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**Original Research Article**

# A computational estimation for alkyl chain effect in Schiff base pyridinium fluoride ionic liquid on chemical reactivity, thermophysical properties, pharmacokinetics, and biological activity by DFT approach

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**ABSTRACT**

Amphiphilic pyridinium fluoride is the novel class of ionic liquid for drug discover for their biological and pharmacological activity. In this case, amphiphilic pyridinium cation was selected to this study. Changing the alkyl chain length, the effect was estimated on thermophysical, chemical, and biological activity. Using density functional theory (DFT), thermophysical and HOMO, LUMO were optimized and calculated. From HOMO, LUMO, the ionization energy, electronegativity, softness, hardness, electrophilicity (ω) and chemical potential (μ) were calculated. The HOMO, LUMO, and HOMO-LUMO gap are near to-8.85, -0.85, and 8.0. From QSAR study, the value of the Log P is from +1.5 to +2.6 as hydrophobic nature. As is observed the pharmacokinetics data, the Lipinski rule, bioavailability score, lead likeness, solubility, and LogP o/w were calculated.

**Keywords:** Pyridine, Ionic Liquids, QSAR, HOMO, LUMO, and Pharmacokinetics

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## Introduction

Schiff bases are considered the most important class of materials for biological chemistry specially antimicrobial agents [1]. Among of them, nowadays, pharmaceutical drug against different micro pathogens is most demanding fields. Secondly, a number of molecules having azomethine Schiff base skeleton are the clinically approved drugs used for treatment of antimicrobial, anticancer, anti-HIV, and anticandidal activities [2]. In the Schift bases, the most common linkage is hydrozone ($RCONHN=CR_1R_2$), which carries on all chemical and pharmaceutical behaviors [3]. The most fascinating properties of pyridine hydrozone are chemotherapeutic nature, and heterocyclic scaffolds [4]. On the other hand, the ionic liquids is known as the designer and green molecule for 21$^{st}$ century due to its tunable chemical and chemical properties which consist of discrete cation and anion with low melting point or melted salt in room temperature. ILs can show the high thermal stability, low volatility, various viscosity, high salvation energy, and low toxicity [5]. In this work, the nitrogen atom of pyridine hydrozene is targeted to convert in the pyridinium salt as ionic liquids to evaluate their biological and chemical behaviors because pyridinium hydrozone salts have already documented as microbial agents last two years. The most important point is specified for pyridinium salts in the alkyl length. With changing the alkyl length in nitrogen atom of hydrozone group, it could be changed its nature. A theoretical investigation using computational approach though the DFT method, the change of alkyl length effect on chemical reactivity, thermophysical properties, pharmacokinetics, and biological activity were estimated [6-12]. The carboxylate anion with ammonium cation can show antimicrobial activity, and halide anion was selected for investigation [13-16]. The computational approach is the best tool to explain the theoretical study of molecule. The HOMO, and LUMO estimation of molecules belongs to the region of electrophilic and electrophonic area. In our previous work [17-21] for ionic liquids and complex of metallic crystal shows the HOMO, LUMO value is near from -9.00 to -7.00, and from -2.00 to 0.50 [6, 18, 22-25]. The second addressing documents for thermophysical and physical properties which contribute a theoretical profile for their application were documented using the computational tools. Finally, the biological activity was evaluated by quantitative structural activity relationship where include the surface area, volume, refractivity, polazibitily, logP, and molecular weight. The logP mention the toxicity and non toxicity having value of positive and negative.

## COMPUTING METHODS FOR SIMULATION

The molecular modeling program permits to build and analyze different molecular structures and determine 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 and chemical structure is converted into 3D structure. In sitting the DFT was fixed via 6G-31G*, and B3-LYP [26-27]. For this calculation, model build was done at first, then fixed the 6G-31G*, total charge zero, spin multiplicity one, UHF, convergence limit is 1e-006. The cut off is fixed 1e-006 with core Hamialtaian calculation and done geometry optimization to record the data of free energy, entropy, dipole moment, binding energy, nuclear energy, electronics energy, the heat of formation, the HOMO, LUMO, 3D mapped structure of electrostatic potential. The QSAR properties were calculated.

## RESULTS AND DISCUSSIONS

## OPTIMIZED STRUCTURE

The optimized structure of molecules using the HyperChem 8.0.10 software is represented in figure. 1. This molecular orbital diagram addressed about the reactivity indices, molecular symmetry, and molecular asymmetry.

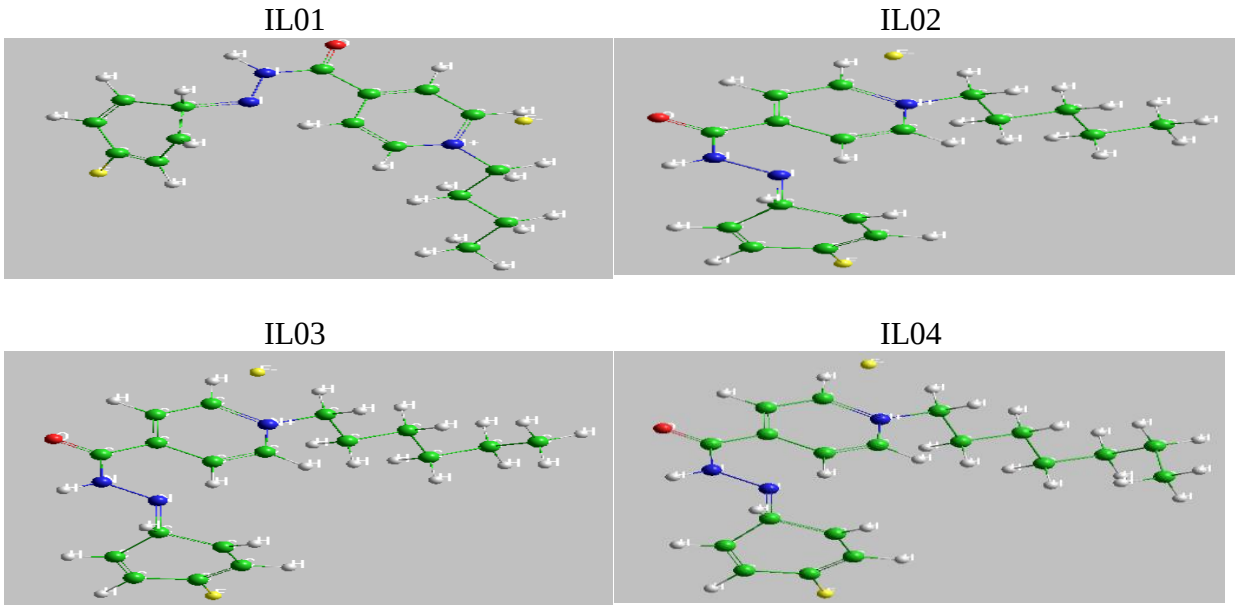


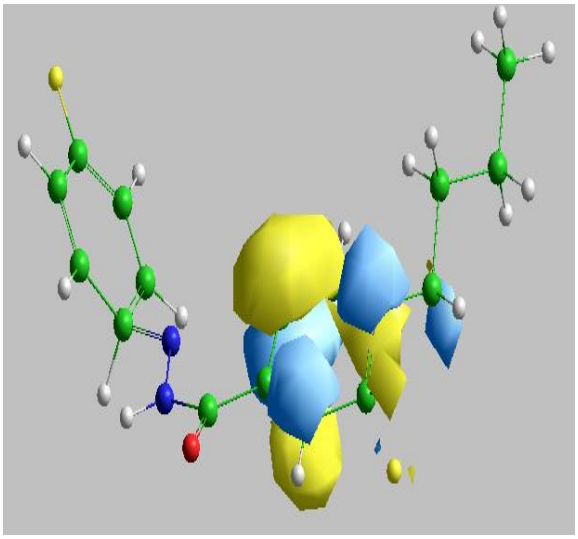

**Figure 1.** Optimized molecular orbital picture

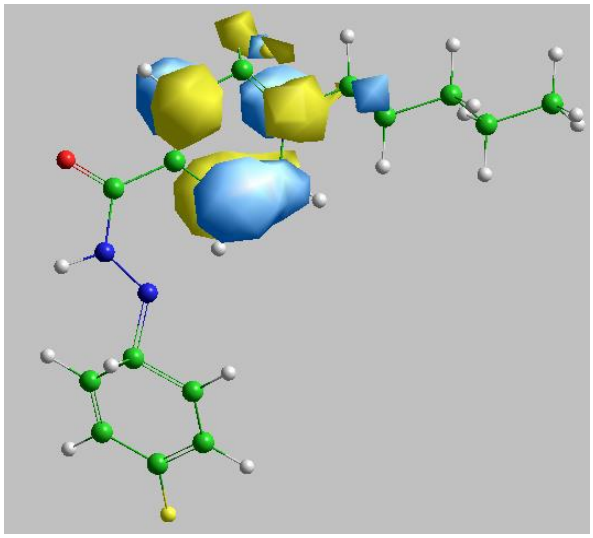
## HOMO-LUMO

The HOMO and LUMO are the best tools to determine the chemical reactivity of molecule, and possible electronic transition. The HOMO and LUMO also indicate the electrophilic and nucleophilic attraction region in molecule. In the 2, documents the positive and negative charge region where the light blue is positive and the yellow is negative. The second reason is that the shorter LUMO-HOMO gap is regarded the grater chemical reactivity. The IL01, IL02, IL03, and IL04 include the HOMO region in hydrozone containing pyridine ring only but the LUMO is surrounding in pyridine and nitrogen-carbon- oxygen atom containing chain. In the time of calculation for HOMO, and LUMO, the orbital contour value for IL01, and IL02 is 0.03, and for IL03, and IL04 is 0.015. From table 2, the magnitude of HOMO for IL01, IL02, IL03, and IL04 are -8.83, 8.86, -8.85, and -8.85 which are almost same. The values of LUMO for IL01, IL02, IL03, and IL04 are -0.71, -0.86, -0.84, and -0.84 respectively. The chemical reactivity parameter relating HOMO, LUMO gap energy is from -8.12 to -8.00. Therefore it can be said that the effect of alkyl chain has no activity on HOMO, LUMO or chemical reactivity.

IL01 IL02

HOMO





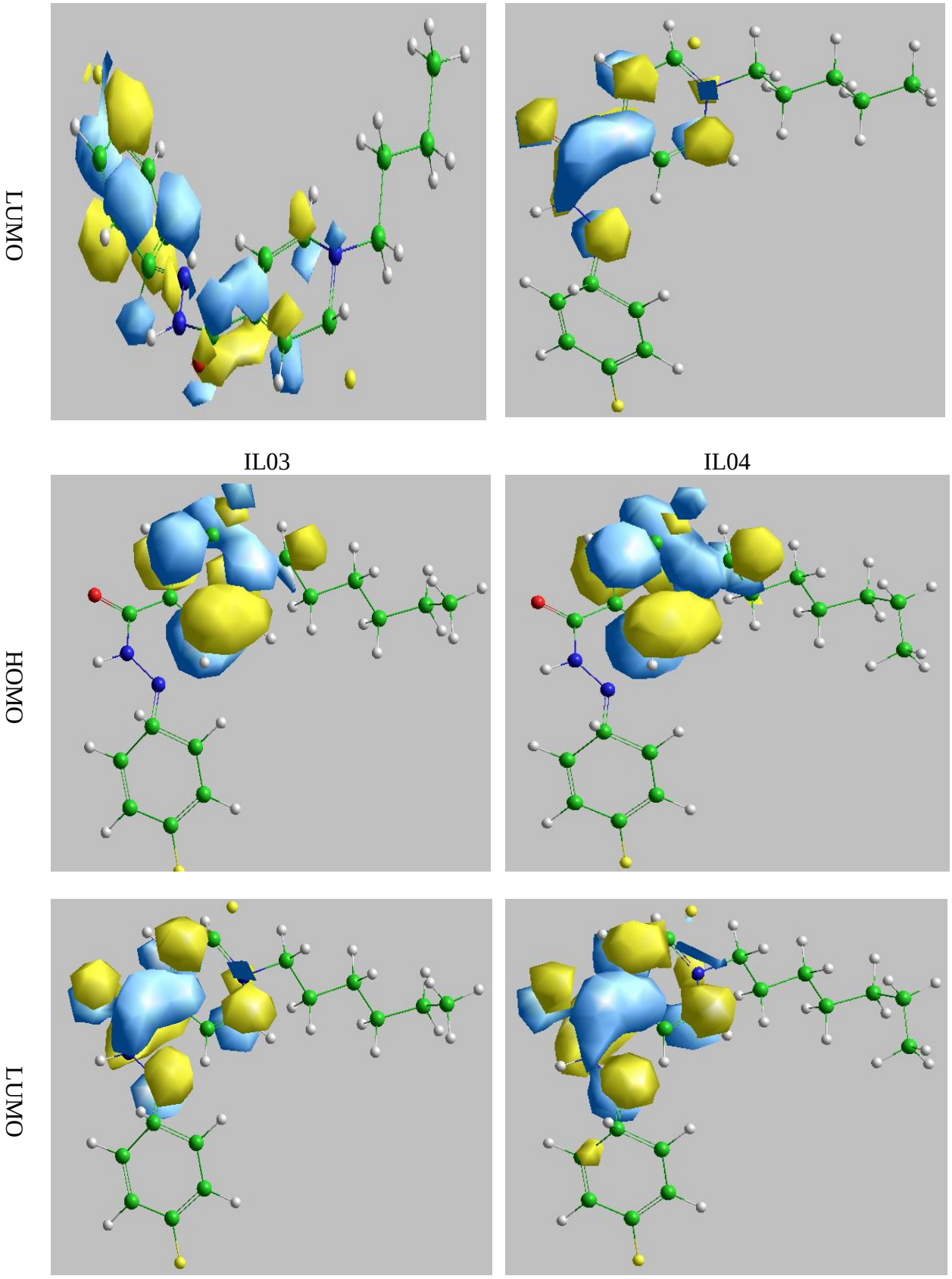



**Figure 2,** HOMO, LUMO orbital picture

| Table 1. Data for Orbital contour value of HOMO, and LUMO | | | | |
|---|---|---|---|---|
| | IL01 | IL02 | IL03 | IL04 |
| Orbital contour value for HOMO | 0.03 | 0.03 | 0.015 | 0.015 |
| Orbital contour value for LUMO | 0.03 | 0.03 | 0.015 | 0.015 |

## Chemical Reactivity Calculations

In addition, according to Koopman's theorem for energy gap ($E_{gap}$) defined as the difference between HOMO and LUMO energy [28].

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

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

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

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

The HOMO and LUMO energies are used for the determination of global reactivity descriptors. The electrophilicity (ω), chemical potential (μ), electronegativity (χ), hardness (η) and softness (S) are calculated using following equation [12].

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

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

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

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

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

Table 2. Data of HOMO, LUMO in different energy levels

| | IL01 | IL02 | IL03 | IL04 |
|---|---|---|---|---|
| HOMO(0), eV | -8.83 | -8.86 | -8.85 | -8.85 |
| LUMO, (0), eV | -0.71 | -0.86 | -0.84 | -0.84 |
| ΔE, (LUMO-HOMO) gap | -8.12 | -8.0 | -8.01 | -8.01 |
| Ionization potential (I),eV | 8.83 | 8.86 | 8.85 | 8.85 |
| Electron affinity (A),eV | 0.71 | 0.86 | 0.84 | 0.84 |
| Hardness, (η) | 4.06 | 4.0 | 4.0 | 4.0 |
| Softness, (S) | 0.24 | 0.25 | 0.25 | 0.25 |
| Electrophilicity (ω), | 2.80 | 2.95 | 2.92 | 2.92 |
| Chemical potential, (μ) | -4.77 | -4.86 | -4.84 | -4.84 |
| Electronegativity, (χ) | 4.77 | 4.86 | 4.84 | 4.84 |

## Thermophysical Properties

The laws of thermodynamics govern drug-molecule binding with targeting molecules where the entropy indicates how tightly a drug binds to its target. If energy is conserved, the amount does not change, and that entropy increases in any biomedical system. When a drug binds to its target, its entropy decreases, so disorder must increase somewhere else in the cell, usually in the abundant water molecules found in a cell, Sharp suggests. That increase in disorder can be detected as heat flowing into the water surrounding the drug-target bond. From table 3, it is found that the entropy is zero without water or drug molecule binding. The binding free energy of the optimized molecules is calculated by DFT before docking with target molecules. It is noted that molecule with minimum binding energy will have the maximum binding affinity. With increasing the alkyl chain, the binding energy increases which indicates the drug affectivity is raising up.

**Table 3.** Thermophysical properties

| Properties | IL01 | IL02 | IL03 | IL04 |
|---|---|---|---|---|
| Total energy, (kcal/mol) | -88713.6 | -92162.3 | -95610.5 | -99058.8 |
| Entropy, (kcal/mol-deg) | 0.0 | 0.0 | 0.0 | 0.0 |
| Free energy, (kcal/mol) | -88713.6 | -92162.3 | -95610.5 | -99058.5 |
| Heat capacity, (kcal/mol-deg) | 0.0 | 0.0 | 0.0 | 0.0 |
| Dipole moment, (D) | 0.0 | 0.0 | 0.0 | 0.0 |
| RMS gradient, (kcal/mol) | 0.0115 | 0.0173 | 0.038 | 0.032 |
| Binding energy, (kcal/mol) | -4188.43 | -4469.10 | -4749.51 | -5029.57 |
| Heat of formation, (kcal/mol) | -27.91 | -33.49 | -38.61 | -43.77 |
| Electronic energy, (kcal/mol) | -595982.02 | -635351.46 | -677857.43 | -723081.47 |
| Nuclear energy, (kcal/mol) | 507268.45 | 543189.19 | 582246.91 | 624022.67 |

## Biological Activity of Optimized Molecules

## The Distribution Electrostatic Potential

Electrostatic potential maps, or electrostatic potential energy maps, or molecular electrical potential surfaces, demonstrate the charge distributions of molecules three dimensionally which mentions to visualize variably charged regions of a molecule, and molecular interaction with one another. Electrostatic potential energy is fundamentally a measure of the strength of the nearby charges, nuclei and electrons, at a particular position. A computer program then imposes the calculated data onto an electron density model of the molecule derived from the Schrödinger equation. To make the electrostatic potential energy data easy to interpret, a color spectrum, with red as the lowest electrostatic potential energy value, and positive charge distribution and blue as the highest and negative charge distribution.

On the other hand, the highest charge distribution of ionic liquids mentions the highest antimicrobial activity because the discrete charge for cation or anion can kill the plasma membrane of pathogen. From the table 4, it is found that the charge distribution highest order for antimicrobial activity is addressed as IL04, > IL01> IL03> IL02. Finally it can be deduced from table 4 data, and 3 for both of chemical reactivity, and biological activity is slightly changed due to change of alkyl chain.

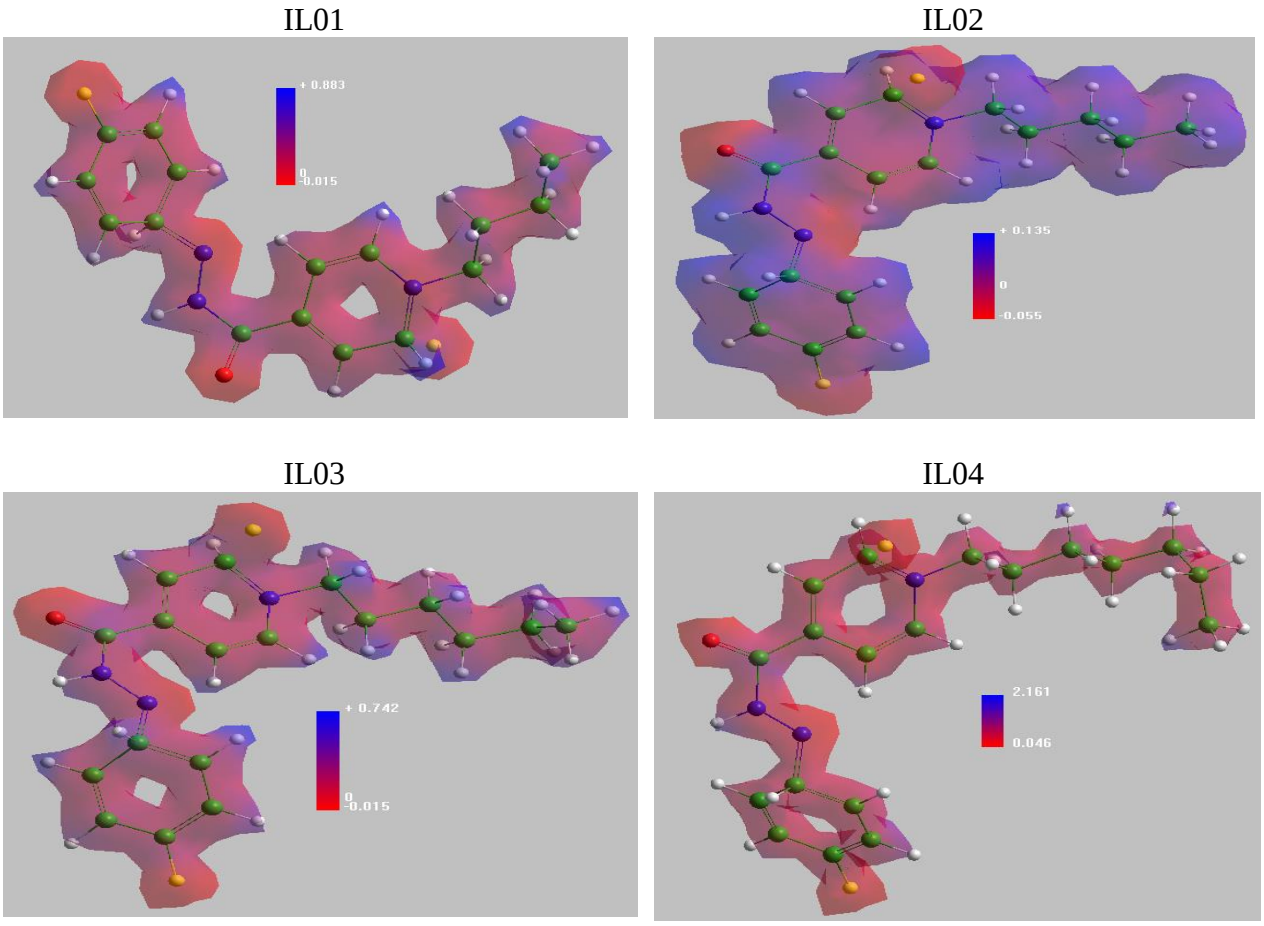



**Figure 3.** distribution electrostatic potential Map

**Table 4.** Data of electrostatic potential energy difference of two levels

| Compounds | IL01 | IL02 | IL02 | IL02 |
|---|---|---|---|---|
| Total charge density | 0.070 | 0.015 | 0.065 | 0.015 |
| E1 | +0.883 | +0.135 | +0.742 | +2.161 |
| E2 | -0.015 | -0.055 | -0.015 | 0.046 |
| ΔE= E2-E1 | -0.898 | -0.190 | -0.757 | -2.115 |

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)

The significance of LogP is on toxicity using positive and negative value. A negative value as the hydrophilicity and positive as the hydrophobicity play an important role in biochemical interactions and bioactivity. 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 molecules and finally are often extensively metabolized. All molecules are hydrophobic and it is changed due to change the alkyl length.

Secondly, the hydration energy documents the attraction of ion or molecules with water, as releases energy, it value is always negative. From the table 5, the change of hydration energy is well poor that is why it is derived that the change of alkyl chain has no effect.

The third point is Polarizibility which is the parameter for determining intermolecular interaction. The higher polarizibilty mentions the lower binding affinity. From table 5, it is found that it is increased more from IL01 to IL02, IL4 but IL03 decreases than IL02, IL04.

**Table 5.** Data for QSAR study

| | IL01 | IL02 | IL03 | IL04 |
|---|---|---|---|---|
| Partial charge, (e) | 0.0 | 0.0 | 0.0 | 0.0 |
| Surface Area(grid), | 562.92 | 623.65 | 617.47 | 642.60 |
| Volume, $Å^3$ | 910.49 | 1050.42 | 1011.70 | 1058.24 |
| Hydration Energy,kcal/mol | -6.69 | -2.63 | -2.95 | -2.70 |
| Log P | 1.49 | 2.59 | 2.20 | 2.59 |
| Refractivity $Å^3$ | 87.60 | 101.40 | 96.80 | 101.40 |
| Polarizibility, $Å^3$ | 31.78 | 37.28 | 35.45 | 37.28 |
| Mass (amu) | 307.34 | 349.42 | 335.40 | 349.20 |

## Calculation Of Pic50

The correlation between the biological activity and descriptor is developed by Zineb Almi et.al. 2014 [29]for the PIC50 value calculation from the Hyperchem simulation value that is given in following equation as

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

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.

**Table 6.** Data of PIC50

| | IL01 | IL02 | IL03 | IL04 |
|---|---|---|---|---|
| PIC50 | 6.57 | 7.45 | 7.57 | 7.59 |

## Pharmacokinetics and Drug likeness Study

For pharmacokinetics study, there are some parameters to describe a molecule as drug. The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion (ADME). However, the rule does not predict if a compound is pharmacologically active. Using Swiss Institute of Bioinformatics online database was used to evaluate the pharmacokinetics, Druglikeness, and toxicity prediction.

Lipinski's rule of five is a rule of thumb to evaluate druglikeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans.

According to Christopher A. Lipinski for drug molecules in 1997 stated that less the 5 hydrogen bond donors, less than 10 hydrogen bond acceptors, 3 rotatable bonds, molecular mass less than 500 Daltons [30]. The second views the octanol-water partition coefficient log P not greater than 5 Note that all numbers are multiples of five, which is the origin of the rule's name**.**

From the table 7, it can be said that the alkyl chain does not have effect on number of H-bond donar (HBD), number of H-bond acceptors (HBA), topological polar surface area (TPSA), but slightly effect on number of rotatable bonds (NRB), molar refractivity (MR), Log P, number arom heavy atom (NAHA).

Table 5. Data for Lipinski rule

| | NRB | HBD | HBA | MR | TPSA (A) | LogP o/w | M .Wt.( g/mol) |
|---|---|---|---|---|---|---|---|
| IL01 | 6 | 2 | 4 | 82.95 | 46.39 | 2.75 | 308.35 |
| IL02 | 7 | 2 | 4 | 87.76 | 46.39 | 3.06 | 322.37 |
| IL03 | 8 | 2 | 4 | 92.57 | 46.39 | 3.37 | 336.40 |
| IL04 | 9 | 2 | 4 | 97.37 | 46.39 | 3.68 | 350.43 |

Lead-like is estimated during the drug discovery, lipophilicity and molecular weight. Hence it is often difficult to maintain drug-likeness during hit and lead optimization. Hence it has been proposed that members of screening libraries from which hits are discovered should be biased toward lower molecular weight and lipophility so that medicinal chemists will have an easier time in delivering optimized drug development candidates that are also drug-like. Hence the rule of five has been extended to the rule of three for defining lead-like compounds.

**Table 8.** Data for Lipinski, Bioavailability, Druglikeness, Solubility

| | Lipinski | | Bioavailability score | Leadlikeness | | Solubility | | |
|---|---|---|---|---|---|---|---|---|
| | status | Violation | | status | Violation | LogS | Value mg/ml | Class |
| IL01 | Yes | 0 | 0.55 | No | 1 | -4,18 | 2.02e-02 | Moderately soluble |
| IL02 | Yes | 0 | 0.55 | No | 1 | -4.54 | 9.36e-03 | Moderately soluble |
| IL03 | Yes | 0 | 0.55 | No | 2 | -4.89 | 4.33e-03 | Moderately soluble |
| IL04 | Yes | 0 | 0.55 | No | 3 | -5.24 | 2.00e-03 | Moderately soluble |

**CONCLUSION**

To summarize, it is concluded that the alkyl chain length effect on thermophysical properties, chemical reactivity, biological activity, and pharmacokinetics study were evaluated. There is no large effect on chemical reactivity but slightly changes in thermophysical properties with increasing alkyl chain. The PIC50 value is 6.0 to 8 where shows the alkyl length effect and it can be said that these molecules biological active. With increasing alkyl chain the biological activity decreases. On the other hand, in views of Lipinski rule, all molecules are satisfied the conditions which recommends the highly pharmaceutical active drugs. The relationship for increasing alkyl chain is that the Lipinski rule, HBA, HBD, and Bioavailability score are not changed but the NBR, molar refractivity, LogP, and solubility are changed in regular fashion.

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