Molecular structure and acidity of captopril, zofenopril and their metabolites captopril disulfide and zofenoprilat

Milan Remko [a,*], Joanna Bojarska [b], Anna Remková [c], Waldemar Maniukiewicz [b]

[a] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Comenius University in Bratislava, Odbojárov 10, SK-832 32 Bratislava, Slovakia
[b] Institute of General and Ecological Chemistry, Lodz University of Technology, Żeromskiego 116, 90-924 Łódź, Poland
[c] Department of Internal Medicine, Faculty of Medicine, Slovak Medical University, Limbová 12, SK-833 03 Bratislava, Slovakia

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ABSTRACT

The geometries of captopril (1-[(2S)-2-methyl-3-sulfanylpropanoyl]-L-proline), captopril disulfide ((2S)-1-[(2S)-3-({3-[(2S)-2-carboxy-1-pyrrolidinyl]-2-methyl-3-oxopropyl} disulfanyl)-2-methylpropanoyl]-2-pyrrolidinecarboxylic acid), zofenopril ((4S)-1-[(2S)-3-(benzoylsulfanyl)-2-methylpropanoyl]-4-(phenylsulfanyl)-L-proline) and zofenoprilat ((4S)-1-[(2S)-2-methyl-3-sulfanylpropanoyl]-4-(phenyl-sulfanyl)-L-proline) were optimized both in gas-phase and solvated state, using the Becke 3LYP/6-311++G(d, p) method. Captopril, zofenopril and zofenoprilat exist in solid state, gas-phase and aqueous solution in the form of more stable *trans* conformers. Based on the Gibbs energy calculations the *trans–trans* isomer of captopril disulfide is the most stable form followed by *cis–trans* one. Of the two acidic groups of captopril and zofenopril the thiol moiety is in the gas phase slightly less acidic.

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1. Introduction

Captopril (1-[(2S)-2-methyl-3-sulfanylpropanoyl]-L-proline) became the first developed angiotensin-converting enzyme (ACE) inhibitor in 1975 [1,2], and differed from other ACE inhibitors due to its short half-life [3]. The sulfhydryl group (—SH) in captopril undergoes oxidative dimerization or conjugation. Captopril disulfide ((2S)-1-[(2S)-3-({3-[(2S)-2-carboxy-1-pyrrolidinyl]-2-methyl-3-oxopropyl}disulfanyl)-2-methylpropanoyl]-2-pyrrolidine-carboxylic acid) is one metabolite and impurity in European Pharmacopeia 6.0 [4,5]. Zofenopril ((4S)-1-[(2S)-3-(benzoylsulfanyl)-2-methylpropanoyl]-4-(phenylsulfanyl)-L-proline) is a prodrug that undergoes metabolic hydrolysis to release the sulfhydryl-containing active metabolite zofenoprilat ((4S)-1-[(2S)-2-methyl-3-sulfanylpropanoyl]-4-(phenylsulfanyl)-L-proline), which is a long-lasting ACE inhibitor [6,7]. Zofenopril and captopril are the only ACE inhibitors with -SH groups and the resultant potential antioxidant activity [8]. Both drugs are chiral molecules. Clinically, these drugs are used as pure (S,S) epimers, which are responsible for the angiotensin-converting enzyme inhibition activity. Knowledge of the molecular and crystal structure of drugs is paramount to structure-aided drug design [9]. The crystal and molecular structure of captopril has been the subject of experimental

[10,11] and theoretical [12,13] investigations. Luke investigated the molecular structure of captopril using semi-empirical AM1 method [12], and Zamarbide et al. performed lower level *ab initio* SCF calculations for neutral and charged captopril species [13]. The three-dimensional structure for the captopril degradation product – captopril disulfide – was recently published [11]. The three-dimensional structure of zofenopril sodium (refcode: TUHMUE) was observed in CSD; however, the solid state structure of zofenoprilat is unknown.

In this work, we report the molecular structure of captopril, captopril disulfide, zofenopril and zofenoprilat (Scheme 1) using density functional theory. The acidity, conformational isomerism and solvent effect (water) on the structure and properties of captopril and zofenopril species was also determined. The theoretical calculations results for the isolated species and solvated structures were compared and discussed using available experimental X-ray crystal data for these compounds.

2. Computational details

All compounds (Fig. 1) were geometrically optimized using the Gaussian 09 program [14] employing the Becke3LYP hybrid function [15–17] of density functional theory [18,19].

Captopril, zofenopril and zofenoprilat were considered using two sets of neutral and ionic complexes. The effect of solvent on the studied compounds was evaluated via the conductor-like

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* Corresponding author.
  E-mail address: remko@fpharm.uniba.sk (M. Remko).
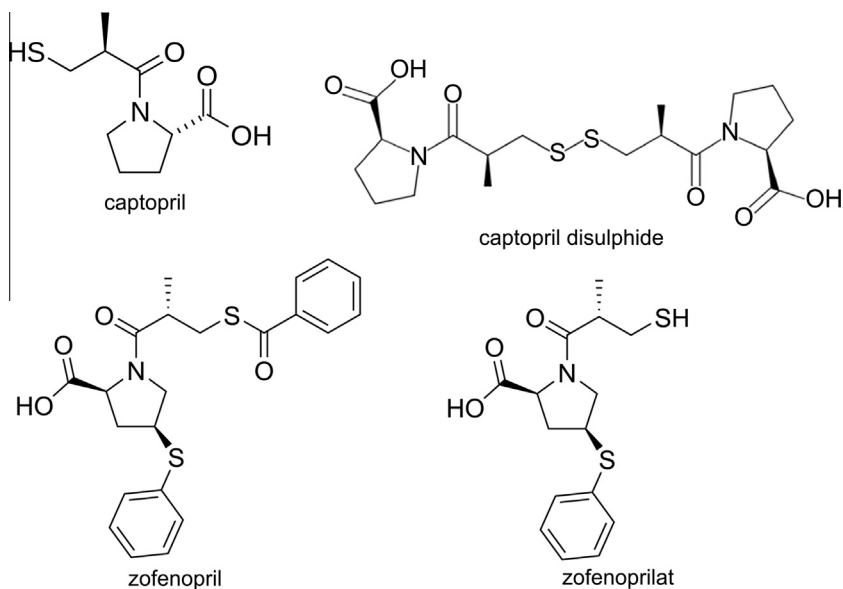
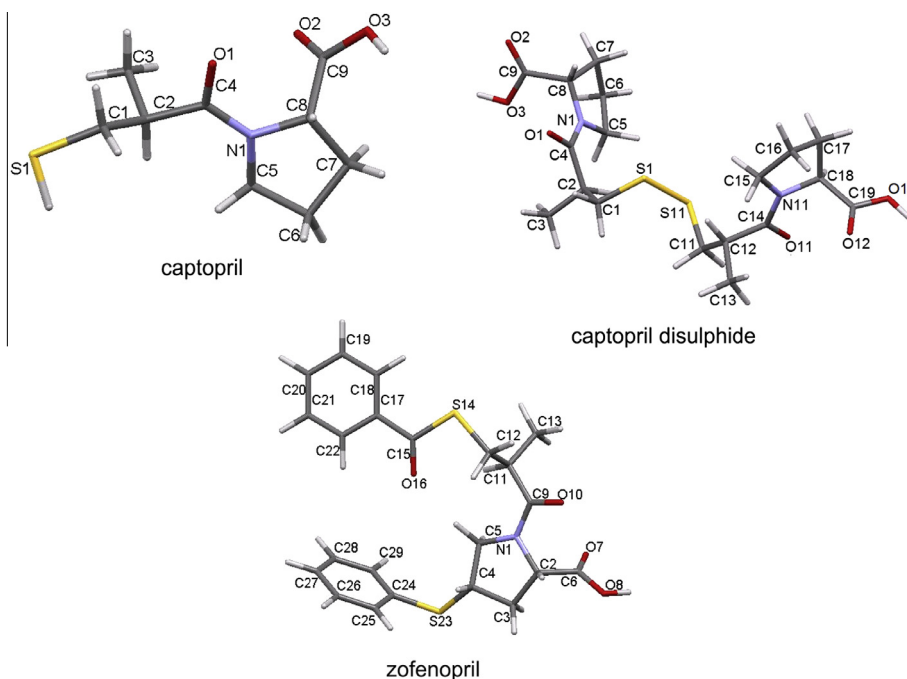**Scheme 1.** Structural formulas of the title compounds.

Fig. 1. Atom numbering of the compounds studied.

polarizable continuum model (CPCM) [20–22]. The structures for all species were fully optimized at the B3LYP level using the 6-311++G(d, p) basis set [23]. Analyzing the harmonic frequencies for the optimized molecules indicated they all were at their minima. The enthalpies and Gibbs energies for the deprotonation of the acidic inhibitors were computed the same way as in our previous publications [24].

3. Results and discussion

3.1. Molecular structures

3.1.1. Captopril

The chiral captopril ((2S)-1-[(2S)-2-methyl-3-sulfanyl-propanoyl]pyrrolidine-2-carboxylic acid) may exist in several

structural forms. The initial geometry for the theoretical calculations for captopril was adapted from the high-resolution X-ray structure of the biologically active *S,S* enantiomer of this drug [11]. Important structural parameters for captopril are given in Table A of the Supplementary Information with experimental X-ray data in the bound state for the angiotensin converting enzyme (ACE) homologue from *Drosophila melanogaster* (AnCE) (**P**rotein **D**ata **B**ank file 1J37) [25], captopril complexed with human testicular ACE (PDB file: 1UZF) [26] and *D*-captopril complexed with zinc *β*-lactamase (PDB file: 1M2X) [27]. Proline may exist in proline-containing peptides as both *cis* and *trans* conformations [28–30]. The thermodynamic parameters for the *cis–trans* isomerization of the proline amide bond (dihedral angle Φ[C(8)—N(1)—C(4)—C(2), Fig. 1) are shown in Table 1. Carboxylic acid in both isomers may exist as the *syn* or *anti* conformer (dihedral angle Φ[O(2)—C(9)—O(3)—H3o]).