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Perindopril and ramipril phosphonate analogues as a new class of angiotensin converting enzyme inhibitors

Catherine Gomez [a], Sabine Berteina-Raboin [a], Guillaume De Nanteuil [b], Gérald Guillaumet [a,*]

[a] Institut de Chimie Organique et Analytique, Université d'Orléans, UMR CNRS 7311, rue de Chartres, BP 6759, 45067 Orléans Cedex 2, France
[b] Institut de Recherche Servier, 125 chemin de Ronde, 78290 Croissy sur Seine, France

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ABSTRACT

A series of phosphonate analogues related to perindopril and ramipril were prepared and tested to estimate their ability to inhibit angiotensin converting enzyme. These new synthesized compounds were active ACE inhibitors with a promising activity.

1. Introduction

The converting-enzymes such as endothelin converting enzyme (ECE), angiotensin converting enzyme (ACE) and neutral endopeptidase (NEP), meanly localised in the endothelium, stand for an interesting target in the drugs development against the cardiovascular pathologies. The well-known diseases involving the most risk factors are arterial hypertension, hypercholesteremia,[1] congestive heart failure,[2] hypertriglyceridemia,[3] tabagism and diabetes. Since 80's, syntheses of compounds acting against these diseases were developed. More particularly against hypertension, the choice has been focused on regulation of enzymes ECE, ACE, NEP having effects on blood pressure. Among these three converting enzymes, our studies have been targeted about angiotensin converting enzyme inhibitors. In previous years, a number of effective antihypertensive drugs have been discovered by the pharmaceutical industry like the Captopril (Lopril®) and several of its variants.[4]

2. Results and discussion

2.1. Determination of targeted structure

At the top ACE is an exopeptidase membrane associated to a zinc atom.[5] This zinc metalloprotease ACE bonds its catalytic site via the zinc atom both to a water molecule and to angiotensin I by the carbonyl group then cleaves the decapeptide into an octapeptide, the angiotensin II. So the accumulation of the potent vasoconstricting octapeptide and the hydrolysis of vasodilator bradykinin by ACE are both responsible to increase blood pressure. To block this effect, angiotensin-converting-enzyme inhibitors (ACEI) are studied and represent an important part in hypertension treatment in acting in hemodynamic regulation.

Among ACE selective inhibitors known in the literature, the discovery of captopril has played an important part in pharmacology in 1977. Indeed, it decreased the arterial pressure in stopping the angiotensin II biosynthesis.[6] This pseudo-peptide contains pyrrolidine, carboxylic acid and thiol functionalities which contribute to have a good affinity toward ACE by binding the Zn atom. Furthermore structure modifications such as in lisinopril[7] or perindopril[8] increase inhibition with an IC_{50} of 0.1 nM (human blood serum ACE) and 1.5 nM, respectively. (Fig. 1).

Other compounds as ramipril,[9] enalapril[10] and quinapril[11] have structural likenesses with the previous series that confer them a potent activity against ACE.

As shown with previous literature models to be specific to catalytic site, inhibitor structures should contain particular functions in specific positions. First, they must be coordinated to a metal by one or several atoms. The zinc-chelating group can be a thiol,[12] a carboxylic acid,[6,7] a hydroxamic acid,[13] a phosphonic acid[14] or a phosphoramidic acid.[15] As indicated in Figure 2 every special position was filled by a specific group in the active site.[16] S_1 subsite constitute hydrophobic domain and could efficiently be occupied by alkyl or aryl moieties in position P_1 to interact with Zn^{2+} ion located in the enzyme's active site. The S_1' site accepts a wide variety of residues in position P_1' like (L)-alanine residue whereas S_2' binding site prefers aromatic amino acids in position P_2'.[17] By analogy with active inhibitors structures in the literature and to respect constraints, the below compounds have been proposed to create new ACEI with a defined configuration.

* Corresponding author. Tel.: +33 2 35 52 24 63; fax: +33 2 35 52 29 71.
E-mail address: gerald.guillaumet@univ-orleans.fr (G. Guillaumet).

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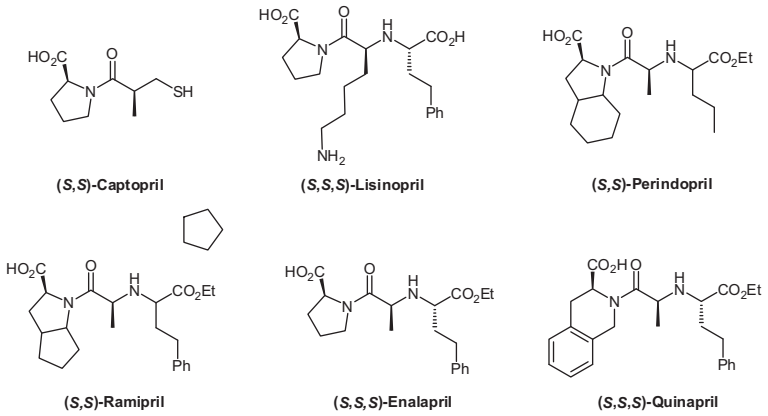


Figure 1. ACE inhibitors known in the literature.

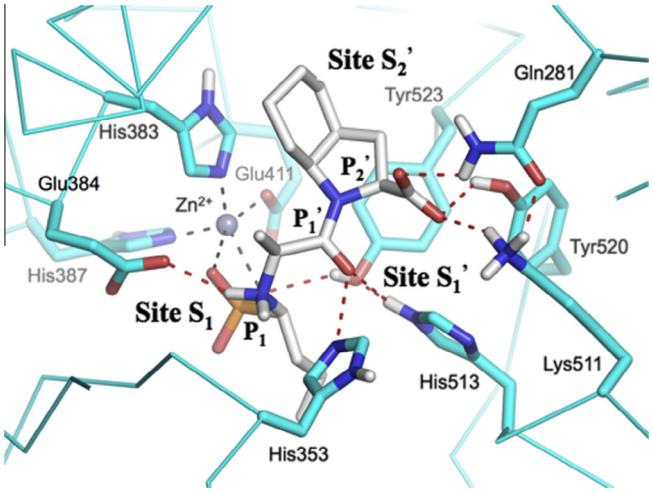


Figure 2. Expected interactions of targeted structure with the enzyme *t*ACE's active site (PDB code 1O86).[18]

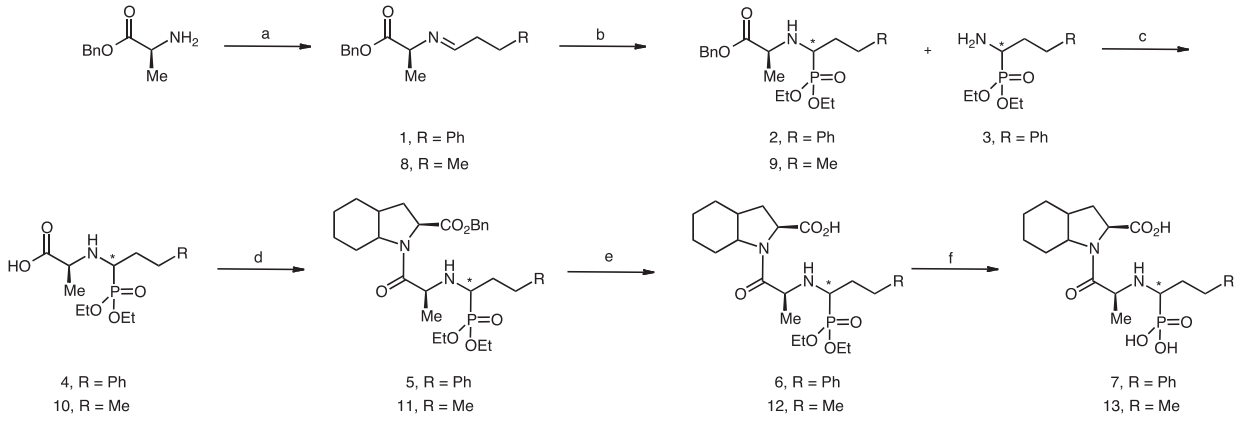
The present work deals with introduce news ACE inhibitors containing zinc-chelating groups such as phosphonates, improving the inhibitor–enzyme coordination, to take the place of thiol or ethyl ester group. In producing isosteres of previous active compounds, physical, chemical and biological properties (greater selectivity, less side effects, decreased toxicity, increased stability and affinity for enzyme) should be improved. Herein we report the results of our studies.

2.2. Synthesis

The synthetic route developed for the preparation of these inhibitors is shown in Scheme 1. The condensation of the commercially available protected L-alanine with 3-phenylpropionaldehyde in dichloromethane under microwaves irradiation gave imine intermediate **1**. The desired substituted diethyl α-aminophosphonate **2** was successfully obtained by optimization of De Lombaert strategy.[19] Use of the Lewis acid $BF_3{\cdot}Et_2O$ promoted triethylphosphite addition according to Arbusov mechanism. Moreover, microwaves activation allowed to get the desired compound in good yield. An optimisation of several parameters of the reaction (catalyst quantities, time, temperature and concentration) has been necessary. Indeed the best conditions were two equivalents of lewis acid $BF_3{\cdot}Et_2O$, in short time (15 min) at 120 °C and in a concentration of 0.3 M to get compound **2** such as two diastereoisomers in 78% yield after purification. These two compounds have been obtained in 6:4 ratio by ^1H NMR then have been separated in the next step.

The by-product **3** often observed could come from intermediate hydrolysis after an isomerization reaction due to the forcing conditions of the phosphite addition.[10] Its formation was minimized when the mixture concentration was increased to 0.3 M.

The following debenzylation step has furnished the desired carboxylic acid α-aminophosphonate **4** under palladium catalysed hydrogenolysis. After separation of diastereoisomers by precipitation in a mixture of dichloromethane/diethylether, one pure isomer was isolated in 47% yield and confirmed by HPLC chiral. So



Scheme 1. Synthetic pathway of ACE inhibitors. Reagents and conditions: (a) NEt_3, 3-phenylpropionaldehyde (R = Ph) or butyraldehyde (R = Me), Na_2SO_4, CH_2Cl_2; (b) triethylphosphite, $BF_3.Et_2O$, CH_2Cl_2; (c) H_2, Pd/C, EtOH; (d) (2*S*, 3a*S*, 7a*S*)-2-[(benzyloxy)carbonyl]perhydroindole, NEt_3, HOBt, DCC, DMF; (e) H_2, Pd/C, EtOH; (f) HCl aq.