SYNTHESIS OF BIOACTIVE IONIC LIQUIDS THROUGH THE REACTION BETWEEN ARYL AMINE AND CARBOXYLIC ACIDS

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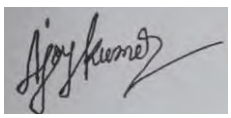

……...……

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Dedicated

to

My Beloved Family, Late grandfather

&

Honorable supervisor

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Abbreviation

	Ionic Liquid	IL
	Ionic Liquids	ILs
	Protic Ionic Liquids	PILs
	Aprotic Ionic Liquids	APILs
	Anilinium Ionic Liquid	AIL
	Ortho- toluidinium Ionic Liquid	OTIL
	Para - toluidinium Ionic Liquid	PTIL
	Meta - toluidinium Ionic Liquid	MTIL
	Diammoniumphenyl ionic Liquid	DPIL
.	Highest occupied molecular orbital	HOMO
.	Lowest occupied molecular orbital	LUMO

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ABSTRACT

Ionic Liquids are recognized as the safer, greener, designer, and engineering chemical for 21st century. As 3rd generation ILs was established as pharmaceutical active ingredients and bioactive molecules, it consists of synthesis, characterization, and computational approaches for synthesis of bioactive ILs. Total twenty five quaternary aryl ammonium ILs were synthesized combination of five different cations like aniline, *o*-toluidine, *m*-toluidine, *p*-toluidine, and 1,2-diaminebenzene and five aliphatic carboxylic acids like formic acid, acetic acid, propanoic acid, butanoic acid and trifluroacetic acid by the Bronsted acid-base neutralization reaction. For confirmation the structure, Fourier Transform Infrared (FT-IR), and Nuclear Magnetic Resonance (1H-NMR) and UV spectroscopy were used. The melting points were found in about 62-86ºC and some have more than 150º C.

To evaluate antimicrobial profiles against eight human pathogenic bacteria, three phytopathogenic fungi were used via well diffusion method and all ILs show the positive result. The minimum inhibition concentration (MIC) was found from 500 mMol/L to 125 mMol/L. Morever, biological studies against plant seed, the phytotoxicity was done using concentrations of 1000mmol/L, 500mmol/L, 250 mmol/L, 0 mmol/L, respectively and obtained the positive result.

Finally, the computational tools were used to evaluate the theoretical investigation of thermo-physical, chemical reactivity and biological interaction by the method of density functional theory (DFT). From the both of computational and biological studies, the anilinium and 1,2- diammoniumphenyl carboxylate in comparatively lower times than others for synthesis and also chemical and biological activity are higher. The alkyl chain length in anion and functional groups in aromatic ring in cations had experienced the change of chemical, biological study. The longer alkyl chain length shows higher chemical and biological activity while substituent group in various position of cation accounted for closer activity. The bi-cation shows much higher the chemical, physical and biological activity than mono ammonium cation. Additionally, halogen atom attaching in anion illustrates the higher biological activity.

CHAPTER 1

INTRODUCTION

1.1 Background

The field of ILs initiated in 1914 with an observation by Paul Walden who synthesized and reported the physical properties of ethylammonium nitrate [$EtNH_3^+$][NO_3^-], and the melting points is (13-14)$^\circ$C, which was formed by the neutralization of ethylamine with concentrated nitric acid [1]. After that, a lot of ILs was synthesized and characterized with variety of cations and anions which are also known as the designer solvent recent time due to have its tunable physical and chemical properties [2].

ILs, considered being a relatively recent magical chemicals due their unique properties, having a large variety of applications in all areas of the chemical industries [3]. ILs are a fascinating class of materials which, although they have been known about since 1914 have only come to prominence over the last decade or so. Commercially, electrochemical applications (e.g., non-volatile electrolytes for batteries) represent just one area in which there is significant interest in the primary thinking of ILs [4]. Publications and patents have grown dramatically since 2000. ILs is the molten salts, comprised of discrete anions and cations. Many are liquid at room temperature some are solid at room temperature. The majority of room temperature molten ILs are salts with large nitrogen or phosphorous-bearing cations with alkyl chain substituent and anions such as halides, fluorophosphates, fluoroborates and so on [5]. Over one million simple ILs are theoretically possible, with mixtures of two or more cations and anions even ILs making the possibilities for new reaction media almost. ILs research has experienced a massive upsurge of interest in the past decade, primarily driven by their application in ‗Green' chemistry, for example, as replacements for conventional organic solvents and volatile organic compounds (VOCs) in the chemical industry, used in large scale for any purposes [6]. Furthermore, ILs has been utilized in multitude of diverse applications from synthetic chemistry (separation/ extraction/ catalysis) to novel biological applications.

The unique behavior of ILs, such as low melting point, negligible vapour pressure and tune-able physicochemical properties make them the ideal candidates for membrane development. ILs is a class of novel solvents composed of large organic cations and organic/inorganic anions that cannot easily form an ordered crystal and thus remain liquid at or near room temperature. These unique solvents are alluring interest as greener alternatives to customary organic solvents with the aim of supporting more environmentally friendly processes of any type of extraction of organic and synthetic chemistry. Room temperature ILs are often referred to as ‗designer solvents' due to the possibility of tuning their physical and chemical properties through a wise combination of cations, anions and/or the introduction of functional groups [7-8].

Quaternary ammonium based ILs is the most expected properties of ILs at which organic ammonium based bases are used as cations to produce a salts with different types of acids as anions. Having different types of cations form ILs with various anions, because of the variety of side chains that can be connected to the central $N^{+,}$ many quaternary ammonium ILs could be prepared to ‗tune'' the physical properties such as melting point, water miscibility, conductivity and viscosity by selection and modification of the anion and cation of the IL. Many ammonium aromatic carboxylates ILs can show the bioactive molecules and low toxic [9-14]. ILs have attracted much attention due to wide spread potential for practical applications such as heat transfer and storage medium in solar thermal energy systems as well as for many areas such as fuel cells, rechargeable batteries and ‗green solvents'' [15].

The widespread use of ILs implies their availability at a reasonable price ammonium based ILs is most common. Choline chloride is special types of ILs due to its significances and structural similarity with ammonium based ILs. Choline chloride also known as 2-hydroxyethyltrimethyl ammonium chloride or vitamin B_4 with the chemical formula $(CH_3)_3N^+(CH_2)_2OHX^-$, where X^- is a counter-ion such as chloride, hydroxide or tartrate is a cheap organic salt, which is used, for instance, as a chicken feed additive. It is a common dietary supplement in the livestock and poultry industries [16-17]. In humans, Choline plays critical roles in fetal development and

may be beneficial when taken as a supplement and also acted as integrity of cell membranes as well as cell signaling, neurotransmission, muscle function and fat transport, and all require choline essential for brain and spinal cord structure and function. They claim that choline supplements may help decrease liver disease, high cholesterol, depression, memory loss, Alzheimer‘s, and asthma [16, 18]. Choline specifically acts to prevent fatty liver syndrome and helps in the formation of the neurotransmitter, acetylcholine, maintaining proper nervous system functioning. Due to have a high melting point 298-304°C, choline chloride has not useful as IL. But Abbott and co-workers obtained ILs by mixing choline chloride with hydrated transition metal salts, or with anhydrous zinc (II) chloride or tin(II) chloride to found choline chloride forms of ILs. That was so-called ―deep eutectic solvents" with hydrogen bond donors and used as like solvents of a mixture of urea and choline chloride in a 2:1 molar ratio were applied for the synthesis of zeolite analogues and for the fictionalization of cellulose [19].

Quaternary ammonium salts (quats) are an economically advantageous class of industrial compounds. They have surface-active properties, possess anti-microbial activity and are known to be bioactive. Contrary, reports regarding low melting tetraalkyl-phosphonium salts were relatively rare in the literature during the last decades.

Although ILs based on quaternary ammonium cations have been known and produced for years, and also numerous phosphonium based ILs have been produced even in ton-scale, these groups of ILs have been more or less ―neglected" in the literature comparing to their imidazolium or pyridinium based counterparts. However, during the last decade significant work has been done, pointing out the advantages and broad application spectrum of these types of ILs. Their improved thermal and chemical stability in comparison to e.g. pyridinium and imidazolium based ILs, their unique miscibility behavior and a solvating property advances their use in specific applications [20]. Several ILs based on these classes of cations are already commercially available and have been successfully applied as phase-transfer

catalysts, solvents, lubricants, gas capture agents, coating materials, or chemical sensors.

1.2 Term of ILs

ILs are generally defined as liquid electrolytes salts composed entirely of ions such as cations and anions, and occasionally a melting point criterion has been proposed to distinguish between molten salts and ILs (mp< 100°C). However, both molten salts and ILs are better described as liquid compounds that display ionic-covalent crystalline structures. Room-temperature ILs based on 1-alkyl-3-methylimidazolium salts were first reported in 1982 by Wilkes et al. as tetrachloroaluminates (first generation) [21]. Replacement of this moisture-sensitive anion by the tetrafluoroborate ion and other anions led, in 1992, to air- and water-stable (second generation) ILs which have since found increasing applications as reaction media for various kinds of organic reactions. At the onset of the new millennium, the concept of task-specific ILs (third generation) was introduced by Davis. These compounds are defined as IL in which the anion, cation, or both covalently incorporate a functional group as a part of the ion structure suitably selected, many combinations of cations and anions allow the design of ILs that meet all the requirements for the chemical reaction under study. This has gained them the alias of ~~"d~~esigner solvents". Properties such as solubility, density, refractive index, and viscosity can be adjusted to suit requirements simply by making changes to the structure of the anion, the cation, or both.

1.3 History of ILs

The history of ILs began in 1914 Walden reported the first synthesis of room temperature molten salt (i.e., Ethylammonium nitrate salt) [22], and reported the physical properties, a melting point of 8º C. This salt is liquid at room temperature; but usually it contains a small amount of water (200-600 ppm). Hurley and Weir developed the first IL with chloroaluminate ions such as ethyl pyridinium bromide/$AlCl_3$ for their use in electroplating aluminium in 1948 at the Rice Institute

[23]. In 1967, Swain et al. described the use of tetra-n-hexylammonium benzoate as a solvent for kinetic and electrochemical investigation [24]. Room temperature ILs (RTILs) became more popular in chemistry fraternity with the reopening of development in this area by the groups of Osteryoung et al. and Hussey et al. in 1970 and 1982 respectively [21, 25]. Ethanol ammonium nitrate (m.p. 52–55°C) was reported in 1887 by S. Gabriel and J. Weiner. In the 1970‘s and 1980‘s, ILs based on alkyl-substituted Imidazolium and pyridinium cations, with halide or tetrahalogenoaluminate anions, were initially developed for use as electrolytes in battery applications. The first major review on room temperature ILs was written by Hussey. The ILs based on $AlCl_3$ can be regarded as the first generation of ILs which was described as new reaction media and catalyst for Friedel–Crafts reaction, was published in 1986 [26].

In 1990, the use of ILs as solvents for homogeneous transition metal catalysts was described for the first time by Chauvin et al. Osteryoung et al. reported the polymerization of ethylene by Ziegler–Natta catalysts in chloroaluminate molten salt [27]. In 1992, Wilkes and Zaworotko reported the first air and moisture stable ILs based on 1-ethyl-3-methylimidazolium cation with either tetrafluoroborate or hexafluorophosphate as anions [28]. Unlike the chloroaluminate ILs, these ILs could be prepared and safely stored outside of an inert atmosphere. Generally, these ILs are water insensitive; however, the exposure to moisture for a long time can cause some changes in their physical and chemical properties. This is due to the formation of HF as a result of decomposition of the ILs in presence of water. Therefore, ILs based on more hydrophobic anions such as trifluoromethanesulfonate ($CF_3SO_3^-$), bis-(trifluoromethanesulfonyl)imide [$(CF_3SO_2)_2N^-$] and tris- (trifluoromethanesulfonyl) methide [$(CF_3SO_2)_3C^-$] were developed. These ILs have received extensive attention not only because of their low reactivity with water but also because of their large electrochemical windows. Usually, these ILs can be well dried with the water contents below 1 ppm under vacuum at temperatures between 100-150º C. Besides Osteryoung, Wilkes, Hussey and Seddon who are the pioneers in the field of ILs, there are several researchers, viz. Rogers, Welton, Wasserscheid, Mac Farlane, Ohno, Endres, Davis, Jr. Abbott, and others, who entered in this field having a strong

impact in introducing the ILs in many applications. Rogers is one of the highly cited authors in the field of ILs and worked on the development of new materials from cellulose utilizing ILs. T. Welton published many papers dealing with the applications of ILs as solvents for synthesis and catalysis. He focused on how the ILs interacts with solute species to affect their reactivity and he worked on replacing environmentally damaging solvents with more benign alternatives. Wasserscheid is an active member of the ILs community who focused on the preparation and characterization of ILs for use in the biphasic catalysis. He showed that the use of hexafluorophosphate ILs allowed selective to biphasic oligomerization of ethylene to 1-olefins. Together with Welton, he edited a very important book entitled –ILs in Synthesis" which represents the synthesis and physicochemical properties of ILs as well as their use in catalysis, polymerization, and organic and inorganic synthesis [29]. Macfarlane worked on the synthesis of new air and water stable ILs with the objective of employing such ILs as indicators for sensing and displaying environmental parameters such as humidity. This process was controlled by the colour change of the ILs where they were synthesized with either a coloured cation or anion, so that the ILs themselves were sensors.

Ohno concentrated his work on the synthesis of a series of polymerizable ILs and their polymerization to prepare a new class of ion conductive polymers. He prepared polymer electrolytes with high ionic conductivity and good elasticity by mixing nitrite rubber [poly(acrylonitrile-cobutadiene) rubber] with the ILs N-ethylimidazolium bis(trifluoromethanesulfonyl)imide with the ILs N-ethylimidazolium bis(trifluoromethanesulfonyl)imide. Recently, he edited a book entitled –Electrochemical Aspects of ILs" which introduces some basic and advanced studies on ILs in the field of electrochemistry [30]. Davis introduced the concept of ‗‗task-specific ILs'' (TSILs) in the field of ILs. TSILs are ILs in which a functional group is incorporated to behave not only as a reaction medium but also as a reagent or catalyst in some reactions or processes. Abbott has recently developed a range of ionic compounds, which are fluid at room temperature Recently, he edited a book entitled –Electro deposition from ILs" which introduces the applications of ILs on electrodeposition of metals [31].

An important property of the Imidazonium halogenoaluminate salts is that their physical properties such as viscosity, melting point, and acidity, that could be adjusted by changing the alkyl substituent and the imidazonium/pyridinium and halide/ halogenoaluminate ratios. Two major drawbacks for some applications were moisture sensitivity and acidity/basicity. In 1992, Wilkes and Zawarotko obtained ILs with 'neutral' weakly coordinating anions such as hexafluorophosphate (PF_6^-) and tetrafluoroborate (BF_4^-), allowing a much wider range of applications. Recently a new class of air– and moisture–stable, neutral ILs became available. Research has also been moving away from hexafluorophosphate and tetrafluoroborate towards less toxic alternatives such as triflimide $[(CF_3SO_2)_2N]^-$or away from halogenated compounds completely. Moves towards less toxic cations have also been growing, with compounds like ammonium salts (such as choline) proving to be as flexible a scaffold as Imidazonium. Long thought to be solely a product of laboratory synthesis, an ionic liquid has recently been found in nature, The material, formed by tawny crazy ants (*Nylanderia fulva*) when they groom after being attacked by fire ants (*Solenopsis invicta*), is a viscous oily protic IL that may be less capable of penetrating the carapace of the would-be ant victim than would be the original venom with which it was attacked.

ILs assigns the task specific properties for a particular need in the both of wide scale nano-scale uses in chemical industries and academia [32]. The researchers can design a specific IL by choosing negatively charged small anions and positively charged large cations, and these specific ILs may be utilized to dissolve a certain chemical or to extract a certain material from a solution. The fine-tuning of the structure provides tailor-designed properties to satisfy the specific application requirements. The physical and chemical properties of ILs are varied by changing the alkyl chain length on the cation and the anion. For example, Huddleston and his co-workers in 1998 concluded that density of ILs increases with a decrease in the alkyl chain length on the cation and an increase in the molecular weight of the anion [33]. Although ILs are studied by a great number of research groups, there are still many questions that scientist are not able to answer.

―Like dissolves like" is seem to be broken by some ILs: Non-polar benzene is up to 50% soluble (by volume) in polar tetrachloroaluminate-based ILs. ILs are able to dissolve un-charged covalent molecules are continuing. Until recently, ILs has been considered to be scarce but it is now known that many salts form liquids at or close to room temperature. There are literally billions of different structures that may form an IL. The composition and the specific properties of these liquids depend on the type of cation and anion in the IL structure. By combining various kinds of cation and anion structures, it is estimated that ILs can be designed as well as uses and application in industries and academia.

1.4 Classification ILs

There are a great number of different cation and anion combinations to synthesize ILs. Different types of ILs give an opportunity to modify the physical and chemical properties of the ILs. The most widely used cations are imidazolium, pyridinium, phosphonium and ammonium. The properties of ILs are determined by mutual fit of cation and anion, size, geometry, and charge distribution. Among the similar class of salts, small changes in types of ions influence the physico-chemical properties. The overall properties of ILs result from the composite properties of the cations and anions and include those that are super-acidic, basic, hydrophilic, water miscible, and water immiscible and hydrophobic. Usually, the anion controls the water miscibility, but the cation also has an influence on the hydrophobicity or hydrogen bonding ability. The structures of most commonly used cations and some possible anion types are tabulated in their structure.

1.4.1 According to the Cations

The cations of IL are generally a bulk organic structure with low symmetry. Most of the ILs are classified based on cation as follow as

- ❖ Ammonium based ILs,
- ❖ Sulfonium based ILs,

- ❖ Phosphonium based ILs,
- ❖ Imidazolium based ILs,
- ❖ Pyridinium based ILs,
- ❖ Picolinium based ILs,
- ❖ Pyrrolidinium based ILs,
- ❖ Thiazolium based ILs,
- ❖ Oxazolium based ILs,
- ❖ Cholinium based ILs,
- ❖ and Pyrazolium based ILs.

The structure of cations are given as

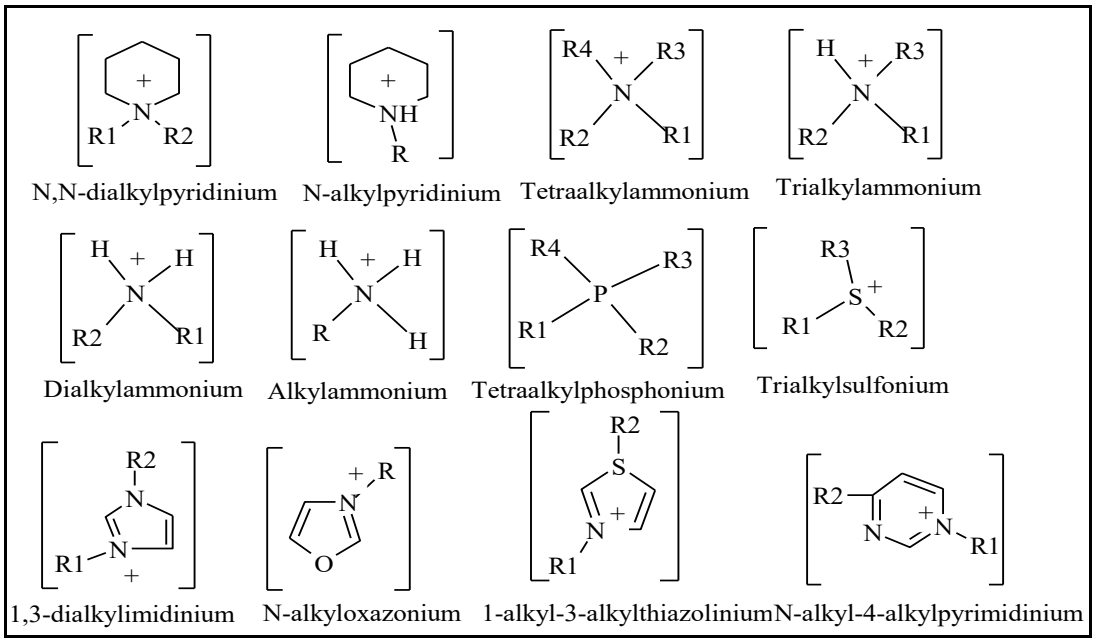


Figure 1: List of cations used in ILs.

1.4.2 On basis on Anions

The major properties of ILs depend on the anion in the molecules. The introduction of different anions results in an increasing number of alternative ILs with various properties. There are two different types of ILs anions:

1. Inorganic anion

It is also two types such as

I. fluorous anions such as PF_6^-, BF_4^-, $CF_3SO_3^-$, $(CF_3SO_3)_2N^-$, hexafluorophosphate, and tetrafluoroborate

II. Non-fluorous anions such as $AlCl_4^-$, chloride, nitrate and sulphate etc.

2. Organic anion

The most popular anions consist of aliphatic and aromatic carboxylate, such as formate, acetate, benzoate, amino or organic acids etc.

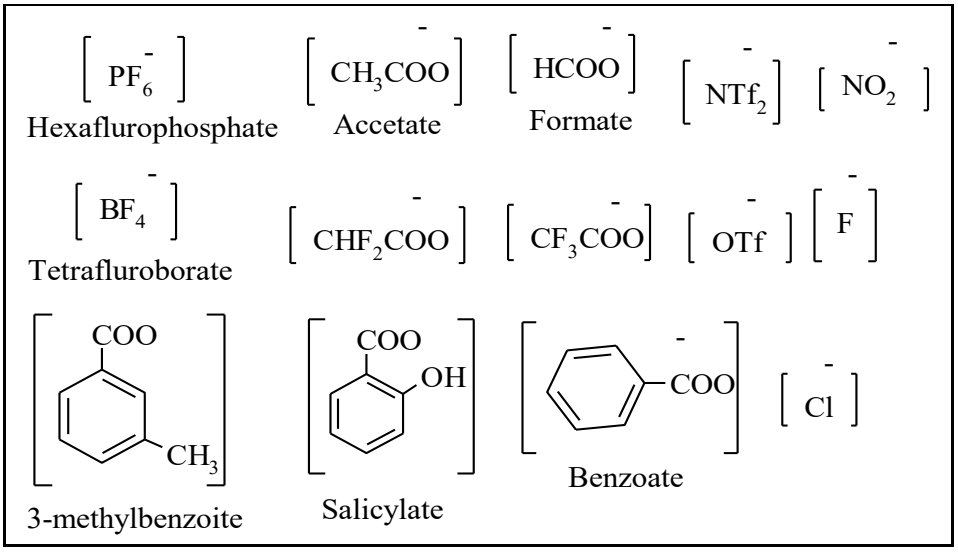


Figure 2: List of anions used in ILs.

Since the anion chemistry has a large effect on the properties of IL, although the cations are the same, there are significant differences between ILs with different anions. This example represents the ‗designer solvent' property of ILs. By changing the anion the hydrophobicity, viscosity, density and salvation of the IL system may be changed. Although PF_6^- and BF_4^- are the two anion types that are utilized in most of IL applications, they have an important disadvantage: these two anions may decompose when heated in the presence of water and liberate HF. After the researchers realized the production of HF in the presence of water, the bonding style

of anion was altered and fluorous anions inert to hydrolysis were used. The fluorine of the anion is bonded to carbon and C–F bond becomes inert to hydrolysis. In this way, ILs such as $CF_3SO_3^-$ and $(CF_3SO_3)_2N^-$ are produced.

1.4.3 On basis of their applications

A simple IL consists of one cation and one anion. The anions are generally small and the cations bulky with alkyl chains. Some usually used anions for simple ionic liquid systems are Cl, Br, BF_4, CF_3SO_3, OTf, $N(SO_2CF_3)_2$, NTf_2 etc. There are a few dissimilar commonly used cations for ILs, the commonly studied ones are the 1-alkyl-3-methyl-imidazolium cations. Other cations are phosphorus or nitrogen containing organic ions with attached alkyl chains of varied length. The name of an ionic liquid first states the cation followed by the anion. For the most commonly studied systems (Imidazolium based cations) the cations are named according to the alkyl chains lengths followed by Imidazolium. A1-butyl-3-methyl-imidazolium cation is sometimes abbreviated as C_4C_1Im, BMIm, BMIM, bmim or BuMeIm. The anions are generally named in accordance to general principles, e.g. Ac is meaning Acetate. More than 600 ILs systems can, in principle, be generated from around 10simple anions such as BF_4^- and PF_6^- and the1-alkyl-3-methylimidazolium cation substituted with various alkyl groups in the 2-, 4-, or 5-position, or N-alkylpridinium substituted in the 3- or 4-position. When hetero-polyanions and tetralkylammonium and tetraalkyl-phosphonium cations are added to the list, a grand total of more than a quarter of a million IL systems is possible. With this enormous variety, it is usually feasible to tailor the solvents to specific chemical reactions. ILs has a range of physical-chemical properties that can be tuned with an accuracy that is hard to see for a given reaction. According to their properties and uses they are classified into following types:

a) a)1st generation ILs;
b) 2nd generation ILs;
c) and 3rd generation ILs.

1.4.3.1 First Generation ILs

The first IL known was ethylammonium nitrate, reported in 1914 by Walden but attracted little interest. The first generation of ILs with widespread utilization was mainly composed of cations like dialkylimidazolium and alkylpyridinium derivatives, and anions like chloroaluminate and other metal halides. The most common anions are chloroaluminate or other metal halide anions that react with water and thus are not suitable for biotransformation. The 1st generation of ILs was also oxygen-sensitive, toxic non-biodegradable,and can only be handled under inert-gas atmosphere due to the hygroscopic nature. In the 1980s, Wilkes et al. started the extensive research on first generation ILs. However, due to these limitations, the progress in their use was limited. For this reason, research was directed towards the synthesis of air- and water-stable ILs, the second generation of ILs.

1.4.3.2 Second generation ILs

After one decade the second generation of ILs was appeared. The water- and oxygen-reactive anions were replaced by halides (Cl^-, Br^-, I^-) or anions such as BF_4^-, PF_6^- and $C_6H_5CO_2$, which are stable to water and air. Cations such as dialkylimidazolium or alkylpyridinium were maintained, and ammonium and phosphonium were added. These ILs present interesting properties such as lower melting points, different solubility, viscosities, etc in classic are organic solvents. Due to these properties, the second generation attracted a great interest in various fields, and research in ILs experienced an important boost from the 1990‘s. The first reports of bio-catalysis with ILs were published in the beginning of 2000´s. One of the dis-advantages of these ILs is the high cost. According to the high costs are related to starting materials (namely fluorinated components) and purification of final product required in the preparation. The most important disadvantage of the second generation is the toxicity, which in general is similar to those of chlorinated and aromatic solvents. However, this second generation of ILs attracted the attention of the wide scientific community and has been providing interesting and novel applications in different areas. The 2nd generation of ILs is a great number of applications in bio-catalysis

activity, stability, kinetic and thermal stability of different enzymes such as oxidases, lipases or celluloses and synthesis of various products with toxicity.

1.4.3.3 Third generation ILs

The third generation of ILs is known as advanced ILs and based on more hydrophobic and stable anions such as $[(CF_3SO_2)_2N^-]$, sugars, amino or organic acids, alkylsulfates, or alkyl phosphates and cations such as choline. The ILs which are biodegradable, readily available, and present lower toxicities, more hydrophilic than the second generation, water-miscible, liquids/melted salt at room temperature, pharmaceutical active ingredient, and bioactive molecule are known as 3rd generation ILs.

The advantages of the third generation are: lower costs (similar to organic solvents), simple to prepare, biodegradable, do not require purification, the purity of the starting materials determines the final purity and uses anions and cations with low toxicity. As this generation is recent, few works have been published. The trans-etherification of ethyl valerate with 1-butanol, showed good activity in DES, and in choline chloride: glycine the activity was similar to activity in toluene for all lipases. The third generation will reach the commercial level soon in market.

1.4.3.4 On the basis of proton

ILs can be divided into two broad categories

1.4.3.4.1 Protic ILs (PILs)

PILs are produced through proton transfer from a Brønsted acid to a Brønsted base.

1.4.3.4.2 Aprotic ILs (APILs)

APILs are produced which cannot transfer proton from a Brønsted acid to a Brønsted base. According to the cation segments, ILs are usually categorized into four types:

alkylammonium, dialkylimidazolium, phosphonium and N-alkylpyridinium based ILs.

1.4.3.5 On the basis of acidity/ basicity

The design and choice of ILs commonly focus on physical properties such as water-miscibility, conductivity, viscosity and solubility properties, although how the chemical structure of the ionic liquid affects these various characteristics is still poorly understood. However, there is another chemical property that imparts a variety of physical characteristics to the ILs that has been little investigated is the relative acidity or basicity of the component ions. Lewis base anions can exhibit a base catalysis phenomenon, which can be utilized. The acidity or basicity of reactive ILs is governed by the strength of the cation or the anion, or by the combination of the cation and anion.

1.4.3.5.1 Neutral Cations and Anions

Typical ionic liquid anions are those that can be described as neutral in the acid/base sense or very weakly basic; these exhibit only weak electrostatic interactions with the cation and thus impart advantageously low melting points and viscosities. hexafluorophosphate, bis(trifluoromethanesulfonyl)amide, tetrafluoroborate, methanesulfonate (mesylate), thiocyanate, tricyanomethide and p-toluenesulfonate (tosylate) are included in this class (figure 2.1). Ionic liquids formed from these anions typically exhibit good thermal and electrochemical stability. They are often utilized as inert solvents in a wide range of applications.

1.4.3.5.2 Acidic Cations and Anions

The most popular acidic ILs includes either protonated alkylimidazole salts or sulfonylalkylimidazolium salts. The simplest examples of slightly acidic ILs are those based on the protic ammonium, pyrrolidinium and imidazolium.

1.4.3.5.3 Basic Cations and Anions

There are a number of ionic liquid forming anions that can be classed as basic. These include the lactate, formate, acetate (and carboxylates generally) and the dicyanamide (DCA) anion. Since the basicity of these anions imparts different advantageous properties to the ILs such as different solubilizing andcatalytic properties. This category of ILs is likely to grow considerably in the coming years. An alternative to the design of ILs utilizing a basic anion is to incorporate a basic site into the cation. This may afford more thermally stable ILs than those containing basic anions, which frequently exhibit relatively low decomposition temperatures.

1.5 Properties

1.5.1.1 Thermal decomposition temperature (T_d)

The thermal stability of ILs commonly depends on the strength of the heteroatom-carbon bond or hetero atom-hydrogen bond. In general, acetate PILs show less thermal stability compared to imidazolium type APILs; this may be due to proton back transfer, which proceeds through equilibrium shifting towards neutral components [34].

The thermal decomposition of hydroxyl ammonium ILs increases with increasing alkyl chain either in the cation or anion. It seems that both cation and anion play a significant role in thermal decomposition of hydroxyl ammonium ILs. The purity of ILs definitely affects the thermal decomposition, as hydroxyl ammonium ILs have tendency to absorb moisture. However, PILs which have carboxylate anions, especially formate, may possess lower thermal stability due to involvement in the condensation reaction to form amides.

1.5.1.2 Heat Capacity and Degradation Temperature

Melting Point, Heat capacity and degradation temperature ILs calorimetric data are not much broadcast on literature. The melting point was not achieved for any of the all protic and ammonium based ILs within the large temperature range. The heat capacity values are presented the ability of aggregation. The heat capacity increases

with temperature, and also showed that the higher molecular weight ILs has the greater energy storage capacity thus implies that ILs requires more energy than the other ILs to increase or decrease its temperature. This behavior shows a poor anion influence on the degradation temperature [35-36].

1.5.1.3 Thermodynamic Properties

Some thermo-dynamical properties, such as the thermal expansion coefficient and the molecular volume can be correlated as a function of temperature. For all ILs, the variation of the thermal expansion coefficient with temperature is small and can be considered independent of the temperature. It showed that entropies are reliably linearly correlated with volume per molecule, $V_{m,}$ thus permitting simple evaluation of standard entropies. For organic liquids, the regression lines generally pass close to the origin. The thermal expansion coefficients, the molecular volumes and the standard entropy at 298.15K for all ammonium based protic ILs [37-38].

1.5.1.4 Molecular volume

The apparent molar volumes, $V(cm^3 \cdot mol^{-1})$, of the ILs in the binaries is the important tools to explain the salvation into any solvent. Therefore, the apparent molar volume at infinite dilution is a measure for the ion-solvent interactions. It shows the ion−ion interactions ammonium ILs. In general, molar volume is positive, but sometimes negative for some electrolytes. It was found that apparent molar volumes at infinite dilution for the ILs increase with the increase in the alkyl chain length of the cations at a given temperature. In addition, the apparent molar volumes at infinite dilution for the ILs also increase with increasing temperature due to the release of solvents from the loose solvation layer of the ILs [39-40].

1.5.1.5 Free volume

The free volume of ammonium ILs was characterized and analyzed for many fundamental physical properties.

It is well proved that the free volume is a main factor to influence the transport properties of liquids. The Cohen-Turnbull equation connects free volume with viscosity and conductivity [41]. This equation is also valid for the ILs.

From the above discussion, it is clear that the free volume is important for the analysis of many fundamental physical properties of liquids. Then it comes the question, of how to determine it. From the previous work for ammonium ILs, a correlation between the molecular volume V_M and the hole volume was observed. The free volumes and molar refraction of ammonium-based ILs are higher than those verified for the sulfonium-based ILs. Furthermore, similar to the molar volumes, the molar refraction and free volume increases with the effective cations.

1.5.2 Physicochemical properties of ILs

The physical properties such as melting point, boiling point, density, surface tension and viscosity are related to the mechanics and engineering components associated with a process. For example, density, viscosity and surface tension will determine important parameters including rates of liquid–liquid phase separation, mass transfer, power requirements of mixing and pumping. Other physical properties, such as refractive index is related to certain chemical properties despite providing a bulk property description. The Physico-chemical properties of ILs can be varied by the selection of suitable cations and anions. Their properties can be adjusted to suit the requirements of a particular process. Because of this reason, the ILs has been referred to as ~~"d~~esigner" solvents. Thus, it is necessary to understand how the physico-chemical properties of ILs are able to affect organic reactivity as well as how they depend upon their structural features. This will be illustrated on the basis of a few selected examples which are as follows:

1.5.2.1 Melting point

The most important property of the IL is the melting point. The melting point of IL lies below 100 °C. With a given cation the choice of anion has a strong effect on the melting point. The coordinating and hydrophilic anions like halides lead to high

melting points, whereas weakly coordinating and hydrophobic anions result in low melting points. Also increase in size of the anion with same charge leads to a decrease in melting points. However, all ILs do not follow this rule of decreasing melting point with increasing anion size. The effect of anion size on the melting point of [emim]X and ammonium IL[42].

1.5.2.2 Viscosity

Viscosity is a key property of ILs. ILs tends to have higher viscosities than conventional solvents. The value of the viscosity varies tremendously with chemical structure, composition, temperature and the presence of solutes of impurities. Viscosities are ranging from 10 mPa·s to about 500 mPa·s at room temperature. A high viscosity may produce a reduction in the rate of many organic reactions and a reduction in the diffusion rate of the redox species [43-44]. It has been shown that the viscosity of Imidazolium based ILs can be decreased by using highly branched and compact alkyl chains. Phosphonium ILs also tends to have higher viscosities than Imidazolium based ILs.A small amount of water tends to decrease the viscosity while high chloride impurities increase the viscosity. The viscosity of an IL is determined by both the cation and anion. For the same cation the viscosity decreases as follows with change in anion: [Cl] $[Cl]^-$ > $[PF6]^-$ > $[BF4]^-$ > $[NO3]^-$ > $[N(SO2CF3)2]^-$. The addition of co-solvent to ILs can dramatically decrease the viscosity of IL without changing the cation or anion of the IL.

1.5.2.3 Conductivity

Conductivity is of vital importance for solvents to be used in electrochemical processes. ILs have many unique properties, one of which is their conductivity which is intrinsic, so supporting electrolytes are not needed, as in the case of traditional organic solvents. Conductivities of our newly developed ammonium based ILs were measured by conductivity meter. Generally speaking, ion size, ion association and viscosity influence the conductivity of a pure IL. The conductivity values ranged from 67 to 77 $S.cm^{-1}$ [45]. Although these salts are purely ionic their conductivity

values are expected to reduce as ion mobility that will be limited by the liquid‘s viscosity. The lowest viscosity recorded for highly polar cation containing ILs showing the highest conductivity value measured (77 $S.cm^{-1}$).

1.5.2.4 Density

Density is one of the basic and important physical properties of ILs. In general, IL is denser than water with values ranging from 1 to 1.6 g cm-3. The density of an IL depends on the length and type of substituent in the cation and also on the kind of the anion. The molar mass of the anion, alkyl chain length and bulkiness in the cation significantly affect the overall density of ILs. The general order of increasing density with respect to the anion is $[CH_3SO_3]^-$ ~ $[BF4]^-$ < $[CF3CO2]^-$ < $[CF3SO3]^-$ < $[C3F7CO2]^-$ < $[N(SO2CF3)2]^-$. In contrast, for ILs with the same anion, the density decreases with increasing cation mass. [beim]+ > [bmim]+ > [eeim]+ > [emim]+ ammonium based ILs tends to have lower densities than all other even imidazolium based ILs. Impurities present in the ILs have a less theatrical effect on the density of ILs compared to their effect on viscosity. The density of IL is also temperature dependent. As temperature changes from 293 to 313 K, the density of [bmim][BF4] decreases linearly with increase in the temperature . The most of ammonium based ILs shows the density 1.13 to 1.60 [46-47].

1.5.2.5 Vapor pressure

These are unique properties of ILs. They have negligible vapour pressure and thus minimizing solvent losses by evaporation into the environment. They are therefore potentially recyclable. Due to their negligible vapour pressure and non-flammable nature, ILs have been developed recently as so called green solvents which are better alternatives for volatile organic solvents (VOS). VOS are the common industrial solvents for synthesis in petrochemical and pharmaceutical industries. The known problems with VOS are that they are quite volatile, highly flammable, and toxic and they tend to damage the earth‘s atmosphere. Non-volatile nature of ILs is a great advantage from an industrial process viewpoint. Product separation by distillation of

a reaction mixture becomes more effective. The well-known problem of azeotrope formation between the solvent and the products does not arise [48-49].

1.5.2.6 Thermal Stability

The thermal stability of ILs is limited by the strength of their heteroatom-carbon and their heteroatom-hydrogen bonds. In general, most of ILs have high thermal stability, the decomposition temperature reported in the literature are generally <400^{o}C, with minimal vapour pressure below their decomposition temperature. Recently, TGA of pyridinium salts have been described and noted that the thermal decomposition was heavily dependent on the salt structure [50]. It indicated that the experiments performed under N_2 or air produces the same results. The beginning of thermal decomposition was nearly similar for the different cations but appeared to decrease as the anion hydrophilicity was increased. It has been suggested that the stability dependence on the anion is $[PF6]^{-}$ >$[NTf2]^{-}$ ~$[BF4]^{-}$ >halides [51]. Halide anions dramatically reduce the thermal stability with the onset of decomposition occurring at least 100 °C below the corresponding ILs with non-halide anions [52].

1.5.2.7 Polarity

It is well known that the solvent chosen could dramatically affect chemical reactions. The solvent effects are considered to be mainly dependent on the solvent polarity. Therefore, polarity is an important property of ILs. The simplest qualitative definition for a polar solvent is one that will dissolve and stabilize dipolar or charged solutes, e.g., 'like dissolves like'. Under this definition, ILs due to their salt nature will be highly polar. ILs has a polarity that lies between those of water and chlorinated organic solvents. Due to the presence of the cation and the anion in the IL, there is most likely to be a much wider range of solvent-solute interaction than with conventional organic solvents. Different solvent-solute interactions in ILs have been reported using solvatochromic dyes such as Nile Red and Reichardt dye [53-54].

1.5.2.8 Water miscibility

The hydrophilic/hydrophobic behavior of IL is important for the salvation properties. It is necessary to dissolve reactants, but it is also significant for the recovery of products by solvent extraction. Furthermore, the water content of ILs can affect the rates and selectivity of reactions. The miscibility of ILs with water is an important factor for the industrial application of these solvents. Extensive data are available on the miscibility of ILs with water. The miscibility of these ILs with water depends on the nature of the anion, temperature and the length of the alkyl chain on the cation. On the basis of IR studies, water molecules absorbed from the air are mostly present in the free state. It has been bonded with $[PF6]^-$ $[BF_4]^-$ $[SbF_6]^-$ $[HSO_4]^-$ $[ClO_4]^-$ $[CF_3SO_3]^-$ and $[NTf_2]^-$ via H bonding. Most of the water molecules should exist in symmetrical 1:2 type H bonded complexes: anion…HOH…anion [55-56].

1.5.2.9 Surface tension

Surface tension may be an important property in multiphase processes. ILs are widely used in transition metal catalyzed reactions, carried out under multiphase conditions [57]. The rates of these processes depend on surface tension. The surface tensions of ILs (e.g. [bmim][PF6] = 48.8 Nm-1 and $[bmim][BF_4]$ = 46.6 Nm-1) are lower than water (72.7 Nm-1 at 20 °C) but higher than n-alkanes (e.g. hexane = 18 Nm-1). Surface tension values vary with temperature and affected by the alkyl chain length [58-59].

1.5.2.10 Biodegradability of ILs

The physicochemical properties of ILs have been studied intensively since their discovery. Diverse modifications of cations and anions have provided ILs with desired properties for many technical applications.

1.5.2.11 ILs in catalysis

Investigations into catalytic reactions using ILs have been performed for more than 35 years. In 1986, Wilkes et al. were the first to report the use of ILs (imidazolium chloroaluminate) as catalysts in Friedel-Crafts acylation [26]. However, extensive interest in a broad range of stoichiometric and catalytic reactions has seen a dramatic

growth of published papers in this area. ILs supported with many catalysts and reagents resulted in improved reaction yields and selectivity in many important reactions. Chauvin and co-workers found that chloroaluminate ILs are good solvents for dimerisation of linear olefins using Ni catalysts. Where, the reaction products can be easily separated by simple decantation, since they are not soluble in the IL, and showed higher yields and selectivity of the required dimers compared to the traditional solvent and solvent less systems [60].

The catalyst activity increases in the presence of ILs. For example, the Diels-Alder reaction of 1,4-naphthoquinone with 1,3-dimethylbutadiene proceeded effectively increase about 30% in [bmim]PF_6 or [bmim]SbF_6 [61].

1.6 Application

1.6.1 ILs as Green Solvents

Clean and green technology concerns the reduction of waste from an industrial chemical process to a minimum: it requires the re-thinking and redesign of many current chemical processes. The term of waste shows that the relative ―dirty" end of the chemical industry, where oil refining and bulk chemicals are actually remarkably waste conscious. It is the fine chemicals and pharmaceutical companies which use inefficient, dirty processes even though they are at a much smaller scale, much of the waste being due to solvent use. In order to reduce this waste factor, there are four main alternate strategies.

- Solvent free synthesis
- Water as a solvent
- Use of supercritical fluids as solvents
- Use of ILs as solvents
- Use recyclable solvent.
- Having high yields.
- Process be less consume energy and time.
- Produced less toxic and hazardous products

The last strategy is the one of interest in this discussion. As mentioned previously ILs has melting points beginning from -96°C. By changing various anions and cations it is estimated that there are one trillion room temperature ILs. The wide range of reactions that have been undertaken in low temperature IL solvents is quite amazing. Many of the processes which shall be mentioned which are now used in industry have been taken through the development process to the point of industrial commercialization. They represent first generation IL processes, principally based on chloroaluminate (III) ILs. These are now ready for industrial uptake at present. The most common production methods involve the use of triethylaluminum catalysts at ~100°C and 100°C atmospheres pressure. The IL solvent/catalyst activates the reaction and the alkylation can be performed even at temperatures as low as -20°C. In the IL solvent, these products have a low solubility and thus are conveniently separated. The two examples above which are being or already have been commercialized are very important if ILs are to be of any real benefit commercially, as it is in industry they need to be beneficial. There are also many reactions which are still in the development stages in laboratories world-wide and it is hoped that with time and effort they will also be used in industry, reducing both cost and waste in various synthetic procedures.

Many of these processes utilize the ability of ILs to selectively immobilize transition metal catalysts for liquid-liquid two phase catalysis, while permitting ease of extraction of products. This alone would have great advantages in industrial processes involving liquid-liquid extraction. It is found that the IL may be recycled and used in a number of reactions which reduces the cost of the procedure by allowing for recycling of both solvent and catalyst and also waste problems may be reduced.

The study of the use of ILs in synthetic procedures has received a vast amount of interest in the last ten years. The study of their use may be divided into two

(i) Their use as a solvent in classical organic reactions.
(ii) And their use in biphasic catalysis.

The synthetic uses of ammonium and others based ILs shall be discussed here with the latter group being the one favored in this research project. Some properties like non volatility, less toxic, cheapness, and recyclable, tunable physical and chemical properties, high thermal range make them as green promising chemical solvents in all fields of science, engineering and technology. ILs was used in

- Solvent in Organic Synthesis
- Lewis acids
- Friedel–Crafts alkylation and acylation
- As a tool to investigate the mechanistic Analysis in NMR
- Catalyst in Diels–Alder reaction
- Fischer indole synthesis as catalyst
- Brønsted acidic ILs (BAILS) as acid catalyst
- Esterification reaction as catalyst
- Mannich reaction as catalyst.
- Ketone synthesis as solvent.
- Knoevenagel reaction
- Henry reaction
- Mannich-type reaction
- ILs are attractive as potential
- Hydroformylation
- Hydroformylation catalysts
- Alkoxycarbonylation
- Heck reactions
- Palladium-catalyzed allylic substitution

1.6.2 Catalysis

In recent years, significant progress has been made in the application of room temperature ILs on catalytic processes, especially in homogenous catalysis. There are many advantages of homogenous catalysis ie. selectivity, activity, low cost and mild,

flexible conditions. Due to these factors heterogeneous catalysis is chosen because this reduces cost and the number of steps in a process [62]. Heterogeneous catalysis involves anchoring the catalyst in one phase while the reactants and products are contained in the other. These two phases are then allowed to mix, the products decanted in one phase, while the catalyst is retained in the other, thus enabling recycling of the catalyst. ILs has solved the hindrance of separation problems in homogenous catalysis. This is due to the fact that ILs are ideal for biphasic catalysis, which is essentially a type of homogenous catalysis but the initial reactants or final products and catalyst are in two separate phases [63-64].

1.6.3 Application in polymer science

The main important view for polymerization media in several types of polymerization processes, including conventional free radical, living/controlling radical polymerizations such as atom transfer radical polymerizations is fastly occurred in the medium of ILs. When radical polymerizations are conducted in an ionic liquid, a significant increase of kp/kt ratio is normally observed in comparison to those carried out in other polar/coordinating solvents. As solvents for ATRP and RAFT, ILs facilitate separation of the polymer from residual catalyst and reduce the extent of side-reactions [65-66].

1.6.4 Friedel–Crafts alkylation and acylation

Aromatic electrophilic substitution reactions such as benzoylation and acetylation catalysed by metal triflates have been conducted in an ionic liquid which were the first to report the alkylation and acylation of benzene using 1-methyl-3-ethylimidazolium–aluminum trichloride IL ([EMIM]Cl–AlCl3), IL, and methyl chloride and acetyl chloride as the alkylating and acylating agents [67] .

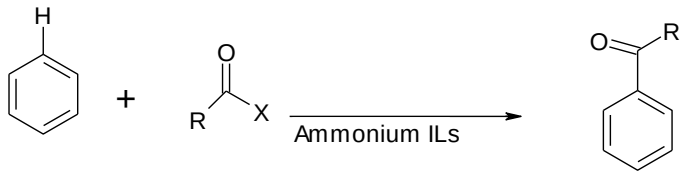


Figure 3: Reaction Scheme for Friedel–Crafts alkylation and acylation

1.6.5 Diels–Alder reaction

Diels–Alder reaction Carols Lee firstly reported the Diels–Alder reaction between cyclopentadiene and methyl acrylate to give endo/exo products using room temperature chloroaluminate ILs as solvent/catalyst. The author reported that the selectivity and reactivity of the reaction were strongly influenced by the Lewis acidity of the chloroaluminate IL. Later on, Abbott et al. reported the choline chloride-based zinc- or tin-containing ILs as water insensitive, recyclable catalysts for Diels–Alder reaction. A novel family of chiral ammonium-based ionic liquids containing a chiral moiety and a free hydroxyl function has been designed and synthesized from isosorbide [68]. The synthesis of these ionic liquids is easy and practical owing to the commercially available starting materials. These new chiral ionic liquids can be used as chiral reaction media as well as catalysts in asymmetric synthesis, which are currently being investigated.

1.6.6 Fischer indole synthesis as Catalyst

Fischer indole synthesis Rebeiro and Khadilkar described the Fischer indole synthesis of different ketones using 1-butylpyridinium–$AlCl_3$ IL as a solvent as well as a catalyst [69]. After that ammonium carboxylate ILs was reported in this reaction to show high yields. The amount of $AlCl_3$ required is much lesser than other reported catalysts. The reaction gives high yield with one equivalent of the IL; exclusive formation of 2, 3-disubstituted indoles is observed in the reaction of alkyl methyl ketones, and the products readily sublime directly from the IL.

1.6.7 Brønsted acidic ILs (BAILS)

Brønsted acidity determination Organic transformations are sensitive to the presence of protons. Therefore, knowledge of the pKa value is important to decide their possible application as reaction media or catalysts. Increasing the alkyl chain length leads to a decrease in acidity. In aliphatic carboxylic acids, the inductive effect of the imidazolium ring drops dramatically with increasing chain length. The first IL ethyl ammonium nitrate reported by Walden is considered to be BAILs. However, in the last decade, the BAILs have been specifically designed as catalysts, reagents, and/or

solvents as organic synthesis was explored designed BAILs containing an alkane sulfonic acid group covalently attached to the IL cation and applied them for transformations such as esterification, ether formation, and the pinacol–pinacolone rearrangement as a catalyst as well as solvent [70].

1.6.8 Esterification reaction as catalyst

Esterification reaction of carboxylic acids using liquid inorganic acid catalysts is well known. However, removal of water/use of excess amount of the reactants is generally needed for satisfactory conversion; also, it is very difficult to recycle the liquid inorganic acid catalysts. Zhu et al. reported a practical and efficient procedure for esterification of carboxylic acids with alcohols, using a BAIL, 1-methylimidazolium tetrafluoroborate [HMim][BF_4] as recyclable catalyst and solvent [71].

The product ester was insoluble and separates from the IL as the reaction proceeds, presumably helping to drive the equilibrium toward products. High yields of products were achieved with a simple separation, and the IL was reused several times [72]. The catalytic activity of these BAILs depends on its anions. It was observed that with the increase of anions, Brønsted acidity increases and hence its catalytic activity and reported esterification reactions of lactic acid with a variety of straight chain aliphatic alcohols, cyclohexanol, and benzyl alcohol using two novel BAILs that bear an aromatic sulfonic acid group on the imidazolium,ammonuim and pyridinium cation under ultrasound irradiation.

1.6.9 Mannich reaction

This is a classical method for the synthesis of b-amino carbonyl compounds. In the Mannich reaction, an amine, two carbonyl compounds, and an acid (or base) catalyst are used to produce amino carbonyl compounds. Zhao et al. [73] synthesized several BAILs which were successfully used as solvents and catalysts for Mannich reactions. The used BAILs include [BMim][HSO_4], [BMim][H_2PO_4], [HMim][PTSA], and [HMim][Tfa]. Out of these BAILs, screened higher yields were obtained in the presence of [HMim][Tfa]. Further, [HMim][Tfa] was reused four times without considerable loss of activity.

Dong et al. (2009) reported tetraalkylammonium and triphenylpho-sphine-bearing sulfonic group-based ILs and investigated the Mannich reaction [74]. A variety of optically active b-amino carbonyl compounds were synthesized with up to 99 % yield.

1.6.10 Brønsted basic ILs Michael addition reaction

The first environmentally benign, highly efficient conjugate addition of aliphatic amines to α,β-unsaturated compounds catalyzed by simple quaternary ammonium salts and ionic liquids in the green solvent, water, is described [74].

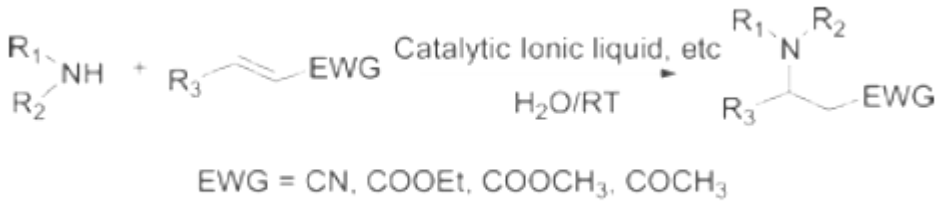


Figure 4: Michael addition reaction using ammonium based ILs

1.6.11 Ketone synthesis

Simple ammonium ionic liquids are efficient catalysts in promoting Saucy–Marbet reactions of unsaturated alcohols with unsaturated ethers to afford the corresponding unsaturated ketones, eliminating the need for volatile organic solvents. The effect of the anions and the cations of ionic liquids, quantity of ionic liquid, temperature, and chain-length of unsaturated alcohols on the reaction were investigated. The results showed that the Saucy–Marbet reaction was heavily influenced by the acidity of ionic liquid and $[Et_3NH][HSO_4]$ had the best catalytic activity. The conversion and selectivity obtained with this method are significantly increased in comparison to those catalyzed by traditional acid. Furthermore, the ionic liquid could be easily separated and reused with a slight loss of its activity. It provided a good alternative way for the industrial synthesis of unsaturated ketones [75].

1.6.12 Knoevenagel reaction

Knoevenagel condensation is widely employed to synthesize intermediates of fine chemicals. A series of Hünig's base tethered ammonium ionic liquids have been used to catalyze the Knoevenagel condensation of aldehyde/ketones with malononitrile and ethyl cyanoacetate. By increasing the distance between the ammonium head group and Hung‘s base the activity of the catalyst was found to increase. Higher activity, in general, was found under homogeneous reaction conditions; however, the recyclability of the catalyst was improved by supporting the BIL under biphasic conditions given by scheme [76].

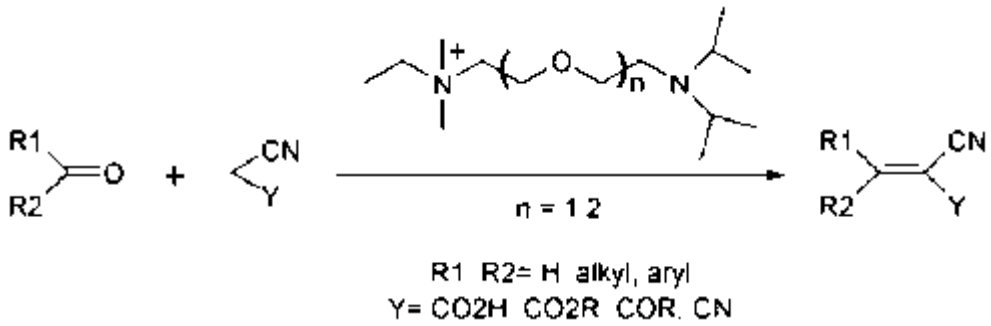


Figure 5: Reaction scheme for Knoevenagel condensation

The reactions proceed at room temperature and are very fast. The significant advantages offered by this methodology were general applicability to a large number of substrates with a very facile reaction of aliphatic aldehyde with diethyl malonate, which was difficult to achieve by other methods, (b) mild reaction conditions (room temperature), (c) clean and fast reaction, (d) high isolated yields of products and (e) reusability of catalyst and cost-effectiveness [77].

1.6.13 Hydroformylation catalysts

Ammonium and phosphonium salts have also been used as hydroformylation catalysts [78-79]. Improved yields were reported when bidentate N-donor or P-donor ligands were added to the reaction mixtures and the principal catalytic species were $[HRu_3(CO)_9\text{-}(L–L)]$— (where (L–L) bidentate ligand).

1.6.14 Heck reactions

The Heck and related C–C coupling reactions are of major importance in organic synthesis and are finding wide applications in the manufacture of fine chemicals. The first example of a Heck coupling in an IL was reported by Kaufmann et al. (1996) [80].

Heck reaction proceeds at ambient temperature (30 °C) with considerably enhanced reaction rate (1.5–3 h) through the formation of Pd–biscarbene complexes and stabilized clusters of zero-valent Pd nanoparticles in ionic liquids under ultrasonic irradiation [81].

This reaction was highly recommended by phosphonium ILs than ammonium ILs. The Heck cross-coupling of aryl iodides and bromides with olefins proceeds in the phosphonium salt ionic liquid trihexyl(tetradecyl)phosphonium chloride (THP-Cl) in excellent yields. Furthermore, it is shown that the counter anion matched to the phosphonium cation exerts a measurable effect on the overall yield [82].

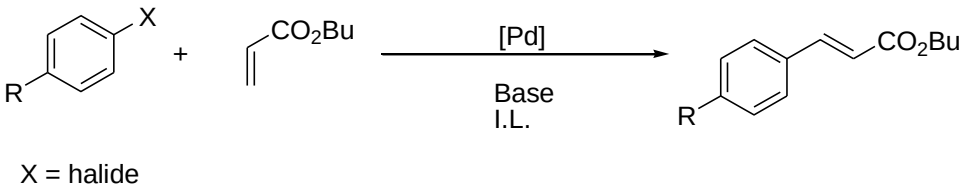


Figure 6: The Heck and related C–C coupling reaction.

1.7 Limitations of ILs

Although ILs is viewed as remarkable class of solvents, there are many issues about some of their features which slow their development in industrial scale. The main limits of ILs are: High cost It is no doubt one of the most limiting factors. Today, ILs is expensive in comparison to common organic solvents, even whether produced on an industrial scale. The high cost of ILs depends not only on the price of raw materials, but especially on the complexity of their manufacturing processes as well as the required qualities. However, a recent study by Helmut Kaiser Consultancy (2015), predicts that there will be a phenomenal increase in demand for ILs during the next fifteen years which will certainly lead to an important reduction of their cost. Obviously, in some cases, the use of slightly expensive ILs may be acceptable if the

advantages related to their application are able to compensate for the additional costs of the solvent. High viscosity of ILs has viscosities comparable of oils with orders of magnitude greater than those of typical organic solvents. Viscosity also impacts the conductivity of ILs and thus their use in electrochemical devices. Toxicity and biodegradability issues ILs are usually viewed and cited as green solvents due to their negligible volatility, their non flammability and their recyclability with high product yields. However, the label ―green solvent" should be attentively applied, because, until now, little is known about the toxicity, biodegradability and mobility in the environment of the most of ILs. So, more researches will be necessary in order to establish the correlation between their ionic structure and toxicity.

1.8 Summary

The ammonium based ILs is the key goal for future uses in all desirable area. But the main problem of this ILs is that lack of scientific data, combine literature and books of ILs. It is still new for our knowledge about the physical, chemical, and biological properties of these fluids is incomplete and limited in comparison with common organic solvents. Besides, for some properties, like the non volatility and the non flammability, it is possible to make generalizations that apply to all classes of ILs. For other properties, applying generalizations to all ILs or to specific groups of ILs are not usually possible.

CHAPTER 2

PRESENT WORK: SYNTHESIS AND CHARACTERIZATION

2.1 Rationale: Introduction of this Research

In this study, the main key point is to synthesize the new molecule of ammonium based ILs (ILs). The theoretically is possible to synthesize billon of IL, it does not say that it is really differ between theoretically study and synthetic study in laboratory. The available of phosphonium, pyridinium, imidazolium, imazolium and ammonium based ILs were synthesized in laboratory. Among of different types of organic solvents that were used in wide fields of chemistry furthermore it is noticed that ILs were less toxic and more environment benighted compounds recognized last three decades. Due to tunable physical and chemical properties of ILs, are easily used in chemicals, pharmaceuticals, industries and research laboratory as solvents and other essential chemicals [78, 83]. Day by day ILs is the target points of researcher, scientist and engineer due to have the tune-able physical and chemical properties. It is also known as the engineering solvent of the 21st century. The 3rd generation ILs is the key point to design as bioactive molecule in pharmaceutical industry. This study deals with the 3rd generation ILs for the use as bioactive molecules in drug discovery.

2.1.1 Problem statement

In the race to synthesize new pharmaceutical drugs, natural product and hetero molecules were used. These molecules have a lot of defect due to large size and high toxicity [84-85].

All the drugs from natural products, complex compound, organ-metallic compound and heterocyclic molecules are to go in complex synthesis and consume a lot of times.

ILs has attracted a great deal of attention due to their variety of potential pharmaceutical applications [86]. IL strategies can take advantage of the dual nature (discrete ions) to realize enhancements which may include controlled solubility (e.g., both hydrophilic and hydrophobic) and are possible bioactivity, antimicrobial agents both prokaryotic and eukaryotic micro-organism [87-88].

The encouraging results of preliminary toxicological studies of synthesized ILs provide good opportunities for the development in biomedical applications for drug discovery. The third generation ILs is active pharmaceutical ingredients. The synthesized third generation ILs provides good opportunities for the replacement to natural bioactive molecule acted as the synthetic bioactive molecule with the satisfactory of green chemistry.

2.1.2 Scope of Research

Firstly In case of invention of new pharmaceutical drugs, ILs has attracted large scope of potential pharmaceutical applications. Due to both of hydrophilic and hydrophobic nature of IL, considered as bioactivity molecule against both prokaryotic and eukaryotic micro-organisms.

Secondly, due to lake of microbial studies of ILs in drug design, open the new fields of research for chemistry, pharmaceutical chemistry and medical chemistry.

The third point to do research on bioactive ILs is explained as greener and designer molecules.

Finally It could be said that a relationship was established in different aryl amine based ILs in term of toxicity.

2.1.3 Objectives and outcomes of Research

In view of remarkable importance of ILs in the field of chemical and pharmaceutical industries, the synthesis of ILs still remains scares. It is planned to synthesize different types new ILs. The possible objectives and outcomes of this research work are as follows:

a. Different aryl amine based bioactive ILs will be synthesized.
b. The synthesized new ILs will be purified by the solvent- separation technique and using vacuum oven.

c. The synthesized new ILs will be characterized by 1H Nuclear Magnetic Resonance Spectroscopy (NMR), 13C Nuclear Magnetic Resonance Spectroscopy (NMR), Fourier Transform Infrared Spectroscopy (FTIR), UV Spectroscopy and Thermo-gravimetric analysis or Thermal gravimetric analysis (TGA).
d. The antibacterial and antifungal profile of synthesized ILs will be estimated.
e. Then Minimum Inhibition concentration (MIC) and Minimum bactericidal/fungicidal concentration (MBC/MFC) will be evaluated for specific use in drug delivery.
f. To confirm their safe use in pharmaceutical industries as drug and active ingredient, the cyto and phyto- toxicological test will be evaluated.
g. Due to have aryl amine as cation, it would be a good bioactive synthetic antibiotic.
h. Due to the satisfactory condition of green chemistry, it would be low toxic.
i. To evaluate the thermochemical properties, HyperChem, material studio were used to optimize all molecules.
j. QSAR was the great goal for pharmaceutical use.
k. A comparison of theoretical and experimental study.

2.1.4 Important of Research

Some of points given below make this research as an essential documentary for the study of ILs in views of pharmaceutical and chemicals area

- To synthesize of new aromatic cation ILs.
- Due to antimicrobial result.
- Due to establish the relationship of different cation on antimicrobial activity.
- The theoretical studies of thermodynamics as like a new area for ILs.
- The QSAR seems them as biological molecule in pharmaceutical Industries.
- This study provides us that ILs is used as environmental benign chemicals.

2.1.5 Summary

To sum up, it could be concluded that all synthesized aromatic cation based ILs could be able to show the high class of antimicrobial activity against different human and phyto-pathogenic bacteria and fungi which gives the best biological evaluation for future uses in the fields of pharmaceutical area. On the other hand the phyto-toxicity of this work also involves the toxicity study and further implement in the area of pesticides especially in herbicides. The most important implement of this work is to use computational chemistry for development of thermo-physical, chemical and biological studies.

2.2 Introduction for synthesis and characterization

This chapter includes the synthetic procedures and purification of aryl ammonium ILs, based ILs in case of both the aliphatic and aromatic ammonium cation. Different types of ammonium cations composed with several carboxylate from the organic acids, such as formic acid, acetic acid, propanoic acid, butanoic acid and trifluroaccetic acid. Simple neutralization reaction occurs in presence of suitable solvents in the reaction system. After the synthesis, the ILs was characterized using spectroscopic technique and elemental analysis. Standard methods from approved organizations were employed in this work. All the experimental data were analyzed by several statistical procedures and explained accordingly. This chapter composed of the synthesis and purification of synthesized ILs.

2.2.1 General procedure for the synthesis by neutralization reaction

Aryls ammonium carboxylate ILs have been synthesized by the acid-base neutralization reaction of alkanolamine or alkanolamine with carboxylate acid, a encapsulated in the scheme shown in figure 7. In this reaction, Acid was solid so that it was added first to solvent and stirring well for dissolving then ammonium base were added drop-wise. This reaction is an exothermic so heat was produced. To control the heat from the reaction, ice-bath was used. To make the inert environment,

nitrogen gas was used as inlet and outlet so that the reaction was proceed quickly and good yields.

As the acid has lower melting point than base, the ratio 1.5: 1 of acid and base was added into round bottle flax at an ambient temperature while the acid was added drop wise in base. Then the flax was placed in Magnetic stirring with condenser for reflux. Then stirring for few minute such that the substrate be dissolved well. Then it was placed in Ice bath on magnetic stirring with reflux condenser and inlet and outlet the Nitrogen gas N_2. Then the stirring was continuous for 6-12 hours even more 30 hours still the reaction monitoring by TLC, using the aluminum sheet coated with silica gel with methanol as a mobile phase that show the formation of expected production. Then the reaction mixture was heated 1.5-2 hours with paraffin bath at 50-55ºC temperature. For the further purification it was kept in vacuum oven at 90ºC temperature for two days where they obtained ILs has more than 200ºC temperature that indicates thermally stable condition of them.

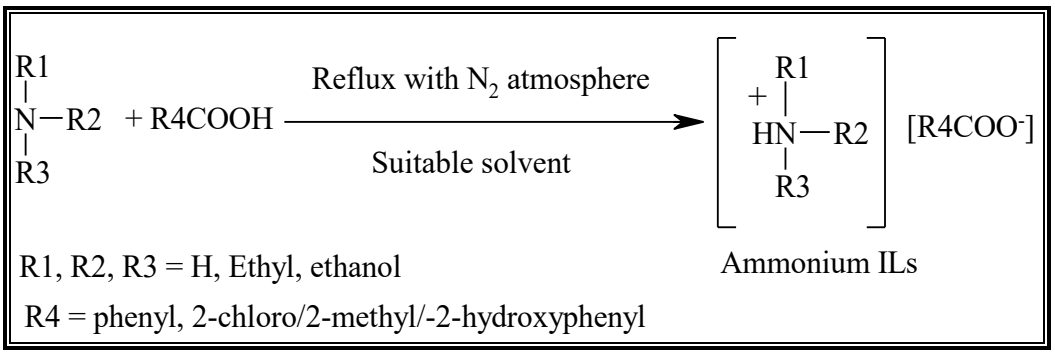


Figure 7: Scheme for Ammonium ILs preparation.

2.3 General method of synthesis for Present work

50 mili mole aryl amine (3.01 ml) was taken in round bottle flax. The round bottle flax with mixture was placed in the icebath on magnetic stirring with magnet. Then 75 (1.5 ratio) m mol carboxylic acid such as formic acid, acetic acid, propanoic acid, butanoic acid and trifluroaccetic acid, was added drop-wise for (30-35) minutes. Then the mixture was stirring various hours for different schemes except for

trifluroaccetic acid about 1.00 hour with reflux containing nitrogen gas for maintaining the inert environment. The reaction was monitored by TLC (MeOH: $CHCl_3$=1:4), where methanol is a mobile phase. After that the mixture was heated with paraffin oil for 2 hours.

2.3.1 Synthesis of anilinium carboxylate ILs (Reaction Scheme-01)

Reaction scheme 01

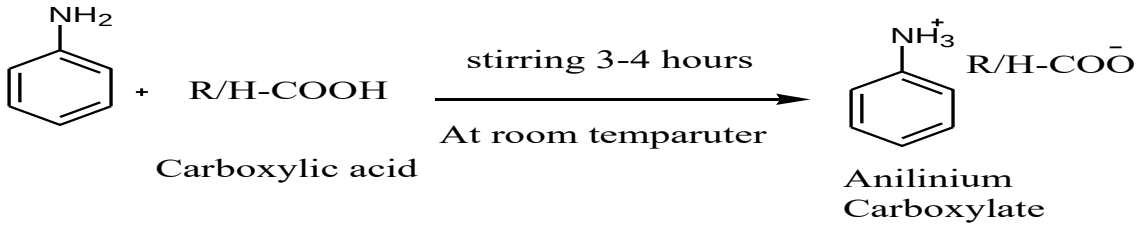
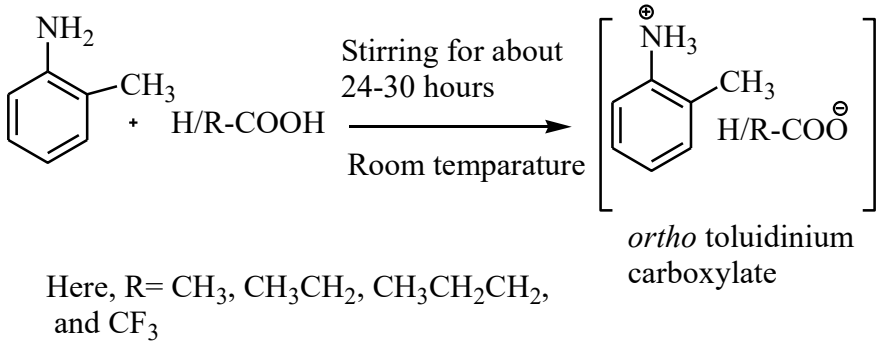


Figure 8: Reaction Scheme 01

2.3.2 Synthesis of *ortho* toluidinium carboxylate ILs (Reaction Scheme-02)

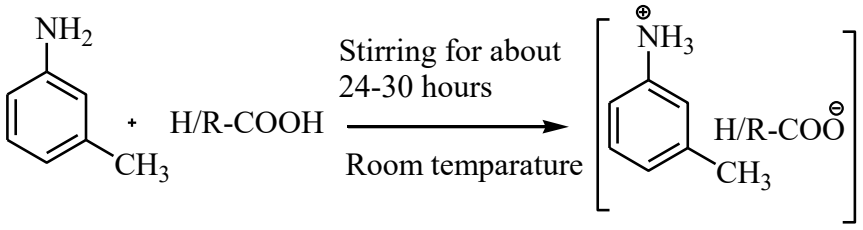


Here, R= CH_3, CH_3CH_2, $CH_3CH_2CH_2$, and CF_3

Figure 9: Reaction Scheme 02

2.3.1 Synthesis of *meta* toluidinium based ILs (Reaction Scheme-03)

2.3.1.1 *Reaction Scheme-03*



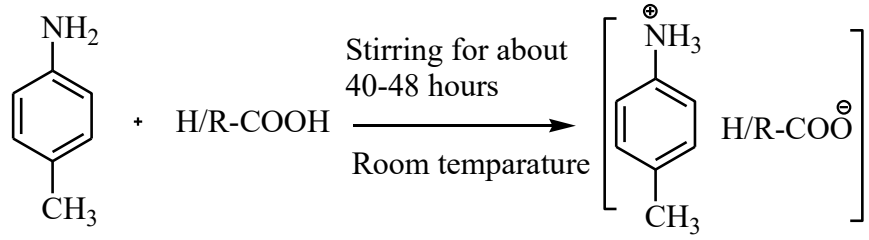
meta toluidinium carboxylate

Here, R= CH_3, CH_3CH_2, $CH_3CH_2CH_2$, and CF_3

Figure 10: Reaction scheme 03

2.3.2 Synthesis of *para* toluidinium Based ILs (Reaction Scheme-04)

2.3.2.1 *Reaction Scheme 04*



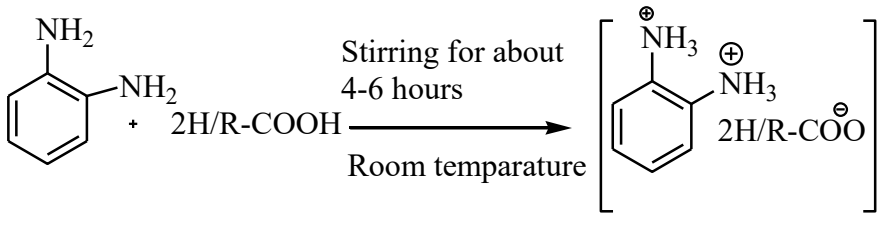
Here, R= CH_3, CH_3CH_2, $CH_3CH_2CH_2$, and CF_3

para toluidinium carboxylate

Figure 11: Reaction scheme-04

2.3.3 Synthesis of Diammniumphenyl based ILs (Reaction Scheme 05)

2.3.3.1 *Reaction Scheme-05*



Here, R= CH_3, CH_3CH_2, $CH_3CH_2CH_2$, and CF_3

Diphenyammonium carboxylate

Figure 12: Reaction Scheme -05

2.4 Purification of ILs

The synthesized ILs was purified after removal of excess amount of unreacted acid from this mixtures using rotary evaporization. After continuous evaporating, all acids were removed from round bottle to stored round bottle under pressure. Then, it was preserved in decicator for 3 days for drying and obtainded semisolid crystal of IL.

2.5 Characterization of Ammonium ILs

The synthesized ILs was characterized using Spectroscopy Fourier-Transform Infrared (FT-IR) (Shimadzu IR Prestige 21, Shimadzu Corporation) and Nuclear Magnetic Resonance (NMR) (Bruker Avance 300 MHz). The purity of the prepared materials was checked chromatographic technique and vacuum evaporation. The functional groups (phenyl, methylene, carbonyl, carboxylate, and ammonum ion) and the unsaturations of the molecules can be identified by FTIR and thus confirm the structure. All the results from FT IR, NMR and UV were in good alignment for the formation of compounds.

2.6 NMR Spectroscopy of Ammonium ILs

The recorded NMR spectral data were summarized for all synthesized ILs. The 1H-NMR spectrum of [$PhNH_3$][R-COO] shows the peaks at δ 2.00 for methyl proton in carboxylate ion and the two identical peaks at δ near 8.00 and 7.00 for two two-proton triplets for C_6H_5- of the alkyl chain, respectively the labile deuterium of the -OD group for the solvent CD_3OD. This can be confirmed by the appearance of a peak with weak intensity at 4.5 to 5.5 ppm, which may be attributed to the NH_3^+ group of CD_3OH. The other ILs represents similar peaks that correspond to the necessary protons in the molecules which confirm the structures. Similar ILs has been reported earlier, which were in good evidence for the existence of ILs in this study.

2.7 Result and Discussion

2.7.1 Characterization for Scheme-01

	AIL 01	AIL 02	AIL 03	AIL 04	AIL 05
Physical State	Liquids	Liquids	Liquids	Solid	Solid
Color	Light Red	Light Red	Light Red	White	white
Odor	No odor	No odor	No odor	No odor	No odor
Boiling Point	>200°C	>200°C	>200°C	>300°C	>350°C
Solubility	H_2O,CH_3OH, DMSO,$CH_3COOC_2H_5$	H_2O,CH_3OH, DMSO,$CH_3COOC_2H_5$	H_2O,CH_3OH, DMSO,$CH_3COOC_2H_5$	H_2O,CH_3OH ,DMSO,$CH_3COOC_2H_5$	H_2O,CH_3OH,DMSO,$CH_3COOC_2H_5$

2.7.2 Structure

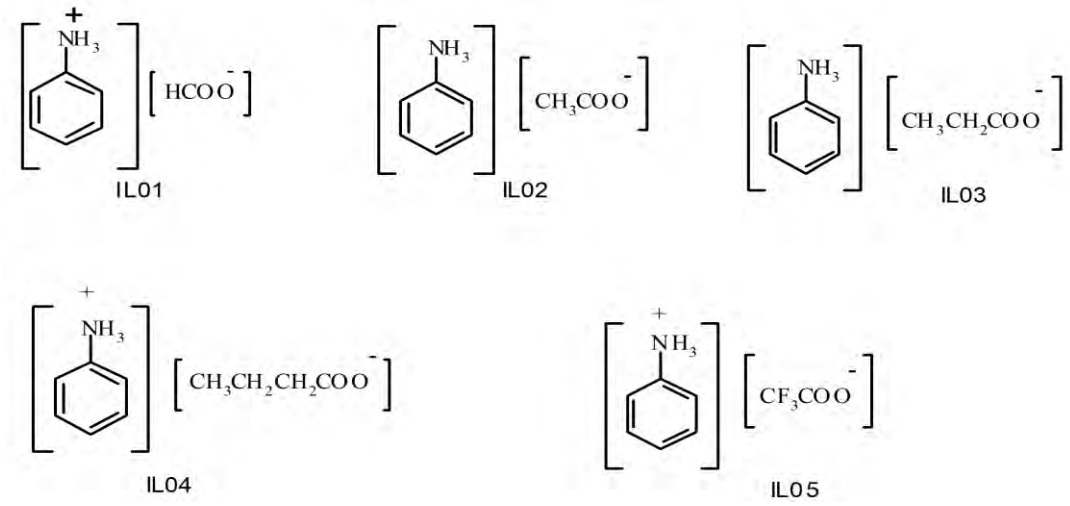


Figure 13: Structure of ILs

Anilinium methanoate (AIL01), [$PhNH_3$] [HCOO], M.W.: 139.0, Yield (%): 94.0%. FT-IR (KBr) in cm^{-1}: 3429 (N-H) asymmetry, 3004 (C=C) in benzene ring, 2956 (N-H) symmetry, 2925 (C-H) asymmetry, 2855 (C-H) symmetry, broad peak in 2695 ($PhNH_3^+$), 1780 (C-O) asymmetry, 1675 (-CO) symmetry cm^{-1}.

Anilinium ethanoate (AIL02), [$PhNH_3$] [C_2OOH_3], M.W.:153, Yield (%): 93.0%

FT-IR (KBr) in cm^{-1}: 3358 (N-H) asymmetry, 3217 (C=C) in benzene ring, 3037 (N-H) symmetry, 2908 (C-H) asymmetry, 2897 (C-H) symmetry, broad peak in 2640 ($PhNH_3^+$), 1681 (C-O) asymmetry, 1621-1602 (-CO) symmetry cm^{-1}.

Anilinium propanoate (AIL03), [$PhNH_3$] [C_3OOH_5], M.W.: 167.0, Yield (%): 91%.FT-IR (KBr) in cm^{-1}: 3334 (N-H) asymmetry, 3087 (C=C) in benzene ring, 3199 (N-H) symmetry, 2977 (C-H) asymmetry, 2910 (C-H) symmetry, 2697 ($PhNH_3^+$), 1667 (C-O) asymmetry, 1603 (-CO) symmetry cm^{-1}.

Anilinium butanoate (AIL04), [$PhNH_3$] [C_4OOH_7], M.W.: 187.0, Yield (%): 91%. FT-IR (KBr) in cm^{-1}: 3287 (N-H) asymmetry, 3000 to 3050 (C=C) in benzene ring, 3197 (N-H) symmetry, 2874 (C-H) asymmetry, 2803 (C-H) symmetry, 2646 ($PhNH_3^+$), 2352 (C-O) asymmetry, 1660 (-CO) symmetry cm^{-1}.

Aniliniumtrifluroaccetate (AIL05), [$PhNH_3$] [$C_2F_3OOH_3$], M.W.: 207.0, Yield (%): 98%. FT-IR (KBr) in cm^{-1}: 3429 (N-H) asymmetry, (3004 (N-H) symmetry, 2800 (C-H) symmetry, 2596 ($PhNH_3^+$), 1780 (C-O) asymmetry, 1675 (-CO) symmetry cm^{-1}.

1H-NMR chemical shifts: 7.93 (s, 3H, $PhNH_3$), 7.21 (s, 4H, Ph), 7.11 (s, 1H, Ph).

2.7.3 Characterization for Scheme-02

	OTIL 01	OTIL 02	OTIL 03	OTIL 04	OTIL 05
Physical State	Liquids	Liquids	Liquids	Solid	Solid
Color	Light Red	Light Red	Light Red	White	White
Odor	No odor	No odor	No odor	No odor	No odor
Boiling point	>200°C	>200 °C	>200 °C	>300 °C	>350 °C
Solubility	Solubility	H_2O,CH_3OH,	H_2O,CH_3O	H_2O,CH_3OH	H_2O,

		DMSO,CH_3CO OC_2H_5	H, DMSO,CH_3 $COOC_2H_5$	, DMSO,CH_3 $COOC_2H_5$	DMSO,

2.7.4 Molecular structure of synthesized ILs

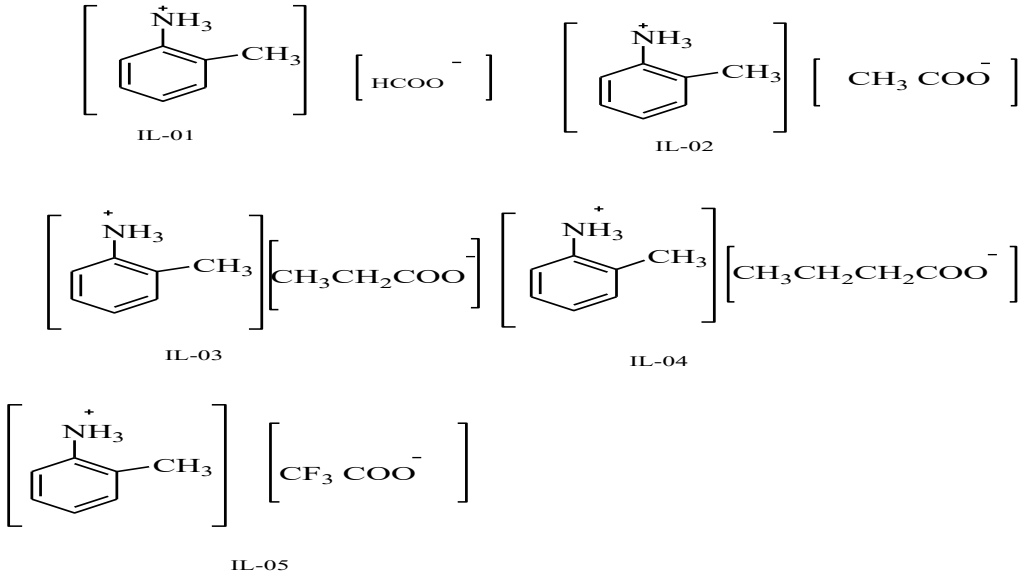


Figure 14: Synthesized ILs

	OTIL 01	OTIL 02	OTIL 03	OTIL 04	OTIL 05
Physical State	Liquids	Liquids	Liquids	Solid	Solid
Color	Light Red	Light Red	Light Red	White	White
Odor	No odor	No odor	No odor	No odor	No odor
Boiling point	>200^oC	>200 $^\circ C$	>200 $^\circ C$	>300 $^\circ C$	>350 $^\circ C$
Solubility	H_2O,CH_3O H, DMSO,CH_3 $COOC_2H_5$	H_2O,CH_3OH, DMSO,CH_3CO OC_2H_5	H_2O,CH_3OH, DMSO,CH_3 $COOC_2H_5$	H_2O,CH_3O H, DMSO,CH_3 $COOC_2H_5$	H_2O, DMSO,

***ortho* toluidiniummethanoate (OTIL01),**[CH_3PhNH_3] [HCOO], M.W.: 153.0,Yield (%): 81.0%., FT-IR (KBr) in cm^{-1}: 3457 (N-H) asymmetry, 3024 (C=C) in benzene ring, 3366 (N-H) symmetry, 2903 (C-H) asymmetry, 2859 (C-H) symmetry, 2596 ($PhNH_3^+$), 1622 (C-O) asymmetry, 1667 (-CO) symmetry cm^{-1}.

***ortho* toluidiniumacetate (OTIL02),**[CH_3PhNH_3] [C_2OOH_3],M.W.:167.0, Yield (%): 78.0%., FT-IR (KBr) in cm^{-1}: 3416 (N-H) asymmetry, 3021 (C=C) in benzene ring, 3361 (N-H) symmetry, 2930 (C-H) asymmetry, 2859 (C-H) symmetry, 2360 ($PhNH_3^+$), 1617 (C-O) asymmetry, 1587 (-CO) symmetry cm^{-1}.

***ortho* toluidiniumpropanoate(OTIL03),** [CH_3PhNH_3] [C_3OOH_5],M.W.: 179.0,Yield (%): 77.0%., FT-IR (KBr) in cm^{-1}: 3433 (N-H) asymmetry, 3020 (C=C) in benzene ring, 3330 (N-H) symmetry, 2990 (C-H) asymmetry, 2874 (C-H) symmetry, 2370 ($PhNH_3^+$), 1621 (C-O) asymmetry, 1612 (-CO) symmetry cm^{-1}.

***ortho* toluidiniumbutanoate (OTIL04),** [CH_3PhNH_3] [C_4OOH_7],M.W.: 195.0, Yield (%): 78.0%., FT-IR (KBr) in cm^{-1}: 3457 (N-H) asymmetry, 3024 (C=C) in benzene ring, 3366 (N-H) symmetry, 2903 (C-H) asymmetry, 2859 (C-H) symmetry, 2360 2596 ($PhNH_3^+$), 1622 (C-O) asymmetry, 1667 (-CO) symmetry cm^{-1}.

***ortho* toluidiniumtrifluroaccetate (OTIL05),**[CH_3PhNH_3] [$C_2F_3OOH_3$], M.W.: 221.0, Yield (%): 88%., FT-IR (KBr) in cm^{-1}: 3440 (N-H) asymmetry, 3007 (N-H) symmetry, 2830 (C-H) symmetry, 2602 ($PhNH_3^+$), 1760 (C-O) asymmetry, 1655 (-CO) symmetry cm^{-1}.

1H-NMR chemical shifts: 8.15 (s, 3H, $PhNH_3$), 7.31 (s, 1H, Ph), 7.30 (s, 1H, Ph), 7.26 (s, 1H, Ph), 7.21 (s, 1H, Ph), 2.27 (s, 3H, $PhCH_3$).

2.7.5 Characterization for Scheme-03

	MTIL 01	MTIL 02	MTIL 03	MTIL 05	MTIL 05
Physical State	Liquids	Liquids	Solid	Solid	Solid
Color	Light Red	Light Red	Red	White	White
Odor	No odor	No odor	No odor	No odor	No odor

Boiling point	>200°C	>200	>200	>300	>350
Solubility	H_2O,CH_3OH, DMSO,$CH_3COOC_2H_5$	H_2O,CH_3OH, DMSO,$CH_3COOC_2H_5$	H_2O,CH_3OH, DMSO,$CH_3COOC_2H_5$	H_2O, DMSO,	H_2O,DMSO

2.7.6 Molecular structure

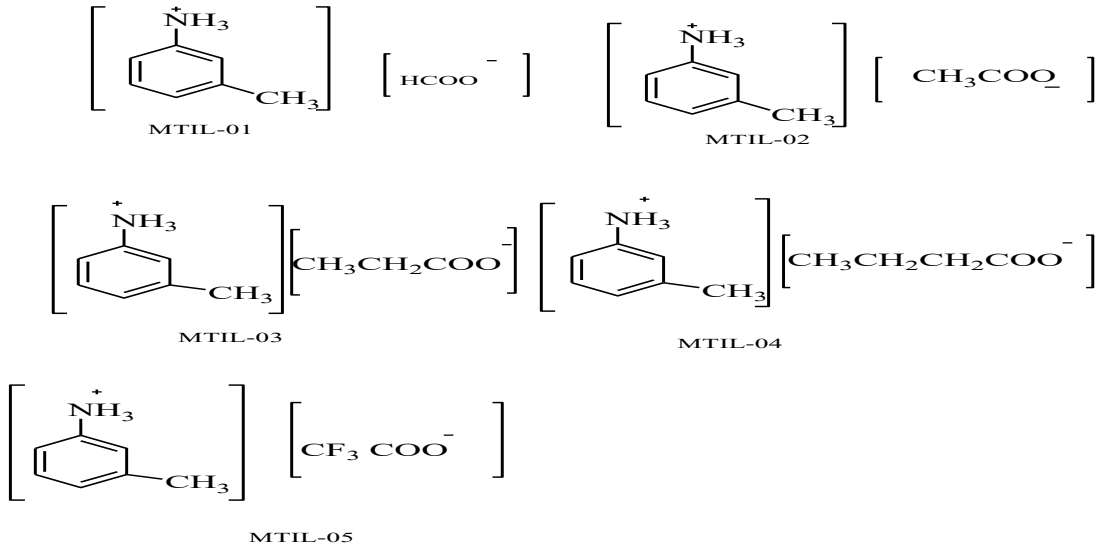


Figure 15: Structure of ILs

***meta* toluidiniummethanoate (MTIL01),**[CH_3PhNH_3] [HCOO], M.W.: 153.0,Yield (%): 81.0%., FT-IR (KBr) in cm^{-1}: 3357 (N-H) asymmetry, 2997 (C=C) in benzene ring, 3312 (N-H) symmetry, 2903 (C-H) asymmetry, 2859 (C-H) symmetry, 2487 ($PhNH_3^+$), 1622 (C-O) asymmetry, 1667 (-CO) symmetry cm^{-1}.

***meta* toluidiniumacetate (MTIL02),** [CH_3PhNH_3] [C_2OOH_3],M.W.:167.0, Yield (%): 78.0%. FT-IR (KBr) in cm^{-1}: 3457 (N-H) asymmetry, 3024 (C=C) in benzene ring, 3366 (N-H) symmetry, 2903 (C-H) asymmetry, 2859 (C-H) symmetry, 2550 ($PhNH_3^+$), 1622 (C-O) asymmetry, 1667 (-CO) symmetry cm^{-1}.

***meta* toluidiniumpropanoate (MTIL03),** [CH_3PhNH_3] [C_3OOH_5],M.W.: 179.0,Yield (%): 76.0%., FT-IR (KBr) in cm^{-1}: 3377 (N-H) asymmetry, 2987 (C=C) in benzene ring, 3334 (N-H) symmetry, 2920 (C-H) asymmetry, 2870 (C-H) symmetry, 2560 ($PhNH_3^+$), 1622 (C-O) asymmetry, 1667 (-CO) symmetry cm^{-1}.

***meta* toluidiniumbutanoate (MTIL04),** $[CH_3PhNH_3]$ $[C_4OOH_7]$,M.W.: 195.0, Yield (%): 74.0%., FT-IR (KBr) in cm^{-1}: 3457 (N-H) asymmetry, 3024 (C=C) in benzene ring, 3366 (N-H) symmetry, 2903 (C-H) asymmetry, 2859 (C-H) symmetry, 2360 2596 ($PhNH_3^+$), 1622 (C-O) asymmetry, 1667 (-CO) symmetry cm^{-1}.

***meta* toluidiniumtrifluroaccetate (MTIL05),** $[CH_3PhNH_3]$ $[C_2F_3OOH_3]$, M.W.: 221.0, Yield (%): 88%., FT-IR (KBr) in cm^{-1}: 3398 (N-H) asymmetry, 3010 (N-H) symmetry, 2900 (C-H) symmetry, 2596 ($PhNH_3^+$), 1783 (C-O) asymmetry, 1671 (-CO) symmetry cm^{-1}.

1H-NMR chemical shifts: 7.96 (s, 3H, $PhNH_3$), 7.18 (s, 1H, Ph), 7.096 (s, 1H, Ph), 7.016 (s, 1H, Ph), 6.99 (s, 1H, Ph), 2.13 (s, 3H, $PhCH_3$).

2.7.7 Characterization of scheme 04

	PTIL 01	PTIL 02	PTIL 03	PTIL 04	PTIL 05
Physical State	Semi solid	Semi solid	Solid	Solid	Solid
Color	Light Red	Light Red	Red	White	White
Odor	No odor	No odor	No odor	No odor	No odor
Boiling point	>200 °C	>200 °C	>200 °C	>300 °C	>350 °C
Solubility	H_2O,CH_3OH, DMSO,$CH_3COOC_2H_5$	H_2O,CH_3OH,DMSO,$CH_3COOC_2H_5$	H_2O,CH_3OH,DMSO,$CH_3COOC_2H_5$	H_2O, DMSO,	H_2O,DMSO

2.7.7.1 Structure of synthesized ILs

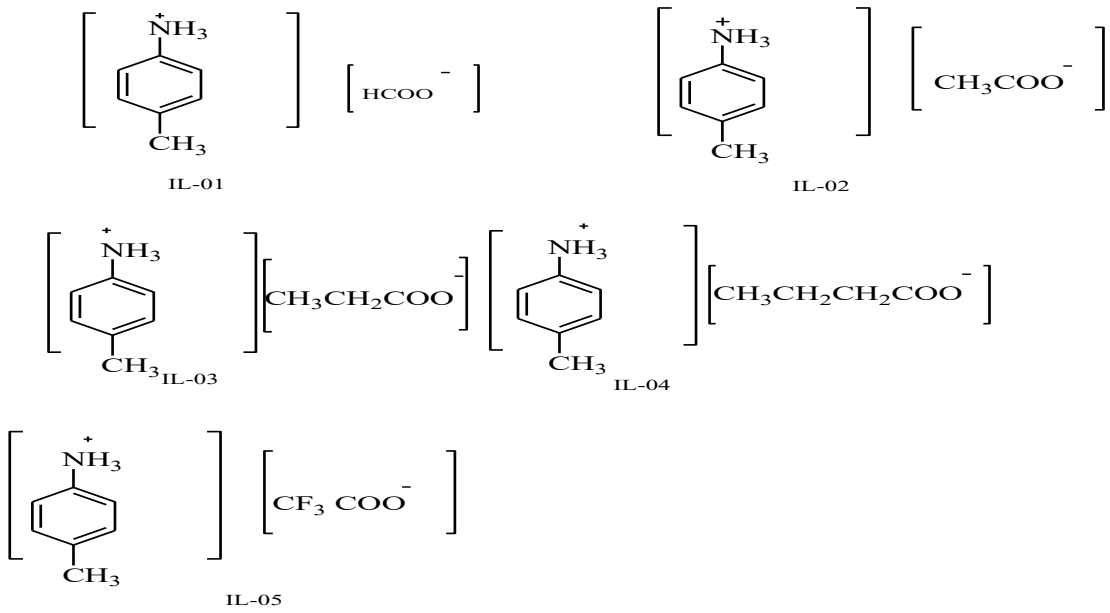


Figure 16: Structure of ILs

***para* toluidiniummethanoate (PTIL01),** $[CH_3PhNH_3]$ [HCOO], M.W.: 153.0,Yield (%): 81.0%., FT-IR (KBr) in cm^{-1}: 3147 (N-H) asymmetry, 3012 (C=C) in benzene ring, 2966 (N-H) symmetry, 2931 (C-H) asymmetry, 2897 (C-H) symmetry, 2360, 1589 (C-O) asymmetry, 1485 (-CO) symmetry cm^{-1}.

***para* toluidiniumacetate (PTIL02),** $[CH_3PhNH_3]$ $[C_2OOH_3]$,M.W.:167.0, Yield (%): 79.0%., FT-IR (KBr) in cm^{-1}: 3457 (N-H) asymmetry, 3024 (C=C) in benzene ring, 3366 (N-H) symmetry, 2903 (C-H) asymmetry, 2859 (C-H) symmetry, 2360 ($PhNH_3^+$), 1622 (C-O) asymmetry, 1667 (-CO) symmetry cm^{-1}.

1H-NMR chemical shifts: 8.46 (m, 3H, $PhNH_3$), 7.28 (t, 2H, Ph), 6.42 (s, 1H, Ph), 2.25 (s, 3H, $PhCH_3$), 1.62 (s, 3H, CH_3COO).

***para* toluidiniumpropanoate(PTIL03),** $[CH_3PhNH_3]$ $[C_3OOH_5]$,M.W.: 179.0,Yield (%): 76.0%., FT-IR (KBr) in cm^{-1}: 3147 (N-H) asymmetry, 3012 (C=C) in benzene ring, 2966 (N-H) symmetry, 2931 (C-H) asymmetry, 2897 (C-H) symmetry, 2360 ($PhNH_3^+$), 1622 (C-O) asymmetry, 1667 (-CO) symmetry cm^{-1}.

***para* toluidiniumbutanoate (PTIL04),** [CH_3PhNH_3] [C_4OOH_7],M.W.: 195.0, Yield (%): 74.0%., FT-IR (KBr) in cm^{-1}: 3457 (N-H) asymmetry, 3024 (C=C) in benzene ring, 3366 (N-H) symmetry, 2903 (C-H) asymmetry, 2859 (C-H) symmetry, 2596 ($PhNH_3^+$), 1622 (C-O) asymmetry, 1667 (-CO) symmetry cm^{-1}.

***para* toluidiniumtrifluroaccetate (PTIL05),**[CH_3PhNH_3] [$C_2F_3OOH_3$], M.W.: 221.0, Yield (%): 88%., FT-IR (KBr) in cm^{-1}: 3147 (N-H) asymmetry, 3012 (C=C) in benzene ring, 2966 (N-H) symmetry, 2931 (C-H) asymmetry, 2897 (C-H) symmetry, 2360, 1589 (C-O) asymmetry, 1485 (-CO) symmetry cm^{-1}.

2.7.8 Characterization of scheme 05

2.7.8.1 Structure of synthesized ILs

	DPIL 01	DPIL 02	DPIL 03	DPIL 05	DPIL 05
Physical State	Solid	Solid	Solid	Solid	Solid
Color	White	White	White	White	White
Odor	No odor	No odor	No odor	No odor	No odor
Melting point	>300^oC	>300	>300	>300	>350
Solubility	H_2O,CH_3OH,DMSO,$CH_3COOC_2H_5$	H_2O,CH_3OH,DMSO,$CH_3COOC_2H_5$	H_2O,CH_3OH,DMSO,$CH_3COOC_2H_5$	H_2O, DMSO,	H_2O, DMSO

2.7.8.2 *Structure of synthesized ILs*

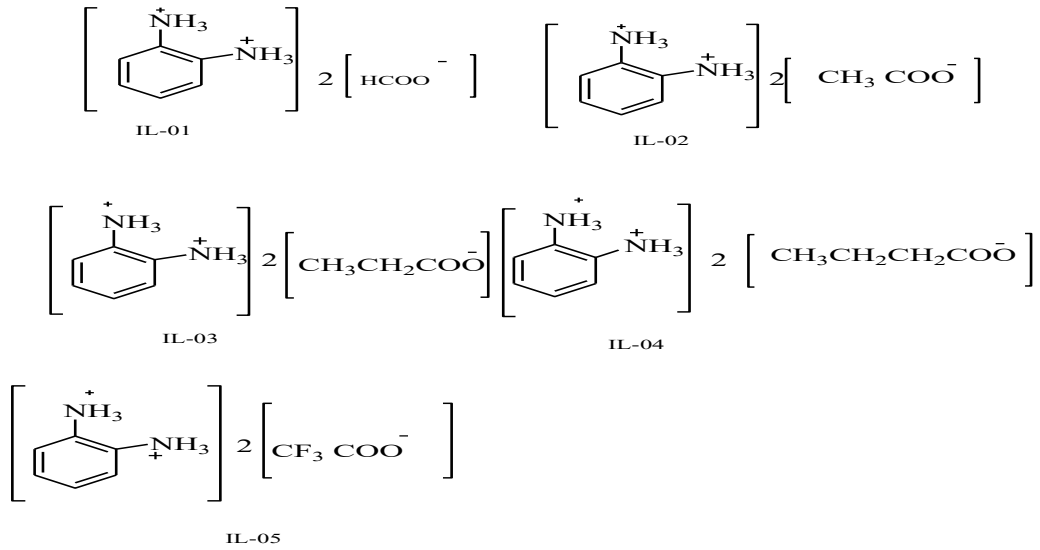


Figure 17: Structure of ILs

1,2-diammoniumphenylmethanoate (DPIL01), $[CH_3PhNH_3]$ [HCOO], M.W.: 153.0,Yield (%): 81.0%., FT-IR (KBr) in cm^{-1}: 3147 (N-H) asymmetry, 3012 (C=C) in benzene ring, 2966 (N-H) symmetry, 2931 (C-H) asymmetry, 2897 (C-H) symmetry, 2360, 1589 (C-O) asymmetry, 1485 (-CO) symmetry cm^{-1}.

1,2 –diammoniumphenylethanoate (DPIL02), $[CH_3PhNH_3]$ $[C_2OOH_3]$, M.W.:167.0, Yield (%): 78.0%., FT-IR (KBr) in cm^{-1}: 3147 (N-H) asymmetry, 3012 (C=C) in benzene ring, 2966 (N-H) symmetry, 2931 (C-H) asymmetry, 2897 (C-H) symmetry, 2360, 1589 (C-O) asymmetry, 1485 (-CO) symmetry cm^{-1}.

1H-NMR chemical shifts: 7.151 (s, 6H, $2PhNH_3$), 7.306 (d, 4H, Ph), 2.27 (s 3H, CH_3COO).

1,2-diammoniumphenylpropanoate(DPIL03),
$[CH_3PhNH_3][C_3OOH_5]$,M.W.:179.0,Yield(%): 76.0%. FT-IR (KBr) in cm^{-1}: 3147 (N-H) asymmetry, 3012 (C=C) in benzene ring, 2966 (N-H) symmetry, 2931 (C-H) asymmetry, 2897 (C-H) symmetry, 2360, 1589 (C-O) asymmetry, 1485 (-CO) symmetry cm^{-1}.

1,2-diammoniumphenylbutanoate (DPIL04),$[CH_3PhNH_3]$ $[C_4OOH_7]$,M.W.:195.0, Yield (%): 74.0%. FT-IR (KBr) in cm^{-1}: 3147 (N-H) asymmetry, 3012 (C=C) in

benzene ring, 2966 (N-H) symmetry, 2931 (C-H) asymmetry, 2897 (C-H) symmetry, 2360, 1589 (C-O) asymmetry, 1485 (-CO) symmetry cm^{-1}.

1,2-diammoniumphenyltrifluroaccetate,(DPIL05),$[CH_3PhNH_3][C_2F_3OOH_3]$, M.W.:221.0,Yield (%): 88%. FT-IR (KBr) in cm^{-1}: 3147 (N-H) asymmetry, 3012 (C=C) in benzene ring, 2966 (N-H) symmetry, 2931 (C-H) asymmetry, 2897 (C-H) symmetry, 2360, 1589 (C-O) asymmetry, 1485 (-CO) symmetry cm^{-1}

2.8 SPECTRA

2.8.1 1H NMR DATA

Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
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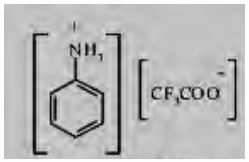
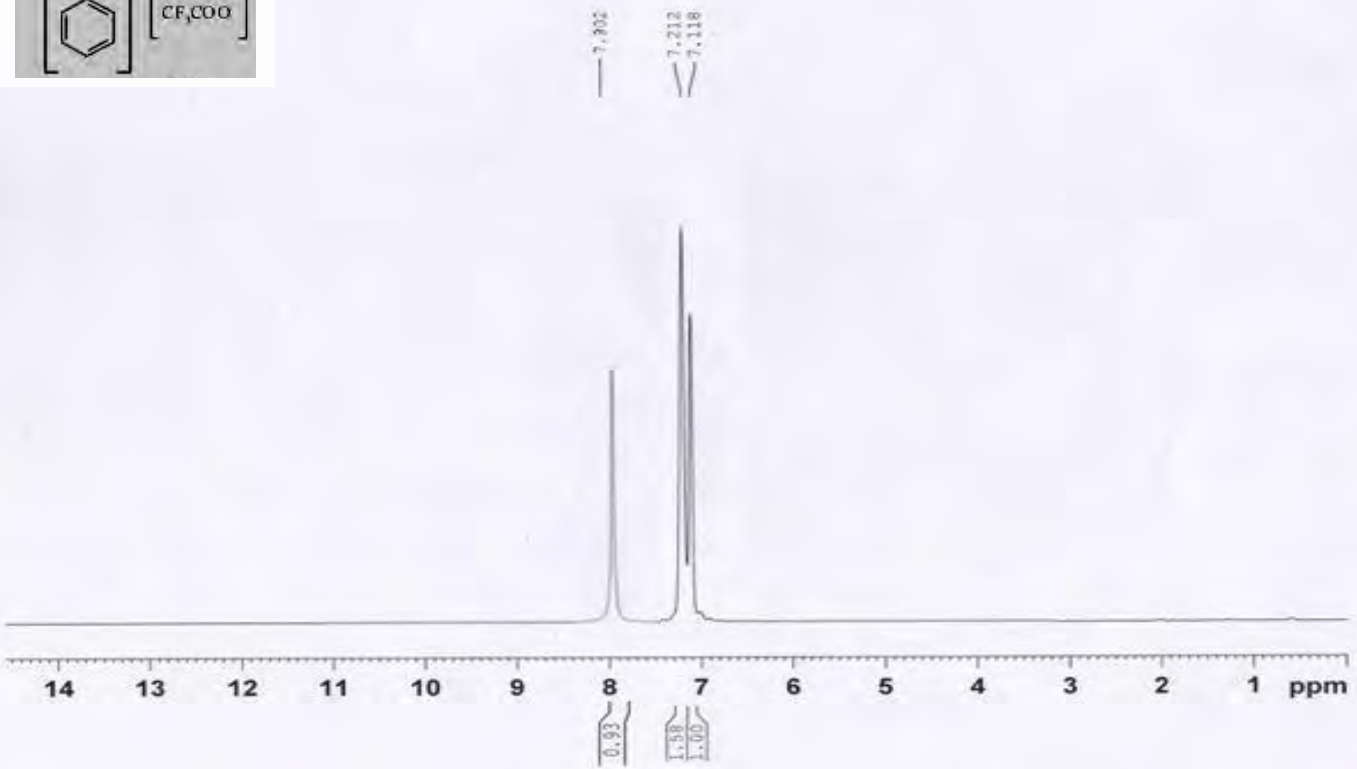
Operated by: Md. Emdad Hossain, Scientist





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DW 62.400 usec
DE 6.50 usec
TE 300.4 K
D1 2.00000000 sec
TD0 1

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NUC1 1H
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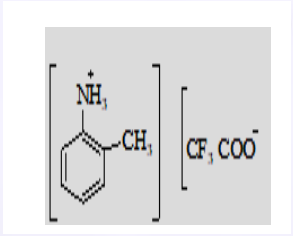
PLW1 12.00000000 W

F2 - Processing parameters
SI 131072
SF 400.2300000 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Sample: OTIL_05
Operated by: Md. Emdad Hossain, Scientist

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FIDRES            0.122266 Hz
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RG                    66.24
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DE                    6.50 usec
TE                   299.4 K
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TD0                      1

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NUC1                    1H
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PLW1           12.00000000 W

F2 - Processing parameters
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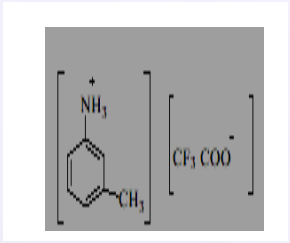
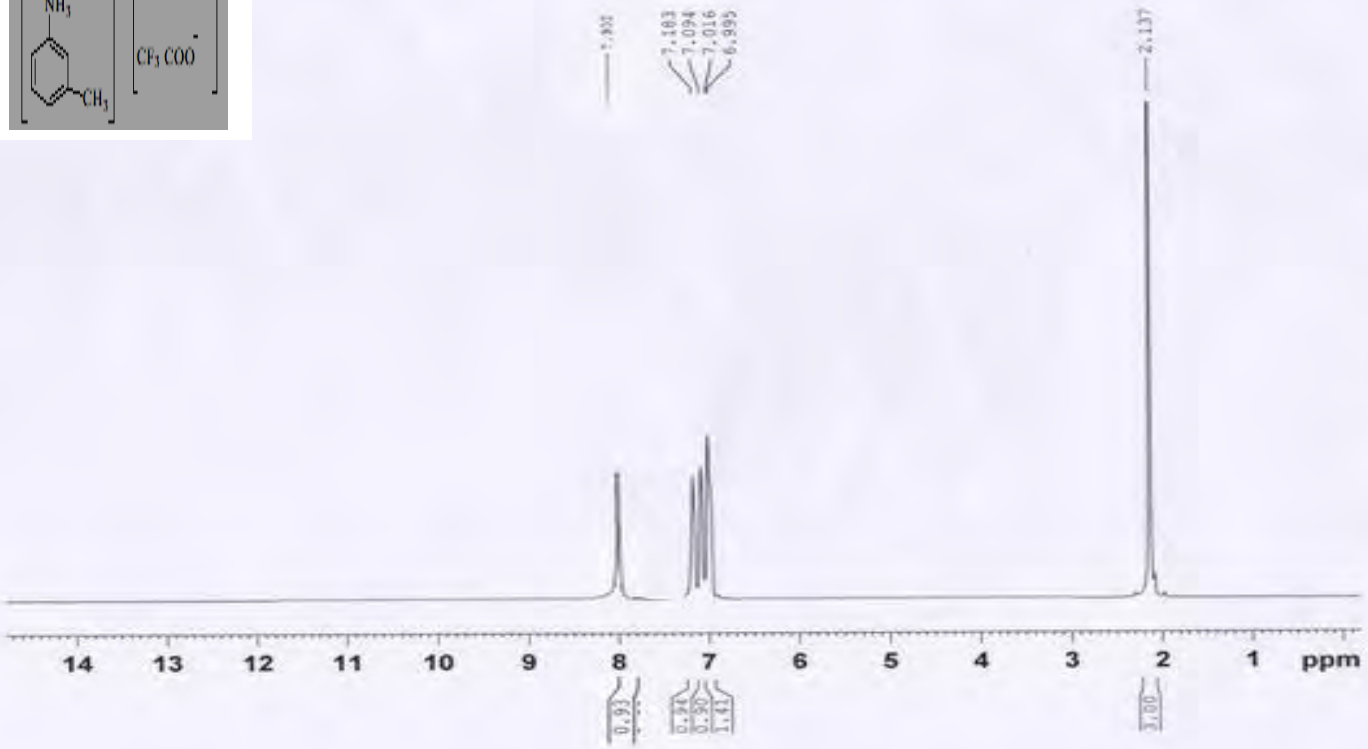
Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Sample: MTIL_05
Operated by: Md. Emdad Hossain, Scientist





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PROCNO 1

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PULPROG zg
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SOLVENT D2O -
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SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 39.71
DW 62.400 usec
DE 6.50 usec
TE 300.2 K
D1 2.00000000 sec
TD0 1

======== CHANNEL f1 ========
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NUC1 1H
P1 11.20 usec
PLW1 12.00000000 W

F2 - Processing parameters
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SF 400.2300000 MHz
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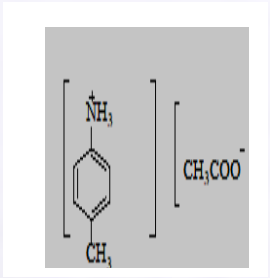
Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Sample: PTIL_01
Operated by: Md. Emdad Hossain, Scientist

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PROCNO                           1

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PULPROG                         zg
TD                           65536
SOLVENT                        D2O
NS                              16
DS                               0
SWH                   8012.820 Hz
FIDRES                0.122266 Hz
AQ                    4.0894465 sec
RG                           22.53
DW                      62.400 usec
DE                       6.50 usec
TE                          300.2 K
D1                    2.00000000 sec
TD0                              1

======== CHANNEL f1 ========
SFO1                400.2320011 MHz
NUC1                           1H
P1                      11.20 usec
PLW1                12.00000000 W

F2 - Processing parameters
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WDW                            EM
SSB                 0
LB                       1.00 Hz
GB                  0
PC                       1.00
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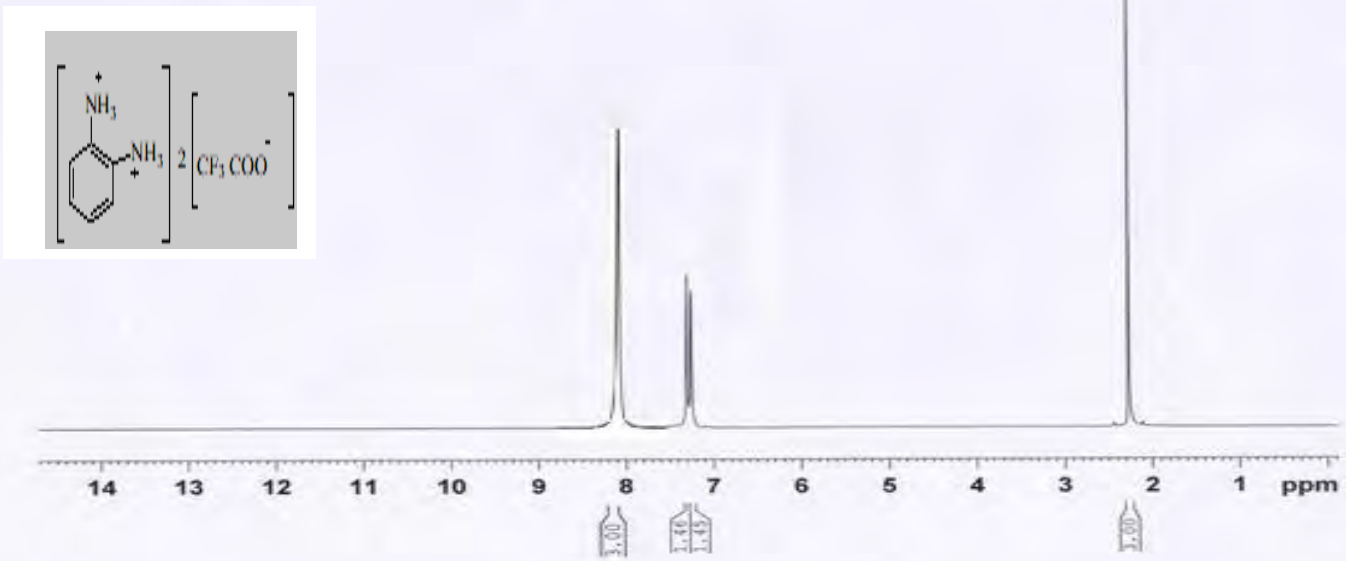
Wazed Miah Science Research Centre (WMSRC)
Jahangirnagar University
Sample: ODPIL_05
Operated by: Md. Emdad Hossain, Scientist

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PROCNO                 1

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PULPROG              zg
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NS                   16
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FIDRES         0.122266 Hz
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RG                 66.24
DW                62.400 usec
DE                 6.50 usec
TE                299.4 K
D1             2.00000000 sec
TD0                    1

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NUC1                   1H
P1                 14.75 usec
PLW1        12.00000000 W

F2 - Processing parameters
SI                131072
SF          400.2300000 MHz
WDW                   EM
SSB          0
LB                 1.00 Hz
GB           0
PC                 1.00
```

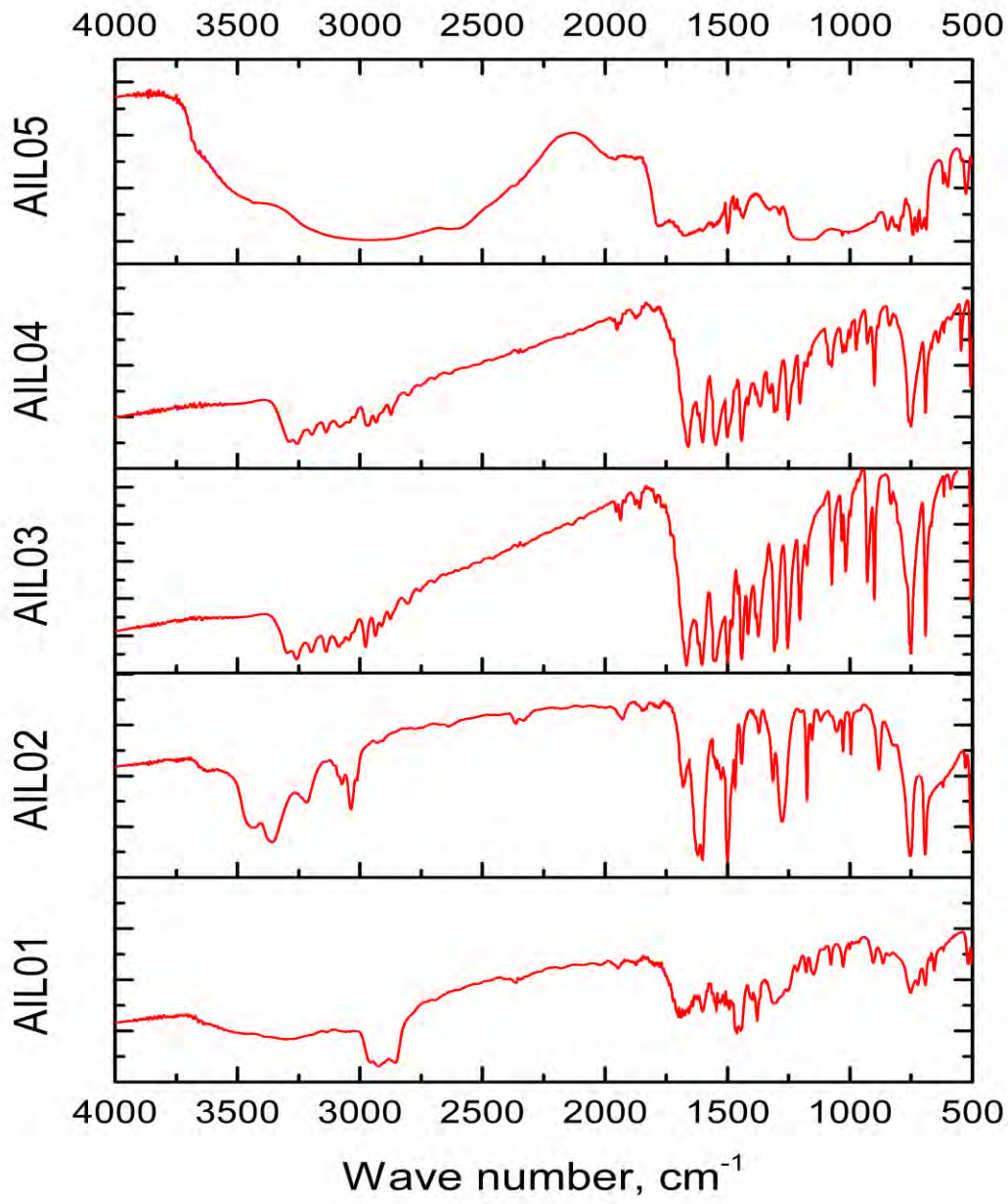
2.8.2 UV spectroscopy data

From the data of UV spectroscopy, it shows that the all spectrum are similar and the 1H NMR and FTIR confirmed the chemical structure of AIL05 that is why all other structure is confirmed their conversion.

Figure 18: UV spectroscopy

2.9 FTIR Spectrum

The aryl ammonium ILs was confirmed by the functional groups located in their structures. The entire absorptions peak was listed in the characterization part. The FTIR spectra of ammonium carboxylate ILs confirmed the presence of ammonium ions at broad 2300 to 3200 cm^{-1} and carboxylate (COO-) ions from the symmetric and asymmetric stretching peak at ~1597 cm^{-1} and ~1338 cm^{-1} respectively, with the former being overlapped by N-H vibrations. The peak at approximately 2940 cm^{-1} and 2910 cm^{-1} correspond to methyl and methylene group for C-H bonds at which 2995 cm^{-1} is for the stretching of Ar-H bond. The Aromatic ring also be assigned the presence of C=C bond stretching of two values at ~1540 to ~1600 cm^{-1} and ~1460 cm^{-1}. Then the C-O bond is also confirmed the peak of 1260-1000 cm^{-1} in the carbonate salts. The presence of Ph-COO group is confirmed the peak at ~1724 cm^{-1}. Alternatively, the presence of Ar-Cl and substituent‘s in benzene ring were confirmed at ~750 cm^{-1} and ~735-770 cm^{-1}. The amines, methyl, ethyl, hydroxyl and aromatic benzene ring structures detected via ^{1}H-NMR were consistent with IR absorption data.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AIL04
AIL03
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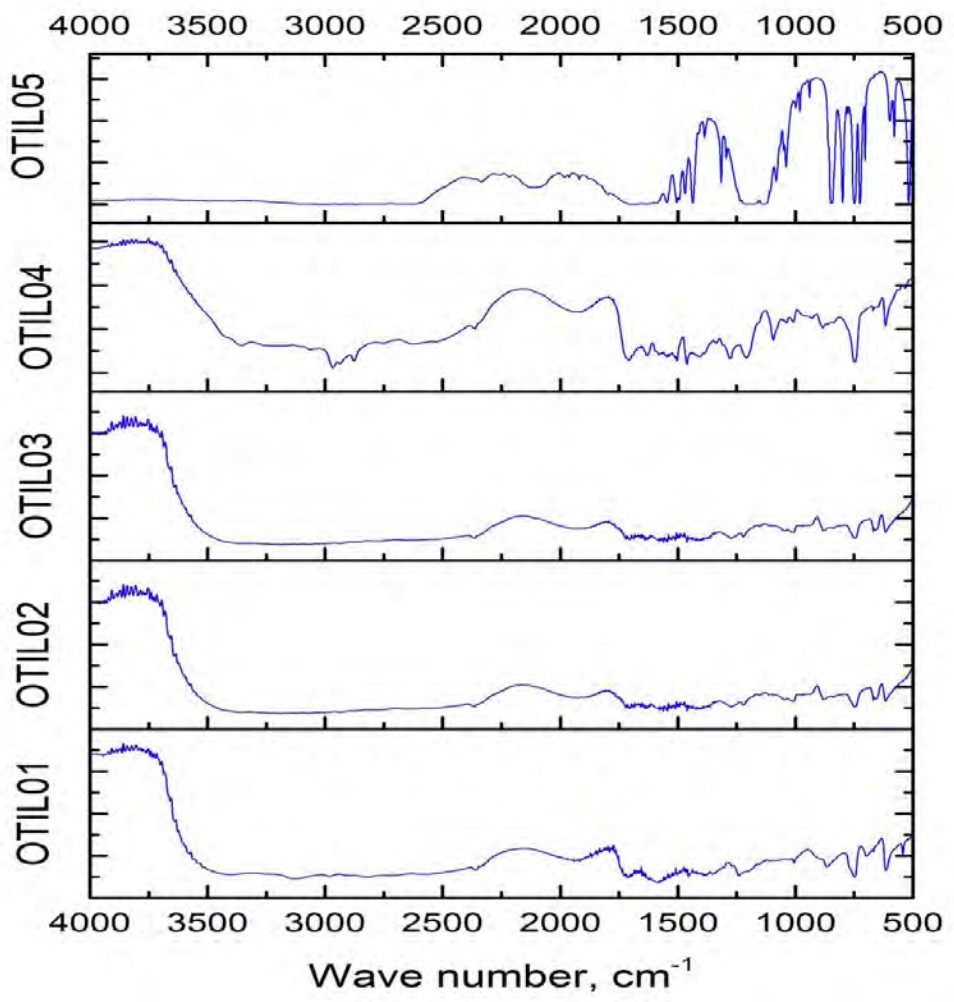


2.10 Conclusion

In conclusion, it could be said that the FTIR, 1H NMR and UV spectroscopy analysis confirmed their conversion from starting materials. In this chapter, the functional group was confirmed by the analysis of FTIR and 1H NMR was used to identify all proton and the UV spectroscopy use for similarity absorption in a similar scheme.

CHAPTER 3

BIOLOGICAL STUDIES

3.1 Introduction

The development of cleaner technologies is a major emphasis in green chemistry. Among the several aspects of green chemistry, the reduction/replacement of ephemeral organic solvents from the reaction medium is of utmost importance [89]. The use of a large excess of conventional fickle solvents required to conduct a chemical reaction creates ecological and economic concerns [90-91]. The search for a non-fickle and recyclable alternative is thus holding a key role in this field of research. The use of fused organic salts, consisting of ions, is now emerging as a possible the remaining options. There were some (eco) toxicological and toxicity studies of ILs with bacteria, phytoplankton, freshwater invertebrates and fishes from newly developed ILs. So it is the demand of time with respect their uses in wide field of chemical industries and academia to insure the toxicological profile that includes the antimicrobial activity study of synthesized ILs [92].

The antimicrobial activity study shows and confirms them about their safe uses in any fields. The antimicrobial activity test is the further measurement to require some views of environmental aspects as standard scale of ILs as a green solvent for uses [93]. To carry out the study, some test are very close for experiment such as Screening of antimicrobial activity, Minimum inhibition concentration (MIC) and Minimum bactericidal/fungicidal concentration (MBC/MFC), Evaluating biofilm susceptibility to antimicrobial agents, etc [94]. These tests were quizzed in this work and show the relative toxicological profile in view of micro-organism of ILs.

3.2 Literature review

In the race to synthesize new pharmaceutical drugs, ILs has attracted a great deal of attention amongst in the scientific community due to their variety of potential pharmaceutical applications [95-96]. ILs represents a big success for industrial and engineering chemistry at the beginning of the 21st century [97]. One of the most appealing features of ILs for pharmaceutical applications is that they are highly customizable materials that can be specially made with pre-selected characteristics

by varying the cations and anions of which they are comprised. Combinations of different cations and anions result in various ILs which provide a wide range of hydrophobicity/hydrophilic, acidity/basicity, viscosities, etc. IL strategies can take advantage of the dual nature (discrete ions) to realize enhancements which may include controlled solubility (e.g., both hydrophilic and hydrophobic ILs are possible, bioavailability or bioactivity, stability, elimination of polymorphism, new delivery options (e.g., slow release or the IL-API as ‗solvent'), or even customized pharmaceutical cocktails. ILs having unique protective metabolic roles can act as antioxidants, protect macromolecules, enhance protein folding and regulate cell volume. ILs have also attracted the scientific community's due to their pharmaceutical properties such as antimicrobial, antiseptic or antifouling actions, acetylcholinesterase (AChE) inhibition, AMP (Adenosine monophosphate) deaminase inhibition, delivery of anti-inflammatory drugs, local anesthetic, anti-nociceptive, anticholinergic, anticancer activities and in protein formulations [98-102]. Enzymes suspended in the ILs could be reused three times, with less than 10% loss of activity per cycle without influencing enantion-selectivity. Based on these interesting properties, ILs appears ready to provide a new research outlook in the field of medicinal chemistry. However the toxicity of some ILs has not been explored much in applications where this property can be desirable and lead to a variety of pharmaceutical applications. Carson *et al.* have reported the broad spectrum antibioflim activity of 1-alkyl-3-methylimidazolium chloride and other imidazolium based ILs against a variety of clinically important microbes. Therefore, ILs with their tunable properties and toxicities could potentially be designed as anti-cancer, anti-viral and other therapeutic agents [103-105]. If a therapeutic response were seen, then the major advantage of ILs would be in tuning their toxicity while tailoring the physio-chemical and pharmacological properties necessary for the desired therapeutic application [106]. Based on these interesting properties, ILs appears ready to provide a new research outlook in the field of medicinal chemistry.

3.3 Causes of studies

The encouraging results of preliminary toxicological studies on ammonium-based ILs provide good opportunities for the development of ILs in biomedical applications. Choline phosphate ILs derivatives have received a great deal of attention due to their pharmacological activity, such as allopurino-ILs, which is still the drug of choice for the treatment of hyperurecemia and gouty arthritis. Pyrazolopyrimidine are purine analogues and as such they have useful properties as antimetabolites in purine biochemical reaction. Moreover, these compounds also display marked antitumor and antileukemic activity. Pyrazolopyrimidine derivatives have demonstrated promising antimicrobial activity against gram-positive bacteria. Synthesis of such biologically important compounds assumes great importance. The use of toxic solvents or expensive is catalysis. In recent years, the interest in room temperature ILs is increasing as green reaction media for synthetic organic chemistry. It is worth to note that Shingare et al. reported the Knoevenagel condensation reactions in ILs ethyl ammonium nitrate of pyrazolone with few aromatic aldehydes gave moderate to high yields. In continuation of our interest in using ILs as a green reaction medium for the synthesis pyrazolopyrimidine derivatives using 3-methyl-1-phenyl-5-pyrazolone with urea and various substituted aldehydes in the presence of 2-methyl-3-butylimidazolium chloride as catalyst [107-109].

An ionic liquid/aqueous two-phase system based on the hydrophilic ionic liquid 1-butyl-3-methylimidazolium chloride and has been employed for direct extraction of proteins from human body fluids for the first time [110]. Proteins present at low levels were quantitatively extracted into the BmimCl-rich upper phase with a distribution ratio of about 10 between the upper and lower phase and an enrichment factor of extraction of proteins from biological fluids by use of an ionic liquid/aqueous two-phase system. Liquid/liquid extraction-bioconversion processes based on functional ILs are emerging as a great potential, simple, and low-cost method in large-scale protein separation and purification. Enzyme-catalyzed hydrolysis of cellulose in ILs is green approach toward the production of biofuels

media by the biodegradation through the microorganism [111-114]. ILs is used as enzymatic catalysis of formation of Z-aspartame, an alternative to enzymatic catalysis in organic solvents. Compatible ionic liquid-celluloses system is for hydrolysis of lignocelluloses biomass.

3.4 Methodology

3.4.1 Introduction

Because of available antimicrobials failure to treat infectious diseases, many researchers have focused on the investigation of ILs as source of new bioactive molecules. A variety of methods are found for this purpose and since not all of them are based on same principles, results obtained will also be profoundly influenced not only by the method selected, but also by the microorganisms used to carry out the test, and by the degree of solubility of each test-compound of ILs. The test systems should ideally be simple, rapid, reproducible, and inexpensive and maximize high sample throughput in order to cope with a varied number of extracts and fractions. The complexity of the bioassay must be defined by laboratory facilities and quality available personnel. The currently available screening methods for the detection of antimicrobial activity of natural products fall into three groups, including bio-autographic, Agar diffusion method, and Disc Diffusion methods [115-116]. The bio-autographic and diffusion methods are known as qualitative techniques since these methods will only give an idea of the presence or absence of substances with antimicrobial activity. On the other hand, dilution methods are considered quantitative assays once they determine the minimal inhibitory concentration. Antimicrobial activities reported in the literature have been evaluated with diverse sets of methodologies, degrees of sensitivity, amount of test compounds and microbial strains, often difficult to compare. For this reason, our purpose is to suggest some recommendations and establish criteria for the use of bio-autographic and diffusion methods.

3.4.2 Different methods for antimicrobial activity evaluation of ILs

A number of methods exist for the accurate determination of microbial susceptibility to antimicrobial/antibiotic compounds. Such methods yield vital data regarding fundamental sensitivity or tolerance to a given antimicrobial biocide or antibiotic and are therefore vital to the successful treatment and management of microbial infections. Furthermore, such tests are useful for determining relative potency of an antimicrobial agent across a range of species and for identifying antimicrobial synergies. The basic testing procedures which have been used in the assessment of the antimicrobial activity of ILs are considered as basic planktonic susceptibility assays (MIC or MBC/MFC) or agar diffusion techniques. Antimicrobial susceptibility testing methods the following three methods have been shown to consistently provide reproducible and repeatable results when followed correctly.

3.4.2.1 Disc diffusion method

Disc diffusion refers to the diffusion of an antimicrobial agent of a specified concentration from discs, tablets or strips, into the solid culture medium that has been seeded with the selected inoculums isolated in a pure culture. Disc diffusion is based on the determination of an inhibition zone proportional to the bacterial susceptibility to the antimicrobial present in the disc. The diffusion of the antimicrobial agent into the seeded culture media results in a gradient of the antimicrobial. When the concentration of the antimicrobial becomes so diluted that it can no longer inhibit the growth of the test bacterium, the zone of inhibition is demarcated. The diameter of this zone of inhibition around the antimicrobial disc is related to MIC for that particular bacterium/antimicrobial combination; the zone of inhibition correlates inversely with the MIC of the test bacterium. Generally, the larger the zone of inhibition, the lower the concentration of antimicrobial required to inhibit the growth of the organisms. However, this depends on the concentration of antibiotic in the disc and its infusibility.

3.4.2.2 Broth and agar dilution method

The aim of the broth and agar dilution methods is to determine the lowest concentration of the assayed antimicrobial that inhibits the visible growth of the bacterium being tested (MIC, usually expressed in µg/mL or mg/L). However, the MIC does not always represent an absolute value. The ‗true' MIC is a point between the lowest test concentration that inhibits the growth of the bacterium and the next lower test concentration. Therefore, MIC determinations performed using a dilution series may be considered to have an inherent variation of one dilution However, antibiotics are usually tested in doubling dilutions, which can produce inexact MIC data. Any laboratory that intends to use a dilution method and set up its own reagents and antibiotic dilutions should have the ability to obtain, prepare and maintain appropriate stock solutions of reagent-grade antimicrobials and to generate working dilutions on a regular basis. It is then essential that such laboratories use quality control organisms to assure accuracy and standardization of their procedures [117].

3.4.2.3 Agar diffusion method

The agar diffusion technique (also known as the Kirby-Bauer test) but described somewhat earlier by Abraham am co-workers in 1941 is a simple and commonly employed technique for determination of MIC on solid media. The basic method requires antibiotic/biocide impregnated discs to be placed on the surface of agar plates seeded or spread with the appropriate test strain of bacteria or fungi. Antimicrobial agent(s) may also be added to wells punched in the agar. The diffusion of antimicrobial agent into the surrounding agar results in inhibition of growth around the reservoir/source and gives rise to zones or clearance where (for sensitive organisms) microbial growth is inhibited. Generally, the diameter of these zones of inhibition or clearance increases with increasing concentration of antimicrobial agent, and this may be measured to determine qualitatively the relative degree of toxicity.

The technique is also useful for empirical determination of antimicrobial activity of a given compound or assessing relative antimicrobial potency by measuring zones of inhibition of bacterial or fungal growth around the antimicrobial site of application.

Few years ago, this method has been championed by Stephens and co-workers as a simple method for rapid determination of relative toxicity of ILs. This simple, inexpensive method has been suggested as a basic requirement in the toxicological assessment of ILs and, since it requires neither specialist equipment nor advanced microbiological techniques, may be performed routinely in laboratories conducting research into ILs with minimum microbiological expertise. Despite this, the use of agar diffusion assays will provide basic toxicity information for a large number of ILs and provides a rapid, high-throughput ‗first look' in the hierarchical screening of antimicrobial activity of ILs.

3.4.2.4 Dilution method

Dilution tests are routinely used for the determination of the two most fundamental parameters in antimicrobial susceptibility testing; the minimum biofilm eradication concentration (MIC) and the minimum bactericidal/fungicidal concentration (MBC/MFC), sometimes referred to as the minimum lethal concentration (MLC). Dilution tests usually involve the use of liquid media but agar may also be used (as discussed above). Following incubation at 35.0±2.5ºC overnight (18 hours), the MIC is determined as the concentration of antimicrobial contained in the first clear tube/well. Therefore the MIC is defined as the minimum concentration of antimicrobial agent that inhibits the growth of an overnight culture of microorganism.

3.4.3 Antibacterial Working Procedure

3.4.3.1 *Chemicals and Equipments*

ILs are used as test chemical for antibacterial work and different concentrations were prepared using serial dilution technique taking one initial concentration as higher (1000 mM). Chemicals were dissolved in water or other suitable solvents, and they act as positive control. Nutrient agar was prepared according to the instruction leveled in the container and kept in freezer for longer use. Dilute alcohol or acetone was used to ensure for septic environment during the culture preparation and

bacterial inoculation. Laminar Air flow was confirmed all the time during the culture preparation and all the tests conducted. Incubator for bacterial growth was maintained at temperature 37±1ºC.

3.4.3.2 *Preparation of Bacterial Inoculums*

The Gram Positive and Gram Negative bacteria were pre-cultured in Nutrient Broth (NB) on overnight in incubator at 37ºC. After incubation centrifuged at 10,000 rpm for 5 min, pellet was suspended in distilled water (DW). The Petri dishes were flooded, 50 ml of sterile distilled water, using sterile cotton buds, micro tips and forceps.

3.4.3.3 *Preparation of IL solutions in different concentrations*

The required amount of the sample was measured in Digital balance with highly carefully so that no impurities were obtained. Then the required 1.5 ml distilled water was added and well shake for well soluble. Some of samples were not soluble in water. These are soluble in Methanol so that methanol was required solvent for these samples.

3.4.3.4 *Antibacterial Screening via Well diffusion test*

A preliminary investigation on the antibacterial activities of pure ILs was performed through measurements of primary screening both the gram-positive and gram-negative bacteria. Antibacterial screening of the test ILs were carried out with eight bacterial pathogens, such as *Bacillus cereus*, *Staphylococcus aureus*, *Sarcina lutea*, *Bacillus subtilis, and four are gram negative such as Escherichia coli*, *Salmonella typhi*, *Pseudomonas aeroginosa* and *Shigella dysenteria*. This method was carried on via well diffusion method taking 20 µL ILs solution in each well [118-119]. The bacterial inhibition zone (including the well diameter 8.0 mm) was measured in mm scale with consideration ±1.0 with all taking value. All the measurements were done in triplicate and the averages were listed in table 01. The initial concentration was maintained for all ILs in 1000 mM/L distilled water. A control plate is always

observed for the ILs if there is any significant inhibition occurred for the solvent. The results showed that all compounds had antimicrobial activity against bacterial pathogens used in this study.

3.4.3.5 *Determination of MIC*

Determination of minimal inhibitory concentration (MIC) was conducted according to the standard procedure developed by the Clinical and Laboratory Standards Institute (CLSI), Pennsylvania, USA [116]. The microbial strains were cultured on a Nutrient Agar media for 24 h. The nutrient agar media was spread through the Petri-pates. The plates remained for 40 to 50 minute for solidification. After solidification, the bacteria suspension was spread by hockey strike through all plates. Then six holes were made serially and put all the serial different concentration of ILs solution was kept as 20 µL per hole. Three replicates and seven different concentrations were studied for each IL. Microbial growth was visually determined after incubation for 24 h at 37°C. The zone of Inhibition was recorded in mm.

MIC for the tested ILs were calculated from the inhibitions showed in the different concentrations via serial dilution such as, 1000 mM/L, 750 mM/L, 500 mM/L, 250 mM/L, and 125mM/L using the well diffusion technique. The all data was plotted in excel file and calculated the MIC point at where the zone of inhibition was zero. From the data of MIC, it was found that the MIC for each ILs against all bacteria from 500 mMol/L to 125 mMol/L.

3.4.4 Antifungal Screening Test

In similar ways the antifungal activity against three phytopathogenic fungi such as *Aspergillus niger, Saccharomyces cerevisiae and Candida albicans* was evaluated through the well diffusion method. At first 100 µL OTILs solution was added into petri plate then the media was added. After solidification, the fungal strain was added in well and kept in incubator for 72 hours. Then the result was recorded in mm scale. The work was done triplet and taken the mean value. All synthesized compounds were dissolved in water or methanol basis on their solubility for making the

concentration 1000 mM. The 100 µL solution of ILs were taken in petri-plate. The Media of PDB was dispersed and solidified. A well of 5 mm were made in the middle of petri-plate using cork-borer and the fungal lead were place there. The plates were then kept in incubator for 96 h at 37°C. After 3 days, the fungal growth in presence of ILs, were measured and analyzed.

The antifungal test was completed and calculated the growth percentage compared with the control where the growth of control is 100% percent. The growth percentage is deduced as the following equation:

$$\%\ \text{Growth percentage} = \frac{\text{Growth of fungi with ILs solution}}{\text{Growth of fungi without ILs solution as control}} \times 100$$

The percentage of inhibition is calculated by following equation

$$\text{Percentage of Inhabitation} = (\text{Growth percentage of control}) - (\text{Growth percentage of ILs sample})$$

2.3.4 Assay of MIC

The MIC test was evaluated via well diffusion method for different concentration against all bacteria for 1000 mM/L, 800 mM/L, 600 mM/L, 400 mM/L, 200 mM/L, and 100 mM/L as similar the assay of anti bacterial and recorded the data and analysis these data via prism and origin graph to calculate the MIC by graphical method.

3.5 Phytotoxicty

One species of sola seed on the Petri dish was paddled with tissue papers. The prepared solutions were shaken properly after preparation and 5 mL were applied directly to the petri dishes containing the seeds and the control experiment was watered with distilled water only. Distilled water (about 10 mL per dish/day) was added to keep the filter paper wet during seeds culture (if the tissue paper became dry). The ionic liquid solutions at concentrations of 1000 mmol/L, 500mmol/L, 250

mmol/L, 0 mmol/L respectively were prepared for doing this test. Each treatment was repeated three times. The test is also done by same way and the result was being recorded. All tested phytotoxicity was be synthesized in the chemistry laboratory at the European University of Bangladesh, Dhaka-1216, Bangladesh. In the present work, the influence ILs introduced to the petri dish on germination and early stages of growth and development of superior plants was investigated using the plant growth test based on the OECD/OECD 208/2006, the growth inhibition assay according to ISO Guideline 11269-2 (2003).The measured endpoint is germination percentage inhibition.

3.6 Result and Discussion

3.6.1 Scheme No 01

3.6.1.1 *Data for antibacterial screening for 1000 mMol/ L solution*

Table 1: Zone of inhibition against bacteria in mm scale without 8 mm hole of well for 1000 mMol/L

	AIL-1	AIL-2	AIL-3	AIL-4	AIL-5	Control	Starting
Bacillus cereus(+)	18	25	28	14	20	0	0
Staphylococcus aureus(+)	18	17	30	14	25	0	0
Bacillus subtilis(+)	16	19	28	15	23	0	0
Sarcina lutea(+)	17	08	30	20	24	0	0
Escherichia coli(-)	16	14	27	18	16	0	0
Salmonella typhi(-)	19	16	15	27	27	0	0
Pseudomona aeroginosa(-)	13	14	27	13	18	0	0
Shigella dysenteriae(-)	16	14	25	17	20	0	0

3.6.1.2 The relative study anion on antibacterial activity

In the antimicrobial activity, the effect of anion was estimated using the formate, acetate, propanoate, butanoate, and trifluroacetate. For the each bacteria pathogen, anion has to be shown reactivity on antibacterial toxicity. The propanoate anion can show the higher activity than formate, acetate. The butanoate anion can also show the antibacterial activity more than formate, acetate but less than propanoate. It was evaluated that anion has slightly antibacterial activity even the antibacterial activity is affected the positive charge of cation and it is presented by fig-29 that proposed a relation for antibacterial activity. It was summarized that increasing the length of anion, the antibacterial activity was increased.

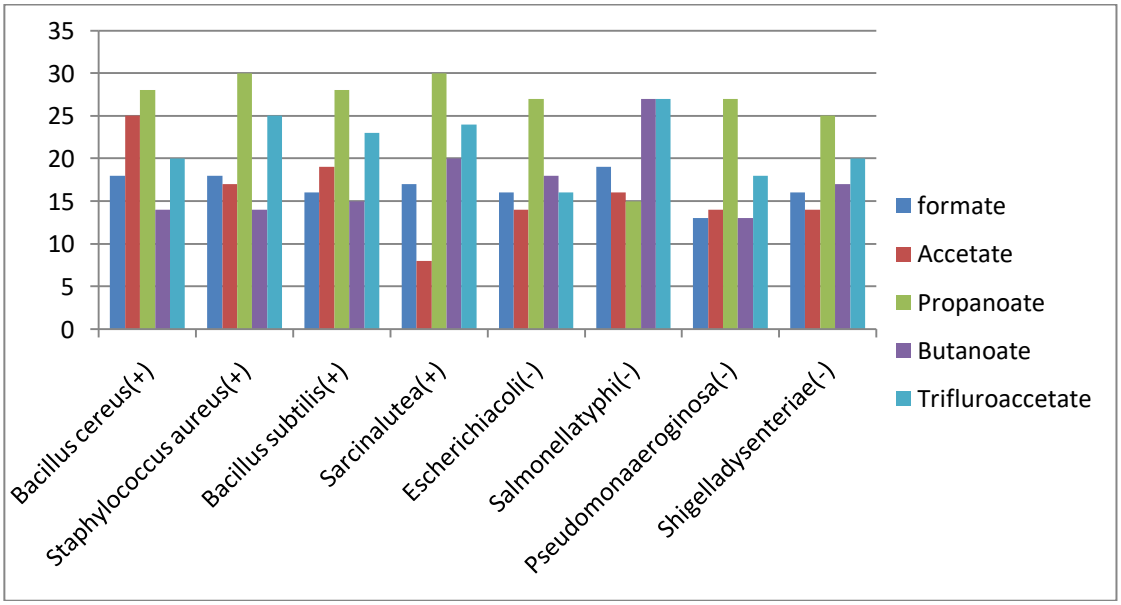


Figure 19: The relative effect of anion on antibacterial activity

3.6.1.3 Calculation of MIC

Table 2: Scheme-01, *Bacillus cereus(+)*						
	1000 mMol/L	750 mMol/L	500 mMol/L	250 mMol/L	125 mMol/L	MIC
AIL01	18	11	6	0	0	250
AIL02	25	16	9	3	0	125
AIL03	28	21	13	6	0	125

AIL04	14	7	0	0	0	500
AIL05	20	12	7	0	0	250
Escherichia coli(-)						
AIL01	16	10	5	0	0	250
AIL02	14	7	0	0	0	500
AIL03	27	21	13	4	0	125
AIL04	18	11	6	0	0	250
AIL05	16	9	3	0	0	250

3.6.1.4 The result and data of antifungal activity

Table 3: **Zone of inhibition of antifungal activity**						
Chemicals tested	Zone of growth (in mm)			%, growth percentage		
	Aspergillus niger	*Saccharomyces cerevisiae*	*Candida albicans*	*Aspergillus niger*	*Saccharomyces cerevisiae*	*Candida albicans*
Control	28 mm	41mm	38 mm	100 %	100%	100 %
Staring material	28 mm	41mm	38 mm	100 %	100 %	100 %
AIL01	15	19	17	53.00 %	46.34%	44.70%
AIL02	14	17	16	50.00 %	41.46%	42.10%
AIL03	13	17	15	46.43 %	41.46%	36.58%
AIL04	11	16	13	39.28%	39.02%	34.21%
AIL05	12	15	13	42.85%	36.58%	34.21%

3.6.1.5 Calculation of Percentage of Inhibition

Table 4: Data for percentage of inhibition			
Chemicals tested	***Percentage of Inhibition***		
	Aspergillus niger	*Saccharomyces cerevisiae*	*Candida albicans*
Control	0%	0%	0 %
Staring material	0%	0%	0%
AIL01	47.00%	53.66%	55.30%
AIL02	50.00%	58.54%	63.43%
AIL03	53.58%	58.54%	55.30%
AIL04	60.72%	60.98%	65.79%
AIL05	57.15%	63.42 %	65.79%

3.6.1.6 The comparative effect anion on antifungal activity in different ILs

From the table 05, the percentage of inhibition was shown that the IL05 was the highest percentage in almost three fungi. The main fact of this reason is that the halogen atom in anion molecule. To test the anion effect on antifungal activity of ILs, the formate, acetate, propanoate, butanoate, and trifluroacetate anion were used in ILs. The butanoate anion can also show the antifungal activity more than formate, acetate but less than propanoate. It was evaluated that anion has slightly antifungal activity even the antibacterial activity is affected the positive charge of cation and that proposed a relation for antifungal activity. It was summarized that increasing the length of anion, the antifungal activity was increased.

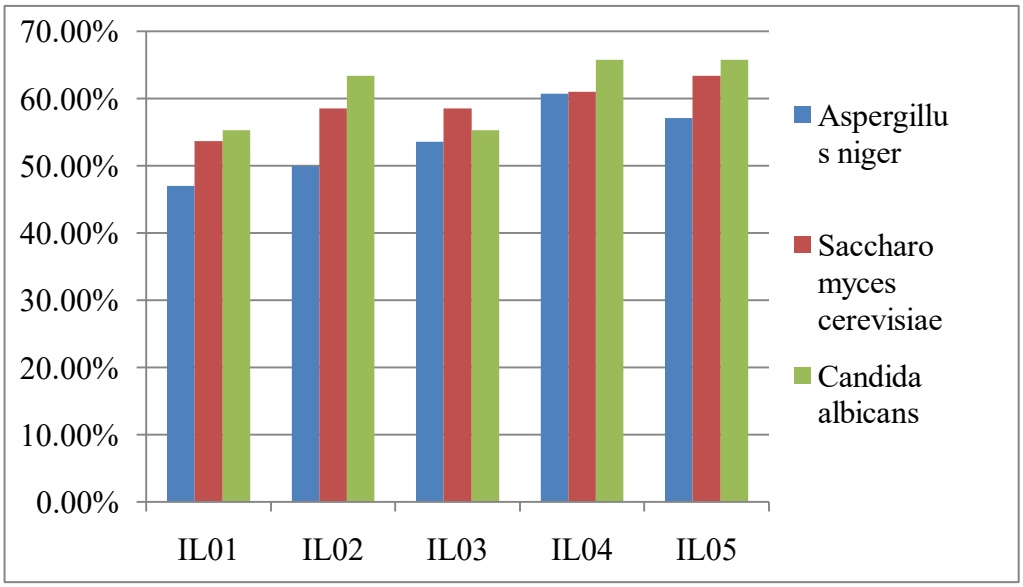


Figure 20: The comparative effect anion on antifungal activity

3.6.1.7 Data of Phytotoxicity

1000 Mmol/L	500 Mmol/L	250 Mmol/L	0.0 Mmol/L

Day-01

Day 04

Figure 21: Picture for anilinium carboxylate, AIL-05

3.6.1.7.1 Change of roots length in different days with different concentration

Table 5: Anilinium carboxylate ILs								
Sample no 01, AIL-01								
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day - 07	
1000	0	0	0	0	0	0	0	
500	0	0	0	0	0	0	0	
250	3	6	12	16	18	20	21	
0	13	22	31	35	37	38	39	

AIL0-2								
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day - 07	
1000	0	0	0	0	0	3	5	
500	0	0	0	0	2	5	7	
250	0	8	13	15	17	22	23	
0	13	24	32	34	36	37	41	
AIL03								
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day - 07	
1000	0	0	0	0	0	0	0	
500	0	0	0	0	4	6	7	
250	4	7	11	17	19	22	24	
0	13	22	31	35	37	38	39	
AIL04								
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day - 07	
1000	0	0	0	0	0	0	0	
500	0	0	0	3	6	7	9	
250	4	7	9	12	15	24	31	
0	13	22	31	35	37	38	39	
AIL05								
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day - 07	
1000	0	0	0	0	0	0	0	
500	0	0	4	6	8	12	14	
250	6	9	13	17	21	25	31	
0	13	22	31	35	37	38	39	

3.6.1.7.2 No of Germination of seeds in different day

Day -01	No of sample	AIL01	AIL02	AIL03	AIL04	AIL05
	Concentration					
	1000	0	3	2	4	1
	500	0	3	6	3	5
	250	1	4	0	2	3
	0	2	3	1	2	2
Day -02	1000	0	4	6	5	6
	500	0	8	7	5	7
	250	1	3	7	5	5
Day -03	1000	0	4	7	8	6
	500	0	4	8	5	6
	250	1	3	8	7	8
	0	5	5	5	7	8
Day -04						
	1000	0	8	7	8	6
	500	0	8	8	6	6
	250	2	4	8	7	8
	0	7	6	5	7	8
Day -05						
	1000	0	8	6	8	6
	500	0	7	8	6	7
	250	0	5	8	7	8
	0	6	6	5	7	8
Day -06						
	1000	0	8	6	8	
	500	0	7	8	6	7
	250	0	7	8	7	8
	0	5	6	5	7	8
Day -07						
	1000	0	8	6	8	6
	500	0	7	8	6	7
	250	0	7	8	8	8
	0	5	6	5	7	8

3.6.2 Scheme No 02

3.6.2.1 Data of antimicrobial activity *o*-toluidinium based ILs

Table 6: Data of Zone of Inhibition for antibacterial activity in mm scale without 8 mm hole of well for 1000mMol/L for *ortho* toluidinium based ILs							
	OTIL-1	OTIL-2	OTIL-3	OTIL-4	OTIL-5	Control	Starting
Bacillus cereus(+)	7	8	14	20	22	0	0
Staphylococcus aureus	12	9	13	18	20	0	0
Bacillus subtilis(+)	12	9	11	19	22	0	0
Sarcina lutea(+)	10	11	12	18	22	0	0
Escherichia coli(-)	13	13	14	18	20	0	0
Salmonella typhi(-)	15	11	13	18	21	0	0
Pseudomona aeroginosa(-)	13	12	14	16	22	0	0
Shigella dysenteriae(-)	12	11	14	18	22	0	0

3.6.2.2 Comparative study against all bacteria

From this table 6 and figure 22, it was shown that the zone of inhabitation of IL-05 is maximum both of gram positive and gram negative bacteria. Then IL-04 was also the 2nd inhabitation zone. It was shown that the alkyl chain has an effect on antibacterial activity even the substituent group in attached with anion.

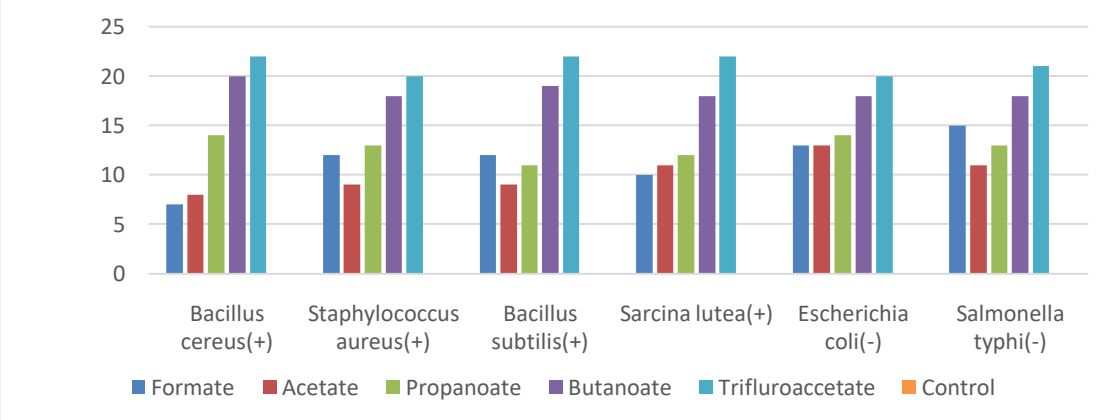


Figure 22: Comparative study for anion on antibacterial activity

3.6.2.3 Profile of MIC for specific concentration

Table 7: Specific value of MIC						
Bacillus cereus(+)						
	1000 mMol/L	750 mMol/L	500 mMol/L	250 mMol/L	125mMol/L	MICmMol/L
OTIL01	7	3	0	0	0	500
OTIL02	8	3	0	0	0	500
OTIL03	14	9	6	0	0	250
OTIL04	20	11	8	3	0	125
OTIL05	22	14	9	5	0	125
Escherichia coli(-)						
OTIL01	13	8	4	0	0	250
OTIL02	13	6	0	0	0	500
OTIL03	14	8	3	0	0	250
OTIL04	18	12	7	3	0	125
OTIL05	20	12	8	3	0	125

3.6.2.4 Result of antifungal activity

Table 8: Data of %, growth percentage against fungal						
Chemicals tested	Zone of growth (in mm)			%, growth percentage		
	Aspergillus niger	*Saccharomyces cerevisiae*	*Candida albicans*	*Aspergillus niger*	*Saccharomyces cerevisiae*	*Candida albicans*
Control	24 mm	37mm	38 mm	100 %	100%	100 %
S. material	22 mm	35mm	35mm	91.67%	94.60 %	92.10 %
OTIL01	16	23	21	66.67 %	62.26%	55.26%
OTIL02	15	21	19	62.50 %	56.75%	50.00%
OTIL03	14	19	18	58.33%	51.35%	47.36%
OTIL04	13	18	17	54.16%	48.65%	44.75%
OTIL05	12	15	17	50.00%	40.54%	44.75%

3.6.2.5 The Percentage of Inhabitation is calculated by following equation

Chemicals tested	Table 9: Percentage of inhibition		
	Aspergillus	*Saccharomyces*	*Candida albicans*

	niger	*cerevisiae*	
Control	0%	0%	0 %
Staring material	8.33%	5.40%	7.90%
OTIL01	33.33%	37.25%	44.74%
OTIL02	37.50%	53.25%	50.00%
OTIL03	41.67%	48.65%	52.25%
OTIL04	45.84%	51.35%	55.25%
OTIL05	50.00%	59.46 %	55.25%

3.6.2.6 Comparative study of the effect of anion on antifungal activity in different ILs

From the table 08, the percentage of inhibition was shown that the IL05 was the highest percentage in almost three fungi. The main fact of this reason is that the halogen atom in anion molecule. To test the anion effect on antifungal activity of ILs, the formate, acetate, propanoate, butanoate, and trifluroacetate anion were used in ILs. The butanoate anion can also show the antifungal activity more than formate, acetate but less than propanoate. It was evaluated that anion has slightly antifungal activity even the antibacterial activity is affected the positive charge of cation and that proposed a relation for antifungal activity. It was summarized that increasing the length of anion, the antifungal activity was increased.

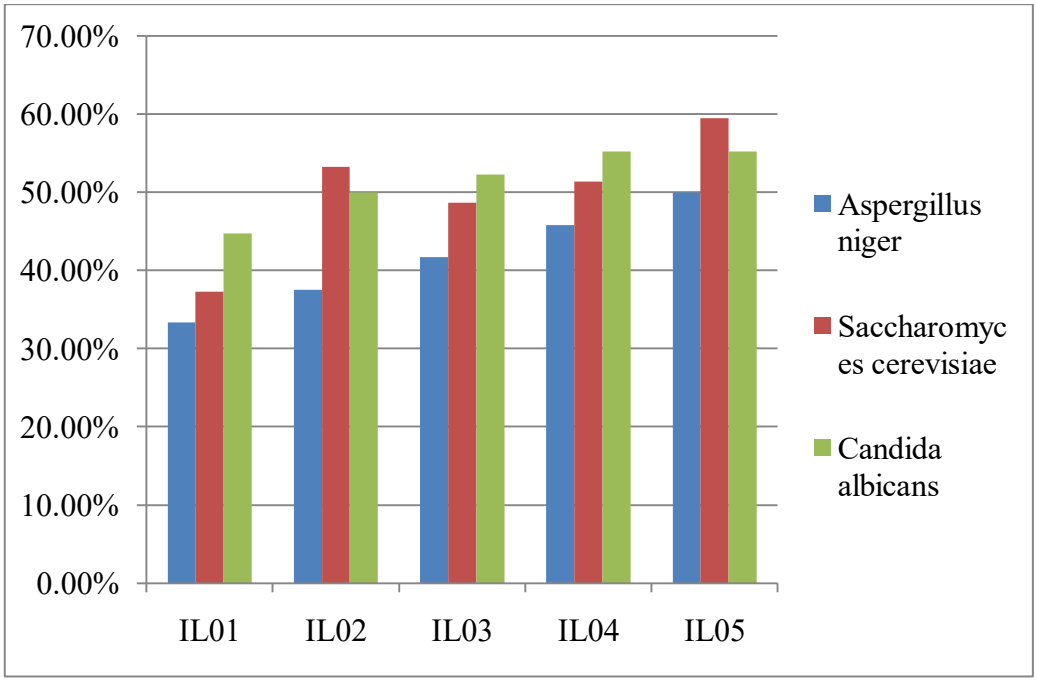


Figure 23: The effect of anion on antifungal activity in different ILs

3.6.2.7 Data of Phytotoxicty

Table 10: Scheme 02. Ortho toluidinium carboxylate Ils							
OTIL-01							
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day -07
1000	0	0	0	0	0	0	0
500	0	0	0	0	0	0	0
250	2	4	10	14	16	19	21
0	13	22	31	35	37	38	39
OTIL0-2							
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day -07
1000	0	0	0	0	0	0	0
500	0	0	0	0	5	8	10
250	5	7	8	12	16	21	24
0	13	22	31	35	37	38	39
OTIL03							
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day -07
1000	0	0	0	0	0	0	0
500	0	0	0	0	0	3	5
250	4	5	7	10	15	18	19

0	13	22	31	35	37	38	39
OTIL04							
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day -07
1000	0	0	0	0	0	0	0
500	0	0	0	2	5	7	10
250	5	9	10	12	15	17	20
0	13	22	31	35	37	38	39
OTIL05							
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day -07
1000	0	0	0	0	0	0	0
500	0	0	0	0	3	5	8
250	2	4	7	11	13	15	18
0	13	22	31	35	37	38	39

3.6.3 Scheme No 03

3.6.3.1 Data of antimicrobial activity *meta* toluidinium based ILs

Table 11: Zone of inhabitation against bacteria in mm scale without 8 mm hole of well for 1000mMol/L

	MTIL-1	MTIL-2	MTIL-3	MTIL-4	MTIL-5	Control	Starting
Bacillus cereus(+)	7	8	13	19	22	0	0
Staphylococcus aureus(+)	11	10	13	17	21	0	0
Bacillus subtilis(+)	11	10	13	16	22	0	0
Sarcina lutea(+)	10	12	14	18	21	0	0
Escherichia coli(-)	10	13	15	18	20	0	0
Salmonella typhi(-)	13	11	13	18	22	0	0
Pseudomona aeroginosa(-)	10	12	14	17	23	0	0
Shigella dysenteriae(-)	10	12	14	19	22	0	0

3.6.3.2 Comparative study against all bacteria

Using the table-11 and Fig no 24, it was shown that the zone of inhabitation of IL-05 is maximum both of gram positive and gram negative bacteria. Then IL-04 was also the 2nd inhabitation zone. It was shown that the alkyl chain has an effect on antibacterial activity even the substituent group in attached with anion.

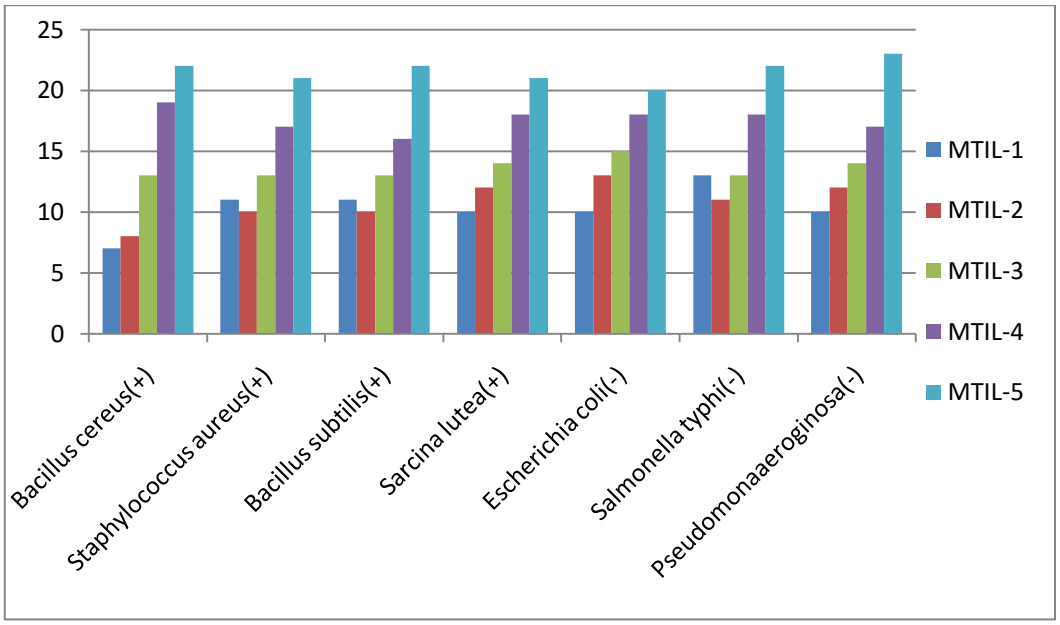


Figure 24: Comparative study of *meta* toluidinium carboxylate ILs

3.6.3.3 Data and determination of MIC

MIC for the tested ILs were calculated from the inhibitions showed in the different concentrations via serial dilution such as, 1000, 800, 600, 400, 200, 100, and 50 mMol/L using the well diffusion technique. The all data was plotted in excel file and calculated the MIC point at where the zone of inhabitation was zero. From table no 12, it was found that the MIC for each ILs against all bacteria from 200 mMol/L to 50 mMol/L.

Table 12: Scheme-03, *Bacillus cereus(+)*						
	1000 mMol/L	750 mMol/L	500 mMol/L	250 mMol/L	125 mMol/L	MIC
MTIL01	7	5	3	0	250	250
MTIL02	8	6	3	0	0	250
MTIL03	13	8	5	0	0	250
MTIL04	19	13	7	4	0	125
MTIL05	22	14	11	6	4	Below 125
Escherichia coli(-)						
MTIL01	13	10	4	0	0	250
MTIL02	13	8	5	0	0	250
MTIL03	14	9	6	2	0	125
MTIL04	18	15	11	6	0	125
MTIL05	20	16	10	5	0	125

3.6.3.4 Result of antifungal activity

Table 13: Data of %, growth percentage against fungal						
Chemicals tested	Zone of growth (in mm)			%, growth percentage		
	Aspergillus niger	*Saccharomyces cerevisiae*	*Candida albicans*	*Aspergillus niger*	*Saccharomyces cerevisiae*	*Candida albicans*
Control	24 mm	37mm	38 mm	100 %	100%	100 %
S. material	22 mm	35mm	35mm	91.67%	94.60 %	92.10 %
MTIL01	17	25	28	70.83 %	67.56%	73.68%
MTIL02	16	22	24	66.66 %	59.45%	63.15%
MTIL03	13	20	22	54.16%	54.05%	57.89%
MTIL04	12	17	19	50.00%	49.94%	50.00%
MTIL05	11	16	19	45.83%	43.24%	50.00%

3.6.3.5 The Percentage of Inhibition

Chemicals tested	Table 14: Percentage of inhibition		
	Aspergillus	*Saccharomyces*	*Candida albicans*

	niger	*cerevisiae*	
Control	0%	0%	0 %
Staring material	8.33%	5.40%	7.90%
MTIL01	29.17%	32.44%	22.32%
MTIL02	33.33%	40.55%	24.85%
MTIL03	45.86%	45.95%	46.11%
MTIL04	50.00%	51.06%	50.00%
MTIL05	54.17%	56.76 %	50.00%

3.6.3.6 Comparative study of the effect of anion on antifungal activity in different ILs

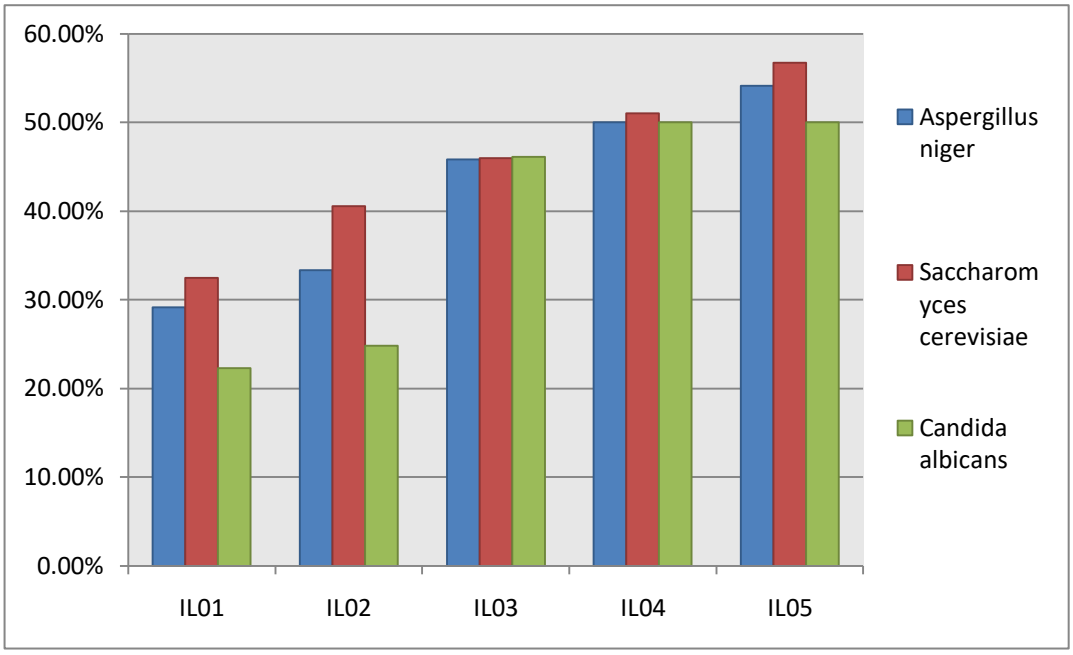


Figure 25: The effect of anion on antifungal activity in different ILs

3.6.3.7 Data of Phytotoxicity

Table 15: Scheme-03, *meta* toluidinium carboxylate ILs

MTIL-01							
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day -07

1000	0	0	3	10	13	20	26
500	0	0	8	10	16	24	30
250	3	6	12	16	18	28	31
0	13	22	31	35	37	38	39
MTIL0-2							
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day -07
1000	3	5	6	16	18	25	41
500	13	16	19	22	23	30	50
250	13	25	22	29	33	38	56
0	15	28	33	41	45	51	63
MTIL03							
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day -07
1000	5	6	7	15	21	24	33
500	8	10	12	22	26	31	45
250	9	10	23	35	37	39	52
0	8	10	36	41	45	46	62
MTIL04							
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day -07
1000	4	6	12	22	26	29	38
500	6	8	18	29	28	33	50
250	8	9	22	40	36	42	54
0	8	10	36	41	45	46	62
MTIL05							
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day -07
1000	3	4	10	21	25	30	41
500	5	6	17	28	35	35	50
250	6	8	25	40	38	40	56
0	7	9	35	41	45	45	65

3.6.4 *para* toluidinium Scheme No 04

3.6.4.1 *Data of antimicrobial activity para toluidinium based ILs*

Table 16:: Zone of inhibition against bacteria in mm scale without 8 mm hole of well for 1000mMol/L							
	PTIL-1	PTIL-2	PTIL-3	PTIL-4	PTIL-5	Control	Starting
Bacillus cereus(+)	8	9	10	11	18	0	0
Staphylococcus aureus(+)	7	9	11	13	19	0	0
Bacillus subtilis(+)	6	8	11	12	15	0	0
Sarcina lutea(+)	7	7	9	12	15	0	0
Escherichia coli(-)	6	8	9	11	16	0	0
Salmonella typhi(-)	8	9	11	13	17	0	0
Pseudomona aeroginosa(-)	6	8	9	11	14	0	0
Shigella dysenteriae(-)	5	6	8	9	11	0	0

3.6.4.2 Comparative study against all bacteria

Using the fig 26, it was shown that the zone of inhabitation of PTIL-05 is maximum both of gram positive and gram negative bacteria. Then IL-04, IL03 were also the 2nd and 3rd inhabitation zone. It was shown that the alkyl chain has an effect on antibacterial activity even the substituent group in attached with anion.

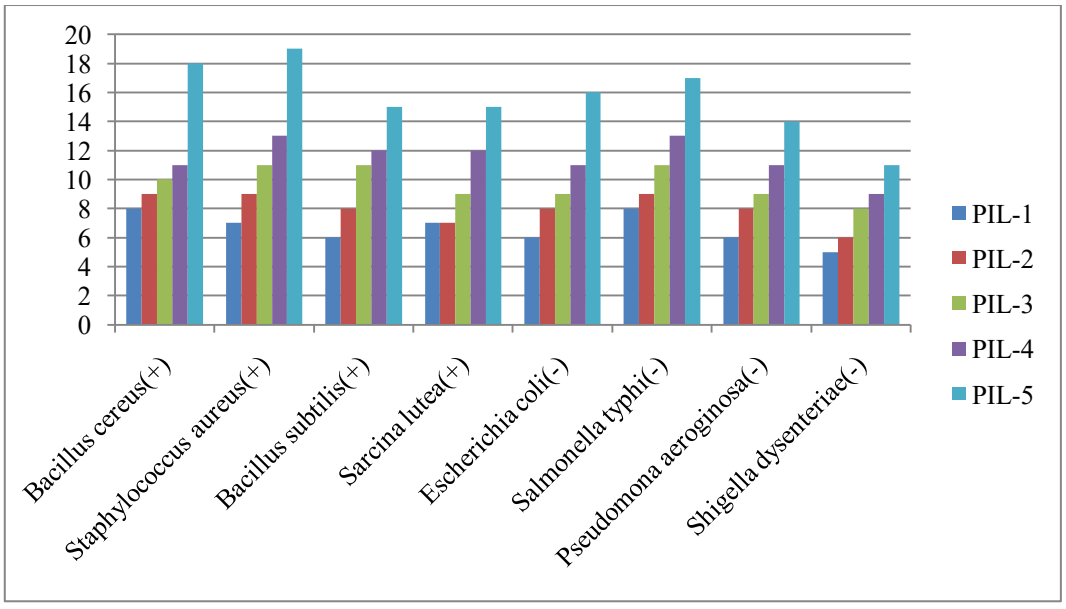


Figure 26: Comparative study against all bacteria

3.6.4.3 Data and determination of MIC

Table 17: Scheme-04, *Bacillus cereus(+)*						
	1000 mMol/L	750 mMol/L	500 mMol/L	250 mMol/L	125 mMol/L	MIC
PIL01	8	5	3	0	0	250
PIL02	9	6	3	0	0	250
PIL03	10	7	4	0	0	250
PIL04	11	7	5	0	0	250
PIL05	18	11	8	6	3	Below125
Escherichia coli(-)						
PIL01	6	4	0	0	0	500
PIL02	8	5	0	0	0	500
PIL03	9	6	4	0	0	250
PIL04	11	8	5	0	0	250
PIL05	16	11	7	4	0	125

3.6.4.4 Result of antifungal activity

Table 18: Data of %, growth percentage against fungal						
Chemicals tested	Zone of growth (in mm)			%, growth percentage		
	Aspergillus niger	*Saccharomyces cerevisiae*	*Candida albicans*	*Aspergillus niger*	*Saccharomyces cerevisiae*	*Candida albicans*
Control	25 mm	38 mm	38 mm	100 %	100%	100 %
S. material	23 mm	36 mm	37 mm	92.00%	94.36 %	97.36 %
PIL01	21	28	28	84.00%	73.34%	73.68%
PIL02	19	26	25	76.00%	68.42%	65.75%
PIL03	16	23	21	64.00%	60.52%	55.26%
PIL04	13	19	18	52.00%	50.00%	47.36%
PIL05	10	16	16	40.00%	42.10%	42.10%

3.6.4.5 The Percentage of Inhibition

Chemicals tested	**Table 19: Percentage of inhibition**

	Aspergillus niger	*Saccharomyces cerevisiae*	*Candida albicans*
Control	0.00%	0.00%	0.00 %
Staring material	8.00%	5.66%	2.64%
PIL01	16.00%	26.66%	24.32%
PIL02	24.00%	31.58%	34.25%
PIL03	36.00%	39.48%	44.74%
PIL04	48.00%	50.00%	52.64%
PIL05	60.00%	57.90%	57.90%

3.6.4.6 Comparative study of the effect of anion on antifungal activity in different ILs

From the table 19 and Figure 27, the percentage of inhibition was shown that the IL05 was the highest percentage in almost three fungi. The main fact of this reason is that the halogen atom in anion molecule. To test the anion effect on antifungal activity of ILs, the formate, acetate, propanoate, butanoate, and trifluroacetate anion were used in ILs. The butanoate anion can also show the antifungal activity more than formate, acetate but less than propanoate. It was evaluated that anion has slightly antifungal activity even the antibacterial activity is affected the positive charge of cation and that proposed a relation for antifungal activity. It was summarized that increasing the length of anion, the antifungal activity was increased.

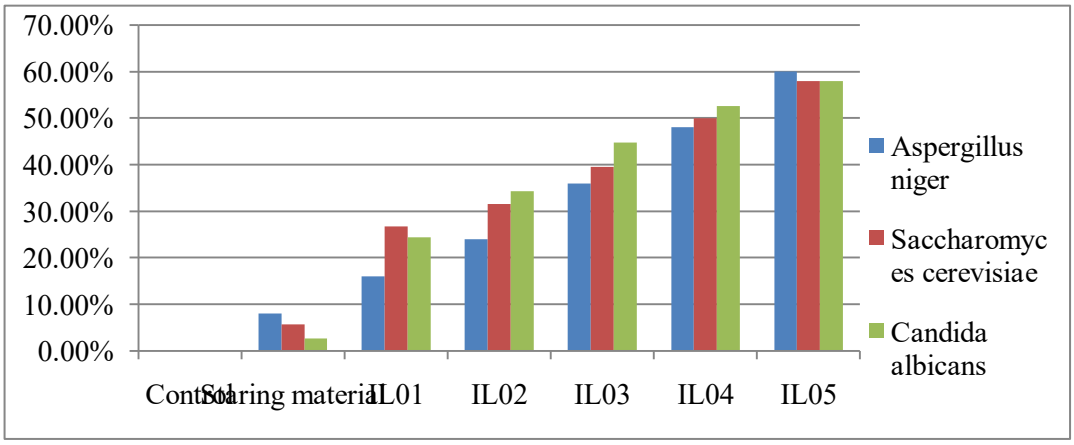


Figure 27: The effect of anion on antifungal activity in different ILs

3.6.4.7 Data of Phytotoxicty

Table 20: Scheme-04, *para* toluidinium carboxylate ILs							
PTIL-01							
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day -07
1000	0	0	4	9	12	21	25
500	0	0	7	11	15	23	29
250	3	6	12	16	17	26	30
0	13	22	31	35	37	38	39
PTIL0-2							
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day -07
1000	0	0	4	16	18	25	34
500	10	11	16	20	21	26	38
250	12	19	22	29	33	36	45
0	15	24	33	41	45	51	56
PTIL03							
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day -07
1000	0	0	5	12	19	22	27
500	0	6	10	20	26	31	48
250	5	10	19	31	37	39	47
0	15	24	33	41	45	51	56
PTIL04							
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day -07
1000	0	0	3	18	21	27	35
500	0	9	14	20	21	26	36
250	8	15	22	28	34	36	45
0	13	22	31	36	44	50	57
PTIL05							
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day - 05	Day - 06	Day -07
1000	0	0	0	5	11	15	24

500	0	3	10	14	21	23	31
250	5	09	12	18	23	26	34
0	12	21	29	35	40	48	52

3.6.5 Scheme No 05

3.6.5.1 Data of antimicrobial activity Diammonium phenyl based ILs

Table 21: Zone of inhibition against bacteria in mm scale without 8 mm hole of well for 1000mMol/L

	DPIL-1	DPIL-2	DPIL-3	DPIL-4	DPIL-5	Control	Starting
Bacillus cereus(+)	33	34	36	37	38	0	0
Staphylococcus aureus(+)	28	29	32	33	33	0	0
Bacillus subtilis(+)	26	27	28	28	33	0	0
Sarcina lutea(+)	24	23	25	27	29	0	0
Escherichia coli(-)	22	24	24	25	26	0	0
Salmonella typhi(-)	22	22	21	24	23	0	0
Pseudomona aeroginosa(-)	24	25	23	26	26	0	0
Shigella dysenteriae(-)	19	21	21	22	23	0	0

3.6.5.2 Comparative study against all bacteria

Using the fig-28, it was shown that the zone of inhabitation of all ILs is to show the almost similar both of gram positive and gram negative bacteria. It was shown that the alkyl chain has an effect on antibacterial activity even the substituent group in attached with anion.

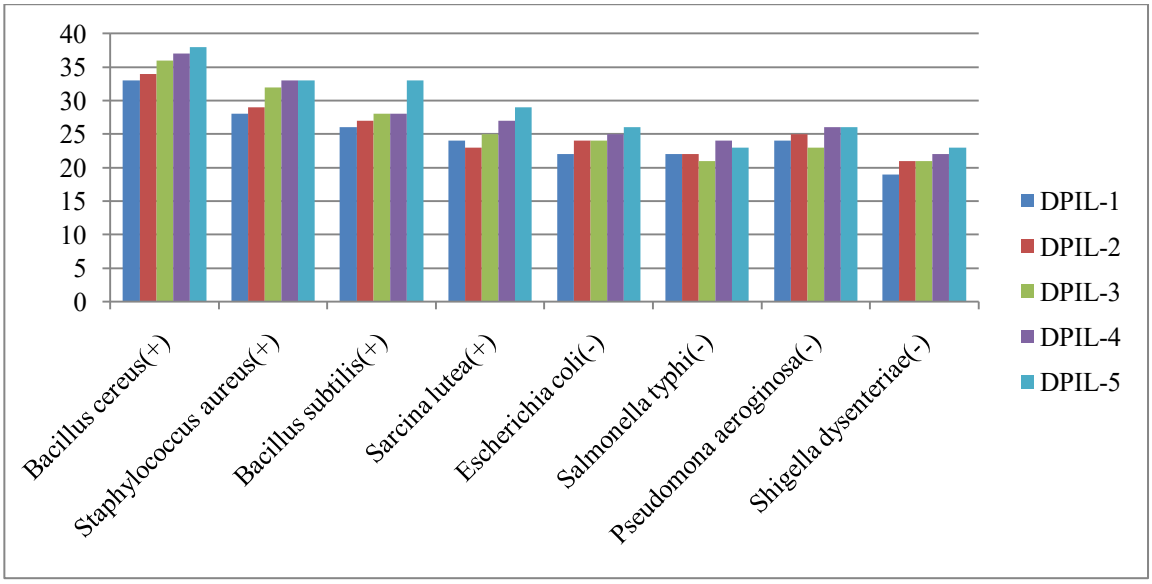


Figure 28: Comparative study against all bacteria

3.6.5.3 Data and determination of MIC

MIC for the tested ILs were calculated from the inhibitions showed in the different concentrations via serial dilution such as, 1000, 750, 500, 250, 125, 62.5, and 0 mMol/L using the well diffusion technique. The all data was plotted in excel file and calculated the MIC point at where the zone of inhabitation was zero.

Table 22: Scheme-05, *Bacillus cereus(+)*							
	1000 mMol/L	750 mMol/L	500 mMol/L	250 mMol/L	125 mMol/L	62.5 mMol/L	MIC
DPL01	33	27	19	10	0	0	125
DPIL02	34	25	18	8	4	0	62.5
DPIL03	36	28	18	10	6	0	62.5
DPIL04	37	26	19	12	5	0	62.5
DPIL05	38	26	20	11	6	0	62.5
Escherichia coli(-)							
DPL01	22	16	8	5	0	0	125
DPIL02	24	15	11	6	0	0	125
DPIL03	24	19	12	7	0	0	125
DPIL04	25	17	12	6	0	0	125
DPIL05	26	19	12	8	5	0	62.5

3.6.5.4 Result for antifungal activity

Table 23: Data of %, growth percentage against fungal						
Chemicals tested	Zone of growth (in mm)			%, growth percentage		
	Aspergillus niger	*Saccharomyces cerevisiae*	*Candida albicans*	*Aspergillus niger*	*Saccharomyces cerevisiae*	*Candida albicans*
Control	28 mm	41 mm	38 mm	100 %	100%	100 %
S. material	25 mm	39 mm	37 mm	89.28%	95.12%	97.36%
DPL01	19	27	29	67.85%	65.85%	76.31%
DPIL02	18	25	26	64.28%	60.97%	68.42%
DPIL03	16	23	24	57.14%	56.09%	63.15%
DPIL04	15	21	23	53.35%	55.26%	60.52%
DPIL05	14	19	20	50.00%	46.34%	52.63%

3.6.5.5 The Percentage of Inhibition

Chemicals tested	Table 24: Percentage of inhibition		
	Aspergillus niger	*Saccharomyces cerevisiae*	*Candida albicans*
Control	0.00%	0.00 %	0.00 %
Staring material	10.72 %	4.88%	2.64%
DPL01	32.15%	34.15%	23.69%
DPIL02	35.72%	39.03%	31.58%
DPIL03	42.86%	43.91%	36.85%
DPIL04	46.65%	44.74%	39.48%
DPIL05	50.00%	53.64%	47.37%

3.6.5.6 Comparative study of the effect of anion on antifungal activity in different ILs

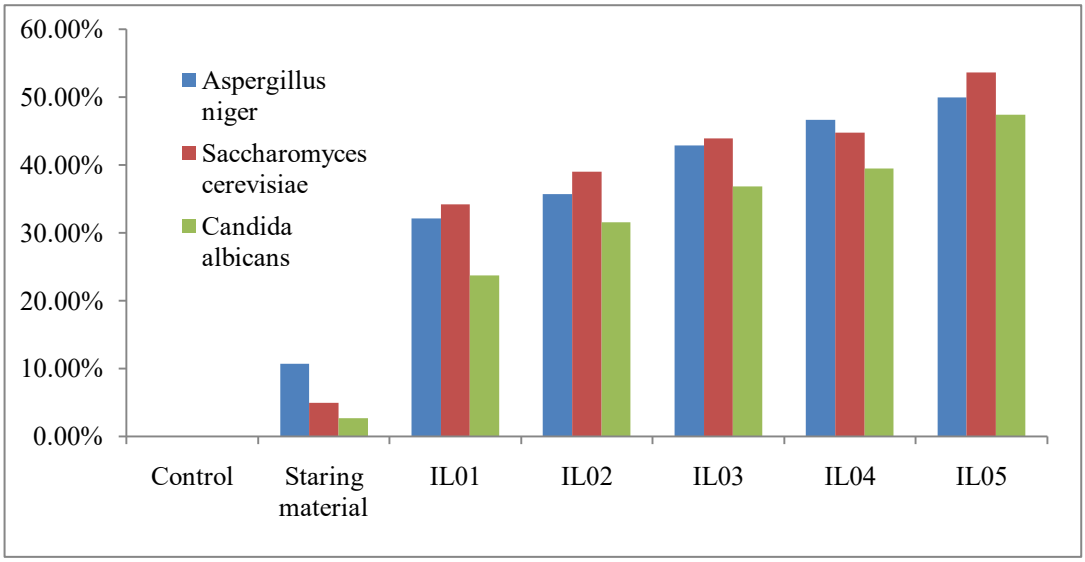


Figure 29: the effect of anion on antifungal activity in different ILs

3.6.5.7 Data of Phytotoxicty

Table 25: Scheme-05. Diammoniumphenyl carboxylate ILs							
DPIL-01							
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day -05	Day - 06	Day -07
1000	0	0	0	0	0	0	0
500	0	0	0	0	0	0	0
250	3	6	12	16	18	20	21
0	13	22	31	35	37	38	39
DPIL0-2							
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day -05	Day - 06	Day -07
1000	0	0	0	0	destroy	-	-
500	0	0	2	3	5	7	10
250	3	6	12	16	18	20	21
0	13	22	31	35	37	38	39
DPIL03							
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day -05	Day - 06	Day -07
1000	0	0	0	0	destroy	-	-
500	0	0	0	1	3	5	9
250	0	3	5	6	8	12	16
0	13	22	31	35	37	38	39
DPIL04							
Concentration	Day -	Day -	Day -	Day -	Day -05	Day -	Day -07

	01	02	03	04		06	
1000	0	0	0	0	0	0	0
500	0	0	0	0	1	3	5
250	0	0	3	5	7	10	14
0	12	20	30	36	39	41	52
DPIL05							
Concentration	Day - 01	Day - 02	Day - 03	Day - 04	Day -05	Day - 06	Day -07
1000	0	0	0	0	0	0	0
500	0	0	0	0	1	2	4
250	0	0	1	4	6	10	12
0	12	18	30	33	35	41	52

3.7 Summary

From the biological activity in case of antibacterial, antifungal and phytotoxicity studies make a comparison between anilinium, *ortho* toluidinium carboxylate, *meta* toluidinum, *para* toluidinium and diammoniumphenyl carboxylate ILs. Among all ILs, the diammoniumphenyl carboxylate ILs could show high biological activity. In conclusion, that the number of anions and cation chain of ILs could play the important role in biological activity.

CHAPTER 4

COMPUTATIONAL APPROACHES

4.1 Computational backgrounds

Computational chemistry is a branch of chemistry that uses computers to solve real problems in chemistry, pharmaceutical science biotechnology and material science [120]. It uses the results of theoretical chemistry, incorporated into efficient computer programs, to calculate the structures and properties of molecules and solids. Computational chemistry is widely used in the design of new drugs and materials.

Computational chemistry is capable of predicting many properties of molecules and reactions, including the following;

- 2D, 3D molecular diagram and bond length angle and order.
- Molecular energies and structures.
- Energies and structures of transition states.
- Bond and reaction energies.
- Molecular orbital.
- Vibration frequencies.
- thermo-chemical properties
- Thermodynamics.
- Reaction pathways.
- Spectroscopic quantities and numerous molecular properties.
- Biological activity.
- Drug design
- Gas phase and in solution, including the ground and excited states.
- Protein and DNA, RNA, hormone theoretical studies, etc.

The methods employed for the computational analysis cover both static and dynamic situations. In all cases the computer time increases rapidly with the size of the system being studied. That system can be a single molecule, a group of molecules or a solid. The methods are thus based on theories which range from highly accurate, but are suitable only for small systems, to very approximate, but suitable for very large systems. The accurate methods used are called *ab* initio methods, as they are based entirely on theory from first principles. The less accurate methods are called empirical or semi-empirical because mathematical truncation or some experimental

results, often from acceptable models of atoms or related molecules, are used along with the underlying theory. Both of these approaches involve approximations, either as generalized forms of first principles equations optimized for computation, from systems with boundary conditions which limit the scope of computation to within a pre-defined window, or ultimately from the necessary approximation of quantum mechanics equations which have not been solved exactly except for single-electron systems (for example, the hydrogen atom). In practice, ab initio methods eventually converge towards the exact solution if all the approximations are made at a small enough magnitude.

4.2 Reasons for Computational works of this research

Computational chemistry will never be a full replacement for doing experiments, but can often supplement experimental work. Very often neither experiment nor computational chemistry can by itself give the desired full insight. In many cases one must therefore piece together whatever information and conclusion that can be drawn from either source. Sometimes computational chemistry can be used to calculate properties that are not at all available from experimental work, while some issues can be difficult both in the laboratory and on the computer. When working with results from modeling and the laboratory one should have a feeling for the quality of the data from different sources so that the most reasonable points for doing computational works as:

Computational chemistry has grown as a field very quickly,

- To save time and expensive due to the potential of its methods.
- To investigate the thermophysical, chemical profiles.
- To estimate the QSAR using theoretical method.
- Compare the experimental and theoretical data.
- To evaluate the theoretical investigation of biological activity.

On the other hand it must also be noted that the systems in the process display considerable complexity. Given the complexity of the system, the amount of experimental data available must actually be considered to be rather sparse. The mechanism of these systems also present challenges for computational chemistry

work. The absence of experimental data at the molecular level also means that it can be difficult to validate models being used and conclusions drawn regarding the nature of the system. The approach in this work has therefore been somewhat pragmatic. The most effort has been put into areas where computational chemistry was thought to give the most valuable new insight, whereas some aspects have been approached tentatively.

4.3 Concept of Computational Chemistry

Computational chemistry involves a mathematical description of systems of chemical species. The goal is to solve the complex equations such as Schrödinger equation for electronic and nuclear motion which accurately describe natural phenomena [121]. In a practical application of computational chemistry, mathematical equations or algorithms are devised to quantitatively describe the physical and chemical phenomena (for example, energy states, structures, reactivity, positions and momenta of atoms) that occur in a particular system. These algorithms are then programmed in the appropriate computer languages and linked together so that the many millions of calculations required to effectively describe the phenomena can be quickly computed. For example, it might be necessary to calculate billions of integrals to accurately describe the repulsion of electrons in a complex molecule.

The end result is a set of computational tools that predict the characteristics and behaviour of the chemical system. The term theoretical chemistry may be defined as a mathematical description of chemistry, whereas computational chemistry is usually used when a mathematical method is sufficiently well developed that it can be automated for implementation on a computer. Note that the words exact and perfect do not appear here, as very few aspects of chemistry can be computed exactly. However, almost every aspect of chemistry can be described in a qualitative or approximate quantitative computational scheme. Molecules consist of nuclei and electrons, so the methods of quantum mechanics apply. Computational chemists often attempt to solve the non-relativistic Schrödinger equation, with relativistic corrections added, although some progress has been made in solving the fully relativistic Schrödinger equation. In principle, it is possible to solve the Schrödinger equation in either its time-dependent or time-independent form, as appropriate for the

problem at hand; in practice, this is not possible except for very small systems. Therefore, a great number of approximate methods strive to achieve the best trade-off between accuracy and computational cost. Accuracy can always be improved with greater computational cost. Significant errors can present themselves in *ab initio* models comprising of many electrons, due to the computational expense of full relativistic-inclusive methods. This complicates the study of molecules interacting with high atomic mass unit atoms, such as transitional metals and their catalytic properties.

The treatment of larger molecules that contain a few dozen electrons is computationally tractable by approximate methods such as density functional theory (DFT). There is some dispute within the field whether or not the latter methods are sufficient to describe complex chemical reactions, such as those in biochemistry. Large molecules can be studied by semi-empirical approximate methods. Even larger molecules are treated by classical mechanics methods that employ what is called molecular mechanics (MM). In QM/MM methods, small portions of large complexes are treated quantum mechanically (QM), and the remainder is treated approximately (MM). In theoretical chemistry, chemists, physicists and mathematicians develop algorithms and computer programs to predict atomic and molecular properties and reaction paths for chemical reactions. Computational chemists, in contrast, may simply apply existing computer programs and methodologies to specific chemical questions.

Storing and searching for data on chemical entities (chemical databases, chemoinformatic) and Identifying correlations between chemical structures and properties (quantitative structure-activity relationships (QSAR) and quantitative structure-property relationships (QSPR) were developed to estimate all molecular properties, chemical properties, and biological activity.

Computational approaches to help in the efficient synthesis of compounds. Computational approaches to design molecules that interact in specific ways with other molecules (for example drug design).

4.4 Computational Chemistry for ILs

Most industrial solvents using these days are organic compounds which are volatile. These compounds have narrow liquid range (~up to 200^{o} C). So the present solvents are major source of environment pollution. These compounds have been studied for more than hundred years and well characterized. There is an intense research effort to replace volatile organic solvents by new class of solvents called ILs. ILs are organic salts mainly composed of organic cations and inorganic anions, which are per definition liquid below 100 °C and exhibit in most cases relatively low viscosities [122]. The definition allows distinguishing them from a classical molten salt, which is mostly a high-melting, highly viscous and very corrosive substance. Conventionally, ILs typically contain bulky asymmetric organic cations, such as imidazolium, pyridinium, pyrrolidinium, quaternary ammonium or tetraalkylphosphonium, with very low symmetry, weak intermolecular interactions and low charge densities [78, 123]. The earliest discovery of an ionic liquid can be dated to the middle of the nineteenth century, when some –red oil" was observed in a Friedel-Crafts reaction [78]. In 1951 AlCl3-based ILs were developed by Hurley and Wier [124] at Rice Institute in Texas as a bath solution for electroplating aluminium. In the 1970s Osteryoung [125] and Wilkes [126] succeeded in preparing room-temperature liquid chloroaluminate melts. The first organic reaction that was carried out in an acidic tetrachloroaluminate ionic liquid was Friedel-Crafts alkylation [127] and since then ILs have been used as reaction solvents in various organic reactions. These ILs are now considered as ideal class of solvents because of their large liquidous range in industrial applications.

4.5 A brief literature of computational chemistry

There are two broad areas within computational chemistry devoted to the structure of molecules and their reactivity: molecular mechanics (MM) and quantum mechanics (QM). They both perform the same basic types of calculations:

Computing the vibrational frequencies of molecules resulting from interatomic motion within the molecule is called evaluating the Hessian. Frequencies depend on

the second derivative of the energy with respect to atomic structure, and frequency calculations may also predict other properties which depend on second derivatives.
These sections provide an overview of the fundamental equations that are used in the construction of computational models. In some sense these sections are historical. However, in order to appreciate differences between modern computational models, and the range over which they may be applicable, it is important to understand the foundation on which all of them are built. There are roughly four different –flavors" to computational chemistry, namely: ab initio methods, semi-empirical methods, density functional theory and molecular mechanics/molecular dynamics.

4.6 Molecular mechanics (MM)

Molecular mechanics uses the laws of classical physics to explain and interpret the structure and properties of molecules. Molecular mechanics methods are available in many computer programs, including MM3, Material studio, HyperChem, Gaussian, Quanta, Sybyl and Alchemy. There are many different molecular mechanics methods. Each one is characterized by its particular force field. A force field has these components. A set of equations defining how the potential energy of a molecule does varies with the locations of its component atoms.
In a MM calculation, an initial guess for the geometry of the system is made. The potential is then minimized through a gradient search method to determine the equilibrium structure and heat of formation. There are several flavors of MM available, such as the MM2 and MM3 methods. Molecular mechanics calculations don‘t explicitly treat electrons in molecular systems. Instead, they perform computations based upon the interactions among the nuclei. Electronic effects are implicitly included in force fields through parameterization.
This approximation makes molecular mechanics computations quite inexpensive computationally, and allows them to be used for very large systems containing many thousands of atoms. However, it also carries several limitations as well. Among the most important are these.

4.7 Quantum mechanics (QM)

Quantum methods are used for the theoretical investigation of molecular properties which depend on the electronic structure of the system. This method uses quantum mechanics rather than classical physics as the basis for its computations. The basis of these methods is the time independent non relativistic Schrödinger equation.

$$\hat{H}\Psi = E\Psi$$

Where, $\hat{H}$ is the Hamiltonian operator, E the energy and Ψ the wave function of the system under consideration. Semi-empirical and *ab* initio methods differ in the trade-off made between computational cost and accuracy of the results. Semi-empirical calculations are relatively inexpensive and provide reasonably qualitative descriptions of molecular systems and fairly accurate quantitative predictions of energies and structures for systems where good parameter sets exist.

In contrast, *ab* initio computations provide high quality quantitative predictions for a broad range of systems. They are not limited to any specific class of systems. Early ab initio programs were quite limited in size of system they could handle. However this is not true for modern ab initio programs. On a typical workstation, Gaussian 09 can compute the energies and related properties for systems containing a dozen heavy atoms in just a few minutes. It can handle jobs of up to a few hundred atoms, and can predict the structures of molecules having as many as a hundred atoms on the same size computer system. Correspondingly larger systems can be handled on supercomputer systems based upon their specific CPU performance characteristics. Semi-empirical methods and ab initio methods are discussed in details in the next two sections.

4.8 Semi-Empirical Methods

Semi-empirical methods, such as Austin Model 1 (AM1), Modified Intermediate Neglect of Differential Overlap (MINDO/3) and Parametric Method Number 3 (PM3), implemented in programs like MOPAC, AMPAC, HyperChem and Gaussian uses parameters derived from experimental data to simplify the computation. They solve an approximate form of the Schrödinger equation that depends on having appropriate parameters available for the type of chemical system under investigation.

Different semi-empirical methods are largely characterized by their different parameter sets.

While the quality of the results is varied, all of these methods can be studied. In addition, semi-empirical models can perform very well for systems for which they have been optimized. They are not so successful in difficult cases, such as radical and ionic species or transition states.

Most semi-empirical models involve an approximation that neglects, to some extent, the overlap of atomic orbital in a molecule. The Austin Model 1 (AM1) semi-empirical method is a variant of the Neglect of Diatomic Differential Overlap approach (NDDO). The overlap approximation states that for integrals that contain the atomic orbital (AOs).

$$\int^{*} s(1) \int s(2) d\tau = 0$$

If r and s are centered on different atoms, even if they are bonded

The Parametric Method Number 3 (PM3) method is similar to AM1 but has an improved parameterization and has been extended to include heavier atoms. In general, PM3 gives improved results over AM1 for molecules containing second row atoms and heavier. It also gives a better account of hydrogen bonding. Still, the typical errors in bond lengths and angles are about twice as large as those resulting from low level (3-21G) ab initio calculations.

4.9 Density Functional Theory (DFT)

An alternative to ab initio methods that has been growing in popularity over the past decade is recognized as density functional theory (DFT). In wave function-based ab initio theory the full electron wave function is calculated, whereas DFT focuses on the total energy and the one electron density distribution. One of the most important reasons for the success of DFT is that it includes the electron correlation in an effective manner. The central underlying idea is the relationship between total energy and electron density. In 1964, Hohenberg and Kohn showed that the electron density $\rho(r)$ uniquely defines the ground-state energy E and other properties of a system (Hohenberg and Kohn, 1964). Therefore, E is a unique functional of $\rho(r)$.

In DFT the energy functional is written as a sum of two terms:

$$E[\rho_i(r)] = \int V_{est}(r)\rho(r)dr + F[\rho(r)]$$

The Born-Oppenheimer Approximation:

The Born-Oppenheimer approximation simplifies the general molecular problem by separating nuclear and electronic motions. This approximation is reasonable since the mass of a typical nucleus is thousands of times greater than that of an electron. The nuclei move very slowly with respect to the electrons, and the electrons react essentially instantaneously to changes in nuclear position. Thus, the electron distribution within a molecular system depends on the positions of the nuclei and not on their velocities. Hence the application of the Born-Oppenheimer approximation yields the electronic Schrödinger equation:

$$\hat{\mathrm{H}}_{el}\Psi_{el} = E_{el}\Psi_{el}$$

The Born-Oppenheimer approximation has a very profound consequence; it enables the calculation of potential energy surface (PES).

4.10 Theoretical Background

4.10.1 Fundamentals of Thermodynamics

Thermodynamics is a branch of physics and physical chemistry where describe the properties of the general macroscopic physical systems and their theory of evolution, calculates all types of changes and heat in the physical and chemical processes [128]. The different activities of living creature done with the conservation of energy which is more complex and governed by the physical law of altering one form of energy to another [129].

A thermodynamic system is a definite macroscopic region or space in the universe in which one or more thermodynamic processes take place. This system has a specific volume consisting of molecules and atoms with continuous movement and concussion by the interaction with the external surrounding. The internal properties and its interaction with the surrounding determine the system behavior [130].

The thermodynamics systems are of three types taking into account the interaction with the external environment which are: (i) Closed system: only the transfer of energy but not mass across the boundary. (ii) Open system: Transfer of both mass

and energy across the boundary. (iii) Isolated system: Do not transfer both mass and energy across the boundary [131-132]. A thermodynamic system can switch from initial state through the intermediate state to final state which is called transformation of state or thermodynamics process[131, 133].

4.11 Computing Part for Simulation

HyperChem 8.0.10, and Material studio 8.00, 2019 version was used for molecular modeling program which permits to build and analyze different molecular structures and to determine their physico-chemical properties.

The PM3 method is derived from Parametric Method number 3 from computational chemistry and included in semi-empirical method for the quantum calculation of molecular structure. PM3 was used the Hamiltonian and it is parameterized to reproduce a large number of molecular properties[134].

In order to create the spatial chemical structure of each calculated molecule, two-dimensional structure of the molecule shall be build step-by-step by drawing. Then hydrogen atoms are automatically added from build option and chemical structure is converted into one 3D structure. 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. It aimed to obtaining the value of total energy, the bonding energy, the heat of formation, the energy of frontier orbital, HOMO (Occupied Molecular Orbital Highest) and LUMO (Lowest Unoccupied Molecular Orbital), the dipole moment, the polarizibility and parameters QSAR (Quantitative Structure - Activity Relationship)

4.12 Computational Chemistry and working procedure

4.12.1 List of Software's and Hardware's and their specifications

This study deals with various software_s collected and purchased from the authentic sources or companies. Some were downloaded as freeware and some could be

accessed as collaboration with the research organizations. The list of software_s includes the DFT based or Statistical or Quantum mechanics based, which were placed in.

Table 3.1: List of most common Softwares

Sl.	Name of the Softwares	Software basis on
	HyperChem	DFT, Quantum mechanics
	Material studio	DFT, Quantum mechanics, Electronic properties, Crystal etc
	Gaussian	DFT, Quantum mechanics
	Sparton	DFT, Quantum mechanics
	COMSOL	DFT, Quantum mechanics
	Schrödinger, LLC	Biological macromolecules, such as proteins
	Python Prescription Virtual Screening Tool	Computer-Aided Drug Design
	Discovery Studio	Computer-Aided Drug Design

4.12.2 Method for Simulation

4.12.3 Molecular Modeling

Molecular modeling is useful tools in many fields such as chemistry, physics, biology, medicine, pharmacy and allows graphical representation of a molecule configuration and calculation of physico-chemical, and biological properties. In the pharmacological research, drug design, biological chemistry, and molecular biology were made easy to continuous research and design new molecules by molecular modeling of computational software. Instigated in various molecular modeling programs, these methods are used to determine properties of drugs, and bioactive molecule found in draft before the actual synthesis.

Molecular modeling methods are numerous, mostly relying on the principles of quantum mechanics and Schrödinger's equation solving [135].

The most important methods that are used in molecular modeling programs are ab-initio methods, empirical methods, semi-empirical methods [136], Density function theory [137]. The most important methods semiempirical: AM1, PM3. In addition to the methods mentioned above, in recent years there was an expansion of the two methods, the method of molecular dynamics and Monte Carlo method, which refers to theoretical models that takes an intermediate between theory and experiment, called numerical methods[138].

Among the most used molecular modeling programs include: Spartan, Gaussian and HyperChem. Most molecular modeling techniques based on the principles of quantum mechanics and Schrödinger's equation solving. Depending on the parameters studied molecular system that are intended to be obtained choosing one or another method[139].

4.13 Thermodynamics quantities

This process assesses the performance of quantum chemical models with regard to the calculation of vibrational frequencies, and describes the evaluation of thermodynamic quantities resulting from vibrational frequencies. The most important of these from the present perspective are associated with bringing energetic data obtained from calculation into juxtaposition with that obtained in a real experiment. The former are energies of non-vibrating molecules while the latter are free energies at some finite temperature. Standard thermodynamic relationships provide necessary connections:

$$\Delta G = \Delta H - T\Delta S$$

$$\Delta H = \Delta E + P\Delta V$$

$$\Delta E = \Delta H - P\Delta V$$

G is the free energy, H is the enthalpy, S is the entropy, E is the energy, and T, P and V are the temperature, pressure and volume.

4.14 Calculations of the HOMO and LUMO Orbital

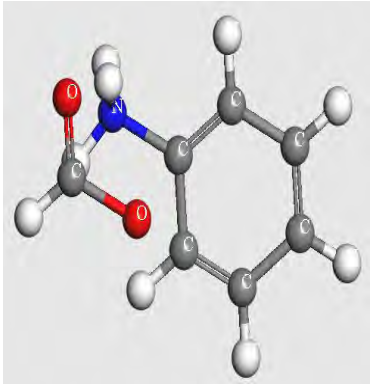
Once the structures of the lowest energy conformers have been confirmed by infrared spectroscopy measurements, the investigation is extended to the electronic properties. In Figure, the comparison among the calculated LUMO orbital of B3PYR, [140] , and calculated at the B3LYP/ level is reported. One can note that in all ions the LUMO extends on the whole ammonium ring and on the methyl group and other alkyl or aromatic ring is directly attached to it. For PYR [140], the orbital extends slightly also on three of the CH groups of the side alkyl chain. In the case of and , the LUMO extends also on the fourth group of the side chain and displays bonding orbital between the first group and the second group of the chain, in contrast to PY Also, the HOMO orbital of the three ions, reported in Figure [141], displays some differences. In all three ions, it extends on the second, third, and fourth groups of the side chain. However, while in PYR the orbital on the second group is smaller than that of the third and fourth atoms of the chain, in and this difference is much smaller [140].

4.15 Results and Discussions

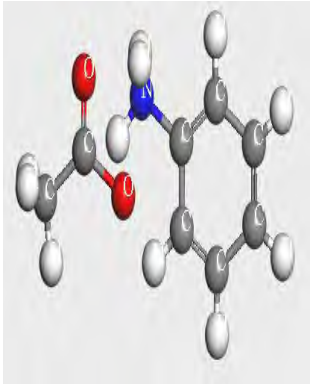
4.15.1 Optimized Structure

Scheme 01**, Anilinium carboxylate**

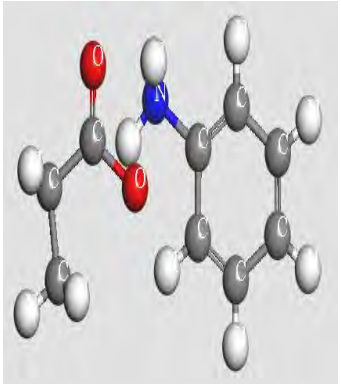
AIL01



AIL02

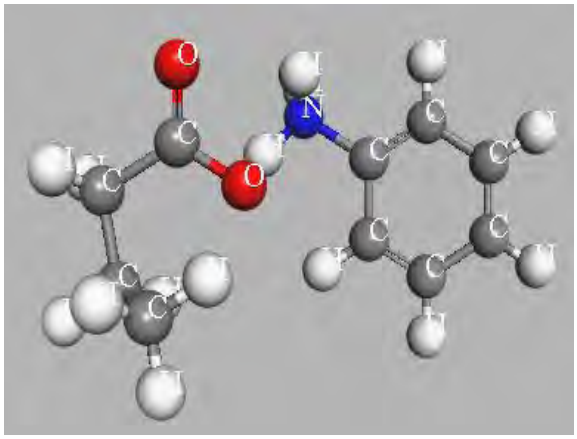
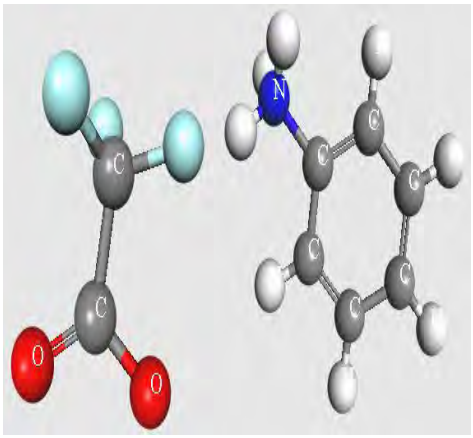


AIL03



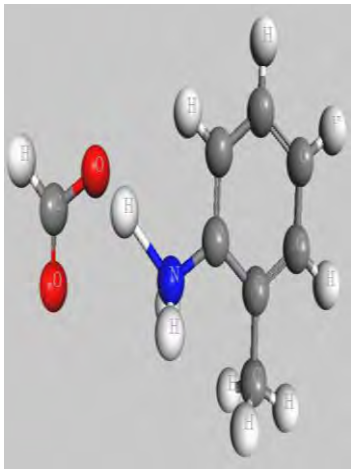
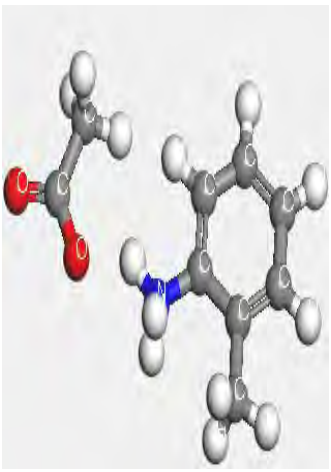
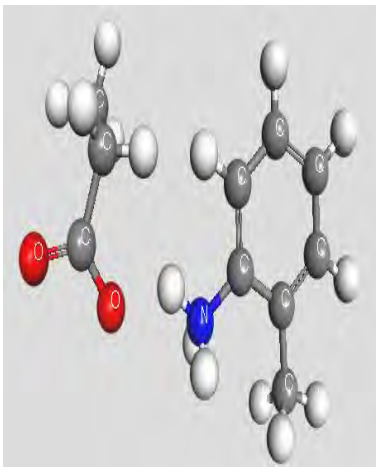
AIL04

AIL05

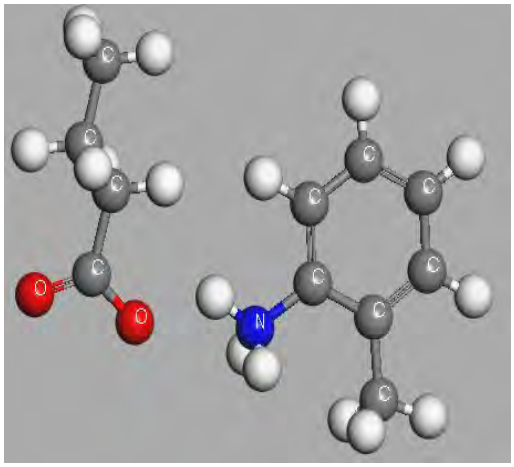
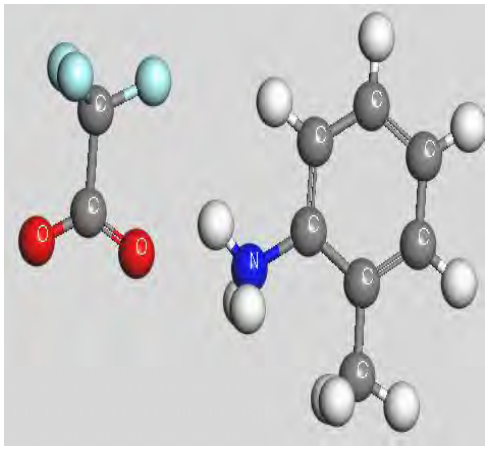



Scheme 02, ***ortho*** **toluidiniumcarboxylate**

OTIL01 OTIL02 OTIL03

OTIL04 OTIL05

Scheme 03, ***meta*** **toluidiniumcarboxylate**

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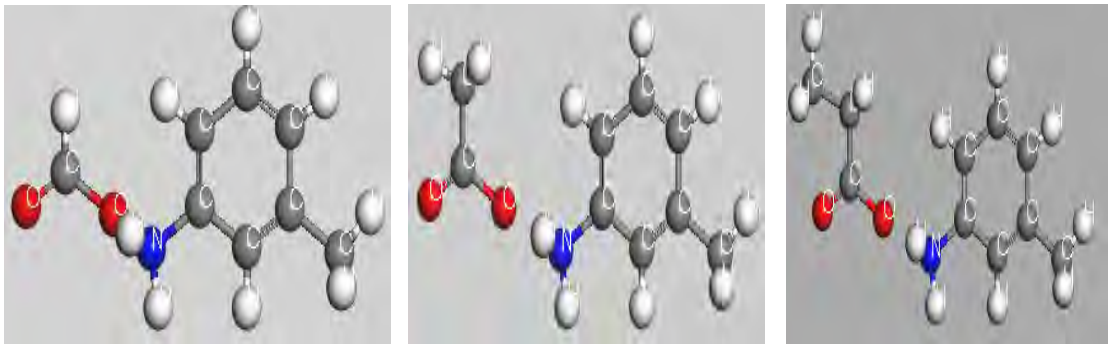
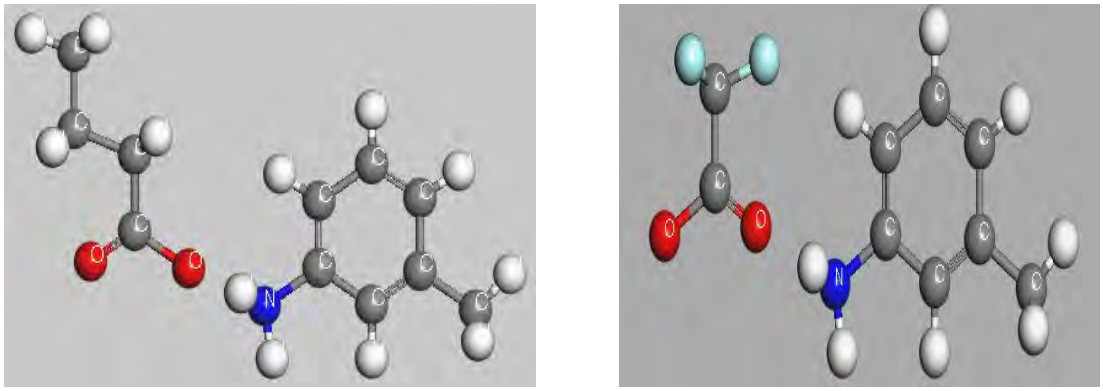
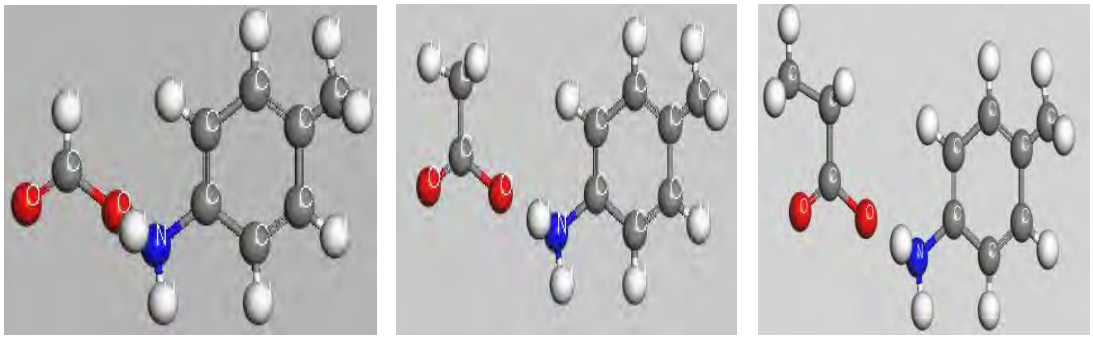


MTIL04 MTIL05

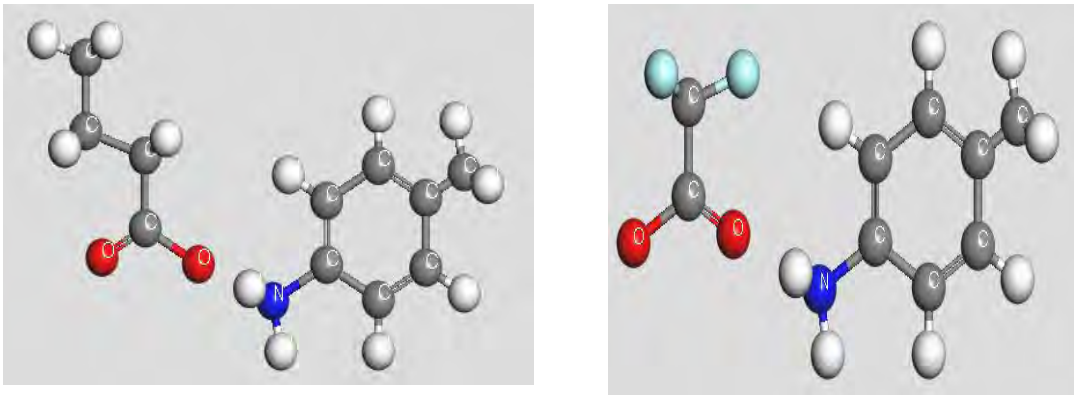


Scheme 04, ***para* toluidiniumcarboxylate**

PTIL01 PTIL02 PTIL03

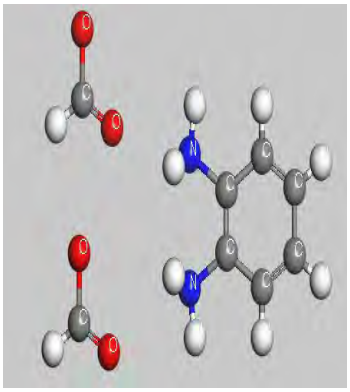


PTIL04 PTIL05

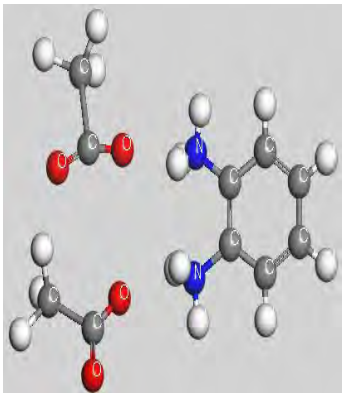


Scheme 05, **1,2 Diammoniumphynylcarboxylate**

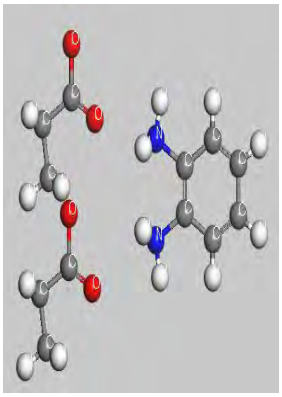
DAIL01



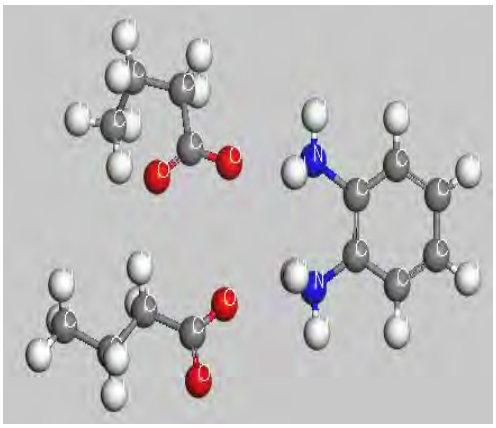
DAIL02



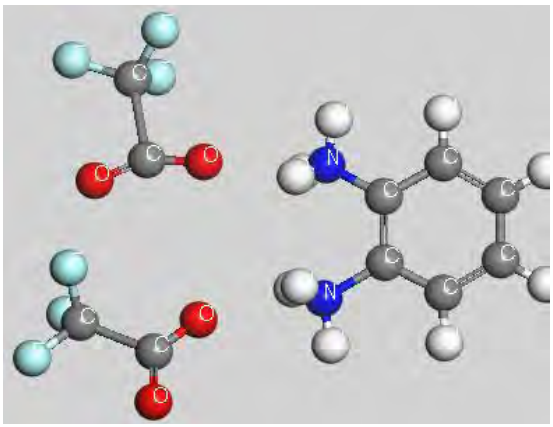
DAIL03



DAIL04



DAIL05

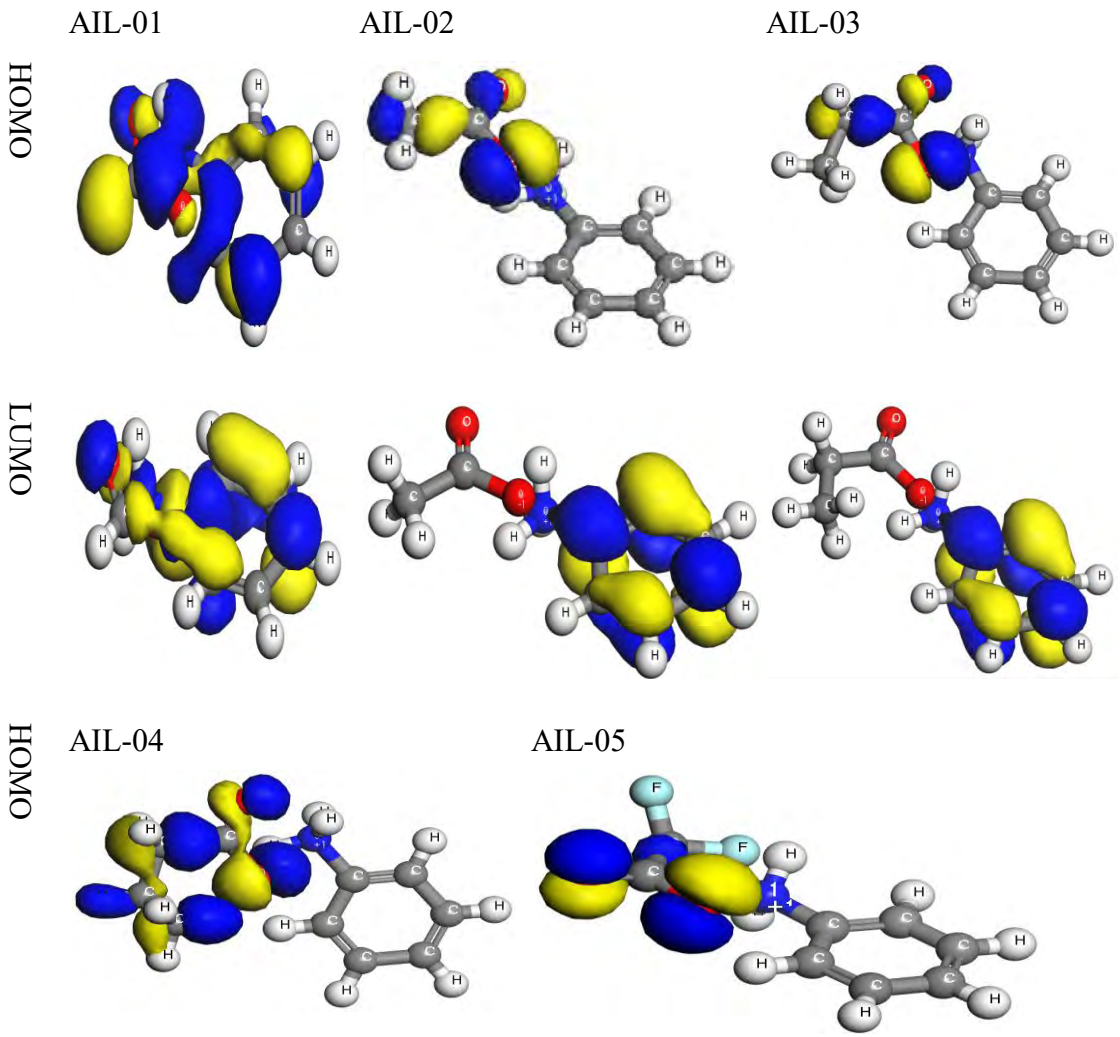


4.15.2 HOMO-LUMO

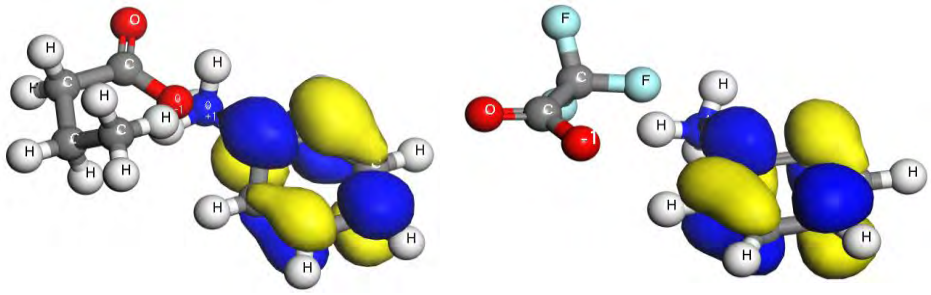
The possible electronic transition is explained by HOMO, and LUMO. The HOMO and LUMO also indicate the electrophilic and nucleophilic attraction region in the

molecule. They are highlighted in figure where the yellow color is a positive value and light blue color is a negative value. The region of HOMO was found on the cation area other two sides of benzene ring, and LUMO on the full benzene ring area. The HOMO can be found of all molecules in near of -7.00 to 9.00 surrounding in cation. On the other hand, the LUMO was addressed in full of anion having -0.2 to 2.0. The magnitude of HOMO and LUMO has attached in table for zero energy level.

Scheme-01



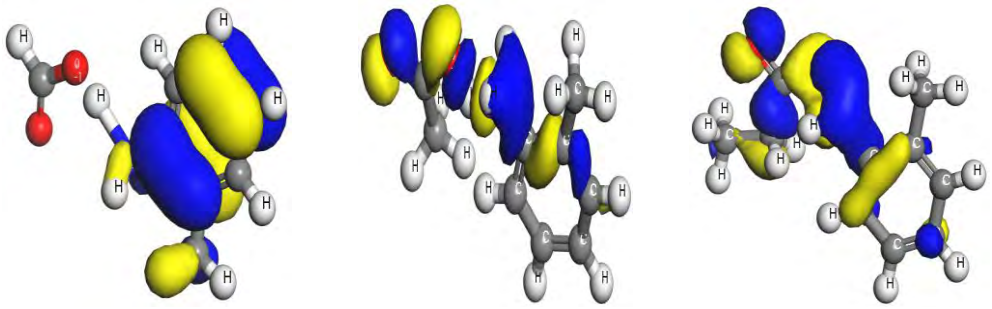
HOMO



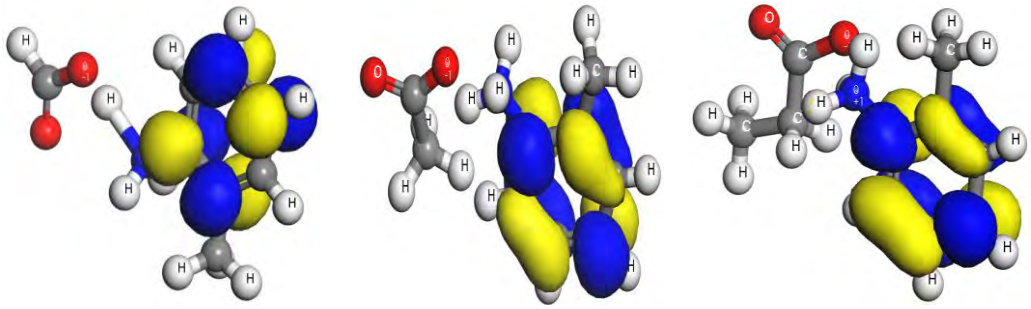
Scheme-02

OTIL-01 OTIL-O2 OTIL-03

HOMO

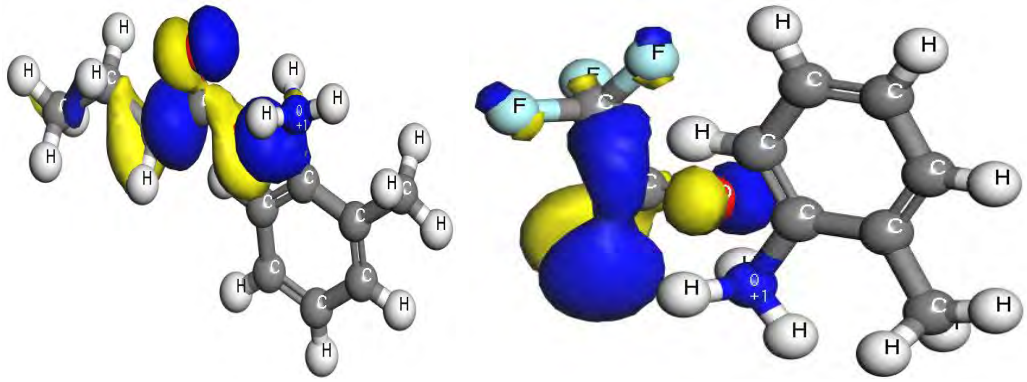


LUMO

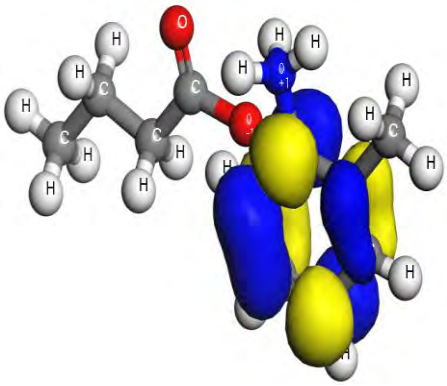


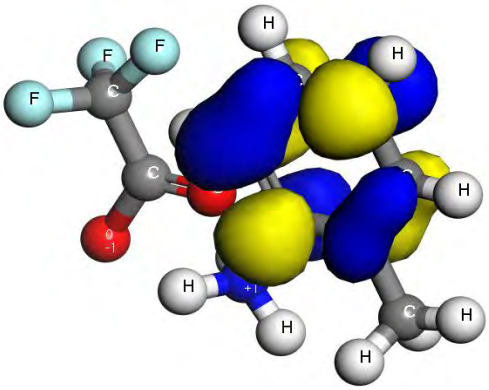
OTIL-04 OTIL-05

HOMO



LUMO

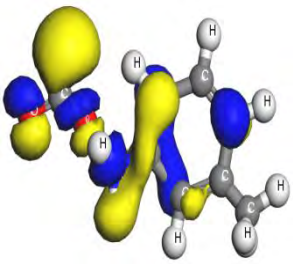


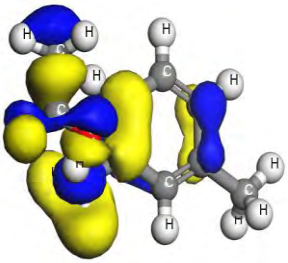


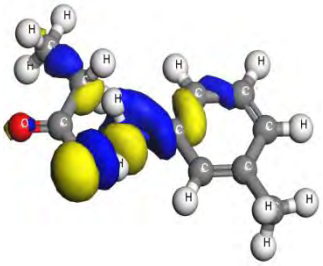
Scheme-03

MTIL-01 MTIL-02 MTIL-3

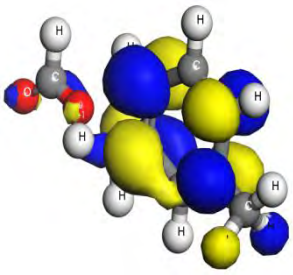
HOMO

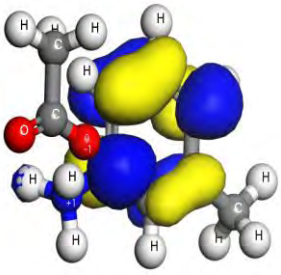


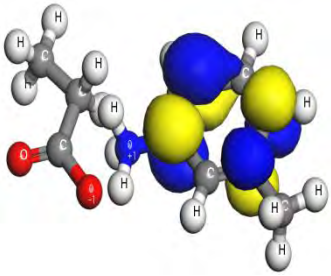




LUMO

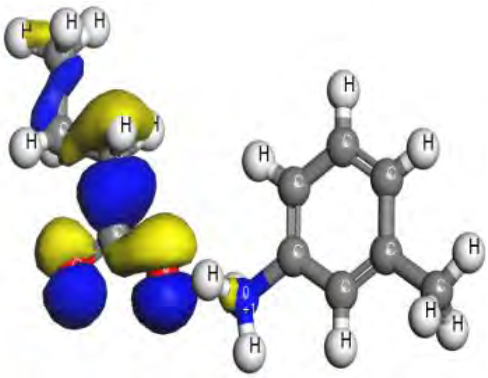


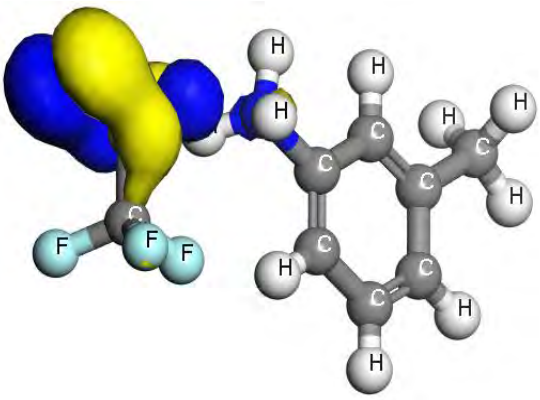




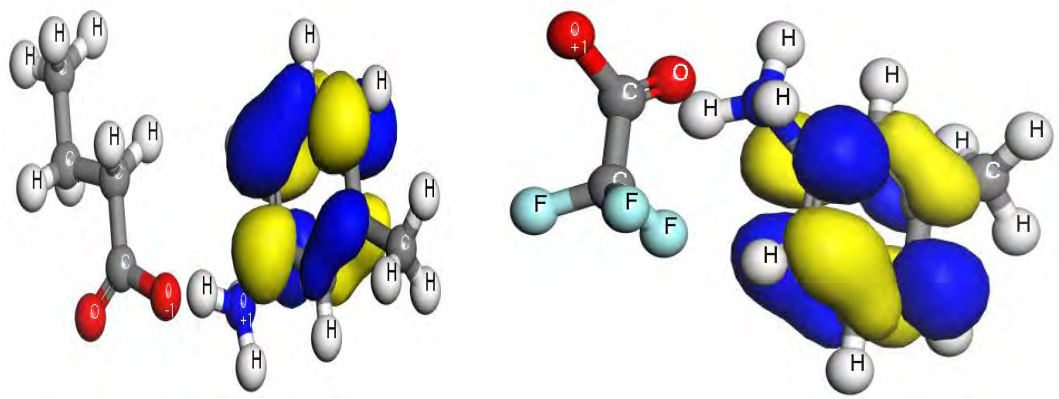
MTIL04 MTIL05

HOMO

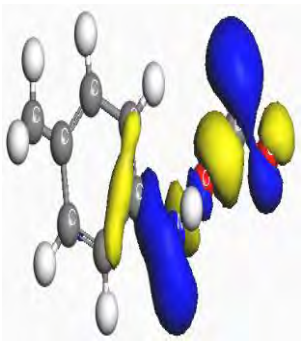
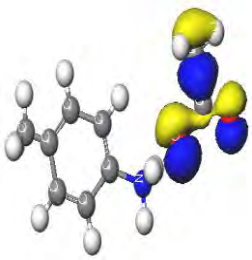
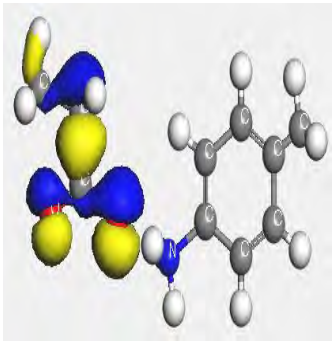
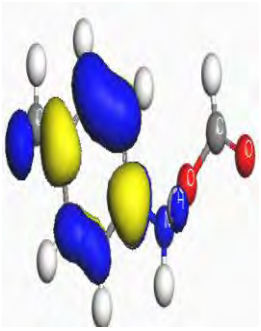
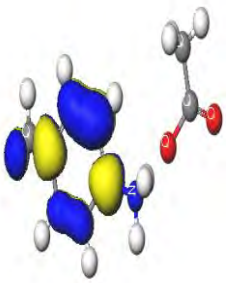
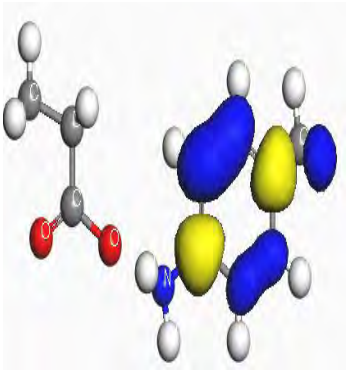




LUMO

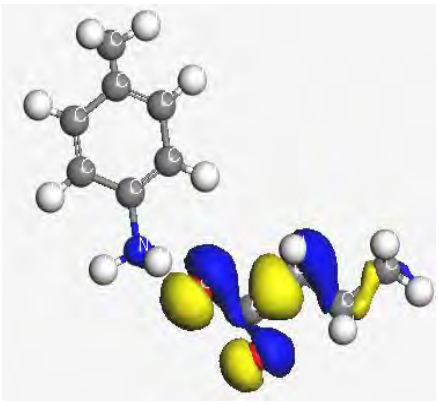


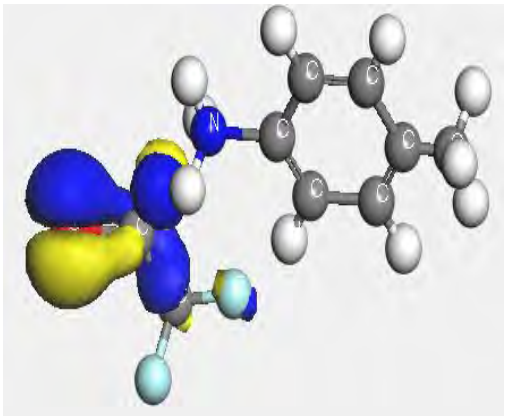
Scheme-04

	PTIL-01	PTIL-02	PTIL-3
HOMO			
LUMO			

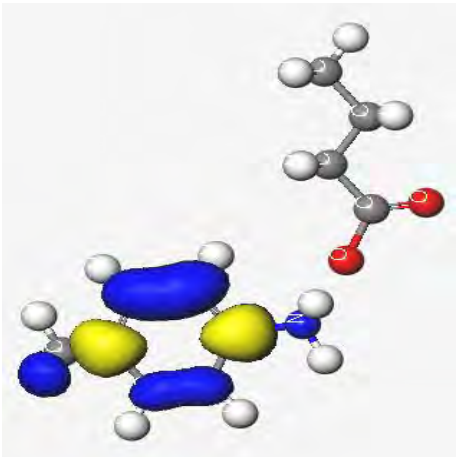
PTIL04 PTIL05

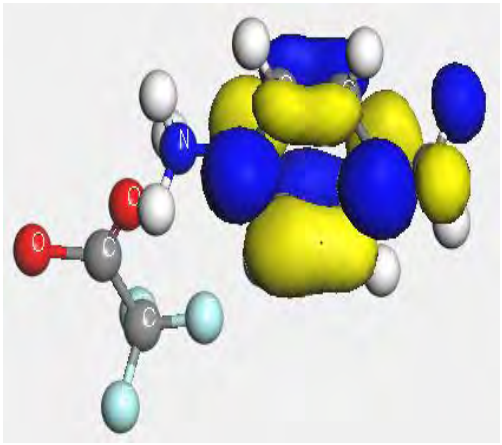
HOMO



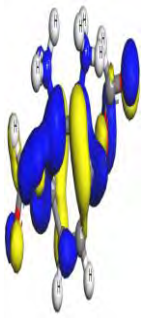
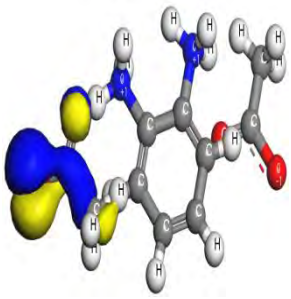
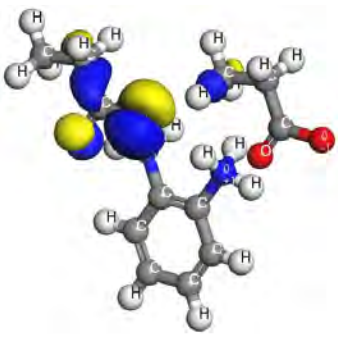


LUMO





Scheme-05

	DPIL-1	DPIL-2	DPIL-3
HOMO			

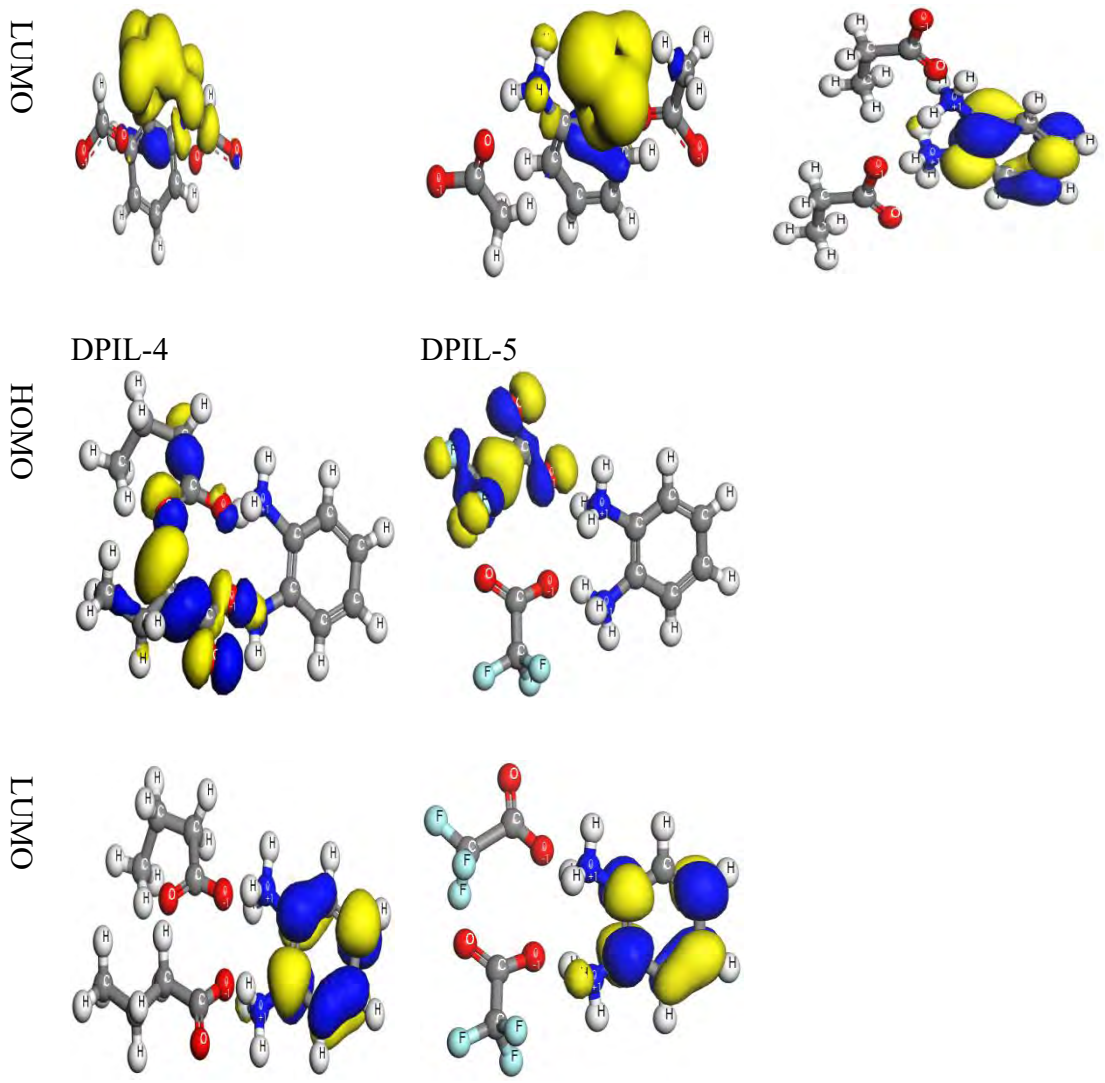


Figure 30: HOMO, LUMO orbital diagram, blue is positive and yellow is negative part

4.15.3 HOMO, LUMO, HOMO–LUMO gap, Ionization potential (I), and Electron affinity

Table 26: HOMO, LUMO, HOMO–LUMO gap, Ionization potential (I), and Electron affinity					
Scheme-01					
	IL01	IL02	IL03	IL04	IL05
HOMO	-14.308	-13.86	-13.856	-13.930	-14.285

LUMO	-5.056	-4.286	-4.279	-4.350	-4.730
HOMO-LUMO gap	-9.252	-9.580	-9.586	-9.580	-9.555
Ionization potential(I), eV	-14.308	-13.86	-13.856	-13.930	-14.285
Electron affinity (A)eV	-5.056	-4.286	-4.279	-4.350	-4.7302
Hardness	-4.626	-4.790	-4.793	-4.790	-4.777
Softness	-0.216	-0.208	-0.208	-0.208	-0.209

Scheme-02					
	IL01	IL02	IL03	IL04	IL05
HOMO	-1.095	-1.317	-2.773	-2.803	-2.915
LUMO	4.414	4.301	4.584	4.571	4.509
HOMO-LUMO gap	-5.500	-5.618	-7.357	-7.374	-7.424
Ionization potential (I), eV	-1.095	-1.317	-2.770	-2.803	-2.915
Electron affinity (A), eV	0	0	0	0	0
Hardness	-2.750	-2.809	-3.678	-3.687	-3.712
Softness	-0.363	-0.355	-0.271	-0.271	-0.269

Scheme-03					
	IL01	IL02	IL03	IL04	IL05
HOMO	-1.053	-2.789	-2.805	-2.859	-2.927
LUMO	4.589	4.574	4.552	4.515	4.469
HOMO-LUMO gap	-5.642	-7.363	-7.357	-7.374	-7.396
Ionization potential, eV	-1.053	-2.789	-2.805	-2.859	-2.927
Electron affinity (A), eV	0	0	0	0	0
Hardness	-2.821	-3.681	-3.678	-3.687	-3.698
Softness	-0.354	-0.271	-0.271	-0.271	-0.270

Scheme-05					
	IL01	IL02	IL03	IL04	IL05
HOMO	7.890	8.432	3.323	2.452	1.695
LUMO	13.758	12.903	8.954	9.502	8.727
HOMO-LUMO gap	-5.868	-4.471	-5.631	-7.050	7.031
Ionization potential (I), eV	0	0	0	0	0
Electron affinity (A), eV	0	0	0	0	0
Hardness	-2.934	-2.235	-2.815	-3.525	-3.515
Softness	-0.340	-0.447	-0.355	-0.282	-0.284

4.16 Thermo physical and thermo chemical properties

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

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 [142-144].

Table 27: Thermo physical and thermo chemical properties

Scheme-01					
Properties	AIL01	AIL02	AIL03	AIL04	AIL05
Total energy,(kcal/mol)	-39442.80	-42876.30	-46324.20	-49770.90	-72268.10
Free energy, (Kcal/mol)	-39442.80	-42876.30	-46324.20	-49770.90	-72268.10
RMS gradient,	0.91	0.63	0.628	1.53	1.49

(Kcal/ mol)					
Binding energy,(Kcal/ mol)	-1794.21	-2059.66	-2339.53	-2618.25	-2087.17
Heat of formation, (Kcal/ mol)	103.05	112.69	107.91	104.29	-14.45
Electronic energy, (Kcal/ mol)	-180333.8	-207002.7	-239052.	-274961.5	-328963.4
Nuclear energy, (Kcal/ mol)	140891.1	164126.4	192728.3	225190.5	256695.3

Scheme-02					
Properties	OTIL01	OTIL02	OTIL03	OTIL04	OTIL05
Total energy, (kcal/mol)	-43084.0	-46536.9	-49985.7	-53434.0	-75987.0
Free energy, (Kcal/mol)	-43084.0	-46536.9	-49985.7	-53434.0	-75967
RMS gradient, (Kcal/ mol)	1.628	1.72	0.93	0.95	0.91
Binding energy, (Kcal/ mol)	-2267.34	-2552.30	-2833.00	-3113.6	-2618.02
Heat of formation, (Kcal/ mol)	-94.98	-104.85	-110.45	-116.05	-270.20
Electronic energy, (Kcal/ mol)	-213174	-243805	-274233	-306476	373639.75
Nuclear energy, (Kcal/ mol)	170090.9	197268.1	224247.55	253042.4	297672.78

Scheme-03					
Properties	MTIL01	MTIL02	MTIL03	MTIL04	MTIL05
Total energy, (kcal/mol)	-43084	-46539	-49986.20	-53435.00	-75967.70
Free energy, (Kcal/mol)	-43084	-46539	-49986	-53435	-75967
RMS gradient, (Kcal/ mol)	2.06	0.90	0.74	0.71	0.55
Binding energy, (Kcal/ mol)	-2267	-2554	-2833	-3114	-2618
Heat of formation, (Kcal/ mol)	-95.09	-106.87	-111.01	-116.70	-270.91
Electronic energy, (Kcal/ mol)	-210607	-239158	-270865	-303056	-369497
Nuclear energy, (Kcal/ mol)	167523	192619	220879	249620	293529

Scheme-05					
Properties	DPIL01	DPIL02	DPIL03	DPIL04	DPIL05
Total energy,(kcal/mol)	-60372	-67075	-74377	-81273	-126380
Free energy, (Kcal/mol)	-60372	-607075	-74377	-81273	-126380
RMS gradient	5.60	5.49	4.45	3.27	2.15
Binding energy	-2274	-2641	-3607	-4167	-3217
Heat of formation	182.37	364.81	-50.26	-60.13	409.72
Electronic energy	-280392	-319706	-415628	-504075	-585737
Nuclear energy	220020	252630	341251	422802	459357

4.16.1 Entropy, Enthalpy and Heat of Capacity

Scheme-01

Entropy

Heat of Capacity

Enthalpy

Entropy, Enthalpy and Heat of Capacity

Scheme-02

Entropy

Heat of Capacity

Enthalpy

Entropy, Enthalpy and Heat of Capacity

Scheme-03

Entropy

Heat of Capacity

Enthalpy

Entropy, Enthalpy and Heat of Capacity

Scheme-04

Entropy

Heat of Capacity

Enthalpy Entropy, Enthalpy and Heat of Capacity

Figure 31: Entropy, enthalpy and heat capacity

4.16.2 Characterization by UV spectroscopy

From computational study, the UV spectra were evaluated while a sharp absorption was in 200 to 215 nm wavelength shown in figure 41.

AIL

DPIL

OTIL

MTIL

Figure 32 : UV Spectra

4.17 Biological Activity

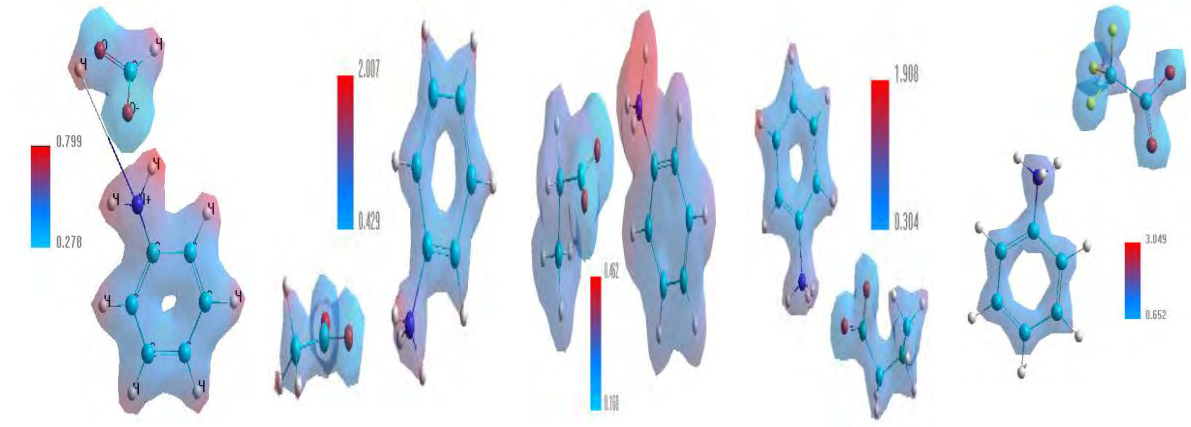
4.17.1 The electrostatic potential Charge Distribution 3D mapped

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 figure 42. 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.

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 [145]. 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.

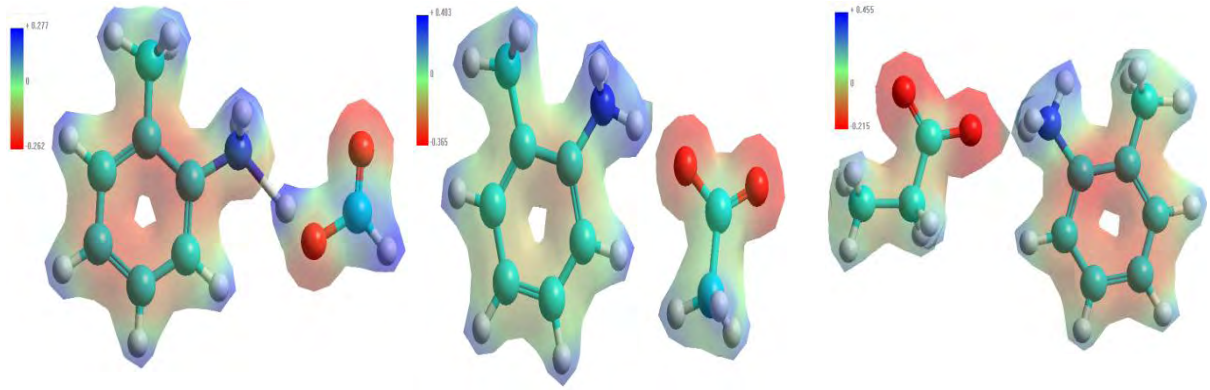
Scheme-01

AIL01 AIL02 AIL03 AIL04 AIL05

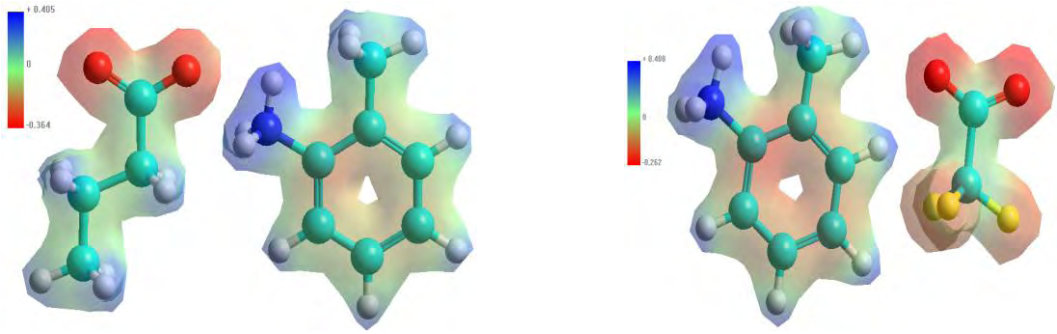


Scheme-2

OTIL-01 OTIL-02 OTIL-03

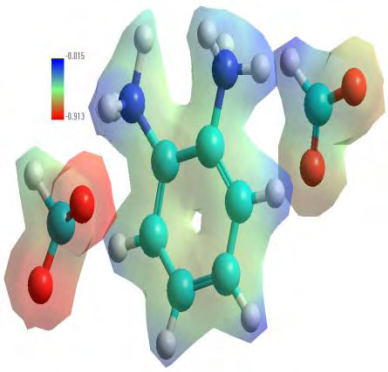


OTIL-04 OTIL-05

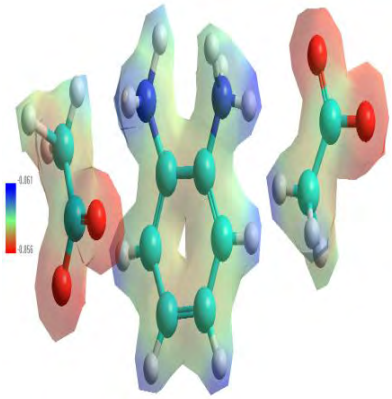


Scheme-3

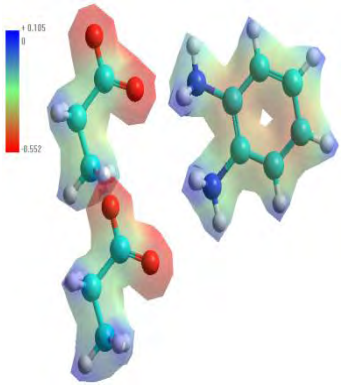
MTIL-01 MTIL-02 MTIL-03

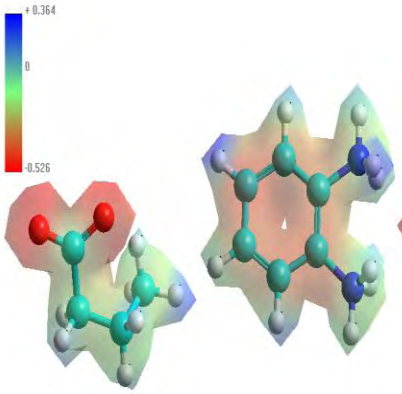


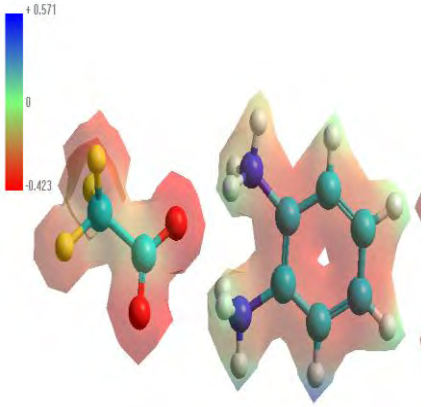
MTIL-04



MTIL-05





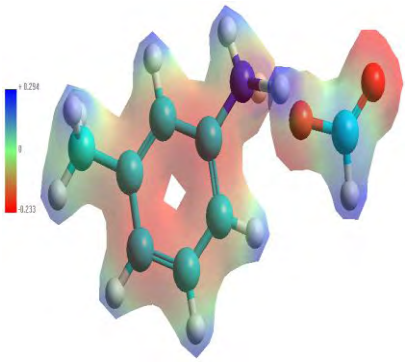


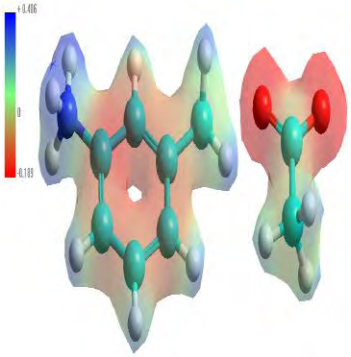
Scheme-4

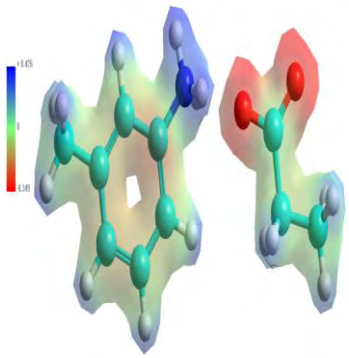
PTIL-01

PTIL-02

PTIL-03

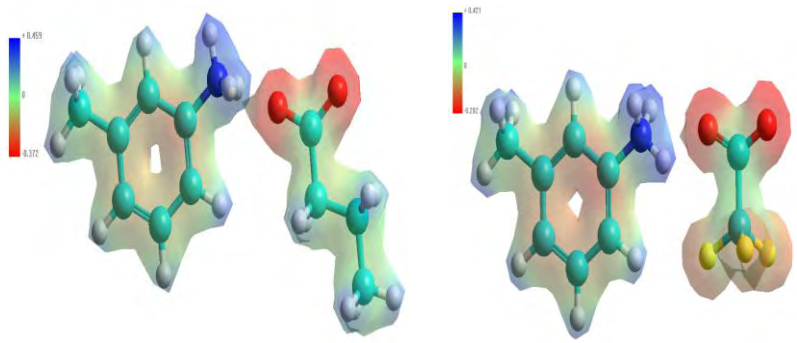






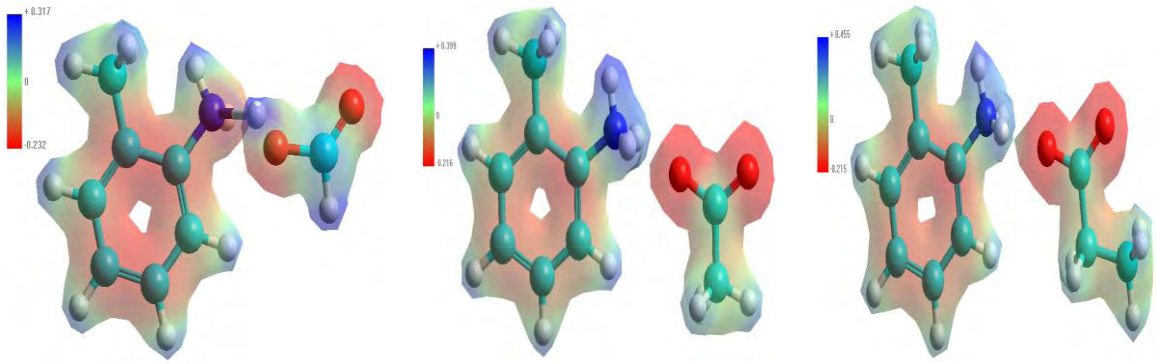
PTIL-04

PTIL-05



Scheme-5

DPIL-01 DPIL-02 DPIL-03



DPIL-04 DPIL-05

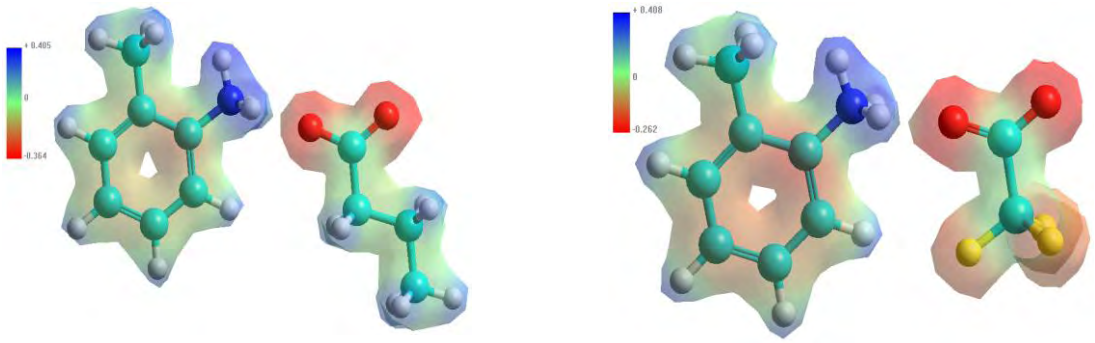


Figure 33: Electrostatic potential charge distribution in molecule

4.17.2 Quantitative Structure Activity Relationships (QSAR)

Table 28: Quantitative Structure - Activity Relationships (QSAR)					
Scheme-01					
	AIL01	AIL02	AIL03	AIL04	AIL05
Partial charge (e)	0	0	0	0	0
Surface Area(grid),	340.91	383.89	406.93	424.60	401.38
Volume, $Å^3$	506.86	565.03	616.49	658.18	600.90
Hydration Energy	-9.10	34.43	-30164.4	-35921.3	28354.43
Log P	0.77	1.07	1.07	-1.08	1.10
Refractivity, $Å^3$	40.90	45.50	50.25	54.68	47.32
Polarizibility, $Å^3$	14.09	15.92	17.76	19.59	15.65
Mass (amu)	139.15	153.18	167.21	181.23	207.15

Scheme-02					
	OTIL01	OTIL02	OTIL03	OTIL04	OTIL05
Partial charge (e)	0	0	0	0	0
Surface Area(grid)	355.48	382.09	417.23	446.01	402.47
Volume, $Å^3$	537.47	586.97	646.43	701.62	618.14
Hydration Energy,	-7.69	857.47	2748.47	-682231	2578.12
Log P	0.44	1.05	1.23	-0.76	1.08
Refractivity, $Å^3$	45.12	49.28	53.98	58.69	51.10
Polarizibility, $Å^3$	15.92	17.76	19.59	21.43	17.48
Mass (amu)	153.18	167.21	181.23	195.65	221.18

Scheme-03					
	MTIL01	MTIL02	MTIL03	MTIL04	MTIL05
Partial charge (e)	0	0	0	0	0
Surface Area(grid),	359.15	391.01	419.76	448.87	408.18

Volume, $Å^3$	542.91	598.94	651.82	704.86	626.73
Hydration Energy, kcal/mol	-8.26	1901.60	7510.0	-48727	5622.7
Log P	0.44	1.05	1.23	-0.76	1.08
Refractivity, $Å^3$	45.12	49.28	53.98	58.45	51.10
Polarizibility, $Å^3$	15.92	17.76	19.59	21.42	17.48
Mass (amu)	153.18	167.21	181.23	195.26	221.8

Schem-05					
	DPIL01	DPIL02	DPIL03	DPIL04	DPIL05
Partial charge (e)	0	0	0	0	0
Surface Area(grid)	539.42	672.34	538.32	586.26	704.78
Volume, $Å^3$	770.43	910.61	886.31	983.25	946.79
Hydration Energy	-12.25	-379.7	-776.0249	-3122.065	-7629.56
Log P	-0.25	0.56	0.14	-4.12	0.25
Refractivity, $Å^3$	50.62	58.98	68.46	77.41	62.68
Polarizibility, $Å^3$	17.74	21.42	25.08	28.75	20.86
Mass (amu)	200.19	228.25	256.30	284.36	336.19

4.17.3 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 [146-151].

4.17.4 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.

4.17.5 Log P

A negative value of log P indicates the hydrophilicity and positive Log P indicates the hydrophobicity that plays 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 proteins and finally are often extensively metabolized. Therefore ideal distribution coefficient for a drug is usually intermediate not too hydrophobic nor too hydrophilic.

4.18 Conclusion

To summarize, an investigation of the confirming of ammonium cations containing an carboxylate ILs has been performed by semi- empirical calculations and validated by HyperChem software. The physio-chemical and thermochemical properties provide the information about their binding affinity, and biological activity. The HOMO, LUMO, HOMO LUMO gap, Hardness and Softness also provide the chemical reactivity of ILs. On the other hand, the QSAR data shows that all ILs are biological active and antibiotic which is similar with experimental data.

SUMMARY AND COMPARISION OF STUDIES

The summary of this study is concluded as following as

- Twenty five bioactive ammonium carboxylate ILs were synthesized.
- This study composes of five reaction schemes for synthesis.
- This synthesis was carried on without solvent as reaction medium.
- The anilinium and 1, 2- diammoniumphenyl carboxylate was synthesized in comparatively lower times.
- All ILs show the biological activity.
- It was deduced that with increasing alkyl chain, the biological activity was increased for all schemes.
- From the biological activity in case of antibacterial, the MIC was found about 250 mMol/Litre concentration.
- For antifungal and phytotoxicty, among all ILs, the diphynylammonium carboxylate ILs could show high biological activity.
- From computational approach, the chemical stability and thermo-physical properties were increased with going up the alkyl chain.
- The number of anions chain and substituent group in cation chain of ILs could play the important role in biological activity and chemical reactivity.

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