mM substrate in a total volume of 2.5 mL. At various times up to 30 min, aliquots (0.3 mL) were removed and quenched with MeOH (4.7 mL). After centrifugation (5000*g*, 10 min), the samples were diluted (1:1) with 0.01 M KH_2PO_4 and 20 μL of the resulting solution was injected directly onto the HPLC column for analysis.

$K_{M(app)}$ and V_{max} Determinations. The $K_{M(app)}$–V_{max} for the hydrolysis of *p*-NP-glc and *p*-NP-gal were determined with use of pooled cecal homogenates (200 mL) as described above. A range of substrate concentrations (56–1000 μM, final volume 2.25 mL), spanning their apparent K_M, was used for each reaction. The amount of cecal homogenate used was 0.04 mL. Reaction mixtures were incubated, in duplicate at 37 °C in a shaking water bath, and the reaction was stopped by addition of 0.2 N NaOH (0.25 mL) after 15 min. Release of *p*-nitrophenol was measured spectrophotometrically at 403 nm. Eadie–Hofstee plots were used to determine the $K_{M(app)}$ (μM) and V_{max} (μmol min^{-1} g^{-1}) of both reactions. The wet weight (g), measured immediately after removal and pooling, was used throughout.

The $K_{M(app)}$ and V_{max} were also measured for the hydrolysis of glycoside prodrugs **1**, **2**, **5**, **7**, and **9**–**12**. Again, cecal contents from four rats were pooled, weighed, diluted (100 mL, 0.01 μM phosphate buffer, pH 7.0), and homogenized. A range of substrate concentrations (0.5–48 μM, final volume 2.5 mL) spanning the apparent K_M was used for each reaction. The amount of cecal homogenate used was 0.8 mL. Reactions were run, in duplicate, at 37 °C in a shaking water bath. After 15 min, the reactions were stopped by removing aliquots (0.3 mL) and quenching them with MeOH (4.7 mL). Following centrifugation (5000*g*, 10 min), the samples were diluted (1:1) with 0.01 M KH_2PO_4 and 20 μL of the resulting solution was injected directly onto the HPLC column for analysis. Eadie–Hofstee plots were used to determine the $K_{M(app)}$ and V_{max}.

Determination of Apparent Partition Coefficients. The partitioning of prodrugs and free steroids between 1-octanol and an aqueous phase (0.01 M phosphate buffer, pH 7.0) were determined at 37 °C. Both octanol and buffer were saturated with the relevant aqueous or organic phase before use. Equal volumes (1.0 mL) of both phases were used and agitated for 30 min. The initial concentration of glycoside was 10 mM, dissolved in the aqueous phase. The initial concentration of steroid was 10 mM dissolved in the organic phase. The amount of glycoside and free steroid in the aqueous phase at equilibrium was measured spectrophotometrically at 239 nm for the dexamethasone and fludrocortisone compounds and 242 nm for the prednisolone and hydrocortisone compounds. The concentration of glycoside or free steroid in the octanol phase was determined by difference.

Note Added in Proof: After this manuscript was accepted, the authors learned of an earlier publication describing the synthesis of steroid glycoside prodrugs for release in the synovial fluid of arthritis victims (Hirschmann, R., Strachan, R. G.; Buchschacher, P.; Sarett, L. H.; Steelman, S. L.; Silber, R. *J. Am. Chem. Soc.* **1964**, *86*, 3903).

Acknowledgment. This work was supported by National Institutes of Health Training Grant GM07379, National Science Foundation Grant PCM19105, and the Cancer Research Coordinating Committee of the University of California, Berkeley.

Registry No. **1**, 88158-43-4; **2**, 88158-44-5; **3**, 50-02-2; **4**, 50-24-8; **5**, 92901-21-8; **6**, 50-23-7; **7**, 92901-22-9; **8**, 127-31-1; **9**, 92901-23-0; **10**, 92901-24-1; **11**, 92901-25-2; **12**, 92901-26-3; **13**, 92901-27-4; **16**, 92901-28-5; **17**, 92901-29-6; **18**, 92901-30-9; **19**, 92901-31-0; **20**, 92937-53-6; **21**, 92901-32-1; **22**, 92901-33-2; **23**, 572-09-8; **24**, 3068-32-4; **25**, 14227-66-8; β-D-glucosidase, 9001-22-3; β-D-galactosidase, 9031-11-2.

Angiotensin-Converting Enzyme Inhibitors. New Orally Active Antihypertensive (Mercaptoalkanoyl)- and [(Acylthio)alkanoyl]glycine Derivatives[1]

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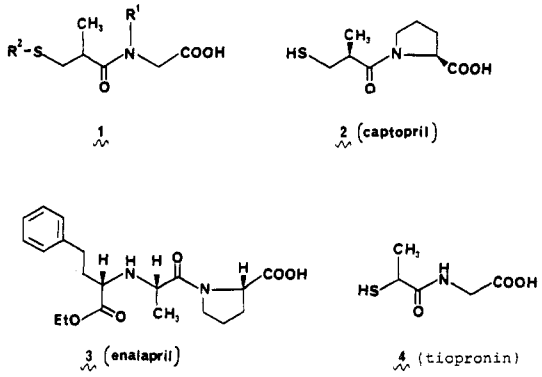
A variety of N-substituted (mercaptoalkanoyl)- and [(acylthio)alkanoyl]glycine derivatives was synthesized and their ability in inhibiting the activity of angiotensin-converting enzyme (ACE) was examined in vitro and in vivo. The acylthio derivatives prepared are assumed to act as prodrugs since they are much less active than the corresponding free SH compounds in vitro and can be expected to act in vivo only after conversion to the free sulfhydryl compounds. A number of these compounds are potent ACE inhibitors that lowered blood pressure in Na-deficient, conscious spontaneously hypertensive rats (SHR), a high renin model. One of the most active members of the series was (*S*)-*N*-cyclopentyl-*N*-[3-[(2,2-dimethyl-1-oxopropyl)thio]-2-methyl-1-oxopropyl]glycine (REV 3659-(S), pivopril). Structure–activity relationships are discussed.

The renin–angiotensin–aldosterone system is an important humoral mechanism involved in the regulation of blood pressure[2-4] and renal function.[5] In particular, the development of antihypertensive drugs that act selectively by inhibiting angiotensin-converting enzyme[6,7] (ACE) has received much attention in recent years. Recently orally active ACE inhibitors have been reported to show promising clinical antihypertensive properties.[8-14] We now report the design and synthesis[15] of an orally active novel series of substituted (mercaptoalkanoyl)glycines of generic formula **1**. Unlike the known inhibitors such as captopril (**2**)[6a,b] and enalapril (**3**),[7e] which embody a C-terminal proline, this series of compounds contains exclusively the nonchiral amino acid glycine.



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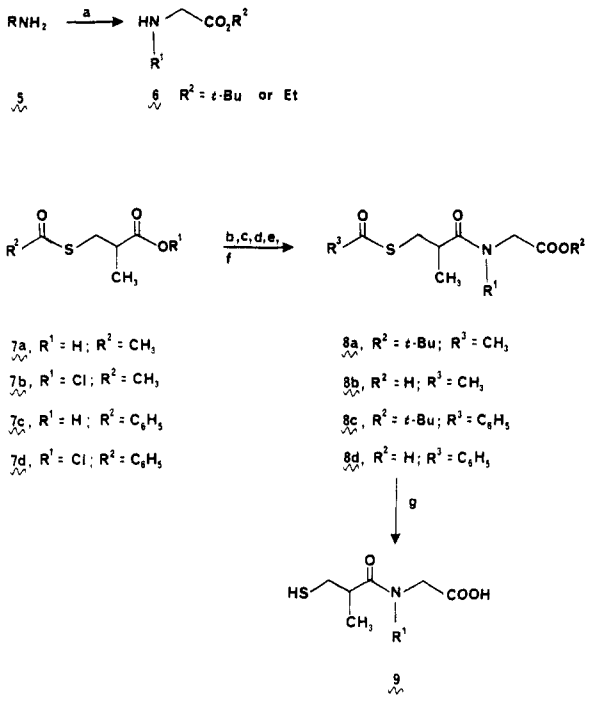
During the course of our investigation we observed that *N*-(2-mercaptopropionyl)glycine (**4**; tiopronin)[16] is a moderately active inhibitor (IC_{50} = 1.9 μM) of rabbit lung ACE in vitro, but the inhibitory activity is diminished in serum or in the presence of other peptidases. This is presumably due to the instability of the unsubstituted amide of tiopronin (**4**) to undergo cleavage by other hydrolytic enzymes. With this hypothesis in mind, a series of potent ACE inhibitory compounds was designed and synthesized in which the amide nitrogen was substituted by various alkyl and aromatic functionality. The compounds of interest are exemplified by the generic formula **1**. Our study differs from the design and synthesis of ACE inhibitors by Ondetti and co-workers, who reported that C-terminal proline was the amino acid that provided the maximum ACE inhibitory activities.[6a,b,17]

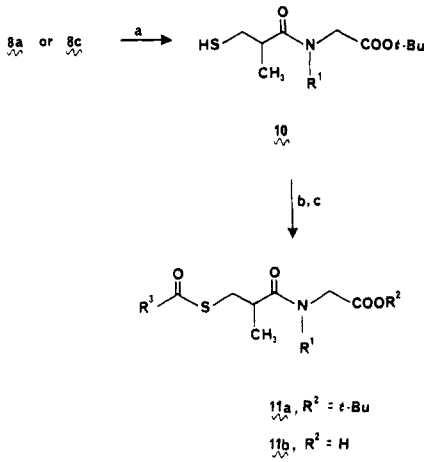
Chemistry. The compounds of Table I were conven-

Scheme I. Synthesis of N-Substituted (3-Mercapto-2-methylpropanoyl)glycines[a]



[a] Reagents: a, $BrCH_2CO_2R^2$; b, **7a**-toluene-$SOCl_2$-pyridine or DMF to give **7b** or **7c**-CH_2Cl_2-$SOCl_2$-DMF to give **7d**; c, **7a**-**6**-CH_2Cl_2-DCC or **7b**-**6**-CH_2Cl_2-Et_3N to give **8a**; d, **7d**-**6**-CH_2Cl_2-Et_3N to give **8c**; e, **8a**-TFA-anisole or **8a**-$(CH_3)_3SiI$-CH_2Cl_2 to give **8b**; f, **8c**-TFA-anisole to give **8d**; g, **8b** or **8d**-anhydrous NH_3-CH_3OH.

Scheme II. Synthesis of Hindered Thio Esters of N-Substituted (3-Mercapto-2-methylpropanoyl)glycines[a]



[a] Reagents: a, **8a** or **8c**-anhydrous NH_3-CH_3OH; b, R^3COCl-CH_2Cl_2-Et_3N to give **11a**; c, **11a**-$(CH_3)_3SiI$-CH_2Cl_2.

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iently prepared as illustrated in Scheme I in an analogous manner to that reported by Cushman and Ondetti[6b] in which 3-(acetylthio)-2-methylpropionic acid (**7a**) was reacted with naturally occurring α-amino acids with use of dicyclohexylcarbodiimide (DCC) as the amide-generating reagent. In our study, non-naturally-occurring N-substituted glycines **6** were utilized. The appropriately substituted glycine esters **6** were prepared by treatment of known primary amines **5** with either *tert*-butyl bromoacetate or ethyl bromoacetate in a polar solvent such as ethanol or acetonitrile. The glycine esters **6** were normally obtained as oils which were used directly and were characterized by NMR, MS, and TLC analysis. In a manner similar to that previously described,[15,18] 3-(acetylthio)-2-methylpropionic acid (**7a**) was prepared by the addition of thiolacetic acid to methacrylic acid in a Michael fashion. The corresponding acid chloride **7b**[15] was prepared conveniently in toluene in the presence of thionyl chloride with a few added drops of pyridine or DMF as initiator. The appropriately substituted amino acid esters **6** were condensed with **7a** in CH_2Cl_2 or Et_2O with DCC as the amide-generating reagent to give **8a**. Alternatively the amides **8a** were also prepared with use of the acid chloride **7b** under standard Schotten–Baumann acylating conditions. In general, the crude amides **8a** were converted directly to the free carboxylic acids **8b** without further purification. In those instances in which **8a** were purified, the general method was high-performance LC using the solvent system of AcOEt/*n*-C_6H_{14} (5:95). The *tert*-butyl esters **8a** were deprotected with either trimethylsilyl iodide ($(CH_3)_3SiI$) in CH_2Cl_2 or by means of trifluoroacetic acid (TFA) in anisole, both at room temperature. In the case of the ethyl esters **8a**, treatment with ethanolic KOH gave directly the mercapto acids **9**. In general, the pure acids **8b** were obtained by high-performance LC over silica gel with the solvent system of *n*-C_6H_{14}/AcOEt/AcOH (60:40:1) as eluent. All acids **8b** were fully characterized by NMR, MS, and elemental analysis. In the case where the acids **8b** are liquids or low melting, the elemental analyses were generally performed on the corresponding dicyclohexylamine (DCHA) or benzathine salts. The free mercaptans **9** were generated from the thio esters **8b** by treatment with anhydrous NH_3 in CH_3OH followed by ion-exchange chromatography (AG-50W-X2, Bio-Rad Laboratories) using CH_3OH as the eluting solvent. The mercaptans **9** were fully characterized by means of NMR, MS, and combustion microanalysis.

In a few selected cases, hindered thio esters **11b**, such as neopentylcarbonyl and pivaloyl, were prepared in order to increase in vivo plasma stability and to decrease nucleophilic displacement of the thio ester carbonyl. These hindered esters were prepared as outlined in Scheme II. The thio esters **8a** were treated with anhydrous NH_3 in CH_3OH to give the mercaptans **10**. Alternatively, optically active amides **8c** were conveniently prepared by conversion of commercially available D-(−)-3-(benzoylthio)isobutyric acid (**7c**) to its corresponding acid chloride **7d** by means of $SOCl_2$ followed by treatment with the appropriately substituted glycine ester **6**. The thiobenzoyl ester **8c** was treated with anhydrous ammonia in CH_3OH to give the optically active thiol **10**. After purification the mercaptans **10** were treated with the appropriate acid chloride under standard Schotten–Baumann acylating conditions to give the hindered thio esters **11a**. The *tert*-butyl esters **11a** were deesterified in CH_2Cl_2 at room temperature by treatment with $(CH_3)_3SiI$ to afford the acids **11b**.

The mercapto acids **9** and the corresponding thio esters **8b** and **11b** which were synthesized and evaluated for ACE inhibition are listed in Table I. Of the over 400 variants of structure **1** prepared, we report hereto approximately 70 representative alkanoylglycines in which the glycine nitrogen is alkylated with various substituents including alkyl, cycloalkyl, bicycloalkyl, aryl, alkynyl, and heterocyclic groups.

Results and Discussion

The compounds presented in Table I represent an important novel class of N-substituted glycines that are very potent and specific competitive inhibitors of ACE in vitro and in vivo. This series of compounds has demonstrated potential as therapeutic agents for hypertension[14] and congestive heart failure. The in vitro IC_{50} values of the most active mercaptans, **17**, **21**, **23**, **25**, **27**, **29**, **37**, **57**, **59**, **63**, and **68**, are in the range of 0.0050–0.035 μM. These values are similar to the IC_{50} obtained in our laboratories for captopril (**2**), IC_{50} = 0.017 μM.

In order to increase the in vitro potency of tiopronin (**4**),[16] which is an (α-mercaptoalkanoyl)glycine, we proceeded to systematically design a series of (β-mercaptoalkanoyl)glycines. It was previously noted by Cushman and Ondetti that (β-mercaptoalkanoyl)prolines are much more potent inhibitors of ACE than their α counterparts.[6b] Upon preparation and evaluation of the glycine analogue **12** in vitro, an IC_{50} of 0.21 μM was obtained. This is to be compared with an IC_{50} of 1.9 μM for tiopronin (**4**). Upon proceeding to substitute the nitrogen of **12** by various alkyl functionalities, **13–15**, **39**, and **40**, the ACE inhibitory IC_{50} values proceeded to decrease from 0.21 μM for **12** to 0.072 μM for the isopropyl analogue **15** and to 0.055 μM for the thio ether **40**. The isopropyl analogue **15** appeared promising and gave us the incentive to prepare the cyclopropyl analogue **17**. The IC_{50} of **17** (0.030 μM) relative to that of **15** (0.072 μM) decreased by a factor of 2–3. With this encouraging result, a series of N-substituted monocycloalkyl analogues **17**, **21**, **23a**, **25**, and **27** was prepared in which the ring varied from cyclopropyl to cycloheptyl. In this series the maximum activity appeared to reside in the cyclobutyl **21** and cyclopentyl **23a** ring systems. The next logical course of action to follow in our systematic design was to prepare a series of *N*-bicycloalkyl-substituted analogues: **29–36**. Suprisingly it was found that the *exo*-norbornyl thio ester **30** was a potent inhibitor of purified rabbit lung ACE having an average IC_{50} of 0.020 μM over many different experiments. This is to be compared with an IC_{50} of 0.032 μM for the thiol **29**. This result was unlike the other analogues of our series in which the acetyl thio esters were a factor of 10 or more less potent than their respective mercaptans when tested in purified rabbit lung ACE.

A series of heterocycloalkyl derivatives, **42**, **44**, **46**, **48**, and **50**, was prepared that exhibited little or no substantial increases in inhibitory potency over the unsubstituted glycine analogue **12** or any of the other substituted analogues. The thienyl derivative **46** had the greatest potency in this series (IC_{50} = 0.055 μM).

A series of *N*-aryl derivatives, **53**, **55**, **57**, **59**, **61**, **63**, **65**, **66**, **68**, **70**, and **72**, was prepared and evaluated. This series was very fruitful in producing the most active member of the compounds prepared by us. The in vitro IC_{50} values of this series ranged from a low of 0.30 μM for the *N*-phenyl analogue **53** to 0.0050 μM for the *p*-tolyl analogue **59**. The *p*-tolyl derivative **59** exhibited the maximum in vitro potency of all of the inhibitors of generic formula **1** prepared by us.

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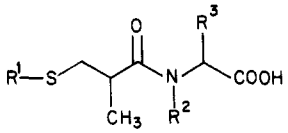
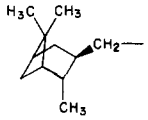
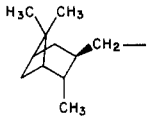
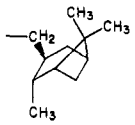
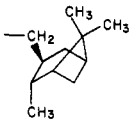
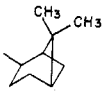
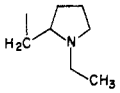
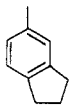
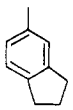
Table I. N-Substituted Mercaptopropanoylglycines and Inhibition of ACE in Vitro



compd[a]	R^1	R^2	R^3	mp,[b] °C	yield,[c] %	procedure[d]	formula[e]	remarks	IC_{50},[f] μM
12	H	H	H	115–117	92	I	$C_6H_{11}NO_3S$		0.21
13	H	CH_3	H	71–73	90	I	$C_7H_{13}NO_3S$		0.13
14	H	C_2H_5	H	131–132	93	I	$C_8H_{15}NO_3S$	DCHA[g]	0.075
15	H	$(CH_3)_2CH$	H	159–160	95	I	$C_9H_{17}NO_3S$	DCHA[g]	0.072
16	CH_3CO	$(CH_3)_2CH$	H	104–105	72	B, D, F	$C_{11}H_{19}NO_4S$		5.9
17	H	c-C_3H_5	H	89–91	84	I	$C_9H_{15}NO_3S$		0.030
18	CH_3CO	c-C_3H_5	H	68–70	61	A, D, F	$C_{11}H_{17}NO_4S$	DCHA[g]	0.54
19	H	c-C_3H_5	CH_3	129–130.5	72	I	$C_{10}H_{17}NO_3S$	DCHA[g]	0.079
20	CH_3CO	c-C_3H_5	CH_3	83–85	42	B, D, F	$C_{12}H_{19}NO_4S$		0.22
21	H	c-C_4H_7	H	liquid	82	I	$C_{10}H_{17}NO_3S$		0.018
22	CH_3CO	c-C_4H_7	H	162.5–164.5	72	B, E, G	$C_{12}H_{19}NO_4S$	DCHA[g]	0.22
23a (*R* + *S*)	H	c-C_5H_9	H	173–176[h]	87	I	$C_{11}H_{18}NO_3S$	calcium salt	0.018[i]
23b (*S*)[j]	H	c-C_5H_9	H	186–188	89 (82)	B, E, G, I (M, N)	$C_{11}H_{18}NO_3S$	calcium salt	0.016
24	CH_3CO	c-C_5H_9	H	172–174	75	B, E, G	$C_{13}H_{21}NO_4S$	DCHA[g]	0.082
25	H	c-C_6H_{11}	H	158–160[k]	92	I	$C_{12}H_{21}NO_3S$	DCHA[g]	0.035[l]
26	CH_3CO	c-C_6H_{11}	H	142–144	83	B, E, G	$C_{14}H_{23}NO_4S$	DCHA[g]	0.27
27	H	c-C_7H_{13}	H	oil[m]	88	I	$C_{13}H_{23}NO_3S$		0.031[n]
28	CH_3CO	c-C_7H_{13}	H	116–117	86	B, E, G	$C_{12}H_{25}NO_4S$	DCHA[g]	0.088
29[o]	H		H	120–122	96	I	$C_{13}H_{21}NO_3S$	DCHA[g]	0.032
30[o]	CH_3CO		H	125–126[p]	86	B, D, F	$C_{15}H_{23}NO_4S$	DCHA[g]	0.020
31[q]	CH_3CO		H	116	21	B, D, F	$C_{15}H_{23}NO_4S$	DCHA[g]	0.052
32	H		H	glass	87	I	$C_{17}H_{29}NO_3S$		0.44
33	CH_3CO		H	117	77	C, D, F	$C_{19}H_{31}NO_4S$		0.085
34	H		H	glass	84	I	$C_{17}H_{29}NO_3S$		0.16
35	CH_3CO		H	120	84	C, D, F	$C_{19}H_{31}NO_4S$		0.14
36	CH_3CO		H	134–138	63	C, D, F	$C_{17}H_{27}NO_4$	DCHA[g]	0.045
37	H		H	186–188[r]	95	I	$C_{15}H_{19}NO_3S$	DCHA[g]	0.031[s]
38	CH_3CO		H	149–150	75	B, E, G	$C_{17}H_{21}NO_4S$	DCHA[g]	0.34
39	H	$CH_3OCH_2CH_2$	H	129–132	90	B, E, G	$C_9H_{17}NO_4S$	DCHA[g]	0.095
40	H	$CH_3S(CH_2)_3$	H	122–128	91	I	$C_{10}H_{19}NO_3S_2$	DCHA[g]	0.055
41	CH_3CO	$CH_3S(CH_2)_3$	H	120–121	82	B, E, G	$C_{12}H_{21}NO_4S_2$	DCHA[g]	0.90
42	H		H	128–130	64	I	$C_{11}H_{19}NO_4S$	DCHA[g]	0.13
43	CH_3CO		H	138–140	80	B, D, F	$C_{13}H_{21}NO_5S$	DCHA[g]	1.9

compd[a]	R^1	R^2	R^3	mp,[b] °C	yield,[c] %	procedure[d]	formula[e]	remarks	IC_{50},[f] μM
44	H		H	150–153	80	I	$C_{11}H_{15}NO_4S$	DCHA[g]	0.17
45	CH_3CO		H	140–141	44	B, E, F	$C_{13}H_{17}NO_5S$	DCHA[g]	0.70
46	H		H	122–128	82	I	$C_{10}H_{19}NO_3S_2$	DCHA[g]	0.055
47	CH_3CO		H	149.5–150.5	49	B, E, G	$C_{13}H_{17}NO_4S_2$	DCHA[g]	0.75
48	H		H	38–40	90	I	$C_{10}H_{17}NO_5S_2$		0.28
49	CH_3CO		H	191–193	85	B, E, G	$C_{12}H_{19}NO_6S_2$	DCHA[g]	0.28
50	H		H	120–122	57	B, D, H	$C_{13}H_{24}N_2O_3S$	DCHA[g]	0.64
51	H	$CH{\equiv}CHCH_2$	H	164–166	91	I	$C_9H_{13}NO_3S$	DCHA[g]	0.27
52	CH_3CO	$CH{\equiv}CHCH_2$	H	154–156	62	B, E, G	$C_{11}H_{15}NO_4S$	DCHA[g]	4.5
53	H	C_6H_5	H	168–170[t]	90	I	$C_{14}H_{17}NO_4S$		0.30[u]
54	CH_3CO	C_6H_5	H	94–94.5	66	B, D, F	$C_{14}H_{17}NO_4S$		0.30
55	H	2-$(CH_3)C_6H_4$	H	97–101	89	I	$C_{13}H_{17}NO_3S$	Benz[v]	0.12
56	CH_3CO	2-$(CH_3)C_6H_4$	H	128–130	91	B, E, G	$C_{15}H_{19}NO_4S$	Benz[v]	0.55
57	H	3-$(CH_3)C_6H_4$	H	121–122	93	I	$C_{13}H_{17}NO_3S$	Benz[v]	0.019
58	CH_3CO	3-$(CH_3)C_6H_4$	H	104–105	87	B, E, G	$C_{15}H_{19}NO_4S$	Benz[v]	0.075
59	H	4-$(CH_3)C_6H_4$	H	134–137	95	I	$C_{13}H_{17}NO_3S$	Benz[v]	0.0050
60	CH_3CO	4-$(CH_3)C_6H_4$	H	146–148	84	B, E, G	$C_{15}H_{19}NO_4S$	Benz[v]	0.13
61	H	3,5-$(CH_3)_2C_6H_3$	H	125–126	96	I	$C_{14}H_{19}NO_3S$		0.044
62	CH_3CO	3,5-$(CH_3)_2C_6H_3$	H	89–92	90	B, E, G	$C_{16}H_{21}NO_4S$		0.044
63	H		H	164–167	92	I	$C_{15}H_{19}NO_3S$	Benz[v]	0.033
64	CH_3CO		H	117–118	82	B, E, G	$C_{17}H_{21}NO_4S$	Benz[v]	0.048
65	CH_3CO	3-$(CH_3O)C_6H_4$	H	103–105	80	B, E, G	$C_{15}H_{19}NO_5S$	Benz[v]	0.11
66	CH_3CO	3-$(CH_3S)C_6H_4$	H	110–112	72	B, E, G	$C_{15}H_{19}NO_4S_2$	Benz[v]	0.075
67	CH_3CO	3-FC_6H_4	H	oil	68	B, E, G	$C_{14}H_{16}FNO_4S$		0.051
68	H	4-FC_6H_4	H	155[w]	92	I	$C_{12}H_{14}FNO_3S$		0.023[x]
69	CH_3CO	4-FC_6H_4	H	oil	82	B, E, G	$C_{14}H_{16}FNO_4S$		0.60
70	H	4-(*n*-$C_4H_9)C_6H_4$	H	137–145[y]	88	I	$C_{16}H_{23}NO_3S$	Benz[v]	0.19[z]
71	CH_3CO	4-(*n*-$C_4H_9)C_6H_4$	H	151–153	66	B, E, G	$C_{18}H_{25}NO_4S$	Benz[v]	0.064
72	CH_3CO	4-(*i*-$C_3H_7)C_6H_4$	H	144	86	B, E, G	$C_{17}H_{23}NO_4S$	Benz[v]	0.060
73	$(CH_3)_3CCH_2CO$	c-C_5H_9	H	85–87	82	E, J, K, L	$C_{17}H_{29}NO_4S$		15
74a[aa]	$(CH_3)_3CCO$	c-C_5H_9	H	140–142	80	E, J, K, L	$C_{16}H_{27}NO_4S$		3.70
74b(*R*)[a,b]	$(CH_3)_3CCO$	c-C_5H_9	H	156	62	E, J, K, L	$C_{16}H_{27}NO_4S$		>100
74c(*S*)[ac] (pivopril)	$(CH_3)_3CCO$	c-C_5H_9	H	155–156	75.1	E, J, K, L	$C_{16}H_{27}NO_4S$		3.60
2 (captopril)									0.017[ad]
3 (enalapril)									8.0[ae]
4 (tiopronin)									1.9[af]

[a] Except where indicated all compounds are racemic. [b] Uncorrected. [c] Yield refers to the last step in each synthetic sequence. [d] See Experimental Section. [e] All compounds had satisfactory C, H, and N microanalyses and were within 0.4% of theoretical values. All compounds exhibited IR, ^1H NMR, and MS spectra consistant with the assigned structures. [f] Concentration inhibiting 50% of the activity of rabbit lung ACE at pH 8.3 in 0.10 M potassium phosphate buffer containing 0.30 M NaCl with the substrate Hip-His-Leu at a concentration of 2 mM. [g] Dicyclohexylamine (DCHA) salt. [h] Literature[6n] mp (DCHA) 143–144 °C. [i] Literature[6n] IC_{50} = 0.007 μM. [j] Corresponds to *S* isomer, $[\alpha]_D$ −12.50° (*c* 1.0, $CHCl_3$). [k] Literature[6n] mp (DCHA) 160–162 °C. [l] Literature[6n] IC_{50} = 0.0075 μM. [m] Literature[6n] mp (DCHA) 143–145 °C. [n] Literature[6n] IC_{50} = 0.0071 μM. [o] Corresponds to exo isomer. [p] Calcium salt mp 157–161 °C. [q] Corresponds to endo isomer. [r] Literature[6n] mp (DCHA) 180–183 °C. [s] Literature[6n] IC_{50} = 0.012 μM. [t] Literature[6n] mp 170–171 °C. [u] Literature[6n] IC_{50} = 0.013 μM. [v] Benzathine salt, *N*,*N*′-dibenzylethylenediamine. [w] Literature[6n] mp 163–165 °C. [x] Literature[6n] IC_{50} = 0.011 μM. [y] Literature[6n] mp (DCHA) 124–126 °C. [z] Literature[6n] IC_{50} = 0.056 μM. [aa] Corresponds to a 1:1 mixture of the *R* and *S* isomers, REV 3659. [ab] Corresponds to *R* isomer, $[\alpha]_D$ +111.05° (*c* 1.0, $CHCl_3$). [ac] Corresponds to *S* isomer, $[\alpha]_D$ −104.64° (*c* 1.0, $CHCl_3$). Corresponds to REV 3659-(S). [ad] Literature[6b] IC_{50} = 0.023 μM. [ae] Literature[7e] IC_{50} = 1.2 μM. [af] Literature[6b] IC_{50} = 1.7 μM.

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