Synthesis, Spectral Characterization, DFT Calculations and *In Silico* ADMET Study of E-(Naphthalen-6-yl) Methylene) Semicarbazide (NMS)

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Abstract

The Schiff base (Naphthalen-6-yl) Methylene) Semi carbazide (NMS) is synthesized and characterised using FT-IR, ^{1}H NMR and ^{13}C NMR spectral methods. A molecular docking experiment was utilised to determine the ADME properties of NMS and forecast their interactions with the oestrogen receptor in order to identify the lead chemical (2IOK).In the ultra-violet absorption spectrum, the substance exhibits absorption at 396 nm. Density functional theory was used to compute the electronic states and molecular characteristics of the molecule.

Keywords: Schiff base; Auto dock; DFT.

Introduction

Schiff base-based metal complexes have received a lot of attention due to their biological activities. Numerous derivatives of the Schiff bases have been created and used to create protein and enzyme imitators [1].

Investigations into the structure can help us to understand the co-ordination characteristics of Schiff bases acting as ligands. The use of Schiff base ligands in inorganic chemistry has been the subject of substantial study throughout the past thirty years. This has led to reports that several of these species make for excellent reagents in biological, pharmacological, therapeutic and analytical applications. We describe here the synthesis and molecular structure of the above mentioned chemical as part of an inquiry into their crystal structures that will help shed light on the coordination characteristics of Schiff bases acting as ligands [2,3].

Nuclear hormone receptors such as the Oestrogen Receptor (ER) bind to DNA and regulate a number of gene-related processes. Antiestrogens, or ER (Estrogen Receptor) blockers, stop the growth of tumours. Numerous antiestrogens, such as bazedoxifene, clomifene, cyclofenil, epimestrol, lasofoxifene, ormeloxifene, raloxifene, tamoxifen and toremifene, have been developed as medications to block the oestrogen signal [3-6]. A potential first step in the creation of cutting-edge and strong anticancer drugs with significant cytotoxic activity against breast and ovarian cancer is represented by symmetrical azine derivatives [6-9]. Density Functional Theory (DFT) computations and spectroscopic investigations are essential to determine the structural link between the groups that affect biological features [9-15].

In the present study, we report the synthesis and molecular structure of a (Naphthalen-6-yl) Methylene) Semi carbazide (NMS). It is a Schiff base derivative and its schematic diagram is shown in Figure 1.
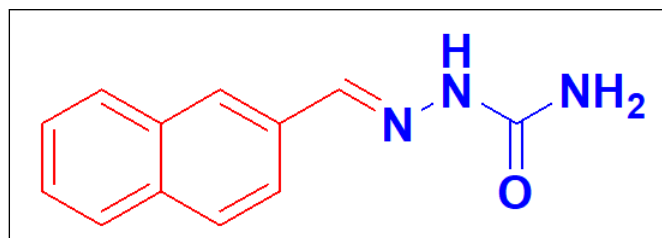

Figure 1: Schematic diagram of Schiff based compound NMS.

Experimental

Synthesis

The ethanoic solution of β-naphthaldehyde (0.4074 g) and semi carbazide (0.4985 g) were stirred with small quantity of Tetra Butyl Ammonium Bromide (TBAB) solution for 4hrs. The resulting solution is poured into ice-water and the precipitate formed was filtered and recrystallized from ethanol (Figure 2).
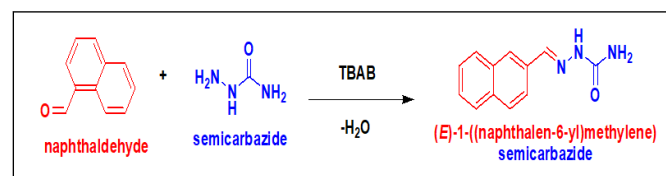

Figure 2: Ethanoic solution of β-naphthaldehyde and semi carbazide.

Results and Discussion

FT-IR
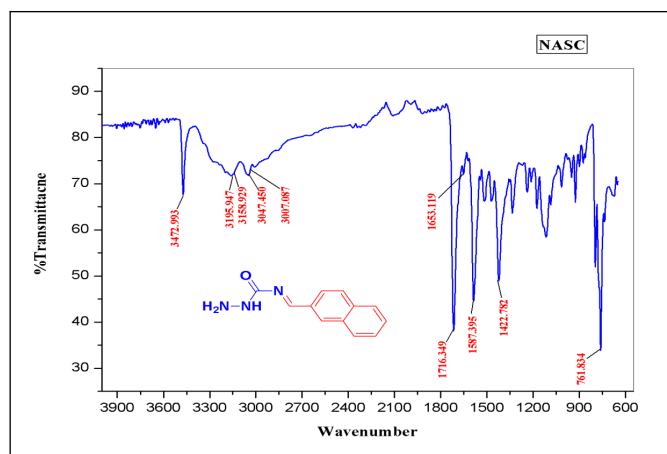
In the IR Spectrum of compound NMS shown in (Figure 3).

Figure 3: FT-IR spectrum of compound NMS.

The >C=O< stretching vibration frequency is observed at 1716 cm^{-1}. The peaks at around 1587 cm^{-1} is due to the >C=C< stretching vibration. >C=N stretching vibration appear at 1653 cm^{-1}.

Ultraviolet absorption spectrum

The ultraviolet absorption spectra are recorded for the newly synthesized symmetrical azine in ethanol the absorption in 395.5 nm might due to the n- π * transition shown in Figure 4.
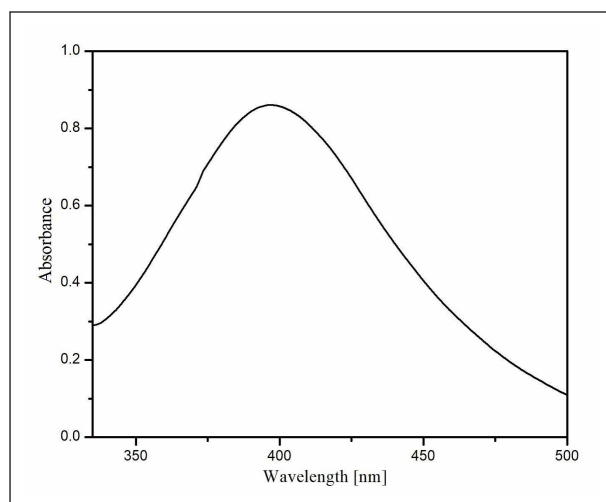

Figure 4: UV-Vis spectrum of compound NMS.

NMR analysis

^{1}H NMR

In the ^{1}H NMR spectrum of compound NMS. The two protons singlet appears at 9.40 ppm are due to the NH2 protons. The benzylidine proton appears as singlet at 8.36 ppm. The NH proton resonates as a singlet at 7.19 ppm. The protons signal ranging from 7.50 ppm-8.0 ppm is obviously due to the aromatic protons (Figure 5).
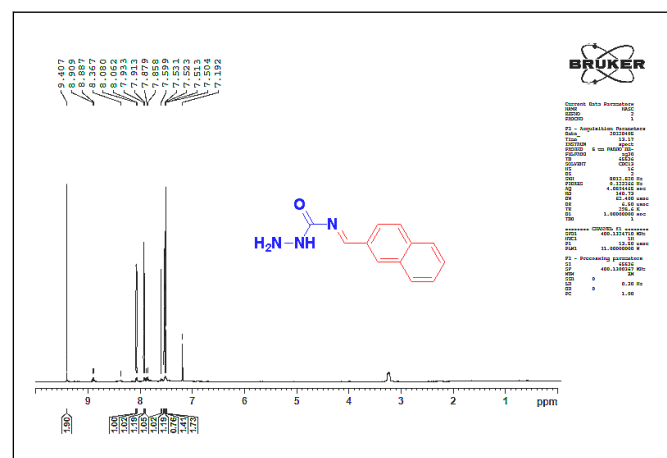

Figure 5: ^{1}H NMR spectrum of compound NMS

^{13}C NMR

In the ^{13}C NMR spectrum of compound the carbons signals at 165.39 ppm and 162.03 ppm is due to the carbonyl carbon and benzylidine carbon respectively. The carbon signal ranging from 124 ppm-133 ppm is due to the aromatic carbons Figure 6.
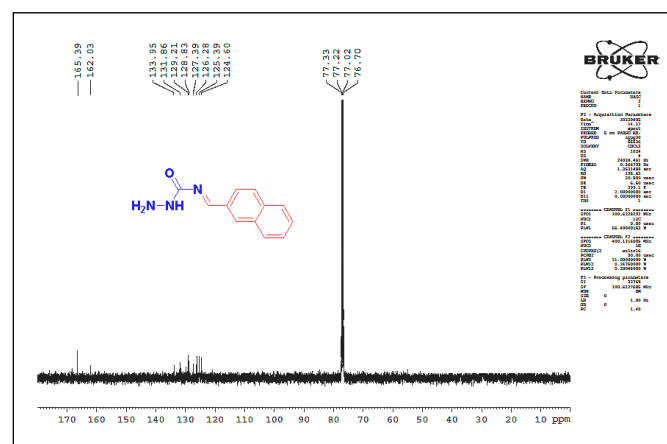

Figure 6: 13C NMR spectrum of compound NMS.

Frontier Molecular Orbital analysis (FMO)

The border orbital gap can be used to explain more clearly the chemical reactivity and kinetic stability of a molecule. An electron donor is present in the HOMO molecular orbital, which has the highest density of occupants, while an electron acceptor is present in the LUMO, which has the lowest density of occupants. The base set B3LYP was used in the calculations. The HOMO-LUMO gap of 0.0319 eV and the characteristics of the molecule indicate that it is soft, reactive and polarizable (Figure 7). Table 1 displays the findings of the compound NMS FMO Analysis.
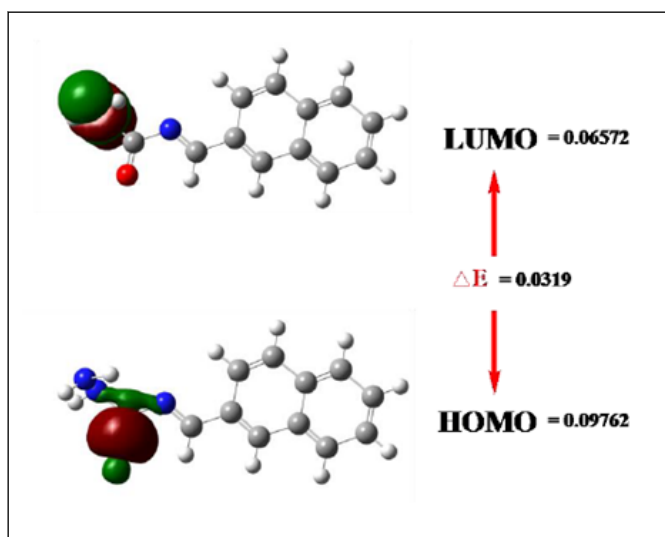
2

Figure 7: FMO analysis.

Properties	NMS
EHOMO (eV)	-0.09762
ELUMO(eV)	-0.06572
Δ E (E$_{HOMO}$-E$_{LUMO}$) eV	0.319
Global hardness (η) (Δ E/2)	0.01595
Softness (S) (1/ Δ E = 1/2 η)	31.3479
Chemical Potential (μ) (–[1/2 EHOMO + ELUMO])	0.08167
Electrophilicity (T) μ ^{2}/2 η	0.41818
Electronegativity (χ) (- μ)	-0.08167
Dipolemoment (Debye)	1.742

Table 1: FMO Analysis of compound NMS.

Mulliken charge distribution

It explains how charges are distributed throughout the different molecular orbital subshells (core, valance and Rydberg). Table 2 displays the buildup of natural charges on particular title-molecule atoms. Quantum chemistry computations of molecular systems depend on the Mulliken atomic charge calculation. Atomic charge has an impact on the system's dipole moment, polariz ability, electronic structure, as well as other molecular characteristics. In Figure 8, the Mulliken charges of atoms were graphically represented.
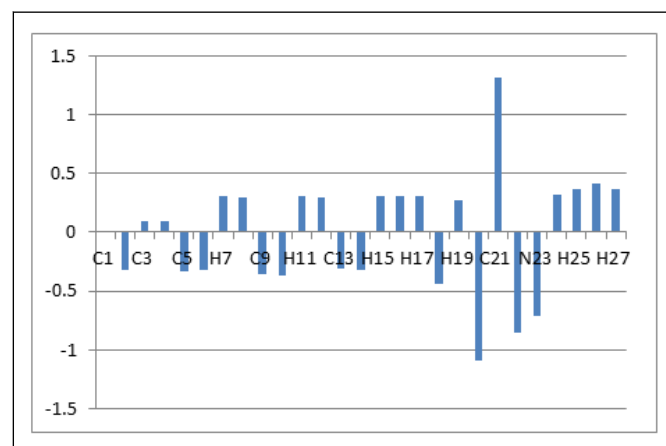
Figure 8: Mulliken charges and graphical representation of compound NMS.

C1	0.014
C2	-0.323
C3	0.093
C4	0.092
C5	-0.328
C6	-0.319
H7	0.304
H8	0.301
C9	-0.353
C10	-0.364
H11	0.306
H12	0.296
C13	-0.313
C14	-0.319
H15	0.304
H16	0.309
H17	0.309
C18	-0.434
H19	0.275
N20	-1.09
C21	1.319
O22	-0.848

N23	-0.707
N24	0.318
H25	0.367
H26	0.409
H27	0.368

Table 2: Mulliken charges of compound NMS.

Molecular docking

In silico molecular docking was used to identify the optimum molecules and molecular interactions for symmetrical azines. Before being used in molecular docking study to ascertain the compounds' binding interactions, the Human Estrogen Receptor Alpha Ligand-Binding Domain in Associa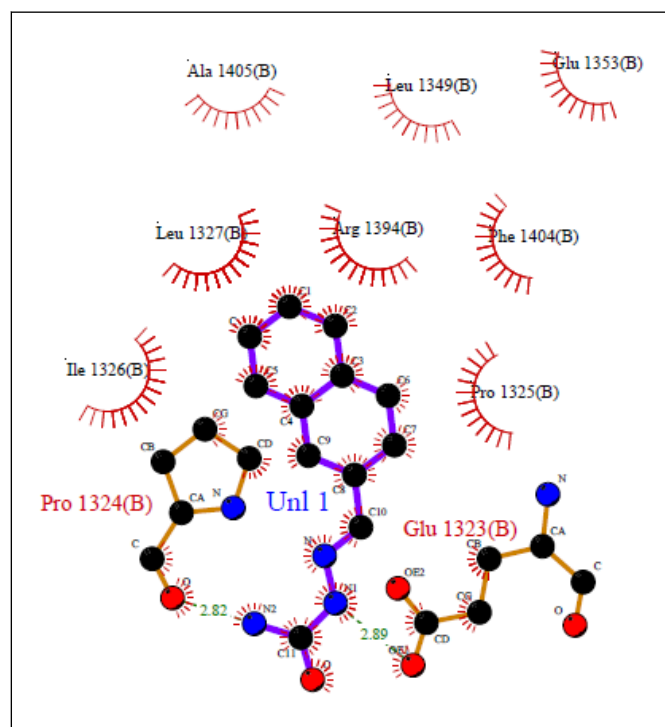tion with Compound 1D (PDB: 2IOK) X-ray crystal structures were retrieved from Protein Data Bank and modified. Figures 9 and 10 display the crucial residues in the binding region together with the best-scoring docking study pose for the compound NMS.
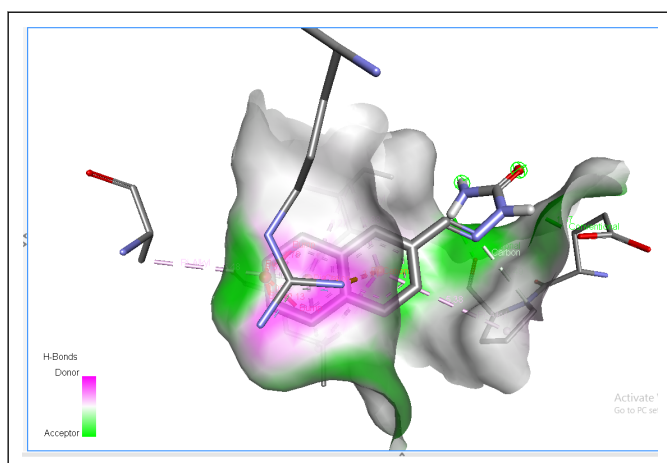
Figure 9: 3D image of compound NMS.

Figure 10: 2D PDB sum image of compound NMS.

The docking investigations revealed that the active chemical NMS had the lowest binding energy, with a value of -6.88. According to glide molecular docking, Table 3 depicts the contact between the protein ligand and the ER as having the least amount of binding energy (PDB: 2IOK).

Ligand	CAHD
Binding energy	-6.88
Ligand efficiency	-0.43
Inhib_Constant	9.13µM
Intermol_energy	-7.47
Vdw_hb_disolve_energy	-7.34
Electrostatic energy	-0.13
Total_internal	-0.21
Torsional energy	0.6
Unbound energy	0.21
refRMS	61.28

Table 3: Lowest binding energy for the ligand NMS and ER protein (PDB: 2IOK).

ADME

Swiss ADME software (www.swissadme.ch) from the Swiss Institute of Bioinformatics (http://www.sib.swiss) was used to estimate individual ADME behaviours of symmetrical

azine compounds in a web server that displays the Swiss ADME Submission page in Google. Simplified Molecular Input Line Entry System (SMILES) defines the list which has one input molecule per line with multiple inputs and the results are provided in Tables 4,5,6 for each molecule Figure 11.
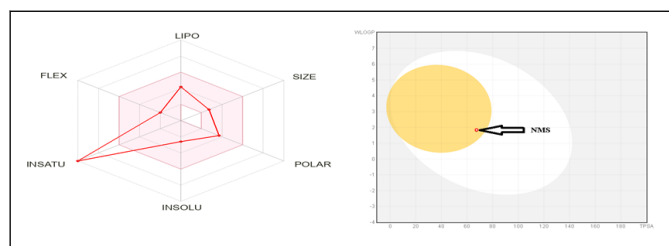
SMILES formula: NC(=O)N\N=C\C1=CC2=C(C=CC=C2)C=C1

Figure 11: SMILES formula.

Molecule	Molecular formula	Molecular weight g/mol	No.of hydrogen bond acceptor	No.Of hydrogen bond donor	Lipophilicity Log Po/w
NMS	C12H11N3O	213.24	2	2	1.68

Table 4: Lipophilicity of the compound NMS.

Water solubility						
Compound	Log S (ESOL)	Class	Log S (Ali)	Class	Log S (SILICO-IT)	Class
NMS	-2.59	Soluble	-2.89	Soluble	-3.81	Soluble

Table 5: Water solubility of the compound NMS.

Compound	Lipinski	Bio avalailability	Pharmacokinetics		Synthetic accessibility
			GI absorption	Log KP (Skin permeation)	
NMS	Yes (Zero violation)	0.55	High	-6.29 cm/s	2.18

Table 6: ADME properties of the compound NMS.

Conclusion

The Schiff's base NMS was synthesized and thoroughly characterized using FT-IR, UV and NMR with all of the results supporting the predicted structures. According to the docking tests the active compound has the lowest binding energy with -6.88. Furthermore the compounds had favorable pharmacokinetic qualities and adhered to Lipinski's rule of five. 6-311(d,p) was also used to optimize the geometrical properties of the compounds. The stability, intermolecular charge transfers and donor-acceptor interactions in the synthesized molecule are clearly supported by DFT. The nucleophilic and electrophilic areas of the molecular surface were investigated using Mulliken atomic charges.

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