Explorations on the electronic structure and spectroscopic IR assignments of 5-methyl-2-(2-oxopropyl)-pyrazolo[5,1-b]quinazolin-9(3H)-one molecule

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Abstract
In the present work, theoretical investigations on a quinazoline derivate, 5-methyl-2-(2-oxopropyl)pyrazolo[5,1-b]quinazolin-9(3H)-one, have been carried out through quantum mechanical density functional B3LYP/6-31G(d,p) method to explore its electronic structure and vibrational features. The normal modes analysis was executed to predict the contributions of different vibrational modes at the required frequencies in the infrared region and the spectral peaks have been assigned accordingly. Besides, certain electronic properties that are associated with chemical reactivity like, HOMO-LUMO energy gap, molecular electrostatic potential, Mulliken partial charges, etc have been estimated and discussed herein. It has been established that the molecule is chemically reactive and may be used in designing drugs as COX-2/5-LOX inhibitor.

1. Introduction
Quinzolines are the organic heterocyclic compounds consisting of fused six-membered benzene and pyrimidine rings. The derivatives of quinzolines played significant roles in the various pharmaceutical applications [1, 2]. Several quinzolines have been approved as drugs by the US Food and Drug Application. Gefitinib(2003) [3], Lapatinib(2007) [4], Erlotinib(2013) [5], and Aftininib(2013) [3] are the quinzoline containing drugs that are used in the treatment of advanced and metastatic breast cancers, which inhibit the functions of protein kinases of epidermal growth factor receptor (EGFR) [6]. Also, quinzolines and quinzoliones find enormous applications in the treatment of bacterial, fungal, inflammatory, malarial, viral, HIV, tuberculosis, etc diseases [7]. Recently, it has been reported that the fusion of pyrazole ring to the quinzoline structure can be used as the dual COX-2/cyclooxygenase)/5-LOX(lipoygenase) inhibitors [8], potential GABAA-R(γ-aminobutyric acid type A) inhibitors [9], novel excitatory amino acid antagonists [10]. The COX-2 and 5-LOX dual inhibitor action possess a wide range of anti-inflammatory activity by acting on arachidonic acid metabolic pathways. Several thioquinazolines have been reported as COX-1/COX-2/LOX inhibitors [11] while chalcone moiety provides a promising effect for the anti-inflammatory activities [12]. Thus, the improvement of chemical structures of quinzolines with potential fragments, nowadays, is the greatly fascinating field of research that promises better anti-inflammatory performances with a lesser occurrence of side effects. Shabaan et al have reported the design and synthesis of several pyrazoloquinazoline derivatives and their biological evaluation as dual COX-2/5-LOX inhibitors [8]. However, theoretical investigations on these compounds are very rare. Given the findings and the importance of pyrazoloquinazoline compounds, we have undertaken the quantum mechanical electronic structure studies and vibrational IR assignments of the 5-methyl-2-(2-oxopropyl)pyrazolo[5,1-b]quinazolin-9(3H)-one molecule [8]. The present work also aims to find out the chemical reactivity of the molecule by calculating HOMO(highest occupied molecular orbitals), LUMO(lowest unoccupied molecular orbitals), partial atomic charges, and
Figure 1. Optimized geometry of 5-methyl-2-(2-oxopropyl)pyrazolo[5,1-b]quinazolin-9(3H)-one molecule as obtained through B3LYP/6-31G** method.

Table 1. Imperative Geometrical parameters of the optimized molecule.

| Bond length (Å) |   |
|-----------------|---|
| C1-C2           | 1.418 |
| C1-C3           | 1.417 |
| C3-C4           | 1.391 |
| C2-C5           | 1.403 |
| C5-C7           | 1.384 |
| C2-C9           | 1.475 |
| C3-C10          | 1.507 |
| C6-C11          | 1.540 |
| C11-C12         | 1.500 |
| C8-C13          | 1.507 |
| C6-C14          | 1.510 |
| C8-N28          | 1.285 |
| C8-N29          | 1.387 |
| C12-N30         | 1.287 |
| C6-O31          | 1.214 |
| Bond angle (°)  |   |
| C2-C1-C3        | 119.70 |
| C1-C3-C4        | 118.23 |
| C1-C2-C5        | 120.48 |
| C2-C5-C7        | 119.59 |
| C1-C2-C9        | 121.03 |
| C1-C3-C10       | 120.19 |
| C6-C11-C12      | 116.30 |
| C11-C12-N30     | 123.19 |
| Dihedral angle (°) |   |
| C2-C1-C3-C4     | 0.01 |
| C3-C1-C2-C5     | −0.05 |
| C1-C2-C5-C7     | 0.06 |
| C3-C1-C2-C9     | −179.94 |
| C2-C1-C3-C10    | −179.97 |
| N28-C1-C8-N29   | −179.99 |
| C6-C11-C12-N30  | 12.72 |
| C1-C2-C9-O32    | 179.45 |
molecular electrostatic potential (MEP) surface as has been reported earlier [13]. The density functional method in conjunction with the 6-31G(d, p) basis set has been employed for the computations.

2. Computational details

The molecular geometry of the 5-methyl-2-(2-oxopropyl)pyrazolo[5,1-b]quinazolin-9(3H)-one molecule was optimized without any constraints using Becke’s three parameters hybrid exchange and Lee-Yang-Parr correlation functional (B3LYP) along with 6-31G(d,p) basis set as implemented within GAUSSIAN03 software [14]. As have been observed from literature, B3LYP/6-31G(d,p) level of the theory is best suited in the case of electronic structure calculations of the organic molecules. The density functional used in the present calculations can be expressed as in the following form [15].

\[ E_{XC} = (1 - \epsilon_0)E_{\text{SDA}} + \epsilon_0 E_{\text{HF}} + \epsilon_x \Delta E_{\text{B}} + \epsilon_c E_{\text{LYP}} + (1 - \epsilon_c) E_{\text{VWN}} \]

The optimized geometry has, then, been used for the calculation of HOMO, LUMO, partial atomic charges, MEP, and IR frequency calculations utilizing the same level of computational theory. The absence of imaginary frequency modes indicated the true minimum of the molecule. GaussView program has been used for the confirmation of the calculated data and visualization purposes [16].

3. Results and discussion

3.1. Geometry optimization

The optimized geometry of the molecule, as obtained through the B3LYP/6-31G** method, has been shown in figure 1. The prominent bond lengths, bond angles, and dihedral angles of the molecule are represented in table 1. It has been observed that the single bond lengths between carbon atoms are about 1.50 Å (except C6–C11) which are slightly less than the normal single bond length values. Inter ring C–C bond lengths are almost to their normal values with an exception of C5–C7. C–N and C–O bond lengths are slightly smaller. We observe that crystallographically CN bonds are much shorter than the expected single bond value, this may be happening due to the protonation-deprotonation type mechanism during complexation [17]. Dihedral angles demonstrate that the benzene and pyrimidine rings are planar while the pyrazole ring is somewhat non-planar. However, the conformation of the side chain is variable. The total electronic energy and the dipole moment of the molecule have been found to -856.04358 Hartree and 4.8339 Debye respectively.

3.2. Frontier molecular orbitals

To describe the chemical reactivity of the molecule, frontier molecular orbitals (HOMO and LUMO) provide a powerful practical model. The idea of frontier orbital symmetries has effectively been used to lessen the cyclo-addition and erstwhile pericyclic reactions. Figure 2 demonstrates the molecular frontier orbitals of the 5-methyl-2-(2-oxopropyl)pyrazolo[5,1-b]quinazolin-9(3H)-one molecule as obtained through quantum mechanical DFT/6-31G(d,p) calculations. Since the electrons from HOMO orbitals are the freest to participate in the reaction, the localization of these orbitals i.e. keto group (C=O) attached to the pyrimidine ring indicate the reaction site of the electrophiles. Similarly, the LUMO localization provides the reaction site where the electrophilic substitution reaction can take place. From figure 2, it can be observed that LUMO orbitals are localized around (C=N) bond of the pyrazole ring which provides a suitable site for the electrophilic substitution.
Figure 3. (a) Mulliken and (b) NBO partial charges as obtained through the B3LYP/6-31G** method.

Figure 4. The MEP surface of 5-methyl-2-(2-oxopropyl)pyrazolo[5,1-b]quinazolin-9(3H)-one molecule on the 0.001 electron/bohr^3 isosurface of the electron density.
reaction. The HOMO and LUMO energies as has been obtained through this calculation are $-0.22711$ and $-0.03929$ Hartree respectively. Consequently, the estimated HOMO-LUMO gap is $117.857$ kcal mol$^{-1}$. The low value of the HOMO-LUMO gap point towards the easy charge transfer indicating high chemical reactivity of the molecule [18].

3.3. Mulliken and NBO partial charges
The asymmetric allocation of electrons in the chemical bonds results in the partial charges in the molecule. These charges are used in the calculation of molecular force fields that play important roles in the classical molecular dynamics simulation studies. Mulliken population analysis [19] is one of the wave function based method for the determination of partial charges. In this method, the overlap population of the density matrix, as obtained through overlapping wave functions, is equally shared between the atoms forming bond. Natural bond orbital (NBO) calculation, useful for the information on the interactions in virtual and filled orbitals, was anticipated for atomic summary of natural localized atomic charges on compounds [20]. Figure 3 demonstrates the calculated Mulliken and NBO charges of the molecule under investigation using the B3LYP/6-31G(d,p) method. It may be observed that all the hydrogen atoms are partially positively charged, nitrogen and oxygen atoms bear partial negative charge while carbon atoms exhibit a substantial positive or negative charge depending upon its situation in the molecule. However, NBO provides more distinctness in partial charges.

3.4. Molecular electrostatic potential
The molecular electrostatic potential (MEP), a very valuable quantity in predicting and analyzing the molecular reactant behavior, illustrates the overall electrical charge distribution, that arises due to the nuclei and electrons of the molecule [21]. The electrophilic and nucleophilic sites within the molecule can also be analyzed using MEP, where reactions may happen. The MEP map of the molecule, shown in figure 4, has different colors depending on the values of the electrostatic potential. Red, green, and blue colors represent, respectively the most negative potential, zero potential, and most positive potential. The electrophilic (most negative) area is visible over the oxygen atom of the carbonyl group. The nucleophilic (positive charge) is localized on the hydrogen atoms of the pyrazole ring. Thus, negative potential sites are exhibited on oxygen and nitrogen atoms whereas hydrogen atoms bear positive potential sites.

3.5. IR assignments
The systematic infrared spectroscopic investigations of the molecule help to identify the presence of rings and other groups attached to the molecule. The experimental IR spectra of the quinazoline compounds have already
Table 2. Infrared vibrational assignments of fundamental wave numbers of the molecule at B3LYP/6-31G** level.

| Frequency (cm⁻¹) | IR intensity (km mol⁻¹) | Assignments |
|-----------------|-------------------------|--------------|
| 719.55          | 7.332                   | C–C out of plane deformation |
| 785.64          | 32.343                  | C–H out of plane deformation |
| 821.46          | 4.842                   | C–H out of plane deformation |
| 862.17          | 6.893                   | C–H out of plane deformation |
| 891.39          | 4.690                   | C–H out of plane deformation |
| 918.22          | 7.163                   | C–H out of plane deformation |
| 993.26          | 0.469                   | C–H out of plane asymmetric vibration |
| 1043.74         | 0.935                   | Inter ring N–N stretching |
| 1055.03         | 12.684                  | CH2 - wagging (side chain) |
| 1067.96         | 2.708                   | C–H2 - wagging (methyl group attached with a benzene ring) |
| 1101.62         | 19.909                  | C–H in-plane wagging symmetric vibration |
| 1109.28         | 24.776                  | C–H in-plane wagging asymmetric vibration |
| 1133.66         | 1.814                   | CH2 asymmetric wagging vibration (pyrazole ring) |
| 1163.61         | 2.747                   | CH2 symmetric wagging (pyrazole ring) |
| 1191.11         | 5.829                   | C–H in-plane symmetric and antisymmetric vibration of benzene ring |
| 1221.50         | 55.728                  | Inter ring N–N stretching (pyrazole ring) |
| 1244.34         | 13.379                  | C–C stretching of benzene- pyrimidine ring |
| 1257.10         | 61.263                  | C–C stretching (side chain) |
| 1346.37         | 111.890                 | C–N out of plane deformations |
| 1364.80         | 46.510                  | C–C stretching of benzene ring |
| 1403.08         | 49.358                  | CH3 wagging vibration of the side chain |
| 1430.64         | 1.245                   | CH3 wagging of the methyl group attached with benzene |
| 1442.68         | 17.880                  | C–H2 scissoring vibrations |
| 1453.94         | 10.078                  | C–H2 scissoring vibrations |
| 1464.27         | 23.615                  | C–H2 scissoring vibrations |
| 1509.97         | 49.597                  | C–H2 scissoring vibrations |
| 1623.87         | 2.005                   | C–C stretching of benzene ring |
| 1649.38         | 73.813                  | C–C stretching of benzene ring |
| 1678.17         | 52.434                  | Out of plane C–N vibrations of the pyrazole ring |
| 1704.73         | 232.105                 | In-plane C–N vibrations of the pyrimidine ring |
| 1799.21         | 355.505                 | C=O stretching (attached with pyrimidine ring) |
| 1822.40         | 192.230                 | C=O stretching of side-chain keto group |
| 3016.75         | 8.126                   | Symmetric C–H stretching of the CH2 group |
| 3051.31         | 7.522                   | Symmetric C–H stretching of side chain methyl group |
| 3052.37         | 24.335                  | Symmetric C–H stretching of the CH3 group attached to benzene ring |
| 3060.11         | 4.002                   | Symmetric C–H stretching of CH2 group attached with pyrazole ring |
| 3092.57         | 2.456                   | Asymmetric C–H stretching of side chain CH2 group |
| 3095.60         | 2.214                   | Asymmetric C–H stretching of CH2 group attached to pyrazole ring |
| 3112.35         | 12.713                  | Asymmetric C–H stretching of CH3-group attached with benzene ring |
| 3120.95         | 6.984                   | Asymmetric C–H stretching of CH3-group of the side chain |
| 3133.06         | 18.284                  | Asymmetric C–H stretching of CH3-group attached with benzene ring |
| 3168.19         | 7.644                   | Asymmetric C–H stretching of CH3-group of the side chain |
| 3179.17         | 14.246                  | Asymmetric C–H vibrations of benzene ring |
| 3200.68         | 16.485                  | Symmetric- asymmetric C–H vibrations of benzene ring |
| 3222.74         | 6.880                   | Symmetric C–H vibrations of benzene ring |

been reported in the literature [22]. Figure 5 and table 2 depict the IR assignments of the 5-methyl-2-(2- oxopropyl)pyrazolo[5,1-b]quinazolin-9(3H)-one molecule, calculated through B3LYP/6-31G(d,p) method in the region of 400 to 3500 cm⁻¹. The vibrational spectra comprise the characteristic vibrations of propanol chain, methyl group, benzene ring, pyrimidine ring, and pyrazole moiety along with C–N, and N–N stretching vibrations. The CH stretching vibrations appear in 3000 to 3250 cm⁻¹ frequency range which consists of symmetric and asymmetric stretching modes of methyl and methylene groups (table 2). Moreover, the CH stretching normal mode vibrations of aromatic moiety as well are the part of this region. The appearance of shoulders in the spectra indicate the presence of overtones of these groups. The vibrations of carbonyl groups appear at 1799 and 1822 cm⁻¹. The peaks in the region of 1440 to 1510 cm⁻¹ are associated with CH2 scissoring vibrations. The 1623 and 1649 cm⁻¹ component of spectra arises due to phenyl C–C stretching vibrations. CN stretching appears at 1678 and 1704 cm⁻¹, 1400 to 1435 cm⁻¹ lines are attributed to CH3 wagging. Other vibrations in the range 1050 to 1200 cm⁻¹ are assigned as CH2 symmetric and asymmetric wagging, and 750 to 1000 cm⁻¹ are attributed to CH out of plane deformations.
4. Conclusion

The density functional B3LYP method along with 6-31G(d,p) basis set has been utilized for the computations of electronic structure properties and IR frequencies of the 5-methyl-2-(2-oxopropyl)pyrazolo[5,1-b]quinazolin-9 (3H)-one molecule. Bond lengths and bond angles of the optimized molecule exhibit slightly less values than the normal values that usually appear in literature. HOMO-LUMO values, MEP surface, and Mulliken charge analyses indicate that the molecule is chemically reactive and may be developed as a drug against COX-2/5-LOX enzymes. The normal mode vibrational frequencies of the molecule as estimated through computations have been assigned accordingly.

Data availability statement

The data that support the findings of this study are available upon reasonable request from the authors.

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