PYRROLIDINE DERIVATIVES — INHIBITORS OF ANGIOTENSIN-CONVERTING ENZYME (REVIEW)

G. I. Chipens, V. A. Slavinskaya,
D. R. Kreile, A. Yu. Krikis,
and A. K. Strautinya

UDC 547.747: 577.15(047)

Methods for the synthesis and the compositions and biological activities of pyrrolidine derivatives that are inhibitors of angiotensin-converting enzyme are discussed. The most active inhibitors are 1-(D-3-mercapto-2-methylpropanoyl)-L-proline (captropril), dehydroproline derivatives, and phosphorus-, zinc-, and germanium-containing derivatives.

Inhibitors of angiotensin-converting enzyme (ACE) are promising medicinal antihypertensive agents. This enzyme participates in the regulatory renin—angiotensin—aldosterone system, the disruption of the function of which leads to the development of most hypertensive states in human beings.

The known inhibitors of ACE can be divided into groups: 1) derivatives of amino acids and other compounds of a nonpeptide nature and 2) low molecular weight peptides.

The general problems of the reaction of inhibitors with the enzyme have been examined in monographs [1-4]. Monographs [5, 6] and reviews [7-34] have been devoted to a discussion of the results with respect to the synthesis of ACE inhibitors, the mechanism of their action, their biological activity, and their application in medicine. In the present review, we set forth information primarily covering the period from 1980 to 1982 regarding the structures and the methods for the synthesis of nonpeptide inhibitors — pyrrolidine derivatives and their biological activity.

General Information Regarding the Enzyme

The angiotensin-converting enzyme (ACE) is a dipeptidylcarboxypentidase (K.F. 3.4.15.1), the properties of which are similar to pancreatic carboxypeptidase A. The antiotensin-converting enzyme (ACE) is a glycopeptide with a relatively high percentage of the carbohydrate part, which, to a great degree, depends on the type of cells, from which the enzyme is isolated. Thus ACE isolated from the lungs of rabbits contains 26% carbohydrates [28, 35, 36]. The enzyme isolated from swine kidneys contains only 8% carbohydrates. The enzyme contains a large number of residues of glutamic and aspartic acids and proline [37]. A high percentage of aromatic amino acid residues, particularly tryptophan, has been noted [28]. The molecular mass of the enzyme determined by equilibrium sedimentation ranges from 129,000 to 136,000 [38]. Angiotensin-converting enzyme (ACE) is a zinc-containing metalloprotein. The percentage of zinc is 1 mole per protein molecule.

Angiotensin-converting enzyme (ACE) is responsible for the hydrolytic cleavage of angiotensin I and bradykinin, as well as being responsible for the hydrolysis of numerous other peptides [28]. In contrast to carboxypeptidase A, ACE cleaves dipeptides rather than individual amino acids from the C-terminal of the peptide chain.

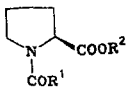
Participation of the Enzyme in the Renin—Angiotensin—Aldosterone System

Angiotensin-converting enzyme (ACE) is of great value in the regulation of blood pressure as a result of an acceleration of two different reactions (see the scheme presented below).

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1443-1454, November, 1984. Original article submitted September 19, 1983; revision submitted March 26, 1984.

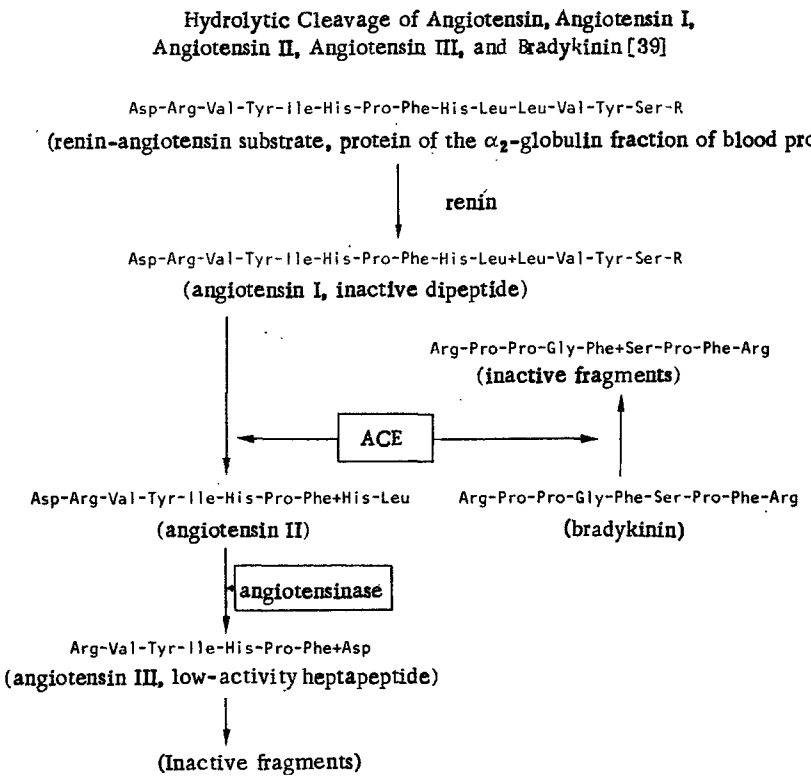
0009-3122/84/2011-1189$08.50

TABLE 1. L-Proline Derivatives and Their Properties as ACE Inhibitors [45-53]



Compound	R^1	R^2	I_{50}[a], μM	Dose mg/kg per day
I[b]	$HSCH_2CH(Me)$[c]	H	0,007 ($2,3 \cdot 10^{-8}$ M)	1,0
II	$HSCH(Me)CH_2$	H	1,1	
III	HSCH(Me)	H	1,1	
IV	$HSCH_2CH(Me)$	H	2,4	
V	$HSCH_2CH_2$	H	0,2	
VI	$HSCH_2CH_2$	*t*-Bu	39	
VII	$HSCH_2CH_2$	Et	17	
VIII	$CH_3SCH_2CH_2$	H	4300	
IX	$HOOCCH(Me)CH_2$	H	2600	
X	$HOOCCH_2CH(Me)$	H	22	
XI	$HOOCCH(Me)CH_2$	H	610	
XII	$HOOCCH_2CH(Me)$	H	1480	

[a]Concentration of the inhibitor at which the activity of the enzyme decreases by 50%. [b]Captopril (SQ 14 225). [c]C-Configuration.



The renin enzyme (K.F. 3.4.99.19) from the blood plasma protein of the angiotensinogen splits out angiotensin I — a decapeptide that does not affect the blood pressure. Angiotensin I is hydrolyzed under the influence of ACE to give a hypertensive octapeptide — angiotensin II and a side product — dipeptide His-Leu [40, 41]. An increase in the blood pressure is due mainly to contraction of the smooth musculature of the blood vessels, as well as to an increase in the aldosterone level. On the other hand, ACE inactivates the antihypertensive peptide — bradykinin, accelerating the hydrolytic splitting out of one or two dipeptides from the C-terminal of bradykinin [42, 43]. Both of the reactions mentioned above lead to an increase in the blood pressure. Inhibitors of ACE are therefore extremely effective antihypertensive agents.

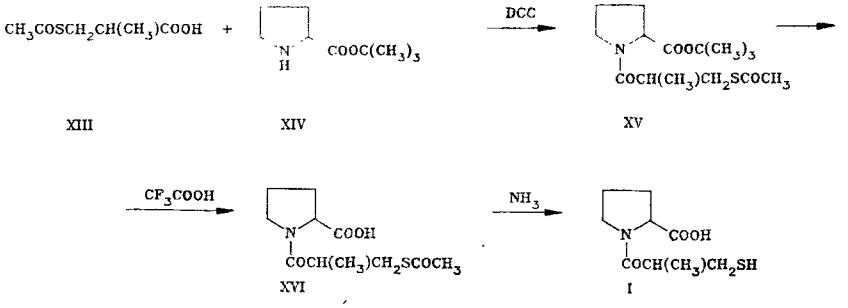
Proline Derivatives and other Amino Acids as Enzyme Inhibitors

The first reports of the development of nonpeptide ACE inhibitors appeared in 1977 [44]. In the design of the medicinal preparations of Cushman and Ondetti it was assumed that the active center of ACE is similar to the active center of carboxypeptidase A and contains at least three sections that interact with the substrate; the known competitive inhibitor of carboxypeptidase A is benzosuccinic acid. With allowance for the differences in the substrate specificity of both enzymes, they advanced the hypothesis that the prototype of the ACE inhibitor may be not succinic acid itself, but rather more likely some type of its amino acid derivative. To verify this hypothesis they synthesized succinyl-L-proline. The latter was selected in view of the fact that all derivatives of ACE peptide inhibitors contain precisely proline as the C-terminal residue. Analysis showed that this compound, although it has low activity, actually is a specific ACE inhibitor.

The subsequent stage in the research consisted of the isolation of the most active proline derivative.

The reactivities of a number of L-proline derivatives in the inhibition of ACE isolated from the lungs of rabbits were investigated (Table 1).

Of the compounds checked, D-2-methyl-3-mercaptopropanoyl-L-proline (I) is characterized by the greatest activity. Methods based on the condensation of acid XIII with L-proline tert-butyl ester (XIV) with subsequent removal of the protective groups have been proposed for the preparation of I [46]:



XIII XIV XV XVI I

The yield of the desired product was 10% based on acid XIII.

Improved methods for the preparation lead to captopril in ∿30% yield [54]. A new variant of the synthesis, which is characterized by the high optical purity of captopril, was proposed in [55]. Compound I was obtained by condensation of 3-chloro-D-2-methylpropanoyl chloride with L-proline with subsequent replacement of the chlorine atom by a sulfhydryl group. Compound I was also obtained by microbiological synthesis [56].

The properties of the inhibition of ACE by a number of other L-proline derivatives have been investigated. The results make it possible to conclude (Table 1) that, first of all, an extremely important structural element that is responsible for the high activity is the sulfhydryl group. Replacement of the sulfhydryl residue by a methylthio group or a carboxy group leads to a sharp decrease in inhibition. Second, a three-carbon chain between the sulfhydryl and carboxy groups is optimal. The presence of an asymmetric carbon atom is extremely important: replacement of the hydrogen atom of the methylene group by a methyl radical leads to a decrease in the I_{50} values by three orders of magnitude. The conformation of the molecule, including the spatial orientation of the methyl group attached to the optically active carbon atom, has a great affect on the properties of the inhibitor. Third, the most active inhibitors are compounds that contain a free carboxy group of proline: the ethyl and tert-butyl esters are less active by factors of 20 to 30 as compared with the corresponding acids.

The inhibiting properties of 3-mercaptopropanoyl derivatives of other amino acids have been evaluated. With respect to the effect of inhibition of ACE, the 3-mercaptopropanoyl derivatives of amino acids can be arranged in the following order: L-Pro > L-Phe > L-Arg> L-Ala > L-Leu > L-Lys > Gly > L-Asp > β-ala > D-Pro.

3-Mercaptopropanoyl-L-proline has the greatest inhibition. The corresponding D-proline derivative has weak inhibiting activity (I_{50} 0.20 and 1800, respectively).

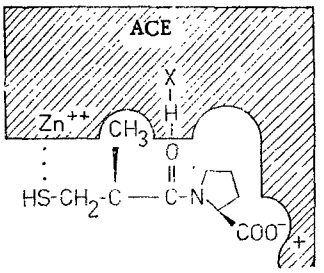


Fig. 1

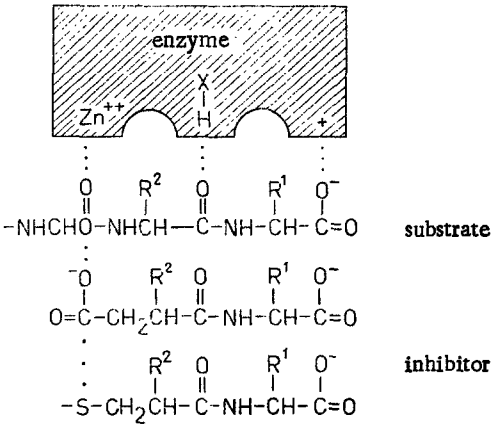


Fig. 2

Fig. 1. Interaction of inhibitor I with the active site of the enzyme.

Fig. 2. Model of the interaction of the enzyme with the inhibitor in the presence of a substrate.

The kinetics of the inhibition of ACE by inhibitor I and other proline derivatives have been investigated [57]. The Michaelis—Menten kinetic model has been used to describe the experimental data. Compound I is a typical competitive inhibitor with inhibition constant $k_i = 1.7 \cdot 10^{-9}$ mole.

The strongly pronounced inhibiting properties of captopril (I) are due to the strong interaction of the inhibitor molecule with the metalloprotein. A model of the interaction of the inhibitor with the enzyme is presented in Fig. 1 [58].

According to the model presented in Fig. 1, the enzyme is tied up with the inhibitor by means of three structural elements. A trans orientation of the peptide bond in the interaction of the carbonyl group with the XH group of the receptor has been postulated [45]. Electrostatic interaction between the anion of the L-proline residue and the positively charged groups of the enzyme [NH_3^+ or $-NHC(=NH_2^+)NH_2$] has been proposed [58]. The methyl group and the hydrophobic part of the proline molecule are included in "pockets" of the enzyme.

When a substrate is present, the enzyme interacts with the inhibitor, as, in general form, is represented in Fig. 2 [46].

In analogy with the preceding model, "packing" of the hydrophobic radicals in "pockets" of the enzyme, interaction of the carbonyl oxygen atom of the substrate and the inhibitor with the hydrogen donor of the enzyme, donor-acceptor interaction between the sulfur atom of the sulfhydryl group of the inhibitor and the zinc ions of the enzyme, and electrostatic interaction between the negatively charged carboxy groups of the substrate and the inhibitor and the positively charged enzyme groups are provided for.

The exceptional importance of the formation of a hydrogen bond between the donor centers of ACE and the oxygen atom of the carbonyl group was emphasized in [59]. Only compounds that are capable of forming a hydrogen bond — amides, esters, ketones, and sulfonamides — are effective inhibitors of the enzyme.

In connection with its high inhibiting capacity, captopril (I) has been studied extensively as a potential medicinal preparation [47-49]. The results of diversified investigations of the mechanism of the action of the above-mentioned substance, which were carried out by Squibb [60-62] and by other firms, have been published. Investigations of the antihypertensive properties of I in various research centers and clinics have shown its effectiveness in experimental and reno-vascular forms of hypertension [63-65], spontaneous hypertension [66, 67], and other hypertensive states [68, 69].

There have been numerous reports regarding the study by means of captopril (I) of the mechanisms of the regulation in the renin—angiotensin—aldosterone system [70, 71]. Studies dealing with its clinical tests have been published [72, 74].

In the treatment of hypertonic disease captopril is frequently used together with diuretic agents [65].

Captopril as a medicinal preparation has been checked over the span of a year in more than 1,000 hypertonic patients. Normalization of the blood pressure was observed in 50% of the patients. When captopril is used together with diuretic agents, the effectiveness of captopril increases sharply, and normalizaion of the blood pressure in this case is observed in 90% of the patients [11].

Unfortunately, undesirable side effects — rash, fever, a tendency for inflammatory processes, disruption of the sense of taste, and membrane glomerulopathy — have been noted [75]. Captopril is characterized by significant toxicity; this is associated with the presence of a sulfhydryl group in the captopril molecule. The latter is also responsible for a decrease in the activity of captopril during storage as a result of dimerization with the formation of a disulfide bridge [76]. Extensive investigations dealing with the synthesis of other pyrrolidine derivatives have therefore been carried out in order to decrease the toxicity and increase the stability of captopril during storage.

The synthesized analogs of captopril — pyrrolidine derivatives — can be divided into the following groups: 1) sulfur-containing analogs of captopril that are substituted in the aliphatic part and in the pyrrolidine ring and 2) those that do not contain the sulfur atom of the captopril analog.

Sulfur-Containing Analogs of Captopril — ACE Inhibitors

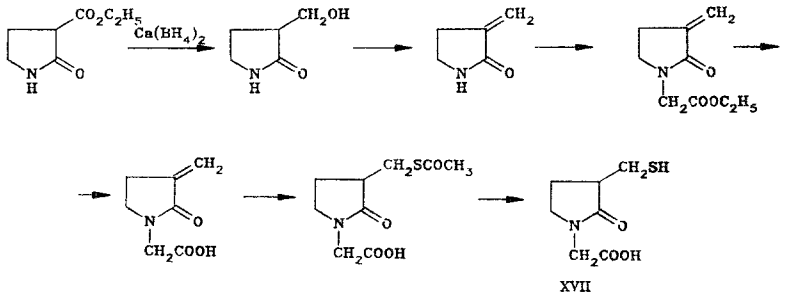
A large number of compounds that are characterized by the presence of a sulfhydryl group (or sulfide and disulfide groupings) and a pyrrolidine ring have been synthesized.

Amides, esters, and hydroxamides of pyrrolidine-carboxylic acids have been synthesized. Below we present a brief list of the information available regarding the structures and properties of sulfur-containing derivatives of pyrrolidine. Replacement of the methyl group of captopril by a phenyl or phenylalkyl substituent leads to inhibitors, the activity of which is comparable to the activity of captopril [77-91].

It is interesting to note that esters of captopril (I) that contain a nitrogen-containing heterocyclic system as the alcohol component, such as 1-(D-3-mercaptopropionyl)-L-proline-(5,6-dihydro-5-oxopyrazolo-1,5-quinolin-2-yl)methyl ester, are both ACE inhibitors and promising preparations for the treatment of allergies and asthma [92].

Analogs of captopril that are characterized by the presence of an L-proline residue substituted in the 3 and 4 positions by lower alkyl and hydroxy groups have been synthesized. Both the acids and their amides and esters have been investigated. These compounds are less active by approximately one order of magnitude compared with captopril.

What we have stated above also applies to analogs of captopril, viz., 2-pyrrolidine derivatives [95]. 3-Mercaptothyomethyl-2-oxo-1-pyrrolodinylacetic acid (XVII) and similar compounds have been synthesized via the following scheme:



XVII

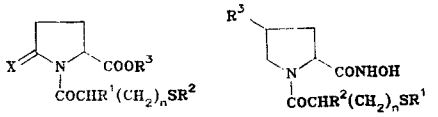
Compound XVII is an ACE inhibitor; however, its activity is lower by a factor of 100 compared with captopril.

In contrast to acid XVII, pyrrolidones and sulfur-containing derivatives of pyrrolidine with the general formula XVIII have high activity [96]. Their daily dose ranges from 0.1 to 100 mg/kg.

3-Oxo-pyrrolidine-2-carboxylic acid derivatives are effective ACE inhibitors [97] (the daily dose ranges from 1 to 15 mg/kg).

Halo-containing pyrrolidines [98] which have low toxicity, are characterized by reduced activity as compared with captopril.

High activity, which is equal to the activity of captopril, is characteristic for halo derivatives of hydroxamic acids [99, 100]:



XVIII XIX

XVIII R^1=H, Alk, CF_3; R^2=H, AlkCO; R^3=H, Alk, Ph_2CH; X=O, S; n=0, 1; XIX R^1=H, Alk, Ar, aralkyl, R^2=H, Alk, CF_3, C_2F_5; R^3=H, OH, Cl, F; n=0—2

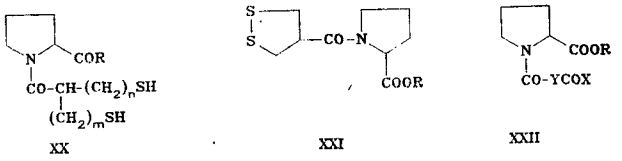
1-Mercaptoacyl-4-azido-L-proline and its esters are promising ACE inhibitors [101]. The activity of the latter is comparable to the activity of captopril.

Compounds of the XX type, which contain two sulfhydryl groups [102] and have similar activities, as well as similar side effects with respect to captopril, have been synthesized.

Aliphatic and cyclic disulfides [97, 103-114] are less active by a factor of 10 as compared with captopril. High stability of cyclic disulfides XXI during storage has been noted [103].

Thioamides such as 1-(3-benzoylthio-2-methylthiopropionyl)-L-proline, etc., also have antihypertensive properties [115, 116]. The activity of the inhibition of ACE is close to the activity of captopril.

Furyl,- benzofuryl-, and benzothienyl derivatives (XXII) of captopril are relatively inactive, and much less research has been devoted to them [117-119]:



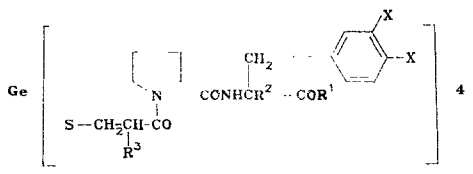
XX XXI XXII

XX R=OH, AlkO; m, n=0, 1; XXI R=H, Alk, aralkyl XXII X= 2- or 3-furyl, 2- or 3-benzofuryl, 2- or 3-benzothienyl; Y=CHR^1—CR^2R^3, CH_2—CHR^1R^3—CHR^2, CHR^3—CHR^4 (R^3—SH, formylthio, benzylthio, alkanothic, etc.; R^4—H, Alk); R—H, Alk, cation

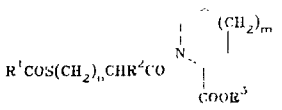
Seleno-containing derivatives of proline [120] and zinc-containing analogs of captopril [121] are capable of interacting with a metalloenzyme that converts angiotensin. Zinc-containing derivatives of proline have antihypertensive properties and are also promising as agents for the treatment of rheumatism.

Highly active analogs of captopril are germanium-containing derivatives of proline XXIII [122], which are obtained by the reaction of germanium oxide with the corresponding mecapto-substituted pyrrolidines. Such germanium derivatives are applicable for the prophylaxis and treatment of essential, reno-vascular, and adrenal forms of hypertension. The daily dose in the case of oral administration ranges from 0.1 to 200 mg/kg. Medicinal forms of these preparations have been developed. The presence of high activity of the zinc- and germanium-containing analogs of captopril for the inhibition of ACE makes it possible to assume that, in addition to the zinc ions of the metalloenzyme, other active charge groupings such as COO^- also participate in tying up the compounds mentioned above with the enzyme.

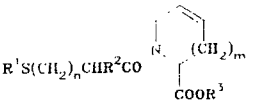
Derivatives of 2,3- and 3,4-dihydropyrrolodinecarboxylic acids XXIV [123-125], XXV [126-128], and tetrahydropropyridinecarboxylic acids have been proposed as effective antihypertensive agents:



XXIII



XXIV



XXV

XXIII R^1=OH, AlkO, NH_2; R^2=H, Me, R^3=H, Alk; X=H, OH; XXIV R^1=H, OH, Hal, Alk; R^2, R^3=H, Alk; m, n=0,1; XXV R^1=H; R^2, R^3=H, Alk; m, n=0, 1

Identical and equal captopril doses, which amount to 0.1 to 100 mg/kg, are characteristic for derivatives of 2,3- and 3,4-dehydropyrrolidinecarboxylic acids.

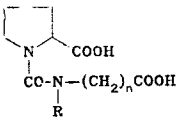
Captopril Analogs that Do Not Contain Sulfur

Since many authors have expressed the assumption that the undesirable phenomena observed in the treatment of hypertonia with captopril are associated with the presence of a SH group and, a sulfur atom in general, more and more attention is being directed by researchers to the synthesis and study of the properties of proline derivatives that do not contain sulfur.

N-[N-Ethyl-N-(2-carboxyethyl)carbamoyl]-L-proline and other compounds of the XXVI type were synthesized in 1979 [129]. Compounds XXVI are ACE inhibitors and have the activity of a coronary vasodilator.

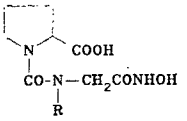
N-(O-Hydroxybenzoyl)-L-proline has also proved to be an ACE inhibitor [130]; however, its activity is considerably lower than the activity of captopril.

As in the case of sulfur-containing derivatives of proline, hydroxamic acids XXVII have high inhibiting properties [131].



XXVI

XXVI R=Alk; n=1, 2



XXVII

XXVII R=Alk

Phosphonoacylprolines [132-138], which are characterized by low toxicity and are promising antihypertensive agents, have been proposed as ACE inhibitors. However, the doses necessary for reducing the blood pressure reach 10 to 1,000 mg/kg.

[(Mercaptoalkanoyl)pyrrolidinyl]phosphic acids, for which the active doses range from 1 to 1,000 mg/kg, also have reduced activity as compared with captopril [139].

In the case of the zinc-containing metalloenzyme thermolysine it has been shown that the phosphoryl group of the inhibitor is tied up with the zinc atom of the active site of the enzyme [140]. It might be assumed that a similar mechanism occurs in the reaction of phosphonoacylprolines with ACE.

Thus, of the synthesized proline derivatives, the most active compounds are those that contain in the aliphatic part an SH group, an amide bond, and the free carboxy group of proline. The optimum number of methylene groups in the aliphatic chain ranges from one to three. The activity increases when a hydrogen atom of the methylene group is replaced by methyl and phenyl groups and other radicals. In the case of captopril the D configuration of the 3-mercapto-2-methylpropanoyl radical is responsible for a sharp increase in activity as compared with the L configuration. Sulfides and disulfides (both aliphatic and cyclic) are less active but are more stable as compared with proline derivatives that contain a sulfhydryl group. Highly activators of ACE inhibitors are derivatives of dehydroproline, zinc- and germanium-containing derivatives of proline, as well as hydroxamates of substituted prolines. Phosphorus-containing derivatives of proline, which, although they are inferior with respect to activity of captopril, are also promising, are characterized by low toxicity. The introduction of an oxygen atom or alkyl radicals into the proline ring basically leads to a decrease in the activity of the inhibitor, which, possibly, is associated with steric hindrance in the formation of the enzyme—inhibitor complex.

In addition to the properties of an ACE inhibitor, esters of substituted prolines in a number of cases have antiallergenic properties.

The high activity of a large number of the most diverse (with respect to composition and structure) derivatives of pyrrolidine, in our opinion, constitutes evidence that the centers

on which the compounds mentioned above are adsorbed have different chemical natures. In addition to the competitive inhibitors adsorbed on the same active centers as the substrate, viz., angiotensin I, there evidently exist a large number of noncompetitive inhibitors that are adsorbed on other parts of the surface of the enzyme than the substrate but retard the decomposition of the enzyme–substrate complex, which also leads to a decrease in the rate of conversion of angiotensin I to II.

LITERATURE CITED

1. G. I. Chipens, L. K. Polevaya, N. I. Veretennikova, and A. Yu. Krikis, Structures and Functions of Low-Molecular-Weight Peptides [in Russian], Zinatne, Riga (1980).
2. S. G. Galaktionov, G. V. Nikiforovich, G. I. Chipens, and M. D. Shenderovich, Angiotensin. Molecular Mechanisms of Its Action [in Russian], Zinatne, Riga (1979).
3. A. A. Klesov and I. V. Berezin, Enzymatic Catalysis [in Russian], Izd. MGU, Moscow (1980).
4. L. Webb, Enzyme and Metabolic Inhibitors, Academic Press (1966).
5. Z. P. Horowitz, Angiotensin-Converting Enzyme Inhibitors: Mechanisms of Action and Clinical Implications, Baltimore, Maryland (1981), p. 451.
6. D. Ganten, M. P. Printz, M. I. Philips, and B. A. Schoelkens, The Renin Angiotensin System in the Brain: A Model for the Synthesis of Peptides in the Brain, Springer-Verlag, Berlin (1982), p. 385.
7. D. W. Cushman, and M. A. Ondetti, Prog. Med. Chem., 17, 41 (1980); Chem. Abstr., 94, 11994 (1981).
8. T. Unger, B. Schuell, G. Speck, and D. Ganten, in: Enzyme Inhibitors, Proc. Meet. (1980), p. 223; Chem. Abstr., 94, 149788 (1981).
9. T. Kobuku and Y. Takada, Igaku No Ayumi, 117, 601 (1981); Chem. Abstr., 95, 94940 (1981).
10. D. W. Cushman, M. A. Ondetti, and B. Rubin, in: Front. Hypertens. Res. [Proc. Int. Symp., 1980] (1981), Springer, New York, p. 595; Chem. Abstr., 95, 56875 (1981).
11. M. A. Ondetti and D. W. Cushman, J. Med. Chem., 24, 355 (1981).
12. J. Iwao, T. Iso, and M. Oya, Yuki Gosei Kagaku Kyokaishi, 38, 1100 (1980): Chem. Abstr., 94, 187440 (1981).
13. E. G. Erdoes, in: Topics in Hypertension, Edited by J. H. Laragh, Yorke Med. Books, New York, p. 21; Chem. Abstr., 94, 44513 (1981).
14. D. W. Cushman, H. S. Cheung, E. F. Sabo, and M. A. Ondetti, in: Adv. Pharmacol. Ther., Proc. 8th Int. Congr. (1981) (Published in 1982), Part 3, p. 249, by H. Yoshida, Y. Hagihara, and S. Ebashi, eds., Pergamon, Oxford, United Kingdom; Chem. Abstr., 96, 212912 (1982).
15. P. S. Semple, Jr., J. Clin. Pharmacol., 12, Supplement 1, 11 (1981); Chem. Abstr., 96, 27997 (1982).
16. B. Rubin, M. J. Antonaccio, and Z. P. Horovitz, in: Captopril Hypertens. [Coll. Papers Symp. 1979] (Published in 1980), p. 115, Edited by D. B. Case, E. H. Sonnenblick, and J. H. Laragh, Plenum Press, New York; Chem. Abstr., 94, 76302 (1981).
17. B. Waeber, H. R. Brunner, J. P. Wauters, and H. Gavras, Adv. Nephrol. Necker Hosp, 10, 111 (1981); Chem. Abstr., 96, 79218 (1982).
18. H. Schweisfurth, Mater. Med. Nordmark, 33, No. 4, 190 (1981); Chem. Abstr., 95, 199525 (1981).
19. K. Miura, T. Yukimura, F. Ikemoto, and K. Yamamoto, Sogo Rinsho, 31, No. 1, 27 (1982); Chem. Abstr., 96, 115307 (1982).
20. D. A. Carretero, A. G. Scicli, and S. R. Maitra, in: Angiotensin-Converting Enzyme Inhibitors [Proc. A. N. Richards Symp. (1980)] (Published in 1981), Edited by Z. P. Horovitz, Urban–Schwarzenberg, Baltimore, Maryland; Chem. Abstr., 95, 59 (1981).
21. C. I. Johnston, M. Yasujima, and B. H. Clappison, in: Angiotensin-Converting Enzyme Inhibitors [Proc. A. N. Ricards Symp. (1980)] (Published in 1981), p. 123, Edited by Z. P. Horovitz, Urban–Schwarzenberg, Baltimore, Maryland; Chem. Abstr., 95, 60 (1981).
22. J. A. Reid, Mod. Pharmacol.-Toxicol., 19, (Hypertens. Res.) 101 (1982); Chem. Abstr., 96, 136005 (1982).
23. M. J. Antonaccio, Clin. Exp. Hypertens, 4, Nos. 1-2, 27 (1982); Chem. Abstr., 96, 192700 (1982).
24. M. R. Lee, Br. J. Clin. Pharmacol., 12, 605 (1981); Chem. Abstr., 96, 46288 (1982).
25. L. B. Klickstein, C. E. Kaempfer, and B. U. Wintroub, J. Biol. Chem., 257, 15042 (1982).
26. K. Yamamoto, K. Miura, Y. Abe, T. Komori, and S. Yoshimoto, Horm. Antagonists, 475 (1982); Chem. Abstr., 96, 174441 (1982).

27. R. L. Soffer, in: Biochemical Regulation of Blood Pressure, Edited by R. L. Soffer, Wiley, New York (1981), p. 123.
28. W. E. Siems and W. Halle, Pharmazie, 37, 539 (1982).
29. M. A. Ondetti, and D. W. Cushman, in: Biochemical Regulation of Blood Pressure, R. L. Soffer, ed., Wiley, New York (1981), p. 165.
30. M. A. Ondetti, D. W. Cushman, E. F. Sabo, S. Natarajan, P. Plusec, and B. Rubin, Dev. Biochem., 19, (Mol. Basis Drug Action), 235 (1981); Chem. Abstr., 97, 16391 (1982).
31. M. J. Antonacci, Ann. Rev. Pharmacol. Toxicol., 22, 57 (1982); Chem. Abstr., 97, 16395 (1982).
32. D. W. Cushman, H. S. Cheung, E. F. Sabo, and M. A. Ondetti, Amer. J. Cardiol., 49, 1390 (1982).
33. E. W. Petrillo and M. A. Ondetti, Med. Res. Rev., 2, No. 1, 1 (1982).
34. P. Buenning and J. F. Riordan, in: Metab. Interconvers. Enzymes, Int. Titische Conf. (1980) (Published in 1981), p. 248; Chem. Abstr., 97, 35074 (1982).
35. M. Das and R. L. Soffer, J. Biol. Chem., 250, 6762 (1975).
36. G. A. Oshima, A. Gesce, and E. G. Erdös, Biochim. Biophys. Acta, 350, 26 (1974).
37. H. A. El-Dorry, H. G. Bull, K. Iwata, N. A. Thornberry, E. H. Cordes, R. L. Soffer, Biol. Chem., 257, 14128 (1982).
38. R. L. Soffer, Annu. Rev. Biochem., 45, 73 (1976).
39. T. Tsuji, K. Hirai, Kagaku (Kyoto), 36, 707 (1981); Chem. Abstr., 95, 16992 (1981).
40. L. T. Skeggs, W. H. Marsch, J. R. Kahn, and N. P. Shumway, J. Exp. Med., 99, 275 (1954).
41. E. G. Erdös, Fed. Proc., 36, 1760 (1977).
42. H. Y. T. Hang, E. G. Erdös and Y. Levin, Biochim. Acta, 214, 374 (1970).
43. S. H. Ferreira, D. C. Bartelt, and L. J. Green, Biochemistry, 9, 2583 (1970).
44. M. A. Ondetti, E. F. Sabo, K. Losse, H. Cheung, D. W. Cushman, and B. Rubin, in: Peptides. Proceedings of the 5th American Symposium (1977), p. 576.
45. C. H. Hassall, A. Kröhn, C. Moody, and W. A. Thomas, FEBS Lett., 147, No. 2, 175 (1982).
46. D. W. Cushman, H. S. Cheung, E. F. Sabo, and M. A. Ondetti, Biochemistry, 16, 5484 (1977).
47. B. Rubin, R. J. Laffan, D. G. Kotler, E. H. O'Keefe, D. A. Demaio, and M. E. Goldberg, Fed. Proc., 36, 1049 (1977).
48. B. Rubin, R. J. Laffan, D. G. Kotler, E. H. O'Keefe, D. A. DeMaio, and M. E. Goldberg, J. Pharmacol. Exp. Ther., 204, 271 (1978).
49. B. Rubin, R. J. Laffan, D. G. Kotler, E. H. O'Keefe, D. A. DeMaio, J. Pharmacol. Exp. Ther., 204, 281 (1978).
50. R. H. Freeman, J. O. Davis, and B. E. Watkins, IRCS Med. Sci., Libr. Compen., 5, 470 (1977); Chem. Abstr., 88, 44944 (1978).
51. D. N. Harris, C. L. Heran, H. J. Goldenberg, J. P. High, R. J. Laffan, B. Rubin, M. J. Antonaccio, and M. E. Goldberg, Eur. J. Pharmacol., 51, 345 (1978).
52. R. F. Meyer, A. D. Essenburg, R. D. Smith, and H. R. Kaplan, J. Med. Chem., 25, 996 (1982).
53. H. Koch, Pharmacol. Int., 2, No. 8, 164 (1981).
54. J. Fischer, L. Rozsa, A. Bakonyi, G. Fazekas, and P. Vago, British Patent No. 2066252; Chem. Abstr., 96, 69426 (1982).
55. M. Shimazaki, J. Hasegawa, K. Kan. K. Nomura, Y. Nose, H. Kondo, T. Ohashi, and K. Watanabe, Chem. Pharm. Bull., 30, 3139 (1982).
56. J. Hasegawa, M. Ogura, S. Hamaguchi, M. Shimazaki, H. Kawaharda, and K. Watanabe, US Patent No. 4310635; Chem. Abstr., 95, 59935 (1981).
57. H. S. Cheung, and D. W. Cushman, Biochim. Biophys. Acta, 293, 451 (1973).
58. D. W. Cushman and M. A. Ondetti, TIPS, No. 6, 260 (1980).
59. M. E. Condon, E. W. Pettrillo Jr., D. E. Ryono, J. A. Reid, R. Neubeck, M. Puar, J. E. Heikes, E. F. Sabo, and K. A. Losee, J. Med. Chem., 25, 250 (1982).
60. B. Watkins, I. D. Davis, R. H. Freeman, and G. Stephens, Proc. Soc. Exp. Biol. Med., 157, 245 (1978).
61. R. G. Bengis, T. G. Coleman, D. B. Young, and R. E. McCaa, Circ. Res., 43, 45 (1978).
62. E. E. Muirhead, R. L. Prewitt, B. Brooks, and W. L. Brosius, Circ. Res., 43, 53 (1978).
63. M. Benuck and N. Marcs, J. Neurochemistry, 30, 1653 (1978).
64. G. J. Trachte and A. M. Leffer, Circ. Res., 43, 576 (1978).
65. E. R. Squibb, Drugs of the Future, 4, No. 11, 844 (1979).
66. R. R. Volmer, J. A. Boccagno, D. N. Harris, and V. S. Murthy, Eur. J. Pharm., 51, 39 (1978).
67. R. R. Volmer and J. A. Boccagno, Eur. J. Pharmacol., 45, 117 (1977).

68. V. S. Murthy, T. Waldron, and M. E. Goldberg, Proc. Soc. Exp. Biol. Med., 157, 121 (1978).
69. R. S. McCaa, IRCS Med.-Sci., Libr. Compend., 5, 207 (1977).
70. V. S. Murthy, T. L. Waldron, and M. E. Goldberg, Circ. Res., 43, 40 (1978).
71. V. S. Murthy and T. L. Waldron, Eur. J. Pharm., 46, 207 (1978).
72. R. K. Furguson, G. Turimi, H. Bruner, H. Gavras, and D. McKinstry, Lancet, No. 8015, 775 (1977).
73. H. Gavras, H. R. Bruner, G. Turini, S. Guttelod, J. Gavras, P. Vukovich, and D. McKinstry, N. Engl. J. Med., 298, 991 (1978).
74. H. R. Bruhner, B. Waeber, J. P. Wauters, G. Turini, D. McKinstry, and H. Gavras, Lancet, No. 8092, 704 (1978).
75. T. Ungerd, D. Gunten, and R. E. Lang, TIPS, 4, No. 12, 514 (1983).
76. F. M. Lai, H. Herzbinger, and P. Eervom, IRCS Med. Sci., Libr. Compend., 9, 625 (1981); Chem. Abstr., 95, 161681 (1981).
77. Z.P. Horowitz and B. Rubin, Belgian Patent No. 873092 Chem. Abstr., 91, 145975 (1979).
78. S. H. Natarajan and M. A. Ondetti, Ger. Offen, No. 2914793; Chem. Abstr., 92, 110842 (1980).
79. Sumitomo Chemical Co., Ltd., Japanese Patent No. 5118456; Chem. Abstr., 94, 120879 (1981).
80. Sumitomo Chemical Co., Ltd., Japanese Patent No. 5122785; Chem. Abstr., 94, 120879 (1981).
81. J. Krapcho, U.S. Patent No. 4217359; Chem. Abstr., 93, 239957.
82. J. Krapcho, M. Oya, and T. Iso, Japanese Patent No. 6086153; Chem. Abstr., 95, 62714 (1981).
83. J. Iwao, M. Oya, and T. Iso, Japanese Patent No. 5015458; Chem. Abstr., 93, 155843 (1980).
84. D. W. Cushman and M. A. Ondetti, USSR Inventor's Certificate No. 694070; Byull. Izobret., No. 39, 240 (1979).
85. C. Malen, P. Roger, and M. Laubie, French Patent No. 2419728 Chem. Abstr., 91, 107888 (1979).
86. R. D. Haugwitz, British Patent No. 2061931; Chem. Abstr., 96, 20460 (1982).
87. T. Sawayama, H. Kinugasa, H. Nishimura, K. Takeyama, and K. Hosoki, European Patent No. 7477; Chem. Abstr., 93, 72299 (1980).
88. A. J. Cohen and K. J. Kripalani, U.S. Patent No. 4179568; Chem. Abstr., 92, 147204 (1980).
89. J. T. Suh, B. E. Williams, and J. W. Skiles, European Patent No. 39804; Chem. Abstr., 96, 122647 (1982).
90. Sumitomo Chemical Co., Japanese Patent No. 7046961; Chem. 97, 6145 (1982).
91. J. N. Korzun, US Patent No. 4332726; Chem. Abstr., 97, 145282 (1982).
92. G. B. Mackaness and K. A. Losee, US Patent No. 4307099; Chem. Abstr., 96, 122821 (1982).
93. B. V. Oce-Andeno, European Patent No. 8831; Chem. Abstr., 93, 114320 (1980).
94. D. D. How, J. Preston, E. R. Walker, and A. H. Ratcliffe, European Patent No. 54017; Chem. Abstr., 97, 39392 (1982).
95. S. Klutchko and M. L. Hoefle, J. Med. Chem., 24, 104 (1981).
96. M. A. Ondetti, E. M. Gordon, and D. E. Ryono, US Patent No. 4234489; Chem. Abstr., 94, 103837 (1981).
97. E. R. Squibb and Sons, Inc. Belgian Patent No. 882366; Chem. Abstr., 94, 175569 (1981).
98. N. Fukuzawa, Japanese Patent No. 6051450; Ref. Zh. Khim., 14013P (1982).
99. E. W. Petrillo and M. A. Ondetti, US Patent No. 4284561; Ref. Zh. Khim., 1009P (1982).
100. E. W. Petrillo and M. A. Ondetti, US Patent No. 4308392; Chem. Abstr., 96, 7079 (1982).
101. E. W. Petrillo and F. L. Weisenborn, US Patent No. 4296033; Ref. Zh. Khim. Zh., 103010P (1982).
102. M. A. Ondetti and F. L. Weisenborn, USSR Inventor's Certificate No. 731891; Byull. Izobret., No. 16, 296 (1980).
103. Y. Oka, T. Aono, and K. Omure, Japanese Patent No. 4125669; Chem. Abstr., 92, 215770 (1980).
104. M. A. Ondetti and P. W. Sprague, US Patent No. 4154936; Chem. Abstr., 91, 74900 (1979).
105. M. A. Ondetti and J. Krapcho, Ger. Offen., No. 2932021; Chem. Abstr., 93, 186788 (1980).
106. J. Krapcho, Dutch Patent No. 7909246; Chem. Abstr., 93, 239216 (1980).
107. M. A. Ondetti and P. W. Sprague, US Patent No. 4241076; Chem. Abstr., 94, 175557 (1981).

108. M. A. Ondetti and P. W. Sprague, Belgian Patent No. 874345; Chem. Abstr., 92, 76268 (1980).
109. F. J. McEvoy, W. B. Wright, G. H. Brinberg, and J. D. Albright, US Patent No. 4299769; Chem. Abstr., 96, 143334 (1982).
110. M. A. Ondetti and M. E. Condon, US Patent No. 4311705; Chem. Abstr., 96, 200175 (1982).
111. J. Krapcho, British Patent NO. 2078733; Chem. Abstr., 97, 24238 (1982).
112. J. Krapcho and P. C. Wade, US Patent No. 4310461; Ref. Zh. Khim., 23019P (1982).
113. J. Krapcho, US Patent No. 4311697; Ref. Zh. Khim., 20018P (1982).
114. M. E. Condon and M. A. Ondetti, US Patent No. 4307110; Ref. Zh. Khim., 16018P (1982).
115. T. Munakata, Japanese Patent No. 6068664; Chem. Abstr., 95, 168986 (1981).
116. T. Munakata, Japanese Patent No. 6068665; Chem. Abstr., 95, 168987 (1981).
117. F. J. McEvoy, W. B. Wright, G. H.Birnberg, and J. D. Albright, US Patent No. 4342691; Ref. Zh. Khim., 9019P (1983).
118. F. J. McEvoy, W. B. Wright, G. H. Birnberg, and J. D. Albright, US Patent No. 4342689; Ref. Zh. Khim., 13018P (1983).
119. F. J. McEvoy, W. B. Wright, G. H. Birnberg, and J. D. Albright, US Patent No. 4342690; Ref. Zh. Khim., 9020P (1983).
120. R. D. Haugwitz and F. L. Weisenborn, US Patent No. 4181663; Chem. Abstr., 93, 8518 (1980).
121. Yoshitomi Pharm. Industries, Japanese Patent No. 5164673; Chem. Abstr., 95, 62700 (1981).
122. Sankyo Co. Ltd., Japanese Patent No. 7058654; Chem. Abstr., 97, 163514 (1982).
123. M. A. Ondetti and M. E. Condon, US Patent No. 4217458; Chem. Abstr., 96, 200175 (1982).
124. A. M. Felix, M. R. Cohen, and J. A. Meienhofer, Japanese Patent No. 5094358; Chem. Abstr., 94, 31074 (1981).
125. S. Natarajan, M. E. Condon, M. S. Cohen, J. Reid, D. W. Cushman, B. Rubin, and M. A. Ondetti, in: Pept. Struct. Biol. Funct., Proc. Am. Pept. Symp., 6th; Chem. Abstr., 94, 98616 (1981).
126. M. A. Ondetti and S. I. Natarajan, US Patent No. 4129566; Chem. Abstr., 90, 151983 (1979).
127. M. A. Ondetti and S. I. Natarajan, British Patent No. 2014573; Chem. Abstr., 90, 151983 (1979).
128. M. A. Ondetti and S. I. Natarajan, Belgian Patent No. 874202; Chem. Abstr., 90, 151983 (1979).
129. Tanabe Seiyaku Co., Ltd., Japanese Patent No. 5151555; Chem. Abstr., 94, 121310 (1981).
130. M. Arimura, H. Ao, and T. Oka, Japanese Patent No. 4019969; Chem. Abstr., 91, 21119 (1979).
131. Tanabe Seiyaku Co., Ltd., Japanese Patent No. 6097266; Chem. Abstr., 95, 220316 (1981).
132. M. A. Ondetti and E. W. Petrillo, US Patent No. 4151172; Chem. Abstr., 91, 108230 (1979).
133. E. R. Squibb and Sons, Inc., European Patent No. 833; Chem. Abstr., 91, 21396 (1979).
134. E. W. Petrillo, US Patent No. 4168267; Chem. Abstr., 92, 76922 (1980).
135. E. W. Petrillo, US Patent No. 4337201; Ref. Zh. Khim., 5015P (1983).
136. E. D. Thorsett, A. A. Patchett, E. E. Harris, and A. L. Maycock, European Patent No. 9183; Chem. Abstr., 93, 72306 (1980).
137. S. Sakakibara, Japanese Patent No. 7085694; Chem. Abstr., 97, 198576 (1982).
138. C. M. Kam, N. Nishino, and J. C. Powers, Biochemistry, 18, 3032 (1978).
139. E. W. Petrillo, British Patent No. 2040944; Chem. Abstr., 93, 8008 (1980).
140. R. W. Lane, J. A. Ibers, R. B. Frankel, G. C. Papaefthymiou, and R. H. Holm, J. Am. Chem. Soc., 99, 84 (1977).