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ORALLY BIOAVAILABLE NONPEPTIDE VITRONECTIN RECEPTOR ANTAGONISTS WITH EFFICACY IN AN OSTEOPOROSIS MODEL

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Abstract: A new series of potent nonpeptide vitronectin receptor antagonists, based on a novel carbocyclic Gly-Asp mimetic, has been discovered. A representative of this series, SB 265123 (**4**), has 100% oral bioavailability in rats, and is orally active in vivo in the ovariectomized rat model of osteoporosis.

Integrin $\alpha_V\beta_3$, also referred to as the vitronectin receptor,[1] is expressed on a variety of cell types, including osteoclasts, vascular smooth muscle cells, and endothelial cells, and is known 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, antagonists of integrin $\alpha_V\beta_3$ are expected to have utility in the treatment of several human diseases, including osteoporosis, restenosis following percutaneous transluminal coronary angioplasty (PTCA), and diseases involving neovascularization.[4c,5,6]

Our preliminary studies[7a] on nonpeptide $\alpha_V\beta_3$ antagonists culminated in the identification of SB 223245 (**1**, Table 1), a potent, nonpeptide $\alpha_V\beta_3$ antagonist that has good selectivity versus the related integrin $\alpha_{IIb}\beta_3$.[8] Unfortunately, **1** has low oral bioavailability and a short half-life in rats (Table 2), which precluded our objective to further evaluate this compound by oral administration in in vivo disease models. During the course of our studies, a potent but nonselective semipeptide $\alpha_V\beta_3$ antagonist, SC 56631,[8a] was reported to be active in the ovariectomized (Ovx) rat model of osteoporosis. While this experiment established that an $\alpha_V\beta_3$ antagonist could prevent the bone loss associated with estrogen deficiency, the experimental design, involving the continuous intravenous infusion of a very high dose of compound, did not address the effectiveness of an $\alpha_V\beta_3$ antagonist following once or twice a day oral administration of a more "drug-like" dose. Our objective in following up our initial studies was to identify compounds with improved pharmacokinetics to allow for an oral proof of concept study. In this communication, we report the results of these efforts.

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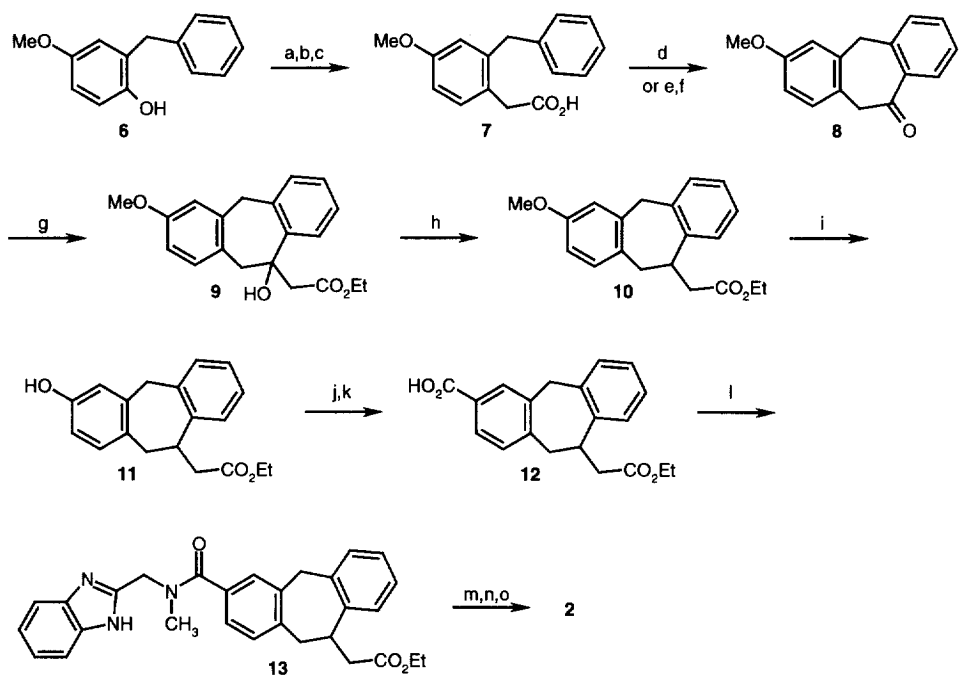
Chemistry The method for preparation of the carbocyclic RGD mimetic **2** is shown in Scheme 1. The known 2-benzyl-4-methoxyphenylacetic acid (**7**) was prepared either according to the reported literature procedure[9] or from the known phenol **6**[10] by allylation[11] of the corresponding triflate followed by cleavage of the olefin with ruthenium tetroxide.[11,12] Cyclization to the tricyclic ketone **8** was accomplished either by brief exposure to warm polyphosphoric acid (PPA) or by the more efficient two-step process involving formation of the acid chloride followed by Friedel–Crafts cyclization. Reaction of **8** with the lithium enolate of ethyl acetate, in the presence of TMEDA to suppress enolization, gave hydroxyester **9**, which was converted to **10** by an in situ dehydration/hydrogenation sequence. Compound **10** was demethylated with ethanethiol in the presence of aluminum trichloride,[13] and the resulting phenol **11** was converted to the carboxylic acid **12** by carboxylation of the corresponding triflate.[14] EDC-mediated coupling gave compound **13**, which on saponification gave **2** (Table 1).

Scheme 1

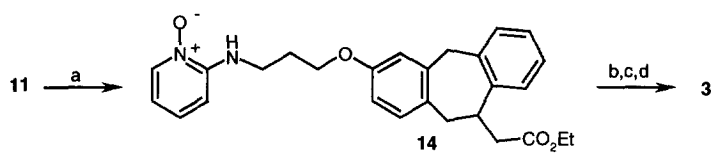


Reagents and conditions: (a) Tf_2O, 2,6-lutidine, CH_2Cl_2, -78 °C to RT (96%); (b) (allyl)$SnBu_3$, LiCl, $(Ph_3P)_2PdCl_2$, DMF, 95 °C (99%); (c) $RuCl_3$, H_5IO_6, CH_3CN, CCl_4, H_2O, 0 °C to RT (74%); (d) PPA, 100-110 °C (48%); (e) $(COCl)_2$, benzene, reflux; (f) $AlCl_3$, CH_2Cl_2, 0 °C to RT (71% for two steps); (g) EtOAc/LiHMDS, THF, -78 °C (73%); (h) H_2, 10% Pd/C, conc HCl, AcOH (91%); (i) EtSH, $AlCl_3$, CH_2Cl_2, 0 °C to RT (95%) (j) Tf_2O, 2,6-lutidine, CH_2Cl_2, -78 °C to RT (92%); (k) CO, $Pd(OAc)_2$, KOAc, dppf, DMSO, 70 °C (95%); (l) 2-(methylamino)methylbenzimidazole dihydrochloride, EDC, HOBt · H_2O, (*i*-Pr)$_2$NEt, DMF (95%); (m) 1.0 N LiOH, THF, H_2O, 40 °C; (n) 1.0 N HCl, H_2O; (o) 5% $NaHCO_3$, MeOH (45% for three steps).

The ether-linked compounds were prepared as illustrated in Scheme 2. The phenol **11**, on reaction with 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide (**15**) in a Mitsunobu reaction,[15] afforded ether **14**. Pyridine **15** was

prepared by reaction of commercially available 2-chloropyridine-N-oxide hydrochloride with 3-amino-1-propanol, according to the general literature procedure for the preparation of 2-aminopyridine derivatives.[16] The N-oxide of **14** was reduced by transfer hydrogenation,[16] and the ester was saponified to afford the racemic derivative **3** (Table 1) Compounds **4** and **5**, the (*S*)- and (*R*)-enantiomers of **3**, respectively, were prepared similarly from the corresponding enantiomerically pure phenols, which were obtained by a chiral HPLC resolution of phenol **11**.[17] The absolute configuration of the phenols was determined by X-ray crystallographic analysis of the (4-bromophenyl)urethane derivative of the (*S*)-phenol.[18]

Scheme 2



Reagents and conditions: (a) 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide (**15**), DEAD, Ph_3P, DMF (75%); (b) cyclohexene, 10% Pd/C, i-PrOH, reflux (63%); (c) 1.0 N NaOH, EtOH, 50 °C; (d) 1.0 N HCl, H_2O (79% for two steps).

Results and Discussion In follow-up studies on **1**,[7b–e] modifications to the 1,4-benzodiazepine system were evaluated in an effort to improve both biological activity and oral bioavailability. Although neither of these parameters could be improved sufficiently in the 1,4-benzodiazepine series, a wide range of functionality, including acidic, basic, lipophilic, and sterically demanding groups, was found to be tolerated at N-4 (the lactam nitrogen). In addition, N-1 could be replaced by a CH_2 group without loss of biological activity. In order to investigate the role of the lactam amide in binding interactions with the receptor, we considered replacement of this amide with an appropriate bioisostere. Since the structure–activity relationship (SAR) suggested that $\alpha_v\beta_3$ afforded considerable free space adjacent to the lactam amide, we reasoned that a fused phenyl ring might be tolerated. We also opted to replace N-1 with a CH_2 group, to afford a novel carbocyclic Gly-Asp mimetic. If the resulting 10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene-10-acetic acid system proved to be a suitable Gly-Asp mimetic, the resulting series would be more lipophilic than the 1,4-benzodiazepine series, and orally bioavailable compounds might result.

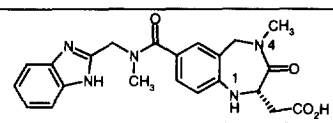
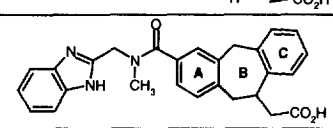
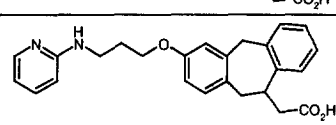
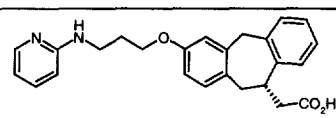
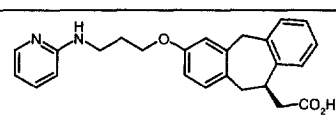
The benzo-fused compound **2** (Table 1) has good affinity for $\alpha_v\beta_3$, with K_i = 23 nM, while affinity for the related RGD-binding integrin, $\alpha_{IIb}\beta_3$ is considerably lower (K_i > 50,000 nM).[19,20] Therefore, replacing the lactam amide with the fused benzo ring resulted in only a small four to five-fold decrease in affinity for $\alpha_v\beta_3$, taking into account that SB 223245 is the pure active (*S*)-enantiomer, while **2** is racemic. This difference in activity is also reflected in the cell adhesion assay.[21] These results clearly indicate that the phenyl ring (ring C) in **2** (Table 1) is an effective bioisostere for the lactam amide in SB 223245.

Although **2** has good affinity for $\alpha_v\beta_3$, its potency at inhibiting cell adhesion is relatively poor. To increase potency, the benzimidazole group was replaced with other Arg mimetics, and the side chain amide was replaced with other linkers. The combination of a pyridylamino Arg mimetic[7d] and a propyloxy linker was very

favorable; the ether-linked compound **3** (Table 1) is significantly more active than the amide-linked compound **2**, with K_i = 8 nM in the $\alpha_v\beta_3$ binding assay and an IC_{50} = 65 nM in the cell adhesion assay. Further, **3** maintained a high degree of selectivity for $\alpha_v\beta_3$ relative to $\alpha_{IIb}\beta_3$.

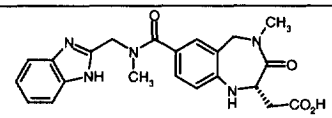
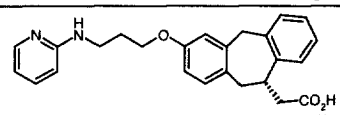
The (*S*)- and (*R*)-enantiomers of **3** (**4** and **5**, respectively) were evaluated in the $\alpha_v\beta_3$ binding assay, and as expected, the activity resided predominantly in the (*S*)-enantiomer, SB 265123 (**4**, Table 1). SB 265123 binds to $\alpha_v\beta_3$ with K_i = 4 nM, and has an IC_{50} = 60 nM in the cell adhesion assay. SB 265123 also binds to the closely related α_v integrin, $\alpha_v\beta_5$, with high affinity (K_i = 1.3 nM), but is >1000-fold less potent at binding to either $\alpha_{IIb}\beta_3$ (K_i = 9 uM) or $\alpha_5\beta_1$ (K_i = 18 uM). Consistent with its poor affinity for $\alpha_{IIb}\beta_3$, SB 265123 has an IC_{50} > 200 uM at inhibiting human platelet aggregation.[22]

Table 1 In vitro activity of nonpeptide $\alpha_v\beta_3$ antagonists

Number	Structure	$\alpha_v\beta_3$ K_i (nM)	$\alpha_{IIb}\beta_3$ K_i (nM)	$\alpha_v\beta_3$-mediated cell adhesion IC_{50} (nM)
1 (SB 223245)		2 ± 0.1	30,000 ± 2000	145
2		23 ± 1	>50,000	1800
3		8 ± 1	30,000 ± 2000	65
4 (SB 265123)		4 ± 1	9000 ± 2000	60
5		550 ± 50	---	---

Since **4** had a level of activity sufficient for in vivo testing, its pharmacokinetic profile (Table 2) was evaluated in rats,[23] where it was found to have a long half life, low clearance, and oral bioavailability on the order of 100%. This level of oral bioavailability appears to be somewhat of an overestimate, as enterohepatic recirculation may be contributing to the pharmacokinetic profile of this compound.[24] Nevertheless, very high oral bioavailability in a non-prodrug compound is unprecedented in the integrin antagonist field. Historically, the discovery of integrin antagonists with oral bioavailability greater than about 10% has been difficult, unless a prodrug strategy is employed as a means to mask the ionic functionality.[25]

Table 2 Pharmacokinetic profiles of $\alpha_V\beta_3$ antagonists

Number	Structure	$t_{1/2}$ (min)	Plasma Clearance (mL/min/kg)	Oral Bioavailability (%)
1 (SB 223245)		9-16	35 ± 2	3-7
4 (SB 265123)		181 - 378	3 ± 1	≈ 100

In biological studies, which are described in greater detail elsewhere,[26] SB 265123 was found to be a potent inhibitor of bone resorption both in vitro and in vivo. In the in vitro human osteoclast resorption assay, SB 265123 has IC_{50} = 48 nM, and in the in vivo thyroparathyroidectomized (TPTx) rat model of bone resorption, on continuous iv infusion at a rate of 2.53 mg/kg/hr, SB 265123 gives 85% inhibition of the calcemic response after 6 hr. Further, and very significantly, on twice a day oral dosing at 3, 10, and 30 mg/kg in the Ovx rat model of osteoporosis, SB 265123 inhibited bone loss in a dose-dependent fashion. This result suggests that $\alpha_V\beta_3$ antagonists have the potential to be orally administered drugs for the treatment of human disease. Further evaluation of members of this carbocyclic class of $\alpha_V\beta_3$ antagonists for the treatment of other human diseases, including restenosis following PTCA and diseases involving neovascularization, is ongoing.

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17. Racemic phenol **11** was resolved into its enantiomers by chiral HPLC using the following conditions: Daicel Chiralcel OJ column (21.2 x 250 mm), 20% ethanol in hexane mobile phase, 10 mL/min flow rate, uv detection at 254 nm, 100 mg injection; t_R for the (*S*)-enantiomer = 17 min; t_R for the (*R*)-enantiomer = 22 min.
18. Tables of crystal data, fractional atomic coordinates, anisotropic thermal parameters for non-hydrogen atoms, bond distances and angles have been included with the deposited supplementary material (deposition number CCDC 120340) sent to the Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge CB2 1EW, United Kingdom. Listings of structure factors are available from the authors upon request.
19. 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. *Mol. Pharm.* **1996**, *50*, 529.
20. 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 Ali, F. E.; Bennett, D. B.; Calvo, R. R.; Elliott, J. D.; Hwang, S.-M.; Ku, T. W.; Lago, M. A.; Nichols, A. J.; Romoff, T. T.; Shah, D. H.; Vasko, J. A.; Wong, A. S.; Yellin, T. O.; Yuan, C.-K.; Samanen, J. M. *J. Med. Chem.* **1994**, *37*, 769.
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