International Journal of Innovative Technology and Interdisciplinary Sciences
https://ijitis.org/index.php/IJITIS
ISSN: 2613-7305
Volume 6, Issue 4
DOI: doi.org/10.15157/IJITIS.2023.6.4.1273-1278
Received: 04.11.2023; Accepted: 25.12.2023

# Activity Correlation of Some Biologically Potent Schiff Bases

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**Abstract**

Imine-functionalized compounds can be modeled as prospective drugs for curing different disease types, particularly those that might be treated via photodynamic therapy. We assess the applicability of these Schiff base ligand systems as model drugs through first-hand in-vitro interaction by deciphering their mode of binding in different biomimicking environments like micelles, reverse micelles, proteins, lipids, DNA, etc. In the present article, we have designed a library of imine-functionalized molecules whose structure-activity correlation has been thoroughly investigated through computational studies employing Density Functional Theory (DFT) using the Gaussian 09 software. The fundamental pharmacological experimental design might be correlated with the theoretical interpretations. In conclusion, we may infer that the design of these biologically imperative compounds, along with their structure-activity correlation study, will serve as colossally important components for future pharmaceutical research.

**Keywords**: Imine-functionalized compounds*;* structure – activity correlation*;* Gaussian 09 software

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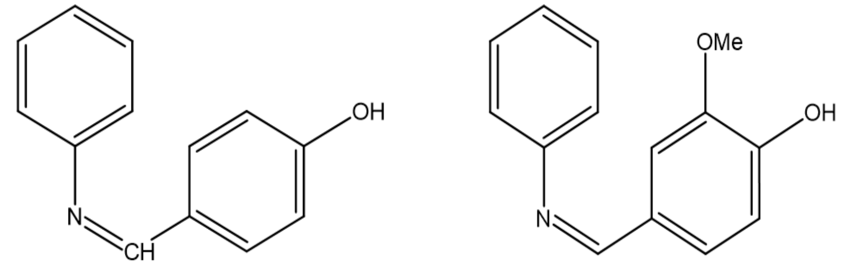
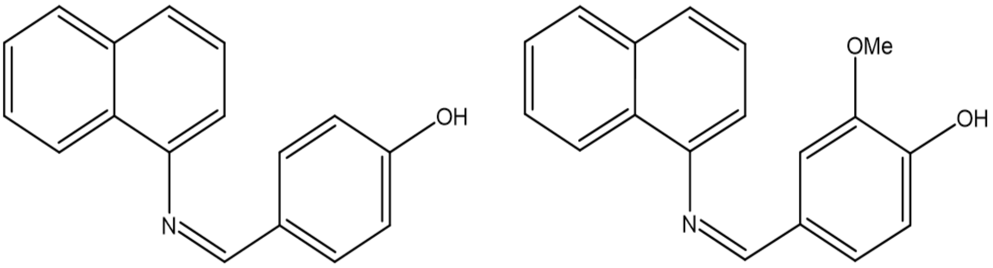
## INTRODUCTION

Schiff bases, named after the famous scientist Hugo Schiff, also referred to as imines or azomethines, are a class of organic compounds that contain a carbon-nitrogen double bond (C=N) where the nitrogen is part of an imine group [1]. Schiff bases play a conducive role in medicinal chemistry [2], such as in the treatment of various cancerous and tumorigenic diseases, particularly in the context of photodynamic therapy. They are excellent biological agents with antiviral, antifungal, and antibacterial activities [3]. They are also promising molecules in the application of pharmaceuticals, serving as active pharmaceutical ingredients (API) [4]. An active pharmaceutical ingredient (API) may be defined as a homogeneous substance or a mixture of substances used in the manufacturing of a pharmaceutical drug that are intended to provide pharmacological activity or other direct effects in the diagnosis, treatment, cure, or prevention of disease [5]. Their structure-activity correlation study facilitates their application window. Through first-hand in-vitro interaction, the applicability of such photosensitizers and Schof base ligands can be assessed experimentally. In this context, in the present article, we have planned and designed a library of novel Schiff bases, and their structure-activity correlation has been explored via computational studies employing Density Functional Theory (DFT). Four new Schiff bases, marked SB5, SB6, SB7, and SB8, are designed (Figure 1) [6]. Two of them (SB5 and SB6) bear phenyl rings, and the remaining two (SB7 and SB8) have naphthalic moieties. Structure-activity correlation provides the roadmap to delineate the experimental synthetic pathway to get fruitful and successful results [7]. This might seem analogous to delving into an AI-driven cuisine recipe before preparing it in the kitchen [8].

The structural analysis of these Schiff bases has been performed by deploying quantum chemical calculations via density functional theory (DFT), which reveals the reactivity order of these Schiff bases [9]. The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) usually come under the purview of frontier molecular orbitals, usually designated as FMOs. Referring to the FMO theory, which conglomerates the idea of the donor/acceptor characteristics of a molecule, where HOMO is the signing orbital for electron donation and LUMO for electron acceptance [10, 11], Based on the above-mentioned idea and theoretical calculations, the reactivity order of the Schiff bases can be finalized as SB6 > SB8 > SB7 > SB5. The energy difference between the HOMO and the LUMO provides the initial hypothesis about the reactivity of the molecule in both ground and excited states. This kind of hypothesis and claim can be found in several scholarly articles [12–14].



(i) (E)-4 (phenylimino) methyl) phenol (**SB5**) (ii) (Z)-2-methoxy-4 ((phenylimino) methyl) phenol (**SB6**)



(iii) (Z)-4-((napthalen-1-ylimino) methyl) phenol (**SB7**) (iv) (Z)-2-methoxy-4-((napthalen-1-ylimino) methyl) phenol (**SB8**)

**Figure 1.** Structural design of the Schiff bases (i) SB5 (ii) SB6 (iii) SB7 (iv) SB8

## COMPUTATIONAL DETAILS

The most coveted technique to decipher the structure-activity correlation of a molecule is theoretical simulation, deploying density functional theory (DFT). This technique gives us high throughput clarity, encompassing the structural characteristics of a many-electron system with its activity [15–17]. With the aid of the computational Gaussian 09 software, the stable ground-state electronic structures of the Schiff bases marked SB5, SB6, SB7, and SB8 are obtained through optimization of their geometrical parameters [17]. DFT was employed to optimize the systems using the B3LYP functional and 6-31++G** basis sets. The Frontier Molecular Orbitals (FMOs) were generated from the optimized/computed chk.point files of the Schiff bases and visualized through the Gauss View 5.0 software. Electronic indices, including the energies of the lowest unoccupied molecular orbital (ELUMO) and the highest occupied molecular orbital (EHOMO) of the designed systems, viz. SB5, SB6, SB7, and SB8, are also computed [18–19]. The distribution of electronic charge with respect to the elements in the Schiff bases is also computed and obtained through DFT analysis via Gaussian [17].

## RESULTS AND DISCUSSION

The ground-state optimized structures of the Schiff bases SB5, SB6, SB7, and SB8 are depicted below in figure 2. The structural analysis of these Schiff bases deploying quantum chemical calculations via density functional theory (DFT) reveals the reactivity order of these Schiff bases [20]. FMO theory states that the lower the difference in energy between its highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), the greater the probability for an electron to ease out and jump from the lower occupied orbital to the higher unoccupied orbital [20, 21]. The complete and illustrative FMO diagrams, along with their corresponding energy differences, are shown below in figure 3.

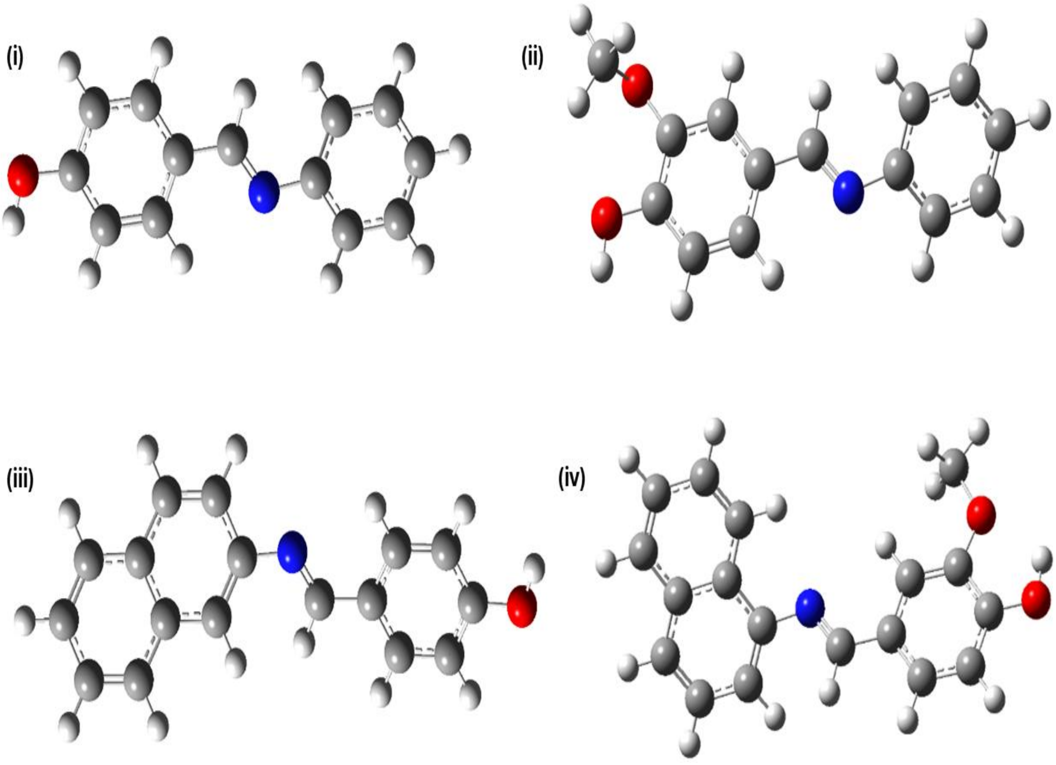


**Figure 2.** Ground state optimized structures of (i) (E)-4 (phenylimino) methyl) phenol **(SB5);** (ii) (Z)-2-methoxy-4 ((phenylimino) methyl) phenol **(SB6);** (iii) (Z)-4-((napthalen-1-ylimino) methyl) phenol **(SB7)** and (iv) (Z)-2-methoxy-4-((napthalen-1-ylimino) methyl) phenol **(SB8).** Color codes: Red – oxygen; Blue – nitrogen; Grey – carbon; white – hydrogen.

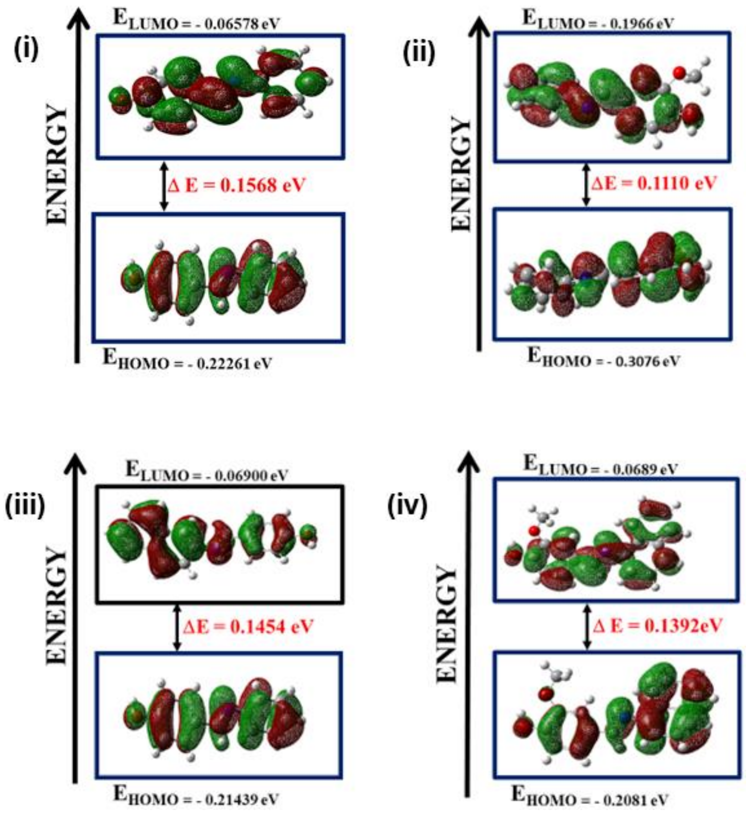


**Figure 3.** FMO diagrams of SB5 (i), SB6 (ii), SB7 (III) and SB8 (iv) depicting the $\Delta E_{LUMO\text{-}HOMO}$.

It could be observed from the table below that the three levels (HOMO/LUMO, HOMO-1, and HOMO-2) are non-degenerate and are separate energy states. In addition, it could be noted that the LUMO-HOMO possesses the lowest energy gap of all four cases. It is hereby anticipated that following the thermodynamic approach, the lowest energy gap for the respective Schiff bases in the ground state (ΔELUMO-HOMO = S0) (as depicted below in Table 1) points to a higher reactivity order as follows: SB6 > SB8 > SB7 > SB5 [20].

**Table 1**: Table showing the difference in energies between the FMOs.

| Name of the Compound | $\Delta E_{LUMO+2\ -\ HOMO-2}$ (eV) | $\Delta E_{LUMO+1\ -\ HOMO-1}$ (eV) | $\Delta E_{LUMO\ -\ HOMO}$ (eV) |
|---|---|---|---|
| **SB5** | 0.2429 | 0.2198 | 0.1568 |
| **SB6** | 0.1915 | 0.1645 | 0.1110 |
| **SB7** | 0.2180 | 0.1916 | 0.1454 |
| **SB8** | 0.2295 | 0.1947 | 0.1392 |

This reactivity order can be theoretically correlated with the structural moieties and substitution of the parent skeleton. A cursory glance at the structures of the four Schiff bases reveals SB5 and SB6 to have phenyl rings, whereas SB7 and SB8 have naphthalic moieties. Following the basic concept of aromaticity and delocalization being one of the strongest contenders to decide the stability of a molecule, naphthyl rings are stabler than phenyl rings

[20]. Hence, the high reactivity of SB6 is justified, with DELUMO-HOMO being the least for SB6, as obtained from theoretical calculations.

The above table additionally reveals SB5 to be the most stable among the four studied Schiff bases; hence, it is to be noted that delocalization alone cannot explain the reactivity order of the Schiff bases: SB6 > SB8 > SB7 > SB5. Pertinent to this order, the substitution effect of the OMe group on both the phenyl and naphthyl rings needed to be considered. The methoxy (OMe) group is an electron-donating group whose presence increases the nucleophilicity of the parent moiety [21]. The result of this methoxy substitution is a decrease in stability, i.e., increased reactivity with respect to their unsubstituted precursors. Hence, SB6 is more reactive than SB5, and SB8 is more reactive than SB7, thus justifying the above-mentioned reactivity order. A more detailed structural analysis also corroborates the obtained fact.

## CONCLUSION

The present article provides a comprehensive insight into the reactivity order of four newly designed Schiff bases in relation to their computed ground-state geometries. By deploying computational density functional theory calculations in the ground state, we can theoretically speculate that the methoxy substituted Schiff base with phenyl ring (SB6) out of the studied four is the most reactive and SB5 the least, as evident from their gross structural scrutiny. At first glance, it might seem unlikely since the more conjugated naphthalic moiety is expected to be stabler than SB5, which contains the benzene ring. But in-depth structural analysis reveals that the quantum chemical calculations provide correct results in terms of the reactivity order as obtained. The reactivity order is SB6 > SB8 > SB7 > SB5, which is explained judiciously following theoretical calculations using the FMO concept and previously accepted conceptual theories.

## ACKNOWLEDGMENT

All the authors acknowledge Amity University Kolkata for the infrastructural support.

## CONFLICT OF INTERESTS

There is no conflict of interests associated with this publication.

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