



# Quantum Computational Exploration of Oxadiazole-Containing Schiff Base Derivatives Using Density Functional Theory

K. B. Chethan Kumar<sup>1</sup>, G. B. Yogesh<sup>1</sup>, C.L. Nisha<sup>2</sup>, and Y. B. Basavaraju<sup>1\*</sup>.

<sup>1</sup>Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore, 570 006, Karnataka, India

<sup>2</sup>Department of Chemistry, St. Anne's degree College, Virajpet, 571218, Karnataka, India

## Abstract

In the field of molecular chemistry, the design and investigation of novel compounds with tailored properties are of paramount importance in various scientific domains, including drug discovery, materials science, and organic electronics. This study delves into the quantum computational exploration of oxadiazole-containing Schiff base derivatives, a class of compounds known for their versatile nature and intriguing characteristics. To comprehensively understand and predict the properties of these derivatives, advanced computational techniques, particularly Density Functional Theory (DFT), were employed. DFT provides a quantum-mechanical foundation for understanding the electronic structure, energy levels, and various properties of molecules. The results of this study provide valuable insights into the electronic structure, energy levels, and molecular properties of these compounds, bridging the gap between theoretical insights and practical applications. This work paves the way for innovative developments in the field of molecular chemistry.

**Keywords:** Oxadiazole, Schiff base, DFT, MEP, HOMO-LUMO.

## 1. Introduction

In the realm of molecular chemistry, the design and analysis of novel compounds with tailored properties have been pivotal to various fields, including drug discovery, materials science, and organic electronics [1-2]. Schiff bases, well-known for their versatile and dynamic nature, serve as a fertile ground for the development of new chemical entities. When combined with oxadiazole moieties, these derivatives exhibit intriguing characteristics that make them attractive for a wide range of applications [3-4].

To thoroughly comprehend and predict the properties of these oxadiazole-containing Schiff base derivatives, it is crucial to employ advanced computational techniques [5-10]. Among these, Density Functional Theory (DFT) has emerged as a powerful tool in the realm of quantum chemistry [11-15]. DFT provides a quantum-mechanical foundation for understanding the electronic structure, energy levels, and various properties of molecules, making it an indispensable method for the computational exploration of new chemical compounds [16-18].

This study delves into the quantum computational exploration of oxadiazole-containing Schiff base derivatives using DFT as the primary analytical approach. By utilizing DFT calculations, we aim to unravel the intricate

details of the electronic structure and properties of these compounds, shedding light on their potential applications in diverse scientific domains. In doing so, we bridge the gap between theoretical insights and practical applications, paving the way for innovative developments in the field of molecular chemistry.

## 2. Materials and Method

We sourced chemicals and reagents from Sigma Aldrich (Merck Pvt. Ltd., India) and utilized Merck Pvt. Ltd. (Mumbai, India) for silica gel in column chromatography. The progression of the reaction was tracked using Thin-Layer Chromatography (TLC).

### *Synthesis of oxadiazoloeschiff base derivatives*

Oxadiazole Schiff bases were synthesized by reacting 2-Amino-5-(4-chlorophenyl)-1,3,4-oxadiazole with various aromatic aldehydes in an ethanol solution, followed by a 4-hour reflux. The evolution and completion of the reaction were monitored through Thin-Layer Chromatography (TLC). Upon reaching completion, we removed the solvent by evaporating it under reduced pressure using a rotary evaporator.

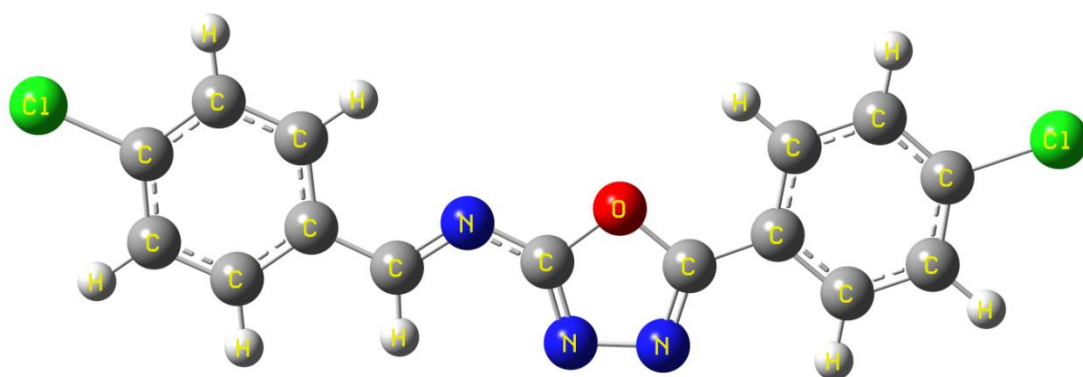
### *Quantum computational details*

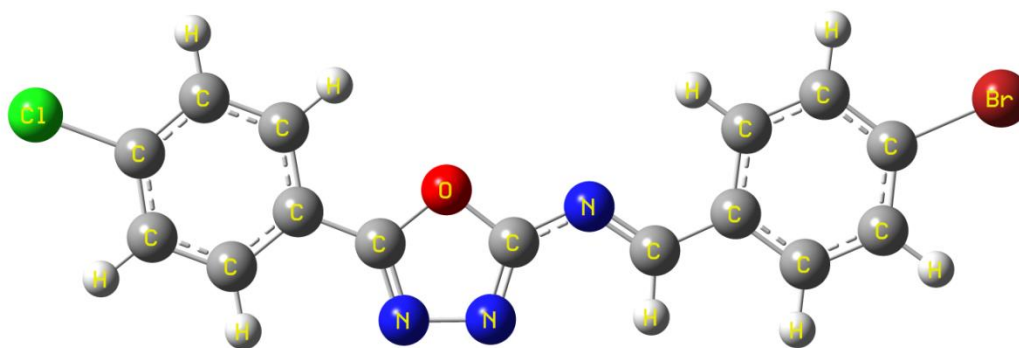
The structural geometry optimization and energy calculations for the oxadiazole Schiff base derivatives were conducted using Density Functional Theory (DFT) with the 6-311++G(d,p) basis set in the Gaussian 09 software [19]. These DFT calculations incorporated a three-parameter hybrid exchange function and the Lee-Yang-Parr (LYP) correlation function [20]. Subsequently, we computed Kohn-Sham Frontier Molecular Orbitals (FMOs) and Molecular Electrostatic Potential (MEP) based on the optimized geometry. To assess the Frontier Molecular Orbitals, their energy gap, and related global reactive parameters, we applied Koopman's approximation [21]. We generated visual representations of the Frontier Molecular Orbitals using GaussView 6.0 [22].

## 3. Result and discussion

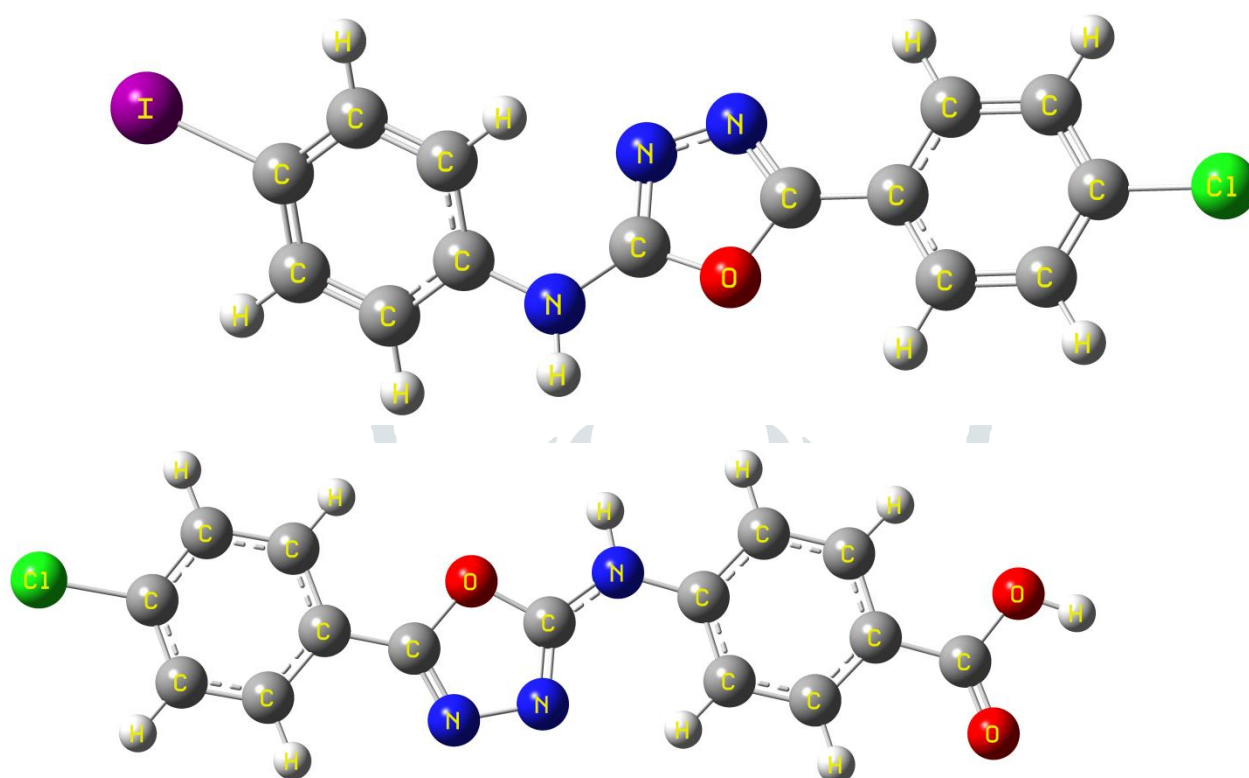
### **Geometry optimization by DFT calculation**

The structural geometry of newly synthesized oxadiazole Schiff base (OSB) derivatives was optimized using density functional theory with the 6-311++G(d,p) basis set in Gaussian 09. In Figure 1 and 2, you can observe the optimized 3D molecular structure of these OSB derivatives, including: 1-(4-chlorophenyl)-N-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)methanimine (OSB1), 1-(4-bromophenyl)-N-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)methanimine (OSB2), N-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-1-(4-iodophenyl)methanimine (OSB3) and 4-(((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)imino)methyl)benzoic acid (OSB4) illustrates the optimized three-dimensional molecular structures of these OSB derivatives.





**Figure 1:** DFT optimized 3D molecular structure of these OSB1 (top) OSB2 (bottom).



**Figure 2:** DFT optimized 3D molecular structure of these OSB3 (top) OSB4 (bottom).

**Frontier molecular orbitals (FMOs):** Figure 3 and 4 provides a visual representation of the 3D plots showcasing the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) for the recently synthesized OSB molecules. The HOMO signifies the highest energy level occupied by electrons within a molecule, playing a pivotal role in chemical reactions by determining the molecule's capacity to donate electrons. Typically, the HOMO is linked to electron-donating or nucleophilic behavior. Conversely, the LUMO corresponds to the lowest energy level that remains unoccupied by electrons within a molecule. It represents the orbital capable of accepting electrons during a chemical reaction and is associated with electron-accepting or electrophilic behavior.

**Table 1:** Global reactive parameters of OSB derivatives.

| Parameters                   | OSB1    | OSB2    | OSB3    | OSB4    |
|------------------------------|---------|---------|---------|---------|
| $E_{\text{HOMO}}(\text{eV})$ | -6.8208 | -6.7628 | -6.1588 | -6.4824 |
| $E_{\text{LUMO}}(\text{eV})$ | -3.0825 | -3.0403 | -2.0675 | -2.1824 |

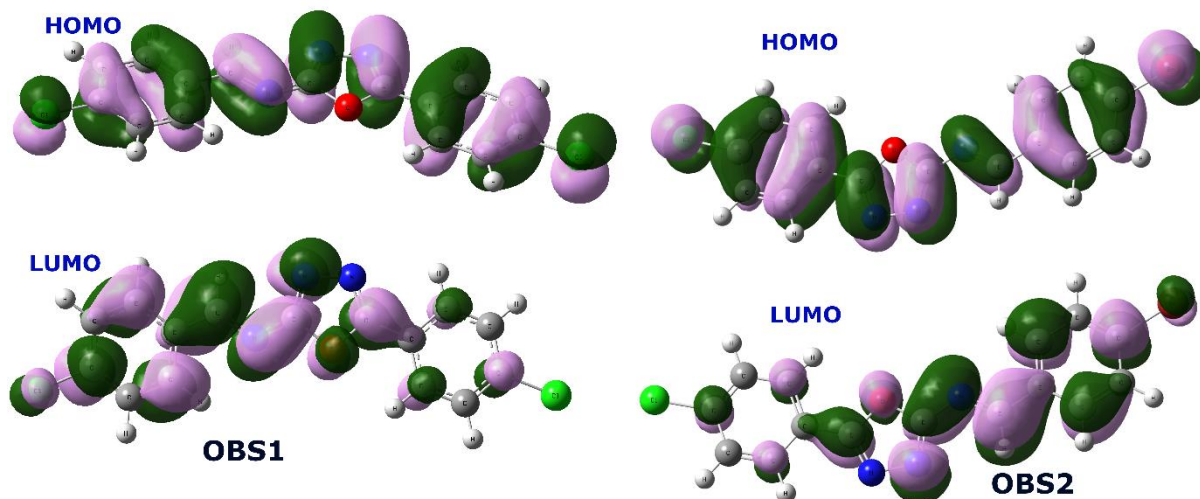
|  |         |         |         |         |
|--|---------|---------|---------|---------|
| Energy gap ( $\Delta E$ ) (eV)           | 3.7383  | 3.7225  | 4.0912  | 4.3002  |
| Ionisation potential (I)(eV)             | 6.8208  | 6.7628  | 6.1588  | 6.4826  |
| Electron affinity (EA)(eV)               | 3.0825  | 3.0403  | 2.0675  | 2.1824  |
| Electronegativity ( $\chi$ )(eV)         | 4.9517  | 4.9016  | 4.1131  | 4.3325  |
| Chemical potential( $\mu$ ) (eV)         | -4.9517 | -4.9016 | -4.1131 | -4.3325 |
| Global Hardness ( $\eta$ ) (eV)          | 1.8692  | 1.8613  | 2.0456  | 2.1501  |
| Softness( $\sigma$ ) (eV <sup>-1</sup> ) | 0.5350  | 0.5373  | 0.4889  | 0.4651  |
| Electrophilicity index ( $\omega$ ) (eV) | 6.5588  | 6.4541  | 4.1352  | 4.3650  |

The Frontier Molecular Orbital (FMO) analysis of OSB1 and OSB2 molecules reveals that the Highest Occupied Molecular Orbital (HOMO) is predominantly distributed throughout the entire molecules, with the exception of oxygen and hydrogen atoms. This distribution suggests its role as an electron donor. Conversely, the Lowest Unoccupied Molecular Orbital (LUMO) exhibits a widespread distribution, primarily centered on the N-(5-(4-chlorophenyl) group, with additional presence on the nitrogen atom in the oxadiazol ring. This distribution hints at its propensity for charge acceptance (see Figure 3).

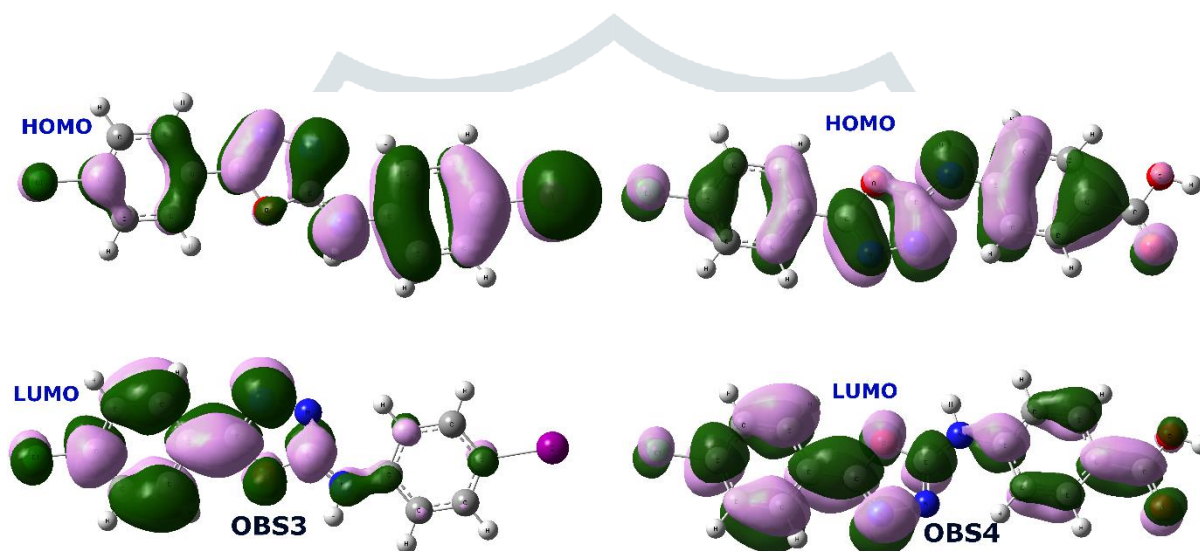
For OSB3, the HOMO is localized on the entire molecule, except for a carbon atom within the 1-(4-chlorophenyl) ring. Meanwhile, in OSB4, the HOMO is localized throughout the entire molecule, except for the benzoic acid group (see Figure 2). The LUMO of OSB3 is distributed across the entire molecule, excluding the 4-iodophenyl)methanimine moiety. On the other hand, the LUMO of OSB4 encompasses the entire molecule except for the nitrogen atom in the oxadiazol ring and the NH group (see Figure 4).

The energy gap observed in all four OSB molecules signifies increased molecular stability, as it indicates a substantial energy barrier separating the occupied and unoccupied states. A negative Chemical Potential value suggests a lower energy barrier for electron extraction, enhancing the likelihood of donating electrons and participating in redox reactions or electron transfer processes. Additional global reactive parameters can be found in Table 1.





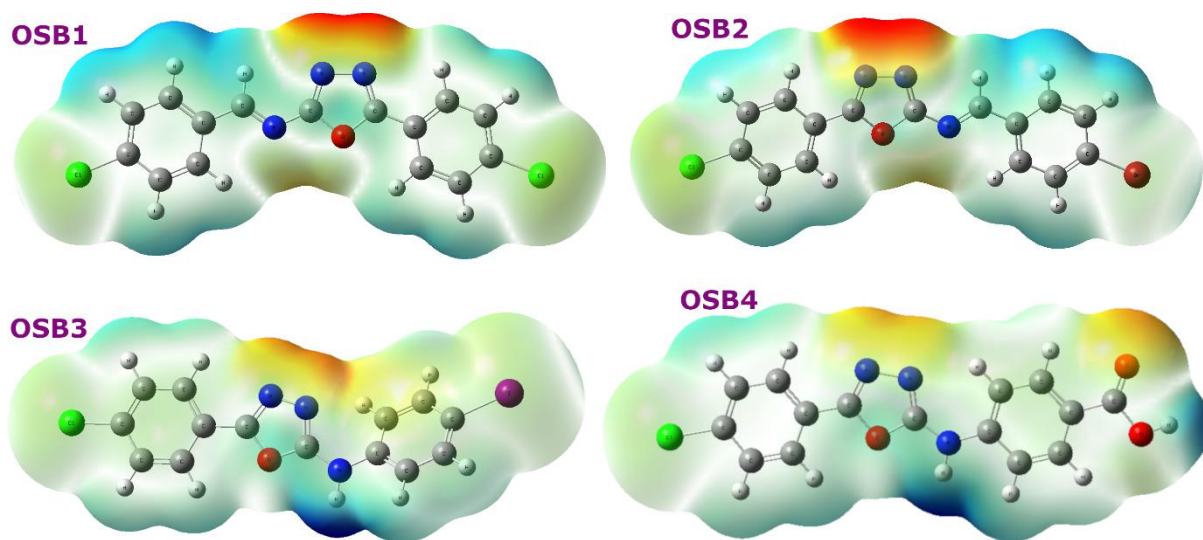
**Figure 3:** The frontier molecular orbitals of OSB1 and OSB2 molecules.



**Figure 4:** The frontier molecular orbitals of OSB3 and OSB4 molecules.

**Molecular electrostatic potential (MEP) analysis:** Molecular Electrostatic Potential (MEP) analysis offers valuable insights into both the physical and chemical characteristics of a synthesized compound, as well as its interactions. By employing software like Gauss View, MEP can be visualized, aiding in the identification of crucial regions within the molecule.

In this visualization, positively charged electrophilic active areas are depicted in red, particularly associated with nitrogen and oxygen groups present in the molecule. This signifies that these regions have a higher tendency to accept electrons or participate in electron-deficient interactions. In Figure 5, we can observe the oxadiazol ring nitrogen atoms and oxygen groups highlighted in red, demonstrating their positive electrostatic potential in the case of OSB1, OSB2, and OSB3 molecules. However, in OSB4, the oxadiazol ring nitrogen atoms and the oxygen atom (C=O) are shown in red (figure 5). Conversely, negatively charged nucleophilic active regions are represented in blue, primarily located on hydrogen atoms associated with the ring systems. These specific areas are characterized by their negative electrostatic potential, with the blue color indicating their propensity to donate electrons or engage in electron-rich interactions.



**Figure 5:** Molecular electrostatic potential graph of OSB1, OSB2, OSB3 and OSB4 molecules.

#### 4. Conclusion

In this study, we conducted a comprehensive exploration of oxadiazole-containing Schiff base derivatives using Density Functional Theory (DFT). The optimized 3D molecular structures were elucidated for four OSB molecules, revealing distinct electronic properties and structural characteristics. The analysis of Frontier Molecular Orbitals (FMOs) highlighted the roles of the Highest Occupied Molecular Orbital (HOMO) as an electron donor and the Lowest Unoccupied Molecular Orbital (LUMO) as an electron acceptor. The calculated global reactive parameters provided further insights into the reactivity and stability of these compounds. Moreover, Molecular Electrostatic Potential (MEP) analysis shed light on the electrostatic properties of the molecules, identifying electrophilic and nucleophilic regions. The presence of positive and negative electrostatic potentials in specific areas suggested their propensity for electron donation or acceptance. This study provides a solid foundation for understanding the electronic and structural properties of oxadiazole-containing Schiff base derivatives, offering valuable insights for potential applications in various scientific domains. It exemplifies the power of quantum computational techniques in bridging the gap between theoretical understanding and practical utilization in the field of molecular chemistry.

#### 5. Reference

1. Das, U., & Dhanaraju, M. D. (2018). A Review on Schiff Bases and Their Biological Applications. *Journal of Pharmaceutical Sciences and Research*, 10(1), 173-177.
2. Patil, S. S., & Patil, R. S. (2016). Design, synthesis and biological evaluation of some novel oxadiazole analogues as potential antimicrobial agents. *European Journal of Medicinal Chemistry*, 123, 378-389.
3. Samarth, N., Sharma, R., Goswami, P., Kumar, P., & Kumar, N. (2019). A Review on Oxadiazole Derivatives and their Biological Activities. *European Journal of Medicinal Chemistry*, 164, 56-72.
4. Jain, R., Chauhan, K., Sharma, A., & Yadav, N. (2020). Synthesis, characterization and biological evaluation of some novel oxadiazole based Schiff bases as potential antibacterial agents. *Journal of Molecular Structure*, 1210, 128064.
5. Biju, S. S., Ahamed, M. S., Aswathy, S. S., Kumar, S. V., Prabhakaran, R., & Ashraf, A. (2020). Oxadiazole Schiff bases: Recent advances in their design, synthesis and anticancer activities. *European*

- Journal of Medicinal Chemistry, 187, 111992.
- Rani, R., Narang, R., Kumar, V., Sharma, P., & Bansal, Y. (2019). Schiff bases and their derivatives as antiviral, antibacterial and antifungal agents: A review. *Journal of Molecular Structure*, 1183, 184-229.
  - Kumar, S., Ali, M. A., Kumar, V., Sharma, P., & Bansal, Y. (2019). Oxadiazole Schiff bases: A review of their synthesis, biological activities and pharmacological applications. *Journal of Molecular Structure*, 1184,
  - Kumar, A., Kumar, S., Srivastava, S. D., & Mishra, P. (2017). Synthesis and evaluation of some novel Schiff bases derived from 1, 3, 4-oxadiazole analogs as potent antimicrobial agents. *Arabian Journal of Chemistry*, 10, S1629-S1639.
  - Al-Masoudi, N.A.; Al-Amiery, A.A.; Kadhun, A.A.; Mohamad, A.B. Synthesis, characterization, and antibacterial activity of new Schiff bases derived from 4-aminosalicylic acid. *Bioinorg. Chem. Appl.* 2012, 1–11.
  - Yasmeen, F.; Khan, K.M.; Shabbir, M.; Latif, S.; Khan, A. Synthesis and evaluation of oxadiazole Schiff bases for their antibacterial activities against multidrug-resistant bacteria. *Med. Chem. Res.* 2014, 23, 3916–39.
  - Jayashankar, J., M. K. Hema, C. S. Karthik, D. Suma, S. R. Kumaraswamy, N. K. Lokanath, P. Mallu, M. Nethaji, and N. Lu. "Enchant OH... O interactions in hydrated 6-amino-2-methoxypyrimidin-4 (3H) one resembles as water flow in the channel: Crystallographic and theoretical investigations." *Journal of Molecular Structure* 1263 (2022) 133098.
  - Hema, M. K., Karthik, C. S., Warad, I., Lokanath, N. K., Zarrouk, A., Kumara, K., and Mallu, P. Regular square planer bis-(4, 4, 4-trifluoro-1-(thiophen-2-yl) butane-1, 3-dione)/copper (II) complex: Trans/cis-DFT isomerization, crystal structure, thermal, solvatochromism, hirshfeld surface and DNA-binding analysis. *Journal of Molecular Structure*, 1157, (2018) 69-77.
  - Lohith, T. N., Hema, M. K., Karthik, C. S., Sandeep, S., Mallesha, L., Mallu, P., and Lokanath, N. K. N-[2-(5-bromo-2-chloro-pyrimidin-4-yl) thio]-4-methoxy-phenyl]-4-chlorobenzenesulfonamide: The existence of H-bond and halogen bond interactions assisted supramolecular architecture—A quantum chemical investigation. *Journal of Molecular Structure*, 1267, (2022) 133476.
  - Hema, M. K., Warad, I., Karthik, C. S., Zarrouk, A., Kumara, K., Pampa, K. J., and Lokanath, N. K. XRD/DFT/HSA-interactions in Cu (II) Cl/phen/β-diketonato complex: Physicochemical, solvatochromism, thermal and DNA-binding analysis. *Journal of Molecular Structure*, 1210, (2020) 128000.
  - Jyothi, K. L., Hema, M. K., Kumara, K., Row, T. G., and Lokanath, N. K. Structural elucidation of 1: 4: 4 stoichiometric form of thymine–gallic acid cocrystal hydrate: Hirshfeld surface analysis, 3D energy framework, DFT calculations, and SARS CoV-2 docking studies. *Journal of Molecular Structure*, 1280, (2023) 135072.
  - Hema, M. K., Karthik, C. S., Pampa, K. J., Mallu, P., and Lokanath, N. K. Solvent induced mononuclear and dinuclear mixed ligand Cu (II) complex: structural diversity, supramolecular packing polymorphism and molecular docking studies. *New Journal of Chemistry*, 44(41), (2020) 18048-18068.
  - Raveesha, T. C., Hema, M. K., Pampa, K. J., Chandrashekara, P. G., Mantelingu, K., Demappa, T., and Lokanath, N. K. Analysis of supramolecular self-assembly of two chromene derivatives: Synthesis, crystal structure, Hirshfeld surface, quantum computational and molecular docking studies. *Journal of Molecular Structure*, 1225, (2021) 129104.

18. Hema, M. K., Karthik, C. S., Warad, I., Lokanath, N. K., Zarrouk, A., Kumara, K., and Mallu, P. Regular square planer bis-(4, 4, 4-trifluoro-1-(thiophen-2-yl) butane-1, 3-dione)/copper (II) complex: Trans/cis-DFT isomerization, crystal structure, thermal, solvatochromism, hirshfeld surface and DNA-binding analysis. *Journal of Molecular Structure*, 1157, (2018) 69-77.
19. M.J. Frisch, F.R. Clemente, Gaussian 09, revision a. 01, mjfrisch, gw trucks, hbschlegel, gescuseria, ma robb, jrcheeseman, g, Scalmani, V. Barone, B. Mennucci, GA Petersson, H. Nakatsuji, M. Caricato, X. Li, HP Hratchian, AF Izmaylov, J. Bloino, G. Zhe. (2009) 20–44.
20. M. B, Y.D. Bodke, N. O, L.T. N, N. G, S. Ma, Coumarin-Benzothiazole Based Azo Dyes: Synthesis, Characterization, Computational, Photophysical and Biological Studies, *Journal of Molecular Structure*. 1246 (2021) 131170.
21. R. Manne, T. Åberg, Koopmans' theorem for inner-shell ionization, *Chemical Physics Letters*. 7 (1970) 282–284.
22. R. Dennington, T. Keith, J. Millam, GaussView, version 6. Semichem Inc.: Shawnee Mission, KS. (2009).

