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Synthesis and Characterization of Antibacterial Ionic Liquids Moieties under Multiple Routes and their Catalytic Responses

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Abstract

Substituted imidazolium salts were prepared under conventional and solvent free condition using silica mediated Muffle furnace methods. Solvent free approach is much more facile than the conventional. We have studied the catalytic activities of imidazolium type of ionic liquids for Pechmann reaction under solvent free as well as conventional approaches using various solvents like THF, acetone, ethanol, methanol and DMSO. Among these solvents, DMSO showed an excellent solvent effect. Solvent free reaction is nearly fifty times faster than the conventional. Antibacterial screening of eight synthesized imidazolium salts were carried out against Gram positive/Gram negative pathogens under disc diffusion and MIC methods. Host-guest interactions are studied between our synthesized ionic liquids and human pathogenic bacteria's *via* hydrogen bonding and Vanderwalls interaction under docking analysis.

Keywords: Ionic liquids; Solid state approach; Antibacterial activity; Well diffusion technique; Human pathogens; Docking model

Introduction

Imidazolium/pyridinium salts acted as a potential candidate with variety of applications in the field of organic catalysis [1-10], biocatalysis [11-14], material synthesis, [15] pharmaceutical chemistry [16], polymerization reactions [17], electro chemical and engineering aspects [18-20]. Ethoxycarbonylethyl substituted imidazolium bromides acted as a good catalyst for aminolysis and trans esterification using greener solvent [21]. Functionalized dicationic imidazolium salts are synthesized and examined the behaviour under the assistance of spectral and analytic instruments [22]. Antibacterial efficacy and antibiofilm activities of Imidazolium Salts (IS's) have been studied.

From the study, authors claimed that minimal inhibitory concentrations are varied depends on the substituents [23-26]. Luczak and co-workers [27] investigated the cytotoxic experiments with hydrophobic cation with different counter anions. The properties of cytotoxicity are purely based on hydrophobicity of counter cation; whereas counter anion showed little importance. Eco-toxicological screening of several classes of ionic liquids demonstrated that, some alkyl substituted imidazolium/pyridinium salts showed cytotoxic behaviours against microorganism [28-31]. Herein, we wish to report the synthesis of substituted imidazolium cation with various counter anions under conventional/solvent free silica supported Muffle furnace approach and studied its catalytic response for Pechmann reaction. Also we have studied the solvent effects for Pechmann reaction from less polar, high polar solvents. Alberto and co-workers prepared the toxic and poisonous behaviours of Selenium containing ionic liquids under multistep reaction in the presence of toxic organic chlorinated solvent. They have been studied the antimicrobial investigation of Selenium containing of ionic liquids against human pathogenic microorganisms. While compared their results, we could say our IS's are acted potential candidate and showed excellent antimicrobial activities under MBC and MIC methods. To the best of our knowledge, our IS's showed excellent antibacterial responses than the available reported work [32].

Materials and Method

General procedure for N-alkylation reaction

2-Methyl-4(5)-nitro-1H-imidazole is (1.573×10^{-2} mmol; 1.0 equi.) mixed with slight excess of benzyl bromide/4-nitro benzyl bromide (1.652×10^{-2} mmol; 1.05 equi.) in the presence of 30 mL of the MeCN under refluxing condition for about 9-13 hours afforded the N-alkylated products of (**1a-b)** in quantitative yield after the purification process.

General procedure for solvent free Muffle furnace condition

The above procedure is repeated except solvent, we have used 5 g of (80-120 mesh) silica gel with fine grinding using mortar & pestle. The reaction mixture is kept in Muffle furnace at 100°C for required period.

2-Methyl-4(5)-nitro(3-methylenebenzene)-imidazoliumbromide 1a: 4.60 g; 97%; Mp: 168-170°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ; 2.35 (s, 3H), 5.28 (s, 2H), 7.08-7.17 (m, 5H), 8.42 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ; 14.1, 50.1, 122.9, 127.6, 128.3, 129.3, 130.9, 136.0, 145.7; MS: m/z: 298.13; Elemental analysis: Molecular formula ($C_{11}H_{12}BrN_3O_2$) Calculated: C: 44.30; H: 4.02; N:14.09; Found C: 44.26; H: 3.96; N: 14.04.

2-Methyl-4(5)-nitro(3-methylene4'-nitrobenzene)-imidazoliumbromide 1b: 5.20 g; 93%; Mp: 98-100°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ; 2.30 (s, 3H), 5.31 (s, 2H), 7.27-7.29 (d, 2H), 7.39-7.41 (d, 2H), 8.46 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ; 15.4, 51.5, 121.3, 125.6, 128.3, 131.4, 139.4, 142.1,147.4; MS: m/z: 343.13; Elemental analysis: Molecular formula ($C_{11}H_{11}BrN_4O_4$) Calculated: C: 38.48; H: 3.26; N: 16.32; Found C: 38.44; H: 3.24; N: 16.28.

General procedure for anion exchange reaction

N-alkylated product of imidazolium bromide **1a,1b** (1.0 equi.) is treated with $NaBF_4$/KPF_6/$LiCF_3SO_3$ (1.05 equi.) in the presence of 10 mL of deionized water at room temperature with stirring for about 1 h afforded the anion exchanged product of imidazolium cation with different anion. After the anion exchanged reaction, we have used Soxhlet extraction to remove metal bromide from imidazolium salts using 100 mL of dry THF for about 1 h refluxtion to give respective imidazolium salts in quantitative yield.

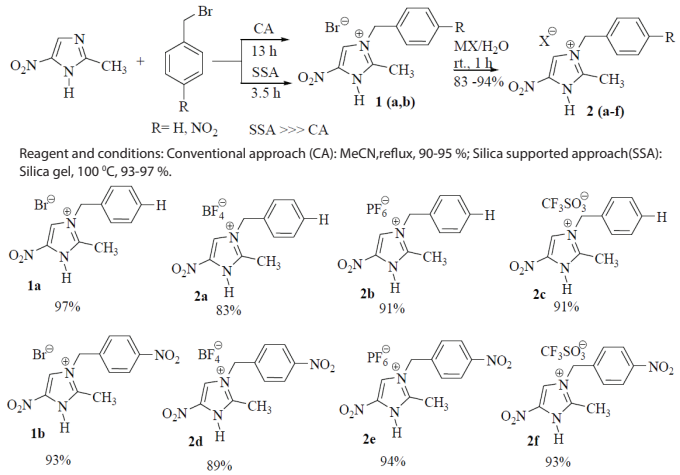
2-Methyl-4(5)-nitro(3-methylenebenzene)-imidazolium tetrafluoroborate 2a: 0.57 g; 83%; Mp: 127-130°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ; 2.38 (s, 3H), 5.26 (s, 2H), 7.12-7.17 (m, 5H), 8.45 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ; 14.2, 50.3, 122.8, 127.9, 128.4, 129.6, 130.8, 136.1, 145.5; MS: m/z: 305.09; Elemental analysis: Molecular formula ($C_{11}H_{12}BF_4N_3O_2$) Calculated: C: 43.26; H: 3.93; N: 13.77; Found C: 43.21; H: 3.88; N: 13.73.

General procedure for imidazolium salt assisted Pechmann reaction

Phenol/4-nitrophenol/4-chlorophenol (2.126×10^{-3} mmol; 1.0 eq.), EAA (2.126×10^{-3} mmol; 1.0 eq.) and solvent (5 mL) are mixed along with optimized concentration of imidazolium salt (2.021×10^{-4} mmol) at room temperature with stirring. After disappearance of starting material monitored by TLC, the reaction mixture was poured into 5 mL and ice cold water and 100 mL of diethyl ether and stirred for 5 min. two layers are formed; the organic layer was then dried over anhydrous Na_2SO_4. The organic layer was evaporated to dryness under reduced pressure to obtain a pure compound.

Results and Discussion

2-Methyl-4(5)-nitroimidazole is treated with slight excess amount of benzyl/4-nitrobenzylbromide in the presence of dry MeCN under refluxing condition between 9-13 h afforded the N-alkylated IS's **1** (**a-b**) in quantitative yield (Scheme 1). The above reaction is conducted under solvent free silica supported Muffle furnace. Equal molar ratios of substituted imidazole and benzyl bromide/4-nitrobenzyl bromide are grained with 5 g of silica gel (80-120 mesh) using mortar and pestle, and kept in Muffle furnace at 100°C; we have monitor the reaction by TLC. We found that solvent free silica supported Muffle furnace reactions were completed from 3-3.5 h. Hence solvent free silica supported reaction are more convenient than the conventional method because of its lesser reactions time, higher yield, solvent free condition and easy work up. N-Alkylated imidazolium bromides **1**(**a-b**) are treated with various inorganic salts such as KPF_6, $NaBF_4$ and $LiCF_3SO_3$ in the presence of deionized water at room temperature for 1 h to afford the anion exchanged product of IS **2** (**a-f**) in quantitative yield. The separation of IS from metal bromide using organic solvent extraction is not easier due to its water-soluble nature. So we carried out the Soxhlet extraction with dry tetrahydrofuran (THF) for 2 h under refluxing condition to afford metal bromide-free IS with higher yield. After completion of Soxhlet extraction, we have confirmed with aqueous $AgNO_3$ solution. The synthesized compounds **2** (**a-f**) are thoroughly characterized by spectral and analytical data.



Scheme 1: Synthesis of substituted imidazolium salts from solvent free silica supported & conventional approaches

Catalytic activities

Calculated equivalent of Pechmann reactants under conventional method without catalyst takes 10 hours to give only 30% yield. The same reaction is tried with optimum concentration of our catalyst using various polar and non-polar solvents which is completed with lesser reaction time and higher yield. We have used varies solvents from less polar to more polar solvents for Pechmann reaction to find out the suitable solvent we observed that, reaction time and percentage of yields are varied from less to the more polar solvent (Tables 1-4). We have studied solvent effect with different solvents like dimethyl sulfoxide (DMSO), ethanol, methanol, acetone and tetrahydrofuran (THF). Among these solvents, DMSO showed less reaction time with higher yield than the other solvents. Polar solvent plays an important role to enhance the Pechmann reaction (Table 1). Reaction between phenol and ethylacetoacetate (EAA) with optimized concentration of our substituted IS under conventional approach afforded 4-methyl-2H-chromen-2-one (**3**), (Scheme 2; Table 1).

Preparation of 4-methyl-6-nitro-2H-chromen-2-one (**4**) from 4-nitrophenol and EAA in the presence of optimized concentration of our synthesized IS at room temperature (Scheme 3). While compared the preparation of 4-methyl-2H-chromen-2-one & 4-methyl-6-nitro-2H-chromen-2-one, the reaction time and yield are not appreciable in scheme 3. Same reaction under solvent free silica supported condition is completed within 20 minutes, whereas conventional heating at 80°C with DMSO required 1 h for completion. Hence solvent free Muffle furnace method is more suitable for preparation of 4-methyl-6-nitro-2H-chromen-2-one (**4**) compared with conventional method (Table 2).

Preparation of 6-chloro-4-methyl-2H-chromen-2-one (**5**) from 4-chlorophenol and EAA with optimized concentration of IS at room temperature (Scheme 4).

4-chloro phenol is much reactive than the 4-nitrophenol in Pechmann reaction due to its electron release towards the arene moiety and facilitate the reaction due to high electron (Table 3). Preparation of 6-chloro-4-methyl-2H-chromen-2-one (**5**) using solvent free Silica Supported Approach (SSA) under Muffle furnace at optimum temperature 100°C; gave the product within 11 minutes whereas under conventional approach took 30 min. So solvent free silica supported methodology is more suitable than conventional condition for Pechmann reaction (Table 3).

To avoid the organic solvents, we tried silica supported solvent free method to afford chromone derivatives under Muffle furnace within 15 min in 97% yield. Hence, Muffle furnace method is more convenient than the conventional method because of its solvent free non-toxic nature, high yield and easy workup.

We have used nearly eight different IS's to study the catalytic responses for the Pechmann reaction. Among these **1a** and **2** (**a-c**) showed excellent catalytic behaviour than the others. Because of the Lewis character than the others. Imidazolium cation with bromide counter anion showed excellent catalytic activity than the other counter anions. The Pechmann reaction under solvent free condition is nearly fifty times faster than conventional approach.

Table 1: Preparation of 4-methyl-2H-chromen-2-one (**3**) under different solvents

S. No	Entry	Different solvents									
		THF		Acetone		Ethanol		Methanol		DMSO	
		Time (h:min)	Yield %	Time (h)	Yield %	Time (h:min)	Yield %	Time (min)	Yield %	Time (min)	Yield %
1	**1a**	4:40	40	4	45	1:30	65	45	81	30	88
2	**2a**	4:40	33	4	40	1:30	60	45	75	30	89
3	**2b**	4:40	36	4	43	1:30	62	45	79	30	83
4	**2c**	4:40	33	4	40	1:30	60	45	75	30	80
5	**1b**	4:40	35	4	42	1:30	62	45	80	30	85
6	**2d**	4:40	30	4	40	1:30	55	45	75	30	78
7	**2e**	4:40	32	4	42	1:30	60	45	76	30	77
8	**2f**	4:40	30	4	41	1:30	58	45	72	30	79
Reagent and conditions: Phenol, EAA, 2.012 × 10^{-4} mmol of IS											

Table 2: Solvent effect for the preparation of 4-methyl-6-nitro-2H-chromen-2-one (**4**)

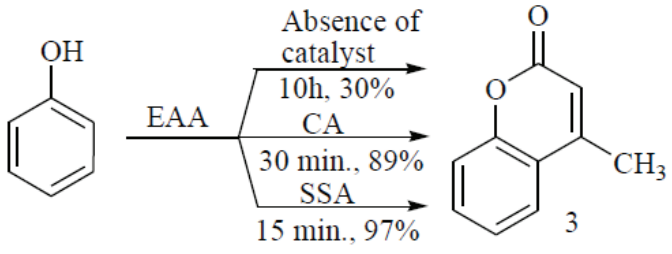
S. No	Entry	Different solvents									
		THF		Acetone		Ethanol		Methanol		DMSO	
		Time (h:min)	Yield %	Time (h)	Yield %	Time	Yield %	Time (h:min)	Yield %	Time (h)	Yield %
1	**1a**	3:40	44	3	55	1:30	60	1:15	70	1	75
2	**2a**	3:40	37	3	47	1:30	54	1:15	65	1	70
3	**2b**	3:40	42	3	52	1:30	57	1:15	68	1	72
4	**2c**	3:40	40	3	50	1:30	55	1:15	66	1	70
5	**1b**	3:40	39	3	50	1:30	55	1:15	65	1	71
6	**2d**	3:40	35	3	45	1:30	50	1:15	60	1	65
7	**2e**	3:40	37	3	48	1:30	52	1:15	62	1	67
8	**2f**	3:40	35	3	47	1:30	50	1:15	60	1	65
Reagent and conditions: 4-nitrophenol, EAA, 2.012 × 10^{-4} mmol of IS.											

Table 3: Preparation of 6-chloro-4-methyl-2H-chromen-2-one (**5**) under different solvents

S. No	Entry	Different solvents									
		THF		Acetone		Ethanol		Methanol		DMSO	
		Time (h:min)	Yield %	Time (h)	Yield %	Time (h)	Yield %	Time (min)	Yield %	Time (min)	Yield %
1	**1a**	1:30	50	2	62	1	65	30	78	30	80
2	**2a**	1:30	45	2	55	1	62	30	70	30	75
3	**2b**	1:30	48	2	60	1	64	30	75	30	78
4	**2c**	1:30	46	2	58	1	64	30	73	30	75
5	**1b**	1:30	48	2	58	1	62	30	74	30	78
6	**2d**	1:30	40	2	40	1	58	30	70	30	70
7	**2e**	1:30	45	2	55	1	60	30	72	30	74
8	**2f**	1:30	40	2	52	1	58	30	70	30	72
Reagent and conditions: 4-chlorophenol, EAA, 2.012 × 10^{-4} mmol of IS.											

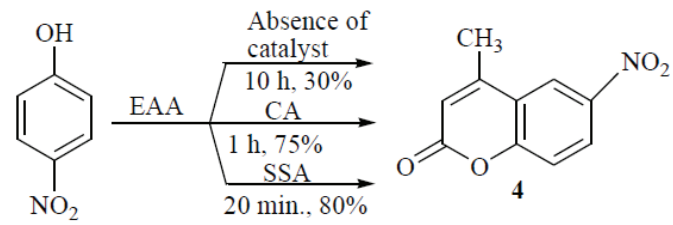
Table 4: Solvent effect for the preparation of 1-methyl-3H-benzo[f]chromen-3-one **(6)**

S. No	Entry	Different solvents									
		THF		Acetone		Ethanol		Methanol		DMSO	
		Time (h:min)	Yield %	Time (h:min)	Yield %	Time (h:min)	Yield %	Time (min)	Yield %	Time (min)	Yield %
1	**1a**	3:20	49	2:30	55	1:15	68	45	82	45	90
2	**2a**	3:20	45	2:30	45	1:15	61	45	75	45	81
3	**2b**	3:20	47	2:30	53	1:15	65	45	80	45	87
4	**2c**	3:20	45	2:30	50	1:15	64	45	78	45	85
5	**1b**	3:20	42	2:30	52	1:15	65	45	80	45	84
6	**2d**	3:20	35	2:30	43	1:15	60	45	76	45	80
7	**2e**	3:20	40	2:30	50	1:15	61	45	75	45	83
8	**2f**	3:20	37	2:30	45	1:15	60	45	73	45	82
Reagent and conditions: 2-napthol, EAA, 2.012 × 10^{-4} mmol of IS.											



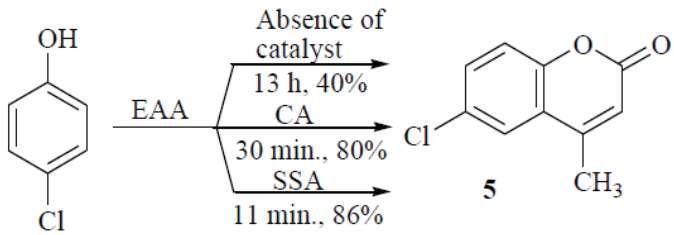
Reagent and conditions:
CA: Different solvents, 2.012X10-4 mmol of IS; SSA: 2.012X10-4 mmol of IS, Muffle furnace, 100 °C.

Scheme 2: Preparation of 4-Methyl-2H-chromen-2-one **(3)** via different method



Reagent and conditions:
CA: Different solvents, 2.012X10-4 mmol of IS; SSA: 2.012X10-4 mmol of IS, Muffle furnace, 100 °C.

Scheme 3: Preparation 4-Methyl-6-nitro-2H-chromen -2-one **(4)** under different method



Reagent and conditions:
CA: different solvents, 2.012X10-4 mmol of IS; SSA: 2.012X10-4 mmol of IS, Muffle furnace, 100 °C.

Scheme 4: Preparation of 6-Chloro-4-methyl-2H-chromen -2-one **(5)** under different method

Preparation of 1-methyl-3H-benzo[f]chromen-3-one (**6**) from 2-naphthol and EAA in the presence of optimized concentration (2.012×10^{-4}) of our IS along with minimum amount of different solvent (5 mL) at room temperature with stirring (Table 4). Under silica supported Muffle furnace at 100°C; formation of 1-methyl-3H-benzo[f]chromen-3-one (**6**) completed within 17 minutes but under conventional method required more reaction time.

We have examined the Pechmann product formation from (schemes 2-6) without IS, there is no appreciable changes even for long periods (Table 5)

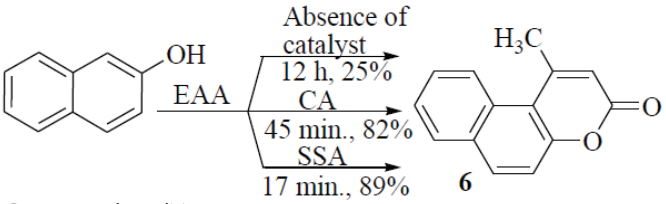
To find out the optimum catalyst concentration for Pechmann reaction of our IS we have used 8.385×10^{-5}, 1.341×10^{-4}, 2.012×10^{-4} and 2.683×10^{-4} mmol concentrations of our IS. We have observed that 2.012×10^{-4} mmol concentration is the optimum catalyst concentration. While increasing the concentration from 2.012×10^{-4} mmol to 2.683×10^{-4} mmol, there is no appreciable changes. The results are described in table 6.

Our synthesized substituted IS are acted as efficient candidates to accelerate the Pechmann reaction as quicker with higher yield.

Synthesized substituted IS are recycled upon fourth cycles and used for preparation of Chromen-one derivatives under same reaction condition. Even after fourth recycle, the product obtained was same as we observed in the fresh use shown in the figure 1.

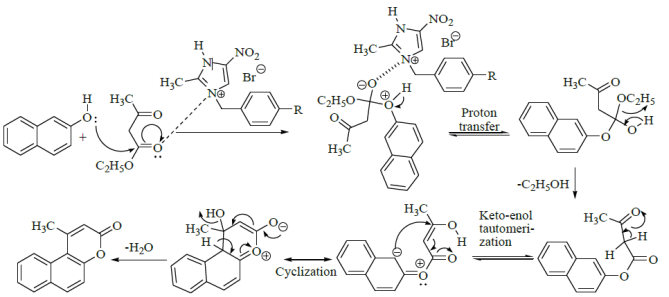
Microbiological study

Imidazolium salts: 2-Methyl-4(5)-nitro(3-methylenebenzene)-imidazolium bromide [(MNMBI)Br$^-$] **1a**; 2-Methyl-4(5)-nitro(3-methylene4'-nitrobenzene)-imidazoliumbromide [(MNMNBI)Br$^-$] **1b**; 2-Methyl-4(5)-nitro(3-methylenebenzene)-imidazolium



Reagent and conditions:
CA: different solvents, 2.012X10-4 mmol of IS; SSA: 2.012X10-4 mmol of IS, Muffle furnace, 100 °C.

Scheme 5: Preparation of 1-methyl-3H-benzo[f]chromen -3-one **(6)** under different method



Scheme 6: Systematic proposed plausible mechanism for Pechmann reaction with IS

Table 5: Pechmann reactions without catalyst

Entry	Scheme	IS	Time (h)	Yield %
1	2	-	10.00	30
2	3	-	10.00	30
3	4	-	13.00	40
4	5	-	12.00	25

Reagent and conditions: Substituted phenol (1.0 equi.), EAA (1.0 equi.), DMSO (5 mL), rt.

Table 6: Different concentrations of IS

Entry	IL's	Time (h: min)	Yield%
1	8.385×10^{-5}	1.00	52
2	1.341×10^{-4}	0.50	69
3	2.012×10^{-4}	0.30	88
4	2.683×10^{-4}	0.30	88

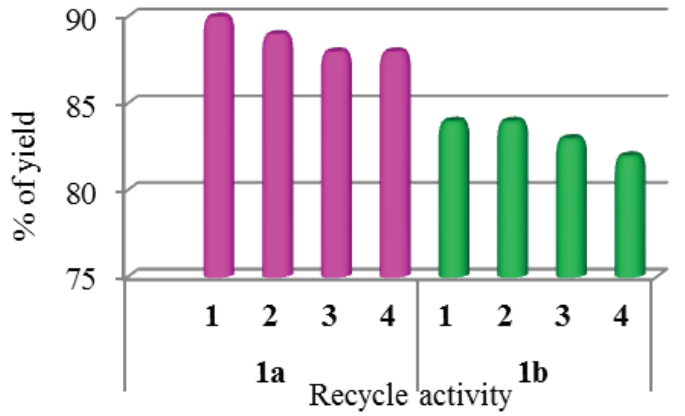


Figure 1: Formation of 1-methyl-3H-benzo[f]chromen-3-one **(6)** derivatives by 4th recycled IS.

tetrafluoroborate [(MNMBI)BF_4^-] **2a**; 2-Methyl-4(5)-nitro(3-methylenebenzene)-imidazoliumhexafluorophosphate [(MNMBI) PF_6^-] **2b**; 2-Methyl-4(5)-nitro(3-methylenebenzene)-imidazolium trifluoromethanesulfonate [(MNMBI)$CF_3SO_3^-$] **2c**; 2-Methyl-4(5)-nitro(3-methylene4'-nitrobenzene)-imidazoliumtetrafluoroborate [(MNMNBI)BF_4^-] **2d**; 2-Methyl-4(5)-nitro(3-methylene4'-nitrobenzene)-imidazolium hexafluorophosphate [(MNMNBI)PF_6^-] **2e**; 2-Methyl-4(5)-nitro(3-methylene4'-nitrobenzene)-imidazolium trifluoromethanesulfonate [(MNMNBI)$CF_3SO_3^-$] **2f**. Tested for both inhibitions, MIC and docking studies are carried out.

Bacterial cultures: Five pathogenic bacteria's have been used for present study as test microorganisms such as Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus vulgaris and Staphylococcus aureus. The bacterial cultures were obtained from Department of Microbiology, Presidency College, Chennai, India. The bacteria are subculture using Nutrient agar (Himedia, India) and stored at 4°C until required for the study.

Sterility test: A loopful of IS were inoculated into Nutrient agar and Sabourauds dextrose agar plates and incubated at 37°C and 20°C for 24 h and 72 h respectively. The compound was found by steriled.

Antibacterial studies

Rajarajan et al. [33] reported that bacterial screening of their synthesized quinolium salts are purely based on length of side chain. While moving from carbon number 8 into 16 the antibacterial responses also enhanced. Based on this report we have screened the antibacterial screening against both Gram positive/negative pathogens, which revealed that our IS's are observed excellent inhibition than the reported literature [33]. Antibacterial activities of IS's are studied by well/disc diffusion methods using Mueller Hinton Agar (MHA) [34]. The stock solution of the IS's are prepared as 1 mg/mL and the dilution were prepared using dimethyl sulfoxide as 25 µg/well (5.091×10^{-4} mmol/mL), 50 µg/well (1.02×0^{-4} mmol/mL), 75 µg/well (1.53×10^{-4} mmol/mL) and 100 µg/well (2.04×10^{-4} mmol/mL) concentrations. The bacterial inoculum was adjusted to 0.5 scale of McFarland standard. The dilutions of IS's were loaded into respective wells of MHA plate. The antibiotic Erythromycin (30 µg/well, Nalidixic acid (30 µg/well) and Amikacin (30 µg/well) are used as standard drugs for studies. The MHA plates were incubated at 37°C for 18-24 h. The zone of inhibition was measured in mm using Vernier Caliper and compared with standard drug disc.

Determination of minimum inhibitory concentration: Minimum Inhibitory Concentration (MIC) and Minimum Bacterial Concentration (MBC) were determined by micro dilution method using Mueller Hinton Broth (MHB) [35]. A stock solution (1 mg/ml) of the IS and the dilution containing 10 µg/well (1.01×10^{-4} mmol/mL), 20 µg/well (2.038×10^{-4} mmol/mL), 30 µg/well (3.059×10^{-4} mmol/mL), 40 µg/well (4.074×10^{-4} mmol/mL), 50 µg/well (5.09×10^{-4} mmol/mL), 60 µg/well (6.11×10^{-4} mmol/mL), 70 µg/well (7.125×10^{-4} mmol/mL) and 80 µg/well (8.14×10^{-4} mmol/mL) Erythromycin (1.362×10^{-4} mmol/mL), Nalidixic acid (4.306×10^{-4} mmol/mL) and Amikacin (1.707×10^{-4} mmol/mL)] concentrations were prepared using MHB. 100 µl of each dilution was loaded in the respective well of the microtitre plate. 100 µl of MHB is used as a control. Erythromycin, Nalidicxic acid and Amikacin were used as standard drugs. The plate was incubated at 37°C for 18-24 h. The dilution showed no growth is termed as bacterial and the dilution showed bacterial growth inhibition was termed as inhibitory activity of IS's.

Recovery plate technique: 20 µl of each well was streaked onto the sterile nutrient agar plates. The plates were incubated at 37°C for 18-24 h. The presence of growth was confirmed by imidazolium salts which have no bactericidal activities and absence of growth is confirmed that that the IS's has bactericidal activities.

Well diffusion technique: Antimicrobial activities of IS's against Gram negative (Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus vulgaris) and Gram positive (Staphylococcus aureus) microorganisms under well diffusion technique. Antimicrobial screening is conducted by well diffusion technique as zone of inhibition with diameters. IS's are screened for their microbial activities under well diffusion method (Figures 2-6). Eight IS's were spread on petri dish plate and screened well diffusion with five test pathogens (Table 7). From the bacterial screening, we found that imidazolium bromide [(MNMNBI) Br^-] **1b** showed effective zone of inhibition while compared with other synthesized drug molecules.

Microdilution technique: We have screened the minimum inhibitory concentration (MIC) and minimum bacterial concentration (MBC) activities of our IS against Gram negative and Gram positive human pathogens under micro dilution technique (Table 8). We have observed that **1b** showed excellent anti-microbial activities against Escherichia coli than the Proteus vulgaris and other pathogens are observed from good to moderate activities.

Binding site prediction via docking studies: Computer assisted molecular docking studies are carried out in order to find out the host-guest binding interaction between our synthesized unsubstituted/nitro substituted IS's with different proteins. Figures 7-11 showed clearly how the pathogens are effectively binds with our IS's via host-gust interactions (ligand bond, hydrogen bonding etc). Compound **2a** showed effective hydrogen bonding with E.coli pathogens. There are two amino acids residue like Cys, 238 A°, Ser 70 A° interacts with **2a** via hydrogen bonding (Figure 7). Similarly we have run the docking studies of other synthesized IS's to analysis host guest interaction with compound **1b** against P. vulgaris and S. aureus observed hydrogen bonding with two amino acid residues (Figures 10 and 11). Compound **2f** and **1b** showed mild interaction with available amino acid residues (Figures 8 and 9).

HB plots of microorganism of E. coli (5DWK), K. pneumonia (5EEC), P. aeruginosa (4Y9P), P. vulgaris (1KOZ) and S. aureus (3VUA) for compound **2a, 2f** and **1b** respectively HB plots give additional evidence for effective binding between various human pathogenic microorganisms against our IS's (Figures 12-16).

Table 7: Antibacterial screening of MNMBI and MNMNBI with different counter anions against human pathogens under disc diffusion method

S. No	Standard drug (30 µg/well) Imidazolium cation with different anions (µg/well)			Zone of inhibition (mm)				
				Gram-negative organism				Gram-positive organism
				Escherichia coli	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	*Proteus vulgaris*	*Staphylococcus aureus*
1	Erythromycin			26.5	25	25.5	31.5	23
2	Nalidixic acid			21	26	20	23	21.5
3	Amikacin			21	19.5	17.5	17.5	19
4	MNMBI with	Br^- 1a	25	5.5	5	5	6	6
			50	7	6	6.5	7.5	8
			75	9	1	10	11	11
			100	11	12	11	12	13
5		BF_4^- 2a	25	5	5	5	5.5	6
			50	6.5	6.5	6	7	8
			75	8	8	8	9	10
			100	11	10	10	11	12
6		PF_6^- 2b	25	6	5.5	6	5.5	6.5
			50	7.5	7	7.5	7.5	8
			75	9	8.5	9	9.5	10
			100	11	10	11	11	12
7		$CF_3SO_3^-$ 2c	25	6.5	6	5	5	7
			50	7.5	7	6.5	6	8.5
			75	9	9	8.5	7.5	10.5
			100	11	11	11	9	12
8	MNMNBI with	Br^- 1b	25	6.5	6	5.5	6	7
			50	8	7.5	7	8	9
			75	10	9	9	10	10.5
			100	12.5	11	11.5	12	13
9		BF_4^- 2d	25	6	6	6	5.5	6.5
			50	7.5	7.5	7	6.5	8
			75	9.5	9	8.5	8	10
			100	12	11.5	10.5	10	12.5
10		PF_6^- 2e	25	5.5	6	5	5	7
			50	6.5	7.5	6.5	6	8.5
			75	8	9	8	8	10
			100	10.5	11	10	10	12.5
11		$CF_3SO_3^-$ 2f	25	5	5	5.5	5.5	6
			50	6.5	6	7	6.5	8
			75	8	7.5	8.5	8	10
			100	10	9	10.5	10	12

Table 8: Antibacterial assay of MNMBI and MNMNBI with different counter anions against test bacteria using micro-dilution method

Microorganism	Study	Imidazolium cation with different anions										
		MNMBI with				MNMNBI with				Standard drug		
		Br^- 1a	BF_4^- 2a	PF_6^- 2b	$CF_3SO_3^-$ 2c	Br^- 1b	BF_4^- 2d	PF_6^- 2e	$CF_3SO_3^-$ 2f	*Erythromycin*	*Nalidixic acid*	*Amikacin*
Escherichia coli	MIC	40	50	50	30	30	40	40	40	10	10	10
	MBC	40	50	50	30	30	40	40	40	10	10	10
Klebsiella pneumoniae	MIC	40	50	50	50	30	40	40	40	10	10	10
	MBC	40	50	50	50	30	40	40	40	10	10	10
Pseudomonas aeruginosa	MIC	40	50	50	50	30	40	40	40	10	10	10
	MBC	40	50	50	50	30	40	40	40	10	10	10
Proteus vulgaris	MIC	40	50	50	50	30	40	40	40	10	10	10
	MBC	40	50	50	50	30	40	40	40	10	10	10
Staphylococcus aureus	MIC	40	50	50	50	30	40	40	40	10	10	10
	MBC	40	50	50	50	30	40	40	40	10	10	10

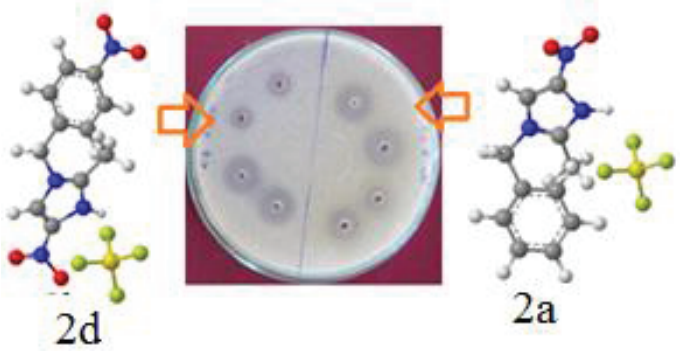


Figure 2: Zone of inhibition against *E. coli* with different concentrations (25, 50, 75 and 100 µg/well) of [MNMBI) BF_4^-] **2a** and [(MNMNBI) BF_4^-] **2d.**

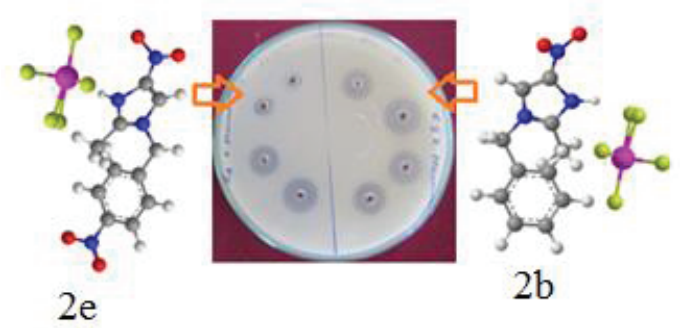


Figure 3: Zone of inhibition against *K. pneumoniae* with different concentrations (25, 50, 75 and 100 µg/well) of [MNMBI) PF_6^-] **2b** and [(MNMNBI) PF_6^-] **2e.**

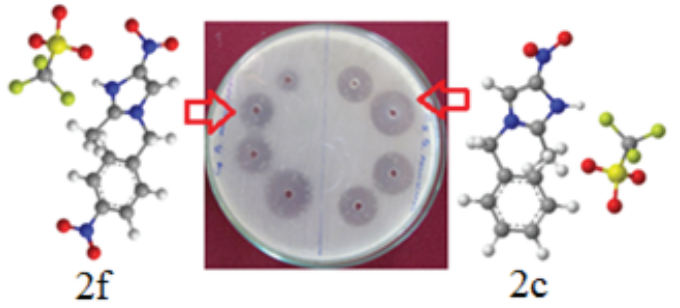


Figure 4: Zone of inhibition against *P. aeruginosa* with different concentrations (25, 50, 75 and 100 µg/well) of [MNMBI) $CO_3SO_3^-$] **2c** and [(MNMNBI) $CO_3SO_3^-$] **2f.**

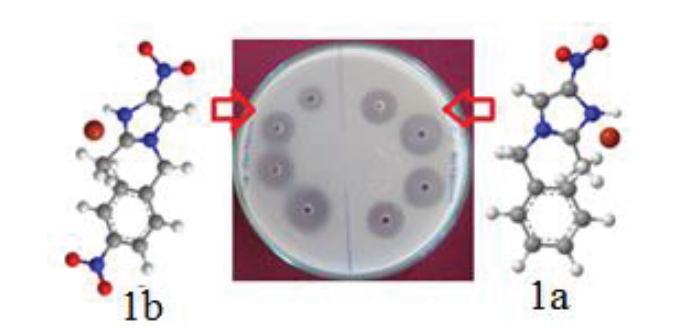


Figure 5: Zone of inhibition against *P. vulgaris* with different concentrations (25, 50, 75 and 100 µg/well) of [MNMBI) Br^-] **1a** and [(MNMNBI) Br^-] **1b.**

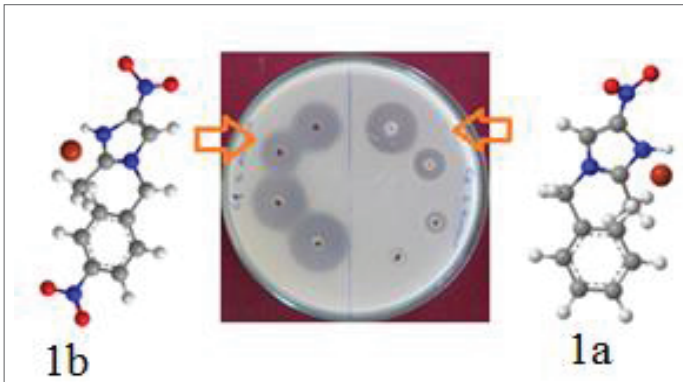


Figure 6: Zone of inhibition against *S. aureus* with different concentrations (25, 50, 75 and 100 µg/well) of [MNMBI) Br^-] **1a** and [(MNMNBI) Br^-] **1b.**

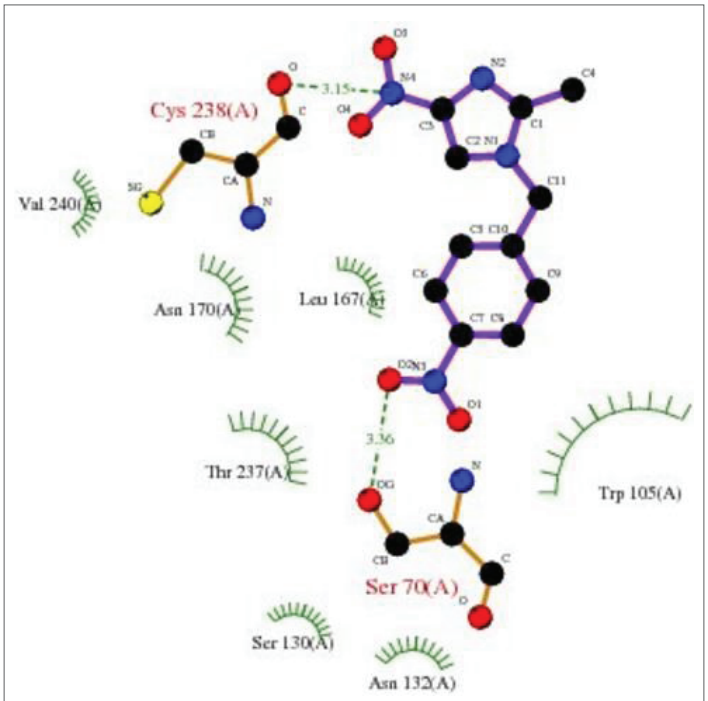


Figure 7: 2D plot of *E. coli* (PDB ID: 5DWK) with [(MNMBI) BF_4^-] **2a.**

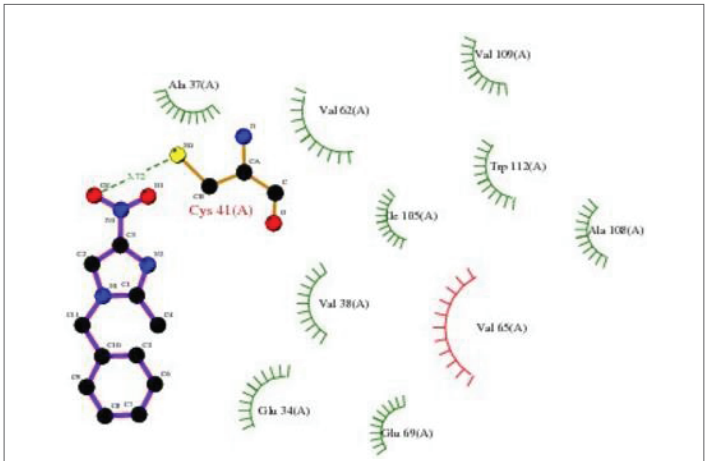


Figure 8: 2D plot of *K. pneumoniae* (PDB ID: 5EEC) with [(MNMNBI) CF_3SO_3-] **2f.**

Citation: Ganapathi P, Ganesan K (2017) Synthesis and Characterization of Antibacterial Ionic Liquids Moieties under Multiple Routes and their Catalytic Responses. J Drug Res Dev 4(1): doi http://dx.doi.org/10.16966/2470-1009.138

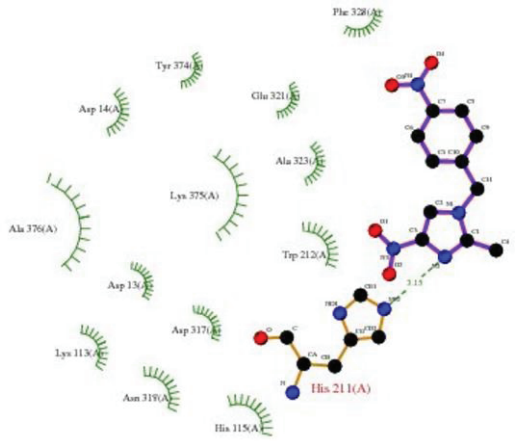


Figure 9: 2D plot of *P. aeruginosa* (PDB ID: 4Y9P) with [(MNMNBI) Br$^-$] **1b.**

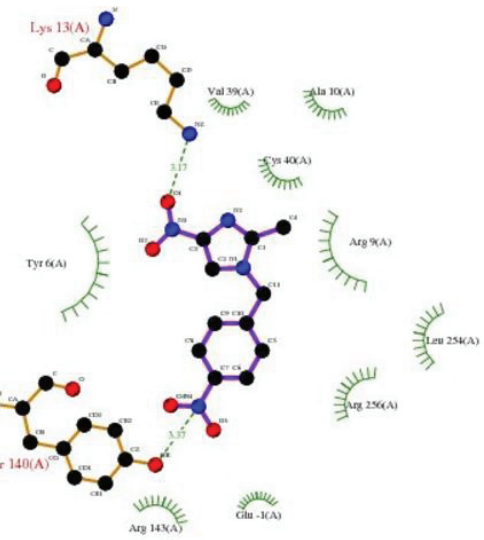


Figure 10: 2D plot of *P. vulgaris* (PDB ID: 1KOZ) with [(MNMNBI) Br$^-$] **1b.**

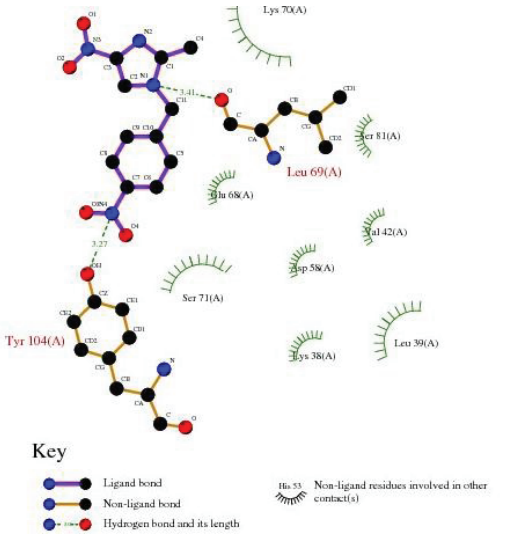


Figure 11: 2D plot of *S. aureus* (PDB ID: 3VUA) with [(MNMNBI) Br$^-$] **1b.**

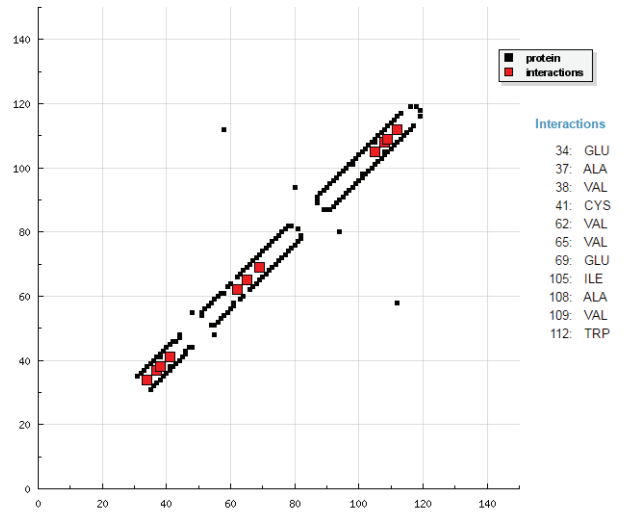


Figure 12: HB plot of *E. coli* (PDB ID: 5DWK) with [(MNMBI) BF_4^-] **2a.**

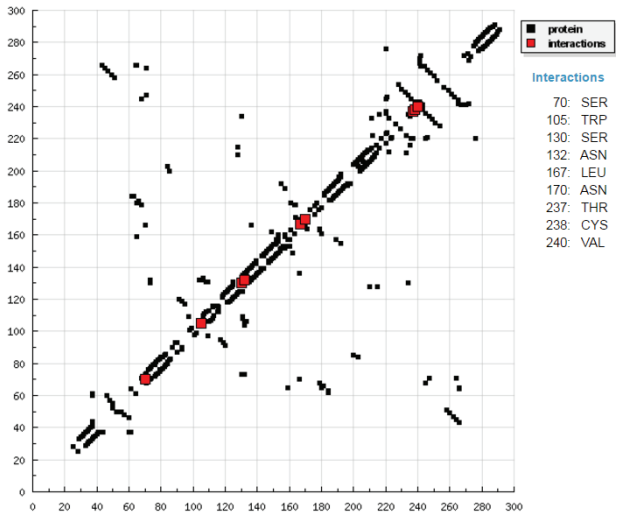


Figure 13: HB plot of *K. pneumoniae* (PDB ID: 5EEC) with [(MNMNBI) $CF_3SO_3^-$] **2f.**

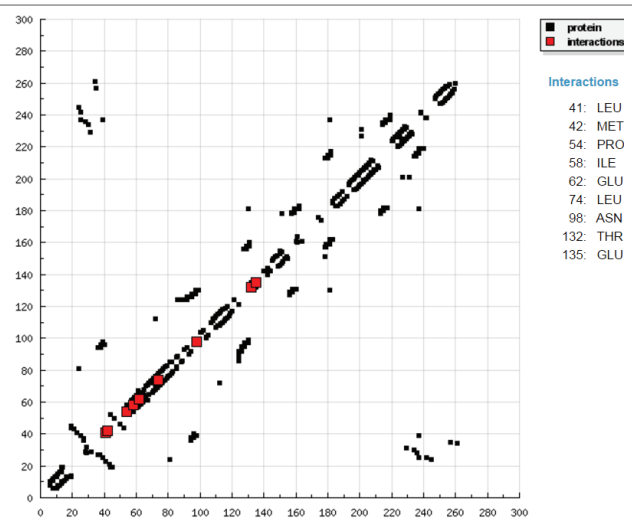


Figure 14: HB plot of *P. aeruginosa* (PDB ID: 4Y9P) with [(MNMNBI) Br$^-$] **1b.**

Citation: Ganapathi P, Ganesan K (2017) Synthesis and Characterization of Antibacterial Ionic Liquids Moieties under Multiple Routes and their Catalytic Responses. J Drug Res Dev 4(1): doi http://dx.doi.org/10.16966/2470-1009.138

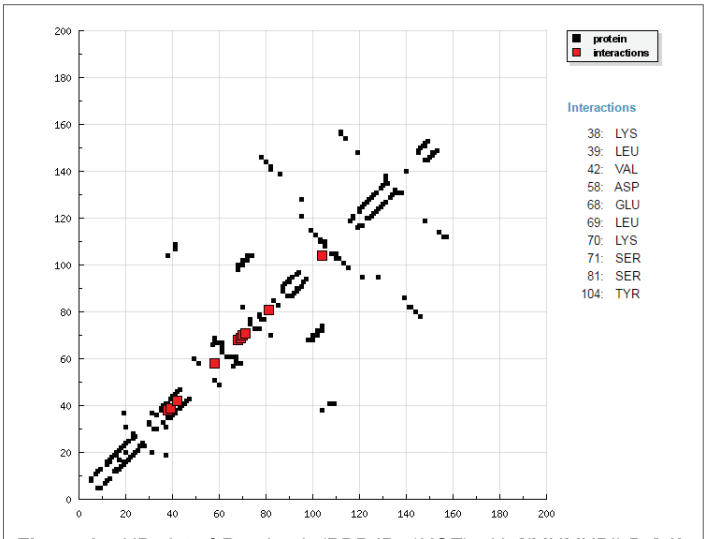


Figure 15: HB plot of *P. vulgaris* (PDB ID: 1KOZ) with [(MNMNBI) Br] **1b.**

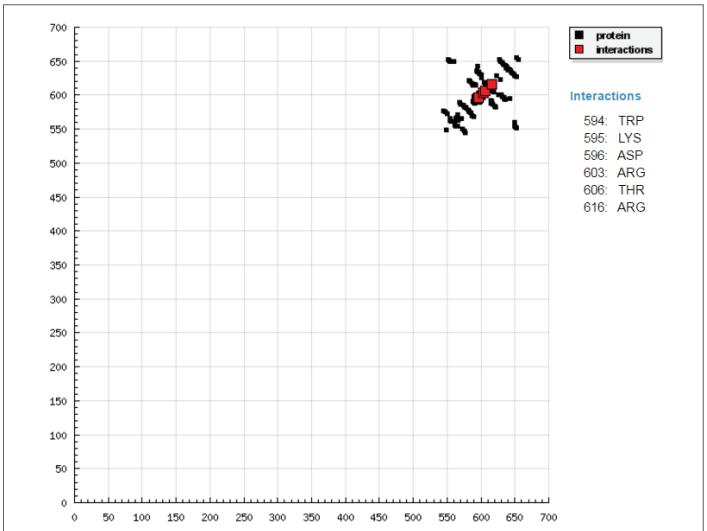


Figure 16: HB plot of *S. aureus* (PDB ID: 3VUA) with [(MNMNBI) Br] **1b.**

From the molecular docking analysis; showed hydrogen bonding, hydrophobicity as well as Vanderwall interactions with different a peptides are observed between E. coli with [(MNMBI) Br] **1a** (Figure 17). Molecular docking studies are extended for other pathogen like K. pnemoniae with [(MNMBI) PF_6^-] **2b** showed effective hydrogen bonding with six different amino acids (Figure 18). Also we found that interesting host-guest interaction from docking analysis are shown effective binding against P. aeruginosa, P. vulgaris and S. aureus against compound **1b** (Figures 19-21). From the bacterial as well as molecular docking studies; host-guest interaction like hydrogen bonding, Vanderwall bonding as well as hydrophobic interaction between test pathogens and IS are very effective.

From the docking studies, observed that effective binding between human pathogenic bacteria's and our synthesized compounds via hydrogen bonding under least energy levels. Nitro substituted imidazolium bromide showed effective hydrogen bonding (TYR 6 (-1.66), TYR arg (-1.224) under lowest intermolecular energy at -7.17 against P. vulgaris. Then we have extended the hydrogen bonding studies with our nitro substituted imidazolium bromide against various pathogens like E. coli, K. Pneumonia, P. aeruginosa, S. aureus. Among these five pathogens our IS's showed binding under least energy level as follows order P. vulgaris>P. aeruginosa>E. coli based on number of hydrogen bonding, intermolecular energy, other physical parameters are available in table 9. Rest of the other our synthesized IS's are showed host-guest between\ human pathogen from good to moderate value.

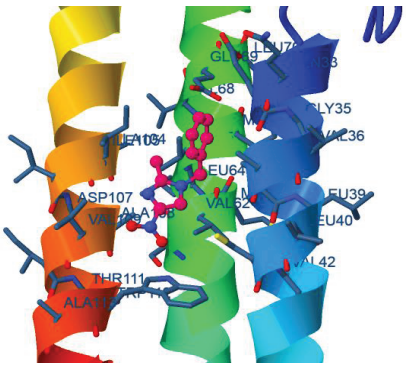


Figure 17: The following amino acid residues from *E. coli* showed effective binding interaction with [(MNMBI) Br] **1a** GLU34 (-0.586), CYS41 (-0.285), TRP112 (-0.533), ALA37 (-0.4145), VAL62 (-0.814), VLA38 (-0.618).

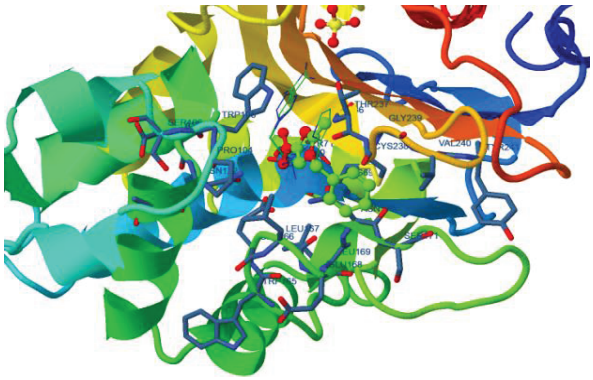


Figure 18: The following amino acid residues from *K. pneumoniae* showed effective binding interaction with [(MNMBI) PF_6^-] **1c** SER70 (-0.30), SER130 (-0.284), TRP105 (-2.562), ASN132 9-0.406), THR237 (-0.677), LYS73 (-0.175).

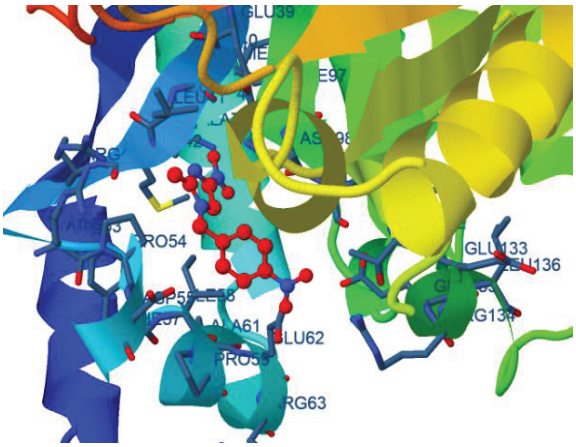


Figure 19: Amino acid residues from *P. aeruginosa* showed effective binding interaction with [(MNMNBI) Br] **1b** HIS211 (-0.724), LYS375 (-0.969), HIS115 (-0.377), ASN318 (-0.329), ALA376 (-1.106), TRP212 (-0.335).

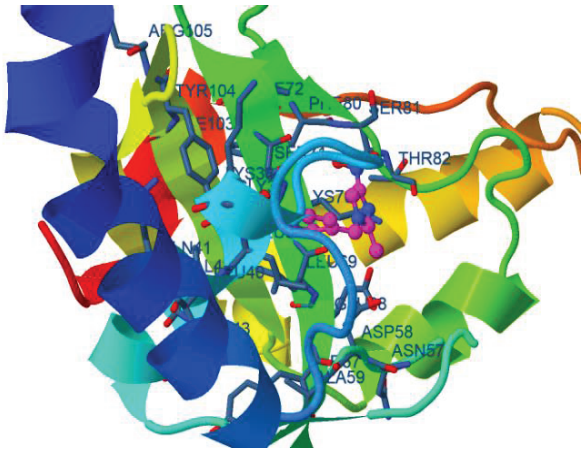


Figure 20: *P. vulgaris* showed effective binding interaction with [(MNMNBI) Br⁻] **1b** LYS13 (-0.553), TYR140 (-0.321), TYR6 (-1.697), ARG143 (-0.439), LEU254 (-0.698), ARG9 (-1.224).

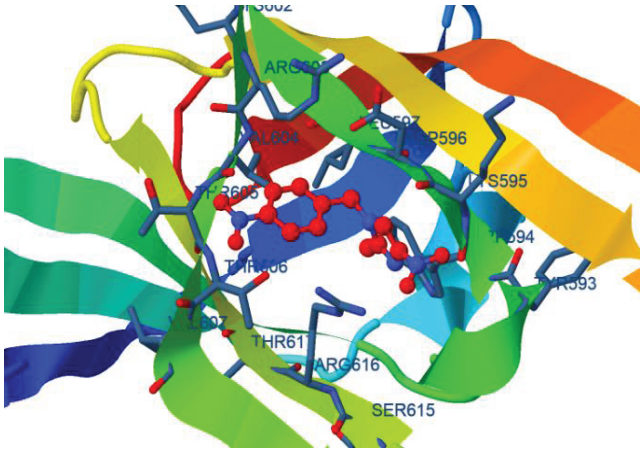


Figure 21: Amino acid residues from *S. aureus* showed effective binding interaction with [(MNMNBI) Br⁻] **1b** LYS695N (-1.09), TRP694 (-0.824), ARG616 (-1.431), THR606 (-0.668), ASP696 (-0.906), ARG603 (-0.584).

Table 9: Physical parameters of Vanderwall, hydrogen bonding, electric force, effective hydrogen bonding between amino acids and IS **1** (**a, b**) and **2** (**a-f**)

Organism	Imidazolium cation with different counter anions								
			1a	2a	2b	2c	1b	2d	2e	2f
Escherichia coli	Est. Free Energy of Binding (kcal/mol)		-4.11	-3.88	-3.93	-3.89	-4.62	-4.61	-4.36	-4.57
	Est. Inhibition Constant, Ki (uM)		972.61	1.44	1.32	1.4	412.03	420.73	638.38	443.83
	vdW+Hbond+desolv Energy		-5.11	-5.01	-4.81	-4.49	-6.06	-6.06	-5.7	-5.96
	Electrostatic Energy		-0.06	0.14	-0.04	-0.31	0.12	0.12	-0.02	0.1
	Total Intermolecular Energy		-5.17	-4.87	-4.85	-4.8	-5.94	-5.94	-5.73	-5.86
	Interact. Surface		495.557	491.356	488.502	471.968	534.45	537.703	542.393	536.232
	Decomposed Interaction Energies (kcal/mol)	Hydrogen bond	GLU34 (-0.586)	VLA109 (-0.794)	VAL38 (-0.408)	GLU34 (-0.996)	ALA108N (-8.65)	TRP112 (-1.773)	TRP112 (-0.676)	TRP112 (-0.688)
			CYS41 (-0.285)	VLA65(-0.693)	ALA106 (-0.343)	GLN33 (-0.573)	VAL62 (-2.641)	VAL65 (1.392)	GLU34 (-0.552)	ALA37 (-0.316)
		Polar	TRP112 (-0.533)	ALA37 (-0.268)	ILE105 (-1.621)	VAL65 (-0.511)	1LE105 (-0.314)	GLU34 (-0.402)	VAL62 (-0.603)	VAL 109 (-0.611)
			ALA37 (-0.4145)	VAL38 (-0.230)	VAL65(-0.475)	ALA37 (-0.506)	VAL109 (-0.571)	ALA112 (-0.426)	ALA37 (-0.451)	VAL65 (-0.545)
		Hydrophopic	VAAL62 (-0.814)	TRP112 (-0.964)	TRP112 (-0.817)	ILE105 (-0.852)	ALA37 (-0.170)	ALA108 (-13.14)	VAL65 (-1.098)	1LE105 (-1.103)
			VLA38 (-0.618)	ILE105 (-0.820)	GLU69 (-0.223)	VAL38 (-0.565)	TRP112 (-0.841)	VAL62 (-2.878)	VAL109 (-0.726)	VAL62 (-0.619)
Klebsiella pneumoniae	Est. Free Energy of Binding (kcal/mol)		-4.41	-4.85	-4.24	-4.09	-4.62	-4.76	-5.16	-4.75
	Est. Inhibition Constant, Ki (uM)		586.32	278.97	777.28	1	412.03	322.22	164.29	331.31
	vdW+Hbond+desolv Energy		-5.31	-5.54	-4.95	-4.81	-6.06	-6	-6.27	-6
	Electrostatic Energy		0.03	-0.39	-0.17	-0.17	0.12	-0.08	-0.15	-0.13
	Total Intermolecular Energy		-5.29	-5.93	-5.13	-4.97	-5.94	-6.08	-6.41	-6.13
	Interact. Surface		527.418	544.622	521.604	523.308	534.45	546.296	574.446	572.792
	Decomposed Interaction Energies (kcal/mol)	Hydrogen bond	TRP105 (-9.42)	THR237 (-0.684)	SER70 (-0.3)	SER70 (-0.344)	ALA108 (-8.656)	ASN132 (-0.507)	ASN170 (-4.034)	SER70 (-0.342)
			SER70 (-0.172)	SER70 (-0.423)	SER130 (-0.284)	THR237 (-0.2)	VAL62 (-2.641)	GLU166 (-0.315)	SER70 (-0.247)	CYS238 (-0.19)
		Polar	ASA170 (-1.105)	SER130 (-0.305)	TRP105 (-2.562)	LEU167 (-0.20)	ILE105 (-0.314)	ASN170 (-1.041)	ASN132 (-0.609)	THR237 (-0.882)
			ASN132 (-0.448)	THR235 (-0.252)	ASN132 (-0.406)	SER130 (-0.19)	VAL109 (-0.66)	LYS73 (-0.153)	LYS73 (-0.62)	SER130 (-0.379)
		Hydrophopic	LEU167 (-0.850)	TRP105 (-1.205)	THR237 (-0.677)	TRP105 (-2.06)	TRP112 (-0.841)	LEU167 (-1.085)	TRP105 (-2.242)	TRP105 (-2.523)
			VAL240 (-0.455)	ASN132 (-0.107)	LYS73 (-0.175)	PRO104 (-0.45)	ALA37 (0.170)	TRP105 (-0.780)	LEU167 (-1.485)	LEU167 (-0.379)

Pseudomonas aeruginosa	Est. Free Energy of Binding (kcal/mol)		-4.74	-4.63	-4.57	-4.74	-6.21	-5.33	-5.32	-5.22
	Est. Inhibition Constant, Ki (uM)		336.07	401.77	447.29	332.6	28.12	124.82	125.8	150.18
	vdW+Hbond+desolv Energy		-5.21	-4.75	-4.8	-5.09	-6.68	-5.86	-5.93	-5.87
	Electrostatic Energy		-0.52	-0.8	-0.71	-0.57	-0.79	-0.72	-0.73	-0.56
	Total Intermolecular Energy		-5.73	-5.54	-5.51	-5.65	-7.47	-6.58	-6.66	-6.43
	Interact. Surface		560.548	654.447	599.396	566.785	612.98	688.314	707.415	620.877
	Decomposed Interaction Energies (kcal/mol)	Hydrogen bond	HIS211 (-0.77)	LYS330 (-0.810)	LYS330 (-0.84)	HIS211 (-0.772)	HIS211 (-0.724)	LYS330 (-0.689)	LYS330 (-0.753)	LYS330 (-0.71)
			LYS375 (-0.606)	GLU74 (-0.651)	VAL72 (-0.753)	LYS375 (-0.62)	LYS375 (-0.969)	GLU321 (-0.319)	GLU321 (-0.275)	TRP212 (-0.83
		Polar	HIS115 (-0.485)	TRP212 (-0.776)	GLU74 (-0.952)	HIS115 (-0.48)	HIS115 (-0.377)	VAL72 (-0.745)	PHE463 (-0.74)	ILE156 (-0.83)
			LYS113 (-0.357)	PHE328 (-0.613)	ILE156 (-0.467)	LYS113 (-0.34)	ASN318 (-0.329)	PHE463 (-0.394)	VAL72 (-0.693)	HIS115 (-0.242)
		Hydrophopic	GLU74 (-1.134)	LEU325 (-0.206)	LYS375 (-0.428)	GLU74 (-1.151)	ALA376 (-1.106)	GLU74 (-0.791)	GLU74 (-0.800)	GLU74 (-1.029)
			TRP212 (-0.357)	ALA323 (-0.168)	THR160 (-0.157)	TRP212 (-0.28)	TRP212 (-0.335)	LYS375 (-0.7433)	LYS375 (-0.724)	HIS211 (-0.452)
Proteus vulgaris	Est. Free Energy of Binding (kcal/mol)		-4.95	-5.17	-5.02	-4.96	-5.97	-5.92	-4.91	-5.89
	Est. Inhibition Constant, Ki (uM)		233.95	162.65	210	232.02	42.25	45.94	251.54	47.8
	vdW+Hbond+desolv Energy		-5.57	-5.72	-5.3	-5.46	-6.59	-6.48	-6.31	-6.4
	Electrostatic Energy		-0.3	-0.39	-0.63	-0.39	-0.57	-0.66	0.09	-0.69
	Total Intermolecular Energy		-5.87	-6.1	-5.93	-5.85	-7.17	-7.14	-6.22	-7.1
	Interact. Surface		616.514	614.411	568.966	622.451	657.381	655.69	694.424	661.55
	Decomposed Interaction Energies (kcal/mol)	Hydrogen bond	GLU1 (-0.297)	ARG256 (-1.286)	LYS13 (-0.562)	ARG143 (-1.14)	LYS13 (-0.553)	TYR140 (-0.286)	ARG143 (-1.119)	GLU253 (-0.748)
			ARG164 (-0.344)	TYR144 (-0.711)	ARG9 (-0.537)	ARG256 (-1.01)	TYR140 (-0.321)	TYR6 (-1.761)	GLU253 (-0.956)	ARG143 (-0.596)
		Polar	ARG143 (-1.097)	LEU254 (-0.729)	TYR6 (-0.889)	TYR6 (-0.773)	TYR6 (-1.697)	ARG143 (-0.396)	ASP252 (-0.740)	TYR6 (-1.942)
			ARG256 (-0.898)	TYR140 (-0.306)	VAL39 (-0.392)	TYR144 (-0.75)	ARG143 (-0.439)	LYS13 (-0.279)	ARG256 (-0.532)	VAL39 (-0.785)
		Hydrophopic	TYR6 (-0.758)	GLU253 (-0.611)	GLU253 (-0.929)	PHE0 (-0.564)	LEU254 (-0.698)	LEU254 (-0.601)	TYR6 (-1.015)	TRY144 (-0.428)
			TYR144 (-0.875)	ASP252 (-0.453)	GLN42 (-0.493)	TYR140 (-0.38)	ARG9 (-1.224)	ARG9 (-1.258)	PHE0 (-0.7922)	TYR140 (-0.343)
Staphylococcus aureus	Est. Free Energy of Binding (kcal/mol)		-4.19	-3.71	-4.22	-4.08	-3.57	-3.78	-3.73	-3.93
	Est. Inhibition Constant, Ki (uM)		853.2	1.91	808.76	1.02	2.42	1.7	1.86	1.32
	vdW+Hbond+desolv Energy		-4.35	-4.5	-4.58	-4.42	-4.91	-5.22	-4.7	-4.85
	Electrostatic Energy		-0.75	-0.07	-0.66	-0.63	-0.1	0.25	-0.22	-0.27
	Total Intermolecular Energy		-5.11	-4.57	-5.25	-5.05	-5.01	-4.97	-4.92	-5.12
	Interact. Surface		404.822	461.717	408.977	404.059	527.058	554.182	463.749	504.888
	Decomposed Interaction Energies (kcal/mol)	Hydrogen bond	LYS09 (-1.129)	TRP594 (-0.1729)	LYS609 (-1.637)	LYS609 (-1.59)	LYS695N (-1.09)	ASP591 (-0.778)	LYS595 (-0.492)	LYS595 (-0.55)
			ASN614 (-0.501)	ASN14 (-0.37)	ASN614 (-0.340)		TRP694 (-0.824)	LYS609 (-0.389)		TRP594 (-0.517)
		Polar	PRO611 (-1.0128)	ARG616 (-1.006)	PRO611 (-1.58)	PRO611 (-0.95)	ARG616 (-1.431)	ASP596 (-0.468)	ARG616 (-1.30)	ARG616 (-1.674)
				LYS609 (-0.783)			THR606 (-0.668)	ARG616 (-0.421)	ASN614 (-0.536)	
		Hydrophopic	ASP591 (-0.585)	ASP591 (-1.004)	ASP591 (-0.589)	ASP591 (-0.43)	ASP696 (-0.906)	ASN614 (-0.229)	ASP591 (-0.888)	ASP591 (-0.422)
							ARG603 (-0.584)		LYS609 (-0.659)	

Conclusions

We have prepared variety of substituted IS's under conventional and silica supported Muffle furnace method. From the preparation, solvent free silica supported method is much appreciable than the conventional due to lesser reaction time, higher yield, non-toxic and easy work up. Catalytic activities of optimized concentration of our eight IS's for Pechmann reaction were studied. Among these, nitro substituted imidazolium cation with bromide counter ion showed effective catalytic response than the others. We have employed several phenols such as phenol, 2-naphthol, 4-chlorophenol, 4-nitrophenol for Pechmann reaction under conventional as well as solvent free approach in absence and presence of IS's. Among these 4-chlorophenol reacts faster than the others. Solvent free Muffle furnace in the presence of optimum concentration of IS's showed nearly 50 times faster than the conventional method. Antimicrobial activities of our synthesized IS's against human pathogenic organisms were studied. We found that our IS's gives much more effective response than the poisonous and toxic Selenium containing of ionic liquids which are reported in literature [35]. Our nitro substituted imidazolium bromide **1b** showed excellent antibacterial activity against tested organisms. Nitro substituted imidazolium cation with PF_6^-, BF_4^- and $CF_3SO_3^-$ counter anions showed good anti-bacterial responses. We found that unsubstituted IS showed moderate response under MIC studies.

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