Available online at www.elixirpublishers.com (Elixir International Journal)

Vibrational Spectroscopy

Elixir Vib. Spec. 96 (2016) 41547-41558

ISSN: 2229-712X

Elucidating Frontier Molecular Orbitals, NLO, Toxicity Risks and Pharmacokinetic Properties of Five-Membered Heterocyclics : In Silico Approach

A. Prabaharan and R. John Xavier*

Department of Physics, Periyar EVR College (Autonomous), Tiruchirappalli – 620 023, India.

ARTICLE INFO

Article history:

Received: 8 June 2016;

Received in revised form:

6 July 2016;

Accepted: 12 July 2016;

Keywords

FMO,

NLO,

DFT,

Drug Likeness,

Drug Score.

ABSTRACT

In silico studies have been helpful in identifying the potential lead molecules with reduced cost. The chemical structure of a drug determines its physicochemical properties, and further determinates its absorption, distribution, metabolism, excretion and toxicity properties and ultimately affect the pharmacological activity. Medical chemists can regulate the pharmacological activity of drug molecule by modifying their structure. Unsaturated (contain two double or triple bonds), partially unsaturated (contain at least one double or triple bond) and saturated(contain no double bond or triple bonds) ring systems are important components of a drug. In this study, a serious of 27 five-membered heterocyclics were subjected to frontier molecular orbital(FMO) analysis and nonlinear optical(NLO) property identification by using density functional theory(DFT) calculations. DFT based global reactivity descriptor calculations have emerged as powerful tools for studying the reactivity, selectivity and stability of chemical and biological systems. Molecular orbital analysis exhibits relatively high(low) energy gap of the studied molecules, indicating that it would be kinetically stable(unstable). Pharmacokinetic properties and toxicity risks were studied using various programs like OSIRIS and Molsoft. In addition, we also verified the drug score, which combines drug likeness, cLogP, LogS, molecular weight(MW), and toxicity risks in one value and this may be used to judge the compounds overall potential to qualify for a drug.

© 2016 Elixir all rights reserved.

1. Introduction

Organic compounds can have a variety of structures. These structures can be acyclic or cyclic. The cyclic systems containing only carbon atoms are called carbocyclic and the cyclic systems containing carbons and at least one other element are called heterocyclic. Though a number of heteroatoms are known to be part of the heterocyclic rings, the most common heteroatoms are nitrogen, oxygen or sulfur. A heterocyclic ring may contain one or more heteroatoms which may or may not be same [1-3]. Also, the rings may be unsaturated (contain two double or triple bonds), partially unsaturated (contain at least one double or triple bond) and saturated (contain no double bond or triple bonds). Nitrogen heterocyclics have paved special attention in pharmaceutical chemistry, due to their diverse medicinal potentials [4]. The chemical structure of a drug determines its physicochemical properties, and further determinates its absorption, distribution, metabolism, excretion and toxicity (ADMET) properties and ultimately affect the pharmacological activity of the drug molecule. The relationship between chemical structure and physicochemical properties has attracted the attention of medicinal chemists as a new drug research and development strategy that complements the structure-activity relationships in the progress of drug design and discovery [5, 6]. In silico approaches are now widely used to study the important parameters that may guide medicinal chemist in evaluating chemical and physicochemical properties of a compound. As these parameters influence pharmacokinetic properties, the main objective of the *in silico* studies is to avoid unnecessary expenses associated with biological assays of compounds with a high probability of presenting future pharmacokinetic problems, and thus save time and investments. In the present investigation a serious of 27 five-membered heterocyclics were subjected to frontier molecular orbital(FMO) analysis, nonlinear optical(NLO) activity, toxicity risks and pharmacokinetic properties calculated using Gaussian 09W [7], OSIRIS [8] and Molsoft [9] programs which estimate both physically significant descriptors and pharmaceutically relevant properties.

2. Materials and methods

The molecular structures of the 27 five-membered heterocyclics were obtained from PubChem [10] database as shown in Fig. 1. All the calculations are performed by using Gauss view 5.0 [11] molecular visualization program and Gaussian 09W [7] program package on the personal computer. The molecular structures of the title compounds in the ground state were optimized by using DFT/B3LYP method with 6-311++G(d,p) basis set. The FMO surfaces were visualized by Chemcraft [12] molecular visualization program. The FMO and hyperpolarizability(β) values of the molecules were taken from the Gaussian 09W [7] output file. Computation of molecular descriptors such as molecular weight(MW), cLogP and a number of hydrogen bond acceptors-donors were carried out using OSIRIS [8] and Molsoft [9] programs.

Tele: +91 431 2780286, +91 94430 73908.

E-mail address: rj_xavier@yahoo.com

© 2016 Elixir All rights reserved

Using these parameters the compounds were checked for their compliance with the Lipinski's rule of five. toxicity risk assessment, drug likeness and overall drug score for all the selected heterocyclics were computed using OSIRIS [8] program.

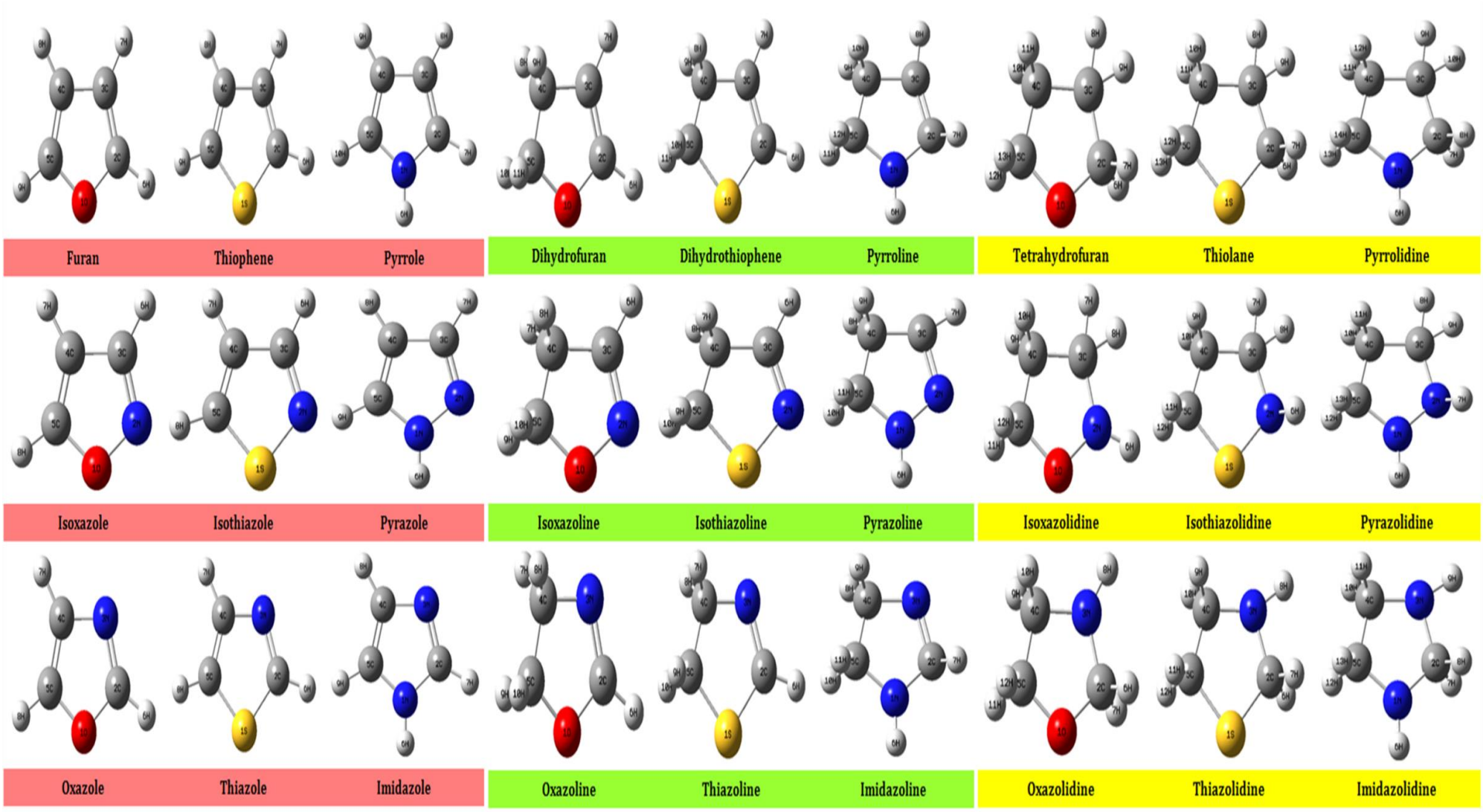

Fig 1. Molecular structures of selected(Unsaturated, Partially Unsaturated and Saturated) heterocyclics.

3. Results and Discussion

3.1 Frontier Molecular Orbital Analysis

The most commonly used theory by chemist is the molecular orbital (MO) theory. The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital(LUMO) are named as FMO. These orbitals take part in an imperative function in the electronic/optical properties and determine the way the molecule interacts with other species. The energy difference between HOMO and LUMO orbital is called as energy gap. The HOMO energy designates the electron donating ability while the LUMO designates the electron accepting ability and the gap between HOMO-LUMO characterizes the molecular chemical stability [13]. The eigenvalues of HOMO and LUMO and their energy gap reflect the biological activity of the molecule [14]. The stability of structures has been explained by energy gap between HOMO and LUMO and this gap helps to characterize some significant issues including the kinetic stability besides chemical reactivity of the molecule. The compound with a small energy gap is more accountable for low kinetic stability and high chemical reactivity. The electronic absorption corresponds that is mainly described by one electron excitation from HOMO to LUMO for these values increase molecule becomes more stable and decreases the intermolecular charge transfer which makes the compound be NLO active [15-17]. For understanding various aspects of pharmacological sciences including drug design and the possible ecotoxicological characteristics of the drug molecules, several new chemical reactivity descriptors have been proposed. The chemical reactivity and site selectivity of the molecular system have been determined by the conceptual density functional theory highly successful in predicting global reactivity trends. The HOMO and LUMO energies for selected heterocyclics obtained by DFT/B3LYP method with 6-311++G(d,p) basis set are presented in Table 1. The stability index [18] defined as the ratio between the HOMO and LUMO energies,

$$f_{H/L} = \frac{E_{HOMO}}{E_{LUMO}}$$

Where $f_{H/L}$ is stability index of the compound. Low values of $f_{H/L}$ are related to the high stability of the molecule.

According to Koopman's theorem [19], the energy of the HOMO is directly related to the ionization potential(IP) and LUMO energy is directly related to the electron affinity(EA), respectively, by the following reactions,

$IP = -E_{HOMO}$

$EA = -E_{LUMO}$

Where IP and EA are ionization potential and electron affinity of the compound respectively. Electron affinity refers to the capability of ligand to accept precisely one electron from a donor. However, in many kinds of bonding viz covalent hydrogen bonding, partial charge transfer takes place. Considering the chemical hardness, a hard molecule means a large energy gap and a soft molecule means a small energy gap. The stability of the molecule is also related to hardness, which indicates that the molecule with small energy gap is more reactive. Absolute electronegativity(χ), Chemical potential(μ) and hardness(η) of the molecule are given by [20],

$$\chi = \frac{IP + EA}{2};$$

$$\mu = -\frac{(IP + EA)}{2} \text{ and}$$

$$\eta = \frac{IP - EA}{2}, \text{ respectively.}$$

Softness (σ) is a property of a compound that measures the extent of chemical reactivity. It is the reciprocal of hardness.

$$\sigma = \frac{1}{\eta}$$

Recently Parr et al. [21] have defined a new descriptor to quantify the global electrophilic power of the molecule as electrophilicity index(ω), which defines a quantitative classification of the global electrophilic nature of a molecule. Parr et al. [22] have proposed electrophilicity index(ω) as a measure of energy lowering due to maximal electron flow between donor and acceptor. They defined electrophilicity index (ω) as follows,

$$\omega = \frac{\mu^2}{2\eta}$$

This index measures the stabilization in energy when the system acquired an additional electronic charge from the environment. Electrophilicity encompasses both the abilities of an electrophile to acquire an additional electronic charge and the resistance of the system to exchange electronic charge with the environment. It contains information about both electron transfer (chemical potential) and stability (hardness) and is a better descriptor of global chemical reactivity. The usefulness of this new reactivity quantity has been recently demonstrated in understanding the toxicity of various pollutants in terms of their reactivity and site selectivity [23]. All the above mentioned molecular properties calculated by using DFT/B3LYP method with 6-311++G(d,p) basis set and are shown in Table 1. It is seen that the chemical potential of the title compound is negative, and it means that the compound is stable. They do not decompose spontaneously into the elements they are made up of. The hardness signifies the resistance towards the deformation of the electron cloud of chemical systems under small perturbation encountered during the chemical process. As it can be seen in Table 1, the energy gap of the heterocyclics increases in the order, saturated < partially unsaturated < unsaturated. The frontier molecular orbitals and its molecular properties for all compounds have been shown in Figs. 2a, 2b and 2c, respectively, it shows that, the location of possible sites responsible for electron transfer between molecules and it's biological target.

3.2 Nonlinear optical properties

Organic molecules with large second order NLO are the subject of substantial research due to their potential applications in optical modulation, molecular switching, optical memory and frequency doubling [24]. As hyperpolarizability is difficult to measure directly, the computational calculation is an alternative choice. The magnitude of the molecular hyperpolarizability value(β) is one of the key factors for more active NLO material. In this context, the first order hyperpolarizabilities of the selected heterocyclic compounds were calculated using DFT/B3LYP method with 6-311++G(d,p) basis set on the basis of the finite field approach. In the presence of an applied electric field, the energy of a system is a function of the electric field. The first order hyperpolarizability is a third rank tensor that can be described by a 3×3×3 matrix. The 27 components of the 3D matrix can be reduced to 10 components due to the Kleinman symmetry [25].

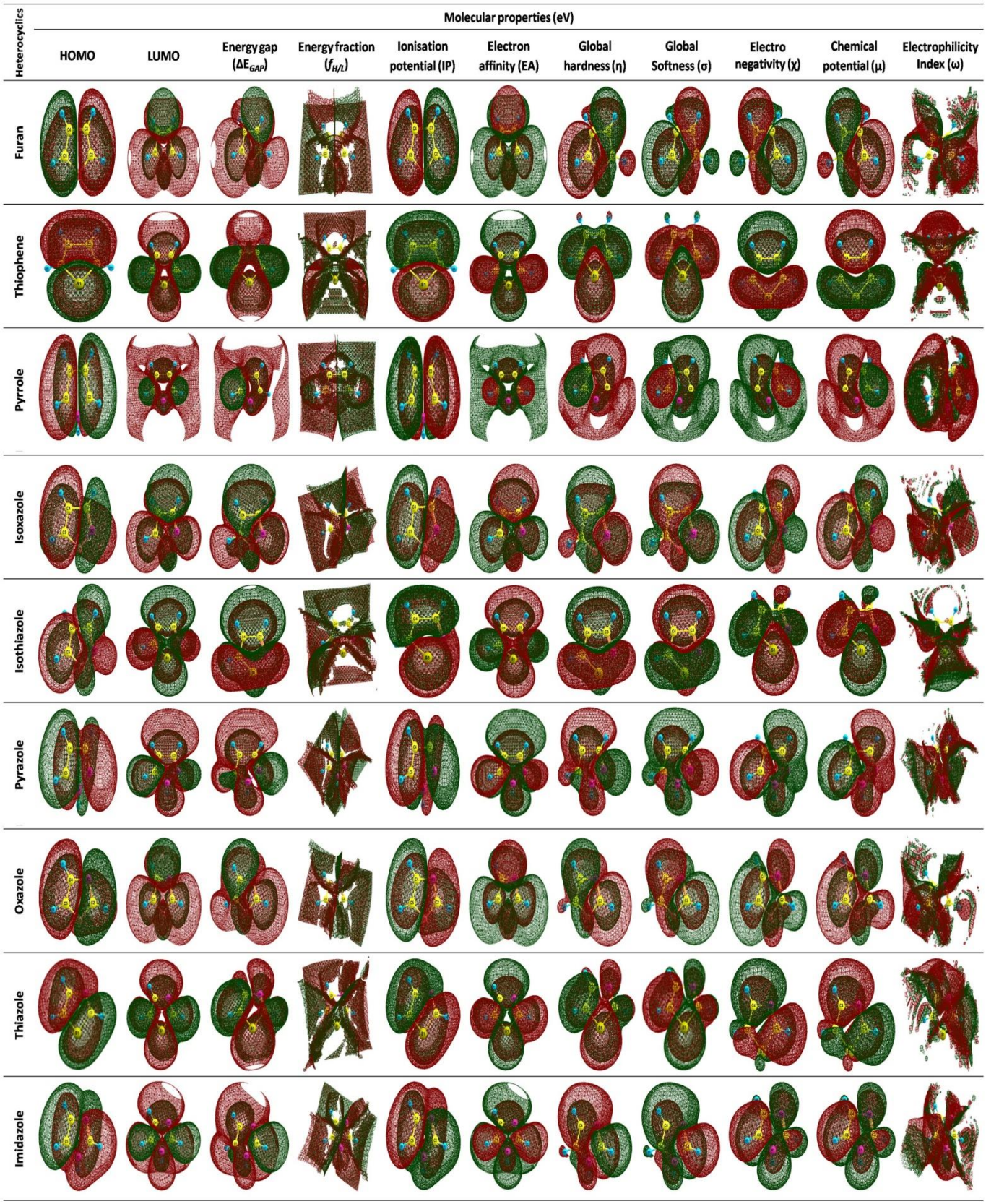

Fig 2a. Pictorial projection of frontier molecular orbitals and related molecular properties of selected unsaturated heterocyclics.

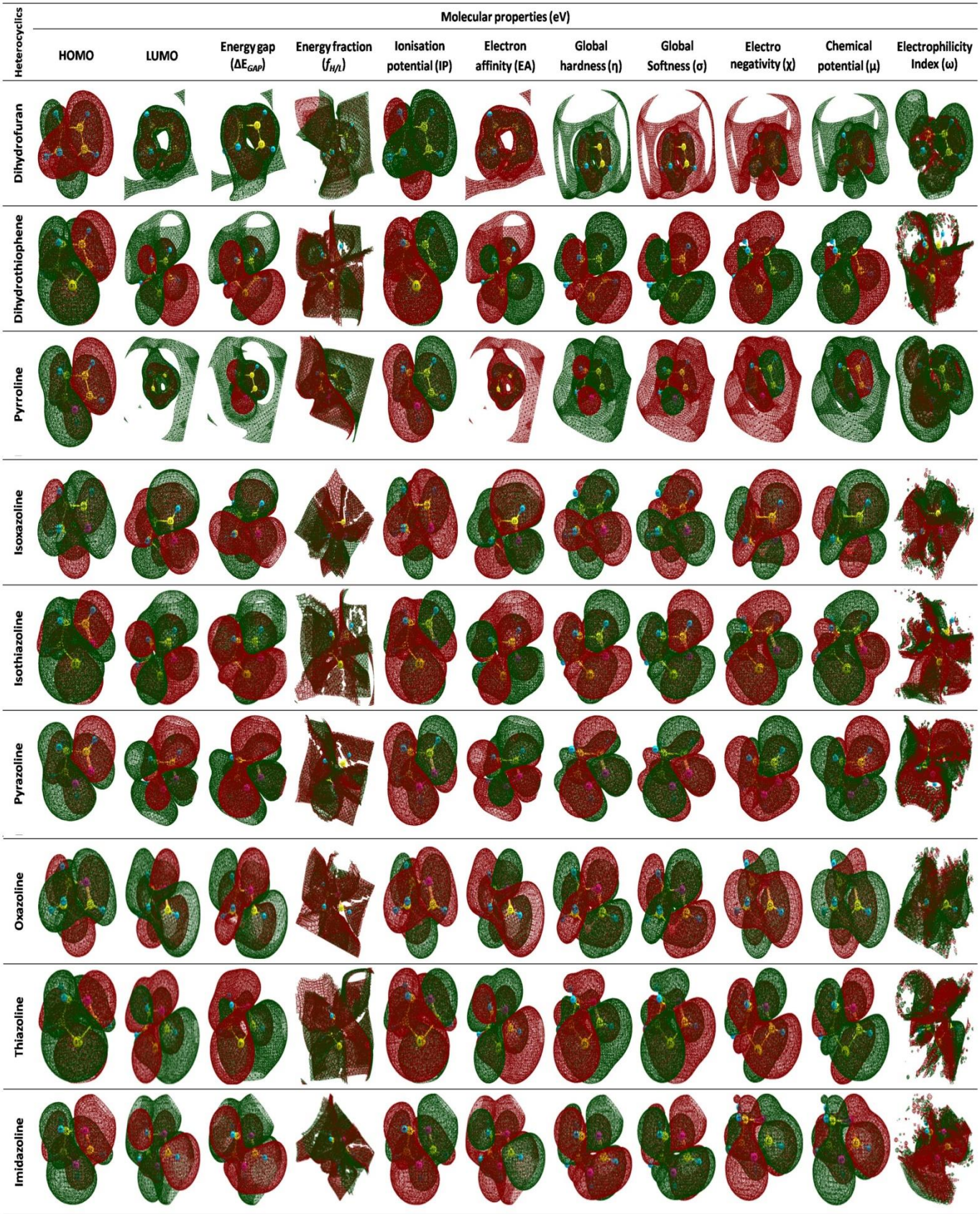

Fig 2b. Pictorial projection of frontier molecular orbitals and related molecular properties of selected partially unsaturated heterocyclics.

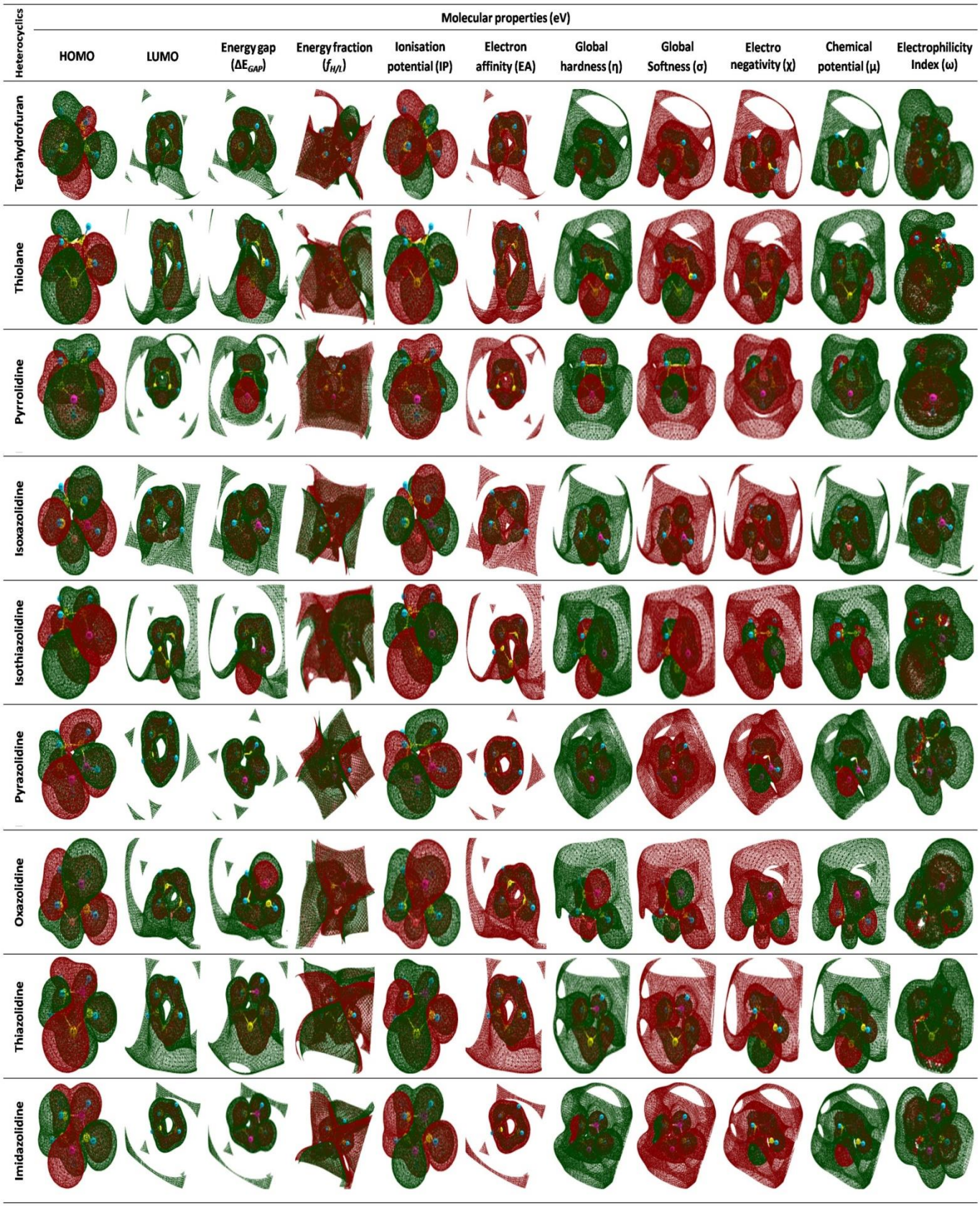

Fig 2c. Pictorial projection of frontier molecular orbitals and related molecular properties of selected saturated heterocyclics.

Table 1. Frontier molecular orbitals and related molecular properties for selected heterocyclics obtained by DFT/B3LYP method with 6-311++G(d,p) basis set.

Heterocyclics		Molecular properties (eV)										
		HOMO	LUMO	Energy gap (ΔE_{GAP})	Energy fraction ($f_{H/L}$)	Ionisation potential (IP)	Electron affinity (EA)	Global hardness (η)	Global softness (σ)	Electro negativity (χ)	Chemical potential (μ)	Electrophilicity Index (ω)
Unsaturated	Furan	-6.704	-0.551	6.153	12.172	6.704	0.551	3.077	0.325	3.627	-3.627	2.138
	Thiophene	-6.775	-0.778	5.998	8.712	6.775	0.778	2.999	0.333	3.777	-3.777	2.378
	Pyrrole	-6.274	-0.270	6.004	23.265	6.274	0.270	3.002	0.333	3.272	-3.272	1.783
	Isoxazole	-7.803	-1.197	6.606	6.519	7.803	1.197	3.303	0.303	4.500	-4.500	3.066
	Isothiazole	-7.167	-1.360	5.807	5.269	7.167	1.360	2.903	0.344	4.264	-4.264	3.131
	Pyrazole	-7.262	-0.798	6.464	9.099	7.262	0.798	3.232	0.309	4.030	-4.030	2.513
	Oxazole	-7.349	-1.049	6.300	7.005	7.349	1.049	3.150	0.317	4.199	-4.199	2.799
	Thiazole	-7.265	-1.245	6.019	5.833	7.265	1.245	3.010	0.332	4.255	-4.255	3.008
	Imidazole	-6.839	-0.668	6.171	10.237	6.839	0.668	3.085	0.324	3.753	-3.753	2.283
Partially Unsaturated	Dihydrofuran	-6.355	-0.154	6.201	41.260	6.355	0.154	3.100	0.323	3.254	-3.254	1.708
	Dihydrothiophene	-5.780	-0.433	5.347	13.350	5.780	0.433	2.673	0.374	3.106	-3.106	1.805
	Pyrroline	-5.721	-0.213	5.508	26.919	5.721	0.213	2.754	0.363	2.967	-2.967	1.598
	Isoxazoline	-7.112	-0.944	6.168	7.532	7.112	0.944	3.084	0.324	4.028	-4.028	2.631
	Isothiazoline	-6.208	-1.136	5.072	5.466	6.208	1.136	2.536	0.394	3.672	-3.672	2.658
	Pyrazoline	-6.410	-0.554	5.856	11.564	6.410	0.554	2.928	0.342	3.482	-3.482	2.071
	Oxazoline	-7.393	-0.890	6.503	8.303	7.393	0.890	3.251	0.308	4.142	-4.142	2.638
	Thiazoline	-6.545	-1.108	5.437	5.907	6.545	1.108	2.719	0.368	3.827	-3.827	2.693
	Imidazoline	-6.620	-0.487	6.133	13.583	6.620	0.487	3.066	0.326	3.554	-3.554	2.059
Saturated	Tetrahydrofuran	-7.005	-0.208	6.797	33.738	7.005	0.208	3.399	0.294	3.606	-3.606	1.913
	Thiolane	-5.881	-0.270	5.611	21.744	5.881	0.270	2.805	0.356	3.076	-3.076	1.686
	Pyrrolidine	-6.335	-0.211	6.124	30.001	6.335	0.211	3.062	0.327	3.273	-3.273	1.749
	Isoxazolidine	-5.443	-0.277	5.166	19.629	5.443	0.277	2.583	0.387	2.860	-2.860	1.584
	Isothiazolidine	-5.089	-0.344	4.745	14.797	5.089	0.344	2.373	0.421	2.717	-2.717	1.555
	Pyrazolidine	-4.747	-0.194	4.553	24.467	4.747	0.194	2.277	0.439	2.471	-2.471	1.341
	Oxazolidine	-6.431	-0.288	6.142	22.315	6.431	0.288	3.071	0.326	3.359	-3.359	1.837
	Thiazolidine	-5.951	-0.330	5.622	18.059	5.951	0.330	2.811	0.356	3.140	-3.140	1.754
	Imidazolidine	-5.811	-0.221	5.590	26.300	5.811	0.221	2.795	0.358	3.016	-3.016	1.627

Table 2. First order hyperpolarizability of selected heterocyclics calculated by DFT/B3LYP method with 6-311++G(d,p) basis set.

Heterocyclics		First order hyperpolarizability							
		β_X (a.u)	β_Y (a.u)	β_Z (a.u)	β_{total} (a.u)	β_{total} x10^{-31}(esu)	NLO		
							> Urea (Times)	< Urea (Times)	Activity
Unsaturated	Furan	-16.53	-75.71	0.00	77.50	6.70	1.80	--	Active
	Thiophene	-28.86	-15.40	0.00	32.71	2.83	--	0.76	Inactive
	Pyrrole	27.11	-52.90	0.00	59.44	5.14	1.38	--	Active
	Isoxazole	18.81	-87.31	-1.59	89.33	7.72	2.07	--	Active
	Isothiazole	38.73	-57.99	-27.53	74.97	6.48	1.74	--	Active
	Pyrazole	-11.76	-85.12	-1.70	85.94	7.43	1.99	--	Active
	Oxazole	20.20	-24.99	16.29	36.03	3.11	--	0.84	Inactive
	Thiazole	92.67	46.50	-15.90	104.89	9.06	2.43	--	Active
	Imidazole	16.44	-32.78	26.91	45.48	3.93	1.05	--	Active
Partially Unsaturated	Dihydrofuran	-74.51	-100.42	-113.38	168.79	14.58	3.91	--	Active
	Dihydrothiophene	-87.95	-35.11	-29.12	99.08	8.56	2.30	--	Active
	Pyrroline	-120.52	-28.57	-118.21	171.22	14.79	3.79	--	Active
	Isoxazoline	-61.86	-93.80	-70.33	132.56	11.45	3.07	--	Active
	Isothiazoline	102.33	-32.98	8.60	107.86	9.32	2.50	--	Active
	Pyrazoline	85.49	-64.41	-71.88	128.93	11.14	2.99	--	Active
	Oxazoline	-24.13	35.08	-47.37	63.69	5.50	1.48	--	Active
	Thiazoline	93.62	31.42	36.43	105.26	9.09	2.44	--	Active
	Imidazoline	8.25	-31.80	-24.14	40.77	3.52	--	0.94	Inactive
Saturated	Tetrahydrofuran	4.88	-104.08	-53.03	116.91	10.10	2.71	--	Active
	Thiolane	47.24	23.81	-13.22	54.53	4.71	1.26	--	Active
	Pyrrolidine	-82.01	-9.90	-158.02	178.31	15.40	4.13	--	Active
	Isoxazolidine	20.08	-112.49	-52.91	125.92	10.88	2.92	--	Active
	Isothiazolidine	-137.85	-59.62	-110.97	186.74	16.13	4.33	--	Active
	Pyrazolidine	-1.42	-64.72	-64.41	91.31	7.89	2.12	--	Active
	Oxazolidine	-15.37	-50.40	-61.89	81.28	7.02	1.88	--	Active
	Thiazolidine	-77.71	23.55	-66.74	105.11	9.08	2.44	--	Active
	Imidazolidine	0.00	0.00	13.55	13.55	1.17	--	0.31	Inactive

The output from Gaussian 09W [7] provides 10 components of this matrix as β_{xxx}, β_{xxy}, β_{xyy}, β_{yyy}, β_{xxz}, β_{xyz}, β_{yyz}, β_{xzz}, β_{yzz}, β_{zzz}, respectively. Many types of hyperpolarizabilities have been discussed in the literature [26] denoted as β_{vec}, $\beta_{\|}$ and β_{total}. β_{vec} which is the component along the dipole moment direction can be measured experimentally using stark spectroscopy. But the theoretical chemists are concerned with $\beta_{\|}$ which is the component parallel to the ground state charge transfer direction and the other is the total hyperpolarizability β_{total}. The components of β can be calculated using the following equation.

$$\beta_i = \beta_{iii} + \frac{1}{3}\sum_{i \neq j}\left(\beta_{ijj} + \beta_{jij} + \beta_{jji}\right)$$

Using the x, y and z components of β, the magnitude of the first hyperpolarizability tensor can be calculated,

$$\beta_{total} = \left(\beta_x^2 + \beta_y^2 + \beta_z^2\right)^{1/2}$$

The complete equation for calculating the magnitude of β from Gaussian 09W output is given as follows,

$$\beta_{total} = \left[\left(\beta_{xxx} + \beta_{xyy} + \beta_{xzz}\right)^2 + \left(\beta_{yyy} + \beta_{yzz} + \beta_{yxx}\right)^2 + \left(\beta_{zzz} + \beta_{zxx} + \beta_{zyy}\right)^2\right]^{1/2}$$

Since the values of the first hyperpolarizability tensors of the output file of Gaussian 09W [7] are reported in atomic units (a.u.), the calculated values were converted into electrostatic units (1 a.u. = 8.6393×10^{-33} esu). The components of first hyperpolarizability β_x, β_y, β_z and the calculated total hyperpolarizability β_{total} for all the selected 27 heterocyclic molecules were listed in Table 2. Urea is one of the prototypical molecules used in the study of the NLO properties of molecular systems(value of Urea [27], β_{total} = 3.729×10^{-31} for B3LYP). Therefore it was used frequently as a threshold value for comparative purposes. NLO analysis of 27 selected heterocyclic compounds were presented in Fig. 3. From Table 2, the calculated β_{total} values of 23 selected heterocyclic compounds are higher than that of Urea. According to the magnitude of the first hyperpolarizability, those 23 heterocyclic compounds may be a potential applicant in the development of NLO materials. As seen from the above results, the NLO activity of the heterocyclics decreases in the order, saturated > partially unsaturated > unsaturated.

3.3 In silico pharmacokinetic and toxicity predictions

In the field of the drug design, it is critical to analyze both a drug's therapeutic activity and its toxicity. Because of the number of molecules that must be tested and the money and time required to perform the testing, quantitative structure-toxicity relationship is useful in prescreening of prospective drug molecules.

3.3.1 Lipinski's rule of five

The entire pharmacokinetic profile is influenced by the physicochemical properties of compounds, such as molecular weight, lipophilicity, hydrogen bond donors and acceptors. Using these molecular properties, Lipinski's [28] established a controversial rule for drug design. Created in 1995 and published in 1997, it is known as the "Lipinski's rule" or "rule of five", it has this name, because each of the four parameters involved uses values that are multiples of five. The rule states that the compounds are more likely to be orally bioavailable if they obey the following criteria: Log P ≤ 5, molecular weight ≤ 500(Dalton), hydrogen bond acceptors ≤ 10, and hydrogen bond donors ≤ 5. Molecules that violate more than one of these rules may have problems with bioavailability. Therefore, this rule establishes some structural parameters relevant to the theoretical prediction of the oral bioavailability profile and is widely used in designing new drugs. The calculated Lipinski's parameters for all heterocyclic compounds using OSIRIS [8] and Molsoft [9] programs were presented in Table 3. The obtained results show that all compounds met the Lipinski's rules of five, suggesting that these compounds would not have problems with oral bioavailability.

3.3.2 Toxicity risk

For any molecule to become a drug, it should not have any toxic or allergenic effects. Drug toxicity is a factor of great importance for a potential commercial drug since a significant number of drugs are disapproved in clinical trials based on their high toxicity profile. Herein, OSIRIS [8] program is used to predict the overall toxicity of 27 heterocyclic compounds as it may point to the presence of some fragments generally responsible for the mutagenic, tumorigenic, irritant and reproductive effects in those molecules. The predicted toxicity risks for 27 heterocyclics were presented in Table 4. The results were visualized using different color codes. Green color shows no risks, yellow color shows the medium and red color shows high risks of toxicity. From Table 1, it can be seen that, the toxicity risks of the heterocyclics increases in the order, partially unsaturated < saturated < unsaturated. As seen from the results, out of 27, 15 heterocyclic compounds were predicted to be safe and expected to show no toxicity regarding mutagenicity, tumorigenicity, irritant effect and effects on the reproductive system. The 15 non-toxic compounds are thiophene, isothiazole, oxazole, dihydrothiophene, pyrroline, isoxazoline, pyrazoline, oxazoline, thiazoline, imidazoline, thiolane, isoxazolidine, pyrazolidine, oxazolidine and imidazolidine.

3.3.3 Drug likeness and drug score

Drug likeness is an important parameter because a drug like molecules exhibit favorable absorption, distribution, metabolism, excretion, toxicological (ADMET) parameters. Currently, there are many approaches to assessing a compound drug likeness based on topological descriptors, fingerprints of molecular drug likeness structure keys or other properties such as cLogP and MW. In this study, OSIRIS [8] program is used for calculating the fragment based drug likeness of the heterocyclic compounds and the calculated results were presented in Table 4. In drug likeness test, a positive value indicates that a molecule contains predominantly fragments commonly present in commercially available drugs, though a negative score does not necessarily mean that the molecule cannot be a potential drug.

The drug score combines drug likeness, cLogP, LogS, molecular weight and toxicity risks in one handy value then may be used to judge the compounds overall potential to qualify for a drug. This value is calculated by multiplying contributions of the individual properties according to the following equation,

$$ds = \Pi(1/2 + 1/2\ s_i)\Pi\ t_i$$

Where,

$$s = 1/1 + e^{ap+b},$$

ds is the drug score. s_i is the contributions calculated directly from cLogP, LogS, molecular weight and drug likeness(p_i) via the second equation, which describes a spline curve. Parameters *a* and *b* are (1, -5), (1, 5), (0.012, -6) and (1, 0) for cLogP, LogS, molecular weight and drug likeness, respectively. The t_i is the contributions taken from the four toxicity risk types and the values are 1.0, 0.8 and 0.6 for no

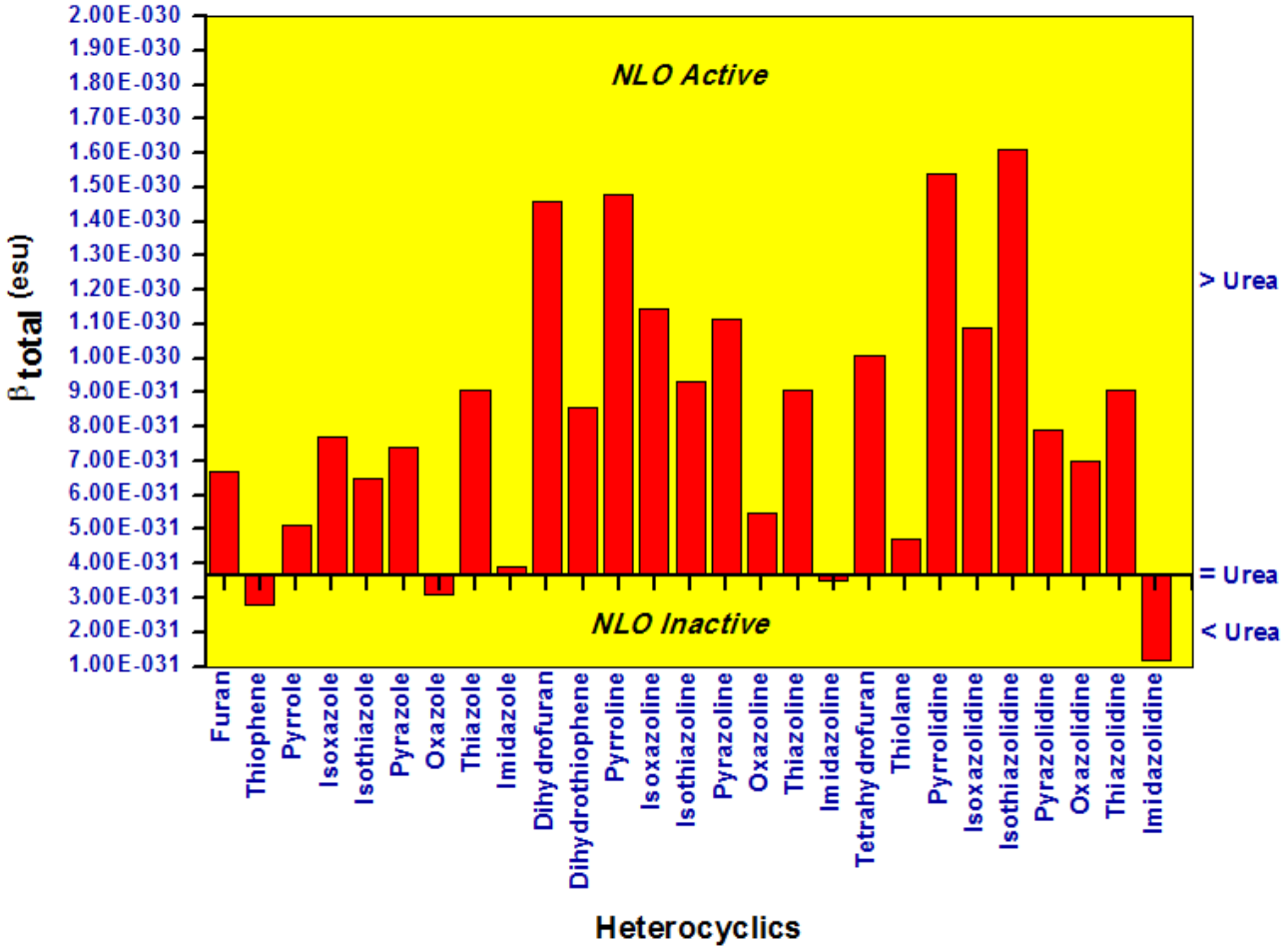

Fig 3. NLO analysis of selected heterocyclics.

Table 3. Lipinski's parameters calculated for selected heterocyclic compounds with OSIRIS and Molsoft programs.

Heterocyclics		Lipinski's rule of 5				
		Molecular Weight (Dalton)	Number of H-bond donors	Number of H-bond acceptors	Log P (oct/wat)	Number of Lipinski's violations
Unsaturated	Furan	68.00	0	1	0.79	0
	Thiophene	84.00	0	1	1.44	0
	Pyrrole	67.00	1	0	0.38	0
	Isoxazole	69.00	0	2	0.07	0
	Isothiazole	85.00	0	2	0.94	0
	Pyrazole	68.00	1	1	-0.45	0
	Oxazole	69.00	0	2	0.23	0
	Thiazole	85.00	0	2	0.44	0
	Imidazole	68.00	1	1	-0.18	0
Partially Unsaturated	Dihydrofuran	70.00	0	1	0.28	0
	Dihydrothiophene	86.00	0	1	1.05	0
	Pyrroline	69.00	1	0	0.14	0
	Isoxazoline	71.00	0	2	1.13	0
	Isothiazoline	87.00	0	2	1.09	0
	Pyrazoline	70.00	1	1	0.16	0
	Oxazoline	71.00	0	2	-0.47	0
	Thiazoline	87.00	0	2	0.18	0
	Imidazoline	70.00	1	1	-0.62	0
Saturated	Tetrahydrofuran	72.00	0	1	0.55	0
	Thiolane	88.00	0	1	0.95	0
	Pyrrolidine	71.00	1	1	0.40	0
	Isoxazolidine	73.00	1	2	-0.27	0
	Isothiazolidine	89.00	1	2	0.46	0
	Pyrazolidine	72.00	2	2	-1.24	0
	Oxazolidine	73.00	1	2	-0.29	0
	Thiazolidine	89.00	1	2	0.28	0
	Imidazolidine	72.00	2	2	-0.43	0

Table 4. Toxicity risks, drug likeness and drug score calculated for selected heterocyclic compounds with OSIRIS program.

Heterocyclics		Toxicity risks				Drug likeness	Drug score
		Mutagenic	Tumorigenic	Irritant	Reproductive effective		
Unsaturated	Furan	High	High	No	High	-2.09	0.12
	Thiophene	No	No	No	No	-0.90	0.62
	Pyrrole	High	No	No	No	-0.57	0.40
	Isoxazole	No	No	No	High	-0.38	0.42
	Isothiazole	No	No	No	No	-0.04	0.73
	Pyrazole	No	No	No	High	2.34	0.57
	Oxazole	No	No	No	No	-1.42	0.59
	Thiazole	High	No	No	No	-0.39	0.41
	Imidazole	High	No	No	High	0.45	0.29
Partially Unsaturated	Dihydrofuran	No	No	Medium	No	-2.62	0.42
	Dihydrothiophene	No	No	No	No	-1.41	0.58
	Pyrroline	No	No	No	No	0.10	0.75
	Isoxazoline	No	No	No	No	-0.23	0.70
	Isothiazoline	High	No	No	No	-0.64	0.39
	Pyrazoline	No	No	No	No	3.11	0.96
	Oxazoline	No	No	No	No	0.46	0.80
	Thiazoline	No	No	No	No	0.49	0.80
	Imidazoline	No	No	No	No	2.46	0.95
Saturated	Tetrahydrofuran	High	High	No	High	-8.26	0.11
	Thiolane	No	No	No	No	-2.69	0.52
	Pyrrolidine	High	High	High	High	-0.72	0.08
	Isoxazolidine	No	No	No	No	-0.54	0.67
	Isothiazolidine	High	No	No	No	-0.08	0.43
	Pyrazolidine	No	No	No	No	1.73	0.91
	Oxazolidine	No	No	No	No	0.30	0.78
	Thiazolidine	High	No	No	No	0.58	0.48
	Imidazolidine	No	No	No	No	1.43	0.89

High: High Risk, Medium: Medium Risk, No: No Risk.

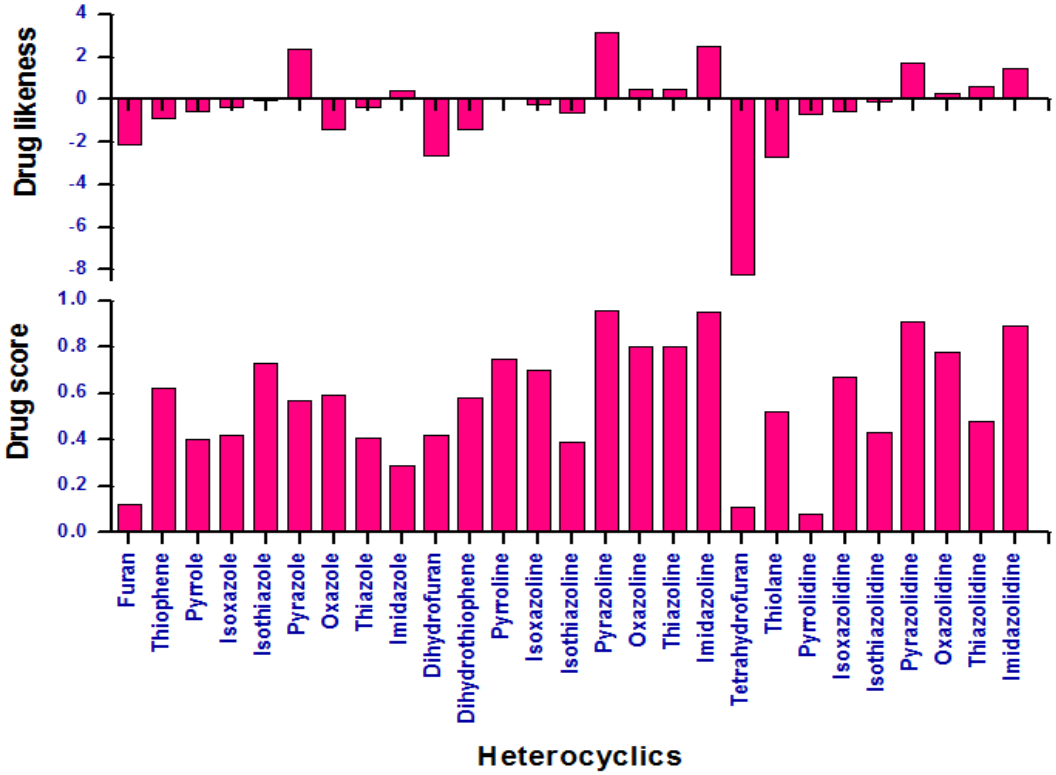

Fig 4. Comparative plot of drug likeness and drug score of selected heterocyclics.

risk, medium risk and high risk, respectively. Computed drug scores were presented in Table 4. Maximum drug score was found out to be 0.96 for compound pyrazoline. From the results presented in Table 4, it can be seen that drug likeness and drug score of the heterocyclics decreases in the order, partially unsaturated > saturated > unsaturated. Comparative plot of drug likeness and drug score is shown in Fig. 4.

4. Conclusion

In the present study, three different(unsaturated, partially unsaturated and saturated) five-membered heterocyclic rings were subjected to the prediction of FMO, NLO, toxicity and pharmacokinetic properties by different programs such as Gaussian 09W, OSIRIS and Molsoft in order to find a suitable five-membered heterocyclic ring for nonlinear applications and drug design. The predicted results were compared and depicted in Fig. 5. From Fig. 5, it is evident that saturated and partially unsaturated heterocyclic compounds have high NLO, non-toxicity and drug score when to compare to unsaturated heterocyclics. This study concludes that the saturated and partially unsaturated heterocyclic compounds have significant biological and pharmaceutical activities and can be used as the therapeutic agent.

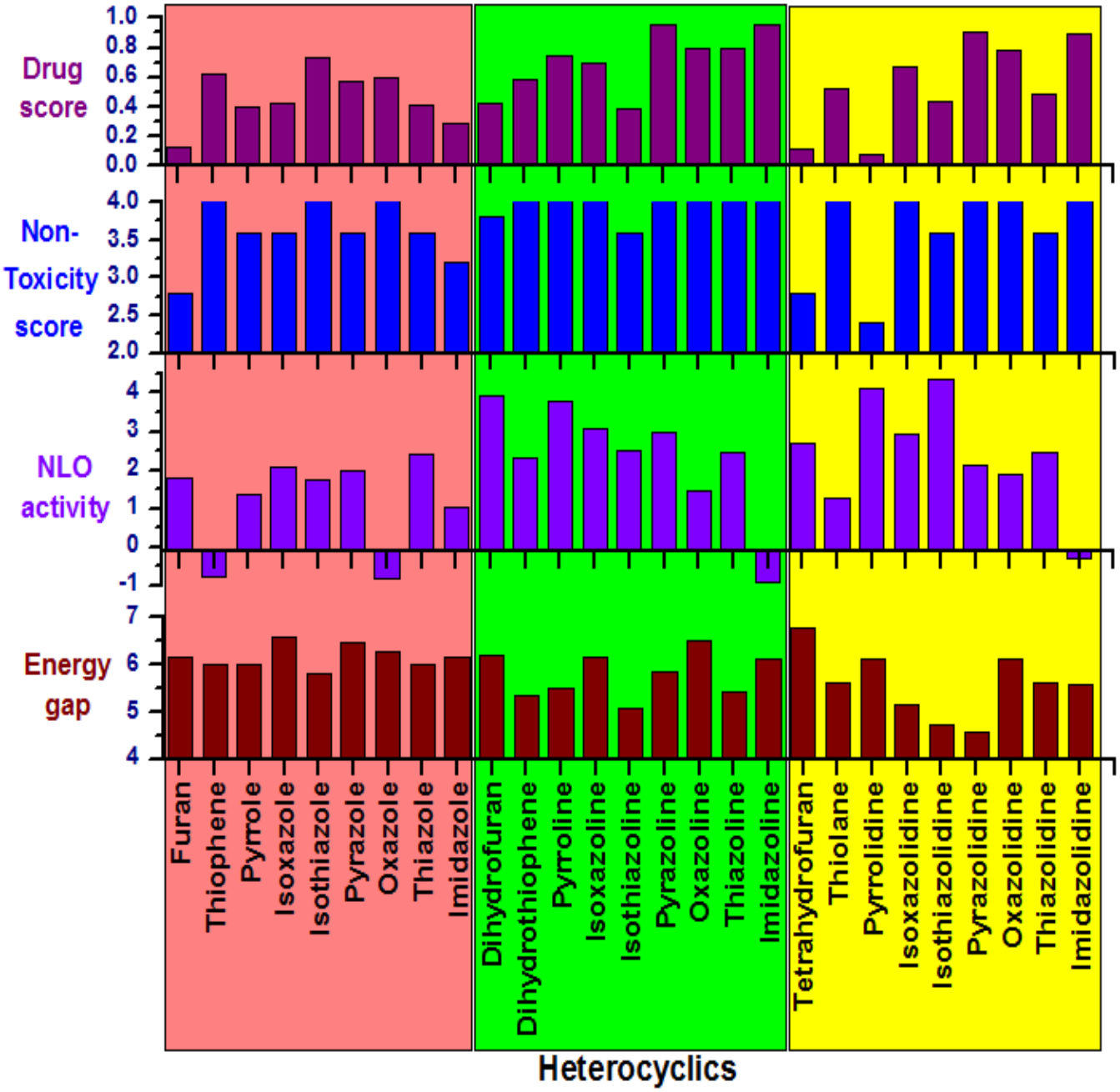

Fig 5. Comparative bar diagram of energy gap, NLO, non-toxicity and drug score of selected heterocyclics.

References

[1] J.J. Li, Heterocyclic chemistry in drug discovery, John Wiley & Sons, 2013.
[2] P. Arora, V. Arora, H. Lamba, D. Wadhwa, IMPORTANCE OF HETEROCYCLIC CHEMISTRY: A REVIEW, International Journal of Pharmaceutical Sciences and Research, 3 (2012) 2947.
[3] M. Malang, G. Kayal, A. Kharia, COMPARATIVE STUDY OF HETEROCYCLICS IN THE TREATMENT OF DIABETES, (2014).
[4] R. Gupta, Biological Significance of Nitrogen Containing Heterocyclic Compounds - A Mini Review, in: International Conference on Advancements in Engineering and Technology, International Journal of Computer Applications 2015, pp. 18-23.
[5] F. Mao, W. Ni, X. Xu, H. Wang, J. Wang, M. Ji, J. Li, Chemical Structure-Related Drug-Like Criteria of Global Approved Drugs, Molecules, 21 (2016) 75.
[6] A. Gomtsyan, Heterocycles in drugs and drug discovery, Chemistry of heterocyclic compounds, 48 (2012) 7-10.
[7] M. Frisch, G. Trucks, H. Schlegel, G. Scuseria, M. Robb, J. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. Petersson, Gaussian 09W, Version 7.0, Gaussian, Wallingford, CT (USA), (2009).
[8] T. Sander, OSIRIS property explorer, Allschwil: Actelion Pharmaceuticals Ltd, (2001).
[9] Molsoft L.L.C.: Drug-Likeness and molecular property prediction. http://molsoft.com/ (accessed May 1, 2016).
[10] PubChem structure search. https://pubchem.ncbi.nlm.nih.gov/search/search.cgi (accessed May 1, 2016).
[11] R. Dennington, T. Keith, J.M.G. Version, 5.0 Semichem Inc, in, KS, 2003.
[12] G. Zhurko, D. Zhurko, ChemCraft, version 1.6, URL: http:// www. chemcraftprog. com, (2009).
[13] E. Kavitha, N. Sundaraganesan, S. Sebastian, Molecular structure, vibrational spectroscopic and HOMO, LUMO studies of 4-nitroaniline by density functional method, Indian J Pure Appl Phys, 48 (2010) 20-30.
[14] A. Prabaharan, J. Xavier, Spectroscopic Aspects, Structural Elucidation, Vibrational and Electronic Investigations of 2-Methoxy-1, 3-Dioxolane: An Interpretation Based on DFT and QTAIM Approach, J Theor Comput Sci, 2 (2015) 2.
[15] Y. Ruiz-Morales, HOMO-LUMO gap as an index of molecular size and structure for polycyclic aromatic hydrocarbons (PAHs) and asphaltenes: A theoretical study. I, The Journal of Physical Chemistry A, 106 (2002) 11283-11308.
[16] A.-M. Sapse, Molecular orbital calculations for biological systems, Oxford University Press, 1998.
[17] R.J. Xavier, A. Prabaharan, Vibrational spectroscopic investigations of 4, 4-dimethyl-2-oxazoline: A density functional theory approach, Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 136 (2015) 1530-1542.
[18] R. Todeschini, V. Consonni, Molecular Descriptors for Chemoinformatics, Volume 41 (2 Volume Set), John Wiley & Sons, 2009.
[19] L. Larabi, Y. Harek, O. Benali, S. Ghalem, Hydrazide derivatives as corrosion inhibitors for mild steel in 1M HCl, Progress in Organic Coatings, 54 (2005) 256-262.
[20] I. Lukovits, I. Bakó, A. Shaban, E. Kálmán, Polynomial model of the inhibition mechanism of thiourea derivatives, Electrochimica Acta, 43 (1998) 131-136.
[21] R.G. Parr, L.v. Szentpaly, S. Liu, Electrophilicity index, Journal of the American Chemical Society, 121 (1999) 1922-1924.
[22] J. Padmanabhan, R. Parthasarathi, V. Subramanian, P. Chattaraj, Electrophilicity-based charge transfer descriptor, The Journal of Physical Chemistry A, 111 (2007) 1358-1361.
[23] R. Parthasarathi, V. Subramanian, D. Roy, P. Chattaraj, Electrophilicity index as a possible descriptor of biological activity, Bioorganic & medicinal chemistry, 12 (2004) 5533-5543.
[24] R.M. Asath, T. Rekha, B.J. Rajkumar, S. Premkumar, A. Jawahar, T. Mathavan, A.M. Franklin Benial, Conformational, vibrational spectroscopic, nonlinear optical activity, and structure–activity studies on 2-hydroxy-3, 5-dinitropyridine: Combined experimental and density functional theory approach, Spectroscopy Letters, 49 (2016) 155-166.
[25] D. Kleinman, Nonlinear dielectric polarization in optical media, Physical Review, 126 (1962) 1977.
[26] K.S. Thanthiriwatte, K.N. De Silva, Non-linear optical properties of novel fluorenyl derivatives—ab initio quantum chemical calculations, Journal of Molecular Structure: THEOCHEM, 617 (2002) 169-175.
[27] Y.-X. Sun, Q.-L. Hao, W.-X. Wei, Z.-X. Yu, L.-D. Lu, X. Wang, Y.-S. Wang, Experimental and density functional studies on 4-(2, 3-dichlorobenzylideneamino) antipyrine and 4-(2, 5-dichlorobenzylideneamino) antipyrine, Journal of Molecular Structure, 929 (2009) 10-21.
[28] C.A. Lipinski, F. Lombardo, B.W. Dominy, P.J. Feeney, Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, Advanced drug delivery reviews, 64 (2012) 4-17.