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Nonpeptide $\alpha_v\beta_3$ antagonists: identification of potent, chain-shortened 7-oxo RGD mimetics

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Abstract—Potent, novel 7-oxo $\alpha_v\beta_3$ antagonists have been prepared. These antagonists offer decreased plasma protein binding and excellent pharmacokinetic profiles.

The vitronectin receptor $\alpha_v\beta_3$ is a member of the integrin superfamily of receptors that is highly expressed in osteoclasts.[1,2] Osteoclasts are hemopoietic multinucleated cells which are responsible for bone resorption. Patients with osteoporosis have decreased bone mass due to an imbalance between osteoclast-mediated bone resorption and bone formation.[3] Peptides and proteins that contain the arginine-glycine-aspartic acid (RGD) tripeptide including osteopontin, vitronectin, and echistatin, and small molecule $\alpha_v\beta_3$ antagonists have been shown to inhibit bone resorption in vitro and in vivo.[4] This report discusses our efforts to discover novel nonpeptide, small molecule $\alpha_v\beta_3$ antagonists for the prevention and treatment of osteoporosis.

Potent nonpeptide $\alpha_v\beta_3$ antagonists that have been reported contain a guanidine mimetic and a carboxylic acid linked together by various tethers and constraints.[5] Previously we detailed the design and synthesis of novel, nonpeptide, 'chain shortened' $\alpha_v\beta_3$ antagonists (**A**, Fig. 1) with significantly improved pharmacokinetics.[6,7] Amide deletion resulted in a class of potent aliphatic compounds (**B**) that have good affinity for $\alpha_v\beta_3$ and excellent dog pharmacokinetics but are highly plasma protein bound.[8] These inhibitors were more lipophilic and displayed high plasma protein binding. High plasma protein binding can be associated with reduced activity at the targeted receptor or enzyme.[9] We therefore directed our efforts toward improving plasma free fraction through the introduction of polar groups on the molecule. Herein we report the identification of a class of

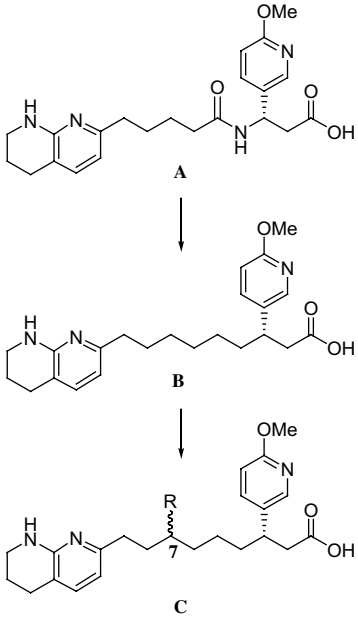

Figure 1. R = O, OH.

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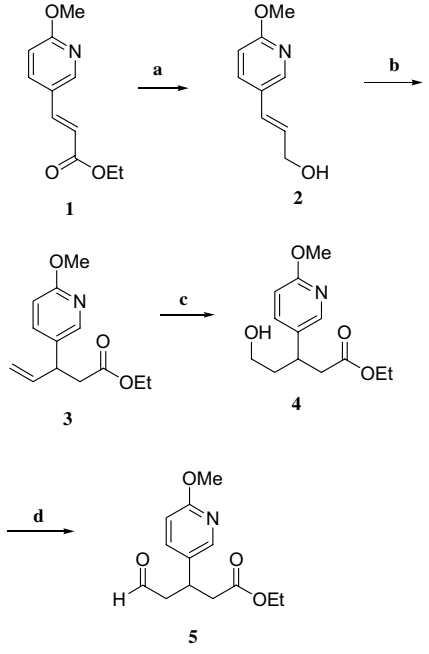
$\alpha_v\beta_3$ antagonists (**C**, Fig. 1) that are substituted with keto and hydroxy groups at the 7-position on the aliphatic tether providing reduced plasma protein binding.

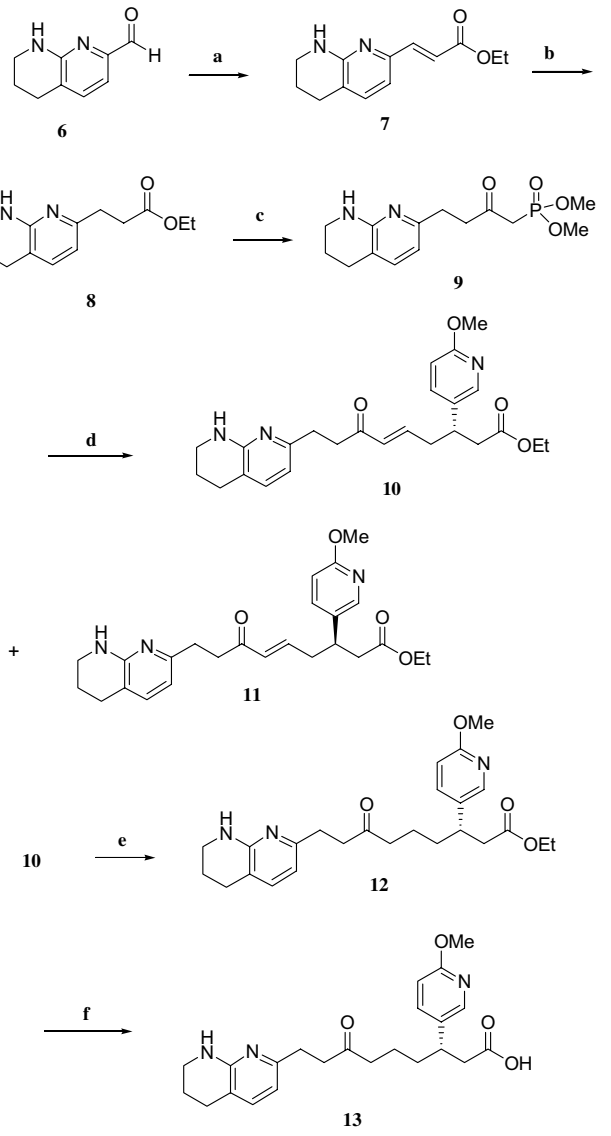
The synthesis of the desired compounds is described in Schemes 1–3. Scheme 1 illustrates the synthesis of the key intermediate, aldehyde **5**. Ethyl (6-methoxypyridin-3-yl) acrylate[10] **1** was reduced to the corresponding alcohol **2** with DIBAL at −78 °C. Next a Johnson–Claisen rearrangement provided the alkene **3**. Hydroboration followed by a Swern oxidation resulted in the desired aldehyde **5**.

Scheme 2 outlines the preparation of the 7-keto antagonist **13**. Ester **7** was prepared through a Wittig olefination with 5,6,7,8-tetrahydro[1,8]naphthyridine-2-aldehyde.[11] Hydrogenation with 10% Pd/C followed by the addition of the lithium anion of dimethyl methylphosphonate provided the desired keto phosphonate **9**. It was then condensed with aldehyde **5** to give the 7-keto esters **10** and **11**. Separation of these enantiomers on a Chiralcel® AS column was followed by reduction of the more mobile enone **10** to its corresponding ketone **12**. Subsequent saponification of **12** provided the tetrahydronaphthyridine 7-keto acid **13**.

Scheme 3 illustrates the catalytic diastereoselective reduction of ketone **10** to the chiral alcohols **16** and **17**. Ketone **10** was reduced to the corresponding alcohols with either (*S*)-2-methyl-CBS-oxazaborolidine or (*R*)-2-methyl-CBS-oxazaborolidine. The configurations of the reduction products were inferred from literature precedent,[12] and diastereomeric excess was determined to be >90% by chiral HPLC comparison to the mixture



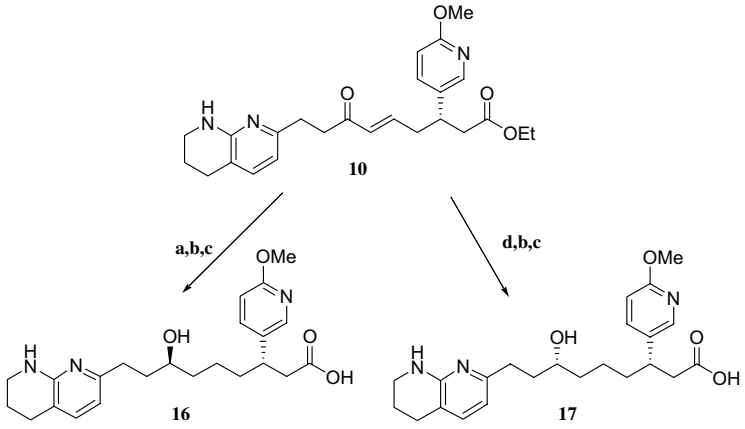
Scheme 1. Reagents and conditions: (a) DIBAL, THF, −78 °C (82%); (b) catalytic propionic acid, $H_3CC(OCH_3)_3$, reflux (77%); (c) 9-BBN, THF, $NaBO_3/NaHCO_3$ (57%); (d) oxalyl chloride, DMSO, triethylamine, CH_2Cl_2 (84%).



Scheme 2. Reagents and conditions: (a) $Ph_3PCHCO_2CH_2CH_3$, toluene, reflux (87%); (b) H_2, Pd/C, ethanol (98%); (c) $CH_3PO(OCH_3)_2$, *n*-BuLi, −78 °C, THF (75%); (d) K_2CO_3, DMF, **5** (64%); (e) H_2, Pd/C, ethanol, (94%); (f) 1 N NaOH, ethanol (47%).

produced by $NaBH_4$ reduction. The alcohols **16** and **17** were subsequently hydrogenated and hydrolyzed to provide the desired alcohols.

Table 1 summarizes the in vitro and pharmacokinetic data of the compounds of interest. For reference, the parent compound, antagonist **B**, showed excellent affinity for the $\alpha_v\beta_3$ integrin in the SPAV3[13] assay and was potent in the OCFORM[14] assay, demonstrating antagonism for $\alpha_v\beta_3$ in a cell based system. In addition, **B** was a highly selective antagonist for the $\alpha_v\beta_3$ integrin over the related $\alpha_{IIb}\beta_3$ integrin demonstrated by its inability to inhibit $\alpha_{IIb}\beta_3$-mediated platelet aggregation (PLAGGIN[15]). In the dog, compound **B** had good oral bioavailability, a low clearance of 4 mL/min/kg, and an excellent iv plasma half-life of 9 h. The compound was, however, highly bound by human protein with a free fraction of <1%. As free drug concentrations have



Scheme 3. Reagents and conditions: (a) (*S*)-2-methyl-CBS-oxazaborolidine, $BH_3{\cdot}S(CH_3)_2$, CH_2Cl_2, −40 °C (86%); (b) H_2, Pd/C, ethanol (94%); (c) 1 N NaOH, ethanol, (63%); (d) (*R*)-2-methyl-CBS-oxazaborolidine, $BH_3{\cdot}S(CH_3)_2$, CH_2Cl_2, −40 °C (73%).

Table 1. In-vitro potencies and pharmacokinetic data

	SPAV3 (IC_{50}, nM)	OCFORM (IC_{50}, nM)	PLAGGIN (IC_{50}, nM)	Log *P*	PB (%)	Dog pharmacokinetics[a]		
						Oral F (%)	Cl (mL/min/kg)	$t_{1/2}$ (h)
B	0.65 ± 0.76	39 ± 5	ND	1.7	>99	49	4 ± 0.3	9 ± 1
13	0.16 ± 0.09	12 ± 1	>10,000	0.0	97.3	75	6.7 ± 0.4	7 ± 2
16	0.24 ± 0.15	8 ± 0.5	>10,000	0.1	93.0	60	2.5 ± 1	6.1 ± 3
17	0.24 ± 0.06	36 ± 7	>10,000	0.0	95.1	ND	ND	ND

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

been shown to correlate well with in vivo efficacy, analogs with reduced protein binding were sought. While maintaining an excellent pharmacokinetic profile, the 7-keto analog **13** demonstrated increased potency in both the SPAV3 and OCFORM assays. As compared to **B**, compound **13** showed the desired decrease in plasma protein binding, which correlated well with an increased polarity as measured by Log *P*.[16] Each of the diastereomeric alcohols **16** and **17** showed further reductions in protein binding. The more potent analog **16** had a 7% plasma free fraction, while offering outstanding potency in the SPAV3 and OCFORM assays. Furthermore, alcohol **16** retained an excellent pharmacokinetic profile in dogs, with a bioavailability of 60%, an iv clearance of 2.5 mL/min/kg and a plasma half-life of 6 h. Selectivity versus $\alpha_{IIb}\beta_3$ is also maintained.

In an attempt to gain insight into the possible role of the C-7 oxo group in the binding of these compounds to the $\alpha_v\beta_3$ integrin, each was modeled in the crystal structure using our published procedure.[17] In each case, no hydrogen bonding interaction was found to occur between the C-7 oxygen and the receptor. It appeared that in the integrin bound state, this atom lay in the solvent exposed region. The addition of this atom did, however, encourage a chain extended conformation suitable for binding to the modeled integrin.

We have thus demonstrated that the introduction of an oxygen atom to position C-7 of compound **B**, in the form of either a ketone or a hydroxyl group, can offer attractive $\alpha_v\beta_3$ antagonists. Compounds from this series are potent and selective inhibitors of $\alpha_v\beta_3$, display reduced plasma protein binding, and retain excellent pharmacokinetic profiles in the dog.

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