Nonpeptide $\alpha_v\beta_3$ Antagonists. 1. Transformation of a Potent, Integrin-Selective $\alpha_{IIb}\beta_3$ Antagonist into a Potent $\alpha_v\beta_3$ Antagonist

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Received March 21, 2000

Modification of the potent fibrinogen receptor ($\alpha_{IIb}\beta_3$) antagonist **1** generated compounds with high affinity for the vitronectin receptor $\alpha_v\beta_3$. Sequential modification of the basic N-terminus of **1** led to the identification of the 5,6,7,8-tetrahydro[1,8]naphthyridine moiety (THN) as a lipophilic, moderately basic N-terminus that provides molecules with excellent potency and selectivity for the integrin receptor $\alpha_v\beta_3$. The THN-containing analogue **5** is a potent inhibitor of bone resorption in vitro and in vivo. In addition, the identification of a novel, nonpeptide radioligand with high affinity to $\alpha_v\beta_3$ is also reported.

Introduction

Osteoporosis is a disease characterized by low bone mass, increased bone fragility, and a higher risk of fractures.[1,2] It is estimated that osteoporosis affects approximately 24 million people, mostly women, in the United States and is associated with over 1.3 million fractures per year at an annual cost of $7−10 billion.[3] Over their lifetime, women can lose up to 50% of their bone mass, whereas men can lose about two-thirds of this amount.[4] Bone loss results from an imbalance between bone resorption and bone formation in the normal remodeling cycle. During remodeling osteoclasts resorb bone over a 2−3-week period and then osteoblasts, the bone forming cells, line the resorption pit and completely replace bone over about a 3-month period.[5] However, when women reach menopause, and estrogen levels decrease, an acceleration in the rate of bone resorption occurs causing a net decrease in bone mass. Diminished bone mass, combined with the fact that, at maturity, women generally have less bone than men, puts them at a high risk for fractures. Reducing the rate of osteoclast-mediated bone resorption constitutes an attractive approach for preventing and treating osteoporosis.

The vitronectin receptor $\alpha_v\beta_3$ is a member of the integrin superfamily of receptors and is highly expressed in osteoclasts but not present in osteoblasts.[6,7] Several proteins that possess the three-amino acid sequence arginine-glycine-aspartic acid (RGD), including vitronectin, osteopontin, and bone sialoprotein, bind with high affinity to $\alpha_v\beta_3$; however, the endogenous matrix protein responsible for $\alpha_v\beta_3$-mediated osteoclast attachment and migration on bone remains undefined.[8,9] Antibodies to $\alpha_v\beta_3$ and the RGD-containing peptide echistatin have been shown to inhibit bone resorption in vitro and in vivo.[10−13] More recently, nonpeptide RGD mimetics have been reported to inhibit bone resorption in vivo.[14−16] These results suggest that low-molecular-weight, high-affinity ligands to $\alpha_v\beta_3$ could have utility as oral agents for the treatment of osteoporosis.

Previously, several reports from these laboratories have appeared that describe our work toward the design of RGD mimetics as potential antithrombotic agents that bind with high affinity to the fibrinogen receptor.[17,18] The fibrinogen receptor, $\alpha_{IIb}\beta_3$, is also a member of the integrin receptor family and possesses the same β-chain as $\alpha_v\beta_3$. In vivo, the fibrinogen receptor is found principally on platelets, and its binding to the plasma protein fibrinogen constitutes the final obligatory step for platelet aggregation.[19,20] In our fibrinogen program, compounds selective for binding to $\alpha_{IIb}\beta_3$ over $\alpha_v\beta_3$ were attained by replacement of the guanidine of the RGD triad with an amine, such as 4-piperidine, and establishment of an appropriate distance between the charged termini.[17,18] Other groups have reported the preparation of integrin-selective fibrinogen receptor antagonists that possess a benzamidine moiety as a guanidine surrogate.[21,22] Taken together, these results demonstrate that the N-terminus of RGD mimetics plays a key role in modulating receptor specificity and suggest that other N-terminal alterations could furnish potent and selective $\alpha_v\beta_3$ antagonists. Utilizing potent fibrinogen receptor antagonists as a starting point, structural features that are important for both integrin specificity and affinity to $\alpha_v\beta_3$ have been derived from cyclic RGD peptides,[23] benzodiazepine-[24,25] and benzazepine-based mimetics,[24,25] and other nonpeptides.[26−28] This report discloses our efforts to discover high-affinity $\alpha_v\beta_3$ ligands that are derived from a potent class of fibrinogen receptor antagonists.

Our strategy for generating high-affinity ligands to $\alpha_v\beta_3$ was to reintroduce the guanidine moiety in place of the piperidine in one of our potent, nonpeptide class of fibrinogen receptor antagonists. This approach was not expected to directly furnish a compound with high integrin specificity for $\alpha_v\beta_3$ over $\alpha_{IIb}\beta_3$ but rather would help to quickly determine whether structures identified

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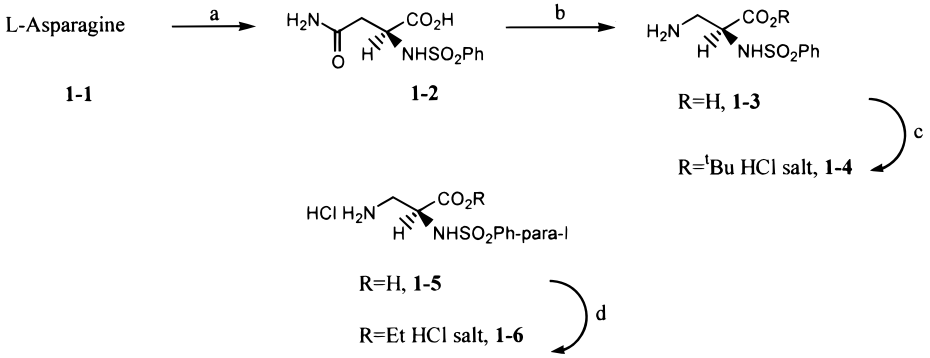
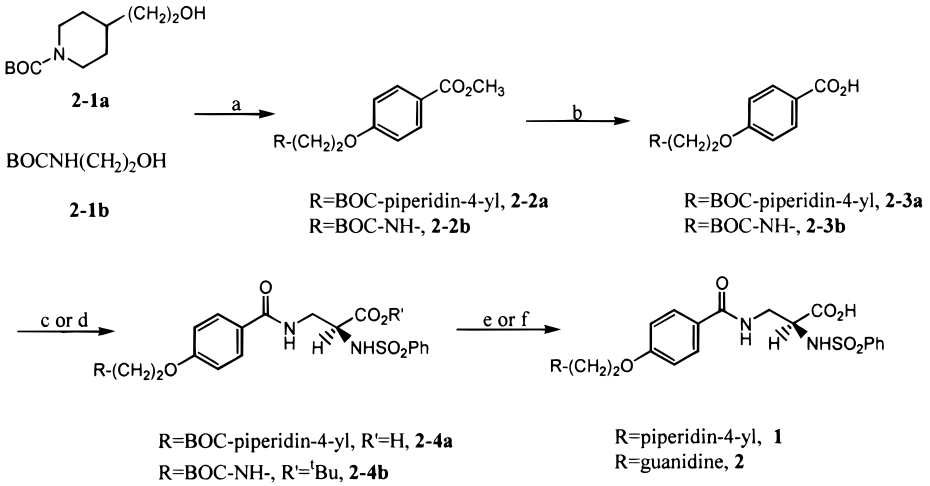
10.1021/jm000133v CCC: $19.00
Published on Web 08/18/2000

Scheme 1. Preparation of 3-Amino-2(*S*)-arylsulfonylaminopropionic Acids and Esters[a]



[a] Reagents: (a) NaOH, H_2O, phenylsulfonyl chloride; (b) NaOH, dioxane, Br_2; (c) isobutylene, H_2SO_4 then 1 N HCl ether; (d) ethanol/HCl.

Scheme 2. Preparation of Compounds **1** and **2**[a]



[a] Reagents: (a) THF, Ph_3P, diethyl diazodicarboxylate, methyl 4-hydroxybenzoate; (b) NaOH; (c) BOP reagent, DMF, 4-methylmorpholine, **1-3**; (d) BOP reagent, CH_3CN, 4-methylmorpholine, **1-4**; (e) TFA, CH_2Cl_2, Me_2S; (f) TFA, CH_2Cl_2 then aq DMF, NEt(*i*-Pr)$_2$, 3,5-dimethylpyrazole-1-carboxamidine nitrate.

in the fibrinogen program could be transformed into potent ligands for $\alpha_v\beta_3$. Upon accomplishing this task, we planned to identify N-termini that displayed enhanced lipophilicity and reduced basicity compared to guanidine and would provide further potency enhancement for $\alpha_v\beta_3$ and improvements in receptor specificity.

Chemistry

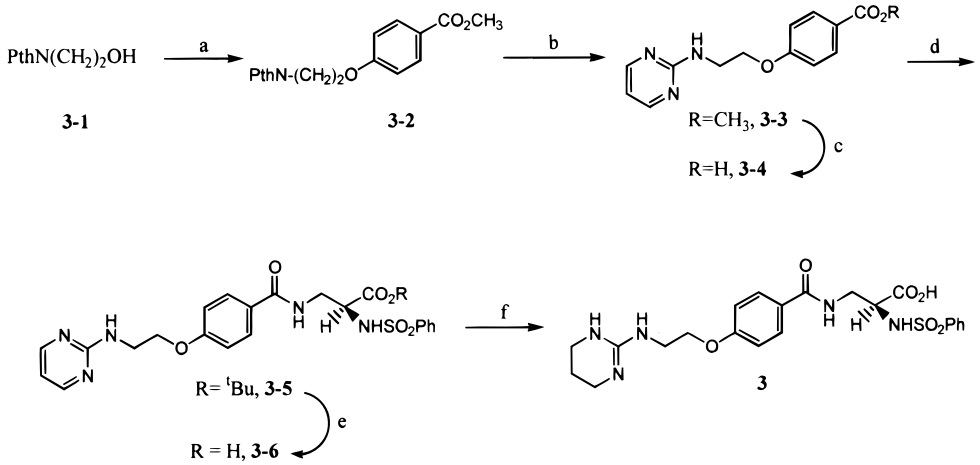
The synthetic pathway to 3-amino-2(*S*)-arylsulfonylaminopropionic acid derivatives is shown in Scheme 1.[29] Sulfonylation of the amino group of L-asparagine was accomplished in high yield upon treatment with phenylsulfonyl chloride in aqueous NaOH to provide **1-2**. A Hofmann rearrangement of **1-2** was effected with bromine in the presence of aqueous NaOH to provide **1-3** in 24% yield, which was converted to the *tert*-butyl ester **1-4** in high yield with isobutylene/H_2SO_4. Following this general procedure, but using 4-iodophenylsulfonyl chloride, **1-5** was prepared and subsequently converted to the ethyl ester **1-6** in ethanolic HCl.

Compounds **1** and **2** were prepared by similar routes as depicted in Scheme 2. Methyl 4-hydroxybenzoate and alcohols **2-1a** and **2-1b** were condensed under Mitsunobu conditions to furnish the ethers **2-2a** and **2-2b** in quantitative yield. Saponification of **2-2a** and **2-2b** gave the carboxylic acids **2-3a** and **2-3b**, which were condensed with **1-3** and **1-4**, respectively, to provide amides **2-4a** and **2-4b** in 43% and 47% yields. Deprotection of the *tert*-butyl ester of **2-4a** was achieved readily with trifluoroacetic acid/Me_2S to provide **1** in 85% yield. The BOC group of **2-4b** was removed upon treatment with trifluoroacetic acid (TFA), and the resulting amine was transformed to **2** with 3,5-dimethylpyrazole-1-carboxamidine nitrate.[30]

The route for preparing **3** is shown in Scheme 3. Key to the synthesis of **3** was the use of the 2-aminopyrimidine group as a protected form of the cyclic guanidine functionality present in **3**. Mitsunobu condensation of **3-1** with methyl 4-hydroxybenzoate provided **3-2** in 73% yield. Removal of the phthalimide protecting group of **3-2** with hydrazine followed by heating of the resulting amine with 2-bromopyrimidine in DMF furnished **3-3** in 50% yield. The poorly soluble ester **3-3** was saponified at elevated temperature, and the resulting acid **3-4** was condensed with **1-4** using EDC/HOBT to produce **3-5** in 44% overall yield. Trifluoroacetic acid deprotection of the *tert*-butyl ester of **3-5** followed by hydrogenation provided **3** in 71% yield.

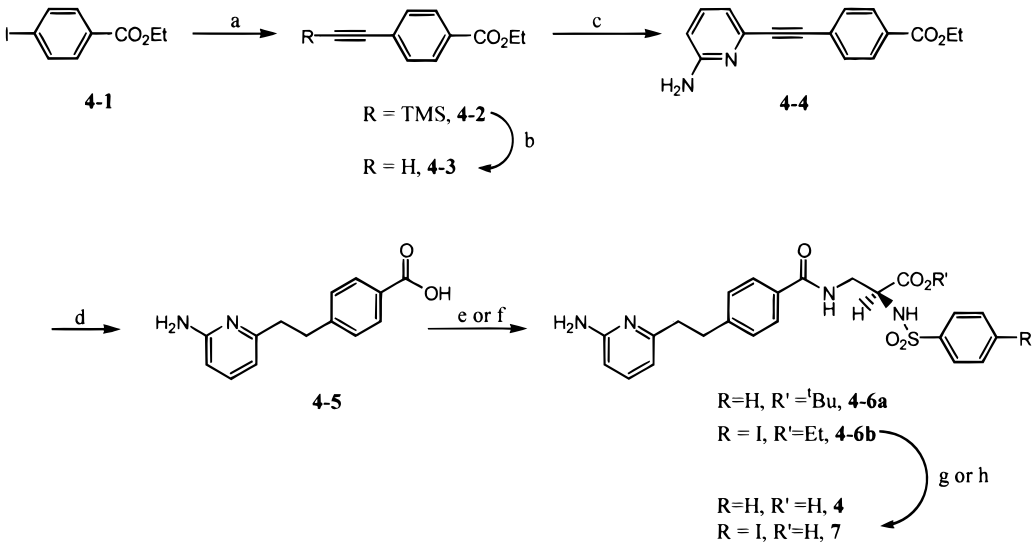
The 2-aminopyridine derivatives **4** and **7** were prepared as shown in Scheme 4. Ethyl 4-iodobenzoate (**4-1**) was coupled to TMS-acetylene in the presence of $(Ph_3P)_2PdCl_2$ and CuI to furnish **4-2** in 93% yield. Removal of the TMS group was effected with K_2CO_3/ethanol, and the resulting terminal acetylene **4-3** was

Scheme 3. Preparation of Compound **3**[a]



[a] Reagents: (a) THF, Ph_3P, diethyl diazodicarboxylate, methyl 4-hydroxybenzoate; (b) hydrazine, MeOH, then DMF, NEt(*i*-Pr)$_2$, 2-bromopyrimidine, 80 °C; (c) NaOH, MeOH, 60 °C; (d) EDC, HOBT, 4-methylmorpholine, **1-4**; (e) TFA, CH_2Cl_2; (f) 10% Pd/C, H_2, HOAc/HCl.

Scheme 4. Preparation of Compounds **4** and **7**[a]



[a] Reagents: (a) TMSC≡CH, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, CH_3CN, 100 °C; (b) K_2CO_3, EtOH; (c) 2-amino-6-bromopyridine, NEt_3, $(Ph_3P)_2PdCl_2$, CH_3CN; (d) 10% Pd/C, H_2, then 6 N HCl; (e) EDC, HOBT, DMF, 4-methylmorpholine, **1-4**; (f) EDC, HOBT, DMF, 4-methylmorpholine, **1-6**; (g) TFA, CH_2Cl_2; (h) 6 N HCl.

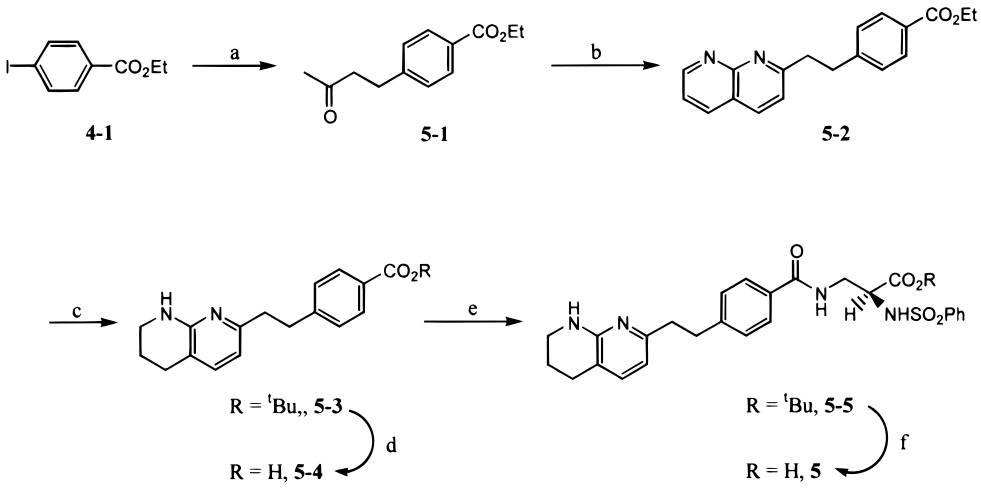
coupled, in the presence of Pd^0, to 2-amino-6-bromopyridine to provide **4-4** in 60% yield. Hydrogenation of the acetylenic moiety of **4-4** in the presence of 10% Pd/C followed by acid hydrolysis of the ethyl ester provided **4-5** in 91% yield. The acid **4-5** was coupled to amine **1-4** to provide **4-6a** which was deprotected in methylene chloride/TFA to afford **4** in 40% yield. Alternatively, the acid **4-5** could be condensed with the amine **1-6** and then deprotected in 6 N HCl to furnish **7** in 22% yield.

The synthesis of **5** was initiated via a Heck coupling of ethyl 4-iodobenzoate (**4-1**) with 3-buten-2-ol to provide the ketone **5-1** in quantitative yield (Scheme 5). A Friedlander condensation of **5-1** with 2-aminopyridine-3-carboxaldehyde[31] provided the [1,8]naphthyridine **5-2** in 60% yield. Hydrogenation of **5-2** in the presence of 10% Pd/C gave a 52% yield of the 5,6,7,8-tetrahydro-[1,8]naphthyridine **5-3**. Hydrolysis of the ester **5-3** in 6 N HCl at 50 °C gave **5-4** which was then coupled to amine **1-4** to provide **5-5** in 97% overall yield. Hydrolysis of the poorly soluble ester was accomplished by heating **5-5** in 6 N HCl at 50 °C for 9 h to afford compound **5** in 72% yield.

Discussion

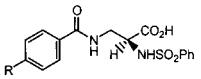
Compound **1**, a member of the "centrally constrained", sulfonamide exo-site class of fibrinogen receptor antagonists, constitutes a synthetically attractive starting point since various C- and N-termini can be readily coupled to commercially available 4-hydroxybenzoic acid.[32] In vitro, **1** was a potent inhibitor of ADP-stimulated platelet aggregation (PLAGGIN)[33] but was ineffective at displacing ^{125}I-echistatin from human recombinant $\alpha_v\beta_3$ (EIB) at 1 μM (Table 1). Replacement of the 4-piperidine moiety of **1** with guanidine afforded **2**, which had an IC_{50} in the EIB assay of 1.8 nM and maintained good antiaggregatory activity. Compound **2** also inhibited rat osteoclast mediated bone resorption in vitro (BONE RES) at sub-micromolar concentrations.[34]

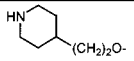
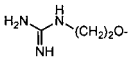
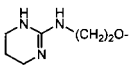
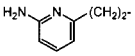
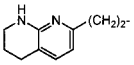
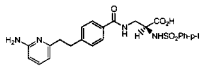
Scheme 5. Preparation of Compound **5**[a]



[a] Reagents: (a) 3-buten-2-ol, $Pd(OAc)_2$, NEt_3, CH_3CN, 100 °C; (b) 2-amino-3-formylpyridine, EtOH, L-proline, reflux; (c) 10% Pd/C, EtOH, H_2; (d) 6 N HCl; (e) BOP reagent, CH_3CN, 4-methylmorpholine, **1-4**; (f) 6 N HCl.

Table 1. In Vitro Potencies



Compound	R	IC50 (nM) EIB[a]	BONE RES[b]	PLAGGIN[c]	SPAV3[d]
1		>1,000[e]	nd	10[e]	>1,000[e]
2		1.8±1.1	300[f]	17[e]	10.7[f]
3		0.7±0.6	46[f]	44[f]	0.93±0.73
4		0.4±0.3	8±6	140[f]	0.44±0.52
5		0.3±0.3	3±3	260[e]	0.07±0.06
6	echistatin	0.5±0.5	2[f]	33[f]	0.10±0.13
7		0.1[e]	nd	1,600[e]	0.08±0.04

[a] Displacement of ^{125}I-labeled echistatin from human $\alpha_v\beta_3$. [b] Inhibition of rat osteoclast-mediated bone resorption in vivo. [c] Inhibition of the rate of ADP-stimulated human gel-filtered platelet aggregation. The error in the IC_{50} values determined in this asay is ±20%. [d] Displacement of ^{125}I-labeled nonpeptide **7** from purified human $\alpha_v\beta_3$ bound to wheatgerm agglutinin scintillation proximity beads. [e] Number of measurements = 1. [f] Number of measurements = 2. The error is reported as standard deviation for the SPAV3, EIB, and BONE RES assays.

Having validated that our structural core, derived from the fibrinogen program, could provide a starting point for the design of $\alpha_v\beta_3$ antagonists, we sought to further optimize the N-terminus of **2** for potency and selectivity. Replacement of the guanidine moiety with 2-aminotetrahydropyrimidine, affording **3**, provided approximately a 3-fold increase in potency in the EIB assay and a 6-fold increase in potency at inhibiting bone resorption in vitro compared to **2**.[34] In addition, a 2.5-fold loss in antiaggregatory potency was realized with this modification. Interestingly, the 2-aminopyrimidine **3-6** (Scheme 3) had an IC_{50} in the EIB assay of 131 nM. The low pK_a of the 2-aminopyrimidine moiety (pK_a 3.1) is one explanation for the diminished potency of **3-6** compared to **3**.[35]

Although **3** provides an advantage in potency and selectivity compared with **2**, the highly basic 2-aminotetrahydropyrimidine moiety contributes substantially to the very polar nature of compound **3** (log P −2.1). A more lipophilic N-terminus would presumably be needed to provide compounds that display acceptable oral absorption. To accomplish this task we explored the utility of 2-aminopyridine as a guanidine replacement that possessed moderate basicity. The 2-aminopyridine derivative **4** provided further increases in potency in the EIB and BONE RES assays, possibly due to the removal of rotational degrees of freedom. Compound **4** was also a less effective inhibitor of platelet aggregation in vitro than **3** and, as proposed, is more lipophilic (log P −1.2) than **3**. The aminopyridine moiety of **4** is an N-terminus with moderate basicity (pK_a 6.9).

Combination of the structural features present at the N-termini of compounds **3** and **4** led to the design of the novel 5,6,7,8-tetrahydro[1,8]naphthyridine (THN) derivative **5**, which has potency similar to that of **4** in the EIB assay but is about 3-fold more potent at inhibiting bone resorption in vitro. While the IC_{50} values for **5** in these two assays are similar to the 49-amino acid, RGD-containing peptide echistatin, **5** exhibits better integrin selectivity than echistatin. In addition, the THN moiety has moderate basicity (pK_a 7.8) and endows **5** with enhanced lipophilicity (log P −0.3). However, as measured by bioassay (EIB), plasma drug levels were <10 nM following a 5 mg/kg oral dose of **5** to male rats (n = 4). Compound **5** also exhibited a short half-life (<30 min) following a 1 mg/kg iv bolus dose to male rats (n = 4).

At this point of the program it was apparent that the correlation between IC_{50} values generated in the echistatin displacement assay (EIB) with those derived from the BONE RES assay began to diverge and that the EIB assay had reached its limit for detecting potency differences between tight-binding compounds. This can be seen by comparing the in vitro values displayed in Table

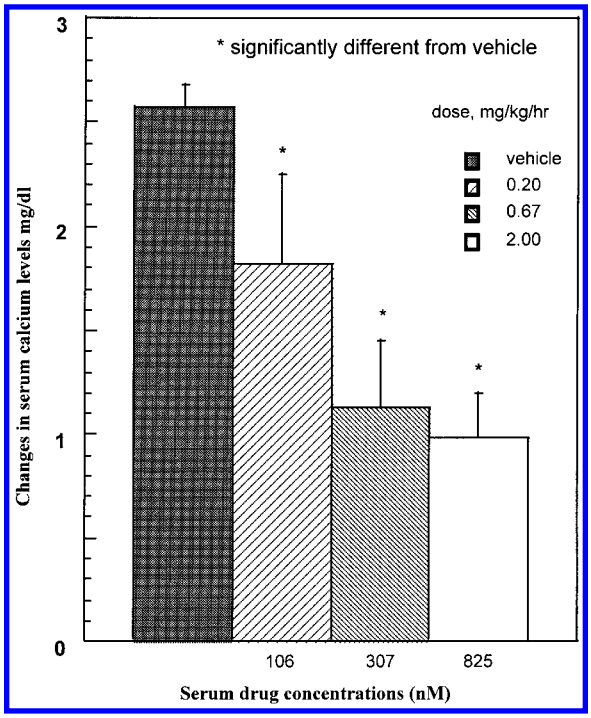


Figure 1. Efficacy of **5** in the TPTX rat model; *$p < 0.05$.

1 for compounds **2**−**5** and echistatin. Therefore, we decided to prepare a radioligand that had more optimal binding characteristics than echistatin. The introduction of an iodide at the para-position of the phenylsulfonyl ring of **4** provided **7**. Since this substituent was well-tolerated (EIB IC_{50} = 0.10 nM), a new scintillation proximity bead-based displacement assay (SPAV3) was developed using ^{125}I-labeled **7** as the displaceable ligand.[36] The K_d of binding of radiolabeled **7** to $\alpha_v\beta_3$ is 0.06 nM, and as seen in Table 1, the IC_{50} values derived from the SPAV3 assay correlate well with those derived from the BONE RES assay. This assay serves as the primary in vitro assay for the program.[37]

Compound **5** was evaluated in vivo in the thyroparathyroidectomized (TPTX) rat model to assess its potential as a therapeutic for osteoporosis. This model tests the ability of a compound to inhibit bone-dependent serum calcium increases produced by exogenous parathyroid hormone. Previously in this model,[10] echistatin was reported to inhibit increases in serum calcium levels in a dose-dependent fashion and was later determined to have an IC_{50} of 100 nM in this model. Subcutaneous infusion of **5** for 6 h to TPTX rats at doses of 0.20, 0.67, and 2.0 mg/kg/h resulted in the inhibition of the increase of serum calcium levels in a dose-dependent fashion with an IC_{50} of 200 nM (Figure 1).[38] The similiar efficacy of **5** and echistatin in this model correlates well with their comparable in vitro IC_{50} values in SPAV3 and BONE RES.

We have established that a fibrinogen receptor antagonist lead compound from the centrally constrained sulfonamide class can be transformed into potent $\alpha_v\beta_3$ antagonists through modification of its N-terminus. The THN moiety has been identified as a novel N-terminus that imparts enhanced potency, integrin selectivity, and lipophilicity to this class of $\alpha_v\beta_3$ antagonists. Compound **5** inhibits bone resorption in vitro and in vivo at concentrations comparable to those observed for the RGD-containing peptide echistatin. A new $\alpha_v\beta_3$ displacement assay was developed using a high-affinity, nonpeptide ligand for $\alpha_v\beta_3$. Alternative structural classes that possess the THN moiety and that display acceptable pharmacokinetic profiles and potency will be the subject of future reports.

Experimental Section

All commercially available chemicals and solvents were used without further purification. EM Science silica gel 60 was used for flash chromatography. All new compounds gave satisfactory ^{1}H NMR, elemental analysis, and mass spectrometry results. ^{1}H NMR spectra were recorded on a Varian Unity 300 spectrometer. Chemical shifts are expressed in parts per million (ppm) relative to tetramethylsilane as the internal standard. Elemental analysis for carbon, hydrogen, and nitrogen was determined on a Leeman Labs CEC 240XA and CE440 elemental analyzer. High-resolution mass spectral data was obtained with a Bruker Daltonics BioApex 3T mass spectometer. Log *P* values were determined in octanol/7.4 phosphate buffer solution and analyzed on a HP 1100 HPLC equipped with a C18 reverse-phase column. pK_a values were determined on a Sirius GlpK_a Titrater.

***N*-Phenylsulfonyl-L-asparagine (1-2).** To a stirred solution of L-asparagine **(1-1)** (50 g, 0.38 mol), NaOH (17 g, 0.42 mol), H_2O (250 mL), and dioxane (250 mL) at 0 °C was added $PhSO_2Cl$ (74 mL, 42 mol). After 1 min, NaOH (17 g) in H_2O (250 mL) was added and the reaction mixture stirred for 30 min. The reaction mixture was then concentrated to remove dioxane then washed with EtOAc. The aqueous phase was then cooled to 0 °C and acidified to pH 5.0 with concentrated HCl to effect product precipitation. The resulting solid was collected by filtration, washed with H_2O (20 mL), and dried at 50 °C under vacuum to give *N*-phenylsulfonyl-L-asparagine **(1-2)** (96 g, 0.35 mol, 93%) as a white solid: R_f 0.40 (silica, 10:1:1 ethanol/H_2O/NH_4OH); ^{1}H NMR (300 MHz, D_2O) δ 7.59 (m, 2H), 7.26 (m, 3H), 3.92 (m, 1H), 3.02 (m, 1H), 2.35 (m, 1H).

3-Amino-2(*S*)-phenylsulfonylaminopropionic Acid (1-3). To a stirred solution of NaOH (101 g, 2.5 mol) in H_2O (455 mL), cooled with an ice bath was added bromine (18 mL, 0.35 mol) dropwise. After 5 min, a cold solution of *N*-phenylsulfonyl-L-asparagine **(1-2)** (95 g, 0.35 mol) and NaOH (28 g) in H_2O (325 mL) was added in one portion. The solution was stirred for 20 min at 0 °C then 30 min at 90 °C. The reaction mixture was recooled to 0 °C, and the pH adjusted to 7 through dropwise addition of concentrated HCl. The white precipitate formed was collected by filtration, washed with ethyl acetate and then dried to give **1-3** (20 g, 82 mmol, 24%) as a white solid: ^{1}H NMR (300 MHz, D_2O) δ 8.00−7.50 (m, 5H), 3.88 (m, 1H), 3.37 (m, 1H), 3.12 (m, 1H).

***tert*-Butyl 3-Amino-2(*S*)-phenylsulfonylaminopropionate Hydrochloride (1-4).** In a Fischer−Porter tube, a mixture of **1-3** (10.2 g, 42 mmol) and DME (150 mL) was sequentially treated with H_2SO_4 (6.4 mL, 0.12 mol), cooled to −78 °C, and then condensed with isobutylene (75 mL). The tube was sealed and the cooling bath was removed. After 24 h, ice/water (250 mL) was added followed by washing with ether (2×). The aqueous phase was basified with aqueous 6 N NaOH, then saturated with NaCl, followed by extraction with EtOAc (3×). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give a white solid. This was dissolved in CH_2Cl_2 and treated with 1 N HCl/ether (22 mL), and then concentrated to give **1-4** (13.2 g, 39 mmol, 94%) as a glassy yellow solid: ^{1}H NMR (400 MHz, DMSO) δ 8.25−8.00 (m, 4H), 7.85−7.58 (m, 5H), 4.08 (m, 1H), 3.10 (m, 1H), 2.73 (m, 1H), 1.17 (s, 9H).

3-Amino-2(*S*)-4-iodophenylsulfonylaminopropionate Hydrochloride (1-5). Compound **1-5** was prepared using the same procedure for preparing **1-3** but using 4-iodophenylsulfonyl chloride in place of phenylsulfonyl chloride: ^{1}H NMR (300 MHz, D_2O) δ 8.02 (d, J = 8 Hz, 2H), 7.63 (d, J = 8 Hz, 2H), 3.21 (m, 1H), 3.92 (m, 1H), 3.33 (m, 1H), 3.06 (m, 1H).

Ethyl 3-Amino-2(*S*)-4-iodophenylsulfonylaminopropionate Hydrochloride (1-6). HCl gas was rapidly bubbled

through a suspension of acid **1-5** (4.0 g, 10.81 mmol) in EtOH (50 mL) at 0 °C for 10 min. The cooling bath was removed and the reaction was heated to 60 °C. After 18 h, the reaction was concentrated to provide ester **1-6** (4.7 g, quantitative) as a white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.98 (d, J = 8 Hz, 2H), 7.63 (d, J = 8 Hz, 2H), 4.25 (q, J = 5 Hz, 2H), 3.92 (m, 2H), 3.33 (m, 1H), 3.06 (m, 1H), 1.01 (t, J = 7 Hz, 3H).

Methyl 4-(2-*N*-BOC-piperidin-4-ylethyloxy)benzoate (2-2a). To a stirred solution of **2-1a** (20 g, 87 mmol), PPh_3 (28.6 g, 108 mmol), and THF (450 mL) at ambient temperature were added methyl 4-hydroxybenzoate (13.3 g, 87 mmol) and DEAD (517.2 mL, 108 mmol; 40% toluene solution) in THF (100 mL) dropwise over a 15-min period. After stirring for 20 h the reaction mixture was diluted with EtOAc and then washed with saturated $NaHCO_3$, 10% $KHSO_4$ and brine, dried ($MgSO_4$) and concentrated. Flash chromatography (silica, 20% EtOAc/hexanes) gave **2-2a** (35 g, 87 mmol, quantitative yield) as a colorless oil: R_f 0.84 (silica, 30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (m, 2H), 6.88 (m, 2H), 4.10 (m, 4H), 3.88 (s, 3H), 2.70 (m, 2H), 1.70 (m, 4H), 1.45 (s, 9H), 1.20 (m, 2H).

4-[2-(*N*-BOC-amino)piperidin-4-yloxy]benzoic Acid (2-3a). A mixture of **2-2a** (35 g, 87 mmol), 1 N NaOH (200 mL) and ethanol (400 mL) was stirred at ambient temperature for 20 h. The reaction mixture was concentrated and the residue dissolved in H_2O and then washed with ether. The aqueous portion was acidified with 10% $KHSO_4$ and then extracted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated to give **2-3a** (29 g, 83 mmol, 95%) as a white solid: R_f 0.26 (silica, 9:1:1 CH_2Cl_2/CH_3OH/AcOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (m, 2H), 6.88 (m, 2H), 4.10 (m, 4H), 2.70 (m, 2H), 1.70 (m, 4H), 1.45 (s, 9H), 1.20 (m, 2H).

3-{4-[2-(*N*-BOC-piperidin-4-yl)ethyloxy]benzoylamino}-2(*S*)-benzenesulfonylaminopropionic Acid (2-4a). To a stirred solution of **2-3a** (14.3 g, 41 mmol), **1-3** (10 g, 41 mmol), NEt_3 (11.4 mL, 82 mmol), and DMF (200 mL) at 0 °C was added BOP reagent (17.2 g, 39 mmol). After 20 h the reaction mixture was diluted with EtOAc and then washed with H_2O, saturated $NaHCO_3$, 10% $KHSO_4$ and brine, dried ($MgSO_4$) and concentrated. Flash chromatography (silica, 40% EtOAc/hexanes) gave **2-4a** (10.0 g, 18 mmol, 45%) as a white solid: R_f 0.19 (silica, 40% EtOAc/hexanes); ^{1}H NMR (300 MHz, CD_3OD) δ 8.10 (m, 1H), 7.62 (m, 2H), 7.50 (m, 2H), 7.24 (m, 3H), 6.74 (m, 2H), 4.00−3.80 (m, 5H), 3.50 (m, 1H), 3.30 (m, 1H), 2.59 (m, 2H), 1.55 (m, 5H), 1.24 (s, 9H), 1.23 (s, 9H), 1.00 (m, 2H).

3-[4-(2-Piperidin-4-ylethyloxy)benzoylamino]-2(*S*)-benzenesulfonylaminopropionic Acid (1). To a stirred solution of **2-4a** (10 g, 17.4 mmol), CH_2Cl_2 (80 mL) and dimethyl sulfide (6.4 mL, 87 mmol) at 0 °C was added trifluoroacetic acid (40 mL) following by removal of the cooling bath. After 1.0 h the reaction mixture was concentrated and the residual trifluoroacetic acid removed via a toluene azeotrope. Flash chromatography (silica, 10:1:1 ethanol/NH_4OH/H_2O) gave a colorless oil which upon trituration with 10:1:1 ethanol/NH_4OH/H_2O gave **1** (7.0 g, 15 mmol, 85%) as a white solid: R_f 0.19 (silica, 40% EtOAc/hexanes); ^{1}H NMR (300 MHz, D_2O) δ 7.72 (d, J = 9 Hz, 2H), 7.50 (d, J = 9 Hz, 2H), 7.32 (m, 3H), 6.96 (d, J = 9 Hz, 2H), 4.20 (m, 1H), 4.13 (m, 2H), 3.72 (m, 1H), 3.50−3.35 (m, 3H), 2.95 (m, 2H), 1.98 (m, 2H), 1.84 (m, 1H), 1.76 (m, 2H), 1.43 (m, 2H); HRMS (FAB, M + 1) calcd 476.1855, found 476.1856.

Methyl 4-(2-*N*-BOC-aminoethyloxy)benzoate (2-2b). To a stirred solution of **2-1b** (5.2 g, 33 mmol), PPh_3 (9.8 g, 41 mmol), and THF (200 mL) at ambient temperature were added methyl 4-hydroxybenzoate (4.6 g, 30 mmol) and DEAD (5.9 mL, 40 mmol; 40% toluene solution) in THF (100 mL) dropwise over a 15-min period. After stirring for 20 h the reaction mixture was diluted with EtOAc and then washed with saturated $NaHCO_3$, 10% $KHSO_4$ and brine, dried ($MgSO_4$) and concentrated. Flash chromatography (silica, 20% EtOAc/hexanes) gave **2-2b** (10 g, 33 mmol, quantitative yield) as a colorless oil: R_f 0.84 (silica, 30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, 2H), 6.93 (d, 2H), 5.02 (m, 1H), 4.11 (m, 2H), 3.89 (s, 3H), 3.58 (m, 2H), 1.46 (s, 9H).

4-[2-(*N*-BOC-amino)ethyloxy]benzoic Acid (2-3b). A mixture of **2-2b** (10 g, 30 mmol), 1 N NaOH (100 mL) and ethanol (150 mL) was stirred at ambient temperature for 20 h. The reaction mixture was concentrated and the residue dissolved in H_2O (15 mL) and then washed with ether. The aqueous portion was acidified with 10% $KHSO_4$ and then extracted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated to give **2-3b** (6.5 g, 14 mmol, 47%) as a white solid: R_f 0.26 (silica, 9:1:1 CH_2Cl_2/CH_3OH/AcOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 9 Hz, 2H), 6.96 (d, J = 9 Hz, 2H), 5.02 (m, 1H), 4.12 (m, 2H), 3.60 (m, 2H), 1.48 (s, 9H).

3-{4-[2-(*N*-BOC-amino)ethyloxy]benzoylamino}-2(*S*)-benzenesulfonylaminopropionic Acid *tert*-Butyl Ester (2-4b). To a stirred solution of **2-3b** (200 mg, 0.71 mmol), **1-4** (260 mg, 0.85 mmol), NMM (313 μL, 2.8 mmol), and CH_3CN (4 mL) at ambient temperature was added BOP reagent (473 mg, 1.1 mmol). After 20 h the reaction mixture was diluted with EtOAc and then washed with H_2O, saturated $NaHCO_3$, 10% $KHSO_4$ and brine, dried ($MgSO_4$) and concentrated. Flash chromatography (silica, 40% EtOAc/hexanes) gave **2-4b** (380 mg, quantitative yield) as a white solid: R_f 0.19 (silica, 40% EtOAc/hexanes); ^{1}H NMR (300 MHz, CD_3OD) δ 7.77 (m, 2H), 7.67 (d, J = 9 Hz, 2H), 7.42 (m, 3H), 6.92 (d, J = 9 Hz, 2H), 4.02 (m, 3H), 3.59 (dd, 1H), 3.42 (dd, 1H), 3.38 (m, 2H), 1.38 (s, 9H), 1.16 (s, 9H).

3-{4-[2-(Guanidino)ethyloxy]benzoylamino}-2(*S*)-benzenesulfonylaminopropionic Acid (2). A solution of **2-4b** (340 mg, 0.64 mmol), TFA (3 mL), and CH_2Cl_2 (3 mL) was stirred at ambient temperature for 1.0 h. Concentration, followed by azeotropic removal of the residual TFA, with toluene, gave an oil which was dissolved in DMF/H_2O (3 mL; 3:1) and then treated with N(i-Pr)$_2$Et (334 μL, 1.9 mmol) and 3,5-dimethylpyrazole-1-carboxamidine nitrate (193 mg, 0.95 mmol). This solution was heated at 60 °C for 4 h and the cooled reaction mixture concentrated. Flash chromatography (silica, 10/0.2/0.2 to 10/1/1 ethanol/NH_4OH/H_2O) gave **2** (150 mg, 0.33 mmol, 52%) as a white powde: R_f 0.20 (silica, 10/1/1 ethanol/NH_4OH/H_2O); ^{1}H NMR (400 MHz, D_2O) δ 7.62 (m, 2H), 7.43 (d, J = 9 Hz, 2H), 7.18 (m, 3H), 6.93 (d, J = 9 Hz, 2H), 4.18 (m, 2H), 3.72 (m, 1H), 3.55 (m, 3H), 3.19 (m, 1H); HRMS (FAB, M + 1) calcd 450.1432, found 450.1447. Anal. ($C_{19}H_{23}N_5O_6S$·2.2H_2O) C, H, N.

Methyl 4-(2-Phthalimidoethyloxy)benzoate (3-2). A solution of *N*-(2-hydroxyethyl)phthalimide **(3-1)** (6.36 g, 33 mmol) and DEAD (5.7 mL, 36 mmol) in 25 mL THF and 10 mL DMF was added to a solution of methyl 4-hydroxybenzoate (5.00 g, 33 mmol) and Ph_3P (9.53 g, 36 mmol) in 100 mL THF during 1 h. After an additional hour the reaction was diluted with ether, washed twice with water, then 1 N NaOH and brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography (silica gel, CH_2Cl_2) provided **3-2** (8.0 g, 24.4 mmol, 73%) as a white solid: R_f 0.18 (silica, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 9 Hz, 2H), 7.87 (m, 2H), 7.74 (m, 2H), 6.84 (d, J = 9 Hz, 2H), 4.28 (t, J = 6 Hz, 2H), 4.14 (t, J = 6 Hz, 2H), 3.87 (s, 3H).

Methyl 4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoate (3-3). 3-2 (8.0 g, 24.4 mmol) was suspended in 25 mL MeOH. Upon addition of hydrazine (10 mL, 320 mmol) the reaction became homogeneous. After 20 h a heavy precipitate had formed. The pH was adjusted to 1 by addition of 6 N HCl, MeOH evaporated, and the solid suspended in 1 N HCl. After filtering through Celite, the filtrate was washed with CH_2Cl_2, the pH was adjusted to 12 with 6 N NaOH. The aqueous layer was extracted with fresh CH_2Cl_2. This organic phase was dried (Na_2SO_4) and concentrated providing crude amine (4.3 g) as a white solid. Amine (4.30 g, 22 mmol), **1-3** (3.51 g, 22 mmol) and DIPEA (3.8 mL, 22 mmol) were heated in 50 mL DMF at 80 °C for 16 h. The cooled mixture was concentrated, then diluted with EtOAc, washed with 1 N NaOH and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 10% acetone/CH_2Cl_2) provided white crystalline **3-3** (3.3 g, 12.1 mmol, 50%): R_f 0.42 (silica, 10% acetone/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, J = 5 Hz, 2H), 7.99 (d, J = 9 Hz,

2H), 6.93 (d, $J = 9$ Hz, 2H), 6.57 (t, $J = 5$ Hz, 1H), 5.53 (br m, 1H), 4.20 (t, $J = 5$ Hz, 2H), 3.88 (s, 3H) 3.88 (overlapped t, 2H).

4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoic Acid (3-4). Pyrimidine ester **3-3** (3.31 g, 12.1 mmol) was combined with 1 N NaOH (30 mL, 30 mmol) in 50 mL EtOH. After 2 h at 60 °C the mixture was cooled and 30 mL 1 N HCl was added (final pH 5). The resulting white precipitate was collected on a frit, washed with water, and dried providing **3-4** (2.0 g, 7.9 mmol, 65%): R_f 0.67 (silica, 10:1:1 EtOH/NH_4OH/H_2O); ^{1}H NMR (300 MHz, DMSO) d 9.02 (d, $J = 5$ Hz, 2H), 8.60 (d, $J = 9$ Hz, 2H), 8.05 (t, $J = 6$ Hz, 1H), 7.76 (d, $J = 9$ Hz, 2H), 7.32 (t, $J = 5$ Hz, 1H), 4.89 (t, $J = 6$ Hz, 2H), 4.38 (q, $J = 6$ Hz, 2H), 4.06 (s, 1H).

3-{4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoylamino}-2(*S*)-benzenesulfonylaminopropionic Acid *tert*-Butyl Ester (3-5). Acid **3-4** (0.770 g, 2.97 mmol), amine **1-4** (1.0 g, 2.97 mmol), NMM (1.14 μL, 10.4 mmol) and HOBT (0.522 g, 3.86 mmol) were combined in 30 mL DMF, cooled to 0 °C, and EDC (0.740 g, 3.86 mmol) was added. The mixture was stirred at room temperature for 3 days, diluted with ethyl acetate, washed twice with water, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 80% EtOAc/hexanes) provided **3-5** (1.1 g, 2.0 mmol, 67%) as a waxy solid: R_f 0.23 (silica, 80% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, $J = 5$ Hz, 2H), 7.85 (d, $J = 7$ Hz, 2H), 7.73 (d, $J = 9$ Hz, 2H), 7.60−7.45 (m, 3H), 6.90 (d, $J = 9$ Hz, 2H), 6.67 (br m, 1H), 6.57 (t, $J = 5$ Hz, 1H), 5.94 (d, $J = 8$ Hz, 1H), 5.68 (br m, 1H), 4.17 (t, $J = 5$ Hz, 2H), 4.00−3.83 (m, 4H), 3.59 (m, 1H), 1.28 (s, 9H).

3-{4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoylamino}-2(*S*)-benzenesulfonylaminopropionic Acid (3-6). Ester **3-5** (1.05 g, 1.86 mmol) and anisole (0.40 mL, 3.7 mmol) were dissolved in CH_2Cl_2 (9 mL), cooled to 0 °C, and TFA (9 mL) was added. After 2 h at 0 °C and 16 h at 20 °C, the reaction was concentrated, azeotroped with toluene, and triturated with Et_2O providing **3-6** (1.1 g, 1.8 mmol, 95%) as a white solid: R_f 0.30 (silica, 22:20:1:1 EtOAc/EtOH/NH_4OH/H_2O). ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (br, 2H), 7.82 (dt, $J = 7$, 2 Hz, 2H), 7.72 (d, $J = 9$ Hz, 2H), 7.50 (tm, $J = 7$ Hz, 1H), 7.42 (tm, $J = 8$ Hz, 2H), 6.99 (d, $J = 9$ Hz, 2H), 6.82 (t, $J = 5$ Hz, 1H), 4.25 (t, $J = 5$ Hz, 2H), 4.18 (dd, $J = 9$, 5 Hz, 1H), 3.88 (t, $J = 5$ Hz, 2H), 3.71 (dd, $J = 14$, 5 Hz, 1H), 3.48 (m, 1H).

3-{4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoylamino}-2(*S*)-benzenesulfonylaminopropionic Acid (3). Pyrimidine **3-6** (1.05 g, 1.75 mmol) was dissolved in a mixture of acetic acid (50 mL) and concentrated HCl (4.5 mL). After addition of 10% Pd/C (450 mg) the mixture was shaken on a Parr hydrogenator under 45 psi H_2 pressure for 2 h. The reaction mixture was filtered, concentrated, azeotroped with toluene, and purified by flash chromatography (silica 20:1:1 then 8:1:1 EtOH/NH_4OH/H_2O) providing **3** (0.66 g, 1.3 mmol, 75%) as a white solid: R_f 0.35 (8:1:1, EtOH/NH_4-OH/H_2O); ^{1}H NMR (300 MHz, CD_3OD + DCl) δ 7.84 (d m, $J = 7$ Hz, 2H), 7.74 (d, $J = 9$ Hz, 2H), 7.50−7.40 (m, 3H), 7.02 (d, $J = 9$ Hz, 2H), 4.22−4.17 (m, 3H), 3.72 (dd, $J = 14$, 5 Hz, 1H), 3.60 (t, $J = 5$ Hz, 2H), 3.49 (dd, $J = 14$, 9 Hz, 1H), 3.38 (t, $J = 5$ Hz, 4H), 1.95 (qn, $J = 6$ Hz, 2H); HRMS (FAB, M + 1) calcd 490.1760, found 490.1759. Anal. ($C_{22}H_{27}N_5O_6S\cdot 1.2H_2O$) C, H, N.

4-Trimethylsilanylethynylbenzoic Acid Ethyl Ester (4-2). TMS-acetylene (5.0 mL, 35.5 mmol), ethyl 4-bromobenzoate **(4-1)** (58 mL, 35.5 mmol) and Et_3N (20 mL, 144 mmol) were combined in 50 mL CH_3CN in a glass pressure tube. $(Ph_3P)_2$-$PdCl_2$ (198 mg, 0.28 mmol) and CuI (100 mg, 0.53 mmol) were added, and the reaction was sealed and heated at 100 °C for 18 h. Dilution with EtOAc, washing twice with water, then brine, drying and concentration provided **4-2** (8.2 g, 33.2 mmol, 93%) as a brown liquid: R_f 0.60 (silica, 10% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, $J = 8$ Hz, 2H), 7.51 (d, $J = 9$ Hz, 2H), 4.37 (q, $J = 7$ Hz, 2H), 1.40 (t, $J = 7$ Hz, 3H), 0.26 (s, 9H).

4-Ethynylbenzoic Acid Ethyl Ester (4-3). Ester **4-2** (8.2 g, 33.2 mmol) was dissolved in 100 mL EtOH, K_2CO_3 (0.25 g 1.8 mmol) was added and the mixture was stirred for 16 h, concentrated, and purified by flash chromatography (silica, 5% Et_2O/hexane) provided **4-3** (5.8 g, 29.9 mmol, 90%) as a yellow oil: R_f 0.47 (silica, 10% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, $J = 8$ Hz, 2H), 7.55 (d, $J = 8$ Hz, 2H), 4.38 (q, $J = 7$ Hz, 2H), 3.22 (s, 1H), 1.40 (t, $J = 7$ Hz, 3H).

Ethyl 4-[2-(2-Aminopyridin-6-yl)ethyl]benzoate (4-4). 2-Amino-6-bromopyridine (0.38 g, 2.4 mmol; available from Davos), **4-3** (0.35 g, 2.0 mmol), Et_3N (1.0 mL, 7.2 mmol), $(Ph_3P)_2PdCl_2$ (76 mg, 0.11 mmol), an CuI (26 mg, 0.14 mmol) were combined in 5 mL CH_3CN, sealed in a glass pressure tube and heated to 100 °C for 3 h. The mixture was diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 5% acetone/hexane), to give **4-4** (293 mg, 1.1 mmol, 55%) as a tan solid: R_f 0.45 (silica, 10% acetone/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, $J = 8$ Hz, 2H), 7.64 (d, $J = 8$ Hz, 2H), 7.44 (t, $J = 8$ Hz, 1H), 6.95 (d, $J = 7$ Hz, 1H), 6.50 (d, $J = 8$ Hz, 1H), 4.55 (br s, 2H), 4.39 (q, $J = 7$ Hz, 2H), 1.40 (t, $J = 7$ Hz, 3H).

4-[2-(2-Aminopyridin-6-yl)ethyl]benzoate (4-5). A mixture of ester **4-4** (700 mg, 2.63 mmol) 10% Pd/C (350 mg) and EtOH were stirred under 1 atm H_2. After 20 h, the reaction was filtered through a Celite pad and then concentrated to provide the crude ester as a brown oil: TLC $R_f = 0.23$ (silica, 40% EtOAc/hexanes). A suspension of ester (650 mg, 2.31 mmol) in 6 N HCl (12 mL) was heated to 60 °C. After ∼20 h, the reaction was concentrated to give acid **4-5** (650 mg, 2.33 mmol, 91%) as a tan solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.96 (d, 2H, $J = 8$ Hz), 7.80 (m, 1H), 7.33 (d, 2H, $J = 8$ Hz), 6.84 (d, 1H, $J = 9$ Hz), 6.69 (d, 1H, $J = 7$ Hz), 3.09 (m, 4H).

3-[4-(6-Aminopyridin-6-ylethynyl)benzoylamino]-2(*S*)-benzenesulfonylaminopropionic Acid *tert*-Butyl Ester (4-6a). Acid **4-5** (234 mg, 0.98 mmol), **1-4** (351 mg, 0.98 mmol), EDC (225 mg, 1.2 mmol), HOBT (159 mg, 1.2 mmol) and NMM (323 μL, 2.9 mmol) were combined in 5 mL DMF. After 16 h the mixture was diluted with EtOAc, washed with water, saturated $NaHCO_3$ and brine, dried ($MgSO_4$), concentrated and chromatographed (silica, 80% EtOAc/hexane) providing **4-6a** (410 mg, 0.78 mmol, 83%): R_f 0.53 (EtOAc, silica); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, $J = 8$ Hz, 2H), 7.76 (d, $J = 9$ Hz, 2H), 7.62 (d, $J = 9$ Hz, 2H), 7.57−7.41 (m, 4H), 6.95 (dd, $J = 7,1$ Hz, 1H), 6.86 (br m, 1H) 6.50 (dd, $J = 8$, 1H, 1H), 5.92 (br m, 1H), 458 (br s, 2H), 4.00−3.84 (m, 2H), 3.36−3.00 (m, 5H), 1.29 (s, 9H).

3-{4-[2-(6-Aminopyridin-6-yl)ethyl]benzoylamino}-2(*S*)-4-iodobenzenesulfonylaminopropionic Acid Ethyl Ester (4-6b). A solution of acid **4-5** (400 mg, 1.43 mmol), amine **1-6** (686 mg, 1.57 mmol), EDC (358 mg, 1.86 mmol), HOBT (252 mg, 1.86 mmol), NMM (632 μL, 5.72 mmol) in DMF (10 mL) was stirred for ∼20 h. The reaction was diluted with EtOAc and then washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated. Flash chromatography (silica, EtOAc then 5% 2-propanol/EtOAc) provided amide **4-6b** (430 mg, 0.69 mmol, 48%) as a white solid: TLC R_f = 0.4 (silica, 10% 2-propanol/EtOAc); ^{1}H NMR (300 MHz, CD_3OD) δ 7.79 (d, 2H, $J = 9$ Hz) 7.61 (d, 2H, $J = 8$ Hz), 7.52 (d, 2H, $J = 9$ Hz), 7.29 (m, 1H), 7.27 (d, 2H, $J = 8$ Hz), 4.20 (m, 1H), 3.95 (q, 2H, $J = 7$ Hz), 3.66 (dd, 1H, $J = 6$ Hz, 14 Hz), 3.49 (dd, 1H, $J = 8$ Hz, 13 Hz), 3.01 (m, 2H), 2.86 (m, 2H), 1.08 (t, 3H, $J = 7$ Hz).

3-{4-[2-(6-Aminopyridin-6-yl)ethyl]benzoylamino}-2(*S*)-benzenesulfonylaminopropionic Acid (4). Ester **4-6a** (375 mg, 0.72 mmol), was dissolved in 1:1 CH_2Cl_2/TFA (7.2 mL). After 2 h the reaction was concentrated, azeotroped with toluene, and triturated with 10:1:1 EtOH/NH_4OH/H_2O, providing **4** (160 mg, 0.34 mmol, 48%) as a light yellow solid: ^{1}H NMR (300 MHz, D_2O + NaOD) δ 7.73 (d, $J = 8$ Hz, 2H), 7.52 (d, $J = 9$ Hz, 2H), 7.34 (d, $J = 8$ Hz, 2H), 7.30−7.15 (m, 3H), 6.67 (d, $J = 7$ Hz, 1H), 6.62 (d, $J = 8$ Hz, 1H), 3.80−3.68 (m, 2H), 3.35−3.05 (m, 5H); HRMS (FAB, M + 1) calcd 469.1546, found 469.1559. Anal. ($C_{23}H_{24}N_4O_5S\cdot 0.4H_2O$) C, H, N.

3-{4-[2-(6-Aminopyridin-6-yl)ethyl]benzoylamino}-2(*S*)-4-iodobenzenesulfonylaminopropionic Acid (7). A solution of ester **4-6b** (200 mg, 0.3213 mmol) and 6 N HCl (30 mL) was heated to 60 °C. After ∼20 h, the reaction mixture was

concentrated. Flash chromatography (silica, 20:20:1:1 EtOAc/EtOH/ NH_4OH/H_2O) provided acid **7** (90 mg, 0.15 mmol, 47%) as a white solid: TLC $R_f = 0.45$ (silica, 20:20:1:1 EtOAc/EtOH/NH_4OH/H_2O); ^{1}H NMR (400 MHz, DMSO) δ 8.40 (m, 1H), 8.14 (Bs, 1H), 7.81 (d, 2H, $J = 8$ Hz), 7.62 (d, 2H, $J = 8$ Hz), 7.48 (d, 2H, $J = 8$ Hz), 7.27 (m, 3H), 6.34 (d, 1H, $J = 7$ Hz), 6.25 (d, 1H, $J = 8$ Hz), 5.85 (bs, 2H), 3.89 (bs, 1H), 3.35 (m, 2H), 2.97 (m, 2H), 2.79 (m, 2H); HRMS (FAB, M + 1) calcd 595.0513, found 595.0518. Anal. ($C_{23}H_{23}N_4O_5S\cdot1.25H_2O$) C, H, N.

4-(3-Oxobutyl)benzoic Acid Ethyl Ester (5-1). 3-Buten-2-ol (16.1 mL, 0.19 mol), ethyl 4-iodobenzoate **(4-1)** (41.4 g, 0.15 mol) and NEt_3 (26.3 mL, 0.19 mol) were combined in 300 mL of CH_3CN under Ar. $Pd(OAc)_2$ (150 mg, 0.6 mmol) was added and the reaction heated to 60 °C for 16 h. The reaction was concentrated. The residue dissolved in EtOAc and then washed with H_2O, 10% $KHSO_4$, saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated to give **5-1** (33.1 g, 0.15 mol, quantitative) as a tan solid: TLC R_f 0.23 (silica, 30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, $J = 8$ Hz, 2H), 7.25 (d, $J = 8$ Hz, 2H), 4.36 (q, $J = 7$ Hz, 2H), 2.95 (t, $J = 7$ Hz, 2H), 2.78 (t, $J = 7$ Hz, 2H), 2.15 (s, 2H), 1.38 (t, $J = 7$ Hz, 3H).

4-(2-[1,8]Naphthyridin-2-ylethyl)benzoic Acid Ethyl Ester (5-2). An ethanol solution of (500 mL) of **5-1** (33.1 g, 0.15 mol), 2-amino-3-carboxaldehyde (17.8 g, 0.15 mol) and L-proline (8.6 g, 75 mmol) was refluxed for 18 h. The cooled reaction mixture was concentrated to dryness. Flash chromatography (silica, 60−70% EtOAc/hex) provided **5-2** (27.6 g, 90 mmol, 60%) as a yellow solid: TLC R_f 0.31 (silica, 70% EtOAc/hex);; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.11 (m, 1H), 8.18 (d, $J = 8$ Hz, 1H), 8.08 (d, $J = 8$ Hz, 1H), 7.95 (d, $J = 8$ Hz, 2H), 7.47 (m, 1H), 7.30 (d, $J = 8$ Hz, 2H), 4.35 (q, $J = 7$ Hz, 2H), 3.35 (m, 4H), 1.38 (t, $J = 7$ Hz, 3H).

4-[2-(5,6,7,8-Tetrahydro[1,8]naphthyridin-2-yl)ethyl]-benzoic Acid Ethyl Ester (5-3). A mixture of **5-2** (27.6 g, 90 mmol), 10% Pd/C (3.0 g), and ethanol (1 L) was stirred under a hydrogen atmosphere for 18 h. Filtration through a Celite pad followed by concentration provided an off-white solid. Trituration with 270 mL Et_2O/hexanes (1:1) gave pure **5-3** (14.5 g, 47 mmol, 52%) as a white solid: TLC R_f 0.75 (silica, 70% EtOAc/hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, $J = 8$ Hz, 2H), 7.26 (d, $J = 8$ Hz, 2H), 7.03 (d, $J = 7$ Hz, 1H), 6.28 (d, $J = 7$ Hz, 1H), 4.81 (s, 1H), 4.35 (q, $J = 7$ Hz, 2H), 3.40 (m, 2H), 3.03 (m, 2H), 2.84 (m, 2H), 2.69 (t, $J = 6$ Hz, 2H), 1.93 (t, $J = 6$ Hz, 2H), 1.38 (t, $J = 7$ Hz, 3H).

4-[2-(5,6,7,8-Tetrahydro[1,8]naphthyridin-2-yl)ethyl]-benzoic Acid (5-4). Ester **5-3** (14.0 g, 45.1 mmol) in 300 mL 6 N HCl was heated to 60 °C for 18 h. Concentration provided **5-4** (15.1 g, quantitative) as a yellow solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.93 (d, $J = 8$ Hz, 2H), 7.52 (d, $J = 8$ Hz, 1H), 7.31 (d, $J = 8$ Hz, 2H), 6.54 (d, $J = 8$ Hz, 1H), 3.48 (t, $J = 5$ Hz, 2H), 3.03 (m, 4H), 2.79 (t, $J = 6$ Hz, 2H), 1.93 (t, $J = 6$ Hz, 2H).

2(*S*)-Benzenesulfonylamino-3-{4-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl]benzoylamino}propionic Acid *tert*-Butyl Ester (5-5). A mixture of **5-4** (33.3 g, 0.10 mol), amine **1-4** (40 g, 0.10 mol), NMM (80.4 mL, 0.73 mol) and BOP reagent (55.4 g, 0.13 mmol) were combined in 1 L CH_3CN. After stirring overnight, the reaction was concentrated, then diluted with EtOAc, washed with H_2O, saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography (silica, EtOAc) provided **5-5** (61.8 g, 0.10 mol, 97%) as an off-white foamy solid: TLC R_f 0.13 (silica, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, $J = 7$ Hz, 2H), 7.69 (d, $J = 8$ Hz, 2H), 7.28−7.34 (m, 3H), 7.25 (d, $J = 8$ Hz, 2H), 7.08 (d, $J = 7$ Hz, 1H), 6.29 (d, $J = 7$ Hz, 1H), 3.78 (m, 1H), 3.58−3.70 (m, 2H), 3.38 (t, $J = 6$ Hz, 2H), 2.97 (t, $J = 6$ Hz, 2H), 2.81 (t, $J = 6$ Hz, 2H), 2.68 (t, $J = 6$ Hz, 2H), 1.86 (m, 2H), 1.20 (S, 9H).

2(*S*)-Benzenesulfonylamino-3-{4-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl]benzoylamino}propionic Acid (5). A mixture of **5-5** (61.8 g, 0.10 mol) and 6 N HCl (1 L) was heated at 50 °C for 9 h. The reaction mixture was concentrated and then diluted with 500 mL of H_2O and neutralized with 1 N NaOH. Concentration and then flash chromatography (silica, 28:10:1:1 EtOAc/EtOH/NH_4OH/H_2O) provided **5** (41 g, 70.3 mmol, 72%) as a white solid: R_f 0.63 (silica, 19:1 EtOH/NH_4OH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.82 (d, $J = 7$ Hz, 2H), 7.69 (d, $J = 8$ Hz, 2H), 7.28−7.34 (m, 3H), 7.25 (d, $J = 8$ Hz, 2H), 7.08 (d, $J = 7$ Hz, 1H), 6.29 (d, $J = 7$ Hz, 1H), 3.78 (m, 1H), 3.58−3.70 (m, 2H), 3.38 (t, $J = 6$ Hz, 2H), 2.97 (t, $J = 6$ Hz, 2H), 2.81 (t, $J = 6$ Hz, 2H), 2.68 (t, $J = 6$ Hz, 2H), 1.86 (m, 2H); HRMS (FAB, M + 1) calcd 509.1859, found 509.18529. Anal. ($C_{26}H_{28}N_4O_5S\cdot0.25SiO_2$) C, H, N.

Echistatin Displacement Assay (EIB). ^{125}I-Echistatin binding to $\alpha_v\beta_3$ integrin was determined by incubating human embryonic kidney (HEK) 293 cell extracts, permanently transfected with human $\alpha_v\beta_3$ integrin expressing $\sim10 \times 10^6$ receptors/cell, with 30 pM ^{125}I-echistatin (1700 Ci/mmol) in binding buffer (100 mM Tris-HCl, pH 7.8, 100 mM NaCl, 1 mM $CaCl_2$/$MgCl_2$, 0.1% BSA) in the presence and absence of 1 μM unlabeled echistatin. Integrin-bound echistatin was separated from unbound by filtration (Skatron cell harvesting system 11021, Sterling, VA) on filters presoaked with 1.5% poly-(ethylenimine). The filters were washed with 6 mL wash buffer (25 mM Tris-HCL, pH 7.8, 1 mM $CaCl_2/MgCl_2$) and counted in a gamma counter (Packard Auto 5650, Meriden, CT).

Rat Bone Resorption Assay (BONE RES). Osteoclasts were isolated from the long bones of 1−3-day-old rat pups (Sprague−Dawley) by modifications of Chambers et al.[39] The resulting suspension (0.75 mL/bone) was gently triturated 90−120 times using a wide bore transfer pipet. The cells were separated from bone fragments by a cell strainer with a 100-μm nylon mesh. 100 μL of the cell suspension was placed onto each bone slice (6 mm) obtained from bovine femur diaphyses. Test compounds were then added at the desired experimental concentrations.

Bone slices exposed to osteoclasts for 20−24 h were processed for staining. Tissue culture media was removed from each bone slice. Each well was washed with 200 μL of H_2O, and the bone slices were then fixed for 20 min in 2.5% glutaraldehyde, 0.1 M cacodylate, pH 7.4. After fixation, any remaining cellular debris was removed by ultrasonication for 2 min in the presence of 0.25 M NH_4OH followed by 2×15 min ultrasonication in H_2O. The bone slices were immediately stained for 6−8 min with filtered 1% toluidine blue and 1% Borax.

After the bone slices dried, resorption pits were counted in test and control slices. Resorption pits were viewed in a Microphot Fx (Nikon) fluorescence microscope using a polarizing Nikon IGS filter cube. Test dosage results were compared with controls, and resulting IC_{50} values were determined for each compound tested.

Platelet Aggregation Assay (PLAGGIN). Platelet aggregation with gel filtered human platelets was measured by the light transmittance method at 37 °C using a Chrono-Log lumi-aggregometer or a BioData platelet aggregation profiler. The reaction mixture containing gel-filtered platelets was adjusted to 2×10^8 platelets/mL. The gel-filtered platelets contained, in addition, 0.1 mg/mL human fibrinogen, 1 mM $CaCl_2$ and test compound or vehicle. Aggregation was initiated by adding 10 μM ADP, and the inhibition of platelet aggregation is reported as a percent of the rate of aggregation.

Human $\alpha_v\beta_3$ Scintillation Proximity Assay (SPAV3). The integrin $\alpha_v\beta_3$ was purified from 293 cells overexpressing human recombinant $\alpha_v\beta_3$ according to Pytela et al.[40] Lyophilized wheatgerm agglutinin scintillation proximity beads (500 mg) were first washed two times with 50 mL of 50-OG buffer (50 mM octylglucoside, 50 mM Tris-HCl, 100 mM NaCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, and 1 mM PMSF, pH 7.5) and once with 50 mL of binding buffer (50 mM HEPES, pH 7.5, 100 mM NaCl, 1 mM Ca^{2+}/Mg^{2+}) and then resuspended in 12.5 mL of binding buffer.

In each assay tube, 2.5 μL of pretreated beads was suspended in 97.5 μL of binding buffer and 20 mL of 50-OG buffer. 5 μL ($\sim$30 ng/μL) of purified receptor was added to the beads in suspension with stirring at room temperature for 30 min. The mixture was then centrifuged at 2500 rpm in a Beckman

GPR benchtop centrifuge for 10 min at 4 °C. The pellets were then resuspended in 50 μL of binding buffer and 25 μL of 50-OG buffer.

The following were sequentially added into Optiplate in corresponding wells: 75 μL of receptor/beads mixture; 25 μL each of the following to corresponding wells (a) compound with known concentration to be tested, (b) binding buffer for total binding, or (c) cold ligand **7** for nonspecific binding (final concentration 1 μM); 25 μL of ^{125}I-labeled **7** in binding buffer (final concentration ~40 pM); and 125 μL of binding buffer. Each plate was sealed with plate sealer from PACKARD and incubated overnight with rocking at 4 °C. Plates were counted using PACKARD TOPCOUNT, and the IC_{50} value for each compound was determined.

TPTX Rat Assay. Rats were anesthetized, weighed, and thyroparathyroidectomized (TPTX). Two subcutaneous pockets (~0.5 × 1 cm) were surgically installed, one in the anterior and another in the posterior dorsal region, to accommodate a polyethylene cannula and an osmotic pump, respectively. Subcutaneous pockets were closed using surgical wound clips. All animals were allowed to recover from surgery with ad libitum access to a low-calcium diet and tap water. On the following day, animals were bled via retro-orbital sinus and serum calcium concentrations determined by colorimetric methods or by atomic absorption spectrophotometry. Rats that were found to have a reduced serum calcium level of <8 mg/dL, as a result of TPTX and dietary calcium restriction, were used for assay.

On the third day after surgery, animals were anesthetized and bled, as above, after which anterior dorsal pockets were opened and connected, via cannulae, to precalibrated digital syringe infusion pumps (Harvard Apparatus, Waltham, MA) delivering <1.3 mL/h of vehicle or test compound. Thirty minutes after the start of of test compound/vehicle infusions, posterior dorsal subcutaneous pockets were opened and pre-equilibrated osmotic minipumps (model 2001D, Alza Corp., Palo Alto, CA), delivering 0.03 nmol/h bovine parathyroid hormone (1−34), were installed.

Animals were maintained in an anesthetized state over 4−6 h, at the end of which time they were bled, as above, and then euthanized. Serum calcium concentrations of baseline and endpoint sera were determined, as above. Statistical analyses of serum calcium data were performed using Statview for PC (version 4.57, Abacus Concepts, Inc.). All surgical procedures were carried out using aseptic technique and according to institutional guidelines for rodent survival surgery.

Acknowledgment. The authors thank the mass spectroscopy and analytical groups for spectral and physical data for compounds disclosed herein. We also thank Joy Hartzell for manuscript preparation and Robert Lynch for PLAGGIN IC_{50} determinations.

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JM000133V