7-Chloroquinoline Sulphonamide Derivatives: Synthesis, Characterization, Biological and Drug-likeness Evaluation

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Abstract: *New quinoline derivatives incorporating sulphonamide moieties have been synthesized from 4,7-dichloroquinoline and characterized using ^{1}HNMR, ^{13}CNMR and FTIR techniques. The compounds were screened for their in-vitro antibacterial activity against Gram-positive (Staphylococcus aureus,Bacillus subtilis) and Gram-negative (Escherichia coli, Klebsiella pneumoniae) bacteria species. The antibacterial activities were determined using standard methods. Among the tested compounds, it was found that compound **2** had the most potent antibacterial activity against all the tested strains except B. subtilis, but lower antibacterial activity than ciprofloxacin. The compounds indicated strong antifungal activity against Penicillium simplicissimum and Aspergillus niger with compound **6** revealing the highest activity with the inhibition zone diameter (IZD) of 28 mm. Compounds **2**, **3**, **4** and **6** showed more potent antifungal inhibitory activities against the two tested fungal species than fluconazole. The ADME (Adsorption, Distribution, Metabolism and Excretion) prediction indicated that the compounds possessed desirable drug-like properties for good bioavailability.*

Keywords: *synthesis, quinoline, sulphonamides, antibacterial, antifungal, in vitro, IZD, ADME.*

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1.0 Introduction

Despite the huge progress in the treatment of infectious diseases, microbial resistance to antimicrobial drugs remains a great threat to human lives (Anslam *et al*. 2018). As a result of drug resistance, several antimicrobial drugs have become ineffective, making infections difficult to treat, and increasing the risk of spread of diseases and long-term treatment

(Ventola, 2015). These emphasize the need for the discovery of novel antimicrobial agents, with subsistent ability to overcome antimicrobial resistant species. Quinoline and sulphonamide compounds have been reported to possess outstanding pharmacological activities (Al-Dosari *et al.*, 2013). Quinoline is a class of aromatic heterocyclic compounds with a double ring structure consisting of benzene and pyridine ring (Murugavel *et al*., 2018). Several quinoline derivatives, either isolated from natural resources or prepared synthetically possess a wide variety of biological activities such as anti-malarial (Christensen, 2021), antibacterial (Chung *et al*., 2015), antifungal (Casal and Asís, 2017), anti-inflammatory, antiviral (Matada *et al*., 2021) etc. Chloroquinoline is a quinoline derivative which has served as an essential building block in the synthesis of more complex new drug candidates with desired biological activities (Abdi *et al*., 2021). On the other hand, sulphonamides belong to an important class of drugs with several types of pharmacological activities including antimicrobial, antihypertensive, anticancer and anti-carbonic anhydrase (Onoabedje *et al*., 2021). Sulphonamide and its derivatives are organo-sulphur compounds containing $-SO_2NH_2$ or $-SO_2NH$ group or both. The most important role of sulphonamide is its use as an antibacterial agent due to the presence of SO_2NH- group (Rehman *et al*., 2018). Sulphonamides inhibit tetrahydrofolate which is required by the synthesis of bacterial DNA and RNA. This inhibition drops the production of new bacteria DNA and RNA due to lack of tetrahydrofolate which eventually kills bacteria (Qadir *et al*., 2015). Some highly active drugs have been synthesized by linking two or more molecules with individual intrinsic activity into a single hybrid molecule (Salahuddin *et al*., 2013, Eze *et al*., 2021, Onoabedje *et al*., 2020, Ibezim *et al*., 2023) The linking of quinoline nucleus with sulphonamide and piperazine moieties in a single molecule is a recent strategy of potentially producing better antimicrobial drugs. Few researchers have reported the antimicrobial activity of quinolone-piperazine-sulphonamide hybrid compounds, hence the purpose of this study.

2.0 Materials and Methods

All reagents and solvents are of analytical grades and were procured from Merck Group in the United States. All reactions were monitored by silica gel pre-coated thin-layer chromatography (TLC). FTIR spectroscopy of the compounds was run in IR M530 Buch Scientific Infrared Spectrophotometer using KBr pellets. The absorptions were given in wavenumbers (cm^{-3}). Melting points were recorded on electrothermal melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on 500 or 600 MHz Advance Brucker Spectrophotometer respectively at room temperature in $DMSOd_6$ using Tetramethylsilane (TMS) as internal standard. Non-commercial compound **2** was prepared according to literature (Salahuddin *et al*., 2018).

2.1 Synthesis of 7-chloro-4-(4-((4-nitrophenyl)sulfonyl)piperazin-1-yl)quinoline (3)

Following a general method (Salahuddin *et al*., 2018) with some modifications, to a stirred solution of 7-chloro-4-(piperazin-1-yl)quinoline (**2**) (0.25 g, 1 mmol) in dichloromethane (10 mL) at 0 ºC was added sodium bicarbonate (0.11 g, 1 mmol). The resulting suspension was stirred at the same temperature for 30 minutes, followed by the addition of p-nitrobenzenesulphonyl chloride (0.22 g, 1 mmol) in portions over a period of 30 minutes. After the addition, the reaction mixture was maintained at the same temperature for another hour, after which the ice bath was removed. Stirring continued at room temperature until completion (6 h) as indicated by thin layer chromatography. The reaction mixture was diluted with water/ dichloromethane and partitioned in a

separating funnel. The layers were separated, and the organic layer was extracted with dichloromethane (3x 30 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. Recrystallization of the crude in DCM: hexane gave the pure compound as a creamy paste (0.32 g, 74%). mp 156-158 ^{o}C; IR (cm^{-1}KBr): 3118, 1614, 1403, 1322, 759;^{1}H NMR (500 MHz, $DMSOd_6$) δ (ppm): 3.41 (s, 8H), 6.09 (d, *J*=7.4 Hz, 2H), 7.35 (dd, *J*=8.7, 2.0 Hz, 2H), 7.61 (d, *J*=2.0 Hz, 1H), 7.96 (d, *J*= 7.4 Hz, 2H), 8.09 (d, *J*=8.6 Hz, 2H);^{13}C NMR (126 MHz, $DMSOd_6$)δ (ppm): 109.5, 118.0, 122.6, 123.8, 124.3, 126.4, 127.4, 127.7, 128.6. 129.3, 137.0, 141.0, 141.2, 152.4, 176.3.

2.2 Synthesis of 4-((4-(7-chloroquinolin-4-yl)piperazin-1-yl)sulfonyl)aniline (4)

Following a general method (Gowda *et al*., 2021) for the reduction of nitro compounds with zinc, a solution of 7-chloro-4-(4-((4-nitrophenyl)sulfonyl)piperazin-1-yl)quinoline **3** (0.2 g, 0.46 mmol) in methanol (3 mL) was placed in a 500 mL round bottom flask equipped with a reflux condenser. Zinc powder (0.36 g, 5.5 mmol) was added to the solution. Concentrated hydrochloric acid (10 mL) was added with a slow stirring for activation of the zinc causing effervescence. An additional 40 mL of the acid was added in batches (10 mL) at intervals of 15 minutes. After the addition, the flask was placed in a preheated oil bath at 60 °C and the reaction mixture was heated for 1 h.The hot solution was filtered to remove zinc residue. The filtrate was slowly cooled to room temperature and the walls of the flask scratched with a glass rod to form crystals. The crystal was filtered and washed with acetone to give the titled compound as orange solid (93 mg, 50%). mp 245-247 ^{o}C; IR (cm^{-1}KBr): 3515, 3401, 3118, 1610, 1326, 792;^{1}H NMR (500 $DMSOd_6$) δ (ppm): 3.67 (s, 8H), 7.82-7.85 (m, 2H), 7.86-8.20 (m, 2H), 8.21 (d, *J*=2.6Hz, 1H) 8.22(s, 1H), 8.23-8.27 (m, 2H), 8.91 (d, *J*=4.7Hz, 1H);^{13}C NMR (126MHz, $DMSOd_6$) δ(ppm): 107.8, 118.8, 122.6, 123.8, 124.8, 126.6, 127.0, 127.4, 128.3, 129.4, 147.8, 149.0, 152.2, 154.6, 176.2.

2.3 Synthesis of N-(4-((4-(7-chloroquinolin-4-yl)piperazin-1-yl)sulfonyl)phenyl)acetamide (5)

A mixture of 4-((4-(7-chloroquinolin-4-yl)piperazin-1-yl)sulfonyl)aniline **4** (0.2 g, 0.5 mmol), glacial acetic acid (10 mL), acetic anhydride (0.11 mmol, 10 mL), zinc dust (16.3 mg, 0.25 mmol) was refluxed under anhydrous condition for 1 h. The hot mixture was poured into a beaker containing ice cold water and was stirred vigorously to precipitate the quinoline acetamide. The crude precipitate was recrystallized in hexane: ethanol to give the pure compound a creamy solid (0.15 g, 68%). mp 320-322 ^{o}C; IR (cm^{-1}KBr): 3493, 3130, 1618, 1438, 665. ^{1}H NMR (600 $DMSOd_6$) δ (ppm): 2.00 (s, 3H), 3.85 (s, 8H), 6.21 (d, *J*=7.2 Hz, 1H), 7.40 (d, *J*=8.9 Hz, 1H) 7.66 (s, 1H), 7.78-7.94 (m, 1H), 7.99 (d, *J*=7.7, 1H), 8.10-8.32(m, 2H), 8.40 (dd, *J*=33.3, 8.2 Hz, 1H), 8.57 (d, *J*=9.2 Hz, 1H), 9.29(s, 1H).

2.4 Synthesis of N-(4-((4-(7-chloroquinolin-4-yl)piperazin-1-yl)sulfonyl)phenyl)-1-(p-tolyl) methanimine (6)

A solution of 4-((4-(7-chloroquinolin-4-yl)piperazin-1-yl)sulfonyl)aniline **4** (0.1 g, 0.25 mmol) in ethanol (10 ml) at room temperature was treated with *p*-tolualdehyde (60µL, 0.5 mmol) and zinc dust (8.2 mg, 0.125 mmol). The mixture was stirred at room temperature until completion as indicated by TLC. The reaction mixture was filtered to remove zinc particles. The filtrate was poured into a beaker containing ice cold water to precipitate the quinoline methanimine. The precipitate was washed with hexane: DCM and air dried to a constant weight to give the titled compound as creamy solid (78 mg, 62%). mp 332-334 ^{o}C; IR (cm^{-1}KBr): 3126, 2943, 1623, 1394, 1000;^{1}H NMR (500 $DMSOd_6$) δ (ppm): 2.51 (s, 3H), 3.62 (s, 8H), 6.46 (d, *J*= 7.2Hz, 1H), 7.51 (d, *J*=8.8Hz, 1H), 7.65-7.88 (m, 5H), 8.19 (dd, *J*=13.6, 8.5Hz, 4H), 8.27-8.37 (m, 2H), 8.91 (s, 1H). ^{13}C NMR

(126MHz, $DMSOd_6$) δ (ppm) 108.6, 118.5, 123.0, 123.8, 125.6, 126.4, 127.0, 127.4, 128.5, 129.3, 129.8, 137.7, 140.9, 142.6, 147.7, 152.3, 154.7, 174.7 (3 carbons signals not observed due to low solubility).

2.5 Antimicrobial sensitivity test of the prepared compounds

The synthesized new quinoline compounds were screened for antimicrobial activity against gram positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*), gram negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*) and pathogenic fungi strain (*Penicillium simplicissimum*, *Aspergillus niger)* using the agar-well dilution technique. Each bacteria isolate was cultured in nutrient broth while the fungi strains were cultured in potato dextrose broth. The compounds were dissolved in dimethylsulphoxide (DMSO). 0.1mL culture of each bacterium and fungi strain was used to inoculate the agar plates using swab sticks. The inoculated plates were well labeled, and uniform wells were bored using plastic-cork borer of 6mm diameter. 20 mg/mL of each compound was delivered into different wells with Pasteur pipette. Ciprofloxacin was used as a standard drug for the bacteria while fluconazole was used as standard drug for the fungi. The plates were incubated for 24 hours at 37 ^oC for bacteria and 48 hours at 22-25 ^oC for fungi. Thereafter, the diameters of zones of growth inhibition were measured.

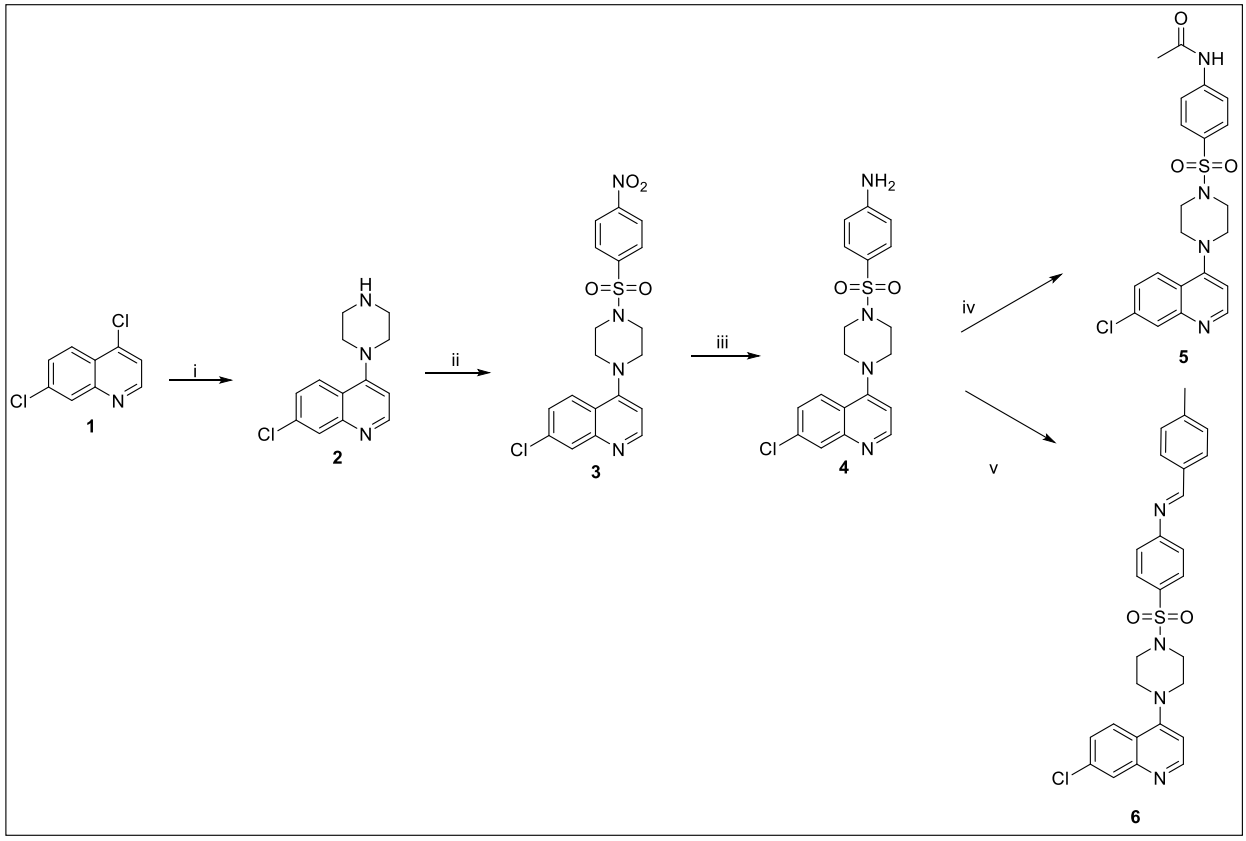
2.6 In silico drug-likeness prediction

The druglikeness assessment of the compounds was done using SwissADME online calculator (https://www.swissadme.ch). Evaluated descriptors include molecular weight, hydrogen bond donor, hydrogen bond acceptor, log *p*, tPSA, number of rotatable bonds.

3.0 Results and Discussion

3.1 Synthesis, characterization and spectral analysis

The nucleophilic aromatic substitution on the 7-chloroquinoline (**1**) with piperazine produced 7-chloro-4-(piperazin-1-yl)quinoline (**2**) in a good yield. The characteristic data is consistent with literature (Salahuddin et al., 2013). The second derivative (7-chloro-4-{4-[(4-nitrophenyl) -sulphonyl]piperizin-1yl}quinoline) (**3**) was formed via the reaction of compound **3** with p-nitrobenzenesulphonyl chloride. Zinc-mediated reduction of compound **3** produced the corresponding amine derivative **4** in a 50% yield. The treatment of compound **4** with acetic anhydride or *p*-tolualdehyde in catalytic amount of zinc dust produced the corresponding quinoline acetamide **5** or methanimine **6,** (**scheme 1**)**.** Purification of the compounds was done by recrystallization in appropriate solvent.The structures of the compounds were characterized by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. In the IR spectra, the bands observed around 1322-1394 cm^{-1} are assigned to the asymmetric SO_2 stretching, and this was evident in all compounds to confirm the presence of SO_2NH group. The N=O asymmetric stretch for compound **3** is observed at 1403 cm^{-1}. Other absorption bands are in good agreement with the proposed structure. The ^{1}H-NMR spectra indicated the presence of a strong singlet around 3.41-3.85 ppm which is assigned to the methylene protons of the piperazine moiety. The doublets and multiplets around 6.21-8.57 ppm reveal the presence of aromatic protons, while the peaks at 2.0 ppm and 2.51 ppm are attributed to the protons of the $–CH_3$ group in compounds **5** and **6** respectively. The ^{13}C-NMR spectrum indicated the expected number of signals.



Scheme 1: Synthetic route to new quinoline-sulphonamides
Condition: (i) piperazine, ethanol, reflux, 12 h (60%), (ii) *p*-nitrobenzenesulphonyl chloride, Na_2CO_3, CH_2Cl_2, 0 °C – rt, 1.5 h (74%), (iii) zinc dust, HCl, methanol, rt – 60 °C. 1 h (50%), (iv) acetic anhydride, glacial acetic acid, zinc dust, reflux, 1 h, (68%), (v) *p*-tolualdehyde, zinc dust, ethanol, rt, 3 h, (62%)

3.2 Antibacterial activity

The synthesized compounds were screened for antibacterial activity against *S. aureus*, *B. subtillis*, *E. coli*, and *K. pneumoniae* using agar-well dilution technique, and the result is presented in Table **1.** All the quinoline derivatives showed weak activity against *B.subtillis*. Compounds **2, 3,** and **4** had moderate activity against *S. aureus*, while compounds **5** and **6** had weak activity. Similarly, compounds **2** and **3** indicated moderate activity against *K. pneumoniae*. Compounds **5** and **6** showed weak inhibition against all the bacteria strains. It became apparent that ciprofloxacin exhibited better antibacterial activity than all the compounds.

Table 1. Zone of inhibition of the synthesized compounds

	Zone of inhibition (mm)					
Organisms	Compound **2**	Compound **3**	Compound **4**	Compound **5**	Compound **6**	Ciprofloxacin
S. aureus	15.00	10.00	15.00	7.00	8.00	22.00
B. subtilis	5.00	5.00	6.00	5.00	5.00	28.00
E. coli	15.00	10.00	5.00	8.00	8.00	24.00
K. pneumoniae	15.00	10.00	6.00	8.00	8.00	26.00

3.3 Antifungal activity

The antifungal activity of the compounds against *P. simplicissimum* and *A. Niger* is presented in Table **2**. Except for compound **5**, all the quinolines showed excellent activity against *P. simplicissimum* with compound **6** indicating the strongest activity with the IZD of 28 mm. Additionally, all the compounds revealed strong activity against *A. Niger* with the IZD in the range of 15-18 mm. In comparison with fluconazole standard, all the compounds exhibited better antifungal activity against the tested strains.

Table 2: Zone of inhibition of the synthesized compounds

	Zone of inhibition (mm)					
Organisms	Compound **2**	Compound **3**	Compound **4**	Compound **5**	Compound **6**	Fluconazole
P.simplicissimum	26.00	24.00	20.00	7.00	28.00	15.00
A.Niger	15.00	17.00	18.00	15.00	17.00	12.00

3.4 ADME assessment

Synthesized compounds were evaluated for ADME compliance with Lipinski's rule of five using Swiss ADME- a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. According to Lipinski rule of five, molecules with MW ≤ 500, HBD ≤ 5, HBA ≤ 10, Log P ≤ 5, RBC ≤ 10 are likely absorbed (Lipinski 2004). In this respect, the results in Table **3** indicate that the compounds showed total compliance with Lipinski rule. All the compounds had molecular weight (MW) <500, except for compound **6**. The cell membrane permeability indicated by the consensus log P ranged from 2.21-4.66 (values <5), which reveal distinct cell membranes tolerability. Further, hydrogen bond donor (HBD) and

hydrogen bond acceptor (HBA) for all the compounds complied with the rule of five. All the compounds showed high GI absorption potential. The topological surface area showed values< 140, which is ideal for good lipophilicity in regard with Veber's rule [19]. The Lipinski rule of 5 provides a framework for predicting the ADME characteristic of the synthesized molecules. Because only compound 6 violated the Lipinski rule by one the synthesized molecules will potentially

exhibit good adsorption or permeability, distribution, metabolic and excretion profile. Thus, the ADME results confirmed the desirable drug-like features of the compounds, Table **3**.

Table 3: Calculated ADME descriptors of the compounds

Compound	MW	HBD	HBA	Log P	RBC	Rule of five	tPSA [Å^2]	Bioavailability score	GI absorption
2	247.72	1	2	2.21	1	0	28.16	0.55	High
3	432.88	0	6	2.29	4	0	107.71	0.55	High
4	402.90	1	4	2.49	3	0	87.91	0.55	High
5	444.93	1	5	2.62	5	0	90.99	0.55	High
6	505.03	0	5	4.66	5	1	74.25	0.55	High
[a]	≤500	≤5	≤10	≤5	≤10	Max 2	≤140[b]		

MW: Molecular weight of the molecule, **HBD**: approximated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution, **HBA**: approximated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution, Rule of five: Number of violations of Lipinski rule, **Log P**: water partition coefficient, **RBC**: approximated number of rotatable bonds**, tPSA:** topological polar surface area.

[a] recommended value based on Lipinski rule

[b] recommended value based on Verber's rule

4.0 Conclusion

The synthesis, characterization and biological studies of new sulphonamide chloroquinolines are reported. The synthesized compounds exhibited weak to moderate antibacterial activity but had excellent antifungal activity against the tested strains. The ADME study indicated desirable drug-likeness of the compounds. The *in-vitro* and ADME results showed that these compounds have the potential to be developed as effective antifungal agents.

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