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Computational study and spectroscopic investigations of antihypertensive drugs

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ABSTRACT

Sartans are orally active non-peptide molecules that competitively block the access of the AT1 receptor to angiotensin II used to treat hypertension and related pathologies. In particular, candesartan and valsartan are currently used in clinical therapy, and it is of interest to characterize them and their anionic forms under physiological conditions by means of their vibrational properties. The Fourier transform Raman (FT-Raman) and Fourier transform infrared (FTIR) spectra of candesartan, valsartan in their protonated and deprotonated forms were recorded in the solid phase. The vibrational wavenumbers, infrared intensities and Raman scattering activities were calculated by density functional B3LYP method with the 6-31+G(d,p) basis set, and theoretical spectrograms have been constructed. The scaled theoretical wavenumbers showed very good agreement with the experimental values. A detailed interpretations of the infrared and Raman spectra were performed for both the synthetic and the bioactive drugs.

1. Introduction

The antihypertensive drugs designated as "sartans" are orally active non-peptide antagonists whose action is based on blocking of the active site of the angiotensin II (Ang II) receptor type 1 (AT1) that causes blood vessels to tighten by a competitive inhibition and, as a result blood vessels relaxed. The renin angiotensin system (RAS) plays a key role in blood pressure regulation and electrolyte homeostasis. The RAS constitutes a proteolytic cascade in which angiotensinogen from the liver is cleaved by the aspartyl protease renin to produce the decapeptide angiotensin I. The biologically inactive angiotensin I is subsequently cleaved by the metalloprotease angiotensin-converting enzyme (ACE) to produce the endogenous vasoconstricting octapeptide hormone angiotensin II. As a result, drugs interfering with the RAS represent potent antihypertensives [1–3]. The sartans are synthetically molecules having in common that they all contain binding sites that at least partially overlap with the one of Ang II. These classes of molecules may approach the active site of the receptor by insertion in the lipid core, followed by lateral diffusion toward the binding site [4,5]. A large number of sartans are now approved for use in the treatment of patients with hypertension. They are all recently developed, patented drugs, so it is of interest to find out their structural characterization by different physicochemical techniques.

Vibrational spectroscopy is one of the most important and promising tools for the characterization of the structural features of molecules (backbone or functional groups). The combination of theoretical calculations with infrared and Raman spectroscopies provide invaluable structural information. In order to compare the vibrational features of pharmacophoric segments of the different sartans, a research activity was initiated in our laboratory related to the study of the vibrational properties of candesartan and valsartan and the results are compared with those of irbesartan [6].

The structure of these sartans have in common a biphenylmethyl moiety with an acidic group (tetrazole) and a 2-ethoxy-1,3-benzodiazole-6-carboxylic acid group (candesartan) or a 3-methyl-pentanamido butanoic acid group (valsartan) (Fig. 1).

At physiological conditions (pH 7.4) both the acidic tetrazole and carboxylate groups of candesartan and valsartan are mostly deprotonated, generating the dianionic forms of both sartans [7].

We have prepared the sodium salts of these drugs by deprotonation of the acidic groups at tetrazole and carboxylic acid moieties in order to establish a better vibrational assignment of the active species under physiological conditions. These comparisons must be systematically undertaken in different studies of bioactive drugs. In particular, candesartan is administered as candesartan cilexetil to increase its bioavalability but it metabolizes during its absorption in the intestinal wall giving the active form, $(cand)^{2-}$ [8].

The FTIR and FT-Raman spectra of the protonated and deprotonated sartans are measured and the vibrational parameters are calculated using B3LYP method with the 6-31+G(d,p) basis sets. The main differences observed for the biological active species of the therapeutic drugs in comparison with their protonated forms are analyzed and discussed herein.

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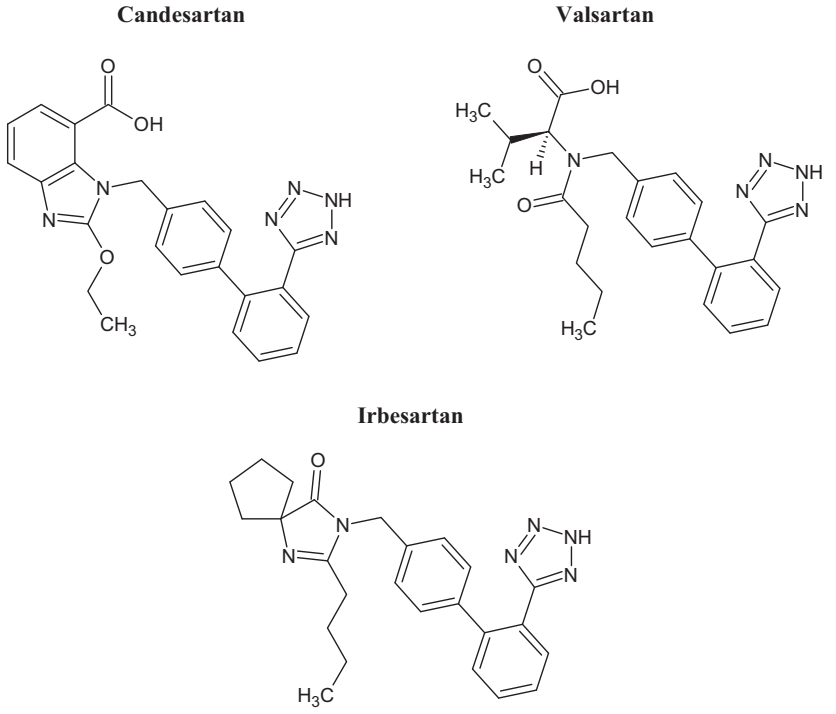

Fig. 1. Schematic structures of candesartan, valsartan and irbesartan.

2. Experimental

2.1. Materials and methods

Pure commercial samples of candesartan and valsartan (Hangzhou Garden Trading Co., Ltd. (China)) were used as supplied. A Bruker IFS 66 FTIR spectrometer in the spectral range between 4000 and 400 cm^{-1} using the KBr pellet technique was used for the FTIR measurements. A total of 60 scans were accumulated. Spectral resolution was $\pm 4\,cm^{-1}$. FT-Raman spectra were measured using the FRA 106 Raman accessory. A continuous-wave Nd:YAG laser working at 1064 nm was employed for Raman excitation. A germanium detector operating at liquid nitrogen temperature was used. Raman scattering radiation was collected with a standard spectral resolution of $\pm 4\,cm^{-1}$.

2.2. Preparative

Considering the acid–base equilibrium constants of valsartan and candesartan [6], the deprotonated sartans were prepared through the alkalinization of ethanolic solutions by addition of an ethanolic 1 M solution of NaOH. To a solution of each sartan (1 mmol) in ethanol (5 mL) was added a solution of sodium hydroxide in ethanol to adjust the pH value to 10. The mixture was stirred

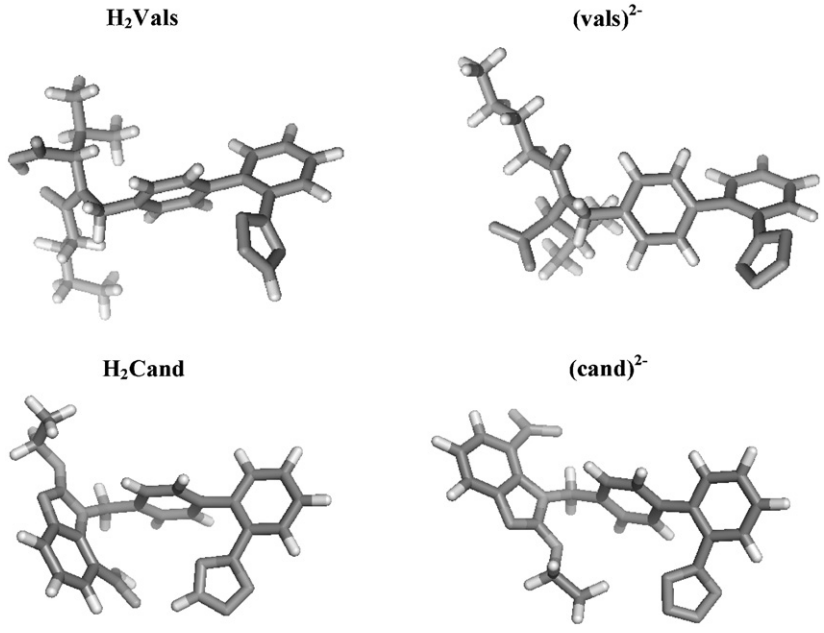

Fig. 2. B3LYP/6-31+G(d,p) optimized geometries of valsartan (H_2Vals), candesartan (H_2Cand), deprotonated valsartan $(vals)^{2-}$ and deprotonated candesartan $(cand)^{2-}$.