Nonpeptide $\alpha_v\beta_3$ Antagonists. Part 11: Discovery and Preclinical Evaluation of Potent $\alpha_v\beta_3$ Antagonists for the Prevention and Treatment of Osteoporosis

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3-(*S*)-Pyrimidin-5-yl-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid **(5e)** and 3-(*S*)-(methylpyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid **(5f)** were identified as potent and selective antagonists of the $\alpha_v\beta_3$ receptor. These compounds have excellent in vitro profiles (IC_{50} = 0.07 and 0.08 nM, respectively), significant unbound fractions in human plasma (6 and 4%), and good pharmacokinetics in rat, dog, and rhesus monkey. On the basis of the efficacy shown in an in vivo model of bone turnover following once-daily oral administration, these two compounds were selected for clinical development for the treatment of osteoporosis.

Introduction

Osteoporosis is a disease of the skeleton characterized by diminishing bone mass and associated with an increased risk of debilitating fracture.[1] Osteoporosis arises from an imbalance between the activities of bone-resorbing osteoclast cells and bone-depositing osteoblast cells.[2] In post-menopausal women, estrogen depletion results in increased bone resorption because of the enhanced activity and number of osteoclasts. Osteoclast cells mediate bone resorption by initial attachment to the bone surface followed by secretion of matrix-degrading proteinases. The attachment of osteoclasts to bone involves the binding of the highly expressed integrin $\alpha_v\beta_3$ to an RGD (arg-gly asp) tripeptide sequence found in extracellular matrix proteins expressed on the bone surface.[3] The integrin $\alpha_v\beta_3$ is thought to be involved not only in cellular adhesion of osteoclasts to the bone surface but also in regulating their migration along the bone surface. Antagonists that block the binding of RGD expressing proteins to $\alpha_v\beta_3$ inhibit bone resorption in rodent models and offer a potential therapy for the prevention and treatment of osteoporosis.[4−12]

Previous reports from these laboratories have demonstrated that "chain-shortened" $\alpha_v\beta_3$ inhibitors are potent receptor antagonists with improved oral pharmacokinetics.[13] RGD peptide mimetics such as **2** are two atoms shorter in chain length than the extended tripeptide or full-length antagonists such as **1** (Figure 1). Although this modification was associated with enhanced pharmacokinetics for **2** (dog pharmacokinetics: F = 99%; Cl = 1.2 mL/min/kg) versus **1** (F = 6%; Cl = 33 mL/min/kg), chain-shortened antagonists such as **2** were less potent than constrained full-length inhibitors such as **1**.[14] Efforts to improve receptor potency within this series while maintaining acceptable pharmacokinetics focused on the incorporation of cyclic constraints,[12,15] N-terminus modifications,[16] C-terminus modifications,[17] and amide deletion. Chain-shortened $\alpha_v\beta_3$ antagonist **3**, which possesses an imidazolidone

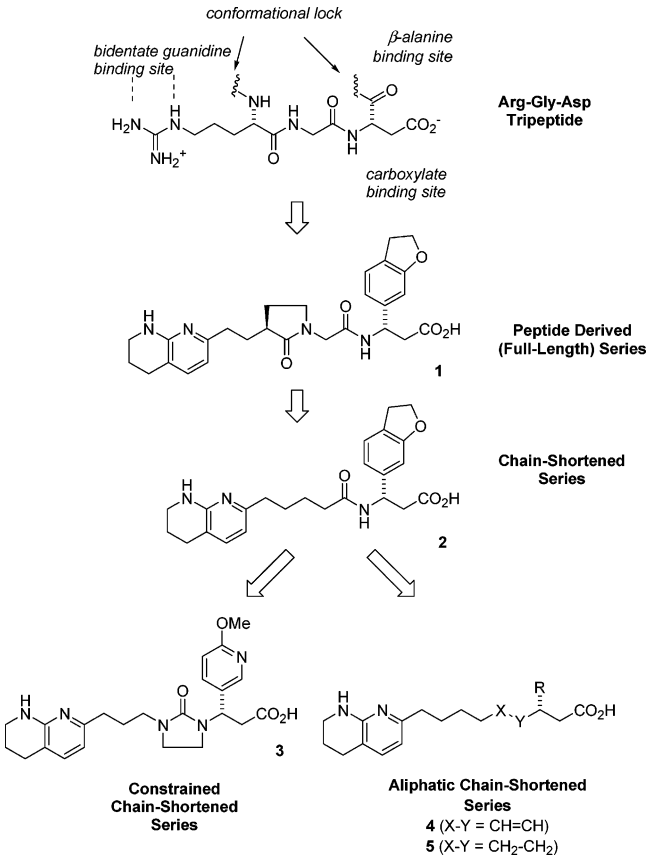

Figure 1. Development of chain-shortened nonanoic acid derivatives **4** and **5**.

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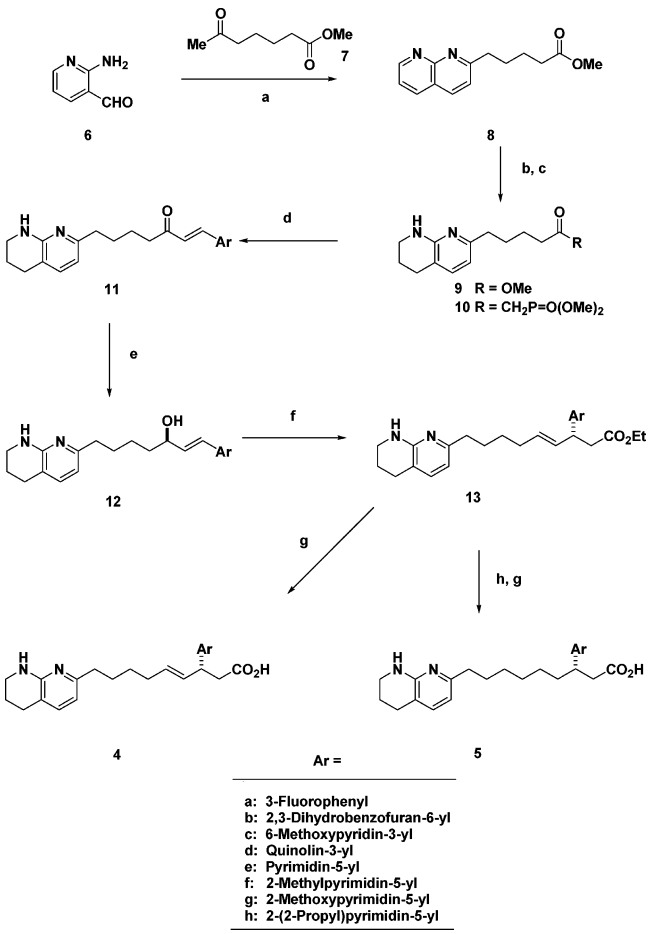
Scheme 1. Synthesis of Nonanoic Acid $\alpha_v\beta_3$ Antagonists[a]



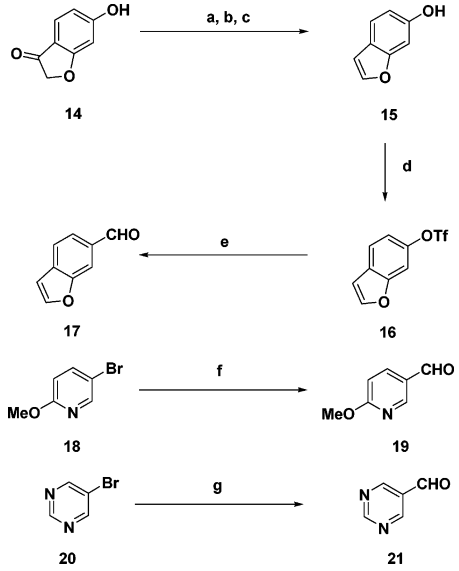
[a] Reagents: (a) Proline, EtOH, reflux, 12 h. (b) PtO_2, H_2(g), EtOH, 48 h, 34%. (c) Dimethylmethylphosphonate, *n*-BuLi, −78 °C, 91%. (d) K_2CO_3, ArCHO, THF, reflux, 1 h. (e) $NaBH_4$, MeOH, chiral HPLC separation. (f) triethylorthoacetate, $EtCO_2H$, 145 °C, 2 h. (g) LiOH, EtOH, rt (h) 10% Pd/C, 1,4-cyclohexadiene, AcOH, 80 °C or Pd/C, H_2(g) 1 atm.

central constraint, is a high-affinity ligand that inhibits bone resorption in vivo and displays good pharmacokinetics in dogs. This compound was previously selected for clinical development on the basis of these attributes. Preclinical metabolism studies on **3** projected that its pharmacokinetic profile in man would likely require twice-daily oral dosing to provide sufficient plasma coverage for the treatment of osteoporosis. A key objective for the project team was therefore to identify structurally novel $\alpha_v\beta_3$ antagonists whose preclinical pharmacokinetic parameters would be predictive of a once-daily dosing regimen in man. In this paper, we describe the synthesis and preclinical characterization of $\alpha_v\beta_3$ inhibitors of general structure **4** and **5**. These studies led to the identification of two potent $\alpha_v\beta_3$ antagonists with improved preclinical pharmacokinetics that have been selected for clinical evaluation in the treatment of osteoporosis.

Chemistry

$\alpha_v\beta_3$ antagonists of general structure **4** and **5** were synthesized by the route shown in Scheme 1. This synthetic sequence utilizes a Johnson ortho ester Claisen[18] rearrangement to establish the 3-aryl nonanoic acid

Scheme 2. Synthesis of Aryl Aldehydes **16**, **18**, and **20**[a]

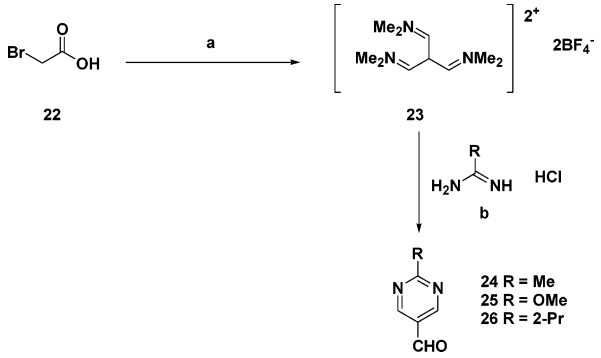


[a] Reagents: (a) TBS−Cl, Et_3N, DMF, rt. (b) $NaBH_4$, MeOH. (c) 3 N aq HCl (99%, 3 steps). (d) $PhNTf_2$, Et_3N, CH_2Cl_2, 94%. (e) $Pd(OAc)_2$, DPPP, DMF, 70 °C, CO(g), Et_3N, $(OCtyl)_3SiH$, 29%. (f) *n*-BuLi, DMF, THF, −78 °C, 95%. (g) *n*-BuLi, −100 °C, EtOCHO, THF, 52%.

derivative **5**. The treatment of 2-amino-3-formylpyridine[19] with methyl ketone **7** using proline as a catalyst provides for a regioselective Friedlander condensation[20] to afford naphthyridine **8**. Selective hydrogenation of **8** with PtO_2/H_2 (g) gives tetrahydronaphthyridine **9**. Low-temperature lithiathion of dimethyl methylphosphonate followed by treatment with **9** affords ketophosphonate **10** in good yield. The Horner−Wadsworth−Emmons reaction of ketophosphonate **10** with various aryl aldehydes under standard conditions provides enone **11**. Reduction of enone **11** with sodium borohydride gives *rac*-allylic alcohol **12**. Because control of the configuration of the stereogenic C3 carbon is critical for gaining receptor potency, allylic alcohol **12** was resolved by chiral stationary phase HPLC[21] to allow for a stereochemical relay in the subsequent Claisen rearrangement. The reaction of **12** with triethylorthoacetate under acid catalysis provides unsaturated ester **13**. In this stereoselective rearrangement, 3-(*R*)-**12** is transformed to 3-(*S*)-**13.** Saturated inhibitors **5a**−**h** were generated by olefin hydrogenation followed by the saponification of the ester. In cases where electron-deficient heterocycles (i.e., pyrimidines and quinoline) were present, the use of transfer hydrogenation protocols proved useful.[22] Unsaturated inhibitor **4a** was prepared by base hydrolysis of ester **13**.

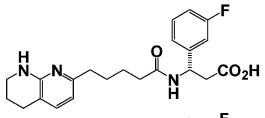
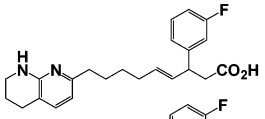
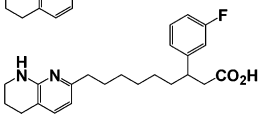
To synthesize $\alpha_v\beta_3$ antagonist **5**, several noncommercially available aryl aldehydes were prepared as shown in Schemes 2 and 3. The synthesis of 6-benzofuran carboxaldehyde **17** began with benzofuranone **14** (Maybridge). Protection of **14** as the silyl ether followed by ketone reduction with $NaBH_4$ and acid-promoted dehydration and desilylation provides **15**.[23] Phenol **15** was transformed to triflate **16** and carbonylated with carbon monoxide under palladium catalysis[24] to yield **17**. The syntheses of 2-methoxypyridine-3-carboxaldehyde (**19**) and pyrimidine-5-carboxaldehyde (**21**) began with the corresponding aryl bromides. Lithium halogen exchange with *n*-butyllithium followed by reaction with either

Scheme 3. Synthesis of 2-Substituted Pyrimidine-5-carboxaldehydes[a]



[a] Reagents: (a) $POCl_3$, DMF, 90 °C, $NaBF_4$, 53%. (b) Amidine, EtOH, NaOEt (48−78%).

Table 1. Amide Replacement in Chain-Shortened $\alpha_v\beta_3$ Antagonists

	compound[a]	SPAV3[b] IC50 (nM)
	**27**	22.7 ± 10.2
	**4a**	7.2 ± 4.2
	**5a**	0.93[c]

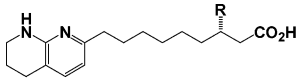
[a] Compounds **4a** and **5a** were tested as racemates. [b] Binding to the $\alpha_v\beta_3$ receptor using a scintillation-proximity assay (SPAV3). [c] $n = 1$.

dimethylformamide or ethyl formate provides the desired aldehydes. In the case of **21**, lithiation was carried out at −100 °C to suppress competing direct alkyllithium addition.[25] Substituted pyrimidines **24**, **25**, and **26** were prepared according to the published methods using vinamidinium salt **23**.[26]

Results and Discussion

In our initial evaluation of these amide-deleted $\alpha_v\beta_3$ antagonists, we incorporated the 3-fluorophenyl moiety at C3 of the alkyl chain (Table 1). Compounds were screened for their affinity to bind to the $\alpha_v\beta_3$ receptor using a scintillation-proximity assay (SPAV3 assay) and a high-affinity radioligand.[27] The replacement of the amide moiety in these chain-shortened antagonists with a trans olefin, a potential amide isostere,[28] afforded more potent $\alpha_v\beta_3$ inhibitor **4a**. Remarkably, saturation of the olefin present in **4a** yielded an inhibitor (**5a**) that was more than 20-fold more potent[28] than corresponding chain-shortened antagonist **27**. With this discovery, we quickly incorporated a set of preferred, potent 3-aryl substituents in this novel series to yield antagonists **5b**, **5c**, and **5d** (Table 2). As a group, this novel class of substituted nonanoic-acid antagonists offered exceptional potency (<1 nM). $\alpha_v\beta_3$ antagonists **5b**, **5c**, and **5d** were synthesized as the enantiomerically enriched 3-(*S*) enantiomers. The corresponding 3-(*R*) isomers were significantly less potent (>10× shift in SPAV3).

Table 2. 3-Aryl Nonanoic Acid $\alpha_v\beta_3$ Antagonists



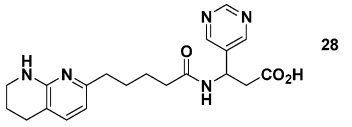
R	compound	SPAV3[a] IC_{50}(nM)	h-protein binding	logP	Dog PK[b] F	T1/2 h	CL ml/min/kg
	**5b**	0.21 ± 0.1	99.9%	2.39	>99%	5.8	7.9
	**5c**	0.65 ± 0.3	99.5%	1.67	49%	9.5	5.1
	**5d**	0.20 ± 0.07	>99.9%	2.39	65%	5.0	3.0

[a] Binding to the $\alpha_v\beta_3$ receptor using a scintillation-proximity assay (SPAV3). [b] Dog PK: compounds dose at 0.2 mpk iv and 1 mpk po in water.

The pharmacokinetic parameters for this class of amide-deleted antagonists were markedly improved in the dog versus chain-shortened amides such as **2** or imidazolone **3** (Table 2). Bioavailability in the dog was good (49−100%) with low plasma clearance (3−8 mL/min/kg) and long plasma $T_{1/2}$ (5.8−9.5 h). Compound **5d** was also bioavailable in the rat (F = 79%) with low clearance (1.4 mL/min/kg) and a good $T_{1/2}$ (5.3 h). Compared to the amide-bearing chain-shortened antagonists, these des-amide inhibitors were significantly more lipophilic, as determined by the measured log *P*.[29] The increase in overall lipophilicity for this class of inhibitors is associated with higher levels of plasma protein binding[30] in both human and rat plasma.

On the basis of its in vitro potency and its excellent rat pharmacokinetics, compound **5d** was evaluated for in vivo efficacy as an inhibitor of bone resorption in an ovariectomized (OVX) rat model.[31] In this assay, ovariectomy of female rats promotes a rapid, time-dependent loss of bone mineral density (BMD) that parallels the bone loss observed in estrogen-deficient, post-menopausal women. Compound **5d** was dosed orally at 10 mpk qd for 28 days, and the effects on BMD were measured at the distal femoral metaphysis were compared to vehicle control and sham-operated rats. At this dose, compound **5d** did not significantly prevent bone loss in this model despite the maintenance of high plasma exposures ($C_{T=1.2\ h} = 44.9 \pm 1.4\ \mu M$; $C_{T=12\ h} = 20.6 \pm 5.3\ \mu M$). The lack of a significant effect on BMD by compound **5d** suggested that plasma protein binding may be controlling in vivo efficacy.

With this result, we directed our efforts toward reducing plasma protein binding in this series of nonanoic acid antagonists. Previous efforts had shown a correlation between log *P* and plasma protein binding, and we therefore sought to design compounds with increased polarity. Because 3-aryl substituents in this class of antagonists exert a profound effect on overall physical properties, we reexamined our earlier series of chain-shortened amides[12] to identify a suitable replacement for the 3-quinolyl substituent in compound **5d**. We had previously incorporated a 3-(5-pyrimidinyl) substituent in the chain-shortened series and found that this $\alpha_v\beta_3$ antagonist **28** (Figure 2) had good receptor potency but very poor dog PK (F = 10%; Cl = 26 mL/min/kg). We attributed this poor PK to the reduced lipophilicity of compound **28** (log *P* = −1.2). However,

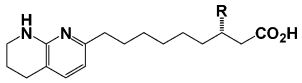


28

SPAV3 IC_{50}(nM) [b]	h-protein binding	logP	Dog PK [c] F	T1/2 hr	CL ml/min/kg
3.3 ± 1.9	44%	-1.2	10%	1.0	26

Figure 2. Evaluation of compound **28**. (a) Evaluated as a racemate. (b) Binding to the $\alpha_v\beta_3$ receptor using a scintillation-proximity assay (SPAV3). (c) Dog PK: compounds dose at 0.2 mpk iv and 1 mpk po in water.

Table 3. 3-Pyrimidinyl Nonanoic Acid $\alpha_v\beta_3$ Antagonists



R	compound	SPAV3[a] IC_{50}(nM)	h-protein binding	logP	dog PK[b] F	T1/2 hr	CL ml/min/kg
	**5e**	0.07 ± 0.01	94%	0.10	66%	6.4	3.9
	**5f**	0.08 ± 0.05	96%	0.43	83%	9.5	2.5
	**5g**	0.11 ± 0.06	97%	0.65	100%	6.8	4.3
	**5h**	0.52 ± 0.17	99%	1.32	ND	ND	ND

[a] Binding to the $\alpha_v\beta_3$ receptor using a scintillation-proximity assay (SPAV3). [b] Dog PK: compounds dose at 0.2 mpk iv and 1 mpk po in water.

compound **28** had an excellent free fraction in human plasma (PB = 44%). We envisioned that merging the polar pyrimidine 3-substituent from compound **28** with an aliphatic chain-shortened backbone might generate an $\alpha_v\beta_3$ antagonist with reduced protein binding, resulting in acceptable in vivo efficacy.

3-(5-Pyrimidinyl) nonanoic acid derivative **5e** was prepared and found to have an IC_{50} of 0.07 nM in the SPAV3 assay (Table 3). As anticipated, replacement of the 3-quinolyl substituent in **5d** with 3-pyrimidine had a profound effect on lipophilicity (log P = 0.1 vs 2.39 for **5d**) and plasma protein binding [PB(h) = 94%]. Remarkably, the favorable PK profile observed with compound **5d** was preserved in compound **5e** despite this significant reduction in lipophilicity. When dosed for dogs, compound **5e** provided excellent bioavailability (F = 66%), low clearance (Cl = 3.9 mL/min/kg), and a good half life (6.4 h).

In an effort to increase lipophilicity and potentially to enhance the PK profile of **5e** further, several substituted pyrimidines were incorporated into this chain-shortened aliphatic series (Table 3). Substitution of the pyrimidine at the 2-position was tolerated in some instances. 5-(2-Methylpyrimidine) and 5-(2-methoxypyrimidine) derivatives **5f** and **5g** had comparable potency to **5e** with decreased polarity. The increases in lipophilicity of **5f** and **5g** were associated with reduced free fractions in human plasma and maintenance of an excellent dog PK profile. In particular, compound **5f** had an exceptional PK profile in the rat with low clearance (Table 4; Cl = 3.6 mL/min/kg) and a long half-life (5.1 h). Remarkably, the inclusion of a methyl group on the pyrimidine of **5e** reduces plasma clearance in the rat by 8-fold and in the monkey by 4-fold. Substitution on the pyrimidine with larger alkyl groups (cf. **5h**) was not tolerated.

Table 4. Rat and Dog Pharmacokinetics for **5e** and **5f**

	rat PK[a]			rhesus PK[b]		
compound	F (%)	$T_{1/2}$ h	Cl ml/min/kg	F (%)	$T_{1/2}$ h	Cl ml/min/kg
5e	45	4.5	30	46	2.3	19
5f	100	5.1	3.6	75	17	4.5

[a] Rat PK: compounds dose at 0.5 mpk iv and 1 mpk po in water. [b] Rhesus PK: compounds dose at 0.2 mpk iv and 1 mpk po in water.

Preclinical modeling of human pharmacokinetics using animal PK data indicated that both **5e** and **5f** have the potential to have excellent bioavailability and plasma half-lives that would permit once-daily oral dosing.

Selectivity against two closely related integrins was also determined for **5e** and **5f**. Against $\alpha_v\beta_5$, compounds **5e** and **5f** demonstrated modest selectivity with IC_{50} values of 0.47 and 0.70 nM, respectively. In a functional platelet aggregation assay that indirectly measures the affinity of compounds **5e** and **5f** for the fibrinogen receptor $\alpha_{IIb}\beta_3$, the EC_{50} values were found to be 133 and 46 μM, respectively.[32]

On the basis of the excellent in vitro and PK profiles of compounds **5e** and **5f**, we evaluated these inhibitors in a OVX rat assay. The endpoints for the OVX rat assay include assessments of bone mass, bone resorption, and bone formation. For bone mass, BMD is determined at the distal femoral metaphysis. For bone resorption, the endpoint is urinary deoxypyridinoline (DPD), a bone collagen breakdown product. For bone formation, the endpoint is mineralizing surface, a histomorphometric measure of the fraction of trabecular bone surface with osteoblast activity.

Compound **5e** was evaluated in a 42-day OVX rat assay (Table 5) with oral administration at 20 and 30 mg/kg/day. At both doses, compound **5e** had statistically significant effects on BMD at the femoral metaphysis. The effect on BMD at 30 mpk of compound **5e** was equivalent to the effect observed with the administration of alendronate at a dose that approximates a typical human exposure. Because of its markedly improved rat PK, compound **5f** was evaluated in a rat OVX assay with oral administration at 1, 3, and 10 mg/kg/day for 28 days (Table 6). Compound **5f** was fully efficacious in BMD when administered orally at 3 mg/kg/day in the rat OVX model.

In this assay of **5f**, urine was collected at 26 days and analyzed for DPD and creatinine (cre) with the results expressed as DPD/cre. In this assay, the urinary DPD/cre ratio was 56% lower in sham rats versus OVX rats. At 3 and 10 mg/kg/day of compound **5f**, DPD/cre levels were significantly lower than those for OVX (−29 and −44%, respectively). For both doses, DPD/cre levels remained significantly above sham. The mineralizing surface, a tissue-level indicator of bone turnover, was 85% lower in sham rats than in OVX rats. The mineralizing surface was significantly lower at all doses of **5f**. $\alpha_v\beta_3$ antagonists **5e** and **5f** are potent inhibitors of bone resorption in vivo.

Table 5. Effects of **5e** on Cancellous Bone of Ovariectomized Female Rats[a]

group	N	DFM[d] BMD[b] (mg/cm^2) (mean ± SEM)	% from OVX + vehicle	$P <$ (vs OVX + vehicle)
sham	13	155.4 ± 2.4	+11.0	0.0005
OVX + vehicle	13	140.0 ± 2.3		
OVX + **5e** (20 mg/kg/d)	13	150.8 ± 3.9	+7.7	0.004
OVX + **5e** (30 mg/kg/d)	13	153.2 ± 4.6	+9.4	0.007
OVX + alendronate (ALN) (0.005 mg/kg/d, s.c.)	9	153.1 ± 2.3	+9.3	0.005

[a] Female rats were ovariectomized (OVX) and, within 24 h, were dosed orally with **5e** at 20 and 30 mg/kg qd for 42 days and compared to age-matched sham operated rats, OVX rats given vehicle, and OVX rats given ALN. [b] BMD denotes bone mineral density. [d] DFM denotes distal femoral metaphysis (region of cancellous bone). Rats treated with **5e** did not differ from either Sham−OVX or OVX + ALN rats. Differences were evaluated by Kruskal−Wallis ANOVA followed by the Student−Neuman−Keuls post-hoc test.

Table 6. Effects of **5f** on Cancellous Bone in Ovariectomized Female Rats[a]

group	N	DFM[d]BMD[b] (mg/cm^2) (mean ± SEM)	% from OVX + vehicle	$P <$ (vs OVX + vehicle)
sham	12	162.6 ± 3.5	+4.0	NS
OVX + vehicle	11	156.4 ± 4.0		
OVX + **5f** (1 mpk)	7	158.3 ± 4.0	+1.2	NS
OVX + **5f** (3 mpk)	10	173.0 ± 3.8	+10.6	0.007
OVX + **5f** (10 mpk)	10	176.0 ± 5.7	+12.5	0.003
alendronate (ALN) (0.003 mg/kg/d, s.c.)	10	167.0 ± 8.0	+6.8	0.10

[a] Female rats were ovariectomized (OVX) and, within 24 h, were dosed orally with **5f** at 1, 3, or 10 mg/kg q.d. for 28 days and compared to sham operated and OVX rats given vehicle or OVX rats given ALN. [b] BMD denotes bone mineral density. [d] DFM denotes distal femoral metaphysis (region of cancellous bone). Rats treated with 3 or 10 mg/kg/d **5f** did not differ from either Sham−OVX or OVX + ALN rats. Differences were evaluated by Kruskal−Wallis ANOVA followed by the Student−Neuman−Keuls post-hoc test.

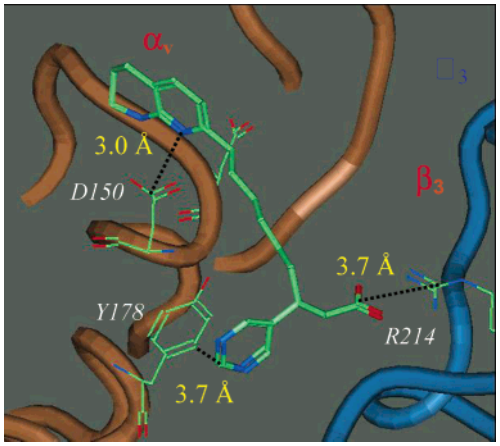


Figure 3. Docking of Compound **14e** to $\alpha_v\beta_3$.

Binding Model for 5e. We have previously reported a binding model for nonpeptide antagonists of the $\alpha_v\beta_3$ integrin on the basis of the published crystal structure of the extracellular domain.[33] In the current study, we have docked antagonist **5e** to $\alpha_v\beta_3$ using these methods and identified key interactions with D150 and Y178 of the α_v subunit (gold ribbon) and R214 of the β_3 subunit (blue ribbon) shown in Figure 3. The naphthyridine of **5e** interacts with the carboxylic acid side chain of D150 in α_v, whereas the C-terminal carboxylic acid is engaged in a salt bridge with R214 in β_3. An additional $\pi-\pi$ stacking interaction between the tyrosine side chain (Y178) of α_v and the 3-pyrimidinyl substituent is observed. The extended backbone in **5e** provides sufficient length (versus amide-containing chain-shortened antagonists) to allow for the key electrostatic interactions of the C- and N-termini with the protein while providing adequate flexibility to gain the binding energy between the aromatic 3-substituent on the ligand and Y178 of the protein.

Conclusions

We have identified **5e** and **5f** as potent and selective antagonists of the $\alpha_v\beta_3$ receptor. These structurally novel inhibitors are effective in a rodent model for preventing bone loss following once-daily oral administration. Critical to the discovery of these two antagonists was the careful monitoring of physical properties and plasma protein binding to optimize pharmacokinetic and pharmacodynamic properties. The merger of polar pyrimidine 3-substituents with the aliphatic chain-shortened backbone afforded a class of $\alpha_v\beta_3$ antagonists with optimal physical properties. Because of the potential for once-daily oral dosing and favorable antiresorptive profiles, both **5e** and **5f** were selected as development candidates for the treatment of osteoporosis.

Experimental Section

General. All commercially available chemicals and solvents were used without further purification. All new compounds gave satisfactory ^{1}H NMR and mass spectrometry analyses. ^{1}H NMR spectra were recorded on a Varian Unity 500-, 400-, or 300-MHz spectrometer, and chemical shifts are reported in ppm relative to tetramethylsilane as an internal standard. High-resolution mass spectral analysis was performed on a Bruker-daltonics BioApex 3T mass spectrometer. All animal studies described herein were approved by the Merck Research Laboratories Institutional Animal Care and Use Committee.

6-Oxo-heptanoic Acid Methyl Ester (7). A solution of 5-acetylvaleric acid (Lancaster, 200 g, 1.38 mol) in dichloroethane/methanol (1000 mL/ 400 mL) was treated with concentrated sulfuric acid (3.69 mL, 6.78 g, 69 mmol) and refluxed for 12 h. The solution was cooled to room temperature and washed with satd aq $NaHCO_3$ (2 × 400 mL). The aqueous washes were back extracted with dichloromethane (200 mL), and the combined organic extracts were washed with brine. The solution was dried over $MgSO_4$, filtered, and concentrated to give ca. 218 g (100%) of methyl ester **7** as a colorless oil. TLC R_f = 0.75 (90% CH_2Cl_2/5% MeOH/5% AcOH; visualized with PMA stain). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.62 (s, 3H), 2.41 (t, 2H), 2.31 (t, 3H), 2.12 (s, 3H), 1.59 (m, 4H).

5-[1,8]Naphthyridin-2-yl-pentanoic Acid Methyl Ester (8). A solution of methyl ketone (**7**) (218 g, 1388 mmol), 2-amino-3-formylpyridine (**6**), and proline (79.8 g, 694 mmol) in anhydrous ethanol (2000 mL) was heated at reflux for 12 h. The solution was cooled to room temperature and concentrated. The residue was taken up in ethyl acetate (1000 mL) and washed with water (2 × 300 mL) to remove the proline. The organic solution was dried over $MgSO_4$, filtered, and concentrated to give 320 g of a 3:1 mixture of desired product **8** and the naphthyridine regioisomer. A small portion of this mixture was purified by flash chromatography (SiO_2; 10% EtOH/CH_2Cl_2) to provide pure **8** for analysis. TLC $R_f = 0.62$ (10% EtOH/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.06 (dd, $J = 2.1$, 4.3 Hz, 1H), 8.14 (dd, $J = 2.0$, 8.0 Hz, 1H), 8.09 (d, $J = 8.2$ Hz, 1H), 7.43 (dd, $J = 4.3$, 8.2 Hz, 1H), 7.37 (d, $J = 8.2$ Hz, 1H), 3.64 (s, 3H), 3.05 (t, $J = 7.6$ Hz, 2H), 2.37 (t, $J = 7.6$ Hz, 2H), 1.93 (m, 2H), 1.75 (m, 2H).

5-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-pentanoic Acid Methyl Ester (9). A solution of **8** (160.0 g, 656 mmol) in anhydrous ethanol (2000 mL) was degassed with argon gas for 20 min. The solution was charged with PtO_2 (ProChem, 16.0 g), and the heterogeneous mixture was placed under 1 atm of H_2(g). The heterogeneous mixture was stirred under H_2(g) for 48 h. The mixture was purged with argon, filtered through Celite, and concentrated to give a dark oil. The residue was purified by flash chromatography (SiO_2, 100% EtOAc) to give an orange waxy solid that was recrystallized from diethyl ether to give 56.0 g (34%, three steps) of desired product **9** as a tan crystalline solid. TLC $R_f = 0.40$ (10% EtOH/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.04 (d, $J = 7.3$ Hz, 1H), 6.32 (d, $J = 7.3$ Hz, 1H), 4.73 (br s, 1H), 3.65 (s, 3H), 3.38 (m, 2H), 2.68 (t, $J = 6.1$ Hz, 2H), 2.54 (m, 2H), 2.33 (m, 2H), 1.89 (m, 2H), 1.67 (m, 4H).

[2-Oxo-6-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-hexyl]-phosphonic Acid Dimethyl Ester (10). A solution of dimethylmethylphosphonate (112 mL, 1030 mmol) in THF (1300 mL) was cooled to −78 °C. A solution of *n*-BuLi (Acros, 412 mL of a 2.5 M soln in hexanes, 1030 mmol) was added via an addition funnel over 1 h. The reaction became heterogeneous at the conclusion of the addition. A solution of methyl ester **9** (64.0 g, 258 mmol) in THF (400 mL) was added via an addition funnel over 45 min. After stirring for an additional 20 min at −78 °C, the mixture was quenched with satd aq NH_4Cl, and the cold bath was removed. After warming to room temperature, the mixture was diluted with EtOAc and washed with H_2O and brine. The organic solution was dried over $MgSO_4$, filtered, and concentrated. The residue was not further purified to give 80.1 g (91%) of ketophosphonate **10** as a pale-yellow oil. TLC $R_f = 0.14$ (10% EtOH/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (d, $J = 7.6$ Hz, 1H), 6.26 (d, $J = 7.6$ Hz, 1H), 4.75 (br s, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.32 (m, 1H), 3.01 (d, $J = 22.8$ Hz, 2H), 2.59 (m, 4H), 2.46 (m, 2H), 1.83 (m, 2H), 1.57 (m, 4H).

Typical Procedure for the Preparation of 3-Aryl-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acids 14. Step 1. 1-Pyrimidin-5-yl-7-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-hept-1-en-3-one (11e). A stirred suspension of anhydrous powdered K_2CO_3 (Aldrich, 325 mesh; 38.44 g, 278.5 mmol), ketophosphonate **10** (46.86 g, 137.8 mmol), and 5-formylpyrimidine (**21**) (12.4 g, 114 mmol) in THF (1400 mL) was heated at reflux for 1 h. After cooling to room temperature, the mixture was diluted with EtOAc (2 L) and washed with water (500 mL) and brine (500 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2; 10% EtOH/CH_2Cl_2) to give 29.0 g (78%) of enone adduct **11e** as a tan solid. TLC $R_f = 0.30$ (10% MeOH/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.8 (s, 1H), 8.8 (s, 2H), 7.43 (d, $J = 16$ Hz, 1H), 7.04 (d, $J = 7.4$ Hz, 1H), 6.84 (d, $J = 16$ Hz, 1H), 6.34 (d, $J = 7.4$ Hz, 1H) 4.68 (br s, 1H), 3.38 (m, 1H), 2.69 (m, 4H), 2.57 (m, 2H), 1.87 (m, 2H), 1.72 (m, 4H).

Step 2. 1-Pyrimidin-5-yl-7-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-hept-1-en-3-ol (12e). Enone **11e** (21.21 g, 65.9 mmol) was dissolved in MeOH (823 mL) and cooled to 0 °C. Solid $NaBH_4$ (3.01 g, 1.2 equiv) was added in three portions. After 15 min of stirring, TLC indicated complete reaction. The reaction was quenched with 10% aq citric acid, and 1 N aq HCl was added to obtain pH 3. The mixture was stirred for 20 min, and then aq 1 N NaOH was added to obtain pH 9. Methanol was removed in vacuo, and the residue was extracted with $CHCl_3$ (3 × 200 mL). The combined organic solutions were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2; 80% $CHCl_3$/10% MeOH/10% EtOAc) to give 17.2 g (81%) of the racemic allylic alcohol as a pale-yellow solid. Enantiomerically enriched *R*-isomer **12e** was isolated by chiral preparative HPLC (5 × 50 cm Chiralpak AD column, 80/20 EtOH/hexanes + 0.1% diethylamine; 0.6 g injection at 60 mL/min) to give 7.7 g (45%) of the first eluting *R*-isomer **12e** (R_T = 40 to 51 min; enantiomer I; > 98% ee) and 8.95 g (52%) of the second eluting *S*-isomer (R_T = 51 to 62 min; Enantiomer II). TLC $R_f = 0.22$ (70% $CHCl_3$/15% MeOH/15% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.06 (s, 1H), 8.72 (s, 2H), 7.09 (d, $J = 7.2$ Hz, 1H), 6.56 (d, $J = 16$ Hz, 1H), 6.40 (dd, $J = 5.6$, 16 Hz, 1H), 6.34 (d, $J = 7.2$ Hz, 1H) 5.30 (br s, 1H), 4.41 (m, 1H), 3.41 (m, 2H), 2.69 (m, 2H), 2.61 (m, 2H), 1.90 (m, 2H), 1.72 (m, 4H), 1.53 (m, 2H).

Step 3. 3-Pyrimidin-5-yl-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-non-4-enoic Acid Ethyl Ester (13e). To a stirred solution of allylic alcohol **12e** (20.4 g, 60.4 mmol) in triethylorthoacetate (380 mL) was added a solution of propionic acid (23.3 mL of a 0.15 M soln in $(EtO)_3CMe$; 0.24 mmol). The solution was heated to reflux (145 °C), and reaction progress was monitored by HPLC. After 120 min at reflux, the solution was cooled to room temperature, and the reaction was treated with 1 N HCl/brine (25 mL/25 mL). After stirring for 10 min, the mixture was extracted with EtOAc (3 × 200 mL), and the combined organic solutions were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2; 80% $CHCl_3$/10% EtOAc/10% MeOH) to give 23.2 g (98%) of **13e** as a brown oil. HPLC $R_T = 10.6$ min (Vydac C18; 95/5 to 5/95 H_2O/MeCN gradient over 15 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.08 (s, 1H), 8.61 (s, 2H), 7.05 (d, $J = 7.3$ Hz, 1H), 6.30 (d, $J = 7.3$ Hz, 1H), 5.54 (m, 2H), 5.09 (br s, 1H), 4.06 (q, $J = 7.1$ Hz, 2H), 3.84 (m, 1H), 2.70 (m, 4H), 2.51 (t, $J = 7.7$ Hz, 2H), 2.04 (m, 2H), 1.90 (m, 2H), 1.63 (m, 2H), 1.40 (m, 2H), 1.24 (t, $J = 7.1$ Hz, 3H).

Step 4. 3-Pyrimidin-5-yl-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic Acid Ethyl Ester. Unsaturated ester **13e** (23.2 g, 58.9 mmol) was dissolved in glacial acetic acid (2.1 L), and the solution was purged with argon gas for 20 min. Ten percent palladium on carbon (23.2 g) was added. Neat 1,4-cyclohexadiene (720 mL) was slowly added by syringe. The heterogeneous reaction was gradually heated to 80 °C, and reaction progress was monitored by HPLC. After 1 h, the reaction mixture was cooled to room temperature, filtered through Celite, and the filtrate was concentrated. The residue was purified by flash chromatography (80% $CHCl_3$/10% MeOH/10% EtOAc) to give 17.9 g (77%) of the ethyl ester of **5e** as a colorless oil. HPLC $R_T = 10.8$ min (Vydac C18; 95/5 to 5/95 H_2O/MeCN gradient over 15 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.09 (s, 1H), 8.59 (s, 2H), 7.18 (d, $J = 7.2$ Hz, 1H), 6.21 (d, $J = 7.2$ Hz, 1H), 4.04 (q, $J = 7.1$ Hz, 2H), 3.45 (t, $J = 7.2$ Hz, 1H), 3.09 (m, 1H), 2.70 (m, 3H), 2.62 (m, 3H), 1.88 (m, 2H), 1.59 (m, 3H), 1.28 (m, 3H), 1.14 (t, $J = 7.1$ Hz, 3H).

Step 5. 3-Pyrimidin-5-yl-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic Acid (5e). To a stirred solution of ester (17.9 g, 45.2 mmol) in MeOH/THF (50 mL/200 mL) was added 1 N NaOH (113 mL, 113 mmol). The reaction was stirred for 16 h at room temperature and then neutralized with 1 N HCl (113 mL). The solvent was removed in vacuo. The residue was purified by flash chromatography (SiO_2; 80% $CHCl_3$/10% MeOH/10% EtOAc) to give a viscous foam that was redissolved in water (600 mL) and lyophilized to yield 11.5 g (69%) of desired acid **5e** as a white amorphous powder. Crystalline material (mp = 91 °C) can be obtained by crystallization from water at pH 6. HPLC $R_T = 9.38$ min (Vydac C18; 95/5 to 5/95 H_2O/MeCN gradient over 15 min). ^{1}H NMR (300

MHz, MeOD): δ 8.98 (s, 1H), 8.69 (s, 2H), 7.39 (d, J = 7.3 Hz, 1H), 6.47 (d, J = 7.3 Hz, 1H), 3.43 (t, J = 5.7 Hz, 2H), 3.20 (m, 1H), 2.76 (t, J = 6.1 Hz, 2H), 2.62 (m, 4H), 1.91 (m, 2H), 1.81 (m, 1H), 1.63 (m, 3H), 1.43 (m, 1H), 1.30 (m, 5H).

Aryl Aldehydes 17, 19, 21, 24, 25, and 26 were Synthesized as below. Benzofuran-6-ol (15). To a solution of 6-hydroxy-[2*H*]-benzofuran-3-one (**14**) (Maybridge; 7.84 g, 52.2 mmol) in DMF (100 mL) at room temperature was added triethylamine (8.17 g, 80.9 mmol) and *tert*-butyldimethylsilyl chloride (10.32 g, 68.4 mmol). After stirring for 2 h, the solution was diluted with Et_2O (300 mL) and washed with satd aq NH_4Cl (150 mL) and brine (100 mL). The solution was dried over $MgSO_4$, filtered, and concentrated to give the benzofuranone as a yellow oil, which solidifed upon standing and was not further purified. A solution of this ketone (44.2 g, 167 mmol) in 400 mL MeOH was treated with $NaBH_4$ (9.5 g, 251 mmol, 1.5 equiv) in four equivalent portions at room temperature until the reaction was complete by TLC (~1 h). The reaction mixture was quenched by the addition of acetone (10 mL). This mixture was then treated with 3 N aq HCl (200 mL) at room temperature until complete by TLC (~24 h). The resulting solution was concentrated in vacuo to 150 mL and was extracted with EtOAc (2 × 250 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (30% EtOAc/hexanes), affording phenol **15** (6.93 g, 99%). TLC R_f = 0.35 (30% ethyl acetate/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, J = 1.5 Hz, 1H), 7.41 (d, J = 6.3 Hz, 1H), 7.1 (br s, 1H), 6.81−6.78 (dd, J = 1.5, 6.3 Hz, 1H), 6.69 (d, J = 1.5 Hz, 1H).

Trifluoromethanesulfonic Acid Benzofuran-6-yl Ester (16). A solution of benzofuran-6-ol (**15**) (4.00 g, 29.85 mmol) and *N*-phenyltriflimide (10.66 g, 29.85 mmol) in CH_2Cl_2 (150 mL) cooled to 0 °C was treated with triethylamine (5.37 mL, 3.92 g, 38.81 mmol). The reaction was warmed to room temperature over 90 min and diluted with Et_2O (200 mL). The organic solution was washed with satd aq NH_4Cl (100 mL) and brine (100 mL). The solution was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (5% EtOAc/hexanes) to give triflate **16** (7.62 g, 96%) as a colorless oil, which solidified upon standing. TLC R_f = 0.39 (10% ethyl acetate/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, J = 1.0 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.48 (br s, 1H), 7.20 (dd, J = 8.4, 1.0 Hz, 1H), 6.82 (br s, 1H).

Benzofuran-6-carbaldehyde (17). A solution of triflate **16** (0.798 g, 3.0 mmol), $Pd(OAc)_2$ (13.5 mg, 0.060 mmol), and diphenylphosphinopropane (24 mg, 0.060 mmol) in DMF (15 mL) was heated to 70 °C with a gentle flow of CO(g) passing through it. Triethylamine (1.66 mL, 12 mmol) was added followed by trioctylsilane (2.70 mL, 6.0 mmol). The solution was maintained at 70 °C for 2 h and then cooled to room temperature. The solution was diluted with water (10 mL). The mixture was extracted with Et_2O (2 × 30 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (5% acetone/hexanes) to give desired aldehyde **17** (0.127 g, 29%). TLC R_f = 0.39 (10% ethyl acetate/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.07 (s, 1H), 8.02 (s, 1H), 7.79 (m, 3H), 6.87 (s, 1H).

6-Methoxy-pyridine-3-carboxaldehyde (19). A solution of *n*-butyllithium (3.46 mL of a 1.6 M solution in hexanes) in THF (18 mL) was cooled to −78 °C and treated with a solution of 5-bromo-2-methoxypyridine (**18**) (1.04 g, 5.53 mmol) in THF (2 mL). The heterogeneous mixture was stirred for 40 min, and neat DMF (1.5 mL) was added. The solution was stirred for 90 min at −78 °C and quenched with satd aq NH_4Cl solution (2 mL). The cold bath was removed, and the mixture was warmed to room temperature. The mixture was extracted with EtOAc (2 × 30 mL), and the combined organic solutions washed with brine, dried over $MgSO_4$, filtered, and concentrated to desired aldehyde **19** (0.72 g, 95%). TLC R_f = 0.45 (10% ethyl acetate/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.94 (s, 1H), 8.62 (d, J = 2.4 Hz, 1H), 8.04 (dd, J = 2.4, 8.1 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 4.01 (s, 3H).

Pyrimidine-5-carboxaldehyde (21). 5-Bromopyrimidine (25 g, 160 mmol) was dissolved in THF (1200 mL) in a three-necked 3-L round-bottom flask equipped with a mechanical stirrer, a thermometer, an addition funnel, and a nitrogen inlet. The solution was cooled to an internal temperature of −100 °C in a MeOH/N_2(l) bath. A small amount of the 4-bromopyrimidine precipitated from the solution. A solution of *n*-BuLi (64 mL of a 2.5 M soln in hexanes, 160 mmol) was added dropwise, maintaining an internal temperature of −100 °C. When the addition was complete, the reaction was stirred for another 20 min at −100 °C, resulting in some precipitation. A solution of ethyl formate (12.9 mL, 160 mmol) in THF (50 mL) was added dropwise, maintaining an internal temperature of −95 °C. After the addition was complete, the pale-yellow solution was stirred for another 20 min at −100 °C. A solution of HCl in ether (82.4 mL of a 2 N soln in ether, 164.8 mmol) was added, keeping the reaction temperature below −85 °C. The cold bath was removed, and the solution was warmed to room temperature. The solution was concentrated to a volume of ca. 200 mL (rotovap bath temp < 30 °C) and treated with 10% K_2CO_3 (200 mL). The mixture was extracted with $CHCl_3$ (3 × 200 mL). The organic solutions were combined, dried ($MgSO_4$), filtered, and concentrated on a rotary evaporator (80 C, no vacuum). The reaction was repeated, and the oily residues were combined (38 g) and purified by flash chromatography (SiO_2, 100% Et_2O) to give 17.98 g (52%) of aldehyde **21** as white crystals. TLC R_f = 0.60 (50% EtOAc/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.1 (s, 1H), 9.4 (s, 1H), 9.19 (s, 2H).

2-Methyl-pyrimidine-5-carboxaldehyde (24). A three-necked 2-L round-bottomed flask with magnetic stirring, an immersion thermometer, and an addition funnel was charged with DMF (209 mL, 2700 mmol) and cooled to 0 °C. Phosphorus oxychloride (54.8 mL, 590 mmol) was carefully added to the reaction via an addition funnel maintaining an internal temperature of 5−10 °C. After 2 h, the red-orange solution was treated with bromoacetic acid (25.0 g, 184 mmol) and heated to 90 °C for 6 h. As the mixture was heated, it began to exotherm and evolve CO_2. The mixture was cooled, and a short-path distillation head was attached. DMF was distilled from the red-orange oil at 120 °C under high vacuum. The tarry residue was cooled to room temperature and treated with ice (ca. 5 g). Aqueous $NaBF_4$ (40 g in 80 mL H_2O) was added. As the solid residue slowly dissolved, a vigorous exotherm occurred. Intermittent immersion in an ice bath controlled the exotherm. The mixture was cooled to 0 °C, and the yellow-orange precipitate that formed was collected by filtration and redissolved in hot MeCN (1 L) and was filtered again to remove excess $NaBF_4$. The filtrate was cooled to −30 °C, and the crystalline precipitate (28 g) was collected by filtration. A second crop provided another 7 g of vinamidinium salt **23** (35 g total, 53% yield).

A suspension of vinamidinium salt **23** (30.0 g, 78.5 mmol) and acetamidine hydrochloride (Acros, 13.45 g, 86.2 mmol) in EtOH (2000 mL) was treated with a solution of NaOEt (Aldrich, 21% by wt, 79.4 mL, 246 mmol) at room temperature. The mixture was heated at reflux for 3 h, cooled to room temperature, and concentrated on a rotovap (bath temp = 30 °C; 40 mmHg). The residue was dissolved in water (100 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2; 40% Et_2O in CH_2Cl_2) to give 4.6 g (48%) of desired product **24** as a tan solid. TLC R_f = 0.40 (40% Et_2O/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.1 (s, 1H), 9.04 (s, 2H), 2.80 (s, 3H).

2-Methoxy-pyrimidine-5-carboxaldehyde (25). Compound **25** was prepared by reaction between vinamidinium salt **23** and methyl isourea by the same procedure described for **24** (57% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 8.96 (s, 2H), 4.10 (s, 3H).

2-(2-Propyl)-pyrimidine-5-carboxaldehyde (26). Compound **26** was prepared by a reaction between vinamidinium salt **23** and 2-methyl propionamide by the same procedure

described for **24** (78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.1 (s, 1H), 9.07 (s, 2H), 3.31 (m, 1H), 1.35 (d, J = 6.8 Hz, 6H).

3-Aryl-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic Acids 5a, 4a, 5b, 5c, 5d, 5f, 5g, and 5h Prepared According to the Methods Described for 5e. 3-(*R, S*)-(3-Fluorophenyl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic Acid (5a). 3-fluorobenzaldehyde was transformed to acid **5a** per Scheme 1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.83 (br s, 1H), 7.24 (m, 2H), 6.88 (m, 3H), 6.28 (m, 1H), 3.42 (m, 2H), 3.05 (m, 1H), 2.70 (m, 6H), 1.88 (m, 2H), 1.59 (m, 4H), 1.19 (m, 7H).

3-(*R, S*)-(3-Fluorophenyl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-non-4-enoic Acid (4a). 3-Fluorobenzaldehyde was transformed to acid **4a** per Scheme 1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (br s, 1H), 7.31 (m, 1H), 6.92 (m, 1H), 6.88 (m, 2H), 6.38 (m, 1H), 5.55 (m, 2H), 3.81 (m, 1H), 3.51 (m, 2H), 2.71 (m, 6 H), 2.18 (m 1H), 1.95 (m, 3H), 1.77 (m, 1H), 1.51 (m, 3H).

3-(*S*)-(2,3-Dihydro-benzofuran-6-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic Acid (5b). Aldehyde **17** was transformed to acid **5b** per Scheme 1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.3 (m, 1H); 7.11 (m, 1H); 6.8 (m, 1H), 6.62 (s, 1H), 6.35 (m, 1H), 4.5 (m, 2H), 3.51 (m, 2H), 3.15 (m, 3H), 2.61 (m, 5H), 1.91 (m, 3H), 1,72 (m, 4H), 1.4 (m, 6H).

3-(*S*)-(6-Methoxypyridin-3-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic Acid (5c). 6-Methoxypyridine-3-carboxaldehyde (**19**) was transformed to acid **5c** per Scheme 1. ^{1}H NMR (300 MHz, CD_3OD): δ 8.31 (m, 1H), 8.19 (s, 1H), 7.59 (m, 1H), 7.45 (m, 1H), 6.60(m, 1H), 4.16 (s, 3H), 3.51 (m, 2H), 3.20 (m, 1H), 2.79 (m, 6H), 1.95 (m, 2H), 1.71 (m, 4H), 1.37 (m, 3H).

3-(*S*)-(Quinolin-3-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic Acid (5d). The 3-quinoline carboxaldehyde was transformed to acid **5d** per Scheme 1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.2 (br s, 1H), 8.92 (d, J = 1.8 Hz, 1H), 8.15 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 1.8 Hz, 1H), 7.82 (d, J = 7.5 Hz, 1H), 7.71 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.05 (d, J = 7.3 Hz, 1H), 6.25 (d, J = 7.3 Hz, 1H), 5.6 (m, 1H), 3.56 (m, 1H), 3.40 (m, 2H), 2.75 (m, 2H), 2.65 (m, 2H), 2.58 (m, 2H), 2.01 (m, 2H), 1.91 (m, 2H), 1.65 (m, 2H), 1.45 (m, 2H).

3-(S)-(Methylpyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic Acid (5f). Aldehyde **24** was transformed to acid **5f** per Scheme 1. HPLC R_T = 9.20 min (Vydac C18; 95/5 to 5/95 H_2O/MeCN gradient over 15 min). ^{1}H NMR (400 MHz, MeOD): δ 8.54 (s, 2H), 7.36 (d, J = 7.2 Hz, 1H), 6.43 (d, J = 7.2 Hz, 1H), 3.39 (t, J = 8.0 Hz, 2H), 3.27 (s, 3H), 3.12 (m, 1H), 2.72 (t, J = 6.0 Hz, 2H), 2.58 (m, 4H), 1.87 (m, 2H), 1.76 (m, 1H), 1.61 (m, 3H), 1.41 (m, 1H), 1.29 (m, 5H).

3-(*S*)-(2-Methoxypyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-Nonanoic Acid (5g). Aldehyde **25** was transformed to acid **5g** per Scheme 1. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (s, 2H), 7.25 (d, J = 7.5 Hz, 1H), 6.28 (d, J = 7.5 Hz, 1H), 4.00 (s, 3H), 3.47 (m, 2H), 3.25 (m, 1H), 2.72 (m, 3H), 2.56 (m, 3H), 1.92 (m, 2H), 1.83 (m, 1H), 1.68 (m, 2H), 1.59 (m, 2H), 1.29 (m, 5H).

3-(*S*)-(2-Isopropylpyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic Acid (5h). The aldehyde **26** was transformed to acid **5h** per Scheme 1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 2H), 7.39 (d, J = 7.3 Hz, 1H), 6.48 (d, J = 7.3 Hz, 1H), 3.43 (m, 2H), 3.16 (m, 2H), 2.76 (m, 2H), 2.60 (m, 3H), 2.53 (m, 1H), 1.91 (m, 2H), 1.79 (m, 1H), 1.63 (m, 3H), 1.47 (m, 1H), 1.30 (m, 1H).

Ovariectomized Rat Model. Female Sprague−Dawley rats aged 7 months (body weight 325 g) were used. They were ovariectomized (OVX) by a dorsal approach and then started on treatment the next day with either **5e** or **5f**. Treatment continued for 28 (**5f** experiment) or 42 days (**5e** experiment). At necropsy, right femurs were collected and placed in 70% ethanol. They were defleshed and analyzed (bone mineral density, BMD) by dual-energy X-ray absorptiometry (DXA). BMD of the central femur (CF), the distal 25% of the femur, and the distal femoral metaphysis (DFM, 12−25% of the distance from distal to proximal end) was conducted. Significant bone loss occurred after ovariectomy ($P < 0.01$).

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