Synthesis, characterization, E/Z-isomerization, DFT, optical and 1BNA docking of new Schiff base derived from naphthalene-2-sulfonohydrazide

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Abstract

The novel N’-((1H-indol-2-yl)methylene)naphthalene-2-sulfonohydrazide Schiff base (S.B) ligand was produced via condensation of 1H-indole-2-carbaldehyde with naphthalene-2-sulfonohydrazide in a high yield. S.B. was then examined using several physicochemical techniques, and the steric structure was consequently confirmed. The highest B3LYP/DFT level theory was used to optimize the 3D E/Z-isomers structure. The stereoisomers computation demonstrated slightly stable E isomers outperformed by Z-one. The ligand displayed decent photosynthetic mid-bandgap semiconductors optical activate range material, and both the E and Z isomers bound to 1BNA DNA recorded many interactions.

Keywords: Sulfonohydrazide; Schiff base; optical; docking; spectral.

1. Introduction

The naphthalene-2-sulfonohydrazide moiety Schiff base is a N,N,O-poly-chelate organic ligands that have been extensively studied for their structural diversity and novel applications in several fields such as science, chemistry, and medicine (Amerreih et al., 2021). Such Schiff base ligands are formed by the reaction of naphthalene-2-sulfonohydrazide with various substituted ketones, or aldehydes resulting in the formation of >C=N- imine bond (Islam et al., 1987, Warad et al., 2020).

The naphthalene-2-sulfonohydrazide Schiff base possess unique optical, electronic and biological applications (Soroceauan and Bargan, 2022). Several studies have investigated the synthesis, structural characterization, and properties of naphthalene-2-sulfonohydrazide for their antimicrobial activity and anti-corrosion inhibitors. Studies have shown that naphthalene-2-sulfonohydrazide can intercalate into DNA, which means it can insert itself between the base pairs of the DNA double helix. This can cause changes in the DNA structure and affect its function (Özmen et al., 2008, Amerreih et al., 2020).
Hydrazine compounds have been investigated as an anticancer treatment for more than 30 years (Dehdhani et al., 2019; Mohammadian et al., 2020; Warad et al., 2021). It has been studied in combination with established treatments both as a chemotherapy agent and cancer-related anorexia (loss of appetite) and cachexia (Khazir et al., 2020; Benvidi et al., 2016; Gorjao et al., 2019).

As a continuation of our efforts to prepare many N-donating ligands and their complexes with the aim of understanding the structural behavior and measuring their biological, catalysis and anti-corrosion effectiveness (Rbaa et al., 2019, Zarrouk et aet al., 2013, Rouif et al., 2020, Abu Saleemh, et al., 2017, Warad, et al., 2013, Rbaa et al., 2020, Lindner et al., 2003). This paper studies N’-((1H-indol-2-yl)methylene)naphthalene-2-sulfonylhydrazide Schiff base ligand synthesized in good yield. The desired S.B ligand was fully characterized by 1H-NMR, FT-IR, UV-vis., CHN-EA, and ESI-MS, moreover, the S.B was subjected also to MEP and DFT-optimization. The optical activity and molecular docking against 1BNA DMA were also evaluated.

2. Materials and Experimental Methods

2.1 Precursors

Condensation of 0.1 mmol of naphthalene-2-sulfonylhydrazide with equivalent amount of 1H-indole-2-carbaldehyde in ethanol through 5 hours reflux resulted in the formation of N’-((1H-indol-2-yl)methylene)naphthalene-2-sulfonylhydrazide Schiff base ligand synthesized in good yield, the mixture was lifted until all the solvent was evaporated, the white product was wash well with water and hexane to ensure the purity. Yield: 83%; white solid; m.p.: 298.0-301.0 °C; IR (KBr): 3261, 3020, 1730, 1622, 1385, 1311, 1158, 871, 588 cm⁻¹. ESI m/z calcd. for C_{19}H_{15}N_{3}O_{2}S 349.09, found 350.1 [M+H]⁺. Calcd elemental analysis: C, 65.31; H, 4.33 and N, 12.03, found C, 65.53; H, 4.28 and N, 11.95. 1H NMR (400 MHz, CDCl₃-d⁶) δ 6.78 (1, 1H, s), 7.20-7.30 (2, 2H, m, benz.), 3.30-7.50 (3, 2H, m, benz.), 7.60-8.10 (4, 7H, m, naph.), 7.83 (5, 1H, s, aldy.), 9.65 (7, 1H, s), 11.37 (6, 1H, s).

2.2 Molecular docking

The small model molecules (E)-N’-((1H-indol-2-yl)methylene)naphthalene-2-sulfonylhydrazide (E-isomer) and (Z)-N’-((1H-indol-2-yl)-methylene)naphthalen-2-sulfonylhydrazide (Z-isomer) were docked against DNA (PDB ID: 1BNA) using AutoDock 4.2v software (Morris, et al., 2009).

3. Results and Discussion

3.1. Synthesis and identification of the desired S.B

New N’-((1H-indol-2-yl)methylene)naphthalene-2-sulfonylhydrazide Schiff base ligand was prepared via condensation of 1H-indole-2-carbaldehyde with naphthalene-2-sulfonylhydrazide in ethanol open reflux condition for 5 hours (Warad et al., 2020) as presented in Scheme 1. The 83%
yield was recorded and the final product was isolated as white solid powder. Moreover, the product found to be soluble in chloroform as chlorinated solvents and hot water, slightly soluble in alcohol, and completely insoluble in hexane. The produced S.B has been characterized via NMR, FT-IR, CHN-EA, and ESI-MS as seen in the experimental section.

![Scheme 1](image)

**Scheme 1:** The desired S.B synthesis.

3.2. DFT optimization and E-Z isomerization.

In order to establish the 3D-structure of the desired S.B ligand as a kind of support for physicochemical measurements and to establish the lengths of the bonds and the values of the angles, the DFT/B3LYB optimization was performed as seen in Table 1 and Figure 1. The steric calculations showed that the compound around the C=N group had the planner form, while the two aromatic rings were perpendicular to each other (Amereih et al., 2021) as seen in Figure 1.

<table>
<thead>
<tr>
<th>Number</th>
<th>Bond type</th>
<th>Å</th>
<th>Number</th>
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<td>1</td>
<td>C2-C1</td>
</tr>
<tr>
<td>2</td>
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<td>2</td>
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<td>28</td>
<td>C25-C26</td>
<td>1.3552</td>
<td>28</td>
<td>N19-C18</td>
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</table>
Figure 1. DFT/B3LYB optimization of the desired S.B.

The ability of Schiff bases to undergo E/Z-isomerization is one of their important characteristics. The forbidden rotation around the double bond that joins the two C=N parts, from E to Z is shown in Scheme 2. Different geometries and electrical characteristics between the Schiff bases' E and Z isomers can have a significant impact on those isomers' chemical and physical characteristics. Depending on the energy amount, the structure of E and Z-isomer was submitted in the gas phase to DFT/B3LYP/6-311G(d,p) optimization, in order to make out the favored isomer. The gaseous state DFT total energy formation of E-isomer -1445.26064924 a.u. lower than the Z-isomer 1,445.255163492 a.u. slightly less stable with the energy difference $\Delta H = 14.32$ kJ/mol. Moreover, the transition state energy $\Delta E_a = 62.52$ kJ/mol is also not large as seen in Figure 2, therefore, it is possible for E isomerize to Z- one even at RT-condition (Amereih et al., 2021).

Scheme 2. E/Z-isomerization in S.B.

Figure 2. Z/E-isomerization in the desired S.B.
3.3. Optical properties

As shown in Figure 3, the desired S.B. underwent an experimental transmittance and UV-Vis. absorption analysis in EtOH at a concentration of $1 \times 10^{-5}$ M, three primary absorption bands between 200 and 350 nm were recorded, but no packs were seen above this wavelength. As shown in Figure 3a, the bands at 240 nm were allocated to the $\pi-\pi^*$ transitions, whereas the bands at 280 and 328 nm were given to the $n-\pi^*$ transitions. The desired S.B.’s transmittance behavior showed three signals at 230, 255, and 300 nm and 100% transmission above 360 nm supported the absorption finding as shown in Figure 3b.

![Figure 3. (a) Absorptance, and (b) Transmittance of the S.B in ethanol.](image)

The experimental direct and indirect bandgap optical energy of the prepared S.B. ligand was evaluated via Tauc’s equation as below (Tauc et al., 1968).

\[
(\alpha h\nu)^\gamma = A(h\nu - E_g)
\]

Where

- $\alpha$ is the absorption coefficient
- $h$ is Planck's constant
- $\nu$ is the photon’s frequency
- $A$ is a proportionality constant
- $E_g$ is the band gap energy

$\gamma$ denotes the nature of the electronic transition

- $\gamma = 2$ direct allowed transitions
- $\gamma = 1/2$ indirect allowed transitions

It was clearly observed that the direct bandgap 5.78 eV (Figure 4a) is higher than the indirect 5.29 eV (Figure 4b) value. Both the bandgap values derived the desired S.B to be under the category of Mid-bandgap semiconductors, whereas the organic materials with an energy gap of 5-6 eV are rare and highly wanted mid-bandgap semiconductors, since it is relatively narrow compared to the wide bandgap materials. Therefore, such S.B Mid-bandgap semiconductors can be used in photovoltaics, power electronics, optoelectronics, chemical sensors, and infrared imaging field of applications (Jassem, et al., 2021).
Interestingly, the two isomers reflected similarity in docking behavior, but a difference in the type and strength of chemical bonding interactions. Both the E/Z-isomers, like the cisplatin binding mode, mimic a very good docking via crosslinking the two chains of the DNA helixes as seen in Figure 5. In this study, we were more interested in the stronger bonds, which is mainly the H-bond interactions, rather than the other relatively weak interactions like Van der Waal forces and π–π stacking bonds. Now, a number of interesting H-bonds interactions between 1BNA DNA and the E/Z-isomer and Van der Waal forces as well as non-covalent interactions involving stacking were detected (Figure 5a and 5b). The higher binding affinity of the E-isomer revealed close link with the molecule surface via mode of minor groove intercalation (Figure 5a) resulting two strong hydrogen bonds: DNA:A:DG10:H21…N with 1.89 Å and DNA:B:DG16:H22…N,O with 2.18 Å (Figure 5c, 5e). Moreover, the strength of these H-bonds is reflected in the binding energy with a -11.4 kcal/mol and total binding energy -12.29 kcal/mol (Table 2) compared to the Z-isomer with a binding energy of -8.25 kcal/mol and total binding energy -9.31 kcal/mol (Table 2), a similar deep groove intercalation with dramatically different H-bonds position and type were observed as in Figure 5b. Z-isomer bind with 1BNA via one H-bonds were detected: DNA:B:DG22:H3….O with 2.21 Å (Figure 5d and 5f).

It is noticeable that in both E/Z-isomer that the O-sulfite functional group played a significant role in the H-bonding with nearby nucleates, whereas the H-N payroll functional group was only active in the E isomer since it was compatible with the appropriate stereochemical shape selectivity method (Singh, et al., 2022, Singh, et al., 2023, Roozbahania et al., 2019, Salehi et al., 2019). As a DNA-binder the E isomer found to be energetically and structurally is more preferred than the Z isomer, such seen may be attributed to the fact that the stereoscopic form of the E isomer is more suitable for such bonding in what is known as shape selectivity. As a conclusion, both E and Z-isomer found to be with high ability to bind to 1BNA DNA and potentially stabilize it can be exploited in various applications, such as gene therapy and cancer treatment.
Figure 5. Docking of the E/Z-isomers with 1BNA DNA.

Table 2. 1BNA DNA Docking data with both E and Z isomers.

<table>
<thead>
<tr>
<th>Conf.</th>
<th>Binding energy kcal/mole</th>
<th>Ligand Efficiency</th>
<th>Inhibition Constant µM T= 298 K</th>
<th>Total binding energy kcal/mol</th>
<th>H-bonds of S.B. with bond length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>-11.4</td>
<td>-0.46</td>
<td>4.39</td>
<td>-12.29</td>
<td>DNA:A:DG10:H21….N (1.89) DNA:B:DG16:22….O (2.18)</td>
</tr>
<tr>
<td>Z</td>
<td>-8.25</td>
<td>-0.33</td>
<td>7.42</td>
<td>-9.31</td>
<td>DNA:B:DG22:H3……O (2.21)</td>
</tr>
</tbody>
</table>
Conclusion

All physicochemical measurements supported the production of the N’-((1H-indol-2-yl)methylene)naphthalene-2-sulfono-hydrazide Schiff base (S.B.) ligand with no side products, which resulted in the preparation of the desired E-isomer naphthalene-2-sulfonohydrazide as kinetic favored compound with 83% yield. The B3LYP/DFT optimization reflected the E-isomer as a slightly favored structure over the Z-one. The UV-Vis absorbance and transmittance yielded the S.B. as a Mid-bandgap semiconductors material with 5.78 and 5.29 eV direct and indirect bandgaps, respectively. Both E and Z-isomers demonstrated a high binding affinity towards 1BAN DNA similar to cisplatin binding mode, but E-isomer is with higher binding since two H-bonds of type DNA:A:DG10:H21….N(1.89) and DNA:B:DG16:H22….O(2.18) compared to one bond DNA:B:DG22:H3…..O(2.21) in Z-isomer were recorded, nevertheless, the desired S.B. isomers with a potential use in the future to aid in the battle against cancer.

Disclosure statement: Conflict of Interest: The authors declare that there are no conflicts of interest. Compliance with Ethical Standards: This article does not contain any studies involving human or animal subjects.

References


(2023); [https://revues.imist.ma/index.php/morjchem/index](https://revues.imist.ma/index.php/morjchem/index)