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Synthesis of *N*-arylquinolone derivatives bearing 2-thiophenoxyquinolines and their antimicrobial evaluation

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ABSTRACT

A new series of 2-thiophenoxyquinolines based trifluoromethyl substituted *N*-aryl quinolone derivatives **8a–f** and **9a–f** have been synthesized *via* a one-pot multicomponent reaction. *In vitro* antimicrobial activity of the synthesized compounds was investigated against a representative panel of pathogenic strains. Compounds **8c**, **9c** and **9e** exhibited comparable antimicrobial activity to first line drugs.

1. Introduction

Recently, multicomponent reactions (MCRs) have been shown to provide an efficient access to highly complex products in a single step. They have proven to be fast, convergent, atom-efficient reactions and often required effortless purifications through give generally high yields of products [1]. These reactions have emerged as a valuable tool in the synthesis of drug libraries because they have greater advantages over conventional strategies to synthesize biologically active compounds with significant structural diversity [2]. Consequently, designing novel MCRs to generate of diverse "drug-like" molecules has been the focus of many medicinal chemists.

Since the discovery of norfloxacin by Koga et al. in the early 1980s [3], fluoroquinolones have been used extensively in clinic because of their extremely potent activity, rapid bactericidal effects, and low incidence of resistance development [4]. These antibiotics exhibit properties like excellent bioavailability and a relatively low incidence of adverse and toxic effects [5]. Also a large number of fluoroquinolone derivatives have been designed and synthesized, and structure activity relationship (SAR) has been accumulated. Cyclopropyl (Ciprofloxacin) and mono/difluorophenyl (Difloxacin or Temafloxacin) groups are generally considered the most favorable substituents at the *N*-1 position of the 4-quinolones [6,7].

Over the past few years, we have been principally engrossed in the synthesis of quinolone-containing structures for biological evaluations [8–11] on the fact that the quinoline moiety is found in a large variety of naturally occurring compounds diverse bioactivities such as antibiotic [12], antimalarial [13], antituberculosis [14], antiHIV [15], anticancer [16], antihypertensive properties [17]. Additionally, some known fluoroquinolones antibiotics such as Ciprofloxacin, Delafloxacin, Sparfloxacin, Temafloxacin, Difloxacin and Norfloxacin are well known drugs. One of the best known drugs with a trifluoromethyl-quinoline nucleus, the antimalarial drug mefloquine is still being used today [18]. Also, a 5-quinolone derivative, 2-(benzylthio)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carbonitrile act as mGlur1 Modulator [19] (Fig. 1).

In this study, we introduce substituted 2-thiophenoxyquinolines at the C-4 position and lipophilic groups, trifluoromethyl substituted aromatic ring at the *N*-1 position on 5-quinolone to probe biological activity. The synthesis of *N*-aryl quinolone bearing 2-thiophenoxyquinolines derivatives was based on the assumption that the incorporation of more than one bioactive moiety into a single scaffold may produce novel heterocycles with good antimicrobial activity.

2. Experimental

All the reagents were obtained commercially and used without further purification. Solvents used were of analytical grade. All melting points were taken in open capillaries and were uncorrected.

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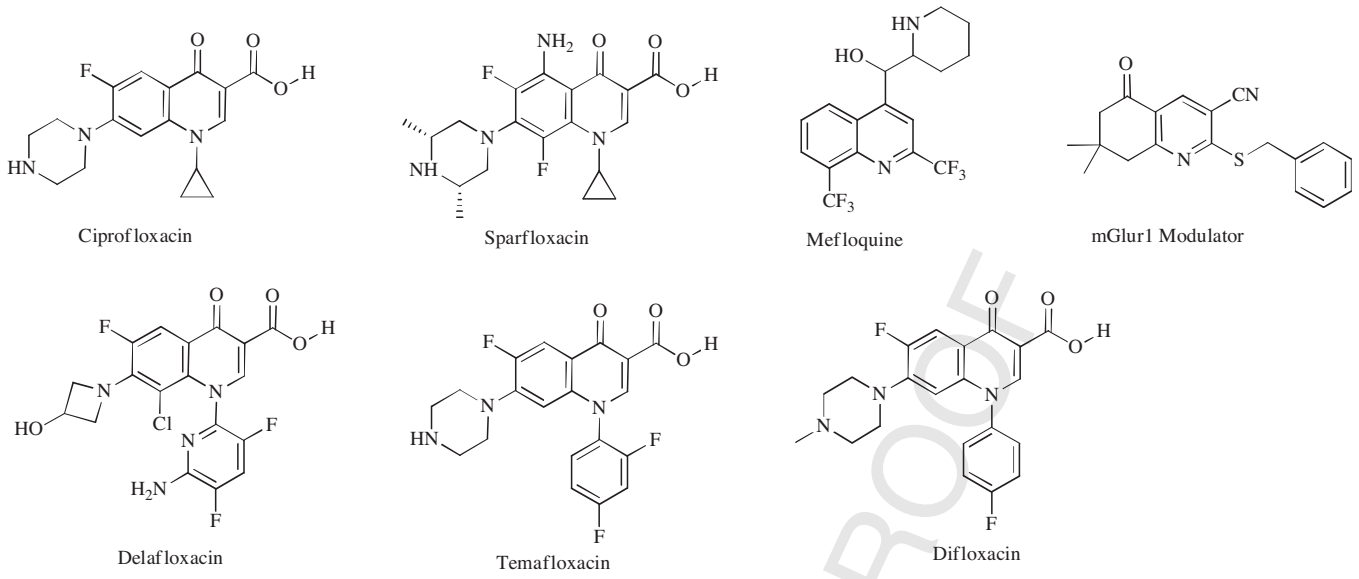
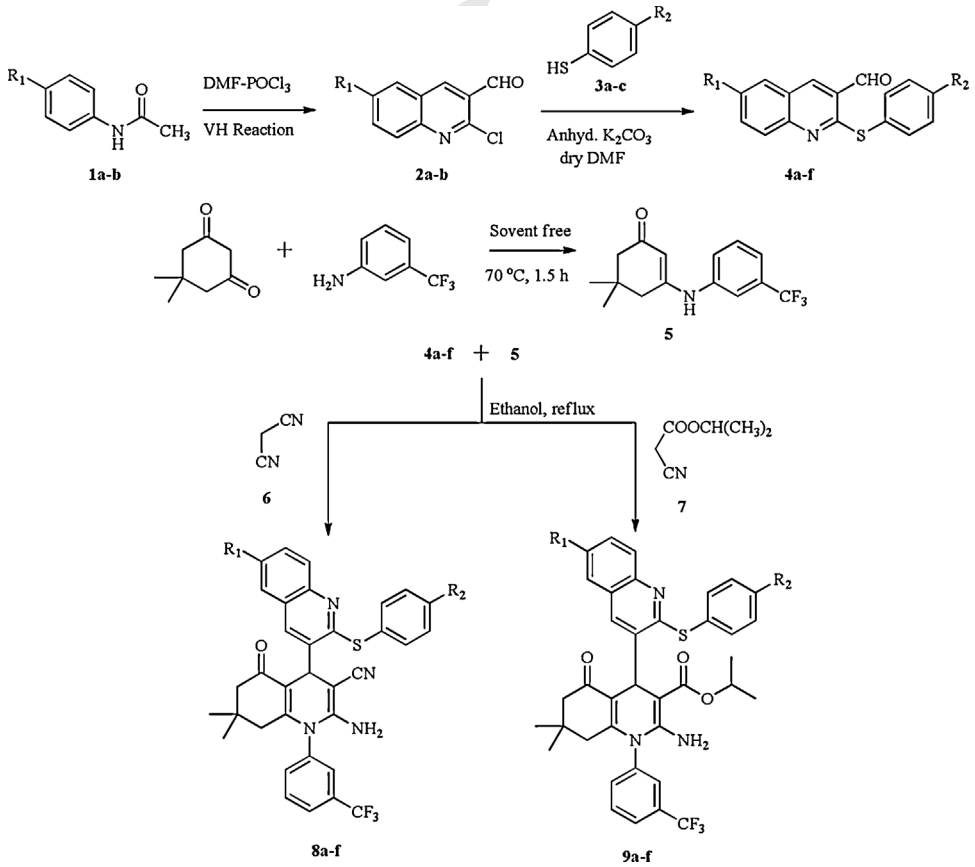


Fig. 1. Example of biologically active quinoline derivatives.

Thin-layer chromatography (TLC, on aluminum plates coated with silica gel 60 F254, 0.25 mm thickness) (Merck, Darmstadt, Germany) was used for monitoring the progress of all reactions, purity and homogeneity of the synthesized compounds. UV radiation and/or iodine were used as the visualizing agents. Elemental analysis (% C, H, N) was carried out using a Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA) and all compounds are within ±0.4% of theoretical values. The IR spectra were recorded in KBr on a Perkin-Elmer Spectrum GX FT-IR Spectrophotometer (Perkin-Elmer, USA) and only the characteristic peaks are reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker Avance 400F (MHz) spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using solvent peak as an internal standard at 400 MHz and 100 MHz respectively. Chemical shifts are reported in parts per million (ppm). Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer (Shimadzu, Tokyo, Japan).



Scheme 1. General synthetic route for the title compounds **8a–f** and **9a–f**.

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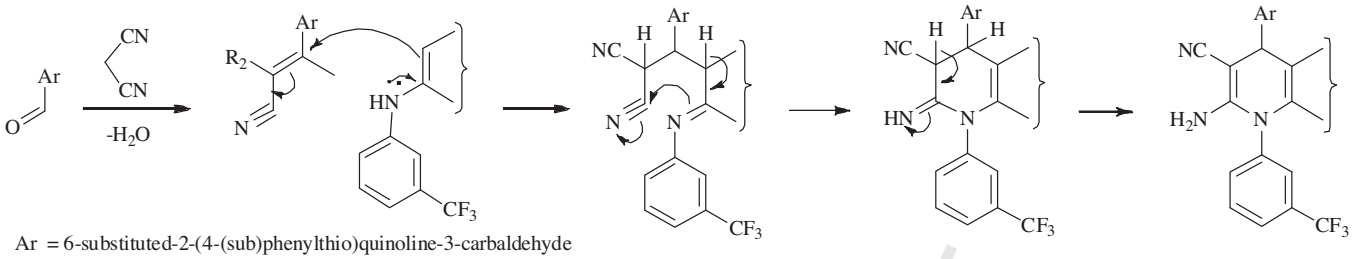

Ar = 6-substituted-2-(4-(sub)phenylthio)quinoline-3-carbaldehyde

Scheme 2. Plausible mechanistic pathway for the synthesis of **8a–f** and **9a–f** biquinoline.

The synthetic approach adopted to obtain 6-(un)substituted-2-((4-(un)substituted phenyl)thio)quinoline-3-carbaldehydes **4a–f** is shown in Scheme 1. The starting material 2-chloro-3-formyl quinolines **2a–b** were prepared by the Vilsmeier–Haack reaction [20] from acetanilides **1a–b** and were conveniently converted into **4a–f** by nucleophilic displacement of chloro group at C-2 in **1a–d** with 4-(un)substituted thiophenols **3a–c** in the presence of anhydrous K_2CO_3 in DMF at 120 °C for 2 h.

The required β-enaminones **5** were prepared by the reaction of 5,5-dimethylcyclohexane-1,3-dione with trifluorinated aromatic amines according to the literature procedures [10]. Subsequently, the one-pot three-component cyclocondensation of a series of **4a–f**, β-enaminones **5** and malononitrile **6** or isopropyl cyanoacetate **7** in ethanol containing a catalytic amount of piperidine afforded the targeted compounds **8a–f** and **9a–f** in good to excellent yields.

A plausible mechanism for the reaction is provided in Scheme 2. The heterylidenenitrile, containing an electron-poor C=C double bond is produced, from the Knoevenagel condensation between **4a–f** and malononitrile **6** or isopropyl cyanoacetate **7** followed by dehydration. Michael addition of β-enaminone **5** to the ylidenic bond forms an acyclic intermediate, which cyclizes by nucleophilic attack of the NH group on the cyano carbon. The subsequent tautomerisation gives the final products **8a–f** and **9a–f**.

The MICs of synthesized compounds 2′-amino-7′,7′-dimethyl-5′-oxo-2-((4-sub)phenylthio)-1′-(3-(trifluoromethyl)phenyl)-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carbonitrile **8a–f** and isopropyl 2′-amino-7′,7′-dimethyl-5′-oxo-2-((4-sub)phenylthio)-1′-(3-(trifluoromethyl)phenyl)-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carboxylate **9a–f** against three Gram-positive and three Gram-negative bacteria as well as two fungi were carried out by the broth microdilution method according to National Committee for Clinical Laboratory Standards (NCCLS) [21].

3. Results and discussion

The values of the MIC against microorganisms showed that these compounds have significant inhibitory effects. The antibacterial data indicate that the synthesized compounds are more effective against Gram-positive strains. It shows that lipophilic character of the molecules plays an important role in their antimicrobial effect. Among them compound **9c** was found to be more active than the comparator against Gram-positive bacterium *S. pneumoniae*. Compounds **8a**, **8c**, **8d** and **8d** showed promising activity against *B. subtilis*. Compounds **8b** and **9d** showed moderate activity against *S. pneumoniae*. Compounds **8a** exhibited good activity toward *C. tetani*. Compound **8c**, **9e** and **9f** were found to be equipotent against Gram-negative bacterium *S. typhi*. Except compounds **8b** and **9b** (R_1 = H and R_2 = CH_3), all the compounds displayed good to excellent inhibitory effects against *C. tetani*. Also, compounds **8c** and **9e** exhibited significant potency against Gram negative bacterium *E. coli* as benchmarked by ampicillin (MIC = 100 μg/mL).

In vitro antifungal activity of the synthesized quinolyl-quinolone derivatives are summarized in Table 1. Compound **9d** was endowed promising activity, while the compounds **8b** and **9f** showed moderate activity against *A. fumigatus*. Unfortunately, none of the synthesized compounds were found sufficiently potent in inhibiting fungal pathogen *C. albicans*.

Table 1
Antimicrobial activity results of compounds **8a–f** and **9a–f** against various microorganisms (MIC, μg/mL).

Compd.	R_1	R_2	Gram-positive bacteria			Gram-negative bacteria			Fungi	
			Bacillus subtilis	*Streptococcus pneumoniae*	*Clostridium tetani*	*Escherichia coli*	*Salmonella typhi*	*Vibrio cholerae*	*Candida albicans*	*Aspergillus fumigatus*
			MTCC 441	MTCC 1936	MTCC 449	MTCC 443	MTCC 98	MTCC 3906	MTCC 227	MTCC 3008
8a	H	H	100	250	100	100	250	500	500	1000
8b	H	CH_3	250	100	500	250	250	500	1000	500
8c	H	Cl	100	250	250	62.5	100	500	200	>1000
8d	CH_3	H	100	250	500	100	200	500	250	>1000
8e	CH_3	CH_3	500	250	200	100	250	200	>1000	>1000
8f	CH_3	Cl	250	200	250	100	200	250	250	500
9a	H	H	250	200	250	200	200	250	500	>1000
9b	H	CH_3	250	250	500	200	250	250	1000	1000
9c	H	Cl	200	62.5	200	500	500	200	500	1000
9d	CH_3	H	100	100	200	200	250	200	>1000	250
9e	CH_3	CH_3	250	250	250	62.5	100	250	500	1000
9f	CH_3	Cl	200	250	500	125	100	500	>1000	1000
Ampicillin			250	100	250	100	100	100	–	–
Norfloxacin			100	10	50	10	10	10	–	–
Griseofulvin			–	–	–	–	–	–	100	500

MTCC: microbial type culture collection; –: not tested.

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4. Conclusion

In conclusion, the aim of the present investigation was to design and synthesis of 5-quinolone derivatives by introducing substituted 2-thiophenoxyquinolines at the C-4 position and diversely trifluoromethyl substituted phenyl ring at *N*-1 position to probe antimicrobial activity. Modification of substituents on both 2-thiophenoxyquinolines ring and *N*-aryl quinolone ring with various electron donatig and electron withdrawing groups improved the activity. Compounds **8c**, **9c** and **9e** exhibited excellent antimicrobial activity. Finally, these compounds represent new scaffolds that could be further optimized to produce more potent and selective antimicrobial agents.

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