Synthesis, computational and anti-oxidant studies of 2-[2-(4-arylamino)-4-phenylaminothiazol-5-oyl]naphthalene

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Abstract
The compound 2-[2-(4-arylamino)-4-phenylamino thiazol-5-oyl]naphthalene was synthesized and characterized by different physico-chemical techniques such as IR, electronic parameters, antioxidant studies etc. The geometrical and electronic characteristics of 2-[2-(4-arylamino)-4-phenylaminothiazol-5-oyl]napht halene were calculated theoretically using the Gaussian 09W software at the B3LYP/6-31G level of theory. The predicted geometrical characteristics are close to those published for 2-[2-(4-arylamino)-4-phenylaminothiazol-5-oyl]naphthalene with similar structures.

Geometrical parameters are dependent on the atom's size, bonding nature and charge transfer according to optimization. The estimated MOs are helpful in determining the optimised compounds' collective electronic characteristics. Energy gap, on the other hand, is a measure of chemical reactivity, kinetic stability and polarizability.

Keywords: B3LYP, DFT, FT-IR, Gaussian, HOMO, LUMO, Mulliken charges.

Introduction

In medicinal chemistry, naphthalene is a versatile and multifunctional platform. Because of the varied biological actions caused by structural alterations, this scaffold emerges as a promising moiety in drug creation. Antimicrobial, anticancer, antiviral, anticonvulsant, antitubercular and anti-inflammatory properties have been described for naphthalene-based compounds. Naphthalene nucleus was also found in a variety of commercially used medications including Nafcillin, Bedaquiline, Naproxen and Nafimidone[7]. Certain analogues of thiazoles are used as a precursor to generate physiologically active molecules in heterocyclic compounds[3,8].

Because of their efficiency, Density Functional Theory (DFT) computations have become an indispensable tool in theoretical organic chemistry[2]. The B3LYP/6-31G approach is accurate and useful for determining vibrational spectrum and structural characteristics. The current study details geometrical and electronic properties of 2-[2-(4-arylamino)-4-phenylaminothiazol-5-oyl]naphthalene, DFT calculations were performed with the Gaussian 09W software as well as by the antioxidant studies. By optimising all geometrical variables such as bond length, bond angle and so on, the molecule's optimal geometry was discovered. The electronic parameters of the molecules were computed including their border molecular orbital energy, ionisation potential, hardness, electronegativity, softness and dipole moment.

Material and Methods

The reagents and solvents used were of AR grade. All chemicals were purchased from Merck Specialties Pvt. Ltd. and Sigma-Aldrich. To a solution of 1-aryl-3-(N,N[1]-diphenylamidino)thiourea in DMF, 2-bromoacetyl naphthalene was added. The reaction mixture was heated on a water bath at 60-70℃ for 5 min. To this, triethylamine was added and the reaction was continued for another 10 min. It was allowed to cool and purged into ice-cold water with stirring. A yellow colored precipitate obtained was filtered, washed with water and dried. The obtained crude product was recrystallized from ethanol: water (2:1) which produces a yellow colored crystalline solid.

Computational: The theoretical calculations were examined using the Gaussian 09 software package and the obtained results were visualised using Gauss View 5.0. DFT methods with B3LYP/ 6-31G basis sets were used to calculate the electronic properties and optimal geometries of the naphthalene derivatives.

Results and Discussion

Optimized geometry: The DFT/B3LYP approach with 6-31G basis sets was used to optimise 2-[2-(4-arylamino)-4-phenylaminothiazol-5-oyl]naphthalene. Figure 1 depicts the theoretically optimised geometric structure. The estimated geometric parameters are listed in table 1. In the 6-31G basis set, the bond lengths of C-C in the naphthalene ring were found to be around 1.40A^0. The preceding data reveals that the electrons in the naphthalene ring are conjugated which means that there is no distinction between single and double bonds.

When the size of an atom increases, the bond length also increases. The SP^2 hybridized carbon pulls electrons more closely compared to the SP^3 hybridized atoms. The length of the bond varies according to the size. The size of the sulphur atom is larger than all the other atoms in the resulting compound, 2-[2-(4-arylamino)-4-phenylaminothiazol-5-oyl]naphthalene, which comprises of C-N, C-C and C-S bonds.

As a result, the bond length for sulphur in these compounds is longer. Based on these findings, it can be concluded that

the B3LYP/6-31G approach reproduces the geometry of the produced naphthalene derivatives as the best.

Mulliken atomic charge: The Mulliken charge distribution structure of 2-[2-(4-arylamino)-4-phenylaminothiazol-5-oyl]naphthalenes was determined with the B3LYP/6-31G basis set as shown in figure 2. The Mulliken charge distribution reveals that all hydrogen and sulphur atoms have positive charges. The atoms of nitrogen and oxygen are all negatively charged. Carbon atoms have Mulliken charges that are either positive or negative, depending on the atoms around them.

Table 1
Geometrical parameters of 2-[2-(4-arylamino)-4-phenylaminothiazol-5-oyl]naphthalene

Position	parameter	C1	C2	C3	C4	C5
Thiazole	C - N	1.3156	1.3525	1.3562	1.3560	1.3542
Thiazole	C = N	1.3088	1.3128	1.3197	1.3198	1.3289
Thiazole	C - S	1.8526	1.8595	1.8460	1.8462	1.8543
Thiazole	C - H	1.0733	1.0782	1.0806	1.0806	1.0798
Naphthalene	C - C	1.4021	1.4047	1.4074	1.4074	1.4071
Naphthalene	C - H	1.0842	1.0643	1.0848	1.0848	1.0855
Phenyl	C - C	1.4056	1.4043	1.4031	1.4031	1.4131
Phenyl	C - H	1.0848	1.0895	1.0872	1.0870	1.0866
Phenyl	C - Cl	1.8350	-	-	-	-
Chain	C - C	-	-	-	1.5190	1.5186
Chain	C - N	1.4152	1.4128	1.4222	1.4224	1.4222
Chain	N - H	1.0168	1.1169	1.0103	1.0103	1.0102
Chain	C - O	-	-	1.3907	1.3896	1.3902

C1- 2-[2,4-bis(phenylamino)thiazol-5-oyl]naphthalene
C2 - 2-[2-(4-chlorophenylamino)-4-phenylaminothiazol-5-oyl]naphthalene
C3 - 2-[2-(4-methylphenylamino)-4-phenylaminothiazol-5-oyl]naphthalene
C4 - 2-[2-(4-methoxyphenylamino)-4-phenylaminothiazol-5-oyl]naphthalene
C5 - 2-[2-(4-ethoxyphenylamino)-4-phenylaminothiazol-5-oyl]naphthalene

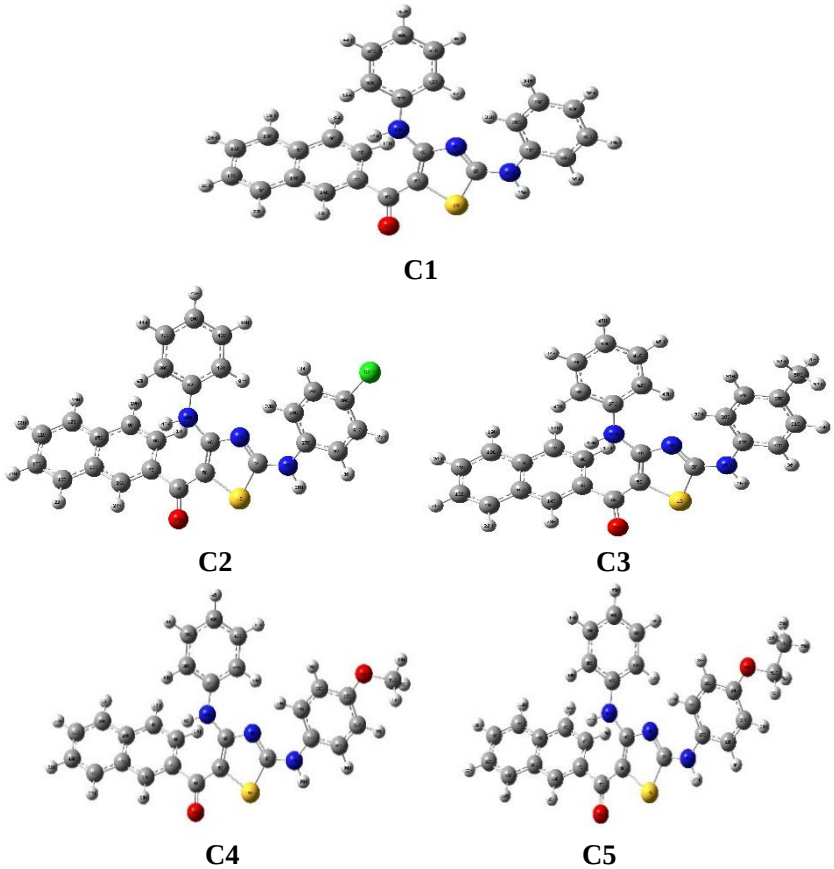

Figure 1: Optimized structure of 2-[2-(4-arylamino)-4-phenylaminothiazol-5-oyl]naphthalenes

Table 2
Mulliken charge distribution of 2-[2-(4-arylamino)-4-phenylaminothiazol-5-oyl]naphthalenes

Atom	Mulliken charge				
	C1	**C2**	**C3**	**C4**	**C5**
S_1	0.445	0.452	0.443	0.441	0.441
C_2	0.175	0.174	0.175	0.174	0.174
N_3	-0.459	-0.461	-0.450	-0.462	-0.462
C_4	0.556	0.556	0.556	0.557	0.556
C_5	-0.403	-0.404	-0.404	-0.404	-0.404
C_6	0.262	0.263	0.262	0.262	0.262
C_7	0.004	0.007	0.005	0.005	0.005
C_8	-0.150	-0.158	-0.151	-0.151	-0.151
C_9	-0.162	-0.163	-0.162	-0.162	-0.162
C_{10}	-0.155	-0.155	-0.155	-0.155	-0.155
C_{11}	-0.126	-0.126	-0.127	-0.127	-0.127
C_{12}	-0.134	-0.134	-0.134	-0.134	-0.134
C_{13}	-0.144	-0.144	-0.144	-0.144	-0.141
C_{14}	-0.165	-0.165	-0.165	-0.165	-0.165
C_{15}	0.075	0.075	0.075	0.075	0.075
C_{16}	0.055	0.054	0.055	0.055	0.055
H_{17}	0.151	0.151	0.151	0.151	0.151
H_{18}	0.138	0.138	0.137	0.137	0.137
H_{19}	0.133	0.134	0.133	0.133	0.133
H_{20}	0.130	0.131	0.130	0.130	0.129
H_{21}	0.131	0.132	0.137	0.130	0.130
H_{22}	0.139	0.140	0.139	0.139	0.139
H_{23}	0.165	0.166	0.165	0.165	0.165
O_{24}	-0.450	-0.449	-0.451	-0.452	-0.452
N_{25}	-0.760	-0.782	-0.760	-0.760	-0.760
H_{26}	0.340	0.342	0.339	-0.339	0.339
C_{27}	0.314	0.319	0.312	0.328	0.319
C_{28}	-0.100	-0.094	-0.097	-0.102	-0.101
C_{29}	-0.156	-0.130	-0.189	-0.156	-0.160
C_{30}	-0.111	-0.225	0.128	0.294	0.300
C_{31}	0.155	-0.107	-0.164	-0.141	-0.142
C_{32}	-0.163	-0.158	-0.162	-0.178	-0.179
H_{33}	0.192	0.203	0.100	0.193	0.192
H_{34}	0.133	0.164	0.127	0.148	0.145
H_{35}	0.131	0.162	0.126	0.134	0.135
H_{36}	0.126	0.137	0.125	0.127	0.127
C_{37}	0.320	0.318	0.321	0.321	0.321
C_{38}	-0.169	-0.165	-0.170	-0.170	-0.170
C_{39}	-0.134	-0.134	-0.134	-0.134	-0.134
C_{40}	-0.115	-0.114	-0.115	-0.115	-0.115
C_{41}	-0.156	-0.156	-0.156	-0.155	-0.156
C_{42}	-0.090	-0.090	-0.091	-0.091	-0.091
H_{43}	0.131	0.131	0.130	0.130	0.130
H_{44}	0.128	0.130	0.127	0.127	0.127
H_{45}	0.124	0.127	0.124	0.124	0.124
H_{46}	0.127	0.129	0.127	0.128	0.128

H_{47}	0.164	0.169	0.165	0.165	0.165
N_{48}	-0.818	-0.815	-0.819	-0.819	-0.820
H_{49}	0.340	0.340	0.340	0.340	0.340
H_{50}	0.128	-	-	-	-
Cl_{50}	-	0.067	-	-	-
C_{50}	-	-	-0.482	-	-
H_{51}	-	-	0.157	-	-
H_{52}	-	-	0.148	0.148	0.142
H_{53}	-	-	0.147	0.172	0.142
O_{50}	-	-	-	-0.561	-0.570
C_{51}	-	-	-	-0.171	-0.013
H_{54}	-	-	-	0.149	-
C_{54}	-	-	-	-	-0.410
H_{55}	-	-	-	-	0.137
H_{56}	-	-	-	-	0.158
H_{57}	-	-	-	-	0.159

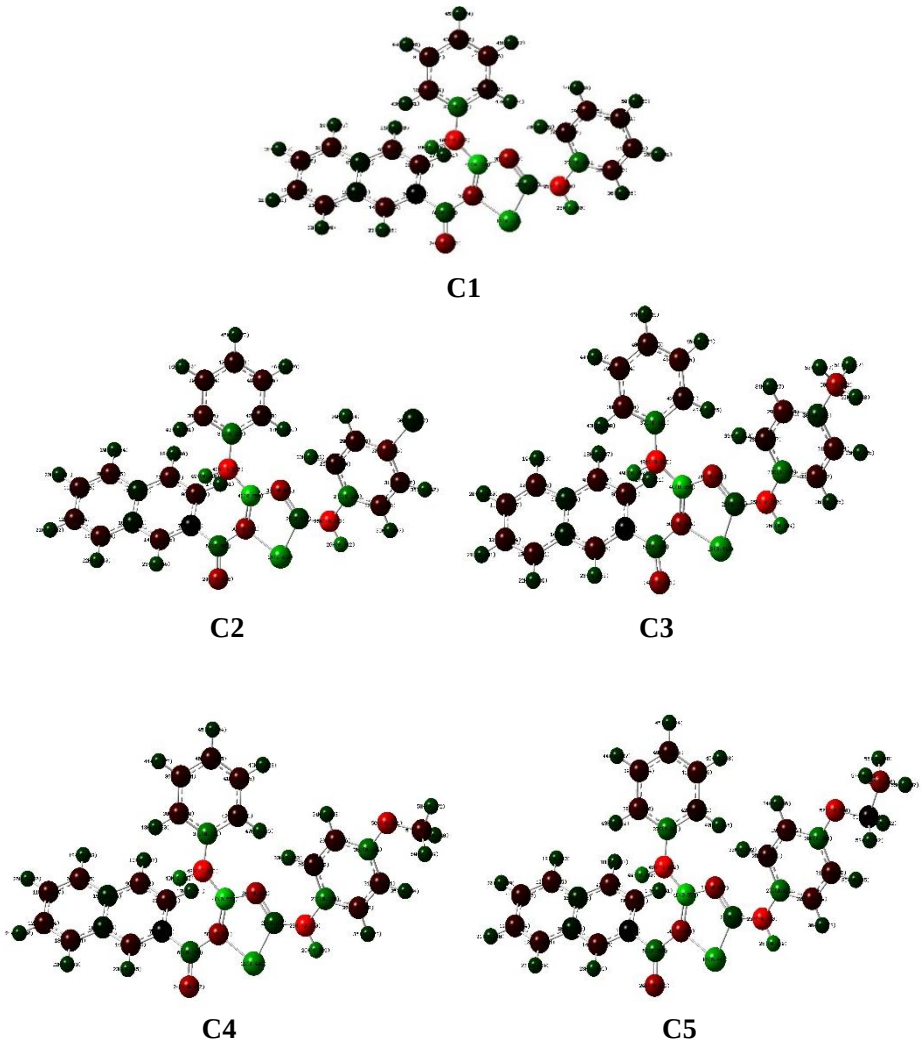

Figure 2: Mulliken charge of 2-[2-(4-arylamino)-4-phenylaminothiazol-5-oyl]naphthalenes

HOMO-LUMO: The shape of the separated molecules affects their electronic properties. The donor orbital is denoted by HOMO while the acceptor orbital is denoted by LUMO. Global reactivity parameters include chemical potential (μ), global hardness (η), global softness (S) and global electrophilicity index (ω). These variables are thought to be useful descriptors of biological activity. The frontier molecular orbital is also used to determine electro negativity

(χ), electron affinity (A) and ionisation potential (I). Electron acceptors, or substances with a positive electron affinity, may participate in charge transfer reactions. The compound is more stable and less reactive if the HOMO-LUMO energy gap is high.

According to Koopmans' theorem[5], the frontier molecular orbital energies are given by:

$-E_{HOMO} = I$ and $- E_{LUMO} = A$. (1)

where I is Ionization potential and A is Electron Affinity.

The equation 1 defines that HOMO energy is the ionization potential and LUMO energy is the electron affinity. Literature survey reveals that the absolute electro negativity (χ), absolute hardness (η) and softness (S) of a compound can be calculated using the HOMO and LUMO energies. The operational definitions for the electronic parameters are:

$\chi = (I+A)/2$, $\eta = (I-A)/2$ and $S = 1/2\eta$ (2)

The electro negativity, hardness and softness can all be determined using equation 2. The B3LYP/6-31G basis set was used to determine the HOMO-LUMO energy gap and electronic characteristics of 2-[2-(4-arylamino)-4-phenylaminothiazol-5-oyl]naphthalene presented in table 2.

The HOMO-LUMO gap in hard molecules is high (E) while the HOMO-LUMO gap in soft molecules is small[10]. Because the excitation of an electron needs more energy, hard molecules are more stable. Excitation energies to the multiple of excited states are small when the HOMO-LUMO gap is narrow. Soft molecules have a smaller gap and are thus more polarizable than hard ones.

The most common quality assigned to soft acids and bases was their high polarizability. C5 is the only one of these four compounds with a small energy gap (0.12518). As a result, it claims that C5 is a soft molecule with a high polarizability. The HOMO-LUMO energy gap is a kinetic stability measure. Because it is energetically unable to add electrons to LUMO[11], a big HOMO-LUMO energy gap indicates minimal chemical reactivity and strong kinetic stability. Because it has a narrow energy gap, C5 is kinetically unstable and has significant chemical reactivity when compared to the other three molecules.

C5, C2, C1, C4 and C3 are the kinetic stability sequences. This indicates that C2 has a large energy gap (0.20174) and is a difficult molecule[1,4,6,9]. As a result, it has a high kinetic stability while also having a low chemical reactivity. The persistent dipole moment exists in all four compounds.

Vibrational Assignments: The purpose of vibrational analysis is to identify vibrational modes that are linked to certain chemical structures in a substance. A non-linear molecule N has 3N-6 degrees of freedom in general. This is due to the fact that all N atoms move in three dimensions (X, Y and Z), resulting in 3N degrees of freedom. When the frequencies estimated using the DFT approach with the 6-31G basis set are compared to the literature values, the B3LYP method exhibits excellent agreement.

The aromatic structure reveals the existence of vibrations in the region 3100-3000cm^{-1} which is the characteristic region for C-H stretching vibrations identification. In the 1420-1000cm^{-1} range, C-H in-plane bending vibrations were found. The stretching absorption of a heteroatomic molecule with an N-H group occurs in the range 3500-3220 cm^{-1}. The absorption bands of primary amine are modest, ranging from 3500 to 3400cm^{-1}.

The symmetric and asymmetric stretching modes are represented by the N-H group in primary amine. C-C stretching vibrations occur in the 1650-1430cm^{-1} range, C=O vibrations in the 1850-1600cm^{-1} range, C-N stretching vibrations in the 150cm^{-1} range and C-S vibrations in the 700cm^{-1} range. The theoretical and experimental IR spectra of 2-[2-(4-chlorophenylamino)-4-phenylaminothiazol-5-oyl]naphthalene are given in figure 3 and 4.

Table 3
Calculated electronic parameters of 2-[2-(4-arylamino)-4-phenylaminothiazol-5-oyl]naphthalene

Parameters	C1	C2	C3	C4	C5
EHOMO	-0.24003	-0.24258	-0.23936	-0.23867	-0.19088
ELUMO	-0.03889	-0.04467	-0.03762	-0.03703	-0.06570
I	0.24003	0.24258	0.23936	0.23867	0.19088
A	0.03889	0.04467	0.03762	0.03703	0.06570
ΔE	0.20114	0.19791	0.20174	0.20164	0.12518
Electronegativity (χ)	0.13946	0.143625	0.13849	0.13785	0.12829
Hardness (η)	0.10057	0.098955	0.10087	0.10082	0.06259
Softness (S)	0.050285	0.049478	0.05044	0.05041	0.03129

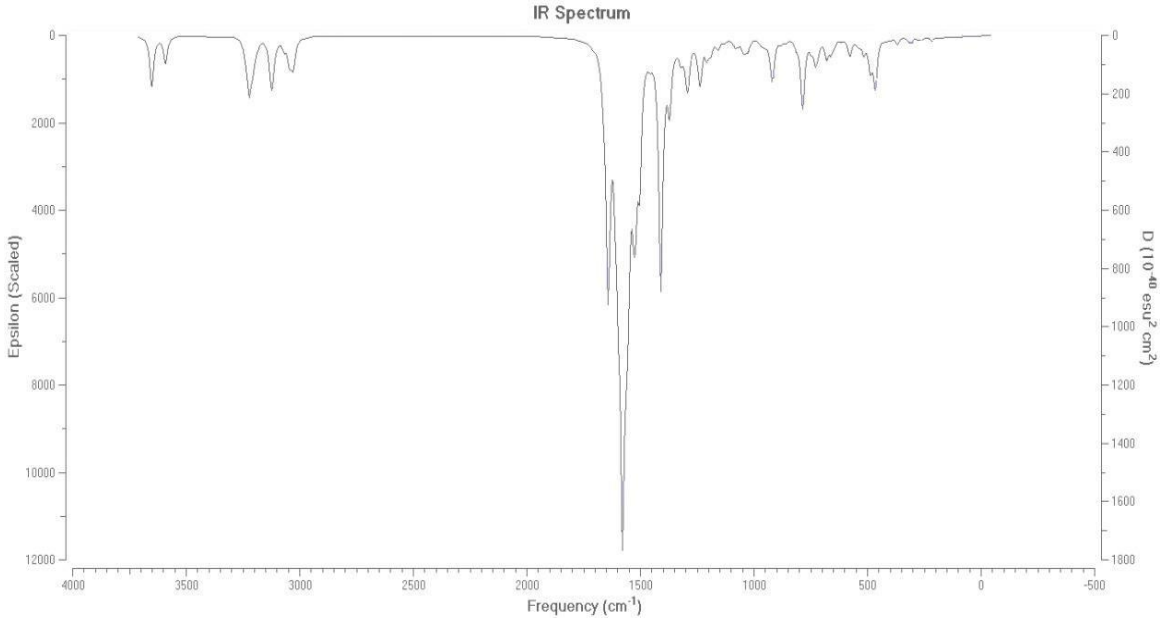

Figure 3: Theoretical IR spectra of 2-[2-(4-chlorophenylamino)-4-phenylaminothiazol-5-oyl]naphthalene

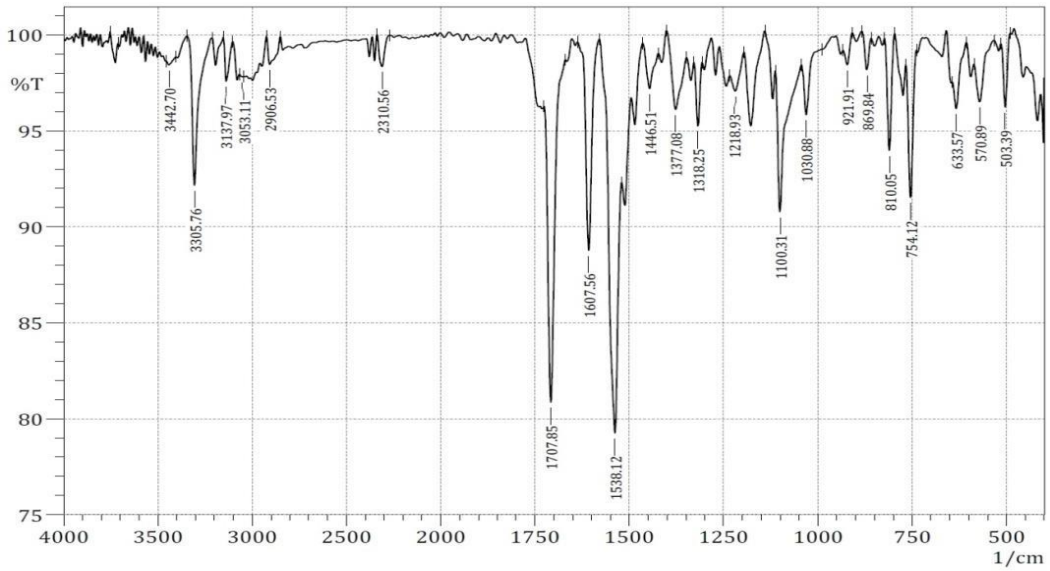

Figure 4: Experimental IR spectra of 2-[2-(4-chlorophenylamino)-4-phenylaminothiazol-5-oyl]naphthalene

Anti-oxidant studies: Antioxidants are defined as the compounds which inhibit oxidation. In the process of oxidation, it can produce free radicals, there by directing to chain reactions that may ruin the cells of organisms. Several antioxidants such as thiols or ascorbic acid (vitamin C) prevent these chain reactions. Some of the antioxidants are produced by our body, they are known as endogenous antioxidants. Antioxidants that come from outer side of the body are called exogenous. Free radicals are squander materials produced by cells. If the body cannot remove free radicals, oxidative stress can result. This can harm cells and body function. These free radicals are commonly known as reactive oxygen species (ROS).

Antioxidants help to neutralize free radicals in our bodies and this is thought to increase overall heal. The simple, quick and inexpensive method to assess antioxidant extent of food involves the use of 2,2-Diphenyl-1-picrylhydrazyl (DPPH) which is commonly used to test the ability of compounds to act as hydrogen donors, free radical scavengers and to estimate antioxidant activity. Hence, the DPPH radicals are broadly used to analyze the radical scavenging activity of compounds.

The free radical DPPH and the odd electrons provide maximum absorption at 517 nm (purple colour). The radical is scavenged by the antioxidants, the absorbance decreases resulting in colour change from purple to pale yellow. The absorbance of DPPH at 517 nm was determined using ultraviolet spectra after 30 minutes. The DPPH concentration in the reaction solution was calculated from the calibration curve plotted at 517 nm at different concentrations and inhibition percentages. Butylated hydroxy anisole (BHA) was used as a standard in our study.

Antioxidant studies of 2-[2-(4-arylamino)-4-phenylaminothiazol-5-oyl]naphthalene: The newly synthesized 2-[2-(4-arylamino)-4-phenylaminothiazol-5-oyl]naphthalene and DPPH were dissolved in ethanol. After 30 minutes, it was screened and percentage of inhibition was calculated using the equation:

$$\% \text{ Inhibition} = \frac{\text{Control absorbance (A0)} - \text{Sample absorbance (A1)}}{\text{Control absorbance (A0)}} \times 100$$

The % inhibition is plotted against the concentration of sample and the value of IC_{50} was calculated. The IC_{50} values of antioxidant study (Table 4) shows that among the compounds, 2-[2-(4-arylamino)-4-phenylaminothiazol-5-oyl]naphthalene and the compound 2-[2-(4-methylamino)-4-phenylaminothiazol-5-oyl]naphthalene (79 µM) have excellent antioxidant activity.

Table 4
Antioxidant activities of 2-[2-(4-arylamino)-4-phenylaminothiazol-5-oyl]naphthalene

Compound	IC_{50} Value (µM)
C1	159
C2	278
C3	79
C4	264
C5	350
BHA(std)	624

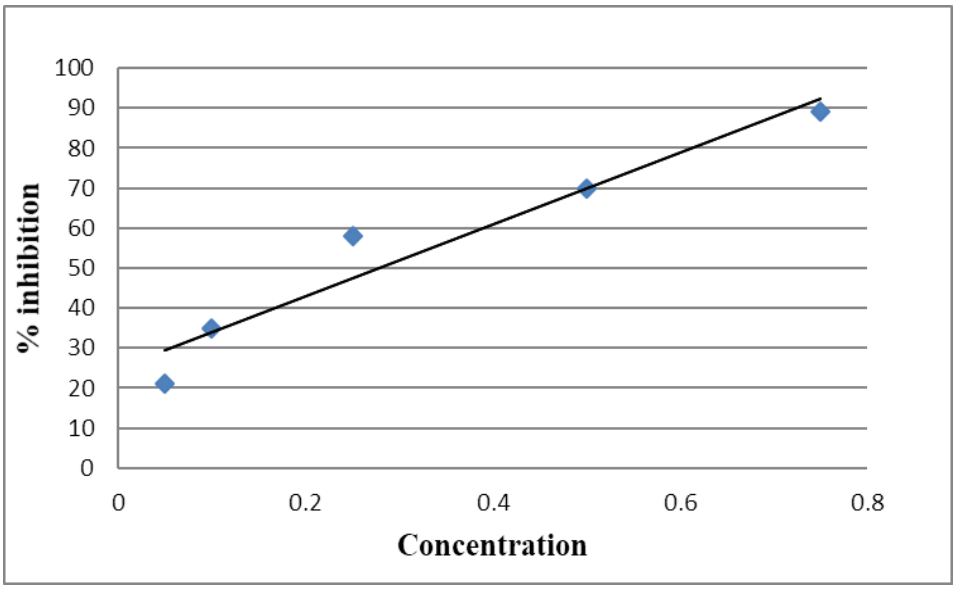

Figure 5: Plot of % inhibition vs concentration of 2-[2,4-bis(phenylamino)thiazol-5-oyl]naphthalene

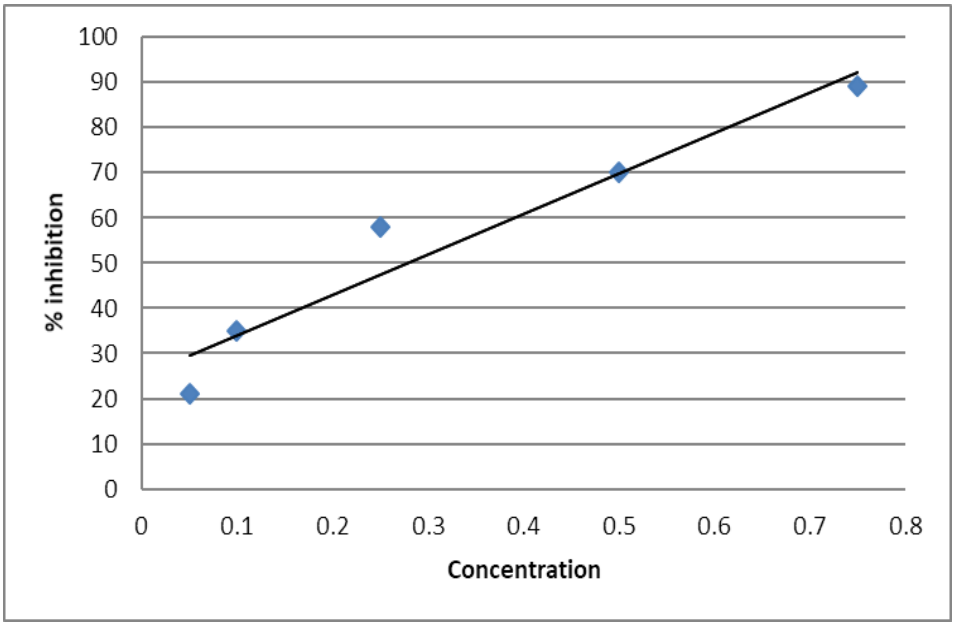

Figure 6: Plot of % inhibition vs concentration of 2-[2-(4-chlorophenylamino)-4-phenylaminothiazol-5-oyl]naphthalene

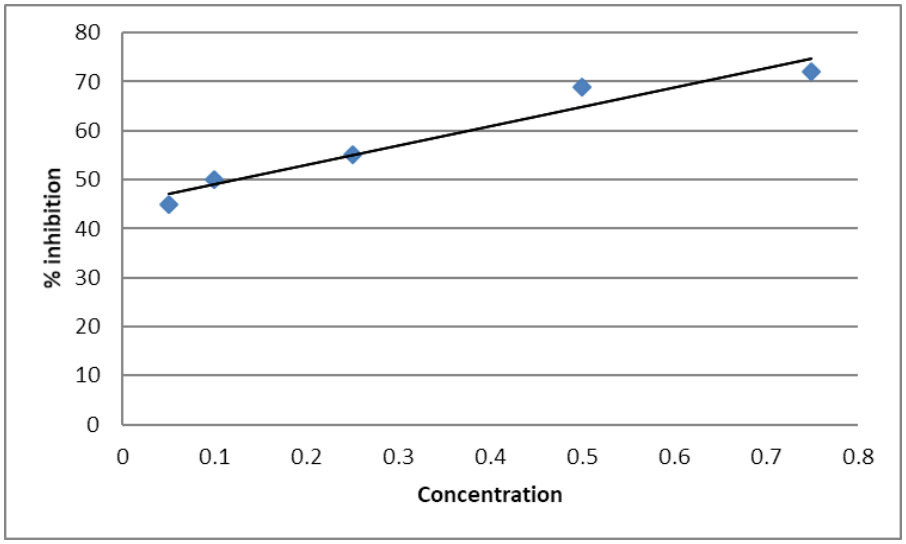

Figure 7: Plot of % inhibition vs concentration of 2-[2-(4-methylphenylamino)-4-phenylaminothiazol-5-oyl]naphthalene

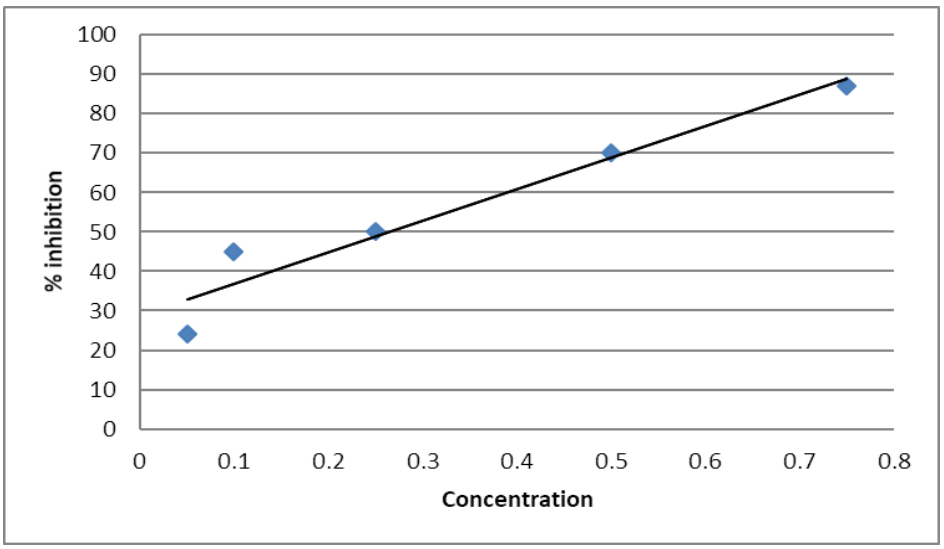

Figure 8: Plot of % inhibition vs concentration of 2-[2-(4-methoxyphenylamino)-4-phenylaminothiazol-5-oyl]naphthalene

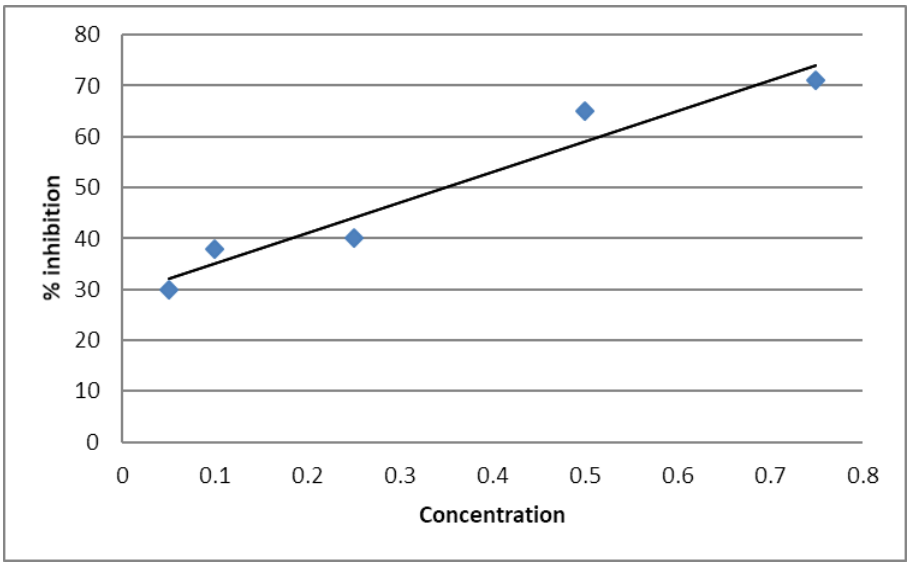

Figure 9: Plot of % inhibition vs concentration of 2-[2-(4-ethoxyphenylamino)-4-phenylaminothiazol-5-oyl]naphthalene

Conclusion

Geometry of the naphthyl thiazoles was optimized by DFT/B3LYP methods using 6-31G basis set. Molecular structural parameters and electronic properties of the optimized geometry of the compounds have been obtained from *ab initio* and DFT calculations. The longest bond distance observed in the naphthalene ring is C_6-C_7. This is due to thiazole moiety at these carbons. The S_1-C_2 bond distance is the longest, while the N_{48}-H_{49} is the shortest. Hence the longest S_1-C_2 distance shows the pure single bond character.

HOMO–LUMO studies explained the intra molecular charge transfer through the conjugated system. The calculated Mulliken atomic charge shows that N_{48} has more negative charge and S_1 has more positive charge. As a result, it has a high kinetic stability and low chemical reactivity. The persistent dipole moment exists in all five compounds. All the compounds are biologically active. The compound 2-[2-(4-methylamino)-4-phenylaminothiazol-5-oyl] naphthalene shows excellent antioxidant activity among the five synthesized compounds.

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