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REVIEW ARTICLE **OPEN ACCESS**

Recent Development and Pharmaceutical Significance of Imidazole Based Ionic Liquids

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ABSTRACT
Objective: *Ionic liquids and silver (Ag-NHC) complexes synthesized from Ionic liquids are a potent analogue shows excellent antimicrobial activity. Some researchers would synthesize novel ILs with imidazole leads, then test them for antimicrobial activity against some bacterial strain. Another major application of metal N-heterocyclic carbenes would be as best possible alternative to existing cytotoxic drugs like cisplatin in treatment of cancer. These analogues work selectively on cancer cells rather than normal cells.Novel analogues of ILs have significant therapeutic importance as anticancer, antimicrobial, mostly antibacterial drugs. The potential ILs would be study worldwide for their antimicrobial and cytotoxic activities. Imidazole-based ionic liquids and silver NHC-complexes have been synthesized are being used as antimicrobial, cytotoxic and many more applications. The increasing applications of ILs in the pharmaceuticals and new drug development fascinating researchers in recent years. This review covers the medical and pharmacological approach, as well as other significant applications of ILs in a variety of sectors.*
Keywords: *Antimicrobial activity, Ionic liquids, silver-N heterocyclic carbenes.*

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INTRODUCTION

These are chemical entity comprising solely ions with melting points below 100 °C. The Paul Walden reported the first ILs in 1914 as ethyl ammonium nitrate, and ILs would be actively explored and a popular scientific topic for nearly a century. Basically, ILs are advanced novel fluids have fascinated extensive attention since the past two decades. ILs categorised into many types by its chemical nature as, Task specific ILs (TSILs), Room temperature ILs (RTILs), Poly ionic liquids (PILs), Chiral ionic liquids, Supported ionic liquid [1]. Ionic-liquids (ILs) has outstanding application in numerous areas of chemistry, including catalytic processes, solar energy cells, bio diesel, solvents for extraction, the electrochemistry, uses in medicine, and many others.[2–4]

Because of their charged nature, ILs and their equivalents have antibacterial activity due to breaking of interactions between molecules. This results in alterations in cellular permeability and cell content leakage.[5]Metal-NHC complexes based on silver (Ag) and gold (Au) have strong bactericidal characteristics. In 1973, Silver Sulfadiazine (SSD) was licenced by the USFDA to treat serious injuries like burn shows wide spectrum of activity against many bacterial strains [6–8]. An imidazole and morpholine-containing salts also their silver-NHCs are explored to have good antibacterial activity[9].ILs and their Ag-NHC counterparts were investigated for cytotoxicity on a human colorectal cancer cell line and found to be effective[10]. When cisplatin was found and licenced by the FDA as an anti-cancer agent for successful therapy in variety of cancers of lung ovaries, breast and prostate researchers became fascinated with metal complex-containing medicinal molecules. Unfortunately, cisplatin has some serious adverse effects like ototoxicity, nephrotoxicity and low blood counts and many more [11].As a result, cisplatin is used as a prototype compound in the discovery and development of new drugs. In this direction researchers were discovered auranofin molecule which has potent anticancer activity comprised of antimitochondrial effects this leads to explore the various metal-based drugs for cancer treatment [12–16].

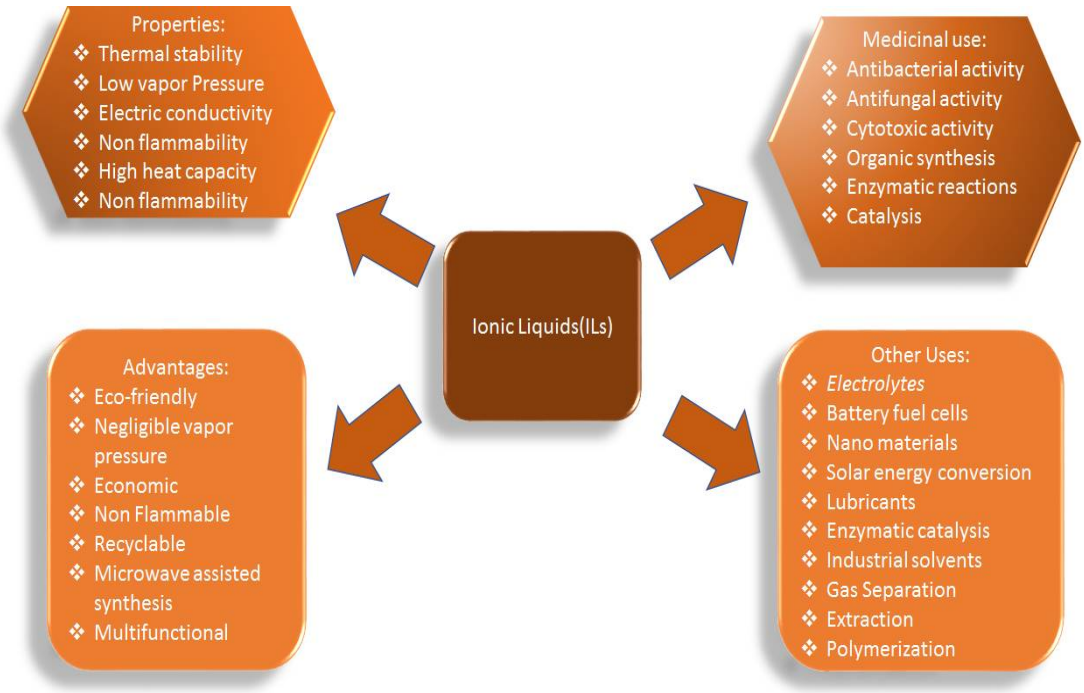


Figure 1: Graphical abstract of Ionic liquids

Structure activity relationship:

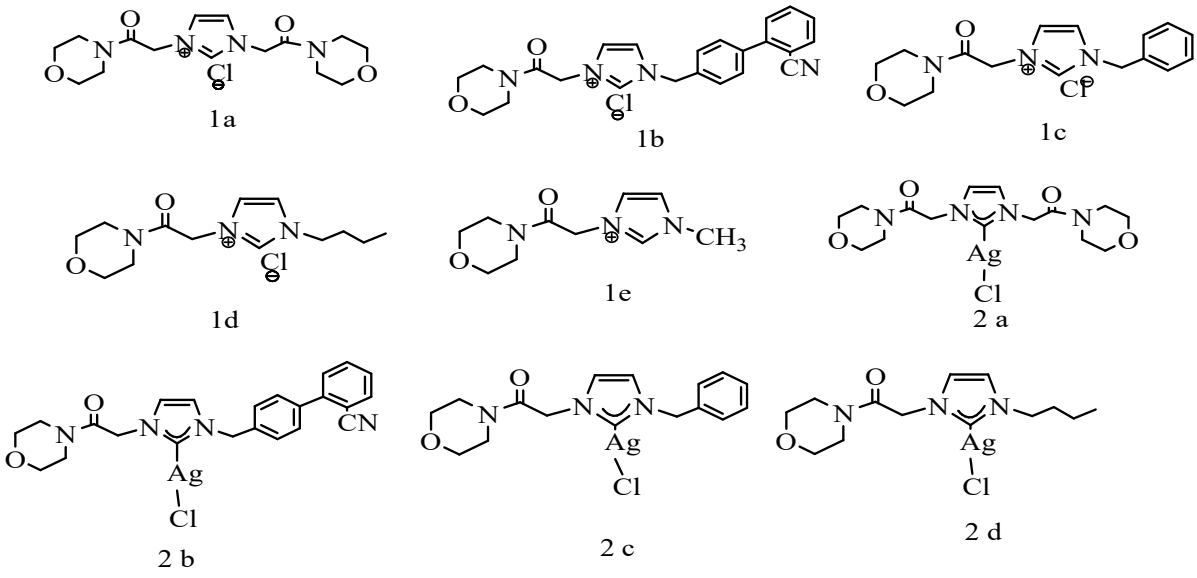
A) Ionic liquids (ILs) and Ag–NHC complexes synthesis evaluation for antimicrobial activity. **Method 1: Derivative 1a:** In RBF, 2-chloro-1-morpholinoethanone (4.89 g), imidazole (0.68 g), and K_2CO_3 (1.38 g) were refluxed by using solvent acetonitrile about 8 to10 hours. Acetonitrile was taken out by reducing pressure, followed by immersing the residue in dichloromethane before filtration. The excess of dichloromethane was removed and residue then re-suspended in acetone. Acetone was then extracted to yield white hygroscopic powder. (Fig.1).

Derivative 1b-1e: N-substituted imidazole and 2-chloro-1-morpholinoethanone were dissolved in tetrahydrofuran (THF) in proportion equivalents (1:1 mol) and heated at 65^0C for about 48 hours, followed by cooling and THF was decanted. Acetone was used for washing the sticky substance, yield hygroscopic white IL powder.

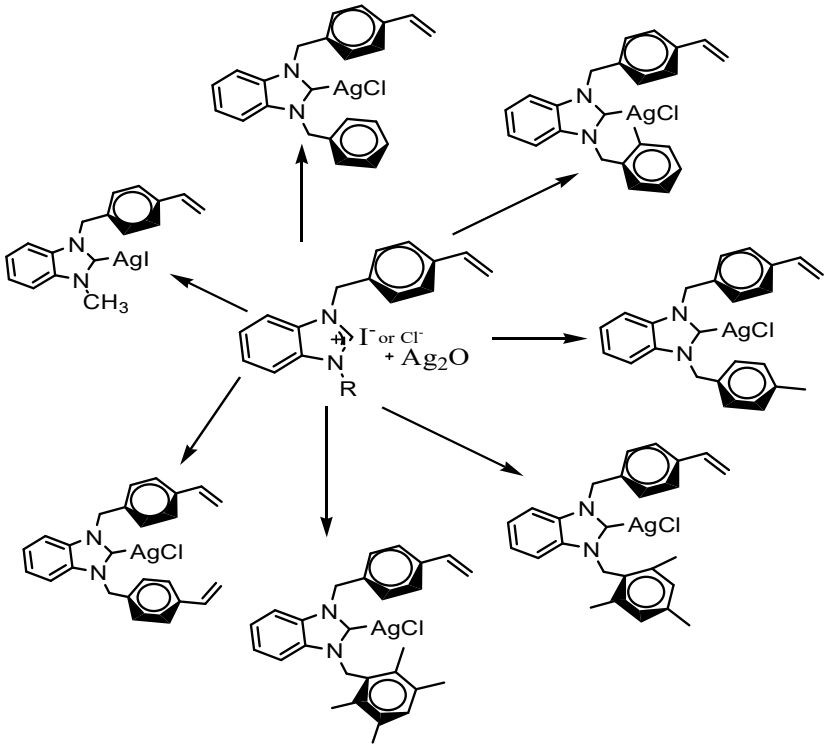
Derivative 2a-2e: Further the imidazolium salts (1b-1e) and Ag_2O were stirred in dichloromethane for 3–4 hours in the dark, followed by filtration over celite. This reaction mixture has been stirred with n-Pentane to generate solid Ag-NHCs. Excess solvent was removed and residual solvents were removed by decreased pressure to get fine powder of silver-NHC complexes [17](Scheme1).

These new imidazolium salts also their Ag-NHCs were synthesized and screened against species as *S. enterica* and S. *aureus*. Many of these tested analogues exhibited a considerable antibacterial action.

Method 2: Some new silver-NHC complexes containing 4-vinylbenzyl substituents. were synthesized and explored for antimicrobial action. These compounds were formed by treating various benzimidazolium-salts and silver oxide using solvent as a DCM at RT. (Scheme2). The new silver-NHC complexes containing 4-vinylbenzyl substituents were synthesized explored to various biological activities. These complexes exhibited strong antibacterial action, primarily against *C. tropicalis,* as well as antifungal efficacy against *C. albicans.* All these synthesized novel compounds were explored for the biological activities. These analogues were shown to have antibacterial activity against *E. coli,P. aeruginosa*, *E. faecalis*, *S. aureus* and also antifungal activity on *C. tropicalis and C. albicans*[18]



Scheme 1: Scheme for synthesis of ILs, Ag-NHC complexes



Scheme 2: Some new silver-NHC complexes containing 4-vinylbenzyl substituents

Figure 2:Some silver-NHC complexes

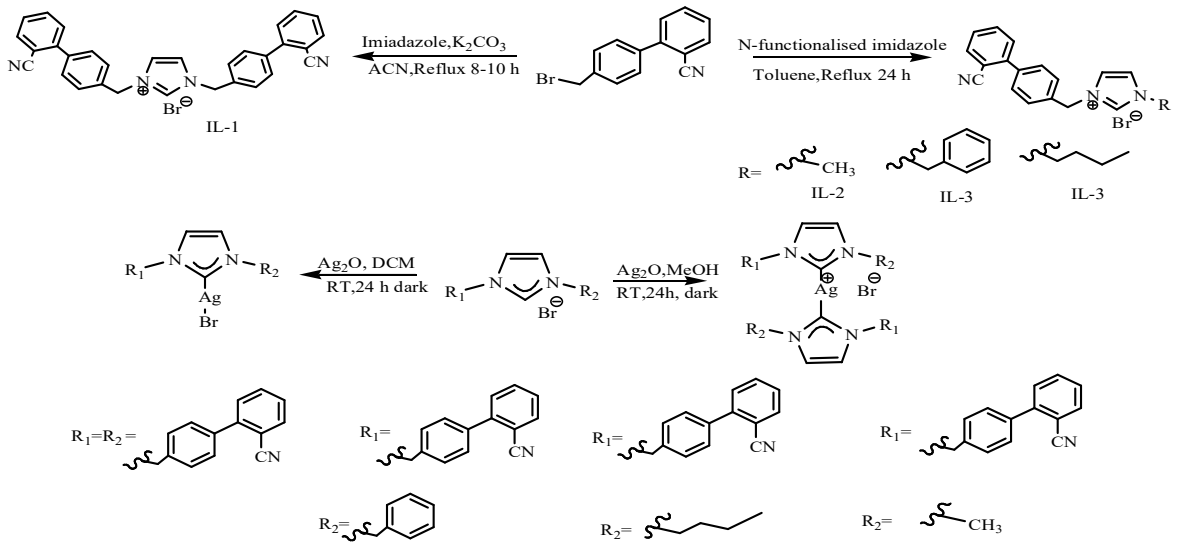
Methods 03: Ionic liquids (ILs) which are Imidazole-based and their silver complexes were synthesized[19]. (Scheme3)This novel analogue was screened for antibacterial activity. Some of analogues were inhibiting microbial growth against *S.aureus* and *S.enterica* showing bacterial growth inhibition for about 21 days.

Methods 04: Disubstituted imidazolium chlorides analogue 1,3-dialkoxymethylimidazolium chloride serve as important precursors used to prepare symmetrical ILs[20]. (Scheme4)These methods utilised one step procedure for synthesis ofdisubstituted ILs with potent analogues having antimicrobial activity as well as anti-electrostatic effect.

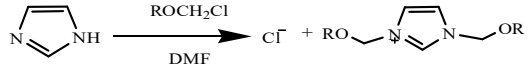
Methods 05: functionalised Ionic liquids with hydroxyl group, they had utilized one phase method of producing uniform monodisperse crystalline silver nanoparticles in aqueous medium prepared by combining mono and dehydroxylated ILs and cationic surfactants[21]. (Scheme5)

This hydroxylated silver nanoparticles stabilized by this salt were screened for certain bacterial and fungal strains by measurement of MIC (in µg/ml). Two series of stabilized Ag-nanoparticles were had potent bactericidal and fungicidal activity.

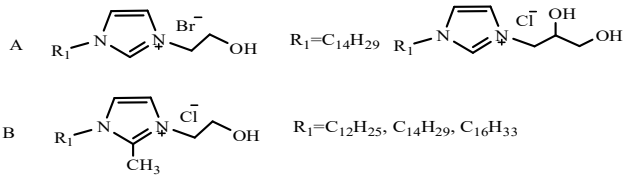
Methods 06: Novel imidazole and triazole containing ILs were synthesized by three step procedure. Triazole or Imidazole reacted with 1,2-butylene oxide followed by ring opening to get N-2-hydroxybutyl-1,2,4 triazole or N-2-hydroxybutylimidazole. This product was resolved by lipase-catalysed transesterification and finally optically active analogues were alkylated [22]. (Scheme6)The antimicrobial action of synthesized analogues was investigated. This ILs were tested against many bacterial strains, as well as eight fungus strains and many analogues found to be effective.



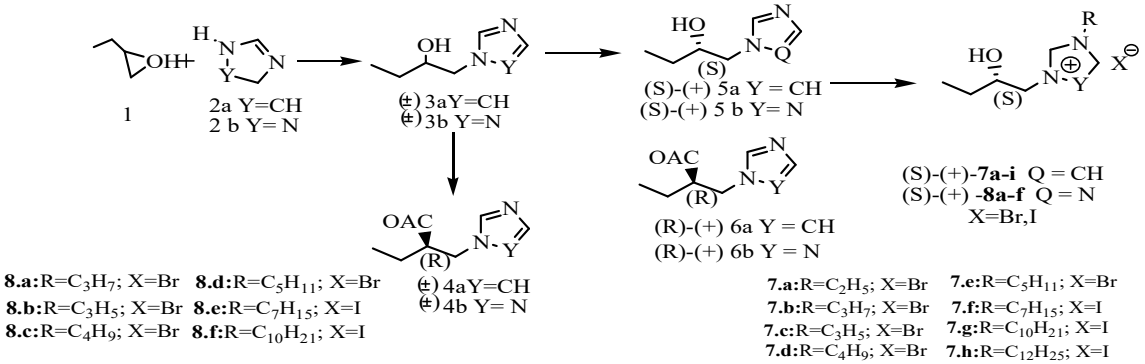
Scheme 3: Synthesis of Ag-NHC complexes



Scheme 4: Some symmetrical ILs



Scheme 05: Some functionalized Ionic liquids



Scheme 06: Some novel imidazole and triazole containing ILs

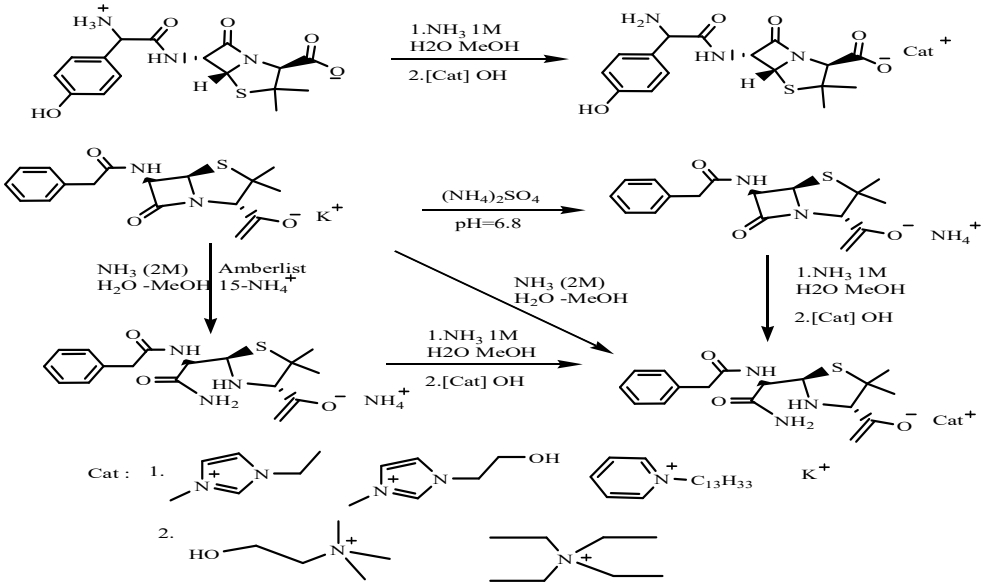
Figure 3:Synthesis of some novel ILs, NHCs

Methods 07: ILs and their organic-salts comprising penicillin-G (anionic) also amoxicillin hydroxylate analogues were synthesized. Eleven novel analogues as hydrolysed β-lactum OSILs were synthesized by precipitation with moderate yield incorporating neutralization of different cation hydroxide salts and basic ammonia buffer[23]. (Scheme 7)All synthesized analogues were tested in contrast to the extensive range of sensitive and resistant bacteria's like S*. aureus*, *E. coli* and *methicillin-resistantS. aureus.*

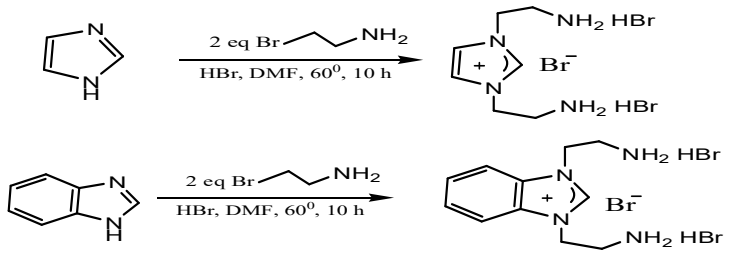
Method 08: Novel six different water-soluble NHC and ionic liquids (ILs were synthesized and tested for antimicrobial activity[24]. (Scheme 08) In this method all synthesized analogues were evaluated for

antimicrobial activity. These compounds were evaluated against some Gram positive bacterial strain as *S. aureus ATCC6538*, *E. faecium*, *B. subtilusATCC 168* also many Gram negative bacterial strain as *E.Coli*, *P.aeruginosa*, *S.typhimurium*, and some fungi as *C.krusei,C.tropicalis*and *C.albican*,

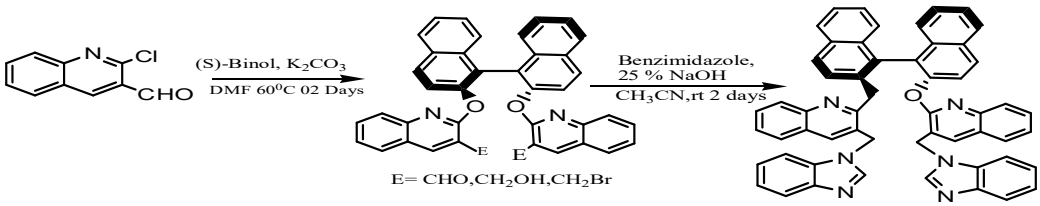
Method 09: The sequential steps were followed to prepare imidazole based chiral quinolinophanes as reaction of chiral dibromide with imidazole in basic medium yield precyclophane[25]. (Scheme 09)In this method all synthesized quinolinophanes were evaluated for antibacterial activity. These compounds were evaluated against some bacteria's like *S. aureus,P. aeruginosa*, *K. pneumoniae*, E*. coli,V. cholera* and *Shigella sp.*



Scheme 7: Synthetic Methodology for ILs & OSILs



Scheme 08: Method to develop NHCs (symmetrical salts)



Scheme 9: Synthesis of Quinolinophanes

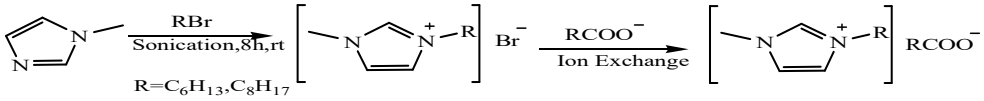
Figure 4:Methods for synthesis ILs and NHCs

Method 10: Many new imidazolium containing carboxylate ILs compounds synthesized by solvent less ultrasound supported reaction as quaternization of 1-methylimidazole with alkyl-bromide followed by ion exchange method mainly anions as some selective carboxylate, cinnamates, salicylates and oxalate[26]. (Scheme 10)In this method all synthesized compounds were tested against fungi like *C. albicans* with MIC less than 1%. Some of the crotonate and oxalate compounds in this series have the lowest cytotoxicity.

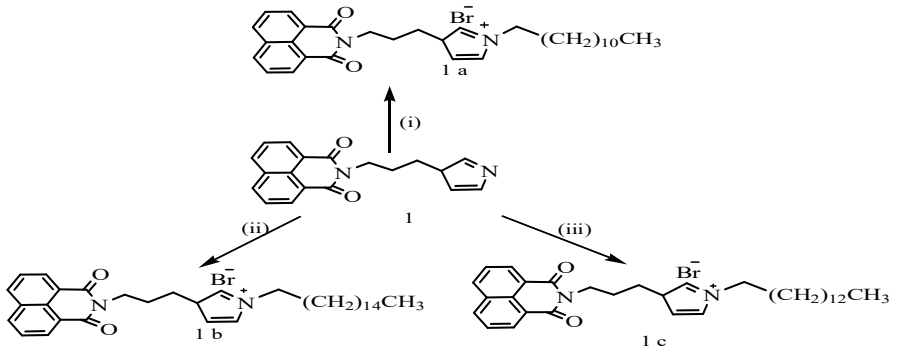
Method 11: Novel analogues comprising different length of alkyl side chains (Imidazolium bromide salts) which are water soluble ILs were synthesized. In this process, Imidazole bromide salt and 1,8 naphthalene was dispersed in chloroform, followed by gradual addition of alkyl bromide providing continuous stirring then refluxed for overnight[27]. (Scheme 11)In this method all synthesized novel imidazolium bromide

salts with different length of alkyl side chains were evaluated for antimicrobial activities by measuring MIC values for many bacterial strains. These imidazolium analogues were found most effective for antibacterial activity.

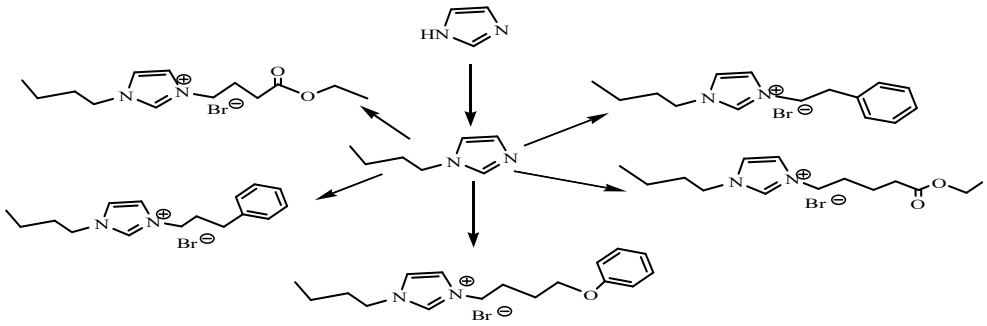
Method 12: Novel functionalized 1-alkyl-3-butylimidazolium ILs were synthesized by an effective green ultrasound assisted method. The conventional synthesis include treatment of imidazole with butyl bromide and acetonitrile with K_2CO_3 /KOH was yield the 1-butyl-1H-imidazole. Subsequently butylimidazole analogues were synthesized by selecting appropriate alkyl bromide with toluene at 80^0C for 18 hours. Further superior ultrasound method was applied to synthesize ILs. In this method butylimidazlium based analogues were synthesized by irradiation of ultrasound in closed vessel containing reactants and reagents[28]. (Scheme 12) In the formation of ILs the superior method was utilised ultrasound irradiation compared with conventional synthesis of ILs. All of these synthesized analogues were tested for antimicrobial and cytotoxic activities. These new analogues shown appreciable antibacterial action against many bacterial strain as *E.Coli, B.Subtilus, K.Penumoniae, P.aeruginosa* also antifungal activity against *S. recemosum, A.fumigatus G.candidum* and *C.albicans*. These compounds also had appreciable cytotoxic activity tested on tumor cell lines.



Scheme 10: Synthetic route for Carboxylate Ionic liquids



Scheme 11: Water soluble ILs as Imidazolium bromide analogues



Scheme 12: Synthetic route 1N-alkylation of N-butylimidazole by convetional preparation also by ultasonic radiation conditon i) R-Br/C.P or U.S : [convetional preparation,C.P: Toluene, 800c18h], [ultasonic radiation,US: toluene, 80 0c 5h] R= -(CH2)3CO2Et

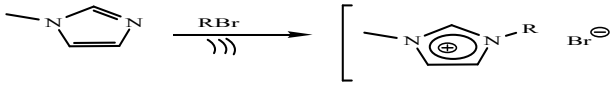
Figure 5:Synthesis methodologies for ILs and NHCs

Method 13: New scaffold 1-alkyl-3-methylimizolium bromide were synthesized by solvent less sonochemical method. New analogues of 1-alkyl-3-methylimizolium bromide ILs were synthesized by ultrasound irradiation on 1-methylimidazole and alkyl-bromide with solvent free environment. Desired products were obtained with higher yields under mild conditions[29,30]. (Scheme 13) In vitro evaluation for antifungal activities was carried out for all synthesized compounds. ILs found to be effective against *C. albicans* also bear antimycotic activity.

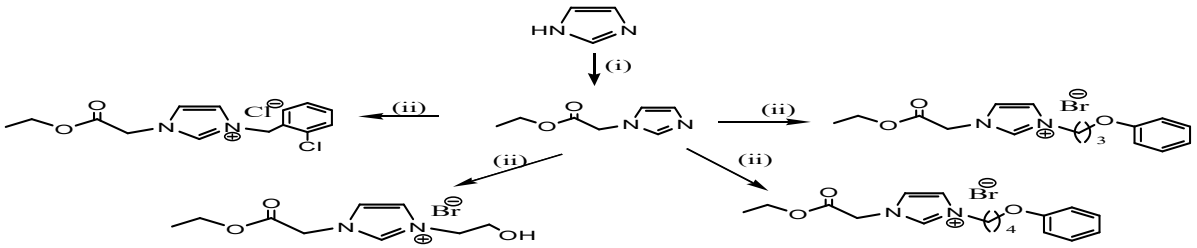
Method 14: Development an efficient method to synthesized 1-(2-alkoxy-2-oxoalkyl) imidazolium ILs analogues was employed. The series of new ILs synthesis utilized alkylation reaction between 2 substituted imidazolyl acetate and numerous alkyl halides by using microwave radiation with good yield.[31](Scheme 14)The nitrogen containing, functionalized imidazolium based ILs were evaluated in vitro against

pathogenic *S.aureus*, *B.subtilis* and *E.Coli*. Also, these newly synthesized compounds were tested against fungi *C. albicans*.

Method 15: New series of imidazolium containing ILs were synthesized by conventional and microwave irradiation methods. This is an environment friendly, simple method to synthesize RTILs by means of both methods as described in the scheme 16. New hexylimidazolium derivatives were synthesized by using of 1-substututed imidazole with 2-bromoalkyl benzene and 1-haloalkyl benzene with toluene at temperature 80^0C for about 18 hours[32][32]. (Scheme 15) The functionalised ILs prepared by both conventional and microwave irradiation method were evaluated against many bacterial strains. Among these novel ILs some of them with phenyl or alkyl group finds efficient antibacterial agent.

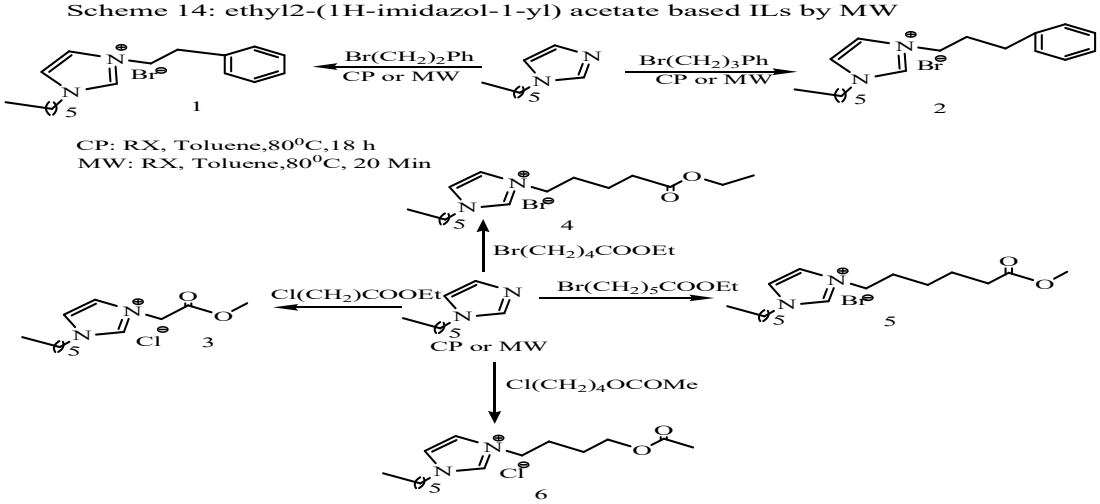


Scheme 13: Solvent free synthesis of -alkyl3-methylimizolium bromide ILs by ultrasound irradiation.



i) : Ethyl chloroacetate ,t-BuOK,CH_3CN, 80^0C 40h ii):R-Br/Cl,8Toluene 0^0C 20 min

Scheme 14: ethyl2-(1H-imidazol-1-yl) acetate based ILs by MW



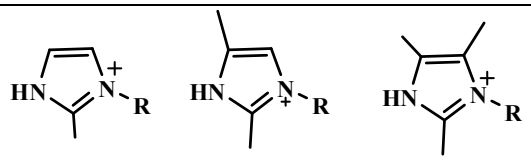
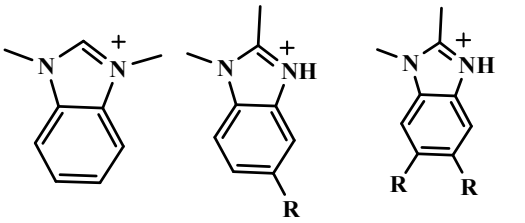
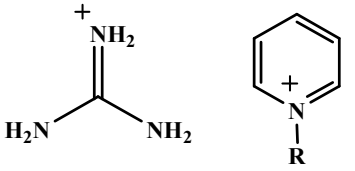
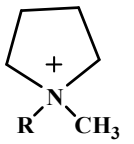
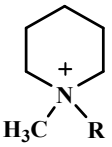
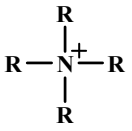
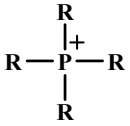
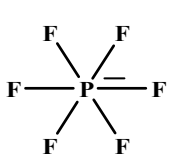
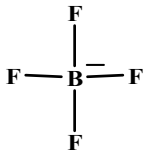
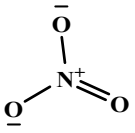
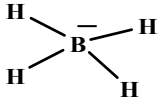
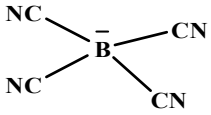
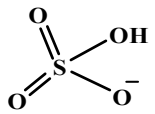
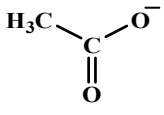
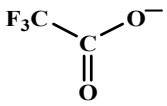
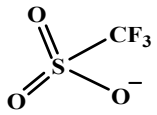
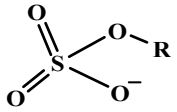
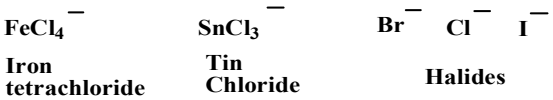
Scheme 15: Synthesis of new ILs with alkyl side chain

Figure 6:New methods for synthesis of ILs and NHCs

Cations and anions used in the formation of ionic liquids:

ILs (Ionic liquids) are union of liquid phases and its ionic nature allows for the development of an extensive array of physical and chemical properties. ILs are fused or molten- organic salts exist as liquids at the temperature less than 100^0c.This ILs have bulky, asymmetrical cationic nature and weak directing anions that destabilise the crystalline structure. Ionic liquids have a molecular structure formed by various anions and cations. The cations are typically organic compound having positive charge whereas anions are significantly smaller than cations (negative charge) also have an inorganic element in it[33].

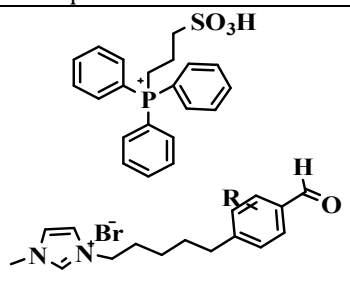
Table 1:Frequently utilized Cations and Anions for Ionic Liquid Preparations

Cations	Anions
 Imidazolium ILs  Benzimidazlium ILs  Guanidinium Alkylpyridinium  Alkylmethylpyrrolidinium  Alkylmethylpyridinium  Ammonium  Phosphonium	 Hexafluorophosphate  Tetrafluroborate  Nitrate  Tetrahydroborate  Tetracyanoborate  Hydrogen sulfate  Acetate  Triflurocaetate  Trifluromethane sulfonate  Alkyl sulphate  Iron tetrachloride; Tin Chloride; Halides

Structural Classification of ILs:

Based on cation and anion combinations and unique biological, physical, chemical, and thermal characteristics such miscibility in aqueous and organic solvents, ionic conductivity, comparative acidity or basicity, among others, ILs are classified into a variety of categories.

Table 2:Types of ILs, Including Task specific ILs, Chiral ILs, Bio- ILs, Poly- ILs with their applications.

Sr.No	Type of ILs	Example	Application
1	Task specific ILs	 Some task specific ILs	TSILs are discussed in detail, with a focus for their use in mainly as synthesis of organic compounds, catalysis process, and nano-particle production[34].

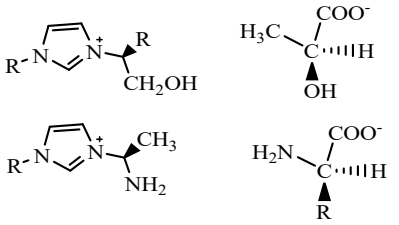
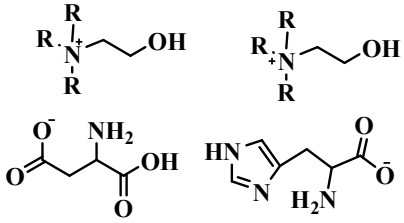
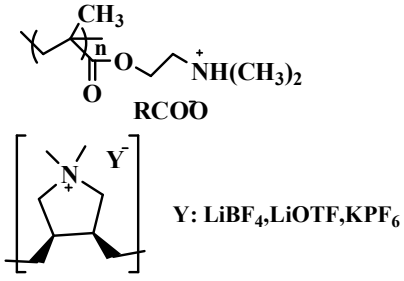
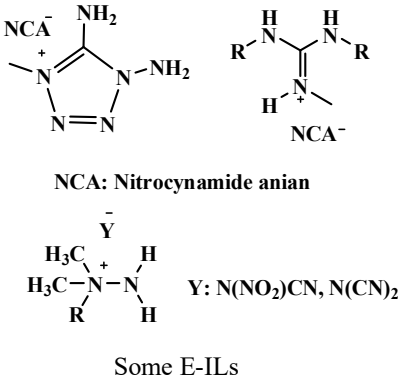
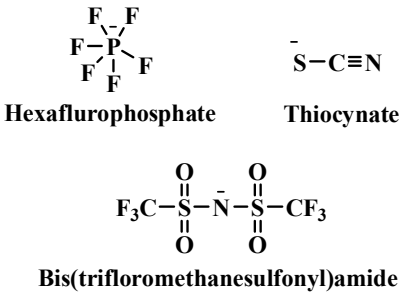
2	Chiral ILs	 Chiral ILs	These ILs serve as catalysts or solvents for chiral chemical asymmetric synthesis[35].
3	Bio- ILs	 Choline based B-ILs	Bio-ILs have been widely employed in ion gel formulations, used in electrochemistry as sensors and modulators, as well as in the biomedical field [36].
4	Poly- ILs	 Some Poly ILs	These polymeric core of ILs like dimers, trimers, oligomers.[37–39]This ILs have many applications as polymer, electrolytes[40,41], membranes for fuel cells[42,43], electrolytes for batteries[44,45], carbon electrodes and sensors[45–47], battery binders[48], photo-responsive materials [49,50], P-IL based antimicrobial materials [51–53], corrosion inhibitors.[54–56]

Table 3:Types of ILs, Including Energetic ILs, Neutral ILs, Protic ILs with their applications.

Sr.No	Type of (ILs)	Example	Application
1	Energetic ILs	 Some E-ILs	Lanthanide-based E-ILs have good to outstanding photochemical stability as well as luminescence characteristics [57]. Anions and cations of hypergolic ILs explored and found this IL has an important role in ignition and combustion, whereas cation plays a small function [58].
2	Neutral ILs	 Counter Neutral anions	N-ILs have a high electro-chemical and thermo-stability, thus commonly used as nuetral solvents in a broad range of open windows.[59–62]

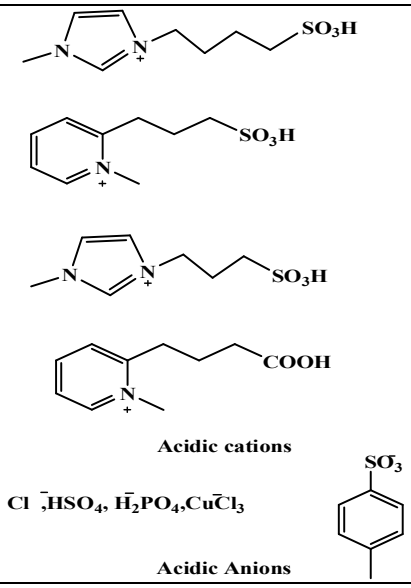
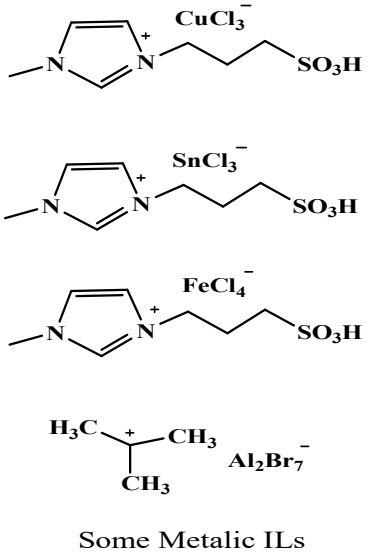
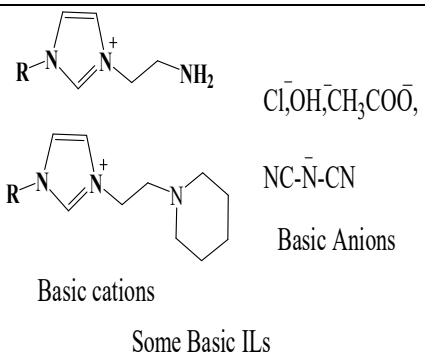
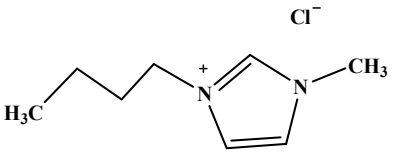
3	Protic ILs		Protic ILs are distinguished due to existence of reversible acid protons. Therefore, this can be utilized as a solvent or a catalyst in a wide range of reactions, including hydrolysis, dehydration, fuel chemistry,.[63,64].

Table 4:Types of ILs, including Metallic ILs, Basic ILs, Supported ILs with their applications

Sr.No	Type of ILs	Example	Application
1	Metallic ILs		The usage of metal-containing ionic liquids in electrochemical applications [65].
2	Basic ILs		This ILs substituted frequently used basic inorganic salts also used in organic reactions such as addition reactions (Michael, and Markovnikov), Aza-Michael reactions, Aldol reaction, etc[66–68].

3	Supported ILs	 Imidazlium based ILs immobilized on supoort (silica SBA-15)	This ILs become very effective and least expensive material for the carbon dioxideand methane separation process[69].

CONCLUSION

Ionic liquids are a fascinating substitute to the numerous widely employed compounds in organic synthesis reactions, solvents, acids, bases. ILs have distinct properties such as non-corrosive, green and eco-friendly natures, as well as a flexible nature with excellent biological, thermal, chemical and physical properties that provides varying combinations of cations and anions ratios resulting into extended industrial and academic applications in recent years.

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CONFLICT OF INTEREST

There is no conflict of interest, according to the authors.

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