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Novel Unsymmetrical Dicationic Pyrrolidinium Ionic Liquids: Synthesis, Characterization and Antimicrobial Activities

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Dicationic ionic liquids (DILs) have sparked a lot of attention due to their high melting point, better solubility, thermal stability and facilitated the creation of molecules with precise functions and application requirements. Dicationic ionic liquids have garnered significant attention in the field of green synthesis media due to their diverse cationic groups. In this work, four environmental friendly unsymmetrical dicationic room temperature ionic liquids with different cationic were synthesized by a simple neutralization process. The structure of the newly synthesized DILs was confirmed by FTIR, ^{1}H NMR, ^{13}C NMR, elemental and ESI-HRMS spectral analyses. All the synthesized DILs were also screened for antifungal, anti-inflammatory and antioxidant activities. When compared the microbial activities of DILs of different cations, the results showed that all the synthesized DILs were effective against *Candida albicans* fungi and had good scavenging activity in DPPH and against protein denaturation with their respective standards. Because of their sulphonic acid and hydroxyl groups in DIL-III and D-IV were the most promising candidates for antifungal, anti-inflammatory and antioxidant properties.

Keywords: Dicationic ionic liquids, Pyrrolidinium ionic liquids, Biological activities, DPPH assay, Protein denaturation.

INTRODUCTION

Green chemistry has grown increasingly relevant in the field of chemical synthesis in recent years. As a result, developing ecologically beneficial activities that may be carried out in aqueous media is extremely desirable. However, numerous environmental friendly procedures for green chemistry have been devised including solvent-free reactions and non-traditional modes of activation such as ultrasound (or) microwave [1]. At room temperature, ionic liquids are salts composed of organic cations and inorganic anions with melting temperatures of less than 100 ºC. The combination of cations with various inorganic or organic anions produced a large volume of liquid salts that exhibit a numerous range of applications [2]. Cations and anions transformed with appropriate functional groups change ionic liquid characteristics [3] and are used in the pharmaceutical sector since they contain water-soluble hydrophilic units and pharmaceutically active hydrophobic units [4].

Recently, research issues centered on the development of a new type of ionic liquid known as dicationic ionic liquids (DILs). It is composed of two cationic head groups linked by a rigid or flexible distinct alkyl chain length. DILs exceed typical monocations in terms of active sites, selectivity and thermal stability. Because of their exceptional qualities, they have been utilized in chromatography as electrolytes, lubricants and stationary phases [5,6]. To achieve their physical properties, dicationic ionic liquids typically contain ammonium, phosphonium, imidazolium, pyridinium or pyrrolidinium in their chemical structures.

DILs have been found to exhibit enhanced application capabilities at low temperatures. Unsymmetrical DILs with two distinct cationic head groups and hetero-anionic ILs with two different anions coupled with the cationic part are both feasible. Unsymmetrical DILs have different physical properties than symmetrical DILs, particularly their melting point. As a result, the cationic groups with different substituents have a significant impact on the properties of ionic liquids [7]. In general, the antimicrobial effects of pyrrolidinium and piperidinium ionic liquids are less pronounced than those of imidazolium salts [8,9]. This fact was attempted to be addressed by adding various

heterocyclic rings and functional groups to the parent pyrrolidinium cationic component of ionic liquids.

Based on this, in this work, four unsymmetrical dicationic ionic liquids were synthesized and successfully characterized. In order to evaluate their antifungal, antioxidant and protein-degradation inhibitory activities, four antimicrobial rings with distinct therapeutic properties were selected and transformed them into four dicationic ionic liquids. In all the synthesized asymmetric DILs, one cation is common in all and the other cation is different. Cationic differentiation was introduced with the help of pyridine, imidazole, quinoline and biphenyl rings.

EXPERIMENTAL

The chemicals *viz*. acetone (99%, Merck), bromoethane (98%, Avra), bromoacetic acid (98%, Avra), chloroethanol (99%, Sigma-Aldrich), chlorosulfonic acid (99%, Merck), 1,2-dichloroethane (98%, Avra), diiodomethane (98%, Avra), DMSO (99%, Merck), DMF (99%, Merck), diphenylamine (95%, SRL), ethylacetate (99%, Merck), ethanol (98%, Avra), 1-methylimidazole (99%, Merck), pyridine (98%, Avra), pyrrolidine (99%, Merck), quinoline (98%, Avra) employed in this study were all analytical grade and utilized without additional purification.

FTIR, ^{1}H & ^{13}C NMR and mass spectrometry were used to characterize all four synthesized dicationic liquids. The FTIR spectra of DILs were recorded using the KBr pellet method (Thermo-Nicolet-50 with inbuilt ATR, Shimadzu, Japan) at 4000-400 cm^{-1}. ^{1}H & ^{13}C NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer at 400 and 101 MHz, respectively using TMS as reference solvent. On the Xevo G2-XS Quadrapole time of flight mass spectrometry, electrospray ionization mass spectra (ESI-MS) were obtained.

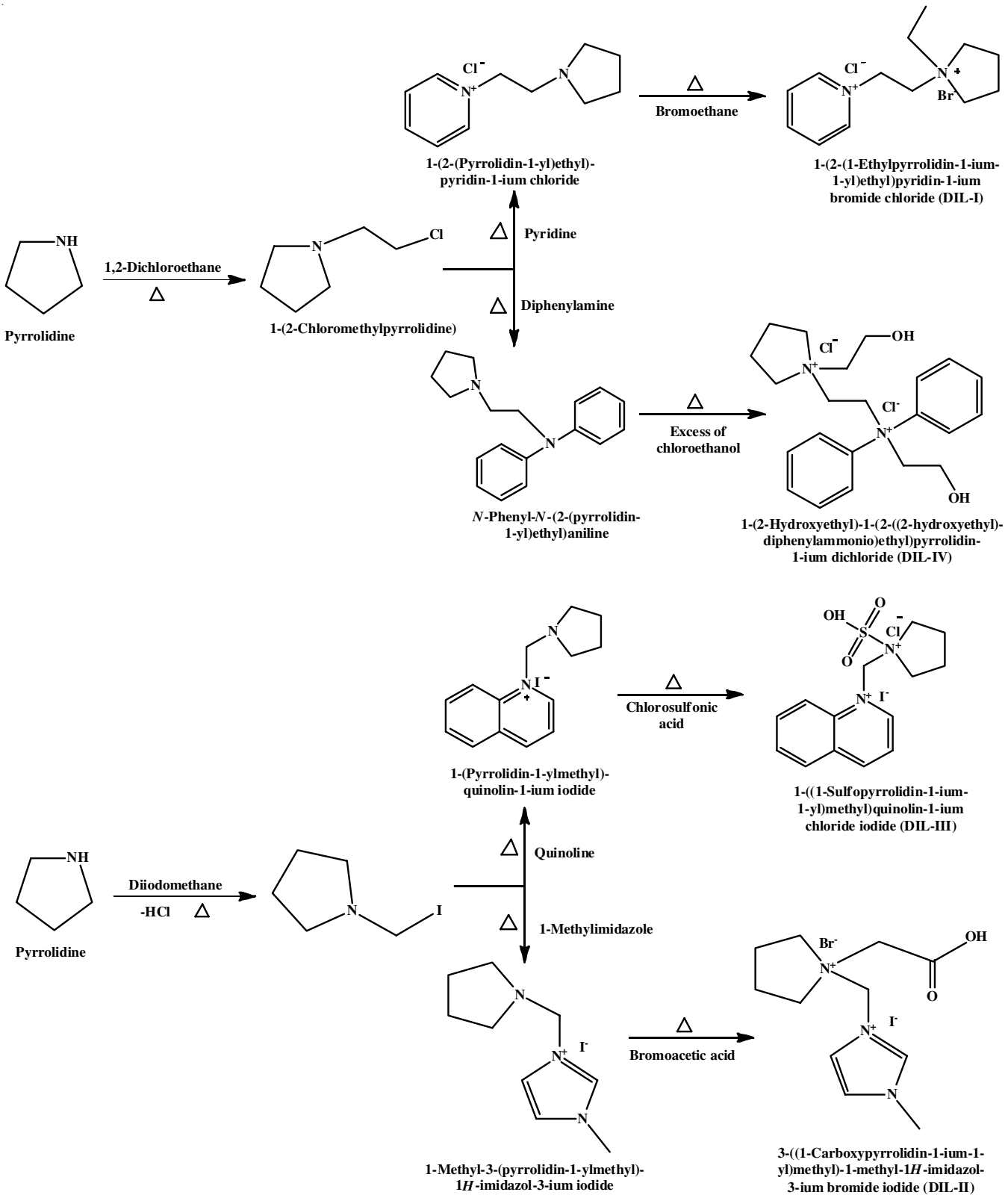
Synthesis of dicationic ionic liquids

Synthesis of 1-(2-(1-ethylpyrrolidin-1-ium-1-yl)ethyl)-pyrridinium bromide chloride (DIL-I): A 0.1 mol of 1-(2-chloroethyl)pyrrolidine (13.3 g) was mixed with 0.1 mol of pyridine (7.9 g) in a two-necked round bottom flask and then refluxed at 80 ºC for 24 h. A brown solid was obtained as an intermediate and the flask was allowed to cool at room temperature. To the above reaction mixture, 0.1 mol of bromoethane (10.8 g) was added and refluxed for another 24 h at 80 ºC in an inert atmosphere. Finally, a brown viscous liquid was obtained. The completion of the reaction was confirmed with TLC. The obtained brown viscous liquid was washed with ethyl acetate in order to remove the unreacted material and the solvent was removed by rotator evaporator (**Scheme-I**). The end product was dried under a vacuum. Brown colloidal liquid, yield: 74%. Elemental analysis for $C_{13}H_{22}N_2BrCl$ (m.w. 321.63) calcd. (found) %: C, 48.50 (48.55); H, 6.84 (6.80); Cl, 11.02 (11.12); N, 8.71 (8.76); Br, 24.87 (24.78). FTIR (KBr, ν_{max}, cm^{-1}): 3278.87, 3112.97, 2966.72, 2749.95, 1588.94, 1492.52, 1173.20, 1073.68, 1026.46; ^{1}H NMR (400 MHz DMSO-d_6) δ ppm: 8.08 (m, 6H, CH) (J = 7.5 Hz), 6.88 (t, 2H, CH_2) (J = 8.4 Hz), 6.58 (t, 3H, CH_2) (J = 7.2 Hz), 3.64 (t, 3H, CH_2), 2.81 (m, 5H, CH_2) (J = 6.9 Hz), 1.54 (t, 3H,CH_2); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 21.26, 23.29, 24.15, 38.97, 39.75, 40.37, 45.09, 53.32, 63.07, 117.16, 120.28, 129.55,143.95; ESI-HRMS: [M$^+$] *m/z* calculated 206.18; found 206.51.

Synthesis of 3-((1-carboxymethyl)pyrrolidin-1-ium-1-yl)methyl)-1-methyl-1*H*-imidazol-3-ium bromide iodide (DIL-II): A mixture containing 0.1 mol of 1-iodomethyl pyrrolidine (21.1 g) and 0.1 mol of 1-methyl imidazole (8.2 g) were discharged into the round bottom flask coupled with a reflux condenser and refluxed at 82 ºC for 24 h. Subsequently, it was allowed to cool at room temperature, then 0.1 mol of bromoacetic acid (13.8 g) was added to the above reaction mixture and the reflux was continued overnight at the same temperature under a nitrogen atmosphere [10] (**Scheme-I**). To remove the unreacted material, ethyl acetate was used and then the product was dried under vacuum. Yield: 82%, Elemental analysis for $C_{10}H_{17}N_3O_2BrI$ (*m.w.* 289.50) calcd. (found) %: C, 28.69 (28.73); H, 4.06 (4.26); Br, 19.13 (19.19); N, 10.04 (10.23); O, 7.65 (7.57); I, 30.36 (29.35). FTIR (KBr, ν_{max}, cm^{-1}): 3407.68, 3135.21, 2977.43, 1720.51, 1618.93, 1581.75, 1227.73, 1170.12, 1087.72; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.29 (s, 1H, OH), 7.34 (m, 3H, CH) (J = 1.9 Hz), 4.67 (q, 4H, CH_2) 3.84 (t, 3H, CH_3), 3.3 (s, 2H, CH_2), 2.50 (q, 4H, CH_2); ^{13}C NMR (400 MHz DMSO-d_6) δ ppm: 20.99, 36.68, 39.28, 39.59, 39.80, 41.01, 129.56, 133.05, 136.20, 152.46; ESI-HRMS: [M$^+$] *m/z* calculated 211.26; found 211.82.

Synthesis of 1-((1-sulfopyrrolidin-1-ium-1-yl)methyl)-quinolinium chloride iodide (DIL-III): An equimolar amount of 1-iodo-methyl pyrrolidine (0.1 mol, 21.1 g) and quinoline (0.1 mol, 12.9 g) were poured into the double-necked round bottom flask connected with a reflux condenser and the mixture was agitated at 82 ºC for 24 h. The reaction was stopped and the reaction mixture was cooled to room temperature followed by the addition of chlorosulphonic acid (0.1 mol, 11.6 g) and refluxed at the same temperature over the nitrogen atmosphere for another 24 h. The black solid of the product formation was confirmed by TLC and the excess of starting materials were removed by ethyl acetate (**Scheme-I**). The product was dried under a vacuum. Black solid, yield: 77%. Elemental analysis for $C_{14}H_{18}N_2O_3SICl$ (*m.w.* 289.50) calcd. (found) %: C, 36.80 (36.74); H, 3.94 (4.01); Cl, 7.77 (7.75); N, 6.13 (6.34); O, 10.31 (10.27); S, 7.01 (7.16); I, 27.67 (27.52). FTIR (KBr, ν_{max}, cm^{-1}): 3431.91, 3056.63, 1640.41, 1596.44, 1560.33, 1380.08, 1301.33, 1155.01, 1027.97; ^{1}H NMR (400 MHz DMSO-d_6) δ ppm: 11.26 (s, 1H, OH), 9.25 (d, 2H, CH) (J = 5.9 Hz), 8.32 (m, 4H, CH) (J = 8.2 Hz), 7.97 (m, 3H, CH) (J = 7.4 Hz), 3.24 (m, 4H, CH_2), 1.78 (q, 4H, CH_2); ^{13}C NMR (400 MHz DMSO-d_6) δ ppm: 23.40, 24.83, 39.97, 54.07, 63.33, 66.33, 77.86, 122.48, 125.63, 128.26, 130.32, 134.55, 134.82, 146.80; ESI-HRMS: [M$^+$] *m/z* calculated 294.10, found 294.41.

Synthesis of 1-(2-hydroxyethyl)-1-2-((2-hydroxyethyl)-diphenyl ammonio)ethyl)pyrrolidin-1-ium dichloride (DIL-IV): A mixture of 1-(2-chloroethyl)pyrrolidine (0.1 mol, 13.3 g) and diphenylamine (0.1 mol, 16.9 g) were placed in the two necked round bottom flask and refluxed at 80 ºC for 24 h. To a reaction mixture, 0.2 mol of chloroethanol was added drop wise and again refluxed for another 20 h. A brownish-black colour liquid was acquired as the final product and the



Scheme-I: Synthesis of dicationic ionic liquid

completion of the reaction was confirmed with TLC. Ethyl acetate was used to remove the unreacted stating materials and finally dried under vacuum (**Scheme-I**). Blackish brown liquid, yield: 80%. Elemental analysis for $C_{22}H_{32}N_2O_2Cl_2$ (*m.w.* 289.50) calcd. (found) %: C, 61.81 (61.76); H, 7.49 (7.56); Cl, 16.60 (16.78); N, 6.56 (6.45); O, 7.49 (7.53). FTIR (KBr, ν_{max}, cm^{-1}): 3373.91, 3063.56, 2974.61, 2603.98, 1633.08, 1178.30, 1030.06; ^{1}H NMR (400 MHz DMSO-d_6) δ ppm: 9.24 (t, 3H, CH_2), 8.02 (m, 7H, CH_2) (J = 8 Hz), 2.50 (m, 8H, CH_2); ^{13}C NMR (400 MHz DMSO-d_6) δ ppm: 19.39, 20.81,

21.67, 35.58, 36.99, 37.29, 37.61, 38.73, 42.49, 50.36, 50.61, 50.93, 51.20, 54.04, 56.73, 61.73, 124.98, 126.48, 134.82,143.56, 144.64, 144.98; ESI-HRMS: [M^+] *m/z* calculated 356.25, found 356.55.

Antifungal activity: An analysis of four newly synthesized dicationic ionic liquids from a microbiological perspective was carried out to ascertain their methods to defend themselves against adverse fungus [11]. *In vitro* antifungal activity of fluconazole and its combined effects with four synthesized DILs were assessed using the well-diffusion method. Stock cultures were kept at 4 ºC on the nutritional agar slopes and potato dextrose agar plates. For 3-5 days, fungus cultures were cultured at 27 ºC. Transferring a loop full of cells from stock cultures into test tubes containing 50 mL nutrient broth created the active culture for studies. After that the fungus was grown at 27 ºC for 3-5 days using the test organism suspension that had been identified on potato dextrose agar. After being moved to nutritional agar media slants, one colony was cultivated for 24 h. A single colony was transferred to nutritional agar media slants and cultured for 24 h at 37 ºC and for 3-5 days at 27 ºC using potato dextrose agar. By using the well-diffusion method, the antifungal activity of crude extract extracts was evaluated [12,13]. A 20 mL of molten medium were poured into sterilized petri plates to develop the MHA plates. A homogeneous 20-25 µL suspension of fungal inoculums was swabbed after the media had solidified. After that 10-40 µL of sample were added to the wells and then incubated for 48 h at 37 ºC. Triplicates of the assay were performed and control plates were kept as well. The zone of inhibition was measured in millimeters from the well's edge to the zone [14].

Anti-inflammation method: Protein denaturation was used to assess the potential *in vitro* anti-inflammatory action of pyridinium-based DILs. Protein denaturation has been linked to the development of inflammatory illnesses such as rheumatoid arthritis, arthritis and cancer as protein loses their biological activity. As a result, a substance's ability to prevent protein denaturation may also help in the prevention of inflammation. A 500 µL of 1% bovine serum albumin and 10-100 µL of DILs make up the reaction mixture. The mixture was then incubated at 37 ºC in an incubator for 15 min before being heated at 51 ºC for 20 min. The absorbance at 660 nm was measured after the sample had been left at room temperature for 10 min using aspirin as a control [15]. The experiment was repeated three times and the percentage of inhibition for protein denaturation was estimated using the formula:

$$\text{Inhibition (\%)} = 100 - \left(\frac{OD_{control} - OD_{product\ test}}{OD_{control}} \right) \times 100$$

Antioxidant method: The antioxidant property of four unsymmetrical dicationic ionic liquids was examined using 1,1-diphenyl-2-picrylhydrazine (DPPH) assay [16]. Different concentrations of samples (10, 20, 40, 60, 80 and 100 µL) were taken in this technique and 50 µL of 0.659 mM DPPH dissolved in methanol solution was added to bring up to one with double distilled water. The vials were incubated at 25 °C for 20 min in complete darkness. When DPPH was combined with samples, the violet solution turned yellow, indicating that the reduced form of DPPH was obtained [17]. The decrease in absorbance at 510 nm was observed using Shimadzu UV 1800 spectrophotometers and vitamin C as the standard reference [18]. The procedure followed for the control with blank.

$$\text{DPPH radical scavenging activity (\%)} = \frac{A_0 - A_1}{A_0} \times 100$$

where A_0 is the absorbance of the control and A_1 is the absorbance of the sample. All tests were performed in triplicate and the average value was computed.

RESULTS AND DISCUSSION

All the synthesized four unsymmetrical dicationic pyrrolidinium ionic liquids (DILs) are soluble in both in water as well as in common organic solvents like ethanol, methanol, isopropyl alcohol, acetonitrile, DMSO, DMF, chloroform, *etc*. In IR spectra of DIL-II, the peaks observed at 3407 and 1618 cm^{-1} are attributed due to the -OH moiety and –C=O group of the carboxyl group, whereas in DIL-III, the peaks observed at 3431and 1301 cm^{-1} are responsible for –OH and S=O groups. The peak found at 3407 and 3373 cm^{-1} are due to the hydroxyl group of DILII and DIL-IV, respectively. The other key bands of the FTIR are shown in Table-1. The mass values of *m/z* for DIL-I, DIL-II, DIL-III and DIL-IV were found at *m/z* 206.51, 211.82, 294.41 and 356. which are equal to $[M\text{-}X]^+$, $M^+ = [C_{13}H_{22}N_2]^+$, $M^+ = [C_{10}H_{17}N_3O_2]^+$, $M^+ = [C_{14}H_{18}N_2O_3S]^+$ and $M^+ = [C_{22}H_{32}N_2O_2]^+$, respectively.

TABLE-1
KEY IR BANDS (cm^{-1}) OF UNSYMMETRICAL DICATIONIC PYRROLIDINIUM IONIC LIQUIDS (DILs)

Functional group	DIL-I	DIL-II	DIL-III	DIL-IV
ν(OH)	–	3407	3431	3373
ν(CH)	2966	2977	2600	2974
ν(C-C)	2749	2749	2550	2603
ν(>C=O)	–	1618	–	–
ν(C-N)	1073	1087	1027	1030
ν(S=O)	–	–	1301	–
ν(>C=C)	1588	1581	1640	1633
ν(N-H)	3278	3135	3056	3063

Biological evaluations

Antifungal activity: Fluconazole and four synthesized DILs were investigated *in vitro* antifungal susceptibility against *Candida albicans*. For comparison, equimolar quantities (10, 20, 30, 40 µL) of each of four DILs were used to quantify the fungal growth impairment. Higher concentrations significantly increased the inhibition activity, which is shown that pathogens responded differently to various DILs. The antifungal activity of DILs rose linearly with increasing concentration [19]. When the results were compared, to standard drug, the results proved that in the DILs for antifungal activity. The order of zone of inhibition was in the following order DIL-III > DIL-IV > DIL-II > DIL-I (Fig. 1).

The highest antifungal activity exhibited by DIL-III is due to the presence of quinolinium cation in its structure. The

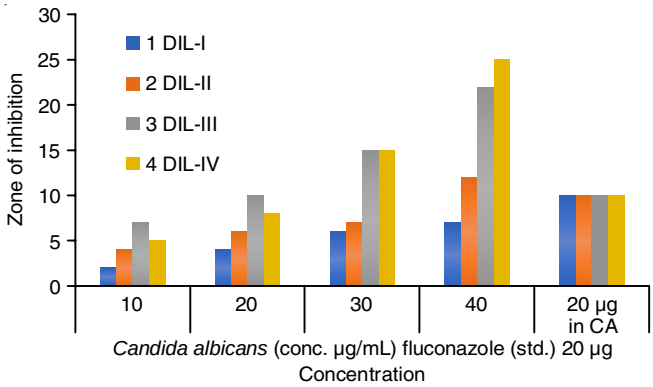


Fig. 1. Comparative study of the antifungal activity of the unsymmetricalal dicationic room temperature ionic liquids

antibacterial activity of synthesized DILs increased at lower pH [20]. Because of this DIL-IV has the superior antibacterial activity than DIL-II. Since DIL-I does not contain any pH responsible groups, it has the least active antibacterial properties.

Anti-inflammatory activity: The current study found the anti-inflammatory properties of four newly synthesized ionic liquids *in vitro*. When the percentage inhibition of four DILs was compared, it was observed that DIL-IV was more active than other three DILs. DIL-IV relied heavily on the pyrrolidinium and diphenyl ammonium cations. Polar groups and their hydrogen bonding were investigated and found that polar groups role to protein conformational stability [21].

The presence of hydroxyl groups found in the side chain contributes positively to protein stability due to the formation of hydrogen bonding. As DIL-IV consists of two hydroxy groups protect the protein from denaturation. Similarly, the sulfonic acid present in the DIL-III also stabilizes the protein against denaturation due to hydrogen bond. The same way, the hydroxyl group in DIL-II molecule also prevents protein denaturation to some extent. DIL-I exhibits less activity against protein degradation than other DILs because it lacks sulfonyl, hydroxyl, carboxyl-like moieties in its structure, which can provide the stabilization by hydrogen bonding. In this investigation, the methanolic extracts of DIL-IV showed a remarkable inhibition of 81% at 50 µL and aspirin was 88% at the same concentration. The anti-inflammatory activities of the DILs are shown as DIL-IV > DIL-III > DIL-II > DIL-I (Fig. 2).

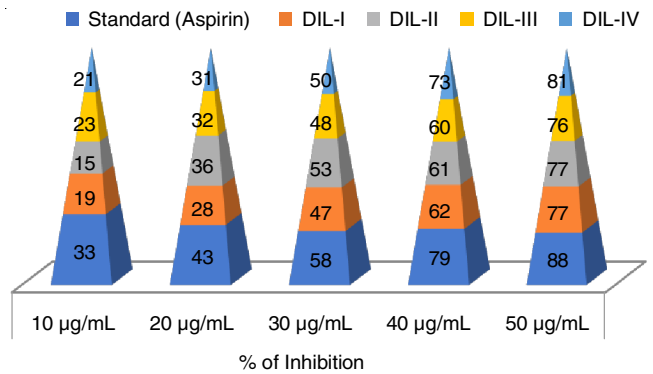


Fig. 2. Comparative study of the anti-inflammatory activity of unsymmetricalal dicationic room temperature ionic liquids

Antioxidant activity: The capacity of the synthesized DILs to neutralize the DPPH radical was evaluated and the IC_{50} values are shown in Table-2. Lower IC_{50} values are interrelated to the higher ionic liquids radical scavenging capacity [22]. D-ascorbic acid (vitamin C) was used as a control for antioxidant activity. The results demonstrated that all synthetic DILs had lower IC_{50} values than the reference, which implied that all the synthetic DILs have greater antioxidant activity than the standard reference.

TABLE-2
ANTIOXIDANT ACTIVITY DATA OF THE SYNTHESIZED UNSYMMETRICAL DICATIONIC PYRROLIDINIUM IONIC LIQUIDS (DILs)

Sample conc. (µg/mL)	Percentage of inhibition				Ascorbic acid
	DIL-I	DIL-II	DIL-III	DIL-IV	
10	13.92	9.01	25.64	43.77	27.85
20	15.45	11.26	42.88	49.56	30.75
40	18.58	15.37	46.74	70.64	48.18
60	22.37	20.68	71.04	77.23	53.75
80	28.32	21.64	83.91	76.11	55.93
100	34.72	22.12	88.09	83.55	62.71
IC_{50}	54.87	25.93	18.97	11.16	19.65

A closer look at the antioxidative activity of the prepared DILs shows that DIL-IV has stronger activity than the other three DILs, which is attributed to the two free OH moieties present in them. DIL-III has a secondary superior activity because it contains a quinine ring that has antimicrobial activity. The stronger activity of DIL-II than DIL-I is due to the presence of imidazole ring present in it.

Conclusion

In this study, a simple solvent-free quaternization approach was adopted to synthesize four unsymmetricalal dicationic ionic liquids successfully. Due to factors like quicker reaction times, easier work procedures and environmental safety, the solvent-free method has proven to be more beneficial than the traditional one. High yields even in favourable conditions show that this approach provides a very efficient synthetic route to ionic liquids. The antimicrobial study's findings demonstrated that four DILs with pyrrolidine-based anti-anxiety medicinal capabilities varied in their antioxidative, antifungal and anti-inflammatory activities due to variations in another ring that was present in them. Functional groups and another ring found in conjugated RTILs play an important role in antimicrobial activity. Among the synthesized compounds, DIL-IV consist of two hydroxyl groups and a pyridine ring shown the excellent activity against fungal, inflammation and oxidation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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