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Research Article

Synthesis, Structural Identification and Biological Potencies of Quinolinium Sulfonamide Ionic Liquids

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ABSTRACT

Members of the quinoline family include several alkaloids. Alkaloids are found in foods and beverages that humans consume daily and in various stimulants. Among many other activities, they act against inflammation, cancer, bacteria, fungi and pain. Modifications of the alkyl chain after N-alkylation can alter the physicochemical properties and affect its multifunctional properties. This article describes the preparation and structural identification of five quinolinium sulfonamide ionic liquids that differ in N-alkylation functional group and chain length. Functional group and alkyl chain length in the N-alkylation of ionic liquids of quinolinium sulfonamide ionic liquids significantly affected the antioxidant activity and C-1 showed the highest antioxidant activity with the lowest IC_{50} of 20.56. Variation of substituents in the N-alkylation of ionic liquids of quinolinium sulfonamide also significantly affected its antibacterial and antifungus activity, with C-1 exhibiting the greatest activity. In addition, experimental results indicate that quinolinium sulfonamide ionic liquids significantly prolong normal human plasma's prothrombin time (PT).

Introduction

In modern days ionic liquids are used as a good alternative to organic solvents. This is because of its negligible vapor pressure, good thermal stability, reversible viscosity, non-volatile, zero non-flammability, low melting, chemical stability and good solubility with water and organic solvents.[1] They are made up of ion pairs bound by non-covalent interactions and have incalculably appealing features that make them useful for a variety of applications.[2,3] Ionic liquids differ from one to another by the nature and size of their cations and anions. In general, heterocyclic compounds such as pyridinium, pyrrolidinium, quinolinium, isoquinolinium, phosphonium and quaternary ammonium salts are used as cations, and halogens, BF_4, PF_6, etc act as anions. The ionic liquids' structural design is crucial for managing the temperature thresholds, self-assembly, and associated functional features.[4] Another key characteristic of ILs is the presence of ions with decreased or no symmetry, which limits the packing of molecules into low-energy crystal structures and thus lowers the melting point.[5,6] Since they can have endless structural variations by changing cations, anions, and substituents, their physical and functional properties could be fine-tuned.[7,8] Imidazolium, pyridinium, pyrrolidinium, quaternary ammonium, or phosphonium cations are the building blocks of the majority of ionic liquids. Due in large part to the fact that it is anticipated that the quinolinium and iso quinolinium ionic liquids will have greater melting temperatures, they have received significantly less attention in research. However, these ionic liquids could be helpful as water-free ways to extract organic compounds.

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Sulfonamides are a significant class of synthetic antimicrobial medications used pharmacologically as broad-spectrum antibiotics for treating bacterial infections in humans and animals.[9,10] Sulfonamides are functional units in a large number of biologically important compounds. Sulfonamide derivatives are known to have a variety of pharmacological effects, including those against Alzheimer's disease,[11] tumor, cancer,[12] inflammation,[13] hypertensive, malarial,[14] convulsant activity, protease inhibitors,[15] and antileishmanial.[16] Because of the above-mentioned salient feature of the sulphonamide group an attempt was made to introduce sulfonamide groups in ionic liquids. By Suzuki coupling reaction, Manoj Kumar *et al.* synthesized sulfonamides, carboxamides, and imidazolium ionic liquid.[17]

Top-selling medications are thought to include heterocyclic compounds, which have pharmacological properties. Heterocyclic compounds are essential components of many therapeutic core structures and play a significant role in biological and pharmacological processes.[18] The heterocycle of relevance in this article, quinoline, is a typical example of a bicyclic heterocyclic molecule. Numerous naturally occurring, physiologically active substances share the quinoline core architecture. The core structure of quinoline is found in many physiologically active alkaloids found in nature. Commonly used pharmaceutical formulations resemble natural heterocycles and exert their power by blocking and disrupting the normal pathways necessary for the growth of dangerous organisms.[19] Here, the heterocyclic core was converted into ionic forms to increase their solubility and facilitate their absorption by animals and plants. Meanwhile, we also revolutionize the number of carbon atoms present in the N-alkylation of the quinoline ring. Accordingly, five diverse ionic liquids were prepared and subjected to basic spectral analysis, the activity of which was also investigated against biological pathogens.

Materials and Methods

Chemistry

The chemicals used were AR grade quinoline, 1-chloroethanol, 1-bromoethane, 1-bromopropane, 1-chlorobutane, 1-bromohexane, sodium amide, benzene sulfonyl chloride, acetone, ethanol, TLC plate coated with silica gel G and deionized water from Sigma-Aldrich. This was used directly without further purification. The synthesized compounds were identified using a well-known KBr pellet method and the ALPHA FTIR (from Bruker, Germany) equipment. Mass spectra were acquired with a Waters Xevo G2-XS-QToF spectrometer. The DMSO-d6 solvent was used to record NMR (proton and carbon) on a JOEL JNM ECX 400P spectrometer operating at 400 MHz. The synthetic steps for the synthesis of quinolinium sulfonamide ionic liquids are given in Scheme 1.

1-(2-hydroxyethyl) quinolin-1-ium Chloride

Equimolar amounts of quinoline (0.1 mole, 12.9 g) and 1-chloroethanol (0.1 mole, 8.05 g) were taken in a two-necked RB flask fitted with a reflux condenser and heated at 70°C simultaneously the reaction mixture was stirred vigorously. After every two-hour interval, the completeness of the reaction was checked by TLC. After 18 hours of reaction completion, the product obtained had a deep honey-like appearance. The product was washed three times with n-hexane to remove the excess reactant involved in the reaction. The yield of the product was about 80% (16.76 g). The same procedure was followed for 1-bromoethane, 1-bromopropane, 1-chlorobutane, and 1-bromohexane.

2-Amino-1-(2-hydroxyethyl) quinolin-1-ium chloride

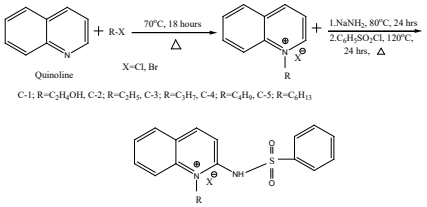
In a two-necked round bottom flask, 0.075 mole of sodium amide (2.9 g) and 0.075 moles of 1-(2-hydroxyethyl) quinolin-1-ium chloride (15.68 g) was added. This combination was heated at 80°C, for around 24 hours. TLC confirmed the product formation. The resulting viscous liquid was subsequently dried under vacuum (yield was 75%, 12.6 g) after being cooled to ambient temperature. The product was washed twice with n-hexane to remove the unreacted starting materials.

1-(2-hydroxyethyl)-2-(phenylsulfonamido)quinolin-1-ium chloride

In a two-necked round bottom flask, an equimolar amount of benzene sulfonyl chloride (0.05 mole, 8.83) and 2-amino-1-(2-hydroxyethyl) quinolin-1-ium chloride (0.05 mole, 11,2 g) was taken. This reaction mixture was vigorously agitated in a nitrogen environment for 24 hours at 120°C. TLC looked at the manufacturing process. After cooling to ambient temperature, the resulting brown solid was filtered to remove the by-product, washed several times with n-hexane and dried under vacuum (yield 82%, 16.5 g). The same procedure was followed for the remaining substituents (C-2 to C-5).

1-(2-hydroxyethyl)-2-(phenylsulfonamido)quinolin-1-ium chloride (C-1)

$C_{17}H_{17}ClN_2O_3S$) was obtained as a brown liquid. Found: FTIR (400–4000cm^{-1}, KBr pellet):
3396.15, 3108.89, 3069.98, 1640.41, 1384.03, 1305.91, 1004.97, 930.73, 692.99; ^{1}H-NMR (400MHz, DMSO-d_6) δ=8.38-8.11 (m, 6H, Ar-H) (J=15.42Hz), 7.99-7.40 (m, 5H,



Scheme 1: Synthesis of quinolinium sulfonamide ionic liquids

Ar-H) (J=15.81Hz), 6.28 (s, 1H, NH), 5.03 (s, 1H, OH), 4.49-4.46 (t, 2H, CH_2) (J=5.8Hz), 3.34-3.30 (t,2H, CH_2) (J=8Hz); ^{13}C-NMR (400MHz, DMSO-d_6) δ=147.57, 144.83, 144.60, 138.74, 137.55, 135.18, 134.15, 130.05, 129.25, 129.15, 128.02, 125.54, 124.61, 121.76,120.12, 62.37, 56.59; ESI-HRMS: [M^+] m/z calculated 329.39; Found:313.46. Elemental Analysis Calculated for $C_{17}H_{17}ClN_2O_3S$: Molecular Weight: 364.84. C, 55.92%; H, 4.66%; Cl, 9.72%; N, 7.67%; O, 13.16%; S, 8.80%. Found: C, 57.60%; H, 4.63%; Cl, 9.66%; N, 7.79%; O, 13.08%; S, 8.75% (Fig. S1-S4).

1-Ethyl-2-(phenylsulfonamido)quinolin-1-ium bromide (C-2:$C_{17}H_{17}BrN_2O_2S$)

was obtained as a brown solid by reaction with benzene sulfonyl chloride (0.05mole) and 2-amino-1-ethyl quinolin-1-ium bromide (yield 85%). Found: FTIR (400-4000cm^{-1}, KBr pellet): 3390.30, 3064.72, 1641.03, 1384.79, 1308.80, 1010.40, 932.44, 690.04; ^{1}H-NMR (400MHz, DMSO-d_6) δ=8.16-7.71 (m, 6H, Ar-H) (J=18Hz), 7.66-7.22 (m, 5H, Ar-H) (J=16Hz), 5.86 (s, 1H, NH) 4.62-4.57 (q, 2H, CH_2) (J=6.66Hz), 1.51–1.48 (t, 3H, CH_3) (J=6Hz); ^{13}C-NMR (400MHz, DMSO-d_6) δ=144.46, 143.36, 141.57, 141.23, 133.97, 130.68, 128.98, 128.60, 126.76, 125.92, 125.67, 124.43, 121.74, 119.93, 119.35, 57.38, 17.47; ESI-HRMS: [M^+] m/z calculated 313.39; Found: 315.41. Elemental Analysis Calculated for $C_{17}H_{17}BrN_2O_2S$: Molecular Weight: 393.29. C, 51.87%; H, 4.32%; Br, 20.34%; N, 7.12%; O, 8.14%; S, 8.14%. Found: C, 51.59%; H, 4.30%; Br, 20.23%; N, 7.08%; O, 8.32%; S, 8.09% (Fig. S5-S8).

1-Propyl-2-(phenylsulfonamido)quinolin-1-ium bromide (C-3:$C_{18}H_{19}BrN_2O_2S$)

was obtained as a brown crystalline solid (yield 88%). Found: FTIR (400-4000cm^{-1}, KBr pellet): 3367.49, 3066.70, 1641.85, 1383.10, 1303.76, 1009.20, 930.68, 689.90; ^{1}H-NMR (400MHz, DMSO-d_6) δ=8.44-7.82 (m, 6H, Ar-H) (J=16Hz), 7.79 -7.54 (m, 5H, Ar-H) (J=12.5Hz), 5.30 (s, 1H, NH), 4.98-4.95 (t, 2H, CH_2) (J=6Hz), 2.26–2.09 (m, 2H, CH_2) (J=6.8Hz)., 1.27–1.23 (t, 3H, CH_3) (J=8Hz); ^{13}C-NMR (400MHz, DMSO-d_6) δ=147.85, 144.85, 144.46, 143.32, 137.45, 135.29, 130.02, 129.58, 129.37, 127.99, 126.63, 125.59, 123.87, 122.42, 121.66, 61.54, 25.12, 12.27; ESI-HRMS: [M^+] m/z calculated 327.42; Found: 329.51. Elemental Analysis Calculated for $C_{18}H_{19}BrN_2O_2S$: Molecular Weight: 407.42. C, 53.02%; H, 4.66%; Br, 19.64%; N, 6.87%; O, 7.85%; S, 7.85%. Found: C, 52.75%; H, 4.64%; Br, 19.54%; N, 6.84%; O, 7.81%; S, 7.84% (Fig. S9-S12).

1-Butyl-2-(phenylsulfonamido)quinolin-1-ium chloride (C-4:$C_{19}H_{21}ClN_2O_2S$)

Was obtained by reaction with benzenesulfonyl chloride and 2-amino-1-butyl quinolin-1-ium chloride. Found: FTIR (400-4000cm^{-1}, KBr pellet): 3401.59, 3067.94, 1638.91, 1383.06, 1305.16, 1006.96, 931.49, 693.77; ^{1}H-NMR (400MHz, DMSO-d_6) δ=8.34-7.82 (m, 6H, Ar-H) (J=16Hz), 7.76-7.26 (m, 5H, Ar-H) (J=16.66Hz)., 5.49 (s, 1H, NH), 4.87-4.84 (t, 2H, CH_2), (J=6Hz), 2.13-2.05 (m, 2H, CH_2) (J=8Hz), 1.42-1.20 (m, 2H, CH_2) (J=4.4Hz), 1.01-0.98 (t, 3H, CH_3) (J=6Hz); ^{13}C-NMR (400MHz, DMSO-d_6) δ=148.52, 147.49, 145.15, 141.79, 138.68, 132.13, 132.09, 131.90, 131.85, 130.82, 130.47, 130.16, 129.13, 123.70, 120.60, 59.18, 37.34, 22.57, 12.51; ESI-HRMS: [M^+] m/z calculated 341.43; Found: 343.45. Elemental Analysis Calculated for $C_{19}H_{21}ClN_2O_2S$: Molecular Weight: 376.88. C, 60.50%; H, 5.57%; Cl, 9.41%; N, 7.43%; O, 8.49%; S, 8.54%. Found: C, 61.17%; H, 5.54%; Cl, 9.36%; N, 6.39%; O, 8.63%; S, 8.75% (Fig. S13-S16).

1-Hexyl-2-(phenylsulfonamido)quinolin-1-ium bromide (C-5:$C_{21}H_{25}BrN_2O_2S$)

Was obtained by reaction with benzenesulfonyl chloride and 2-amino-1-hexyl quinolin-1-ium bromide. Found: FTIR (400-4000cm^{-1}, KBr pellet): 3405.90, 3062.31, 1636.00, 1383.01, 1305.21, 1014.85, 932.23, 692.86; ^{1}H-NMR (400MHz, DMSO-d_6) δ=8.74-7.95 (m, 6H, Ar-H) (J=18Hz), 7.75-7.07 (m, 5H, Ar-H) (J=13.6Hz), 5.79 (s, 1H NH), 3.28-3.24 (t, 2H, CH_2) (J=8Hz), 2.49-2.32 (m, 2H, CH_2) (J=6Hz), 1.53-1.25 (m, 6H, CH_2) (J=6.6Hz)., 122-1.18 (t, 3H, CH_3) (J=8Hz); ^{13}C-NMR (400MHz, DMSO-d_6) δ=146.21, 144.82, 144.23, 143.73, 143.04, 142.22, 141.84, 141.43, 135.07, 133.50, 132.16, 130.17, 128.50, 125.22, 122.95, 56.73, 35.38, 27.48, 26.23, 22.27, 14.06; ESI-HRMS: [M^+] m/z calculated 369.50; Found: 371.49. Elemental Analysis Calculated for $C_{21}H_{25}BrN_2O_2S$: Molecular Weight: 449.50. C, 56.66%; H, 5.56%; Br, 17.80%; N, 6.23%; O, 7.12%; S, 7.05%. Found: C, 55.82%; H, 5.54%; Br, 17.72%; N, 6.21%; O, 7.09%; S, 7.04%(Fig. S17-S20).

Biological Activities

Antioxidant Activity

The 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging test was used to assess the *in-vitro* antioxidant activity using the recommended literature technique.[20–22] The spectrophotometric method utilized by DPPH to measure free radical scavenging activities were slightly modified. A 3 mL aliquot of the freshly made DPPH in methanol (6×10^{-5} M) solution was added to 1-mL of the samples at various concentrations (12.5, 25, 50, 100, 200, and 400 µg/mL). After giving the solutions in tubes 1–5 a thorough shake, they were left to sit at room temperature for 15 minutes in the dark. At 517 nm, the absorbance started to decline. Ascorbic acid served as the reference material. The graph was drawn using the mean values from each test, which were carried out in triplicate. To calculate the %inhibition, the absorbance values of the control and test samples were compared. The formula was used to compute the %inhibition[23]

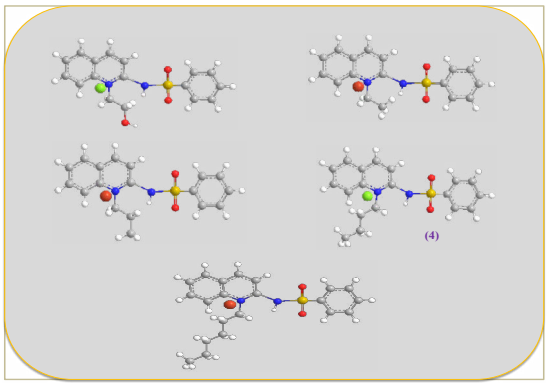


Fig. 1: 3D Structures of the synthesized Quinolinium sulfonamide ionic liquids

$$\text{DPPH scavenging effect (\% inhibition)} = \frac{(A_0 - A_1)}{A_0} \text{ X } 100$$

A_0 denotes the absorbance of the control sample and A_1 that of the test samples. The findings of each test were averaged after being run in triplicates.

Antibacterial and Antifungal Activity

The antibacterial and antifungal properties of quinolinium sulfonamide ionic liquids have been studied[24–27] using the well diffusion method. 25–100 µL of the synthesized compound (in ethanol) was supplementary to the wells. After that, the plates were incubated for 24 hours at 37°C. Assays were run in triplicate, and control plates were also kept. The distance between the well's edge and the inhibition zone was measured in millimeters. Using sterile forceps, the potato dextrose agar wells were put into the agar medium after the cell suspension under test was spread out on a Muller-Hinton agar plate. The thus-created compounds were added to the wells. The plates were then incubated for roughly 24 hours at 37°C while maintaining the control. The free zone was used to measure the zone of inhibition in mm.

Anticoagulant Activity Assay

The anticoagulant activity investigation that was conducted in this article followed the guidelines provided in the literature.[28]

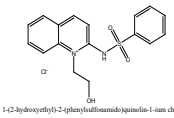
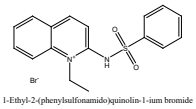
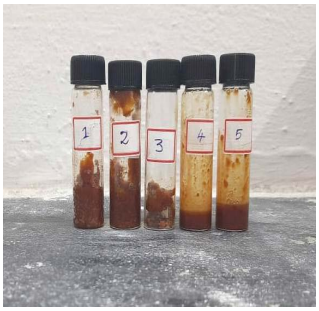
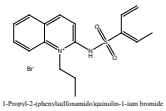
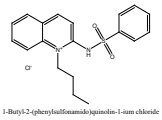
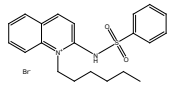
Results and Discussion

The IL structure, chemical name, physical state, color and solubility of the synthesized quinolinium sulfonamide ionic liquids are summarized in Table 1. Fig. 1 depicts the 3D structures of the quinolinium sulfonamide ionic liquids. Table 2 provided the significant IR peak values of the ILs. The peak appearing at around 3,300 cm^{-1} for all the compounds in the five quinolinium sulfonamide ionic liquids prepared is for the stretching frequency of –NH of secondary amine. The peak that appeared at 3108 cm^{-1} for C-1 is due to the presence of the -OH group in the C-1 compound. This peak appeared weak because it was involved in the intra-molecular hydrogen bonding with the lone pair of electrons on the oxygen and sulphur of the sulfonamide moiety. This peak was not seen in other compounds due to the absence of the -OH group. When comparing the IR spectral frequencies of the produced compounds, we can notice slight variations between them since the N-alkylation of the quinoline ring changed the number of carbons in the N-alkylation of quinolinium sulfonamide ionic liquids. The ILs' structures were elucidated by investigations of their elemental and other spectra, which were well validated by their mass spectra. By careful examination of the NMR spectrum of the ILs shows the variation in the values caused by substitutions. The presence of the -OH group is confirmed by the peak at 5.03(singlet) in the NMR spectrum of C-1. The molecular structure of the ILs was studied using electron spray ionization (ESI-HRMS) mass spectrometry. In the mass spectra, the C-1, C-2, C-3, C-4, and C-5 each show a molecular ion peak at m/z 313.46., 315.41, 329.51, 343.45 and 371.49, which is equal to $[M\text{-}X]^+$, $[M = C_{17}H_{17}N_2O_3S]^+$, $[M= C_{17}H_{17}N_2O_2S]^+$, $[M=C_{18}H_{19}N_2O_2S]^+$, $[M= C_{19}H_{21}N_2O_2S]^+$ and $[M = C_{21}H_{25}N_2O_2S]^+$. The molecular ion peak in compound C-1 appears at m/z 313.46. Additionally, upon closely examining the C-1 values obtained from the mass analysis, gained mass is 18 mass units less than the actual mass of the compound. This is because in an alcoholic compound, the -OH group lost its hydration before forming a molecular ion peak and subsequently underwent fragmentation.

Antioxidant Activity

In terms of antioxidant activity, the compounds' ability to snare the DPPH radical was identified and expressed as an IC_{50} value. Antioxidants in the five newly created sulfonium compounds were evaluated. Ascorbic acid was used as the benchmark in this instance. Since ascorbic acid has greater antioxidant activity, the compounds' activity was compared to IC_{50}, which is the concentration of a molecule required to diminish DPPH by 50%. Scheme 2 depicts the mechanism underlying antioxidant activity.[29] Compounds with lower IC_{50} values have higher antioxidant activity. Based on these results documented in Table 3, the IC_{50} values of all synthesized compounds were below standard one(Ascorbic acid). Therefore, these have higher oxidant scores than ascorbic acid. Among the compounds prepared, C-1 achieved the highest antioxidant activity, and the degree of antioxidant among them was in the following order C-1 > C-5 > C-4 > C-3 > C-2. The antioxidant test result showed that the antioxidant property increases as the number of carbons in the quinoline ring's N-alkylation increases. Moreover, compound-1 had higher activity than compound-2 even when both compounds had the same carbon number. The reason for the greater activity of C-1 is the presence of the hydroxyl group.

Table 1: IL structure, name, physical state, color and solubility of the synthesized quinolinium sulfonamide ionic liquids

Compound Code	*Structure of the IL and its name*	*Physical state & Color*	*Solubility*	
			Completely Miscible	*Partially Miscible*
C-1	 1-(2-hydroxyethyl)-2-(phenylsulfonamido)quinolin-1-ium chloride			
C-2	 1-Ethyl-2-(phenylsulfonamido)quinolin-1-ium bromide		Methanol Ethanol DMSO DMF H_2O Isopropanol	DCM Acetone $CHCl_3$
C-3	 1-Propyl-2-(phenylsulfonamido)quinolin-1-ium bromide			
C-4	 1-Butyl-2-(phenylsulfonamido)quinolin-1-ium chloride			
C-5	 1-Hexyl-2-(phenylsulfonamido)quinolin-1-ium bromide			

The enhanced antioxidant activity of compound C-1, compared to the other four produced compounds, is caused by its capacity to donate the hydrogen atom present in -OH in the N-alkylation. Additionally, when the number of carbons in the N-alkylation increases, the DPPH-reducing nature increases.

Antibacterial Activity

Two bacterial strains, *Escherichia coli* and *Staphylococcus aureus*, were chosen, and their antibacterial activity was assessed using the zone of inhibition (ZOI) (Table S1) method at doses ranging from 25 to 100 µg/µL. Gentamycin was utilized as the positive control. The synthesized compounds had the following order of antibacterial activity against *E. coli*:

C-1 is followed by C-5, C-4=C-2, and C-3.

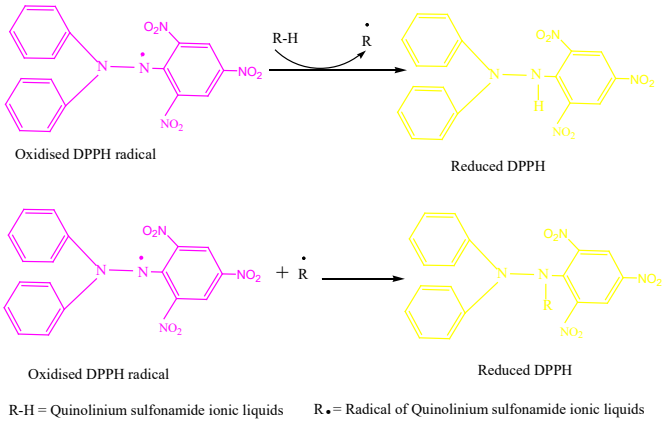
The synthetic compounds' anti-*Staphy-lococcus aureus* activities in order

C-1 is followed by C-5, C-4=C-3, and C-2.

The measured zones of inhibition developed as a function of the different substitutions in the quinoline (at N-alkylation) ring of the sulfonamide are shown in Fig. 2. The zone of inhibition, which evaluates a compound's inhibitory impact on a certain microbe, is the region in which bacterial growth is stopped as a result of the compound's bacteriostatic activity. It is clear that the antibacterial activity of sulfonamide increased as the number of carbon atoms at the N-alkylation of the quinoline ring increased.[30] The higher activity of C-1 than the other compounds is due to the –OH group in

Table 2: FTIR data of the synthesized quinolinium sulfonamide ionic liquids

FTIR Peak Assignment (cm^{-1})	*Quinolinium sulfonamide ionic liquids*				
	C-1	*C-2*	*C-3*	*C-4*	*C-5*
υ(N-H) stretching of secondary amine	3396.15	3390.30	3367.49	3401.59	3405.90
Weak intra-molecular υ(OH)	3738.49	-	-	-	-
υ(C-H) of alkane	3069.98	3064.72	3066.70	3067.94	3062.31
υ (N-H) bending	1640.41	1641.03	1641.55	1638.91	1636.00
υ(S=O) stretching	1384.03	1384.79	1383.10	1383.06	1383.01
υ(C-N)aromatic	1305.91	1308.80	1303.76	1305.16	1305.21
υ(C-N) aliphatic	1004.97	1010.40	1009.20	1006.96	1041.85
υ(N-S) stretching	930.73	932.44	930.68	931.49	932.23
υ(C-S) stretching	692.99	690.04	689.90	693.77	692.86



Scheme 2: Mechanism of the antioxidant activity of quinolinium sulfonamide ionic Liquids

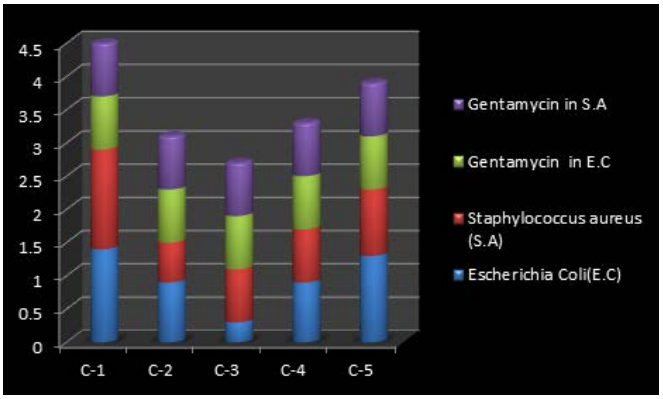


Fig. 2: Antibacterial activity of the synthesized quinolinium sulfonamide ionic liquids

the N-substituent. The numbers of carbons in the alkyl groups found in C-2 to C-5 of the synthesized compounds are 2, 3, 4 and 6, respectively. Therefore, C-5 and C-4 of the synthesized compounds, which contain more carbon atoms than C-3 and C-2, which contain fewer carbon atoms, exhibit higher zones of inhibition.

Antifungal Activity

The *Candida albicans* fungus was used to test the antifungal activity of the newly synthesized sulfonamide functionalized quinolinium ionic liquids. Here, fluconazole was used as the standard. The synthesized compounds have the following order of antifungal activity (Fig. 3).
C-1 comes before C-5, C-4, C-3, and C-2.
In all cases, antifungal activity increases with increasing in compound concentration. Similar to the antibacterial activity of the synthesized compounds, the antifungal activity of C-1 was higher than that of the other compounds (C-2 to C-5) when the alcohol moiety replaced the alkyl moiety. As with antibacterial activity, increasing the number of carbon atoms in the N-alkylation of the quinoline ring also increases its antifungal activity. In general, acidic compounds destroy the cell viability of bacteria and enter the cell, causing changes in the bacterial cell membrane, affecting its protein and nucleic acid synthesis, and acting against the metabolism of bacteria. The presence of the -OH group in C-1 makes it somewhat more acidic than the

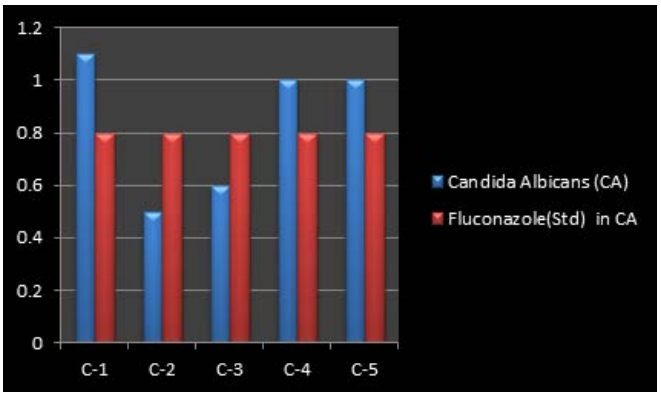


Fig. 3: Antifungal activity of the synthesized quinolinium sulfonamide ionic liquids

other compounds and hence its activity is similar to the above and therefore making it more effective than other compounds against bacteria and fungus.

Anticoagulant Activity

The anticoagulant test for blood clotting effects in normal human plasma was performed in the synthesized sulfonium C-1. Experimental results show that normal human plasma's prothrombin time (PT) was significantly prolonged. Anticoagulation was tested in different solvents (methanol, ethanol, and acetone) with different compound concentrations. Here, heparin was taken as a

Table 3: Antioxidant activity of the synthesized quinolinium sulfonamide ionic liquids

S. No	Compound code	The Concentration of the Sample (µg/mL)						IC_{50}
		12.5	25	50	100	200	400	
1	C-1	23.05 ± 1.0	35.42 ± 1.5	50.34 ± 1.2	62.03 ± 1.7	67.63 ± 0.5	78.98 ± 0.9	20.56
2	C-2	11.19 ± 0.6	20.68 ± 1.5	33.56 ± 1.0	52.37 ± 0.8	65.93 ± 0.8	77.80 ± 1.2	28.13
3	C-3	12.88 ± 1.0	23.05 ± 0.7	35.42 ± 1.0	48.47 ± 0.7	55.42 ± 0.6	80.00 ± 1.2	26.31
4	C-4	16.44 ± 0.5	30.85 ± 1.3	45.59 ± 0.9	51.86 ± 0.8	63.05 ± 1.3	75.76 ± 1.0	24.39
5	C-5	16.61 ± 0.3	31.53 ± 0.6	46.78 ± 0.8	60.34 ± 0.8	74.75 ± 1.2	83.39 ± 0.7	23.14
6	Ascorbic acid (Std)	15.53 ± 1.2	19.74 ± 0.8	28.68 ± 1.0	58.51 ± 1.1	72.37 ± 0.5	81.49 ± 0.5	29.56

Table 4: Anticoagulant activity of the synthesized IL (C-1)

Sample ID	*Solvent*	*Concentration (µg)*	*PT in Sec*	*APTT in Sec*
		100	35.4	62.4
	Ethanol	200	46.5	70.5
		300	57.3	78.4
		100	26.3	51.6
C-1		200	34.5	60.3
	Methanol	300	42.6	67.1
		100	41.1	68.5
		200	46.8	78.2
	Acetone	300	56.3	86.6
Negative control	DMSO	200	14.9	41.8
Positive control.	Heparin	200	>100	>150

Table 5: Nomenclature

ILs	*Ionic Liquids*
Compound-1	1-(2-hydroxyethyl)-2-(phenylsulfonamido) quinolin-1-ium chloride
Compound-2	1-Ethyl-2-(phenylsulfonamido)quinolin-1-ium bromide
Compound-3	1-Propyl-2-(phenylsulfonamido)quinolin-1-ium bromide
Compound-4	1-Butyl-2-(phenylsulfonamido)quinolin-1-ium chloride
Compound-5	1-Hexyl-2-(phenylsulfonamido)quinolin-1-ium bromide

positive control (standard). DMSO was taken as a negative control. Heparin has superior anticoagulant activity, so the activity of C-1 prepared with it was compared. Table 4 shows the anticoagulant activity of C-1 at different concentrations. Acetone has a prolonged clotting time of 68.5, 78.2, and 86.6 seconds. Ethanol has a prolonged clotting time of 62.4, 70.5, 78.4 seconds and methanol has a prolonged clotting time of 51.6, 60.3, and 67.1 seconds at concentrations of 100, 200 and 300 µg, respectively. From the anticoagulant dosage ratio, it is seen that the clotting time increases with increasing compound concentration. Acetone showed great activity among the three solvents. In turn, the activity of the synthesized compound is lower than that of heparin.

Nomenclature

Nomenclature is shown in Table 5

Conclusion

Quinoline base compounds exhibit various therapeutic properties. It is a secondary metabolite of the category of natural nitrogen compounds and belongs to the family of alkaloids. Some of the most important drugs based on quinoline and its derivatives include drugs against malaria, bacteria, cancer, local anesthetics and tuberculosis. Likewise, there are various pharmacological effects associated with sulfonamide derivatives. In this article, an attempt was made to drag both the core properties in a single compound. Based on the above, we have prepared five different N-alkylated quinolinium sulfonamide ionic liquids, which differ in the length of the alkyl chain and the presence of a functional group. Their structures were analyzed using basic spectroscopic analyses such as FTIR, NMR (^{1}H and ^{13}C), and mass spectroscopy. According to the findings of pharmacological screening experiments, the activity of quinolinium sulfonamide ILs varied depending on the presence of the functional group and the length of the alkyl group at the N-alkylation quinoline ring. According to the results of the antioxidant activity tests, C-1 had the highest potency, with an IC_{50} value of 20.56. Among the prepared compounds, C-1 had the largest zone of inhibition value of 1.4 and 1.5 mm. Like the activity against bacteria, the value of C-1 obtained higher activity against *C. albicans* fungus than other compounds and has an inhibition zone of about 1.5 mm. Moreover, it is also observed that as the number of carbon atoms present in the N-alkylation increases, its activity against oxidants, bacteria, and fungi increases. As already mentioned, the biological activities of the synthesized compounds were found to be potent due to the presence of the sulfonamide group found in the side chain of the quinolinium ring and of the quinoline ring. Hence their activity was higher than that of the reference taken for pathogenic effects.

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References

1. Sudhalakshmi J, Rajathi K. Data on creation and description of mono and dicationic bi-functionalized ionic liquids derived from aldehydic functionalized imidazolium ionic liquids. Chemical Data Collections 2023; 43: 100973. https://doi.org/10.1016/j.cdc.2022.100973
2. Smiglak M, Pringle JM, Lu X, Han L, Zhang S, Gao H, MacFarlane DR, Rogers RD. Ionic liquids for energy, materials, and medicine. Chem. Commun. 2014; 50: 9228-9250. https://doi.org/10.1039/C4CC2021A
3. Khupse ND, Kumar A. Ionic liquids: New materials with wide applications. Indian J. Chem. 2010; 49A: 635-648. https://nopr.niscpr.res.in/bitstream/123456789/9662/1/IJCA%2049A%2805-06%29%20635-648.pdf
4. Devaki SJ, Sasi R. Ionic Liquids/Ionic Liquid Crystals for Safe and Sustainable Energy Storage Systems. Progress and Developments in Ionic Liquids 2017; DOI: 10.5772/65888.
5. Xu W, Wang T, Cheng N, Hu Q, Bi Y, Gong Y, Yu L. Experimental and DFT studies on the aggregation behavior of imidazolium-based surface-active ionic liquids with aromatic counter ions in aqueous solution. Langmuir 2015; 31(4): 1272-1282. https://doi.org/10.1021/la503884v

6. Kobayashi D, Fujita K, Nakamura N, Ohno H. A simple recovery process for biodegradable plastics accumulated in cyanobacteria treated with ionic liquids. Appl. Microbiol. Biotechnol. 2015; 99: 1647-1653. DOI:10.1007/s00253-014-6234-1
7. Rodrigues ASMC, Rocha MAA, Almeida HFD, Neves CMSS, Lopes-da-Silva JA, Freire MG, Coutinho JAP, Santos LMNBF. Effect of the methylation and N–H acidic group on the physicochemical properties of imidazolium-based ionic liquids. J. Phys. Chem. B. 2015; 119: 8781-8792. https://doi.org/10.1021/acs.jpcb.5b05354
8. Wang M, Pan X, Chen J, Dai S. Regulating the mesogenic properties of imidazolium salts by modifying N_3-substituents. Sci. China Chem. 2015; 58(12): 1884-1890. doi: 10.1007/s11426-015-5390-1
9. Supuran CT, Casini A, Scozzafava A. Protease inhibitors of the sulfonamide type: anticancer, antiinflammatory, and antiviral agents. Med. Res. Rev. 2003; 23(5): 535-558. doi: 10.1002/med.10047
10. Ovung A, Bhattacharyya J. Sulfonamide drugs: structure, antibacterial property, toxicity, and biophysical interactions. Biophysical Reviews 2021; 13(2): 259-272. https://doi.org/10.1007%2Fs12551-021-00795-9
11. Li N, Wang Y, Li W, Li H, Yang L**, Wang J,** Mahdy HA, Mehany ABM, Jaiash DA, Santali EY, Eissa IH. Screening of Some Sulfonamide and Sulfonylurea Derivatives as Anti-Alzheimer's Agents Targeting BACE1 and PPARγ. Journal of Chemistry 2020. https://doi.org/10.1155/2020/1631243
12. Owa T, Nagasu T. Novel sulphonamide derivatives for the treatment of cancer. Expert Opinion on Therapeutic Patents 2000; 10(11): 1725-1740. https://doi.org/10.1517/13543776.10.11.1725
13. Ozdemir UO, Guvenç P, Sahin E, Hamurcu F. Synthesis, characterization and antibacterial activity of new sulfonamide derivatives and their nickel (II), cobalt (II) complexes. Inorganica Chimica Acta 2009; 362(8): 2613-2618. https://doi.org/10.1016/j.ica.2008.11.029
14. Askar FW, Aldhalf YA, Jinzeel NA. Synthesis and Biological Evaluation of New Sulfonamide Derivatives. International Journal of Chemical Science 2007; 15(3): 173. https://www.tsijournals.com/articles/synthesis-and-biological-evaluation-of-new-sulfonamide-derivatives-13360.html
15. Siddiqui N, Arshad MF, Kan SA, Ahsan W. Sulfonamide derivatives of thiazolidin-4-ones with anticonvulsant activity against two seizure models: synthesis and pharmacological evaluation. Journal of Enzyme Inhibition and Medicinal Chemistry 2010; 25(4): 485-491. doi: 10.3109/14756360903282833
16. Kumar N, Khanna A, Kaur K, Kaur H, Sharma A, Singh Bedi PM. Quinoline derivatives volunteering against antimicrobial resistance: rational approaches, design strategies, structure activity relationship and mechanistic insights. Mol. Divers 2022. https://doi.org/10.1007/s11030-022-10537-y
17. Manoj Kumar M, Bhupender S, Chhikara, Parang K, Anil Kumar. Ionic Liquid-Supported Synthesis of Sulfonamides and Carboxamides. ACS Comb. Sci. 2012; 14: 60-65. https://doi.org/10.1021/co200149m
18. Ajani OO, Iyaye KT, Ademosun OT. Recent advances in chemistry and therapeutic potential of functionalized quinoline motifs– a review, RSC Adv. 2022; **12:** 18594-18614. https://doi.org/10.1039/D2RA02896D
19. Snehi V, Pathak D. Synthesis, Characterization and Biological Evaluation of Novel Isoxazolo [5,4-b] Quinolines as Potent Antimicrobial Agents. International Journal of Pharmaceutical Sciences and Drug Research 2022; 14(6): 725-733. https://doi.org/10.25004/IJPSDR.2022.140609
20. Okolo EN, Ugwu DI, Ezema BE, Ndefo JC, Eze FU, Ezema CG, Ezugwu JA, Ujam OT. New chalcone derivatives as potential antimicrobial and antioxidant agent. Scientific Reports 2021; 11: 21781. https://doi.org/10.1038/s41598-021-01292-5
21. Venkatesh T, Bodke YD, Kenchappa R, Eilkar S. Synthesis, Antimicrobial and Antioxidant Activity of Chalcone Derivatives Containing Thiobarbitone Nucleus. Med. Chem. 2016; 6(7): 440-448. DOI: 10.4172/2161-0444.1000383
22. Santosh R, Selvam MK, Kanekar SU, Nagaraja GK. Synthesis, Characterization, Antibacterial and Antioxidant Studies of Some Heterocyclic Compounds from Triazole-Linked Chalcone Derivatives. ChemistrySelect 2018; 3: 6338-6343. https://doi.org/10.1002/slct.201800905
23. Mirani Nezhad S, NazarzadehZare E, Davarpanah A, Pourmousavi SA, Ashrafizadeh M, Kumar AP. Ionic Liquid-Assisted Fabrication of Bioactive Heterogeneous Magnetic Nanocatalyst with Antioxidant and Antibacterial Activities for the Synthesis of Poly hydro quinoline Derivatives. Molecules 2022; 27(5): 1748. https://doi.org/10.3390/molecules27051748
24. Su PW, Yang CH, Yang JF, Su PY, Chuang LY. Antibacterial Activities and Antibacterial Mechanism of Polygonum cuspidatum extracts against Nosocomial Drug-Resistant Pathogens. Molecules 2015; 20(6): 11119-11130. https://doi.org/10.3390/molecules200611119
25. Burman S, Bhattacharya K, Mukherjee D, Chandra G. Antibacterial efficacy of leaf extracts of Combretum album Pers. against some pathogenic bacteria. BMC Complementary and Alternative Medicine 2018; 18: 213-220. https://doi.org/10.1186/s12906-018-2271-0
26. Atef NM, Shanab SM, Negm SI, Abbas YA. Evaluation of antimicrobial activity of some plant extracts against antibiotic susceptible and resistant bacterial strains causing wound infection. Bulletin of the National Research Centre 2019; 43:144-156. https://doi.org/10.1186/s42269-019-0184-9
27. Foudah AI, Alam A, Soliman GA, Salkini MA, Ibnouf Ahmed EO, Yusufoglu HS. Pharmacognostical, Antibacterial and Antioxidant Studies of Aerial Parts of Pulicaria somalensis (Family: Asteraceae). Asian J. Biol.Sci. 2016; 9(1-2): 19-26. https://scialert.net/abstract/?doi=ajbs.2016.19.26
28. Ashokan D, Rajathi K. A green Approach for Synthesis of Pyridinium Sulfonamide Ionic Liquids: Characterization and Their Biological Activities. Chemistry Africa 2023. https://doi.org/10.1007/s42250-023-00653-z
29. Hamlaoui I, Bencheraiet R, Bensegueni R, Bencharif M. Experimental and theoretical study on DPPH radical scavenging mechanism of some chalcone quinoline derivatives. Journal of molecular structure 2018; 1156: 385-389. https://doi.org/10.1016/j.molstruc.2017.11.118
30. Kim J, Yub H, Yang E, Choi Y, Chang PS. Effects of alkyl chain length on the interfacial, antibacterial, and antioxidative properties of erythorbyl fatty acid esters. LWT-Food science and Technology 2023; 174: 1144. https://doi.org/10.1016/j.lwt.2022.114421

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