine[11] **15** to yield the naphthyridine product **16**. Reduction of the naphthyridine to tetrahydronaphthyridine was accomplished using palladium hydroxide on carbon in ethanol. Resolution on a chiral OD column isolated the more slowly eluting enantiomer, and subsequent

saponification provided the tetrahydronaphthyridinyl tricyclic acid **17**.

Syntheses of the tetrahydronaphthyridinyl-pentanoic acid side chain and its 3-cyclopropyl derivative, as well as the β-substituted β-alanines, have been previously described.[12]

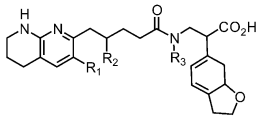
Results and Discussion

Compounds were evaluated for their ability to inhibit the binding of a high affinity radioligand to human $\alpha_v\beta_3$ immobilized on scintillation proximity beads (SPAV3).[13] Table 1 depicts a comparison of the IC_{50} values in this assay for the corresponding 2- and 3-aryl-substituted chain-shortened analogues. With the exception of **1-1B**, all of the 3-aryl analogues were tested as the single (*S*)-enantiomer. The racemic 2-aryl analogues exhibited in vitro potencies that were comparable to or better than the corresponding 3-aryl analogues. Interestingly, the rank order for the aryl substituents is the same in both series, suggesting that in both cases the aryl substituents might be accessing the same binding site in the receptor.

Further potency enhancements were investigated in the 2-aryl series (Table 2). The *N*-methyl amide analogue **2-2** did not significantly increase SPAV3 potency over the N–H analogue. The 3-cyclopropyl analogue **2-3** gave a significant 3-fold increase in potency. However, incorporation of these two substitutions (**2-4**) did not provide a further increase in potency. Although the constrained tricyclic analogue **2-5** did not provide an increase in potency over **1-4A**, the corresponding *N*-methyl amide tricyclic did afford a 3-fold increase in SPAV3 potency.

Pharmacokinetic data following oral and iv dosing in dogs for selected compounds are summarized in Table 3. Entry **1-4B**, the 3-substituted dihydrobenzofuran analogue, demonstrated excellent oral bioavailability with low clearance and a moderate half-life. The 2-aryl analogue **1-4A** also demonstrated good oral bioavailability, with low clearance and an improved half-life. The cyclopropyl analogue **2–3** displayed good oral bioavailability, but also possessed a greatly reduced half-life. The tricyclic analogues **2–5** and **2–6** displayed low oral bioavailability and short half-lives.

Table 2. Additional structural modifications and their associated SPAV3 binding affinities



Entry	R1	R2	R3	SPAV3, IC_{50} (nM)
1–4A	H	H	H	1.01
2–2	H	H	CH_3	0.74
2–3		H	H	0.29
2–4		H	CH_3	0.49
2–5			H	0.72
2–6			CH_3	0.35

Table 3. Pharmacokinetic data for selected compounds following oral and iv dosing in dogs

Entry	F (%)	CI (mL/min/kg)	$T_{1/2}$
1-4B	99	2.0	3.5
1-4A	47	6.6	4.7
2-3	40	13.7	0.7
2-5	1.1	18.9	1.1
2-6	18	10.3	1.6

Conclusion

In summary, we have identified a new class of highly potent, non-peptide $\alpha_v\beta_3$ receptor antagonists, with favorable pharmacokinetic profiles, where a 2-aryl β-amino acid functions as a potent aspartic acid replacement. In particular, analogue **1-4A** shows improved (3-fold) binding affinity for the $\alpha_v\beta_3$ receptor versus **1-4B**, while maintaining a good pharmacokinetic profile. Further improvements in potency were realized in this series through substitution on the tetrahydronaphthyridine moiety, incorporation of a tricyclic N-terminus, or methylation of the amide moiety.

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13. SPAV3 is a binding assay that uses purified human recombinant $\alpha_v\beta_3$ and 4-[2-(2-aminopyridin-6-yl)ethyl]benzoyl-2(*S*)4-^{125}Iodophenylsulfonylamino-β-alanine. For protocol, see: Duggan, M. E.; Hartman, G. D.; Hoffman, W. F.; Meissner, R. S.; Perkins, J. J.; Askew, B. C.; Coleman, P. J.; Hutchinson, J. H.; Naylor-Olsen, A. M. US Patent 5,981,546, 1999.