Ann. Rev. Pharmacol. Toxicol. 1985. 25:307–23

SYNTHETIC AND FERMENTATION-DERIVED ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Marlene L. Cohen

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285

INTRODUCTION

Interest in the development of inhibitors of angiotensin-converting enzyme (EC 3.4.15.1) (ACE) has exploded since the announced discovery in 1977 of captopril (1), an orally effective inhibitor of ACE, by Cushman & Ondetti of the Squibb Institute for Medical Research. Following extensive clinical studies, ACE inhibitors have been heralded as a "major therapeutic advance" (2) and a "new approach to the therapy of hypertension" (3). ACE inhibitors have been the subject of numerous review articles (3–9), many symposia (10–12), editorials (13), and texts (14) during the last two years.

Based primarily on clinical studies with captopril, the utility of ACE inhibitors in most forms of hypertension has been established. In addition, the beneficial effect of captopril in congestive heart failure (15–17) has led to its recent approval for this use. Because of the ubiquitousness of ACE and the expanding research to identify those diseases associated with elevations in ACE activity (sarcoidosis, Gaucher's disease, diabetes mellitus, and hyperthyroidism), clinical studies with ACE inhibitors may expand into other pathological states (8, 18, 19). That ACE inhibitors may be useful in limiting experimental infarct size has also been reported (20).

Recently, a focal point in the research on ACE inhibitors has been the mechanism(s) by which ACE inhibitors exert their antihypertensive effects. This topic has been addressed in several excellent recent reviews (7, 9, 21–23) and will only be briefly mentioned here. In this regard, it is generally accepted that the inhibition of plasma angiotensin-converting enzyme, although known

0362-1642/85/0415-0307$02.00

to occur with ACE inhibitors, does not sufficiently explain their antihypertensive effects. Because of this, several theories have been advanced to explain the antihypertensive activity of ACE inhibitors. These include (*a*) inhibition of angiotensin II-induced facilitation of sympathetic neurotransmission in blood vessels, (*b*) tissue-specific inhibition of ACE, possibly within the central nervous system, kidney, or vasculature, (*c*) other actions of ACE inhibitors unrelated to the inhibition of the direct effects of angiotensin II. These latter actions include potential postsynaptic α-blocking activities, potential elevations in bradykinin or other peptides (substance P, enkephalins, etc) degraded by ACE, and possible indirect effects of angiotensin II mediated via prostaglandin derivatives. Clarification of this controversy awaits additional comparative data on the actions of multiple ACE inhibitors with regard to each of the mechanisms specified above.

We are currently entering an era that will see a rapidly expanding armamentarium of ACE inhibitors. The race to develop such inhibitors has begun in earnest, and over the next few years we shall no doubt see an emerging literature on subtle differences in the pharmacological activity of the newer ACE inhibitors. Such differences will help to ellucidate the precise mechanism for their antihypertensive activity and may provide a rational basis for specific clinical implications for some of the newer agents.

This review focuses on the development of these newer ACE inhibitors, their structural relationship to captopril, and their current clinical status. Although I have attempted to present all of the ACE inhibitors under development, the rapid and dramatic growth in the plethora of available ACE inhibitors makes this task a formidable one. I have chosen to discuss only compounds on which published data, including recent abstracts, are available, and with only minor exceptions to review data generated within the last two years. No attempt has been made to review the voluminous patent literature.

ACE INHIBITORS FROM NATURAL PRODUCTS

The evolution of synthetic ACE inhibitors (Figure 1) began with the discovery that certain peptides isolated from the venom of the snake *Bothrops jararaca* were inhibitors of ACE (24). Of the several peptides isolated and examined for ACE inhibitory activity, the nonapeptide, later known as teprotide (SQ 20,881), was the most potent inhibitor [for reviews see (25–27)]. Since that discovery in the early 1970s, structure-activity correlations developed with the snake venom peptides have been used to synthesize small molecular-weight compounds with even greater bioavailability and affinity for ACE, and hence greater clinical utility. However, more recently, interest in the possibility of discovering novel structures (unrelated to teprotide or captopril) from natural products has been renewed.

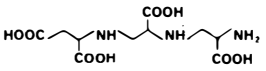
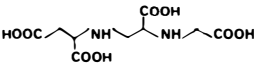
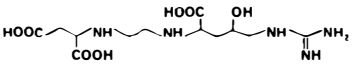
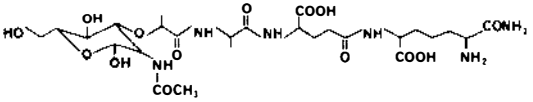
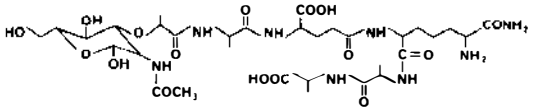
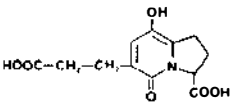
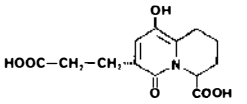
COMPOUND	SOURCE	STRUCTURE	REFERENCE
TEPROTIDE	BOTHROPS JARARACA	NONAPEPTIDE	25
ANCOVENIN	STREPTOMYCES	HEXADECAPEPTIDE	28
ASPERGILLOMARASMINE	ASPERGILLUS COLLETOTRICHUM FUSARIUM PYRENOPHORA	A  B 	29
L-681,176	STREPTOMYCES		30-31
MURACEIN	NOCARDIA	A  B 	32
A58365	STREPTOMYCES	A  B 	33-34

Figure 1 The structure and source of ACE inhibitors derived from natural products.

Ancovenin (28) is a hexadecapeptide isolated from streptomyces. It has been found to be approximately six-fold less potent than captopril as an ACE inhibitor. Other microorganism-derived peptide inhibitors (Figure 1) with even lower ACE inhibitory activity include the aspergillomarasmines (29), L-681,176 (30–31), and muramyl peptides (muraceins) (32). Clearly, the low inhibitory activity and minimal bioavailability of such agents precludes any direct therapeutic or clinical utility for them.

The utility of natural products produced from microorganisms to provide small molecular-weight structural leads for the future development of novel

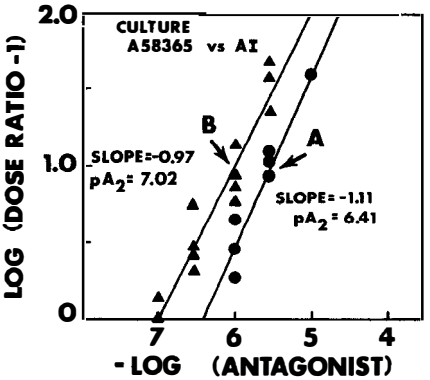


Figure 2 Schild plot for the effect of A58365A and A58365B to antagonize angiotensin I contractile responses in the isolated guinea pig ileum. Plot of the logarithm of dose ratio − 1 against the negative logarithm of the molar concentration of antagonists yielded a straight line whose slope approximated one, indicating a competitive interaction of the antagonists with ACE. The intercept along the abcissa is the pA_2 value, which is equal to the negative logarithm of the dissociation constant (*i.e.* $-\log K_B$).

ACE inhibitors was advanced by the recent discovery of the angiotensin-converting enzyme inhibitors A58365A and A58365B produced by streptomyces chromofuscus (33–34). These natural products are nonpeptide compounds. A58365A and B were competitive antagonists of angiotensin-converting enzyme as determined by the antagonism of angiotensin I contractile responses in the guinea pig ileum (Figure 2). These simple bicyclic dicarboxcylic acid molecules showed relatively high in vitro affinity for ACE and may be considered natural product analogues of the newer bicyclic ACE inhibitors (see below). The identification of these agents supports the contention that efforts directed toward isolating microbially derived ACE inhibitors may well provide an avenue for the development of second and third generation ACE inhibitors of novel structures.

Other naturally occurring peptide ACE inhibitors have been identified from mammalian sources. These include a peptide derived from fibrin (35), ACTH-related peptides (36), and metabolites of thyrotropin-releasing hormone (37). The physiological function of such endogenous peptide inhibitors is a subject of current research and remains to be clarified.

SULFUR-CONTAINING ACE INHIBITORS

Based on the ACE inhibitory activity of the nonapeptide, teprotide, and the contention that an orally effective ACE inhibitor would find utility in hypertension, Cushman & Ondetti generated an elegant SAR that led to the discovery of the first potent and orally active ACE inhibitor, captopril (25–27). This discov-

ery was soon followed by the demonstration that captopril was effective in many animal models of hypertension and in almost all clinical forms of hypertension, including essential hypertension associated wth low or normal plasma renin levels.

The fact that the clinical use of captopril exceeded initial expectations spurred interest in the development of other ACE inhibitors. Initially, synthesis was directed toward compounds structurally similar to captopril (Figure 3). These included YS980 (36–39), SA446 (40–44), pivalopril (RHC 3659) (45–47), CL242,817 (48–50), and zofenopril (51), all sulfur-containing structures with an affinity for ACE lower than or similar to that of captopril. YS980 and SA446 are more lipophilic structures than captopril; hence, they may distribute to the central nervous system (CNS) to inhibit brain ACE to a greater extent than captopril. Pivalopril, CL242,817, and zofenopril contain protected sulfhydryl groups and may serve as prodrugs. More recently, chemists from both Ciba-Geigy (52) and Wyeth Laboratories (53, 54) independently reported on the synthesis of the bicyclic molecule WY-44,221, a compound shown to be 10–20 times more potent than captopril. It is interesting to note that such a minor chemical change could result in a marked improvement in ACE inhibition. In general, however, little novel chemistry and only minor pharmacological advantage emerged with these new sulfur-containing compounds.

Using computer graphics to postulate the favored spatial orientation of functional groups for ACE inhibition, Hassall and co-workers (55) designed the bicyclic rigid molecule compound III, which had in vitro activity close to that of captopril. Also using computer modeling to generate energy minimized conformations, Thorsett and colleagues (56) investigated a series of mercaptomethyl lactams similar to those previously reported by Klutchko and colleagues (57) and found that seven or eight membered lactam rings optimized ACE inhibitory activity. The mercapto lactam 5d compared favorably with captopril in terms of ACE inhibition in vitro. Both these latter sulfhydryl-containing compounds served as prototypes for the development of non-sulfhydryl rigid lactam ACE inhibitors (see below).

Of the sulfur-containing ACE inhibitors that followed in the wake of captopril, clinical studies have been reported only for pivalopril (47). These studies suggest that pivalopril has a rapid onset of action with a short duration based on serum ACE inhibition. No clinical data are reported on pivalopril in hypertensive patients or on the other sulfur-containing compounds, although zofenopril has been selected for clinical study (51).

During this flurry of chemical activity, captopril continued to be evaluated clinically. Initial clinical tests used relatively high doses of captopril to insure clinical efficacy. As clinical experience expanded, side effects attributed to captopril emerged (58–60). These included skin rashes and loss of taste, along with proteinurea and alterations in the haematopoietic system. Although the

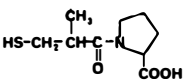
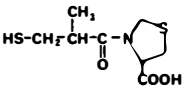
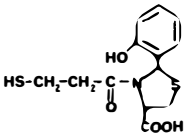
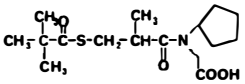
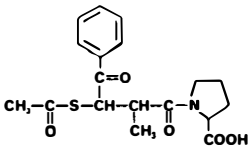
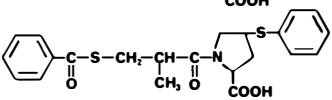
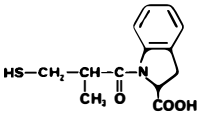
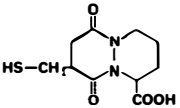
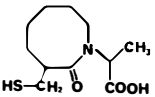
COMPOUND	STRUCTURE	REFERENCE
CAPTOPRIL		25–27
YS 980		36–39
SA 446		40–42
PIVALOPRIL (RHC 3659)		45–47
CL 242,817		48–50
ZOFENOPRIL (SQ26,991)		51
WY-44,221		52–54
III		55
MERCAPTOLACTAM (5d)		56

Figure 3 The structures of ACE inhibitors that contain sulfur.

cause of these side effects remains unclear, their resemblance to side effects produced by penicillamine, another sulfhydryl-containing molecule, led some to implicate captopril's sulfhydryl moiety as a causative factor (60). This possibility, coupled with the potential for multiple interactions of sulfur-containing molecules, led to a rapid redirection of synthetic effort in the development of ACE inhibitors, although reduced dosage has minimized the occurrence of side effects in the use of captopril (61, 62).

NON-SULFHYDRYL ACE INHIBITORS

Patchett and co-workers elegantly accomplished the replacement of the sulfhydryl moiety in captopril by designing a series of substituted N-carboxymethyl-dipeptides (63) (Figure 4). The dicarboxylic acid compound, enalaprilic acid (MC422), was a potent inhibitor of ACE with approximately ten times greater affinity for ACE than captopril (64, 65). Although enalaprilic acid showed high affinity for ACE, oral bioavailability was poor in both animals (65) and man (66). This problem was partially overcome by the development of the ethyl ester, enalapril (MK421). Enalapril has become a prototype for a generation of ACE inhibitors that are prodrugs that must be hydrolyzed for ACE inhibition. Relative to captopril, enalapril has a slower onset of action (65, 67), which may be related both to the need for hydrolysis to the active moiety and to poor oral absorption (although oral absorption is improved compared to enalaprilic acid) (68). The major clinical advantage of enalapril resides in its relatively long duration of action (69, 70), which should permit once or at most twice daily dosing for maintenance of blood pressure reduction. In addition, unlike captopril, plasma ACE inhibition can be used as a rough index of plasma levels of enalapril, since enalapril-induced ACE inhibition was stable on storage whereas captopril-induced ACE inhibition was not (23). Although developed to minimize captopril-like side effects, mucocutaneous reactions (71, 72) and reversible leucopenia have been reported with enalapril (73). The occurrence of such side effects will be placed in perspective as the clinical use of enalapril expands pending its approval by the Food and Drug Administration.

During the development of enalapril, the lysine derivative of enalaprilic acid (lisinopril, MK521) was found to be a potent ACE inhibitor with affinity for ACE similar to enalaprilic acid. Lisinopril offered the singular advantage of oral activity similar to enalapril, in spite of the fact that it was a dicarboxylic acid (66, 74, 75). Blood pressure after lisinopril (2.5 and 5 mg) was significantly reduced for more than twenty-four hours in hypertensive patients, indicating that once daily dosing will be likely with this agent (76, 77).

The development of these two novel ACE inhibitors has opened a new era in the synthesis of ACE inhibitors. Shortly after the identification of enalapril and lisinopril, researchers at both Schering Corporation (78, 79) and Warner-Lambert/Parke-Davis Research Laboratories (80–82) independently reported on the synthesis and development of indolapril (SCH31846, CI907), a close analog of enalapril. Like enalapril, indolapril is a prodrug that must be hydrolyzed to the diacid for ACE inhibition. Indolapril's duration of action appears similar to that of enalapril. The ethyl ester, CI-906, is an analog of both enalapril and indolapril (80, 81). However, unlike these other ethyl ester derivatives, CI906 showed relatively high affinity for ACE, an affinity that was

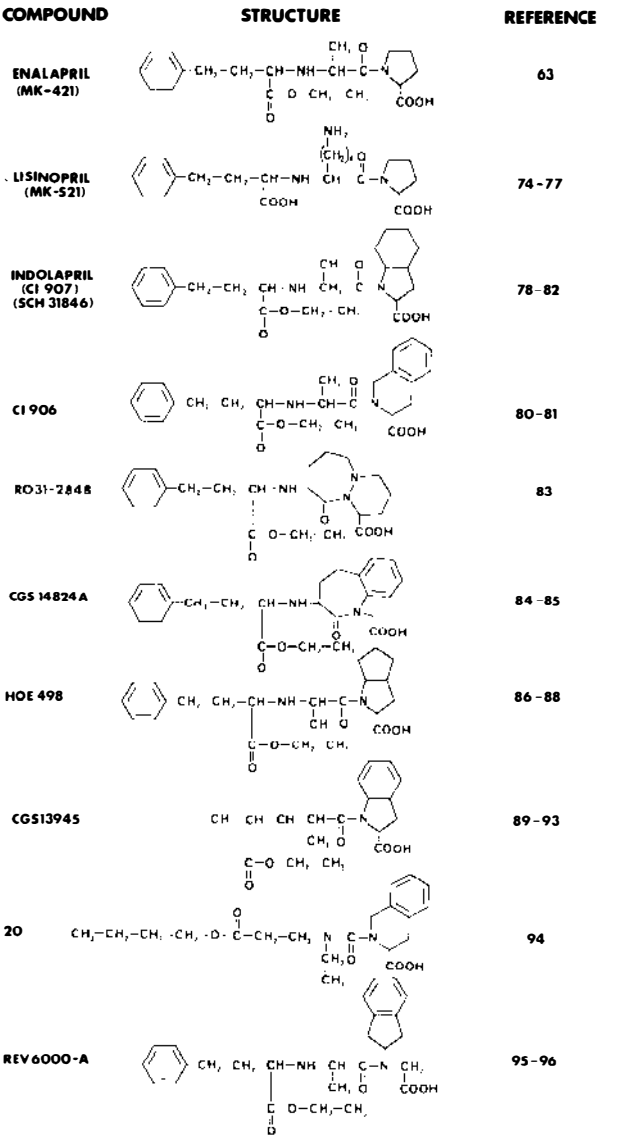


Figure 4 The structures of ACE inhibitors that do not contain sulfur or sulfhydryl moieties.

only three-fold less than that of its diacid metabolite (81). Why CI-906 showed such high affinity for ACE relative to enalapril and indolapril remains to be determined. Should this in vitro activity be translated to the in vivo situation, CI-906 might have a more rapid onset of action (due to activity of the parent compound) and a longer duration of action (due to activity of the diacid) than

enalapril or CI-907. However, initial preclinical data evaluating inhibition of an angiotensin I pressor response in conscious rats and dogs did not reveal any major differences in the time course among these three ACE inhibitors (80). Clinically, CI-906 (5 and 10 mg, p.o.) lowered blood pressure for twelve to twenty-four hours without adverse effects in hypertensive patients (82), effectiveness similar to enalapril and lisinopril. CI-925, the dimethoxy derivative of CI-906, has a rapid onset and long duration of ACE inhibition in preclinical studies and is currently also undergoing clinical evaluation (H. Kaplan, personal communication).

Following the identification of indolapril and CI-906, several additional bicyclic ACE inhibitors have been synthesized. These include bicyclic lactam derivatives that possess a seven-membered lactam ring as in R031-2848 (83) and CGS14824A (84), the active isomer of the seven-membered lactams reported by Parsons et al (85). The increase in lactam ring size from five and six carbons improved affinity for ACE.

The bicyclic ACE inhibitor HOE-498 is a structural variant of enalapril and indolapril. Based on blockade of angiotensin I (AI) pressor response, intravenously administered HOE 498 showed similar potency to enalapril, yet oral or intraduodenal administration of HOE-498 resulted in approximately ten-fold greater potency than enalapril (86). Thus the bioavailability of HOE-498 was greater than that of enalapril, consistent with previous observations suggesting the relatively poor oral bioavailability of enalapril. The greater oral activity of HOE-498 relative to enalapril was also reflected in a better reduction in blood pressure and inhibition of plasma and tissue ACE following oral administration to stroke-prone, spontaneously hypertensive rats (87). Initial reports (87) with HOE-498 also suggest a different distribution of tissue ACE inhibitory effectiveness (heart, adrenal, and brain ACE were markedly inhibited by HOE-498 and not by MK-421 at 10 mg/kg, p.o.). Furthermore, clinical data with HOE-498 confirm the high potency and long duration of activity with regard to plasma ACE inhibition in normal volunteers (88). Should these differences observed with HOE-498 relative to indolapril or enalapril be maintained with further scrutiny, the dramatic effect on pharmacological activity produced by minor structural modification of ACE inhibitors will become obvious.

As a departure from the phenethylamine ester side chain in previously discovered ACE inhibitors, scientists at Ciba-Geigy and Tanabe Seiyaku Company have synthesized bicyclic ACE inhibitors with markedly different side chains (Figure 4). This modification resulted in a disappointing reduction in activity. Both these compounds, CGS 13945 (89–93) and compound 20 (94), are esters that must be hydrolyzed for in vivo ACE inhibitory activity. In vitro affinity for ACE of the diacid forms of these molecules, as well as in vivo activity of the esters, was lower than that reported for compounds with the

phenethylamine side chain, such as in enalapril. In fact, CGS 13945, although possessing a long duration of action, was less effective than captopril in inhibiting the AI pressor response in both rats and dogs after intravenous and oral administration (90). Likewise, CGS 13945 was less potent in inhibiting human plasma ACE activity after oral administration than was captopril (92, 93). The effectiveness of CGS 13945 in hypertensive patients has not yet been reported.

Lastly, REV 6000A is a newly revealed ACE inhibitor of a nonrigid bicyclic structure in which the proline nitrogen is not enclosed in a ring structure. Although REV 6000A possesses a long duration of action, it appears to be less potent than enalapril after oral administration to animals (95, 96). Clinical data on this compound are not yet available.

PHOSPHOROUS-CONTAINING ACE INHIBITORS

In a search for ACE inhibitors with novel properties, Holmquist & Vallee (97) and Galardy (98–100) were the first to demonstrate that the carboxyl or mercapto moiety proposed as the ligand for the active site zinc ion on ACE could be replaced by a phosphorous group with the retention of reasonable ACE inhibitory activity (Figure 5). This observation paved the way for Thorsett and colleagues (101) in the Merck Sharp & Dohme Laboratories and Powell and colleagues (102) from the Squibb Institute for Medical Research to design phosphorous-containing molecules as potential candidates for clinical therapy.

As with other described ACE inhibitors, SQ 28,555 is a prodrug with in vitro ACE inhibitory activity similar to that of captopril. SQ 28,555 was orally effective in animal studies and had a relatively long duration of action based on reductions in mean arterial pressure following oral administration in animals (102). Although clinical data on phosphorous-containing ACE inhibitors has not yet been reported, this new class of ACE inhibitors, when studied in more detail, may produce a new profile of pharmacological activity.

MISCELLANEOUS INHIBITORS

On route to the discovery of the potent ACE inhibitors previously mentioned, several other compounds have been reported (Figure 6). Reports of di-peptide and tri-peptides as weak inhibitors of angiotensin-converting enzyme have prompted Almquist and colleagues (103–106) to direct a synthetic effort toward the development of potent and orally effective tri-peptide analogs as inhibitors of ACE. In general, this effort has not met with great success. However, the most recent preclinical demonstration of antihypertensive activity following the oral administration of peptides that inhibit ACE may prompt further synthetic effort in this area (107). The possibility of success here must be

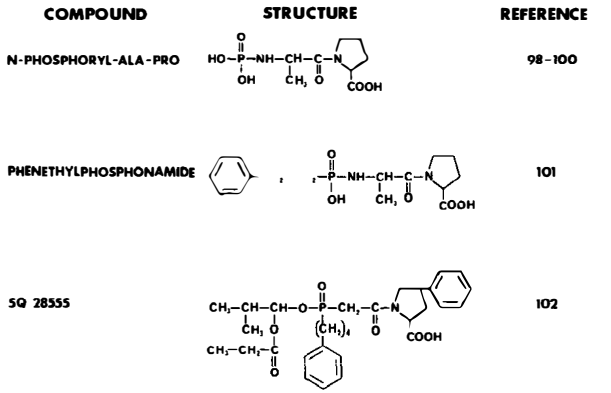


Figure 5 The structure of ACE inhibitors that contain phosphorous.

tempered by the suggestion that, although such peptides possess ACE inhibitory activity, the antihypertensive activity may result from other actions of these peptides.

Replacement of the amide moiety in compounds such as captopril with a ketone has resulted in active ACE inhibitors, although activity was somewhat lower than that found for the corresponding amide analogs (108). In vivo and clinical data on such compounds are not available.

Harris and colleagues (109) have demonstrated that hydroxamate derivatives of di-peptides, known to be inhibitors of other zinc-containing enzymes, are

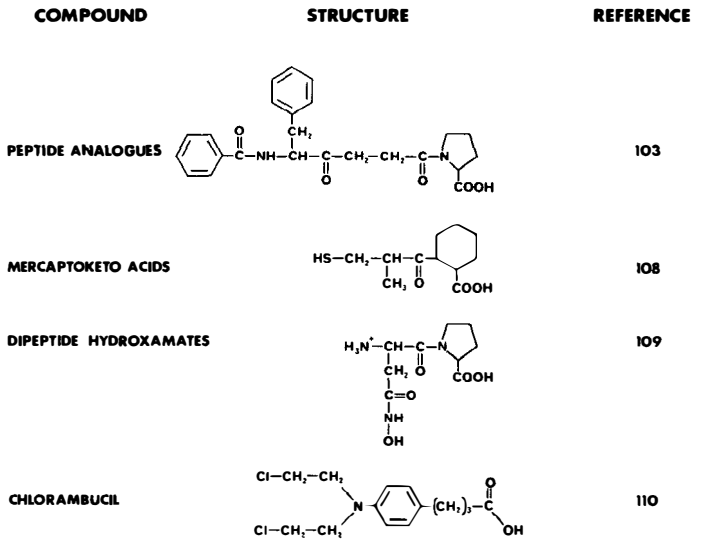


Figure 6 The structure of miscellaneous ACE inhibitors.

also relatively weak inhibitors of angiotensin-converting enzyme. Such inhibitors appear less potent than captopril and may lack specificity for angiotensin-converting enzyme. Furthermore, no in vivo data are reported on di-peptide hydroxamates.

Chlorambucil and its proline derivative have been reported to produce irreversible inhibition of ACE (110). Because this anticarcinogenic agent is a nitrogen mustard alkylating agent, specificity of action may be minimal.

SUMMARY AND CONCLUSIONS

The availability of potent and orally effective angiotensin-converting enzyme inhibitors will no doubt have a major impact on the future clinical therapy of hypertension and probably other disease states. It remains the challenge of the pharmacologist to decipher the subtle differences in the pharmacological profile of activity of these various ACE inhibitors and to capitalize on that information in order to determine the precise mechanism or mechanisms responsible for the antihypertensive activity of this class of agents. With the availability of these agents, this will be the challenge of the next few years.

The area of research involving ACE inhibitors, from their synthesis to the unravelling of their pharmacological activities, is a major example of a therapeutic breakthrough and benefit resulting entirely from the dedication and motivation of research accomplished within the pharmaceutical industry. Irvine H. Page has made this point before with reference to the overall development of antihypertensive agents (111). In his words:

> It must be evident that this was an extraordinary period in the history of the treatment of hypertension. Within about fifteen years, a panoply of highly effective drugs had been made available wholly through the skills of chemists in the pharmaceutical industry. These scientists have received little or no recognition by the medical community for this amazing achievement. . . . *It is important to realize that* drug *innovation begins with investigators who* work in the chemical laboratories in cooperation with pharmacologists, is followed by studies in patients by clinicians, and results in large-scale government finance and committee-directed studies. Each of these steps has its importance, but to date the first has been generally ignored.

The perceived importance of this group of antihypertensive agents has fostered considerable competition within the pharmaceutical industry. This is perhaps best reflected in the number of patents filed on ACE inhibitors and in the dual development of chemical compounds by different pharmaceutical companies (i.e. indolapril, WY44,221 and CGS14824A). This healthy competition will undoubtedly result in the improved therapy of hypertension, congestive heart failure, and other disease states.

ACKNOWLEDGEMENTS

I am grateful to Dr. Jon Mynderse for his helpful discussion and assistance, to Ms. Kathryn Schenck for preparing the chemical structures, to Ms. Laura Wittenauer for compiling the references, and to Ms. Elaine Gardner for her expert typing of the manuscript.

Literature Cited

1. Ondetti, M. A., Rubin, B., Cushman, D. W. 1977. Design of specific inhibitors of angiotensin-converting enzyme: New class of orally active antihypertensive agents. *Science* 196:441–43
2. Stronger role forecast for ACE inhibitors. 1984. *Practitioner* 228:368–69
3. Johnston, C. I., Arnolda, L., Hiwatari, M. 1984. Angiotensin-converting enzyme inhibitors in the treatment of hypertension. *Drugs* 27:271–77
4. Ondetti, M. A., Cushman, D. W. 1982. Enzymes of the renin-angiotensin system and their inhibitors. *Ann. Rev. Biochem.* 51:283–308
5. Antonaccio, M. J. 1982. Angiotensin-converting enzyme (ACE) inhibitors. *Ann. Rev. Pharmacol. Toxicol.* 22:57–87
6. Petrillo, E. W. Jr., Ondetti, M. A. 1982. Angiotensin-converting enzyme inhibitors: Medicinal chemistry and biological actions. *Med. Res. Rev.* 2(1):1–41
7. Van Zwieten, P.A., DeJonge, A., Timmermans, P. B. 1983. Inhibitors of the angiotensin-I converting enzyme as antihypertensive drugs. *Pharmaceut. Wklbd. Sci. Ed.* 5:197–204
8. Studdy, P. R., Lapworth, R., Bird, R. 1983. Angiotensin-converting enzyme and its clinical significance—A review. *J. Clin. Pathol.* 36:938–47
9. Antonaccio, M. J. 1983. Development and pharmacology of angiotensin converting enzyme inhibitors. *J. Pharmacol.* 14:29–45
10. Doyle, A. E., ed. 1982. Symposium on angiotensin converting enzyme inhibition. *Clin. Exp. Pharmacol. Physiol.* 6(Suppl. 7):1–144
11. Zanchetti, A., Tarazi, R. C., eds. 1982. Symposium on angiotensin converting enzyme inhibition: A developing concept. *Am. J. Cardiol.* 49:1381–580
12. Abrams, W. B. 1984. Research forum: Angiotensin-converting enzyme inhibitors. *Fed. Proc.* 43:1313–50
13. Dargie, H. J., Ball, S. G., Atkinson, A. B., Robertson, J. I. S. 1983. Converting enzyme inhibitors in hypertension and heart failure. *Br. Heart J.* 49:305–8
14. Doyle, A. E., Beam, A. G., eds. 1984. *Hypertension and the Angiotensin System Therapeutic Approaches*. New York: Raven. 304 pp.
15. Awan, N. A., Massie, B. M. 1982. Therapy of severe chronic congestive heart failure. *Am. Heart J.* 104: 1125–26
16. Sullivan, J. M. 1983. Drug suppression of the angiotensin system in congestive heart failure. *Ann. Rev. Med.* 34:169–77
17. Romankiewicz, J. A., Brogden, R. N., Heel, R. C., Speight, T. M., Avery G. S. 1983. Captopril: An update review of its pharmacological properties and therapeutic efficacy in congestive heart failure. *Drugs* 25:6–40
18. Rohatgi, P. K. 1982. Serum angiotensin converting enzyme in pulmonary disease. *Lung* 160:287–301
19. Smallridge, R. C., Rogers, J., Verma, P. S. 1983. Serum angiotensin-converting enzyme. Alterations in hyperthyroidism, hypothyroidism, and subacute thyroiditis. *J. Am. Med. Assoc.* 250:2489–93
20. Ertl, G., Kloner, R. A., Alexander, R. W., Braunwald, E. 1982. Limitation of experimental infarct size by an angiotensin-converting enzyme inhibitor. *Circulation* 65:40–8
21. Unger, T., Ganten, D., Lang, R. E. 1983. Converting enzyme inhibitors: Antihypertensive drugs with unexpected mechanisms. *Trends Pharmacol. Sci.* 4:514–19
22. Unger, T., Ganten, D., Lang, R. E. 1983. Pharmacology of converting enzyme inhibitors: New aspects. *Clin. Exper. Hyper.* A5:1333–54
23. Cohen, M. L., Kurz, K. 1983. Captopril and MK-421: Stability on storage, distribution to the central nervous system, and onset of activity. *Fed. Proc.* 42:171–75
24. Bakhle, Y. S. 1968. Conversion of angiotensin I to angiotensin II by cell-free extracts of dog lung. *Nature* 220:919–20
25. Cushman, D. W., Ondetti, M. A. 1980. Inhibitors of angiotensin-converting enzyme for treatment of hypertension. *Biochem. Pharmacol.* 29:1871–77

26. Cushman, D. W., Ondetti, M. A. 1982. Inhibitors of angiotensin-converting enzyme. *Chemtech* 12:620–24
27. Cushman, D. W., Cheung, H. S., Sabo, E. F., Ondetti, M. A. 1982. Development and design of specific inhibitors of angiotensin-converting enzyme. *Am. J. Cardiol.* 49:1390–94
28. Kido, Y., Hamakado, T., Yoshida, T., Anno, M., Motoki, Y. 1983. Isolation and characterization of ancovenin, a new inhibitor of angiotensin I converting enzyme, produced by actinomycetes. *J. Antibiot.* 36:1295–99
29. Mikami, Y., Suzuki, T. 1983. Novel microbial inhibitors of angiotensin-converting enzyme, aspergillomarasmines A and B. *Agric. Biol. Chem.* 47:2693–95
30. Huang, L., Rowin, G., Dunn, J., Sykes, R., Dobna, R., et al. 1983. Discovery of an angiotensin converting enzyme inhibitor, L-681,176 in the culture filtrate of *streptomyces sp. 83rd Ann. Meet. Am. Soc. Microbiol. New Orleans, 6–11 March 1983,* p. 244 (Abstr.)
31. Huang, L., Rowin, G., Dunn, J., Sykes, R., Dobna, R., et al. 1984. Discovery, purification and characterization of the angiotensin converting enzyme inhibitor, L-681,176, produced by *streptomyces sp.* MA 5143a. *J. Antibiot.* 37:462–68
32. Singh, P. D., Johnson, J. H. 1984. Muraceins—Muramyl peptides produced by *nocardia orientalis* as angiotensin-converting enzyme inhibitors. *J. Antibiot.* 37:336–43
33. Dubus, R., Fukuda, D., Samlaska, S., Baker, P., Hunt, A. et al. 1984. Isolation of A58365A and A58365B, angiotensin converting enzyme inhibitors produced by streptomyces chromofuscus. *84th Ann. Meet. Am. Soc. Microbiol., St. Louis, 4–9 March 1984,* p. 198 (Abstr.)
34. Hunt, A. H., Mynderse, J. S., Maciak, G. M., Jones, N. D., Samlaska, S., et al. 1984. Structure elucidation of A58365A and A58365B, angiotensin converting enzyme inhibitors produced by streptomyces chromofuscus. *187th Natl. Meet. Am. Chem. Soc., St. Louis, 8–13 April 1984, p. 145* (Abstr.)
35. Saldeen, T., Ryan, J. W., Berryer, P. 1981. A peptide derived from fibrin-(ogen) inhibits angiotensin converting enzyme and potentiates the effects of bradykinin. *Thrombosis Res.* 23:465–70
36. Verma, P. S., Miller, R. L., Taylor, R. E., O'Donohue, T. L., Adams, R. G. 1982. Inhibition of canine lung angiotensin converting enzyme by ACTH and structurally related peptides. *Biochem. Biophys. Res. Commun.* 104:1484–88
37. MacGregor, J. S., Resnick, L. M., Laragh, J. H. 1982. Metabolites of thyrotropin releasing hormone inhibit angiotensin converting enzyme *in vitro. Biochem. Biophys. Res. Commun.* 109:556–61
38. Unger, T., Rockhold, R. W., Schaz, K., Vescei, P., Bonner, G., et al. 1979. A novel orally active converting-enzyme inhibitor YS 980: Effects on blood pressure in spontaneously hypertensive rats. *Clin. Sci.* 57:157s–60s
39. Funae, Y., Komori, T., Sasaki, D., Yamamoto, K. 1980. Inhibitor of angiotensin I converting enzyme: (4R)-3-[(2S)-3-mercapto-2-methylpropranoyl]-4-thiazolidinecarboxylic acid (YS-980). *Biochem. Pharmacol.* 29:1543–47
40. Abe, Y., Miura, K., Imanishi, M., Yukimura, T., Komori, T., et al. 1980. Effects of an orally active converting enzyme inhibitor (YS-980) on renal function in dogs. *J. Pharmacol. Exp. Ther.* 214:166–70
41. Komori, T., Yamamoto, K. 1981. Effects of YS-980, an orally active converting enzyme inhibitor, on blood pressure in normotensive and hypertensive rats. *Jpn. J. Pharmacol.* 31:401–7
42. Iso, T., Yamauchi, H., Suda, H., Nakata, K., Nishimura, K., et al., 1981. A new potent inhibitor of converting enzyme: (2R,4R)-2-(2-hydroxyphenyl)-3-(3-mercaptopropionyl)-4-thiazolidinecarboxylic acid (SA446). *Jpn. J. Pharmacol.* 31:875–82
43. Unger, T., Yukimura, T., Marin-Grez, M., Lang, R. E., Rascher, W., et al. 1982. SA446, a new orally active converting enzyme inhibitor: Antihypertensive action and comparison with captopril in stroke-prone spontaneously hypertensive rats. *Eur. J. Pharmacol.* 78:411–20
44. Takata, Y., DiNicolantonio, R., Hutchinson, J. S., Mendelsohn, F. A. O., Doyle, A. E. 1982. *In vivo* comparison of three orally active inhibitors of angiotensin-converting enzyme. *Am. J. Cardiol.* 49:1502–4
45. Schwab, A., Weinryb, I., Macerata, R., Rogers, W., Suh, J., et al. 1983. Inhibition of angiotensin-converting enzyme by derivatives of 3-mercapto-2-methylpropanoyl glycine. *Biochem. Pharmacol.* 32:1957–60
46. Wolf, P. S., Mann, W. S., Suh, J. T., Loev, B., Smith, R. D. 1984. Angiotensin-converting enzyme inhibitory and antihypertensive activities of pivalopril [RHC 3659-(S)]. *Fed. Proc.* 43:1322–25

47. Burnier, M., Turini, G. A., Brunner, H. R., Porchet, M., Kruithof, D., Vukovich, R. A., Gavras, H. 1981. RHC 3659: A new orally active angiotensin converting enzyme inhibitor in normal volunteers. *Br. J. Clin. Pharmacol.* 12:893–99
48. Lai, F. M., Chan, P. S., Cervoni, P., Tanikclla, T., Shepherd, C., et al. 1982. Antihypertensive activity of [S-(*R**,*S**)]-1-[3-(acetylthio)-3-benzoyl-2-methylpropionyl] - L - proline (CL 242,817), an inhibitor of angiotensin converting enzyme (ACE). *Fed. Proc.* 41:1647
49. McEvoy, F. J., Lai, F. M., Albright, J. D. 1983. Antihypertensive agents: Angiotensin converting enzyme inhibitors. 1-[3-(acylthio)-3-aroylpropionyl]-L-prolines. *J. Med. Chem.* 26:381–93
50. Lai, F. M., Cervoni, P., Tanikella, T., Shepherd, C., Quirk, G., et al. 1983. Some *in vitro* and *in vivo* studies of a new angiotensin I-converting enzyme inhibitor [[S-(*R**,*S**)]-1-[(3-Acetylthio)-3-benzoyl-2-methylpropionyl]-L-proline] (CL 242,817) in comparison with captopril. *Drug Develop. Res.* 3:261–69
51. Dean, A. V., Kripalani, K. J., Migdalof, B. H. 1984. Disposition of SQ 26,991 (zofenopril) and SQ 26,900, new angiotensin converting enzyme (ACE) inhibitors in rats. *Fed. Proc.* 43:349
52. Stanton, J. L., Gruenfeld, N., Babiarz, J. E., Ackerman, M. H., Friedmann, R. C., et al. 1983. Angiotensin converting enzyme inhibitors: N-substituted monocyclic and bicyclic amino acid derivatives. *J. Med. Chem.* 26:1267–76
53. Kim, D. H., Guinosso, C. J., Buzby, G. C. Jr., Herbst, D. R., McCaully, R. J., et al. 1983. (Mercaptopropanoyl)indoline-2-carboxylic acids and related compounds as potent angiotensin converting enzyme inhibitors and antihypertensive agents. *J. Med. Chem.* 26:394–403
54. Lappe, R. W., Kocmund, S., Todt, J. A., Wendt, R. L. 1984. Effects of Wy-44,221, a new angiotensin converting enzyme inhibitor, on regional vascular resistance in the conscious SHR. *Fed. Proc.* 43:554
55. Hassall, C. H., Krohn, A., Moody, C. J., Thomas, W. A. 1982. The design of a new group of angiotensin-converting enzyme inhibitors. *FEBS Letts.* 147:175–79
56. Thorsett, E. D., Harris, E. E., Aster, S., Peterson, E. R., Taub, D., Patchett, A. A. 1983. Dipeptide mimics. Conformationally restricted inhibitors of angiotensin-converting enzyme. *Biochem. Biophys. Res. Commun.* 111:166–71
57. Klutchko, S., Hoefle, M. L. 1981. Synthesis and angiotensin-converting enzyme inhibitory activity of 3-(mercaptomethyl)-2-oxo-1-pyrrolidineacetic acids and 3-(mercaptomethyl)-2-oxo-1-piperidineacetic acids. *J. Med. Chem.* 24:104–9
58. Wilkin, J. K., Hammond, J. J., Kirkendall, W. M. 1980. The captopril-induced eruption. A possible mechanism: Cutaneous kinin potentiation. *Arch. Dermatol.* 116:902–5
59. Waeber, B., Gavras, I., Brunner, H. R., Gavras, H. 1981. Safety and efficacy of chronic therapy with captopril in hypertensive patients: An update. *J. Clin. Pharmacol.* 21:508–16
60. Rotmensch, H. H., Vlasses, P. H., Ferguson, R. K. 1982. Inhibition of angiotensin-converting enzyme: Therapeutic implications. *Israel. J. Med. Sci.* 18:981–85
61. Veterans Administration Cooperative Study Group on Antihypertensive Agents. 1982. Captopril: evaluation of low doses, twice-daily doses and the addition of diuretic for the treatment of mild to moderate hypertension. *Clin. Sci.* 63:443s–45s
62. Drayer, J. I. M., Weber, M. A. 1983. Monotherapy of essential hypertension with a converting-enzyme inhibitor. *Hypertension* 5:III–108–13
63. Patchett, A. A., Harris, E., Tristram, E. W., Wyvratt, M. J., Wu, M. T., et al. 1980. A new class of angiotensin-converting enzyme inhibitors. *Nature* 288:280–83
64. Gross, D. M., Sweet, C. S., Ulm, E. H., Backlund, E. P., Morris, A. A. et al. 1981. Effect of N-[(S)-1-carboxy-3-phenylpropyl]-L-Ala-L-Pro and its ethyl ester (MK-421) on angiotensin converting enzyme *in vitro* and angiotensin I pressor responses *in vivo*. *J. Pharmacol. Exp. Ther.* 216:552–57
65. Sweet, C. S. 1983. Pharmacological properties of the converting enzyme inhibitor, enalapril maleate (MK-421). *Fed. Proc.* 42:167–70
66. Biollaz, J., Burnier, M., Turini, G. A., Brunner, D. B., Porchet, M., et al. 1981. Three new long-acting converting-enzyme inhibitors: Relationship between plasma converting-enzyme activity and response to angiotensin I. *Clin. Pharmacol. Ther.* 29:665–70
67. Cohen, M. L., Kurz, K. D. 1982. Angiotensin converting enzyme inhibition in tissues from spontaneously hypertensive rats after treatment with

captopril or MK-421. *J. Pharmacol. Exp. Ther.* 220:63–69
68. Cohen, M. L., Kurz, K. D., Schenck, K. W. 1983. Tissue angiotensin converting enzyme inhibition as an index of the disposition of enalapril (MK-421) and metabolite MK-422. *J. Pharmacol. Exp. Ther.* 226:192–96
69. Abrams, W. B., Davies, R. O., Ferguson, R. K. 1984. Overview: The role of angiotensin-converting enzyme inhibitors in cardiovascular therapy. *Fed. Proc.* 43:1314–21
70. Gavras, H., Waeber, B., Gavras, I., Biollaz, J., Brunner, H. R., Davies, R. O. 1981. Antihypertensive effect of the new oral angiotensin converting enzyme inhibitor "MK-421". *Lancet* 2:543–46
71. Kubo, S. H., Cody, R. J. 1984. Enalapril, a rash, and captopril. *Ann. Int. Med.* 100:616
72. Vlasses, P. H., Rotmensch, H. H., Ferguson, R. K., and Sheaffer, S. L. 1982. "Scalded mouth" caused by angiotensin-converting enzyme inhibitors. *Br. Med. J.* 284:1672–73
73. Studer, A., Vetter, W. 1982. Reversible leucopenia associated with angiotensin-converting-enzyme inhibitor MK-421. *Lancet* 1:458
74. Brunner, D. B., Desponds, G., Biollaz, J., Keller, I., Ferber, F., et al. 1981. Effect of a new angiotensin converting enzyme inhibitor MK 421 and its lysine analogue on the components of the renin system in healthy subjects. *Br. J. Clin. Pharmac.* 11:461–67
75. Ulm, E. H., Hichens, M., Gomez, H. J., Till, A. E., Hand, E., et al. 1982. Enalapril maleate and a lysine analogue (MK-521): Disposition in man. *Br. J. Clin. Pharmac.* 14:357–62
76. Rotmensch, H. H., Vincent, M., Vlasses, P. H., Swanson, B. N., Irvin, J. D., et al. 1984. Initial evaluation of the nonsulfhydryl-containing converting enzyme inhibitor MK-521 in hypertensive humans. *Fed. Proc.* 43:1333–35
77. Rotmensch, H. H., Vlasses, P. H., Swanson, B. N., Irvin, J. D., Harris, K. E., et al. 1984. Antihypertensive efficacy of once daily MK-521, a new nonsulfhydryl angiotensin-converting enzyme inhibitor. *Am. J. Cardiol.* 53:116–19
78. Baum, T., Sybertz, E. J., Watkins, R. W., Ahn, H. S., Nelson, S., et al. 1983. Antihypertensive activity of SCH 31846, a non-sulfhydryl angiotensin-converting enzyme inhibitor. *J. Cardiovasc. Pharmacol.* 5:655–67
79. Sybertz, E. J., Baum, T., Ahn, H. S., Nelson, S., Eynon, E., et al. 1983. Angiotensin-converting enzyme inhibitory activity of SCH 31846, a new nonsulfhyrdryl inhibitor. *J. Cardiovasc. Pharmacol.* 5:643–54
80. Ryan, M. J., Boucher, D. M., Cohen, D. M., Olszewski, B. J., Singer, R. M., et al. 1984. Antihypertensive profile of the angiotensin-converting enzyme inhibitors CI-906 and CI-907. *Fed. Proc.* 43:1330–32
81. Kaplan, H. R., Cohen, D. M., Essenburg, A. D., Major, T. C., Mertz, T. E., et al. 1984. CI-906 and CI-907: New orally active nonsulfhydryl angiotensin-converting enzyme inhibitors. *Fed. Proc.* 43:1326–29
82. Gavras, I., Vlahakos, D., Melby, J. C., Gavras, H. 1984. Effects of the angiotensin converting enzyme inhibitor CI-906 on patients with essential hypertension. *Clin. Res.* 32:480A
83. Attwood, M. R., Francis, R. J., Hassall, C. H., Krohn, A., Lawton, G., et al. 1984. New potent inhibitors of angiotensin converting enzyme. *FEBS Letts.* 165:201–6
84. Miller, D., Hopkins, M. F., Tonnesen, S. T., Watkins, B. E. 1983. Antihypertensive assessment of CGS 14824A, an orally effective angiotensin-converting enzyme (ACE) inhibitor. *Pharmacologist* 25:102
85. Parsons, W. H., Davidson, J. L., Taub, D., Aster, S. D., Thorsett, E. D., Patchett, A. A. 1983. Benzolactams. A new class of converting enzyme inhibitors. *Biochem. Biophys. Res. Commun.* 117: 108–13
86. Becker, R. H. A., Scholkens, B. A., Unger, T., Linz, W. 1983. HOE 498: An orally active non-sulfhydryl ce-inhibitor. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 324:R42
87. Unger, T., Scholkens, B. A., Ganten, D., Lang, R. E. 1983. Chronic administration of the novel converting enzyme inhibitor HOE 498 in spontaneously hypertensive rats (SHRSP): Comparison with MK 421. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 324:R43
88. Witte, P. U., Metzger, H., Irmisch, R. 1983. Pharmacodynamics of a new orally active long acting angiotensin converting enzyme inhibitor (HOE 498) in healthy subjects. *IRCS Med. Sci.* 11:1053
89. Gruenfeld, N., Stanton, J. L., Yuan, A. M., Ebetino, F. H., Browne, L. J., et al. 1983. Angiotensin converting enzyme inhibitors: 1-glutarylindoline-2-carboxylic acid derivatives. *J. Med. Chem.* 26:1277–82
90. Chen, D. S., Watkins, B. E., Ku, E. C., Dotson, R. A., Burrell, R. D. Jr. 1984. Pharmacological profiles of two new

angiotensin-converting enzyme (ACE) inhibitors: CGS 13945 and CGS 13934. *Drug Develop. Res.* 4:167–78

91. Miller, D., Watkins, B. E., Hopkins, M. F., Tonnesen, S. T., Van Orsdell, D. 1984. Antihypertensive assessment of two new angiotensin-converting enzyme (ACE) inhibitors: CGS 13945 and CGS 13934. *Drug Develop. Res.* 4:179–89
92. Chen, D. S., Brunner, H. R., Waeber, B. 1984. *In vitro* response of plasma angiotensin converting enzyme to precursors and active forms of converting enzyme inhibitors. *Curr. Ther. Res.* 35:-253–62
93. des Combes, B. J., Turini, G. A., Brunner, H. R., Porchet, M., Chen, D. S., et al. 1983. CGS 13945: A new orally active angiotensin-converting enzyme inhibitor in normal volunteers. *J. Cardiovasc. Pharmacol.* 5:511–16
94. Hayashi, K., Nunami, K. I., Sakai, K., Ozaki, Y., Kato, J., et al. 1983. Studies on angiotensin converting enzyme inhibitors. II. Syntheses and angiotensin converting enzyme inhibitory activities of carboxyethylcarbamoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives. *Chem. Pharm. Bull.* 31: 3553–61
95. Mann, W. S., Samuels, A. I., Bauer, K., Schwab, A., Wolf, P. S., et al. 1984. Indalapril (I), a new non-sulfur containing ACE inhibitor: Pharmacological characterization in rats and dogs. *Fed. Proc.* 43:733
96. Town, C., Knipe, J. O., Freiler, L., Tantillo, N., Magnien, E., et al. 1984. The disposition of indalapril (REV 6000-A(SS)), an orally active, non-sulfhydryl angiotensin-converting enzyme inhibitor, in animals. *Fed. Proc.* 43:958
97. Holmquist, B., Vallee, B. L. 1979. Metal-coordinating substrate analogs as inhibitors of metalloenzymes. *Proc. Natl. Acad. Sci. USA* 76:6216–20
98. Galardy, R. E. 1980. Inhibition of angiotensin converting enzyme with N^{α}-phosphoryl-L-alanyl-L-proline and N^{α}-phosphoryl-L-valyl-L-tryptophan. *Biochem. Biophys. Res. Commun.* 97:94–99
99. Galardy, R. E. 1982. Inhibition of angiotensin converting enzyme by phosphoramidates and polyphosphates. *Biochemistry* 21:5777–81
100. Galardy, R. E., Kontoyiannidou-Ostrem, V., Kortylewicz, Z. P. 1983. Inhibition of angiotensin converting enzyme by phosphonic amides and phosphonic acids. *Biochemistry* 22:1990–95
101. Thorsett, E. D., Harris, E. E., Peterson, E. R., Greenlee, W. J., Patchett, A. A., et al. 1982. Phosphorous-containing inhibitors of angiotensin-converting enzyme. *Proc. Natl. Acad. Sci. USA* 79:2176–80
102. Powell, J. R., DeForrest, J. M., Cushman, D. W., Rubin, B., Petrillo, E. W. 1984. Antihypertensive effects of a new angiotensin converting enzyme (ACE) inhibitor, SQ 28,555. *Fed. Proc.* 43:733
103. Almquist, R. G., Chao, W. R., Ellis, M. E., Johnson, H. L. 1980. Synthesis and biological activity of a ketomethylene analogue of a tripeptide inhibitor of angiotensin converting enzyme. *J. Med. Chem.* 23:1392–98
104. Almquist, R. G., Crase, J., Jennings-White, C., Meyer, R. F., Hoefle, M. L., et al. 1982. Derivatives of the potent angiotensin converting enzyme inhibitor 5(S)-Benzamido-4-oxo-6-phenylhexanoyl-L-proline: Effect of changes at positions 2 and 5 of the hexanoic acid portion. *J. Med. Chem.* 25:1292–99
105. Meyer, R. F., Essenburg, A. D., Smith, R. D., Kaplan, H. R. 1982. Angiotensin converting enzyme inhibitors: Modifications of a tripeptide analogue. *J. Med. Chem.* 25:996–99
106. Almquist, R. G., Christie, P. H., Chao, W. R., Johnson, H. L. 1983. Synthesis and biological activity of an amino analogue of a tripeptide inhibitor of angiotensin-converting enzyme. *J. Pharm. Sci.* 72:63–67
107. Morikawa, T., Takada, K., Kimura, T., Sakakibara, S., Kurauchi, M., et al. 1984. Novel peptides with orally active and long-lasting antihypertensive activity. *Biochem. Biophys. Res. Commun.* 119:1205–10
108. Condon, M. E., Petrillo, E. W. Jr., Ryono, D. E., Reid, J. A., Neubeck, R., et al. 1982. Angiotensin-converting enzyme inhibitors: Importance of the amide carbonyl of mercaptoacyl amino acids for hydrogen bonding to the enzyme. *J. Med. Chem.* 25:250–58
109. Harris, R. B., Strong, P. D. M., Wilson, I. B. 1983. Dipeptide-hydroxamates are good inhibitors of the angiotensin I-converting enzyme. *Biochem. Biophys. Res. Commun.* 116:394–99
110. Harris, R. B., Wilson, I. B. 1982. Irreversible inhibition of bovine lung angiotensin I-converting enzyme with p-[N,N-Bis(chloroethyl)amino]phenylbutyric acid (chlorambucil) and chlorambucyl L-proline with evidence that an active site carboxyl group is labeled. *J. Biol. Chem.* 257:811–15
111. Page, I. H. 1981. Antihypertensive drugs. Our debt to industrial chemists. *New Eng. J. Med.* 304:615–18