Iranian Journal of Pharmaceutical Research (2005) 1: 37-41
Received: May 2004
Accepted: March 2005

Original Article

Design and Synthesis of New Imidazole Derivatives of Captopril

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Abstract

A new series of alkylthio imidazole analogues of captopril, an ACE inhibitor used in the treatment of hypertension, was designed and synthesized in order to obtain agents more active than captopril with less side effects. All the compounds thus prepared were purified and characterized by IR, NMR and Mass analytical instruments.

Keywords: ACE inhibitor; Synthesis; Captopril; Alkylthio imidazole derivatives.

Introduction

Angiotensin converting Enzyme (ACE) plays an important role in the control of arterial blood pressure. The enzyme is responsible for conversion of the decapeptide angiotensin I into the vasopressor agent, angiotensin II. It is a zinc-containing enzyme that cleaves dipeptide units from its peptide substrate (1). An important competitive inhibitor of ACE is captopril, which inhibits conversion of the relatively inactive angiotensin I to the angiotensin II. According to the mechanism proposed by Ondetti and colleagues (2), captopril interacts with the enzyme through several bonds, i.e. electrostatic, hydrogenic and lipophilic connections (Fig 1). Among these is a coordinance bond formed between the free thiol group of captopril and zinc ion in the active site of ACE. Captopril, although is an important orally active ACE inhibitor, produces some side effects. The two most common side effects, skin rashes and taste disturbances are attributed to the presence of the sulfhydryl group (3). An alternative approach to ACE inhibitors developed by Patchett and colleagues is the preparation of N-carboxyalkyl dipeptides which with some modification gives enalaprilat, a compound approximately ten fold more potent than captopril (4). Enalaprilat, a di-acid in which the SH group of captopril is replaced by a carboxyl moiety, has however poor oral absorption. But the ethyl ester derivative, enalapril, a mono acid, is a prodrug form which is orally well absorbed. In fact, the addition of some lipophilic groups at the ends and in the middle of the structure can improve oral absorption of ACEI molecules (2,5,6). In the present study several molecules have been designed and synthesized as imidazole derivatives of captopril in such a way that cover those factors necessary for tight binding to ACE with acceptable oral absorption and less side effects comparing to captopril.

Experimental

For molecular modeling and design a PC Model® 6.0 software implementing MMX force field program was used (7). Synthesis of the compounds was performed by chemical reagents purchased from Merck company. The synthesized compounds were visualized by UV light of λ=254 nm. IR spectra were recorded on perkin Elmer model 840. ^{1}HNMR spectra

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were recorded on a varian-400 spectrometer and Mass spectrometry was performed on a finnigan TSQ 70 Mass spectrometer at 70 ev. Elemental analyses (C, H, N) were realized on a Carlo-Erba EA 1108-elemental analyzer.

Molecular Design

Some new imidazole derivatives of captopril were designed as shown in Figure 2. The structure of captopril was used as the starting point. Since proline is the C-terminal part of usual ACEI molecules, this amino acid structure was preserved in the present molecular design. As the second part of ACEI molecules, an imidazole ring was constructed to mimic histidine residue in ACE main substrate, angiotensin I. N-Methyl group on the imidazole N-1 was proposed to occupy S_1 site of the enzyme. Alkylated thiol on this ring was designed to save connection with zinc ion of the enzyme as well as to fill S_1 site of ACE as an additional lipophilic site as proposed by Patchett *et al* (2). By designing the complete ACEI structures employing PC Model®, the molecules were energy minimized and then superimposed on captopril structure using MMX force field analysis (Figure 3).

Chemistry

The designed molecules were synthesized following the steps outlined in scheme 1. At first 5-hydroxymethyl-1-methyl-2-thio-imidazole I was prepared using dihydroxy acetone (8,9). Reaction of I with alkyl iodide afforded corresponding substituted alkylthio imidazole II (10). As the next step, oxidation of the carbinol group was prerequisite for amide bond formation between the imidazole moiety and amino acid proline. Oxidation may give carboxylic acid directly from alcohol or indirectly through aldehyde formation. Considering yield and availability of reagents, preparation of carboxylic acid via aldehyde was practiced. For the final step, condensation of proline with the imidazole was put forward. This condensation may proceed by several routes:

1) Direct coupling of proline with imidazole in alkaline medium (11) or in the presence of DCC in DMF (12),

2) Coupling of proline with the imidazole acyl chloride in THF (12) and dioxane (13),

3) Coupling of esterified proline with the imidazole by using ethyl chloroformate and triethylamine (14).

In practice, coupling in alkaline solution gave low yield since amide formation was reversible. Condensation reaction by DCC showed difficulty in working up of the product. Furthermore, coupling by imidazole acyl chloride did not proceed well. However, esterified proline could couple well with the imidazole in the presence of ethyl chloroformate. Hydrolysis of the resultant product gave the desired derivative. The purity of all compounds was determined by thin-layer chromatography using several solvent systems of different polarities.

Synthetic Methods

1) 1-Methyl-2-mercapto-5-hydroxy methylimidazole (I)

A mixture of potassium thiocynate (0.7 mol, 69 g), methylamine HCl (0.6 mol, 41.3 g) and dihydroxyacetone (0.46 mol, 42.6 g) in a solution of acetic acid (54 ml) and 1-butanol (340 ml) was stirred at room temperature for 60 h. Water (70 ml) was then added to the reaction mixture and the precipitate thus formed was filtered and washed with water (200 ml), then ether (200 ml) and dried at 50-60ºC. The product I (40 g) was obtained at 58% yield, mp 202-207ºC (ref. (8) 203-205 ºC),

IR(KBr): ν 3180 (OH), 2570 (SH), 1620 (C=C), 1450, 1375 cm^{-1}(CH3).

2) 1-Methyl-2-alkylthio-5-hydroxy methylimidazole (II):

To the stirring solution of compound I (21 mmol, 3 g) and sodium hydroxide (25 mmol, 1 g) in 5 ml of hydromethanol, a solution of alkyl iodide (30 mmol) in methanol was added dropwise. The reaction mixture was stirred at room temperature for 3 h. Methanol and excess alkyl iodide were removed under reduced pressure. The residue was saturated with NaCl and then extracted three times (3×20 ml) with choroform. After solvent evaporation, a yellow precipitate was obtained; yields 70-82 %, mps.:(methyl) 182ºC, (ethyl) 179ºC, (propyl) 175ºC. (ref. (9). 182ºC (methyl), 180ºC (ethyl), 174ºC (propyl)), IR(KBr): ν 3300 (OH), 1600 (C=C).

3) 5-Formyl-1-methyl-2-alkylthio imidazole (III):

A mixture of compound II (12 mmol, 2.88 g) with activated manganese dioxide (~120 mmol) in chloroform (50 ml) was refluxed for 12 h. After cooling, the mixture was filtered on celite and the filtrate was separated and the solvent was then evaporated.

The aldehydes were thus obtained as fine yellow powders; yields 93-95%, mps: (methyl) 120ºC (ethyl) 118ºC (propyl) 116ºC. (ref. (9). 122ºC (methyl), 120ºC (ethyl), 115ºC (propyl)), IR(KBr): ν 2800 (C-H aldehyde), 1660-1680 (C=O), 1600 cm^{-1} (C=C).

4) 1-Methyl-2-alkylthio-5-imidazolyl carboxylic acid (IV):

Addition of silver nitrate (in water, 26.4 mmol) to sodium hydroxide solution (52.5 mmol) gave silver oxide as an oxidating reagent. To an ice-cooled reagent mixture, III (12.8 mmol) was gradually added with stirring. Oxidation was completed after 15 min. The reduced silver was filtered on celite. The filtrate was pH adjusted (5-5.5) and then extracted by n-butanol. After solvent evaporation, a yellow powder was obtained: yields 60-63%; mps: (methyl)155ºC, (ethyl)187ºC, (propyl) 230ºC.

IR(KBr): ν 3300 (OH), 1680 (C=O), 1600 cm^{-1} (C=C). Elemental microanalyses were within ± 0.4% of the theoritical values for C, H, N.

5) Ethyl L-prolinate (V)[12] :

L-proline (25 mmol) was suspended in absolute ethanol (20 ml) under dried HCl gas. After 30 min, the excess ethanol was evaporated and an oily residue was obtained; yield 97%, IR($CHCl_3$): ν 3400 (NH), 1740 (C=O), 1220 cm^{-1}(C-O).

6) 1-(2-Alkylthio-1-methyl-5-imdazolyl)-ethyl-L-prolinate (VI):

To a mixture of dried triethylamine (50 mmol, 5.0 g) dissolved in dried chloroform (30 ml), compound IV (25 mmol) was added under nitrogen. The mixture was cooled at 0ºC in ice-water bath. Ethyl chloroformate (25 mmol, 2.7 g) was added dropwise to the mixture while keeping the temperature at 0ºC. After 15 min stirring at this temperature, a solution of compound V (25 mmol, 3.6 g) in dried chloroform as well as dried triethylamine (5.0 g) were added gradually to the mixture and the reaction was left for 30 min at room temperature and then refluxed for 10 min at 50ºC. The reaction mixture was then washed several times with water and sodium hydrogen carbonate solution (0.5M). After solvent evaporation, a yellow solid was obtained which following chromatography on silica gel gave the product as an oily compound: For (methyl derivative) : yield 68 %, IR($CHCl_3$): ν 1740, 1700 cm^{-1} (C=O)

H-NMR ($CDCl_3$) ppm: 7.7 (s, 1H, imidazole), 4.2 (m, 3H, OCH_2, Proline 2-CH), 3,83 (s, 3H, N-Me), 3.53 (m, 2H, proline 5-CH_2), 2.7 (s, 3H, S-Me), 1.7-2.3 (m, 4H, proline 3-CH_2, 4-CH_2), 1.25 (m, 3H, Me)

Ms: m/e 297 (25), 252 (30), 155(32), 142(100), 97(25), 70(65), 45(38).

For (ethyl derivative) : yield 82 % , IR($CHCl_3$): ν 1750, 1710 cm^{-1} (C=O)

^{1}H-NMR ($CDCl_3$) ppm: 7.7 (s, 1H, imidazole), 4.2 (m, 3H, OCH_2, Proline 2-CH), 3,82 (s, 3H, N-Me), 3.5 (m, 2H, proline 5-CH_2), 3.2 (m, 2H, CH_2-S), 1.6-2.3 (m, 4H, proline 3-CH_2, 4-CH_2), 1.1-1.4 (m, 6H, CH_3), Ms: m/e 311 (10), 153 (90), 142(100), 112(22), 70(53).

For (Propyl derivative):yield 81 %, IR($CHCl_3$): ν 1750, 1710 cm^{-1} (C=O)

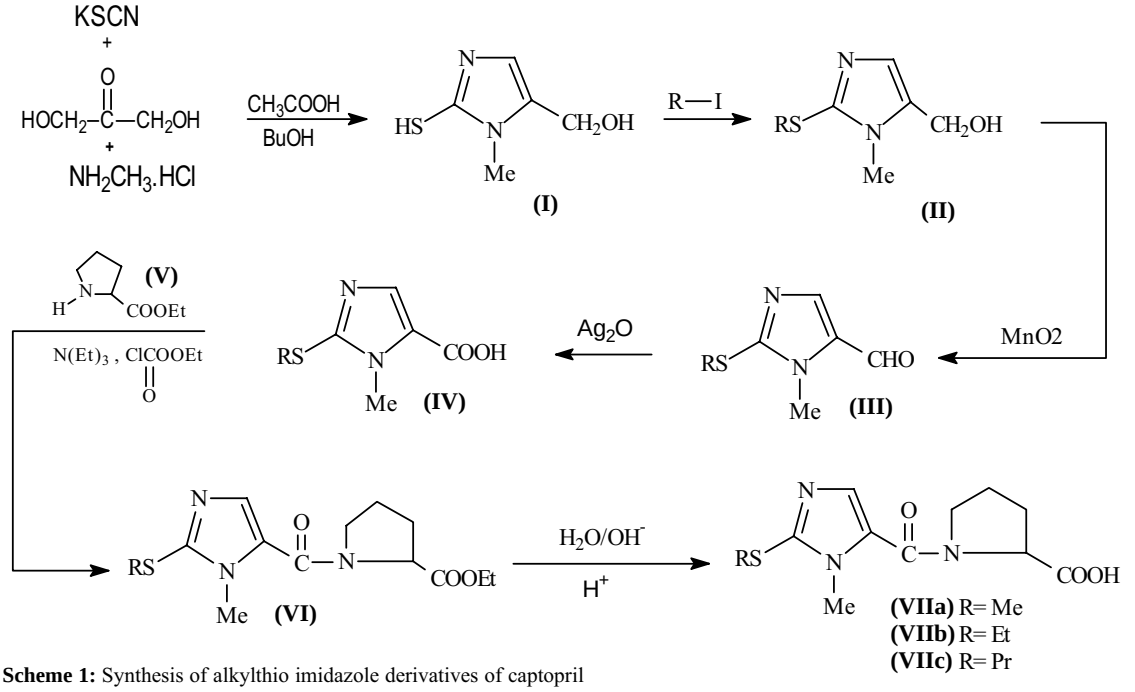
H-NMR ($CDCl_3$) ppm: 7.7 (s, 1H, imidazole), 4.2 (m, 3H, OCH_2, Proline 2-CH), 3,83 (s, 3H, N-Me), 3.5 (m, 2H, proline 5-CH_2), 3.2 (m, 2H, CH_2-S), 1.5-2.2 (m, 6H, $\underline{CH_2}$ CH_2S, proline 3-CH_2, 4-CH_2), 1.25 (m, 3H, OCH_2 $\underline{CH_3}$), 1.0 (m, 3H, SCH_2 CH_2 $\underline{CH_3}$).

Ms: m/e 325 (5), 228 (65), 154(55), 142(38), 112(37).

7) 1-(1-Alkylthio-5-imidazolyl)-L-proline (VII):

To a hydroethanolic solution of VI (6.73 mmol), sodium hydroxide (10%, 30 ml) was added. The mixture was refluxed for 30 min. Ethanol was removed by evaporation and the residue was pH adjusted to 5-5.5. Saturation with NaCl and extraction by chloroform-isopropanol (10:1), gave an oily product after solvent evaporation: yield 77-85%;

IR($CHCl_3$): ν 3440 (OH), 1700, 1680 cm^{-1} (C=O). Elemental microanalyses were within ± 0.4% of the theoritical values for C, H, N.



Scheme 1: Synthesis of alkylthio imidazole derivatives of captopril

Results and Discussion

In molecular designing of some imidazole derivatives of captopril, the designed structures had the main captopril pharmacophores. In order to confirm whether the designed compounds could mimic proper conformation for binding to ACE, they were superimposed on captopril molecule. Superimposition of energy minimized conformers showed that the main proposed pharmacophores i.e. carboxylic, carbonyl and mercapto groups were well matched with captopril functional groups. Moreover, the addition of alkyl groups on the terminal SH did not interfere with superimposition. It should be mentioned that alkylation makes the molecule more tight binding to ACE (2) as well as more lipophilic so that potency along with oral absorptivity of the synthesized molecules can be increased.

In captopril molecule the SH group has a key role in the interaction with zinc ion of ACE (2). However, the alkylthio group on the designed molecules should play that role since the lone pair electrons of sulfur atom is still available. On the other hand, the alkylthio is not expected to produce side effects like the free SH group on captopril molecule. This study also showed that the synthesis strategy for the imidazole derivatives of captopril, as depicted in Scheme 1, is quite applicable. That is because it consists only few steps which are feasible and afford overall acceptable yields.

The present new imidazole derivatives of captopril are promising to give more potent ACEI compounds with better oral bioavailability.

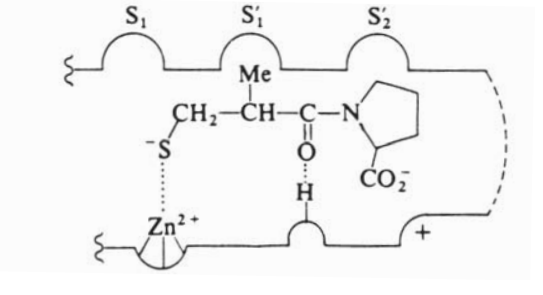


Figure 1. Binding interactions of captopril with the active site of ACE (2).

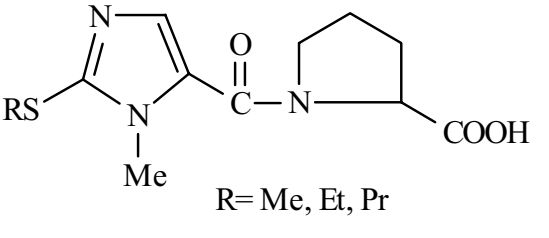


Figure 2: The structure of designed imidazole derivatives of captopril.

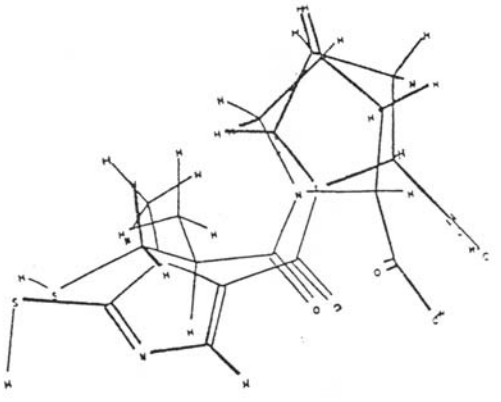


Figure 3. Superimposition of the energy minima conformers of captopril and the designed compound.

However, *in vitro* binding assay on purified ACE as well as *in vivo* experiments on animals are needed to prove such expectation.

Acknowledgments

This research was supported by a grant from the deputy for research of Shaheed Beheshti University of Medical Sciences, Iran.

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