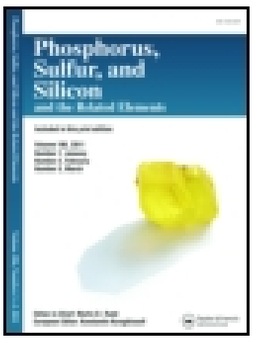

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Synthesis and antimicrobial evaluation of some new *N*-pyridinium, quinolinium and isoquinolinium sulfonate derivatives

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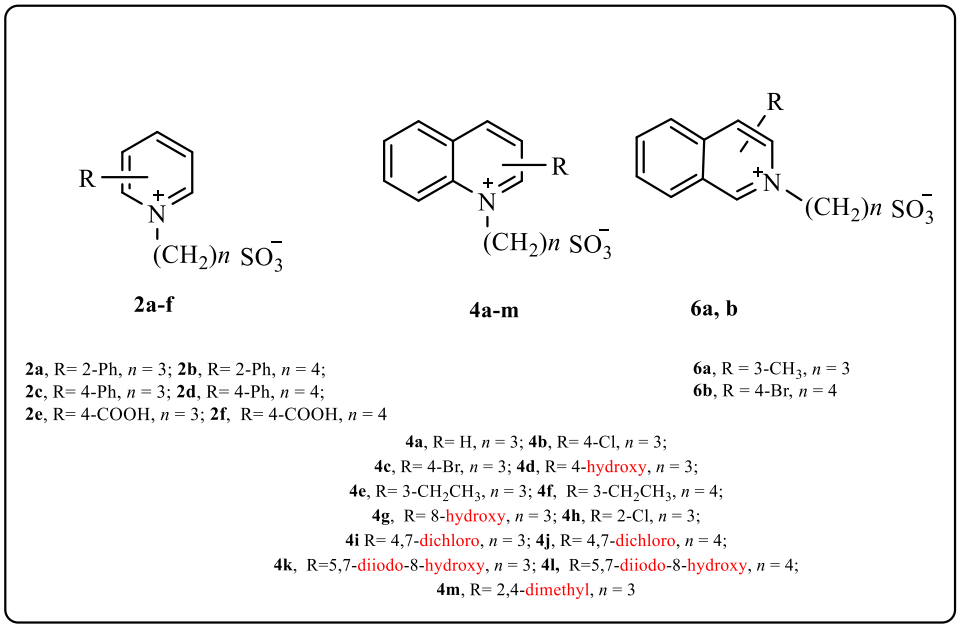
1,3-propane- and/or 1,4-butane sultone (sultones are internal esters of hydroxyl sulfonic acid) are used as a chemical intermediate to introduce the sulfopropyl and/or sulfobutyl groups into heterocyclic molecules and to confer water solubility and an anionic character to the molecules. Therefore, the synthesis of three novel functionalized *N*-sulfonates are described. These sulfonates containing pyridyl **(2a-f)**, quinolyl **(4a-m)** and isoquinolyl **(6a,b)** functional groups with potential biological activity. The synthesized quaternary ammonium salts 3-(2 or 4-arylpyridinium-1-yl)propane or butane-1-sulfonate **(2a-f)**, 3-(alkylquinolinium-1-yl)propane or butane-1-sulfonate **(4a-m)** and

3-(alkylisoquinolinium-1-yl)propane or butane-1-sulfonate **(6a,b)** were screened for their antimicrobial and antifungal activities. Among all tested compounds, it was found that

compound 4-(4-carboxypyridinium-1-yl)butane-1-sulfonate **(2f)** showed high activity against Gram-positive bacteria, Gram-negative bacteria and tested fungi. Most of the compounds showed a moderate degree of antimicrobial activity. The structures of these compounds were confirmed on the basis of their analytical and spectral data (IR, ^{1}HNMR, ^{13}CNMR spectroscopy and mass spectral data).



Keywords

1,3-Propane sultone; 1,4-Butane sultone; Antibacterial; Antifungal; Pyridinium; Quinolinium; Quaternary ammonium

Introduction

The synthesis and characterization of pyridine and S-alkylpyridine derivatives has become a main focus of this research group. This is because these derivatives have significant and versatile biological and pharmacological activities, such as antimalarial [1], antiproliferative [2], antimicrobial [3], inhibition of cyclin-dependent kinases [4], cardiovascular [5], antiviral [6] and antileishmanial activities [7]. In addition, the quinoline ring system occurs in various natural products, especially in alkaloids. The quinoline and isoquinoline [8] skeletons are one of the privileged medicinal scaffolds that show a wide range of pharmaceutical activities. The presence of quinoline framework of various pharmacologically active compounds with antiasthmatic [9], antifungal [10], antimalarial [11], antiviral [12], antitumor [13], and anti-inflammatory [14] activities continues to promote their synthetic efforts. Sulfoalkylic heterocyclic compounds are widely used in the production of medicinal materials [15], various dyes [16], and in other areas. Even though 1,3-propane sultone and 1,4-butane sultone, used for the synthesis of sulfoalkylic heterocyclic compounds, have a high reactivity, they are also sensitive to hydrolysis and to the influence of alkalis. Therefore, a water-free medium is essential for the synthesis of sulfonates; however, they make the sulfoalkylation process more difficult and expensive. The sulfoalkyl group has been used extensively to improve the aqueous solubility and otherwise enhance the hydrophilicity of a variety of surfactants [17], dyes [18] nucleosides [19], proteins [20] and polymers [21]. Compounds having a combination of pyridine derivatives with sulfopropyl and/ or sulfobutyl moieties are expected to possess interesting medicinal properties. Encouraged by these reports and in continuation of our work in this field [22-26], we report here the synthesis of

some new *N*-sulfoalkylpyridine derivatives of biological interest and their evaluation as antimicrobial agents.

The use of pyridinium salts in organic synthesis is now receiving considerable interest. As a part of our program of developing new, simple and efficient procedures for the synthesis of new aromatic compounds using readily available pyridinium salts, we recently affected the conversion of pyridinium salts into anilines and aminobiphenyls [27-33]. This procedure appeared to be a fundamental type of pyridine-into-benzene ring transformation. We have been particularly interested to study if reactions of such pyridinium salts might be extended to include a more general synthesis of other classes of new heterocyclic compounds.

Results and Discussion

Chemistry

The present work reports on the synthesis of several new sulfoalkylpyridinium salts and their evaluation as antimicrobial agent. However, no details regarding with the synthesis and biological evaluation of such compounds are reported. The fusion of pyridine derivatives **1a-c** with 1,3-propane sultone and/or 1,4-butane sultone afforded the corresponding quaternary pyridinium salts **2a-f** (**Scheme 1**) ~~such reaction require a drastic condition~~. The generation of these types of salts was attributed to the large charge-dipole destabilization effect introduced upon the formation of the pyridinium salts **2a-f**.

Structures **2a-f** were established based on both spectral and analytical analyses. In general, the IR spectra showed absorption frequencies at *ύ* 3105-3048, 1625-1615, and 1300-1110 cm^{-1} corresponding to aromatic CH, C = N and SO_3 function groups, respectively. In the pyridine rings, the ring nitrogen significantly influences substituents at the position **1** in quaternary salts.

Conversely, the inductive and mesomeric effects of substituents influence the chemical shifts of the protons and carbons of the pyridinium ring. The quaternization shift increments or deshielded the pyridine protons depend on the nature of pyridine substituents (1-alkyl and 1-aryl groups) and on the experimental conditions. The ^{1}H-NMR spectrum of structure **2e** showed multiplet signals at δ 2.10 ppm due to the middle CH_2 protons ($^{+}NCH_2CH_2CH_2SO_3^{-}$), also two triplet signals at δ 2.60 and 4.45 ppm attributable to CH_2-S and CH_2-N^{+} protons, respectively, while four aromatic protons of pyridinium ring appeared at δ 8.50-9.34 ppm as two doublets (AA'BB') system and COOH proton appeared as singlet signal at δ 10.90 ppm. On the other hand, the structure of the compound **2e** was well confirmed by its mass spectral studies. Compound **2e** exhibited a molecular ion peak at *m/z* (EI, 70 ev) = 247 (M^{+}+2, 74) corresponding to the molecular formula ($C_9H_{13}NO_5S$).Additionally, the ^{13}C-NMR spectra revealed a more confirmation of structures **2a-f** (*c.f.* Experimental part).

We also studied the possibility of obtaining various quinolinium salts **4a-m** and isoquinolinium salts **6a**,**b** containing sulfonate groups by the above mentioned strategy.in which they were prepared by fusion of the aromatic bases **3a-j** and **5a**,**b** with 1,3-propane or 1,4-butane sultones (**Schemes 2** & **3**).

The identity of the products was determined by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral studies. Structures **4a-m** were elucidated on the basis of their correct spectral and analytical data. In general, IR spectra revealed absorption bands at $\acute{\upsilon}$ 3110-3059, 1620-1612 and 1356- 1150 cm^{-1} attributable to aromatic CH, C = N and SO_3 groups. In ^{1}H-NMR spectrum of quinolinium salt **4f** displayed two multiplet signals at δ 1.96 and 2.67 ppm attributable to two middle CH_2 protons ($^{-}O_3SCH_2\underline{CH_2}\underline{CH_2}CH_2N^{+}$),three triplet signals at δ 2.15, 2.92 and 4.41 ppm

corresponding to CH_3, CH_2-S and CH_2-N^+ protons and quartet signal at δ 3.40 ppm due to CH_2. It also revealed multiplet signals at δ 7.14-8.42 ppm corresponding to six aromatic protons. Compound **4f** showed a distinct molecular ion peak at *m/z* (EI, 70 ev) = 295 (M^++2, 88%) corresponding to its molecular formula ($C_{15}H_{19}NO_3S$). Furthermore, the IR spectrum of isoquinolinium salt **6a** showed absorption frequencies at $\acute{\upsilon}$ 2895 and 1351-1153 cm^{-1} corresponding to CH_3 and SO_3 function groups. The ^{1}H-NMR spectrum showed a characteristic multiplet signals at δ 2.31 ppm due to the central CH_2 protons, two singlet signals at δ 2.71 and 9.52 ppm corresponding to CH_3 and $^+$N = CH and two characteristic triplet signals at δ 2.89 and 4.69 attributable to CH_2-S and CH_2-N^+. The ^{13}C-NMR spectrum of structures **4a-m** and **6a, b** is in good agreement with the structure assigned. The elemental analysis values are in good agreement with the theoretical data.

Biological implementation

Antimicrobial activity

Fifteen of the newly synthesized targeted compounds were evaluated for their *in vitro* antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis* as examples of Gram-positive bacteria and *Escherichia coli* and *Pseudomonase aerugunosa* as examples of Gram-negative bacteria. Also, they were evaluated for their *in vitro* antifungal potential against *Aspergillus flavus* and *Aspergillus nieger*.

Agar-diffusion method [34] was used for the determination of the antibacterial and antifungal activity. Chloramphenicol, Cephalothin, Cycloheximide and Ampicillin were used as reference drugs. The results were recorded for each tested compound as the average diameter of inhibition zones (IZ) of bacterial or fungal growth around the disks in mm. The minimum inhibitory

concentration (MIC) measurement was determined for compounds showed significant growth inhibition zones (> 14 mm) using two fold serial dilution method [35].

Tables S 1 and S 2 (Supplemental materials) present that antimicrobial effects of new N-sulfoalkylpyridinium, quinolinium and isoquinolinium derivatives. All the synthesized compounds have mild to high antibacterial effects especially against Gram-positive bacteria.

Experimental

Instruments

All melting points are uncorrected in degree centigrade and determined on Gallenkamp electric melting point apparatus. The infrared (IR) spectra were recorded (KBr disk) on a Mattson 5000 FTIR spectrometer at the Faculty of Science, Mansoura University, Egypt. The ^{1}HNMR spectra were determined on a Bruker WPSY 200 MHz spectrometer with tetramethylsilane (TMS) as an internal standard and the chemical shifts are in δ ppm using deuterated water (D_2O) and dimethyl sulfoxide (DMSO) as a solvent. The mass spectra were recorded at 70 eV with a Varian MAT 311 at the Microanalytical Center, Faculty of Science, Cairo University. Elemental analyses (C, H and N) were carried out at the Faculty of Science, Cairo University. The results were found to be in a good agreement with the calculated values. The following microorganisms were used as diluted samples with broth culture: *Staphylococcus aureus*, *Bacillus subtilis*, *Listeria. monocytogenes*, *Escherichia. coli*, *Pseudomonas aeruginosa*, *Salmonella enteritidis*, *Candida. albicans*, *Aspergillus.niger* an *Aspergillu. flavus*. All microorganisms were obtained from Persian Type Culture Collection (PTCC). Mueller-Hinton broth (Merk, Germany) and RPMI-1640 (Gibco, Scotland) were used for the growth of bacteria and fungi respectively. Deuterated water (D_2O) was purchased from Merck, Germany.

Chemistry

*General procedure for the synthesis of quaternary salts **2a-f**, **4a-m** and **6a, b***

Compounds **1a-c**, **3a-j** and **5a**, **b** (10 mmol) were carefully mixed with 1,3-propane sultone and / or butane sultone (8.17 mmol), the reaction mixture was fused in an oil bath at 140 °C for 0.5-4 h (TLC control). The reaction mixture was then cooled to room temperature. The obtained solid product was washed firstly with diethyl ether then triturated with ethanol and filtered off. The solid products were recrystallized from diluted ethanol to give compounds **2a-f**, **4a-g** and **6a**, **b**, respectively.

*3-(2-Phenylpyridinium-1-yl) propane-1-sulfonate **(2a)***

Yield 74%; yellowish white crystals; m.p. 202-204 °C; IR (KBr): v/cm^{-1} = 3044 (Ar-CH), 2978 (CH_2), 1626 (C = N), 1288, 1199 (2 S = O), 646 (S-O); ^{1}H-NMR (D_2O): δ/ppm = 2.00 (m, J = 6.1, 2H, CH_2), 2.50 (t, J = 6.5, 2H, CH_2-SO_3), 4.43 (t, J = 5.9, 2H, CH_2-N^+), 7.33-7.50 (m, J = 6.5, 5H, Ar-H), 7.75 (d, J = 6.5, 1H, CH), 7.85 (d.d, J = 6.6, 1H, CH), 8.32 (d.d, J = 6.4, 1H, CH), 8.72 (d, J = 6.4, 1H, CH). ^{13}C-NMR: δ (ppm): 25.7, 47.2, 57.0, 127.3, 128.7, 129.4, 130.8, 131.1, 131.2, 145.2, 145.7, 155.8; MS: (EI, 70 ev)(*m/z*, %) 279 (M^++2, 30%), 199 (40%), 171 (33%), 157 (50%), 131 (57%), 105 (67%), 81 (100%), 55 (62%). Anal.Calcd for $C_{14}H_{15}NO_3S$ (277): C, 60.63; H, 5.45; N, 5.10%. Found: C, 60.67; H, 5.35; N, 5.05%.

*3-(2-Phenylpyridinium-1-yl) butane-1-sulfonate **(2b)***

Yield 52%; white crystals; m.p. > 300 °C; IR (KBr): v/cm^{-1} = 3144 (Ar-CH), 2972 (CH_2), 1620 (C = N), 1298, 1169 (2 S = O), 665 (S-O); ^{1}H-NMR (D_2O): δ/ppm = 1.65 (m, J = 4.2, 2H, CH_2), 2.00 (m, J = 4.3, 2H, CH_2), 2.51 (t, J = 4.4, 2H, CH_2-SO_3), 3.93 (t, J = 4.3, 2H, CH_2-N^+), 7.10-

7.55 (m, J = 6.1, 5H, Ar-H), 7.75 (d, J = 6.2, 1H, CH), 7.85 (d.d, J = 6.2, 1H, CH), 8.32 (d.d, J = 6.1, 1H, CH), 8.72 (d, J = 6.2, 1H, CH). ^{13}C-NMR: δ (ppm): 25.7, 28.4, 47.2, 57.0, 127.3, 128.7, 129.4, 130.8, 131.1, 131.2, 145.2, 145.7, 155.8; MS: (EI, 70 ev) (*m/z*, %) 293 (M^++2, 4.60%), 292 (16%), 291 (100%), 213 (74%), 199 (20%), 172 (37%), 156 (52%), 131 (53%), 106 (67%), 81 (12%), 54 (52%). Anal.Calcd for $C_{15}H_{17}NO_3S$ (291): C, 61.83; H, 5.88; N, 4.81%. Found: C, 61.67; H, 5.35; N, 4.95%.

3-(4-Phenylpyridinium-1-yl) propane-1-sulfonate ***(2c)***.

Yield 70%; yellowish white crystals; m.p. 110-112 °C; IR (KBr): ν/cm^{-1} = 3048 (Ar-CH), 2968 (CH_2), 1624 (C = N), 1294, 1191 (2 S = O), 868 (S-O). ^{1}H-NMR (D_2O): δ/ppm = 2.20 (m, J = 4.6, 2H, CH_2), 2.79 (t, J = 4.7, 2H, CH_2-SO_3), 4.50 (t, J = 5.1, 2H, CH_2-N^+), 7.25-7.61 (m, J = 6.1, 5H, Ar-H), 7.90 (d, J = 6.0, 2H, 2CH), 8.49 (d, J = 7.1, 2H, 2CH); ^{13}C-NMR: δ (ppm): 26.0, 26.1, 47.1, 58.9, 100.1, 124.5, 124.8, 127.8, 129.7, 132.3, 144.1; MS: (EI, 70 ev) (*m/z*, %) 279 (M^++2, 47%), 198 (20%), 171 (23%), 157 (50%), 132 (84%), 105 (66%), 81 (100%), 55 (54%). Anal. Calcd for $C_{14}H_{15}NO_3S$ (277): C, 60.63; H, 5.45; N, 5.05%. Found: C, 60.65; H, 5.40; N, 5.00%.

4-(4-Phenylpyridinium-1-yl)butane-1-sulfonate ***(2d)***

Yield 70%; yellowish white crystals; m.p. 198-200 °C; IR (KBr): ν/cm^{-1} = 3046 (Ar-CH), 2958 (CH_2), 1622 (C = N), 1293, 1190 (2 S = O), 869 (S-O); ^{1}H-NMR (D_2O): δ/ppm = 1.62 (m, J = 4.5, 2H, CH_2), 1.92 (m, J = 4.2, 2H, CH_2), 2.76 (t, J = 4.1, 2H, CH_2-SO_3), 4.43 (t, J = 5.3, 2H, CH_2-N^+), 7.27-7.65 (m, J = 6.1, 5H, Ar-H), 7.85 (d, J = 6.2, 1H, 2CH), 8.69 (d, J = 6.2, 2H, 2CH); MS: (EI, 70 ev) (*m/z*, %) 293 (M^++2, 71%), 213 (68%), 199 (18%), 185 (59%), 171

(54%), 157 (33%), 131 (52%), 105 (68%), 81(100%), 55 (62%). Anal.Calcd.for $C_{15}H_{17}NO_3S$ (291): C, 61.83; H, 5.88; N, 4.81%. Found: C, 61.85; H, 5.83; N, 4.78%.

3-(4-Carboxypyridinium-1-yl)propane-1-sulfonate ***(2e)***

Yield 62%; yellow crystals; m.p. 220-222 °C; IR (KBr): ν/cm^{-1} = 3038 (Ar-CH), 2967 (CH_2), 1732 (C = O), 1616 (C = N), 1301, 1091 (2 S = O), 668 (S-O); ^{1}H-NMR (D_2O) δ/ppm = 2.10 (m, J = 4.3, 2H, CH_2), 2.60 (t, J = 4.2, 2H, CH_2-SO_3), 4.45 (t, J = 6.2, 2H, CH_2-N^+), 8.50 (d, J = 4.1, 2H, 2CH), 9.34 (d, J = 7.2, 2H, 2CH), 10.90 (s, J = 6.1, 1H, COOH); ^{13}C-NMR (DMSO-d_6) δ (ppm): 24.3, 46.9, 60.0, 127.2, 143.8, 146.4, 162.1; MS: (EI, 70 ev) (*m/z*, %) 247 (M^++2, 74%), 165 (25%), 141 (23%), 96 (100%), 70 (47%). Anal.Calcd for $C_9H_{11}NO_5S$ (245): C, 44.08; H, 4.89; N, 5.71%. Found: C, 44.10; H, 4.80; N, 5.75%.

4-(4-Carboxypyridinium-1-yl)butane-1-sulfonate ***(2f)***

Yield 62%; yellow crystals; m.p. 175-177 °C; IR (KBr): ν/cm^{-1} = 3042 (Ar-H), 2968 (CH_2), 1732 (C = O), 1616 (C = N), 1301, 1091 (2 S = O), 668 (S-O); ^{1}H-NMR (D_2O) δ/ppm = 1.65 (m, J = 4.5, 2H, CH_2), 1.90 (m, J = 4.3, 2H, CH_2), 2.79 (t, J = 4.2, 2H, CH_2-SO_3), 4.40 (t, J = 6.5, 2H, CH_2-N^+), 8.35 (d, J = 6.3, 2H, 2CH), 8.82 (d, J = 6.3, 2H, 2CH), 10.80 (s, J = 7.2, 1H, COOH); ^{13}C-NMR (DMSO-d_6) δ (ppm): 20.7, 29.3, 49.8, 61.4, 127.8, 145.6, 147.1, 165.8; MS: (EI, 70 ev) (*m/z*, %) 301 (M^++2, 45%), 221 (45%), 185 (63%), 140 (100%). Anal.Calcd for $C_{10}H_{13}NO_5S$ (259): C, 46.32; H, 5.01; N, 5.40%. Found: C, 46.29; H, 4.48; N, 5.41%.

3-(Quinolinium-1-yl)propane-1-sulfonate ***(4a)***

Yield 52%; colorless crystals; m.p. 190-192 °C; IR (KBr): ν/cm^{-1} = 3058 (Ar-H), 2998 (CH_2), 1615 (C = N), 1311, 1091 (2 S = O), 698 (S-O); ^{1}H-NMR (D_2O) δ/ppm = 2.11 (m, J = 4.2, 2H, CH_2), 2.55 (t, J = 4.1, 2H, CH_2-SO_3), 4.40 (t, J = 6.0, 2H, CH_2-N^+), 7.52-7.98 (m, J = 6.4, 7H, Ar-H); ^{13}C-NMR: δ (ppm): 27.2, 44.2, 54.9, 123.1, 126.3, 127.5, 131.2, 132.2, 135.3, 137.6, 149.0; MS:(EI, 70 ev) (*m/z*, %) 253 (M^++2, 58%), 147 (60%), 121 (100%), 95 (52%), 70 (45%). Anal.Calcd for $C_{12}H_{13}NO_3S$ (251): C, 57.35; H, 5.21; N, 5.57%. Found: C, 57.30; H, 5.20; N, 5.50%.

3-(4-Chloroquinolinium-1-yl)propane-1-sulfonate ***(4b)***

Yield 61%; yellowish white crystals; m.p. 240-242 °C; IR (KBr): ν/cm^{-1} = 3058 (Ar-CH), 2998 (CH_2), 1616 (C = N), 1321, 1191 (2 S = O), 798 (S-O), 742 (C-Cl); ^{1}H-NMR (D_2O) δ/ppm = 2.30 (m, J = 6.2, 2H, CH_2), 2.87 (t, J = 6.1, 2H, CH_2-SO_3), 4.92 (t, J = 4.5, 2H, CH_2-N^+), 7.79-9.00 (m, J = 6.1, 7H, Ar-H), ^{13}C-NMR (DMSO-d_6) δ (ppm): 26.1, 47.1, 59.9, 123.0, 126.3, 131.1, 132.2, 135.3, 138.6, 149.1; MS: (EI, 70 ev) (*m/z*, %) 289 (M^++4, 30%), 252 (43%), 170 (36%), 146(100%), 120 (65%), 106(19%), 80 (62%).Anal.Calcd for $C_{12}H_{12}NO_3SCl$ (285): C, 50.44; H, 4.23; N, 4.90%. Found: C, 50.41; H, 4.20; N, 5.10%

3-(4-Bromoquinolinium-1-yl)propane-1-sulfonate ***(4c)***

Yield 61%; yellowish white crystals; m.p. 248-250 °C; IR (KBr): ν/cm^{-1} = 3048 (Ar-CH), 2973 (CH_2), 1620 (C = N), 1304, 1167 (2 S = O), 660 (S-O), 589 (C-Br); ^{1}H-NMR (D_2O) δ/ppm = 2.45 (m, J = 6.3, 2H, CH_2), 2.84 (t, J = 6.4, 2H, CH_2-SO_3), 4.70 (t, J = 4.3, 2H, CH_2-N^+), 6.80-9.60 (m, J = 6.2, 7H, Ar-H);^{13}C-NMR δ (ppm): 24.8, 47.3, 47.5, 56.3, 118.7, 122.4, 127.0, 131.0, 136.9, 148.2; MS:(EI, 70 ev) (*m/z*, %) 333 (M^++4, 100%), 252 (44%), 171 (66%), 147 (100%),

121 (22%), 105(7%), 80 (52%). Anal.Calcd for $C_{12}H_{12}NO_3SBr$ (331): C, 43.50; H, 3.62; N, 4.22%. Found: C, 43.48; H, 3.74; N, 4.30%.

3-(4-Hydroxyquinolinium-1-yl)propane-1-sulfonate ***(4d)***

Yield 61%; yellowish white crystals; m.p. 186-188 °C; IR (KBr): ν/cm^{-1} = 3410 (OH), 3111 (Ar-CH), 2928 (CH_2), 1613 (C = N), 1314, 1151 (2 S = O), 662 (S-O); ^{1}H-NMR (D_2O) δ/ppm = 2.18 (m, J = 6.3, 2H, CH_2), 2.92 (t, J = 6.4, 2H, CH_2-SO_3), 4.30 (t, J = 6.4, 2H, CH_2-N^+), (s, J = 6.4, 1H, OH), 6.90-8.51 (m, J = 6.0, 6H, Ar-H);MS: (EI, 70 ev) (*m/z*, %) 269 (M^++2, 65%), 252 (45%), 171 (36%), 145 (100%), 121 (65%), 104 (22%), 82 (52%). Anal.Calcd.for $C_{12}H_{13}NO_4S$ (267): C, 53.92; H, 4.86; N, 5.24%. Found: C, 53.89; H, 4.80; N, 5.2%.

3-(3-Ethylquinolinium-1-yl)propane-1-sulfonate ***(4e)***

Yield 61%; yellowish white crystals; m.p. 260-262 °C; IR (KBr): ν/cm^{-1} = 3080 (Ar-H), 2968 (CH_2), 1623 (C = N), 1316, 1194 (2 S = O), 646 (S-O); ^{1}H-NMR (D_2O) δ/ppm = 2.15 (t, J = 6.1, 3H, CH_3), 2.67 (m, J = 6.2, 2H, CH_2), 2.92 (t, J = 6.0, 2H, CH_2-SO_3), 3.40 (q, J = 6.2, 2H, CH_2), 4.28 (t, J = 6.4, 2H, CH_2-N^+), 6.94-8.48 (m, J = 6.6, 6H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 13.9, 24.9, 25.3, 47.4, 55.8, 117.6, 129.8, 134.9, 136.2, 138.4, 145.7, 146.0, 145.8, 149.2; MS: (EI, 70 ev)(*m/z*, %) 281 (M^++2, 30), 264 (29%), 182 (56%), 158 (100%), 132 (75%), 106 (19%), 92 (62%). Anal. Calcd for $C_{14}H_{17}NO_3S$ (279): C, 60.21; H, 6.09; N, 5.01%. Found: C, 60.19; H, 6.28; N, 5.00%.

4-(3-Ethylquinolinium-1-yl)butane-1-sulfonate ***(4f)***

Yield 71%; yellowish white crystals; m.p. 180-182 °C; IR (KBr): ν/cm^{-1} = 3180 (Ar-H), 2961 (CH_2), 1621 (C = N), 1326, 1194 (2 S = O), 656 (S-O); ^{1}H-NMR (D_2O) δ/ppm = 1.90 (m, J = 4.1, 2H, CH_2), 2.15 (t, J = 4.5, 3H, CH_3), 2.67 (m, J = 6.4, 2H, CH_2), 2.92 (t, J = 4.2, 2H, CH_2-SO_3), 3.40 (q, J = 6.2, 2H, CH_2), 4.41 (t, J = 5.1, 2H, CH_2-N^+), 7.14-8.42 (m, J = 6.1, 6H, Ar-H);^{13}C-NMR (DMSO-d_6) δ (ppm): 13.9, 24.9, 25.3, 29.3, 47.4, 55.8, 117.6, 129.8, 134.9, 136.2, 138.4, 145.7, 146.0, 145.8, 149.2; MS: (EI, 70 ev) (*m/z*, %) 295 (M^++2, 88%), 266 (69%), 184 (51%), 160 (15%), 136 (100%), 111 (14%), 85 (66%). Anal.Calcd for $C_{15}H_{19}NO_3S$ (293): C, 61.43; H, 6.48; N, 4.77%. Found: C, 61.39; H, 6.50; N, 4.79%.

3-(8-Hydroxyquinolinium-1-yl)propane-1-sulfonate ***(4g)***

Yield 61%; yellowish white crystals; m.p. 260-262 °C; IR (KBr): ν/cm^{-1} = 3342 (OH), 3080 (Ar-CH), 2998 (CH_2), 1620 (C = N), 1312, 1155 (2 S = O), 746 (S-O); ^{1}H-NMR (D_2O) δ/ppm = 2.20 (m, J = 6.4, 2H, CH_2), 2.79 (t, J = 6.2, 2H, CH_2-SO_3), 3 5.06 (t, J = 5.2, 2H, CH_2-N^+), 7.18-8.78 (m, J = 7.2, 6H, Ar-H), (s, J = 5.7, 1H, OH); MS: (EI, 70 ev) (*m/z*, %) 269 (M^++2, 75%), 251 (45%), 173 (77%), 144 (100%), 120 (45%), 104 (32%), 81 (50%). Anal.Calcd for $C_{12}H_{13}NO_4S$ (267): C, 53.92; H, 4.86; N, 5.24%. Found: C, 53.89; H, 4.80; N, 5.19%.

3-(2-chloroquinolinium-1-yl)propane-1-sulfonate ***(4h)***

Yield 32%; yellow crystals; m.p. 130-132 °C; IR (KBr): ν/cm^{-1} = 3088 (Ar-CH), 2978 (CH_2), 1619 (C = N), 1321, 1191 (2 S = O), 798 (S-O), 742 (C-Cl); ^{1}H-NMR (D_2O) δ/ppm = 2.35 (m, J = 6.2, 2H, CH_2), 2.97 (t, J = 7.1, 2H, CH_2-SO_3), 4.32 (t, J = 6.4, 2H, CH_2-N^+), 7.99-9.30 (m, J = 6.5, 6H, Ar-H), ^{13}C-NMR (D_2O) δ (ppm): 26.1, 46.3, 60.9, 123.1, 125.3, 131.2, 132.2, 135.3, 138.6, 150.0; MS: (EI, 70 ev) (*m/z*, %) 289 (M^++4, 59%), 252 (43%), 171 (32%), 146 (100%),

120 (65%), 106 (19%), 80 (62%). Anal.Calcd for $C_{12}H_{12}NO_3SCl$ (285): C, 50.43; H, 4.33; N, 4.91%. Found: C, 50.42; H, 4.29; N, 5.00%.

3-(4,7-dichloroquinolinium-1-yl)propane-1-sulfonate ***(4i)***

Yield 54%; orange crystals; m.p. 240-242 °C; IR (KBr): ν/cm^{-1} = 3002 (Ar-CH), 2991 (CH_2), 1630 (C = N), 1326, 1195 (2 S = O), 790 (S-O), 742, 749 (2 C-Cl); ^{1}H-NMR (D_2O) δ/ppm = 2.15 (m, J = 6.5, 2H, CH_2), 3.17 (t, J = 6.1, 2H, CH_2-SO_3), 4.42 (t, J = 6.2, 2H, CH_2-N^+), 7.99-9.30 (m, J = 4.5, 4H, Ar-H), ^{13}C-NMR (D_2O) δ (ppm): 20.3, 50.4, 62.8, 128.8, 128.9, 129.4, 130.4, 134.3, 140.9, 147.4, 153.7; MS: (EI, 70 ev) (*m/z*, %) 322 (M^++2, 100%), 242 (42%), 228 (32%), 200 (19%), 186 (25%), 163 (54%), 128 (62%), 116 (56%), 91 (71%), 56 (85%). Anal.Calcd for $C_{12}H_{11}NO_3SCl_2$ (320): C, 45.01; H, 3.46; N, 4.37%. Found: C, 45.02; H, 3.40; N, 4.32%.

3-(4,7-dichloroquinolinium-1-yl)butane-1-sulfonate ***(4j)***

Yield 63%; brown crystals; m.p. > 300 °C; IR (KBr): ν/cm^{-1} = 3002 (Ar-CH), 2991 (CH_2), 1630 (C = N), 1326, 1195 (2 S = O), 790 (S-O), 742, 749 (2 C-Cl); ^{1}H-NMR (D_2O) δ/ppm = 1.92 (m, 2H, CH_2), 2.25 (m, 2H, CH_2), 3.47 (t, J = 6.2, 2H, CH_2-SO_3), 4.47 (t, J = 6.7, 2H, CH_2-N^+), 7.94-9.23 (m, J = 7.1, 4H, Ar-H), ^{13}C-NMR (D_2O) δ (ppm): 21.3, 25.0, 51.4, 63.8, 129.0, 128.9, 129.4, 130.4, 134.3, 141.9, 147.1, 152.7; MS: (EI, 70 ev) (*m/z*, %) 322 (M^++2, 100%), 242 (32%), 228 (33%), 200 (40%), 186 (75%), 163 (50%), 128 (68%), 116 (50%), 91 (22%), 56 (54%). Anal.Calcd for $C_{12}H_{11}NO_3SCl_2$ (320): C, 45.01; H, 3.46; N, 4.37%. Found: C, 45.02; H, 3.40; N, 4.32%.

3-(8-hydroxy-5,7-diiodoquinolinium-1-yl)propane-1-sulfonate ***(4k)***

Yield 23%; white crystals; m.p. 100-102 °C; IR (KBr): ν/cm^{-1} = 3342 (OH), 3032 (Ar-CH), 2996 (CH_2), 1634 (C = N), 1326, 1190 (2 S = O), 784 (S-O), 622, 579 (2 C-I); ^{1}H-NMR (D_2O) δ/ppm = 2.20 (m, J = 4.0, 2H, CH_2), 3.41 (t, J = 4.3, 2H, CH_2-SO_3), 4.31 (t, J = 7.0, 2H, CH_2-N^+), 7.85 (s, J = 4.5, 1H, Ar-H), 8.50-9.21 (m, J = 5.9, 2H, Ar-H), 9.83 (s, J = 6.1, 1H, OH); ^{13}C-NMR (D_2O) δ (ppm): 21.3, 51.4, 63.8, 129.0, 128.9, 129.4, 130.4, 134.3, 141.9, 147.1, 152.7; MS: (EI, 70 ev) (*m/z*, %) 519 (M^++2, 30%), 393 (52%), 313 (39%), 299 (43%), 283 (25%), 259 (100%), 245 (62%), 219 (46%), 93 (75%), 69 (54%), 45 (69%). Anal.Calcd for $C_{12}H_{11}NO_4SI_2$ (517): C, 27.77; H, 2.14; N, 2.70%. Found: C, 27.74; H, 2.16; N, 2.73%.

3-(8-hydroxy-5,7-diiodoquinolinium-1-yl)butane-1-sulfonate ***(4l)***

Yield 69%; white crystals; m.p. 250-252 °C; IR (KBr): ν/cm^{-1} = 3325 (OH), 3039 (Ar-CH), 2976 (CH_2), 1630 (C = N), 1326, 1195 (2 S = O), 786 (S-O), 632, 580 (2 C-I); ^{1}H-NMR (D_2O) δ/ppm = 1.96 (m, J = 4.6, 2H, CH_2), 2.23 (m, J = 5.9, 2H, CH_2), 3.24 (t, J = 6.7, 2H, CH_2-SO_3), 4.36 (t, J = 7.2, 2H, CH_2-N^+), 7.84 (s, J = 6.2, 1H, Ar-H), 8.52-9.26 (m, J = 6.0, 2H, Ar-H), 9.86 (s, J = 5.9, 1H, OH); ^{13}C-NMR (D_2O) δ (ppm): 21.3, 25.0, 51.4, 63.8, 129.0, 128.9, 129.4, 130.4, 134.3, 141.9, 147.1, 152.7; MS: (EI, 70 ev) (*m/z*, %) 533 (M^++2, 100%), 453 (58%), 327 (86%), 202 (62%), 185 (46%), 143 (75%), 129 (54%), 103 (69%). Anal. Calcd for $C_{13}H_{13}NO_4SI_2$ (531): C, 29.27; H, 2.44; N, 2.63%. Found: C, 29.27; H, 2.46; N, 2.65%.

3-(2,4-diquinolinium-1-yl)propane-1-sulfonate ***(4m)***

Yield 61%; yellowish white crystals; m.p. 260-262 °C; IR (KBr): ν/cm^{-1} = 3052 (Ar-CH), 2900 (CH_2), 1626 (C = N), 1322, 1215 (2 S = O), 749 (S-O); ^{1}H-NMR (D_2O) δ/ppm = 1.99 (s, J = 6 .1, 3H, CH_3), 2.10 (s, J = 6.0, 3H, CH_3), 2.26 (m, J = 6.4, 2H, CH_2), 2.69 (t, J = 5.9, 2H, CH_2-SO_3),

3.06 (t, J = 6.5, 2H, CH_2-N^+), 7.18-8.78 (m, J = 7.0, 6H, Ar-H); MS: (EI, 70 ev) (*m/z*, %) 279 (M^+, 84%), 199 (75%), 184 (67%), 169 (100%), 145 (49%), 117 (69%), 91 (33%). Anal. Calcd for $C_{14}H_{17}NO_3S$ (279): C, 60.19; H, 6.13; N, 5.03%. Found: C, 60.23; H, 6.15; N, 5.09%.

3-(3-Methylisoquinolinium-1-yl)propane-1-sulfonate ***(6a)***.

Yield 69%; yellowish white crystals; m.p. 220-222 °C; IR (KBr): ν/cm^{-1} = 3180 (Ar-CH), 2998 (CH_2), 2895 (CH_3), 1623 (C = N), 1351, 1153 (2 S = O), 640 (S-O); ^{1}H-NMR (D_2O) *δ*/ppm = 2.31 (m, J = 5.8, 2H, CH_2), 2.70 (s, J = 6.0, 1H, CH_3), 2.89 (t, J = 6.2, 2H, CH_2-SO_3), 4.69 (t, J = 7.4, 2H, CH_2-N^+), 6.69-8.18 (m, J = 6.1, 5H, Ar-H), 9.52 (s, J = 6.2, 1H, CH);. MS: (EI, 70 ev) (*m/z*, %) 267 (M^++2, 38%), 252 (70%), 172 (42%), 145 (100%), 122 (72%), 106 (36%), 80 (27%). Anal.Calcd for $C_{13}H_{15}NO_3S$ (265): C, 58.85; H, 5.66; N, 5.28%. Found: C, 58.82; H, 5.60; N, 5.20%.

4-(3-Bromoisoquinolinium-1-yl)butane-1-sulfonate ***(6b)***

Yield 69%; yellowish white crystals; m.p. 120-122 °C; IR (KBr): ν/cm^{-1} = 3080 (Ar-H), 2988 (CH_2), 1623 (C = N), 1312, 1125 (2 S = O), 646 (S-O); ^{1}H-NMR (D_2O) *δ*/ppm = 1.68 (m, J = 5.6, 2H, CH_2), 2.11 (m, J = 5.2, 2H, CH_2), 2.80 (t, J = 6.5, 2H, CH_2-SO_3), 4.61 (t, J = 6.8, 2H, CH_2-N^+), 7.80-8.38 (m, J = 7.1, 4H, Ar-H), 8.78 (s, J = 6.7, 1H, CH), 9.61 (s, J = 5.7, 1H, CH); MS: (EI, 70 ev) (*m/z*, %) 334 (M^++4, 84%), 254 (43%), 173 (60%), 149 (100%), 123 (55%), 107(71%), 82 (24%). Anal.Calcd for $C_{12}H_{12}NO_3SBr$ (330): C, 43.63; H, 3.63; N, 4.24%. Found: C, 43.63; H, 3.60; N, 4.25%.

Biological activity

Antimicrobial method

Standard sterilized filter paper disks (5 mm diameter) impregnated with a solution of the tested compound in DMF (1 mg/mL) was placed on an agar plate seeded with the appropriate test organism in triplicates. The utilized test organisms were:*B. subtilis* and *S. aureus* examples of Gram-positive bacteria and *E. Coli* and *P. aeruginosaas* examples of Gram-negative bacteria. They were also evaluated for their *in vitro* antifungal potential against *A.nieger* and A. flavus fungal strains. Chloramphenicol, Cephalothin, Cycloheximide and Ampicillin were used as standard antibacterial and antifungal agents, respectively [34, 35]. DMF alone was used as control at the same above-mentioned concentration. The plates were incubated at 37°C for 24 h for bacteria and 48 days for fungi. Compounds that showed significant growth inhibition zones (>14 mm) using the twofold serial dilution technique, were further evaluated for their minimum inhibitory concentration (MICs) [35, 36].

Minimum inhibitory concentration (MIC) and minimum bacterial concentration (MBC) measurements [36]

The minimum inhibitory and bactericidal concentrations (MICs and MBCs) were determined using 96-well microtitre plates. The microdilution susceptibility test in MüllereHinton Broth (Oxoid) and Sabouraud Liquid Medium (Oxoid) was used for the determination of antibacterial and antifungal activity, respectively. Stock solutions of the tested compounds, Chloramphenicol, Cephalothin,

Cycloheximide and Ampicillin were prepared in DMF at concentration of 1000 mg/mL followed by twofold dilution at concentrations of (500, 250, 3.125 mg/mL). The microorganism suspensions at 10^6 CFU/mL (Colony Forming U/mL) concentrations were inoculated to the

corresponding wells. Plates were incubated at 36°C for 24-48 h and the minimum inhibitory concentration (MICs) were determined. Control experiments were also done. The MIC and MBC values were expressed in mg/mL as shown in Tables S 1 and S 2 (Supplemental Materials).

Conclusion

In conclusion, the wider objective of the present study was to synthesize and investigate antimicrobial activities of some new functionalized hetarenium salts such as pyridinium **2a-f**, quinolinium **4a-m** and isoquinolinium **6a, b** salts with hope of discovering new structure leads to serving as potent antimicrobial agents. The obtained results clearly revealed that heterocyclic compounds incorporated with electron withdrawing groups and the length of *N*-sulfoalkyl group exhibited better antimicrobial activity than their analogues.

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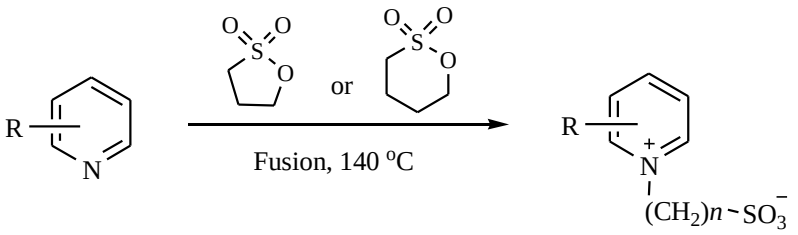
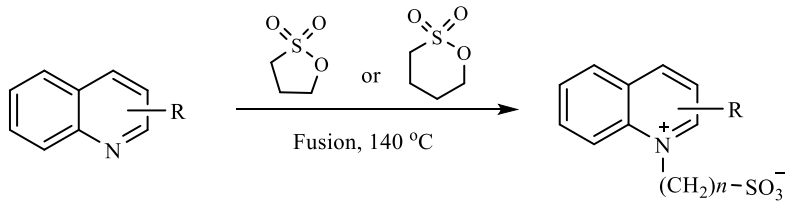


1a-c **2a-f**

1a, R= 2-Ph; **1b**, R= 4-Ph;
1c, R= 4-COOH

2a, R= 2-Ph, *n* = 3; **2b**, R= 2-Ph, *n* = 4;
2c, R= 4-Ph, *n* = 3; **2d**, R= 4-Ph, *n* = 4;
2e, R= 4-COOH, *n* = 3; **2f**, R= 4-COOH, *n* = 4

Scheme 1. Synthesis of pyridinium salts **2a-f**



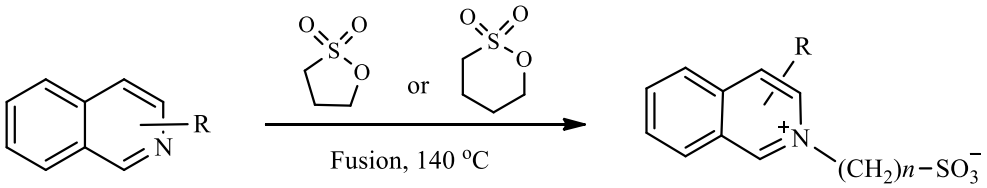
3a-j

3a, R= H; **3b**, R= 4-Cl;
3c, R= 4-Br; **3d**, R= 4-hydroxy;
3e , R= 3-CH_2CH_3; **3f**, R= 8-OH;
3g, R= 2-Cl; **3h**, R= 4,7-diChloro
3i, R= 5,7-diiodo-8-hydroxy; **3j**, R= 2,4-dimethyl

4a-m

4a, R= H, *n* = 3; **4b**, R= 4-Cl, *n* = 3;
4c, R= 4-Br, *n* = 3; **4d**, R= 4-hydroxy, *n* = 3;
4e, R= 3-CH_2CH_3, *n* = 3; **4f**, R= 3-CH_2CH_3, *n* = 4;
4g, R= 8-hydroxy, *n* = 3; **4h**, R= 2-Cl, *n* = 3;
4i R= 4,7-dichloro, *n* = 3; **4j**, R= 4,7-dichloro, *n* = 4;
4k, R=5,7-diiodo-8-hydroxy, *n* = 3; **4l**, R=5,7-diiodo-8-hydroxy, *n* = 4;
4m, R= 2,4-dimethyl, *n* = 3

Scheme 2. Synthesis of some quinolinium salts **4a-m**



5a, b

5a, R= 3-CH_3
5b, R= 4-Br

6a, b

6a, R = 3-CH_3, n = 3
6b, R = 4-Br, n = 4

Scheme 3. Synthesis of some isoquinolinium salts **6a, b**