Research article

Speculative analysis on the electronic structure, IR assignments and molecular docking of N-{4-[4-amino-3-phenyl-1H-pyrazolo[3,4-d]pyrimidin-1-yl]sulfonyl]phenyl}acetamide, an anti-amoebic agent

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ABSTRACT

An exhaustive quantum mechanical calculations on a pharmaceutically critical molecule N-{4-[4-amino-3-phenyl-1H-pyrazolo[3,4-d]pyrimidin-1-yl]sulfonyl]phenyl}acetamide have been investigated through the B3LYP/6-31G** Density Functional and HF/6-31G** Wave Function techniques. Physicochemical parameters along with the advanced electronic structure parameters like; MEP (molecular electrostatic potentials) and highest occupied & lowest unoccupied molecular orbitals (HOMO-LUMO) analysis have additionally been scanned over both methods. The computed HOMO-LUMO energy demonstrates that charge exchange takes place inside the molecule. The estimated small HOMO-LUMO energy gap, through both methods, indicates that the molecule is chemically reactive. Further, the IR vibrational spectra of the molecule have been assigned in the region 400-4000 cm⁻¹ through the DFT technique. The anticipated vibrational assignments have been compared with the experimental values accounted for in the literature. To comprehend the mode of binding, docking investigations of the molecule alongwith the co-crystallized metronidazole (MNZ) molecule were accomplished with O-acetyl-serine-sulphydrylase (OASS) enzyme using GLIDE-SP and GLIDE-XP modules. Docking simulations and reported biological activities (IC50) demonstrate that the title molecule may act as a lead molecule for constraining the progression of Entamoeba histolytica illness.

1. Introduction

Amoebiasis, one of the most pouring reasons of the death from intestinal protozoan parasite Entamoeba histolytica, is a notable medical issue in the Third World Nations [1]. The situation influences over 10% of the total residents, and unprocessed contamination may prompt extreme inconveniences, including hepatic amoebiasis and intestinal tissue obliteration [2]. The E. histolytica causes about 50 million medical circumstances per year out of which around one million people die [3]. Usually, the luminal parasite is spread into the colon wall and beyond which can lyse and devastate the intestinal tissue and the amoebiasis is caused [4]. The E. histolytica genome provide the key understanding of this multistage process. There are enormous promise for the novel drug development using the metabolic and signaling pathways of the Entamoeba histolytica parasite [5]. Metronidazole (MNZ) is the mainline drug against amoebiasis, yet late examinations have demonstrated that this medication has a few dangerous impacts, such as, genotoxicity, gastric bodily fluid disturbance, and spermatozoid harm [6, 7]. Moreover, disappointments in the treatment of a few abdominal protozoan fleas may come about because of medication impervious to parasites [8, 9]. These issues impelled us to scan for new antiamoebic representatives. Pyrazolo[3-4,d]pyrimidine molecules are endowed with antiamoebic actions [10, 11, 12, 13], alongwith the inhibition of anti-coagulation and inflammation activities of viper PLA2 [14], β-oxidation trifunctional enzyme of Mycobacterium tuberculosis [15] and other potential pharmaceutical activities [16, 17, 18]. Additionally, pyrazolo[3,4-d]pyrimidine compounds are the outstanding archetypal frameworks utilized for examining the intra- and intermolecular aromatic π-π interactions [19, 20]. These compounds have successfully proven to find applications in the treatment of thyroid carcinoma human cancers [20]. Also, the in-vitro anti amoebic activity of such a compound namely, N-{4-[4-amino-3-phenyl-1H-pyrazolo[3,4-d]pyrimidin-1-yl]sulfonyl]phenyl}acetamide against HM1:IMSS strain of Entamoeba histolytica, demonstrates the

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better inhibitor action in contrast to the known drug metronidazole (MNZ) [13, 14].

In the present examination, electronic structure along with its physicochemical properties, HOMO-LUMO molecular frontier orbitals, molecular electrostatic potential (MEP) map, and spectroscopic assignments of the typical modes of the title molecule have been performed using Density Functional Theory and ab-initio Hartree-Fock wave function techniques. The results obtained through these quantum computational methods have been compared. The present inspection has been executed with a view purpose of vibrational frequencies analyzed and equated with experimental results as described in the literature [21]. Keeping in mind the end goal to think about the relative restricting affinities and noncovalent interactions, molecular docking investigations of the title molecule along with the co-crystallized drug metronidazole (MNZ) have been performed using the Gaussian-03 program package [22]. Both methods are established techniques and can be used successfully in the case of small organic molecules.

2. Methodology

2.1. Electronic structure calculation

The whole investigations were achieved at Hartree-Fock and Density Functional techniques in conjugation with the 6-31G** basis set utilizing the Gaussian-03 program package [22].

| Bond length (Å) | Bond Angle (°) | Dihedral angle (°) |
|----------------|---------------|--------------------|
| Parameter      | HF            | B3LYP              | Parameter      | HF            | B3LYP              |
| N1-C2          | 1.335         | 1.341              | N1-C2-N3       | 129.0         | 128.5              | N1-C2-N3-C4        | 1.8            | 1.9          |
| C2-N3          | 1.301         | 1.333              | C2-N3-C4       | 112.8         | 111.8              | C2-N3-C4-C5        | 1.6            | 1.9          |
| N3-C4          | 1.332         | 1.336              | N3-C4-C5       | 125.0         | 127.1              | N3-C2-N1-C6        | -2.2           | -2.2         |
| C4-C5          | 1.392         | 1.406              | C4-C5-C6       | 117.7         | 118.3              | N3-C4-C5-C7        | 179.4          | 178.0        |
| N1-C6          | 1.319         | 1.344              | C4-C5-C7       | 104.4         | 105.2              | C4-C5-C7-C8        | -179.5         | -179.5       |
| C5-C7          | 1.440         | 1.443              | C5-C7-C8       | 130.2         | 130.0              | C5-C7-C8-C9        | -138.0          | -142.2       |
| C7-C8          | 1.482         | 1.476              | C7-C8-C9       | 119.7         | 119.8              | C7-C8-C9-C10       | -179.0          | -179.2       |
| C8-C9          | 1.392         | 1.404              | C8-C9-C10      | 120.4         | 120.4              | C8-C9-C10-C11      | 0.0             | -0.0         |
| C9-C10         | 1.383         | 1.393              | C9-C10-C11     | 120.3         | 120.3              | C9-C10-C11-C12     | 0.4             | 0.7          |
| C10-C11        | 1.386         | 1.397              | C10-C11-C12    | 119.6         | 119.7              | C10-C11-C12-C13    | -0.3            | -0.4         |
| C11-C12        | 1.383         | 1.396              | C11-C12-C13    | 120.2         | 120.2              | C2-N3-C4-N14       | -176.4          | -177.9       |
| C12-C13        | 1.386         | 1.396              | N3-C4-N14      | 128.5         | 127.3              | C4-C5-C7-N15       | 1.0             | 0.7          |
| C4-N14         | 1.354         | 1.381              | C5-C7-N15      | 109.9         | 110.6              | C2-N1-O6-N16       | 179.6           | 179.2        |
| C7-N15         | 1.284         | 1.322              | N1-C6-N16      | 115.9         | 116.7              | N3-C4-N14-S17      | -8.4            | -5.7         |
| C6-N16         | 1.361         | 1.359              | C4-N14-S17     | 130.1         | 127.9              | C4-N14-S17-O18     | 161.5           | 179.1        |
| N14-S17        | 1.727         | 1.737              | N14-S17-O18    | 104.4         | 106.1              | C4-N14-S17-O19     | 36.1            | 46.9         |
| S17-O18        | 1.429         | 1.458              | N14-S17-O19    | 104.0         | 106.8              | C4-N14-S17-C20     | -81.4           | -67.7        |
| S17-O19        | 1.429         | 1.457              | N14-S17-C20    | 107.2         | 97.9               | N14-S17-C20-N21    | 5.0             | 167.3        |
| S17-C20        | 1.878         | 1.907              | S17-C20-N21    | 110.9         | 114.9              | S17-C20-N21-C22    | 179.2           | 3.02         |
| C20-N21        | 1.279         | 1.351              | C20-N21-C22    | 120.3         | 129.8              | C20-N21-C22-C23    | -179.1          | 66.4         |
| N21-C22        | 1.394         | 1.436              | N21-C22-C23    | 116.1         | 120.6              | N21-C22-C23-C24    | -180.0          | 178.0        |
| C22-C23        | 1.400         | 1.396              | C22-C23-C24    | 121.7         | 119.5              | C22-C23-C24-C25    | 0.0             | -1.2         |
| C23-C24        | 1.378         | 1.394              | C23-C24-C25    | 121.3         | 121.3              | C23-C24-C25-C26    | 0.1             | 0.1          |
| C24-C25        | 1.393         | 1.400              | C24-C25-C26    | 117.1         | 118.1              | C24-C25-C26-C27    | -0.2            | 0.9          |
| C25-C26        | 1.384         | 1.403              | C25-C26-C27    | 122.3         | 121.1              | C25-C26-C27        | 2.3             | 3.5          |
| C26-C27        | 1.387         | 1.392              |                   |                   |                   |                   |                   |              |

Parameters having significant variations, as calculated through DFT and HF methods.
molecules [23]. We have used these two methods for the comparative examinations of the electronic structure performances on the molecule under study. The geometries were first decided using the Hartree-Fock method, after that, compared with the values obtained by DFT utilizing the Becke’s three-parameter hybrid functional joined with Lee-Yang-Parr correlation functional strategy (B3LYP) [24]. The enhanced structural parameters were utilized as a part of the vibrational IR frequency (velocity of light in vacuum times wave number) calculations at DFT levels to portray the standing point as least. The optimized geometries were exploited to figure out all the physicochemical parameters alongside harmonic vibrational wave numbers of the selected molecule. The HOMO- LUMO and molecular electrostatic potential (MEP) surfaces of the improved structures have likewise been examined [25].

2.2. Molecular docking

The DFT optimized geometry of the title molecule along with the reference medicate metronidazole (MNZ) has been prepared utilizing the LIGPREP module of the Schrödinger Suite to adjust the bond orders as per their information and, diverse conformers were created utilizing CONFGEN. These prepared ligands were utilized for ligand docking. The 3-D structure of the target OASS (PDB ID: 4IL5) [26] was

| Atom No. | Atom | Atomic charge | Atomic charge |
|----------|------|---------------|---------------|
|          |      | HF            | B3LYP         |
| 1        | N    | -0.671        | -0.431        |
| 2        | C    | 0.342         | 0.184         |
| 3        | N    | -0.560        | -0.404        |
| 4        | C    | 0.665         | 0.592         |
| 5        | C    | -0.266        | -0.024        |
| 6        | C    | 0.686         | 0.357         |
| 7        | C    | 0.222         | 0.174         |
| 8        | C    | -0.029        | 0.081         |
| 9        | C    | -0.119        | -0.091        |
| 10       | C    | -0.145        | -0.093        |
| 11       | C    | -0.153        | -0.078        |
| 12       | C    | -0.147        | -0.095        |
| 13       | C    | -0.157        | -0.145        |
| 14       | N    | -0.679        | -0.519        |
| 15       | N    | -0.230        | -0.254        |
| 16       | N    | -0.754        | -0.597        |
| 17       | S    | 1.601         | 1.239         |
| 18       | O    | -0.670        | -0.493        |
| 19       | O    | -0.666        | -0.483        |
| 20       | C    | 0.460         | 0.317         |
| 21       | N    | -0.703        | -0.535        |
| 22       | C    | 0.244         | 0.172         |
| 23       | C    | -0.166        | -0.056        |
| 24       | C    | -0.133        | -0.132        |
| 25       | C    | -0.049        | 0.135         |
| 26       | C    | -0.141        | -0.129        |
| 27       | C    | -0.184        | -0.067        |
| 28       | O    | -0.660        | -0.394        |
| 29       | C    | -0.332        | -0.377        |
| 30       | H    | 0.147         | 0.109         |
| 31       | H    | 0.187         | 0.116         |
| 32       | H    | 0.141         | 0.095         |
| 33       | H    | 0.135         | 0.091         |
| 34       | H    | 0.138         | 0.092         |
| 35       | H    | 0.176         | 0.110         |
| 36       | H    | 0.307         | 0.276         |
| 37       | H    | 0.308         | 0.283         |
| 38       | H    | 0.132         | 0.292         |
| 39       | H    | 0.105         | 0.124         |
| 40       | H    | 0.109         | 0.093         |
| 41       | H    | 0.192         | 0.089         |
| 42       | H    | 0.104         | 0.101         |
| 43       | H    | 0.104         | 0.115         |
| 44       | H    | 0.108         | 0.116         |
| 45       | H    | -0.167        | 0.135         |
downloaded from Protein Data Bank (http://www.rcsb.org/); which was prepared utilizing protein preparation wizard of the suite, to beat the assortment of potential issues, e.g. chain breaks, included water molecules, bond orders, missing residues, and so forth. The affinity and electrostatic potential grid were ascertained for each kind of atom in ligands at various grid points at the active site of the receptor. The location of MNZ remained the center of the active site. The docking calculations of prepared ligands were performed in the Standard precision (SP) and Extra precision (XP) modes of the GLIDE [27]. During docking, the target macromolecule was held fixed while ligands were dealt with as flexible. Full force field minimization of those poses which were considered for the last scoring was accomplished. The outcomes were utilized for binding energy calculations and docking scores.

3. Results and discussion

3.1. Molecular geometry

In the present investigation, the optimized geometries in gaseous state of the title compound using B3LYP (density functional theory) and Hartree-Fock (wave function theory) strategies in conjunction with the standard 6-31G** basis set are depicted in Figure 1. The imperative bond lengths, bond angles, and dihedral angles, as obtained through both techniques have been compared and are displayed in Table 1. The calculated net Mulliken charges on every atomic center have been presented in Table 2. It is inspected that the processed geometrical parameters viz; bond lengths, bond angles, and dihedral angles acquired from both techniques are similar for core-ring regions while there are some

Figure 2. The molecular electrostatic potential using (a) density functional and (b) Hartree- Fock methods of the N-{4-[(4-amino-3-phenyl-1H-pyrazolo[3,4-d]pyrimidin-1-yl)sulfonyl]phenyl}acetamide molecule projected on the 0.001 electrons/bohr³ isodensity surface. (c) colour strip representing the strength of electrostatic potential (Red color represents the regions of negative electrostatic potential, blue ones represent regions of positive electrostatic potential and white colour represents regions of zero potential).

Figure 3. HOMO and LUMO of N-{4-[(4-amino-3-phenyl-1H-pyrazolo[3,4-d]pyrimidin-1-yl)sulfonyl]phenyl}acetamide molecule using (a) density functional method and (b) Hartree-Fock method. (The orbital wave functions are positive in the red regions and negative in the blue region).
MEPs have been explored utilizing astounding wave function through that are utilized in order to observe molecular interactions [28].

3.2. Molecular electrostatic potential (MEP) and HOMO-LUMO analysis

Molecular electrostatic potentials (MEP) are important parameters that are utilized in order to observe molecular interactions [28]. The MEPs have been explored utilizing astounding wave function through B3LYP and Hartree Fock (HF) techniques at the self-consistent field level. The MEP surface of N-{4-[(4-amino-3-phenyl-1H-pyrazolo[3,4-d]pyrimidin-1-yl)sulfonyl]phenyl}acetamide on the 0.002 electron/bohr³ isosurface density is shown in Figure 2. It is observed that electron densities are low at the exterior portion and close to hydrogen molecules (blue and light blue regions). Consequently, electrostatic potential around these regions is positive. Comparatively higher electron densities (yellow and green regions) are observed in the interior portion of the molecule, because of the proximity of the less electronegative carbon atoms. The electron densities are high close to the strong electronegative atoms like oxygen and nitrogen, the result is that the MEP scan exhibits negative potential destinations on oxygen and nitrogen atoms while positive potential locales are around the hydrogen atoms.

The HOMO and LUMO of the studied molecule as ascertained by B3LYP/6-31G** and HF/6-31G** techniques are displayed in Figure 3. The HOMO of the molecule is exceptionally fixed on phenyl rings including carbon atoms while less focused on the oxygen and nitrogen atoms. Partial charges on nitrogen atoms indicate the overlap of nitrogen atoms on the adjacent carbon atoms, which shortens the bond length between these atoms. The C-N group is likewise exceedingly controlled. In LUMO, the delocalization of valence (virtual) orbitals all through the atom has ensued. Nitrogen atoms of the bond assemble overlap each other and carbon atoms of the central linkage cover adjoining carbon atoms of the phenyl rings. Since phenyl rings are nearly co-planar, both HOMO and LUMO are proportioned. The aggregate electronic energy, dipole moment, HOMO, and LUMO energies and energy gap (ΔE) for the molecule are presented in Table 3. A molecule with a smaller energy gap is expected to have higher reactivity and lower stability in the chemical process with electron exchange or leap [23, 29]. It is seen from Table 3, the HOMO-LUMO energy gap is 0.4036 Hartree through the B3LYP strategy and 0.3414 Hartree through the HF method, which is diminutive and demonstrates that the molecule under study is synthetically reactive.

| Parameters | HF | B3LYP |
|------------|----|-------|
| Total energy E (Hartree) | -1677.018 | -1685.958 |
| Dipole moment (Debye) | 5.8623 | 1.1706 |
| HOMO (Hartree) | -0.15490 | -0.31556 |
| LUMO (Hartree) | 0.18647 | 0.88104 |
| HOMO-LUMO energy gap (Hartree) | 0.34137 | 0.4036 |

| Parameters | DFT | HF |
|------------|-----|----|
| Zero-Point vibrational energy(kcal/mol) | 211.505 | 218.683 |
| Rotational temperature (Kelvin) | | |
| 0.017 | 0.009 |
| 0.004 | 0.005 |
| 0.003 | 0.004 |
| Rotational constants(GHA) | | |
| 0.348 | 0.267 |
| 0.079 | 0.089 |
| 0.070 | 0.079 |
| Energy (kcal/mol) | | |
| Total | 227.331 | 239.405 |
| Transtional | 0.889 | 0.889 |
| Rotational | 0.889 | 0.889 |
| Vibrational | 225.553 | 237.465 |
| Molecular Capacity at constant volume(cal/mol-kelvin) | | |
| Total | 96.026 | 87.324 |
| Transtional | 2.981 | 2.981 |
| Rotational | 2.981 | 2.981 |
| Vibrational | 90.064 | 81.362 |
| Entropy (cal/mol-kelvin) | | |
| Total | 178.585 | 173.318 |
| Transtional | 43.910 | 43.903 |
| Rotational | 36.363 | 36.402 |
| Vibrational | 98.312 | 93.013 |
3.3. Thermodynamical parameters

A few thermodynamic properties like heat capacity, zero-point vibrational energy, entropy alongside the global least energy of the title compound as acquired by \textit{ab-initio} Hartree Fock and Density Functional Theory strategies utilizing B3LYP/6-31G** are presented in Table 4. The distinction in the values figured out by both strategies is just minimal. Scale factors have been suggested for an exact forecast in deciding the zero-point vibrational energy, and the entropy. The variations in zero-point vibrational energy is by all accounts insignificant [30]. The aggregate energy and the adjustment in the aggregate entropy at room temperature are additionally exhibited. As obvious from Table 4, as the rotational temperature changes, rotational constants likewise change. The rotational constant declines with the reduction in rotational temperature. The rotational constant is inversely related to the moment of inertia of the molecule. Hence, decrease in rotational constant demonstrates increase in the moment of inertia of the molecule.

| Experimental wave numbers (cm\(^{-1}\)) | Theoretical wave numbers (cm\(^{-1}\)) | Intensity (km/mol) | Vibrational assignments |
|-----------------------------------------|----------------------------------------|--------------------|-------------------------|
| 411                                     | 424.02                                 | 11.375             | Ring out of plane deformation |
|                                         | 425.11                                 | 0.084              |                         |
|                                         | 436.10                                 | 45.404             |                         |
|                                         | 466.45                                 | 22.710             |                         |
| 474                                     | 509.98                                 | 15.757             |                         |
| 527                                     | 537.72                                 | 29.734             |                         |
| 551                                     | 553.72                                 | 9.581              |                         |
| 637                                     | 63173                                  | 1.826              |                         |
|                                         | 651.69                                 | 30595              |                         |
| 693                                     | 694.78                                 | 32.962             |                          |
|                                         | 715.86                                 | 35.309             |                          |
| 776                                     | 775.87                                 | 26.379             | C-H out of plane deformation |
| 807                                     | 793.43                                 | 3.038              |                         |
| 824                                     | 826.19                                 | 11.240             |                         |
|                                         | 834.39                                 | 28.614             |                         |
|                                         | 845.45                                 | 1.549              |                         |
| 885                                     | 870.36                                 | 1.259              | C-H3 Rocking            |
| 1003                                    | 1004.26                                | 0.368              | Inter ring C-C stretching |
| 1019                                    | 1016.24                                | 0.506              | C-C stretching          |
| 1061                                    | 1065.55                                | 7.363              |                          |
| 1121                                    | 1121.57                                | 193.653            | In-plane ring HCC bending |
| 1179                                    | 1182.14                                | 182.655            |                          |
| 1215                                    | 1221.09                                | 22.67              | C-H in-plane bending    |
| 1265                                    | 1229.42                                | 25.080             |                          |
|                                         | 1237.70                                | 8.582              |                          |
| 1306                                    | 1321.00                                | 40.786             | N-N stretching          |
| 1339                                    | 1336.41                                | 18.929             | C-N stretching          |
|                                         | 1354.16                                | 39.119             |                          |
|                                         | 1359.07                                | 88.426             |                          |
|                                         | 1364.31                                | 3.300              |                          |
|                                         | 1376.90                                | 19.203             |                          |
| 1466                                    | 1464.65                                | 8.394              | C-C Stretching          |
| 1478                                    | 1484.62                                | 4.940              |                          |
|                                         | 1501.37                                | 6.774              |                          |
| 1674                                    | 1667.29                                | 0.154              | NH\(_2\) Scissoring     |
| 3032                                    | 3043.14                                | 25.575             | Aromatic C-H stretching |
| 3070                                    | 3104.00                                | 18.829             |                          |
| 3125                                    | 3130.25                                | 13.563             |                          |
|                                         | 3183.76                                | 27.761             |                          |
|                                         | 3186.06                                | 12.611             |                          |
|                                         | 3190.10                                | 12.871             |                          |
|                                         | 3192.40                                | 7.209              |                          |
|                                         | 3201.46                                | 19.031             |                          |
|                                         | 3209.53                                | 19.632             |                          |
|                                         | 3220.76                                | 4.462              |                          |
|                                         | 3226.79                                | 0.728              |                          |
| 3472                                    | 3569.44                                | 47.942             | NH\(_2\) asymmetric stretching |
|                                         | 3599.99                                | 84.400             | NH\(_2\) symmetric stretching |
3.4. Vibrational analysis

Vibrational spectroscopy has noteworthy contributions towards the investigations of the structure and physicochemical properties of crystals and molecular systems. The vibrational examination of a picked compound has been made utilizing FTIR spectroscopy. An attractive assignment of the fundamental vibrations has been made by the position, shape, nature, and relative intensity. The vibrational IR spectra of N-{4-[(4-amino-3-phenyl-1H-pyrazolo[3,4-d]pyrimidin-1-yl)sulfonyl]phenyl}acetamide molecule in the region 400-4000 cm\(^{-1}\) comprises of vibrations characteristics of pyrazole and pyrimidine moieties, alkyl chains, CH and CN stretching modes, etc. Theoretically predicted vibrational (IR) frequencies of the molecule have been compared with the experimental observations and are introduced in Table 5, while the related spectrum is depicted in Figure 4.

3.4.1. The C–H vibrations

The C–H stretching vibrational modes of the aromatic and heteroaromatic structures occur in the wave number region 3000-3200 cm\(^{-1}\) [31]. The C–H stretching vibrations of N-[(4-amino-3-phenyl-1H-pyrazolo[3,4-d]pyrimidin-1-yl)sulfonyl]phenyl)acetamide are predicted at 3043.14, 3104.00, 3130.25, 3183.76, 3186.06, 3190.10, 3192.40, 3201.46, 3209.53, 3220.76, 3226.79 cm\(^{-1}\) in the FT-IR spectra, while experimentally they are found at 3032, 3070, and 3125 cm\(^{-1}\). The CH in-plane bands seen at 1221.09, 1229.42, 1237.70 cm\(^{-1}\), with CH out-of-plane bending, were observed to be well inside the evocative region. The small differences in the wave numbers may be because of calculations in gaseous state of the molecule while reported experimental values are in solid states. Several values of the same type of vibrations represent their presence in different chemical environments.

3.4.2. The C–N vibrations

The unconjugated C–N linkage in the amine group offers average to weak groups close to 1250–1020 cm\(^{-1}\) as a result of C–N stretching vibration [32]. The IR groups seen at 1336.41, 1354.16, 1359.07, 1364.31, and 1376.90 cm\(^{-1}\) are in the great concurrence with the experimentally observed values (1339 cm\(^{-1}\)). The slight distinction in wave number is because of the way the force constants of the C–N band expanded due to resonance with the ring.

3.4.3. C–C stretching vibrations

The vibrational band between 1400-1650 cm\(^{-1}\) is assigned to carbon-carbon vibrations. The FT-IR groups predicted at 1464.65, 1484.62, 1501.37, and 1506.73 cm\(^{-1}\) are allocated to C–C extending vibrations, which are in agreement with the probing esteems of 1466, 1478, 1677 cm\(^{-1}\).

3.4.4. Ring vibrations

For the title molecule, the bands seen at 1121.57, 1182.14, and 1188.34 cm\(^{-1}\) in FT-IR are credited to ring in-plane bending types, while experimentally they are seen at 1121 and 1179 cm\(^{-1}\). The twisting mode frequencies due to ring out-of-plane vibrations are observed at 424.02, 425.11, 436.10 cm\(^{-1}\), while experimentally they are found at 411 cm\(^{-1}\).

| Compounds | Hydrogen bondings | Hydrophobic interactions | Polar interactions | Other interactions |
|-----------|-------------------|-------------------------|-------------------|-------------------|
| SP docking |                  |                         |                   |                   |
| Title molecule | GLN235, ASN88, THR85, GLN159 | MET112, TYR313, ALA239, PHE241, MET136, PRO137, ILE140 | SER113, THR89, SER86, SER84 | PHE650(Cation ...x) |
| MNZ | SER86, ASN88, LLP58, GLN159, GLY236 | MET136, PHE160, ILE237, ALA239 | THR85, THR89, THR193 | LLP58(Cation ...x) |

| XP Docking |                  |                         |                   |                   |
| Title molecule | GLN235, ASN88, THR85, GLN159 | MET112, TYR313, ALA239, PHE241, MET136, PRO137, ILE140 | SER113, THR89, SER86, SER84 | PHE650(Cation ...x) |
| MNZ | THR85, THR89, LLP58, GLY236 | MET136, PHE160, ILE237, ALA239 | GLN159, THR85, SER86, ASN88, THR193 | LLP58(Salt bridge) |
3.4.5. Amino group vibrations

Generally, the wave numbers of amino groups show up in the region 3300-3500 cm\(^{-1}\) for N-H stretching, 1600-1700 cm\(^{-1}\) for NH\(_2\) scissoring, and 900-1150 cm\(^{-1}\) for rocking distortion. For the examined molecule asymmetric and symmetric extending vibrations are assigned out at 3569.44 and 3599.99 cm\(^{-1}\) respectively. NH\(_2\) is assigned at 1674 cm\(^{-1}\).

3.5. Molecular docking simulation

The estimation of different energy terms viz; Glide energy, van der Waal energy, Coulomb energy, and so on and Glide-score as acquired through standard precision (SP) and Extra Precisions (XP) protocols of Glide, along with the experimentally reported IC50 activities, are presented in Table 6. Docking of the title molecule with O-acetyl Serine Sulphhydrylase (OASS) compound uncovered an enormous variation in their binding energies. Even though the ascertained free energy of binding is a productive descriptor of ligand-receptor complementarities, the choice of the “best” docking model was at least articulated by an assortment of parameters of ADME study. It has been seen through SP docking that the title molecule has the best G-score (-6.839 kcal/mol) contrasted with reference medicate metronidazole (MNZ) (-4.217 kcal/mol). In the XP module of GLIDE, protein-ligand structural motifs promoting improved binding affinity were incorporated into expansion to one of a kind water destruction energy terms. The Glide docking effects of the XP protocol also revealed the title molecule with the highest docking score (-5.463 kcal/mol) compare to the reference drug metronidazole (-4.171 kcal/mol). Glide energies for title molecule were more negative (-50.001 kcal/mol) than the reference medicate metronidazole. Several non-covalent interactions of the ligands with the residues of the active site, similar to hydrogen bonding, aromatic π-π stacking, and hydrophobic interactions, are observed. As obvious from Table 7, Figure 5, and Figure 6, the title molecule display four numbers of hydrogen bonding interactions through both protocols of the docking with residues GLN235, ASN88, GLN159, THR85, while the reference drug metronidazole indicate five number of hydrogen bonds with residues SER86, ASN88, GLN159, GLY236, and LLP58 through SP-docking while four number of hydrogen bonds involving residues THR85, GLY236, TH89 and LLP58 by XP docking. Aromatic π-π interaction is

![Figure 5. Hydrogen bonding and other non-covalent interactions in the best docking poses of the title molecule and MNZ as obtained through SP and XP docking protocols of Glide.](image-url)
exhibited by the title molecule with the residue Phe160. The MNZ, within binding site, exhibit cation-π and salt bridge interactions with LLP58. Binding site residues MET112, TYR313, ALA239, PHE241, MET136, PRO137, ILE140, PHE160, ILE237, ALA239 etc form hydrophobic enclosure while SER113, THR89, SER86, SER84, THR85, THR193, GLN159, etc. are responsible for polar interactions. Estimations show that the title molecule has a better binding capability with O-acetyl Serine Sulfhydrylase enzyme against *Entamoeba histolytica* as compared to the established drug metronidazole (MNZ).

### 3.6. ADME property

ADME properties figured out utilizing QikProp3.5 [33] anticipated 44 properties for title molecule, comprising of primary descriptors and physicochemical properties. Adequacy of the analogs in light of “Lipinski’s rule of five” is additionally computed, which is fundamental for a reasonable medication plan. It has been observed that the title molecule and the reference drug MNZ both exhibit one violation of the Lipinski’s rule of ‘5’ (Table 8). The violation of more than one or two rules of ‘5’ may have issues with bioavailability. ADME estimations and docking simulations come about to show that the considered molecule might be developed as a lead compound as the inhibitor of the OASS enzyme.

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### Table 8. ADME properties of the title molecule and metronidazole (MNZ).

| Properties | Log P | M. W. | nON | nOHNH | nRotb | PSA | Volume | Abs. | nViol. |
|------------|-------|-------|-----|-------|-------|-----|--------|------|--------|
| Title molecule | 25.391 | 408.434 | 10.500 | 3.000 | 4 | 136.493 | 1192.941 | 72.267 | 1 |
| MNZ | 25.405 | 444.424 | 11.700 | 3.000 | 8 | 173.486 | 1207.119 | 41.683 | 1 |
| Range of 95% drugs | -2.0 to 6.5 | 130 to 725 | 2.0 to 20 | 0.0 to 6.0 | 0.0 to 15.0 | 7.0 to 200.0 | 500 to 2000 | >25% | 0.4 |

### 4. Conclusion

An attempt has been made in the present investigations to analyzed molecular geometry, HOMO-LUMO, MEP surface and vibrational spectra of N-[(4-amino-3-phenyl-1H-pyrazolo[3,4-d]pyrimidin-1-yl)sulfonyl] phenylacetamide molecule utilizing Density Functional theory (B3LYP/6-31G**) and wave function theory (HF/6-31G**) methods. The parameters (bond length and bond angle) of the optimized geometry figured through both IIF and B3LYP strategies in conjugation with a 6-31G** basis set are observed to be in great concurrence with each other. However, variations have been observed in the conformations of the molecule at the sulfonyl site. MEP indicates that electrophilic ability reinforces besides nucleophilic capacity deteriorates as one moves away from the internal center of the molecule. The calculated HOMO and LUMO energies demonstrate that possible charge exchange happens inside the molecule, and little value of the HOMO-LUMO gap demonstrated that the title molecule is chemically reactive. The total vibrational assignment of wavenumbers is made on the premise of aggregate energy distribution. The computed vibrational frequencies were found in great harmony with the experimental results accessible in literature. The DFT optimized geometry of the molecule has been used for docking within binding site of the OASS enzyme of the *Entamoeba Histolytica*. The partial charges demonstrated by MEP map helped in the creation of affinity grid.
map during docking. Molecular docking simulation and ADME property estimations demonstrate that the title molecule has a better binding ability with the target OASS than the reference medicate metronidazole (MN2), which are very similar to those of experimentally reported biological IC50 values for inhibiting the development of amoebiasis due to Entamoeba histolytica.

Declarations

Author contribution statement

Umesh Yadava: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.
Bindesh Kumar Shukla: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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