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Epoxyalkanoyls as Novel ACE Inhibitors

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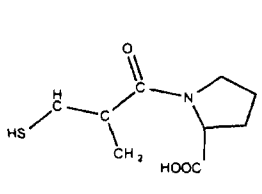
The epoxyalkanoyl derivatives were designed and synthesized as ACE inhibitors. Coupling of unsaturated carboxylic acids with amino acids and following epoxidation with dimethyldioxirane gave the epoxyalkanoyls with high yield. The inhibitory activity of synthesized compounds on angiotensin converting enzyme was IC_{50} values of 0.06~5.5 μM.

Key words : Epoxides, Angiotensin converting enzyme inhibitor, Irreversible inhibition

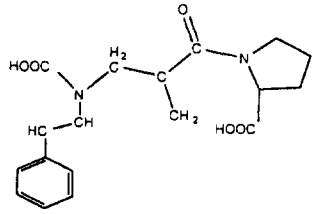
INTRODUCTION

Angiotensin converting enzyme (ACE) is a nonspecific peptidase that cleaves dipeptides from a wide variety of natural and synthetic peptides including angiotensin I. It has been known that the active site of ACE is structurally similar to that of carboxypeptidase A (CPA). The only difference is that the distance between the basic arginine residue which forms a salt bridge with the carboxylate and the zinc ion which is known to activate the scissile amide carbonyl group of substrate through coordination to the oxygen atom (Cushman *et al.*, 1977).

ACE inhibitors are widely used in clinics for hypertension and congestive heart failure. Since the discovery of captopril, there have been reported numerous ACE inhibitors, most of which are structually related to captopril (Ondetti *et al.*, 1977). In these inhibitors a free carboxyl group presumably forms hydrogen bonds with arginine residue of ACE, another essential structural feature found in these inhibitors in common is a zinc-binding ligand; for example sulfhydryl group in captopril, carboxyl group in enalaprilat, or phosphoryl group in fosenopril (Kostis *et al.*, 1987).



Captopril



Enalaprilat

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Recently, 2-benzyl-3,4-epoxy-butanoic acid (BEBA) was reported as a pseudomechanism-based inactivator for CPA, in which the epoxy group was thought to be activated through ligation to the active site zinc

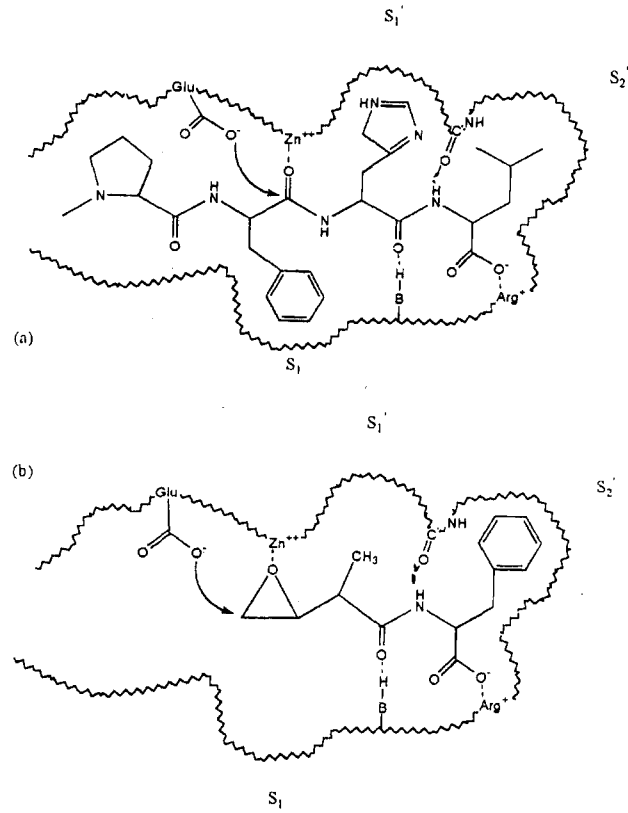


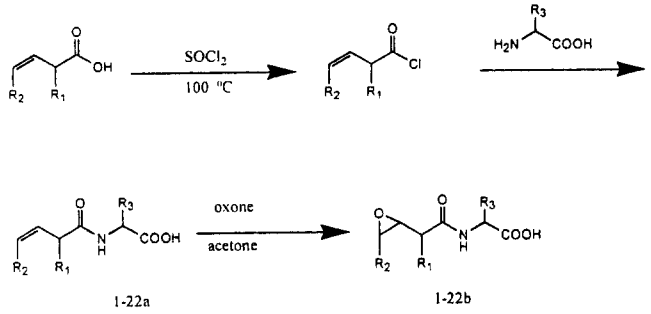
Fig. 1. (a) Hypothetical active site model of ACE illustrating the cleavage of angiotensin I to give angiotensin II and His-Leu (Kostis *et al.*, 1987). (b) The hypothesized binding mode of epoxyalkanoyl amino acid to the active site of ACE.

ion (Kim and Kim, 1991). Thus it covalently modifies the carboxylate of Glu-270 present at the active site of the enzyme.

We have designed ACE substrate analogs which bear an oxirane as potential pseudomechanism-based inactivator for ACE (Fig. 1). Such inactivators are supposedly superior to the existing inhibitors of ACE because they are expected to cause permanent loss of the enzyme activity. This report describes synthesis and evaluation of these potential inactivators for ACE.

MATERIALS AND METHODS

All of the epoxy amides and esters reported herein were prepared from unsaturated carboxylic acids as shown in scheme 1. Unsaturated carboxylic acids were converted to acyl chlorides which were then treated with amino acids to give the amides (Ondetti and Cushman, 1977). Subsequent reaction of the amides with dimethyldioxirane provided epoxy amides (Corey and Ward, 1986; Yoo *et al.*, 1991). For the synthesis of epoxy ketones, typical malonic ester alkylation methods were employed (Beckwith *et al.*, 1988; Sum and Weiler, 1979; Weiler, 1970). Pertinent spectral data for the compounds thus synthesized are listed in Table I, II.



Scheme 1.

General procedure for the coupling

A mixture of thionyl chloride (1.785 g, 15 mmole) and alkenoic acid (0.01 mole) was stirred at 80°C for 2 hrs. When no more white gas was evolved, the remaining thionyl choride was removed by rotatory evaporator. L-Amino acid (6.5 mmole) was dissolved in 1 N sodium hydroxide solution (6.5 ml) and the solution was chilled in an ice-water bath. To the ice chilled solution was added sodium hydroxide (2 N, 3.5 ml) and the acid chlorides prepared (6.5 mole) and the mixture was stirred vigorously at room temperature for 3 hrs. The reaction mixture was washed with ether and the water layer was acidified to pH 1~2 with conc. HCl and extracted with ethyl acetate. The ethyl

Table I. Yield and spectral data of amides, esters and ketones

Compound No	Yield (%)	mp (°C)	IR (cm^{-1})	MS (m/z)	H^1-NMR (ppm)
1a	76	98-102	3350, 3400-2500, 1620	233 (M^+)	2.9 (d, 2H), 3.1 (t, 2H), 4.9 (q, 1H), 5.2 (d, 2H), 5.6-5.9 (m, 1H), 6.3 (d, 1H), 7.2 (s, 5H), 12.6 (s, 1H)
2a	92	-	3300, 3400-2500, 1620	248 (MH^+)	1.6 (t, 3H), 2.8 (d, 2H), 3.1 (q, 2H), 4.8 (q, 1H), 5.3-5.6 (m, 2H), 6.2 (d, 1H), 7.2 (s, 5H), 10.2 (s, 1H)
3a	80	85-87	3300, 3400-2700, 1630	261 (M^+)	1.0 (t, 3H), 2.1 (q, 2H), 2.9 (d, 2H), 3.1-3.3 (m, 2H), 4.8 (q, 1H), 5.2-5.8 (m, 2H), 6.3 (d, 1H), 7.2 (s, 5H), 8.1 (s, 1H)
4a	41	-	3250, 3400-2700, 1630	292 (MH^+)	2.1 (d, 2H), 2.9-3.2 (m, 2H), 4.8 (q, 1H), 5.5-5.8 (m, 2H), 7.3 (s, 5H), 8.3 (s, 1H)
5a	75	60-63	3250, 3400-2700, 1430	234 (MH^+)	1.8 (dd, 3H), 3.1 (t, 2H), 4.9 (q, 1H), 5.7 (d, 1H), 5.9 (d, 1H), 6.5 (d, 1H), 7.2 (s, 5H), 11.4 (s, 1H)
6a	79	-	3350, 3400-2600, 1600	234 (MH^+)	1.9 (s, 3H), 3.2 (d, 2H), 4.9 (q, 1H), 5.3 (s, 1H), 5.6 (s, 1H), 6.5 (d, 1H), 7.2 (s, 5H), 9.6 (s, 1H)
7a	88	-	3300, 3400-2600, 1630	247 (M^+)	1.3 (dd, 3H), 2.9-3.0 (m, 1H), 3.1-3.3 (m, 2H), 4.9 (q, 1H), 5.1-5.2 (m, 2H), 5.8-6.0 (m, 1H), 6.3 (s, 1H), 7.3 (s, 5H), 10.3 (s, 1H)
8a	87	-	3320, 3400-2600, 1620	276 (MH^+)	1.2 (d, 6H), 2.3 (t, 2H), 3.1 (t, 2H), 4.8 (q, 1H), 5.1 (d, 2H), 5.4-5.7 (m, 1H), 6.3 (d, 1H), 7.2 (s, 5H), 11.5 (s, 1H)
9a	80	99-101	3300, 3400-2500, 1650	282 (MH^+)	1.2 (dd, 3H), 3.0-3.1 (m, 2H), 3.2 (m, 1H), 4.8 (m, 1H), 5.2 (t, 2H), 5.7-5.9 (mm, 1H), 6.2 (t, 1H), 7.1 (t, 2H), 7.3 (t, 2H), 9.7 (s, 1H)
10a	79	124-126	3300, 3400-2600, 1650	293 (MH^+)	1.3 (dd, 3H), 3.0 (t, 1H), 3.2-3.4 (m, 2H), 4.9 (m, 1H), 5.2 (t, 2H), 5.7-5.8 (m, 1H), 6.2 (t, 1H), 7.4 (q, 2H), 8.1 (t, 2H), 9.5 (S, 1H)
11a	67	-	3300, 3400-2700, 1630	264 (MH^+)	1.2 (dd, 3H), 2.0-2.1 (m, 2H), 3.0-3.2 (m, 2H), 4.7-4.8 (m, 2H), 5.0-5.2 (m, 2H), 5.8-5.9 (m, 1H), 6.4 (q, 1H), 6.8-6.9 (9d, 2H), 7.1-7.2 (m, 2H), 8.4 (s, 1H)
12a	63	-	3250, 3400-2600, 1600	198 (MH^+)	1.2 (dd, 3H), 2.0 (s, 4H), 3.0-3.2 (m, 1H), 3.6 (t, 2H), 4.5 (t, 1H), 5.0-5.1 (m, 2H), 5.7-5.9 (m, 1H), 10.6 (s, 1H)

Table I. Continued

Compound No	Yield (%)	mp (°C)	IR (cm^{-1})	MS (m/z)	H^1-NMR (ppm)
13a	84.5	-	3500-2600, 1650	-	1.3 (dd, 3H), 3.1-3.5 (m, 2H), 5.0 (9s, 1H), 5.0-5.2 (m, 2H), 5. 8-6.0 (m, 1H), 7.2 (t, 4H), 10.2 (s, 1H)
14a	96	-	3500-2500, 1650	-	1.3 (dd, 3H), 1.8 (s, 2H), 3.3 (d, 2H), 4.6 (s, 1H), 5.0-5.3 (m, 2H), 5.6-6.0 (m, 1H), 10.5 (s, 1H)
15a	60	-	3500-2700, 1650	-	1.3 (dd, 3H), 1.9 (d, 2H), 3.1-3.3 (m, 2H), 3.7 (s, 1H), 4.7 (t, 1H), 5.2 (d, 2H), 5.8-6.1 (m, 1H), 8.6 (s, 1H)
16a	82	-	3400, 3450-2500, 1650	-	1.3 (dd, 3H), 3.0-3.3 (m, 2H), 4.9-5.2 (mM, 1H), 5.7-6.1 (m, 1H), 7.0-7.6 (m, 4H), 9.5 (s, 1H), 10.0 (s, 1H)
17a	68.6	-	3400-2700	249 (MH^+)	1.3 (dd, 3H), 3.2 (d, 2H), 5.0 (s, 1H), 5.1-5.4 (m, 2H), 5.6-6.0 (m, 1H), 7.3 (s, 5H), 9.6 (s, 1H)
18a	93.6	-	3600-2800, 1650	235 (MH^+)	1.8 (d, 3H), 3.2 (d, 2H), 5.2-5.4 (m, 1H), 5.8 (d, 1H), 6.9-7.1 (m, 1H), 7.2 (s, 5H), 10.6 (s, 1H)
19a	91.5	-	3400-2800	235 (MH^+)	3.2 (d, 2H), 5.0-5.4 (m, 2H), 5.3 (s, 1H), 5.6-6.6 (m, 1H), 7.2 (s, 5H), 10.0 (s, 1H)
20a	44	-	3700-2600, 1680	-	2.2 (s, 2H), 2.6-3.0 (mm, 4H), 5.2 (t, 2H), 5.6-5.7 (m, 1H), 7.2 (s, 5H), 8.9 (s, 1H)
21a	20.4	-	3800-2800, 1650	-	1.5 (d, 3H), 2.0-2.1 (m, 2H), 2.6 (d, 2H), 2.9 (d, 2H), 5.1-5.3 (m, 1H), 6.4-6.6 (d, 2H), 7.0-7.8 (m, 5H)
22a	99	194-197	3500-2500	262 (MH^+)	3.2-3.6 (m, 2H), 5.4 (dd, 1H), 6.7 (d, 1H), 7.1-7.3 (m, 4H), 8.1 (d, 1H)

Table II. Yield and spectral data of epoxyalkanoyls

Compound No	Yield (%)	IR (cm^{-1})	MS-CI (m/z)	H^1-NMR (ppm)
1b	68	3400-2400, 1700	250 (MH^+)	2.5 (s, 2H), 3.1 (s, 2H), 3.4-3.5 (m, 1H), 4.0-4.3 (m, 2H), 4.8 (q, 1H), 7.2 (s, 5H), 8.6 (d, 1H)
2b	71	3300, 3400-2500	264	1.5 (t, 3H), 2.6 (d, 2H), 3.1 (m, 2H), 3.9-4.2 (m, 2H), 4.8 (q, 1H), 7.
3b	71	3300, 3400-2700	278	1.0 (t, 3H), 1.5-1.9 (m, 2H), 2.5 (d, 2H), 2.9-3.2 (m, 2H), 3.6-4.2 (m, 2H), 4.8 (q, 1H), 7.2 (s, 5H), 7.8 (d, 1H)
4b	62	3300, 3400-2700	307	1.9 (q, 2H), 2.4-3.1 (m, 4H), 3.9-4.1 (m, 2H), 4.8 (q, 1H), 7.2 (s, 5H), 8.3 (d, 1H)
5b	70	3400, 3400-2600	250	1.4 (s, 3H), 3.2 (d, 2H), 3.5-3.8 (m, 1H), 4.0-4.2 (m, 1H), 4.8 (q, 1H), 6.8 (d, 1H), 7.2 (s, 5H), 8.1 (s, 1H)
6b	68	3300, 3400-2600	264	1.3 (dd, 3H), 2.7-2.8 (m, 1H), 3.0-3.3 (m, 2H), 3.4-3.6 (m, 1H), 3.8-4.2 (m, 2H), 4.8 (q, 1H), 7.2 (s, 5H), 8.1 (d, 1H)
7b	59	3300, 3400-2700	250	1.2 (m, 3H), 3.1 (d, 2H), 3.9-4.3 (m, 2H), 4.8 (q, 1H), 6.5 (d, 1H), 7.2 (s, 5H), 10.0 (s, 1H)
8b	47	3400, 3400-2600	-	1.2 (d, 6H), 1.8 (t, 2H), 2.0 (d, 2H), 3.5 (t, 1H), 3.7-4.0 (m, 2H), 4.6 (q, 1H), 7.2 (s, 5H)
9b	83	3300, 3400-2500	298	1.2-1.3 (dd, 3H), 2.6-2.8 (m, 2H), 2.9-3.1 (m, 1H), 3.3-3.6 (m, 2H), 3.9-4.1 (m, 1H), 4.8 (m, 1H), 7.2 (s, 2H), 7.3 (s, 2H), 8.0 (d, 1H)
10b	81	3330, 3400-2600	309	1.3 (dd, 3H), 2.6-2.8 (m, 1H), 3.1-3.3 (m, 2H), 3.4-3.7 (m, 2H), 4.0-4.1 (q, 1H), 4.9 (m, 1H), 7.4 (q, 2H), 8.1 (d, 2H), 8.6 (d, 1H)
11b	72	3400, 3400-2700	280	1.3 (dd, 3H), 2.6-2.9 (m, 2H), 3.2 (q, 1H), 3.6 (q, 1H), 4.0-4.2 (m, 2H), 4.8 (m, 1H), 6.8-7.1 (m, 4H), 8.0 (d, 1H)
12b	83	3400, 3400-2600	214	1.2 (dd, 3H), 2.0 (s, 4H), 2.7-2.9 (m, 1H), 3.6 (d, 2H), 3.8-4.1 (m, 3H), 4.4 (t, 1H), 8.0 (s, 1H)
13b	81	3500-2800, 1730	262	1.3 (dd,3H), 2.6-2.7 (m, 1H), 3.3 (d, 2H), 3.5-3.8 (m, 2H), 3.9-4.3 (m, 1H), 5.1-5.3 (m, 1H), 7.2 (t, 4H), 8.3 (s, 1H)
14b	91	3500-2800, 1730	-	1.3 (d, 3H), 1.9-2.1 (m, 2H), 2.7-2.8 (m, 1H), 3.2 (d, 2H), 3.5-3.7 (m, 1H), 4.3-4.4 (m, 2H), 9.4 (s, 1H)
15b	80	3500-2700, 1700	-	1.3 (dd, 3H), 1.9 (d, 2H), 2.5-2.8 (m, 1H), 3.0-3.1 (m, 2H), 3.6-3.8 (m, 2H), 3.9-4.1 (m, 1H), 4.6 (s, 1H), 10.0 (s, 1H)

Table II. Continued

Compound No	Yield (%)	IR (cm^{-1})	MS-CI (m/z)	H^1-NMR (ppm)
16b	80	3400, 3600-2600	-	1.3 (dd, 3H), 2.5-2.7 (m, 1H), 3.1 (d, 2H), 3.5-3.8 (m, 2H), 4.0-4.3 (m, 1H), 5.0 (s, 1H), 7.0-8.5 (m, 4H)
17b	90	3600-2700, 1720	265	1.7 (dd, 3H), 2.5-2.8 (m, 1H), 3.2 (s, 2H), 3.4-3.7 (m, 2H), 3.8-4.2 (m, 1H), 5.3 (s, 1H), 7.2 (s, 5H), 8.0 (s, 1H)
18b	76	3400-2700, 1720	252	1.8 (d, 3H), 3.2 (d, 2H), 3.2 (d, 1H), 4.2-4.5 (m, 1H), 5.3 (s, 1H), 7. 2 (s, 5H), 10.3 (s, 1H)
19b	57	3500-2800, 1750		2.7 (d, 2H), 3.2 (d, 2H), 3.5-3.7 (m, 2H), 4.0-4.4 (m, 1H), 5.3 (s, 1H), 7.2 (s, 5H)
20b	89	3700-2700, 1750	-	2.2 (d, 2H), 2.6-3.0 (m, 4H), 3.4-3.6 (m, 2H), 4.0-4.4 (m, 1H), 7.2 (s, 5H)
21b	90	3700-2500, 1720	-	1.5 (d, 3H), 2.0 (d, 2H), 2.6-2.7 (m, 2H), 3.0 (d, 2H), 3.3-3.6 (m, 2H), 4.4-4.6 (m, 1H), 7.2 (s, 5H), 9.7 (s, 1H)
22b	47	3500-2500, 1760	-	3.58 (g, 2H), 3.61 (m, 1H), 4.10 (m, 1H), 5.48 (dd, 1H), 7.08-7.26 (m, 4H), 8.13 (d, 1H), 13.0 (s, 1H)

acetate layer was washed with water and dried over magnesium sulfate. The solvent was removed *in vacuo* and the residue was recrystallized from ether and chloroform.

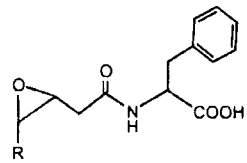
General procedure for epoxidation of amides

Unsaturated amides (1 mmole) were dissolved in 5 ml of acetone and 3 ml of water. With vigorous stirring sodium bicarbonate (14 mmol) and oxone (4 mmol) were added to this solution. The stirring was continued for 0.5~8 hrs. at room temperature. The reaction mixture was acidified to pH 1~2 with conc. HCl, then extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and the solvent was removed *in vacuo*. The epoxides were obtained after column chromatography on silica gel (hexane: ether:methanol 1:4:1).

Evaluation of ACE inhibition

Potassium phosphate buffer (pH 8.4) (100 mM, 0.2 ml), sodium chloride (60 μmol), rabbit lung homogenate (0.14 μg) and inhibitors were preincubated for 20 min. at 37°C. The substrate hippuryl-L-histidyl-L-leucine (1 mM) was added to the mixture to start the reaction. After 15 min. 6 N hydrochloric acid (15 μl) was added and extracted with 0.4 ml ethyl acetate. The hydrolysis product hippuric acid was quantitated using HPLC (Pascard *et al.*, 1991).

Table III. ACE inhibition of epoxides without alkyl group at α- to the carbonyl group



Compound No	R	ACE inhibition IC_{50} (mM)
1	H	NE
2	CH_3	NE
3	CH_2CH_3	NE
4	CH_2COOH	NE

NE: not effective up to 5 or 10 mM.

RESULTS AND DISCUSSION

It is generally believed that the structure of the active site of ACE is very similar to that of the well studied zinc protease, carboxypeptidase A. Figure 1 depicts the presumed active site of ACE which was occupied by substrate. It has been well known that

Table IV. ACE inhibition of α,β-, β,γ- and γ,δ-epoxides

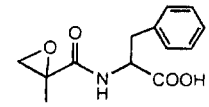
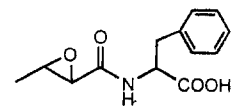
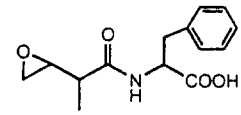
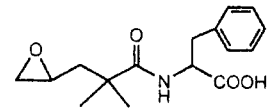
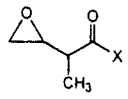
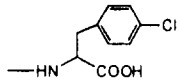
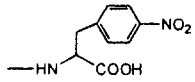
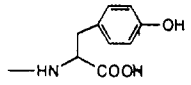
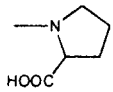
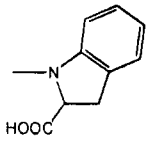
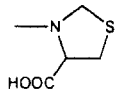
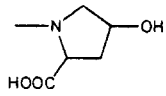
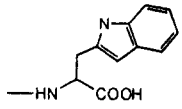
Compound No	Structure	ACE inhibition IC_{50} (mM)
5		2.4
6		NE
7		1.0
8		0.7

Table V. ACE inhibition of analogues modified in terminal amino acids

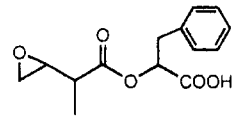
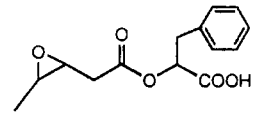
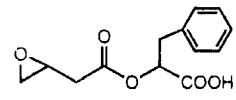
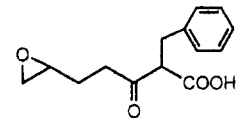
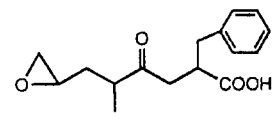
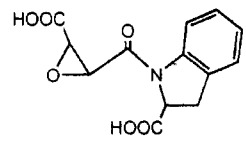


Compound	-X	ACE inhibition IC_{50} (mM)
9		NE
10		NE
11		NE
12		5.5
13		0.25
14		NE
15		NE
16		NE

there is a large hydrophobic pocket at the S2' subsite of ACE (Kim *et al.*, 1983). It was thought that compounds obtained by incorporation an oxirane ring into the structure similar to that of substrate would be accommodated in the active site of ACE with the oxirane moiety being ligated to the active site zinc ion. Such oxirane ring would be activated by the metal ion and interacts with a nucleophile such as the carboxylate of the catalytically essential Glu present at the active site of ACE, leading to covalent modification of the carboxylate to impair the catalytic activity (Fig. 1b).

Compound 1-4 and 6 which lack the methyl group at the α-position to the amide carbonyl were not active up to 5 or 10 mM concentration. The effect on the ACE inhibition caused by changing the distance between the carbonyl and epoxide groups are summerized in Table III. It appears that the presence of the methyl group at the α-position to the amide carbonyl is essential for the inhibition of ACE. The importance of the S2' residue on the inhibitory activity can be seen from Table IV. As observed with captopril (IC_{50}, 10^{-5} mM) and 9-16, proline and indolinecarboxylic acid are most suited as the S2' residue (Table V). Compound 13 and 22 which have indolinecarboxylic acid moiety were found to be active ACE inhibitor.

Table VI. ACE inhibition of epoxyesters and epoxyketones

Compound No	Structure	ACE inhibition IC_{50} (mM)
17		NE
18		NE
19		NE
20		NE
21		NE
22		0.06

The replacement of the amide nitrogen with oxygen atom or a methylene unit resulted in the loss of the inhibitory activity as shown in Table VI. Presumably, the amide hydrogen atom forms a hydrogen bond with peptide carbonyl oxygen of the backbone chain which constitutes the active site wall.

The occurance of irreversible binding, at least in part, was presumed by the fact that the inhibited enzyme activity by compound 22 was restored only 58% after dialysis.

In conclusion, we have designed and synthesized a series of potential irreversible ACE inhibitors bearing an oxirane ring which was thought to be activated by

the active site zinc ion when the inhibitors bind the enzyme. The activated oxirane would then covalently modify the carboxylate, inactivating the enzyme. Contrary to the expectation, only some of them, i.e., 7, 8 and 13 exhibited moderately potent inhibitory activity against ACE.

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