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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Schiff's base derivatives bearing 2-thiophenoxyquinoline nucleus as new antibacterial agents

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Abstract A series of new Schiff's base derivatives **4a–x** bearing 2-thiophenoxyquinoline nucleus have been designed and synthesized by reaction of 2-thiophenoxyquinoline-3-carbaldehydes **2a–d** with various benzohydrazides **3a–f** in the presence of $Ni(NO_3)_2{\cdot}6H_2O$ as a catalyst. In vitro antibacterial screening was carried out against two Gram-positive bacteria (*Bacillus subtilis* ATCC 6633 and *Staphylococcus aureus* ATCC 6538) and two Gram-negative bacteria (*Escherichia coli* ATCC 35218 and *Pseudomonas aeruginosa* ATCC 13525). Of the compounds studied, compound **4e** showed chief activity (MIC = 3.13 μg/mL) against *S. aureus*, and compounds **4p**, **4k**, and **4w** were found to possess effective antibacterial activity against employed strains compared with standards used. The structures of Schiff's base derivatives were established by using various spectroscopic methods. A crystal structure of compound **4k** has been determined by X-ray diffraction analysis.

Keywords Schiff's base · Quinoline · Antibacterial activity · X-ray diffraction

Introduction

The frequency of infectious diseases in humans has increased dramatically because of multidrug resistance. The increasing clinical significance of drug-resistant bacterial and fungal pathogens has impelled additional urgency to research for more effective agents. Consequently, searching for new antimicrobial agents with specific activity, possibly acting through mechanism, which are distinct from those of well-known classes is of prime interest. The molecular manipulation of promising lead compounds is still an organized and ruler approach to widen the vicinity of antimicrobial medicine research. It involves an initiative to merge the separate pharmacophoric groups of analogous activity into one compound, thus making structural changes in the biological activity.

Schiff's bases constitute an important class of biologically active drug molecules, which have attracted attention of medicinal chemists because of their wide range of pharmacological properties. These compounds are being synthesized as drugs by many researchers to combat diseases with minimal toxicity and maximal effects. These predictions have provided therapeutic pathway to develop new effective biologically active Schiff's base derivatives. A number of Schiff's base derivatives have been reported to exert notably antibacterial (Joshi *et al.*, 2008), antitubercular (Hearn *et al.*, 2009), antitumor (Zhong *et al.*, 2007), antileishmanial (Rando *et al.*, 2008), DNA-binding activities, etc. On the other hand, quinoline derivatives are also known for their well-known biological properties including antibacterial (Kalluraya *et al.*, 2008), antimycobacterial (Mital *et al.*, 2006), antimalarial (Dave *et al.*, 2009; Charris *et al.*, 2005), analgesic (Bhovi *et al.*, 2010), anticonvulsant (Xie *et al.*, 2005), antioxidant, hemolytic, and cytotoxic activities (Roopan and Khan, 2009). Encouraged by their potential clinical applications and in continuation of our previous investigations on biopotent heterocycles (Song *et al.*, 2009; Li *et al.*, 2011; Xiao *et al.*, 2011; Makawana *et al.*, 2011a, b, 2012a, b, c), our efforts are focused to design and synthesize biologically potent hydrazone derivatives by reaction between 2-thiophenoxyquinoline-3-carbaldehyde and benzohydrazide derivatives.

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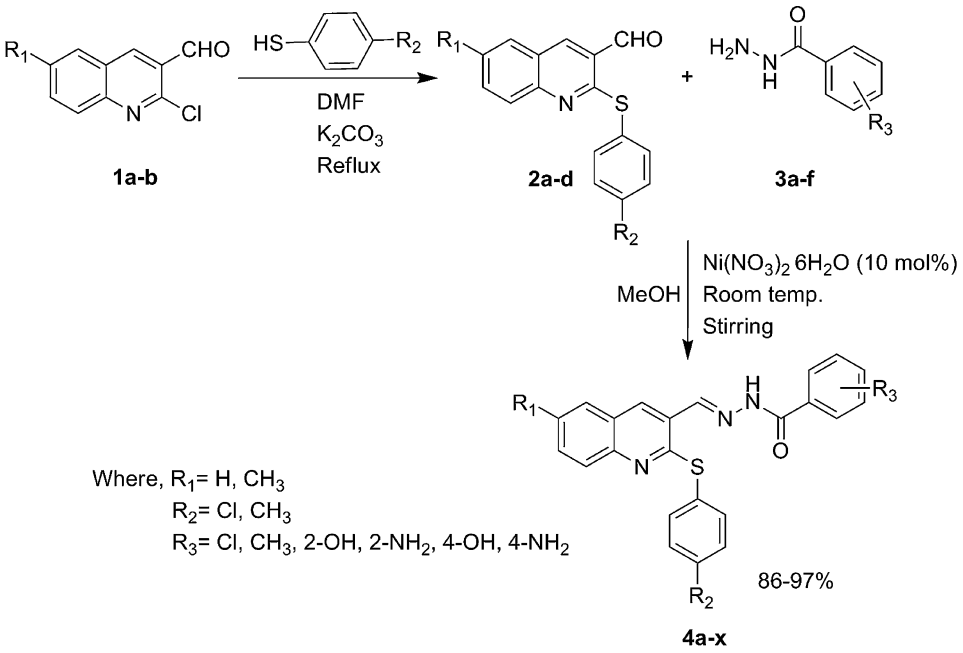
Results and discussion

Chemistry

Schiff's base derivatives **4a–x** have been synthesized by reaction between 2-thiophenoxyquinoline-3-carbaldehyde **2a–d** and various benzohydrazides **3a–f** in the presence of nickel(II) nitrate as a catalyst in methanol at room temperature, obtaining good yield (86–97 %) (Scheme 1). The reaction was also attempted using AcOH (Sirisoma *et al.*, 2009; Li *et al.*, 2009), and conc. H_2SO_4 (Jorge *et al.*, 2009); however, some shortcomings were observed, such as incompletion of reaction, long reaction time, loss of yield, and purification problems. Therefore, we applied $Ni(NO_3)_2{\cdot}6H_2O$ as a catalyst for this reaction to avoid such drawbacks as well as to develop easy and efficient method for the synthesis of new Schiff's base derivatives **4a–x**.

The key intermediate, 2-thiophenoxyquinoline-3-carbaldehyde **2a–d** has been synthesized by refluxing 2-chloroquinoline-3-carbaldehyde **1a–b** and various thiophenols for 2–3 h in DMF in the presence of K_2CO_3 as a catalyst. The required 2-chloroquinoline-3-carbaldehyde **1a–b** was prepared by Vilsmeier–Haack reaction according to the literature procedure (Meth-Cohn and Bramha, 1978).



Compound	R_1	R_2	R_3	Compound	R_1	R_2	R_3
4a	H	CH_3	CH_3	**4m**	H	Cl	CH_3
4b	H	CH_3	Cl	**4n**	H	Cl	Cl
4c	H	CH_3	2-OH	**4o**	H	Cl	2-OH
4d	H	CH_3	4-OH	**4p**	H	Cl	4-OH
4e	H	CH_3	$2\text{-}NH_2$	**4q**	H	Cl	$2\text{-}NH_2$
4f	H	CH_3	$4\text{-}NH_2$	**4r**	H	Cl	$4\text{-}NH_2$
4g	CH_3	CH_3	CH_3	**4s**	CH_3	Cl	CH_3
4h	CH_3	CH_3	Cl	**4t**	CH_3	Cl	Cl
4i	CH_3	CH_3	2-OH	**4u**	CH_3	Cl	2-OH
4j	CH_3	CH_3	4-OH	**4v**	CH_3	Cl	4-OH
4k	CH_3	CH_3	$2\text{-}NH_2$	**4w**	CH_3	Cl	$2\text{-}NH_2$
4l	CH_3	CH_3	$4\text{-}NH_2$	**4x**	CH_3	Cl	$4\text{-}NH_2$

Scheme 1 Synthetic pathway for the compounds **4a–x**

The structures of all the new synthesized compounds were established by ^{1}H NMR, ^{13}C NMR, FT-IR, elemental analysis, and molecular weights of some selected compounds confirmed by mass spectrometry. Mass spectroscopy of compounds showed molecular ion peak (M+1) corresponding to the exact mass.

Crystal structure determination

Crystal structure determination of compound **4k** has been carried out on a Nonius CAD4 diffractometer equipped with graphite monochromated Mo Ka ($k = 0.71073$ Å) radiation (Fig. 1). The structure was resolved by direct methods and refined on F^2 by full matrix least-squares methods using SHELX-97 (Sheldrick, 1997). All non-hydrogen atoms of compound **4k** were refined with anisotropic thermal parameters. All hydrogen atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms. The crystal data, data collection, and refinement parameters for the compound **4k** are listed in Table 1.

Among these compounds, a crystal structure for compound **4k** has been determined by X-ray diffraction analysis. Crystal was obtained by slow evaporation of diluted solution of **4k** in ethanol. The crystal unit of compound is composed of itself and ethanol molecule, but compound **4k** is not linked with ethanol. Figure 1 gives perspective views of **4k** with the atomic labeling system.

Table 1 Crystal data for compound **4k**

Crystal parameters	Compound **4k**
Moiety formula	$C_{25}H_{22}N_4OS$
MW (g/mol)	426.53
Moiety + ethanol trapped	$C_{27}H_{28}N_4O_2S$ (472.60)
Crystal size (mm)	0.2 × 0.2 × 0.1
Crystal system	Orthorhombic
V (Å^3)	5,067
Z	9.0
a (Å)	9.394
b (Å)	21.544
c (Å)	25.040
α (°)	90
β (°)	90
γ (°)	90
F (000)	2,000
θ limits (°)	$2.37 \leq \theta \leq 25.32$
hkl limits	$-23 \leq h \leq 26$, $-11 \leq k \leq 10$, $-30 \leq l \leq 30$
Data/restraints/parameters	4,827/0/315
Absorption coefficient (mm^{-1})	0.776
Reflection collected	4,827
Independent reflections	2,189
R_1	0.0563
wR_2	0.2165
GOF	0.991

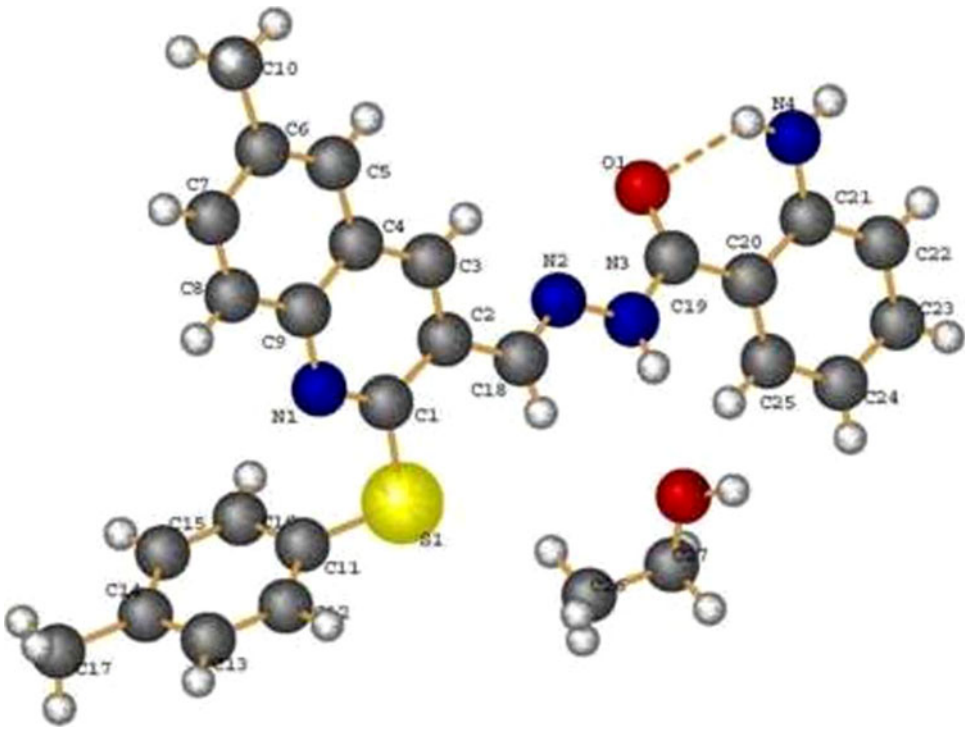


Fig. 1 Crystal structure of compound **4k**

Antimicrobial activity

In vitro antibacterial activity assay

The antibacterial activity of the synthesized compounds was tested against *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *S. aureus* using MH medium (Mueller–Hinton medium: casein hydrolysate 17.5 g, soluble starch 1.5 g, beef extract 1,000 mL). The minimum inhibitory concentrations (MICs) of the test compounds were determined by a colorimetric method using the dye (3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazoliumbromide) (MTT) (Meletiadis *et al.*, 2000). A stock solution of the synthesized compound (100 μg/mL) in DMSO was prepared and graded quantities of the test compounds were incorporated in specified quantity of sterilized liquid MH medium. A specified quantity of the medium containing the compound was poured into microtitration plates. Suspension of the microorganism was prepared to contain approximately 10^5 cfu/mL and applied to microtitration plates with serially diluted compounds in DMSO to be tested and incubated at 37 °C for 24 h. After the MICs were visually determined on each of the microtitration plates, 50 μL of PBS (phosphate buffered saline 0.01 mol/L, pH 7.4, $Na_2HPO_4{\cdot}12H_2O$ 2.9 g, KH_2PO_4 0.2 g, NaCl 8.0 g, KCl 0.2 g, distilled water 1,000 mL) containing 2 mg of MTT/mL was added to each well. Incubation was continued at room temperature for 4–5 h. The content of each well was removed, and 100 μL of isopropanol containing 5 % 1 mol/L HCl was added to extract the dye. After 12 h of incubation at room temperature, the optical density was measured with a microplate reader at 550 nm. The observed MICs are presented in Table 2.

Upon examination of antibacterial activity data, it has been observed that a majority of the compounds were found to be active against employed strains.

Against Gram-positive bacteria *S. aureus*, compound **4e** (MIC = 3.13 μg/mL) showed excellent activity, and compound **4p** (MIC = 6.25 μg/mL) showed comparable activity relative to penicillin G (MIC = 6.25 μg/mL). Compound **4k** (MIC = 6.25 μg/mL) has shown activity against Gram-negative bacteria *E. coli* equal to those of both standards used (MIC = 6.25 μg/mL). Against Gram-negative bacteria *P. aeruginosa*, compound **4e** (MIC = 6.25 μg/mL) and **4w** (MIC = 6.25 μg/mL) showed activities equal to that of penicillin G (MIC = 6.25 μg/mL). The rest of the compounds showed effective antibacterial activities against respective employed strains.

Moreover, reviewing and comparing the activity data, it is worthy to mention that the antimicrobial activity of the target compounds depends not only on the heteroaromatic pharmacophore, but also on the nature of the substituents and their spatial relationship. Compounds having $–NH_2$ at the 2nd position and –OH at the 4th position of benzohydrazide ring were found to be more effective in the series compared with other compounds.

Table 2 Antibacterial activity of compounds **4a–x**

Minimum inhibitory concentration (MIC) expressed in μg/mL				
Compounds	Gram-positive bacteria		Gram-negative bacteria	
	B. subtilis ATCC 6633	*S. aureus* ATCC 6538	*E. coli* ATCC 35218	*P. aeruginosa* ATCC 13525
4a	50	100	100	100
4b	6.25	>100	50	>100
4c	100	>100	50	100
4d	25	>100	100	50
4e	25	3.13	12.5	6.25
4f	50	25	25	25
4g	100	100	100	25
4h	100	50	>100	25
4i	100	12.5	100	12.5
4j	12.5	50	100	100
4k	3.13	12.5	3.13	100
4l	100	100	100	>100
4m	6.25	100	100	>100
4n	100	25	100	100
4o	>100	25	25	3.13
4p	100	6.25	50	100
4q	50	100	100	100
4r	50	100	100	>100
4s	50	50	100	>100
4t	100	50	100	25
4u	3.13	50	50	100
4v	100	12.5	50	100
4w	25	50	50	6.25
4x	25	50	>100	100
Kanamycin B	1.56	1.56	3.13	3.13
Penicillin G	1.56	6.25	3.13	6.25

Experimental

Materials and measurements

All chemicals and reagents used in the current study were of analytic grade. Melting points (uncorrected) were determined on an XT4 MP apparatus (Taike Corp., Beijing, China). All the ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX300 model Spectrometer in DMSO-d_6, and chemical shifts were reported in ppm (d). FTIR spectra (KBr) were run on a Nexus 870 FT-IR spectrophotometer. ESI–MS spectra were recorded on a

Mariner System 5304 Mass spectrometer. Elemental analyses were performed on a CHN-O-Rapid instrument. TLC was performed on the glass-supported silica gel sheets (Silica Gel 60 GF254) and visualized in UV light (254 nm).

*General synthetic procedure for the compounds **4a–x***

2-Thiophenoxyquinoline-3-carbaldehyde **2a–d** (1.0 mol), benzohydrazide **3a–f** (1.25 mol), and $Ni(NO_3)_2{\cdot}6H_2O$ (10 mol%) were mixed together in methanol (7 mL) and stirred at room temperature for 1–2 h. After the completion of reaction (checked by TLC), the solid separated was filtered, washed well with methanol (5 mL) and water (10 mL), and finally dried and recrystallized from ethanol to get the pure solid sample **4a–x**. Physical, analytic, and spectroscopic characterization data of the compounds **4a–x** are presented hereafter.

*(E)-4-methyl-N′-((2-(p-tolylthio)quinoline-3-yl)methylene) benzohydrazide (**4a**)* Yield 92 %, m.p. 248–250 °C, anal. calcd. for $C_{25}H_{21}N_3OS$ (411.52 g/mol): C 72.97, H 5.14, N 10.21 %. Found: C 72.81, H 5.01, N 10.33 %. IR (KBr, ν, cm^{-1}): 3180 (NH str.), 3020 (ArC–H str.), 1695 (C=O str.), 1590 (CH=N str.), 790 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 2.35 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 7.23–9.01 (m, 14H, –CH=N + Ar–H), 12.20 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 20.67 (C-16; CH_3), 21.12 (C-25; CH_3), 126.09, 127.04, 127.98, 128.89, 129.10, 129.56, 130.36, 131.15, 132.00, 133.90, 134.18, 136.09, 137.88, 138.16, 142.90, 143.78, 145.37 (–CH=N–), 156.87 (Ar–C), 163.65 (C=O). MS: 412 (M+1).

*(E)-4-chloro-N′-((2-(p-tolylthio)quinolin-3-yl)methylene) benzohydrazide (**4b**)* Yield 86 %, m.p. 292–294 °C, anal. calcd. for $C_{24}H_{18}ClN_3OS$ (431.94 g/mol): C 66.74, H 4.20, N 9.73 %. Found: C 66.55, H 4.32, N 9.59 %. IR (KBr, ν, cm^{-1}): 3190 (NH str.), 3025 (ArC–H str.), 1690 (C=O str.), 1595 (CH=N str.), 793 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 2.36 (s, 3H, CH_3), 7.27–8.96 (m, 14H, –CH=N + Ar–H), 12.23 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 20.79 (C-16; CH_3), 125.07, 126.15, 128.12, 128.68, 129.44, 131.56, 133.66, 134.05, 136.70, 137.44, 139.99, 140.33, 142.12, 142.78, 143.59, 145.18 (–CH=N–), 146.18, 157.10 (Ar–C), 163.69 (C=O). MS: 432.0 (M+1).

*(E)-2-hydroxy-N′-((2-(p-tolylthio)quinolin-3-yl)methylene) benzohydrazide (**4c**)* Yield 96 %, m.p. 258–260 °C, anal. calcd. for $C_{24}H_{19}N_3O_2S$ (413.49 g/mol): C 69.71, H 4.63, N 10.16 %. Found: C 69.80, H 4.56, N 10.12 %. IR (KBr, ν, cm^{-1}): 3185 (NH str.), 3010 (ArC–H str.), 1690 (C=O str.), 1585 (CH=N str.), 794 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 2.36 (s, 3H, CH_3), 6.91–8.89 (m, 14H, –CH=N + Ar–H), 12.13 (s, broad peak, 2H, OH + NH). ^{13}C NMR (DMSO-d_6) δ ppm: δ 21.34 (C-16; CH_3), 122.07, 123.29, 127.09, 127.78, 128.07, 129.29, 129.90, 130.06, 132.67, 133.89, 134.00, 134.69, 136.87, 138.00, 139.18, 142.07, 143.79, 144.59 (–CH=N–), 155.80, 157.30 (Ar–C), 163.59 (C=O).

*(E)-4-hydroxy-N′-((2-(p-tolylthio)quinolin-3-yl)methylene) benzohydrazide (**4d**)* Yield 90 %, m.p. 232–234 °C, anal. calcd. for $C_{24}H_{19}N_3O_2S$ (413.49 g/mol): C 69.71, H 4.63, N 10.16 %. Found: C 69.55, H 4.81, N 10.24 %. IR (KBr, ν, cm^{-1}): 3190 (NH str.), 3020 (ArC–H str.), 1695 (C=O str.), 1590 (CH=N str.), 792 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 2.38 (s, 3H, CH_3), 6.97–9.10 (m, 14H, –CH=N + Ar–H), 12.08 (s, broad peak, 2H, OH + NH). ^{13}C NMR (DMSO-d_6) δ ppm: 20.89 (C-16; CH_3), 125.15, 126.18, 127.88, 128.03, 128.93, 129.44, 130.19, 130.47, 132.00, 133.10, 134.00, 135.09, 136.57, 138.32, 142.52, 144.90 (–CH=N–), 155.30, 157.30 (Ar–C), 163.63 (C=O). MS: 414 (M+1).

*(E)-2-amino-N′-((2-(p-tolylthio)quinolin-3-yl)methylene) benzohydrazide (**4e**)* Yield 88 %, m.p. 284–286 °C, anal. calcd. for $C_{24}H_{20}N_4OS$ (412.51 g/mol): C 69.88, H 4.89, N 13.58 %. Found: C 69.72, H 4.78, N 13.61 %. IR (KBr, ν, cm^{-1}): 3195 (NH str.), 3020 (ArC–H str.), 1695 (C=O str.), 1580 (CH=N str.), 796 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 2.37 (s, 3H, CH_3), 5.83 (s, 2H, NH_2), 6.57–8.95 (m, 14H, –CH=N + Ar–H), 11.93 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 21.29 (C-16; CH_3), 125.18, 126.33, 127.12, 128.80, 129.72, 131.09, 133.15, 134.70, 135.14, 137.43, 138.35, 139.78, 140.00, 141.12, 142.08, 143.74, 145.35 (–CH=N–), 146.90, 155.19, 157.66 (Ar–C), 163.38 (C=O). MS: 413 (M+1).

*(E)-4-amino-N′-((2-(p-tolylthio)quinolin-3-yl)methylene) benzohydrazide (**4f**)* Yield 91 %, m.p. 244–246 °C, anal. calcd. for $C_{24}H_{20}N_4OS$ (412.51 g/mol): C 69.88, H 4.89, N 13.58 %. Found: C 69.65, H 5.01, N 13.71 %. IR (KBr, ν, cm^{-1}): 3190 (NH str.), 3000 (ArC–H str.), 1695 (C=O str.), 1585 (CH=N str.), 793 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 2.36 (s, 3H, CH_3), 5.78 (s, 2H, NH_2), 6.60–8.90 (m, 13H, –CH=N + Ar–H), 11.77 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 21.37 (C-16; CH_3), 125.90, 127.08, 127.83, 128.35, 129.90, 131.00, 132.98, 134.67, 135.42, 137.02, 139.77, 140.19, 141.58, 142.15, 143.60, 145.87 (–CH=N–), 146.53, 156.44 (Ar–C), 163.57 (C=O). MS: 413 (M+1).

*(E)-4-methyl-N′-((6-methyl-2-(p-tolylthio)quinolin-3-yl)methylene)benzohydrazide (**4g**)* Yield 97 %, m.p. 256–258 °C, anal. calcd. for $C_{26}H_{23}N_3OS$ (425.55 g/mol): C 73.38, H 5.45, N 9.87 %. Found: C 73.21, H 5.67, N 9.72 %. IR (KBr, ν, cm^{-1}): 3180 (NH str.), 3010 (ArC–H str.), 1690 (C=O str.), 1595 (CH=N str.), 795 (C–S–C str.). ^{1}H NMR

(DMSO-d_6) δ ppm: 2.35 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 7.26–9.07 (m, 13H, –CH=N + Ar–H), 12.03 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 20.67 (C-10; CH_3), 21.20 (C-17; CH_3), 21.41 (C-26; CH_3), 126.57, 127.00, 128.08, 128.67, 129.49, 130.56, 131.46, 132.93, 133.10, 133.53, 134.81, 136.00, 137.14, 138.05, 141.18, 143.36, 145.12 (–CH=N–), 156.39 (Ar–C), 163.71 (C=O). MS: 426 (M+1).

*(E)-4-chloro-N′-((6-methyl-2-(p-tolylthio)quinolin-3-yl)methylene)benzohydrazide (**4h**)* Yield 95 %, m.p. 296–298 °C, anal. calcd. for $C_{25}H_{20}ClN_3OS$ (445.96 g/mol): C 67.33, H 4.52, N 9.42 %. Found: C 67.09, H 4.66, N 9.30 %. IR (KBr, ν, cm^{-1}): 3190 (NH str.), 3020 (ArC–H str.), 1690 (C=O str.), 1590 (CH=N str.), 792 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 2.37 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 7.25–8.99 (m, 13H, –CH=N + Ar–H), 12.21 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 20.87 (C-10; CH_3), 21.25 (C-17; CH_3), 125.15, 127.78, 128.15, 129.77, 130.44, 132.91, 133.00, 134.17, 136.83, 137.25, 139.62, 140.20, 142.02, 142.53, 143.10, 145.52 (–CH=N–), 146.68, 157.53 (Ar–C), 163.51 (C=O). MS: 446 (M+1).

*(E)-2-hydroxy-N′-((6-methyl-2-(p-tolylthio)quinolin-3-yl)methylene)benzohydrazide (**4i**)* Yield 93 %, m.p. 238–240 °C, anal. calcd. for $C_{25}H_{21}N_3O_2S$ (427.52 g/mol): C 70.24, H 4.95, N 9.83 %. Found: C 70.20, H 5.13, N 9.66 %. IR (KBr, ν, cm^{-1}): 3185 (NH str.), 3000 (ArC–H str.), 1690 (C=O str.), 1590 (CH=N str.), 790 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 2.35 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 6.99–9.08 (m, 13H, –CH=N + Ar–H), 12.07 (s, broad peak, 2H, OH + NH). ^{13}C NMR (DMSO-d_6) δ ppm: 20.93 (C-10; CH_3), 21.31 (C-17; CH_3), 122.18, 125.30, 126.73, 127.09, 128.32, 129.41, 129.72, 130.42, 132.00, 133.15, 134.90, 136.87, 137.15, 138.00, 139.83, 142.17, 143.42, 145.20 (–CH=N–), 155.14, 156.30 (Ar–C), 163.67 (C=O). MS: 428 (M+1).

*(E)-4-hydroxy-N′-((6-methyl-2-(p-tolylthio)quinolin-3-yl)methylene)benzohydrazide (**4j**)* Yield 90 %, m.p. 274–276 °C, anal. calcd. for $C_{25}H_{21}N_3O_2S$ (427.52 g/mol): C 70.24, H 4.95, N, 9.83 %. Found: C 70.43, H 4.78, N 9.69 %. IR (KBr, ν, cm^{-1}): 3190 (NH str.), 3000 (ArC–H str.), 1695 (C=O str.), 1580 (CH=N str.), 794 (C–S–C str.) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ ppm: 2.36 (s, 3H, CH_3), 2,45 (s, 3H, CH_3), 6.92–9.12 (m, 13H, –CH=N + Ar–H), 12.15 (s, broad peak, 2H, OH + NH). ^{13}C NMR (DMSO-d_6) δ ppm: 20.89 (C-10; CH_3), 21.24 (C-17; CH_3), 125.33, 126.89, 127.13, 128.14, 128.67, 129.77, 130.09, 130.45, 132.10, 133.43, 134.16, 135.00, 136.18, 138.23, 142.12, 145.07 (–CH=N–), 155.16, 157.87 (Ar–C), 163.49 (C=O). MS: 428 (M+1).

*(E)-2-amino-N′-((6-methyl-2-(p-tolylthio)quinolin-3-yl)methylene)benzohydrazide (**4k**)* Yield 87 %, m.p. 254–256 °C, anal. calcd. for $C_{25}H_{22}N_4OS$ (426.53 g/mol): C 70.40, H 5.20, N 13.14 %. Found: C 70.22, H 5.53, N 13.09 %. IR (KBr, ν, cm^{-1}): 3195 (NH str.), 3020 (ArC–H str.), 1690 (C=O str.), 1590 (CH=N str.), 792 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 2.35 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 5.75 (s, 2H, NH_2), 6.58–8.80 (m, 13H, –CH=N + Ar–H), 11.90 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 20.68 (C-10; CH_3), 21.33 (C-17; CH_3), 125.09, 126.17, 127.32, 128.93, 129.35, 131.00, 133.89, 134.53, 135.12, 137.10, 138.24, 139.00, 140.78, 141.48, 142.19, 143.10, 145.42 (–CH=N–), 146.57, 155.11, 157.36 (Ar–C), 163.41 (C=O). MS: 427 (M+1).

*(E)-4-amino-N′-((6-methyl-2-(p-tolylthio)quinolin-3-yl)methylene)benzohydrazide (**4l**)* Yield 91 %, m.p. 288–290 °C, anal. calcd. for $C_{25}H_{22}N_4OS$ (426.53 g/mol): C 70.40, H 5.20, N 13.14 %. Found: C 70.21, H 5.34, N 13.27 %. IR (KBr, ν, cm^{-1}): 3190 (NH str.), 3015 (ArC–H str.), 1695 (C=O str.), 1585 (CH=N str.), 793 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 2.38 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 5.94 (s, 2H, NH_2), 6.64–8.93 (m, 13H, –CH=N + Ar–H), 11.85 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 21.03 (C-10; CH_3), 21.29 (C-17; CH_3), 125.16, 127.47, 127.91, 128.89, 129.10, 131.14, 132.35, 134.78, 135.31, 137.10, 139.16, 140.00, 141.18, 142.67, 143.36, 145.19 (–CH=N–), 146.77, 156.14 (Ar–C), 163.50 (C=O). MS: 427 (M+1).

*(E)-4-methyl-N′-((2-(4-chlorophenylthio)quinolin-3-yl)methylene)benzohydrazide (**4m**)* Yield 86 %, m.p. 290–292 °C, anal. calcd. for $C_{24}H_{18}ClN_3OS$ (431.94 g/mol): C 66.74, H 4.20, N 9.73 %. Found: C 66.53, H 4.05, N 9.92 %. IR (KBr, ν, cm^{-1}): 3190 (NH str.), 3015 (ArC–H str.), 1690 (C=O str.), 1590 (CH=N str.), 795 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 2.36 (s, 3H, CH_3), 7.23–9.05 (m, 14H, –CH=N + Ar–H), 12.23 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 21.37 (C-24; CH_3), 126.78, 127.51, 127.92, 128.09, 129.29, 129.67, 130.65, 131.32, 132.09, 133.16, 134.10, 136.75, 137.45, 138.23, 142.89, 143.31, 145.68 (–CH=N–), 156.77 (Ar–C), 163.50 (C=O). MS: 432 (M+1).

*(E)-4-chloro-N′-((2-(4-chlorophenylthio)quinolin-3-yl)methylene)benzohydrazide (**4n**)* Yield. 89 %, m.p. 268–270 °C, anal. calcd. for $C_{23}H_{15}Cl_2N_3OS$ (452.36 g/mol): C 61.07, H 3.34, N 9.29 %. Found: C 60.89, H 3.08, N 9.53 %. IR (KBr, ν, cm^{-1}): 3195 (NH str.), 3000 (ArC–H str.), 1695 (C=O str.), 1585 (CH=N str.), 792 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 7.25–8.98 (m, 17H, –CH=N + Ar–H), 12.25 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 125.30, 126.51, 128.80, 129.17, 129.72, 131.90,

133.14, 134.10, 136.55, 137.02, 139.00, 140.18, 142.39, 142.80, 143.13, 145.30 (–CH=N–), 146.62, 157.36 (Ar–C), 163.61 (C=O). MS: 452 (M+1).

*(E)-2-hydroxy-N′-((2-(4-chlorophenylthio)quinolin-3-yl)methylene)benzohydrazide (**4o**)* Yield 94 %, m.p. >300 °C, anal. calcd. for $C_{23}H_{16}ClN_3O_2S$ (433.91 g/mol): C 63.66, H 3.72, N 9.68 %. Found: C 63.39, H 3.55, N 9.74 %. IR (KBr, ν, cm^{-1}): 3195 (NH str.), 3005 (ArC–H str.), 1690 (C=O str.), 1580 (CH=N str.), 793 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 6.92–8.85 (m, 14H, –CH=N + Ar–H), 12.23 (s, broad peak, 2H, OH + NH). ^{13}C NMR (DMSO-d_6) δ ppm: 125.15, 126.10, 127.87, 128.19, 128.53, 129.70, 129.98, 130.20, 132.82, 133.16, 134.77, 134.91, 136.43, 138.08, 139.17, 142.32, 143.18, 144.37 (–CH=N–), 155.51, 157.81 (Ar–C), 163.40 (C=O). MS: 434 (M+1).

*(E)-4-hydroxy-N′-((2-(4-chlorophenylthio)quinolin-3-yl)methylene)benzohydrazide (**4p**)* Yield 87 %, m.p. 262–264 °C, anal. calcd. for $C_{23}H_{16}ClN_3O_2S$ (433.91 g/mol): C 63.66, H 3.72, N 9.68 %. Found: C 63.56, H 3.81, N 9.79 %. IR (KBr, ν, cm^{-1}): 3195 (NH str.), 3020 (ArC–H str.), 1690 (C=O str.), 1595 (CH=N str.), 795 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 6.89–8.90 (m, 14H, –CH=N + Ar–H), 12.19 (s, broad peak, 2H, OH + NH). ^{13}C NMR (DMSO-d_6) δ ppm: 125.71, 126.18, 127.37, 128.00, 128.47, 129.03, 130.18, 130.62, 132.10, 133.29, 134.41, 135.67, 136.18, 138.52, 142.40, 144.25 (–CH=N–), 155.49, 157.15 (Ar–C), 163.67 (C=O). MS: 434 (M+1).

*(E)-2-amino-N′-((2-(4-chlorophenylthio)quinolin-3-yl)methylene)benzohydrazide (**4q**)* Yield 90 %, m.p. 296–298 °C, anal. calcd. for $C_{23}H_{17}ClN_4OS$ (432.93 g/mol): C 63.81, H 3.96, N 12.94 %. Found: C 63.57, H 4.08, N 12.76 %. IR (KBr, ν, cm^{-1}): 3190 (NH str.), 3020 (ArC–H str.), 1695 (C=O str.), 1585 (CH=N str.), 790 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 6.33 (s, 2H, NH_2), 6.59–8.85 (m, 14H, –CH=N + Ar–H), 11.83 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 125.37, 126.12, 127.74, 128.32, 129.45, 131.10, 133.00, 134.01, 135.19, 137.61, 138.20, 139.17, 140.91, 141.29, 142.43, 143.18, 145.11 (–CH=N–), 146.83, 155.39, 157.59 (Ar–C), 163.48 (C=O). MS: 433 (M+1).

*(E)-4-amino-N′-((2-(4-chlorophenylthio)quinolin-3-yl)methylene)benzohydrazide (**4r**)* Yield 92 %, m.p. 286–288 °C, anal. calcd. for $C_{23}H_{17}ClN_4OS$ (432.93 g/mol): C 63.81, H 3.96, N 12.94 %. Found: C 63.69, H 3.80, N 13.09 %. IR (KBr, ν, cm^{-1}): 3195 (NH str.), 3020 (ArC–H str.), 1690 (C=O str.), 1590 (CH=N str.), 792 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 5.95 (s, 2H, NH_2), 6.54–8.79 (m, 14H, –CH=N + Ar–H), 11.77 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 125.67, 127.09, 127.59, 128.14, 129.63, 131.00, 132.50, 134.13, 135.47, 137.00, 139.52, 140.19, 141.30, 142.81, 143.00, 145.79 (–CH=N–), 146.32, 156.18 (Ar–C), 163.62 (C=O). MS: 433 (M+1).

*(E)-4-methyl-N′-((2-(4-chlorophenylthio)-6-methylquinolin-3-yl)methylene)benzohydrazide (**4s**)* Yield 86 %, m.p. 250–252 °C, anal. calcd. for $C_{25}H_{20}ClN_3OS$ (445.96 g/mol): C 67.33, H 4.52, N 9.42 %. Found: C, 67.56; H, 4.28; N, 9.31 %. IR (KBr, ν, cm^{-1}): 3190 (NH str.), 2995 (ArC–H str.), 1690 (C=O str.), 1590 (CH=N str.), 791 (C–S–C str.) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ ppm: 2.37 (s, 3H, CH3), 2.46 (s, 3H, CH3), 7.28–8.99 (m, 13H, –CH=N + Ar–H), 12.19 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 21.33 (C-10; CH_3), 21.52 (C-25; CH_3), 126.34, 126.92, 127.78, 127.86, 128.70, 129.01, 130.36, 132.43, 133.51, 133.62, 134.94, 136.38, 137.12, 138.95, 143.76, 145.39 (–CH=N), 146.62, 156.25 (Ar–C), 163.65 (C=O). MS: 446 (M+1).

*(E)-4-chloro-N′-((2-(4-chlorophenylthio)-6-methylquinolin-3-yl)methylene)benzohydrazide (**4t**)* Yield 95 %, m.p. 244–246 °C, anal. calcd. for $C_{24}H_{17}Cl_2N_3OS$ (466.38 g/mol): C 61.81, H 3.67, N 9.01 %. Found: C 61.93, H 3.70, N 9.12 %. IR (KBr, ν, cm^{-1}): 3190 (NH str.), 3010 (ArC–H str.), 1690 (C=O str.), 1590 (CH=N str.), 794 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 2.39 (s, 3H, CH_3), 7.25–8.99 (m, 13H, –CH=N + Ar–H), 12.20 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 21.27 (C-10; CH_3), 125.32, 127.81, 128.19, 129.13, 130.33, 132.10, 133.52, 134.19, 136.77, 137.29, 139.11, 140.54, 142.90, 143.53, 144.10, 145.39 (–CH=N–), 146.30, 157.29 (Ar–C), 163.53 (C=O). MS: 466 (M+1).

*(E)-2-hydroxy-N′-((2-(4-chlorophenylthio)-6-methylquinolin-3-yl)methylene)benzohydrazide (**4u**)* Yield 97 %, m.p. 282–284 °C, anal. calcd. for $C_{24}H_{18}ClN_3O_2S$ (447.94 g/mol): C 64.35, H 4.05, N 9.38 %. Found: C 64.41, H 3.91, N 9.20 %. IR (KBr, ν, cm^{-1}): 3190 (NH str.), 3000 (ArC–H str.), 1690 (C=O str.), 1590 (CH=N str.), 794 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 2.43 (s, 3H, CH_3), 6.91–9.09 (m, 13H, –CH=N + Ar–H), 12.11 (s, broad peak, 2H, OH + NH). ^{13}C NMR (DMSO-d_6) δ ppm: 21.39 (C-10; CH_3), 122.64, 125.19, 126.00, 127.73, 128.10, 129.53, 129.94, 130.15, 132.29, 133.42, 134.83, 136.64, 137.33, 138.00, 139.15, 142.92, 143.03, 145.27 (–CH=N–), 155.18, 156.62 (Ar–C), 163.60 (C=O). MS: 448 (M+1).

*(E)-4-hydroxy-N′-((2-(4-chlorophenylthio)-6-methylquinolin-3-yl)methylene)benzohydrazide (**4v**)* Yield 88 %, m.p. 270–272 °C, anal. calcd. for $C_{24}H_{18}ClN_3O_2S$ (447.94 g/mol): C 64.35, H 4.05, N 9.38 %. Found: C 64.51, H 4.23, N 9.53 %. IR (KBr, ν, cm^{-1}): 3195 (NH str.), 3020 (ArC–H str.), 1695 (C=O str.), 1595 (CH=N str.), 795 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 2.36

(s, 3H, CH_3), 6.94–9.10 (m, 13H, –CH=N + Ar–H), 12.07 (s, broad peak, 2H, OH + NH). ^{13}C NMR (DMSO-d_6) δ ppm: 21.31 (C-10; CH_3), 125.00, 126.40, 127.18, 128.23, 128.92, 129.10, 130.32, 130.60, 132.15, 133.03, 134.19, 135.00, 136.32, 138.12, 142.09, 145.32 (–CH=N–), 155.19, 157.38 (Ar–C), 163.53 (C=O). MS: 448 (M+1).

*(E)-2-amino-N′-((2-(4-chlorophenylthio)-6-methylquinolin-3-yl)methylene)benzohydrazide (**4w**)* Yield 93 %, m.p. >300 °C, anal. calcd. for $C_{24}H_{19}ClN_4OS$ (446.95 g/mol): C 64.49, H 4.28, N 12.54 %. Found: C 64.35, H 4.09, N 12.67 %. IR (KBr, ν, cm^{-1}): 3190 (NH str.), 2995 (ArC–H str.), 1690 (C=O str.), 1590 (CH=N str.), 791 (C–S–C str.). ^{1}H NMR (DMSO- d_6) δ ppm: 2.45 (s, 3H, CH_3), 6.43 (s, 2H, NH_2), 6.56–8.85 (m, 13H, –CH=N + Ar–H), 11.92 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 21.25 (C-10; CH_3), 125.42, 126.00, 127.16, 128.87, 129.32, 131.04, 133.19, 134.55, 135.13, 137.91, 138.32, 139.00, 140.63, 141.07, 142.15, 143.84, 145.36 (–CH=N–), 146.18, 155.42, 157.30 (Ar–C), 163.61 (C=O). MS: 447 (M+1).

*(E)-4-amino-N′-((2-(4-chlorophenylthio)-6-methylquinolin-3-yl)methylene)benzohydrazide (**4x**)* Yield 90 %, m.p. 264–266 °C, anal. calcd. for $C_{24}H_{19}ClN_4OS$ (446.95 g/mol): C 64.49, H 4.28, N 12.54 %. Found: C 64.32, H 4.30, N 12.76 %. IR (KBr, ν, cm^{-1}): 3190 (NH str.), 3005 (ArC–H str.), 1690 (C=O str.), 1595 (CH=N str.), 790 (C–S–C str.). ^{1}H NMR (DMSO-d_6) δ ppm: 2.38 (s, 3H, CH_3), 6.18 (s, 2H, NH_2), 6.61–8.97 (m, 13H, –CH=N + Ar–H), 12.01 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 21.27 (C-10; CH_3), 125.54, 127.32, 127.98, 128.65, 129.03, 131.17, 132.89, 134.31, 135.88, 137.00, 139.62, 140.09, 141.10, 142.25, 143.92, 145.64 (–CH=N–), 146.00, 156.37 (Ar–C), 163.58 (C=O). MS: 447 (M+1).

Conclusion

In conclusion, new Schiff's base derivatives bearing 2-thiophenoxyquinoline nucleus have been synthesized using ecofriendly catalyst in a short reaction time with good yield. This synthetic strategy allows for the assimilation of 2-thiophenoxyquinoline and benzohydrazide in a single scaffold through an easy way. Of the compounds studied, **4e**, **4p**, **4k,** and **4w** have proven as the efficient antimicrobial member. Further, a majority of the compounds were found to be active against employed strains, and a –NH_2– and –OH-substituted benzohydrazide ring plays an important role in the activity. Based on this conclusion, it is worth mentioning that Schiff's base derivatives bearing thioether linkage in quinoline nucleus have emerged as a spotlight in the field of antibacterial medicine research.

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