Journal of Molecular Structure 1245 (2021) 131087

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstr

Synthesis, characterization, antimicrobial activity and computational exploration of ortho toludinium carboxylate ionic liquids

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ARTICLE INFO

Article history:
Received 22 April 2021
Revised 6 July 2021
Accepted 9 July 2021
Available online 17 July 2021

Keywords:
FTIR
Antimicrobial activity
Well-diffusion method
DFT
HOMO
LUMO and Docking

ABSTRACT

As Ionic Liquids (IL) was considered as designer molecules for use in chemical and biological sectors, its demands and researches have been increasing day by day. To design new ILs and evaluate its antimicrobial activities, the ortho-toludinium carboxylate ionic liquids (OTILs) were synthesized through the Brønsted acid-base neutralization reaction between ortho toluidine and carboxylic acids with yields (74 to 88)%. The synthesized OTILs were characterized by FT-IR, UV and ^{1}H-NMR, which had confirmed their conversion of the reaction and their structure. The eight human pathogenic bacteria were used for antibacterial screening, as well as three antifungal activities had estimated against three fungi. However, the synthesized ILs showed the good result to antimicrobial activity against both bacteria and fungi. Due to show high antimicrobial activity, MIC was performed against two bacteria whereas the MIC had found the range 250 to 500 mM. Furthermore, density functional theory (DFT) had used for determining the HOMO, LUMO and chemical reactivity descriptors for the computational investigation of OTILs, as well as molecular docking screening had performed against three pathogens. By the molecular docking score as binding affinity and chemical descriptors, the effect of alkyl chain and electronegative atom in anion had direct contribution on antimicrobial activity which was the similar result from the experimental data of antimicrobial activity. Finally, attaching Fluorine atom in anion could show the highest antimicrobial activity and docking score among chlorine, bromine, iodine even alkyl chain.

1. Introduction

ILs, a fascinating class of materials for concurrent era, composes of discrete cation and anion. Initially, it was synthesized in 1914 as ethanolammonium nitrate for commercial use in electrochemical applications, especially in non-volatile electrolytes for batteries [1]. Afterwards, it was attracted to research for its tunable chemical and thermophysical and chemical properties, such as high ionic conductivity and a wide electrochemical window [2], good thermal stability [3], low flammability [4], tunable polarity, solvation power for organic [5] and inorganic compounds [6], surface activity [7], low melting point and negligible vapor pressure [8]. Due to its desirable properties, ILs was used in membrane development [9], reaction catalyst [10], biochemistry [11], bioorganic process or engineering [12], chemical process [13], organic synthesis [14], electrochemistry [15], analytical chemistry [16], extraction of nano particles [17, 18], absorber of CO_2 and SO_2 [10]. With beginning of 21st century, ILs has considered as the alternative organic solvent or traditional reaction solvent in synthesis placing as green solvent [19, 20]. Besides, it was opened a new window for drug discovery in pharmaceutics and medicine [21] as bioactive molecules of anticancer [22], antimicrobial agents [23-27], antiviral [28, 29], antifungal and antiparasitic drugs [30, 31], anti-infective defense, as well as in the pharmaceutical and food industries, agrochemistry, artificial enzymes biocides and biotechnology [32, 33]. Regarding the biological activity, the phosphonium and ammonium-based ionic liquids have been used as potential molecules for treatment of cancer [34], insect detergents [35], blood and tissue preservatives [36], phenol degradation [37] wood preservatives [38], antibacterial agents, antiviral agents, antifungal agents, antiparasitic drugs and herbisides [39, 40] due to its low toxicity [41, 42]. Mainly, the chains, that can be connected to the central N^+ atom forming 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 ILs [43, 44]. Moreover, it was illustrated that alkyl chain was shown a vast antimicrobial potency in various infection diseases as that larger alkyl chain was illustrated the higher activity [45], and come to think of bifuctional group [46] or multi functional group [47]. It must be added that dicationic part of ILs can show a variable effect on microbial potency

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https://doi.org/10.1016/j.molstruc.2021.131087
0022-2860/

[48]. In addition, according to Holbrey and Rogers et al., reported the various factors with main importance on biological activity of ILs are the charge, size, alkyl chain, electronegative group and distribution of charge on the ions and small changes in the shape of covalent bonds with protein or micromolecules interaction, as well as its thermal properties [49-51]. One of the most recent fields by ILs to be explored is that of biologically active compounds [30, 52]. Thus, Smiglak et al. highlighted the potential use of ILs drug deliverers through the improvement of solubility of active pharmaceutical ingredients (APIs) proteins and amino acids in ILs with strong hydrogen bond acceptors [53] which had considered the 3rd generation ILs. Among of 3rd generation ILs, hydrophobic quaternary ammonium-based salts can show dual biological tasks, such as sweet and anti-microbial activity [54] that led to select the aniline base for acting the cation making ammonium ion in IL, called as the protic ILs (PILs), to estimate the antimicrobial agents of human pathogenic micro-organism. To kick off about the PILs, it is a sub-division of ILs which are easily synthesized by preparation formula of a Brønsted acid and a Brønsted base [55], and used as potential selective drug design and delivery system [56]. As a result, the quaternary ammonium-based ILs was chosen for investigation of study with organic alkyl chain and electronegative atom effect examination combining organic base as cations to produce ammonium salt with different types of organic acids as an anion. The ammonium-based ILs is introduced as new fields of bioactive against different bacteria, fungi, and plant and virus pathogen [57-59]. With experimental work, to evaluate the hydrogen bonding and hydrophobic bonding, the molecular docking was performed against the pathogens which were compared with the experimental data of antimicrobial activity. Before docking, chemical reactivity descriptors was estimated by DFT functional to say about its ligand acceptability in part of HOMO or LUMO and chemical stability.

2. Methodology and Experiment

2.1. Materials and reagents

The Formic acid, acetic acid, propanoic acid, butanoic acid, trifluroacetic acid, ortho toluidine, thin layer chromatography powder and agar media were analytical grade purchased and used without purification, but solvents were distilled before use. The bacterial and fungal strains were collected from the Department of Pharmacy in the University of Dhaka and conducted as sub culture before use each time. The FT-IR spectrophotometer, (Model: IRAffinity-1S and type Double beam) SHIMADZU, Japan, range 600-4500 cm^{-1} was used with KBr disc technique for taking the FTIR spectra. The work of synthesis, purification and analysis were done at the department of chemistry in Bangladesh University of Engineering and Technology (BUET), Dhaka-1000, Bangladesh. The antimicrobial activity was done at Pharmacy at University of Dhaka, Bangladesh. The ^1H NMR Spectroscopy (Bruker, 400 MHz, Switzerland, Model: Avance-III HD) was recorded in Jahangirnagar University, Bangladesh.

2.2. Synthesis and Purification of Ionic Liquids

The ortho toluidinium carboxylate ILs was synthesized by an acid-base neutralization reaction [60]. The base, ortho toluidine, was added with carboxylic acids under stirring maintaining low temperature by ice-bath around the round bottle flux. At first, the equimolar carboxylic acid was added in a slow by dropwise about 15- 20 minutes, maintaining the temperature. Then the mixture was stirred for 18-24 hours at room temperature until obtaining a clear, viscous liquid which was monitored by thin-layer chromatography (TLC). The reaction product was a viscous salt of ortho toluidinium carboxylate [60]. The ILs purification process consisted of a strong agitation and slight heating, at 100º C under pressure, under a vacuum of 20 KPa and found a limpid and viscous appearance liquid. The ortho toluidinium salt formation and their structure were confirmed by FT-IR spectra, UV spectra and ^1H NMR. The structure of synthesized IL is shown in the figure 3 and synthesized reaction scheme was presented in figure 1.

2.3. Characterization

For the characterization by ^1H NMR spectrum of ortho toluidiniumtrifluroaccetate (IL05) was accounted for the chemical shift at 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, $PhCH_3$). There was not presence any chemical shift at 3.55 ppm which was confirmed the absence of peak for -NH_2 group, and in case of the –COOH group, the original peak of that functional group was not shown at 11.42 ppm considering its conversion. However, the absence chemical shift at original peak region of –COOH and -NH_2 group pointed out the conversion into carboxylate groups and ammonium group in ammonium carboxylate ILs. For the fact of FTIR, the strongest peaks at about 3440 cm^{-1} (N-H) asymmetry and 3007 cm^{-1} (N-H) symmetry make available the existence of ammonium ion [61], on top of the another two peaks at 1760 cm^{-1} (C-O) asymmetry, 1655 cm^{-1} (-CO) symmetry prove the existence of carboxylate ion [62]. Finally, the FTIR spectrum of IL01, IL02, IL03 and IL04 were similar to ILs and confirmed their functional groups as ILs. Withal, the UV spectra for IL05 shows the similar absorption at about 240 nm wavelength which is almost same for IL01, IL02, IL03 and IL04.

ortho toluidiniummethanoate (IL01), [CH_3PhNH_3] [HCOO], M.W.: 153.0,Yield (%): 81.0%., Physical state: liquids, 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.

ortho toluidiniumacetate (IL02), [CH_3PhNH_3] [C_2OOH_3], M.W.:167.0, Yield (%): 78.0%., Physical state: liquids, 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.

ortho toluidiniumpropanoate (IL03), [CH_3PhNH_3] [C_3OOH_5], M.W.: 179.0,Yield (%): 77.0%., Physical state: semi-melted, 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 and 1612 (-CO) symmetry.

ortho toluidiniumbutanoate (IL04), [CH_3PhNH_3] [C_4OOH_7], M.W.: 195.0, Yield (%): 78.0%., Physical state: melted solid, 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 and 2596 ($PhNH_3^+$), 1622 (C-O) asymmetry, 1667 (-CO) symmetry.

ortho toluidiniumtrifluroaccetate (IL05), [CH_3PhNH_3] [$C_2F_3OOH_3$], M.W.: 221.0, Yield (%): 88%., Physical state: white solid crystal, 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. ^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, $PhCH_3$).

2.4. Antimicrobial test against bacteria and fungi

2.4.1. Preparation of IL solutions in different concentrations

For preparation of sample, the ILs sample was measured for preparation of mili-Molar (mM) solution with high level of accurately so that no impurities were obtained. Moreover, the five various solutions, such as 1000 mM, 750 mM, 500 mM, 250 mM, and

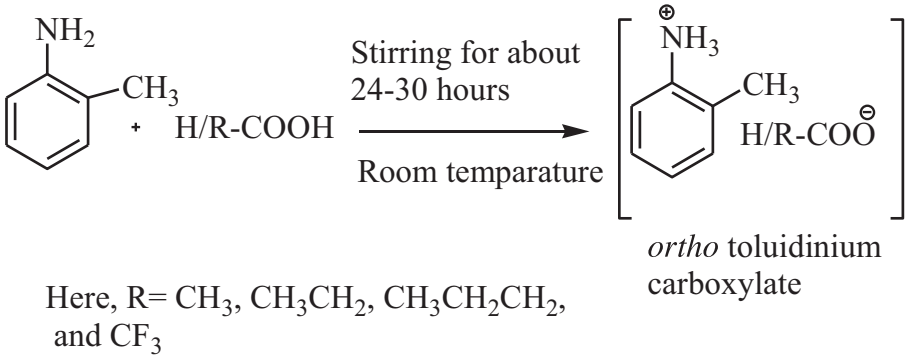

Fig. 1. Reaction scheme for synthesis

Table 1
Data of Zone of Inhibition for antibacterial activity

	IL-1	IL-2	IL-3	IL-4	IL-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
Pseudomonaaeroginosa(-)	13	12	14	16	22	0	0
Shigella dysenteriae(-)	12	11	14	18	22	0	0

125 mM, were prepared for determination of minimum inhibitor concentration (MIC).

2.4.2. Antibacterial test

A beginning examination for the antibacterial activities of pure ILs, well diffusion method taking 20 µL ILs solution in each well with concentration 1000 mM was executed for primary screening both gram-positive, Bacillus cereus, Staphylococcus aureus, Sarcina lutea and Bacillus subtilis, and gram-negative bacteria, Escherichia coli, Salmonella typhi, Pseudomonas aeroginosa and Shigella dysenteria [63, 64]. For this procedure the auto-clave (Systec V-40 and Systec V-55: 220-240 V, 50/60 Hz, 16A) was used for sterilized and this full work was done in Laminar flow [Model: HHS-1000/1300/1600/1800 (-U)] for removal of contamination. The zone of inhibition (including the well diameter 8.0 mili meter as mm) was measured in mm scale with consideration ±1.0 with all taking values. All the measurements were done in triplicate, and the average value was listed in table 1. The initial concentration was maintained for all ILs in 1000 mM distilled water. A control plate was always observed during working procedure by the solvent.

2.4.3. Antifungal test

In analogous ways, antifungal investigation against three phytopathogenic fungi, such as Aspergillus niger, Saccharomyces cerevisiae and Candida albicans, was finished from end to end well diffusion method. With beginning, the amount of 100 µL of ILs solution for 1000 mM was kept in petri plate before adding the freshly prepared media with well shaking for right proportion of mixing. After waiting about 30 minutes for solidification, the fungal strain was transferred in incubator for growing the fungal strain during 72 hours. Finally, the result was traced in mm scale, and this procedure was performed triplet time for avoiding errors.

2.4.4. Determination of MIC

The five subsequence concentrations, such as 1000 milimolar (mM), 750 mM, 500 mM, 250 mM, and 125 mM were taken for determination the MIC against two antibacterial stain and analyzed the recorded mean result using origin graph to calculate the MIC by graphical method.

2.5. Computational Methods

For molecular modelling and theoretical investigation, Material studio 8.0 (Accelrys, now BIOVIA 2019) [65] were used for molecular optimization and determination the chemical descriptor using DFT functional [66-69] of DMol code [70, 71]. Afterwards, the optimized structure was taken in to protein data bank (pdb) file for molecular docking as ligand. The molecular docking was performed by PyRx software using autodocking option by obtaining required condition to calculate the binding affinity while ILs was the ligand, and protein of pathogens as micromolecules. Then, the docking complex of ligand-protein was analysis by discovery studio [72]. Lastly, the ADMET was obtained the online data base admetSAR (http://lmmd.ecust.edu.cn/admetsar2/) [73] for calculating absorption, distribution, metabolism, excretion and toxicity parameters, and other online portal named SwissADME (http://www.swissadme.ch/) [74] was used to calculate the Lipinski rule.

To explain the chemical descriptors calculating from the computational tools using DFT functionals, the HOMO and LUMO are the crucial parameters which are used to calculate the ionization potential (I), electron affinity (A), energy gap, chemical potential, electronegativity, electrophilic index, hardness and softness by the following equations 1-8.

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

$$I = -E_{HOMO} \quad (2)$$

$$A = -E_{LUMO} \quad (3)$$

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

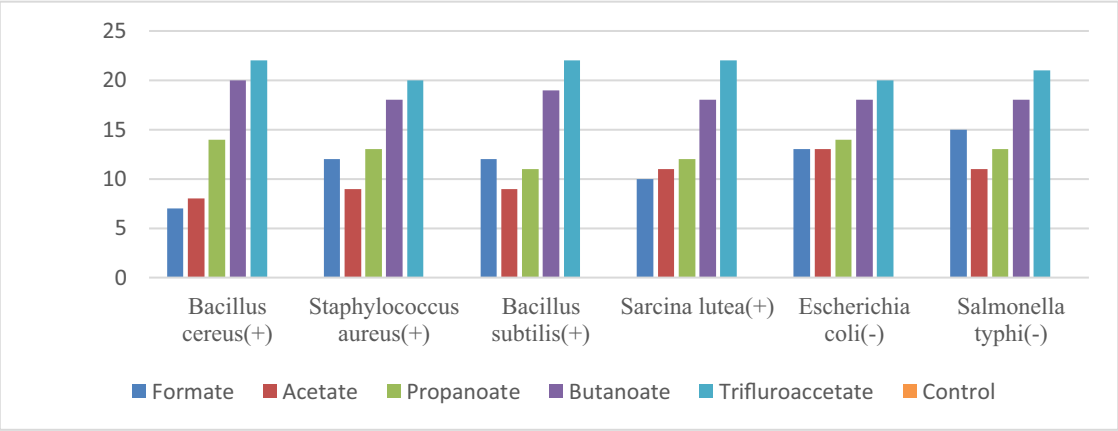

Fig. 2. Comparative study for anion on antibacterial activity

$$(\eta) = \frac{I - A}{2} \tag{5}$$

$$(S) = \frac{1}{\eta} \tag{6}$$

$$(\chi) = \frac{I + A}{2} \tag{7}$$

$$(\omega) = \frac{\mu^2}{2\eta} \tag{8}$$

3. Results and Discussions

The protic Ionic Liquids (PILs) consists of Brønsted acid and Brønsted base. In this study, the use acids, aliphatic carboxylic acids, as anion in ILs have considered the Brønsted acid and ortho toluidine acting as cation in IL has recognized as Brønsted based. According to that literature, the IL01-IL09 is called PILs, and reported their computational and biological study with in-silico study.

3.1. Antibacterial studies

To evaluate the antibacterial activity of synthesized five ILs, well diffusion method was performed for taking zone of inhibition in mm scale without 8 mm hole of well for 1000mM for ortho toluidinium based Ionic Liquids, and it was listed in table 1 while the four Gram positive bacteria and Gram negative bacteria was taken. It must be noted that there were no effect of the control and starting material (ortho toluidine), and when it was converted into ionic liquids by adding carboxylic acids, the antibacterial activity was increased.

From the table 1 and figure 2, it was shown that the zone of inhibition of IL05 is maximum both of gram-positive and gram-negative bacteria, showing about more than 20 mm while the IL04 was placed below the IL05 having about 17 mm. It could be concluded that the alkyl chain has an effect on antibacterial activity even the substituent group attaching with anion where electronegative atom (Fluorine) can show the height activity among others.

3.2. Antifungal activity

Regarding the antifungal analysis, the growth percentage compared with the control was illustrated by following formula where the growth percentage of control was 100%.

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

The antifungal analysis was as well measured by the term of the growth percentage compared with the control while the growth of control is 100% percent using the following formula which shows a ILs how can be able to show it potency agonist any fungal stain.

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

From table 3, the percentage of inhibition was shown that the IL05 was found the highest percentage in almost three fungi. The main fact of this reason is to be noted that the halogen atom in the anion molecule is the main fact. To test the anion effect on antifungal activity of ILs, the formate, acetate, propanoate, butanoate, and trifluoroacetate anion were used whereas 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 was affected the negative charge distribution of anion although the same cation was attached for all ILs. It was summarized that increasing the length of anion, the antifungal activity was increased while attaching electronegative atom (F) could show similar effect.

3.3. Minimum inhibition concentration(MIC)

To explain the MIC, the zone of inhibition was accounted for different concentrations, such as 1000 mM, 750 mM, 500 mM, 250 mM and 125 mM. These calculated results were plotted in view of zone of inhibition touching at zero point called the MIC value. The MIC was presented in table 4 against the Bacillus cereus(+) and Escherichia coli(-) pathogens. It was found for the MIC for tested ILs about ranging 500 mM to 125 mM, and it was the lowest magnitude for IL05 and IL04 for bacteria.

4. Computational Approaches

4.1. Optimized structure of ILs

The molecular structural geometry or stable configuration after optimization through computational functional of DFT, which contains the values of the reactivity indices and biological activity, is presented in the in figure 3 for nine ILs. The molecules belong to the class asymmetry, and non-planar, and they have more than one element of symmetry and the plane of the molecule with their charge.

4.2. Chemical reactivity using HOMO and LUMO

The energy levels of the molecular orbitals using the terms, HOMO and LUMO, provides in rank on the possible electronic tran-

Table 2
Data of %, growth percentage against fungal

Chemicals	Zone of growth (in mm)			%, growth percentage		
	Aspergillus niger	Saccharomyces cerevisiae	Candida albicans	Aspergillus niger	Saccharomyces cerevisiae	Candida albicans
Control	24	37	38	100 %	100%	100 %
S. material	22	35	35	91.67%	94.60 %	92.10 %
IL01	16	23	21	66.67 %	62.26%	55.26%
IL02	15	21	19	62.50 %	56.75%	50.00%
IL03	14	19	18	58.33%	51.35%	47.36%
IL04	13	18	17	54.16%	48.65%	44.75%
IL05	12	15	17	50.00%	40.54%	44.75%

Table 3
Percentage of inhibition

Tested chemicals	Aspergillus niger	Saccharomyces cerevisiae	Candida albicans
Control	0%	0%	0 %
Staring material	8.33%	5.40%	7.90%
IL01	33.33%	37.25%	44.74%
IL02	37.50%	53.25%	50.00%
IL03	41.67%	48.65%	52.25%
IL04	45.84%	51.35%	55.25%
IL05	50.00%	59.46 %	55.25%

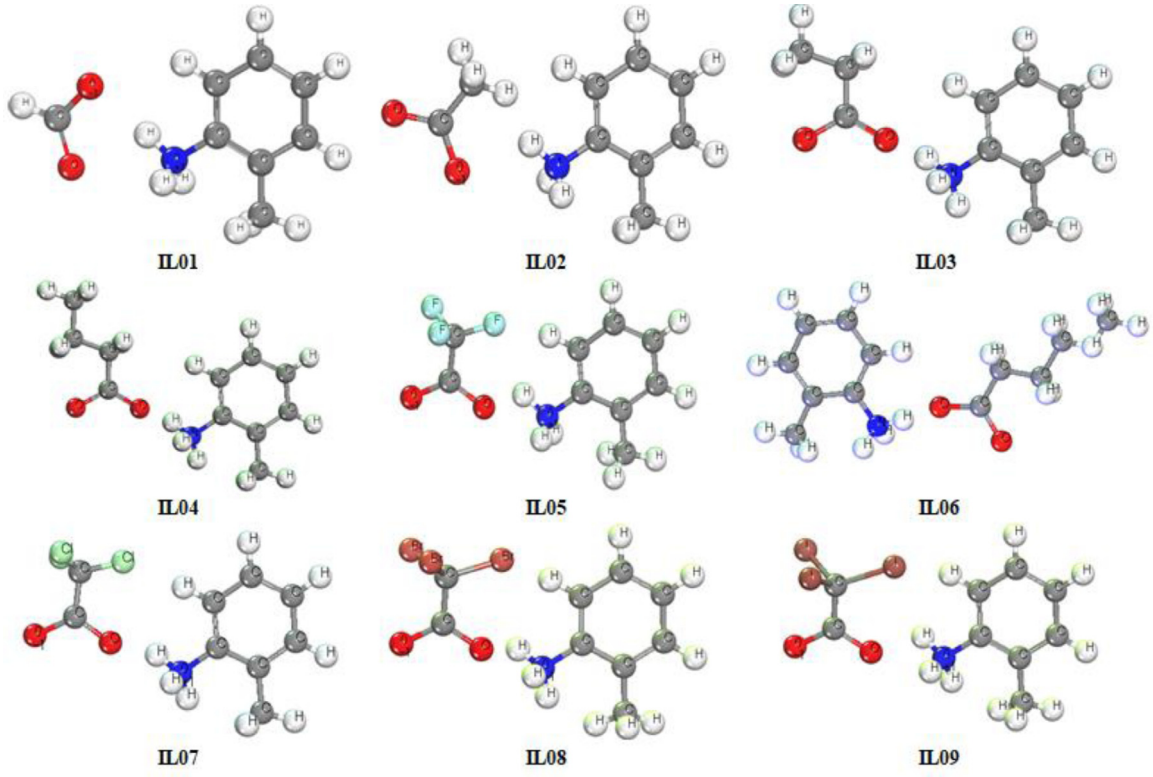

Fig. 3. Optimized structure of ILs

sition, electron upcast and downcast part in molecule which are highlighted in figure 4. The larger value of the LUMO indicates the easily attached to the protein of pathogens which has shown in figure 5, and the colors: deep yellow is a positive value, and light blue is a negative value. In addition, the HOMO is the region of the molecule whereas the electrophilic group can be attached. Energy difference between HOMO and LUMO orbital, known as energy gap, indicates the chemical stability for structure or molecules which is listed in table 5, and greater value of energy gap indicates lower chemical stability [75-83]. From the table 5, it has found that the energy gap is about 6.579 kcal/mol to 5.329 kcal/mol, but IL04 showed the highest energy gap 8.144 kcal/mol.

To make a comparative study and alkyl chain effect on biological study, the optimized alkyl chain and halogen atoms containing ILs was designed. The hardness and softness are directly related with Lewis acid and base and chemical stability. A small HOMO-LUMO gap automatically means small excitation energies to the manifold of excited states. The softness and hardness are listed in table 5 where the softness are in 0.304, 0.375, 0.323, 0.245, 0.303, 0.297, 0.323, 0.304 and 0.335 and hardness are in 3.289, 2.664, 3.092, 4.072, 3.292, 3.358, 3.095, 3.286 and 2.981, respectively of IL01 to IL09.

Electrophilicity index of a molecule reports to about the binding ability of a compound with biomolecules, and the greater value of

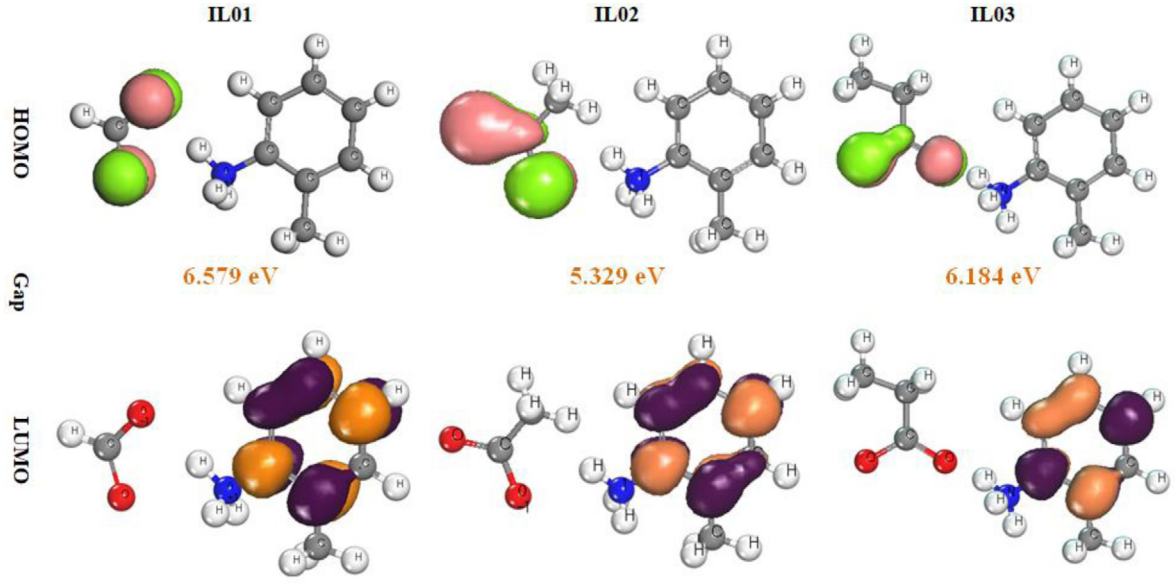

Fig. 4. Orbital picture of HOMO and LUMO

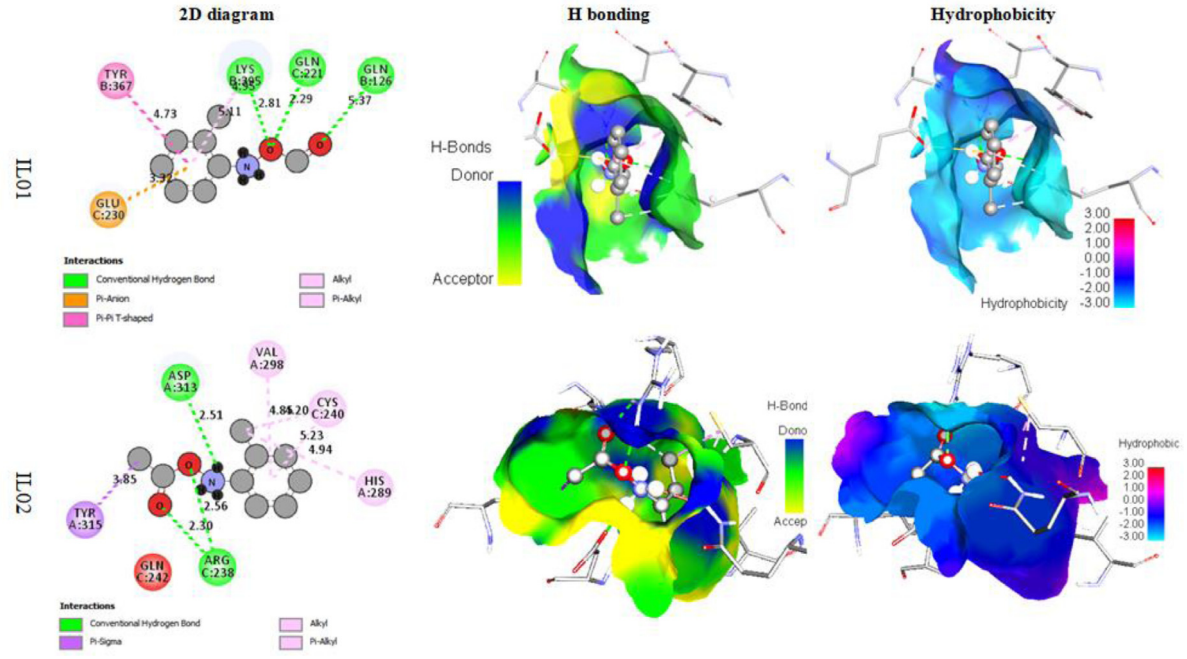

Fig. 5. Docking interaction diagram of 2D and 3D

Table 4
Specific value of MIC

	1000 mM	750 mM	500 mM	250 mM	125mM	MIC mM
Bacillus cereus(+)						
IL01	7	3	0	0	0	500
IL02	8	3	0	0	0	500
IL03	14	9	6	0	0	250
IL04	20	11	8	3	0	125
IL05	22	14	9	5	0	125
Escherichia coli(-)						
IL01	13	8	4	0	0	250
IL02	13	6	0	0	0	500
IL03	14	8	3	0	0	250
IL04	18	12	7	3	0	125
IL05	20	12	8	3	0	125

electrophilicity index of molecule demonstrated the higher binding capacity with proteins acting as an electrophilic species. The obtained value of electrophilicity index is about 3.243 to 3.937 eV while the larger value is for IL02 and second larger value is IL09.

4.3. Molecular Docking

The foremost undertaking of docking study has employed to investigate the possible interaction between ligands (ILs) and macromolecules, such as Bacillus cereus (+), Escherichia coli (-), and Aspergillus niger (fungi).The protein pocket, hydrogen bonding and 2D diagram have showed in figure 5, S2 and S3, and their binding affinity with these pathogens in table 6. It already was established that the binding affinity of standard drug is almost 6.0 kcal/mol or above [84, 85]. From the table 6, it is shown that the starting

Table 5
Data for HOMO LUMO and chemical reactivity parameters

Chemical descriptors	IL01	IL02	IL03	IL04	IL05	IL06	IL07	IL08	IL09
HOMO, eV	-7.909	-7.245	-7.598	-8.704	-8.243	-7.748	-7.827	-8.241	-7.747
LUMO, eV	-1.330	-1.916	-1.414	-0.560	-1.659	-1.031	-1.637	-1.668	-1.785
LUMO–HOMO gap, eV	6.579	5.329	6.184	8.144	6.584	6.717	6.190	6.573	5.962
Ionization potential (I), eV	7.909	7.245	7.598	8.704	8.243	7.748	7.827	8.241	7.747
Electron affinity (A), eV	1.330	1.916	1.414	0.560	1.659	1.031	1.637	1.668	1.785
Chemical Hardness, (η), eV	3.289	2.664	3.092	4.072	3.292	3.358	3.095	3.286	2.981
Chemical Softness, (S), eV	0.304	0.375	0.323	0.245	0.303	0.297	0.323	0.304	0.335
Electronegativity, (χ), eV	4.619	4.580	4.506	4.632	4.951	4.389	4.732	4.954	4.766
Chemical Potential, (μ), eV	-4.619	-4.580	-4.506	-4.632	-4.951	-4.389	-4.732	-4.954	-4.766
Electrophilicity Index, (ω),eV	3.243	3.937	3.283	2.634	3.723	3.242	3.617	3.737	3.809

Table 6
Docking score by interaction between ligand and macromolecule

	Bacillus cereus(+)			Escherichia coli(-)			Aspergillus niger (1ks5)		
	Binding affinity (kcal/mol)	No of H bond	Total bonds	Binding affinity (kcal/mol)	No of H bond	Total bonds	Binding affinity (kcal/mol)	No of H bond	Total bonds
IL01	-5.3	0	07	-4.9	00	07	-5.0	03	04
IL02	-5.7	01	03	-5.1	02	05	-5.2	03	05
IL03	-6.2	00	06	-5.5	05	10	-5.6	03	05
IL04	-5.9	00	04	-5.2	01	05	-5.5	02	04
IL05	-6.4	03	06	-5.7	02	06	-6.0	04	09
IL06	-5.8	05	08	-5.6	06	09	-5.5	03	05
IL07	-5.8	03	07	-5.8	03	07	-5.6	03	07
IL08	-5.3	03	07	-5.8	03	07	-5.6	03	07
IL09	-5.9	02	06	-5.8	02	06	-5.6	02	06
starting	-2.8	00	03	-2.9	00	03	-2.7	00	04

material named aniline can show very poor binding affinity which is about -2.8, -2.9, -2.7 kcal/mol. But it was increased almost two times after converting into ortho toluidinium carboxylate ILs showing in table 6. From the table 6, it is noted that IL05 illustrates the highest binding affinity, which is more than 6.0 kcal/mol against three pathogens although all are about slightly below 6.0 kcal/mol. From the full analysis of table 6, containing docking score, it can be summarized that alkyl chain of anion has a regular effect on biological activity with protein while fluorine atoms on anion (IL05) can show the highest binding score.

On the other hand, the orbital picture of H bonding, hydrophobicity, 2D diagram and molecular interaction shown in table S1, and S2, it is clear that the hydrogen bonding, hydrophobic bonding and van dar Waal force with protein are occurred for binding as drug presented in figure 5. In case of IL05, showing higher binding affinity causes the extra halogen bond forming which are not formed for other ILs. Moreover, IL04 can show the second highest binding affinity although there are not formed halogen bonds. Though the halogen atoms are attached in the IL07, IL08 and IL09, they can not form the halogen bond with proteins which lead a vast contribution for making larger binding affinity.

4.4. ADMET Study

The ADMET stands for absorption, distribution, metabolism, excretion and toxicity, which have been considered as

The crucial parts of any drug development program and essential for compliance with regulatory guidelines. It conveys a theoretical model involved whole-animal to save time-consumption and cost.

First of all, table-S3 conveys that all ILs are satisfied by Lipinski rule, means that they have good binding affinity. The hydrophilicity, logp, has been increased with increasing the alkyl chain and attaching halogens atoms in anion.

All of ILs are negative response in P- I glycoprotein inhibitor, P-II glycoprotein substrate, Renal Organic Cation Transporter, CYP450 2C9 Substrate and CYP450 1A2 Inhibitor listed table S4. But they illustrate the positive response for Human Intestinal Absorption, Caco-2 Permeability and Blood Brain Barrier. In addition, the subcellular localization is found at Lissome.

In case of toxicity shown in table S5, all ILs are non carcinogenic molecules although they have medium water solubility, LogS, which have been changed with increasing alkyl chain and found the maximum value for IL09. For case of AMES toxicity, all can not show this toxicity except IL01, IL02 and IL03. They show the medium affinity to Acute Oral Toxicity, Oral Rat Acute Toxicity (LD50), Fish Toxicity pLC_{50} and T.Pyriformis toxicity.

5. Conclusion

The synthesis of ortho toluidinium carboxylate ILs is synthesized with high yield without solvent just 24-30 hours stirring by the acid-base neutralization. Afterward, the purification, analytical data of IR, UV and NMR give the supports for the confirmation of reaction and structure of the molecule. To estimate the bioactivity of OTILs, the well diffusion methods was use while the starting material was near to zero or very poor zone of inhibition as antimicrobial agent against all taken pathogens. But, there were a huge change of antimicrobial activity of ILs from starting, and the zone of inhibition was found almost 07 nm to 22 nm whereas the IL05 showed the highest antibacterial activity. In case of antifungal activity, it was found that the antifungal activity was increased about 60% in term of zone of inhibition compared with control, and IL05 illustrated the same result like antibacterial. It could be said that the effect on alkyl chain of anion on the antibacterial and antifungal activity of ILs had to be change with increasing the length of anion although adding fluorine atom with ethanoate anion can show the best result among tested ILs. On the other hand, the theoretical investigation through computational approaches, the chemical reactivity and molecular docking score have been changed in a regular fashion on base their chain length of anions. The chemical reactivity regarding the term

of LUMO-HOMO gap gradually increases with increasing the alkyl chain, and found the highest in IL04, as well as the inverse effect was found for softness. According to molecular docking, with increasing alkyl chain, the binding affinity was increased though electronegative atoms fluorine could make the best docking score rather than other halogen atoms, and the IL05 could show the superior binding affinity against antimicrobial pathogens. Moreover, it was estimated that halogen bond was created for IL05 not other halogen containing ILs. However, halogen atom has a capacity to form the interaction with protein of pathogens in anion of ILs. From the AMDET study, it could be said that all of tested ILs are non carcinogenic, low toxic with low water solubility.

Declaration of Competing Interest

The authors declare that they have no conflict of interest. All authors gave final approval for publication.

Acknowledgement

I am grateful to the Department of Chemistry, Bangladesh University of Engineering and Technology (BUET), Dhaka-1000, Bangladesh, for all kind of supports. I am also grateful to Prof. Dr. M. Abdur Rashid, Professor, Department of Pharmacy, University of Dhaka, Dhaka, Bangladesh, for all kind of support for the working of antimicrobial studies.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2021.131087.

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