STRUCTURE, ELECTRONIC AND VIBRATIONAL STUDY OF 7-METHYL-2,3-DIHYDRO-(1,3) THIAZOLO(3,2-A)PYRIMIDIN-5-ONE BY USING DENSITY FUNCTIONAL THEORY

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ABSTRACT

We have presented molecular structure and vibrational wavenumber assignments of 7-methyl-2,3-dihydro-(1,3)thiazolo(3,2-a)pyrimidin-5-one. Both ab initio Hartree-Fock and density functional theory employing 6-311++G(d,p) basis set have been used for the calculations. The scaled values of the calculated vibrational frequencies were used for assignments on the basis of potential energy distribution. The structure-activity relation has been interpreted by mapping molecular electrostatic potential surface. Electronic properties have been analyzed by using time dependent density functional theory (TD-DFT) for both gaseous and solvent phase. The calculated HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) energy values show that the charge transfer occurs within the molecule.

Keywords: MeTPDN, DFT, Vibrational spectroscopy, HOMO and LUMO.

INTRODUCTION

In recent years, there is an urgent need to develop new antimicrobial drugs with potent activities in order to overcome the global problem of bacterial drug resistance. Heterocyclic compounds containing pyrimidine moiety are of great interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities and clinical applications (Bradley et al., 2007; Panililo et al., 1992; Brown, 1984; Elderfield, 1957). Electron-rich nitrogen heterocycles and sulphur compounds play an important role in diverse biological activities. Thiazolo(3,2-a)pyrimidine derivatives are known for their broad spectrum of biological activities such as potential purine antagonists and antioxidants (El-Bayouki & Basyouni, 2010; Nagarajaiah et al., 2012). They exhibit anti-inflammatory (Tozkoparan et al., 1999), antihypertensive (Jeanneau-Nicole et al., 1992), antimicrobial (Jachak et al., 2005), antiviral (Mohamed et al., 2010), antifungal (Pan et al., 2011), antitumor (Flefel et al., 2007; Al-Omary et al., 2012), anti-HIV (Danel et al., 1998), antitubercular (Geist et al., 2010), calcium channel blocking (Balkan et al., 1992; Cai et al., 2015) etc. as their common activities. Park et al. (2013), designed and synthesized the oxazolopyridine and thiazolopyridine derivatives, and biologically evaluated their inhibitory activities against monoamine oxidase B (MAO-B) with greater optimal therapeutic potential towards Parkinson’s disease. Recently, Cai et al. (2015), reported antibacterial and antitubercular activities of some of the S-alkylated pyrimidine derivatives. Literature reveals that many synthesis and structure-activity related works on these pyrimidine derivatives had been reported, but their vibrational analysis has still not been studied. So, the aim of present study was to fully determine the molecular structure, vibrational modes and the absorption bands of 7-methyl-2,3-dihydro-(1,3)thiazolo(3,2-a)pyrimidin-5-one (MeTPDN) theoretically. Both Raman and infrared (IR) are the traditional spectroscopic methods for non-destructive characterization of substances (Chamers & Griffiths, 2002). Along with the quantum chemical studies, the equilibrium geometry, harmonic vibrational wavenumbers, molecular electrostatic potential surfaces, absolute Raman scattering
activities and IR absorption intensities have been calculated to support our wavenumber assignments using both ab initio Hartree-Fock (HF) and density functional theory (DFT) (Hohenberg & Kohn, 1964; Jha et al., 2018; Kumar et al., 2017; Govindarajan et al., 2012). Frontier levels energy gap (ΔE), dipole moments and the total energy has been obtained from the optimized geometry of the molecule. Most of the calculations have been performed for a single (or isolated) molecule in the gaseous system.

MATERIALS AND METHODS
Computational details
The DFT calculations were mainly carried out on the framework of Becke’s three parameter (local, non-local, Hartree-Fock) hybrid exchange functional with Lee-yang-Parr correlation functional (B3LYP) (Casida & Chong, 1995; Casida et al., 1998; Lee et al., 1998). Molecular structure, vibrational frequencies and energies of the optimized structure of the molecule were calculated using Gaussian 09 (Frisch et al., 2009) program package employing 6-311+G(d,p) basis set (Becke, 1993; Parr & Yang, 1989). The absolute Raman scattering and IR intensities were calculated at the same level as used for the optimization of geometry. The vibrational assignments of the normal modes were done as by Pulay’s recommendation (Pulay et al., 1983) along the internal coordinates employing localized symmetry using GAR2PED (Martin & Van Aslenoy, 1995). Visualization and confirmation of the calculated data were done by CHEMCRRAFT program (Zhurko & Zhurko, 2005). The graphical presentation of molecular electrostatic potential surface, HOMO - LUMO, and the calculated IR and Raman spectra obtained from the Gaussian output were made using GaussView program (Frisch et al., 2000).

RESULTS AND DISCUSSION
Geometry optimization
Using the standard geometric parameters, obtained from structure search data base (https://pubchem.ncbi.nlm), the geometry optimization has been performed as the first task, without using any constraints. These optimized geometric parameters were used for all the other calculations. Calculated vibrational frequency and the equilibrium geometry have been determined by the energy minimization. The ground state optimized molecular structure is shown in the figure 1. The relative energies of the molecule are calculated employing ab initio HF functions and DFT functional. The energy calculated by DFT (-536301.423 kcal/mol) is lower showing more stability than the calculated by HF (-534115.669 kcal/mol).

Fig. 1. Optimized structure of MeTPDN molecule.

The enthalpy difference between these two theories is 6.442 kcal/mol. The optimized parameters obtained by DFT method were very close to those obtained by the HF method. In this study, the bond lengths did not differ by more than 0.015Å except S1-C6, O2=C8, N3-C8 and N4=C7, which differed by 0.022Å, 0.0249Å, 0.0254Å and 0.0226Å, respectively. Relative to the bond lengths, both the bond angles and the dihedral angles were very similar (Srivastava et al., 2010) in the two theories.

Molecular electrostatic potential surface
The molecular electrostatic potential (MEP) in a molecule at any point r(x,y,z) is a force on unit positive charge at that point due to the net charge of the system (electronic and the nuclear charge). It is given by:

$$V(r) = \sum_{A=1}^{N} \frac{Z_A}{|R_A - r|} - \int \frac{\rho(r')dr'}{|r - r'|}$$  \hspace{1cm} (1)

where $Z_A$ is the charge on nucleus A located at $R_A$ and $\rho(r')$ is the electron density. The first term is due to the nucleus and the second due to electron cloud.

The MEP is a visualization tool to understand the relative polarization of the molecules (Chidangil et al., 1998). Such surfaces depict the size, shape, charge density, and site of chemical reactivity of the molecules. In the surface generated, negative electrostatic potential (shades of red color)
corresponds to an attraction of the proton by the concentrated electron density in the molecules (from lone pairs, pi-bonds, etc.) and positive electrostatic potential (shades of blue color) corresponds to repulsion of the proton by the atomic nuclei in the regions where low electron density exists and the nuclear charge is incompletely shielded. The spatial distribution and the values of the electrostatic potential are in fact largely responsible for the binding of a substrate to its receptor binding site. Different values of the electrostatic potential at the surface of a molecule appear with the different colors. The largely white or lighter color shades on the surface indicate that the molecule is mostly non-polar. The potential increases in the order red < orange < yellow < green < blue.

The electrostatic potential surface (ESP), electron density (ED), and the molecular electrostatic potential (MEP) of the molecule mapped with the output obtained by B3LYP/ 6-311++G(d,p) basis are shown in the figures 2(a-d).

From the figure, the highest negative potential (red region) is localized over the oxygen atom O2, as a functional group atom, of pyrimidine ring (R2). A less negative area occurs over the nitrogen atom N4 and sulphur atom S1. Similarly, the lowest potential (blue) is localized over the hydrogen atoms of the ethylene group of the thiazole ring (R1). ED mapping shows the uniform charge distribution over the molecular surface.

**Electronic absorption and frontier molecular orbitals (FMOs)**

In order to understand the electronic transitions in terms of energies and oscillator strengths, the time dependent density functional theory (TD-DFT)/6-31G (Petersson & Allaham, 1991) calculations were performed in the gaseous phase as well as in the solvent (EtOH) environment (integral equation formalism polarizable continuum model, IEF-PCM model) (Mishra et al., 2015, Perepichka & Bryce, 2005). The theoretical UV-vis absorption spectra are shown in the figure 3. Both the frontier molecular orbitals (FMOs), HOMO and LUMO are the main orbitals taking part in the chemical reaction (Singh et al., 2012). Energy difference between these two orbitals is the principal factor for determining the reactivity of the system.

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**Fig. 2. Graphical representation: (a) electrostatic potential surface in-plane, (b) electrostatic potential surface perpendicular to the plane, (c) electron density, and (d) molecular electrostatic potential (mapped from -5.730e-2 to 5.730e-2).**
To understand the electronic transitions, positions of experimental absorption peaks, calculated wavelengths ($\lambda_{\text{max}}$), vertical excitation energies, oscillator strengths ($f$), dipole moments, and excitation transition with spectral assignments for gas and solvent environment were carried out, which is given in Table 1. From the table, the main dipole transition in gas phase occurs at 264.70 nm ($H \rightarrow L$) with the oscillator strength 0.1246. Another strong transition is at 211.27 nm ($H \rightarrow L+1$) with the oscillator strength 0.0708. Similarly, in solvent phase, the transitions are centered at 265.14 / 216.21 nm ($H \rightarrow L$ / $H \rightarrow L+1$) with the oscillator strengths 0.1726 / 0.1096, respectively. It was clearly visible that both in gaseous and solvent phase in HOMO as well as in LUMO, the charge was mainly accumulated over the rings. The plots are shown in the figure 4. The main transition types occurring are $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$.

### Table 1: Electronic transitions, absorption wavelength $\lambda_{\text{max}}$ (nm), excitation energy (eV), oscillator strengths ($f$), frontier orbital energies (eV) and dipole moment, $\mu$ (Debye).

<table>
<thead>
<tr>
<th>Excited states</th>
<th>Gas phase</th>
<th>Solvent (EtOH) phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transitions</td>
<td>$\lambda$ (nm)</td>
</tr>
<tr>
<td>1</td>
<td>$H \rightarrow L$</td>
<td>264.70</td>
</tr>
<tr>
<td>2</td>
<td>$H-1 \rightarrow L$</td>
<td>256.39</td>
</tr>
<tr>
<td>3</td>
<td>$H-3 \rightarrow L$</td>
<td>247.37</td>
</tr>
<tr>
<td>4</td>
<td>$H-2 \rightarrow L$</td>
<td>227.86</td>
</tr>
<tr>
<td>5</td>
<td>$H \rightarrow L+1$</td>
<td>211.27</td>
</tr>
<tr>
<td></td>
<td>$E_{\text{HOMO}}$ (eV)</td>
<td>-6.370298</td>
</tr>
<tr>
<td></td>
<td>$E_{\text{LUMO}}$ (eV)</td>
<td>-1.161845</td>
</tr>
</tbody>
</table>

$E_{\text{HOMO}}$: Frontier orbital energies (eV) and dipole moment, $\mu$ (Debye).
Vibrational spectrum
The number of atoms in this molecule is 19 and it gives 51 (3N-6, N number of atom) number of vibrations. All the vibrations are both Raman and IR active. DFT calculations yield Raman scattering amplitudes which cannot be taken directly to be the Raman intensities. The Raman scattering cross section, \( \frac{\partial \sigma}{\partial \Omega} \), which are proportional to Raman intensity may be calculated from Raman scattering amplitude and predicted wavenumbers for each normal mode using the relationship (Guirgis et al., 2003; Polavarapu, 1990):

\[
\frac{\partial \sigma_j}{\partial \Omega} = \left( \frac{2^4 \pi^4}{45} \right) \left( \frac{\left( v_0 - v_j \right)^4}{1 - \exp \left( \frac{-h \omega_j}{kT} \right)} \right) \left( \frac{h}{8\pi^2 \omega_j^3} \right) S_j
\]

where \( S_j \) and \( v_j \) are the scattering activities and the predicted wavenumbers, respectively of the \( j^{th} \) normal mode, \( v_0 \) is the wavenumber of Raman excitation line and \( h \), \( c \) and \( k \) are universal constants.

Since, the DFT and HF vibrational wavenumbers are known to be higher than the actual values due to neglect of anharmonicity effects, they were scaled down by the wavenumber linear scaling procedure (WLS) \((v_{\text{obs}} = (1.0087 - 0.0000163 v_{\text{calc}}) \text{ cm}^{-1})\) of Yoshida et al., 2002. Comparison of the wavenumbers shows that the DFT methods give smaller value of the wavenumbers than the HF due to inclusion of the electron correlation in the first. The wavenumbers, intensities and the PED distributions obtained by HF and DFT methods with 6-311++G(d,p) basis set are listed in the Table 2. Calculated FT-IR and Raman spectra are shown in the figures 5 & 6. The assignments of some selected mode of vibration are discussed below:

Methyl group vibrations
Methyl (\( \text{CH}_3 \)) group has several modes associated with it, such as symmetric and asymmetric stretches, bends, rocks, and torsional modes. There is a methyl group attached to the pyrimidine ring as a functional group as shown in the figure 1. The asymmetric stretching of \( \text{CH}_3 \) was predicted at 2993 and 2960 cm\(^{-1}\) with medium intensity in the Raman and weak in the IR spectra. The symmetric stretching related to this mode corresponds at 2911
cm$^{-1}$ with strong intensity of 262 arb. units (i.e., Å$^3$/amu) in the Raman spectrum. Asymmetric and symmetric stretches were predicted at 1457 / 1451 and 1404 / 1368 cm$^{-1}$, respectively. The mixed rocking vibration of CH$_3$ was calculated at 1052 and 1038 cm$^{-1}$.

<table>
<thead>
<tr>
<th>Table 2: Calculated FT-IR and FT-Raman wavenumbers (cm$^{-1}$) with their intensities.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unscaled</strong></td>
</tr>
<tr>
<td>DFT</td>
</tr>
</tbody>
</table>
In this study, the symmetric stretching vibration was predicted at 3071 cm$^{-1}$, while the asymmetric stretching vibration of CH groups was calculated at 3007 and 2990 cm$^{-1}$ (Joshi et al., 2011). The asymmetric CH stretching vibrations are generally observed in the region of 2900–2900 cm$^{-1}$, while the CH$_2$ symmetric stretch appears in the region 2900–2800 cm$^{-1}$ (Sajan et al., 2004; Balachandran & Parimala, 2012). In this study, the asymmetric stretching vibration of CH$_2$ group was calculated at 3007 and 2990 cm$^{-1}$ while the symmetric stretching vibration was predicted at 2947 and 2918 cm$^{-1}$. The deformation was predicted at 1489 and 1468 cm$^{-1}$. Wagging, twisting and rocking vibrations were predicted below 1390 cm$^{-1}$ as shown in the Table 2. The mixed SC stretching vibration was calculated at 906, 685 and 429 cm$^{-1}$. CC stretching was predicted at 981 cm$^{-1}$.

**Thiazole ring (R1) vibrations**

The methylene (CH$_2$) groups are characterized by six fundamental modes of vibration. Out of them symmetric and asymmetric stretch, bending and rocking modes belong to polarized in-plane vibration. Similarly, wagging and twisting modes belong to the depolarized out-of-plane vibration. The asymmetric CH$_2$ stretching vibrations are generally observed in the region of 3000–2900 cm$^{-1}$, while the CH$_2$ symmetric stretch appears in the region 2900–2800 cm$^{-1}$ (Sajan et al., 2004; Balachandran & Parimala, 2012). In this study, the asymmetric stretching vibration of CH$_2$ group was calculated at 3007 and 2990 cm$^{-1}$ while the symmetric stretching vibration was predicted at 2947 and 2918 cm$^{-1}$. The deformation was predicted at 1489 and 1468 cm$^{-1}$. Wagging, twisting and rocking vibrations were predicted below 1390 cm$^{-1}$ as shown in the Table 2. The mixed SC stretching vibration was calculated at 906, 685 and 429 cm$^{-1}$. CC stretching was predicted at 981 cm$^{-1}$.

**Pyrimidine ring (R2) vibrations**

The CH stretching was predicted at 3071 cm$^{-1}$. The in-plane and out-of-plane bending vibration of this group were predicted at 1210 and 846 cm$^{-1}$, respectively. The most of the characteristic features of the carboxylic group are observed usually in the region 1700-1800 cm$^{-1}$ (Banwell & McCash, 1994). In this study, C=O stretching was predicted at 1705 cm$^{-1}$ which has very strong intensity of 665 arb. units (i.e., km/mole) in the IR spectrum and medium intensity of 40 units in the Raman spectrum. The in-plane bending related to this group modes vibration was calculated at 631 cm$^{-1}$.
Fig. 5. Calculated FT-IR spectra between the ranges 100-3200 cm\(^{-1}\) (frequency ranges 1300-1800 cm\(^{-1}\) with high absorbance is given in the inset section). Absorbances of selected characteristic modes are assigned.

C=C ring stretching was predicted at 1598 cm\(^{-1}\) with strong intensity in the IR spectrum and weak intensity in the Raman spectrum. N=C stretching was calculated at 1528 cm\(^{-1}\), which has very strong intensity in the IR spectrum (407 km/mole) and medium intensity in the Raman spectrum (67 km/mole). The mixed CC stretching was predicted at 1119 cm\(^{-1}\). Similarly, the NC stretching vibration was predicted at 988 cm\(^{-1}\).

The highly mixed ring puckering, deformation, torsion were predicted at 745, 741 and 200 cm\(^{-1}\), respectively.

Fig. 6. Calculated FT- Raman spectra between the ranges 100-3200 cm\(^{-1}\) (intensity of selected characteristic modes are assigned).
CONCLUSION
We have mainly concentrated to study the wavenumber calculations theoretically. All the assigned 51 modes of vibration are both IR and Raman active. The MEP mapping gives the size, shape, charge density distribution and sites of chemical reactivity of the title molecule which would be a good starting point for studying the detailed potential surface of the molecule. From the HOMO-LUMO plot it is clear that the charge accumulation mainly takes place from HOMO to LUMO both in the gaseous and solvent phases. The gap energy between these two frontier energy levels 5.21 eV (gaseous phase) indicates the high stability of the molecule.

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