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Synthesis, Antimicrobial Activity and Molecular Docking Studies of 7-Bromoquinoline-5,8-dione containing Aryl sulphonamides

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Abstract

Some quinoline-5,8-dione derivatives incorporating aryl sulphonamides have been synthesized. This was achieved by direct nucleophilic amination of 7-bromoquinoline-5,8-dione using different aryl sulphonamides. The chemical structures of the compounds were confirmed on the basis of UV, FTIR, ^{1}H-NMR and ^{13}C-NMR spectral data. The synthesized compounds were considered as fragments due to their low MW (314.32 – 359.31 Da) and reasonable lipophilicity (1.14 – 1.79), an important property for putative drug hit, and docking results showed the sulphonamides interacted with bacteria dihydropteroate synthase at K_i range of 529.80 µM - 1.42 mM. Hence, *in vitro* antimicrobial activity of the newly synthesized compounds against some bacterial and fungal strains was investigated and the results confirmed their antibiotic potency with MIC ranges of 0.80 – 1.00 mg/ml. The two compounds, **5b** and **5d** can be used to design new drug selective for *K. Pneumonia* and *S. typhi* respectively.

Keywords: Amination; Biological activity; Derivatives; Quinoline-5,8-dione; Sulphonamides;

1. INTRODUCTION

The chemistry of quinolin-5,8-dione compounds has continued to attract great interest especially in the field of medicine due to their broad range of pharmacological activities [1]. They are indispensible targets in the synthesis of biologically active compounds [2]. Substituted quinoline-5,8-diones are important antifungal, antibacterial, tuberculostatic and cytostatic agents [3]. Quinolinedione derivatives have been used as anti-inflammatory, anticancer, antihypertensive, and anti HIV agents as well as tryokinase PDGF-RTK inhibitors [4-11]. Quinoline-5,8-dione moiety has continued to undergo various modifications in order to discover more potent drugs [12] . Prominent quinolinedione-based drugs include antibacterials; such as ciprofloxacin and sparfoxacin, antimalarials; such as quinidine, chloroquine and primaquine, antifungal; such as clioqinol, and antiviral; such as saquinavir.

The quinoline-5,8-dione nucleus is a vital component of many naturally occurring bioactive agents including Lavendamycin and Streptonigrin, which are well-known antibiotic and antitumor agents [13, 14]. Report has shown that Strptonigrin also possesses potent antiviral, cytotoxic, and antimicrobial properties [15]. Furthermore, the synthesis of a series of 5,8-quinolinedione derivatives containing alkoxy [16], alkynyloxy [17] and amino [18] groups, which were found to show strong cytotoxicity activity against human cancer cells have been reported. In most cases the activity was found to vary with the type of substituent and the tumor cell lines tested [17].

Several compounds with wide range of biological activities have been synthesized by manipulating the substituents around the quinoline5,8-dione nucleus [18-33]. However, studies have shown that the presence of substituents such as amine, halogen, hydroxyl or thiol, at 6 or 7 position of the 5, 8-quinolinedione moiety gives rise to improved biological activity [17].

There are particularly many studies on the synthesis and biological activity of the amine derivatives of 5,8-quinolinedione [16], but reports on sulphonamide analogues are quite limited in the literature. Sulphonamide group is an important pharmacophore that is found in many biologically active molecules. Sulphonamide derivatives have been recognized as antimicrobial agents [34-37], anti-inflammatory agents [38], anticancer [39], and carbonic anhydrase inhibitor [40-44]. Chemically modified sulphonamides are synthesized to obtain more effective antimicrobials with more prolonged action.

In continuation of our study on quinoline-5,8-diones [3,16] and sulphonamides [37] we herein report the facile synthesis of various 7-bromoquinoline-5,8-dione aryl sulphonamides. Our focus in this study is to synergize the antimicrobial activity of quinoline-5,8-dione and sulphonamide in an effort to obtain potent antimicrobial leads. Hence the molecular docking study and antimicrobial screening of the synthesized compounds were also done.

Molecular modeling techniques are commonly employed in studying properties of small and macro-molecules because of their cost and time effectiveness relatively to

experimental techniques [45, 46]. Moreover, growth in computational power and accuracy have increased the correlation between computational and experimental results and hence applicability and acceptance of the techniques in scientific research [47, 48].

2. EXPERIMENTAL SECTION

The reagents used were products of Sigma Aldrich Chemicals and were used without further purification. Melting points were determined using electrothermal melting point apparatus in open capillaries and were uncorrected. Ultraviolet and visible spectra were recorded on UV-25500 PC spectrometer using matched 1 cm quart cell. The IR spectra were recorded on 8400S FTIR spectrometer using KBr discs. The ^{1}H-NMR and ^{13}C-NMR were determined using varian NMR 500MHz and 126MHz spectrometer respectively. The antimicrobial screening was done at the Faculty of Pharmaceutical Science University of Nigeria Nsukka.

Procedure for the synthesis of the compounds

Synthesis of 5,7-dibromo-8-hydroxyquinoline, 2

A solution of bromine (10 ml) in methanol (100ml) was added to a mixture of 8-hydroxyquinoline **1** (0.065 mol), sodium hydrogen carbonate (0.12 mol) and methanol (100 ml) drop by drop under stirring for 5 minutes at room temperature. Then sodium trioxosulphate (iv) (0.04 mol) was added to react with the excess bromine. The mixture was then filtered and the crude product obtained was washed with distilled water, and dried in vacuo to give the titled compound as a white solid. The yield was 82.9 %.

Synthesis of 7-bromoquinoline-5,8-dione, 3

5,7-Dibromo-8-hydroxyquinoline **2** (0.034 mol) was dissolved in concentrated sulphuric acid (40 ml). To this solution, nitric acid (61%, 5 ml) was added cautiously for 30 minutes under stirring at 0 ◦C in ice bath. Ice water (300 ml) was added to the mixture and extracted with dichloromethane. The organic layer was dried over sodium sulphate and concentrated in vacuo to give the final product as a brown solid. The yield was 97.9 %.

General procedure for the synthesis of the target compounds 5a-e

The various benzene sulphonamides **4a-e** (0.0053 mol) were added to a solution of 7-bromoquinoline-5,8-dione **3** (0.0021 mol) in dichloromethane (15 ml). The resulting mixture was stirred for 2 hours at room temperature. The mixture was then treated with distilled water (45 ml), and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude product obtained was recrystallized from methanol to furnish the desired compounds, **5a-e** in good yields.

Synthesis of N-(7-bromoquinoline-5,8-dione-6-yl)-benzenesulphonamide, 5a

Following the general procedure described, compound **5a** was obtained as a brown crystalline solid on reacting 7-bromoquinoline-5,8-dione with benzene sulphonamide. Yield: 86.4%. mp: 118-120 ◦C. UV-Vis (MeOH) λ_{max} (nm): 403, 464. IR (KBr) cm^{-1}: 3431 (N-H), 2984 (C-H aromatic), 1766 (C=O), 1326, 1284 (SO_2), 794 (C-Br). ^{1}H-NMR (500 MHz; DMSO-d_6) δ (ppm): 8.78 (1H, s, NH), 7.54-7.63 (3H, m, Ar-H), 7.35-7.59 (5H, m, Ar-H). ^{1}C-NMR (126 MHz; DMSO-d^6) δ (ppm): 144.62, 132.36, 132.17, 129.52, 129.31, 126.09, 126.00 (aromatic carbons).

Synthesis of N-(7-bromoquinoline-5,8-dione-6-yl)-4-methylphenylsulphonamide, 5b.

Following the general procedure, p-toluenesulphonamide and 7-bromoquinoline-5,8-dione were converted to the titled compound **5b** as a dark brown crystalline solid. Yield: 58.7%. mp: 86-88 ◦C. UV-Vis (MeOH) λ_{max} (nm): 465. IR (KBr) cm^{-1}: 3354 (N-H), 3053 (C-H aromatic), 1727 (C=O), 1272, 1210 (SO_2), 695 (C-Br).^{1} H-NMR (500 MHz; DMSO-d_6) δ (ppm): 7.72 (1H, s, NH), 7.71 (2H, d, J = 8.24 Hz, Ar-H), 7.37 (2H, d, J = 7.97 Hz, Ar-H) 7.33-7.36 (2H, m, Ar-H), 2.38 (3H, s, CH_3). ^{1}C-NMR (126 MHz; DMSO-d^6) δ (ppm): 142.34, 141.89, 129.86, 129.71, 126.17, 126.02 (aromatic carbons).

Synthesis of N-(7-bromoquinoline-5,8-dione-6-yl)-4-chlorophenylsulphonamide, 5c

Following the general procedure, compound **5c** was furnished as a brown crystalline solid by the reaction between 4-chlorobenzenesulphonamide and 7-bromoquinoline-5,8-dione. Yield: 62.2 %. mp: 108-110 ◦C. UV-Vis (MeOH) λ_{max} (nm): 401, 465. IR (KBr) cm^{-1}: 3470 (N-H), 3158 (C-H aromatic), 1689 (C=O), 1286, 1176 (SO_2), 578 (C-Br).^{1} H-NMR (500 MHz; DMSO-d_6) δ (ppm): 7.74 (1H, s, NH), 7.83 (1H, d, J = 7.87 Hz, Ar-H), 7.66 (1H, d, J = 8.02 Hz, Ar-H) 7.66 (1H, d, J = 7.76 Hz, Ar-H) . ^{1}C-NMR (126 MHz; DMSO-d^6) δ (ppm): 143.47, 137.03, 129.68, 129.65, 129.60, 129.46, 129.42, 128.12, 128.03 (aromatic carbons).

Synthesis of N-(7-bromoquinoline-5,8-dione-6-yl)-4-nitrophenylsulphonamide, 5d

By the reaction of 4-nitrophenylsulphonamide with 7-bromoquinoline-5,8-dione following the general procedure, compound **5d** was furnished as a dark brown crystalline solid. Yield: 64.7 %. mp: 119-121 ◦C. UV-Vis (MeOH) λ_{max} (nm): 464. IR (KBr) cm^{-1}: 3485 (N-H), 3184 (C-H aromatic), 1743 (C=O), 1312, 1263 (SO_2), 579 (C-Br).^{1} H-NMR (500 MHz; DMSO-d_6) δ (ppm): 8.77 (1H, s, NH), 9.14 (3H,dd, J = 4.58, 1.53 Hz, Ar-H), 9.00 (4H, br d, J = 4.27 Hz, Ar-H) . ^{1}C-NMR (126 MHz; DMSO-d^6) δ (ppm): 149.67, 128.69, 127.70, 124.94 (aromatic carbons).

Synthesis of N-(7-bromoquinoline-5,8-dione-6-yl)-4-methoxyphenylsulphonamide, 5e

The general procedure was employed to synthesize compound **5e** by the reaction of 4-methoxybenzenesulphonamide and 7-bromoquinoline-5,8-dione. IR (KBr) cm^{-1}: 3421 (N-H), 3123 (C-H aromatic), 1693 (C=O), 1310, 1214 (SO_2), 624 (C-Br). ^{1}H-NMR (500 MHz; DMSO-d_6) δ (ppm): 7.78 (1H, s, NH), 7.52-7.75 (3H, m, Ar-H), 7.07 (2H, d, Ar-H), 7.10 (2H, d, Ar-H), 3.28 (3H, s, CH_3) . ^{1}C-NMR (126 MHz;

DMSO-d^6) δ (ppm): 140.84, 136.21, 127.72, 114.04, 112.79 (aromatic carbons).

Molecular docking Studies

The X-ray crystal structure of dihydopteroate synthase (dhps) with its co-crystallized inhibitor was retrieved from protein databank (PDB code 5u14) [49]. The 3-dimension of dhps was prepared for docking studies using molecular operating environment (MOE) as described in our earlier work [45]. Molecule builder interface in MOE was used to generate the 3-D chemical structures of the newly synthesized sulphonamide compounds. The five molecular descriptors represented in Lipinski's determination of drug-likeness: molecular weight (MW), lipophilicity (logP), hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), and number of rotatable bond (NRB), were computed for each of the sulphur compounds using QuSAR module implemented in MOE. The dock-tool and scoring method implemented in AutoDock 4.2.0 were employed in docking and scoring the poses of the sulfa compounds in the dhps binding site. A grid box size of 40, 40, 40 A^3 points (spacing between the grid points of 0.375 A) was used which centered on the mass center (71.574, -0.376, 101.64) of the crystallographic macromolecule encompassing all the active site atoms. Root mean square deviation of the dock-pose from the X-ray crystal pose was calculated to validate the docking protocol [46].

Antimicrobial Activity Test

Agar-well diffusion method was used to determine antimicrobial sensitivity test and the minimum inhibitory concentration (MIC) of the synthesized compounds [50,51]. Serial dilutions of the compounds were prepared from 1 mg/ml solution of the quinolinedione sulphonamide derivatives to give 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, and 0.1 mg/ml. After dilution, the test solutions were added into their corresponding cups previously made in the molten agar, starting from the lowest concentration (0.1 mg/ml). This was followed by incubation at 37 °C for 24 h for bacteria and 48 h for fungi. The resultant inhibition zones of diameter (IZD) were measured and the values subtracted from the diameter of the borer (8 mm) to give the inhibition zone diameter (IZD). The graph of IZD^2 against log of concentration was plotted for each plate and the antilogarithm of the intercept on x-axis gave the MIC. The procedure was also repeated for Ciprofloxacin and Nystatine standards.

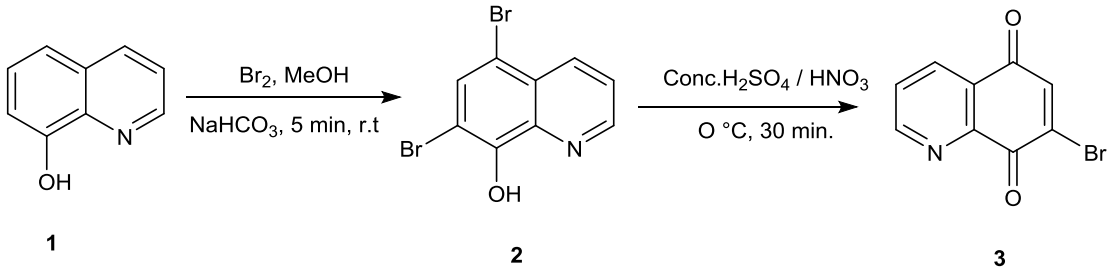
3. RESULTS AND DISCUSSION

Chemistry

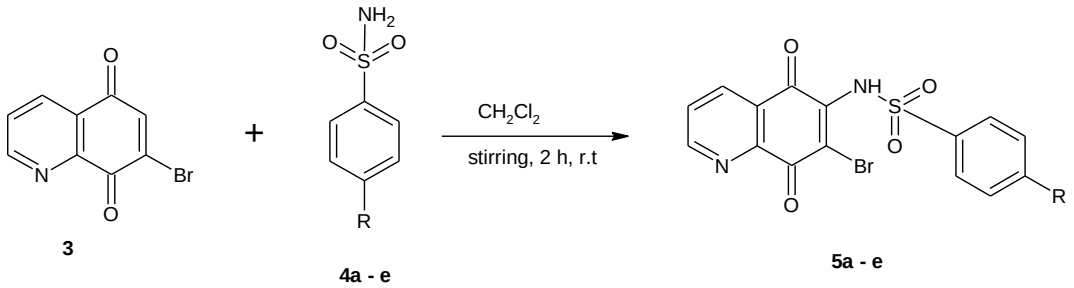
The room temperature bromination of 8-hydroxyquinoline afforded 5,7-dibromo-8-hydroxyquinoline, which upon oxidation gave the key intermediate 7-bromoquinoline-5,8-dione [18] (S**cheme 1)**. The aryl sulphonylchlorides were converted to their corresponding sulphonamides using previously reported procedure [52]. The target compounds, (**5a-e**), were furnished by nucleophilic amination of 7-

bromoquinoline-5,8-dione using the various aryl sulphonamides (S**cheme 2)**. Only the 6-sulphonamides of 7-bromoquinoline diones 5a – e were obtained. This is in conformity with previous reports [18, 19]. The proposed mechanism of the reaction involves Michael addition with regioselectivity on the basis of steric effect caused by the bulkiness of the bromine atom at C7 [19], which makes attack at ipso position difficult. This results in a favourable attack by the sulphonamide group at the C6 position of the quinolinedione system, which is at α-position with respect to 5-carbonyl. In addition, intramolecular hydrogen bonding between the OH at C8 and N1 can also contribute to the observed nucleophilic attack on C6 position [19] (**Scheme 3**.) From the reaction mechanism, the intermediate compound can exist as a keto or enol compound. However, the enol form will be more stable because of possible hydrogen bonding. Consequently, oxidation of the enol intermediate yields 7-bromoquinoline-5,8-dione- 6-arylsulphonamides.

The structures of the target compounds **5a-e** were characterized by UV, IR, ^{1}H-NMR and ^{13}C-NMR spectral data. The UV absorption bands for the compounds around 403-464 nm showed the extended pi-conjugation nature of the compounds. N-H asymmetric stretching for all the compounds are observed around 3421-3354 cm^{-1} in the infrared spectra. The strong absorption signals observed around 132-1176 cm^{-1} are assigned to the asymmetric and symmetric SO_2 stretching vibrations, and this was evident in all the compounds, confirming the presence of SO_2-NH group in the structures. Other absorption signals are in good agreement with the structures of synthesized compounds. In the ^{1}H-NMR spectra, the singlets around 8.78-7.47 ppm are for the –NH moiety in the structures. The doublets and multiplets around 7.07-9.14 ppm reveals the presence of Ar-H in the ring of the structures, while the peaks at 2.38-3.82 are assigned to the protons of the $–CH_3$ group in compounds **5b** and **5e** respectively. The peaks in the ^{13}C-NMR spectra are for aromatic carbons in the structures. The IR bands, proton and carbon signals observed strongly support the proposed structures.



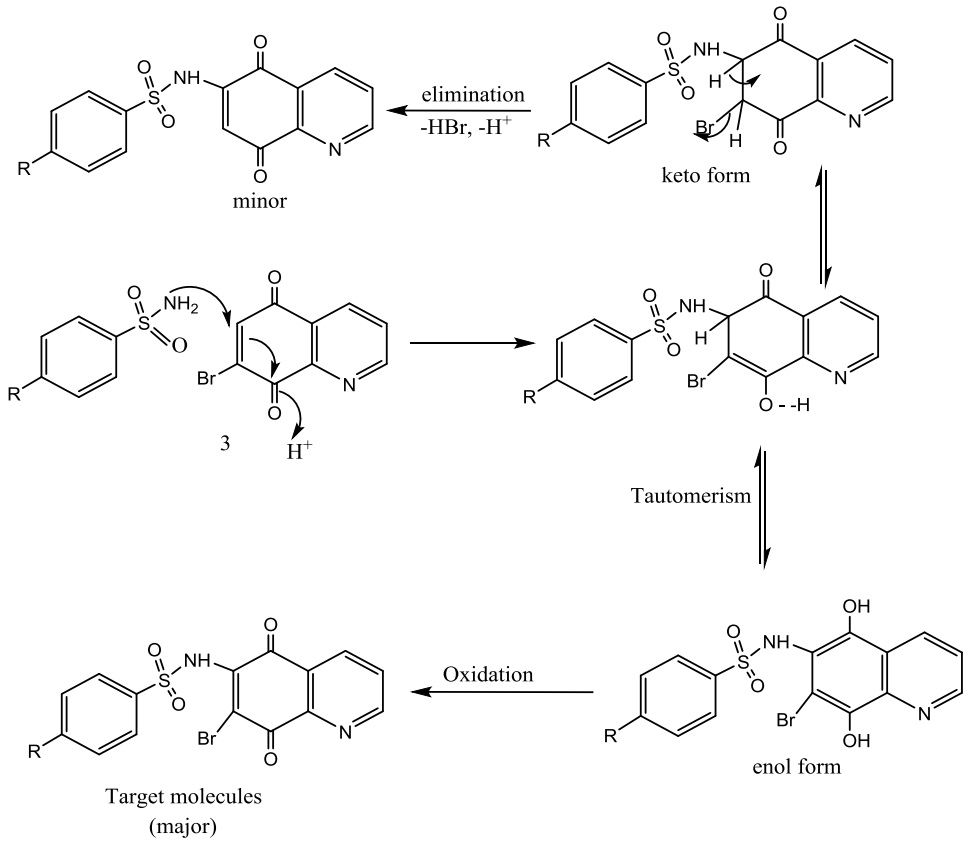
Scheme 1. Pathway for the synthesis of 7-bromoquinoline-5,8-dione



3 **4a - e** **5a - e**

R: a = H, b = CH_3, c = Cl, d = NO_2, e = OCH_3

Scheme 2. Pathway for the synthesis of N-(7-bromoquinoline-5,8-dione-6-yl)sulphonamides



Scheme 3. Proposed plausible reaction mechanism for synthesis of N-(7-bromoquinoline-5,8-dione-6-yl)sulphonamides from their precursors

Molecular modeling

Poor pharmacokinetic property has resulted in failure of many potential drug molecules. Therefore, it has become a common practice to determine the property at early stage of drug discovery. The basic physicochemical feature of the five

sulphonamides as described by the computed molecular descriptors suggests they are drug-like (Table 1) according to the set rule for oral bioavailability [53]. In fact, the sulphonamides were considered as fragments due to their low MW (314.32 – 359.31 Da) and reasonable lipophilicity (1.14 – 1.79), an important property for putative drug hit [48].

Sulphonamides are well known to inhibit *dhps*, a key enzyme in the folate pathway of bacteria and primitive eukaryotes, in exhibiting their antibiotic activity [54]. Therefore, the newly synthesized sulphonamides were evaluated for ability to interact with the enzyme. The lowest theoretical binding energies as shown in Table 2 depict all the sulphonamides favourably interacted with the bacteria dhps. Variation in the C4-position of the compounds produced significant effect in their binding interaction. It was observed that **5e** with methoxy group at C4 position demonstrated the highest binding affinity (K_i = 409.52 µM), followed by **5a** and **5b** with hydrogen and methyl atom / group (K_i = 1.42 mM and 529.80 µM) respectively. This implies that interaction with the protein is enhanced by the presence of moieties at C4 position that can engage in hydrogen bonding and hydrophobic interaction with the active site protein residues as was noticed in the binding poses of **5e** (Figure 1).

Table 1. Main Physical features of the sulphonamides

Compds	**NRB**	**HBA**	**HBD**	**logP(o/w)**	**MW**
5a	3	6	1	1.20	314.32
5b	3	6	1	1.50	328.34
5c	3	6	1	1.79	348.76
5d	4	9	1	1.14	359.31
5e	4	7	1	1.16	344.34

Table 2: Docking scores of the sulphonamides

Compds	**ΔG**	**K_i**	**LE**	**run**
5a	-4.01	1.15	0.18	9
5b	-4.47	529.80*	0.19	10
5c	-3.9	1.39	0.17	6
5d	-3.88	1.42	0.16	1
5e	-4.62	409.52*	0.19	5

K_i values with * are in µM units

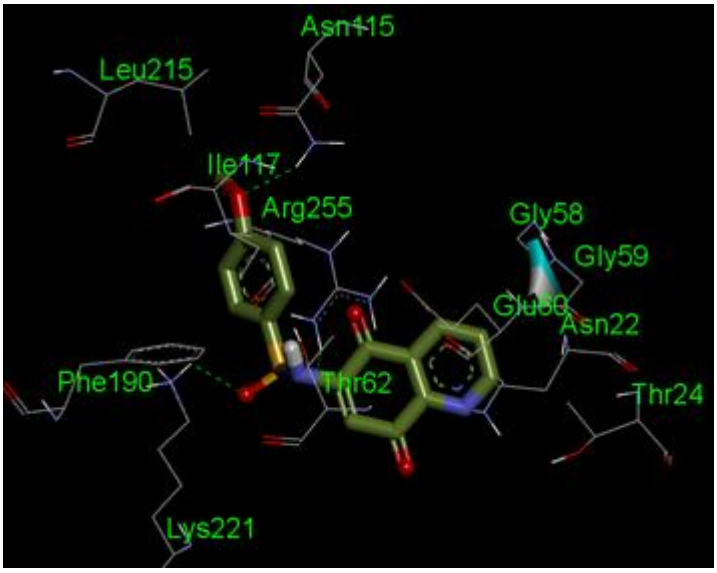


Figure 1. Binding pose of **5e** in the bacterial dihydropteroate synthase active site

Biological evaluation

Having shown high degree of drug-likeness and excellent binding affinity with the bacteria dhps, it became necessary to screen the synthesized compounds for in vitro antibacterial and antifungal activities against some pathogens, which include *S. aureus, E. coli, K. pneumonae, B. subtilis, S. typhi, C. albican,* and *A. niger*, and compare the results with Ciprofloxacin standard antibacterial and Nystatine standard antifungal drugs. These pathogens are known to cause infections associated with skin, urinary and chronic obstructive pulmonary, as well as gastrointestinal tract damage and renal failure. The results of the MIC tests are given in **Table 3**. The results showed that *E. coli, C. albican, and S. niger* strains are resistant to all the compounds. Compounds 5**a, 5b,** and **5e** were more active than **5d** and **5c** against *S. aureus*, each with the MIC of 0.9 mg/ml. Compound **5b**, the derivative bearing electron donating group (CH_3) showed better activity against *K. pneumonae* than all the other derivatives. The derivative **5c**, bearing electron withdrawing –Cl substituent had the least activity among all the derivatives against all the microbial strains. On the other hand, derivative **5d**, bearing electron withdrawing NO_2 substituent revealed the highest activity among all the compounds with the MIC of 0.8 mg/ml against *S. typhi*. This could be as a result of the polar nature of NO_2 group, which offer chances for H-bonding. However, it is noteworthy to say that none of the synthesized compounds showed a better activity than the Ciproflocaxin and Nystatine standard drugs. But compounds **5b** and **5d** could be incorporated into novel antibacterial drugs to boost their potency against bacterial infections like pneumoni, bloodstream infections, wound infections, urinary tract infections, meningitis, typhoid fever, food poisoning, gastroenteritis and enteric fever associated with *K. pneumonia* and S. typhi.

Table 3: Results of the minimum inhibition concentration (mg/ml) of the compounds and the standard drugs

Microorganisms→ Compounds↓	*Staphylococcus Aureus*	*E.coli*	*Klebsiella Pneumonia*	*Bacillus subtilis*	*Salmonella Typhi*	*C.albicans*	*A.niger*
5a	0.9	+	1	0.9	0.9	+	+
5b	0.9	+	0.9	0.9	0.9	+	+
5c	1	+	1	1	1	+	+
5d	1	+	1	0.9	0.8	+	+
5e	0.9	+	+	0.9	0.9	+	+
Cypro 30ug/ml	30	30	30	30	30	+	+
Nystatine 30ug/ml	+	+	+	+	+	30	30

+ = Resistant to the compound or drug

CONCLUSION

In summary, N-(7-bromoquinoline-5,8-dione) sulphonamide derivatives have been synthesized by the reaction of 7-bromoquinoline-5,8-dione with aryl sulphonamides, characterized by spectral analysis, and evaluated for their in vitro antimicrobial activity. The compounds obtained showed excellent drug-likeness and varying degree of activity against the tested strains, but none of them was more active compared to the standard drugs used.

Conflict of interest: The authors declare that they do not have any conflict of interest.

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