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ORIGINAL ARTICLE

Synthesis and Antimicrobial Activity of 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-Quinolinoxide

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KEYWORDS

8-hydroxyquinoline;
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Precipitating agent

ABSTRACT: A new 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide was synthesized starting from diethyloxalate via a four-reaction step. The new compound obtained in a simple and efficient procedure in the solvent and solvent-free with good yield and methanol served as a precipitating agent to isolate compound **2**. The purity of 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide was tested by thin-layer chromatography (TLC) and characterized by Fourier transform infrared spectroscopy (FT-IR), proton nuclear magnetic resonance (NMR), Carbon-13 (C13) nuclear magnetic resonance (^{13}C-NMR), and DEPT 135 to confirm the presence and nature of CH_2. The solvent-free reaction of compound **1** was better in relation to green chemistry and better yield. The presence of solvent responsible for a color change that differentiates between compound **1** and **2** as they have the same physical data, functional group, and the chemical shift studied. The newly synthesized compound was evaluated and screened *in vitro* against Gram-positive *(methicillin-susceptible Staphylococcus aureus, methicillin-resistant Staphylococcus aureus*, and *Bacillus subtilis)*, Gram-negative (*Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae)* bacterial strains, and *Candida albicans* using the standard microbiological method. 5-Chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide exhibited weak activities when compared with the standard drug ciprofloxacin and itraconazole used for many bacterial and fungal infections respectively.

INTRODUCTION

Quinoline is one of the *N*-heterocycle with many binding properties that encourage different structural modification of functional group. 8-Hydroxyquinolines are useful in the preparation of antiseptics, deodorants, antiperspirants, and fungicides. They are important in metals separation because of there precipitating or chelating properties. Also, to formulate anti-dandruff agents for shampoo. Compounds with 8-hydroxyquinoline have therapeutics potential, for instance, antibacterial [1], antimicrobial [2-3], anti-cancer [4-6], anti-oxidant [1, 7], antitrypanosomal [8], anti-HIV [4, 9], anti-phytopathogenic [10]. Therefore they can be used for the design and synthesis of novel drugs.

Imidazole is an aromatic heterocycle five-membered ring, planar, almost pentagon in shape with two nitrogen atoms in one and three positions. Imidazole shows similar properties to pyrrole and pyridine. The position one

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nitrogen is a "pyrrole" type and the position three positions is a "pyridine" type nitrogen. The former contributes to two electrons to the π ring-system meanwhile the non-bonding electron pair of the pyridine *N*-atom is perpendicular to, and thus not involved in, the aromatic system. Imidazoles are unique heterocyclic compounds in agricultural, medicinal, and industrial chemistry. They are present in histidine, vitamin B_{12}, histamine, biotin among others.

Imidazole was first prepared in 1858 by Heinrich Debus, and different approaches are used for its synthesis. Wallach reaction is one of the methods of synthesizing 5-chlorimidazole. Wallach Synthesis is an exothermic reaction that involves heating of *N,N*-disubstituted oxamides with phosphorus pentachloride discovered by O. Wallach in the presence of $POCl_3$ as a solvent [11].

Antimicrobial activities refer to the process of inhibiting the growth of or kills the pathogens or microbes causing diseases. Antimicrobial agents, maybe anti-bacterial, antifungal or antiviral. Ciprofloxacin and itraconazole are antimicrobial agents used for many bacterial and fungal infections respectively. They are on the List of Essential Medicines as the most effective, significant, and safe medicines needed in a health system [12].

To search for new antimicrobial agents due to high chemotherapeutic and chelating properties of the 8-hydroxyquinoline. 8-Hydroxyquinoline was reacted with 5-chloro-1-ethyl-2-methylimidazole-4-sulfonylchloride for the synthesizing of 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide and screened for microbial activities to serve as a template for drug discovery.

MATERIALS AND METHODS

Ethylamine, ethyl oxalate, phosphorus pentachloride, chlorosulphonic acid, 8-hydroxyquinoline, calcium chloride, triethylamine, and chloroform were analytical grade.

Characterization

Melting points (MP) were measured uncorrected on Stuart SMP-10, serial no R000103248 apparatus. Fourier-transform infrared spectra (ATR, FT-IR) of the neat samples were measured using CARY 630 Agilent product. NMR spectra for ^{1}H, ^{13}C and the nature of C, CH, CH_2 were determined by DEPT 135 recorded in $CDCl_3$ on a Bruker Avance 500 spectrometer. Thin-layer chromatography was performed on 0.25 mm Kieselgel 60, Merck DC pre-coated aluminum plates, and viewed with UV_{254} lamp.

Synthesis of N, N^1–diethyloxamide

Diethyl oxalate (5 mL) (i) in a dropping funnel was added dropwise to 70% aqueous ethylamine (5.5 mL) cooled in an ice-water bath with constant stirring. The white crystals formed were filtered under vacuum, triturated in cold water, and air-dried to produce 4.34 g *N*, N^1-diethyloxamide (ii) (83%), MP 179-180°C (lit, 180-181 °C) (Figure 1) [13].

Synthesis of 5-chloro-1-ethyl-2-methylimidazole

N, N^1-diethyloxamide (4 g, 0.028 mol) (ii) and PCl_5 (12 g, 0.057 mol) were mixed thoroughly in a 50-mL flat bottom flask equipped with the wide-open reflux condenser and placed in hot water for 30 min for the reaction to commenced in a fume hood. The content was left overnight at ambient temperature. The solution was cooled in crushed ice bath and made alkaline with 50% Na_2CO_3 solution to give (3.05 g, 75.51%) with a single spot on thin-layer chromatography, used without further purification with R_f, 83.33% in $CHCl_3$.

Synthesis of 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl chloride

5-Chloro-1-ethyl-2-methylimidazole (4 g, 0.0277 mol) (iii) and freshly distilled chlorosulphonic acid (18 ml, 0.272 mol) were heated to reflux for 3 h. The solution was cooled, poured in crushed ice and filtered immediately under vacuum to get brownish solid product used without further purification (iv) (3.6 g, 53.52%) R_f, 88.56 in $CHCl_3$, MP 116-117 ^{o}C.

Synthesis of 5-chloro-1-ethyl-2-methylimidazole-4-

sulfonyl-8-quinolinoxide

A mixture of equimolar (0.005 mol) of 5-chloro-4-chlorosulfonyl-1-ethyl-2-methyl-imidazole (1.22 g) (iv) and 0.73 g of distilled 8-hydroxyquinoline were dissolved in 10 ml of triethylamine and stirred at 300 rpm, in-room temperature for 12 h, quenched with water to remove the base to form a precipitate yield 1.389 g, 78.80% when recrystallized from ethanol to produce brownish grain-like crystal with R_f 0.74 (3 MeOH:7 Pet) and MP 130-131 ^oC to have compound **1**. Compound **2** was prepared in 10 mL chloroform and 5 mL triethylamine followed the same reaction condition but solution blue-grey solution formed when quenched with water, and added small methanol that resulted in the precipitation, recrystallized in ethanol to produce blue-grey grain-like crystals, R_f 0.33 (7 EtOAc: 3 Hex) and MP 129-131 ^oC.

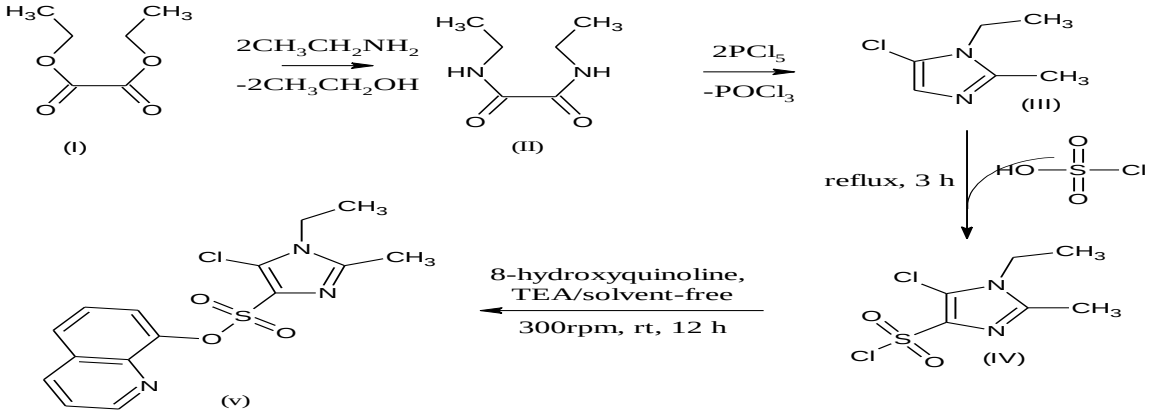


Figure 1. Synthesis of 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide.

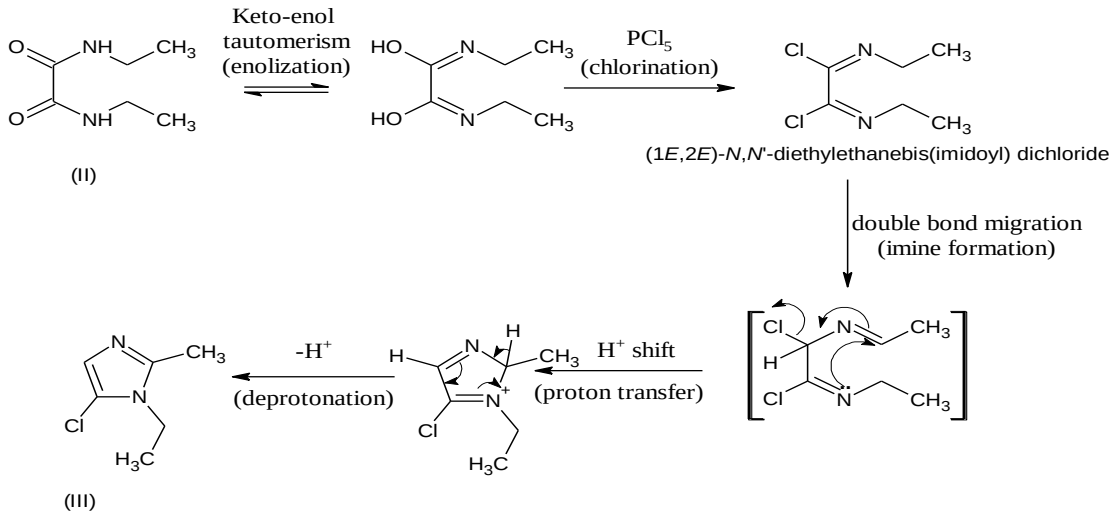


Figure 2. Proposed mechanism of 5-chloro-1-ethyl-2-methylimidazole.

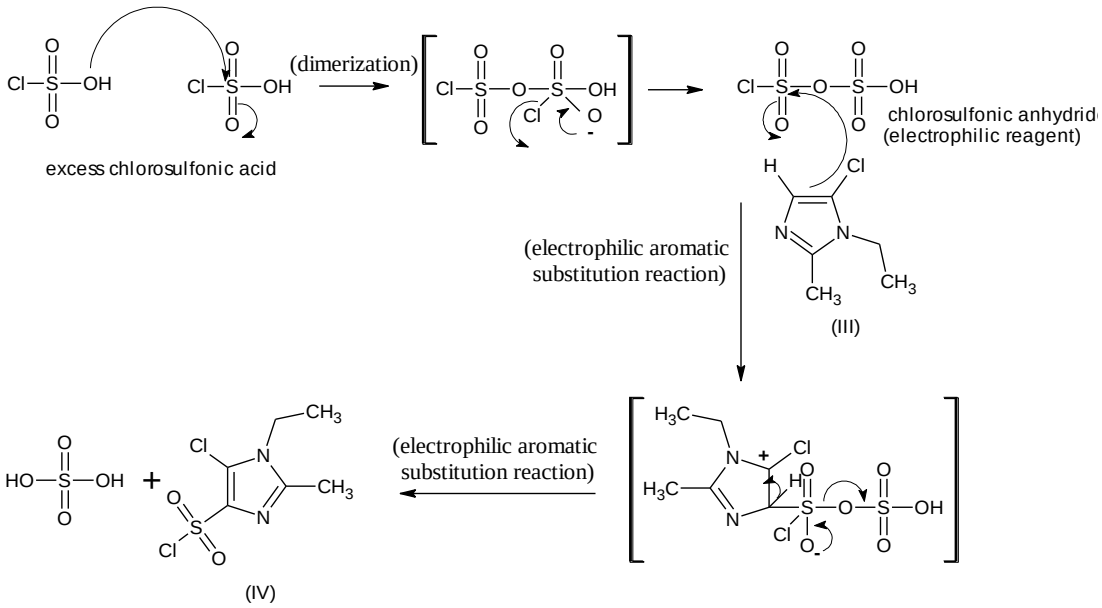


Figure 3. Proposed mechanism for the chlorosulfonylation of 5-chloro-1-ethyl-2-methylimidazole.

Antimicrobial activity

P. aeruginosa, E. coli, K. pneumoniae, B. subtilis, and *C. albicans* investigated in this study were procured from the University of Benin Teaching Hospital while methicillin-susceptible *S. aureus*, methicillin-resistant *S. aureus*, and *B. subtilis* NCTC 8236 obtained from Pharmaceutical Microbiology, University of Benin. All bacterial strains were cultured and subcultured from the stock into sterile nutrient agar, *C. albicans* on Sabouraud dextrose agar plate at 37 °C for 48 h and standardized to 10^6 CFU.mL^{-1} in 12 h sterile broth before use. Each media was prepared according to the manufacturer's specifications. 5-Chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide (60 mg.mL^{-1}) was dissolved in dichloromethane and distilled water 1:1 as diluent (solvent control). Ciprofloxacin and itraconazole (30 and 50 mg.mL^{-1} respectively) were used as the reference drug for antibacterial and antifungal activities respectively.

Preliminary screening

A rectangular cavity (rectangle: 4 × 30 mm^2) was bored on an agar plate and the base was sealed with sufficient warm nutrient agar. A 2 mm diameter wire loop was used to streak six different standardized inoculums along the cavity and emptied 0.5mL synthesized 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide into the cavity [14]. The plate was left standing for 1h at room temperature, incubated at 37^{o}C for 18 h and measured the zones of inhibition diameter. All experiments were carried out in triplicates.

Determination of zone of inhibition using agar-well method

Standardized inoculums of the test microorganisms were radially streaked with an individual cotton swab aseptically on their respective agar plates. A stainless steel sterile borer (8 mm) was used to bore six uniform sizes well, each was uniformly sealed, and filled with 100 µL of four different concentration ranges of the synthesized compound, one for standard, and sixth the control (diluent). The plate was left standing for 1 h at room temperature, incubated at 37 ^{o}C for 18 h, and measured the zones of inhibition diameter. All experiments were carried out in triplicates [15].

Determination of MIC using microdilution broth method

The minimum inhibitory concentration (MIC) values of 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-

quinolinoxide was determined using the microdilution broth method. Four different concentration range of 100 µL of synthesized 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide diluted in double strength sterile Mueller Hinton broth in test tubes, 20 µL of standardized organisms was added and incubated at 37 ^{o}C overnight. The test compound was the positive control and diluent as the negative control against the microorganisms for the experiment [14]. The MIC recorded as the lowest concentrations without any visible growth (turbidity) for each of the test organisms. All experiments were carried out in triplicates.

RESULTS AND DISCUSSION

A novel 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide was synthesized and screened for microbial activity. The preparation of 5-chloro-1-ethyl-2-methyl imidazole was from diethyloxalate and ethylamine using the Wallach reaction [11]. A chlorosulfonylation reaction of 5-chloro-1-ethyl-2-methyl imidazole was carried out by heating at reflux temperature. The chlorosulfonylated compound with 8-hydroxyquinoline was catalyzed in triethylamine in solvent and solvent-free at room temperature in good yields with one isolable product each from there respective TLC. The compound **2** was carried out in chloroform isolated with a small amount of methanol, which was able to precipitate the compound from chloroform and the aqueous two-phase system as a precipitating agent. The compound **1** was carried out in solvent-free reaction was better as being more greener and simpler without the use of hazardous and toxic solvents such as chloroform and methanol that poses health and safety problems. 5-Chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide was assigned structure based on substantiated spectral data (Figure 4-7) and (Table 1-3) gives the physical data, functional group, and the chemical shift summarized as FTIR (ATR, neat) cm^{-1}: 3060 (Ar, imidazole C—H), 2978, 2929 (CH_3), 2885 (CH_2), 2766, (CH_2–N), 1633, 1595 (C=N, m), 1498 (C=C), 1379, 1174 (S=O, SO_2), 1260 (C-N bend, str) these correlated with a published book [16] and in line with related reported work [17]. The presence of solvent responsible for a color change that differentiates between compound **1** and **2** as they have the same physical data, functional group, and the chemical shift studied.

FT-IR (ATR, neat υ max cm-^{1}): 3060 (Ar, imidazole C-H), 2978 (CH_3), 2929, (CH_2), 2766 (CH_2–N), 2356, 2158, 2091, 1961, 1733 (Ar, NH^+ overtones, w), 1633, 1595 (C=N), 1528, 1498 (C=C, str), 1405 (ring C-H), 1379 (S=O, SO_2 as, str), 1315, 1260 (C-N bend, str), 1174, (S=O, SO_2 sy, str), 1126 (C–O st.), 1077, 1047, 969, 890, 835 (S-O, str), 779, 708, 678 (C–Cl str).

^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 1.13 - 1.16 (t, 3H, *J* = 15 Hz, $CH_2CH_{3,\ imidazole}$), 2.31 (s, 3H, $CH_{3,\ imidazole}$), 3.83 - 3.84 (q, 2H, $CH_2CH_{3,\ imidazole}$), 7.33 - 7.36 (q, H, 7-H $_{quinoline}$), 7.45 - 7.48 (m, H, 5-H $_{quinoline}$) 7.63 - 7.71 (m, 2H, 3, 6-H $_{quinoline}$), 8.10 - 8.12 (d, H, *J* =10 Hz, 4-H $_{quinoline}$), 8.74 - 8.76 (d, H, *J* = 10 Hz, 2-H $_{quinoline}$).

^{13}C NMR ($CDCl_3$, δ ppm) 13.73 ($CH_{3,\ imidazole}$), 14.72 ($CH_2CH_{3,\ imidazole}$), 39.97 ($CH_2\mathit{CH_{3,\ imidazole}}$), 121.76 (7-C quinoline), 122.64 (5-C $_{quinoline}$), 123.03 (3-C $_{quinoline}$), 126.19 (C-Cl), 127.10 (6-C $_{quinoline}$), 128.97 (C-SO_2) 129.48 (bridge quinoline), 136.00 (4-C $_{quinoline}$), 141.40 (bridge quinoline), 144.81 (C $_{imidazole}$), 145.45 (2-C $_{quinoline}$), 150.45 (8-C $_{quinoline}$).

DEPT 135 confirmed the presence of methylene carbon 39.97 ppm of ^{13}C NMR in the compound (Figure 7).

The proposed mechanism of regiospecific reaction of 5-chloro-1-ethyl-2-methylimidazole from an exothermic reaction of *N, N^1*-diethyloxamide with PCl_5 in the presence of an *in situ* $POCl_3$ as a solvent [11]. *N, N^1*-diethyloxamide (II) enolized in the acidic environment of PCl_5 followed by chlorination. The chlorinated *(1E,2E)-N,N'*-diethylethanebis (imidoyl) dichloride underwent hydride shift from double bond migration that responsible for imine formation and stabilized by $POCl_3$. The imine formed was then cyclized to form a new N-C bond with loss of proton and subsequent electronic distribution to give 5-chloro-1-ethyl-2-methylimidazole (Figure 2).

In excess chlorosulfonic acid, chlorosulfonic acid underwent a dimerization reaction to produce chlorosulfonic anhydride, as an electrophilic reagent. The electrophilic reagent reacted with 5-chloro-1-ethyl-2-

methylimidazole through an electrophilic aromatic substitution reaction to produce 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl chloride. The pi bond between carbon 4 and 5 of the imidazole reacted with the electrophilic sulfur atom of chlorosulfonic anhydride, where the pi electrons of carbon 4 reacted with a sulfur atom, so the S=O pi bond broke to place a –I charge on O atom whereas the carbon 5 of the imidazole took on +I charge. The electrons on the negatively charged oxygen, then shift back to regenerate S=O pi bond and pushed out bisulfate. Thereafter, an H atom at carbon 4 of the imidazole released its electrons to regain the pi bond of the imidazole to restore the aromaticity with the release of sulfuric acid (Figure 3).

Table 1. Physical data of 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide

Compound	Molecular formula	Appearance	MP (°C)	Yield (%)	R_f
1	$C_{15}H_{14}ClN_3O_3S$	Brownish grain-like crystals	130-131	78.80	0.74(3 MeOH:7 Pet)
2	$C_{15}H_{14}ClN_3O_3S$	Blue-grey grain-like crystals	129-131	76.85	0.33(7 EtOAc: 3 Hex)

Table 2. FTIR of 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide

Compound	S=O	C=N	C-N	C=C	CH_2	CH_3	Ar C-H
1	1379, 1174	1633, 1590	1260	1528, 1498	2929	2978	3060
2	1378, 1170	1633	1263	1463	2854	2953	3060

Table 3: NMR of 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide

Compound	CH_3	CH_3	CH_2	CH_3	CH_2CH_3	CH_2	C-5	C-4	C-2
1	1.13-1.16, t	2.31, s	3.83-3.84, q	13.73	14.72	39.97	126.19	128.97	144.81

Multiplicity abbreviations: q-quartet, s-singlet, t-triplet.

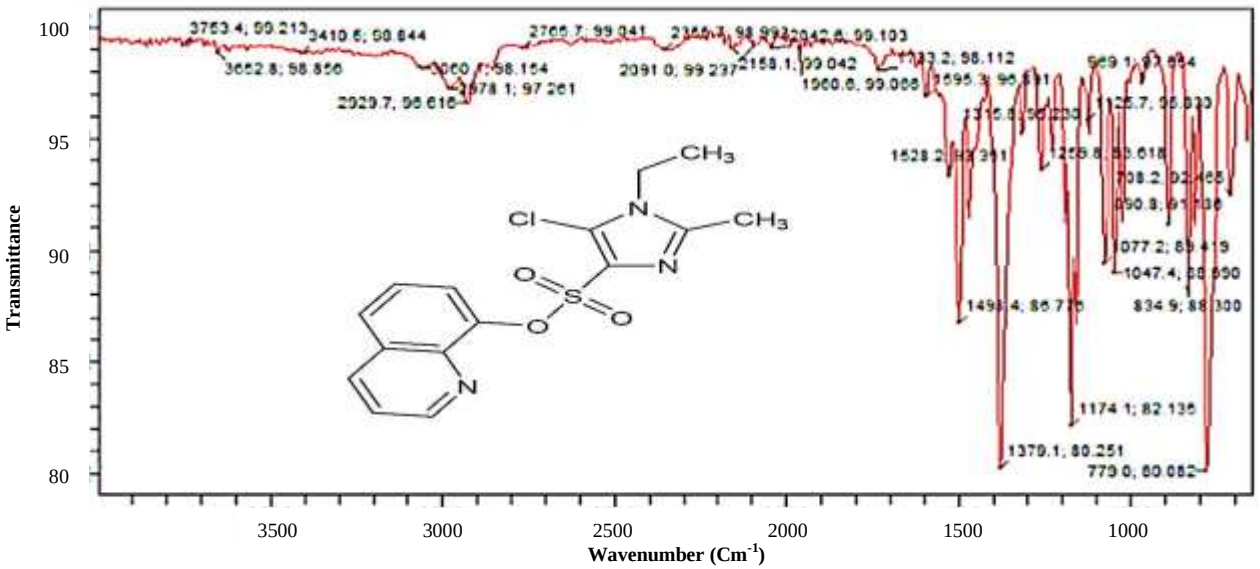


Figure 4. FTIR of 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide.

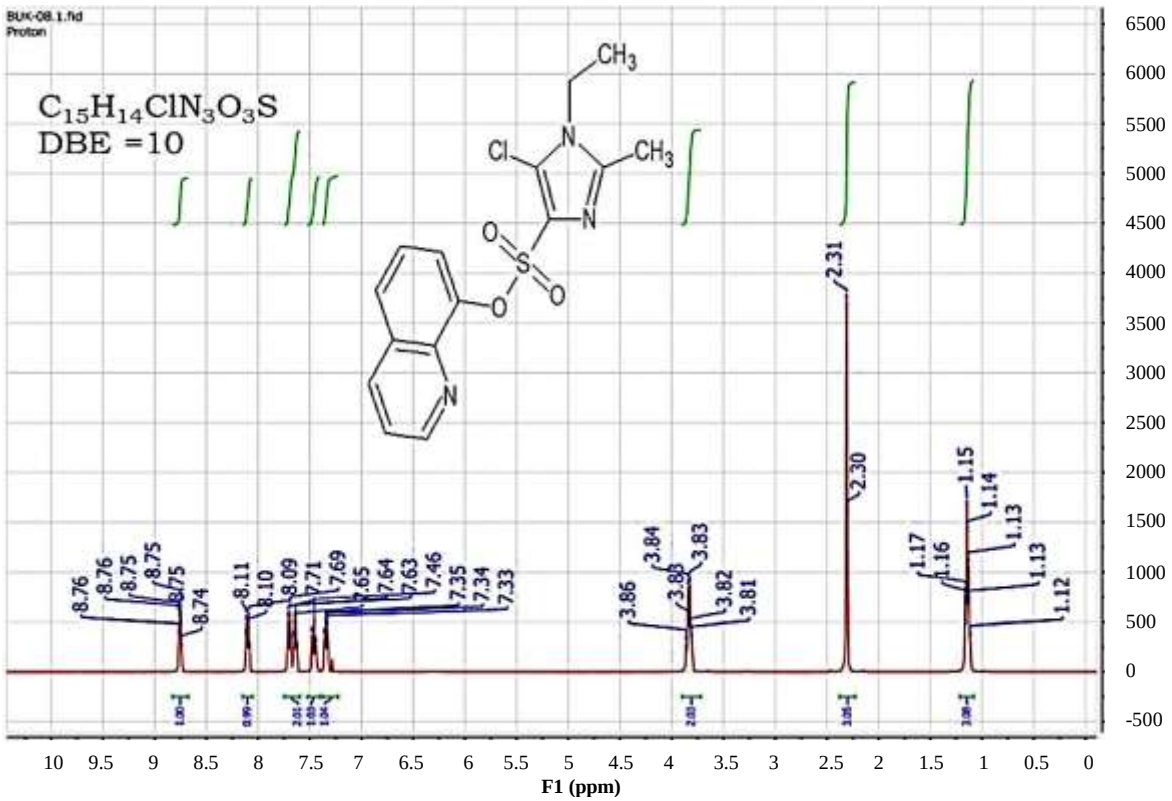
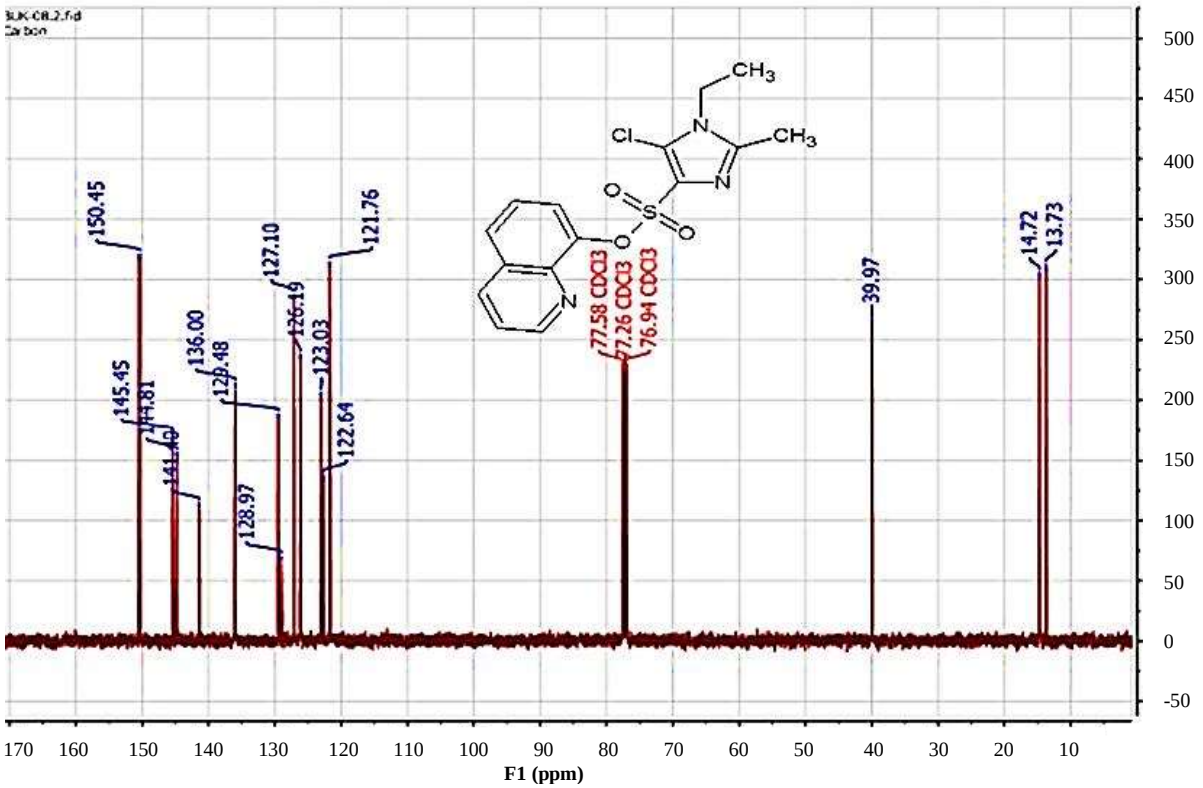


Figure 5. ^{1}H spectra of 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide in $CDCl_3$.



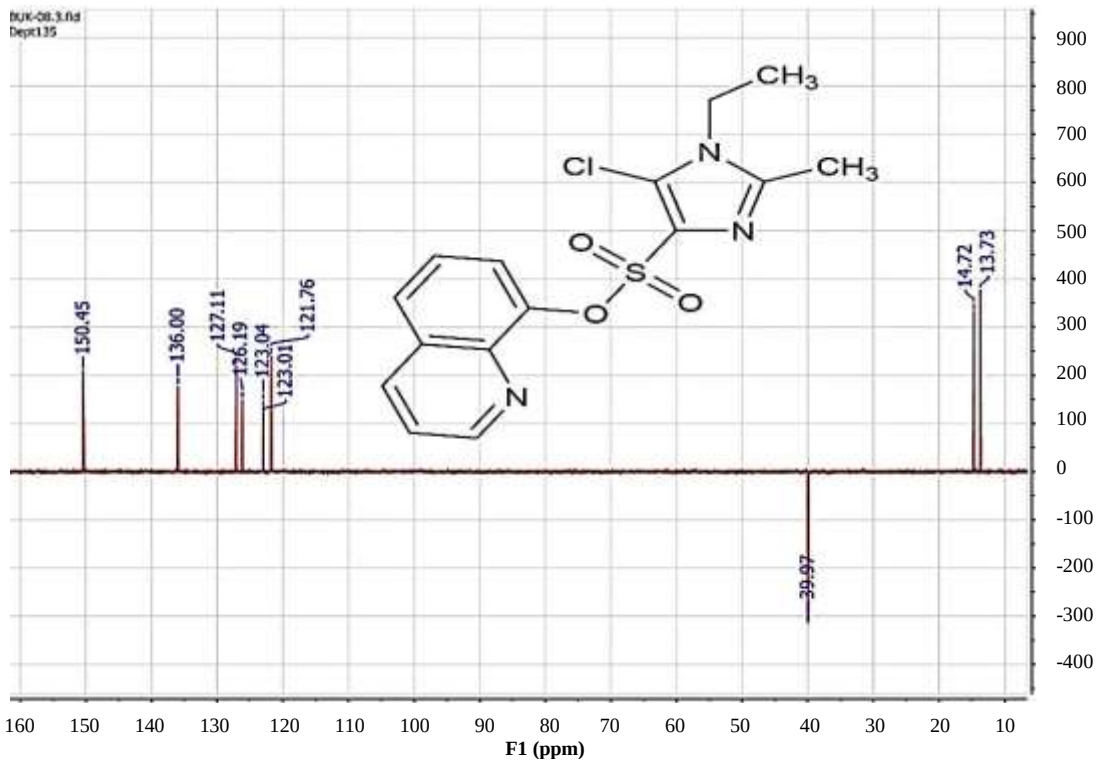


Figure 7. DEPT 135 spectra of 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide in $CDCl_3$.

The synthesized 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide was first screened against all tested microbial strains using a modified cup-plate method for further studies and compound **1** shown activities only against *B. subtilis (T), K. pneumonia, E. coli* (Table 4). Thereafter, the zone of inhibition and the MIC which is the lowest concentrations for each of the tested organisms with sign of turbidity were evaluated using the agar-well method and microbroth dilution method respectively. The result of zones of inhibition of 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide in comparison with reference drug ciprofloxacin and itraconazole are in (Table 5) (Figure 8). The MIC of compound **1** has a reasonable range of 8.00 and 25.00 $mg.mL^{-1}$ for *P. aeruginosa* and *E. coli* respectively. The result above shows that compound **1** with quinoline exhibits weak activities when compared with the reference drug ciprofloxacin and itraconazole.

Table 4. Preliminary screening of 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide for microbial activity (mm)

Compound	*P. aeruginosa*	*MSSA*	*E. coli*	*K. pneumoniae*	*B. subtilis (T)*	*B. subtilis*	*C. albicans*
1	N	N	8.50	18.00	N	12.50	N

N indicates no activity at concentration prepared

Table 5. Zone of inhibition of 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide for microbial activity (mm)

Compound	*P. aeruginosa*	*MSSA*	*E. coli*	*K. pneumoniae*	*B. subtilis (T)*	*B. subtilis*	*C. albicans*	*MRSA*
1	14.00	N	11.00	N	N	N	N	N
Ciprofloxacin	27.00	31.00	27.00	26.00	25.00	28.00		31.00
Itraconazole							21.50	

N indicates no activity at concentration prepared

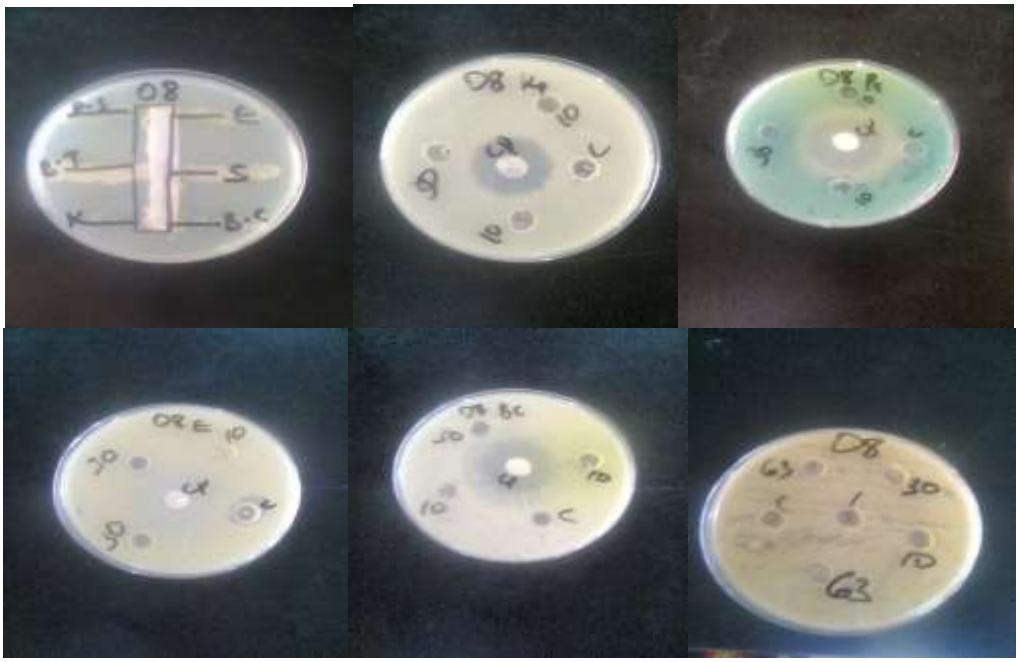


Figure 8. A preliminary screening and zones of inhibition of 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide for microbial activities.

CONCLUSIONS

In summary, we have prepared a four-reaction step of 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl-8-quinolinoxide from diethyloxalate. The new compound obtained in a simple and efficient way in solvent-free and solvent with good yield and methanol served as a precipitating agent to isolate compound **2**. The solvent-free reaction of compound **1** was better in relation to green chemistry and better yield. The presence of the solvent was responsible for the color change that differentiates between compound **1** and **2**, but they have the same physical data, functional group, and the chemical shift studied as confirmed by FT-IR, NMR, and DEPT 135 spectra analysis. The microbial evaluation of compound **1** against tested microbial strains compared with the reference drug ciprofloxacin and itraconazole exhibited weak activities.

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Conflict of interests

The authors declare no conflict of interest regarding this manuscript.

REFERENCES

1. El Faydy M., Djassinra T., Haida S., Rbaa M., Ounine K., Kribii A., Lakhrissi B., 2017. Synthesis and investigation of antibacterial and antioxidants properties of some new 5-substituted-8-hydroxyquinoline derivatives. *J. M. E. S.* 8(11), 3855-3863.

2. Srisung S., Suksrichavalit T., Prachayasittikul S., Ruchirawat S., Prachayasittikul V., 2013. Antimicrobial Activity of 8-Hydroxyquinoline and Transition Metal Complexes. International Journal of Pharmacology. 9, 170-175.

3. Cherdtrakulkiat R., Boonpangrak S., Sinthupoom N., Prachayasittikul S., Ruchirawatd S., Prachayasittikul V., 2016. Derivatives (halogen, nitro, and amino) of 8-hydroxyquinoline with highly potent antimicrobial and

antioxidant activities. Biochemistry and Biophysics Reports. 6, 135-141. https :// doi. Org /10. 1016/j.bbrep. 2016.03.014.

4. Shah P., Abadi L.F., Gaikwad S., Chaudhari D., Kushwah V., Jain S., Bhutani K.K., Kulkarni S., Singh Inder P., 2018. Synthesis and Biological Evaluation of 8-Hydroxyquinoline- hydrazones for Anti- HIV- 1 and Anticancer Potential. Chemistry select 3. 38, 10727-10731. https://doi.org/10.1002/slct.201802283.

5. Krawczyk M., Pastuch-Gawolek G., Mrozek-Wilczkiewicz A., Kuczak M., Skonieczna M., Musiol R., 2019. Synthesis of 8-hydroxyquinoline glycoconjugates and preliminary assay of their β1,4-GalT inhibitory and anti-cancer properties. Bioorg Chem. 84, 326-338. https://doi.org/10.1016/j.bioorg.2018.11.047.

6. Krawczyk M., Pastuch-Gawolek G., Pluta A., Erfurt K., Domiński A., Kurcok P., 2019. 8-Hydroxyquinoline Glycoconjugates: Modifications in the Linker Structure and Their Effect on the Cytotoxicity of the Obtained Compounds. Molecules. 24(22), 4181-4220. https://doi.org/10.3390/molecules24224181.

7. Gümüş A., Okumuş V., Gümüş S., 2018. Synthesis of 2-substituted 8-propargyloxyquinoline derivatives and determination of their antioxidant, antibacterial, and DNA binding activities. Turk J Chem.42, 1358 – 1369© TÜBİTAK doi:10.3906/kim-1805-77.

8. Scalese G., Machado I., Correia I., Pessoa J.C., Bilbao L., Pérez-Diaz L., Gambino D., 2019. Exploring oxidovanadium (iv) homoleptic complexes with 8-hydroxyquinoline derivatives as prospective antitrypanosomal agents. *New J Chem.* 43, 17756-17773. DOI: 10.1039/C9NJ02589H.

9. Velthuisen E.J., Johns B.A., Temelkoff D.P., Brown K.W., Danehower S.C., 2016. The design of 8-hydroxyquinoline tetracyclic lactams as HIV-1 integrase strand transfer inhibitors. *Eur J Med Chem.* 117, 99-112. doi: 10.1016/j.ejmech.2016.03.038.

10. Yin X.D., Sun Y., Lawoe R.K., Yang G.Z., Liu Y.Q., Shang X.F., Liu H., Yang Y.D., Zhu J.K., Huang X.L., 2019. Synthesis and anti-phytopathogenic activity of 8-hydroxyquinoline derivatives. R S C Adv. 9, 30087-30099.

11. Aleksandrova E.V., Kravchenko A.N., Kochergin P.M., 2011. Methods for the synthesis of Haloimidazoles (Review). Chemistry of Heterocyclic Compounds. 46(11), 1295-1317.

12. World Health Organization., 2017. WHO Model List of Essential Medicines (20th List). 13, 18, 49.

13. Trout G.E., 1966. Imidazoles and imidazole metabolism. Thesis submitted to the University of the Witwatersrand, Johannesburg, South Africa. pp. 60-64.

14. Ovonramwen O.B., Owolabi B.J., Oviawe A.P., 2019. Synthesis of (2*Z*)-4,6-Diphenyl-*N*-((2-(Piperidin-1yl)Ethyl]-2*H*-1,3-Thiazin-2-Imino Hydrochloride and its Antimicrobial Activities. Asian Journal of Physical and Chemical Sciences. 7(3), 1-9.

15. Babaiwa U.F., Erharuyi O., Falodun A., Akerele J.O., 2017. Antimicrobial activity of ethyl acetate extract of *Citrullus lanatus* seeds, Tropical Journal of Pharmaceutical Research. 16(7), 1631-1636.

16. Pretsch E., B¨uhlmann P., Badertscher M., 2009. *Structure Determination of Organic Compounds.* Springer-Verlag Berlin Heidelberg Fourth Ed. pp. 269-324. ISBN 978-3-540-93809-5.

17. Sigma-Aldrich (330248 Aldrich). (Accessed December 2019). 5-Chloro-1-ethyl-2-methylimidazole. Specification Sheet FTNMR (PDF).