Original Research Article

The prediction of thermo physical, vibrational spectroscopy, chemical reactivity, biological properties of morpholinium borate, phosphate, chloride and bromide Ionic Liquid: A DFT Study

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ABSTRACT

In the light of computational chemistry, based on morpholinium cation-based Ionic Liquid, their different types of physical, chemical, and biological properties is highlighted. The physical properties are evaluated through the Density Functional Theory (DFT) of Molecular Mechanics and also examine the chemical and biological properties. The difference between Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) is starting from 11.19 to 4.00, which means that their chemical reactions change as soon as an anion change is done. Biological activity of predictions given by QSAR calculation is forecasted. Where the value of all the LogP that is available is positive, which indicates hydrophobic, on the other hand, PIC50 calculations are found that all the values below 5 are biologically active. To identify these molecules, computational data is used to determine the vibrational spectrum and electronic spectrum.

Introduction

At present, morpholine is widely used in rubber and color industries as additive materials (1). The second use area in chemical industries as solvents for their low polar nature and low cost. The great deal is as solvents in synthetic process in solvent in organic synthesis, reactions and chemical industry research (2-4). It is also used in the manufacture of paper, glass, soap, detergent, dye and synthetic fiber (5). Morpholine is colorless and free of suspended matter. In recent time, it is finding as target additive molecule in both fossil fuel and nuclear power plant steam systems due to have pH adjustment (6, 7). The another key point of morpholine is a heterocyclic chemical compound containing both of nitrogen and oxygen atoms, which indicates amine and ether functional groups and focusing the amine groups becoming as morpholinium salt. Morpholine is a base due to the presence of the amine showing nucleophilic character typical of secondary amines (8). On the other hand, in the medical sciences, new discoveries of scientists have to be searched for new drugs day by day. The reason is that side effects of these medicines on human body and searching more effective medicines developed from rows. In medical science, about 20 drugs contain the morpholine moiety which was approved by FDA, although it is often metabolically labile. Morpholine-based analogues may advantageously alter important pharmacokinetic properties such as lipophilicity and metabolic stability (9). It was grafted into molecular scaffolds in previous case. The overall pharmacokinetics, it was inactive in experimental models of systemic mycoses. In reason strong protein binding and/or rapid metabolism and toxicity considerations have so far not allowed the further development of systemically active morpholines based drugs. If we go into our body after using morpholine as a drug, it may lead to headaches, stomach problems, respiratory problems, lightheadedness, kidney problems, and obstruction of blood circulation. Again, as an alternative to morpholine, scientists are trying to detect any other drug. On the other hand, since 2007, Ionic Liquid has played an important role in liquid drug discovery. Another quality of the third generation of Ionic liquid is bio active and they are called designer molecule. For these reasons it is very easy to invent new drugs by Ionic Liquid (10-12) for its tunable physical and chemical properties. During last five years, some researchers added different types of anion with morpholine to synthesize some morpholinium based ionic liquids for different purposes. Some ammonium carboxylate anion based ionic liquids were established as bioactive molecules by M. Ismail and A. Kumer 2017, 2018 (13-16). Some of which are biologically active and toxic much less than it parent molecule. It is extremely important for its anti-microbial activity to use one of the ingredients as a drug. If anti-microbial activity

can show good activity, he is nominated for use as a drug. Starting from the preparations, all their biological chemical thermo chemical properties are made to be used by experimental test. These are time-consuming and cost-effective. Through the use of computational chemistry, a lot of drugs are designed to detect chemicals, biochemical, and physiochemical properties. It is possible to establish a molecule of appropriate drugs by the properties. Morphine is a target for the discovery, with which different anion is made to produce various types of ionic liquids (17). Tetrafluroborate, Cl^-, BF_4^-, I-, NO_2-, NO_3^-, CO_3^{2-} and hexaflurophosphate are used for making ionic liquids. Our work has shown that due to any anion, biological activity is more available. From our some previous works, through computational chemistry, different chemicals such as HOMO, LOMO and HOMO LOMO gap differ by determining their chemical reactivity, QSAR study, how effective it is to find out how active the drug is in the human body, and how active the reactant environment. Thermophysical properties include banding power, entropy, electronics energy, heat of formation, and dipole moment of molecules tend to adapt to the environment where it is to use. Partitioning, Refractivity, Polarizibility, Hydration Energy is extracted through QSAR analysis for biological studies (18-24).

Computing methods for simulation

In case of drawing molecule, drawing default was selected and builds and analyzes different molecular structures and determines the molecular, electronic, and biological properties. 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. The first step in getting the main characteristic parameters of molecules is to optimize the molecular structure to obtain a configuration characterized by minimum free energy. In sitting the DFT was fixed via 6G-31G*, and B3-LYP(25). After completing optimization, the theoretical properties of the studied compound such as free energy, entropy, dipole moment, binding energy, nuclear energy, electronics energy, the heat of formation, the HOMO, LUMO are recorded. The QSAR properties of molecules like charge density, surface area grid, volume, LogP, polarizability, refractivity, molecular mass, were calculated. Using the computing in vibrational optimization, the UV Visible spectroscopy and Roman spectroscopy were determined.
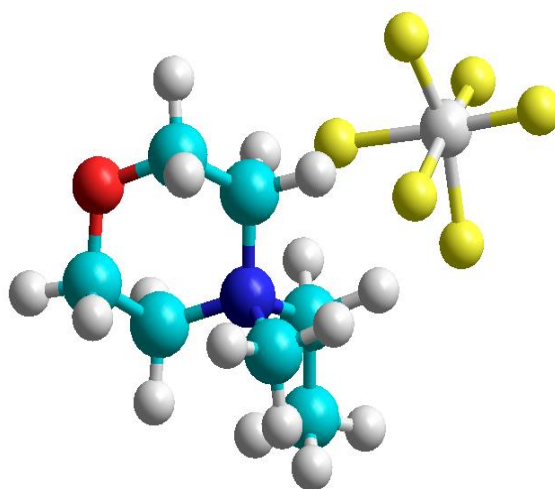
Results and discussions
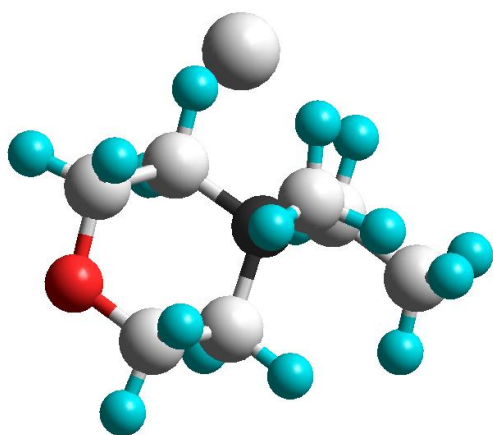
Optimized structure

Their plane of symmetry and asymmetry are found by optimizing the above mentioned compositional molecules shown in below fig-1. Using Computational Methods, the composition of the molecules is dissimilar and have more than 3 of plane of symmetry.
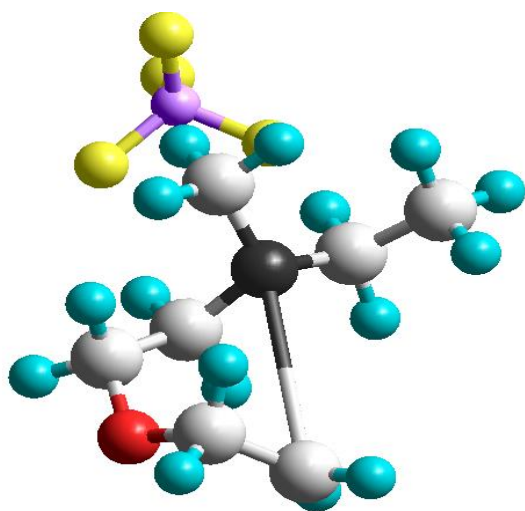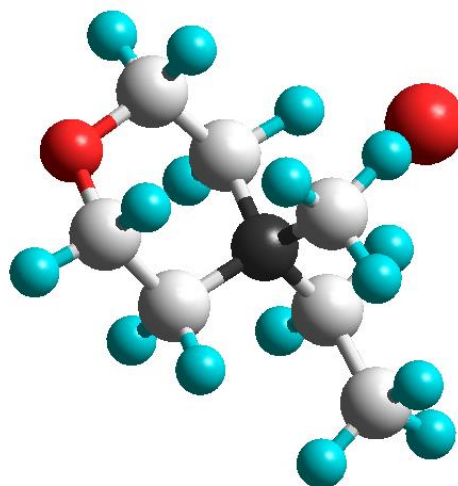

morpholiniumtetrafluroborate (IL01)   Morpholiniumhexaflurophosphate (IL02)

morpholiniumbromide (IL03)   Morpholiniumchloride (IL04)

Figure 1. Optimized structure in the cylinder shape, Color: Red is oxygen, cyan is hydrogen, yellow is fluorine, brown is carbon, gray is boron and white is phosphorous.

HOMO-LUMO

The energy levels of the molecular orbitals order HOMO and LUMO for different ILs give information on the possible electronic transition. The HOMO and LUMO also indicate the electrophilic and nucleophilic attraction region in molecule and the shorter LUMO- HOMO gap is considered as the high reactivity, they are highlighted in figure 2 (color: green is positive value and blue is negative value).
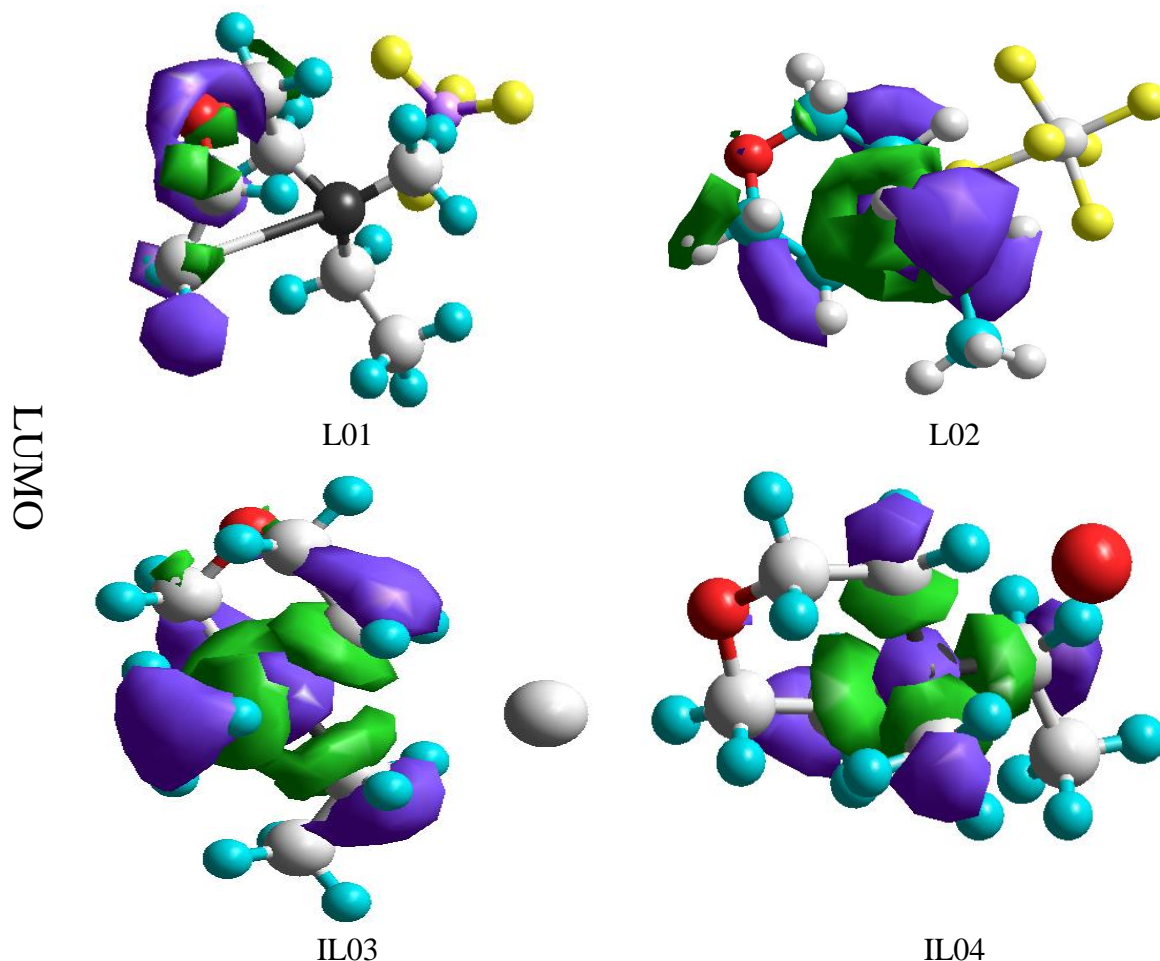

IL01

IL02

IL03

IL04
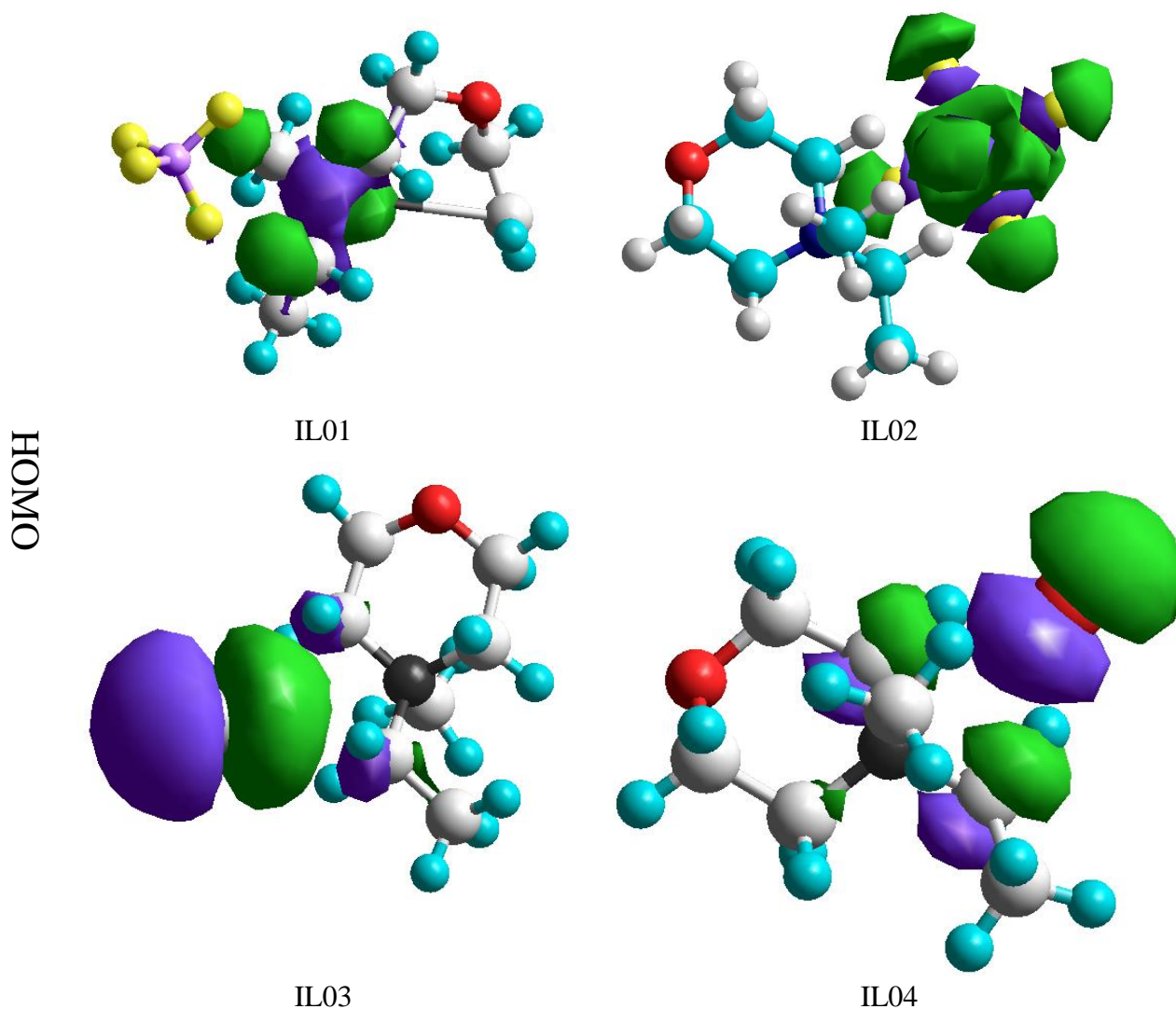
Figure 2. The frontier orbitals: a) HOMO and b) LUMO

Chemical reactivity by DFT Calculations:

The Energy of the HOMO is directly related to the ionization potential and LUMO Energy is directly related to the electron affinity. Energy difference between HOMO and LUMO orbital is called as energy gap which is an important parameter that determines the stability of the structures. The energy gap is used in determining molecular electrical transport properties and listed in table -1. In addition, according to Koopmans theorem the energy gap, Egap, defined as the difference between HOMO and LUMO energy (26).

$$E_{gap} = (E_{LUMO} - E_{HOMO}) \approx IP - EA$$

The ionization potential (I) and electron affinity (A) can be estimated from the HOMO and LUMO energy values as following

$$I = -E_{HOMO} \qquad (1)$$

$$A = -E_{LUMO} \qquad (2)$$

Table 1. Data for HOMO, LUMO, IP, EA, and LUMO- HOMO gap (ΔE)

	IL01	IL02	IL03	IL04
HOMO, (eV)	-5.9315	-1.4754	-7.9751	-8.8781
LUMO, (eV)	5.2661	3.2024	-0.7024	0.0766
ΔE, (LUMO-HOMO	11.1976	4.6778	7.2486	8.9547
Ionization potential (I),eV	5.9315	1.4754	7.9751	8.8781
Electron affinity (A),eV	-5.2661	-3.2024	0.7024	-0.0766

The HOMO and LUMO energies are used for the determination of global reactivity descriptors. It is important that electrophilicity (ω), chemical potential (μ), electronegativity (χ), hardness (η) and softness (S) be put into a molecular orbital's framework in table-2. We focus on the HOMO and LUMO energies in order to determine the interesting molecular or atomic properties and chemical quantities. These are calculated as following equations

$$(\mu) = -\frac{I+A}{2} \qquad (3)$$

$$(\eta) = \frac{I-A}{2} \qquad (4)$$

$$(S) = \frac{1}{\eta} \qquad (5)$$

$$(\chi) = \frac{I+A}{2} \qquad (6)$$

$$(\omega) = \frac{\mu^2}{2\eta} \qquad (7)$$

Table 2. Chemical reactivity

	IL01	**IL02**	**IL03**	**IL04**
Hardness, (η)	5.5988	2.3389	3.6363	4.4773
Softness, (S)	0.1786	0.4275	0.2750	0.2233
Electrophilicity (ω),	0.0098	0.1593	2.5883	2.1620
Chemical potential, (μ)	-0.3327	0.8635	-4.3387	-4.400
Electronegativity, (χ)	0.3327	-0.8635	4.3387	4.400

Thermophysical properties

Binding energy is a key parameter to use as a drug that can be used for drug discovery. Binding energy standards can be either positive or negative. It is better to have a large value negative for drugs, where the value is more negative, the tendency to get involved is so much that the molecule is so good as a drug. From the table 3 below, it is seen that the binding energy of IL1 and IL2 is close to three thousand, which is much more involved now. On the other hand, Heat Of formation is an important feature by which the ductility of the molecules indicates the stability of the IL1 and IL2 is 8 to 10 times the stability than IL3 and IL4 from table 3.

Table 3. Thermophysical properties

Properties	IL01	IL02	IL03	IL04
Total energy, (kcal/mol)	-77784.1712	-99209.4126	-43483.9728	-42641.0422
Entropy, (kcal/mol-deg)	0	0	0	0
Free energy, (kcal/mol)	-77784.1712	-99209.4126	-43483.9728	-42641.0422
Heat capacity, (kcal/mol-deg)	0	0	0	0
Dipole moment, (D)	0	17.35	14.4	9.095
RMS gradient, (kcal/mol)	0.1771	0.0007	0.000074	0.000098
Binding energy, (kcal/mol)	-2891.2676	-2865.2821	-2267.6471	-2285.9296
Heat of Formation	-477.5866	-473.9511	-38.4861	-54.5186
Electronic energy, (kcal/mol)	-393521.9751	-557792.9106	-239014.9015	-241284.8532
Nuclear energy, (kcal/mol)	315737.8039	458583.4979	195530.9286	198643.8109

Table 4 shows that with the increase in temperature, all the entropy and heat capacity are changed in a specific way thus both the parameters of IL01 andIL02 are increasing. On the other hand IL03 IL04 is increasing both parameters which are less than IL01 and IL02. So it can be said that the IL01 and IL02 enlargement entropy and heat capacity are increasing with the

increase in temperature as compared to others. Entropy rules mean that the disturbing of the ordered will increase.

Table 4. Temperature effect on Entropy and Heat of capacity					
273 K		298 K		323 K	
Entropy	Heat capacity, (kcal/mol-deg)	Entropy	Heat capacity, (kcal/mol-deg)	Entropy	Heat capacity, (kcal/mol-deg))
IL01	0.1358	0.0561	0.1411	0.0600	0.1462	0.0639
IL02	0.1200	0.0641	0.1260	0.0686	0.1318	0.0729
IL03	0.1019	0.0400	0.1058	0.0436	0.1096	0.0472
IL03	0.0949	0.0389	0.0986	0.0725	0.1024	0.0462

Vibrational spectrum

The existence of the functional group in the molecule can be identified through the vibrational spectroscopy. Since Morpholinium cation creates ionic liquids in combination with various types of inorganic anion, and then there is a large spectrum of between 3000 to 3500 cm^{-1} for NH levels of morpholinium cation shown in fig-3. It is also found available for 2500 to 2200 cm^{-1} spectrums for CH of morpholinium cation. The calculating different modes for vibrational spectroscopy are given in table-05.
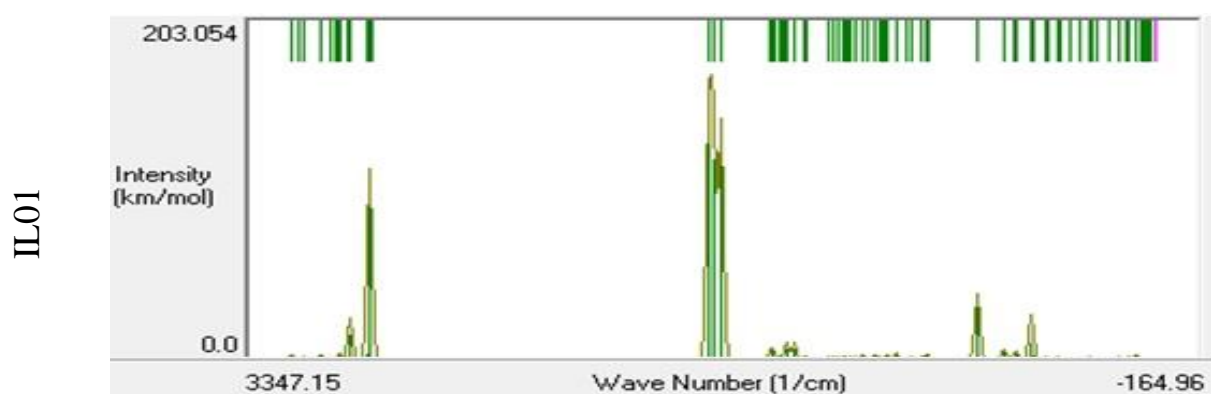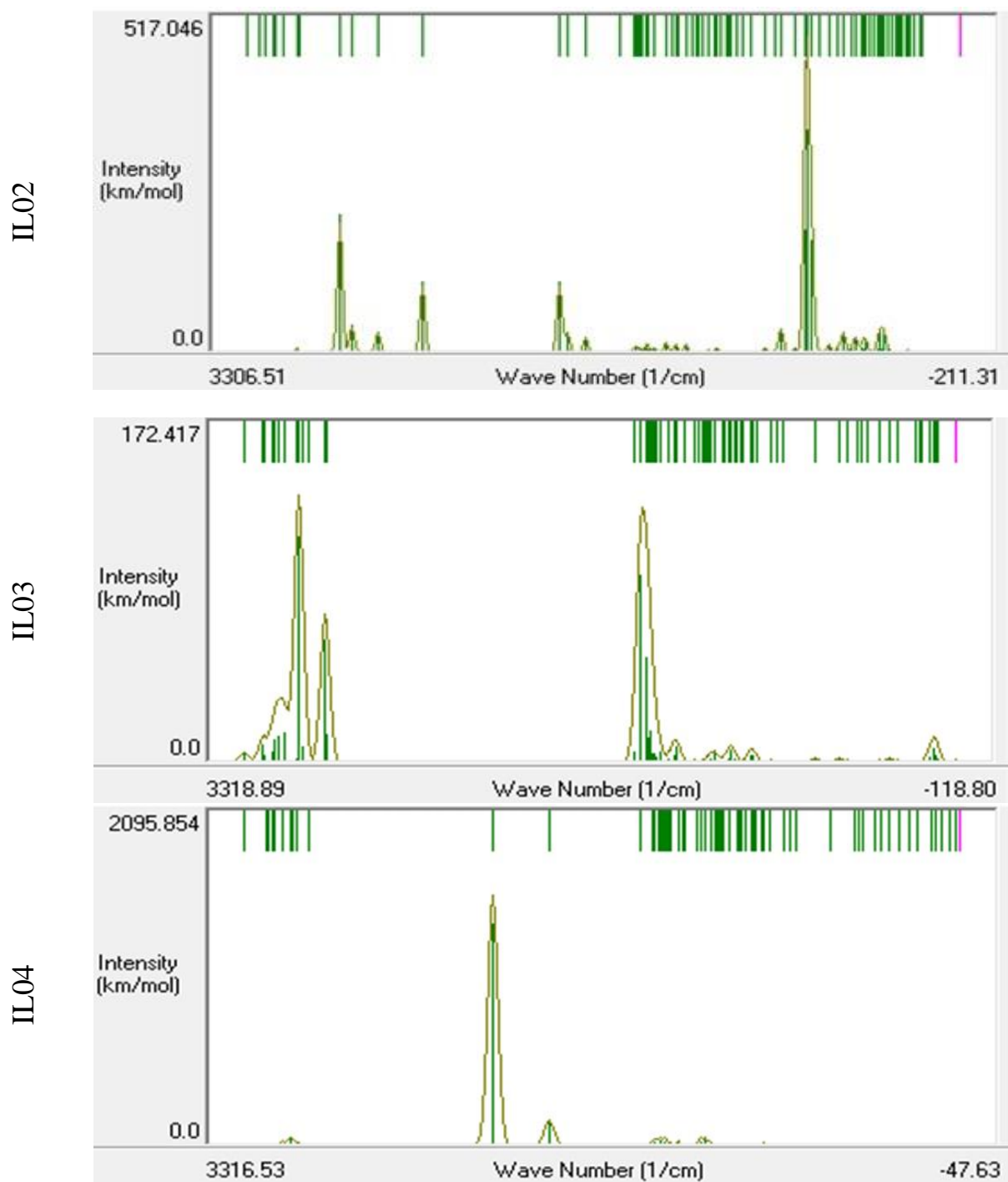
Figure 3. Vibrational spectrum

Table 4. Data for vibrational spectroscopy

	Normal Mode	Degeneracy	Frequency	Intensity	Symmetry
IL01	1	1	-5.32	0.076	1 A

IL02	1	1	-51.41	0.943	1 A
IL03	1	1	37.46	0.906	1A
IL03	1	1	105.28	1.195	1A

UV-visible Spectrum

UV-visible Spectrum provides a powerful technique by which the nature of nitrogen ion with anion bonding may be identified (27). The UV-visible spectrum of the morpholinium based ILs shows a strong transition (near 150 and 190 nm) shown in fig 4. The calculating different modes for UV visible spectroscopy are given in table 5.
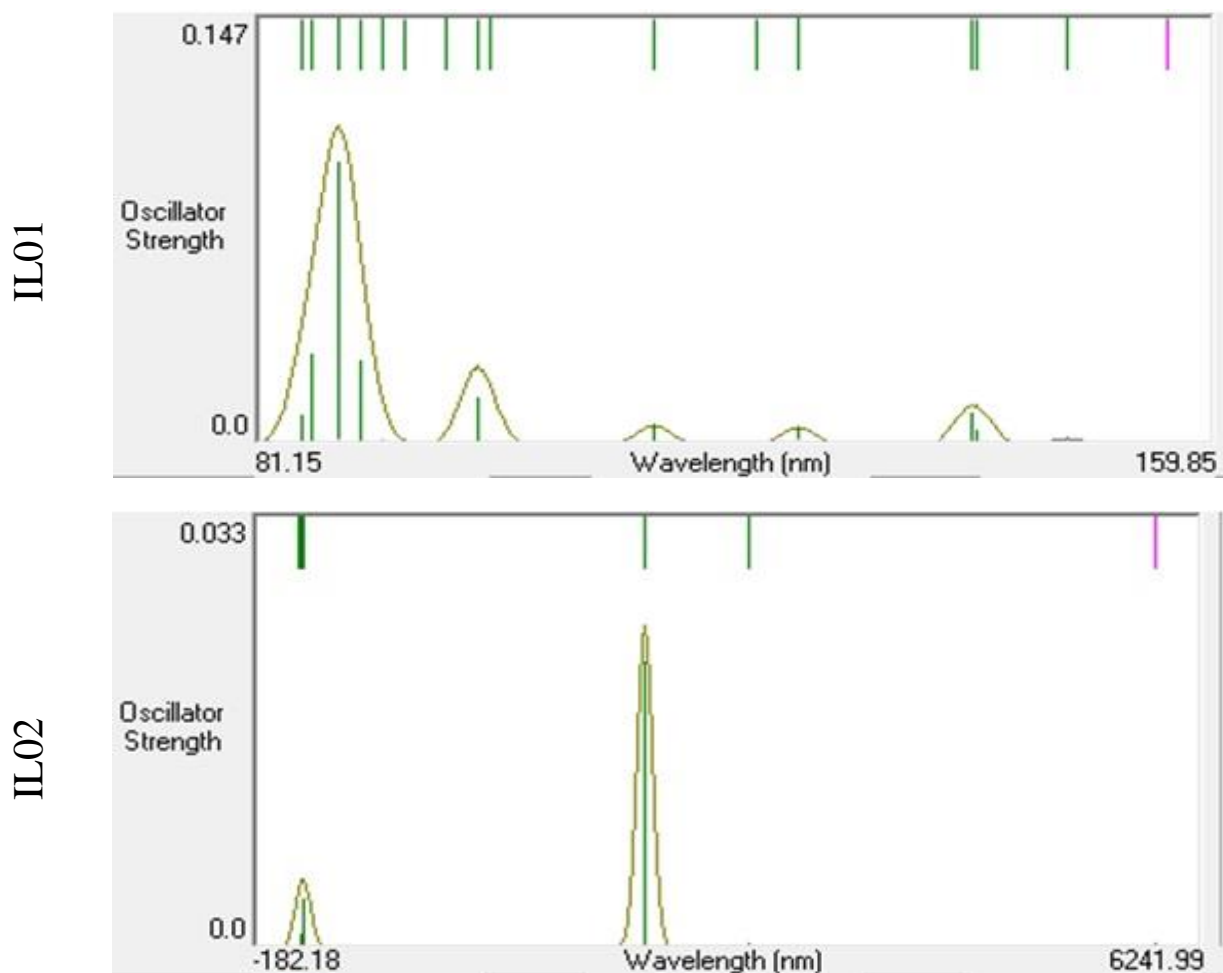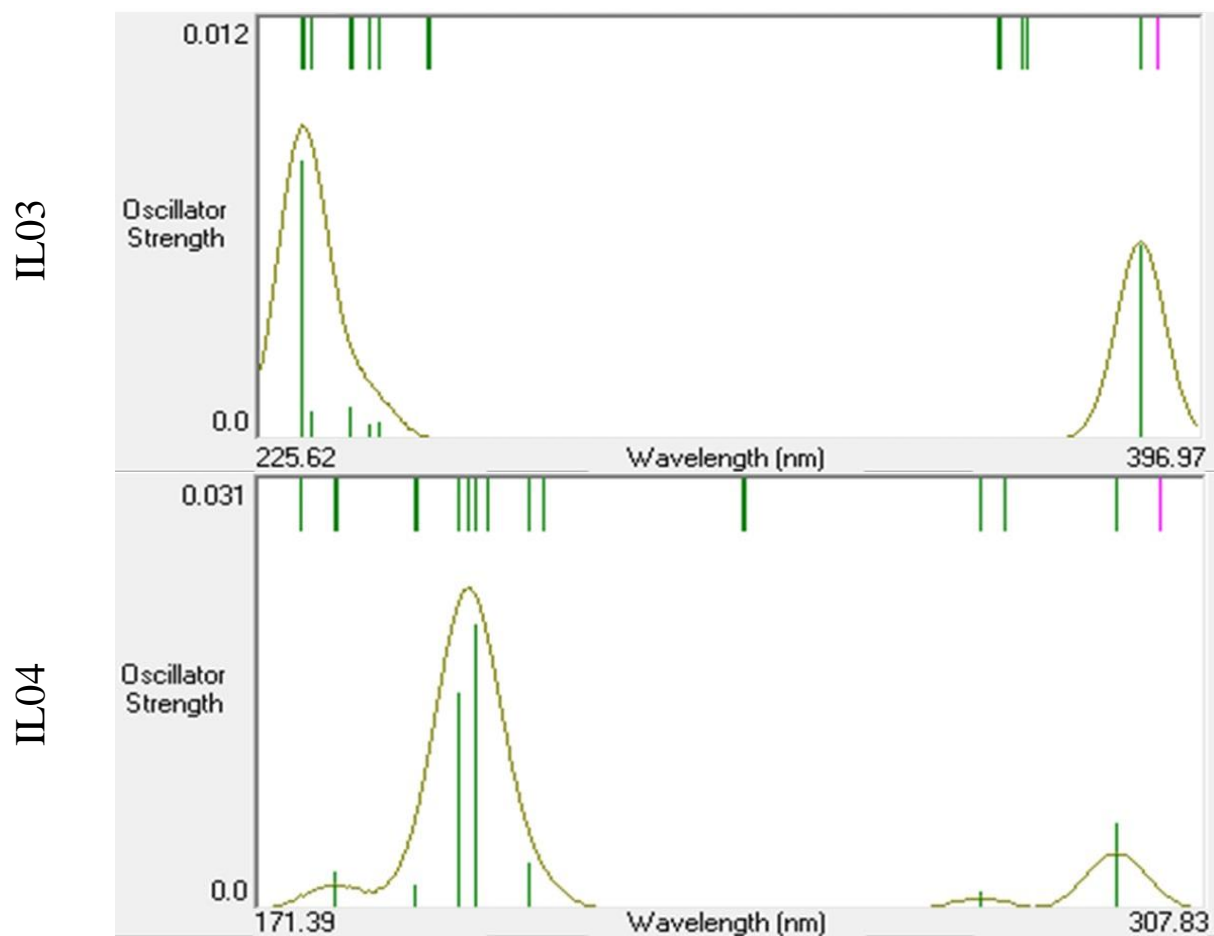
Figure 4. UV spectroscopy

Table 5. Data for electronic spectroscopy

|	Transition	Degeneracy	Spin Multiplicity	Wavelength	Oscillator Strength
IL01	1	1	triplet	156.27	0.0
IL02	1	1	doublet	5949.98	0.0
IL03	1	1	triplet	389.18	0.0
IL04	1	1	triplet	301.63	0.0

Biological activity by distribution electrostatic potential due to 3D mapped structure

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 given in table-05. This difference, ΔE represents the electronic excitation energy which is possible in a molecule. The electrostatic potential in view of the 3D

mapped structure indicates positive and negative charge region and the charged surface area in a molecule that is considered as the best tools to estimate the biological activity parameter (28).
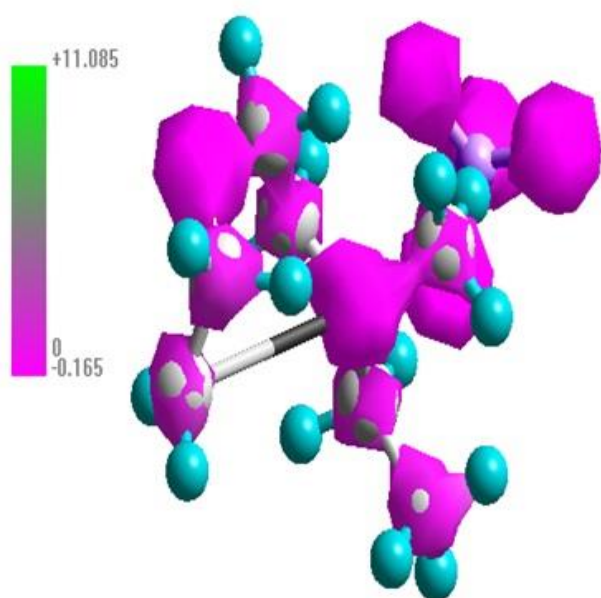
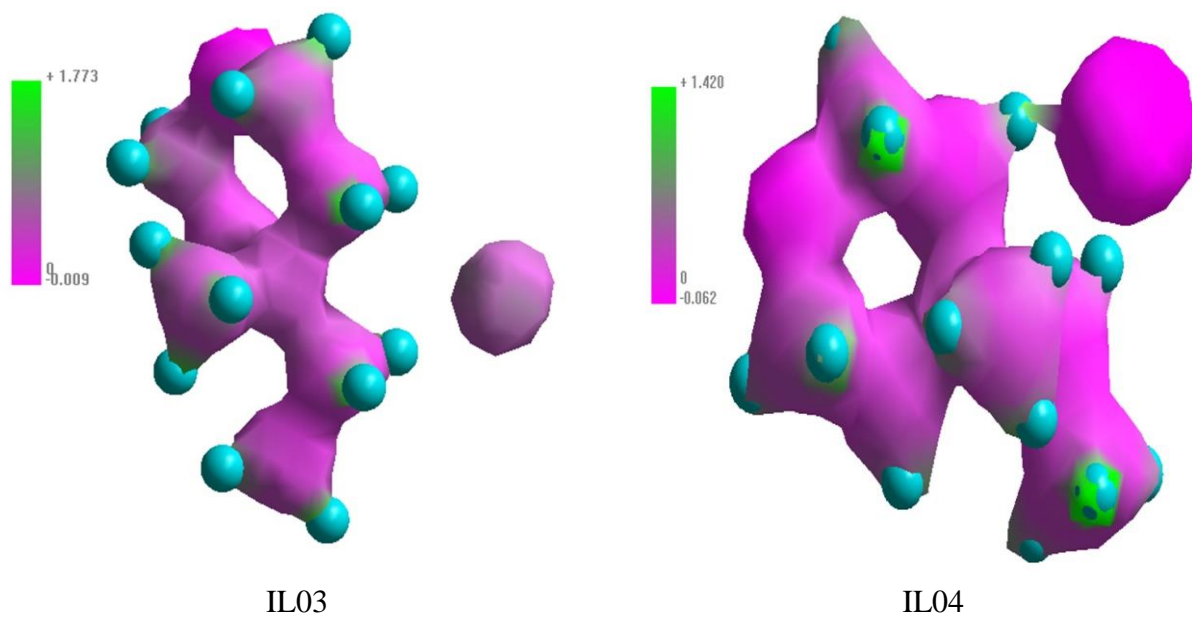IL01   IL02
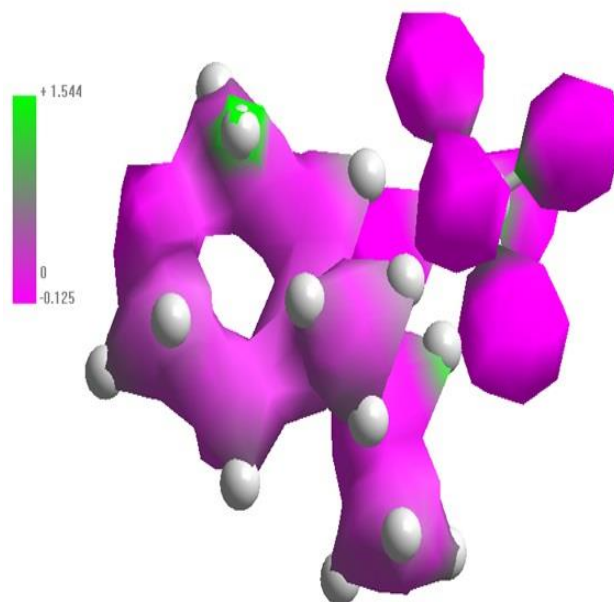
IL03   IL04

Figure 7. The 3D geometry of the distribution electrostatic potential

Table 6. Data of electrostatic potential energy difference of two levels

	IL01	IL02	IL03	IL04
E1	+11.085	1.544	+1.773	+1.420
E2	-0.165	-0.125	-0.009	-0.062
ΔE= E2-E1	-11.25	-1.669	-1.782	-1.482

Here, E1 = Electrostatic potential energy in positive value, E2 = Electrostatic potential energy in negative value and ΔE = Electrostatic potential energy difference of two level.

Quantitative structure-activity relationships (QSAR)

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 (29). To kill the different human pathogenic microorganism, the region of molecules was used the positive charge area of the molecule. In this case, the most important factors are explained that the higher surface area having a positive charge is considered as the high antimicrobial activity. From table -7, it was found that LogP is 1.35, 2.19, 0.62, and 0.32 respectively IL01, IL02, IL03, and IL04 and indicates hydrophobic nature and more toxic.

Table 7. Data for QSAR study

	IL01	IL02	IL03	IL04
Partial charge (e)	0.0	0.0	0.0	0.0
Surface Area(grid),	404.82	394.31	352.31	338.10
Volume, Å^3	643.0	636.80	554.69	527.67
Hydration Energy kcal/mol	0.61	0.30	0.59	0.59
Log P	1.35	2.19	0.62	0.32
Refractivity Å^3	40.10	41.84	45.34	42.75
Polarizibility, Å^3	16.72	16.03	17.27	16.57
Mass (amu)	217.01	275.17	210.11	165.66

Calculation of PIC50

The correlation between the biological activity and descriptor is developed by Zineb Almi et.al. 2014 (**30**)for the PIC50 value calculation from the HyperChem simulation value that is given in following equation as

$$PIC50 = 3.028 - 0.542logP + 0.352\,HE - 1.272\,Pol + 0.863MR - 0.038\,MV - 0.024MW + 19.120q01 + 0.024SAG$$

Here, HE=Hydration Energy, Pol= Polazibility, MR= Molecular Refractivity, LogP= Partition coefficient, MV= Molar Volume, MW= Molar Weight, SAG= Surface Area Grid, q01= atomic net charges.

Similar ways, we know that, pIC50 = -log IC50

Table 8. Data of PIC50

Data of PIC50				
	IL01	IL02	IL03	IL04
PIC50	-4.4077	-3.6426	2.399	3.0

The PIC50 value is important for biological properties evaluation, where PIC50 is below -5, then the IC50 value falls below 10000 ppm which can be used as an acceptable mark of standard antibiotic. The value of PIC50 obtained from table 8 can be seen that the value of PIC50 for the newly designed molecules is given below -5 where the value of IC50, can be considered as a standard antibiotic less than 100,00 ppm. Finally, our goal was to design a bioactive new molecule. All the Ionic liquids can be used as high-level antibiotics, whose toxic labels must be limited.

Conclusion

Finally, it is possible to see a change in the physical properties of new bioactive molecules, on the basis of anion change. However, the appropriate anions for drug designs with morpholinium cation are a tetrafluroborate and hexafluorophosphate anion. In the presence of these two anions, morpholinium can show the most biological activity, but not how much increases in the presence of morpholinium. Likewise, the value of LogP is increased, in the presence of the chloride and bromide ion with morpholinium, means that toxicity increases. So it can be said that the best drug can be made by adding tetrafluroborate and hexaflurophosphate anion to the morpholinium cation.

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