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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and in vitro antimicrobial evaluation of novel 2-amino-6-(phenylthio)-4-(2-(phenylthio)quinolin-3-yl)pyridine-3,5-dicarbonitriles

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Abstract A new series of 2-thiophenoxyquinoline-based penta-substituted pyridine derivatives, **6(a–r)**, has been synthesized by base-catalyzed cyclocondensation reaction through multi-component reaction (MCR) approach. In vitro antimicrobial activity of the synthesized compounds was investigated against a representative panel of pathogenic strains, specifically three Gram-positive bacteria (*Streptococcus pneumoniae, Bacillus subtilis*, *Clostridium tetani*), three Gram-negative bacteria (*Escherichia coli*, *Salmonella typhi*, *Vibrio cholerae*) and two fungi (*Aspergllus fumigatus*, *Candida albicans*). Majority of the compounds were found to be equipotent or more potent than that of the standard drugs.

Keywords Penta-substituted pyridine · Quinoline · One-pot reaction · Antimicrobial activity

Introduction

The pyridine ring system is considered to be one of the most imperative heterocycle in nature as it has the distinction of being the parent nucleus in countless derivatives of biologic relevance. Among them, 2-amino-3-cyanopyridine derivatives are well known for their antimicrobial activity (Makawana *et al*., 2011a; Mahmoud *et al*., 2007; Mungra *et al*., 2009), isoniazid derivatives bearing the pyridine nucleus possess anti-tubercular activity (Ashrafali *et al*., 2010; Lourenco *et al*., 2007) and 3-cyano-2-pyridone derivatives possess anti-inflammatory activity (Amr and Abdulla, 2006). Moreover, the polysubstituted pyridines represent molecular framework that serves as a platform for the development of new antimicrobial agents. Of the pharmacologically active pyridine derivatives, pyridine-3,5-dicarbonitriles have attracted much interest in recent years because of their significant synthetic as well as medicinal utility. Thus, the synthesis of highly functionalized pyridine derivatives has become an active area of research (Anabha *et al*., 2007; Fletcher *et al*., 2006; Movassaghi and Hill, 2006; Shinde *et al*., 2010).

On the premise that the quinoline moiety is found in a large variety of naturally occurring compounds and also chemically useful synthons bearing diverse bioactivities like antimicrobial (Kategaonkar *et al*., 2010), antituberculosis (Kumar *et al*., 2011), anti-inflammatory (Bava and Kumar 2009), antitumor (Li *et al*., 2006), analgesic (Kidwai and Negi, 1997), antimalarial (Dave *et al*., 2009, Charris *et al*., 2005 and Kaur *et al*., 2010), anticancer activity (Shi *et al*., 2008), and anti-HIV (Strekowski *et al*., 1991). Over the past few years, we have been principally engrossed in the synthesis of quinoline incorporating structures for antimicrobial evaluations (Jardosh and Patel, 2012; Mungra *et al*., 2011a, b; Shah *et al*., 2011; Makawana *et al*., 2011b, c; Thumar and Patel, 2009a, b; Kathrotiya *et al*., 2012).

It has been established that the presence of a thiophenoxy group at the 2nd position of the quinoline nucleus influences antimicrobial activity of quinoline derivatives and thus plays a vital role in the development of new antimicrobial drugs (Makawana *et al*., 2011d).

Various methods for the synthesis of penta-substituted pyridines from aromatic and heterocyclic aldehydes using different catalysts (Wang *et al*., 2009; Lakshmikantam *et al*., 2010; Evdokimov *et al*., 2006; Heravi *et al*., 2010; Mamgain *et al*., 2009; Sridhar *et al*., 2009; Singh and

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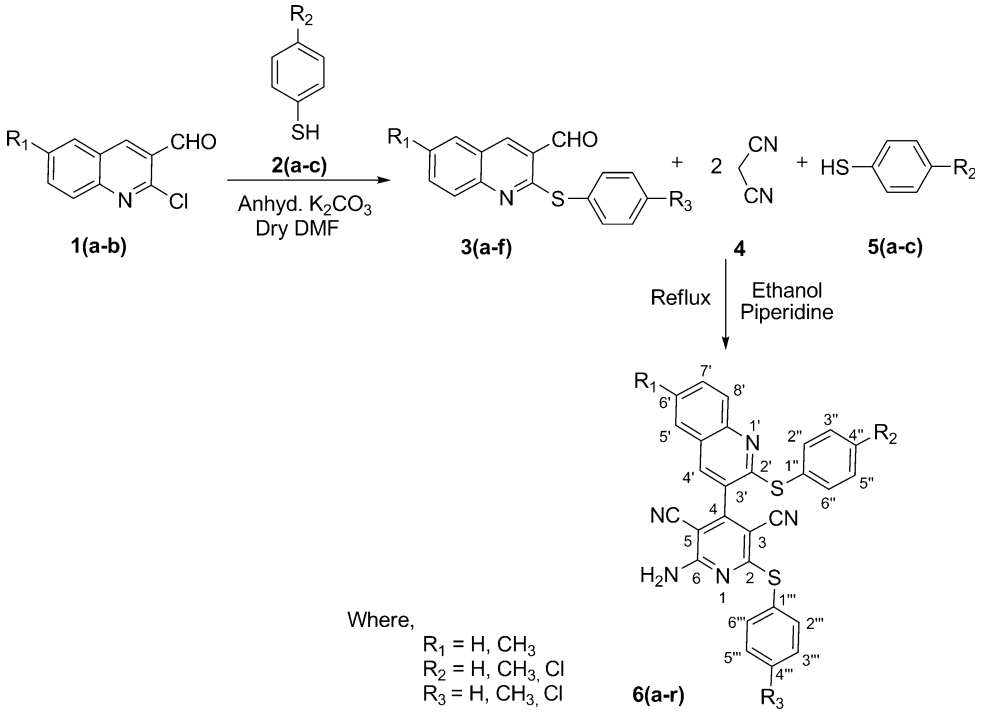
Singh, 2009; Banerjee and Sereda, 2009; Ranu *et al*., 2007) are reported in the literature but not a single report has been found where 2-thiophenoxy-3-formyl quinoline using piperidine as the catalyst. Also, the most suitable protocol for the synthesis of functionalized organic compounds would be a one-pot reaction because the synthesis can be performed without the isolation of intermediates and within a short time (Boulard *et al*., 2004). Thus, in a view to obtain biologically more potent heterocyclic system containing two therapeutically active moieties, quinoline and pyridine, the synthesis of some new penta-substituted pyridine derivatives bearing quinoline nucleus by means of the approach of multi-component reaction (MCR) is reported in this article.

Result and discussion

Chemistry

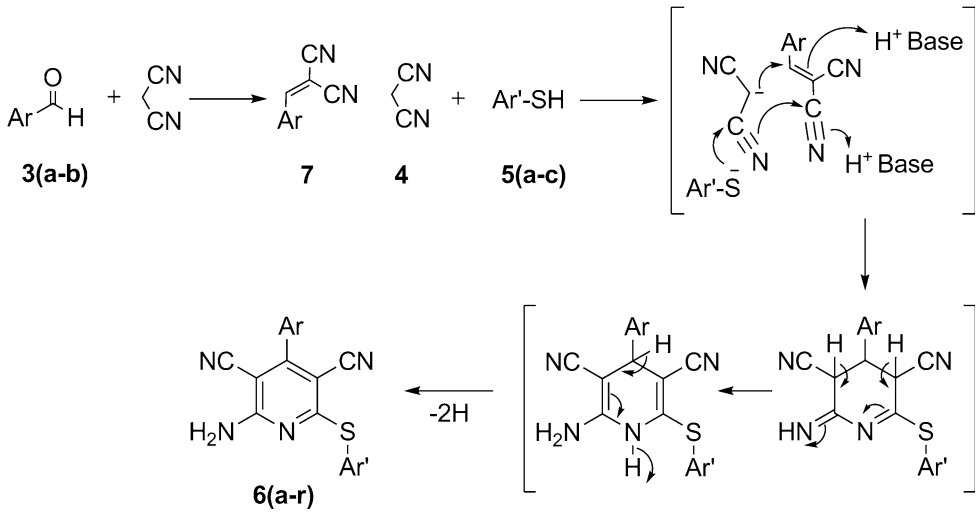
The reaction sequence employed for the syntheses of the title compounds **3(a–f)** and **6(a–r)** is depicted in Schemes 1, 2. The starting materials 2-chloro-3-formylquinolines **1(a–b)** were synthesized according to the Vilsmeier-Haack reaction (Meth-Cohn and Bramha, 1978) and converted to 2-thiophenoxyquinolin-3-carbaldehydes **3(a–f)** by nucleophilic displacement of a chloro group at C-2 of **1(a–b)** with substituted thiophenoxy groups in the presence of dimethylformamide and anhydrous potassium carbonate. Subsequently, the one-pot three component cyclocondensation of 2-thiphenoxyquinolin-3-carbaldehydes **3(a–f)**, malononitrile **4** and thiophenols **5(a–c)** in ethanol, containing a catalytic amount of piperidine at reflux temperature to afforded the target compounds **6(a–r)** in good to excellent yield (71–90 %). The formation of compounds **6(a–r)** may proceed via the initial formation of an intermediate **7** afforded by Knoevenagel condensation of an aldehyde with malononitrile, which would undergo intermolecular cyclization, driven through the nucleophilic attack of thiophenols in basic reaction medium.

The structures of all the synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR, and FTIR spectrometry. Elemental analysis and mass spectrometry were performed for few selected compounds. In the ^{1}H NMR (DMSO-d_6) spectrum of compound **6n**, aromatic protons, as well as –NH_2 protons, resonate as multiplets at $\delta = 7.256$–8.375 ppm and protons from three methyl groups resonate as multiplets at $\delta = 2.35$, 2.37 and 2.38 ppm. The ^{13}C NMR spectrum of compound **6n** exhibited signals at $\delta = 21.34$, 21.42, and 21.48 ppm for three methyl groups in the molecule. All the aromatic carbon atoms of compound **6n** showed signals $\delta = 115$–166 ppm in the ^{13}C NMR spectrum. The C-3 and C-5 carbon atoms of the pyridine ring, attached to the nitrile group, exhibited signals at $\delta = 88.59$ and 94.58 ppm, respectively. The IR spectrum of compound **6n** exhibited two characteristic absorption bands at 3470–3372 cm^{-1} for symmetric and asymmetric N–H stretching and one band at for 2210 –C≡N stretching. Absorption band at 759 cm^{-1} is mainly attributed to thioether linkage. The structures of the selected compounds, **6c**, **6l,** and **6n,** were confirmed by mass spectrometry. The mass spectra detected the expected



Scheme 1 Synthetic pathway for the synthesis of pyridine derivatives of 2-thiophenoxyquinoline **6(a–r)**

Scheme 2 Plausibe mechanistic pathway for the synthesis of pyridine derivatives **6(a–r)**



Ar = 2 -(un)-substited phenylthio-6-(un)-substituted quinolin-3-carbaldehyde
Ar' = 4-(un)-substituted thiophenol

molecular ion signals corresponding to respective molecular formula of synthesized compounds. Mass spectra of compound **6n** gave molecular ion peak at 529.7 (M + 1) corresponding to the molecular formula $C_{31}H_{23}N_5S_2$. The spectroscopic data for all the synthesized compound are given in the experimental section.

Antimicrobial activity

All the glasswares were sterilized before use. Antimicrobial activity of all the synthesized compounds was carried out by broth microdilution method [National Committee for Clinical Laboratory Standards (NCCLS) (2002)]. Mueller–Hinton broth was used as the nutrient medium for the test bacteria and Sabouraud dextrose broth was for the test fungi. Inoculum size for the test strains was adjusted to 10^8 CFU [Colony Forming Unit] per milliliter by comparing the Mac Fernald standard turbidity. The strains used for [MTCC—Microbial Type Culture Collection] antimicrobial activity were procured from the Institute of Microbial Technology, Chandigarh, India. Each synthesized compound was diluted with DMSO so as to have the stock solution of 2000 μg/mL concentration as a stock solution. The results were recorded in the form of primary and secondary screening. The compounds **3**(**a**–**f**) and **6**(**a**–**r**) were screened for their antibacterial activity against *Streptococcus pneumoniae* (MTCC 1936), *Clostridium tetani* (MTCC 449), *Bacillus subtilis* (MTCC 441), *Salmonella typhi* (MTCC 98), *Vibrio cholerae* (MTCC 3906), and *Escherichia coli* (MTCC 443) as well as for antifungal activity against *Aspergillus fumigatus* (MTCC 3008) and *Candida albicans* (MTCC 227) at concentrations of 1000, 500, and 250 μg/mL for primary screening. Dimethyl sulfoxide (DMSO) was used as the vehicle to get the desired concentrations of compounds. The compounds showing activity against microbes in the primary screening were further screened in a second set of dilution at concentrations of 200, 100, 62.5, 50, and 25 μg/mL. The suspension of 10 μL was further inoculated in a 96-well plate and growth was noted after 24 and 48 h. The lowest concentration, which showed no visible growth (turbidity) after spot subculture, was considered as the minimum inhibitory concentration (MIC) for each compound. In the present study, ampicillin and norfloxacin were used as standard antibacterial drugs, whereas griseofulvin was used as standard antifungal drug. The values of MIC are summarized in Table 1.

The examination of the data summarized in Table 1 reveals that many compounds were found to be active against Gram-positive bacteria, while some of the compounds were found to be active against Gram-negative bacterial and fungal species compared to that of standard antimicrobial drugs.

Review of the antimicrobial activities of 2-thiophenoxyquinolines and their pyridine derivatives (Table 1) indicated that compounds **3c** (R_1 = H, R_2 = Cl) and **3f** (R_1 = CH_3, R_2 = Cl) showed MIC = 200 μg mL^{-1} and 100 μg mL^{-1}, respectively against *E. coli*; but, upon cyclocondensation of these compounds with malononitrile and 4-chlorothiophenol the result compounds **6h** (R_1 = H, R_2 = Cl, R_3 = Cl) and **6p** (R_1 = CH_3, R_2 = Cl, R_3 = Cl) have been found to possess increased potency since MIC for both the compounds was 62.5 μg mL^{-1} against *E. coli*. Similarly, compounds **3d** (R_1 = CH_3, R_2 = H) and **3f** (R_1 = CH_3, R_2 = Cl) showed MIC = 200 μg mL^{-1} and MIC = 100 μg mL^{-1}, respectively, against gram negative bacteria *E. coli*, but their cyclocondensed derivatives, **6l** (R_1 = CH_3, R_2 = H, R_3 = Cl)

Table 1 In vitro antimicrobial activity of 2-thiophenoxyquinolines **3a–f** and their pyridine derivatives **6a–r**

Compound	Minimum inhibitory concentration (MIC, μg/ml)							
	Gram-positive bacteria			Gram-negative bacteria			Fungi	
	S.P. MTCC 1936	*C.T.* MTCC 449	*B.S.* MTCC 441	*S.T.* MTCC 98	*V.C.* MTCC 3906	*E.C.* MTCC 443	*A.F.* MTCC 3008	*C.A.* MTCC 227
3a(R_1 = H, R_2 = H)	200	250	200	250	200	200	1000	**250**
3b(R_1 = H, R_2 = CH_3)	250	**250**	**250**	250	250	200	200	1000
3c(R_1 = H, R_2 = Cl)	**100**	**200**	**250**	250	200	250	>1000	1000
3d(R_1 = CH_3, R_2 = H)	500	**250**	**500**	200	250	200	>1000	>1000
3e(R_1 = CH_3, R_2 = CH_3)	250	**250**	**250**	200	125	250	250	**500**
3f(R_1 = CH_3, R_2 = Cl)	500	**500**	**500**	125	**100**	**100**	1000	**200**
6a(R_1 = H, R_2 = H, R_3 = H)	500	500	500	200	200	250	500	**250**
6b(R_1 = H, R_2 = H, R_3 = CH_3)	250	**250**	**200**	125	250	**100**	250	1000
6c(R_1 = H, R_2 = H, R_3 = Cl)	500	**200**	**250**	250	250	250	1000	1000
6d(R_1 = H, R_2 = CH_3, R_3 = H)	250	**200**	**250**	125	200	200	>1000	**500**
6e(R_1 = H, R_2 = CH_3, R_3 = CH_3)	200	**250**	**250**	250	200	250	1000	1000
6f(R_1 = H, R_2 = CH_3, R_3 = Cl)	250	**100**	**200**	200	200	200	>1000	>1000
6g(R_1 = H, R_2 = Cl, R_3 = H)	200	**200**	**100**	200	**100**	**100**	1000	**200**
6h(R_1 = H, R_2 = Cl, R_3 = CH_3)	200	**250**	**100**	**100**	200	**62.5**	>1000	**250**
6i(R_1 = H, R_2 = Cl, R_3 = Cl)	**100**	500	**250**	200	200	200	1000	**500**
6j(R_1 = CH_3, R_2 = H, R_3 = H)	250	**250**	**250**	200	250	200	250	1000
6k(R_1 = CH_3, R_2 = H, R_3 = CH_3)	250	**200**	500	**100**	500	250	500	1000
6l(R_1 = CH_3, R_2 = H, R_3 = Cl)	500	**200**	500	**100**	200	**50**	250	>1000
6m(R_1 = CH_3, R_2 = CH_3, R_3 = H)	250	500	**250**	200	250	**100**	500	>1000
6n(R_1 = CH_3, R_2 = CH_3, R_3 = CH_3)	200	**250**	**100**	125	250	200	1000	**250**
6o(R_1 = CH_3, R_2 = CH_3, R_3 = Cl)	250	**100**	**250**	**100**	200	**100**	>1000	1000
6p(R_1 = CH_3, R_2 = Cl, R_3 = H)	250	**250**	**250**	200	**100**	**62.5**	>1000	1000
6q(R_1 = CH_3, R_2 = Cl, R_3 = CH_3)	**100**	**250**	**100**	200	250	200	250	>1000
6r(R_1 = CH_3, R_2 = Cl, R_3 = Cl)	500	500	500	**100**	200	**50**	500	**500**
Ampicillin	100	250	250	100	100	100	–	–
Norfloxacin	10	50	100	10	10	10	–	–
Ciprofloxacin	50	100	50	25	25	25	–	–
Griseofulvin	–	–	–	–	–	–	100	500
Nystatin	–	–	–	–	–	–	100	100

S.P., *Streptococcus pneumoniae*; C.T., *Clostridium tetani*; B.S., *Bacillus subtilis*; S.T., *Salmonella typhi*; V.C., *Vibrio cholerae*; E.C., *Escherichia coli*; A.F., *Aspergillus fumigatus*; C.A., *Candida albicans*

'–' represents 'not tested'

Bold numbers indicate more or equally potent compounds compared to standard drugs

and **6r** (R_1 = CH_3, R_2 = Cl, R_3 = Cl) displayed excellent activity (MIC = 50 μg mL^{-1}) against *E. coli*.

Compounds **6f** and **6o** (MIC = 100 μg mL^{-1}) showed excellent activity toward *C. tetani* compared to ampicillin (MIC = 250 μg mL^{-1}). Against Gram-positive bacteria *B. Subtilis*, compound **6g**, **6h**, **6n**, and **6q** (MIC = 100 μgmL^{-1}) showed activity higher than that of ampicillin (MIC = 250 μg mL^{-1}) and equivalent to norfloxacin (MIC = 100 μg mL^{-1}). Compounds **6c**, **6d**, **6g**, and **6k** (MIC = 200 μg mL^{-1}) displayed activity better than ampicillin toward *C. tetani*. Compound **6g** (MIC = 200 μg mL^{-1}) was found to be more effective against *C. albicans* than griseofulvin (MIC = 500 μg mL^{-1}).

Against *B. subtilis*, compounds **6c**, **6d**, **6e**, **6i**, **6j**, **6m**, **6o**, and **6p** (MIC = 250 μg mL^{-1}) were found to be equipotent with ampicillin (MIC = 250 μg mL^{-1}). In case of *S. typhi,* compounds **6h**, **6k**, **6l**, **6o**, and **6r** (MIC = 100 μg mL^{-1}) displayed inhibition similar to ampicillin (MIC = 100 μg mL^{-1}). Compounds **6i** and **6q** (MIC = 100 μg mL^{-1}) showed results equivalent to that of ampicillin (MIC = 100 μg mL^{-1}) toward *S. pneumonia.* Against *C.tetani*, compounds **6b**, **6e**, **6h**, **6j**, **6n**, **6p**, and **6q**

(MIC = 250 μg mL^{-1}) were found to be equipotent with ampicillin (MIC = 250 μg mL^{-1}).

Moreover, against *C. albicans*, compounds **6a**, **6h**, and **6n** (MIC = 250 μg mL^{-1}) revealed better inhibitory action as compared to the standard drug griseofulvin (MIC = 500 μg mL^{-1}), whereas compounds **6d**, **6i**, and **6r** (MIC = 500 μg mL^{-1}) showed activity comparable to griseofulvin (MIC = 500 μg mL^{-1}). Majority of the compounds were active toward *E. coli, B. subtilis*, and *C. tetani*. Unfortunately, none of the synthesized compounds were found sufficiently potent to inhibit fungal pathogen *A. fumigatus.*

The compounds **6**(**a**–**r**) exerted significant inhibitory activities against the growth of tested bacterial and fungal strains (Table 1). The data also revealed that derivatization at positions $\mathbf{R_1}$, $\mathbf{R_2}$, and $\mathbf{R_3}$ of the parent molecule produced marked improvement in the potency of the synthesized analogs as antimicrobial agents and demonstrated the following assumptions regarding the structural activity relationship (SAR).

Compound **6h** (R_1 = H, R_2 = Cl, R_3 = Cl) revealed outstanding inhibitory action against most of the tested bacteria and fungi but replacement of H by CH_3 at R_1 decreased the potency of the resulting compound **6q** (R_1 = CH_3, R_2 = Cl, R_3 = Cl) against *E. coli and S. typhi*. Moreover, Compounds having electron-withdrawing Cl group at position $\mathbf{R_2}$ improves the antimicrobial activity of the compounds **6h**, **6i**, **6q,** and **6r** against *S. typhi* and *E. coli*. Furthermore, the replacement of –H with –CH_3 at the 6-position of the quinoline nucleus makes a marked difference in the antimicrobial effectiveness of the tested compounds. Compound **6h** (R_1 = H, R_2 = Cl, R_3 = CH_3) revealed outstanding inhibitory action against *E. coli* (MIC = 62.5 μg mL^{-1}), *S. typhi* (MIC = 100 μg mL^{-1}), and *C. albicans* (MIC = 250 μg mL^{-1}); but, upon replacing (R_1 = H) by (R_1 = CH_3) increase the potency of the resulting compound **6q** (R_1 = CH_3, R_2 = Cl, R_3 = CH_3) against *E. coli* (MIC = 62.5 μg mL^{-1}), *S. typhi* (MIC = 100 μg mL^{-1}) and *C. albicans* (MIC = 250 μg mL^{-1}) was observed.

Experimental

All the reagents were obtained commercially and after further purification. Solvents used were of analytical grade. All the melting points were taken in open capillaries and are uncorrected. Thin-layer chromatography (TLC, on aluminum plates precoated with silica gel 60 F_{254}, 0.25-mm thickness, Merck Darmstadt, Germany) was used for monitoring the progress of all reactions. Hexane:Ethyl-acetate (1:1) was used as an eluent and UV radiation and/or iodine were used as the visualizing agents. Elemental analysis (% C, H, N) was carried out using Perkin-Elmer 2400 series-II elemental analyzer and all compounds are within the range of ±0.4 %. The IR spectra were recorded by KBr pellet method on a Perkin-Elmer Spectrum GX FT-IR spectrophotometer. The characteristic peaks are reported in cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker Avance NMR spectrometer using TMS 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).

General procedure for the synthesis of compounds 6(a–r)

A mixture of 2-thiophenoxy-quinoline **3**(**a**–**f**) (5 mmol), malononitrile **4** (10 mmol), thiophenol **5**(**a**–**c**) (5 mmol), and piperidine (5 mol%) in ethanol (10 ml) was charged in a 100-ml round bottom flask equipped using a condenser. The reaction mixture was stirred at reflux temperature for 3.5 h. After completion of a reaction, monitored by TLC, the separated solid was filtered, washed with methanol, and recrystallized from chloroform to obtain the pure solid compounds **6**(**a**–**r**). The physicochemical and spectroscopic characterization data of the synthesized compounds **6**(**a**–**r**) are given below.

*2-Amino-6-(phenylthio)-4-(2′-(phenylthio)quinolin-3′-yl)pyridine-3,5-dicarbonitrile (**6a**)*

Yield 76 %, m.p. 229 °C, Anal. Calcd. for $C_{28}H_{17}N_5S_2$ (487.09 gm/mol): C 68.97, H 3.51, N 14.36 % Found: C 68.74, H 3.29, N 14.16 %. IR (KBr, cm^{-1}): 3400 and 3370 (N–H str), 2215 (C≡N str), 756 (C–S–C thioether str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.41–8.93 (m, 17H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 88.70 (C–C≡N), 94.73 (C–C≡N), 128.23, 128.91, 129.60, 129.88, 129.94, 130.08, 130.42, 132.32, 134.51, 135.51, 138.08, 114.93, 115.25, 125.74, 127.12, 127.71, 127.75, 148.01(Ar–C), 155.51, 155.69, 159.82, 166.68 (Ar–C–S).

*2-Amino-4-(2′-(phenylthio)quinolin-3′-yl)-6-(p-tolylthio)pyridine-3,5-dicarbonitrile (**6b**)*

Yield 71 %, m.p.211 °C, Anal. Calcd. for $C_{29}H_{19}N_5S_2$ (501.11 gm/mol) C 69.44, H 3.82, N 13.96 % Found: C 6924, H 3.70, N 13.71 %. IR (KBr, cm^{-1}): 3412 and 3315 (N–H str), 2203 (C≡N str), 761 (C–S–C thioether str). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.31 (s, 3H, CH_3), 7.41–8.93 (m, 16H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.36 (CH_3), 88.61 (C–C≡N), 94.49 (C–C≡N), 128.70, 129.40., 129.69, 129.84, 130.19, 130.32, 130.52, 134.68, 135.61, 138.50, 115.07, 115.15, 125.20,

125.89, 127.57, 127.61, 128.43, 148.10 (Ar–C), 155.31, 155.51, 159.91, 167.03 (Ar–C–S).

*2-Amino-6-(4″-chlorophenylthio)-4-(2′-(phenylthio)quinolin-3′-yl)pyridine-3,5-dicarbonitrile (**6c**)*

Yield 86 %, m.p. 219 °C, Anal. Calcd. for $C_{28}H_{16}ClN_5S_2$ (521.05 gm/mol) C 64.42, H 3.09, N 13.42 % Found: C 64.25, H 2.7, N 13.29 %. IR (KBr, cm^{-1}): 3480 and 3320 (N–H str), 2212 (C≡N str), 772 (C–S–C thioether str). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 7.41–8.93 (m, 16H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 88.73 (C–C≡N), 94.51 (C–C≡N), 128.71, 129.71, 129.81, 130.01, 130.38, 130.82, 132.42, 134.61, 135.81, 138.02, 114.87, 115.17, 125.47, 127.21, 127.69, 127.57, 128.31, 148.30(Ar–C), 155.31, 155.61, 159.92, 165.90 (Ar–C–S). MS (*m*/*z*): 522 (M^+), 523 (M + 2).

*2-Amino-6-(phenylthio)-4-(2′-(p-tolylthio)quinolin-3′-yl)pyridine-3,5-dicarbonitrile (**6d**)*

Yield 82 %, m.p. 232 °C, Anal. Calcd. for $C_{29}H_{19}N_5S_2$ (501.11 gm/mol) C 69.44, H 3.82, N 13.96 % Found: C 69.35, H 3.67, N 13.69 %. IR (KBr, cm^{-1}): 3460 and 3340 (N–H str), 2210 (C≡N str), 749 (C–S–C thioether str). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.34 (s, 3H, CH_3), 7.41–8.93 (m, 16H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.41 (CH_3), 88.69 (C–C≡N), 94.69 (C–C≡N), 128.90, 129.69, 130.01, 130.20, 130.69, 130.97, 132.41, 134.91, 135.61, 138.07, 115.08, 115.25, 125.69, 127.32, 127.79, 127.89, 128.32, 148.50 (Ar–C), 155.71, 155.73, 159.92, 166.94 (Ar–C–S).

*2-Amino-6-(p-tolylthio)-4-(2′-(p-tolylthio)quinolin-3′-yl)pyridine-3,5-dicarbonitrile (**6e**)*

Yield 80 %, m.p. 232 °C, Anal. Calcd. for $C_{30}H_{21}N_5S_2$ (515.12gm/mol) C 69.88, H 4.10, N 13.58 % Found: C 69.53, H 3.80, N 13.29 %. IR (KBr, cm^{-1}): 3400 and 3370 (N–H str), 2209 (C≡N str), 730 (C–S-C thioether str). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.30 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 7.41–8.93 (m, 15H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.32 (CH_3), 21.39 (CH_3), 88.68 (C–C≡N), 94.59 (C–C≡N), 129.50, 129.50, 129.50, 130.29, 130.42, 132.63, 134.89, 135.71, 138.52, 115.19, 115.19, 125.98, 127.30, 127.69, 127.76, 128.39, 128.79, 148.20 (Ar–C), 155.21, 155.61, 159.10, 166.61 (Ar–C–S).

*2-Amino-6-(4″-chlorophenylthio)-4-(2′-(p-tolylthio)quinolin-3′-yl)pyridine-3,5-dicarbonitrile (**6f**)*

Yield 77 %, m.p.218 °C, Anal. Calcd. for $C_{29}H_{18}ClN_5S_2$ (535.07gm/mol) C 64.97, H 3.38, N 13.06 % Found: C 64.61, H 3.10, N 12.77 %. IR (KBr, cm^{-1}): 3425 and 3365 (N–H str), 2217 (C≡N str), 739 (C–S–C thioether str). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.35 (s, 3H, CH_3), 7.41–8.93 (m, 15H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.35 (CH_3), 88.51 (C–C≡N), 94.68 (C–C≡N), 129.61, 129.81, 129.97, 130.09, 130.24, 132.49, 134.61, 135.61, 138.10, 114.91, 115.24, 125.77, 127.17, 127.81, 127.91, 128.29, 128.49, 148.19 (Ar–C), 155.49, 155.71, 159.72, 166.19 (Ar–C–S).

*2-Amino-4-(2′-(4″-chlorophenylthio)quinolin-3′-yl)-6-(phenylthio)pyridine-3,5-dicarbonitrile (**6g**)*

Yield 74 %, m.p. 227 °C, Anal. Calcd. for $C_{28}H_{16}ClN_5S_2$ (521.05 gm/mol) C 64.42, H 3.09, N 13.42 % Found: C 64.33, H 2.88, N 13.07 %. IR (KBr, cm^{-1}): 3438 and 3350 (N–H str), 2207 (C≡N str), 745 (C–S–C thioether str). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 7.41–8.93 (m, 16H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 88.74 (C–C≡N), 94.75 (C–C≡N), 128.99, 129.61, 129.87, 129.89, 130.09, 130.59, 132.69, 134.51, 135.91, 138.09, 114.97, 115.29, 125.79, 127.17, 127.59, 127.79, 128.31, 148.11 (Ar–C), 155.52, 155.01, 159.01, 166.03 (Ar–C–S).

*2-Amino-4-(2′-(4″-chlorophenylthio)quinolin-3′-yl)-6-(p-tolylthio)pyridine-3,5-dicarbonitrile (**6h**)*

Yield 90 %, m.p. 237 °C, Anal. Calcd. for $C_{29}H_{18}ClN_5S_2$ (535.07 gm/mol): C 64.97, H 3.38, N 13.06 % Found: C 64.73, H 3.21, N 12.97 %. IR (KBr, cm^{-1}): IR, ν/cm^{-1}: 3450 and 3310 (N–H str), 2213 (C≡N str), 759 (C–S–C thioether str). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.34 (s, 3H, CH_3), 7.41–8.93 (m, 15H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.45 (CH_3), 88.8 (C–C≡N), 94.51 (C–C≡N), 128.06, 130.72, 133.39, 134.28, 134.71, 135.64, 137.29, 139.39, 140.31, 115.07, 115.39, 123.67, 125.7, 126.78, 126.86, 127.53, 128.89, 146.71 (Ar–C), 154.91, 155.61, 159.71, 166.59 (Ar–C–S).

*2-Amino-6-(4″-chlorophenylthio)-4-(2′-(4‴-chlorophenylthio)quinolin-3′-yl)pyridine-3,5-dicarbonitrile (**6i**)*

Yield 79 %, m.p. 231 °C, Anal. Calcd. for $C_{28}H_{15}N_5S_2Cl$ (555.01 gm/mol): C 60.43, H 2.72, N 12.58 % Found: C 60.23, H 2.41, N 12.35 %. IR (KBr, cm^{-1}): 3468 and 3323 (N–H str), 2201 (C≡N str), 765 (C–S–C thioether str). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 7.41–8.93 (m, 15H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 88.53 (C–C≡N), 94.70 (C–C≡N), 128.01, 130.74, 132.78, 133.40, 134.48, 134.81, 135.61, 137.30, 139.41, 140.21114.91, 115.29, 123.69, 125.79, 126.89, 127.51, 127.90, 146.73 (Ar–C), 154.92, 155.63, 159.70, 166.69 (Ar–C–S).

*2-Amino-4-(6′-methyl-2′-(phenylthio)quinolin-3′-yl)-6-(phenylythio)pyridine-3,5-dicarbonitrile (**6j**)*

Yield 73 %, m.p. 209 °C, Anal. Calcd. for $C_{29}H_{19}N_5S_2$ (501.11 gm/mol): C 69.44, H 3.82, N 13.96 % Found: C 69.23, H 3.69, N 13.66 %. IR (KBr, cm^{-1}): 3415 and 3340 (N–H str), 2209 (C≡N str), 747 (C–S–C thioether str). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.38 (s, 3H, CH_3), 7.41–8.93 (m, 16H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.46 (CH_3), 88.48 (C–C≡N), 94.69 (C–C≡N), 128.08, 130.72, 130.79, 133.31, 134.21, 134.62, 135.45, 137.29, 139.34, 140.31, 115.04, 115.39, 129.69, 125.70, 126.89, 127.86, 127.60, 127.81, 146.81 (Ar–C), 154.89, 155.61, 159.85, 166.91(Ar–C–S).

*2-Amino-4-(6-methyl-2′-(phenylthio)quinolin-3′-yl)-6-(p-tolythio)pyridine-3,5-dicarbonitrile (**6k**)*

Yield 77 %, m.p. 215 °C, Anal. Calcd. for $C_{30}H_{21}N_5S_2$ (515.12 gm/mol): C 69.88, H 4.10, N 13.58 % Found: C 69.57, H 3.90, N 13.29 %. IR (KBr, cm^{-1}): 3455 and 3380 (N–H str), 2214 (C≡N str), 751 (C–S–C thioether str).^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.36 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 7.41–8.93 (m, 15H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.41 (CH_3), 21.49 (CH_3), 88.49 (C–C≡N), 94.52 (C–C≡N), 130.53, 130.61, 133.29, 134.16, 134.46, 135.49, 137.16, 139.34, 140.31 115.06, 115.31, 123.70, 125.89, 126.69, 127.54, 127.89, 129.09, 146.81(Ar–C), 154.91, 155.69, 155.89, 166.82 (Ar–C–S).

*2-Amino-6-(4″-chlorophenylthio)-4-(6′-methyl-2′-(phenylthio)quinolin-3′-yl)pyridine-3,5-dicarbonitrile (**6l**)*

Yield 82 %, m.p. 225 °C, Anal. Calcd. for $C_{29}H_{18}ClN_5S_2$ (535.07 gm/mol): C 64.97, H 3.38, N 13.06 % Found: C 64.57, H 3.21, N 12.89 %. IR (KBr, cm^{-1}): 3430 and 3380 (N–H str), 2217 (C≡N str), 741 (C–S–C thioether str). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.34 (s, 3H, CH_3), 7.41–8.93 (m, 15H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.49 (CH_3), 88.61 (C–C≡N), 94.63 (C–C≡N), 130.53, 130.70, 133.29, 134.29, 134.71, 135.61, 137.29, 139.51, 140.31, 115.07, 115.37, 123.69, 125.84, 126.81, 127.54, 127.84, 128.09, 146.71(Ar–C), 154.91, 155.71, 159.93, 166.99(Ar–C–S). MS (*m/z*): 535.8 (M^+), 536.8(M + 2).

*2-Amino-4-(6′-methyl-2′-(p-tolylthio)quinolin-3′-yl)-6-(phenylthio)pyridine-3,5-dicarbonitrile (**6m**)*

Yield 83 %, m.p. 217 °C, Anal. Calcd. for $C_{30}H_{21}N_5S_2$ (515.12 gm/mol): C 69.88, H 4.10, N 13.58 % Found: C 69.60, H 3.85, N 13.25 %. IR (KBr, cm^{-1}): 3430 and 3380 (N–H str), 2243 (C≡N str), 741 (C–S–C thioether str). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.39 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 7.42–8.93 (m, 15H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.39 (CH_3), 21.43 (CH_3), 88.64 (C–C≡N), 94.59 (C–C≡N), 129.61, 129.88, 129.93, 130.09, 130.41, 132.41, 134.59, 135.47, 138.07, 114.99, 115.49, 125.39, 127.31, 127.79, 128.07, 128.41, 128.99, 148.09(Ar–C), 155.71, 155.71, 159.91, 166.81(Ar–C–S).

*2-Amino-4-(6′-methyl-2′-(p-tolylthio)quinolin-3′-yl)-6-(p-tolylthio)pyridine-3,5-dicarbonitrile (**6n**)*

Yield 87 %, m.p. 235 °C, Anal. Calcd. for $C_{31}H_{23}N_5S_2$ (529.14 gm/mol): C 70.29, H 4.38, N 13.22 % Found: C 70.01, H 4.19, N 13.07 %. IR (KBr, cm^{-1}): 3470 and 3372 (N–H str), 2210 (C≡N str), 759 (C–S–C thioether str). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.37 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 7.41–8.93 (m, 14H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.34 (CH_3), 21.42 (CH_3), 21.48 (CH_3), 88.59 (C–C≡N), 94.58 (C–C≡N), 128.05, 130.52, 130.72, 133.28, 134.18, 134.61, 135.46, 137.26, 115.02, 115.29, 123.66, 125.74, 126.68, 127.50, 127.80, 139.25, 140.21, 146.70(Ar–C), 154.96, 155.67, 159.90, 166.98(Ar–C–S). MS (*m/z*): 529.7 (M^+).

*2-Amino-6-(4″-chlorophenylthio)-4-(6′-methyl-2′-(p-tolylthio)quinolin-3′-yl)pyridine-3,5-dicarbonitrile (**6o**)*

Yield 75 %, m.p. 230 °C, Anal. Calcd. for $C_{30}H_{20}ClN_5S_2$ (549.08 gm/mol): C 65.50, H 3.66, N 12.73 % Found: C 65.21, H 3.42, N 12.57 %. IR (KBr, cm^{-1}): 3465 and 3370 (N–H str), 2206 (C≡N str), 768 (C–S–C thioether str). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.35 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 7.41–8.93 (m, 14H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.33 (CH_3), 21.41 (CH_3), 88.62 (C–C≡N), 94.69 (C–C≡N), 130.77, 133.29, 134.28, 134.67, 135.47, 132916, 139.14, 140.27, 115.07, 115.32, 123.63, 125.77, 126.68, 127.51, 127.80, 129.07, 130.57, 146.77(Ar–C), 154.90, 155.77, 155.98, 167.03(Ar–C–S).

*2-Amino-4-(2′-(4″-chlorophenylthio)-6′-methylquinolin-3′-yl)-6-(phenylthio)pyridine-3,5-dicarbonitrile (**6p**)*

Yield 73 %, m.p.223 °C, Anal. Calcd. for $C_{29}H_{18}ClN_5S_2$ (535.07 gm/mol): C 64.97, H 3.38, N 13.06 % Found: C 64.73, H 3.17, N 12.81 %. IR (KBr, cm^{-1}): 3455 and 3350 (N–H str), 2211 (C≡N str), 721 (C–S–C thioether str). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.41 (s, 3H, CH_3), 7.41–8.93 (m, 15H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.47 (CH_3), 88.53 (C–C≡N), 94.64 (C–C≡N), 130.73, 133.29, 134.19, 134.71, 135.47, 137.29,

139.25, 140.29, 115.30, 115.21, 123.61, 125.70, 126.71, 127.59, 127.89, 129.19, 130.62, 146.74(Ar–C), 154.98, 155.97, 155.96, 166.91(Ar–C–S).

*2-Amino-4-(2′-(4″-chlorophenylthio)-6′-methylquinolin-3′-yl)-6-(p-tolylthio)pyridine-3,5-dicarbonitrile (**6q**)*

Yield 75 %, m.p. 230 °C, Anal. Calcd. for $C_{30}H_{20}ClN_5S_2$ (549.08 gm/mol): C 65.50, H 3.66, N 12.73 % Found: C 65.29, H 3.38, N 12.50 %. IR (KBr, cm^{-1}): 3485 and 3315 (N–H str), 2214 (C≡N str), 744 (C–S–C thioether str). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.43 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 7.41–8.93 (m, 14H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.37 (CH_3), 21.43 (CH_3), 88.69 (C–C≡N), 94.71 (C–C≡N), 130.59, 130.79, 133.29, 134.16, 134.67, 135.47, 137.36, 139.54, 140.63, 115.08, 115.34, 126.71, 125.79, 126.73, 127.53, 127.89, 128.19, 146.89(Ar–C), 154.51, 155.39, 159.97, 166.80(Ar–C–S).

*2-Amino-6-((4‴-chlorophenylthio)-(2′-(4″-chlorophenyl)thio)-6′-methylquinolin-3′-yl)-pyridine-3,5-dicarbonitrile (**6r**)*

Yield 75 %, m.p. 230 °C, Anal. Calcd. for $C_{29}H_{17}ClN_5S_2$ (569.03 gm/mol): C 61.05, H 3.00, N 12.28 % Found: C 60.81, H 2.86, N 12.09 %. IR (KBr, cm^{-1}): 3460 and 3345 (N–H str), 2205 (C≡N str), 753 (C–S–C thioether str). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.51 (s, 3H, CH_3), 7.41–8.93 (m 14H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.45 (CH_3), 88.51 (C–C≡N), 94.79 (C–C≡N), 133.47, 134.51, 134.91, 135.71, 136.15, 137.41, 139.41, 140.41, 114.92, 115.28, 123.69, 125.81, 126.99, 127.61, 127.92, 128.03, 130.75, 146.89(Ar–C), 154.91, 155.67, 159.80, 166.89(Ar–C–S).

Conclusions

In conclusion, we report the synthesis and antimicrobial activity of new pentasubstituted pyridine derivatives bearing 2-thiophenoxy quinoline nucleus. This synthetic strategy allows the assimilation of two promising bioactive heterocycles into a single scaffold through an easy way. Reviewing and comparing the antimicrobial activity data, compounds **6g**, **6h,** and **6o** have found to be more efficient members of this series. The present study opens the scope and boundaries of both allied candidate for further detailed preclinical investigations.

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