Research article

Conformational analysis and quantum descriptors of two new imidazole derivatives by experimental, DFT, AIM, molecular docking studies and adsorption activity on graphene

Veena S. Kumar, Y. Sheena Mary, Kiran Pradhan, Dhiraj Brahman, Y. Shyma Mary, Gonzagül Serdaroğlu, Ali Shokuhi Rad, M.S. Roxy

a Department of Physics, SN College, Kollam, Research Centre, University of Kerala, Kerala, India
b Department of Physics, Fatima Mata National College(Autonomous), Kollam, Kerala, India
c Department of Chemistry, St. Joseph’s College, P.O. North Point, Dist. Darjeeling 734104, India
d Sivas Cumhuriyet University, Faculty of Education, Math. and Sci. Edu., 58140 Sivas TURKEY
e Department of Chemical Engineering, Qaemshahr Branch, Islamic Azad University, Qaemshahr, Iran

ARTICLE INFO

Keywords:
Organic chemistry
Pharmaceutical chemistry
Theoretical chemistry
DFT
Imidazole
MEP
QTAIM
Docking

ABSTRACT

1-[2-(2-hydroxy-3-methoxy-5-(4-methoxyphenylazo)benzaldeneamino)ethyl]-3-methyl-3H-imidazole (HMY) and 1-[2-(2-hydroxy-3-methoxy-5-(4-methylphenylazo)benzaldene amino)ethyl]-3-methyl-3H-imidazole (HMM) were synthesized and characterized using spectral analysis. Conformational analysis has been achieved using potential energy scan for different rotatable bonds for obtaining the lowest energy conformer. Conformer with minimum energy is obtained along the dihedral angle N30-C31-C34-N37. QTAIM analysis gives nature and strength of hydrogen bonding interactions. UV-Vis, electrostatic potential and chemical descriptors are analyzed. Interaction of HMY and HMM with graphene is analyzed in terms of SERS activity. Chemical reactivity descriptors were investigated for graphene-drug systems. NLO activity of parent drugs and its graphene complexes show good activity. The wavenumber downshift of different modes is noted. Title molecules exhibit inhibitory activity against cytochrome C peroxidase. Interactions with graphene sheets are theoretically predicted for the title compounds.

1. Introduction

Imidazoles are materials for chemical synthesis with remarkable biological activities [1]. Some derivatives are characterized by properties of electroluminescence and have fluorophores in diodes that emit light [2, 3]. Azo compounds are industrial organic colorants and used in various fields, electronics, foods, drugs, cosmetics and textiles due to the versatile applications [4]. Imidazole drugs have uses in medical field of anticancer, antiviral, antibacterial and anti-diabetic activities [5, 6]. They are very important in materials chemistry as ionic liquids [7, 8] and in organic reactions as carbene precursors which are more stable [9]. Imidazole drugs show anti-hypertensive activities [10, 11]. They are also efficient corrosion inhibitors [12]. Khodja et al. recently reported a series of imidazole derivative’s design, synthesis and biological evaluation [13]. Kandasamy et al. recently reported the synthesis of zinc binding groups based on imidazole inhibitors that target lung cancer [14]. Recently green synthesis of an ionic liquid is reported based on imidazole [15]. Shahi et al. presented synthesis and distribution of electron density in imidazole derivatives [16]. Mary et al. reported a number of imidazole derivative’s spectroscopic studies [17, 18, 19, 20, 21, 22, 23]. In literature, broad research has been reported on graphene activity [24, 25, 26, 27, 28, 29]. Hydrophobic interaction is a major adsorption mechanisms of drugs with graphene [30, 31, 32, 33]. GQDs provide high SERS signals for detecting drugs due to electronic properties [34, 35, 36, 37, 38, 39, 40, 41, 42, 43]. Adsorption of drugs with graphene is reported by many authors experimentally and theoretically [44, 45, 46, 47, 48, 49, 50, 51, 52]. Coronene structures are reported as mimic of graphene [53, 54, 55]. Mary et al. reported the interaction of organic molecules with graphene/fullerene and doped graphene sheets [56, 57, 58, 59]. In the present study, DFT investigations, spectral analysis and docking study of title molecules, HMY and HMM were employed to determine the various properties including adsorption on coronene like graphene [60, 61, 62, 63].

* Corresponding author.
E-mail address: marysheena2018@rediffmail.com (Y.S. Mary).

https://doi.org/10.1016/j.heliyon.2020.e05182
Received 30 July 2020; Received in revised form 29 August 2020; Accepted 2 October 2020
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2. Methods of calculation and experimental

All calculations related to this study have been executed with computational chemistry software package Gaussian09 program [64]. In order to obtain correct structural feature of HMY and HMM (Figure 1), DFT theory with B3LYP with 6–311++G (d,p) basis have been taken. B3LYP is most popular DFT functional and widely used in density functional calculations [65, 66, 67, 68]. GAR2PED and Gasuview programs has been utilized to compute percentage potential energy distribution and hence to correctly assign vibrational wavenumbers of the title compound [69, 70]. QTAIM is a powerful method used to investigate the nature of all bonds in the course of HMY and HMM compounds [71, 72]. The QTAIM approach is useful to obtain electron density values and bonding characteristics of the configurations [71]. The charge density (n(r)), Laplacian of charge density (∇²n(r)), ellipticities (α) are calculated by AIMALL program [72] with all default options, were used to evaluate nature of the interaction. Based on the QTAIM approach, every two interacting atoms were connected by the bond path (BP), and one point (saddle point) in the BP had a maximum value of electron density named bond critical point (BCP).

HMY and HMM are prepared according to reported protocol [21, 22]. Perkin Elmer spectrometer was used for FT-IR spectrum (Figure 2) and Raman spectrum (Figure 3) of the sample were using Bruker UFS 66V model interferometer using Nd:YAG laser source.

3. Results and discussion

3.1. Conformational studies

To find least energy structure (Figure 1) of HMY and HMM, PES scan is performed at B3LYP/6-311++G (d,p) on C1-N11, N12-C13,
C16-C28, N30-C31, C31-C34, C34-N37 and C17-O20. In addition to this C4-O49 is also selected for HMY. The dihedral angles corresponding to these bonds are C6-C1-N11-N12, N11-N12-C13-C14, C14-C16-C28-N30, C28-N30-C31-C34, N30-C31-C34-N37, C31-C34-N37-C38 and C15-C17-O20-C23 for both HMY and HMM with an additional torsion angle C3-C4-O49-C50 for HMY. The structure obtained at global and local minima from the PES graph is again optimized to illustrate most stable conformer. All together 8 and 7 conformers are obtained after optimization corresponding to local and global minima for HMY and HMM. The energy as well as relative energies are predicted (Table 1). The PES curves and energies of structures are shown in Figures 4 and 5. Stable least energy form is along N30-C31-C34-N37 and is calculated to be -1313.87821 and -1238.67223 Hartree for HMY and HMM respectively.

Table 1. Ground state optimized energy and energy difference of all the possible conformers of HMY and HMM predicted at B3LYP/6-311++G (d,p) level.

| code | Dihedral angle | Conformers | Energy (Hartree) | Energy difference* (Hartree) |
|------|----------------|------------|-----------------|-------------------------------|
| **HMY** | | | | |
| φ1(N30-C31-C34-N37) | I | -1313.87821 | 0.00000 |
| φ2(N11-N12-C13-C14) | II | -1313.87012 | 0.00809 |
| φ3(C28-N30-C31-C34) | III | -1313.86797 | 0.01024 |
| φ4(C31-C34-N37-C38) | IV | -1313.86796 | 0.01025 |
| φ5(C6-C1-N11-N12) | V | -1313.86795 | 0.01026 |
| φ6(C14-C16-C28-N30) | VI | -1313.86357 | 0.01464 |
| φ7(C15-C17-O20-C23) | VII | -1313.85791 | 0.02030 |
| φ8(C3-C4-O49-C50) | VIII | -1313.8579 | 0.01031 |
| **HMM** | | | | |
| φ1(N30-C31-C34-N37) | I | -1238.67223 | 0.00000 |
| φ2(N11-N12-C13-C14) | II | -1238.66361 | 0.00862 |
| φ3(C28-N30-C31-C34) | III | -1238.66191 | 0.01032 |
| φ4(C31-C34-N37-C38) | IV | -1238.6619 | 0.01033 |
| φ5(C6-C1-N11-N12) | V | -1238.66175 | 0.01048 |
| φ6(C14-C16-C28-N30) | VI | -1238.65737 | 0.01486 |
| φ7(C15-C17-O20-C23) | VII | -1238.64908 | 0.02315 |

* Relative energies of the other conformers with respect to the lowest energy of conformer I.

Figure 4. (1): Potential energy surface scan with varying dihedral angle for HMY. (2): Potential energy surface scan with varying dihedral angle for HMM.
Figure 5. (1): Optimized structure of all the conformers of HMY. (2): Optimized structure of all the conformers of HMM.

Figure 6. The molecular graph of HMY. Nuclei and bond critical points are represented by big and small spheres small, respectively (green and red circles are bond and ring critical points, respectively). The lines are bond paths.
3.2. AIM analysis

Atom in molecule (AIM) analysis was used to find inter-molecular interactions. AIM molecular graph of stable geometry of HMY and HMM was illustrated in Figures 6 and 7, respectively, while the status of all BPs and BCPs related to these systems were clearly indicated. The densities (electron and Laplacian) and ellipticity parameters ($\epsilon$) at critical points for all bonds of HMY and HMM compounds were depicted in Tables 2 and 3, respectively. The values of electron density, 0.022–0.294 au shows a good interaction between atoms. Increase in $\rho$ caused the reduced distance between atoms. The $\rho$ valued for all bonds except O20-H22 in both HMY and HMM are in the range of covalent while for the stated bond is the range of hydrogen bonding. The Laplacian of charge density ($\nabla^2\rho(r)$) for all bonds at critical points also are listed in Tables 2 and 3. There is very good agreement between charge density and Laplacian of charge density. As can be seen in Tables 2 and 3, the Laplacian of charge density for all bonds except O20-H22 is negative which points towards the covalent interaction. For the O20-H22 bond, the value is positive which a proof of noncovalent interaction is. Results of Tables 2 and 3 showed that the $\epsilon$ of O20-H22 had values higher than the $\epsilon$ of the other bonds. This was due to the hydrogen interaction between them.

3.3. Molecular reactivity analyses, electronic spectra, MEP and NLO studies

The HOMO-LUMO band gap is a basic parameter in deciding atomic transport effects such as the chemical reactivity of a substance and kinetic stability of a molecule since it is a measure of electron conductivity [73, 74, 75]. Values of band gaps ($\Delta E_{LH}$) of HMY and HMM are 2.381 and 2.240 respectively (Table 4). HOMO (Figure 8), is over entire part of HMY and for HMM except in ring R3, CH2 groups and OCH3 atoms of rings R1 and R2 whereas LUMO spread the same regions as in HMY and HMM. Using the PDB's, 1QMQ, 4JB4, 2WYA, 4KF0, HMY and HMM were docked [88, 89]. Lamarckian Genetic Algorithm [90] included in Autodock software has been implemented for docking. Interactions are HMY and HMM are electrophilic regions whereas the blue color regions across R3 for both HMY and HMM shows low electron density (nucleophilic). The orientation of charge levels among the molecular site in the compound are usually measured different order such as first and second order [83]. Normally, the first order is measured loosely bounded electron delocalization and they occupied with high pressure generated by interactive and repulsive forces among the molecular sites and leads static chemical potential for regulate drug activity. In the second order, the bounded electrons with strong binding forces with nucleus delocalized with frenkel pressure generates enforced asymmetrical polarization called hyperpolarization causing intra atomic static potential which is the root cause of sensitive drug commotion. First order hyperpolarizability ($10^{-30}$ esu) of HMY (40.147) is greater than that of HMM (24.359) which are 308.82 and 187.38 times that of urea while next order values are -30.166 $\times 10^{-30}$ esu and -28.116 $\times 10^{-32}$ esu for HMY and HMM (Table 5). Here the first order polarization for both chain and ring was enabled and causing strong drug hardness capability. Here, the second order polarizability of the compound was also enables strongly which showed stabilization of consistent drug potential in the compound and this compound was able to have additional ligand groups for making multifunctional drug movement [84].

3.4. NBO analysis

The important NBO [85] interactions are: O49$\rightarrow$$\pi^*(C3-C14)$, N44$\rightarrow$$\pi^*(C9-C41)$, N44$\rightarrow$$\pi^*(N37-C38)$, O21$\rightarrow$$\pi^*(C16-C19)$, O20$\rightarrow$$\pi^*(C15-C17)$ with energies, 31.98, 29.08, 78.82, 29.30, 26.27 kcal/mol for HMY and N44$\rightarrow$$\pi^*(N37-C38)$, N44$\rightarrow$$\pi^*(C29-C41)$, O21$\rightarrow$$\pi^*(C16-C19)$, O20$\rightarrow$$\pi^*(C15-C17)$, C16-C19$\rightarrow$$\pi^*(C13-C14)$, C15-C17$\rightarrow$$\pi^*(C16-C19)$ with energies, 78.86, 29.07, 29.48, 26.34, 20.94, 20.41, 20.42 kcal/mol for HMM.

3.5. Molecular docking

To explore the drug properties, ligand-protein interaction is essential to be investigated to get more insights into the binding sites of biologically active molecules with amino acids of the protein and docking has been carried out by using Autodock software [86]. Targets, Chemo sensitizer, APOA1 expression enhancer, HMGC52 expression enhancer and CYP2C19 inducer as predicted by online PASS analysis [87] for HMY and HMM. Using the PDBs, 1QMQ, 4JB4, 2WYA, 4KF0, HMY and HMM are docked [88, 89]. Lamarckian Genetic Algorithm [90] included in Autodock software has been implemented for docking. Interactions are
Table 2. The charge density ($\rho(r)$), Laplacian of charge density ($\nabla^2\rho(r)$), and ellipticities ($\varepsilon$) of all bonds in the HMY molecule.

| BCP # | Bonds         | $\rho(r)$  | $\nabla^2\rho(r)$ | Ellipticities ($\varepsilon$) |
|-------|---------------|------------|-------------------|-------------------------------|
| 1     | C1 - C2       | +0.293474  | -0.679263         | +0.157327                     |
| 2     | C4 - O49      | +0.260343  | -0.431654         | +0.00025                      |
| 3     | C2 - H7       | +0.267002  | -0.817221         | +0.000368                     |
| 4     | C3 - C4       | +0.290659  | -0.663510         | +0.165621                     |
| 5     | O49 - C50     | +0.214792  | -0.264160         | +0.004719                     |
| 6     | C2 - C3       | +0.293051  | -0.675996         | +0.159697                     |
| 7     | C4 - C5       | +0.289159  | -0.667390         | +0.148286                     |
| 8     | C1 - C6       | +0.285618  | -0.636701         | +0.132554                     |
| 9     | C1 - N11      | +0.278641  | -0.685598         | +0.061311                     |
| 10    | C5 - C6       | +0.299533  | -0.707720         | +0.159039                     |
| 11    | C5 - H9       | +0.266947  | -0.818374         | +0.010984                     |
| 12    | C3 - H8       | +0.265824  | -0.796857         | +0.015527                     |
| 13    | C6 - H10      | +0.269218  | -0.841686         | +0.000434                     |
| 14    | N11 - N12     | +0.400618  | -0.685853         | +0.100118                     |
| 15    | N12 - C13     | +0.276321  | -0.649895         | +0.053436                     |
| 16    | C14 - H27     | +0.270792  | -0.864558         | +0.004650                     |
| 17    | C13 - C14     | +0.294548  | -0.675199         | +0.153297                     |
| 18    | C13 - C15     | +0.286707  | -0.647805         | +0.149354                     |
| 19    | C15 - C17     | +0.299385  | -0.708768         | +0.182515                     |
| 20    | C14 - C16     | +0.286702  | -0.644364         | +0.137671                     |
| 21    | C17 - C20     | +0.253129  | -0.411917         | +0.023050                     |
| 22    | C15 - H18     | +0.267546  | -0.826837         | +0.008688                     |
| 23    | C23 - H26     | +0.264248  | -0.784377         | +0.049591                     |
| 24    | C17 - C19     | +0.292935  | -0.672649         | +0.202456                     |
| 25    | O20 - C23     | +0.211152  | -0.232825         | +0.007834                     |
| 26    | C16 - C19     | +0.290678  | -0.668725         | +0.181251                     |
| 27    | C19 - O21     | +0.263285  | -0.449991         | +0.005436                     |
| 28    | C23 - H25     | +0.268898  | -0.829214         | +0.047328                     |
| 29    | O20 - H22     | +0.021809  | +0.086103         | +0.378981                     |
| 30    | O21 - H22     | +0.323275  | -1.542628         | +0.019628                     |
| 31    | C23 - H24     | +0.264192  | -0.783579         | +0.049784                     |
| 32    | C16 - C28     | +0.263245  | -0.551444         | +0.073764                     |
| 33    | C28 - H29     | +0.264062  | -0.791729         | +0.001822                     |
| 34    | C28 - N30     | +0.351235  | -0.918510         | +0.065149                     |
| 35    | N30 - C31     | +0.254153  | -0.509720         | +0.020824                     |
| 36    | C31 - H32     | +0.259967  | -0.745527         | +0.011215                     |
| 37    | C31 - H33     | +0.256538  | -0.711519         | +0.014103                     |
| 38    | C31 - C34     | +0.227665  | -0.416098         | +0.069474                     |
| 39    | C34 - H35     | +0.268104  | -0.827327         | +0.046342                     |
| 40    | C34 - H36     | +0.266464  | -0.803683         | +0.048723                     |
| 41    | N37 - C38     | +0.313346  | -0.823800         | +0.199277                     |
| 42    | C34 - N37     | +0.217735  | -0.347959         | +0.018929                     |
| 43    | N44 - C45     | +0.224133  | -0.391916         | +0.023152                     |
| 44    | C38 - H40     | +0.275304  | -0.934888         | +0.033530                     |
| 45    | C38 - N44     | +0.310572  | -0.795118         | +0.194983                     |
| 46    | N37 - C39     | +0.276296  | -0.615939         | +0.091254                     |
| 47    | C41 - N44     | +0.275030  | -0.595892         | +0.096469                     |
| 48    | C41 - H43     | +0.273403  | -0.908601         | +0.032106                     |
| 49    | C39 - C41     | +0.312757  | -0.759861         | +0.261251                     |
| 50    | C39 - H42     | +0.273698  | -0.913111         | +0.030626                     |
| 51    | C45 - H48     | +0.266036  | -0.808271         | +0.045458                     |
| 52    | C45 - H46     | +0.265719  | -0.809716         | +0.046971                     |
| 53    | C45 - H47     | +0.265764  | -0.810060         | +0.046948                     |
| 54    | C50 - H53     | +0.263083  | -0.772022         | +0.046892                     |
| 55    | C50 - H51     | +0.263012  | -0.771275         | +0.047014                     |
| 56    | C50 - H52     | +0.268911  | -0.828553         | +0.043833                     |
Table 3. The charge density ($\rho(r)$), Laplacian of charge density ($\nabla^2 \rho(r)$), and ellipticities ($\varepsilon$) of all bonds in the HMM molecule.

| BCP # | Bonds | $\rho(r)$ | $\nabla^2 \rho(r)$ | Ellipticities ($\varepsilon$) |
|-------|-------|-----------|-------------------|--------------------------|
| 1     | C4 - C49 | 0.237480  | -0.450813        | 0.016833               |
| 2     | C1 - C2  | 0.293578  | -0.680858        | 0.152152               |
| 3     | C2 - H7  | 0.264687  | -0.812454        | 0.000392               |
| 4     | C3 - C4  | 0.290342  | -0.665012        | 0.144914               |
| 5     | C49 - H50| 0.258736  | -0.733113        | 0.012426               |
| 6     | C2 - C3  | 0.294256  | -0.684823        | 0.144086               |
| 7     | C4 - C5  | 0.286480  | -0.642914        | 0.132693               |
| 8     | C1 - C6  | 0.287941  | -0.648139        | 0.134745               |
| 9     | C1 - N11 | 0.275607  | -0.669105        | 0.048672               |
| 10    | C5 - C5  | 0.296966  | -0.694978        | 0.148439               |
| 11    | C5 - H9  | 0.264822  | -0.791661        | 0.050762               |
| 12    | C3 - H8  | 0.264949  | -0.791596        | 0.070051               |
| 13    | C49 - H52| 0.255417  | -0.713519        | 0.013510               |
| 14    | C6 - H10 | 0.268680  | -0.834937        | 0.000778               |
| 15    | N11 - N12| 0.402635  | -0.694275        | 0.099312               |
| 16    | N12 - C13| 0.275774  | -0.647636        | 0.052971               |
| 17    | C14 - H27| 0.270928  | -0.865671        | 0.004230               |
| 18    | C13 - C14| 0.294706  | -0.677070        | 0.152886               |
| 19    | C13 - C15| 0.286835  | -0.648398        | 0.149715               |
| 20    | C14 - C16| 0.286986  | -0.645763        | 0.137194               |
| 21    | C15 - C17| 0.299386  | -0.708688        | 0.182348               |
| 22    | C15 - H18| 0.267569  | -0.827299        | 0.008687               |
| 23    | C17 - C19| 0.292758  | -0.671782        | 0.201752               |
| 24    | O20 - C23| 0.211007  | -0.231834        | 0.007492               |
| 25    | C16 - C19| 0.290733  | -0.669185        | 0.180553               |
| 26    | C17 - O20| 0.253347  | -0.412865        | 0.023387               |
| 27    | O20 - H22| 0.021834  | +0.086191        | 0.379276               |
| 28    | C19 - O21| 0.263723  | -0.451270        | 0.006519               |
| 29    | O21 - H22| 0.323184  | -1.542509        | 0.018957               |
| 30    | C23 - H25| 0.268941  | -0.829750        | 0.047355               |
| 31    | C23 - H24| 0.264715  | -0.783563        | 0.049871               |
| 32    | C23 - H26| 0.264239  | -0.784367        | 0.049730               |
| 33    | C16 - C28| 0.263013  | -0.550401        | 0.073451               |
| 34    | C28 - H29| 0.264114  | -0.792403        | 0.001748               |
| 35    | C28 - N30| 0.351451  | -0.916326        | 0.065704               |
| 36    | N30 - C31| 0.254052  | -0.509962        | 0.020945               |
| 37    | C31 - H32| 0.259907  | -0.745154        | 0.011359               |
| 38    | C31 - H33| 0.256590  | -0.712158        | 0.014084               |
| 39    | C31 - C34| 0.227775  | -0.411188        | 0.069549               |
| 40    | C34 - N37| 0.217772  | -0.348057        | 0.018836               |
| 41    | C34 - H35| 0.268137  | -0.827833        | 0.046234               |
| 42    | C34 - H36| 0.264548  | -0.803609        | 0.048634               |
| 43    | N37 - C38| 0.313314  | -0.823559        | 0.199193               |
| 44    | N44 - C45| 0.224123  | -0.391781        | 0.023195               |
| 45    | C38 - N44| 0.310590  | -0.795435        | 0.195059               |
| 46    | N37 - C39| 0.276278  | -0.615669        | 0.091125               |
| 47    | C41 - N44| 0.275023  | -0.595883        | 0.096209               |
| 48    | C28 - H40| 0.275312  | -0.934903        | 0.033534               |
| 49    | C41 - H42| 0.272395  | -0.908676        | 0.032075               |
| 50    | C29 - C41| 0.312778  | -0.759980        | 0.261217               |
| 51    | C29 - H42| 0.273687  | -0.913183        | 0.030605               |
| 52    | C45 - H48| 0.266031  | -0.808233        | 0.045476               |
| 53    | C45 - H46| 0.265749  | -0.810020        | 0.046940               |
| 54    | C45 - H47| 0.265744  | -0.809902        | 0.046989               |
| 55    | C49 - H51| 0.255374  | -0.713113        | 0.013558               |
Table 4. Chemical descriptors.

| Compound | $I - \varepsilon_{\text{HOMO}}$ | $A - \varepsilon_{\text{LUMO}}$ | Gap     | $\eta = (I - A)/2$ | $\mu = -(I + A)/2$ | $\omega = \mu^2/2\eta$ |
|----------|----------------|----------------|---------|-------------------|--------------------|--------------------|
| HMY      | 7.822          | 5.441          | 2.381   | 1.191             | -6.632             | 18.465             |
| HMM      | 7.833          | 5.593          | 2.240   | 1.120             | -6.713             | 20.118             |
| HMY-G    | 7.813          | 5.732          | 2.081   | 1.041             | -6.773             | 22.033             |
| HMM-G    | 7.887          | 5.738          | 2.149   | 1.075             | -6.813             | 21.589             |

Figure 8. HOMO-LUMO plots of (a) HMY, (b) HMM (c) HMY-G (d) HMM-G.
presented in Figures 12 and 13. The maximum energy values of HMY and HMM are -9.8 and -10.7 kcal/mol for 4JB4 respectively (Table 6). These results suggest that HMY and HMM shows activity against these cytochrome C peroxidase. However further experimental studies are needed to confirm its activity.

3.6. IR and Raman spectra

A sharp peak observed at 3435, 3430 cm\(^{-1}\) and 3447 cm\(^{-1}\) experimentally (Table S1) and at 3451 cm\(^{-1}\) (DFT) are \(\nu\)OH [91, 92]. \(\delta\)OH was 1250 (DFT) and seen at 1251/1252 cm\(^{-1}\) (IR) for HMY/HMM and at 1248 cm\(^{-1}\) (Raman) for HMM. \(\tau\)OH is at 544 cm\(^{-1}\) (Raman) for HMM but DFT give this at 539 (HMY) and 542 cm\(^{-1}\) (HMM). The prominent peaks observed at 3068, 3002, 2925, 2850/3205, 3067, 3011, 2958, 2918, 2850 cm\(^{-1}\) and 3180, 3128, 3020, 2865, 2934, 2850/3130, 2970, 2922, 2850 cm\(^{-1}\) (IR/Raman) are \(\nu\)CH modes and DFT values are 3221-2850/3220-2858 cm\(^{-1}\) for HMY and HMM respectively. The \(\nu\)C = CR3 is assigned at 1547 cm\(^{-1}\) and at 1549/1547 cm\(^{-1}\) (IR) spectrum for HMY and HMM.

3.7. Adsorption behavior on graphene sheet

Adsorption process of graphene-drugs is reported by many researchers [93, 94, 95, 96, 97, 98]. Adsorption energies are -0.65833 and -0.63937 eV for HMY-G and HMM-G complexes [99]. Chemical potential and electrophilicity indices (Table 4) for graphene complex with
Figure 11. MEP plots of (a) HMY (b) HMM (c) HMY-G (d) HMM-G.

Table 5. NLO properties.

| Molecule | Dipole moment (Debye) | Polarizability ($\times 10^{-25}$) | First order hyperpolarizability ($\times 10^{-26}$) | Second order hyperpolarizability ($\times 10^{-27}$) |
|----------|-----------------------|-----------------------------------|-----------------------------------------------|-----------------------------------------------|
| HMY      | 25.787                | 4.785                             | 40.147                                        | -30.166                                       |
| HMM      | 23.843                | 4.589                             | 24.359                                        | -28.116                                       |
| HMY-G    | 40.784                | 8.952                             | 45.493                                        | -61.096                                       |
| HMM-G    | 12.352                | 8.435                             | 19.521                                        | -88.326                                       |

Figure 12. The docked ligands HMY (A) and HMM (B) interaction with the amino acids of (a) 1QMQ (b) 4JB4 (c) 2WYA (d) 4KF0.
HMY and HMM show more stability. The HOMO-LUMO plots and MEP plots (Figures 8 and 11) show the charge transfer between graphene sheet and molecules with a lowering of hardness values. Table 5 data shows that NLO property of graphene-MHY/HMM increase and hyperpolarizability values are very high. For HMY/HMM-G complexes (Table S2), intensity multiplication is for 3074 cm\(^{-1}\) from 10.05/12.92 to 46.04/40.55, with enhancement factors, 358/214, which is significant (Figures 14 and 15). Multiplication of 237 and 230 are seen for 1440 cm\(^{-1}\) and 1348 in HMY-G complex, corresponding to CH\(_3\) and CH\(_2\) deformations with blue and redshift to 1463 and 1336 cm\(^{-1}\). But for HMM-G, enhancement of these deformation modes is high and enhancement factors of 1172 and 1168 for the modes 1486 cm\(^{-1}\) and 1468 cm\(^{-1}\). For both complexes \(\nu_{CH3}, \nu_{C=CH}\) and \(\nu_{Ring}\) modes are in SERS spectrum with low enhancement factors. Enhancement of different modes shows that graphene can be used as sensor for detection of drugs [100, 101].

4. Conclusion

In the present work, quantum chemical descriptors, and vibrational spectral studies of HMY and HMM were studied. Conformational analysis identifies the most stable conformer. The theoretically obtained data are in agreement with experimental results. The FMO’s determined energy gap shows the chemical stability. NBO results account for the natural charge accumulation in the investigated molecule. QTAIM study shows that ellipticity of OH bond had values

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Table 6. Docking analysis of receptors with ligands.

| Molecule | Receptors name | Binding energy (kcal/mol) | Residues involved in hydrogen bonding | Residues involved in electrostatic interactions | Residues involved in hydrophobic interactions |
|----------|----------------|--------------------------|----------------------------------------|-----------------------------------------------|-----------------------------------------------|
| HMY      | 1QMQ          | -8.9                     | ASP297, GLN322, TYR96, PHE350, HIS355  | ASP297                                       | THR252, VAL295, CYS357, ALA363               |
|          | 4JB4          | -9.8                     | THR234, SER185, LYS179                 | TRP51,                                        | TRP51, PRO145, LEU171, ALA174               |
|          | 2WYA          | -8.1                     | SER14, GLY87, ASN204                   | ALA205, PRO303                                |                                               |
|          | 4KF0          | -8.3                     | THR266, SER72, ALA30                   | PHE87, ALA328                                |                                               |
| HMM      | 1QMQ          | -9.5                     | ASP297, GLN32, VA; 247, PHE350, HIS355 | GLN322, ASP297, ALA363, PHE350                | VAL295, PHE350, VAL253, LEU298, ALA50, ILE367, CYS357, PHE256, |
|          | 4JB4          | -10.7                    | THR234, TRP51, SER185, LYS179, LEU171, ALA174 | TRP51                                        | TRP51, LEU171, ALA174, LEU269, PRO145, PHE262, |
|          | 2WYA          | -8.1                     | ASN204, TYR412                         | CYS400, ALA205, PRO303, HIS301               |                                               |
|          | 4KF0          | -9.0                     | LYS69, ARG398, ASN395, ILE401,         | ARG398, CYS400                               | CYS400, PHE87, ILE153, ALA264, PHE107, PHE405 |

HMY and HMM shows more stability. The HOMO-LUMO plots and MEP plots (Figures 8 and 11) show the charge transfer between graphene sheet and molecules with a lowering of hardness values. Table 5 data shows that NLO property of graphene-MHY/HMM increase and hyperpolarizability values are very high. For HMY/HMM-G complexes (Table S2), intensity multiplication is for 3074 cm\(^{-1}\) from 10.05/12.92 to 46.04/40.55, with enhancement factors, 358/214, which is significant (Figures 14 and 15). Multiplication of 237 and 230 are seen for 1440 cm\(^{-1}\) and 1348 in HMY-G complex, corresponding to CH\(_3\) and CH\(_2\) deformations with blue and redshift to 1463 and 1336 cm\(^{-1}\). But for HMM-G, enhancement of these deformation modes is high and enhancement factors of 1172 and 1168 for the modes 1486 cm\(^{-1}\) and 1468 cm\(^{-1}\). For both complexes \(\nu_{CH3}, \nu_{C=CH}\) and \(\nu_{Ring}\) modes are in SERS spectrum with low enhancement factors. Enhancement of different modes shows that graphene can be used as sensor for detection of drugs [100, 101].

4. Conclusion

In the present work, quantum chemical descriptors, and vibrational spectral studies of HMY and HMM were studied. Conformational analysis identifies the most stable conformer. The theoretically obtained data are in agreement with experimental results. The FMO’s determined energy gap shows the chemical stability. NBO results account for the natural charge accumulation in the investigated molecule. QTAIM study shows that ellipticity of OH bond had values
higher than the ellipticity of the other bonds which is due to hydrogen interactions. SERS data of HMY/HMM with graphene gives enhancement of Raman signals.

Docking simulation obtained shows good binding affinities with the receptors. The predicted docked models will be the starting point of drug discovery. This study could hopefully serve as a base for further drug research and development.

Declarations

Author contribution statement

Veena S. Kumar, Y. Sheena Mary, Kiran Pradhan, Dhiraj Brahman: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Y. Shyma Mary, Goncagül Serdaroglu, Ali Shokuhi Rad, M. S. Roxy.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interest statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at doi:10.1016/j.heliyon.2020.e05182.

Acknowledgements

All calculations have been carried out at TUBITAK ULAKBIM, High Performance and Grid Computing Center (TR-Grid e-Infrastructure).

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