

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

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Abstract

The novel N'-((1H-indol-2-yl)methylene)naphthalene-2-sulfonylhydrazide Schiff base (S.B) ligand was produced via condensation of 1H-indole-2-carbaldehyde with naphthalene-2-sulfonylhydrazide in a high yield. S.B. was then examined using several physicochemical techniques, and the steric structure was consequently confirmed. The highest B3LYB/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: Sulfonylhydrazide; Schiff base; optical; docking; spectral.

1. Introduction

The naphthalene-2-sulfonylhydrazide 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 (Amereih *et al.*, 2021). Such Schiff base ligands are formed by the reaction of naphthalene-2-sulfonylhydrazide 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-sulfonylhydrazide Schiff base possess unique optical, electronic and biological applications (Soroceanu and Bargan, 2022). Several studies have investigated the synthesis, structural characterization, and properties of naphthalene-2-sulfonylhydrazide for their antimicrobial activity and anti-corrosion inhibitors. Studies have shown that naphthalene-2-sulfonylhydrazide 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).

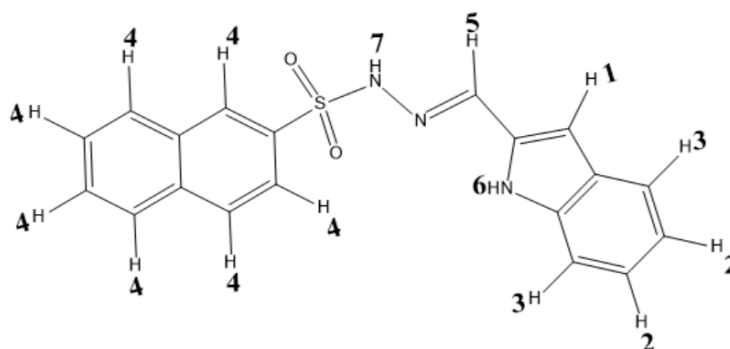
Hydrazine compounds have been investigated as an anticancer treatment for more than 30 years (Dehdhani *et al.*, 2019; Mohammadian *et al.*, 2020; Warad *et al.*, 2021). It has been studied in combination with established treatments both as a chemotherapy agent and cancer-related anorexia (loss of appetite) 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 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-sulfonohydrazide 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-sulfonohydrazide 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 C₁₉H₁₅N₃O₂S 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-d¹) 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

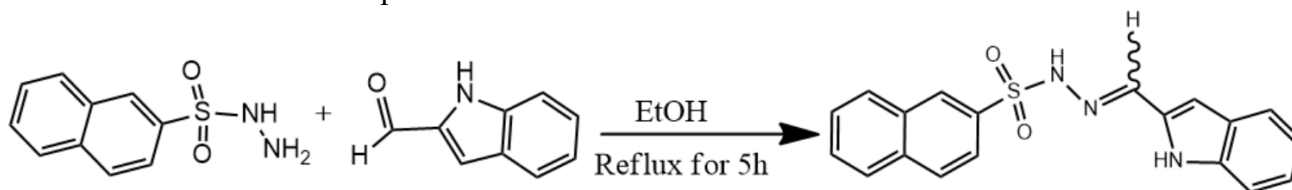
The small model molecules (E)-N'-((1H-indol-2-yl)methylene)naphthalene-2-sulfonohydrazide (E-isomer) and (Z)-N'-((1H-indol-2-yl)-methylene)naphthalen-2-sulfonohydrazide (Z-isomer) were docked against DNA (PDB ID: 1BNA) using AutoDock 4.2v software (Morris, *et al.*, 2009).

3. Results and Discussion

3.1. Synthesis and identification of the desired S.B

New N'-((1H-indol-2-yl)methylene)naphthalene-2-sulfonohydrazide 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: 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 1. Angles and bond lengths values of the desired S.B.

Number	Bond type	Å	No.	Angle	(°)
1	C1 C2	1.3064	1	C2 C1 C6	120.89
2	C6 C1	1.3652	2	C1 C2 C3	117.95
3	C2 C3	1.3278	3	C2 C3 C4	122.92
4	C3 C4	1.3373	4	C3 C4 C5	120.27
5	C5 C4	1.3434	5	C3 C4 C7	123.15
6	C4 C7	1.3618	6	C5 C4 C7	116.5
7	C5 C6	1.3634	7	C4 C5 C6	116.65
8	C10 C5	1.3631	8	C4 C5 C10	122.46
9	C8 C7	1.3399	9	C6 C5 C10	120.89
10	C8 C9	1.4067	10	C1 C6 C5	120.84
11	C9 C10	1.3817	11	C4 C7 C8	120.43
12	C9 S11	1.7967	12	C7 C8 C9	125.37
13	S11 O12	1.4582	13	C8 C9 C10	110.18
14	S11 O13	1.4309	14	C8 C9 S11	126.58
15	S11 N14	1.6895	15	C10 C9 S11	123.22
16	N14 N15	1.3389	16	C5 C10 C9	123.34
17	N15 C16	1.2648	17	C9 S11 O12	108.84
18	C16 C18	1.3824	18	C9 S11 O13	109.74
19	N19 C18	1.2461	19	C9 S11 N14	107.49
20	C18 C22	1.3654	20	O12 S11 O13	115.75
21	C20 N19	1.2514	21	O12 S11 N14	111.33
22	C20 C21	1.3106	22	O13 S11 N14	103.33
23	C23 C20	1.3388	23	S11 N14 N15	111.98
24	C22 C21	1.3657	24	N14 N15 C16	127.03
25	C21 C26	1.374	25	N15 C16 C18	131.79
26	C24 C23	1.3175	26	C16 C18 N19	122.51
27	C25 C24	1.3405	27	C16 C18 C22	129.32
28	C25 C26	1.3552	28	N19 C18 C22	108.11

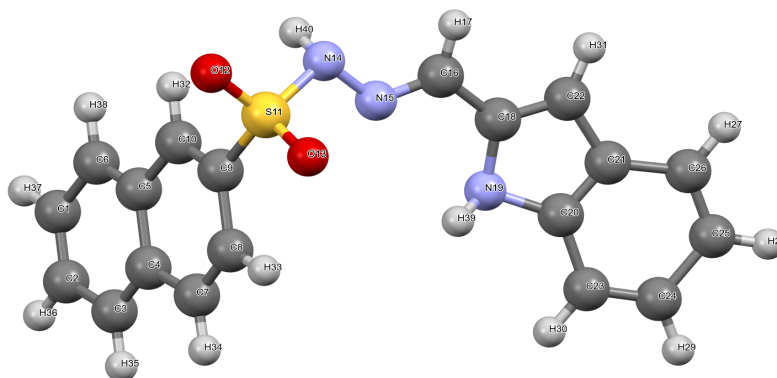
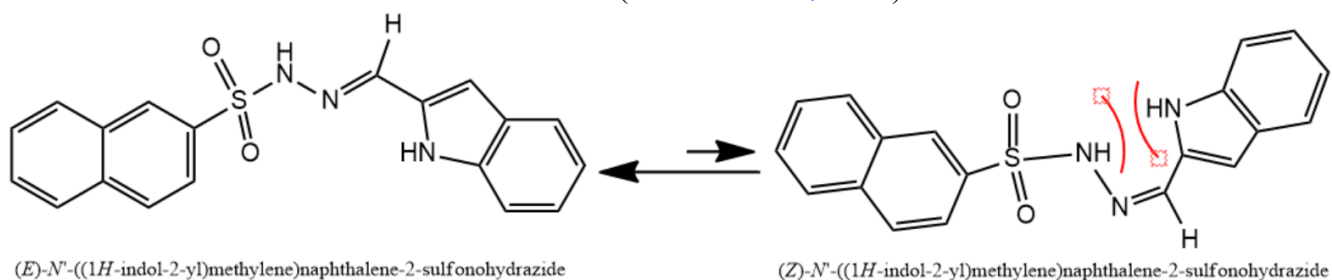


Figure 1. DFT/B3LYB optimization of the desired S.B.

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.

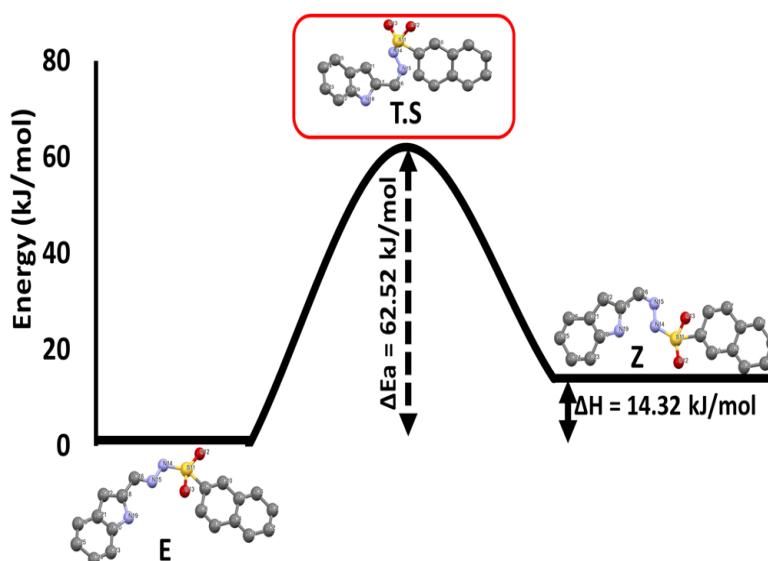


Figure 2. Z/E-isomerization in the desired S.B.

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 $1 \times 10^{-5} \text{M}$, three primary absorption bands between 200 and 350 nm were recorded, but no peaks were seen above this wavelength. As shown in **Figure 3a**, the bands at 240 nm were allocated to the $\pi\text{-}\pi^*$ transitions, whereas the bands at 280 and 328 nm were given to the $n\text{-}\pi^*$ 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**.

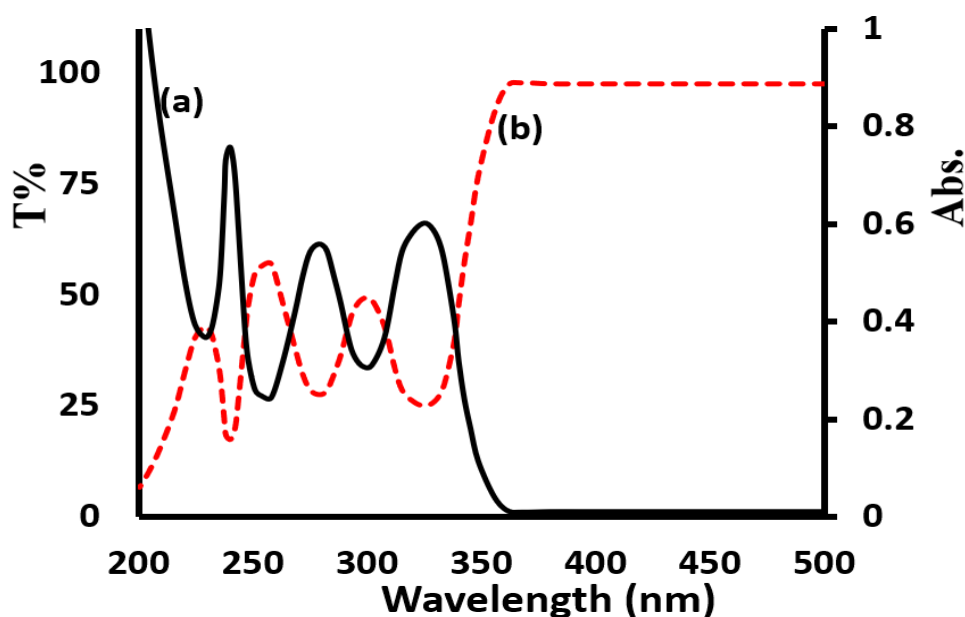


Figure 3. (a) Absorbance, and (b) Transmittance of the S.B in ethanol.

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

α is the absorption coefficient

h is Planck's constant

ν is the photon's frequency

A is a proportionality constant

E_g is the band gap energy

γ 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).

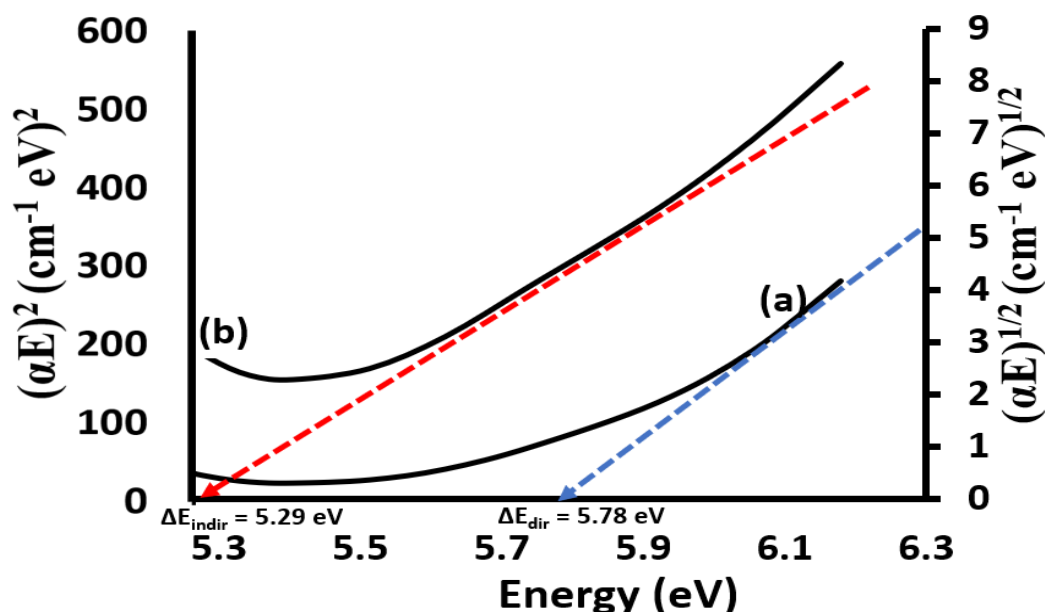


Figure 4. (a) Direct and (b) indirect bandgap.

3.5. E/Z-isomers docking with 1BNA DNA

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 helices 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.

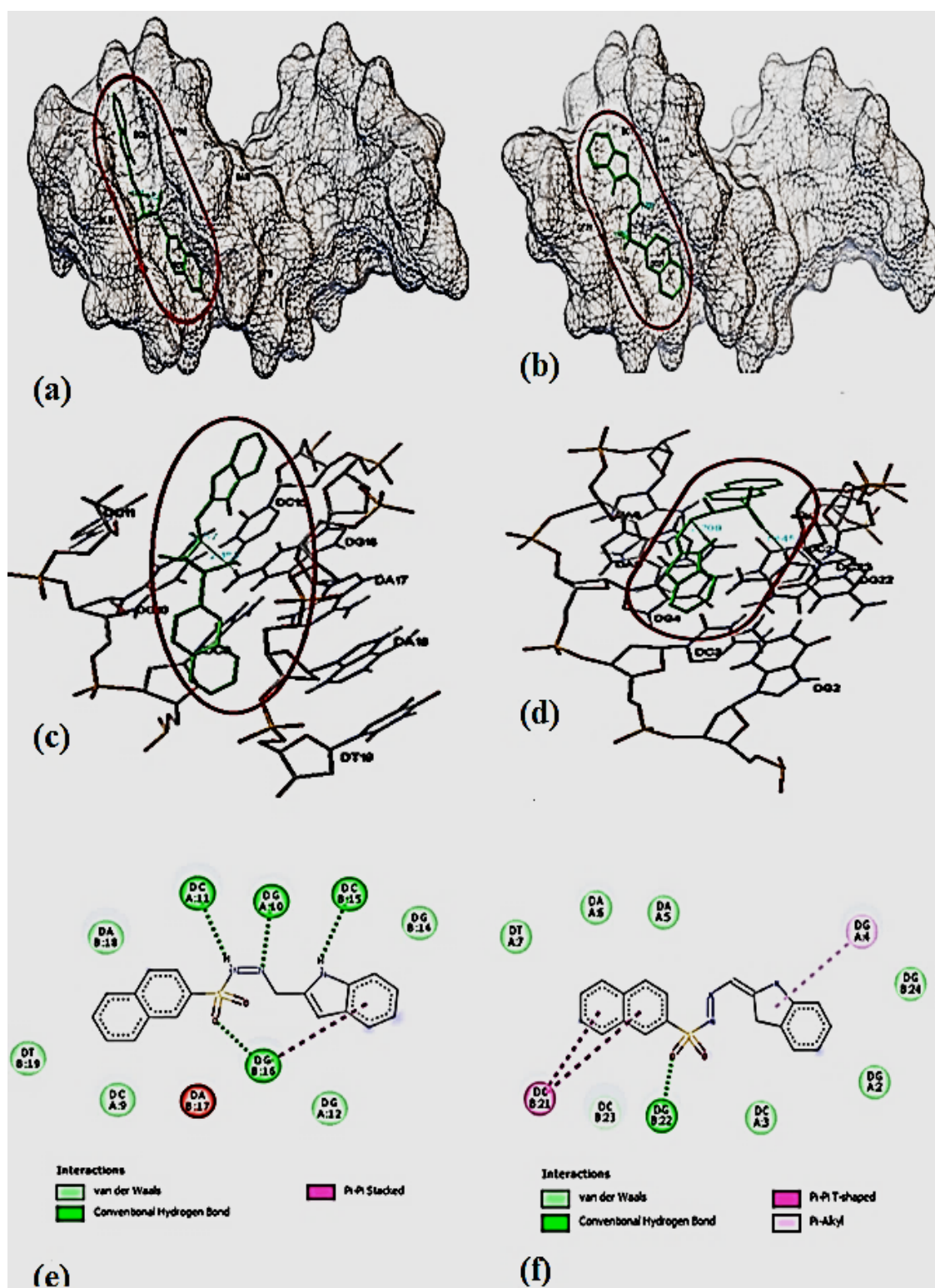


Figure 5. Docking of the E/Z-isomers with 1BNA DNA.

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

Conf.	Binding energy kcal/mole	Ligand Efficiency	Inhibition Constant μM T= 298 K	Total binding energy kcal/mol	H-bonds of S.B. with bond length (Å)
E	-11.4	-0.46	4.39	-12.29	DNA:A:DG10:H21.....N (1.89) DNA:B:DG16:H22.....O (2.18)
Z	-8.25	-0.33	7.42	-9.31	DNA:B:DG22:H3.....O (2.21)

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.

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