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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

An efficient one-pot cyclization of quinoline thiosemicarbazones to quinolines derivatized with 1,3,4-thiadiazole as anticancer and anti-tubercular agents

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Abstract A series of 6,7,8-substituted thiosemicarbazones (**2a–j**) of 2-chloro-3-formyl-quinoline derivatives were cyclized to the title compounds (**3a–j**) using acetic anhydride. The structures of the final compounds (**3a–j**) were confirmed by elemental and spectral (IR, ^{1}H NMR and MS) analysis. Some of the title compounds have shown promising anticancer and antitubercular activities.

Keywords Quinoline · 1,3,4-Thiadiazole · Cyclization · Anticancer activity · Antitubercular activity · SAR · *c* log *P*

Introduction

The design as well as identification of new molecules for the treatment of diseases such as the cancer and tuberculosis is an important undertaking in medicinal chemistry research. The quinoline derivatives have been known to possess wide spectrum of pharmacological properties (Nayar and Jain, 2008; Lilienkampf *et al.*, 2009; Mital *et al.*, 2006; Leclerc *et al.*, 1986). They are the backbone in numerous commercial products such as perfumes, dyes including pharmaceuticals. Quinoline derivatives viz., ofloxacin, norfloxacin, ciprofloxacin, chloroquine, etc., have been used as efficient drugs till date (Fig. 1). 2-Chloroquinoline constitutes one of the most active classes of compounds possessing diversified biological activities (Hirao *et al.*, 1976; Pokalwar *et al.*, 2006; Kategaonkar *et al.*, 2010).

Literature survey reveals that 1,3,4-thiadiazole derivatives have been incorporated into a large number of compounds with potential medicinal values such as antibacterial, antifungal, antitubercular and antitumor activities (Solak and Rollas, 2006; Padmavathi *et al.*, 2010; Lamani *et al.*, 2009; Meng *et al.*, 2009). Many drugs containing 1,3,4-thiadiazole as lead nucleus such as acetazolamide, methazolamide, sulfamethizole, are presently available in the market (Fig. 1).

Tuberculosis is the single largest infectious disease having a high mortality rate and due to this every year 0.10–0.30% of population is being infected in the developing as well as in the developed countries. It is commonly known that *Mycobacterium tuberculosis* has developed resistance to the majority of the existing drugs. Ring substituted quinolines have been reported as new structural class of anti-TB agents which can act by their mechanism and these are different from those of currently used drugs against a panel of drug sensitive and drug resistant strains (Vangapandu *et al.*, 2004). Cancer is another major cause of the death in the world. It is a devastating disease caused due to the uncontrolled growth of the cells which are characterized by their out of limit growth. In view of the above mentioned facts and as a part of SAR studies we have made an attempt to achieve novel molecules with better anticancer and anti-TB properties. And hence in this report 1,3,4-thiadiazole as a substituent is incorporated on 2-chloroquinoline nucleus viz., *N*-[4-acetyl-5-(6,7,8-substituted-2-chloroquinolin-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]-acetamides (**3a–j**) and further screened them for anticancer activity against cervical cancer cell (Hela)

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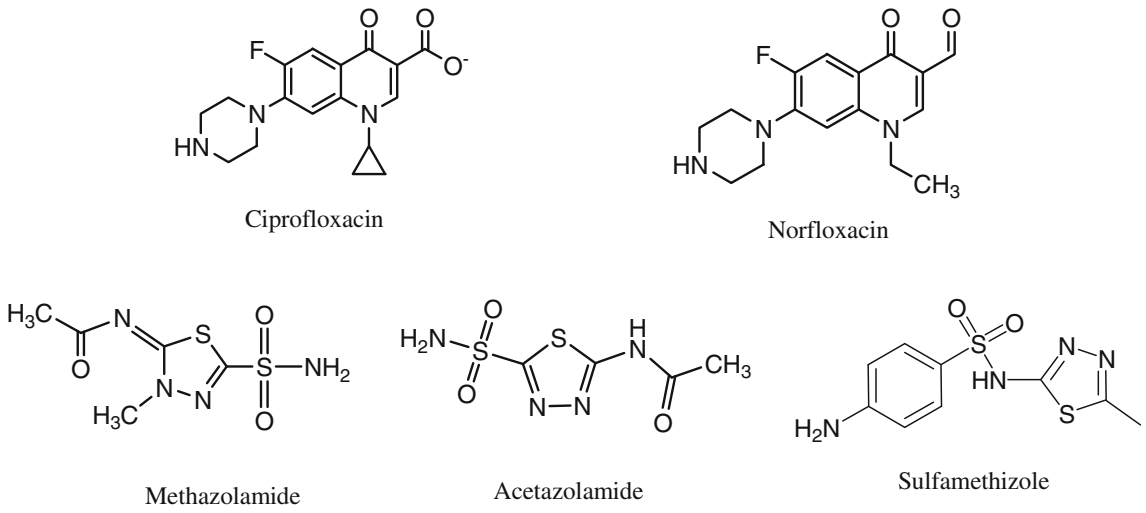


Fig. 1 Structurally related bio-active compounds

and antitubercular activity assay against *Mycobacterium tuberculosis* $H_{37}Rv$.

Chemistry

The thiosemicarbazones (**2a–j**) were prepared by the condensation of 6,7,8-substituted-2-chloro-3-formyl-quinolines (**1a–j**) with thiosemicarbazide in ethanol. The intermediate thiosemicarbazones (**2a–j**) were further converted to *N*-[4-acetyl-5-(6,7,8-substituted-2-chloroquinolin-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]-acetamides (**3a–j**) by the action of acetic anhydride on the compounds (**2a–j**) (Scheme 1). The proposed mechanism for the conversion of thiosemicarbazones (**2a–j**) to the quinolines derivatized with 1,3,4-thiadiazoles (**3a–j**) is given in (Scheme 2).

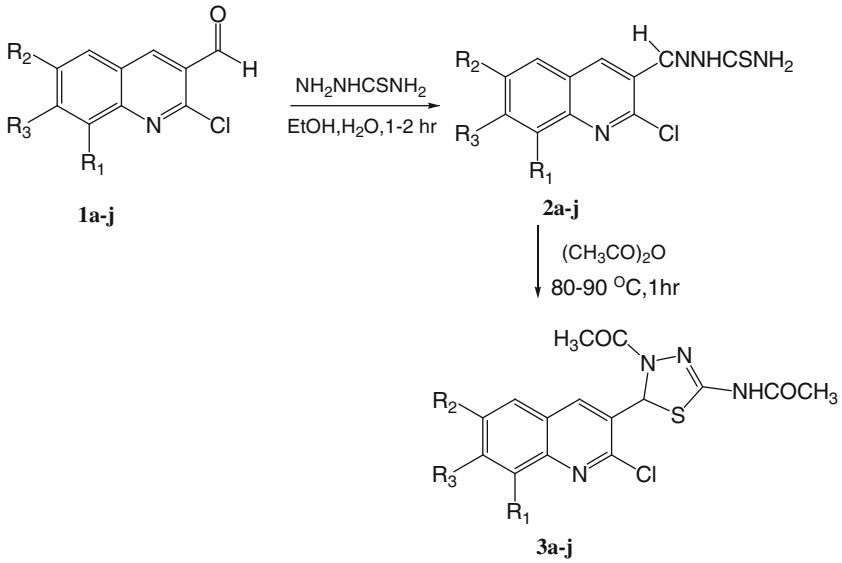
Results and discussion

The structures of the final compounds (**3a–j**) were confirmed by their elemental analysis, IR, ^{1}H NMR and mass spectral data.

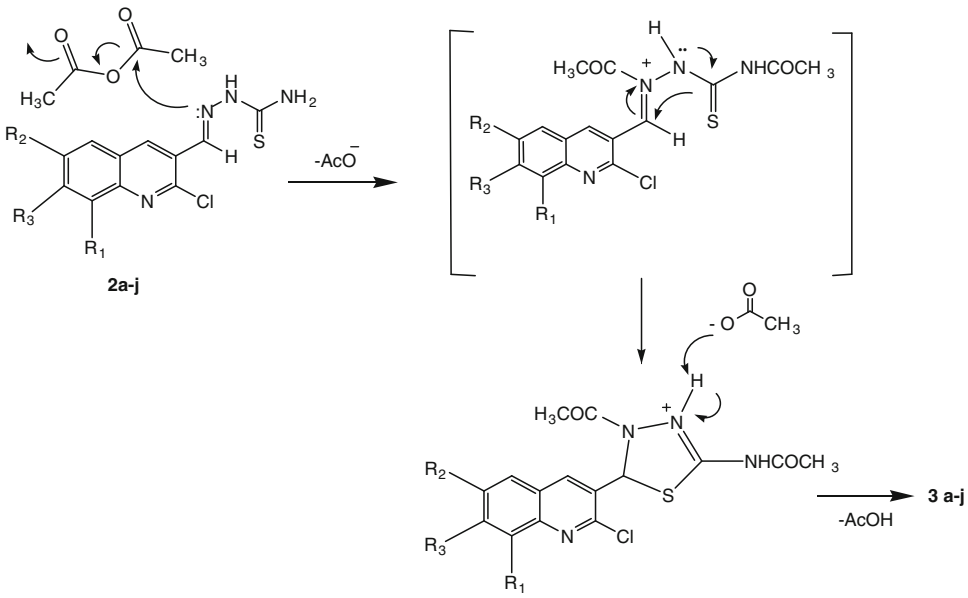
The IR spectra of the title compounds (**3a–j**) have shown mainly a sharp strong absorption band around 1655–1685 cm^{-1} which corresponds to amide carbonyl group. Another medium absorption band was observed at around 1602–1642 cm^{-1} due to C=N stretching.

The ^{1}H NMR spectral analysis of the title compounds (**3a–j**) has shown a characteristic singlet in the range δ 6.2–7.3 ppm responsible for C_5–H of the 1,3,4-thiadiazole ring. The aldehydic proton (–CH=N) in the corresponding thiosemicarbazones (**2a–j**) appeared around δ 8.05–8.35 ppm. This shift in the signal to δ 6.2–7.3 ppm in the

Scheme 1 Overview of synthetic pathway of *N*-[4-acetyl-5-(6,7,8-substituted-2-chloroquinolin-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]-acetamides (**3a–j**)



1a-j **2a-j** **3a-j**



Scheme 2 Proposed mechanism for the transformation of thiosemicarbazones **2** (**a**–**j**) to 1,3,4-thiadiazole derivatives **3** (**a**–**j**)

title compounds (**3a**–**j**) confirmed the cyclization of thiosemicarbazone to 1,3,4-thiadiazole. The protons of the substituent groups and the aromatic protons appeared in their respective regions.

A lead molecule to consider it as a drug candidate, parameters set by Lipinski's rule of five is analyzed. The *c* log *P* is an important physiochemical property indicating the lipophilicity which determines the ability of molecule to cross the various biological membranes. The calculations of *c* log *P* values of compounds were done at self consistent field theory level using PM_3 (Hamiltonian Inc.) in MOPAC 6.0 PACKAGE (Stewart, 1989, 1990) and are tabulated in Table 1. According to Lipinski's rule of five the *c* log *P* value below 5 is feasible for a compound to be future drug (Lipinski *et al.*, 1997). The synthesized compounds showed a marginal lipophilicity within the range of 1.91–3.25, indicating that these compounds have better penetrating power into the cell membrane. The molecular weight property of the compound is related to its in vivo administration and all the synthesized compounds have molecular weight within acceptable range (200–500). The synthesized compounds did not show any of the toxic properties like, mutagenicity, tumorigenicity, irritant nature, reproductive effect. On the basis of these properties, we can ascertain that these may exhibit better drug likeliness property and drug score.

Anticancer activity was carried out against cervical cancer cell lines (Hela). The activity of the compounds **3b** (methyl at C_6 of quinoline), **3c** (methoxy at C_6 of quinoline) and **3h** (two methoxy groups at C_7 and C_8 of quinoline) are encouraging. These compounds have shown very good anticancer activity and the cell lyses occurred only at 10 μg/ml. However, the compounds **3a** (with no substituent), **3f** (methoxy group at C_8 of quinoline) and **3g** (methoxy group at C_7 of quinoline) have also exhibited anticancer activity and the cell lyses was found at 15 μg/ml. Where as the compounds **3d**, **3e**, **3i** and **3j** have shown poor activity (Table 2; Fig. 2).

Table 1 Physical data and yields of *N*-[4-acetyl-5-(6,7,8-substituted-2-chloroquinolin-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]-acetamides (**3a**–**j**)

Compound	R_1	R_2	R_3	Formula	Mol. wt.	*c* log *P*	Drug likeliness	Drug score
3a	H	H	H	$C_{15}H_{13}ClN_4O_2S$	348.80	2.91	4.49	0.76
3b	H	CH_3	H	$C_{16}H_{15}ClN_4O_2S$	362.83	3.22	3.48	0.70
3c	H	OCH_3	H	$C_{16}H_{15}ClN_4O_3S$	378.83	2.02	3.10	0.81
3d	CH_3	H	H	$C_{16}H_{15}ClN_4O_2S$	362.83	3.22	4.70	0.71
3e	H	H	CH_3	$C_{16}H_{15}ClN_4O_2S$	362.83	3.22	3.48	0.70
3f	OCH_3	H	H	$C_{16}H_{15}ClN_4O_3S$	378.83	2.80	4.74	0.74
3g	H	H	OCH_3	$C_{16}H_{15}ClN_4O_3S$	378.83	2.02	3.10	0.80
3h	H	OCH_3	OCH_3	$C_{17}H_{17}ClN_4O_4S$	408.86	1.91	3.52	0.80
3i	H	H	Cl	$C_{15}H_{12}Cl_2N_4O_2S$	383.25	2.74	3.25	0.74
3j	H	Br	H	$C_{15}H_{12}BrClN_4O_2S$	427.70	2.74	3.02	0.74

Table 2 Anticancer activity of the compounds (**3a–j**) against human cervical cancer cell lines (HELA)

Entry no.	Concentration[a] (μg/ml)
3a	15.0
3b	10.0
3c	10.0
3d	25.0
3e	20.0
3f	15.0
3g	15.0
3h	10.0
3i	20.0
3j	20.0

[a] Minimum concentration at which cell mortality (lyses) occur

Antitubercular activity was carried out against *Mycobacterium tuberculosis* $H_{37}Rv$. The assay reveals that the compounds **3d** and **3f** (with methyl and methoxy groups at the C_8 of quinoline nucleus, respectively) have shown the inhibition (MIC) at 5 μg/ml. The remaining compounds **3a**, **3b**, **3c**, **3e**, **3g**, **3h**, **3i** and **3j** have shown the activity at 10 μg/ml. Encouraging activity may be attributed to the presence of electron donating groups viz., OCH_3 and CH_3 at C_8 of quinoline nucleus (Table 3). It is interesting to note that the compounds which have shown anticancer activity have not exhibited the antitubercular activity and vice versa, suggesting that the compounds exhibited selectivity either as anticancer or as antitubercular agents.

Table 3 Antitubercular activities of the synthesized compounds (**3a–j**)

Entry no.	Concentration (μg/ml)		
	5	10	25
3a	R	S	S
3b	R	S	S
3c	R	S	S
3d	S	S	S
3e	R	S	S
3f	S	S	S
3g	R	S	S
3h	R	S	S
3i	R	S	S
3j	R	S	S

Standard: streptomycin (inhibition at 10 μg/ml)

R resistant, *S* sensitive

Experimental

Melting points were measured with open capillary in a melting point apparatus. FT-IR spectra were recorded on Nicolet 5700 using KBr pellets. The ^1H NMR spectra were recorded on a Varian (300 MHz) FT-NMR spectrometer in DMSO-d_6 with TMS as an internal standard. Mass spectra were recorded on a GCMS-SC\AD\17-004 Mass spectrometer. Elemental analyses were performed on Heraus CHN analyzer. All the reagents and solvents were of analytical grade, and used as supplied unless otherwise stated. TLC was performed on silica gel coated plates for monitoring the reactions. 2-Chloro-3-formyl-quinoline derivatives (**1a–j**) and the corresponding thiosemicarbazones (**2a–j**) were prepared as per the reported method (Otto and Bramha, 1978, 1981). Anticancer and antitubercular activity assay were carried out according to the literature method (Doyle and Griffiths, 2000) at the Department of Molecular Biology and Immunology, N.G.H. Institute of

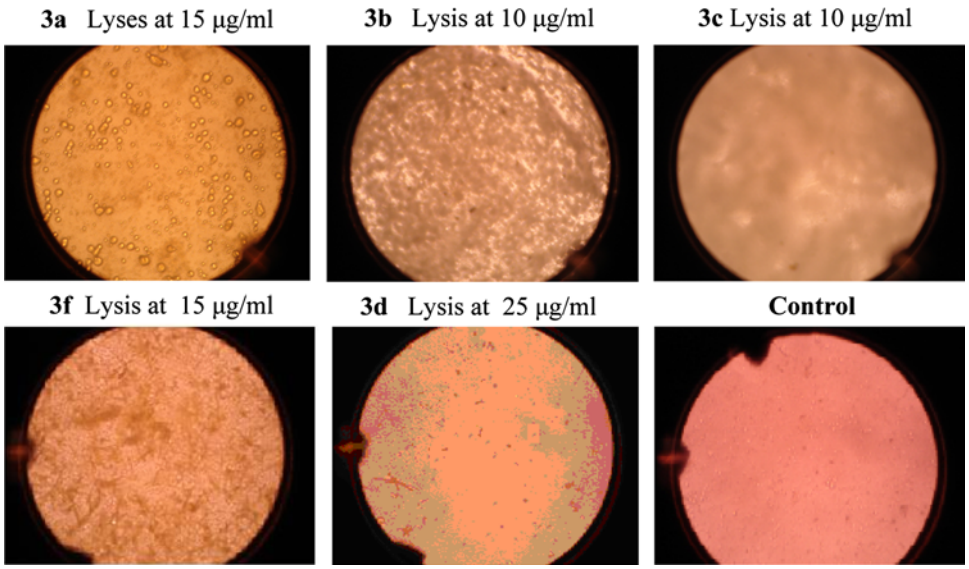


Fig. 2 Photographs showing the cervical cancer cell lysis at different concentrations by the title compounds **3a**, **3b**, **3c**, **3d**, **3f** and the control

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General procedure for the preparation of *N*-(4-acetyl-5-(6,7,8-substituted-2-chloroquinolin-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)-acetamides (**3a–j**)

A mixture of the compounds (**2a–j**) (0.005 mol) and acetic anhydride (4 ml) was heated at 80–90°C for 1 h. The reaction mixture was cooled to room temperature and then poured into the ice-cold water. The precipitate thus obtained was filtered off, washed with water, dried and crystallized from alcohol to get pale yellow to brown needles of the compounds (**3a–j**).

*N-(4-Acetyl-5-(2-chloroquinolin-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)-acetamide (**3a**)*

Pale yellow crystals. Yield; 65% mp (°C); 210–213. IR (ν_{max} in cm^{-1}); 3421, 2926, 1659, 1615. ^1H NMR (300 MHz, δ ppm, DMSO-d_6); 2.14 (s, 3H, CH_3 of $NHCOCH_3$), 2.21 (s, 3H, CH_3 of N_4–$COCH_3$), 6.59 (s, 1H, C_5–H), 8.30–8.16 (m, 4H, Ar–H, quin C_5–H, C_6–H, C_7–H, C_8–H), 8.78 (s, 1H, quin C_4–H), 11.72 (s, 1H, NHCO). LCMS (70 eV, *m/z*); 352.2 (M + 1, 18.3), 188 (8.2), 153 (100). CHN Analysis; Calculated for $C_{15}H_{13}ClN_4O_2S$: C, 51.65; H, 3.76; N, 16.06. Found: C, 51.60; H, 3.70; N, 15.99.

*N-(4-Acetyl-5-(2-chloro-6-methylquinolin-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)-acetamide (**3b**)*

Yellow crystals. Yield; 75% mp (°C); 168–170. IR (ν_{max} in cm^{-1}); 3430, 2922, 1655, 1612. ^1H NMR (300 MHz, δ ppm, DMSO-d_6); 2.16 (s, 3H, CH_3 of $NHCOCH_3$), 2.18 (s, 3H, CH_3 of N_4–$COCH_3$), 2.34 (s, 3H, CH_3 of Ar–CH_3), 7.00 (s, 1H, C_5–H), 8.97 (s, 1H, ArH, quin C_4–H) 8.06–8.16 (m, 3H, Ar–H, quin C_5–H, C_7–H, C_8–H), 11.86 (s, 1H, NHCO). LC–MS (70 eV, *m/z*); 363.2 (M + 1, 30.3), 197.6 (22.2), 162.5 (100). CHN Analysis; Calculated for $C_{16}H_{15}ClN_4O_2S$: C, 52.96; H, 4.17; N, 15.44. Found: C, 53.06; H, 4.08; N, 15.52.

*N-(4-Acetyl-5-(2-chloro-6-methoxyquinolin-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)-acetamide (**3c**)*

Yellow crystals. Yield; 72% mp (°C); 200–205. IR (ν_{max} in cm^{-1}); 3434, 2974, 1660, 1620. ^1H NMR (300 MHz, δ ppm, DMSO-d_6); 2.13 (s, 3H, CH_3 of $NHCOCH_3$), 2.16 (s, 3H, CH_3 of N_4–$COCH_3$), 3.45 (s, 3H, of OCH_3), 6.91 (s, 1H, C_5–H), 8.22–8.32 (m, 3H, Ar–H, quin C_5–H, C_7–H, C_8–H), 8.82 (s, 1H, quin C_4–H), 11.80 (s, 1H, NHCO). LC–MS (70 eV, *m/z*); 380.0 (M + 1, 31.0), 216 (20), 153 (100). CHN Analysis: Calculated for $C_{16}H_{15}ClN_4O_3S$: C, 50.79; H, 4.00; N, 14.79. Found: C, 50.84; H, 4.08; N, 14.81.

*N-(4-Acetyl-5-(2-chloro-8-methylquinolin-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)-acetamide (**3d**)*

Yellow crystals. Yield; 65.2% mp (°C); 200–203. IR (ν_{max} in cm^{-1}); 3430, 2922, 1655, 1612. ^1H NMR (300 MHz, δ ppm, DMSO-d_6); 2.18 (s, 3H, CH_3 of $NHCOCH_3$), 2.20 (s, 3H, CH_3 of N_4–$COCH_3$), 2.34 (s, 3H, CH_3 of Ar–CH_3), 7.20 (s, 1H, C_5–H), 8.22 (m, 3H, Ar–H, quin C_5–H, C_6–H, C_7–H), 8.92 (s, 1H, Ar–H, quin C_4–H), 11.69 (s, 1H, NHCO). LC–MS (70 eV, *m/z*); 363.0 (M + 1, 32.3), 197.2 (21.2), 161.8 (100). CHN Analysis; Calculated for $C_{16}H_{15}ClN_4O_2S$: C, 52.98; H, 4.17; N,15.44. Found: C, 53.08; H, 4.23; N, 15.50.

*N-(4-Acetyl-5-(2-chloro-7-methylquinolin-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)-acetamide (**3e**)*

Yellow crystals. Yield; 72.3% mp (°C); 195–197. IR (ν_{max} in cm^{-1}); 3400, 2899, 1668, 1618. ^1H NMR (300 MHz, δ ppm, DMSO-d_6); 2.08 (s, 3H, CH_3 of $NHCOCH_3$), 2.11 (s, 3H, CH_3 of N_4–$COCH_3$), 2.29 (s, 3H, CH_3 of Ar–CH_3), 6.88 (s, 1H, C_5–H), 8.80 (s, 1H, ArH, quin C_4–H), 8.02–8.25 (m, 3H, Ar–H quin C_5–H, C_6–H, C_8–H), 11.54 (s, 1H, NHCO). LC–MS (70 eV, *m/z*); 362.2 (M + 1, 25.3), 198.2 (20.2), 161.0 (100). CHN Analysis; Calculated for $C_{16}H_{15}ClN_4O_2S$: C, 52.82; H, 4.15; N, 15.32. Found: C, 52.88; H, 4.12; N, 15.38.

*N-(4-Acetyl-5-(2-chloro-8-methoxyquinolin-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)-acetamide (**3f**)*

Yellow crystals. Yield; 75.8% mp (°C); 205–207. IR (ν_{max} in cm^{-1}); 3389, 2984, 1669, 1617. ^1H NMR (300 MHz, δ ppm, DMSO-d_6); 2.13 (s, 3H, CH_3 of $NHCOCH_3$), 2.18 (s, 3H, CH_3 of N_4–$COCH_3$), 3.55 (s, 3H, OCH_3 of OCH_3), 6.86 (s, 1H, C_5–H), 8.25–8.40 (m, 3H, Ar–H, quin C_5–H, C_6–H, C_7–H), 8.78 (s, 1H, Ar–H, quin C_4–H), 11.89 (s, 1H, NHCO). LC–MS (70 eV, *m/z*); 380.2 (M + 1, 33.0), 215.8 (20.3), 153.5 (100). CHN Analysis; Calculated for $C_{16}H_{15}ClN_4O_3S$: C, 50.72; H, 3.3.78; N, 14.62. Found: C, 50.80; H, 3.85; N, 14.69.

*N-(4-Acetyl-5-(2-chloro-7-methoxyquinolin-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)-acetamide (**3g**)*

Yellow crystals. Yield; 64.3% mp (°C); 203–205. IR (ν_{max} in cm^{-1}); 3299, 2872, 1672, 1616. ^1H NMR (300 MHz, δ ppm, DMSO-d_6); 2.11 (s, 3H, CH_3 of $NHCOCH_3$), 2.14 (s, 3H, CH_3 of N_4–$COCH_3$), 3.68 (s, 3H, OCH_3), 6.98 (s, 1H, C_5–H), 8.32–8.42 (m, 3H, Ar–H, quin C_5–H, C_6–H, C_8–H),

8.82 (s, 1H, Ar–H, quin C_4–H) 11.40 (s, 1H, NHCO). LC–MS (70 eV, *m/z*); 380.2 (M + 1, 28.0), 215.2 (18.3), 153.8 (100). CHN Analysis; Calculated for $C_{16}H_{15}ClN_4O_3S$: C, 50.84; H, 3.82; N, 14.85 Found: C, 50.91; H, 3.88; N, 14.87.

*N-(4-Acetyl-5-(2-chloro-6,7-dimethoxyquinolin-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)-acetamide (**3h**)*

Pale brown crystals. Yield; 68.8% mp (°C); 220–222. IR (ν_{max} in cm^{-1}); 3339, 2962, 1682, 1614. ^1H NMR (300 MHz, δ ppm, DMSO-d_6); 2.13 (s, 3H, CH_3 of $NHCOCH_3$), 2.18 (s, 3H, CH_3 of N_4–$COCH_3$), 3.59 (s, 6H, OCH_3 of Ar–OCH_3), 6.78 (s, 1H, C_5–H), 8.62 (s, 1H, ArH, quin C_4–H), 7.94 (s, 1H, ArH, quin C_5–H), 7.99 (s, 1H, ArH, quin C_8–H), 11.32 (s, 1H, NHCO). LC–MS (70 eV, *m/z*); 409.6 (M + 1, 31.0), 250.2 (18.3), 208.8 (100). CHN Analysis; Calculated for $C_{17}H_{17}ClN_4O_4S$: C, 49.94; H, 4.19; N, 13.70. Found: C, 50.11; H, 4.22; N, 13.66.

*N-(4-Acetyl-5-(2,6-dichloroquinolin-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)-acetamide (**3i**)*

Pale brown crystals. Yield; 63.7% mp (°C); 205–207. IR (ν_{max} in cm^{-1}); 3359, 2951, 1687, 1619. ^1H NMR (300 MHz, δ ppm, DMSO-d_6); 2.08 (s, 3H, CH_3 of $NHCOCH_3$), 2.15 (s, 3H, CH_3 of N_4–$COCH_3$), 6.50 (s, 1H, C_5–H), 8.78 (s, 1H, ArH, quin C_4–H), 8.65 (s, 1H, ArH, quin C_5–H), 8.12–8.26 (m, 2H, ArH, quin C_7–H, C_8–H), 11.46 (s, 1H, NHCO). LC–MS (70 eV, *m/z*); 384.3 (M + 1, 27.0), 220.2 (20.3), 185.8 (100). CHN Analysis; Calculated for $C_{15}H_{12}Cl_2N_4O_2S$: C, 47.10; H, 3.16; N, 14.62. Found: C, 47.18; H, 3.22; N, 14.59.

*N-(4-Acetyl-5-(6-bromo-2-chloroquinolin-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)-acetamide (**3j**)*

Dark yellow crystals. Yield; 60.8% mp (°C); 222–223. IR (ν_{max} in cm^{-1}); 3400, 2998, 1689, 1617. ^1H NMR (300 MHz, δ ppm, DMSO-d_6); 2.05 (s, 3H, CH_3 of $NHCOCH_3$), 2.20 (s, 3H, CH_3 of N_4–$COCH_3$), 6.78 (s, 1H, C_5–H), 8.69 (s, 1H, ArH, quin C_4–H), 8.58 (s, 1H, Ar–H, quin C_5–H), 8.22–8.34 (m, 2H, ArH, quin C_6–H, C_7–H), 11.46 (s, 1H, NHCO). LC–MS (70 eV, *m/z*); 427.7 (M + 1, 27.0), 310.6 (20.3), 230.7 (100). CHN Analysis; Calculated for $C_{15}H_{12}BrClN_4O_2S$: C, 42.12; H, 2.83; N, 13.10. Found: C, 42.18; H, 2.89; N, 13.15.

Pharmacological evaluation

The title compounds were subjected to pharmacological evaluation viz., anticancer and anti-tubercular activities.

Anticancer activity

Anticancer activity assay was carried out against cervical cancer cell lines (Hela) and involves the following steps. The cell lines were detached by tapping and centrifuged for 6 min at 300 rpm. Eagle's medium was prepared by adding Eagle's powder (500 mg) and sodium bicarbonate (93.74 mg) to 50 ml of distilled warm water. To this, a mixture of antibiotic solution (streptopenicillin, 1 ml), FBS (2.5 ml), gentamycin (25 µl) and fluconazole (50 µl) was added. The prepared media of 200 µl was added into the wells of micro titre culture plate in laminar air flow cabinet. Supernatant solution from the centrifuged cell line was discarded and required quantity of the cell line was transferred into the well containing the media. The test solutions of different concentrations (10, 15, 20, 25 µg/ml) were transferred to well. One well was left without the test solution (control). The cell lines were observed under inverted microscope after 24, 36, 48, 72 h for cell line lyses. The results were recorded and photographs were taken out.

Antitubercular assay

The antitubercular activity of the test compounds was evaluated against standard strain of *Mycobacterium tuberculosis* $H_{37}Rv$. Antibiotic standards used were streptomycin and pyrazinamide. The procedure followed for antitubercular activity involves the use of Middlebrook 7H-9 broth and standard strain of *M. tuberculosis* $H_{37}Rv$. The basal medium was prepared according to manufacturer's instructions (Hi-Media) and sterilized by autoclaving. Then 4.5 ml of broth was poured into each one of the sterile bottles. To this, 0.5 ml of ADC supplement was added. The supplement consists of catalase, dextrose and BSA fraction v. A stock solution was prepared (10 mg/ml). From this, an appropriate amount of solution was transferred to media bottles to achieve final concentrations of 5, 10 and 25 µg/ml. Finally 10 µl suspension of *M. tuberculosis* $H_{37}Rv$ strain (1 lakh organisms/ml adjusted by McFarmland's turbidity standard) was transferred to each of the tubes and incubated at 37°C. Along with this, one growth control without compound and drug controls were also set up. The bottles were inspected for growth twice a week for a period of 3 weeks. The appearance of turbidity indicated the growth and infers the resistance to the compound. The growth was confirmed by making a smear from each bottle and performing a ZN stain.

Conclusions

We have successfully derivatized a potent quinoline moiety with 1,3,4-thiadiazole. The newly synthesized compounds

(**3a**–**j**) have exhibited pharmacological properties viz., anticancer and antitubercular activities. As all these compounds have shown better drug likeliness, drug score and suitable *c* log *P* values, there is a scope for the in vivo and quantitative evaluation for their activities and also for their bioavailability by silico study. SAR study confirmed that **3c**, **3d** and **3f** are potent lead compounds for drug discovery with negligible toxicity.

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