Dual Angiotensin Converting Enzyme/Thromboxane Synthase Inhibitors

Gary M. Ksander,* Mark Erion,† Andrew M. Yuan, Clive G. Diefenbacher, Lena El-Chehabi, Don Cote, and Nigel Levens

Research Department, Pharmaceuticals Division, CIBA-GEIGY Corporation, 556 Morris Avenue, Summit, New Jersey 07901

Received July 2, 1993®

A variety of compounds were prepared to determine whether dual angiotensin converting enzyme (ACE)/thromboxane synthase (TxS) inhibition could be obtained in the same molecule. These compounds would be used to explore the concept that a dual inhibitor would have superior antihypertensive activity in the spontaneous hypertensive rat compared to an ACE inhibitor. Potent *in vitro* dual ACE and TxS inhibition was obtained in the same molecule with five series of compounds. Potent blood pressure lowering in the SHR was observed after oral administration of **8b** and **11**. However, a correlation between blood pressure lowering and the A1 pressor response inhibition was not observed. The blood pressure-lowering actions of enalapril were significantly potentiated by concurrent administration of **3**, a thromboxane synthase inhibitor. Analysis of the area under the curve for 24 h showed nearly a doubling of the blood pressure-lowering effect.

Angiotensin converting enzyme (ACE) inhibitors lower blood pressure in patients with essential hypertension and in various animal models of hypertension.[1] Furthermore, combination therapy of ACE inhibitors[2] with diuretics, calcium channel blockers, and β-blockers has been shown to impart greater efficacy in hypertensive patients and animal models. In contrast, thromboxane synthase (TxS) inhibitors do not lower blood pressure acutely when administered to spontaneous hypertensive rats (SHR).[3] Long-term administration of TxS inhibitors does, however, lower blood pressure in adult SHR and retards the development of hypertension in young SHR.[4] Such observations suggest that the vasoconstrictor thromboxane A2 (TxA_2) does not in the short term contribute to the increased vascular resistance that is characteristic of the SHR but that TxA_2 may play a role in the long-term control of blood pressure in this animal model. Since inhibition of ACE increases levels of bradykinin and bradykinin evokes the release of prostaglandins,[5] it was considered that concomitant blockade of ACE and TxA_2 formation through inhibition of TxS and subsequent shunting to the vasodilatory prostaglandins PGE_2 and PGI_2 *via* the endoperoxide PGH_2 could result in an additional antihypertensive effect. We have published preclinical data from spontaneous hypertensive rats that show concomitant inhibition of TxA_2 formation, *via* inhibition of TxS, does potentiate the blood pressure-lowering effects of converting enzyme inhibitors.[6] However, presently, there is no evidence to support a role for bradykinin in this mechanism.[7] Although the mechanism underlying this effect in the SHR model is unclear, it probably involves the increase in vasodilatory prostaglandins and not just the blockade of TxA_2 formation, since neither Indomethacin, a cyclooxygenase inhibitor, nor BM13505, a TxA_2 antagonist, affected the blood pressure-lowering effects of the ACE inhibitors tested in this model.[6]

In this paper, we describe our approach to the incorporation of dual ACE and TxS inhibitory activity within the same molecule. The approaches taken were (a) P_1 amide-linked mixed inhibitors, (b) glutaric acid amides, where the lipophilic portion of the TxS moiety occupies the P_1 site in the ACE template, (c) phosphonates, where the lipophilic portion of the TxS moiety again occupies the P_1 site while the phosphonate group satisfies both criteria for good ACE and TxS binding, and (d) dual *in vitro* active labile combinations which could generate the individual components *in vivo*.

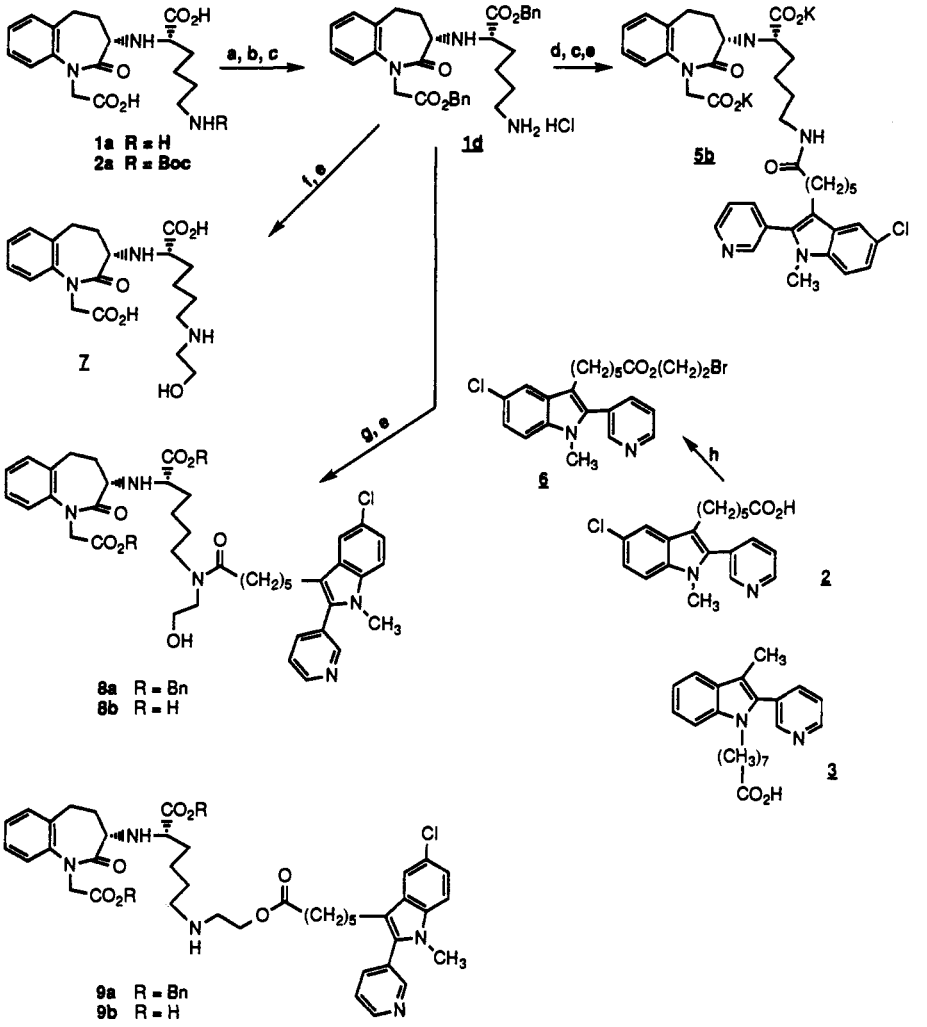
Chemistry

The amide diacid **5b**, Scheme 1, was prepared by manipulating protecting groups on compound **1a**[8] followed by acylation of the primary amine with the acid chloride of the pyridylindole thromboxane synthase inhibitor **2**.[9] The diesters **8a** and **9a** were prepared by alkylating **1d** in the presence of triethylamine with the 2-bromoethyl ester of **2**. Compound **8a** probably occurs *via* a base-catalyzed intramolecular acyl migration. The ethanol amide **8a** was quite stable, while the amino ester **9a** gave ester-cleavage products as well as small amounts of **8a** upon standing. Hydrogenation gave the respective diacids **8b** and **9b**. As expected, the amino ester **9b** was also unstable. The related amine analogs **8c** and **9c** were prepared as outlined in Scheme 2. The primary amine **1d** was condensed with *N*-Cbz-glycine aldehyde, reduced with sodium cyanoborohydride, reacted with Boc anhydride, and then, hydrogenated to give the extended amino ethane derivative **7d**. EDCI activation of **7d**, coupling with **2** followed by hydrolysis of the diethyl esters with potassium hydroxide, and removal of the Boc protecting group with hydrochloric acid gave the desired compound **9c**. The related compound **8c** was prepared using similar reactions by modifying the order of addition and removal of protecting groups. The aminopiperidine-linked dual inhibitor **11** was readily available by reductive amination of **1a** with the acylated piperidone **10**, Scheme 3. The glutaric acid derivative **17** was prepared as outlined in Scheme 4. Hydrolysis of the triester **13** followed by thermal decarboxylation of **14** gave the mixed acid ester **15**. EDCI-activated coupling with indoline-2-carboxylic acid methyl ester followed by potassium hydroxide hydrolysis gave the desired inhibitor **17**. Scheme 5 outlines the preparation of the 2-pyridylindole phosphonate derivatives. Alkylation of 2-pyridyl-3-methylindole with the appropriate four-carbon-extended diethyl phosphonate gave **18a**. Hydrolysis of the phosphodiester with trimethylsilyl iodide gave the phosphonic acid **18b**.

* Author to whom correspondence should be addressed.
† Present address: Gensia Pharmaceuticals.
® Abstract published in *Advance ACS Abstracts*, May 15, 1994.

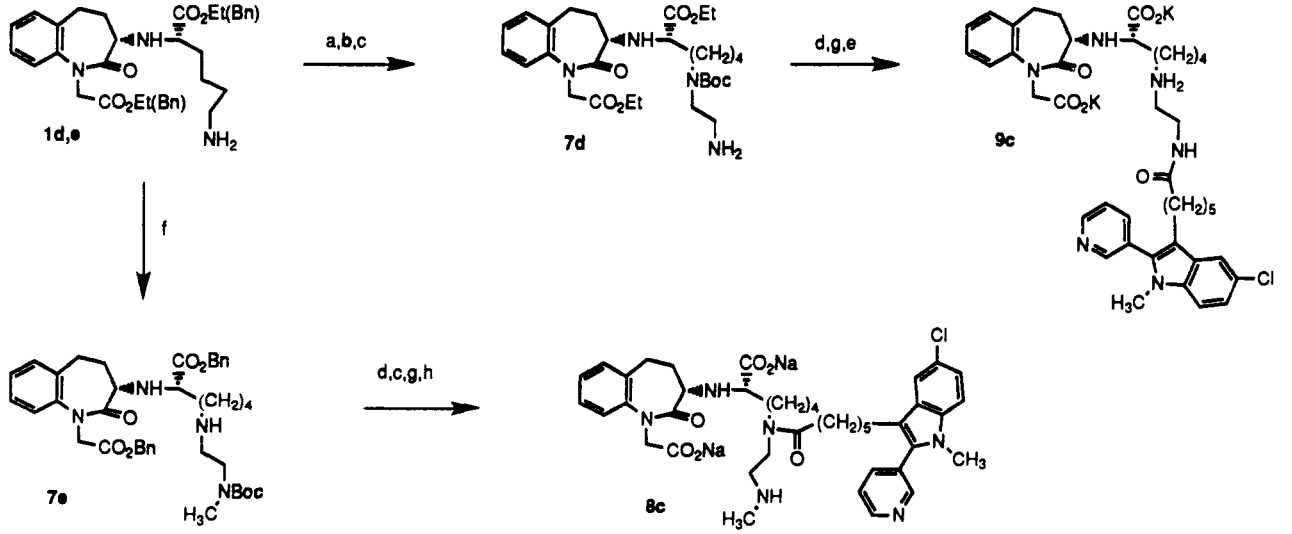
0022-2623/94/1837-1823$04.50/0

Scheme 1[a]



[a] (a) Boc_2O; (b) BnBr, Cs_2CO_3; (c) HCl; (d) EDCI, **2**; (e) H_2/Pd–C; (f) $Br(CH_2)_2OBn$, Et_3N; (g) **6**, Et_3N; (h) EDCI, $HO(CH_2)_2Br$.

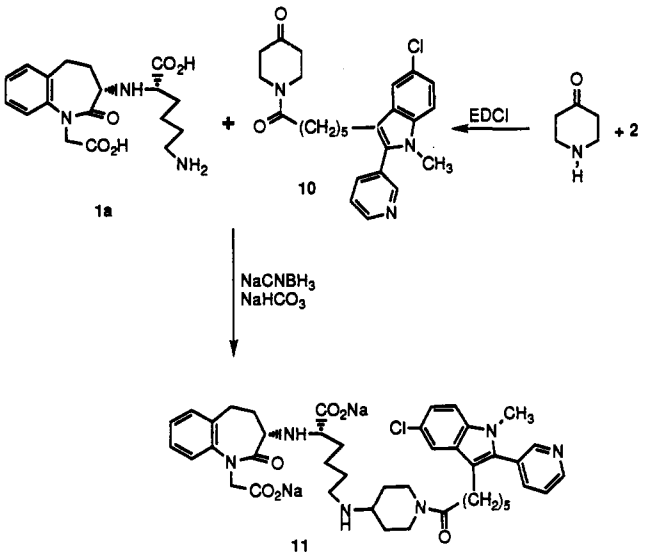
Scheme 2[a]



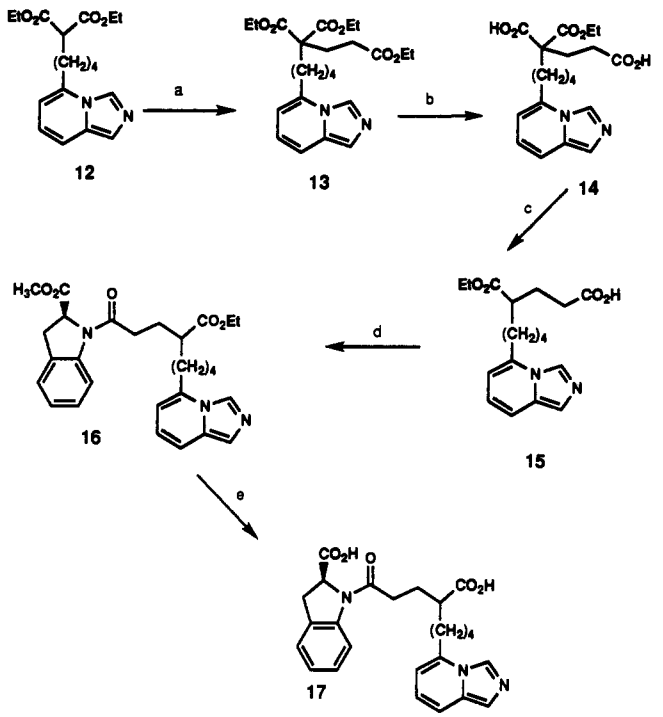
[a] (a) $CbzNHCH_2CHO$, $NaBH_3CN$; (b) Boc_2O; (c) H_2, Pd–C; (d) **2**, isobutyl chloroformate; (e) KOH; (f) $BocCH_3NCH_2CHO$, $NaBH_3CN$; (g) HCl; (h) NaOH.

The reaction of **18a** with 1 equiv of sodium hydroxide afforded the monophosphonic acid ester **18c**. The preparation of the benazepine phosphonate derivatives is outlined in Scheme 6. Alkylation of the 3-bromobenzolactam[11] with the substituted monophosphonic acid benzyl ester cesium salt in DMF gave a good yield of **19**. Alkylation of the lactam nitrogen with benzyl bromoacetate and K_2CO_3/acetone followed by hydrogenolysis of the dibenzyl ester gave the desired product **21a**. The pyridylindole phosphonate **21b** was prepared in an analogous fashion, although the corresponding reaction yields were decreased. The 5-oxy-substituted benazepines were pre-

Scheme 3



Scheme 4[a]



[a] (a) Ethyl acrylate; (b) NaOH; (c) 150 °C; (d) (2S)-carboxyindoline methyl ester, DCC; (e) KOH.

pared as outlined in Scheme 7. *N*-Acetyl-L-tryptophan was subjected to ozonolysis, selectively *N*-protected with Boc anhydride, and cyclized with EDCI to the 5-ketolactam **24**. Alkylation of the lactam nitrogen with *tert*-butyl bromoacetate/Cs_2CO_3/DMF and reduction of the ketone with sodium borohydride gave one diastereomer, **26**, presumably the α-OH isomer. Acylation of the 5-hydroxy function and acid hydrolysis of the *tert*-butyl ester and the *N*-Boc groups gave the amino acid **28**. Borch condensation of **28** with ethyl (2-phenylethyl)pyruvate gave a chromatographically separable mixture of diastereomers. Both diastereomers were carried through the synthesis to determine the active isomer. Hydrolysis and dibenzylation with Cs_2CO_3/benzyl bromide in DMF gave **31**. Appropriate acylation of the 5-hydroxy group followed by palladium-catalyzed hydrogenation afforded **33a–c**.

Table 1. *In Vitro* ACE and TxS Inhibition

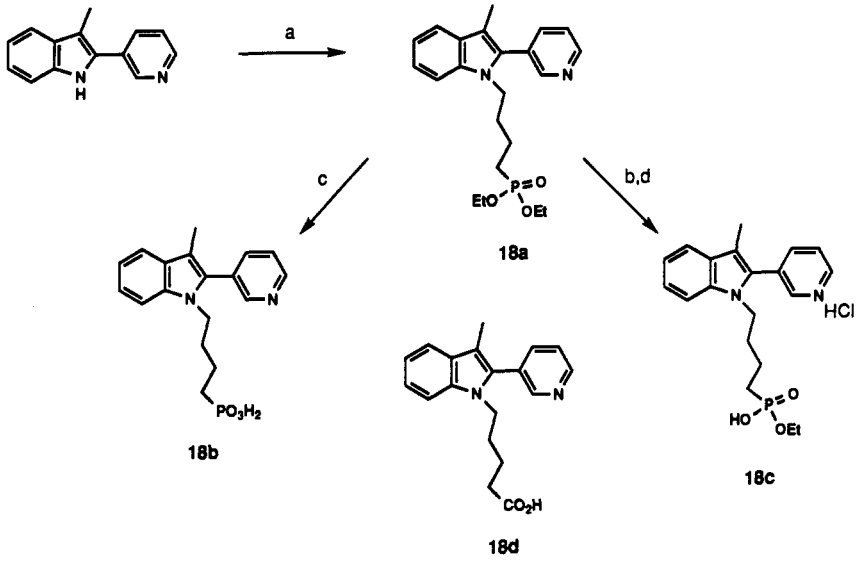
compound	ACE IC_{50} (nM)	TxSI IC_{50} (nM)
1a	7	NA
2	NA	2
3	NA	12
5b	6	4
7	7	NA
8b	10	20
8c	10	18
9c	4	10
11	12	20
17	20	70
18b	NA	100
18c	NA	9
18d	NA	10
21a	20	NA
21b	30	20
33a	6	NA
33b	8	NA
33c	90	20
enalapril	2	NA
benazapril	2	NA

In Vitro Structure–Activity Discussion

It has been previously reported[8] that substantial modifications, such as *N*-Boc, and *N*-Cbz derivatives of the P_1 butylamine substitutent of **1a**, have minor effects on ACE inhibitory potency, with IC_{50}'s varying from 5 to 20 nM. As shown in Table 1, acylation of the butylamine side chain with the bulky thromboxane synthase inhibitor **2** gave compound **5b** with an ACE IC_{50} of 6 nM. Other examples, the *N*-hydroxyethyl derivative **7**, the *N*-hydroxyethyl pyridylindole **8b**, the *N*-aminoethyl pyridylindoles **8c** and **9c**, and the piperidine-linked inhibitor **11**, inhibited ACE with IC_{50} values of 7, 10, 10, 4, and 12 nM, respectively, demonstrating the flexibility of the P_1-binding site in the ACE template. These P_1 substituents probably reach outside the active site of the enzyme. The thromboxane synthase inhibitory activities for **5b**, **8b,c**, **9c**, and **11** were 4, 20, 18, 10, and 20 nM, respectively. Amide substitution of the acid moiety of a potent TxSI appears to decrease activity 5–20-fold. Compound **17**, a glutaric acid derivative, uses the flexibility of the P_1 site to obtain good inhibitory ACE activity (IC_{50} = 20 nM). In addition, the glutaric acid carboxy group acts in a dual capacity as the zinc ligand to the angiotensin converting enzyme and as the carboxy functionality found in many potent TxS inhibitors. Of course, individual molecules interact separately with each enzyme. For this case, the TxS inhibitory activity is a modest 70 nM. The decrease in activity is possibly due to the large α-carboxy substituent.

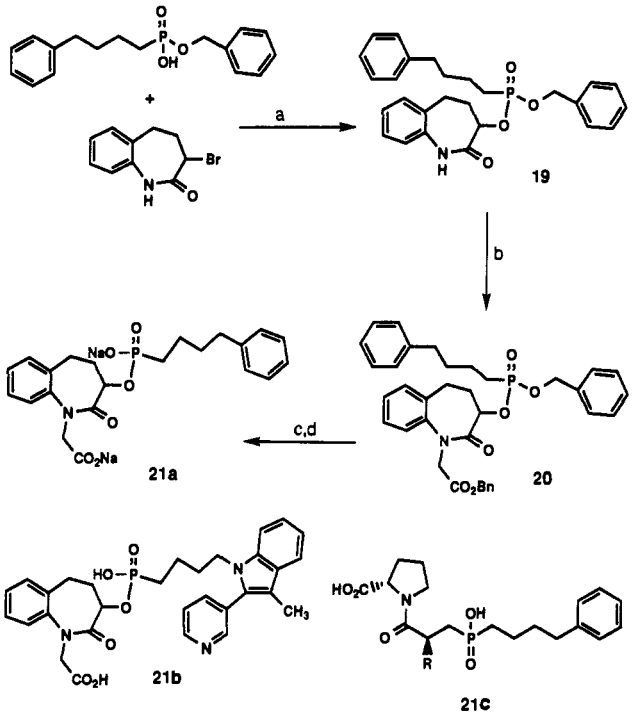
The target molecule **21b**, a monophosphonic acid ester, was envisioned as a dual inhibitor, where the phosphonate would chelate with the zinc atom in the active ACE site and act as the acid moiety for good thromboxane synthase inhibitory activity. There are no reports of replacing the carboxy group of a TxS inhibitor with a phosphonic acid or monophosphonic acid ester. The TxSI portion of the molecule was prepared to assess the feasibility of the class of compounds represented by **21b**. Therefore, the first critical experiment was the replacement of the carboxylic acid moiety of the *N*-(carboxyalkyl)-2-pyridylindole **18d** with a phosphonic acid and monophosphonic acid ester. Replacement of the carboxy group in **18d** with a phosphonic acid, **18b**, significantly decreased activity from 7 to 100 nM, respectively. Although the phosphonic acid

Scheme 5[a]



[a] (a) $Cl(CH_2)_4PO(OEt)_2$/NaI/NaH; (b) NaOH; (c) TMSI; (d) HCl.

Scheme 6[a]



[a] (a) Cs_2CO_3; (b) benzyl bromoacetate; (c) H_2/Pd–C; (d) NaOH.

group increases the distance from the acidic functionality to the structurally required pyridylindole, this probably does not play a significant role since methylene extension by even three units does not significantly alter the TxSI activity in the caboxylic acid series. The increase in acidity of the phosphonic acid as compared to that of the carboxylic acid may play a more important role in the observed decrease in activity. Fortunately, the monophosphonic acid ester **18c** inhibited TxS equivalent to the carboxylic acid analog **18d**. The pK_a's of a carboxylic acid and a monophosphonic acid ester are similar. Therefore, this similarity may play a more dominat role in governing the activity of these compounds.

Phosphonates used as ACE inhibitors are not new. The structure–activity in the proline phosphonate series **21c** has been published.[10] For example, the three chiral phosphonates differing at the P_1' site by aminobutyl, methyl, and phenylethyl substituents have good to moderate *in vitro* potency (36, 55, and 640 nM), respectively. Interestingly, the rigid benazepine analog **21a** increases ACE inhibitory potency, with IC_{50} = 20 nM. The compound **21a** is racemic and would be expected to have all its inhibitory activity in only one enantiomer (*S*) as is the case for the proline phosphonates. Therefore, a 4- to 5-fold increase in potency is gained using the benazepine template. Combining the two structural types **18c** (TxS) and **21a** (ACE) resulted in the formation of the racemic hybrid dual inhibitor **21b**, IC_{50} = 30 nM (ACE), 20 nM (TxS).

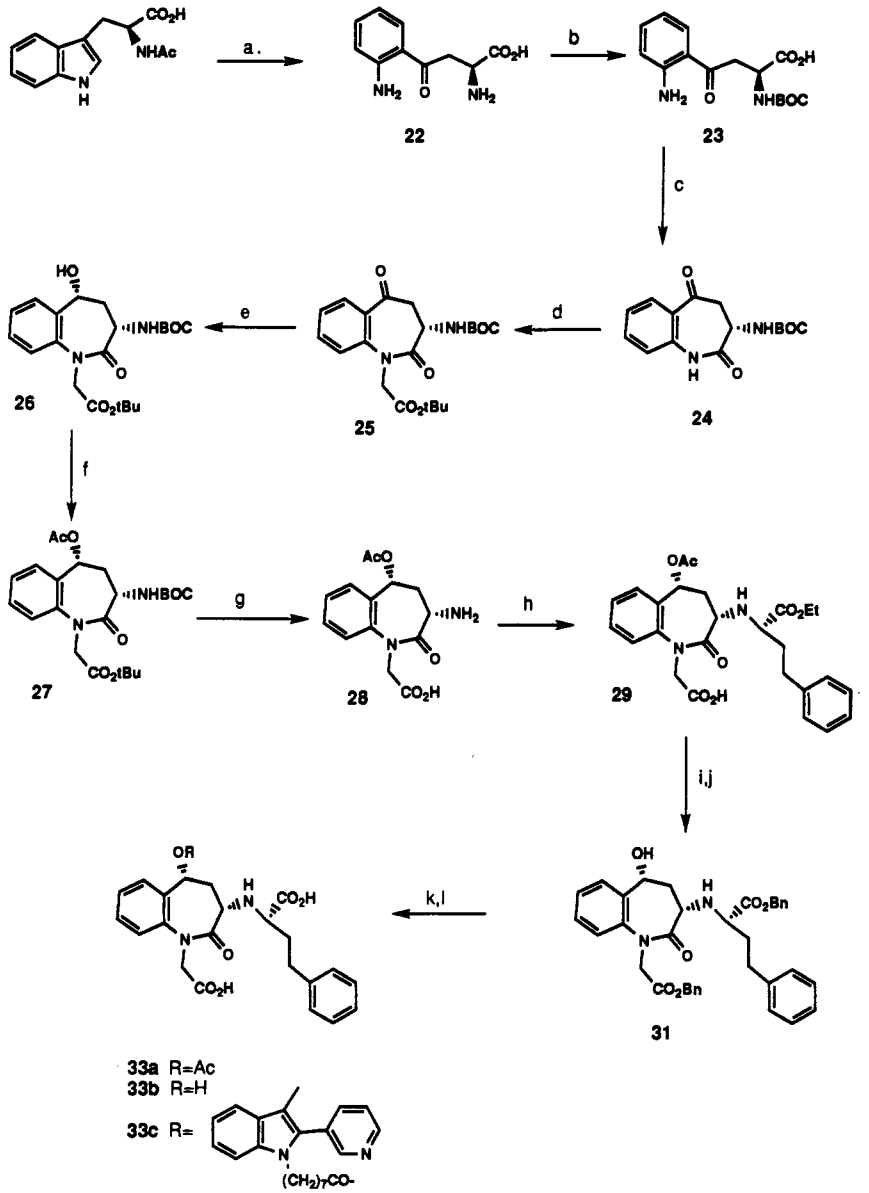
The 5-oxybenzazepine derivatives **33a,b** were effective inhibitors of ACE (IC_{50} = 6 and 8 nM, respectively). The 5-hydroxy or acetoxy derivatives only slightly affected the inhibitory activity as compared to the parent compound benazapril[11] (5-desoxy derivative, IC_{50} = 2 nM). However, when the bulky pyridylindole derivative **33c** was prepared, the ACE activity decreased to 90 nM while the TxS inhibitory activity was maintained at 20 nM.

In Vivo Activity

The potentiation of the antihypertensive action of an ACE inhibitor by a TxSI is demonstrated with enalapril and compound **3**, Figure 1. The oral administration of 10 mg/kg of **3**[12] completely inhibited plasma thromboxane (TxA_2) formation[6] from 1 to 24 h but failed to significantly lower blood pressure from control values. The ACE inhibitor enalapril at 5 mg/kg po significantly lowered blood pressure for 6 h in the unrestrained intraarterial catheterized spontaneously hypertensive rat (SHR). The blood pressure-lowering actions of enalapril at this submaximal dose was significantly potentiated by concurrent administration of **3** (TxSI) from 1 to 24 h (Figure 1). Analysis of the area under the curve for 0–6 and 0–24 h showed nearly a doubling of the blood pressure-lowering effect. The mechanism whereby **3** potentiates the antihypertensive action of enalapril has not been conclusively determined, and an effect of **3** on the pharmacokinetics of enalapril has not been ruled out.[6,7]

The *in vivo* activity of selective ACE/TxS dual inhibitors is summarized in Table 2. The potent dual inhibitor **5b** after interarterial (ia) administration did not lower blood

Scheme 7[a]



[a] (a) O_3; (b) Boc_2O; (c) EDCI; (d) *tert*-butyl bromoacetate; (e) $NaBH_4$; (f) Ac_2O/DMAP; (g) HCl; (h) $NaCNBH_3$/ethyl 4-phenyl-2-ketobutanoate; (i) NaOH; (j) Cs_2CO_3/benzyl bromide; (k) HOAc/EDCI; (l) H_2/Pd–C.

Table 2. Antihypertensive Effects in the SHR

compound	dose (route)	SHR max Δ BP (mmHg) (*t*, h)	SHR Δ BP (mmHg) 24 h	max AI pressor response % inhibition (*t*, h)
1a	10 MPK (po)	−30 (4)	−18	70 (2)
5b	1 MPK (ia)	NS	NS	81 (0.5)
7	30 MPK (po)	−28 (4)	NS	84 (4)
8b	10 MPK (po)	−42 (5)	−30	30 (5)
8b	1 MPK (ia)	−23 (5)	NS	76 (0.5)
8c	30 MPK (po)	−39 (6)	−20	71 (6)
11	10 MPK (po)	−35 (4)	NS	51 (4)
11	1 MPK (ia)	−24 (4)	NS	76 (2)
9c	10 MPK (po)	−38 (6)	−23	39 (5)
enalapril	5 MPK (po)	−28 (3)	−17	100 (2)

pressure measured between 1 and 6 h postdosing. The lack of an antihypertensive action was probably due to rapid removal from the systemic circulation, evident by the 81 ± 6.1% inhibition of the angiotensin I (AI) pressor response at 0.5 h, while insignificant inhibition was observed after 2 h. In contrast, compound **5b** and the *N*-hydroxyethyl derivative **8b** lowered blood pressure after ia and po administration in the SHR at 1 and 10 mg/kg, respectively. The AI pressor response inhibition after ia injection of **8b** at 1 mg/kg was 76 ± 5.5%, 30 min postdosing, similar to **5b**. The inhibitory activity decayed to 50 ± 5.5% at 4 h postdosing and was not significant after 6 h. However, over the first 6 h, the blood pressure decreased −23 ± 7.1 mmHg, while returning to control values at 24 h postdosing. Oral dosing of **8b** at 10 mg/kg lowered blood pressure −42 ± 5.1 mmHg up to 6 h, and a −30 ± 5.8 mmHg decrease in blood pressure was still present after 24 h (Figure 2). Interestingly, while a potent antihypertensive effect was observed, the AI pressor response inhibition reached a maximum of only 30% throughout the entire 6-h period and was not significant at 24 h. Although the hypotensive effects of ACE inhibitors are not always correlated to plasma enzyme inhibition, a potent hypotensive effect *via* this mechanism with 30% AI pressor response inhibition is unusual. This indicates that only low levels of **8b** are present in the circulation, since inhibition of AI pressor response is directly correlated

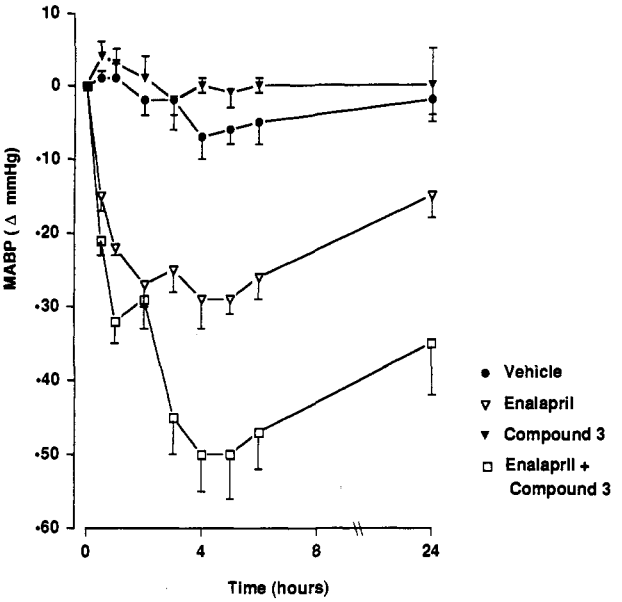


Figure 1. ACE/TxSI potentiation of mean arterial blood pressure in spontaneously hypertensive rats: enalapril, 5 mg/kg po; compound **3**, 10 mg/kg po; vehicles, 1 mL/kg po.

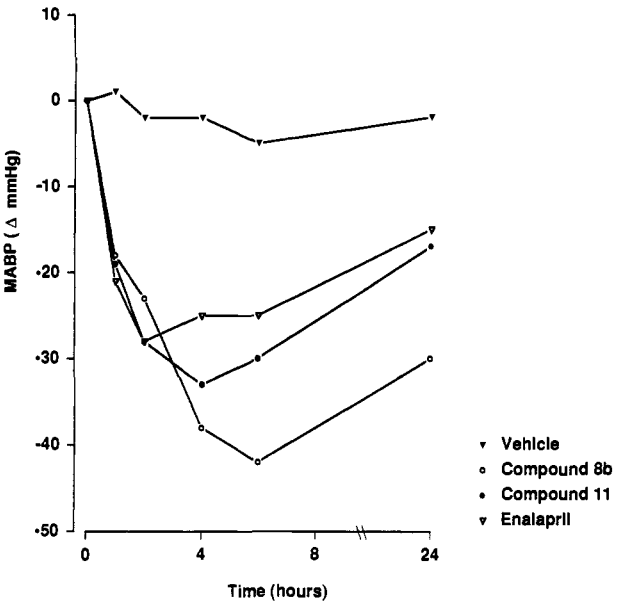


Figure 2. Change in mean arterial blood pressure in spontaneously hypertensive rats of **8b** (10 mg/kg po), 11 (10 mg/kg po), and enalapril (5 mg/kg po).

to inhibitor plasma concentrations. Whether the unexpected decrease in blood pressure for **8b** is due to formation of vasodilatory prostaglandins *via* inhibition of TxS or rapid removal from circulation into tissues or specific metabolism is not known. Since good blood pressure lowering was observed acutely, a 4-daily-dosing regiment of 10 mg/kg po of **8b** in the SHR to address chronic administration was performed. A -40 to -50 mmHg drop in blood pressure was sustained for the entire 4-day study. After withdrawal of **8b** on day 5, the blood pressure of these animals returned to its initial hypertensive base line (day 6). Examining the thromboxane synthase inhibitory activity *ex vivo*, we found that platelet-derived TxA_2 formation was inhibited 95% by **8b**, 6 h postdosing in the SHR at 10 mg/kg po.

Similarly, **8c** lowered blood pressure after oral administration in the SHR. The dose required to reach comparable blood pressure effects was 3 times higher than that observed with **8b**. In contrast to **8b**, the A1 pressor response inhibition effects of **8c** increased with time, paralleling the fall in blood pressure. At 6 h, the blood pressure and the A1 pressor response inhibition reached maximal, -39 mmHg and 71% inhibition, respectively.

The piperidine-linked dual inhibitor **11** displayed a very similar profile as **8b** except its duration of action was shorter. Oral dosing of **11** at 10 mg/kg lowered blood pressure -30 ± 4.9 mmHg up to 6 h postdosing. However, the antihypertensive effect was not significant at 24 h. The AI pressor response inhibition was 30–50% over a period of 2–6 h. *via* increasing the dose to 30 mg/kg po, the maximum change in blood pressure was -42 ± 5.6 mmHg with AI pressor response inhibition reaching a maximum of -61 ± 3.1% 5 h post-dosing. In contrast to the lack of correlation of AI pressor response inhibition to the hypotensive effects of **8b** and **11**, enalapril gives a classical response to the AI challenge. At an enalapie dose of 5 mg/kg po, the AI pressor response inhibition was 100–50% from 1 to 6 h postdosing. The comparative blood pressure-lowering data at 12 mmol/kg po for **8b**, **11**, and enalapril are shown in Figure 2. As previously mentioned, the lack of correlation between blood pressure lowering and AI pressor response inhibition for both **8b** and **11** could be the formation of vasodilitory prostaglandins. However, **8b** and **11** are highly plasma protein bound, >98%, determined by ultracentrifugation. Therefore, whether ACE interacts with a plasma-bound inhibitor or only a free unbound inhibitor and whether we are observing a tissue selectivity or specific uptake of these compounds by cells or unidentified metabolism are not known.

In summary, we have demonstrated that *in vitro* ACE/TxS inhibition is obtainable with a variety of structural types. The P_1 linked inhibitors show good antihypertensive effects after oral administration. The lack of correlation of the hypotensive effects to AI pressor response inhibition is not known.

Experimental Section

General Procedures. ^1H NMR spectra were recorded on a Varian XL 400-MHz, Varian VR 300-MHz, and/or Bruker AC 250-MHz spectrometer with tetramethylsilane as internal standard. Infrared spectra were recorded on a Nicolet 5SXFT spectrometer. Optical rotations were measured with a Perkin-Elmer Model 241 polamiter. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected.

Biology *in Vitro* Studies. Measurement of Thromboxane Synthetase Activity. Thromboxane synthetase activity was measured according to previously described methods.[9b,13] In this assay, [1-^{14}C]arachadonic acid was incubated with partially purified thromboxane synthetase obtained from human platelets. At the end of the incubation period, the (thromboxane B_2; TxB_2) product was extracted into ethyl acetate, and the extract was evaporated to dryness. The residue was redissolved in acetone and this solution spotted onto a thin-layer chromatography plate. After development, the plates were scanned and the radioactive spot corresponding to TxB_2 was scrapped off and counted. The IC_{50} values were determined by employing a range of concentrations of test compounds over the linear range of the assay and analyzed graphically. All determinations were done in duplicate and repeated once.

Measurement of Angiotensin Converting Enzyme Activity. Angiotensin converting enzyme activity was measured according to a previously described method.[13] In this assay, a synthetic peptide substrate, Hip-His-Leu, was incubated with partially purified angiotensin converting enzyme obtained from rabbit lung. At the end of the incubation period, the hipperic acid product was assayed spectrophotometrically. The IC_{50} values

were determined as described in the previous section, Measurement of Thromboxane Synthetase Activity.

***In Vitro* Studies. Animals.** These studies were conducted with spontaneously hypertensive rats (SHR; taconic Forms, NY) weighing between 250 and 280 g. All rats were maintained on a normal pellet diet (purina rat chow), allowed free access to tap water, and housed in a room with a 12-h light cycle (6:00 a.m.–6:00 p.m.) at 70 ± 5 °F and 55% relative humidity.

Determination of Blood Pressure. Blood pressure was measured in conscious rats. Rats were anesthetized with methoxy furan (Pitman-Moore, Inc., Washington Crossing, NJ), and the femoral artery was cannulated with clear vinyl tubing (0.28-mm inside diameter × 0.61-mm outside diameter; Dural Plastics and Engineering, Dural, Australia). The arterial catheter was tunneled subcutaneously and scited from the animals through a small stab wound on the dosal surface, 1 cm from the base of the tail. The arterial catheter was connected to a single-channel infusion swivel (Instech Labs, Horsham, PA) and protected along its length by an 18-in. stainless steel spring anchored to the animal with a stainless steel button (Instech Labs). This arrangement enabled blood pressure to be recorded from conscious, fully ambulatory animals. The animals were allowed 24 h to recover from surgery and were housed individually in plexiglass cabinets (width 31.5 cm, depth 32.5 cm, height 38.5 cm) for the duration of the experiment period. Measurements of blood pressure were subsequently performed over a 6-h period.

Determination of Angiotensin I Pressor Responses. Rats were prepared for the measurement of blood pressure as described above. At an appropriate time, 300 mg/kg angiotensin I was administered intraarterially in a volume of 0.5 mL and the increase in blood pressure recorded.

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-[1-[[(benzyloxy)carbonyl]methyl]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3-yl]hexanoic Acid Benzyl Ester (1c). To a suspension of **1b**[8] (26.0 g, 0.056 mol) in 200 mL of DMF was added cesium carbonate (36.6 g, 0.112 mol). The mixture was stirred at room temperature for 1 h. Benzyl bromide (14 mL, 0.118 mol) was added and the mixture stirred for 2 days. The reaction mixture was concentrated and partitioned between ethyl acetate (EtOAc) and water. The organic layer was washed with H_2O, saturated $NaHCO_3$, and NaCl, filtered, and concentrated to give 36.0 g (90%) of **1c** as a viscous oil. ^{1}H NMR ($CDCl_3$): δ 7.4–7.0 (m, 15 H), 5.1 (ABq, J = 5 Hz, 2 H), 5.02 (ABq, J = 11 and 15 Hz, 2 H), 4.6 (m, 1 H), 4.55 (ABq, J = 15 and 45 Hz), 3.4–2.95 (m, 5 H), 2.45 (m, 2H), 2.05 (m, 1 H), 1.7 (m, 2 H), 1.4 (s, 9 H), 1.4 (m, 4 H).

6-Amino-2-[[1-[[(benzyloxy)carbonyl]methyl]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3-yl]amino]hexanoic Acid Benzyl Ester (1d). Dry HCl (g) was bubbled through a solution of **1c** (35.9 g) in 300 mL of EtOAc for 20 min. The mixture was stirred for 16 h. The solid was collected, washed with EtOAc, and dried under high vacuum to give 27.5 g (90%) of **1d**.

2-[[1-(Carboxymethyl)-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3-yl]amino]-6-[[5-[5-chloro-1-methyl-2-(3-pyridinyl)-1*H*-indol-3-yl]pentanoyl]amino]hexanoic Acid Dibenzyl Ester (5a). Triethylamine (0.45 g, 4.4 mmol) was added to a suspension of **1d** (1.36 g, 2.2 mmol) in 20 mL of CH_2Cl_2. To this solution were added **2** (1.0 g, 2.2 mmol) and 1-[3-(dimethylamino)-propyl]-2-ethylcarbodiimide HCl (EDCI) (0.45 g, 2.3 mmol). The reaction mixture was stirred for 16 h, diluted with EtOAc, and washed with saturated $NaHCO_3$ and H_2O, dried ($MgSO_4$), filtered, concentrated, and flash chromatographed on SiO_2 eluting with 95% EtOAc:5% CH_3OH to give 1.2 g (52%) of **5a**, mp 47–50 °C. ^{1}H NMR ($CDCl_3$): δ 8.78 (s, 1 H), 8.7 (d, J = 4 Hz, 1 H), 7.75 (d, J = 9 Hz, 1 H), 7.57 (s, 1 H), 7.48 (m, 1 H), 7.23 (m, 15 H), 6.98 (d, J = 9 Hz, 1 H), 6.5 (br, 1 H), 5.1 (2 overlapping ABq, 4 H), 4.52 (s, 2 H), 3.8 (br, 1 H), 3.6 (m, 1 H), 3.5 (s, 3 H), 3.15 (m, 2 H), 2.7–1.1 (m, 21 H).

2-[[1-(Carboxymethyl)-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3-yl]amino]-6-[[5-[5-chloro-1-methyl-2-(3-pyridinyl)-1*H*-indol-3-yl]pentanoyl]amino]hexanoic Acid (5b). A solution of **5a** in 30 mL of EtOH containing 1.1 g of 10% Pd–C was hydrogenated for 24 h at atmospheric pressure. The catalyst was filtered off and the filtrate concentrated and slurried with ether. The solid was collected and dried at 70 °C, high vacuum, to give 0.75 g (98%) of **5b**. The dipotassium salt was formed by mixing 2 equiv of KOH in water with **5b**, mp 140–143 °C. ^{1}H NMR (DMSO-d_6): δ 8.66 (m, 2 H), 7.95 (m, 1 H), 7.7 (t, J = 5 Hz, 1 H), 7.6 (s, 2 H), 7.52 (d, J = 9 Hz, 1 H), 7.25 (m, 5 H), 4.55 (ABq, J = 15, and 38 Hz, 2 H), 3.7 (m, 2 H), 3.52 (s, 3 H), 3.5 (br, 1 H), 3.2 (m, 1 H), 2.98 (m, 2 H), 2.7–1.1 (m, 19 H). Anal. ($C_{38}H_{42}ClK_2N_2O_6 \cdot 2H_2O$) C, H, N.

[[1-[[(Benzyloxy)carbonyl]methyl]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3-yl]amino]-6-[[5-[5-chloro-1-methyl-2-(3-pyridinyl)-1*H*-indol-3-yl]pentanoyl](2-hydroxyethyl)-amino]hexanoic Acid Benzyl Ester (8a) and 2-[[1-[[(Benzyloxy)carbonyl]methyl]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3-yl]amino]-7-[[2-[[5-[5-chloro-1-methyl-2-(3-pyridinyl)-1*H*-indol-3-yl]pentanoyl]oxy]ethyl]amino]heptanoic Acid Benzyl Ester (9b). To a solution of **1d** (6.0 g, 11.0 mmol) in 20 mL of DMF with triethylamine (1.12 g, 11.0 mmol) was added **6** (4.5 g, 10.0 mmol). The ester **6** was prepared by EDCI/DMAP coupling of **2** with 2-bromoethanol. The mixture was stirred for 18 h at 60 °C, concentrated, and flash chromatographed eluting with 9:1 EtOAc:CH_3OH to give 1.7 g of **8a**. Eluting the column with 90:5:5 EtOAc:CH_3OH:Et_3N gave 1.3 g of **9a**. **Compound 8a.** ^{1}H NMR ($CDCl_3$): δ 8.6 (m, 2H), 7.7 (d, J = 7 Hz, 1 H), 7.57 (s, 1 H), 7.42 (m, 1 H), 7.2 (m, 15 H), 6.97 (d, J = 7 Hz, 1 H), 5.15–4.9 (m, 4 H), 4.65 (m, 1 H), 4.4 (m, 1 H), 3.68 (t, J = 4 Hz, 2 H), 3.51 (s, 3 H), 3.45 (t, J = 4 Hz, 1 H), 3.2 (m, 5 H), 2.7–1.1 (m, 20 H). **Compound 9a.** ^{1}H NMR ($CDCl_3$): δ 8.68 (d, J = 7 Hz, 1 H), 8.62 (s, 1 H), 7.67 (d, J = 7 Hz, 1 H), 7.55 (s, 1 H), 7.4 (m, 1 H), 7.2 (m, 15 H), 6.96 (d, J = 7 Hz, 1 H), 7.55 (s, 1 H), 7.4 (m, 1 H), 7.2 (m, 15 H), 6.96 (d, J = 7 Hz, 1 H), 5.5 (s, 2 H), 5.0 (ABq, J = 11 and 35 Hz, 2 H), 4.54 (ABq, J = 19 and 93 Hz, 2 H), 4.10 (t, J = 5 Hz, 2 H), 3.50 (s, 3 H), 3.17 (m, 3 H), 2.75 (t, J = 5 Hz, 2 H), 2.60 (t, J = 7 Hz, 2 H), 2.51 (t, J = 7 Hz, 2 H), 2.4–1.5 (m, 19 H).

2-[[1-(Carboxymethyl)-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3-yl]amino]-6-[[5-[5-chloro-1-methyl-2-(3-pyridinyl)-1*H*-indol-3-yl]pentanoyl](2-hydroxyethyl)amino]hexanoic Acid (8b). A solution of **8a** in 80 mL of ethanol containing 1 g of 10% Pd–C was hydrogenated for 16 h under atmospheric pressure. The mixture was filtered and the filtrate concentrated and triturated with ether. The solid was collected and dried at 50 °C under high vacuum to give 1.1 g (87%) of **8b**. The dipotassium salt was prepared by mixing **8b** with 2 equiv of potassium hydroxide in water, mp 137–140 °C. MS: m/z 746.3. GCMS: 0.1% NH_4OAc, 40–90 CH_3OH in 10 min, pH 4.7 (5% of the des-Cl compound, m/z 712.3, detected). ^{1}H NMR (DMSO-d_6): δ 8.68 (d, J = 5 Hz, 1 H), 8.65 (s, 1 H), 7.91 (d, J = 7 Hz, 1 H), 7.6–7.0 (m, 8 H), 3.95 (ABq, J = 15 and 90 Hz), 3.56 (s, 3 H), 3.5–1.5 (m, 30 H). Anal. ($C_{40}H_{46}ClK_2N_5O_7 \cdot 2H_2O$) C, H, N.

2-[[1-(Carboxymethyl)-2,3,4,5-tetrahydro-2-oxo-1*H*-benzazepin-3-yl]amino]-7-[[2-[[5-[5-chloro-1-methyl-2-(3-pyridinyl)-1*H*-indol-3-yl]pentanoyl]oxy]ethyl]amino]heptanoic Acid (9b). **9b** was prepared similarly as **8b** except it was hydrogenated for 2 days. MS: m/z 746.3. GCMS: 0.1% NH_4OAc, 40–90 CH_3OH in 10 min, pH 4.7. Significant amount of the des-Cl indole was present.

6-[[(2-Aminoethyl)carbobenzoxy]amino]-2-[[1-[(ethoxycarbonyl)methyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-benz[*b*]azepin-3-yl]amino]hexanoic Acid Ethyl Ester (7b). A solution of *N*-Cbz-glycine aldehyde (3.0 g, 15.54 mmol) and **1e** (8.47 g, 20.2 mmol) in 200 mL of methanol with 10 g of molecular sieves was stirred for 18 h. The mixture was filtered through Celite, concentrated, and dissolved in EtOAc. The organic layer was washed with H_2O, 5 N HCl, and $NaHCO_3$, dried ($MgSO_4$), and concentrated to give 2.2 g of **7b**. The 5 N HCl was reextracted with 10% CH_3OH/CH_2Cl_2 three times. The organic phase was washed with $NaHCO_3$, dried ($MgSO_4$), and concentrated to give an additional 2.5 g of the crude product **7b**.

6-[[(2-Aminoethyl)carbobenzoxy](*tert*-butoxycarbonyl)-amino]-2-[[1-[(ethoxycarbonyl)methyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-benz[*b*]azepin-3-yl]amino]hexanoic Acid Ethyl Ester (7c). A solution of **7b** (4.6 g, 7.7 mmol) and $(Boc)_2O$ (1.6 g, 7.7 mmol) in 15 mL of CH_2Cl_2 was left standing for 18 h at room temperature and then poured into H_2O, extracted with CH_2Cl_2, dried ($MgSO_4$), concentrated, and flash chromatographed on silica gel eluting with 1% CH_3OH/CH_2Cl_2 to give 4.2 g of **7c**. ^{1}H NMR ($CDCl_3$): δ 7.2–7.1 (m, 9 H), 5.1 (m, 2 H), 4.65 (m, 1 H), 4.4 (m,

1 H), 4.15 (m, 2 H), 4.0 (m, 2 H), 3.4–3.0 (m, 7 H), 2.55 (m, 1 H), 2.37 (m, 1 H), 1.95 (m, 2 H), 1.8–1.1 (m, 2 H).

6-[(2-Aminoethyl)(*tert*-butoxycarbonyl)amino]-2-[[1-[(ethoxycarbonyl)methyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-benz[*b*]azepin-3-yl]amino]hexanoic Acid Ethyl Ester (7d). A suspension of **7c** (4.0 g) in 25 mL of EtOH and 1.0 g of 10% Pd–C was hydrogenated at 50 psi for 20 h. Acetic acid (10 mL) and 0.5 g of 10% Pd–C was added and the mixture hydrogenated for an additional 5 h. The mixture was filtered through Celite, concentrated, and flash chromatographed on silica gel, eluting gradient 1% CH_3OH/CH_2Cl_2 to 10% $CH_3OH/1\%$ Et_3N/CH_2Cl_2, affording 2.0 g of starting material and 1.5 g of **7c**. ^1H NMR (CD_3OD): δ 7.35–7.2 (m, 4 H), 4.57 (ABq, J = 23 and 30 Hz, 2 H), 4.17 (q, J = 8 Hz, 2 H), 4.0 (q, J = 8 Hz, 2 H), 3.4–3.1 (m, 8 H), 2.63 (m, 1 H), 2.35 (m, 1 H), 1.8–1.2 (m, 17 H), 1.22 (t, J = 8 Hz, 3 H), 1.05 (t, J = 8 Hz, 3 H).

2-[[1-(Carboxymethyl)-2,3,4,5-tetrahydro-2-oxo-1*H*-benzazepin-3-yl]amino]-7-[[2-[[5-[5-chloro-1-methyl-2-(3-pyridinyl)-1-1*H*-indol-3-yl]pentanoyl]amino]ethyl](*tert*-butoxycarbonyl)amino]heptanoic Acid (9d). To a solution of **2** (904 mg, 2.64 mmol) and triethylamine (338 mL, 2.64 mmol) in 15 mL of THF at –10 °C was added isobutyl chloroformate (312 mL, 2.58 mmol). The mixture was stirred for 1 h at –10 °C, **7d** (1.30 g, 2.5 mmol) in a minimal amount of CH_2Cl_2 was added, and the mixture was allowed to warm to room temperature and was stirred for 5 h. The mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with H_2O and $NaHCO_3$, dried ($MgSO_4$), concentrated, and flash chromatographed on silica gel eluting with 2% CH_3OH/CH_2Cl_2 to give 703 mg of **9d**. ^1H NMR (CD_3OD): δ 8.6 (m, 2 H), 7.92 (d, J = 10 Hz, 1 H), 7.6 (m, 1 H), 7.55 (s, 1 H), 7.4–7.1 (m, 6 H), 5.1 (m, 1 H), 4.54 (m, 2 H), 4.14 (m, 2 H), 3.98 (t, J = 8 Hz, 2 H), 3.56 (s, 3 H), 3.3–3.0 (m, 7 H), 2.68 (t, J = 7 Hz, 2 H), 2.57 (m, 2 H), 2.34 (m, 1 H), 2.1 (q, J = 8 Hz, 1 H), 1.94 (m, 1 H), 1.7–1.2 (m, 13 H), 1.46 (s, 9 H), 1.2 (m, 3 H), 1.05 (t, J = 8 Hz, 3 H).

2-[[1-(Carboxymethyl)-2,3,4,5-tetrahydro-2-oxo-1*H*-benzazepin-3-yl]amino]-7-[[2-[[5-[5-chloro-1-methyl-2-(3-pyridinyl)-1*H*-indol-3-yl]pentanoyl]amino]ethyl]amino]heptanoic Acid (9c). To a room-temperature solution of **9d** (0.67 g, 0.75 mmol) in 2 mL of CH_3OH was added 1 N KOH (1.5 mL). The reaction mixture was stirred for 5 h, 1 N HCl was added to adjust to pH 8, and the mixture was concentrated to give 450 mg of **9f**. To the crude product was added 10 mL of trifluoroacetic acid at room temperature for 1 h; the mixture was concentrated affording 112 mg of **9c**, isolated after preparative HPLC eluting with A = 90% CH_2CN/H_2O + 0.09% TFA, B = 100% H_2O + 0.09% TFA, gradient A/B 1:9 to 100% A over 2 h, mp 141–143 °C (dipotassium salt). ^1H NMR (HCl salt) (CD_3OD): δ 9.1 (s, 1 H), 9.0 (s, 1 H), 8.78 (d, J = 7.5 Hz), 8.3 (m, 1 H), 7.62 (s, 1 H), 7.5–7.2 (m, 6 H), 4.68 (ABq, J = 17 and 30 Hz, 2 H), 3.9 (m, 3 H), 2.65 (s, 3 H), 3.48 (m, 1 H), 3.3 (m, 1 H), 3.1 (m, 1 H), 3.05 (m, 1 H), 2.75 (m, 5 H), 2.4 (q, J = 7 Hz), 2.2 (t, J = 7 Hz), 2.02 (m, 4 H), 1.8–1.2 (m, 8 H). Anal. ($C_{40}H_{47}N_6O_6ClK_2 \cdot 2\ H_2O$) C, H, N.

2-[[1-(Carboxymethyl)-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3-yl]amino]-6-[[5-[5-chloro-1-methyl-2-(3-pyridinyl)-1*H*-indol-3-yl]pentanoyl][2-(methylamino)ethyl]amino]hexanoic Acid (8c). Prepared in an analogous fashion to **9c**, the desired product **8c** was isolated after reverse-phase chromatography, $MeOH/H_2O$ as the disodium salt, mp 170–172 °C, m/z 816.5. ^1H NMR (CD_3OD·TFA): δ 9.0 (s, 1 H), 8.91 (s, 1 H), 8.57 (d, J = 10 Hz, 1 H), 8.15 (t, J = 10 Hz, 1 H), 7.64 (s, 1 H), 7.2–7.5 (m, 6 H), 4.6 (ABq, J = 25 and 30 Hz, 2 H), 3.9 (m, 3 H), 3.65 (s, 3 H), 3.15 (m, 2 H), 2.72 (m, 2 H), 2.68 (s, 3 H), 2.36 (m, 2 H), 1.98 (m, 2 H), 1.7–1.2 (m, 14 H). Anal. ($C_{41}H_{49}N_6O_6ClNa_2$) C, H, N.

1-[5-[5-Chloro-1-methyl-2-(3-pyridinyl)-1*H*-indol-3-yl]pentanoyl]piperidin-4-one (10). To a 0 °C solution of **1a**[8] (3.0 g, 8.8 mmol), 4-piperidone monohydrate HCl (0.96 g, 6.3 mmol), and TEA (0.96 mL, 6.9 mmol) in 175 mL of CH_2Cl_2 was added EDCI (3.59 g, 19 mmol). The mixture was stirred at room temperature overnight, concentrated, and diluted with Et_2O and H_2O. The organic layer was washed with H_2O (3×) and $NaHCO_3$ (1×), dried, concentrated, and flash chromatographed on SiO_2 eluting with 5% $MeOH/CH_2Cl_2$ to give 1.81 g of **10**. ^1H NMR ($CDCl_3$): δ 8.7 (m, 2 H), 7.8 (d, J = 9 Hz, 1 H), 7.57 (s, 1 H), 7.55 (m, 1 H), 7.2 (m, 2 H), 3.84 9 t, J = 6 Hz, 2 H), 3.7 (t, J = 6 Hz, 2 H), 3.56 (s, 3 H), 3.95 (s, 3 H), 2.62 (t, J = 6 Hz, 2 H), 2.42 (t, J = 6 Hz, 4 H), 2.3 (t, J = 6 Hz, 2 H), 1.5 (m, 6 H).

2-[[1-(Carboxymethyl)-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3-yl]amino]-6-[[1-[5-[5-chloro-1-methyl-2-(3-pyridinyl)-1*H*-indol-3-yl]pentanoyl]piperidin-4-yl]amino]hexanoic Acid (11). To a solution of **10** (470 mg, 1.09 mmol) in 2 mL of MeOH was added **1** (200 mg, 0.56 mmol) in 4 mL of acetic acid. The cloudy solution was stirred at room temperature for 1 h, $NaBH_3CN$ (102 mg, 1.63 mmol) in 2 mL of methanol was added over a 4-h period using a syringe pump, and the reaction mixture was stirred overnight. The reaction was quenched with 4 mL of 1 N HCl. The mixture stood for 30 min. The solvent was removed under reduced pressure, sodium bicarbonate added, and the aqueous phase extracted 3 times with EtOAc. The sodium bicarbonate solution was concentrated and chromatographed on a reverse-phase column (C-18 resin) eluting with water to remove 1 followed by 75% methanol/H_2O to give 250 mg of **11** isolated as the disodium salt which contained small amounts of $NaHCO_3$. An analytical sample was prepared by repeating the reverse-phase column, mp 164–166 °C. ^1H NMR (CD_3OD): δ 8.6 (m, 2 H), 7.9 (m, 1 H), 7.6 (m, 1 H), 7.55 (s, 1 H), 7.19 (d, J = 7 Hz, 1 H), 7.1 (m, 5 H), 4.38 (ABq, J = 12 and 74 Hz, 2 H), 4.42 (d, J = 11 Hz, 1 H), 3.84 (d, J = 11 Hz, 1 H), 3.57 (s, 3 H), 3.4 (m, 1 H), 3.0 (t, J = 11 Hz, 2 H), 2.9 (t, J = 6 Hz, 1 H), 2.6–1.1 (m, 27 H). Anal. ($C_{43}H_{51}N_6O_6ClNa_2$) C, H, N.

2-[4-(Ethoxycarbonyl)-8-(5-imidazo[1,5-*a*]pyridinyl)octanoyl]-2,3-dihydro-1*H*-1-isoindole-1-carboxylic Acid Methyl Ester (16). To a 0 °C solution of **15** (250 mg, 0.79 mmol) and indoline-(2*S*)-carboxylic acid methyl ester (170 mg, 0.94 mmol) in 4 mL of methylene chloride was added DCC (240 mg, 1.2 mmol). The reaction mixture was stirred overnight and filtered, CH_2Cl_2 was added, and the organic layer was washed with $NaHCO_3$ and brine, concentrated, and chromatographed on SiO_2 eluting with 2:1 EtOAc/hexane to give 240 mg of **16**. ^1H NMR ($CDCl_3$): δ 8.0 (s, 1 H), 7.3 (d, J = 8 Hz, 2 H), 7.1 (m, 1 H), 7.07 (s, 1 H), 6.6 (d, J = 9 Hz, 1 H), 6.5 (d, J = 9 Hz, 1 H), 6.35 (s, 1 H), 6.21 (s, 1 H), 4.8 (m, 1 H), 4.1 (q, J = 7 Hz, 2 H), 3.75 (s, 3 H), 3.3 (m, 1 H), 2.8 (m, 2 H), 2.4 (m, 2 H), 2.2–1.0 (m, 7 H), 1.25 (t, J = 7 Hz, 3 H).

2-[4-Carboxy-8-(5-imidazo[1,5-*a*]pyridinyl)octanoyl]-2,3-dihydro-1*H*-1-isoindole-1-carboxylic Acid (17). To a 0 °C solution of **16** (110 mg, 0.22 mmol) in 10 mL of EtOH was added 10 mL of 2.5 N KOH. The reaction mixture was stirred for 90 min and then the reaction neutralized with 1 N HCl. The mixture was concentrated and the residue taken up in water and chromatographed on a revers-phase column eluting with H_2O/MeOH (increasing methanol from 5% to 40%) to give 40 mg of **17**, mp 114–124 °C. ^1H NMR (CD_3OD): δ 8.56 (d, J = 5 Hz, 1 H), 8.14 (d, J = 8 Hz, 1 H), 7.5 (s, 1 H), 7.47 (d, J = 8 Hz, 1 H), 7.2 (m, 2 H), 7.0 (m, 1 H), 6.9 (m, 1 H), 6.62 (d, J = 7 Hz, 1 H), 5.07 (m, 1 H), 3.6 (m, 1 H), 2.9 (m, 2 H), 2.5–1.5 (m, 12 H). Anal. ($C_{25}H_{27}N_3O_5 \cdot H2O$) C, H, N.

[4-[3-Methyl-2-(3-pyridinyl)-1*H*-indol-1-yl]butyl]phosphonic Acid Diethyl Ester (18a). To a hexane-washed suspension of NaH (0.25 g, 5.3 mmol, 50% oil dispersion) in 5 mL of DMF was added 2-pyridyl-3-methylindole (1.0 g, 4.8 mmol) in 5 mL of DMF dropwise. The mixture was stirred for 1 h at room temperature under an atmosphere of nitrogen. Diethyl (4-chlorobutyl)phosphonate (1.1 g, 4.8 mmol) and NaI (0.072 g, 0.48 mmol) were added, and the mixture was heated to 70 °C overnight. The DMF was removed under reduced pressure and the residue partioned between Et_2O and H_2O. The ether layer was washed (2×) with H_2O, dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 eluting with 95:5 CH_2Cl_2/CH_3OH to give 1.2 g of **18a** as an oil. ^1H NMR ($CDCl_3$): δ 8.75 (m, 2 H), 7.1–7.8 (m, 6 H), 4.0 (q, J = 7.5 Hz, 4 H), 4.10 (t, J = 8 Hz, 2 H), 2.2 (s, 3 H), 1.5 (m, 6 H), 1.2 (t, J = 7.5 Hz, 6 H).

[4-[3-Methyl-2-(3-pyridinyl)-1*H*-indol-1-yl]butyl]phosphonic Acid (18b). To a room-temperature solution of **18a** (1.05 g, 2.62 mmol) was added iodotrimethylsilane (1.0 g, 5.2 mmol) in 30 mL of CH_2Cl_2. The reaction mixture was stirred for 17 h and the reaction quenched with 10 mL of H_2O followed by stirring for an additional 2 h. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated. The residue was triturated with Et_2O and the solid collected and recrystallized from acetone

to give 0.43 g of solid **18b**, mp 194–196 °C. ^{1}H NMR (DMSO-d_6): δ 8.75 (s, 1 H), 8.73 (s, 1 H), 7.90 (d, J = 8 Hz, 1 H), 7.55 (m, 3 H), 7.2 (t, J = 8 Hz, 1 H), 7.1 (t, J = 8 Hz, 1 H), 4.95 (t, J = 7 Hz, 2 H), 2.15 (s, 3 H), 1.55 (t, J = 8 Hz, 2 H), 1.3 (m, 4 H). Anal. ($C_{18}H_{21}N_2O_3P$) C, H, N.

[4-[3-Methyl-2-(3-pyridinyl)-1*H*-indol-1-yl]butyl]phosphonic Acid Monoethyl Ester (18c). A mixture of **18a** (0.18 g, 0.45 mmol) and 1 mL of 10% NaOH was refluxed for 90 min. The mixture was cooled, 2.5 mL of 1 N HCl added, and the mixture extracted twice with CH_2Cl_2. The organic layer was washed with H_2O, dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in 5 mL of EtOAc, filtered, treated with dry HCl gas, and concentrated. The residue was stirred with Et_2O and the solid collected and dried under high vacuum to give 45 mg of **18c**, mp 60–62 °C. ^{1}H NMR (DMSO-d_6): δ 8.9 (s, 1 H), 8.83 (d, J = 6 Hz), 8.38 (d, J = 8 Hz, 1 H), 7.92 (t, J = 8 Hz, 1 H), 7.59 (t, J = 8 Hz, 3 H), 7.15 (t, J = 8 Hz, 1 H), 7.10 (t, J = 8 Hz, 1 H), 4.1 (t, J = 7 Hz, 2 H), 3.8 (q, J = 8 Hz, 2 H), 2.20 (s, 3 H), 1.5 (t, J = 7 Hz, 2 H), 1.3 (m, 4 H), 1.1 (t, J = 8 Hz, 3 H). Anal. ($C_{20}H_{26}ClN_2O_3P$) C, H, N.

(4-Phenylbutyl)phosphonic Acid Benzyl 2-Oxo-1,2,3,4,5,7-hexahydrocyclohept[*b*]azepin-3-yl Ester (19). Cesium carbonate (0.557 g, 1.7 mmol) and (4-phenylbutyl)phosphonic acid benzyl ester (1.04 g, 3.4 mmol) were dissolved in 30 mL of hot MeOH, and 3-bromo-1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one[8] (0.82 g, 3.4 mmol) in 10 mL of DMF was added. The mixture was heated at 55 °C for 50 h. The DMF was removed under reduced pressure. The residue was extracted with Et_2O/EtOAc (1:1) and the organic layer washed with $NaHCO_3$ and saturated NaCl, dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 eluting with toluene/EtOAc (1:2) to give 840 mg of diester diastereomers **19**. ^{1}H NMR ($CDCl_3$): δ 7.7 (s, 1 H), 7.0–7.4 (m, 13 H), 6.9 (d, J = 7 Hz, 1 H), 5.1 (m, 2 H), 4.87 (ABq, J = 7 and 7 Hz, 1 H), 2.95 (m, 1 H), 2.6 (m, 4 H), 2.3 (m, 1 H), 1.7 (m, 6 H).

[3-[[(Benzyloxy)(4-phenylbutyl)phosphinoyl]oxy]-2-oxo-3,4,5,7-tetrahydro-2*H*-cyclohept[*b*]azepin-1-yl]acetic Acid Benzyl Ester (20). A mixture of **19** (410 mg, 0.88 mmol), benzyl bromoacetate (203 mg, 0.88 mmol), and K_2CO_3 (0.60 mg, 4.4 mmol) in 8 mL of acetone was stirred for 30 h. The mixture was concentrated and extracted with EtOAc/Et_2O (1:1), and the organic layer was washed with $NaHCO_3$ and saturated NaCl, dried ($MgSO_4$), filtered, concentrated, and chromatographed on SiO_2 eluting with EtOAc/toluene (1:1) to give 0.49 g of **20** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.3–7.0 (m, 19 H), 5.1 (s, 2 H), 5.05 (m, 1 H), 4.95 (m, 3 H), 4.80 (2 doublets, J = 3 Hz, 1 H), 2.5–2.1 (m, 5 H), 2.0–1.1 (m, 6 H).

[3-[(Benzyloxy)(4-phenylbutyl)phosphinoxy]-2-oxo-3,4,5,7-tetrahydro-2*H*-cyclohept[*b*]azepin-1-yl]acetic Acid (21a). A suspension of **20** (480 mg) and 5% Pd–C (250 mg) in 25 mL of absolute EtOH was hydrogenated at 1 atm pressure for 3 h. The solution was filtered through a pad of Celite and concentrated to give 300 mg of colorless oil. The diacid was converted to the disodium salt by treatment with 2 equiv of NaOH in MeOH. The solution was evaporated to dryness and suspended in Et_2O. The solid was collected and dried at 50 °C under high vacuum to give 270 mg of colorless solid **21a**, mp 215–220 °C. ^{1}H NMR (DMSO-d_6): δ 8.7 (br s, 2 H), 7.4–7.0 (m, 9 H), 4.8 (m, 2 H), 4.2 (m, 1 H), 3.0–2.0 (m, 6 H), 1.9–1.4 (m, 6 H). Anal. ($C_{22}H_{24}NNa_2O_6P\cdot H_2O$) C, H, N.

[3-[[Hydroxy[4-[3-methyl-2-(3-pyridinyl)indol-1-yl]butyl]-phosphinyl]oxy]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-1-yl]acetic Acid (21b) was prepared in a similar manner as described for **21a**: mp 132–135 °C, m/z 590 (thermospray ionization MS after treatment with diazomethane). ^{1}H NMR (DMSO-d_6/D_2O): δ 8.65 (br s, 2 H), 7.9 (d, J = 7 Hz, 1 H), 7.54 (m, 2 H), 7.49 (d, J = 7 Hz, 1 H), 7.3 (m, 4 H), 7.18 (t, J = 5 Hz, 1 H), 7.08 (t, J = 5 Hz, 1 H), 4.46 (ABq, J = 15 and 28 Hz, 2 H), 4.57 (m, 1 H), 4.05 (m, 2 H), 2.25 (s, 3 H), 3.0–1.0 (mutiplets, 12 H).

[3-[[(1,1-Dimethylethoxy)carbonyl]amino]-2,3,4,5-tetrahydro-2,5-dioxo-1*H*-1-benzazepin-1-yl]acetic Acid 1,1-Dimethyl Ethyl Ester (25). To a solution of **24** (2.25 g, 7.75 mmol) and potassium carbonate (2.25 g) in 150 mL of acetone was added *tert*-butyl bromoacetate (2.20 g, 11.0 mmol). The mixture was stirred for 16 h and concentrated. The residue was slurried with toluene, filtered, dried ($MgSO_4$), filtered, and concentrated to give 3.35 g of **25** as a thick oil. ^{1}H NMR ($CDCl_3$): δ 7.7–7.1 (m, 4 H), 5.75 (d, J = 7 Hz, 1 H), 4.9 (m, 1 H), 4.4 (ABq, J = 18 and 30 Hz, 2 H), 3.1 (m, 2 H), 1.3 (s, 18 H).

[3-[[(1,1-Dimethylethoxy)carbonyl]amino]-2,3,4,5-tetrahydro-5-hydroxy-2-oxo-1*H*-1-benzazepin-1-yl]acetic Acid 1,1-Dimethylethyl Ester (26). To a 0 °C solution of **25** (3.35 g, 8.3 mmol) in 100 mL of methanol was added sodium borohydride (0.31 g, 8.3 mmol). The reaction mixture was stirred for 1 h at 0 °C, the reaction quenched with acetic acid and then H_2O, and the mixture concentrated. The residue was extracted with EtOAc and washed with $NaHCO_3$ and brine. The organic layer was concentrated and chromatographed on SiO_2 eluting with toluene/EtOAc 3:1 to give 1.9 g of **26** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.6 (m, 1 H), 7.3 (m, 2 H), 7.1 (m, 1 H), 5.5 (2 overlapping multiplets, 2 H), 4.4 (ABq, J = 15 and 152 Hz, 2 H), 4.15 (m, 1 H), 2.5–2.3 (m, 2 H), 1.42 (s, 9 H), 1.36 (s, 9 H).

[5-Acetoxy-3-[[(1,1-dimethylethoxy)carbonyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-1-yl]acetic Acid 1,1-Dimethyl Ethyl Ester (27). To a solution of **26** (1.0 g, 246 mmol), pyridine (5 mL), and DMAP (0.70 g, 5.7 mmol) in 25 mL of methylene chloride was added 5 mL of acetic anhydride. The mixture was stirred for 4 h and the reaction quenched with 50 mL of 1:1 MeOH/EtOAc. The reaction mixture was concentrated to dryness and the residue taken up in EtOAc. The organic layer was extracted with 0.5 M citric acid, H_2O, $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated to give 1.02 g of **27**, mp 166–168 °C. ^{1}H NMR ($CDCl_3$): δ 7.3 (m, 4 H), 6.4 (t, J = 10 Hz, 1 H), 5.7 (d, J = 7 Hz), 4.4 (ABq, J = 15 and 18 Hz, 2 H), 4.2 (m, 1 H), 2.5 (m, 2 H), 2.15 (s, 3 H), 1.4 (s, 18 H).

(5-Acetoxy-3-amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-1-yl)acetic Acid (28). To a solution of **27** (0.93 g) in 100 mL of methylene chloride was added HCl gas for 10 min. The solution sat overnight, was concentrated, and then, triturated with ether to give 750 mg of **28**, mp 121–126 °C. The hydrochloride salt was used as obtained is in the next step.

2-[[5-Acetoxy-1-(carboxymethyl)-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3-yl]amino]-4-phenylbutanoic Acid Ethyl Ester (29). A mixture of **28** (1.33 g, 4.05 mmol), ethyl 4-phenyl-2-ketobutanoate (2.5 g, 2.02 mmol) ,and sodium acetate (1.0 g, 4.0 mmol) were dissolved in 20 mL of 1:1 glacial acetic acid/EtOH. The mixture was gently refluxed and then cooled to room temperature. Sodium cyanoborohydride (0.50 g, 8.0 mmol) in 10 mL of cold EtOH was added in 1-mL portions, each over a 30-min period. The mixture was stirred overnight. To the reaction mixture was added another portion of ethyl 4-phenyl-2-ketobutanoate (2.5 g, 2.02 mmol) in 5 mL of glacial acetic acid. Another portion of sodium cyanoborohydride (0.50 g, 8.0 mmol) was added as before. The mixture was stirred overnight and the reaction quenched with 25 mL of 2 N HCl. The solvent was concentrated and the residue diluted with 100 mL of sodium bicarbonate and 400 mL of ether. The organic layer was extracted three times with aqueous sodium bicarbonate. The basic aqueous extracts were combined and washed with ether to remove neutral organics. The basic layer was acidified with 50 mL of glacial acetic acid and extracted with Et_2O/EtOAc. The organic layer was dried ($MgSO_4$) and concentrated to give 1.15 g of yellow oil **29** as a mixture of diastereomers. The mixture of diastereomers was carried on and separated at compound **31**.

2-[[5-Hydroxy-1-(carboxymethyl)-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3-yl]amino]-4-phenylbutanoic Acid (30). Aqueous sodium hydroxide (1.0 N, 15 g) was added to **29** (1.15 g, 2.4 mmol) and the mixture stirred overnight. Aqueous hydrochloric acid (1.0 N, 14.5 g) was added and the mixture concentrated under high vacuum. The residue was stirred with 200 mL of hot 9:1 CH_2Cl_2/MeOH, dried (Na_2SO_4), and filtered through a pad of Celite. The organics were concentrated to give 1.1 g of **30** as a yellow oil. The crude product was used in the next reaction.

2-[[1-[[(Benzyloxy)carbonyl]methyl]-2,3,4,5-tetrahydro-5-hydroxy-2-oxo-1*H*-1-benzazepin-3-yl]amino]-4-phenylbutanoic Acid Benzyl Ester (31). A suspension of **30** (1.01 g, 2.45 mmol) and cesium carbonate (798 mg, 2.45 mmol) in 50 mL of absolute methanol was gently refluxed for 1 min. The solution was concentrated, and the solid cesium salt was dried under high vacuum overnight. The cesium salt was dissolved in 20 mL of

DMF, benzyl bromide (838 mg, 4.9 mmol) was added, and the mixture was stirred overnight at room temperature. The DMF was removed under high vacuum. The crude mixture was chromatographed on SiO_2 eluting with 70% toluene and 30% EtOAc to give 170 mg of the undesired diastereomer, 60 mg of mixed fractions, and 300 mg of **31** (R_f, 0.12) as a colorless oil. ^1H NMR ($CDCl_3$): δ 7.6 (m, 1 H), 7.4–6.9 (m, 18 H), 5.27 (dd, J = 7 and 11 Hz, 1 H), 5.1–4.9 (multiplets, 5 H), 4.55 (ABq, J = 14 and 120 Hz, 2 H), 3.3 (m, 2 H), 2.61 (t, J = 7 Hz, 2 H), 2.5 (m, 1 H), 2.3 (m, 1 H), 2.0 (m, 2 H).

2-[[1-[(Benzyloxy)carbonyl]methyl]-2,3,4,5-tetrahydro-5-acetoxy-2-oxo-1*H*-1-benzazepin-3-yl]amino]-4-phenylbutanoic Acid Benzyl Ester (32). To a flask containing **31** (130 mg, 0.19 mmol), DMAP (27 mg, 0.19 mmol), and EDCI (84 mg, 0.38 mmol) was added acetic acid (26 mg, 0.38 mmol) in 4 mL of CH_2Cl_2. The reaction mixture was stirred at room temperature overnight, diluted with Et_2O/EtOAc (1:1), and washed three times with H_2O and brine. The organic layer was dried ($MgSO_4$) and concentrated to give 130 mg of **32** as a yellow oil. ^1H NMR ($CDCl_3$): δ 7.4–7.0 (m, 19 H), 6.3 (t, J = 9 Hz, 1 H), 5.12, 5.0 (2 overlapping ABq, 4 H), 4.57 (ABq, J = 14 and 42 Hz), 3.34 (m, 2 H), 2.64 (t, J = 7 Hz, 2 H), 2.45 (m, 2 H), 2.15 (s, 3 H), 2.0 (m, 2 H).

2-[[5-Acetoxy-1-(carboxymethyl)-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3-yl]amino]-4-phenylbutanoic Acid (33a). To a solution of **32** (130 mg, 0.2 mmol) in 20 mL of 1:1 EtOAc/EtOH was added 200 mg of 5% Pd–C. The suspension was hydrogenated at atmospheric pressure for 3 h. The mixture was filtered through Celite, concentrated, and triturated with Et_2O to give 70 mg of **33a**, mp 147–149 °C. ^1H NMR (DMSO-d_6): δ 7.5–7.1 (m, 9 H), 6.27 (t, J = 7 Hz, 1 H), 4.37 (ABq, J = 14 and 38 Hz, 2 H), 3.19 (t, J = 11 Hz, 1 H), 3.02 (t, J = 7 Hz, 1 H), 2.6 (t, J = 7 Hz, 2 H), 2.4 (m, 2 H), 2.15 (s, 3 H), 1.75 (m, 2 H). Anal. ($C_{24}H_{24}N_2Na_2O_7$) C, H, N.

Prepared in a similar manner were the following compounds.

2-[[1-(Carboxymethyl)-2,3,4,5-tetrahydro-5-hydroxy-2-oxo-1*H*-1-benzazepin-3-yl]amino]-4-phenylbutanoic Acid (33b). Mp: 168–170 °C. ^1H NMR (DMSO-d_6): δ 7.48 (d, J = 7 Hz, 1 H), 7.3–7.1 (m, 9 H), 5.33 (t, J = 10 Hz, 1 H), 4.2 (ABq, J = 16 and 34 Hz, 2 H), 3.19 (t, J = 9 Hz, 1 H), 2.97 (t, J = 7 Hz, 1 H), 2.6 (t, J = 7 Hz, 2 H), 2.5 (s, 1 H), 2.25 (m, 1 H), 2.05 (m, 1 H), 1.77 (m, 2 H). Anal. ($C_{22}H_{24}N_2O_6$) C, H, N.

8-[2-(3-Pyridinyl)-1*H*-indol-1-yl]octanoic Acid 1-(Carboxymethyl)-3-[(1-carboxy-3-phenylpropyl)amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-5-yl Ester (33c). Mp: 114–119 °C. ^1H NMR (DMSO-d_6): δ 8.25 (s, 2 H), 7.75 (d, J = 7 Hz, 1 H), 7.57 (d, J = 7 Hz, 2 H), 7.48 (d, J = 7 Hz, 1 H), 7.4–7.0 (m, 11 H), 6.25 (m, 1 H), 4.38 (ABq, J = 14 and 37 Hz, 2 H), 4.04 (t, J = 6 Hz, 2 H), 3.2–2.9 (m, 2 H), 2.6 (t, J = 8 Hz, 1 H), 2.5 (s, 1 H), 2.34 (t, J = 5 Hz, 2 H), 2.15 (s, 3 H), 2.4–2.1 (m, 2 H), 1.7 (m, 2 H), 1.45 (m, 4 H), 1.1 (m, 8 H). Anal. ($C_{44}H_{48}N_4O_7 \cdot H_2O$) C, H, N.

Acknowledgment. We are grateful to Karl Gunderson for ^1H NMR spectra and Michael Hatolski for IR spectra. We are also grateful to Dr. Raj Ghai, Ms. Yumi Sakane, Ms. Carol Berry, and Mr. Warren Lee for *in vitro* measurements.

References

(1) (a) Sweet, C. S.; Blaine, E. H. Angiotensin converting enzyme and renin inhibitors. *Cardiovascular Pharmacology*, 2nd ed.; Raven Press: New York, 1984; pp 119–154. (b) Salvetti, A. Newer ACE inhibitors A look at the future. *Drugs* **1990**, *40*, 800–828.

(2) (a) Barton, J. N.; Plwinski, J. J.; Skiles, J. W.; Regan, J. R.; Menard, P. R.; Desai, R.; Golec, F. S.; Reilly, L. W.; Goetzen, T.; Ueng, S. N.; Warus, J. D.; Schwab, A.; Samuels, A. I.; Neiss, E. S.; Suh, J. T. Angiotensin-converting enzyme inhibitors. 9. Novel [[*N*-(1-carboxy-3-phenyl-propyl)amino]acyl] glycine derivatives with diuretic activity. *J. Med. Chem.* **1990**, *33*, 1600–1606. (b) Mencel, J. J.; Regan, J. R.; Barton, J.; Menard, P. R.; Bruno, J. G.; Calvo, R. R.; Kornberg, B. E.; Schwab, A.; Neiss, E. S.; Suh, J. T. Angiotensin converting enzyme inhibitors. 10. Aryl sulfonamide substituted *N*-[1-carboxy-3-phenylpropyl]-L]alanyl-L-proline derivatives as novel antihypertensives. *J. Med. Chem.* **1990**, *33*, 1606–1615. (c) Kudo, K.; Abe, K.; Saturo, C.; Sato, M.; Yasujima, M.; Kohzuki, M.; Omata, K.; Tanno, M.; Tsunoda, K.; Yoshinaga, K. Role of thromboxane A_2 in the hypotensive effect of captopril in essential hypertension. *Hypertension.* **1988**, *11*,147–152. (d) Everett, D. W.; Singhvi, S. M.; DeForrest, J. M.; Morrison, R. A.; Weinstein, S. H.; Migdalof, B. H.; *Drug Des. Delivery* **1987**, *2*, 22–34. (e) DeForrest, J. M.; Waldron, T. L.; Powell, J. R.; Floyd, D. M.; Sundeen, J. E. SQ 27,786 and SQ 28,853: Two Angiotensin Converting Enzyme Inhibitors with Potent Diuretic Activity. *J. Cardiovasc. Pharmacol.* **1987**, *9*, 154–159. (f) Middlefell, V. C.; Ennis, C.; Ward, T. J.; *Cardiovasc. Drug Rev.* **1990**, *8*, 117–131. (g) Allan, G.; Cambridge, D.; Hardy, G. W.; Follenfant, M. J. BW A575C, a chemically novel agent with ACEI and beta-adrenoceptor blocking properties. *Br. J. Pharmacol.* **1987**, *90*, 609–615. (h) Chan, C.; Ford-Hutchinson, A. *Eur. J. Pharmacol.* **1985**, *110*, 323–328. (i) Hardy, G. W.; Allan, G. *Drugs Future* **1988**, *13*, 3.

(3) (a) Grone, H. J.; Grippo, R. S.; Arendshort, W. J.; Dunn, M. F. Role of thromboxane in control of arterial pressure and renal function in young spontaneously hypertensive rats. *Am. J. Physiol.* **1986**, *250*, F488–F496. (b) Shibouta, Y.; Terashita, Z.; Inada, Y.; Kato, K.; Nishikawa, K. Renal effects of pinane-thromboxane A_2 and indomethacin in saline volume-expanded spontaneously hypertensive rats. *Eur. J. Pharmacol.* **1992**, *85*, 51–59.

(4) (a) Underman, H. D.; Jackson, E. K.; Puett, D.; Workman, R. J. Thromboxane synthase inhibitor UK 38,485 lowers blood pressure in the adult spontaneously hypertensive rat. *J. Cardiovasc. Pharmacol.* **1984**, *6*, 969–972. (b) Underman, H. D.; Workman, R. J.; Jackson, E. K. Attenuation of the development of hypertension in spontaneously hypertensive rats by the thromboxane synthase inhibitor, 4′-(imidazol-1-yl)acetophenone. *Prostaglandins* **1982**, *24*, 237–244.

(5) (a) Mullane, K. M.; Moncada, S. PGI_2 mediates the potentiated hypotensive effect of bradykinin following captopril treatment. *Eur. J. Pharmacol.* **1980**, *66*, 355–365. (b) McGiff, J. C.; Itskovitz, H. D.; Terrango, N. A. The actions of bradykinin and eledoisin in the canine isolated kidney: Relationships to prostaglandins. *Clin. Sci. Mol. Med.* **1975**, *49*, 125–131. (c) Murthy, V. S.; Waldron, T.; Goldbert, M. E. The mechanism of bradykinin potentiation after inhibition of angiotensin converting enzyme by SQ 14,225 in concious rabbits. *Circ. Res.* **1978**, *43* (Suppl. 1), 1–40.

(6) Levens, N. R.; Ksander, G. M.; Zimmerman, B. G.; Mullane, K. M. Thromboxane synthase inhibition enhances action of converting enzyme inhibitors. *Hypertension* **1989**, *13*, 51–62.

(7) Levens, N.; Cote, D.; Ksander, G. Inhibition of thromboxane synthase potentiates the antihypertensive action of an ACE inhibitor by a prostaglandin dependant but kinin independant mechanism. *J. Pharmacol. Exp. Ther.* **1991**, *259*, 219.

(8) Stanton, J. L.; Watthey, J. W. H.; Desai, M. N.; Finn, B. M.; Babiarz, J. E.; Tomaselli, H. C. Angiotensin converting enzyme inhibitors: Structure-activity profile of 1-benzazepin-2-one derivatives. *J. Med. Chem.* **1985**, *28*, 1603–1606.

(9) (a) Renfroe, H. B. Eur. Pat. Appl. EP 129051, Dec 27, 1984. (b) Olson, R. W.; Cohen, D. S.; Ku, E. C.; Kimble, E. F.; Renfroe, H. B.; Smith, E. F., III. *Eur. J. Pharmacol.* **1987**, *133*, 265–273.

(10) Karanewsky, D. S.; Badia, M. C.; Cushman, D. W.; DeForrest, J. M.; Dejneka, T.; Loots, M. J.; Perri, M. G.; Petrillo, E. W., Jr.; Powell, J. R. (Phosphinyloxy)acyl amino acid inhibitors of angiotensin converting enzyme (ACE) 1. Discovery of (*S*)-1-[6-amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline, a novel orally active inhibitor of ACE. *J. Med. Chem.* **1988**, *31*, 204–212.

(11) Watthey, J. W. H.; Stanton, J. L.; Desai, M.; Babiarz, J. E.; Finn, B. M. Synthesis and biological properties of (carboxyalkyl)amino-substituted bicyclic lactam inhibitors of angiotensin converting enzyme. *J. Med. Chem.* **1985**, *28*, 1511–1516.

(12) Renfroe, H. B. U.S. Patent Appl. 4478842, Nov 1, 1982.

(13) Ku, E. C.; McPherson, S. E.; Signor, C.; Chertock, H.; Cash, W. D. Characterization of imidazo[1,5-a]pyradine-5-arcanoic acid (CGS 13080) as a selective thromboxane synthetase inhibitor using *in vitro* biochemical models. *Biochem. Biophys. Res. Commun.* **1983**, *112*, 899.

(14) Cheung; Cushman. *Biochim. Biophys. Acta* **1973**, *293*, 451.