Vasopeptidase Inhibitors: Incorporation of Geminal and Spirocyclic Substituted Azepinones in Mercaptoacyl Dipeptides

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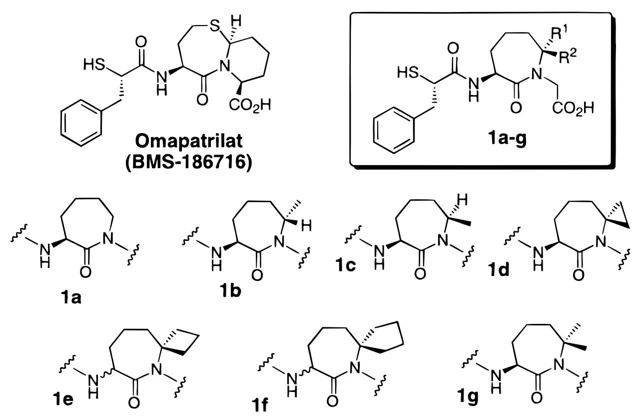
A series of 7-(di)alkyl and spirocyclic substituted azepinones were generated and incorporated as conformationally restricted dipeptide surrogates in mercaptoacyl dipeptides. Clear structure−activity relationships with respect to both angiotensin-converting enzyme (ACE) and neutral endopeptidase (NEP) activity in vitro were observed. The best in this series, compound **1g**, a geminally dimethylated C-7-substituted azepinone, demonstrated excellent blood pressure lowering in animal models. Compound **1g** (BMS-189921) is characterized by a good duration of activity and excellent oral efficacy in models relevant to ACE or NEP inhibition, and its activity is comparable to that of the clinically efficacious agent omapatrilat. Consequently this inhibitor has been advanced clinically for the treatment of hypertension and congestive heart failure.

Introduction

Angiotensin-converting enzyme (ACE) and neutral endopeptidase (NEP) are zinc metalloproteases responsible for angiotensin II (AII) formation and atrial natriuretic peptide (ANP) degradation, respectively. AII serves to raise blood pressure by both vasoconstriction and release of aldosterone. In contrast ANP, a peptidic hormone secreted by the heart in response to atrial distention, promotes the generation of cGMP via guanylate cyclase activation, which in turn causes vasodilatation, natriuresis, diuresis, and possibly inhibition of aldosterone formation. Because of the functionally opposed hormonal actions of AII and ANP, coinhibition of ACE and NEP has the potential to act synergistically to lower vascular resistance and inhibit activation of the renin−angiotensin−aldosterone system. Additionally, simultaneous inhibition of ACE and NEP may be effective in potentiating other vasoactive endogenous peptides such as bradykinin, a peptide which has been shown to be important in cardiovascular protection.[1] Hence, to fully represent the scope of ACE/NEP inhibitors in vivo, we have termed this class of compounds as vasopeptidase inhibitors (VPIs).

A number of pharmaceutical groups have engaged in developing single agents that act as an inhibitor to both enzymes. Several review articles have highlighted advances in this field.[2] In recent reports,[3,4] we described the design, synthesis, in vitro characterization, and in vivo pharmacology of a series of conformationally restricted mercaptoacetyls possessing a core bicyclic azepinone framework. From this series, BMS-186716 (omapatrilat) was selected for clinical development and is currently in phase III clinical trials for hypertension. Preliminary data in humans has demonstrated that omapatrilat is a well-tolerated and highly effective oral antihypertensive agent with a once daily duration of activity.[5] Preclinically, omapatrilat was only one of a few compounds to exhibit good in vitro potency against both ACE and NEP *and* to exhibit a prolonged duration of activity in animal models. As demonstrated in previous studies,[6] the ability of these compounds to perform in vivo is subject to many factors, one of which is the nature of the dipeptide mimetic framework.

Chart 1



Although omapatrilat continues to distinguish itself from other classes of established antihypertensive drugs, it was felt desirable to advance other potential agents with modified biological properties into the clinic. Our interest in the monocyclic based azepinone series in part was derived from the observation that appropriate substitution on the lactam ring could confer better in vitro potency and enhanced pharmacodyamic activity[7] (compare C-7 methyl-substituted lactam **1b** with its unsubstituted counterpart **1a**, Chart 1). Compound **1b** was significantly more potent against NEP and ACE in vitro and exhibited a more robust response and greater duration of activity in a functional assay of in vivo ACE inhibition (AI pressor assay). Noting the effect of this modification and suspecting that metabolism at the C-7 position of the lactam ring could be limiting efficacy in vivo, we generated a series of C-7 geminally and spirocyclic substituted lactams, generically repre-

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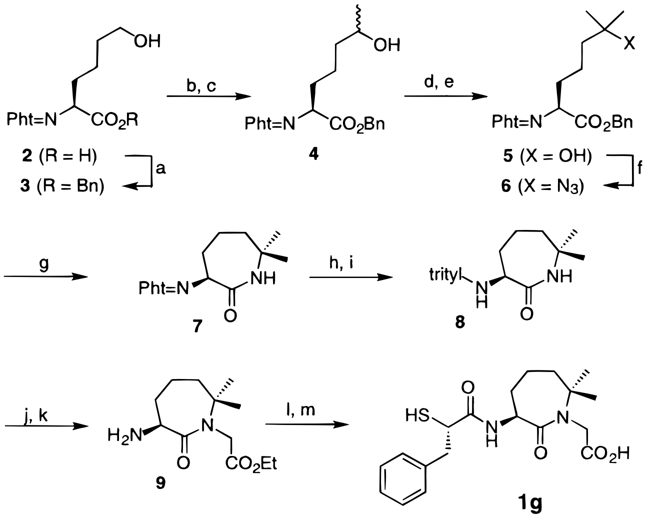
Scheme 1[a]



[a] (a) BnBr, Cs_2CO_3, DMF, 95%; (b) Swern oxidation; (c) Me_3Al in hexanes, CH_2Cl_2, 91% (2 steps); (d) Swern oxidation, 97%; (e) $MeTiCl_3$, Et_2O, 0 °C, 87%; (f) $TMSN_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt 5 days, 81%; (g) H_2, Pd/C, DMF, then EDAC, HOAt, 88%; (h) $H_2N-NH_2{\cdot}H_2O$, MeOH; (i) Ph_3CCl, TEA, CH_2Cl_2, 96% (2 steps); (j) xs $LiN(TMS)_2$, xs $BrCH_2CO_2Et$, THF; (k) TFA, CH_2Cl_2, 85% (2 steps); (l) (*S*)-$AcSCH(CH_2Ph)CO_2H$, EDAC, CH_2Cl_2; (m) NaOH, H_2O, MeOH, then H_3O^+, 95% (2 steps).

sented by the structure **1**, and determined their effect on NEP and ACE inhibition.

Chemistry

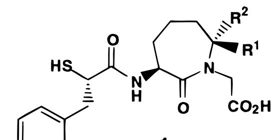
We have previously reported biological and chemical information on vasopeptidase inhibitors **1a**–**c**.[7] Chemical methods for the generation of the requisite azepinones in **1d**–**g** have been outlined as well by selective (**1d**) and nonstereoselective (**1e**–**g**) routes.[8] The potent activity observed with **1g** (BMS-189921) in our assays prompted the development of a homochiral synthesis of this compound which is outlined in Scheme 1. Benzylation of (*S*)-6-hydroxy-2-phthalimidohexanoic acid (**2**)[3] followed by Swern oxidation of the alcohol functionality and methyl addition[9] with Me_3Al afforded **4** in good yield as a 1:1 mixture of diastereomers. Swern oxidation provided the intermediate ketone. Treatment of the ketone with Me_3Al failed to provide the desired tertiary alcohol, and addition of more conventional agents (MeMgCl, MeLi) led to the destruction of the phthalimdo protecting group. In contrast, reaction with methyltitanium trichloride,[10] generated in situ by the addition of MeLi to $TiCl_4$, afforded tertiary alcohol **5** in reasonable overall yield. Treatment of **5** with $TMSN_3$ and $BF_3{\cdot}OEt_2$ rapidly formed a mixture of azide **6** and the related olefin elimination product,[11] which slowly underwent conversion to the desired azide over several days. Palladium-catalyzed hydrogenation of **6** effected both reduction of the azide to the amine and hydrogenolysis of the benzyl ester. EDAC-mediated cyclization of the intermediate amino acid gave azepinone **7** in good overall yield. We have demonstrated that C-7 monoalkyl-substituted lactams related to **7** can be cleanly and quickly alkylated at the lactam nitrogen under near stoichiometric conditions.[12] In contrast, the steric environment of geminally substituted azepinones severely retards this desired transformation. For example, alkylation of the racemic Boc-protected azepinone of **8** under forcing conditions afforded a mixture of unreacted and N-alkylated products which were difficult to separate.[8] To circumvent this problem, a trityl group was utilized as the primary amine-protecting group, leading exclusively to the formation of the desired lactam alkylation product. Thus, treatment of **8** with a 5-fold excess of $LiN(TMS)_2$ and ethyl bromoacetate afforded a crude alkylation mixture. Amine **9** could be isolated in nearly pure form after trityl deprotection and acid–base extraction. EDAC-mediated coupling of amine **9** with (*S*)-2-(acetylthio)benzenepropanoic acid afforded the coupling product with little or no racemization. Saponification under anaerobic conditions thus afforded **1g**. Utilizing similar coupling/deprotection procedures, compounds **1a**–**f** were also prepared.

Discussion

Table 1 lists in vitro data and ED_{50} AI pressor responses (intravenous administration in rats) for compounds **1a**–**g** as well as for omapatrilat. All of the compounds were effective inhibitors against ACE with IC_{50}'s ranging from 6 to 29 nM. As a general trend, the C-7 alkyl-substituted azepinones appeared less active versus NEP than ACE in vitro, with a greater disparity between ACE and NEP potency observed in the C-7 spirocyclic analogues. These structure–activity relationships outline the subtle yet distinct structural requirement necessary for effective inhibition of both enzymes. Spirocyclopropane **1d** and dimethyl lactam **1g** differ structurally by only two hydrogen atoms and a single bond, yet they display equivalent in vitro ACE activity but a 6-fold difference with respect to NEP. The reason for this disparity is unclear, but the data suggests that the geminal dimethyl groups in **1g** may be bisecting a critical residue in the P1 pocket of NEP that cannot be avoided by the spirocyclic compounds due to increased steric bulk and covalent bonding between the R^1 and R^2 substituents. The observation that ACE activity is marginally affected by these changes argues against major conformational differences among the spirocyclic and nonspirocyclic substituted azepinones. Despite its apparent modest IC_{50} values, Lineweaver–Burk analysis of **1g** against rabbit lung ACE and rat kidney NEP indicate that it is a linear competitive inhibitor of these enzymes with inhibitor constants (K_i) of 5.3 and 16 nM, respectively. These values compare favorably with the current clinical compound omapatrilat (ACE K_i = 6.0 nM, NEP K_i = 8.9 nM).

The nature of the substitution at the C-7 position had a pronounced effect on in vivo activity as well.[7] Both the monomethyl (**1b**) and dimethyl (**1g**) azepinones were approximately 8-fold more potent than their unsubstituted analogue **1a** in the acute AI pressor response assay (Table 1). Despite similar ED_{50}'s, **1g** also exhibited a greater duration of activity (data not shown) in this assay, suggesting this compound may have a better pharmacodynamic profile and be suitable for once daily dosing. Importantly, compound **1g** distinguished itself from other compounds in this class with its high level of oral efficacy (ED_{50} = 0.6 μmol/kg, po) in the AI pressor assay (Figure 1) and exhibited a more robust response as compared to either compound **1b** or the clinically efficacious, once-a-day, selective ACE inhibitor fosinopril. Based on its in vitro activity and performance in

Table 1. Inhibition of ACE and NEP in Vitro and AI Pressor Responses for Compounds **1a**−**g**



1a-g

no.	R^1	R^2	formula[a]	IC_{50} (nM) ACE[b]	IC_{50} (nM) NEP[c]	AI pressor ED_{50}[d] (μmol/kg, iv)
omapatrilat				5	8	0.07
1a	H	H	$C_{17}H_{22}N_2O_4S$	22	82	0.84
1b	H	Me	$C_{18}H_{24}N_2O_4S$	8.2	49	0.11
1c	Me	H	$C_{18}H_{24}N_2O_4S{\cdot}0.31H_2O$	16	149	ND
1d	$-(CH_2)_2-$		$C_{19}H_{24}N_2O_4S{\cdot}0.5H_2O$	9.6	377	ND
1e[e]	$-(CH_2)_3-$		$C_{20}H_{26}N_2O_4S{\cdot}0.33$toluene	29	641	ND
1f[e]	$-(CH_2)_4-$		$C_{21}H_{28}N_2O_4S{\cdot}0.8$EtOAc[f]	6	426	ND
1g	Me	Me	$C_{19}H_{26}N_2O_4S$	12	63	0.1

[a] All spectral data were consistent with the assigned structures. All compounds were analyzed for C, H, N, and S for the formula shown. [b] Compounds were assayed against angiotensin-converting enzyme isolated from rabbit lung extract using hippuryl-L-histidyl-L-leucine (HHL) as the substrate. [c] Compounds were assayed against purified rat kidney neutral endopeptidase using a fluorometric assay with dansyl-Gly-Phe-Arg as the substrate. [d] Represents dose required for 50% inhibition of the AI pressor response in normotensive rats. [e] Compounds 1e and 1f were prepared as a 1:1 mixture of diastereomers from the racemic lactam. [f] Anal. ($C_{21}H_{26}N_2O_4S{\cdot}0.8$EtOAc) C, H, N; S: calcd, 61.96; found, 60.61.

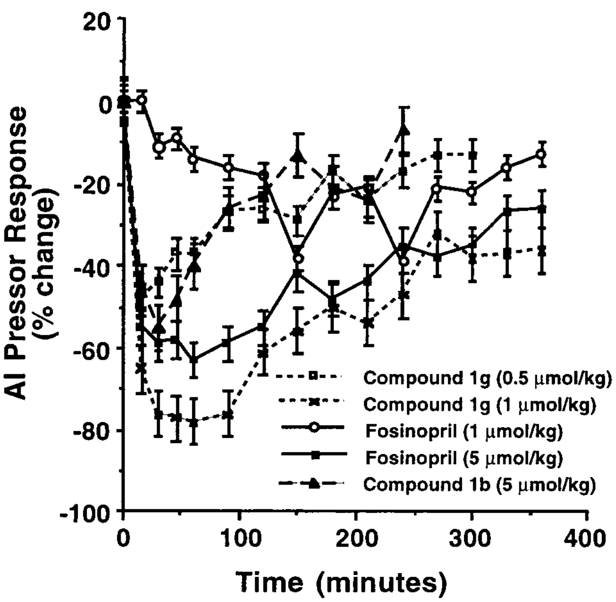


Figure 1. Inhibition of the MAP response to AI (iv administration) in conscious rats after oral (po) administration of fosinopril, compound **1g**, or compound **1b** was determined according to procedures previously described.[13] Conscious animals ($n = 4$/group), instrumented with implanted arterial and venous catheters at least 2 weeks prior to study, were prepared for direct recording of aterial blood pressure using a pressure transducer. Changes in MAP in response to iv injections of AI (310 ng/kg) were obtained before (control) and at intervals after the administration of fosinopril, compound **1g**, or compound **1b**. The percent change (mean ± SE) from the control response (percent inhibition) was determined for each response after drug or vehicle administration.

the AI pressor assay, **1g** was selected for further evaluation in other relevant animal models.[13]

The spontaneously hypertensive rat (SHR) is a model widely used for essential hypertension and generally has normal plasma renin activity in the sodium replete state. The antihypertensive effects of **1g** and omapatrilat at 100 μmol/kg, once daily, were determined in unrestrained SHR by telemetry. This method allows measurements of mean arterial pressure (MAP) in a relatively undisturbed manner. Compound **1g** elicited a progressive fall in 24-h averaged MAP during the first 5−6 days of dosing (Figure 2A). At the end of 9 days, 24-h MAP decreased by approximately 30 mmHg in the drug-treated group. The changes in MAP averaged over 2-h periods during the ninth day of study are depicted in Figure 2B. Starting at 3 h after administration of **1g**, MAP decreased by approximately 40 mmHg and increased slightly over the next 20 h. At completion of the study, MAP was clearly lower in the drug-treated as compared to the vehicle-treated group, indicating that the duration of antihypertensive activity was at least 23 h. The activity of **1g** was comparable to, if not slightly greater than, that of omapatrilat under the same conditions.

In vivo inhibition of NEP for **1g** was demonstrated in 1-kidney DOCA salt hypertensive rats, a sodium-dependent model of hypertension that is responsive to NEP inhibitors but refractory to selective ACE inhibitors. In this assay, compound **1g** was administered orally at 100 μmol/kg for 4 consecutive days and systolic blood pressure (SBP) was measured by tail-cuff 4 h after each dose (Figure 3). Compound **1g** demonstrated a rapid onset of action, lowering SBP by approximately 60 mmHg over the duration of the study. Qualitatively, the results were similar to those in a separate study[3] performed with omapatrilat, which gave ≈45 mmHg SBP lowering but a slower onset of action.

To ascertain the pharmacodynamics of **1g** in a non-rodent animal model, conscious cynomologus monkeys were dosed with compound (50 μmol/kg, po) once daily and the AI pressor response was measured at 24 h after each dose (Figure 4A). Inhibition of NEP activity was assessed in these monkeys by measuring the urinary ANP response to iv injection of human ANP 24 h after the second and fourth doses (Figure 4B). The results indicate that **1g** inhibits ACE and renal NEP activities in vivo for at least 24 h and that inhibition of both enzymes is sustained during 4 days of repeat dosing in conscious monkeys.

The overall in vitro and in vivo pharmacology of **1g** is consistent with potent inhibition of both ACE and NEP, and like omapatrilat, **1g** is characterized by a good

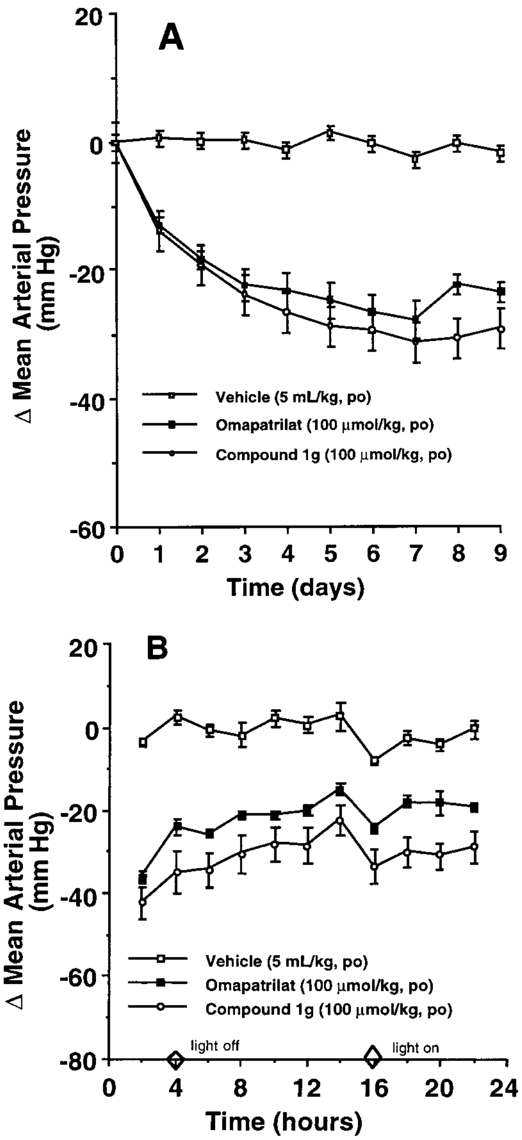


Figure 2. Changes in MAP in conscious unrestrained SHR after once daily oral administration of vehicle (5% $NaHCO_3$, $n = 10$), omapatrilat ($n = 9$), or compound **1g** ($n = 9$) as measured by telemetry. Mean arterial pressures before administration of agents were (mean ± SE): 130 ± 4, 138 ± 5, and 145 ± 2 mmHg in the vehicle, omapatrilat, and compound **1g** groups, respectively. (A) Changes in MAP averaged over a 24-h period for 9 days of dosing. (B) Changes in MAP averaged over 2-h periods during the ninth day of the study.

duration of action consistent with once daily oral dosing. Both compound **1g** and omapatrilat display favorable similarities in their preclinical pharmacological profiles, although preliminary pharmacological data suggest that **1g** may have a somewhat greater effect on NEP inhibition in vivo. Additional preclinical and clinical studies are warranted to ascertain a better differentiation among these compounds. Compound **1g** (BMS-189921) was selected for further development and is currently in phase II clinical trials for the treatment of hypertension and congestive heart failure, where early data from these trials confirm a favorable safety and efficacy profile with this inhibitor.

Experimental Section

All reactions were carried out under a static atmosphere of argon and stirred magnetically unless otherwise noted. All reagents used were of commercial quality and were obtained from Aldrich Chemical Co. or Sigma Chemical Co. Melting points were obtained on a Hoover Uni-melt melting point apparatus and are uncorrected. Infrared spectra were recorded on a Mattson Sirius 100-FTIR spectrophotometer. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a JEOL GSX400 spectrometer using Me_4Si as an internal standard. Optical rotations were measured in a 1-dm cell on a Perkin-Elmer 241 polarimeter, and *c* is expressed in g/100 mL. All flash chromatographic separations were performed using E. Merck silica gel (60, particle size 0.040−0.063 mm). Reactions were monitored by TLC using 0.25-mm E. Merck silica gel plates (60 F_{254}) and were visualized with UV light or 5% phosphomolybdic acid in 95% EtOH. Omapatrilat (BMS-186716) and fosinopril were synthesized at The Bristol-Myers Squibb Pharmaceutical Research Institute (Princeton, NJ).

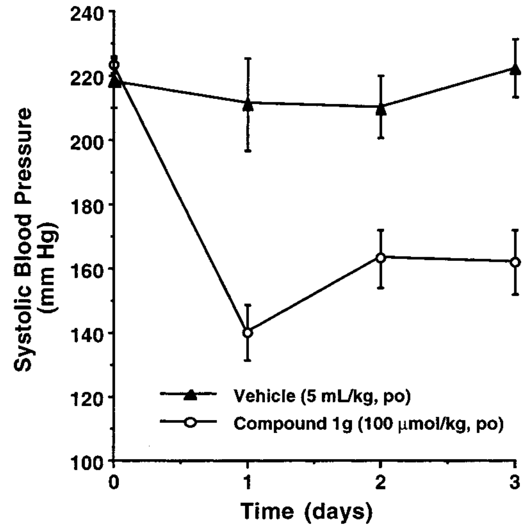


Figure 3. Effect on systolic blood pressure upon oral administration once daily of vehicle (5% $NaHCO_3$) or compound **1g** in 1-K DOCA salt hypertensive rats. Systolic blood pressure was measured 4 h after each dose by the tail-cuff method after conditioning rats to the procedure for 3 consecutive days prior. Dosing was initiated on day 1.

(*S*)-2-Phthalimido-6-hydroxyhexanoic Acid, Phenylmethyl Ester (3). A slurry of Cs_2CO_3 (3.82 g, 11.7 mmol) and (*S*)-2-phthalimido-6-hydroxyhexanoic acid (**2**; 6.000 g, 21.6 mmol) in DMF (60 mL) was treated with benzyl bromide (3.30 mL, 4.75 g, 27.7 mmol). After stirring at room temperature for 2 h, the mixture was partitioned between EtOAc and H_2O. The organic extract was washed twice with H_2O and brine, then dried (Na_2SO_4), filtered, and concentrated in vacuo to give an oil. The oil was flash-chromatographed (6:4 EtOAc:hexanes as eluant) to give essentially pure **3** as a solid. Recrystallization from EtOAc:hexane gave 7.57 g (95%) of analytically pure compound **3**: TLC R_f 0.43 (75:25 EtOAc:hexanes); mp 106−108.5 °C; $[\alpha]_D$ −27.5° (*c* 1.5, MeOH); ^1H NMR ($CDCl_3$) δ 1.50 (m, 4H), 2.32 (m, 2H), 3.62 (m, 2H), 4.91 (dd, 1H), 5.22 (d, 2H), 7.31 (m, 5H), 7.77 (m, 2H), 7.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.62, 28.46, 31.91, 52.32, 62.32, 67.46, 123.55, 128.06, 128.31, 128.53, 131.77, 134.23, 135.28, 167.76, 169.25.

(2*S*)-2-Phthalimido-6-hydroxyheptanoic Acid, Phenylmethyl Ester (4). A −78 °C solution of oxalyl chloride (3.0 mL, 4.36 g, 34.4 mmol) in CH_2Cl_2 (100 mL) was treated dropwise with a solution of dry DMSO (4.8 mL, 5.28 g, 67.6 mmol) in CH_2Cl_2 (2.0 mL). After 10 min, a solution of alcohol **3** (10.365 g, 28.2 mmol) in CH_2Cl_2 (20 mL) was added over a 7-min period. After an additional 15 min, dry TEA (17 mL) was added, and the mixture was stirred at −78 °C for 5 min and then let gradually warm to 0 °C. The mixture was partitioned between Et_2O and H_2O. The organic layer was washed with 1 N HCl and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give the desired intermediate aldehyde as an oil: TLC R_f 0.56 (6:4 EtOAc:hexanes); ^1H NMR

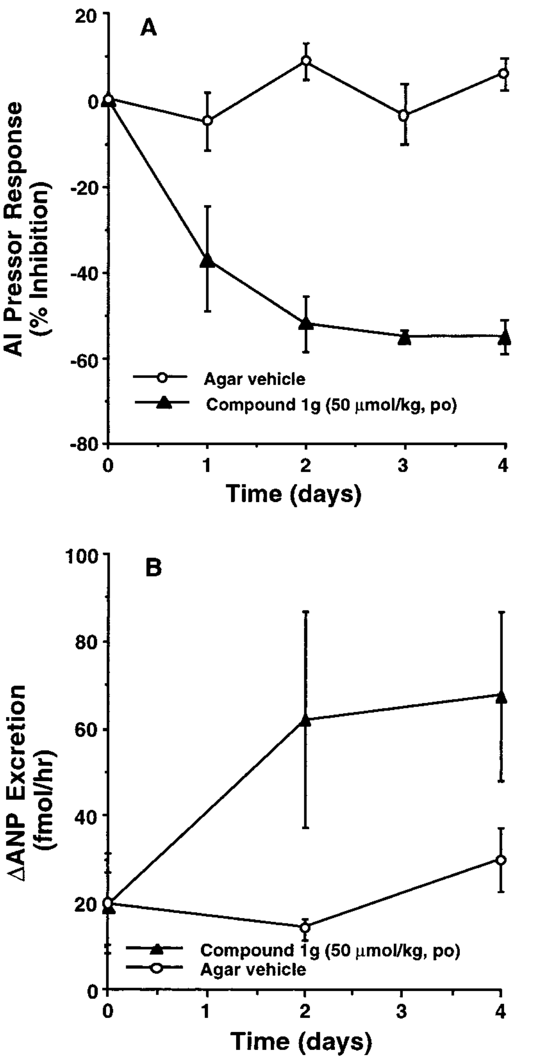


Figure 4. (A) Inhibition of the MAP response to AI in conscious cynomologus monkeys after oral administration once daily with vehicle (agar) or compound **1g** (50 μmol/kg) and measured 24 h after each dose. Changes in MAP in response to iv injections of AI (310 ng/kg) were obtained before (control) and at intervals after the administration of vehicle or compound **1g**. The percent change (mean ± SE) from the control response (percent inhibition) was determined for each response after drug or vehicle administration. (B) Potentiation of urinary ANP response to iv injections of 1 nmol/kg human ANP 99-126 in conscious cynomologus monkeys treated once daily with vehicle (agar) or compound **1g** (50 μmol/kg) and measured 24 h after each dose. Changes in ANP excretion were obtained before (control) and at intervals after the administration of vehicle or compound **1g**. The percent change (mean ± SE) from the control response (percent inhibition) was determined for each response after drug or vehicle administration.

($CDCl_3$) δ 1.66 (m, 2H), 2.40 (m, 4H), 4.90 (dd, 1H), 5.18 (d, 2H), 7.35 (m, 5H), 7.74 (m, 2H), 7.86 (m, 2H), 9.72 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.66, 27.99, 42.87, 51.83, 67.47, 123.50, 128.00,128.26, 128.44, 131.58, 134.21, 135.04, 167.55, 168.80, 201.31.

The crude aldehyde was redissolved in dry CH_2Cl_2 (170 mL), chilled to 0 °C, and then treated dropwise with Me_3Al (2.0 M in hexanes, 20.0 mL).[9] After 20 min, additional Me_3Al solution (5.0 mL) was added, and stirring was continued for 10 min. The mixture was cautiously quenched by the addition of saturated NH_4Cl and then partitioned between Et_2O and H_2O. The aqueous layer was back-extracted with EtOAc, and the pooled organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give a near-colorless oil. Flash chromatography (6:4 EtOAc:hexanes as eluant) afforded pure alcohol **4** (9.836 g, 91% from **3**) as a colorless oil (1:1 mixture of diastereomers): TLC R_f 0.42 (6:4 EtOAc:hexanes); ^1H NMR ($CDCl_3$) δ 1.12 (d, 3H), 1.43 (m, 4H), 3.73 (m, 2H), 4.90 (dd, 1H), 5.19 (d, 2H), 7.30 (m, 5H), 7.76 (m, 2H), 7.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.5, 23.40, 28.47, 28.59, 38.20, 38.34, 52.20.67.35, 67.51, 123.43, 127.94, 128.19, 128.41, 131.65, 134.11, 135.16, 167.62, 167.67, 169.13.

(*S*)-2-Phthalimido-6-methyl-6-hydroxyheptanoic Acid, Phenylmethyl Ester (5). A −78 °C solution of oxalyl chloride (1.52 mL, 2.21 g, 17.4 mmol) in CH_2Cl_2 (120 mL) was treated dropwise with a solution of dry DMSO (2.50 mL, 2.75 g, 35.2 mmol) in CH_2Cl_2 (2.0 mL). After 10 min, a solution of alcohol **4** (5.078 g, 13.3 mmol) in CH_2Cl_2 (30 mL) was added. After an additional 15 min, dry TEA (10 mL) was added, and the mixture was stirred at −78 °C for 5 min and then let gradually warm to 0 °C. The mixture was partitioned between Et_2O and 1 N aqueous HCl. The aqueous layer was back-extracted with Et_2O, and the pooled organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (1:1 EtOAc:hexanes as eluant) afforded the intermediate ketone (4.89 g, 97%) as a colorless oil: TLC R_f 0.32 (1:1 EtOAc:hexanes); $[\alpha]_D$ −10.7° (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.60 (m, 2H), 2.10 (s, 3H), 2.26 (m, 2H), 2.47 (m, 2H), 4.90 (dd, 1H), 5.19 (d, 2H), 7.30 (m, 5H), 7.74 (m, 2H), 7.84 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.15, 27.93, 29.84, 42.47, 51.89, 67.40, 123.46, 127.97, 128.23, 128.43, 131,61, 134.17, 135.10, 167.57, 168.93, 207.80.

Neat $TiCl_4$ (2.48 mL, 4.28 g, 22.5 mmol) was added dropwise to dry Et_2O (150 mL) at −78 °C, resulting in a bright-yellow suspension. Addition of MeLi (1.4 M in Et_2O, 16.1 mL, 22.5 mmol) over a 5-min period afforded a dark-brown nonhomogeneous mixture. Gradual warming to −35 °C resulted in a deep-brown-purple near-homogeneous solution. The intermediate ketone (5.68 g, 15.0 mmol) in Et_2O (30 mL) was added dropwise to the above solution, affording a gummy intractable reaction mixture. The reaction was warmed to 0 °C and occasionally agitated with a spatula in order to augment magnetic stirring. After 4 h at 0 °C, the mixture was quenched with saturated NH_4Cl, diluted with H_2O, and extracted with EtOAc. The organic layer was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was flash-chromatographed (1:1 EtOAc:hexanes as eluant) to afford compound **5** (5.17 g, 87%) as an oil: TLC R_f 0.25 (1:1 EtOAc:hexanes); $[\alpha]_D$ −3.4° (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.14 (s, 6H), 1.45 (m, 4H), 2.30 (m, 2H), 4.90 (dd, 1H), 5.19 (d, 2H), 7.30 (m, 5H), 7.74 (m, 2H), 7.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.88, 29.00, 29.17, 42.78, 52.13, 67.35, 70.47, 123.44, 127.95, 128.19, 128.41, 131.66, 134.11, 167.66, 169.14. The above reactions were also executed in greater scale (0.4 mol) with no discernible difference in yield.

(*S*)-2-Phthalimido-6-methyl-6-azidoheptanoic Acid, Phenylmethyl Ester (6). A solution of alcohol **5** (144.3 g, 364.9 mmol) and azidotrimethylsilane (63.06 g, 547.3 mmol) in dry CH_2Cl_2 (2.2 L) at room temperature under argon was treated with neat $BF_3{\cdot}OEt_2$ (67.32 g, 474.4 mmol). After stirring for 5 days, the resulting solution was quenched with water (1.5 L). The organic layer was separated, washed with saturated $NaHCO_3$, water, and brine, then dried ($MgSO_4$), and concentrated in vacuo. The residue was flash-chromatographed (1:3 EtOAc:hexane as eluant) to afford azide **6** (124.9 g, 81%) as a light-yellow oil: TLC R_f 0.35 (35:65 EtOAc:hexanes); $[\alpha]_D$ −9.2° (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.20 (s, 6H), 1.45 (m, 4H), 2.30 (m, 2H), 4.90 (dd, 1H), 5.19 (d, 2H), 7.30 (m, 5H), 7.74 (m, 2H), 7.86 (m, 2H), ^{13}C NMR ($CDCl_3$) δ 20.97, 25.67, 25.92, 28.80, 40.53, 52.02, 61.16, 67.40, 123.47, 127.97, 128.23, 128.43, 131.66, 134.14, 135.12, 167.60, 169.01.

(*S*)-Hexahydro-6-phthalimido-2,2-dimethyl-2*H*-azepin-7-one (7). A solution of azide **6** (124.8 g, 296.8 mmol) and 10% Pd/C (32 g) in dry DMF (2.0 L) was hydrogenated (balloon) for 24 h. After completion of the reaction, argon was bubbled through the mixture to remove excess hydrogen, and methyl sulfide (2.6 mL) was added to poison the palladium catalyst. To this solution was added 1-hydroxybenzotriazole hydrate

(HOBT; 46.74 g, 346 mmol) followed by ethyl-3-(3-dimethylamino)propylcarbodiimide hydrochloride salt (EDAC; 68.74 g, 360 mmol). After stirring at room temperature under argon for 3.5 h, the reaction was diluted with EtOAc (2 L) and filtered through a pad of Celite. The filtrate was washed in succession with 0.5 N aqueous HCl, saturated $NaHCO_3$, and brine, then dried ($MgSO_4$), and concentrated in vacuo to give a gum. Trituration with 2:1 Et_2O:hexanes afforded pure lactam **7** (74.5 g, 88%) as a white solid: TLC R_f 0.35 (3:7 EtOAc:hexanes); mp 193−194 °C; $[\alpha]_D$ +58.5° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.45 (s, 3H), 1.74 (m, 2H), 1.96 (m, 3H), 2.74 (m, 1H), 4.98 (d, 1H), 6.00 (s, 1H), 7.20 (m, 2H), 7.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.89, 26.65, 29.58, 33.32, 40.68, 52.69, 54.51, 123.34, 123.15, 133.87, 168.06, 171.03. Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 66.83; H, 6.31; N, 9.74.

(*S*)-Hexahydro-7,7-dimethyl-3-[(triphenylmethyl)amino]-2*H*-azepin-2-one (8). A solution of lactam **7** (74.5 g, 260.2 mmol) in CH_3OH (900 mL) and CH_2Cl_2 (250 mL) at room temperature under argon was treated with hydrazine monohydrate (18.24 g, 364.3 mmol). After 48 h, the precipitate was removed by filtration, and the filtrate was concentrated in vacuo to give a solid (≈41 g). The solid was dissolved in CH_2Cl_2 (2 L) and subsequently treated with triethylamine (50 mL) and triphenylmethyl chloride (83.41 g) at room temperature. After stirring for 1.5 h, the resulting slurry was diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give a gum. Trituration with Et_2O:pentane afforded compound **8** (100.1 g, 96%) as a white solid: TLC R_f 0.53 (6:4 EtOAc:hexanes); ^1H NMR ($CDCl_3$) δ 1.00 (s, 3H), 1.10 (s, 3H), 1.46 (m, 6H), 3.36 (m, 1H), 4.03 (m, 1H), 5.20 (d, 1H), 6.00 (s, 1H), 7.20 (m, 2H), 7.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.86, 25.81, 33.50, 34.23, 40.16, 51.97, 55.60, 71.89, 126.22, 127.61,128.96, 146.48, 176.71.

(*S*)-6-Aminohexahydro-2,2-dimethyl-7-oxo-1*H*-azepine-1-acetic Acid Ethyl Ester (9). To a well-stirred solution of lactam **8** (50 g, 125 mmol) in dry THF (1.02 L) at room temperature was added simultaneously and at the same rate a solution of lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 627.3 mL, 627.3 mmol) and ethyl bromoacetate (104.8 g, 627.3 mmol) in THF (523 mL) over a 1-h period. After stirring for 30 h, the reaction was quenched with saturated NH_4Cl (1.0 L) and extracted with EtOAc (3 × 700 mL). The EtOAc extracts were combined, washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo to afford a black oil. The experiment was repeated on the same scale to give a similar result. The combined oils were flash-chromatographed (1:4 EtOAc:hexanes as eluant) to give the impure alkylated lactam as a light-yellow oil. The oil was dissolved in dry CH_2Cl_2 (2 L) and treated with trifluoroacetic acid (78 mL) at room temperature. After 1 h the solvent was removed by rotary evaporation, and the residue was dissolved in 1.0 N aqueous HCl (400 mL) and washed with Et_2O (2 × 400 mL, discarded). The aqueous layer was carefully neutralized to pH 7−8 with solid $NaHCO_3$ (foaming!!) and extracted with CH_2Cl_2 (3 × 1.2 L). The CH_2Cl_2 extracts were combined, dried (Na_2SO_4), and concentrated in vacuo to afford pure amine **9** (51.5 g, 85%) as a light-brown oil: TLC R_f 0.30 (8:1:1 CH_2Cl_2:CH_3OH:AcOH); ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H), 1.36 (s, 3H), 1.38 (s, 3H) 1.60 (m, 1H), 1.90 (m, 5H), 3.75 (m, 1H), 4.00 (d, 1H), 4.22 (q, 2H), 4.28 (d, 2H); ^{13}C NMR ($CDCl_3$) δ 14.00, 20.06, 28.19, 30.07, 32.29, 39.98, 46.87, 53.20, 58.38, 60.73, 170.35, 177.06.

[*S*-(*R,*R**)]-Hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1*H*-azepine-1-acetic acid (1g).** (*S*)-2-(Acetylthio)benzenepropanoic acid, dicyclohexylamine salt (58.9 g, 145.3 mmol) was suspended in EtOAc (1.2 L), washed twice with 5% $KHSO_4$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The gummy residue was dried under high vacuum to afford the crude free acid. To a chilled (0 °C, ice bath) solution of the acid and amine **9** (32 g, 132.5 mmol) in CH_2Cl_2 (500 mL) under argon was added EDAC (27.8 g, 145.3 mmol). The reaction mixture was stirred at 0 °C for 2 h, poured into 1.0 N aqueous HCl (1.7 L), and extracted with EtOAc (3 × 1.2 L). The EtOAc extracts were combined, washed with water, saturated $NaHCO_3$, and brine, then dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (1.6 kg of SiO_2, 35:65 EtOAc:hexanes as eluant) afforded the penultimate coupled intermediate (54.5 g, 92%) as a gum: TLC R_f 0.20 (4:6 EtOAc:hexanes); ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H), 1.35 (s, 3H), 1.43 (s, 3H), 1.46 (m, 1H), 1.92 (m, 4H), 2.13 (m, 1H), 3.01 (dd, 1H), 3.30 (dd, 3H), 4.00 (d, 1H), 4.22 (q, 2H), 4.28 (d, 1H), 4.32 (d, 2H), 4.74 (m, 1H), 7.24 (s, 5H), 7.40 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.03, 20.00, 27.78, 29.65, 30.26, 30.57, 36.75, 39.85, 46.67, 48.15, 52.14, 58.90, 60.98, 126.66, 128.25, 129.12, 137.51, 168.84, 170.04, 172.38, 178.00.

A chilled (0 °C, ice bath) solution of the above coupling product (54.5 g, 121.5 mmol) in CH_3OH (400 mL, oxygen purged via argon bubbling) was treated dropwise with a solution of 1.0 N NaOH (688 mL, previously sparged with argon). After addition was complete, the ice bath was removed, and the reaction was stirred for an additional 5.5 h. The mixture was continuously purged with argon during the reaction sequence. The resulting solution was carefully acidified to pH 2 with 6.0 N HCl and extracted with EtOAc (3 × 1 L). The EtOAc extracts were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give a foam. Trituration with 1:1 Et_2O:hexane afforded a white solid which was filtered, washed with water and Et_2O, and dried under high vacuum to afford **1g** (BMS-189921; 43.6 g, 95%): TLC R_f 0.61 (2:98 HOAc:EtOAc); $[\alpha]_D$ −18.9° (*c* 0.38, $CHCl_3$); mp 173−177 °C; ^1H NMR ($CDCl_3$) δ 1.39 (t, 3H), 1.43 (s, 3H), 1.53 (m, 1H), 1.96 (m, 6H), 3.04 (dd, 1H), 3.25 (dd, 1H), 3.58 (m, 1H), 4.02 (d, 1H), 4.32 (d, 1H), 4.79 (m, 2H), 7.24 (m, 5H), 7.68 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.04, 27.83, 29.57, 30,50,39.66, 41.14, 44.53, 46.65, 52.05, 59.07, 126.78, 128.27, 129.32, 137.43, 171.06, 172.88, 174.14. Anal. Calcd for $C_{19}H_{26}N_2O_4S$: C, 60.30; H, 6.92; N, 7.40; S, 8.47. Found: C, 60.16; H, 7.06; N, 7.06; S, 8.10.

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