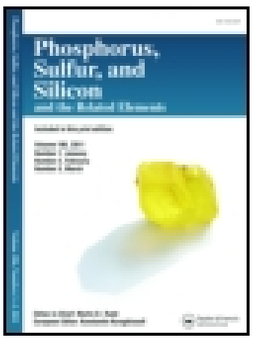

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Chemoselective synthesis of 5-amino-7-bromoquinolin-8-yl sulfonate derivatives and their antimicrobial evaluation

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ABSTRACT

A series of new 5-amino-7-bromoquinolin-8-ol sulfonate derivatives **5**(**a**–**j**) were synthesized from 8-hydroxyquinoline through multi-step process with high yields using mild, efficient and conventional methods. Chemoselectivity was observed during the transformation of 5-amino-7-bromoquinolin-8-ol to 5-amino-7-bromoquinolin-8-ol sulfonate with various sulfonylchlorides exclusively to afford sulfonate derivatives. Also, the products were investigated for their *in vitro* antimicrobial activities and compared with the standard drugs. Among all the synthesized compounds 5-amino-7-bromoquinolin-8-yl biphenyl-4-sulfonate (**5b**) and 5-amino-7-bromoquinolin-8-yl 2-hydroxy-5-nitrobenzenesulfonate (**5g**) have showed potent antibacterial activity, whereas 5-amino-7-bromoquinolin-8-yl biphenyl-4-sulfonate (**5b**) and 5-amino-7-bromoquinolin-8-yl 2-hydroxy-5-nitrobenzenesulfonate (**5g**) possessed potent antifungal activities among all the tested pathogens.

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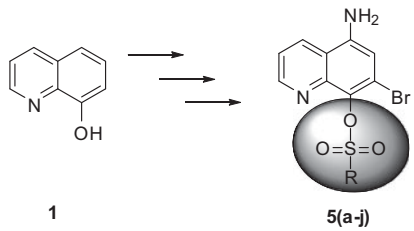
8-Hydroxy quinoline; 5-amino-7-bromoquinolin-8-ol; chemoselectivity; sulfonation; antimicrobial activity

GRAPHICAL ABSTRACT



Introduction

Quinoline derivatives are the most important antimalarial drugs (quinine, chloroquine and amodiaquine) constantly used historically and these scaffolds are precursors in a wide variety of pharmacologically active synthetic and natural compounds.[1] In recent years, the synthesis of quinoline and its derivatives have been of interest for chemists because of its various applications in fields like medicine, food, catalysts, dye materials, refineries and electronics were well established. In addition, these derivatives possess attractive ionophoric properties towards a variety of metal ions. Quinolones and aminoquinolines are the group of synthetic quinolines used as antimicrobials for the treatment of many infections[2] and have been considered as pivotal constituents in a number of pharmaceutically important compounds.[3] In particular, aminoquinoline derivatives possess potent biological activities including antiviral,[4] anticancer,[5] antibacterial,[6] antifungal,[7] antiobesity,[8] antiinflammatory[9] and antimalarial activity. It is reported that many antimalarial compounds have shown antiprion activity because of the incorporation of the quinoline rings.[10]

8-Hydroxyquinoline (8HQ) is a quinoline derivative originating from plants as well as from synthesis and it is known as simple fungicidal compound since the 1920s.[11] The derivatives of 8HQ are widely used as analytical reagents due to their ability to form stable complexes with many metal ions.[12] In addition they have also use in biological applications such as for example, antimicrobial,[13–15] antimalarial,[16–18] antiviral,[19] antitubercular[20] and antidental plaque activities.[21,22] Another derivative of 8HQ, Clioquinol (5-chloro-7-iodo-8-hydoxyquinoline) which has found use as an antifungal and antiprotozoal drug with metal-binding properties.[23–26]

Sulfonates are known as important intermediates in organic synthesis and precursors of sulfonamides. They act as alkylating agents and leaving groups in substitution reactions.[27] On the other hand, compounds containing aryl sulfonate moiety have received considerable attention during last two decades due to their biological activities such as papillomavirus microbicidal,[28] anti-HIV-1,[29] antineoplastic[30] and anticancer activity.[31,32] In addition, various sulfonate derivatives of quinoline exhibit interesting pharmacological activities.[33] To the best of our knowledge,

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no reports were found on sulfonate derivatives of 5-amino-7-bromoquinolin-8-ol.

Led by the above facts, we focused on the synthesis of 5-amino-7-bromoquinolin-8-ol sulfonate **5**(**a**–**j**) derivatives from 8-hydroxy quinoline (**1**) in excellent yields through a multi-step reaction process. All the newly synthesized 5-amino-7-bromoquinolin-8-ol sulfonate derivatives **5**(**a**–**j**) were screened for their antibacterial and antifungal activities.

Results and discussion

Chemistry

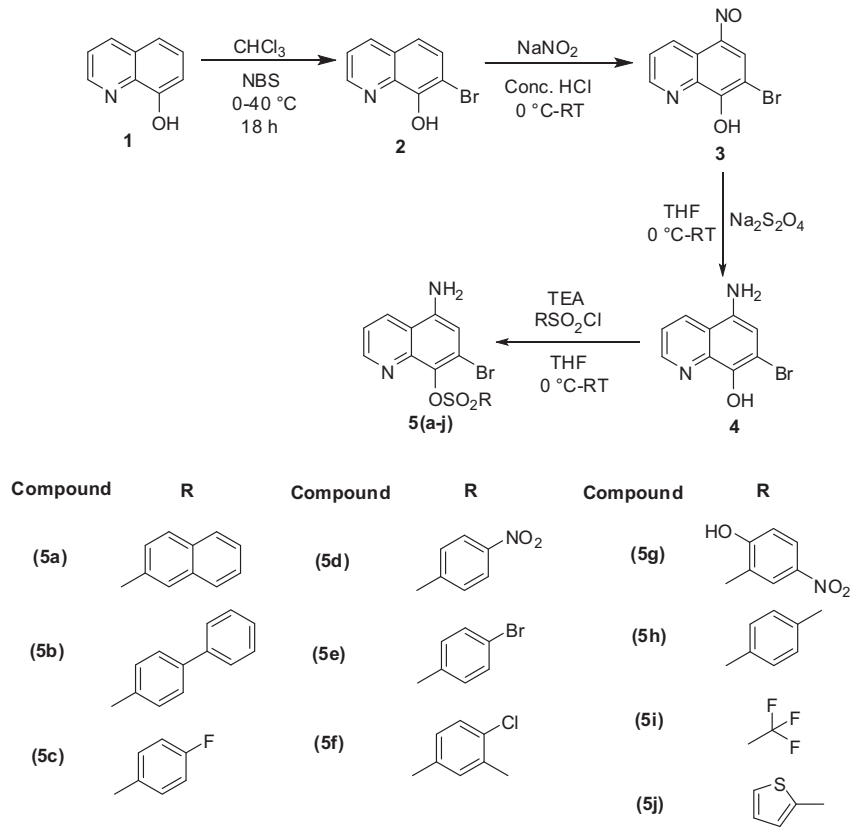
We have synthesized a series of new 5-amino-7-bromoquinolin-8-ol sulfonate derivatives **5**(**a**–**j**) from 8-hydroxy quinoline (**1**) in four steps bromination, nitrosation, reduction and sulfonation with high yields (86–93%) (Scheme 1).

Compound (**1**), on reaction with *N*-bromosuccinimide in chloroform,[34] afforded 7-bromoquinolin-8-ol (**2**), which upon nitrosation[35] with conc. HCl and $NaNO_2$ in water yielded 7-bromo-5-nitrosoquinolin-8-ol (**3**). Compound (**3**) was reduced to amino[36] derivative 5-amino-7-bromoquinolin-8-ol (**4**) by reaction with $Na_2S_2O_4$ in 1:1 THF and water. Finally, sulfonate derivatives **5**(**a**–**j**) were achieved from compound (**4**) by reaction with various sulfonyl chlorides in dry THF in the presence of triethylamine (TEA) to chemoselectively afford sulfonate derivatives.

In general, primary amines and alkyl/aryl alcohols were converted to their corresponding sulfonamides and sulfonates by treating with an appropriated sulfonyl chloride in the presence of a base.[37,38] According to Da Silva et al., the sulfonyl chloride group was chemoseletively[39] attacked by OH group instead of NH_2 group exclusively to get sulfonate derivatives. This can be attributed to the conjugation and resonance delocalization of the lone pair electrons of the amino group nitrogen atom with the aromatic ring enhancing the nucleophilicity of the quinolinic nitrogen.[39] It plays the role of nucleophilic catalyst to transfer the arylsulfonyl moiety to the phenol oxygen atom via intramolecular nucleophilic attack. Here, triethylamine act as a base to deprotonate the pyridine nitrogen after re-aromatization of the product molecule.

In the present study, we have investigated that compounds having a bromo substitution at ortho-position to hydroxy group show high chemoselectivity to obtain the quinoline sulfonate **5**(**a**–**j**) (Figure 1) instead of the formation of sulfonamides under the conditions of triethylamine at 0 °C to room temperature (RT). In ^{1}H NMR spectroscopy, NH_2 peak was appeared as a singlet in the region δ 5.68–6.18 ppm designated for 2 protons, which clearly indicates that the formed products are sulfonates.

All the newly synthesized compounds were characterized by IR, NMR (^{1}H and 13C), mass spectra and elemental analysis spectral data and were presented in experimental data. In IR spectrum, the two absorption bands were observed in the region of 3337–3500 cm^{-1} corresponds to the stretching vibrations of N-H for all the title compounds. The absorption bands in the region 1370–1405 and 560–645 cm^{-1} correspond to the stretching vibrations of S=O and C–Br



Scheme 1. Chemoselective synthesis of 5-amino-7-bromoquinolin-8-ol sulfonate derivatives **5**(**a**–**j**).

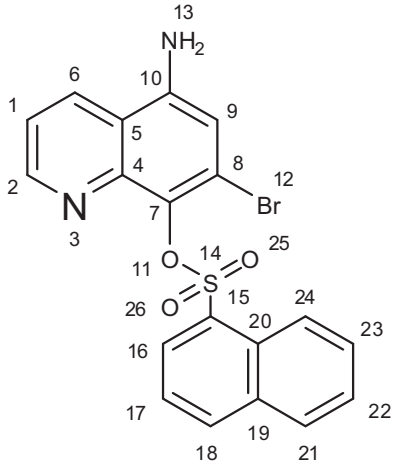


Figure 1. Structure and numbering of sulfonate derivative 5(a–j).

respectively. In the ^{1}H NMR spectra, the chemical shift values observed in the region δ 5.68–6.18, 6.66–7.35, 7.49–8.07, 8.55–9.12 ppm are assigned to NH_2, H_1, H_9 and H_2 protons respectively. In 13C NMR spectra, the chemical shift values resonated in the region δ 106.2–110.0, 117.6–146.4, 119.1–121.6, 121.6–123.8, 136.9–141.4, 139.8–148.9 and 149.6–153.0 ppm corresponds to C_9, C_{15}, C_1, C_8, C_{10}, C_7 and C_2 carbon atoms. The chemical shift values were observed in the region δ 127.3, 129.4, 129.4, 137.8, 155.2 and 165.3 ppm corresponds to C–Br, C–Cl, C–OH, C–CH_3, C–NO_2 and C–F respectively.

Biological activity

Antibacterial activity

The *in vitro* antibacterial activity of the newly synthesized compounds **5**(**a**–**j**) were tested against two bacterial strains such as *Staphylococcus aureus, Bacillus megaterium* (Gram positive bacteria), *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* (Gram negative bacteria); two Gram negative antibiotic resistant *E. coli* bacterial strains such as Mutant *E. coli* (*Streptomycin resistant*) and Donor *E. coli* (*Rifampin resistant*) bacteria by agar well diffusion method[40,41] using Amoxiclav Ac[30] (SD063, Himedia) as a standard drug.

Among the synthesized compounds **5a**, **5b** and **5h** have shown potent activity against donor *E. coli* bacteria. Compound **5b** has shown potent activity against *Staphylococcus aureus* and mutant *E. coli* bacteria due to biphenyl, compounds **5c** and **5j** showed potent activity against *Bacillus megaterium* might be due to the presence of fluorine and sulfur. Compounds **5h** has shown potent activity against *Klebsiella pneumonia* might be due to the presence of 4-methoxy benzene whereas, compounds **5c** and **5g** have shown potent activity against *Pseudomonas aeruginosa* might be due to the presence of fluorine and nitro substituents. Compounds, **5b** and **5h** have shown good antibacterial activity against all the tested pathogens, might be due to the presence of biphenyl and 4-methoxy benzene on the sulfonyl group (Table S1, Supplemental Materials).

Antifungal activity

The *in vitro* antifungal activity was screened for the compounds which have shown good antibacterial activity (**5b**, **5c**, **5f**, **5g** and **5h**) against two fungal strains such as *Aspergillus niger* and *Penicillium spinulosum* by the poison plate technique[42] using Fluconazole *Fu*[10] (SD 114, Himedia) as a standard drug.

Among the tested compounds, **5b** and **5g** have exhibited potent antifungal activity against *Aspergillus niger* and *Pencillium spinulosum,* might be due to the presence of biphenyl, 2-nitro 5-hydroxy benzene ring on sulfonyl group. However, compounds **5c** and **5f** have shown good antifungal activity due to the presence of fluorine and chlorine substituent in the aromatic ring against all tested pathogens. Compound **5h** possessed moderate activity against *Aspergillus niger* (Table S2, Supplemental Materials)

Experimental

All chemicals were purchased from Sigma-Aldrich, Merck and Lancaster, and were used without further purification. Compound (**1**) was purchased from Avra laboratory, Hyderabad. All solvents used for spectroscopic and other physical studies were reagent grade and were further purified by literature methods. Melting points were determined using a calibrated thermometer by Guna digital melting point apparatus. IR Spectra were recorded as KBr discs on a Nicolet 380 FT-IR spectrophotometer. ^{1}H and 13C NMR spectra were recorded as solutions in DMSO-d_6 on a Bruker AMX 400 MHz spectrometer operating at 400 MHz for ^{1}H NMR, 100 MHz for 13C NMR. The ^{1}H NMR and 13C NMR chemical shifts were referenced to internal standards using tetramethylsilane. Chemical shifts were reported in ppm (δ) and the signals are described as singlet (s), doublet (d), triplet (t), quartet (q), broad (br), broad singlet (br s) and multiplet (m). The model structure and numbering of 5-amino-7-bromoquinolin-8-ol sulfonate derivatives is given in Figure 1. The Supplemental Materials contains sample ^{1}H and ^{13}C NMR spectra for 5a (Figures S4–S5).

Synthesis of 7-bromoquinolin-8-ol (2)

To a stirred solution of quinolin-8-ol **(1)** (5 g, 1 mmol) in chloroform (10 mL), *N*-bromo succinimide (6.13 g, 1 mmol) was added portion wise at 0 °C, slowly raising the temperature to 40 °C and stirred for 18 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as an eluent (1:9).

After completion of the reaction, the reaction mixture was evaporated under vacuum and washed with water to give the crude 7-bromoquinolin-8-ol (2) (6.53 g), which was then washed with hexane and diethyl ether to yield 7-bromoquinolin-8-ol as a white solid in 85% yield. m.p: 138–143 °C; EI-MS: *m*/*z* (%): 224 (M^+ H (100)), 145 (32).

Synthesis of 7-bromo-5-nitrosoquinolin-8-ol (3)

To 7-bromoquinolin-8-ol (6.53 g, 1 mmol) (**2**) in minimum amount of conc. HCl (3 mL), $NaNO_2$ (2.02 g, 1 mmol) in water was added drop wise through dropping funnel at 0 °C and stirred for 30 min at room temperature. Formation of 7-bromo-5-nitrosoquinolin-8-ol (**3**) was confirmed by TLC (ethyl acetate and hexane, 2:8). After completion, the reaction mixture was poured into ice water and filtered by washings with water to get the residue, which was purified by washings with hexane and diethyl ether to obtain an orange red solid 7-bromo-5-nitrosoquinolin-8-ol (6.05g) (**3**) with 82% yield. m.p: 230–233 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.98 (dd, 1H, $J = 4.4$, 3.6 Hz, H_1), 8.38 (s, 1H, H_9), 8.78 (dd, 1H, $J = 4.4$, 4.0 Hz, H_6), 9.10 (d, 1H, $J = 5.2$ Hz, H_2), 13.8 (s, 1H, OH); EI-MS: *m/z* (%): 254 (M^+ H (32)), 236 (21), 157 (100), 149 (46), 131 (21).

Synthesis of 5-amino-7-bromoquinolin-8-ol (4)

To a solution of 7-bromo-5-nitrosoquinolin-8-ol (**3**) (6.05 g, 1 mmol) in a 1:1 THF and water (10 mL), was added $Na_2S_2O_4$ (4.2 g, 1 mmol) in portions at 0 °C and resulting mixture was stirred for 1 h. Formation of the 5-amino-7-bromoquinolin-8-ol (**4**) was ascertained by TLC using ethyl acetate and hexane (2:8) as an eluent. The reaction mixture was quenched with saturated sodium bicarbonate solution to remove unreacted $Na_2S_2O_4$ and extracted with ethyl acetate (200 mL). The organic layer was washed with water for several times, it was separated and concentrated under vacuum to give the crude compound, which was purified by silica gel column chromatography, using ethyl acetate/hexane (1:4, v/v) as eluent to obtain 5-amino-7-bromoquinolin-8-ol (4.45g) (**4**) as white solid with 78% yield.m.p: 237–240 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.31 (s, 2H, NH_2), 7.31 (dd, 1H, $J = 4.4$, 3.6 Hz, H_3), 7.46 (s, 1H, H_7), 8.18 (dd, 1H, $J = 4.4$, 4.0 Hz, H_4), 8.72 (d, 1 H, $J = 5.2$ Hz, H_2), 9.39 (s, 1 H, OH); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 108.1 (C_9), 120.1 (C_1), 122.6 (C_8), 122.9(C_5), 130.3(C_6), 136.1(C_4), 139.8(C_{10}), 141.4 (C_7), 150.8 (C_2); EI-MS: *m/z* (%): 239 (M^+ H (100)), 196 (8), 160 (37), 131 (10).

General procedure for the preparation of 5-amino-7-bromoquinolin-8-ol sulfonate derivatives 5(a–j) is illustrated by the synthesis of compound (5a)

To a mixture of 5-amino-7-bromoquinolin-8-ol (**4**) (1 mmol, 0.5 g) and TEA (2 mmol, 0.385 mL) in dry THF (10 ml) at 0 °C, naphthalene-1-sulfonyl chloride (1 mmol, 0.47g) in dry THF was added drop wise and stirred for 6 h at room temperature. After completion, the reaction mixture was evaporated under vacuum to obtain the residue, which was purified by washings with n-hexane and diethyl ether to obtain pure product 5-amino-7-bromoquinolin-8-yl naphthalene-1-sulfonate (0.79g) **(5a)**.

Yield: 88%, White solid, m.p.: 187–189 °C. IR (KBr, cm^{-1}): 3500, 3450 (-N-H, str), 1405 (-S = O, str), 620 (-C-Br, str); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.89 (s, 2 H, NH_2), 7.21 (dd, $J = 4.4$, 4.0 Hz, 1 H, H_1), 7.68 (s, 1 H, H_9), 7.79–7.81 (m, 2 H, $H_{23,24}$), 8.15–8.25 (m, 5 H, $H_{6,16,17,18,21}$), 8.38 (d, $J = 2.40$ Hz, 1 H, H_{24}), 8.79 (d, $J = 1.6$ Hz, 1 H, H_2); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 108.1 (C_9), 119.1 (C_1), 121.6 (C_8), 122.6 (C_5), 123.7 (C_{17}), 127.5 (C_{22}), 127.9 (C_{16}), 128.9 ($C_{21,23}$), 129.4 (C_{24}), 129.5 (C_{20}), 131.0 (C_6), 131.6 (C_{18}), 133.2 (C_{19}), 135.8 (C_4), 139.8 (C_{10}), 141.4 (C_{15}), 146.7 (C_7), 151.1 (C_2); EI-MS: m/z (%): 429 (M^+ H (10)), 262 (44), 239 (100), 192 (34), 167 (16), 127 (13). Anal. Calcd. for $C_{19}H_{13}BrN_2O_3S$ C, 53.16; H, 3.05; N, 6.53; Found: C, 53.10; H, 3.23; N, 6.42.

Biological activity

Antibacterial activity

Antibacterial activity of the newly synthesized sulfonate derivatives of 5-amino-7-bromoquinolin-8-ol **5(a–j)** was assayed against Gram positive bacteria *Staphylococcus aureus* and *Bacillus Megaterium*; Gram negative bacteria *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* and Gram negative antibiotic resistant *E. coli* bacterial strains Mutant *E. coli* (Streptomycin resistant) and Donor *E. coli* (Rifampin resistant) by agar well diffusion method. The results are presented in Table S1 (Supplemental Materials).

Antifungal activity

The compounds which have shown good antibacterial activity were tested for antifungal activity against the fungal strains like *Aspergillus niger* and *Penicillium spinulosum* by the poison plate technique. The results are presented in Table S2 (Supplemental Materials).

Conclusion

In this study, we have synthesized a series of new 5-amino-7-bromoquinolin-8-ol sulfonate derivatives containing biologically potent groups through mild, efficient and convenient synthetic methods & evaluated their antimicrobial activity. In the final step, the chemoselectivity was observed to exclusively afford 5-amino-7-bromoquinolin-8-ol sulfonate derivatives. The *in vitro* antimicrobial activity results revealed that compounds **5b** and **5h** exhibited potent antibacterial activity, whereas, **5b** and **5g** possessed potent antifungal activity compared with the remaining synthesized compounds against all pathogens in tested doses. It is concluded that, the chemoselective synthetic process might be useful to the researchers for the synthesis of biologically active organic compounds. Incorporation of the sulfonyl group on quinoline enhanced the pharmacological effect, and hence they are suited for further modifications to obtain efficient antimicrobial agents.

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