Discovery of Orally Active Nonpeptide Vitronectin Receptor Antagonists Based on a 2-Benzazepine Gly-Asp Mimetic

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Received August 30, 1999

Introduction. The vitronectin receptor, also known as αvβ3, is a member of the integrin family of heterodimeric transmembrane glycoprotein complexes that function in cellular adhesion events and signal transduction processes.[1] Integrin αvβ3 is expressed on almost all cells originating from the mesenchyme and has been shown to mediate several biologically relevant processes, including adhesion of osteoclasts to the bone matrix,[2−5] migration of vascular smooth muscle cells,[6−8] and angiogenesis.[9] As a result, antagonists of integrin αvβ3 are expected to have utility in the treatment of several human diseases, including osteoporosis,[10] restenosis following percutaneous transluminal coronary angioplasty (PTCA),[6,7] and diseases involving neovascularization, such as rheumatoid arthritis,[11,12] cancer,[13−16] and ocular diseases.[17,18] Like many, but not all, integrins αvβ3 is known to recognize the arginine−glycine−aspartic acid (RGD) tripeptide sequence.[1] Therefore, we[19−23] and others[10,13,24−27] have investigated peptidomimetic approaches to identify αvβ3 antagonists. In this communication, we describe a new series of small molecule RGD mimetics that are highly potent, orally active αvβ3 antagonists. Selected members of this series are potent inhibitors of bone resorption in vitro and in vivo and have activity in an animal model of osteoporosis.

Chemistry. The benzazepine derivatives were prepared by the procedures outlined in Schemes 1−3. The syntheses of **5** and **7** illustrate the methods. Commercially available 4-bromo-3-methylanisole (**8**) was converted to benzazepine **14** using a slight modification of our general method for the synthesis of 2-benzazepine derivatives (Scheme 1).[28] The racemic benzazepine **14** was resolved into its (*R*)- and (*S*)-enantiomers by chiral HPLC.[29] The absolute configurations were assigned following X-ray crystallographic analysis of the (*S*)-phenol **16**,[30] which was obtained by demethylation of **15** with BBr_3.

For the synthesis of **5**, the (*S*)-phenol **16** was reacted with the pyridine derivative **18** in a Mitsunobu reaction (Scheme 2).[31,32] The resulting ether derivative **19** was converted to **5** by a reduction/saponification sequence described previously for related compounds.[23,33]

Compound **7** was prepared from the (*S*)-phenol **16** and 6-(methylamino)-2-pyridylethanol (**26**), which was prepared straightforwardly from 2-amino-6-picoline (Scheme 3). Compound **26** was conveniently purified by crystallization of the corresponding formate salt.

Results and Discussion. In our preliminary studies,[19] we identified **1** (Table 1), a potent, 1,4-benzodiazepine-based αvβ3 antagonist with a good in vitro profile but with low oral bioavailability in rats. Followup studies on **1**[20−22] indicated that neither biological activity nor oral bioavailability could be improved substantially in the 1,4-benzodiazepine series. However, **1** proved to be a suitable template for the design of second-generation αvβ3 antagonists with improved properties. An initial success was the identification of **2**,[23] wherein the lactam amide, the linking amide, and N-1 of the 1,4-benzodiazepine system were replaced with more hydrophobic groups and the benzimidazole arginine (Arg) mimetic was replaced with an aminopyridine Arg mimetic. Compound **2** has improved biological activity relative to **1** and has high oral bioavailability in rats (approximately 100%).[34] We were concerned, however, about the level of biological activity of **2** in cell-based assays,[35] so we continued our investigations in search of orally bioavailable αvβ3 antagonists with improved biological activity.

Beginning with **1**, we envisioned replacing the linking amide with an ether linkage, similar to that in **2**, while retaining the seven-membered ring lactam (Figure 1). Previously, in our work leading to **2**, we found that replacing the lactam amide with a phenyl ring caused a 4-fold drop in affinity for αvβ3,[23] which suggests that the lactam amide may interact favorably with the receptor. Since replacing the linking amide with an ether linkage in the 1,4-benzodiazepine series would generate a 4-alkoxyaniline derivative, we were con-

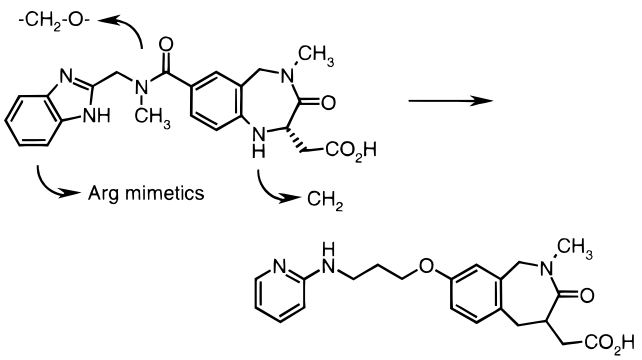

Figure 1. Strategy for modification of **1**.

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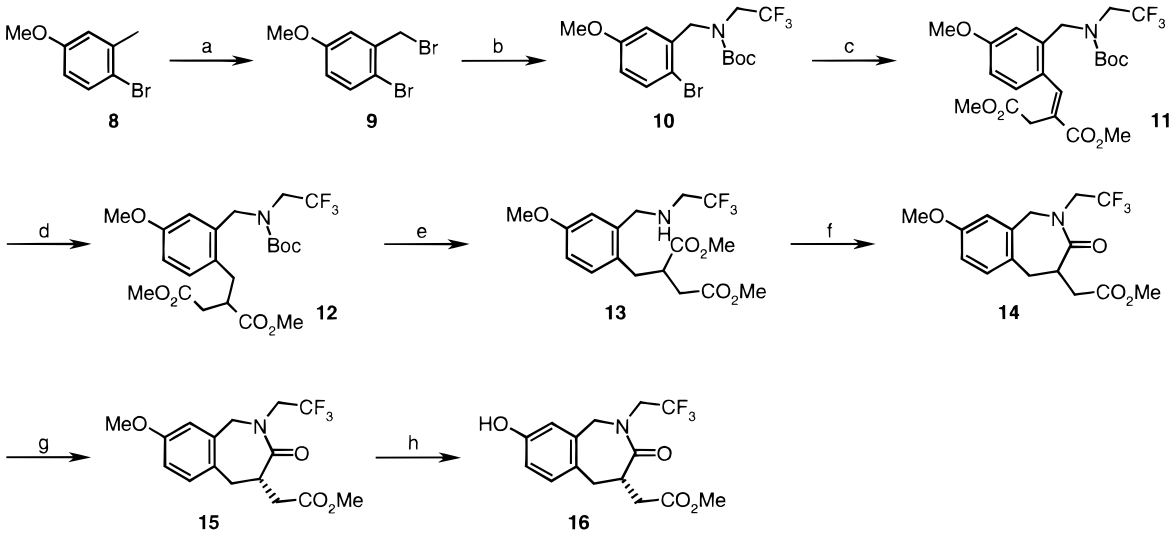
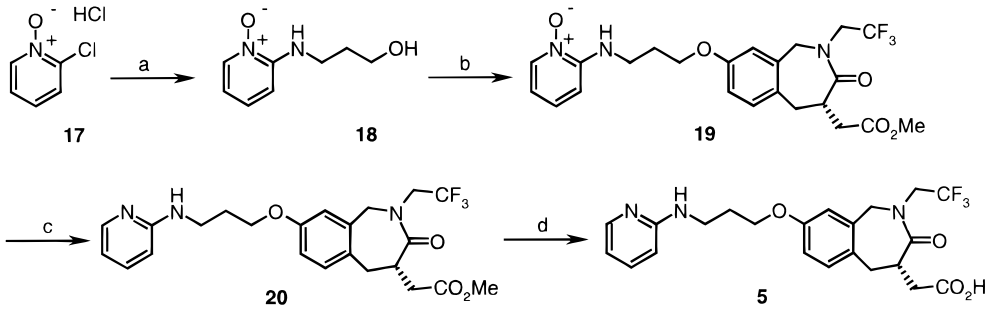
10.1021/jm990446u CCC: $19.00 © 2000 American Chemical Society
Published on Web 12/23/1999

Scheme 1[a]



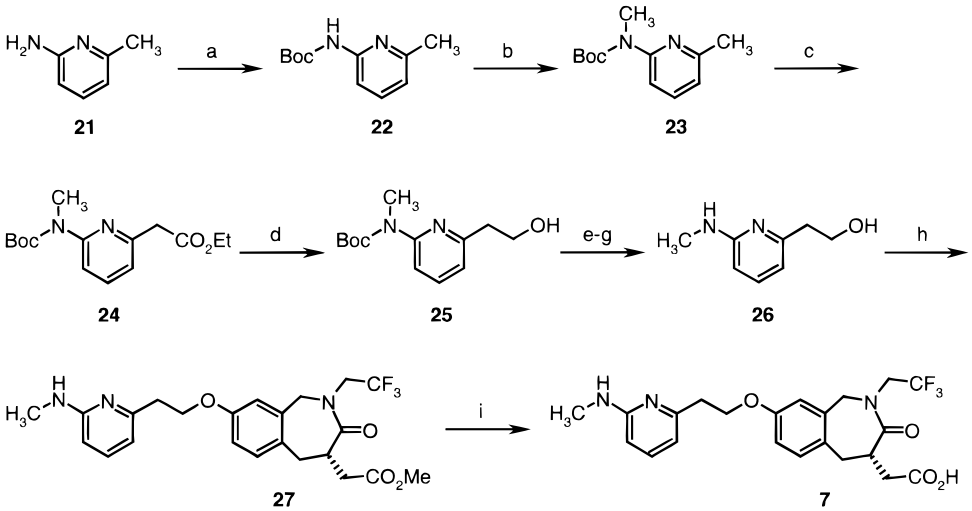
[a] (a) NBS, $(BzO)_2$, *hν*, CH_2Cl_2 (81%); (b) $NaN(Boc)CH_2CF_3$, DMF (77%); (c) dimethyl itaconate, $Pd(OAc)_2$, $P(o\text{-tol})_3$, $(i\text{-Pr})_2NEt$, CH_3CH_2CN, reflux (92%); (d) H_2, Pd/C, EtOAc (90%); (e) TFA, anisole, CH_2Cl_2 (86%); (f) $(n\text{-Pr})_3N$, TFA, xylenes, reflux (81%); (g) chiral HPLC (46%, 99+% ee); (h) BBr_3, CH_2Cl_2 (99%).

Scheme 2[a]



[a] (a) 3-Amino-1-propanol, $NaHCO_3$, *tert*-amyl alcohol, reflux (96%); (b) **16**, Ph_3P, DIAD, THF (75%); (c) cyclohexene, 10% Pd/C, *i*-PrOH, reflux (76%); (d) 1.0 N NaOH, dioxane, then 1.0 N HCl (86%).

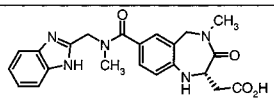
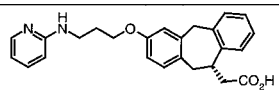
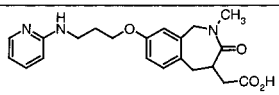
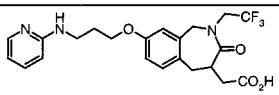
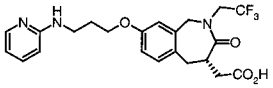
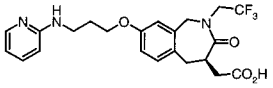
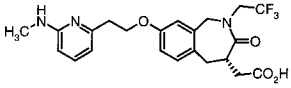
Scheme 3[a]



[a] (a) $(Boc)_2O$, neat, 50 °C (99%); (b) NaH, CH_3I, DMF (87%); (c) LDA, $(EtO)_2C{=}O$, THF, 0 °C (100%); (d) $LiBH_4$, THF, reflux (100%); (e) 4 N HCl/dioxane, anisole, then aq NaOH; (f) HCO_2H, EtOAc; (g) aq NH_4OH (52% from **25**); (h) **16**, Ph_3P, DIAD, THF (91%); (i) 1.0 N NaOH, MeOH, then acetic acid (82%).

cerned about potential oxidative instability. We therefore elected to replace the aniline nitrogen with a methylene group, as we expected these groups to be interchangeable based on the results of previous SAR studies. We also chose to incorporate aminopyridine Arg mimetics,[33] as our previous studies indicated that 1,4-benzodiazepine derivatives containing aminopyridine Arg mimetics had somewhat improved oral bioavailability relative to those with a benzimidazole Arg mimetic.[22] Our initial target was benzazepine **3**, which

Table 1. In Vitro Activity and Pharmacokinetic Profiles of Nonpeptide αvβ3 Antagonists

Number	Structure	αvβ3 Binding K_i (nM)	αIIbβ3 Binding K_i (nM)	αvβ3/HEK Cell Adhesion IC_{50} (nM)	$T_{1/2}$ (min)	Clp (mL/min/kg)	Oral F (%)
1		2.0 ± 0.1	30,000 ± 2000	145	9-16	35 ± 2	3-7
2		4.0 ± 0.3	9000 ± 2000	60	192 ± 79	4 ± 2	≈ 100
3		1.9 ± 0.1	30,000 ± 3000	75	16 ± 3	50 ± 4	9 ± 0.5
4		1.3 ± 0.2	9000 ± 1000	53	25 ± 3	63 ± 14	19 ± 13
5		0.9 ± 0.2	3300 ± 700	12	360 ± 32	16 ± 5	34 ± 10
6		20.0 ± 2.0	---	390	19 ± 5	60 ± 7	4 ± 2
7		1.2 ± 0.2	3800 ± 1000	3	53 ± 19	25 ± 1	72 ± 16

was prepared by the general methods described previously and above.

The benzazepine ether derivative **3** has $K_i = 1.9$ nM in an αvβ3 binding assay,[36] while affinity for the related RGD-binding integrin, αIIbβ3,[37] is considerably lower ($K_i = 30\,000$ nM). Benzazepine **3** also has $IC_{50} = 75$ nM in an αvβ3-mediated cell adhesion assay,[38] which measures the affinity of a compound for αvβ3 in a cellular context. Since **3** is racemic, whereas both **1** and **2** are the single, biologically active (*S*)-enantiomers, these results clearly indicate that benzazepine ethers are potent αvβ3 antagonists with improved activity relative to both the 1,4-benzodiazepine series (**1**) and the tricyclic series (**2**).

The pharmacokinetic profile[39] of benzazepine **3** in rats is not appreciably different from that of **1** (Table 1). The compounds have similar half-lives and oral bioavailabilities, while the plasma clearance is only marginally higher in **3**. Although **3** (ClogP = 2.6) is more lipophilic than **1** (ClogP = 1.4), the modest increase in lipophilicity was not sufficient to confer improved oral bioavailability. We therefore investigated methods for further increasing lipophilicity.

In the benzazepine series, lipophilicity can be conveniently increased by appropriate manipulation of the 2-position substituent. An investigation into 2-position substituents revealed a trend toward improved in vitro biological activity and improved oral bioavailability as lipophilicity is increased. For example, the trifluoromethyl-substituted derivative **4**, with ClogP of 3.9, has $K_i = 1.3$ nM in the αvβ3 binding assay and $IC_{50} = 53$ nM in the cell adhesion assay. In addition, **4** appears to have somewhat improved oral bioavailability in rats relative to **3** (19% for **4** vs 9% for **3**). Although individually none of these results are significantly different from those of **3**, taken together they seem to suggest that increasing lipophilicity has had a positive effect on both in vitro biological activity and oral bioavailability.

Since **4** has good biological activity, as well as good oral bioavailability, the individual enantiomers were prepared and evaluated. As expected, the (*S*)-enantiomer **5**, with $K_i = 0.9$ nM in the αvβ3 binding assay and $IC_{50} = 12$ nM in the cell adhesion assay, was more active than the (*R*)-enantiomer **6**, which has $K_i = 20$ nM in the αvβ3 binding assay and $IC_{50} = 390$ nM in the cell adhesion assay. Interestingly, however, the pharmacokinetic profiles in rats were very different. The (*S*)-enantiomer **5** has an outstanding pharmacokinetic profile, with a long half-life (360 min), low to moderate clearance (16 mL/min/kg), and good oral bioavailability (34%). In contrast, the pharmacokinetic profile of the (*R*)-enantiomer **6** is relatively poor, with a short half-life (19 min), high clearance (60 mL/min/kg), and low oral bioavailability (4%). The reasons for the differences

in the pharmacokinetic profiles of the enantiomers are not clear at this time but may be due to enantiospecific clearance or metabolism.

Interestingly, incorporation of the isomeric 6-(methylamino)pyridine Arg mimetic[22] has a significant impact on both biological activity and oral bioavailability. Compound **7** has $K_i = 1.2$ nM in the $\alpha v\beta 3$ binding assay, comparable to that of **5**, but has $IC_{50} = 3$ nM in the cell adhesion assay, which is a 4-fold improvement relative to **5**. Further, **7** has improved oral bioavailability in rats (72%).

The affinity of **5** and **7** for other RGD-binding integrins was evaluated, and both were found to bind to the closely related αv integrin, $\alpha v\beta 5$, with low nanomolar affinity (**5** $\alpha v\beta 5$ $K_i = 0.6 \pm 0.2$ nM; **7** $\alpha v\beta 5$ $K_i = 0.3 \pm 0.1$ nM). In contrast, the compounds both show minimal affinity for either $\alpha IIb\beta 3$ (**5** $\alpha IIb\beta 3$ $K_i = 3300 \pm 700$ nM; **7** $\alpha IIb\beta 3$ $K_i = 3800 \pm 1000$ nM) or $\alpha 5\beta 1$ (**5** $\alpha 5\beta 1$ $K_i = 1000 \pm 400$ nM; **7** $\alpha 5\beta 1$ $K_i = 110 \pm 30$ nM). Consistent with their low affinity for $\alpha IIb\beta 3$, both compounds have $IC_{50} > 200$ μM at inhibiting human platelet aggregation.[40]

In biological studies,[41,42] both **5** and **7** were found to be active in models of bone resorption and osteoporosis. In an in vitro human osteoclast resorption assay,[43] which measures the ability of a compound to inhibit human osteoclast-mediated bone resorption, compound **5** has $IC_{50} = 29$ nM and compound **7** has $IC_{50} = 11$ nM. Both compounds were also active in the in vivo thyroidectomized−parathyroidectomized (TPTx) rat model of bone resorption, which measures the ability of a compound to inhibit the parathyroid hormone-stimulated calcemic response in hypocalcemic TPTx rats.[35] In this model, on continuous intravenous infusion, compound **5** has $EC_{50} = 35$ μM and compound **7** has $EC_{50} = 20$ μM. The compounds were also tested in the ovariectomized (Ovx) rat model of osteoporosis, a well-established model for evaluating the potential of a compound to prevent bone loss associated with estrogen deficiency. Significantly, on twice a day oral dosing in the Ovx rat, both **5** (at 5, 15, and 60 mg/kg) and **7** (at 3, 10, and 30 mg/kg) inhibited bone loss in a dose-dependent fashion. For both compounds, the level of inhibition was greater than 50% at the highest dose. The results of these biological studies will be described in greater detail elsewhere.

In conclusion, we have discovered a new class of potent and orally bioavailable $\alpha v\beta 3$ antagonists based on a 2-benzazepine Gly-Asp. Two representatives from this class, benzazepines **5** and **7**, inhibit bone resorption in vitro and in vivo and are orally active in an Ovx rat model of osteoporosis. These results suggest that $\alpha v\beta 3$ antagonists have the potential to be orally administered drugs for the treatment of osteoporosis in humans. Further evaluation of members of this benzazepine 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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JM990446U