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Synthesis, optimization, DFT/TD-DFT and COX/LOX docking of new Schiff base N'-((9-ethyl-9H-carbazol-1-yl)methylene)naphthalene-2-sulfonohydrazide

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Abstract Condensing naphthalene-2-sulfonylhydrazide with 9-ethyl-9H-carbazole-1-carbaldehyde starting materials resulting the formation of novel N'-((9-ethyl-9H-carbazol-1-yl)methylene)naphthalene-2-sulfonohydrazide Schiff base (S.B.) ligand with high yield and without having any unwanted side products. A wide range of physicochemical measurements, such as CHN-EA, UV-Vis., NMR, FT-IR, and ESI-MS were used to extensively investigate the structural properties of the desired S.B. ligand, the highest level of B3LYB/DFT also served to optimize the 3D structure of the S.B. ligand. Moreover, the experimental optical properties via the UV-Vis absorption measurements were compared to the theoretical DFT/TD-DFT study under identical conditions and using The DCM as solvent. Furthermore, to evaluate the prepared S.B. ligand as a future work drug for treating different types of infections, the LOX and COX anti-inflammatory computation capability was evaluated via the in silico molecular docking using the suitable enzymes.

Keywords: Schiff base; NMR; LOX/COX; docking; spectral; DFT/TD-DFT.

1. Introduction

Due to their numerous uses in a variety of industries, including chemistry, business, healthcare, and pharmacy, interest in these interesting molecules has significantly increased (Boulechfar *et al.*, 2023; Warad *et al.*, 2020). The azomethine (>C=N-) group, as the substituents can include heterocyclic or aryl/alkyl is a good example of what distinguishes Schiff bases (SBs) from other types of bases (Catalano, 2023). Notably, although the nitrogen atom in the identical link has a highly active free pair of electrons capable of finding stable solid complexes with metal ions, moreover, the sp^2-carbon center

in the imine unsaturated bond is sensitive to nucleophilic addition reactions. Schiff bases have proven to be versatile in a variety of applications, including catalytic activity, corrosion inhibition properties, photosensitizing abilities, fluorescence chemo-sensor devices designed for the sensing of M^{2+} metal ions, and photosensitizing behavior (Gupta *et al.*, 2008; Afshari *et al.*, 2023; Upendranath *et al.*, 2022). Schiff bases (SBs), which have a wide spectrum of biological functions, have received a lot of attention in the literature. Key enzymes like butyrylcholinesterase (BChE), acetylcholinesterase (AChE), and carbonic anhydrase have been shown to be inhibited by these compounds (Çakmak *et al.*, 2022; El-Azab *et al.*, 2022; Camadan *et al.*, 2022; Barakat *et al.*, 2013). Aside from that, they have shown positive antimalarial, antitumoral, neuroprotective, antimicrobial, antidepressant, antioxidant, antidiabetic, and anti-inflammatory properties (Tople *et al.*, 2023; Yuldasheva *et al.*, 2022; Hamid *et al.*, 2022).

Additionally, it has been discovered that SBs coatings increase material bioactivity, increasing the scope of their possible medical uses (Mondal *et al.*, 2023). The observed biological effects are thought to be caused by the azomethine nitrogen found in SBs, which acts as a site for interacting with different biomolecules, including proteins and amino acids. The development of compounds with noticeably higher activity is typically caused by the formation of relatively stable complexes between SBs and transition metals, the chemistry, materials science, and pharmacology have all identified uses for this phenomenon for various medicinal applications (Tighadouini *et al.*, 2022; Ashraf *et al.*, 2023; Abu-Yamin et al., 2022; Alezzy *et al.*, 2022). Despite the enormous number of produced SBs ligands, there is still a demand for more of these materials due to the diversity of their prospective applications in scientific domain wide range.

In this article, the composition of a new naphthalene-2-sulfonohydrazide S.B was verified using numerous known physical methods, including DFT/TD-DFT and DFT-optimization studies to determine the existence of the favored isomer. Furthermore, the LOX/COX anti-inflammatory aspects of the desired S.B. were investigated theoretically using the in-silico COX/LOX docking technique.

2. Materials and Experimental Methods

2.1 synthesis of the S.B.

N'-((9-ethyl-9H-carbazol-1-yl)methylene)naphthalene-2-sulfono-hydrazide was successfully formed when 0.1 mmol of 9-ethyl-9H-carbazole-1-carbaldehyde was treated to condensation with an equal quantity of naphthalene-2-sulfonylhydrazide in methanol under reflux conditions for a duration of 5 hours. The reaction mixture was then let to evaporate until all of the solvent had gone away the yield was an admirable 87%. The yellow powder was thoroughly washed with *n*-hexane and water to assure the purity of the resultant chemical product.

Yellow solid; m.p.: 288.0- 290.0 °C; FT-IR (KBr): 3304, 3033, 1745, 1631, 1390, 1309, 162, 880, 579 cm^{-1}. Calcd. m/z for $C_{25}H_{21}N_3O_2S$, 427.2, found 428.4, $[M+H]^+$. Calcd. CHN-EA analysis: C, 70.24; H, 4.95 and N, 9.83, found C, 70.13; H, 4.88 and N, 9.75. ^{1}H-NMR ($CDCl_3$-d^1, 400 MHz), δ 1.58 (3H, t,), 4.55 (2H, q), 7.13-7.95 (14H, m), 8.33 (1H, s, aldy.), and 9.75 (1HN=C, s).

2.1. Materials, computations and docking *details*

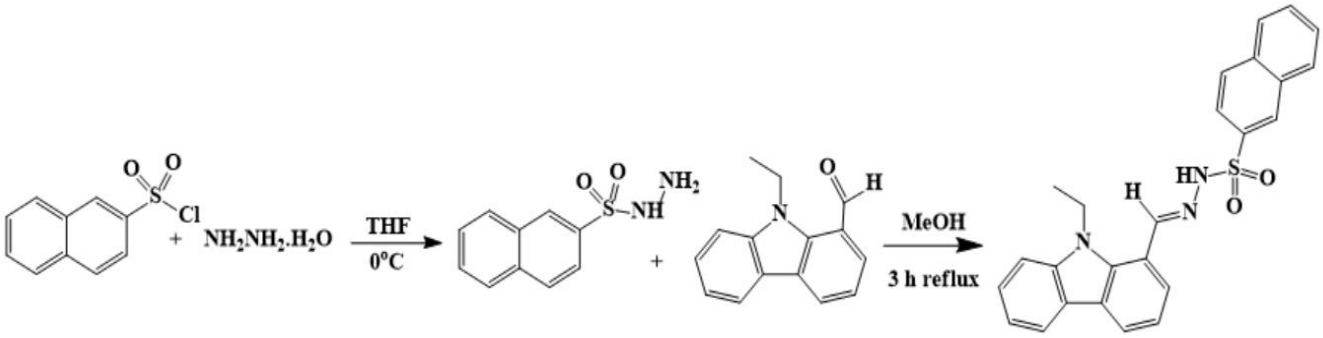
The chemicals were purchased from Sigma-Aldrich and used without further purification. The IR was recorded in solid state in the range of 400-4000 cm^{-1} using a Shimadzu FTIR-8010 M spectrometer. The ^{1}H-NMR were acquired in $CDCl_3$ using a Jeol GSX WB spectrometer at 400 MHz. The Gaussian09W program was utilized for the gaseous state DFT calculations at DFT/B3LYP/6-311G (d,p) (Frisch *et al.*, 2009; Al Hamzi *et al.*, 2013; Barhoumi *et al.*, 2020). Using the AutoDock 4.2v

program (Morris *et al.*, 2009; Zaki *et al.*, 2017; El Aissouq *et al.*, 2022), the COX/LOX against the ligand was docked (AlAli *et al.*, 2023a; Rudrapal *et al.*, 2023).

3. Results and Discussion

3.1. S.B ligand preparation and identification

The naphthalene-2-sulfonylhydrazide starting material was obtained by combining of naphthalene-2-sulfonyl chloride with an excess amount of $NH_2NH_2.H_2O$ at 0 ^oC in THF (Warad *et al.*, 2020; Daraghmeh *et al.*, 2019). By condensation of 9-ethyl-9H-carbazole-1-carbaldehyde with freshly prepared naphthalene-2-sulfonylhydrazide in an reflux medium using methanol solvent, a novel solid yellow Schiff base N'-((9-ethyl-9H-carbazol-1-yl)methylene)naphthalene-2-sulfono-hydrazide ligand was prepared with high yield 87% (Amereih *et al.*, 2020; Amereih *et al.*, 2021; Warad *et al.*, 2013; Abu-Rayyan *et al.*, 2023; Saleemh *et al.*, 2017) as see (**Scheme 1**). The product's solubility profile was also examined, and the results showed that it easily to be dissolved in hot water, and other chlorinated solvents like chloroform, although it was hardly soluble in heave ROH, and totally insoluble in hexane.



Scheme 1: The desired S.B synthesis.

As described in the experimental section, the synthesized Schiff base was thoroughly characterized via several available analytical tools, such as NMR, UV-Vis., FT-IR spectroscopy, CHN elemental analysis, and ESI-MS.

3.2. DFT-optimization

To optimize the desired S.B., the DFT mode optimization was computationally perfumed via B3LYP/6-311 basis set level. The theoretical calculations confirmed the condensation reaction occurred and the imine >C=N- unit formation as observed in (**Scheme 1**). **Figure 1** shows the S.B. with E-isomer structure as the stable optimized isomer over the Z-isomer one (Amereih *et al.*, 2019, Takfaoui *et al.*, 2014; Lindner *et al.*, 2003). All the dihedral angles, angles, and bond lengths of the named S.B are illustrated in **Table 1**.

3.3. UV-Vis and TD-DFT investigations

The exp. UV-vis and theoretical TD-DFT simulations were performed using the same solvent (CH_2Cl_2) to comprehend the electronic and the optical properties of the desired S.B. Since the desired S.B existence with 5 rings (4 aromatic and 1 heterocyclic) in his backbone, the UV-Vis outcome revealed the presence of 3 absorption band at λ_{max} = 231, 266 and 307 nm, that can be resonated to π to π^* e-transfer (**Figure 2**).

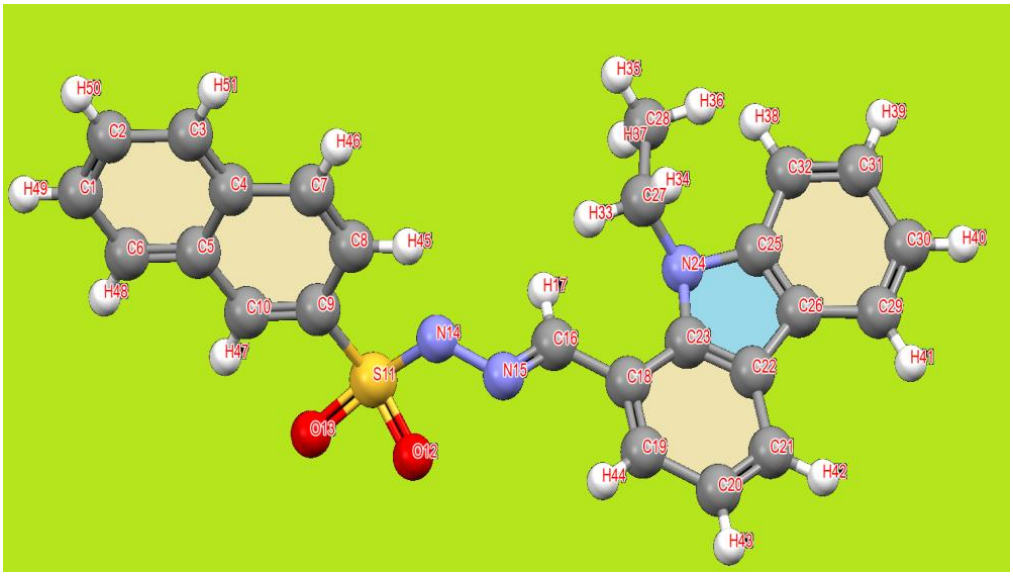


Figure 1. DFT/B3LYB E-isomer optimization of the desired S.B.

Table 1. Angles, bond lengths and dihedral angles of the desired S.B.

No.	Bond		A	No.	Angle			(º)	No.	Torsion				(º)
1	C1	C2	1.3407	1	C2	C1	C6	119.84	1	C6	C1	C2	C3	0.2
2	C6	C1	1.3418	2	C1	C2	C3	119.79	2	C5	C6	C1	C2	-0.06
3	C2	C3	1.3418	3	C2	C3	C4	120.6	3	C1	C2	C3	C4	-0.06
4	C3	C4	1.3458	4	C3	C4	C5	119.66	4	C2	C3	C4	C5	-0.22
5	C5	C4	1.3478	5	C3	C4	C7	121.16	5	C6	C5	C4	C3	0.36
6	C4	C7	1.3448	6	C5	C4	C7	119.18	6	C6	C5	C4	C7	-180
7	C5	C6	1.346	7	C4	C5	C6	119.42	7	C10	C5	C4	C3	-180
8	C10	C5	1.3457	8	C4	C5	C10	119.54	8	C10	C5	C4	C7	0.45
9	C8	C7	1.3419	9	C6	C5	C10	121.04	9	C3	C4	C7	C8	180
10	C8	C9	1.343	10	C1	C6	C5	120.69	10	C5	C4	C7	C8	-0.19
11	C9	C10	1.3446	11	C4	C7	C8	120.78	11	C4	C5	C6	C1	-0.22
12	C9	S11	1.7938	12	C7	C8	C9	120.5	12	C10	C5	C6	C1	180
13	S11	O12	1.4542	13	C8	C9	C10	118.56	13	C9	C10	C5	C6	180
14	S11	O13	1.4526	14	C8	C9	S11	122.24	14	C9	C8	C7	C4	-0.4
15	S11	N14	1.6974	15	C10	C9	S11	119.2	15	C7	C8	C9	S11	-179
16	N14	N15	1.3521	16	C5	C10	C9	121.44	16	C8	C9	C10	C5	-0.43
17	N15	C16	1.2675	17	C9	S11	O12	107.66	17	S11	C9	C10	C5	179
18	C16	C18	1.351	18	C9	S11	O13	108.3	18	C8	C9	S11	O12	-124
19	C19	C18	1.3523	19	C9	S11	N14	113.15	19	C8	C9	S11	O13	112
20	C23	C18	1.3582	20	O12	S11	O13	114.45	20	C8	C9	S11	N14	-6.79
21	C19	C20	1.3417	21	O12	S11	N14	106	21	C10	C9	S11	O12	57
22	C20	C21	1.3365	22	O13	S11	N14	107.41	22	C10	C9	S11	O13	-67.2
23	C21	C22	1.3369	23	S11	N14	N15	113.74	23	C10	C9	S11	N14	174
24	C22	C23	1.3517	24	N15	C16	C18	135.75	24	C9	S11	N14	N15	61.7
25	C22	C26	1.3389	25	H17	C16	C18	118.72	25	O12	S11	N14	N15	179
26	C23	N24	1.2816	26	C16	C18	C19	119.63	26	O13	S11	N14	N15	-57.8
27	N24	C25	1.2741	27	C16	C18	C23	124.6	27	S11	N14	N15	C16	-174
28	N24	C27	1.4818	28	C19	C18	C23	115.77	28	N14	N15	C16	C18	-2.27
29	C25	C26	1.3386	29	C18	C19	C20	124.07	29	N15	C16	C18	C19	-0.62

30	C25	C32	1.3426
31	C29	C26	1.3395
32	C27	C28	1.5341
33	C30	C29	1.343
34	C31	C30	1.3437
35	C32	C31	1.3443

30	C19	C20	C21	119.8
31	C20	C21	C22	117.11
32	C21	C22	C23	123.7
33	C21	C22	C26	126.82
34	C23	C22	C26	109.48
35	C18	C23	C22	119.52
36	C18	C23	N24	137.43
37	C22	C23	N24	103.04
38	C23	N24	C25	115.37
39	C23	N24	C27	126.36
40	C25	N24	C27	118.27
41	N24	C25	C26	106.04
42	N24	C25	C32	134.42
43	C26	C25	C32	119.54
44	C22	C26	C25	106.06
45	C22	C26	C29	131.81
46	C25	C26	C29	122.13
47	N24	C27	C28	111.97
48	C26	C29	C30	118.1
49	C29	C30	C31	120.36
50	C30	C31	C32	120.92
51	C25	C32	C31	118.94

30	N15	C16	C18	C23	179
31	C20	C19	C18	C16	178
32	C20	C19	C18	C23	-0.79
33	C22	C23	C18	C16	-178
34	C22	C23	C18	C19	1.6
35	N24	C23	C18	C16	1.53
36	N24	C23	C18	C19	-179
37	C18	C19	C20	C21	-0.42
38	C19	C20	C21	C22	0.79
39	C20	C21	C22	C23	0.07
40	C20	C21	C22	C26	-180
41	C21	C22	C23	C18	-1.32
42	C21	C22	C23	N24	179
43	C26	C22	C23	C18	179
44	C26	C22	C23	N24	-0.88
45	C21	C22	C26	C25	-180
46	C21	C22	C26	C29	0.36
47	C23	C22	C26	C25	0.38
48	C23	C22	C26	C29	-179
49	C18	C23	N24	C25	-178
50	C18	C23	N24	C27	2.29
51	C22	C23	N24	C25	1.14
52	C22	C23	N24	C27	-178
53	C23	N24	C25	C26	-0.93
54	C23	N24	C25	C32	179
55	C27	N24	C25	C26	179
56	C27	N24	C25	C32	-1.7
57	C23	N24	C27	C28	-86
58	C25	N24	C27	C28	94.4
59	N24	C25	C26	C22	0.28
60	N24	C25	C26	C29	-180
61	C32	C25	C26	C22	-179
62	C32	C25	C26	C29	0.5
63	N24	C25	C32	C31	-180
64	C26	C25	C32	C31	-0.38
65	C30	C29	C26	C22	180
66	C30	C29	C26	C25	-0.26
67	C31	C30	C29	C26	-0.1
68	C32	C31	C30	C29	0.2
69	C25	C32	C31	C30	0.04

Likewise, TD-DFT computation reflected also three bands at λ_{max} at 238 nm assigned to H=>L+1(80%) and H-2=>L (20%), with $\Delta\lambda$= 7 nm regarding the exp. peak, the second λ_{max} at 260 nm resonated to H=>L(75%) and H-2=>L+1 (25%) with $\Delta\lambda$= -6 nm, the third λ_{max} at 314 nm attributed to H-1=>L(65%) and H-1=>L+1 (35%) with $\Delta\lambda$= 7 nm shift. The degree of agreement between practical UV-Vis and theoretical TD-DFT studies was more than remarkable, as the shift in absorption maxima $\Delta\lambda$ did not exceed 7 nm at the greatest value as seen in **Figure 2**

3.4. COX/LOX *Molecular docking*

The ligand's anti-inflammatory potential was assessed theoretically using in silico docking studies targeting essential inflammation-related proteins such as COX-2 (pdb ID: 4COX), 5-LOX (pdb ID: 6N2W) and COX-1 (pdb ID: 2OYU), which are all recognized as critical targets for anti-inflammatory medicines (Salehi *et al.*, 2019). In order to determine the natural and the power of interactions as well as the overall binding energy, docking studies were conducted (Toubi *et al.*, 2024; AlAli *et al.*, 2023a; AlAli *et al.*, 2023b; Faris *et al.*, 2023; El Masaoudy *et al.*, 2023). The docking studies considerable H-bond interactions constructed between the ligand and the target enzymes as the key to evaluating the power and nature of binding with the nearby amino acids (**Figure 3c-f**). Notably, the ligand had differential binding sites for various enzymes: for COX-1 and COX-2, it occupied the groove center of the enzyme body (**Figure 3a** and **3b**), while for LOX, it migrated to a more terminal position (**Figure 3c**).

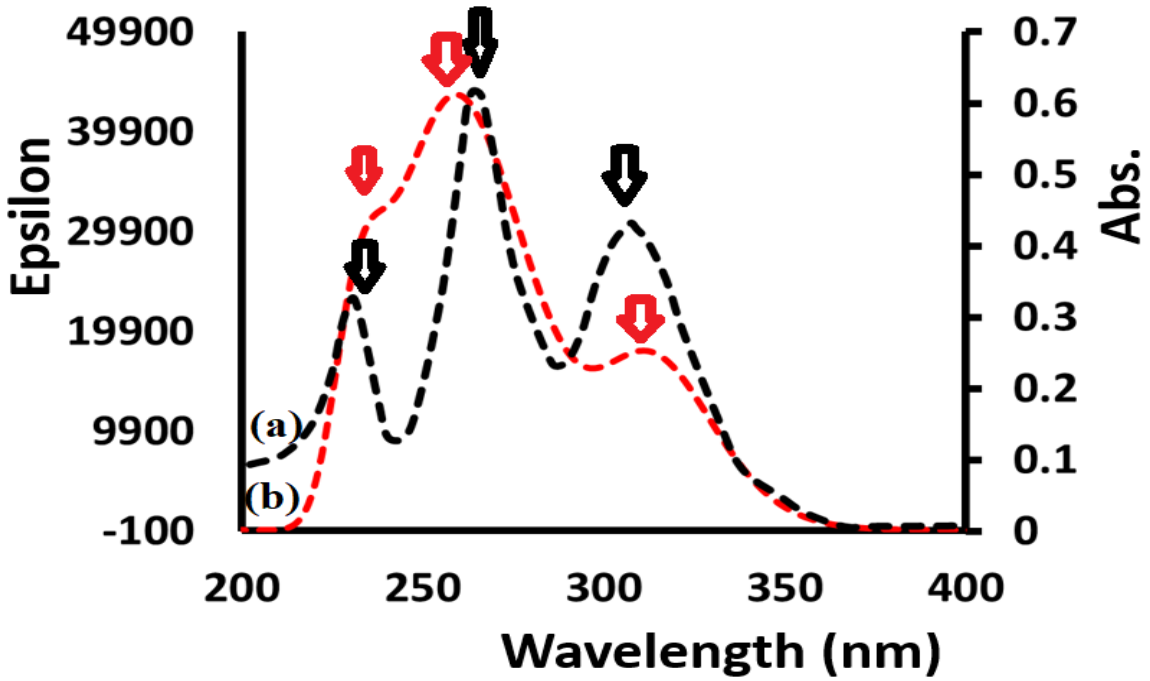


Figure 2. (a) UV-Vis, and (b) TD-DFT for the desired S.B in CH_2Cl_2 solvent.

In COX-1 (**Figure 3d**), both O of SO2 acted as e-donors to generate H-bond, and when 5-LOX was utilized, one S of SO2 was involved in H-bond formation (**Figure 3e**). In COX-2, the H of NH acted as an e-acceptor to generate a new H-bond interaction (**Figure 3f**) in addition to the O of SO2 interactions. Moreover, the interactions between the S.B molecule and the COX-2 protein had three H-bonds formed, N-H...O of GLN372 with 1.985 A, O....HZ3 of LYS532 with 2.028 Å, and O....HZ1 of LYS532 with 1.961 Å bond length (**Figure 3g**). These connections result in the highest binding energy value among enzymes, -12.67 kcal/mol, as shown in (**Table 2**). COX-1 protein had two H-bonds O….HE2 of HIS388 with 1.897 Å and O….HE2 of HIS207 with 2.059 Å bond distance (Fig.3h) indicating the binding energy of -11.04 kcal/mol. On another hand, the 5-LOX protein had one H-bonds O….HD21 of ASN328 with 2.236 Å (**Figure 3i**). resulting in the binding energy being the lowest one with -9.94 kcal/mol, as seen in (**Table 2**). These collected results were consistent with other recently published ones (Elizabeth *et al.*, 2023; Amit *et al.*, 2023).

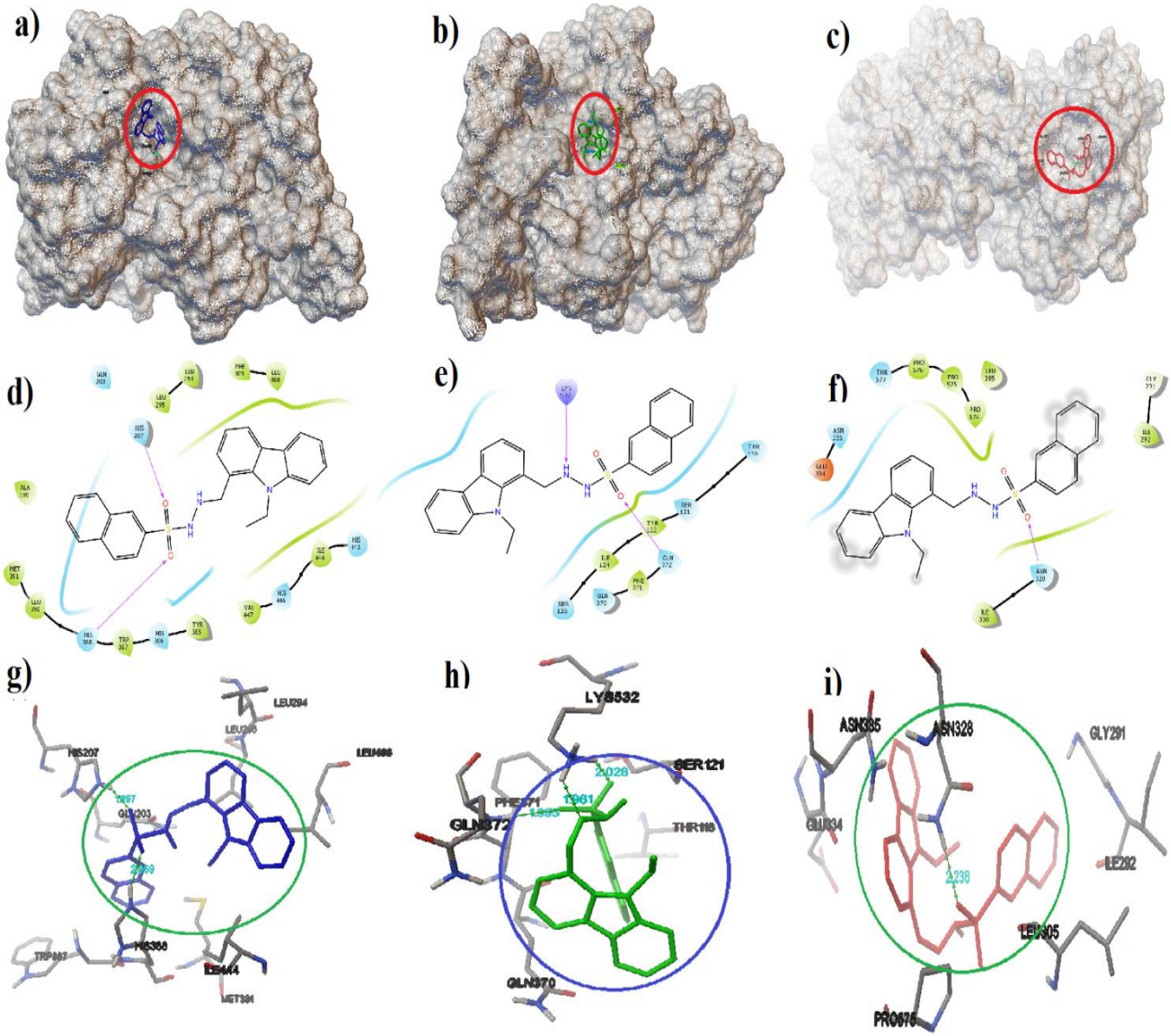


Figure 3. Ligand- inflammation enzyme docking result, (a) 2OYU (COX-1), (b) 4COX (COX-2), (c) 6N2W (5-LOX) ligand locations, (d) COX-1, (e) COX-2, (f) 5-LOX 2-D-interactions, (j) COX-1, (h) COX-2, (i) 5-LOX H-bonds natural.

Table 2. In silico COX/LOX docking results.

Conf. No.	Protein-Code	B.E (kcal/mole)	L. E	I. C, µM T= 298. 15 K	VdW- Hb- Des-energy kcal/mol	Hb of residues and S.B with bond length (Å)
S.B	COX-1 2OYU	-11.04	-0.36	8.06	-12.53	HIS388:HE2:O (1.897) HIS207:HE2:O (2.059)
	COX-2 4COX	-12.67	-0.41	5.64	-14.16	GLN372:NH:O (1.985) LYS532:HZ1:O (1.961) LYS532:HZ3:O (2.028)
	5-LOX 6N2W	-9.94	-0.32	9.57	-11.42	ASN328:HD21:O (2.236)

Conclusion

All physico-measurements outs consistently confirmed the efficient synthesis of of N'-((9-ethyl-9H-carbazol-1-yl)methylene)naphthalene-2-sulfono-hydrazide ligand, with no side products and a remarkable 87% yield. According to computational DFT-calculation, the E-isomer structure was only slightly favored above the Z-isomer one. Moreover, the UV-Vis spectroscopic analysis revealed that the S.B with three broad-bands which were consistent with the theoretical DFT/TD-DFT computation result.

The ligand's anti-inflammatory activities were theoretically explained using COX/LOX molecular docking experiments. The H-bonding numbers and types reflect the strength of the [ligand: enzyme] complexes interactions. When COX-2 was docked with the S.B ligand, three hydrogen bonds were obtained with a very high bonding energy, whereas only two hydrogen bonds were obtained with a medium energy with the COX-1 enzyme and one hydrogen bond with a lower energy with the LOX-enzyme; thus, the desired ligand can be classified as an excellent COX-2 better than the COX-1 and LOX enzymes. Finally, in silico docking approaches employed in this research paper yielded promising results that could help in understanding the experimental in vitro/in vivo anti-inflammatory medicines behavior.

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

Abu-Rayyan A., Suleiman M., Daraghmeh A., Al Ali A., Zarrouk A., Kumara K., Warad I., (2023) Synthesis, characterization, E/Z-isomerization, DFT, optical and 1BNA docking of new Schiff base derived from naphthalene-2-sulfonohydrazide. *Mor. J. Chem.*, 11, 613. https://doi.org/10.48317/IMIST.PRSM/morjchem-v11i3.39715

Abu-Yamin A. A., Abduh M. S., Saghir S. A. M., Al-Gabri N., (2022) Synthesis, characterization and biological activities of new Schiff base compound and its lanthanide complexes. *Pharmaceuticals*, 15, 454. https://doi.org/10.3390/ph15040454

Afshari F., Ghomi E. R., Dinari. M., Ramakrishna S., (2023) Recent advances on the corrosion inhibition behavior of Schiff base compounds on mild steel in acidic media. *ChemistrySelect*, 8, e202203231. https://doi.org/10.1002/slct.202203231

AlAli A., Al-Noaimi M., AlObaid A., Khamees H. A., Zarrouk A., Kumara K., Warad I., Khanum S. A., (2023) Jahn-Teller distortion in SP-like [Cu (bipy)(triamine)]. 2BF4 complexes with novel NH… F/CH… F synthon: XRD/HSA-interactions, physicochemical, electrochemical, DFT, docking and COX/LOX inhibition. *J. Mol. Liq.*, *387*, 122689. https://doi.org/10.1016/j.molliq.2023.122689

AlAli A., Khamees H. A., Madegowda M., Zarrouk A., Kumara K., El-khatatneh N., Warad I., Khanum, S. A. (2023) One-pot reproducible Sono-synthesis of trans-[Br(N⋂N')Cu(μBr)$_2$Cu(N⋂ N') Br] dimer:[H…. Br S (9)] synthons, spectral, DFT/XRD/HSA, thermal, docking and novel LOX/COX enzyme inhibition. *J. Mol. Struct.*, 1275, 134626. https://doi.org/10.1016/j.molstruc.2022.134626

Alezzy A. A., Alnahari H., Al-horibi S. A., (2022) Short review on metal complexes of Schiff bases containing antibiotic, and bioactivity applications. *J. Chem. Nutrit. Biochem.*, 3, 44. https://doi.org/10.48185/jcnb.v3i2.671

Al Hamzi A. H., Zarrok, H. Zarrouk A., Salghi R., Hammouti B., Al-Deyab S.S., Bouachrine M., Amine A., Guenoun F. (2013), The Role of Acridin-9(10H)-one in the Inhibition of Carbon Steel Corrosion: Thermodynamic, Electrochemical and DFT Studies, *Int. J. Electrochem. Sci.*, 8 N°2, 2586-2605

Amereih S., Al Ali A., Zarrouk A., Chetouni A., Kumara K., Lokanath N. K., Warad I., (2019) Synthesis, XRD, DFT-optimization, MEP and Hirshfeld surface analysis of di-μ-Chloro-bis[chloro (1, 10-phenanthroline)Cd(II) dimer. *Mor. J. Chem.*, *7*(2), 392-400.

https://doi.org/10.48317/IMIST.PRSM/morjchem-v7i2.16070
Amereih S., Daraghmeh A., Al-Nuri M., Suleiman M., Zarrouk A., Warad I. (2021) Synthesis, NMR, DFT, GRD, MEP, FMO's analysis and comparison of E and Z-isomer of N'-((4-bromothiophen-2-yl)methylene)naphthalene-2-sulfonohydrazide. *Mor. J. Chem.* 9, 232. https://doi.org/10.48317/IMIST.PRSM/morjchem-v9i2.26239
Amereih S., Daraghmeh, A., Warad, I., Al-Nuri, M. (2020). Synthesis, Characterization and Evaluation of Biological Activity of Sulfonylhydrazide Schiff Base (E)- N'-(2,5-dimethoxybenzalidene) naphthalene-2-sulfonohydrazide. *Palest. Tech. Univ. Res. J.* 8, 1.
Amit A. P., Mubarak H. S., Badrinarayan G. C., Vijay N. B., Baban K. M., (2023) Pyridine-1,3,4-Thiadiazole-Schiff Base Derivatives, as Antioxidant and Antimitotic Agent: Synthesis and in Silico ADME Studies, *Polycycl. Aromat. Compd.*, 43, 1247. https://doi.org/10.1080/10406638.2022.2026988
Ashraf T., Ali B., Qayyum H., Haroone M. S., Shabbir G., (2023) Pharmacological aspects of Schiff base metal complexes: A critical review. *Inorg. Chem. Commun.*, 150, 110449. https://doi.org/10.1016/j.inoche.2023.110449
Barhoumi A., El Idrissi M., Bakkas S., Zeroual A., Tounsi A., El Hajbi A. (2020) A DFT study of the mechanism and regioselectivity of the reaction between diethyl trichloro-methyl phosphonate and diphenyl methyl phosphinite, *Mor. J. Chem.*, 8 No 4, 830-840; https://doi.org/10.48317/IMIST.PRSM/morjchem-v8i4.20720
Barakat A., Al-Noaimi M., Suleiman M., Aldwayyan A.S., Hammouti B., Hadda T.B., Haddad S.F., Boshaala A., Warad I. (2013) One Step Synthesis of NiO Nanoparticles via Solid-State Thermal Decomposition at Low-Temperature of Novel Aqua(2,9-dimethyl-1,10-phenanthroline)NiCl2 Complex. *International Journal of Molecular Sciences*, 14(12), 23941-23954. https://doi.org/10.3390/ijms141223941
Boulechfar C., Ferkous H., Delimi A., Djedouani A., Kahlouche A., Boublia A., Darwish A. S., Lemaoui T., Verma R., Benguerba Y., (2023) Schiff bases and their metal complexes: A review on the history, synthesis, and applications. *Inorg. Chem. Commun.*, 150, 110451. https://doi.org/10.1016/j.inoche.2023.110451
Çakmak R., Ba¸saran E., Sentürk M., (2022) Synthesis, characterization, and biological evaluation of some novel Schiff bases as potential metabolic enzyme inhibitors. *Archiv. Pharm.*, 355, 2100430. https://doi.org/10.1002/ardp.202100430
Camadan Y., Çiçek B., Adem S., Çali Ü., Akkemik E., (2022) Investigation of in vitro and in silico effects of some novel carbazole Schiff bases on human carbonic anhydrase isoforms I and II. *J. Biomol. Struct. Dyn.*, 40, 6965. https://doi.org/10.1080/07391102.2021.1892527
Catalano A., (2023) Schiff bases: A short survey on a promising scaffold in drug discovery. *Curr. Med. Chem.*,*30*, 4170. https://doi.org/10.2174/0929867330666230201121432
Daraghmeh, A. F.A. (2019). Synthesis and Characterization of Sulfonylhydrazide-Schiff Bases, their Biological Activities and Molecular Docking. M. Sc Thesis, *An- Najah National University*, 1-87.
El Aissouq A., Lachhab A., El Rhabori S., Bouachrine M., Ouammou A., & Khalil F., (2022) Computer-aided drug design applied to a series of pyridinyl imidazole derivatives targeting p38α MAP kinase: 2D-QSAR, docking, MD simulation, and ADMET investigations. *New J. Chem.*, 46, 20786. https://doi.org/10.1007/s11224-022-01903-5
El Masaoudy Y., Tabti K., Koubi Y., Maghat H., Lakhlifi T., & Bouachrine M., (2023) In silico design of new pyrimidine-2, 4-dione derivatives as promising inhibitors for HIV Reverse Transcriptase-associated RNase H using 2D-QSAR modeling and (ADME/Tox) properties. *Mor. J. Chem.*, 11, 300. https://doi.org/10.48317/IMIST.PRSM/morjchem-v11i2.35455
El-Azab A. S., Abdel-Aziz A. A. M., Ghabbour H. A., Bua S., Nocentini A., Alkahtani H. M., Alsaif N. A., Al-Agamy M. H. M., Supuran C. T., (2022) Carbonic anhydrase inhibition activities of Schiff's bases based on quinazoline-linked benzenesulfonamide, *Molecules*, 27, 7703 https://doi.org/10.3390/molecules27227703
Elizabeth N., Pilar M., Michelle M.O., Yesseny V.M., Fernando G., Tamara M., Angel M., Erick F., Carolina M., (2023) Evaluating the inhibitory activity of ferrocenyl Schiff bases derivatives on 5-lipoxygenase: Computational and biological studies, *J. Inorg. Biochem.*, 245, 112233. https://doi.org/10.1016/j.jinorgbio.2023.112233
Faris A., Edder Y., Louchachha I., Ait Lahcen I., Azzaoui K., Hammouti B., Merzouki M., Challioui A., Boualy B., Karim A., Hanbali G., Jodeh S. (2023) From Himachalenes to trans-Himachalol: Unveiling

Bioactivity through Hemisynthesis and Molecular Docking Analysis, *Scientific reports*, 13, 17653. https://doi.org/10.1038/s41598-023-44652-z

Frisch M. J., Trucks G. W., Schlegel H. B., Scuseria G. E., (2009) Gaussian 09W, Gaussian Inc., Wallingford CT. http://www.gaussian.com

Gupta K. C., Sutar A. K., (2008) Catalytic activities of Schiff base transition metal complexes. *Coord. Chem. Rev*, 252, 1420. https://doi.org/10.1016/j.ccr.2007.09.005

Hamid S. J., Salih T., (2022) Design, synthesis, and anti-inflammatory activity of some coumarin Schiff base derivatives: In silico and in vitro study. *Drug Des. Develop. Ther.*, 16, 2275. https://doi.org/10.2147/DDDT.S364746

Lindner E., Warad I., Eichele K., & Mayer H. A., (2003) Supported organometallic complexes Part 34: synthesis and structures of an array of diamine (ether–phosphine) ruthenium(II) complexes and their application in the catalytic hydrogenation of trans-4-phenyl-3-butene-2-one. *Inorganica Chim. Acta*, 350, 49. https://doi.org/10.1016/S0020-1693(02)01535-9

Mondal K., Mistri S., (2023) Schiff base-based metal complexes: A review of their catalytic activity on aldol and henry reaction. *Comments Inorg. Chem.*, 43, 77. https://doi.org/10.1080/02603594.2022.2094919

Morris G. M., Huey, R., Lindstrom, W., Sanner, M. F., Belew, R. K., Goodsell, D. S. Olson, A. J. (2009) Autodock4 and AutoDockTools4: automated docking with selective receptor flexibility. *J. Comp. Chem.* 16, 2785. https://doi.org/10.1002/jcc.21256

Rudrapal M., Eltayeb W. A., Rakshit G., El-Arabey A. A., Khan J., Aldosari S. M., Alshehri B., Abdalla M. (2023) Dual synergistic inhibition of COX and LOX by potential chemicals from Indian daily spices investigated through detailed computational studies. *Scientific Reports*, 13(1), 8656. doi: 10.1038/s41598-023-35161-0

Saleemh F. A., Musameh S., Sawafta A., Brandao P., Tavares C. J., Ferdov S., Barakat A., Al Ali A., Al-Noaimi M., Warad I. (2017) Diethylenetriamine/diamines/copper(II) complexes [Cu(dien)(NN)]Br_2: Synthesis, solvatochromism, thermal, electrochemistry, single crystal, Hirshfeld surface analysis and antibacterial activity. *Arab. J. Chem.* 10 (6) 845. https://doi.org/10.1016/j.arabjc.2016.10.008

Salehi M., Kubicki, M., Galini, M., Jafari, M., Malekshah, R. E. (2019) Synthesis, characterization and crystal structures of two novel sulfa drug Schiff base ligands derived sulfonamide and molecular docking study. *J. Mol. Struct.*,1180, 595. https://doi.org/10.1016/j.molstruc.2018.12.002.

Takfaoui A., Lakehal I., Bouabdallah I., Halaimia F., Nacer H., Hammouti B., Touzani R. (2014) New imines bearing alkyl armed for catecholase activity, *J. Mater. Environ. Sci.* 5 (3), 753-756

Tighadouini S., Roby O., Mortada S., Lakbaibi Z., Radi S., Al-Ali A., Warad I., (2022). Crystal structure, physicochemical, DFT, optical, keto-enol tautomerization, docking, and anti-diabetic studies of (Z)-pyrazol β-keto-enol derivative. *J. Mol. Struct.*, 1247, 131308. https://doi.org/10.1016/j.molstruc.2021.131308

Tople M. S., Patel N. B., Patel P. P., Purohit A. C., Ahmad I., Patel H., (2023) An in silico-in vitro antimalarial and antimicrobial investigation of newer 7-chloroquinoline based Schiff-bases. *J. Mol. Struct.*, 1271, 134016. https://doi.org/10.1016/j.molstruc.2022.134016

Toubi Y., Hakmaoui Y., EL Ajlaoui R., Abrigach F., Zahri D., Radi S., Rakib E. M., Lgaz H., Hammouti B. (2024) Unexpected Efficient One-Pot Synthesis, DFT Calculations, and Docking study of new 4-hydroxy-2H-chromen-2-one Derivatives predicted to target SARS-CoV-2 spike protein, *Journal of Molecular Structure*, 2024, 136789, , https://doi.org/10.1016/j.molstruc.2023.136789

Upendranath K., Venkatesh T., Nayaka Y. A., Shashank M., Nagaraju G., (2022) Optoelectronic, DFT and current-voltage performance of new Schiff base 6-nitro-benzimidazole derivatives. *Inorg. Chem. Commun.*, 139, 109354. https://doi.org/10.1016/j.inoche.2022.109354

Warad I., Ali O., Al Ali A., Jaradat N. A., Hussein F., Abdallah L., Al-Zaqri N. Alharthi F. A. (2020) Synthesis and spectral Identification of three Schiff bases with a 2-(piperazin-1-yl)-N-(thiophen-2-yl methylene) ethanamine moiety acting as novel pancreatic lipase inhibitors: Thermal, DFT, antioxidant, antibacterial, and molecular docking investigations. *Molecules*, 25, 2253. https://doi.org/10.3390/molecules25092253

Warad I., Daraghmeh A., Al-Nuri M., Zarrouk A., Mousa M., Al-Ali A., Shraim A. M., (2020) Method for synthesizing 1-(naphthalen-2-ylsulfonyl)-3-(thiophen-2-yl) diaziridine. *U.S. Patent* No. 10,836,752 B1.

Washington, DC: U.S. Patent and Trademark Office. https://patents.google.com/patent/US10836752B1/en

Warad I., Eftaiha, A. A. F., Al-Nuri, M. A., Husein, A. I., Assal, M., Abu-Obaid, A., Hammouti, B. (2013) Metal ions as Antitumor Complexes. *J. Mater. Environ. Sci.* 4, 542.

Yuldasheva N., Acikyildiz N., Akyuz M., Yabo-Dambagi L., Aydin T., Cakir A., Kazaz C., (2022) The synthesis of Schiff bases and new secondary amine derivatives of *p*-vanillin and evaluation of their neuroprotective, antidiabetic, antidepressant and antioxidant potentials. *J. Mol. Struct.*, 1270, 133883. https://doi.org/10.1016/j.molstruc.2022.133883

Zaki H., Bourass M., Haddaji G., Ouammou K., Benlyass M., & Bouachrine M., (2017) QSAR analyses of Octahydroquinazolinone for insecticidal activity against spodoptera litura and its in-silico validation using molecular Docking study. *Mor. J. Chem.*, 5, 202. https://doi.org/10.48317/IMIST.PRSM/morjchem-v5i1.7834

(2024); https://revues.imist.ma/index.php/morjchem/index