

**THE SIMULATING STUDY OF HOMO, LUMO, THERMO PHYSICAL AND
QUANTITATIVE STRUCTURE OF ACTIVITY RELATIONSHIP (QSAR) OF
SOME ANTICANCER ACTIVE IONIC LIQUIDS**

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Received: dd/mm/yyyy Accepted: 03/02/2019

ABSTRACT

Cancer is one of the pathologies and trouble diseases in the present time, and the first time anti-tumor activity of phosphonium and ammonium-based ILs (ILs) has been studied in view of computational chemistry. The thermochemical, chemical reactivity and biological interaction of most expected phosphonium and ammonium cations ILs is considered under theoretical study by HyperChem 8.010. Some thermodynamic parameters such as free energy, entropy, dipole moment, binding energy, nuclear energy, electronics energy, heat of formation and QSAR properties of molecules like charge density, surface area, volume, LogP, polarizability, refractivity, molecular mass, and reactivity properties of molecule like HOMO, LUMO, HOMO-LUMO gap, ionization potential and electron affinity were determined using the HyperChem 8.0.10 program. To optimize the IL molecules, the tributylmethylphosphonium cation were chosen as anticancer active with tri-(pentafluoroethyl)fluorophosphate, tetrafluoroborate, tetrafluorophosphate and chloride to obtain phosphonium ILs IL-01, IL-02, IL-03 and IL-04 respectively. The computed QSAR parameters have a significant role in estimation the biological activity and metabolism action in the human body when these are entered in the body using as the anticancer drug or therapy.

Keywords: ILs, QSAR, HOMO, LUMO, Vibrational Spectra.

1. INTRODUCTION

The Ionic Liquids (ILs) are melted salts below temperature 100° C or low melting points, liquid at or close to room temperature. The main point of liquid state is explained in view of the asymmetry of their ionic structure and the dispersion of their charges widely in full molecules which is responsible for lower intermolecular attractions and, thus decreasing the energy of the lattice (Hanke, Price et al. 2001). Due to their almost null vapor pressure and tunable physiochemical properties (Greaves, Weerawardena et al. 2006), low volatility, low toxicity, and environment friendly behavior makes them unusually green solvents in all the area of chemical industries, pharmaceutical industries, electrochemical engineering and material engineering (Earle and Seddon 2000, Holbrey, Reichert et al. 2003, Rogers and Seddon 2003, Zhao, Xia et al. 2005).

Nowadays, the pharmaceutical industry is facing many problems and many challenges in the discovery of innovative and effective drugs and their following therapies. Roughly 50% of available drugs are administrated as salts, which could imply many disadvantages (Morissette, Almarsson et al. 2004), some of them related with polymorphism of drugs which have tendency of a compound to endure structural conversions between distinct crystalline forms. The development of strategies using ILs is promising for the pharmaceutical industry. Indeed, despite the general definition

of ILs being based on a physical property, the combination of favorable biological properties with the fact that the drug may be in the liquid state can be an important feature.

They were primarily proposed as replacements to the common organic old-fashioned solvent but, as soon as their chemistry has developed due to expected opportunities in different areas. They possess a series of unusual properties, namely high chemical and thermal stability, high ionic conductivity, desirable viscosity, low inflammable, low toxicity and a wide electrochemical potential window (Seddon, Stark et al. 2000, Tokuda, Hayamizu et al. 2004, Greaves, Weerawardena et al. 2006). Although ILs were initially defined as green solvents making them as leading chemicals of 21st century almost all fields of natural science, engineering and pharmaceutical industry. As a general rule even though there is a certain contribution from the anion, toxicity, antimicrobial activity of the IL is largely determined by the head group of the cation most of the scientist and chemist. The cation also contributes the bio activity of ILs against different bacteria and fungal. Cholinium cation is considered as the most common bioactive cation(Liu, Ji et al. 2017) by which ILs consists of. After that some other cation such as amino acid, imazonium, ammonium, and phosphonium based ILs are used as bioactive molecules(Ferraz, Branco et al. 2011, Egorova, Gordeev et al. 2017). Due to the large demand of the natural products in pharmaceutical industries, scientist searches the alternative chemical in this area which exit the smaller size and easy to handle in synthesis. The another important key point of the ILs in the environment friendly in the term of green chemistry including low cost, smaller time in synthesis, easy purification, and tunable physicochemical properties that are seemed as the target and vital chemical in this time. Due to the tunable properties, some scientists worked for use them in anticancer and antitumor drug using different cation which is main responsible for the activity of biological molecules(Dias, Costa□Rodrigues et al. 2017). Vineet Kumar et al, (2010) evaluated the first time of anticancer drug of imidazolium, phosphonium and ammonium based ILs (KUMAR and MALHOTRA 2010). So based on this study, the four ILs of phosphonium based cations were optimized in the thermo-physical, chemical reactivity, biological prediction, and Vibrational spectra study. In this study the phosphonium based ILs was designed which have been experimental study for anticancer drug named as tributylmethylphosphoniumpentafluoroethyl) fluorphosphate(IL-01), tributylmethylphosponim tri(pentafluoroethyl) fluorphosphate (IL02),tritybutylmethylphosphoniumtetra fluoroborate (IL03),and tributylmethylphosphonium chloride (IL04).

HyperChem 8.0.1 is a path of molecular modeling program which permits to build and analyze different molecular structures and to determine the physicochemical properties.

There are different basis set like Molecular Mechanics, Semi-empirical method, *Ab initio* and Density Function Theory, The PM3 method is derived from Parametric Method number 3 from computational chemistry and included in the semi-empirical method for the quantum calculation of the molecular structure. PM3 was used the Hamiltonian and it is parameterized to reproduce a large number of molecular properties (Howard, McIver et al. 1994).

In order to create the spatial chemical structure of each calculated molecule, the two-dimensional structure of the molecule shall be built step-by-step by drawing. Then hydrogen atoms are automatically added from building option and chemical structure is converted into 3D structure and model built. The first step in getting the main characteristic parameters of molecules is to optimize the molecular structure to obtain a configuration characterized by a minimum free energy. This is usually done using the algorithm Polak - Ribiere with maximum gradient set at 0.001 kcal/(mol*Å).

After optimization is achieved, the theoretical properties of the studied compound are calculated such as free energy, entropy, dipole moment, binding energy, nuclear energy, electronics energy, heat of formation the energy of frontier orbital, HOMO (Occupied Molecular Orbital Highest), LUMO (Lowest Unoccupied Molecular Orbital). The QSAR properties of molecules like charge density, surface area grid, volume, LogP, polarizability, refractivity, molecular mass, were calculated using the by QSAR (Quantitative Structure-Activity Relationship). Using the compute in NMR, the coupling, shielding and shielding tensor were determined.

3 RESULT AND DISCUSSION

The symmetry is a very powerful tool established on the basis of HyperChem. All the ILs belongs to the class of asymmetry, the molecules of this group are non-planar and they have more than one element of symmetry and the plane of the molecule.

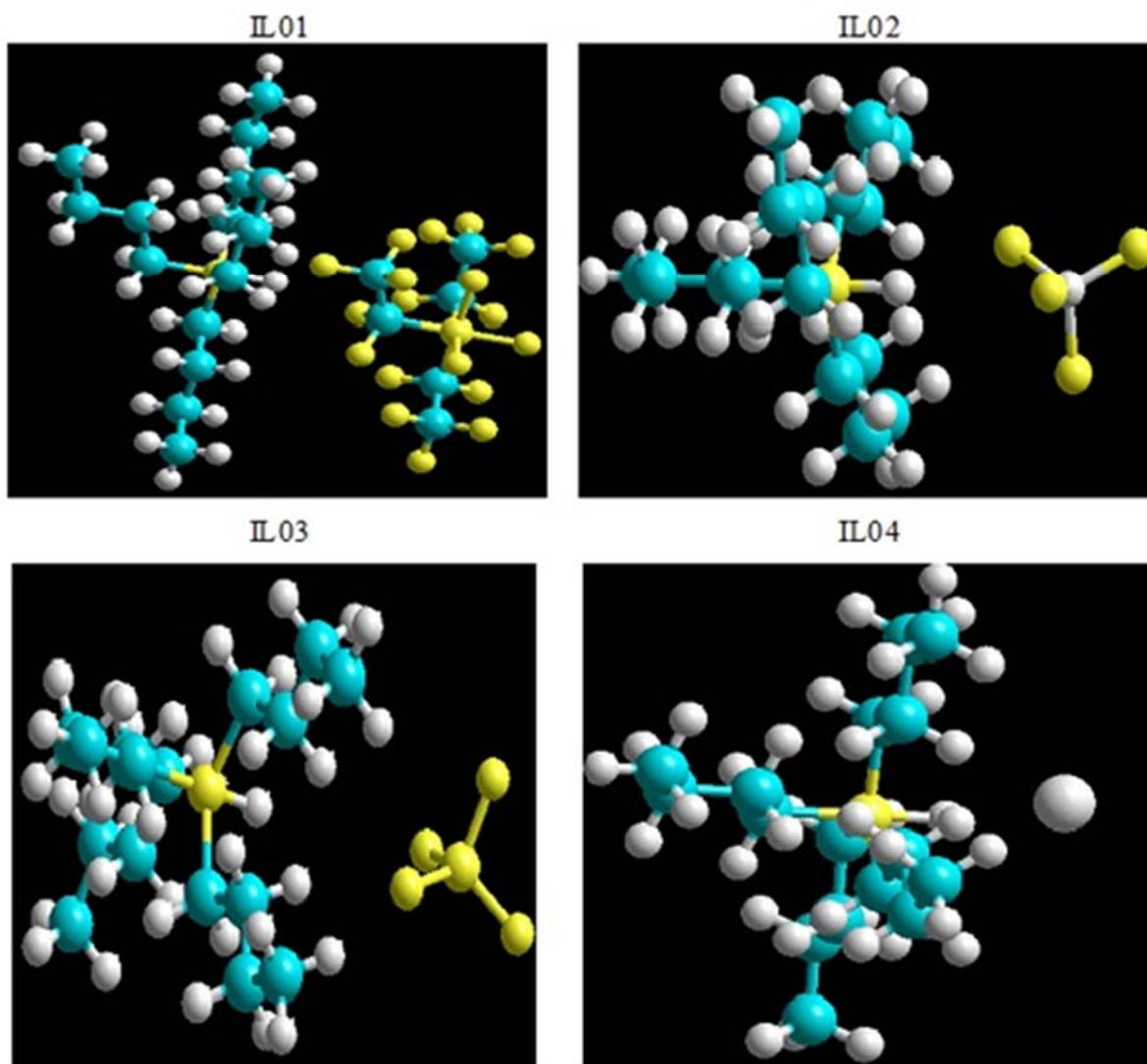


Figure 1; Optimized structure in cylinder shape, Color: yellow is fluoride, cyan is carbon, white is hydrogen, White in big shape is chloride, and phosphorus is yellow as big shape.

The atomic charges computed by hyperchem

It is seen that the negative and positive charges are almost zero located near C F, and P atoms.

Bond length

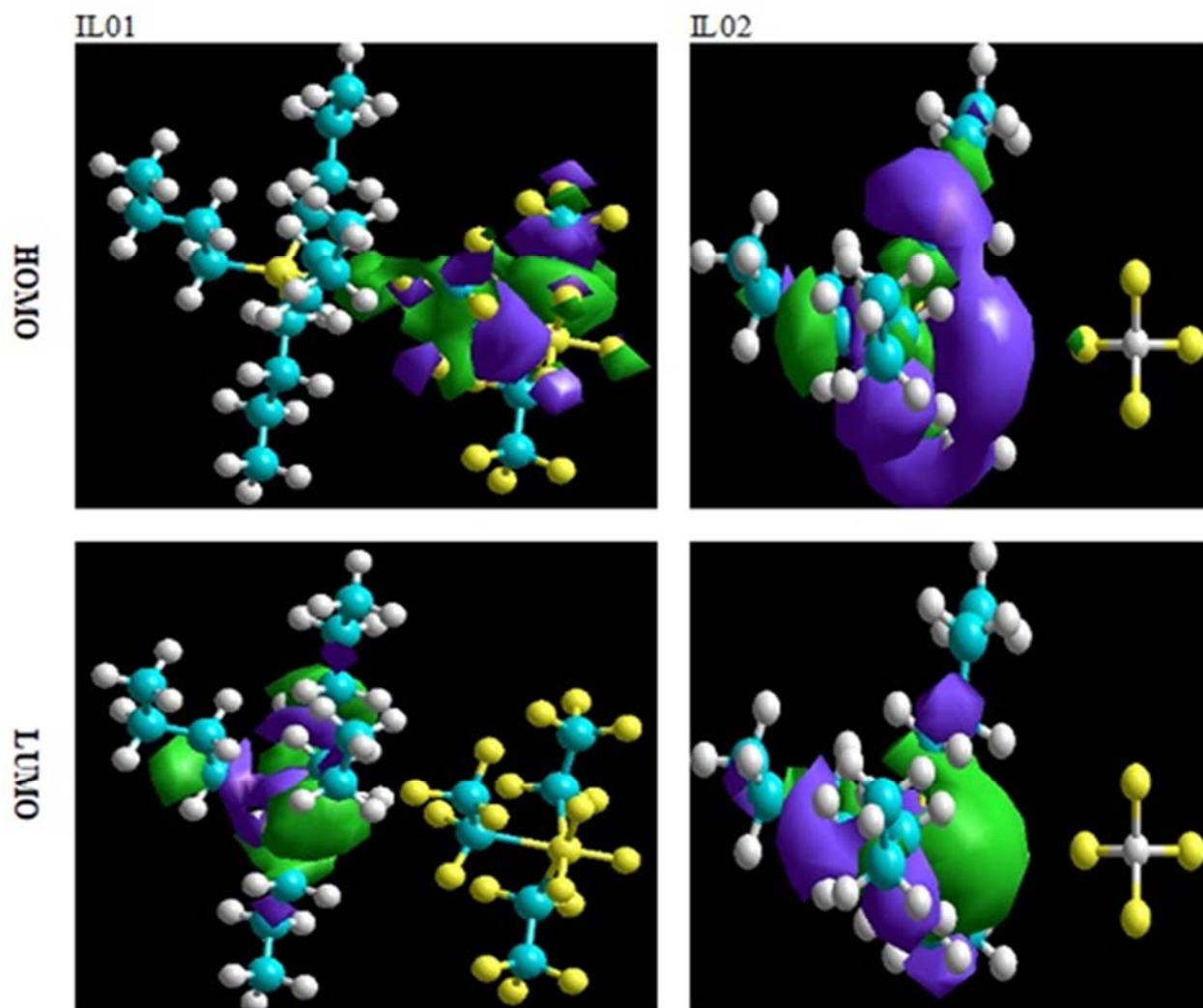
Generally, the length of the bond between two atoms is approximately the sum of the covalent radii of the two atoms. For covalent bonds, bond energies and bond lengths depend on many factors: electron affinities, sizes of atoms involved in the bond, differences in their electronegativity, and the overall structure of the molecule. There is a general trend in that the shorter the bond length, the higher the bond energy. Similar bond length indicates the similarity and molecular symmetry.

Bond order

The higher the bond order, are considered as the stronger the pull between the two atoms and the shorter the bond length. The shorter bond length indicates the higher required energy as a result the rate of reaction decreases. From the figure -3, all ILs shows bond order 1.

HUMO-LUMO

The energy levels of the molecular orbitals order HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) for different aromatic carboxylic acid molecules give information on the possible electronic transition. They are highlighted in fig. 6 (color: green is positive value and blue is negative value).



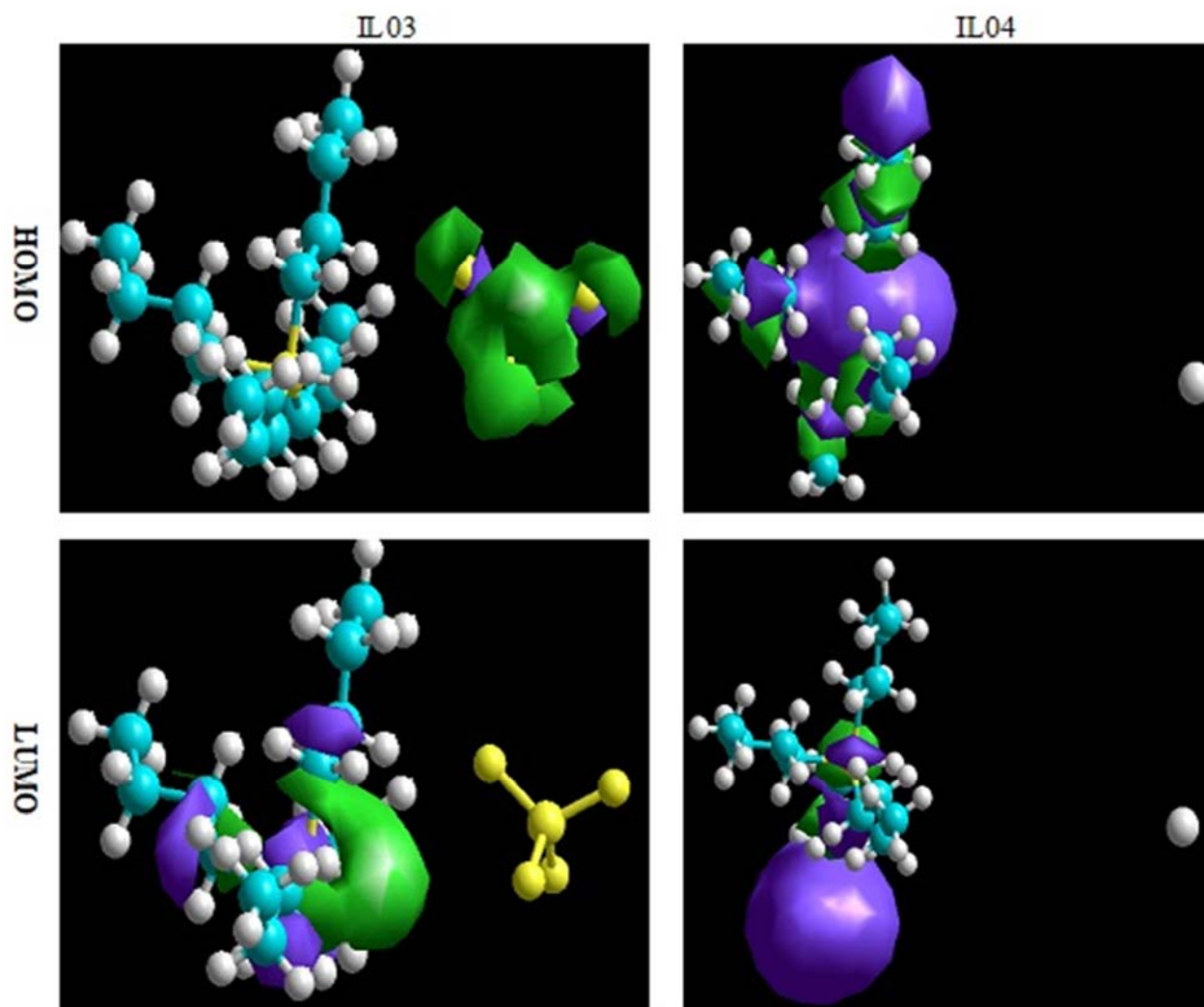


Figure 2: The frontier orbitals HOMO and LUMO in the zero energy level

The electrophilic (Positive charge groups or atoms) attack to the most likely to the atomic site with a high density of orbital HOMO, while nucleophile (Negative charge groups or atoms) attack LUMO that is correlated with atomic high-density of orbital LUMO. The ionization potential (I) and electron affinity (A) can be estimated from the HOMO and LUMO energy values. Here IP = Negative of the energy of HOMO, EA = Negative of the energy of LUMO.

	L01	IL02	IL03	IL04
HOMU(0)	-9.64	-5.51	-2.133	2.256
LUMO(0)	-2.29	3.42	3.290	9.274
HOMU(1)	-9.81	-7.55	-5.718	1.581
LUMO(1)	-1.07	4.29	4.541	9.501
HOMU(2)	-11.49	-7.75	-7.859	0.4577
LUMO(2)	-0.87	4.80	4.766	9.598
HOMU(3)	-11.98	-8.84	-8.235	-1.132
LUMO(3)	-0.74	5.26	4.296	9.788

	L01	IL02	IL03	IL04
HOMO-LUMO gap (o level)	-7.35	-8.93	-5.423	-7.018
HOMO-LUMO gap (1 level)	-8.74	-11.84	-10.259	-7.920

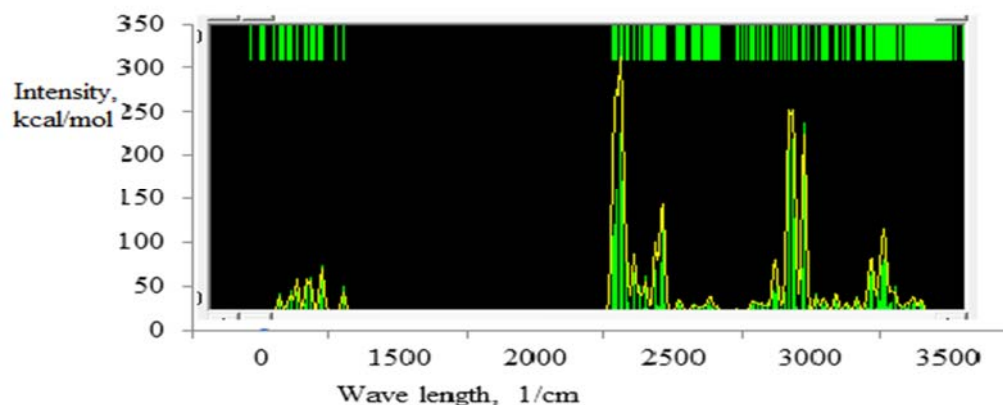
HOMO-LUMO gap (2 level)	-10.620	-12.550	-12.625	-9.141
HOMO-LUMO gap (3 level)	-11.24	-14.09	-12.530	-10.920

Properties	IL01	IL02	IL03	IL04
Total energy, (kcal/mol)	-261765	-102165	-103269	-66873
Entropy, (Kcal/mol-deg)	0	0	0	0
Free energy, (Kcal/mol)	-261765	-102165	-103269	-66873
Heat capacity, (Kcal/mol-deg)	0	0	0	0
Dipole moment, (D)	0	0	0	0
RMS gradient, (Kcal/ mol)	3.191	1.557	1.27	3.74
Binding energy, (Kcal/ mol)	-7125.761	-5442.66	-5274.666	-4688.240
Heat of formation, (Kcal/ mol)	-947.2474	-493.81	-385.952	78.333
Electronic energy, (Kcal/ mol)	-2448900.461	-767786.5244	-770054.534	-512545.35
Nuclear energy, (Kcal/ mol)	2187135.48	665621.2789	666785.215	445672.321

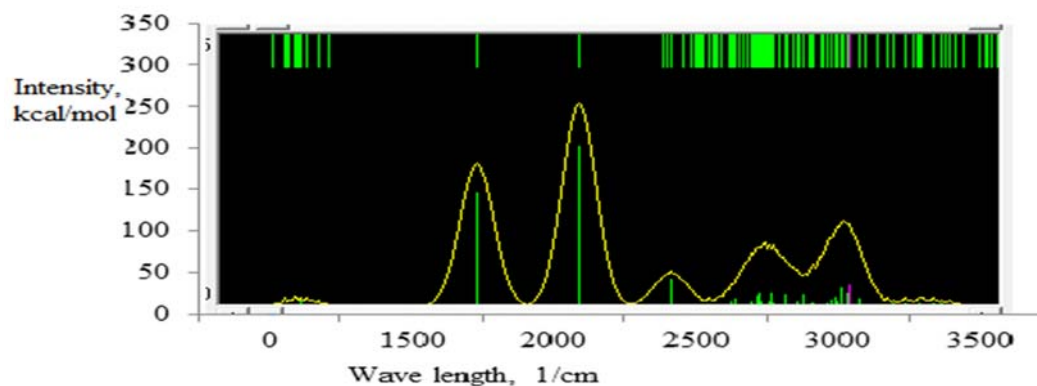
Characterization by electrostatic vibrational spectra (IR)

The most characterized peak of phosphonium ILs in vibrational electrostatic spectra was found as a broad peak in 2400 to 3000 cm^{-1} which indicates the confirmation of phosphonium cation.

IL01



IL02



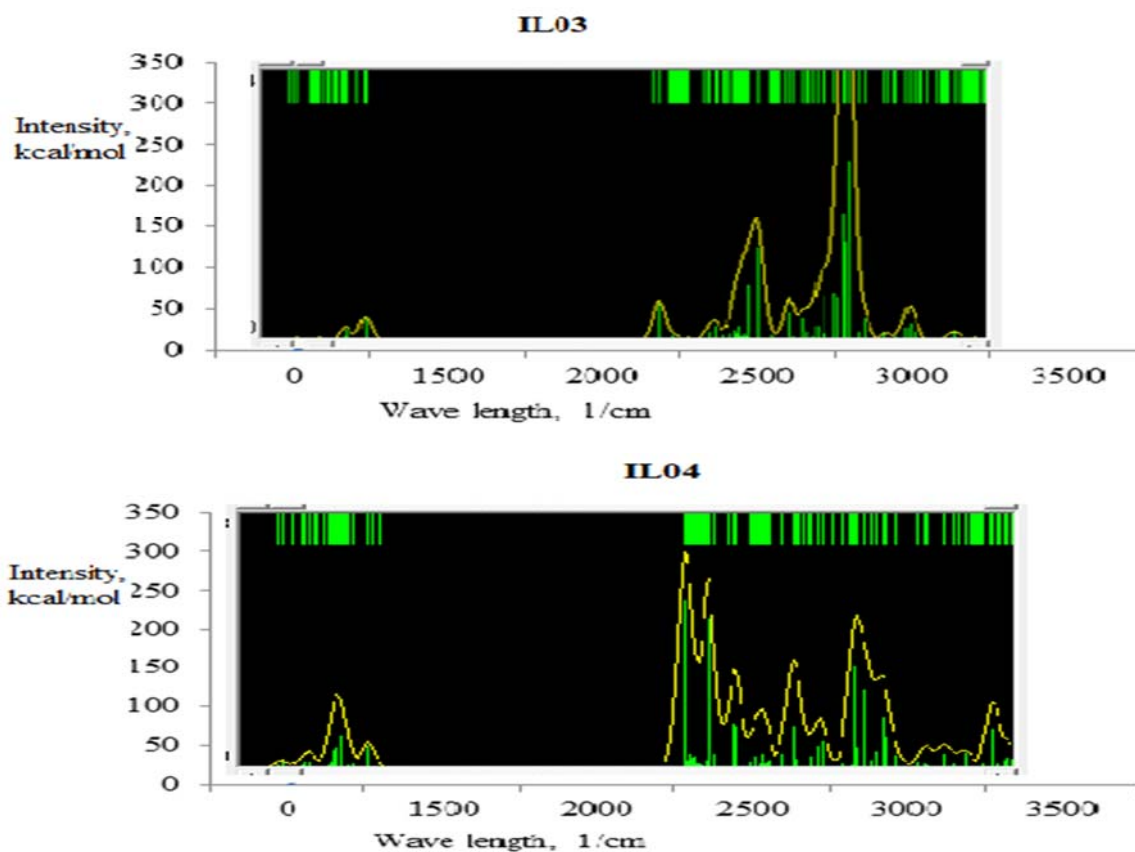


Figure 3: The vibrational spectrum of ILs

The stability of the studied molecular structure is given by the higher negative values of total energy. The biological activity of a compound can be estimated on the basis of the energy difference ΔE frontier orbitals. This difference, ΔE represents the electronic excitation energy which is possible in a molecule. According to the mechanism of antimicrobial activity and antimicrobial agents of bioactive molecules, the positive charge end of molecules is responsible to damage the plasma membrane of pathogens (Timofeeva and Kleshcheva 2011). The electrostatic potential in view of 3D mapped structure indicates positive and negative charge region and charged surface area in a molecule that is considered as the best tools to estimate the biological activity parameter. For the anticancer properties, greater value of ΔE indicates the higher activity. The surface distribution of molecular electrostatic potential is an indicator of the specific reactive regions of the molecule.

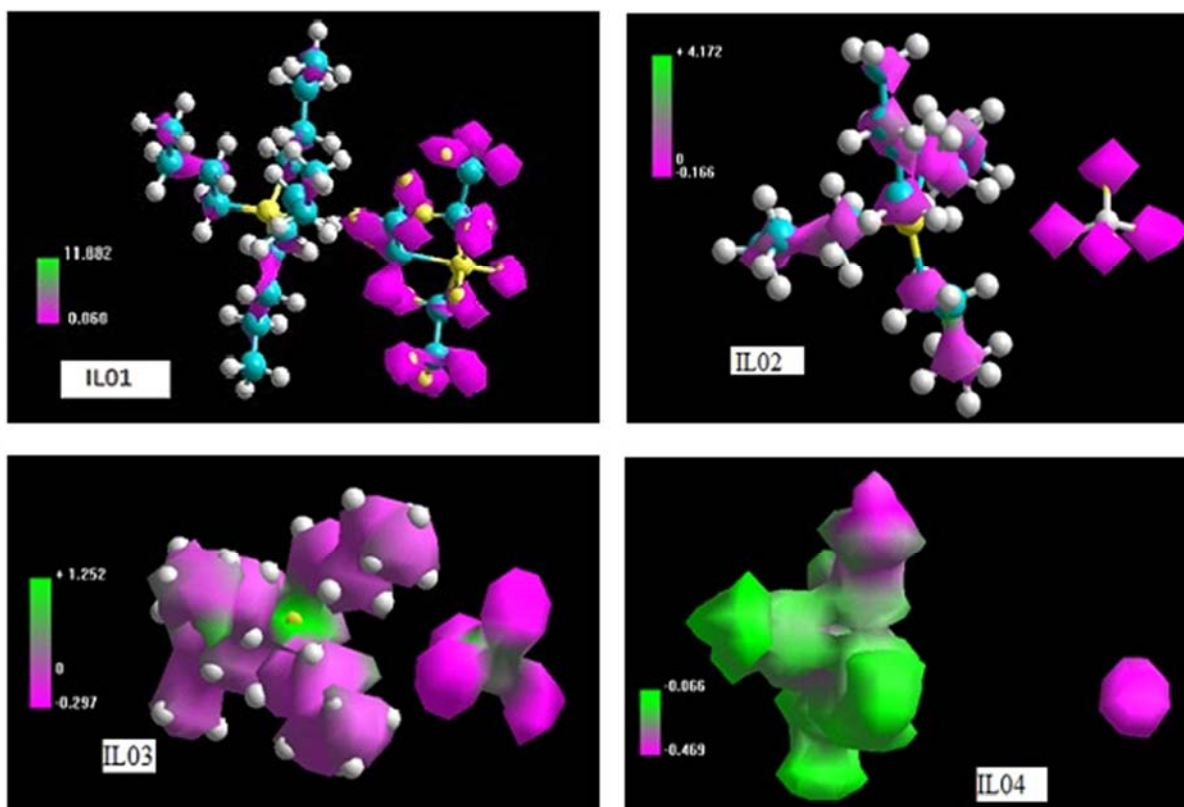


Figure 4: 3D mapped structure of electrostatic potential energy distribution

Table 4: Energy gap of 3D geometry of the distribution electrostatic potential				
	IL01	IL02	IL03	IL05
E1	+11.882	+4.172	+1.252	-0.066
E2	-0.060	-0.166	-0.296	-0.460
ΔE	11.942	4.338	1.548	3.94

Here, E1= Electrostatic potential energy in positive value, E2= Electrostatic potential energy in negative value, and ΔE = Electrostatic potential energy difference of two level. The highlights the existence of three regions with increased electronegativity in which oxygen atoms are involved, and that play a role in their coupling to different structures in which ions are positively charged.

QUANTITATIVE STRUCTURE - ACTIVITY RELATIONSHIPS (QSAR)

Correlate the molecular structure or properties derived from molecular structure with a particular chemical or biochemical activity (Gallegos, 2004)(Martras, Alvarez et al. 2004, Moreira, Fraga et al. 2004). This method is widely used in pharmaceutical chemistry in the environment and in the search for certain properties.

Table 5: Quantitative Structure - Activity Relationships (QSAR)				
	IL01	IL02	IL03	IL04
Partial charge (e)	0	0	0	0
Surface Area(grid),	790.06	607.17	649.0	711.58
Volume, Å ³	1511.31	1077.55	1156.21	1153.05
Hydration Energy	29733×10 ⁻²⁸	5.64	6.01	6.54
Log P	3.71	5.56	3.93	4.82
Refractivity, Å ³	105.42	85.08	90.62	85.22
Polarizibility, Å ³	42.99	33.76	32.48	33.61
Mass (amu)	705.49	347.25	367.41	295.90

Binding Energy

The binding free energy of the optimized molecules is calculated by performing docking process. The molecule with minimum binding energy will have the maximum binding affinity. The binding free energy is calculated by the formula

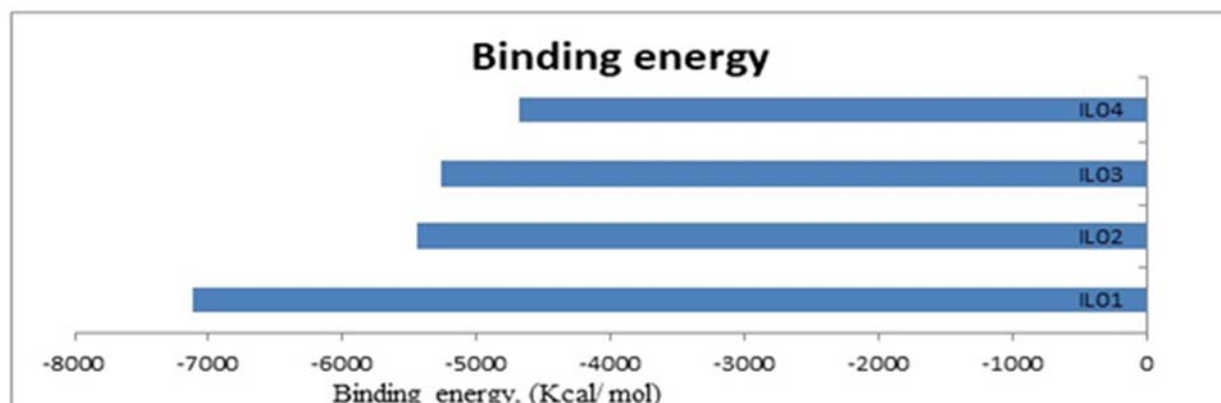


Figure 5: Binding energy of ILs

The binding free energy of the designed molecules is obtained by eliminating the energy of the main molecule. Having the maximum binding affinity, indicating as the best molecule for drug leads molecules targeting computationally. We can find out the drug binding affinity by using fitness of the drug, which can bind to target molecule during the docking process and second way is using Gibbs free energy calculations. According to this more negative value, we can consider as more effective drug. From the fig-03, it was found that the IL01 have the highest negative value of binding energy among all others so that it can be able to show the high effective activity as drug.

Surface area

In case of biological activity of molecule, the surface area is considered as the important parameter. Greater charge surface area of a molecule can be able to kill more pathogens. The charged distribution from electrostatic potential completely depends on the surface area. The greater positive charge surface area means the higher biological activity. From the table, the IL01 includes the highest surface area similar to binding energy then IL04, IL03, and IL02.

Hydration Energy

The hydration energy is defined as the energy absorbed when the substance is dissolved in water. The lower hydration energy is considered as the greater capacity to dissolve in water so that it acts as the hydrophilic nature and predict the best properties of drug. From the table-05, the important note for the IL01 contains a large number of hydrophobic energy which predicts that the dissolution of IL01 in water is quick difficult. As it is the best anticancer activity, but in view of hydration energy showing 29733×10⁻²⁸ that is unexpected but all others have lower hydration energy.

Log P

A negative value of log P indicates the hydrophobicity and positive Log P indicates the hydrophobicity that plays an important role in biochemical interactions and bioactivity in living cell. Hydrophobic drugs tend to be more toxic because, in general, are kept longer, have a wider distribution in the body, are somewhat less selective in their binding to proteins and finally are often extensively metabolized. Therefore ideal distribution coefficient for a drug is usually intermediate (not too hydrophobic nor too hydrophilic). QSAR data table shows that all molecules tend as hydrophobic nature in human body that range is 3.71 to 5.56. The IL01 has lower value of LogP that is recognized as that low toxic drug. It is derived the activity order IL01<IL04<IL03<IL02.

4. CONCLUSION

The semi-empirical PM3 method of the program HyperChem 8.01 was used to characterize and optimize of tributylmethylphosphonium pentafluoroethyl) fluorophosphate (IL-01), tributylmethylphosphoniumtri- (pentafluoroethyl) fluorophosphate (IL02), tributylmethylphosphonium tetrafluoroborate (IL03), and tributylmethylphosphoniumchloride (IL04). The physico-chemical parameters and thermodynamic properties were estimated for specific use to each molecule including 3D structure, bond lengths, the atomic charges, total energy, free energy, entropy, dipole moment, formation energy, binding energy, electrostatic energy, and nuclear energy. The molecular descriptors QSAR was used to calculate charge, surface area, volume, hydration energy, Log P, refractivity, polarizability, and molecular mass.

The most important properties for biological chemistry, reactivity and drug design, the HOMO, LUMO, HOMO-LUMO Difference, ionization potential, electron affinity, and electrostatic potential in case of charge distribution in molecule were optimized and recorded using semi-empirical modeling methods. The vibration and electronic spectra were evaluated by molecular modeling programs. Obtaining by modeling the distribution of molecular electrostatic potential reactive sites led to the identification and characterization of the molecules. It is summarized that the result optimized molecules of ILs was developed a comparative studies on their chemical reactivity, thermochemical profile and biological activity in view of theoretical studies.

ACKNOWLEDGMENT

I am thankful to Prof. Dr. Mukbul Ahmed Khan, V.C of European University of Bangladesh for his distinctive inspiration and I am also thankful to Zemam Ahmed Head of IT department and Mr. Moinul Islam, Assistant IT Officer, European University of Bangladesh, for all kind of technical supports.

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