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In Situ Characterization of Lopinavir by ATR-FTIR Biospectroscopy

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Abstract

Lopinavir is an antiretroviral of the protease inhibitor class (Figure 1 and Figure 2). It is used against HIV infections as a fixed-dose combination with another protease inhibitor, ritonavir (lopinavir/ritonavir). In the current research, the stimulated ATR-FTIR biospectroscopy of liquid sample of Lopinavir was investigated. The stimulated ATR-FTIR diffractions emitted through focusing the second harmonic laser beam Nd:YAG into the sample were recorded by Echelle spectrometer and ICCD detector. Increasing the energy of laser beam from 2.6 (mJ) to 16 (mJ) led to increase in stimulated ATR-FTIR signal but after breakdown threshold of liquid sample, further increasing energy led to the decrease in stimulating ATR-FTIR signals and for energies higher than 20 (mJ), they were disappeared.

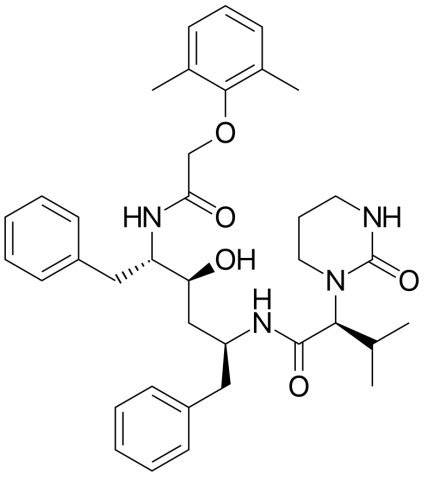

Figure 1. Molecular structure of Lopinavir.

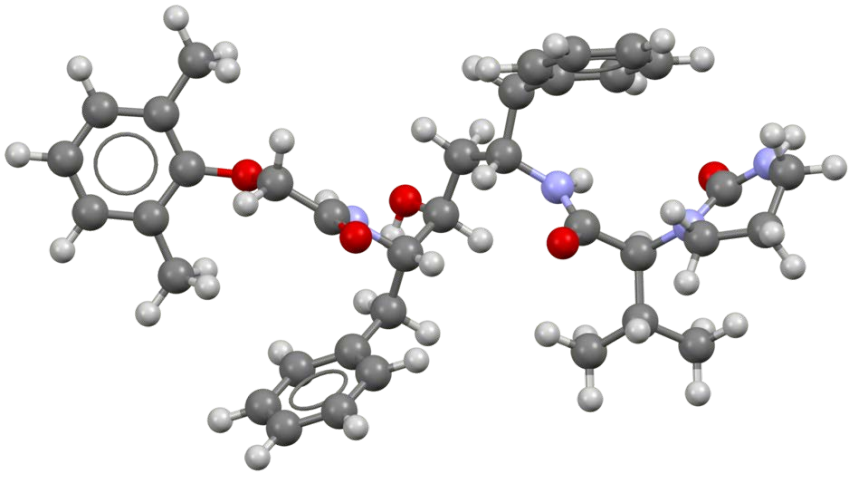

Figure 2. Ball-and-stick model of a Lopinavir molecule, $C_{37}H_{48}N_4O_5$ was found in the crystal structure of HIV-1 protease in complex with Lopinavir, reported in [1] (PDB entry: 1MUI; PDB ligand entry: AB1; PDBe ligand entry: AB1). **Colour code:** Carbon, C: grey Hydrogen, H: white Nitrogen, N: blue Oxygen, O: red Model manipulated and image generated in CCDC Mercury 3.8.

Keywords

ATR-FTIR Biospectroscopy, Simulation, Lopinavir, Breakdown, Coronavirus Disease-2019, COVID-19, Infection, Protective and Therapeutic Effect, Potent Drug

1. Introduction

ATR-FTIR biospectroscopy is a vibration biospectroscopy based on the influence of ATR-FTIR [2]-[17]. The influence of ATR-FTIR is elastically diffracting the electromagnetic ray due to rotational and vibrational transitions in molecules and its characteristic is changing the energy of diffracted beam photons compared to incident beam [18]-[33]. The difference between wavelength of incident beam light and diffracted light is related to molecular vibrations and is considered as exclusive "chemical finger print" of sample and can be used in identification of molecular compounds on a surface, into a liquid or into the air [34]-[49].

The stimulated ATR-FTIR diffraction is a non-linear effect [50]-[65]. If the pumping intensity exceeds the threshold of this effect, it observes [66]-[81]. The pumping threshold limit for stimulated ATR-FTIR depends on ATR-FTIR active material [82]-[98]. Regarding the spectral characteristics, stimulated ATR-FTIR can be distinguished from normal ATR-FTIR [1] [99] [100] [101] [102] [103]. While the intensity of ATR-FTIR bands are several times smaller than pumping laser intensity in normal ATR-FTIR, the intensity of ATR-FTIR bands in stimulated ATR-FTIR can be similar to laser intensity and for most materials, only strongest ATR-FTIR bands of material are intensified and are dominant in the

recorded spectrum of material.

In the current research, the stimulated ATR-FTIR spectrum is obtained through pumping the second harmonic beam laser Nd:YAG and it is performed by a spectrometer and detector. The resulted spectra and their characteristics are investigated here.

The severe acute respiratory syndrome (SARS) is a life threatening viral infection caused by a positive, single stranded RNA virus from the enveloped coronaviruse family. Associated with fever, cough, and respiratory complications, the illness causes more than 15% mortality worldwide. So far, there is no remedy for the illness except supportive treatments. However, the main viral proteinase has recently been regarded as a suitable target for drug design against SARS infection due to its vital role in polyproteins processing necessary for coronavirus reproduction.

The present in silico study was designed to evaluate the effects of anti-HIV-1 proteases inhibitors, approved for clinical applications by US FDA, on SARS proteinase inhibition.

In the present study, docking and molecular dynamic experiments were applied to examine the effect of inhibitors on coronavirus proteinase under physiological conditions of similar pH, temperature, and pressure in aqueous solution. Hex software version 5.1 and GROMACS 4.5.5 were used for docking analysis throughout this work.

The calculated parameters such as RMSD, RMSF, MSD, dipole moment, diffusion coefficient, binding energy, and binding site similarity indicated effective binding of inhibitors to SARS proteinase resulting in their structural changes, which coincide with proteinase inhibition.

The inhibitory potency of HIV-1 protease inhibitors to cronovirus proteinase was as follows: LPV > RTV > APV > TPV > SQV. Lopinavir and Saquinavir were the most and the least powerful inhibitors of cronovirus proteinase, respectively.

2. Experimental Arrangement

The experimental arrangement used in the current study is schematically shown in **Figure 3**. The first harmonic bicolor mirror reflects 1064 nm but passes the second harmonic one. As a result, the first harmonic removes from laser beam. The second harmonic laser Nd:YAG with wavelength of 532 nm and pulse width of 8 ns interacts with the sample after passing through bicolor mirror and lens with focal length of 3.5 cm. The resulted emissions from this interaction filters by an optical system consisting of some lens and optical fiber conducts to Eschelle spectrometer. The necessary time range for collecting spectra and its start time in ICCD detector controls by delayer device. Optical emissions of sample collect and intensifies from the striking moment of laser to sample until 5 ms after that moment. Test was repeated five times for each energy level for laser energy from 2.4 mJ to 29 mJ.

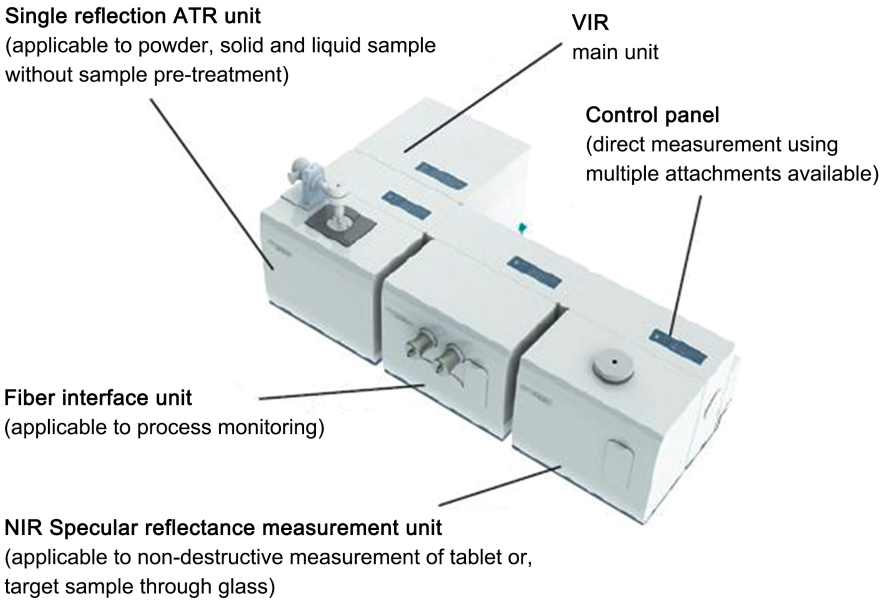

Figure 3. Schematic of stimulated ATR-FTIR biospectroscopy test arrangement.

3. Results and Discussion

Figure 4 shows the normal and stimulated ATR-FTIR spectra. Normal ATR-FTIR spectrum can be obtained when laser beam is not focused on the sample. When laser beam focuses on sample using a lens, non-linear effects stimulate and stronger bands of ATR-FTIR spectrum intensify up to some levels of laser intensity.

By increasing the energy of laser beam, the intensity of main bands of 3333 cm^{-1} and 3563 cm^{-1} also are increased and for energy levels higher than 8 mJ, anti-Stokes ATR-FTIR band corresponding to 3333 cm^{-1} intensifies in the spectrum and can be observed at left hand side of laser line in ATR-FTIR shift of -3333 cm^{-1}. Recording the anti-Stokes band necessitates the occupation of corresponding vibration level through diffraction of Stokes ATR-FTIR (Table 1).

By more increasing the energy level higher than 16 mJ, all four graphs of Figure 5 shows reduction in intensity. The reason for this reduction is creation of spark in the Lopinavir liquid due to increase in energy of laser more than the breakdown threshold of liquid. As a result of this spark, which creates in the center of liquid, laser beam absorbs by liquid and some part of it diffracts and only this part plays a role in creation of stimulated ATR-FTIR. By increasing the energy, beam has higher contribution in making the spark and the diffracted emission which reaches to detector decreases.

4. Conclusions, Summary, Useful Suggestions, Outlook, Perspective and Future Studies

The stimulated ATR-FTIR biospectroscopy test was performed for liquid sample of Lopinavir. The main band at 3333 cm^{-1} shows an intensity level comparable to pumping laser intensity. The intensity of stimulated ATR-FTIR spectrum at

Table 1. ATR-FTIR modes for Lopinavir.

	ATR-FTIR Shift (cm^{-1})	ATR-FTIR Mode
1	1085 cm^{-1}	C-H Stretch
2	1593 cm^{-1}	CH_2 Rocking
4	1927 cm^{-1}	CH_2 Wagging
5	3333 cm^{-1}	CH_2 Symmetric Stretch
7	3563 cm^{-1}	C-H Asymmetric Stretch

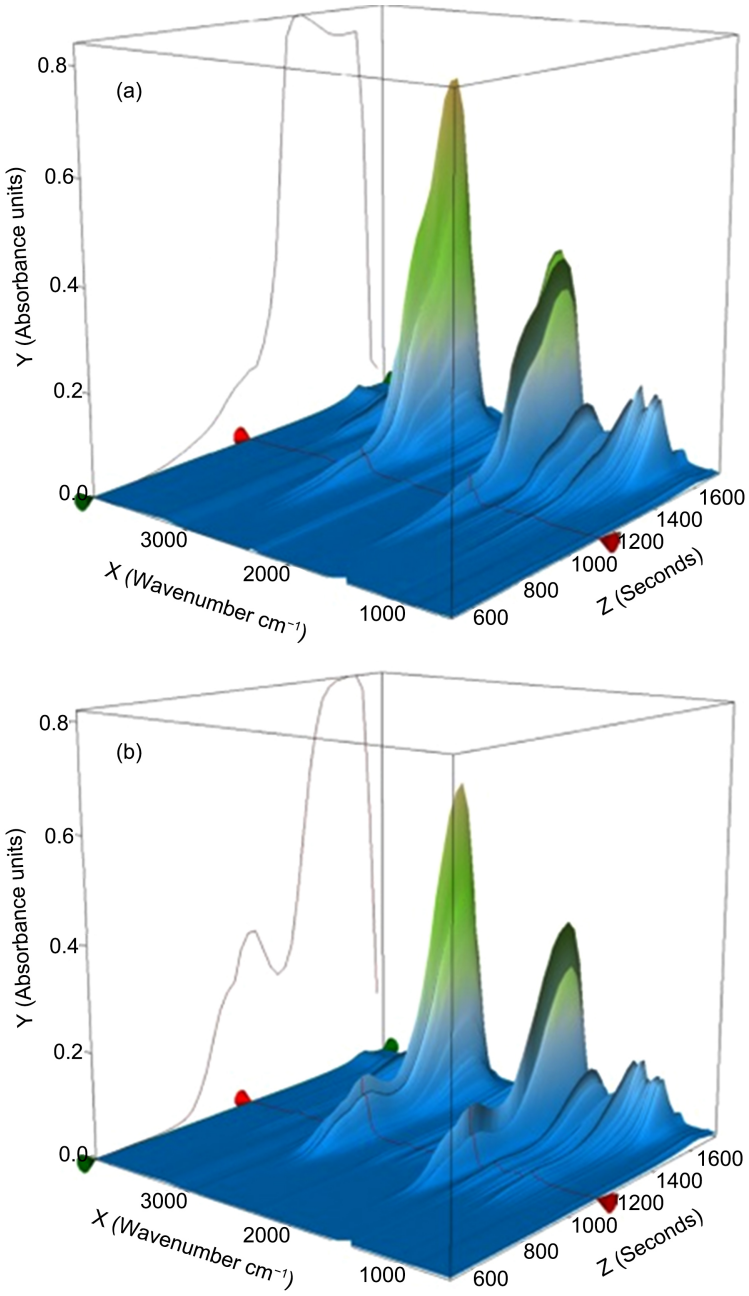

Figure 4. (a) Normal and (b) stimulated ATR-FTIR spectra for Lopinavir.

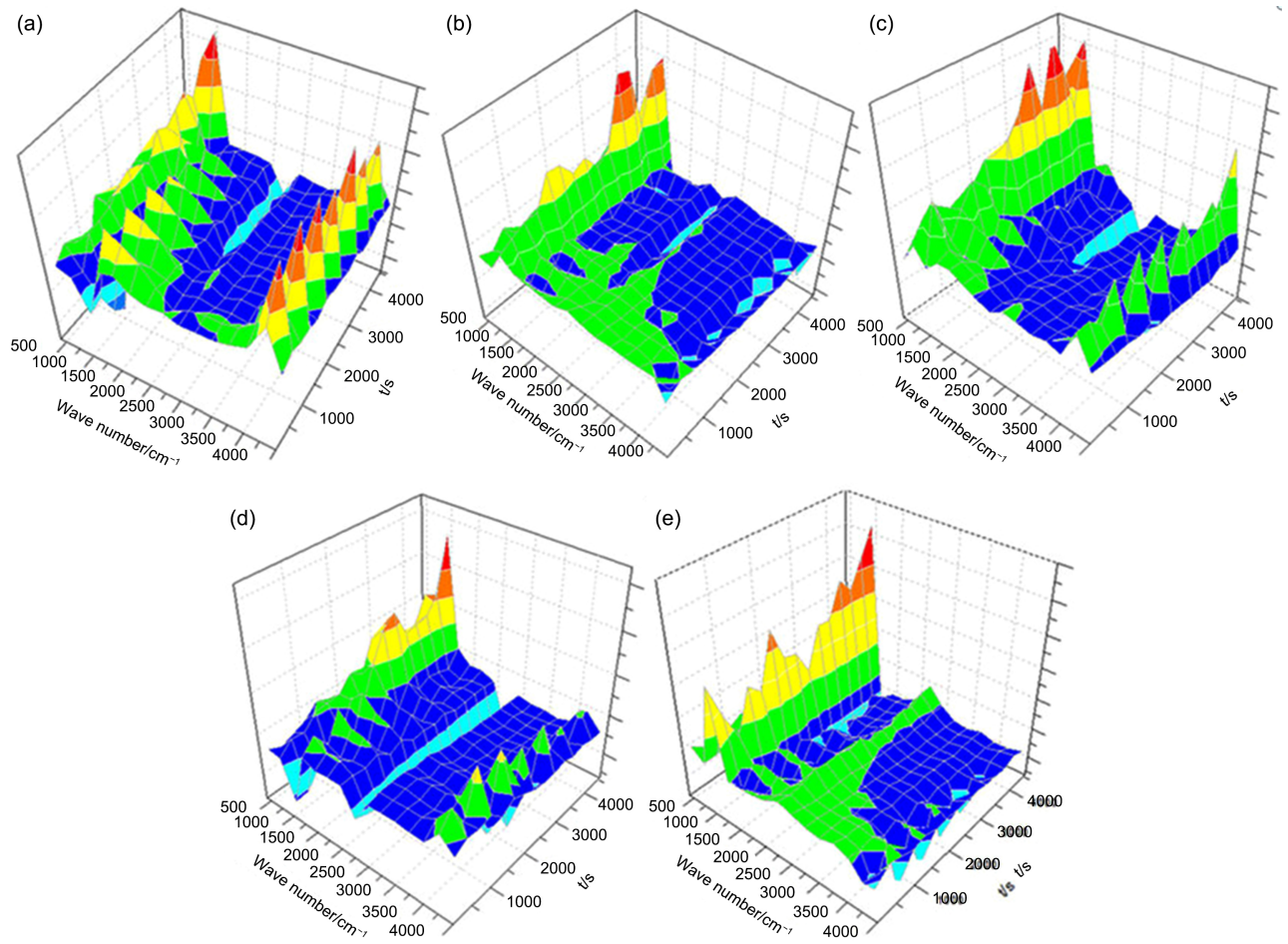

Figure 5. Peak intensity (a) band 1593 cm^{-1}, (b) 1927 cm^{-1}, (c) band 3333 cm^{-1}, (d) band 3563 cm^{-1} and (e) band −3333 cm^{-1} based on increase in energy level of beam focused on the liquid.

16 mJ energy level is the highest intensity in this test and more increasing the energy level reduces the intensity of spectrum. The reason for this reduction is creation of spark in the Lopinavir liquid due to increase in energy of laser more than the breakdown threshold of Lopinavir.

Taking into consideration our findings and the available clinical evidence on the usefulness of anti-HIV-1 protease inhibitors for SARS infection treatment, tested inhibitors can be ranked based on their inhibitory potency as follows: LPV < RTV < APV < TPV < SQV. In the absence of even a single effective drug for SARS treatment, our findings represent a promising pharmaceutical perspective for the disease therapy via Mpro inhibition.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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