

# THERMO-DYNAMICAL, ELECTRONIC STRUCTURE, SPECTROSCOPIC AND SOLVENT EFFECT OF FLUORINE AND CHLORINE SUBSTITUTED COUMARIN CHLOROBENZOYL ISOXAZOLINE

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## ABSTRACT

The Density Functional Theory (DFT) calculations have been performed to investigate the thermo-dynamical, electronic structure, spectroscopic properties and solvent effect on electronic absorption spectra of fluorine and chlorine substituted coumarin isoxazolines (Ia) and (Ib) by using PBE1PBE functional with 6-311g basis set. The results revealed that the electronegativity of halogen group affect the bond length, atomic charges, excited wavelength, molecular orbital energy gap, vibration frequency, thermo-chemical parameters and stability of compounds.

**Keywords:** FT, electronegativity, stability, HOMO-LUMO gap

## 1. INTRODUCTION

The synthesis of halogen substituted isoxazoline derivatives has increase the attention as a source of new pharmacological agents. The isoxazoline derivatives have been reported to possess antifungal<sup>1</sup>, antimicrobial<sup>2</sup>, antitumor<sup>3</sup>, anti-inflammatory<sup>4,5</sup>, antidepressant<sup>6,7</sup> and analgesic<sup>8</sup> activity. The halogen group can alter the course of the reaction as well as the biological activities. In addition, isoxazoline derivatives have played a crucial role in the theoretical development of heterocyclic chemistry and are also used extensively in organic synthesis<sup>9,10</sup>.

For study of halogen substituted isoxazoline drug, mainly study the effect of halogen group over the drug activity is important. To study such effect the synthesis of isoxazoline is not necessary. Many theoretical methods are available like QSAR, *ab-initio*, semi-imperical, DFT, HF method etc, to predict such drug activity without synthesis. Amongst these, the DFT method has commonly used to determined molecular effect of halogen group on pharmacological activity<sup>11</sup>.

In this work we have studied the computational method for 8-(5-((4-fluoro phenyl)amino)-4-(4-chlorobenzoyl)-4,5-dihydroisoxazole-3-yl)-7-hydroxy-4-methyl-2H-chromen-2-one (Ia) and 8-(5-((4-chlorophenyl)amino)-4-(4-chlorobenzoyl)-4,5-dihydroisoxazole-3-yl)-7-hydroxy-4-methyl-2H-chromen-2-one (Ib) including electronic structure spectroscopic and thermo-dynamical properties.

## 2. COMPUTATIONAL DETAILS

The ground state geometry optimizations were carried out at the DFT<sup>12-16</sup> using the modified hybrid functional of Perdew, Burke and Ernzerhof (PBE1PBE)<sup>17,18</sup> with the 6-311g basis set<sup>19-23</sup>. Electronic absorption spectra were computed as vertical electronic excitations from the ground state using TD-DFT<sup>24-26</sup> with PBE1PBE/6-311g basis set. The optimized structural parameters were used for vibrational frequency calculation to characterize all the stationary points as minima. All the calculations performed with Gaussian-03 package<sup>27</sup>. Molecular visualization and the vibrational frequency assignment were made by using Gauss View 3.07 program. The gauge-including atomic orbital (GIAO) approach<sup>28</sup> was used to ensure gauge invariance of the result. The calculated chemical shifts were transformed to the  $\delta$ -scale as the difference between the isotropic part of magnetic shielding tensor and that of TMS.

### 3. RESULTS AND DISCUSSION

#### 3.1 Geometry optimization

The molecules were first optimized using DFT method with PBE1PBE function using 6-311g basis set in gas phase. The geometry optimization has started without symmetry constraints and after optimization; the structure converged to  $C_1$  symmetrical species. The calculated geometrical parameters are the basis for calculating other parameters such as vibrational frequency, UV-Vis spectra, chemical shift and thermodynamical properties of compounds.

The geometry was optimized in a lowest energy singlet ground state and the optimized structures of Ia and Ib shown in Fig. 1 and 2 respectively. The optimized geometric parameters of Ia and Ib are recorded in supplementary information Table S1 and S2 respectively.

The heterocyclic ring bond lengths of 48C-49C, 49C-35O and 34N-33C were slightly more in Ia than Ib. The 35O-34N bond length is slightly more in Ib than Ia. The 15O-16H bond length was almost same and was important in formation of metal complexes (Table 1).

Dihedral angles of Ia; 2C-6C-33C-34N, 22O-21C-48C-49C, 37H-36N-49C-35O were showed the values 126.71564, 66.16824, 93.63012 Å respectively with respect to the isoxazoline ring and was slightly smaller than Ib (except 2C-6C-33C-34N). It showed the three aromatic rings were non-planar to the isoxazoline ring and also non planar to each other. The geometry of both the compounds was non-planar because of strong distortion between electron cloud of three aromatic rings and isoxazoline ring.

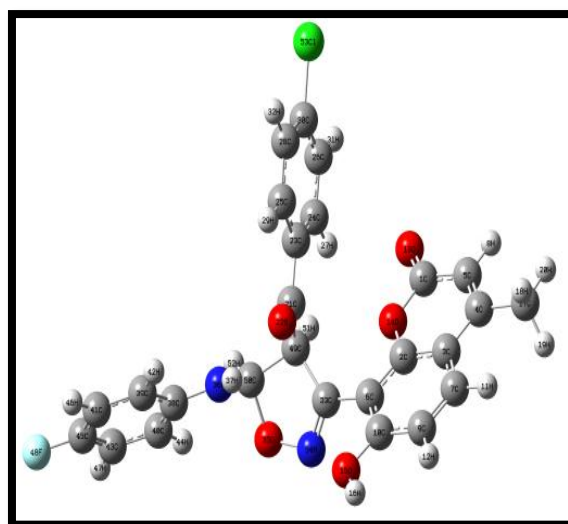


Fig. 1: Optimized structure of Ia in gas phase

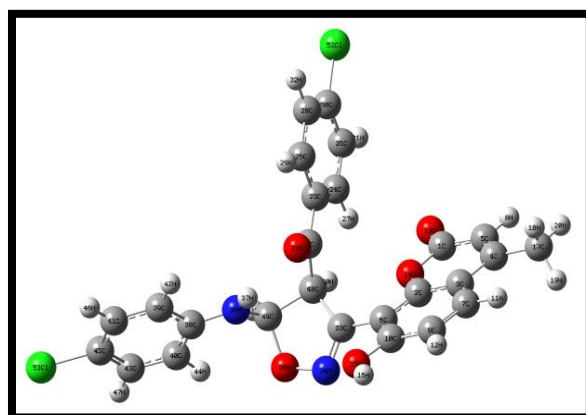


Fig. 2: Optimized structure of Ib in gas phase

**Table 1: Bond length and Dihedral angle of Ia and Ib**

Type	Bond Length (Å)		Type	Dihedral angle	
	Ia	Ib		Ia	Ib
48C-49C	1.54612	1.54580	2C-6C-33C-34N	126.71564	126.45997
49C-35O	1.51954	1.51626	22O-21C-48C-49C	66.16824	66.67280
35O-34N	1.42132	1.42236	37H-36N-49C-35O	93.63012	94.65076
34N-33C	1.29109	1.29093	10C-6C-33C-48C	129.08951	128.95267
33C-48C	1.52045	1.52082	36N-49C-48C-33C	94.97477	94.81292
15O-16H	0.96848	0.96847			
49C-36N	1.40075	1.40260			
36N-37H	1.00933	1.00956			
48C-21C	1.50898	1.50924			
21C-22O	1.24910	1.24929			

### 3.2 NBO Charges:

The natural bond orbital (NBO) atomic charges calculated in gas phase (

Table 2). The atomic charge gives information about oxidation states of atoms in molecule, which provides important information for the complex formation.

The carbon atoms connected to the high electronegative (F, O, and N) atoms were positive in nature except 45C in Ib compound was contained negative charge. 45C was contained 0.372 and -0.031 charges in Ia and Ib respectively. This may be happened due to high electronegativity of fluorine. Amongst all oxygen and hydrogen atoms the 15O and 16H contained high negative and positive charge respectively. It means the 15O-16H will provide the binding site for metal ion.

**Table 2: NBO charges of Ia and Ib**

Atoms	Ia	Atoms	Ia	Atoms	Ib	Atoms	Ib
1C	0.732	30C	0.017	1C	0.732	30C	0.017
2C	0.382	31H	0.243	2C	0.382	31H	0.243
3C	0.164	32H	0.235	3C	0.164	32H	0.235
4C	0.088	33C	0.199	4C	0.088	33C	0.200
5C	-0.332	34N	-0.053	5C	-0.332	34N	-0.652
6C	-0.149	35O	-0.431	6C	-0.150	35O	-0.429
7C	-0.148	36N	-0.641	7C	-0.148	36N	-0.637
8H	0.239	37H	0.421	8H	0.239	37H	0.422
9C	-0.284	38C	0.162	9C	-0.284	38C	0.174
10C	0.382	39C	-0.225	10C	0.382	39C	-0.227
11H	0.222	40C	-0.245	11H	0.222	40C	-0.246
12H	0.219	41C	-0.258	12H	0.219	41C	-0.224
13O	-0.557	42H	0.216	13O	-0.557	42H	0.217
14O	-0.529	43C	-0.253	14O	-0.530	43C	-0.219
15O	-0.640	44H	0.231	15O	-0.640	44H	0.232
16H	0.473	45C	0.372	16H	0.474	45C	-0.031
17C	-0.625	46H	0.231	17C	-0.625	46H	0.230
18H	0.229	47H	0.232	18H	0.229	47H	0.230
19H	0.229	48F	-0.362	19H	0.229	48C	-0.376
20H	0.226	49C	-0.377	20H	0.226	49C	0.278
21C	0.557	50C	0.278	21C	0.557	50H	0.268
22O	-0.576	51H	0.267	22O	-0.576	51H	0.216
23C	-0.154	52H	0.215	23C	-0.154	52Cl	-0.013
24C	-0.153	53Cl	-0.014	24C	-0.153	53Cl	-0.047
25C	-0.133			25C	-0.133		
26C	-0.235			26C	-0.235		
27H	0.243			27H	0.243		
28C	-0.240			28C	-0.240		
29H	0.240			29H	0.240		

### 3.3 Electronic absorption spectra

The electronic absorption spectra has computed as lowest 20 vertical electronic excitations from the singlet ground state to singlet excited state using TD-DFT and the effect of solvent was simulated by IEFPCM (

Table 3).

In both compounds, polarity of solvent affect on wavelength, and excitation at higher wavelength in DMSO. Decrease in electronegativity of halogen group increases the excited wavelengths in both phases, because as electronegativity decrease the electron cloud slightly shifted towards HOMO and then electron excited to LUMO by low energy<sup>11</sup>.

**Table 3: Electronic absorption data of Ia and Ib in different phases**

Excited state	Gas		Acetonitrile		THF		DMSO	
	$\lambda$ (nm)	f	$\lambda$ (nm)	f	$\lambda$ (nm)	f	$\lambda$ (nm)	f
<b>Ia</b>								
1 <sup>st</sup>	445.78	0.0012	415.97	0.0015	420.78	0.0016	415.36	0.0016
2 <sup>nd</sup>	394.50	0.0002	346.00	0.0051	347.27	0.0011	345.88	0.0053
3 <sup>rd</sup>	340.95	0.0025	340.17	0.0017	343.89	0.0057	340.07	0.0017
4 <sup>th</sup>	327.55	0.0115	329.88	0.0014	330.46	0.0022	330.13	0.0016
5 <sup>th</sup>	312.91	0.0471	311.33	0.0327	311.76	0.0335	311.25	0.0390
6 <sup>th</sup>	309.61	0.0214	301.61	0.2737	302.48	0.2673	302.87	0.2952
7 <sup>th</sup>	303.68	0.0052	292.42	0.0425	294.06	0.0440	292.34	0.0457
8 <sup>th</sup>	293.17	0.1845	288.73	0.0181	290.69	0.0376	288.91	0.0181
9 <sup>th</sup>	276.42	0.0001	269.54	0.1211	268.49	0.1624	269.86	0.1548
10 <sup>th</sup>	271.19	0.0018	269.19	0.0796	268.14	0.0531	269.39	0.0607
11 <sup>th</sup>	268.43	0.0007	265.80	0.0003	267.31	0.0023	265.50	0.0006
12 <sup>th</sup>	265.07	0.1154	263.93	0.5441	263.91	0.5379	264.59	0.5740
13 <sup>th</sup>	262.93	0.0220	257.43	0.0467	258.10	0.0472	257.79	0.0511
14 <sup>th</sup>	261.91	0.0511	255.30	0.0793	255.97	0.0031	255.30	0.0727
15 <sup>th</sup>	261.73	0.0849	253.58	0.0025	255.12	0.0875	253.42	0.0026
16 <sup>th</sup>	259.99	0.3340	251.52	0.0024	254.74	0.0047	251.37	0.0024
17 <sup>th</sup>	257.66	0.0423	247.43	0.0008	249.18	0.0018	247.52	0.0008
18 <sup>th</sup>	255.87	0.0080	239.48	0.2380	240.96	0.0005	239.69	0.2483
19 <sup>th</sup>	250.65	0.0292	237.88	0.0003	240.15	0.2165	237.81	0.0004
20 <sup>th</sup>	248.19	0.0221	236.21	0.0232	237.79	0.0160	236.36	0.0244
<b>Ib</b>								
1 <sup>st</sup>	440.12	0.0012	408.50	0.0016	413.48	0.0016	408.66	0.0017
2 <sup>nd</sup>	388.89	0.0003	346.62	0.0049	344.46	0.0054	346.89	0.0052
3 <sup>rd</sup>	340.72	0.0026	334.70	0.0020	341.65	0.0016	334.58	0.0021
4 <sup>th</sup>	327.44	0.0111	329.95	0.0014	330.61	0.0020	330.05	0.0015
5 <sup>th</sup>	311.28	0.0502	311.33	0.0328	311.83	0.0334	311.51	0.0378
6 <sup>th</sup>	306.61	0.0283	301.44	0.2759	302.24	0.2732	302.62	0.2992
7 <sup>th</sup>	304.38	0.0036	289.07	0.0684	290.85	0.0807	289.21	0.0724
8 <sup>th</sup>	293.08	0.1818	287.98	0.0033	289.75	0.0083	288.09	0.0027
9 <sup>th</sup>	276.28	0.0001	269.87	0.0465	268.77	0.1150	270.15	0.1351
10 <sup>th</sup>	268.58	0.0027	269.61	0.1611	268.67	0.1119	270.04	0.0882
11 <sup>th</sup>	268.38	0.0009	264.76	0.0001	266.41	0.0006	265.19	0.6085
12 <sup>th</sup>	265.32	0.1365	264.45	0.5807	264.44	0.5724	264.82	0.0002
13 <sup>th</sup>	263.40	0.0388	257.07	0.0356	257.68	0.0376	257.32	0.0389
14 <sup>th</sup>	261.95	0.1725	255.53	0.0778	255.86	0.0045	255.66	0.0722
15 <sup>th</sup>	260.75	0.0005	253.54	0.0025	255.42	0.0862	253.49	0.0025
16 <sup>th</sup>	260.39	0.2907	248.35	0.0026	251.66	0.0026	248.42	0.0028
17 <sup>th</sup>	257.96	0.0313	247.37	0.0006	249.08	0.0015	247.24	0.0007
18 <sup>th</sup>	253.81	0.0171	239.92	0.3016	240.68	0.2531	240.18	0.3197
19 <sup>th</sup>	251.06	0.0166	236.64	0.0029	239.65	0.0001	236.59	0.0040
20 <sup>th</sup>	249.58	0.0722	236.09	0.0152	237.57	0.0334	236.09	0.0153

Note:  $\lambda$  = Wavelength and f= Oscillator strength.

### 3.4 Frontier Molecular Orbital

Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are important parameters in quantum chemistry. HOMO is the outermost orbital containing electrons and tends to donate these electrons, while LUMO is the innermost orbital containing free places to accept electrons. The  $\lambda_{\text{max}}$  of compound formed due to excitation of electron from HOMO to LUMO. HOMO and LUMO of Ia and Ib in different phases shown in Fig. 3 and 4 respectively.

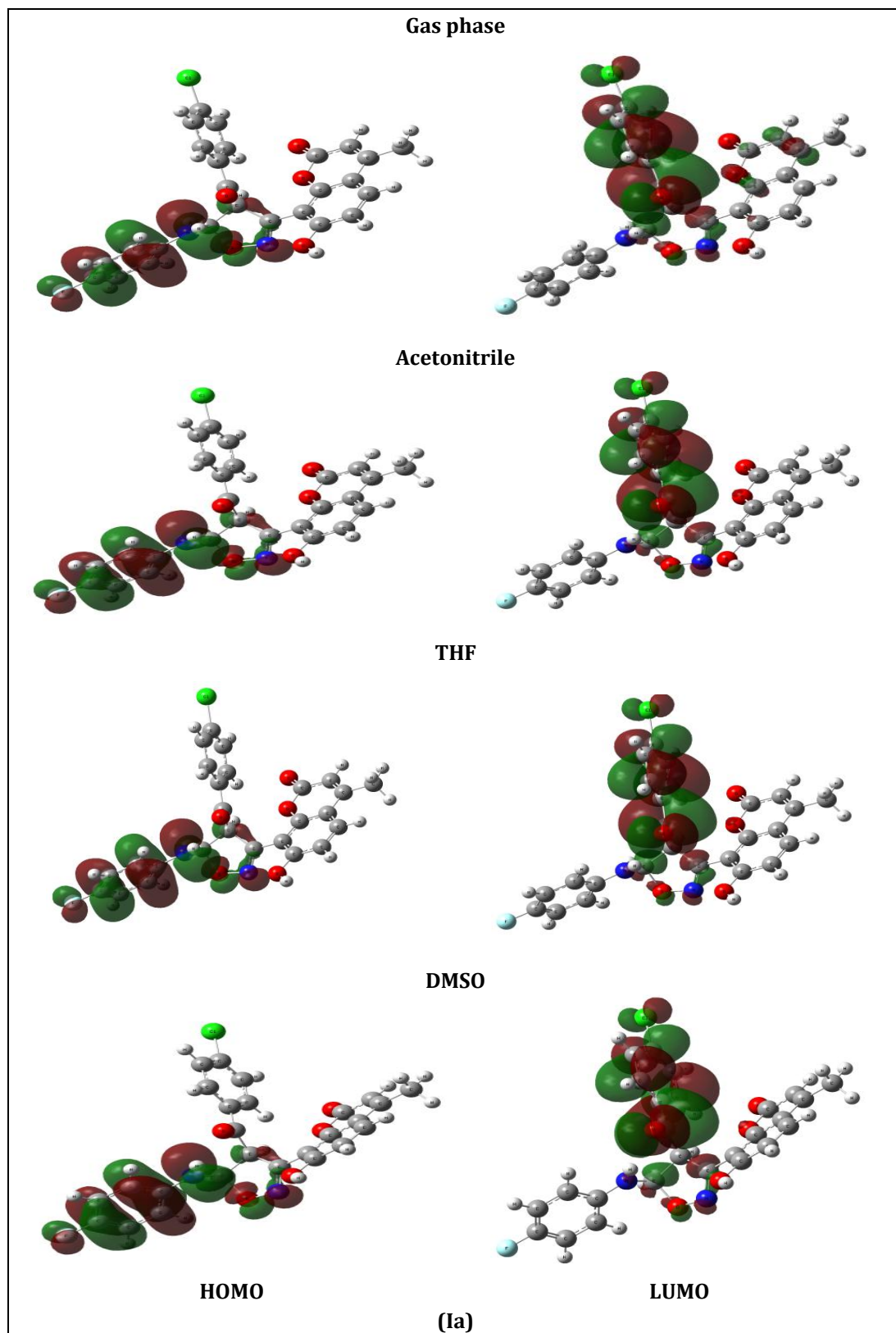


Fig. 3: HOMO and LUMO of Ia (Isodensity value=0.02)

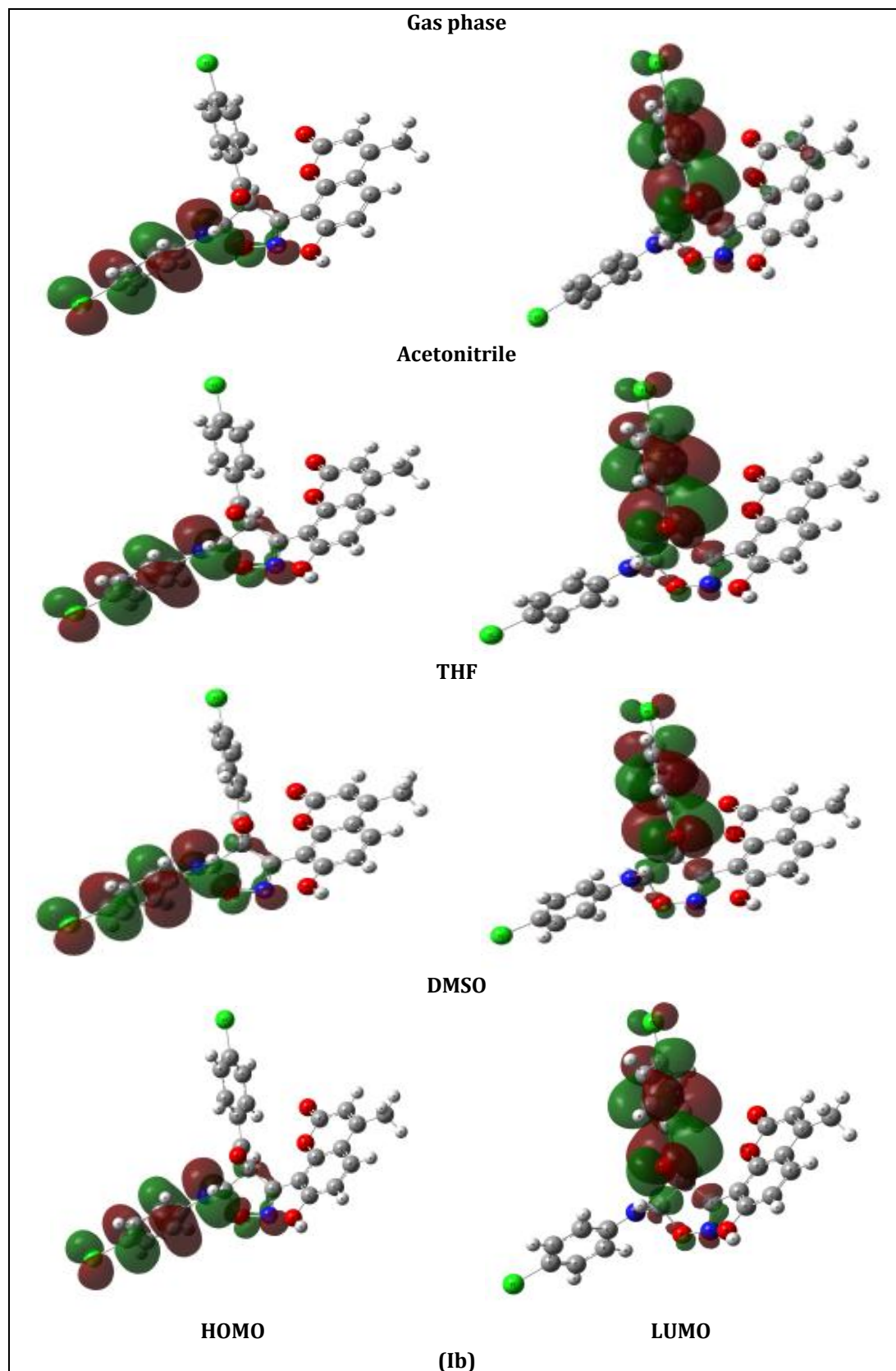


Fig. 4: HOMO and LUMO of Ib (Isodensity value=0.02)



The calculations indicated that the titled compounds have 127 and 131 occupied MOs in Ia and Ib respectively. In gas and solvent phases the HOMO is located on the heterocyclic, fluorophenylamine and chlorophenylamine ring of Ia and Ib. The HOMO was formed due to the  $\pi$  bonding and non-bonding electron density of fluoro/chloro-phenylamine and heterocyclic ring. LUMO is located over the chlorobenzoyl ring, heterocyclic ring and slightly on coumarine ring in gas phase. HOMO-LUMO transition of both molecules in gas phase implies an electron density transfer to the chlorobenzoyl ring. In solvent phase the LUMO is located over the chlorobenzoyl ring and heterocyclic ring and it increases the acceptor character of the ring.

The calculated HOMO-LUMO gap for the compounds at the 6-311g level is in the range 0.1306 - 0.1401 eV in different phases.

The molecular orbital energy gap was very important to study the photo-physics and kinetic stability of isoxazoline. E (LUMO), E (HOMO) and molecular orbital energy gap of Ia and Ib were shown in

Table 4 in different phase.

A large HOMO-LUMO gap implies high kinetic stability and low chemical reactivity because it is energetically unfavorable to add electrons to a high-lying LUMO. Meanwhile, a molecule with a small frontier orbital gap is more polarizable, is generally associated with a high chemical reactivity, low kinetic stability and is termed as soft molecule<sup>29</sup>.

In both compounds, the energy of LUMO is low in THF solvent than other solvents. This is may be due to the interaction of non-bonding orbital of oxygen atom and carbonyl group of coumarin ring with LUMO. Hence, it affects to lower the energy gap.

The energy gap was lowest in gas phase and in solvent phases showed the following order.

$$\Delta E_{\text{THF}} < \Delta E_{\text{Acetonitrile}} < \Delta E_{\text{DMSO}}.$$

This may be happened due to polarity order of solvents.

The important properties like global hardness ( $\eta$ ), global softness ( $\sigma$ ), electronegativity ( $\chi$ ), chemical potential ( $\mu$ ), and electrophilicity index ( $\omega$ ) were calculated by using these HOMO-LUMO energy values.

**The hardness ( $\eta$ )** of a species:  $\eta = (E_{\text{LUMO}} - E_{\text{HOMO}})/2$  is a qualitative indication of how polarizable it is.

**The softness ( $\sigma$ )** is the reciprocal of the hardness:  $\sigma = 1/\eta$ <sup>30-32</sup>.

**Electronegativity** is the tendency of molecules to attract electrons:

$$\chi = -(E_{\text{LUMO}} + E_{\text{HOMO}})/2.$$

**Chemical potential** is defined as the first derivative of the total energy with respect to the number of electrons in a molecule<sup>33</sup>, chemical potential is simply the negative of electronegativity value;  $\mu = -\chi$ .

**Electrophilicity index** is a measure of the electrophilic power of a molecule and it can be measured through the equation:

$$\omega = (\mu^2/2\eta)^{34}$$

In gas phase the Ia was soft molecule, having low electronegativity, high chemical potential and high electrophilicity index. Ib showed high electronegativity, higher hardness, low chemical potential and low electrophilicity index. But in solvent phases, Ia in THF solvent showed higher hardness, low electronegativity, high chemical potential and high electrophilicity index; that showed the solvent effect over the energy gap.

As compared to Ia the Ib was soft molecule having high electronegativity; it means solvent increases the electronegativity, softness and decreases the hardness, chemical potential, and electrophilicity index.

**Table 4: Energy gap (a.u.) for Ia and Ib.**

Solvent	E <sub>LUMO</sub>	E <sub>HOMO</sub>	$\Delta E$	$\eta$	$\sigma$	$\chi$	$\mu$	$\omega$
<b>Ia</b>								
Gas phase	-0.0886	-0.2192	0.1306	-0.0653	-15.3139	0.1539	-0.1539	-0.00077
Acetonitrile	-0.0899	-0.2284	0.1385	-0.06925	-14.4404	0.15915	-0.15915	-0.00088

THF	-0.0894	-0.2266	0.1372	-0.0686	-14.5773	0.15800	-0.15800	-0.00086
DMSO	-0.0898	-0.2285	0.1387	-0.06935	-14.4196	0.15915	-0.15915	-0.00088
<b>Ib</b>								
Gas phase	-0.0903	-0.2215	0.1312	-0.0656	-15.2439	0.1559	-0.1559	-0.0008
Acetonitrile	-0.0905	-0.2306	0.1401	-0.07005	-14.2755	0.16055	-0.16055	-0.0009
THF	-0.0902	-0.2288	0.1386	-0.0693	-14.4300	0.1595	-0.1595	-0.00088
DMSO	-0.0906	-0.2306	0.1400	-0.0700	-14.2857	0.1606	-0.1606	-0.0009

### 3.5 Vibration mode

The molecules have  $C_1$  point group symmetry and hence, all the calculated frequency transforming to the same symmetry species (A). Both the molecule consists of 53 atoms and has 153 normal modes of vibrations. The IR spectra were calculated by Gaussian using PBE1PBE 6311g basis set. The calculated IR spectra were compared with reported values. Table 5 presents the calculated frequencies and reported values. We have compared our calculated values with reported values<sup>35</sup>. Some difference is seen in between calculated spectra and reported values.

**Table 5: IR spectral data of Ia and Ib**

Type	Vibration mode	Frequency (cm <sup>-1</sup> )		
		Ia	Ib	Reported
Isoxazoline ring	N-O str.	907.253	906.468	850-800
	C=N str.	1629.06	1629.28	1690-1640
Amine	N-H str.	3593.78	3589.69	3400-3200
Phenolic OH	O-H str.	3759.69	3759.63	3200-3600
	O-H def. (out of plane)	357.373	357.637	290-320
	O-H def. (in plane)	1221.44	1221.14	1150-1250
Carbonyl	C=O Str.	1664.64	1676.16	1650-1800

The heterocyclic ring stretching mode of N-O and C=N was observed at 907.253 cm<sup>-1</sup> and 1629.06 cm<sup>-1</sup> for Ia and 906.468 cm<sup>-1</sup> and 1629.96 cm<sup>-1</sup> for Ib respectively. Other characteristic vibration modes of compounds are N-H stretching and O-H stretching. N-H stretching mode was observed in the region 3589.69-3593.78 cm<sup>-1</sup> and O-H stretching mode was observed in the region 3759.63-3759.69 cm<sup>-1</sup> for both compounds respectively. The O-H deformed out of plane vibration observed at 357.373-357.637 cm<sup>-1</sup> and O-H in plane bending vibration observed in the region 1221.14-1221.44 cm<sup>-1</sup> for Ia and Ib respectively. The C=O stretching mode was observed at 1664.64 and 1676.16 cm<sup>-1</sup> for Ia and Ib and is in good agreement with reported wave numbers.

### 3.6 Thermo-chemical study

The thermo-chemical parameters were calculated to their ideal gas state at 298.15 K and 101.325 kPa for Ia and Ib. The thermodynamic parameters including total electronic energy ( $E_t$ ), enthalpy ( $H^\theta$ ), entropy ( $S^\theta$ ), Gibbs free energy ( $G^\theta$ ) and standard heat capacity at constant volume ( $C_v^\theta$ ) were obtained from the Gaussian frequency output files (Table 6). The equations used for computing thermo-chemical data in Gaussian programs have derived from statistical thermodynamics<sup>36</sup>. The thermal energy ( $E_{thermal}$ ) calculated as the sum of zero-point energy and thermal energy corrections for molecular translation ( $E_{trans}$ ), rotation ( $E_{rot}$ ), and vibration ( $E_{vib}$ ). The enthalpy ( $H^\theta$ ) was obtained by adding  $RT$  to the total electronic energy ( $E_t$ ) and thermal energy at 298.15 K and 101.325 kPa.

**Table 6: Thermo-dynamical properties of Ia and Ib**

Thermo-dynamical Properties	Ia	Ib
$E_t$ (Hartree)	266.191	265.635
$H^\theta$ (Hartree)	-2044.7789	-2405.0600
$G^\theta$ (Hartree)	-2044.8716	-2405.1616
$C_v^\theta$ (cal/mole- K)	112.762	113.564
$S^\theta$ (cal/mole- K)	195.001	197.620

With decrease in electronegativity of halogen group, the values of  $E_t$ ,  $H^\theta$ , and  $G^\theta$  decreased and the value of  $C_v^\theta$  and  $S^\theta$  increased. It has known that the compounds with higher free energies are less stable than



those with lower free energies. The Ib was more stable because it has low free energy i.e. -2405.1616 Hartree.

#### 4. CONCLUSION

Some conclusive remarks can be derived from the results obtained from density functional theory calculations. The electronic structure, thermo-dynamical properties and spectroscopic properties were satisfactorily explained by DFT with PBE1PBE function using 6-311g basis set. DFT explained the solvent effects on energy gap, hardness, softness of molecule, electronegativity, electrophilicity index. From these properties the Ia was soft molecule and highly electronegative. Less polar solvent (THF) increases the electronegativity and softness of molecules. With decrease in electronegativity of halogen group the values of  $E_b$ ,  $H^o$ , and  $G^o$  decreased and the value of  $C^o_v$  and  $S^o$  increased.

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#### SUPPLEMENTARY INFORMATION

Table S1:

#	Symbol	NA	NB	NC	Bond	Angle	Dihedral	X	Y	Z
1	C							-3.5458050	-0.1877180	1.6912250
2	C	1			2.4538758			-2.3659880	-1.7927800	0.2582860
3	C	2	1		1.4034355	91.3964111		-3.5761110	-2.2449990	-0.2901040
4	C	3	2	1	1.4486988	118.5437556	-1.0043287	-4.8131990	-1.6609470	0.1865770
5	C	4	3	2	1.3600675	119.4269984	0.7061598	-4.7704810	-0.6870480	1.1349860
6	C	2	1	5	1.3959764	145.0255873	-178.3923853	-1.1169530	-2.3005800	-0.1033780
7	C	3	2	1	1.4040841	117.1877144	179.5307004	-3.5016880	-3.2519780	-1.2657610
8	H	5	4	3	1.0796038	121.4799527	179.8573095	-5.6716490	-0.2274830	1.5121340
9	C	7	3	2	1.3806704	120.8597672	-0.1363722	-2.2828210	-3.7651940	-1.6622750
10	C	6	2	1	1.4001529	117.1009107	-179.1337829	-1.0935120	-3.2935980	-1.0901880
11	H	7	3	2	1.0809451	119.7616828	179.9510525	-4.4084580	-3.6315950	-1.7153180
12	H	9	7	3	1.0830154	120.1089905	-179.3938499	-2.2389370	-4.5348400	-2.4229600
13	O	1	5	4	1.2270376	127.7201835	177.5996028	-3.4069230	0.7107730	2.5152680
14	O	2	1	13	1.3798334	29.0614815	3.4465528	-2.3602200	-0.8014200	1.2180320
15	O	10	6	2	1.3668765	117.4360545	178.1065748	0.1285650	-3.7674570	-1.4779210
16	H	15	10	6	0.9684751	112.6912788	-178.7357687	0.0657750	-4.4361450	-2.1756730
17	C	4	3	2	1.4969836	119.7618031	-179.2806539	-6.1206050	-2.1344250	-0.3679210
18	H	17	4	3	1.0930918	111.1441157	-59.6587179	-6.1696890	-1.9795950	-1.4488780
19	H	17	4	3	1.0930939	111.1230065	59.8226426	-6.2623790	-3.2027230	-0.1849080
20	H	17	4	3	1.0883552	110.9800330	-179.9208196	-6.9529830	-1.6009700	0.0871500
21	C	6	2	1	3.1177078	94.5105714	-49.7491878	0.1643280	0.5042740	-0.5629590
22	O	21	6	2	1.2490982	86.9593519	-128.8465134	0.5345470	0.0788850	-1.6775120
23	C	21	6	2	1.4748927	126.3520733	-2.8578154	-0.5197620	1.8063720	-0.4540090
24	C	23	21	6	1.4013481	123.4621164	57.0201391	-1.1807250	2.2374430	0.7040420
25	C	23	21	6	1.4045780	117.4640754	-122.0728483	-0.5144170	2.6376550	-1.5861660
26	C	24	23	21	1.3916968	120.5200478	-178.9848025	-1.8248400	3.4707810	0.7325580
27	H	24	23	21	1.0801598	121.7134220	-2.2322141	-1.2546080	1.6121730	1.5817230
28	C	25	23	21	1.3861191	120.8553835	179.8572105	-1.1386090	3.8750520	-1.5625190
29	H	25	23	21	1.0811403	118.3929295	-0.2210762	-0.0102920	2.2897330	-2.4770490
30	C	26	24	23	1.3860366	118.8689809	-0.8465219	-1.7860830	4.2722650	-0.3975830
31	H	26	24	23	1.0795544	120.2957195	178.3965605	-2.3548080	3.7880530	1.6179450
32	H	28	25	23	1.0800216	121.0600321	179.3226541	-1.1272530	4.5215070	-2.4276280
33	C	6	2	1	1.4653230	120.5005838	0.2819407	0.1038590	-1.7912550	0.5270010
34	N	33	6	2	1.2910871	121.2970386	126.7156403	0.9556570	-2.5882310	1.0803320
35	O	34	33	6	1.4213179	108.9717793	-179.9594181	2.0314670	-1.8222190	1.6056920
36	N	35	34	33	2.4265741	108.3183749	-50.1166922	2.8208230	-0.3238400	-0.1321340
37	H	36	35	34	1.0093251	113.9001990	-8.4310400	2.4118950	-0.4973310	-1.0384540
38	C	36	35	34	1.3966787	109.7899368	-144.2977642	4.2068120	-0.1792090	-0.0381780
39	C	38	36	35	1.4037846	119.0998359	158.2269529	4.9273040	0.2423400	-1.1668050
40	C	38	36	35	1.4023439	121.8372697	-22.3834051	4.8976230	-0.4312720	1.1558960
41	C	39	38	36	1.3892202	120.6975017	178.8799280	6.3037550	0.4194770	-1.1040530
42	H	39	38	36	1.0826441	119.4055772	-0.3224615	4.3990520	0.4427730	-2.0903280
43	C	40	38	36	1.3930605	120.2998273	-177.7584968	6.2745360	-0.2320180	1.2267900
44	H	40	38	36	1.0805244	120.0949395	5.4580300	4.3726260	-0.8309340	2.0115720
45	C	43	40	38	1.3809426	119.0224651	-1.3598083	6.9495640	0.1889250	0.0980090
46	H	41	39	38	1.0805288	121.3665834	179.9836897	6.8690280	0.7433030	-0.9661120
47	H	43	40	38	1.0805161	121.0856778	-179.8073834	6.8199320	-0.4251450	2.1393470

48	F	45	43	40	1.3942744	119.0097253	-179.4305591	8.3294570	0.3767280	0.1660260
49	C	21	6	2	1.5089788	58.0846506	104.5509762	0.4714240	-0.3220680	0.6617320
50	C	36	35	34	1.4007516	35.3986541	95.4166588	1.9795830	-0.4375090	0.9820920
51	H	49	21	6	1.0883253	111.5183938	-105.0683318	-0.0345360	0.0672420	1.5431480
52	H	50	36	35	1.0878631	111.6243269	115.4996215	2.2977820	0.2143440	1.7928220
53	Cl	30	26	24	1.7996802	119.0913136	-179.6032030	-2.6078580	5.8730100	-0.3636700

Table S2:

#	Symbol	NA	NB	NC	Bond	Angle	Dihedral	X	Y	Z
1	C							-3.8212330	-0.1578920	1.7030230
2	C	1			2.4538495			-2.6631330	-1.7731980	0.2639370
3	C	2	1		1.4033773	91.4029606		-3.8797320	-2.2129770	-0.2800750
4	C	3	2	1	1.4487576	118.5386610	-1.0257251	-5.1091540	-1.6174790	0.2024210
5	C	4	3	2	1.3600686	119.4236334	0.7219018	-5.0529600	-0.6450170	1.1516030
6	C	2	1	5	1.3959235	145.0334218	-178.3564243	-1.4207950	-2.2932280	-0.1031700
7	C	3	2	1	1.4041000	117.1867029	179.5196471	-3.8189930	-3.2195730	-1.2570970
8	H	5	4	3	1.0795995	121.4774369	179.8589506	-5.9480410	-0.1771750	1.5330330
9	C	7	3	2	1.3807056	120.8694916	-0.1314116	-2.6068530	-3.7444240	-1.6590870
10	C	6	2	1	1.4001074	117.1247102	-179.1341017	-1.4107400	-3.2853940	-1.0909990
11	H	7	3	2	1.0809452	119.7526622	179.9604734	-4.7312750	-3.5896350	-1.7034580
12	H	9	7	3	1.0829942	120.1110244	-179.3905210	-2.5736280	-4.5135680	-2.4207890
13	O	1	5	4	1.2269786	127.7331271	177.5525467	-3.6699640	0.7388440	2.5267090
14	O	2	1	13	1.3797435	29.0713500	3.5015816	-2.6434620	-0.7828830	1.2244480
15	O	10	6	2	1.3668203	117.4201233	178.0996607	-0.1946830	-3.7705050	-1.4835170
16	H	15	10	6	0.9684735	112.7160619	-178.8729412	-0.2660550	-4.4394390	-2.1802050
17	C	4	3	2	1.4969562	119.7636881	-179.2541486	-6.4234080	-2.0778770	-0.3468040
18	H	17	4	3	1.0930874	111.1504620	-59.6397253	-6.4756450	-1.9219980	-1.4274580
19	H	17	4	3	1.0930937	111.1187337	59.8452487	-6.5747620	-3.1448400	-0.1636760
20	H	17	4	3	1.0883475	110.9800653	-179.9030117	-7.2486240	-1.5366260	0.1120710
21	C	6	2	1	3.1186247	94.6129634	-49.7714818	-0.1081460	0.4972950	-0.5676630
22	O	21	6	2	1.2492903	87.2549313	-129.2036817	0.2620170	0.0708150	-1.6820330
23	C	21	6	2	1.4745326	125.9684564	-3.1185299	-0.7860610	1.8022070	-0.4586570
24	C	23	21	6	1.4014347	123.4710084	57.2846543	-1.4402180	2.2388510	0.7012740
25	C	23	21	6	1.4046904	117.4590710	-121.8539387	-0.7812260	2.6313550	-1.5925200
26	C	24	23	21	1.3916054	120.5209147	-179.0274937	-2.0781150	3.4753100	0.7299480
27	H	24	23	21	1.0801446	121.7280947	-2.2628063	-1.5135650	1.6159810	1.5806860
28	C	25	23	21	1.3860358	120.8541817	179.8848915	-1.3994480	3.8716510	-1.5687990
29	H	25	23	21	1.0811334	118.4009613	-0.1990318	-0.2821990	2.2795220	-2.4847280
30	C	26	24	23	1.3860874	118.8725931	-0.8370603	-2.0402550	4.2743640	-0.4020050
31	H	26	24	23	1.0795512	120.2911233	178.4055983	-2.6027580	3.7969170	1.6169370
32	H	28	25	23	1.0800172	121.0563838	179.3299624	-1.3885050	4.5163060	-2.4352500
33	C	6	2	1	1.4653595	120.4874953	0.3364453	-0.1926510	-1.7975820	0.5239470
34	N	33	6	2	1.2909350	121.2946972	126.4599670	0.6503460	-2.6037600	1.0770710
35	O	34	33	6	1.4223610	108.9413518	-179.9243415	1.7364820	-1.8486760	1.5998210
36	N	35	34	33	2.4236763	108.2244472	-50.2531379	2.5399590	-0.3694320	-0.1438730
37	H	36	35	34	1.0095603	114.4485684	-7.4997819	2.1219630	-0.5253350	-1.0495140
38	C	36	35	34	1.3931080	109.8582215	-144.0719492	3.9247140	-0.2441240	-0.0572620
39	C	38	36	35	1.4036948	119.1793808	156.7800946	4.6503560	0.1337350	-1.1978870
40	C	38	36	35	1.4021557	121.9479257	-23.8209161	4.6168770	-0.4724290	1.1405810
41	C	39	38	36	1.3884528	120.7804549	178.6685592	6.0282560	0.2952650	-1.1422020
42	H	39	38	36	1.0828137	120.4757325	-0.4608018	4.1255150	0.3144490	-2.1276020
43	C	40	38	36	1.3923818	120.3733535	-177.7059942	5.9960860	-0.2915650	1.2022080
44	H	40	38	36	1.0806098	120.2202939	5.5632582	4.0920520	-0.8411860	2.0102330
45	C	43	40	38	1.3846964	119.4699778	-1.2503595	6.6845380	0.0910040	0.0633230
46	H	41	39	38	1.0804853	120.4890802	-179.9236600	6.5820000	0.5874470	-2.0227960
47	H	43	40	38	1.0804507	120.1956294	-179.8155113	6.5269730	-0.4711840	2.1259340
48	C	21	6	2	1.5092408	58.0752394	104.4744557	0.1927850	-0.3324090	0.6566080
49	C	36	35	34	1.4025970	35.3931711	95.5502555	1.6994390	-0.4677820	0.9746670
50	H	48	21	6	1.0883296	111.5074164	-105.0449325	-0.3065710	0.0628880	1.5391300
51	H	49	36	35	1.0878408	111.6349978	115.6086969	2.0274890	0.1840750	1.7814280
52	Cl	30	26	24	1.7993443	119.0929944	-179.6085007	-2.8540160	5.8788180	-0.3679410
53	Cl	45	43	40	1.8098220	119.4145249	-179.5778749	8.4787690	0.3145020	0.1423130

## REFERENCES

1. Basappa, Sadashiva MP, Mantelingu K, Nanjunda Swamy S and Rangappa KS. Solution-phase synthesis of novel  $\Delta^2$ -isoxazoline libraries via 1,3dipolar cycloaddition and their antifungal properties. *Bioorg Med Chem*. 2003;11(21):4539-4544.
2. Gaonkar SL, Lokanatha Rai KM and Prabhuswamy B. Synthesis of novel 3-[5-ethyl-2-(2-phenoxyethyl) pyridin]-5-substituted isoxazoline libraries via 1,3dipolar cycloaddition and evaluation of antimicrobial activities. *Med Chem Res*. 2007;15:407-417.
3. Taylor EC and Patel HH. Synthesis of pyrazolo 3,4-d pyrimidine analogues of the potent agent N-4-2-2-amino-4 3H-oxo-7H-pyrrolo 2,3-d pyrimidin-5-yl ethyl benzoyl-L-glutamic acid. *Tetrahedron*. 1992;48:8089-8100.
4. Chen YL, Zhao YL, Lu CM, Tzenga CC and Wang JP. Synthesis, cytotoxicity, and anti-inflammatory evaluation of 2-(furan-2-yl)-4-(phenoxy)quinoline derivatives. Part 4 *Bioorg Med Chem*. 2006;14:4373-4378.
5. Jayashankar B, Lokanath Rai KM, Baskaran N and Sathish HS. Synthesis and pharmacological evaluation of 1,3,4-oxadiazole bearing bis(heterocycle) derivatives as anti-inflammatory and analgesic agents. *Eur J Med Chem*. 2009;44:3898-3902.
6. Edwin W and Lilianna B. Synthesis and pharmacological assessment of derivatives of isoxazolo[4,5-d]pyrimidine. *Bioorg Med Chem*. 2004;12:265-272.
7. Palaska E, Aytemir M, Uzbay IT and Erol D. *Eur J Med Chem*. 2001;36:539-543.
8. Manna F, Chimenti F, Balasco A, Cenicola ML, Amico M, Parrilo C, Rossi F and Marmo E. anti-inflammatory, analgesic and antioytratic N-acetyl- $\Delta^2$ -pyrazolines and dihydrothienocoumarines. *Eur J Med Chem*. 1992;27:633-639.
9. Shi L, Hu R, Wei Y, Liang Y, Yang Z and Ke S. Anthranilic acid-based diamides derivatives incorporating aryl-isoxazoline pharmacophore as potential anticancer agents: design, synthesis and biological evaluation. *Eur J Med Chem*. 2012;54:549-556.
10. Kamal JS, Reddy MJ, Ramaiah D, Dastagiri EV, Bharathi MA, Azhar F, Sultana SNCVL, Pushpavalli M, Pal-Bhadra A, Juvekar S, Sen S and Zingde. Design, synthesis and biological evaluation of 3,5-diaryl-isoxazoline/ isoxazole-pyrrolobenzodiazepine conjugates as potential anticancer agents. *Eur J Med Chem*. 2010;45:3924-3937.
11. Jadhao NU and Naik AB. Effect of electronegativity on structural, spectrophotometric and thermochemical properties of fluorine and chlorine substituted isoxazoles by DFT method. *Cogent Chemistry*. 2017;3(1):1296342.
12. Hohenberg P and Kohn W. Inhomogeneous electron gas. *Phys Rev*. 1964;136:B864.
13. Kohn W and Sham LJ. Self-consistent equations including exchange and correlation effects. *Phys. Rev*. 1965;140:A1133.
14. Slater JC. Quantum theory of molecular and solids. vol. 4: the self-consistent field for molecular and solids. McGraw-Hill. 1974, New York.
15. Pople JA, Gill PMW and Johnson BG. Kohn-Sham density-functional theory within a finite basis set. *Chem Phys Lett*. 1992;199(6):557-560.
16. Becke AD. Density functional thermochemistry. III. The role of exact exchange. *J Chem Phys*. 1993;98(7):5648-5652.
17. Perdew JP, Burke JK and Ernzerhof M. Generalized gradient approximation made simple. *Phys Rev Lett*. 1996;77:3865-3868.
18. Perdew JP, Burke JK and Ernzerhof M. Generalized gradient approximation made simple. *Phys Rev Lett*. 1997;78:1396.
19. McLean AD and Chandler GS. Contracted Gaussian basis sets for molecular calculations. I. Second row atoms, Z = 11-18. *J Chem Phys*. 1980;72:5639-5648.
20. Krishnan R, Binkley JS, Seeger R and Pople JA. Self-consistent molecular orbital methods. XX. A basis set for correlated wave functions. *J Chem Phys*. 1980;72:650-654.
21. Binning Jr. RC and Curtiss LA. Compact contracted basis sets for third-row atoms: gallium-krypton. *J Comp Chem*. 1990;11:1206-1219.
22. McGrath MP and Radom L. Extension of Gaussian-1(G1) theory of the bromine containing molecules. *J Chem Phys*. 1991;94:511-516.
23. Curtiss LA, McGrath MP, Blaudeau JP, Davis Jr. NE, Binning RC and Radom L. Extension of Gaussian-2 theory to molecules containing third-row atoms Ga-Kr. *J Chem Phys*. 1995;103:6104-6113.
24. Stratmann RE, Scuseria GE and Frisch MJ. An efficient implementation of time-dependent density-functional theory for the calculation of excitation energies of large molecules. *J Chem Phys*. 1998;109: 8218-8224.

25. Bauernschmitt R and Ahlrichs R. Treatment of electronic excitations within the adiabatic approximation of time dependent density functional theory. *Chem Phys Lett.* 1996;256:454-464.
26. Casida ME, Jamorski C, Casida KC and Salahub DR. Molecular excitation energies to high-lying bound states from time-dependent density-functional response theory: Characterization and correction of the time-dependent local density approximation ionization threshold. *J Chem Phys.* 1998;108(11):4439-4449.
27. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery JA Jr., Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C and Pople JA. Gaussian 03, Revision D. 01, Gaussian, Inc., Wallingford CT, 2004.
28. Wolinski K, Hilton JF and P. Efficient implementation of the gauge-independent atomic orbital method for NMR chemical shift calculations. *J Am Chem Soc.* 1990;112: 8251-8260.
29. Fleming I. *Frontier orbitals and organic chemical reaction.* 1976, New York: John Wiley and Sons.
30. Gázquez JL, Martínez A and Méndez F. Relationship between energy and hardness differences. *J Phys Chem.* 1993;97:4059-4063.
31. Pearson RG. Hard and soft acids and bases. *J Am Chem Soc.* 1963;85:3533-3539.
32. Pearson RG. Acids and bases. *Science.* 1966;151:172-177.
33. Kavitha E, Sundaraganesan N and Sebastian S. Molecular structure, vibrational spectroscopic and HOMO-LUMO studies of 4-nitroaniline by density functional method. *Ind J Pure App Phy.* 2010; 48:20-30.
34. Parr RG, Szentpály LV and Liu S. Electrophilicity index. *J Am Chem Soc.* 1999;121:1922-1924.
35. Silverstein RM, Bassler GC and Morrill TC. *Spectrometric identification of organic compounds.* New York: 1981, 4th Ed.: John Wiley and Sons.
36. Foresman JB and Frisch E. *Exploring chemistry with Electronic structure method: A Guide to Using Gaussian.* 1996;Pittsburg, PA.