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Synthesis and anti-tuberculosis activity of 2,4-disubstituted quinolines

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Synthesis and anti-tuberculosis activity of a new series of 2,4-disubstituted quinolines have been reported. The most promising compounds have been found to exhibit 99% inhibition at 6.25 μg/mL against drug-sensitive *M. tuberculosis H37Rv* strain and >90% inhibition at 12.5 μg/mL against isoniazid resistant TB strain.

Keywords: Tuberculosis, ring-substituted quinolines, drug-sensitive TB, drug-resistant TB, multi-drug resistant TB, extreme drug-resistant TB

Tuberculosis (TB) has staged a lethal comeback and kills approximately 2 million people each year primarily because of the development of multidrug resistant strains (MDR) by the causative organism, *Mycobacterium tuberculosis* against at least two main first-line anti-TB drugs-isoniazid and rifampicin[1]. Recently, deadly new strains of tuberculosis (TB), virtually untreatable using the drugs currently available, appear to be spreading across the globe. The new strains are known as extreme drug-resistant TB (XDR-TB) is MDR-TB that is resistant to first-line drugs and at least three out of six classes of second-line drugs. Importantly, second-line drugs are the last line of defence against TB and there are no third-line drugs. Moreover, XDR-TB has a mortality rate of >90% and appears to be the main cause of deaths (60-70%) in patients with HIV/TB coinfection[2,3]. However, no new TB specific drug has been introduced in past forty years possibly due to lack of interest. To overcome the menace of MDR and XDR-TB, new structural classes of anti-TB drugs are urgently required[4]. The new structural classes of drugs possibly acting on TB drug targets different from that known for existing drugs may allow emergence of new treatment regimens and/or supplement existing regimens to combat MDR and XDR-TB.

Previously, we have reported discovery of ring-substituted quinolines as an entirely new structural class of anti-TB agents[5-11]. The analogs of this class have exhibited promising anti-TB activities against a panel of drug-sensitive and drug-resistant strains. The absence of cross-resistance with known TB drugs indicate that ring-substituted quinoline analogs possibly act by mechanism(s) of action different to those known for currently used drugs. Therefore, ring-substituted quinolines are considered an important and promising new structural class of anti-TB drugs. In continuation of our efforts in structural optimization of this class, this paper reports synthesis and anti-tuberculosis activity of a new series of 2,4-disubstituted quinolines **10**-**14** (**Figure 1**).

Results and Discussion

Chemistry

The synthesis of intermediate 2-hydroxy-4-quinolinecarboxylic acid **6** required for the synthesis of **10**-**14** was accomplished using two step procedure starting from isatin. The treatment of commercially available isatin **4** with acetic anhydride for 30 min at 160-170°C afforded 1-acetyl-1*H*-indole-2,3-dione **5**. The compound, **5** upon reaction with aqueous 1.5 *N* NaOH at 100°C for 1 hr produced 2-hydroxy-4-quinolinecarboxylic acid **6**. The one-pot reaction of **6** with thionyl chloride ($SOCl_2$) in anhydrous dichloroethane (DCE) at 80°C for 2 hr gave an intermediate acid chloride **7**, which upon reaction *in situ* with various aliphatic/aromatic/cyclic amines (e.g., aniline, benzylamine, *n*-hexylamine, morpholine and *N*-methylpiperazine) in the presence of triethylamine

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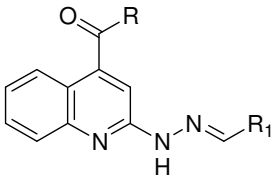
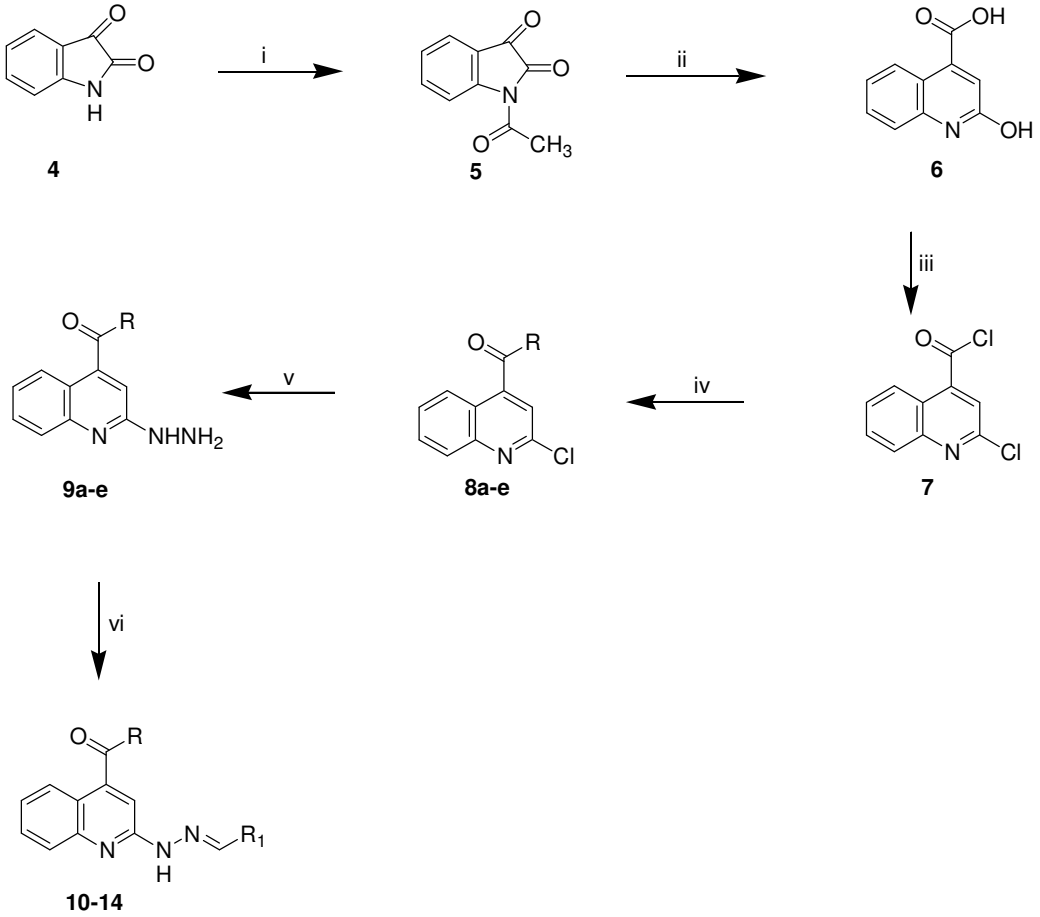


Fig. 1. General structure of synthesized 2,4-disubstituted quinolines



Scheme I, (i). $(CH_3CO)_2O$, 160-170 °C, 30 min; (ii). 1.5 N NaOH, reflux, 100 °C, 1h; (iii). $SOCl_2$, DCE, 80 °C, 2h; (iv). amine, Et_3N , DCM, 4 °C, 2h; (v). $NH_2NH_2.H_2O$, 95%EtOH, 80 °C, 8h; (vi). R_1CHO, abs. EtOH, 80 °C, 2h.

(Et_3N) in anhydrous dichloromethane (DCM) at 4°C for 2 hr afforded 2-chloro-quinoline-4-carboxylic acid alkylamides **8a-c** and (2-chloro-quinolin-4-yl)alkyl-methanones **8d-e**. The latter compounds **8a-e** upon reaction with hydrazine hydrate in 95% ethyl alcohol at 80°C for 8 hr produced hydrazino ring-substituted quinoline derivatives **9a-e**. Finally, hydrazines **9a-e** upon reaction with several commercially available aliphatic, aromatic or heteroaromatic aldehydes in abs. ethyl alcohol at 80°C for 2 hr produced *N*4-substituted-2-(*N′*-substitutedhydrazino)-4-quinoline-carboxamides **10-12** and 2-substitutedhydrazino-4-quinolylmethanones **13-14** (**Scheme I**) in varying yields.

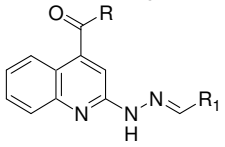
Biological activity

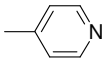
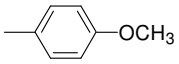
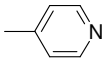
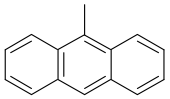
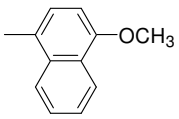
In vitro activity of the synthesized derivatives against *M. tuberculosis H37Rv* strains (ATCC 27294, susceptible both to rifampicin and isoniazid) was carried out using the Microplate Alamar Blue Assay

(MABA) at a concentration of 6.25 μg/mL[12]. Compounds exhibiting fluorescence were then tested in the BACTEC 460 radiometric system[13] and the % inhibition are summarized in **Table I**. Isoniazid (99% inhibition, MIC = 1 μg/mL) was included, as a standard drug, for comparison.

Most of the phenylamide derivatives (**10a-h**, **Table I**) exhibit modest inhibition against drug sensitive *M. tuberculosis H37Rv* at 6.25 μg/mL. The most potent analog **10h** (R = 4-OCH_3-C_6H_4) displayed 99% inhibition at the test concentration (MIC = 6.25 μg/mL). Similarly, benzylamide derivatives (**11a-j**,

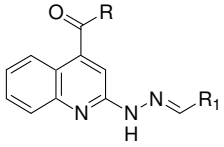
Table I — *In vitro* antimycobacterial activity evaluation of *N*4-substituted-2-(*N'*-substitutedhydrazino)-4-quinolinecarboxamides **10-12** and 2-substitutedhydrazino-4-quinolylmethanones **13-14** against drug-sensitive *M. tuberculosis H37Rv* strain.



Compd	R	R_1	(%) Inhibition
10a	NHC_6H_5		14
10b	NHC_6H_5		10
10c	NHC_6H_5		10
10d	NHC_6H_5		26
10e	NHC_6H_5	$CH(CH_3)_2$	11
10f	NHC_6H_5	CH_2CH_3	12
10g	NHC_6H_5	C_6H_5	11
10h	NHC_6H_5		99
11a	$NHCH_2C_6H_5$		14
11b	$NHCH_2C_6H_5$		23
11c	$NHCH_2C_6H_5$		20
11d	$NHCH_2C_6H_5$		30
11e	$NHCH_2C_6H_5$		20
11f	$NHCH_2C_6H_5$		16
11g	$NHCH_2C_6H_5$	$CH(CH_3)_2$	42
11h	$NHCH_2C_6H_5$	CH_2CH_3	27
11i	$NHCH_2C_6H_5$	C_6H_5	21

—*Contd*

Table I — *In vitro* antimycobacterial activity evaluation of *N*4-substituted-2-(*N′*-substitutedhydrazino)-4-quinolinecarboxamides **10-12** and 2-substitutedhydrazino-4-quinolylmethanones **13-14** against drug-sensitive *M. tuberculosis H37Rv* strain.(— *Contd)*



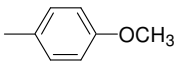
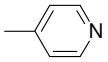
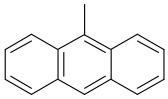
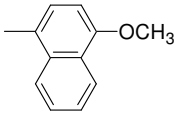
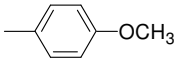
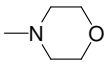
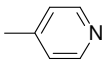
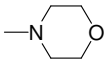
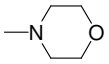
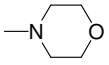
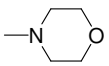
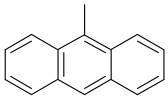
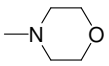
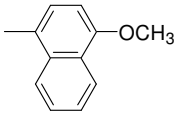
Compd	R	R_1	(%) Inhibition
11j	$NHCH_2C_6H_5$		99
12a	$NH(CH_2)_5CH_3$		30
12b	$NH(CH_2)_5CH_3$		10
12c	$NH(CH_2)_5CH_3$		15
12d	$NH(CH_2)_5CH_3$		21
12e	$NH(CH_2)_5CH_3$		23
12f	$NH(CH_2)_5CH_3$		40
12g	$NH(CH_2)_5CH_3$	$CH(CH_3)_2$	42
12h	$NH(CH_2)_5CH_3$	C_6H_5	21
12i	$NH(CH_2)_5CH_3$		40
13a			0
13b			0
13c			0
13d			0
13e			0
13f			7

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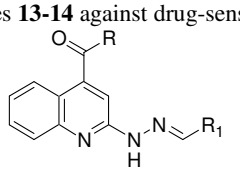
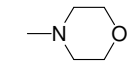
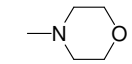
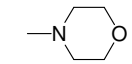
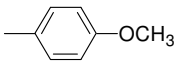
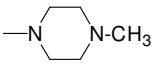
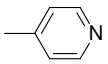
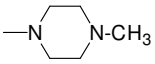
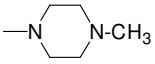
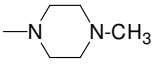
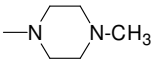
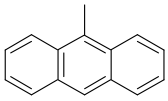
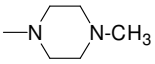
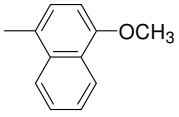
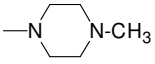
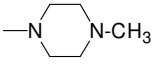
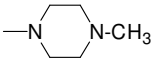
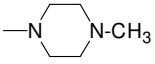
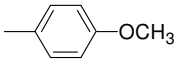
Table I — *In vitro* antimycobacterial activity evaluation of *N*4-substituted-2-(*N'*-substitutedhydrazino)-4-quinolinecarboxamides **10-12** and 2-substitutedhydrazino-4-quinolylmethanones **13-14** against drug-sensitive *M. tuberculosis H37Rv* strain. (— *Contd*)



Compd	R	R_1	(%) Inhibition
13g		$CH(CH_3)_2$	0
13h		C_6H_5	3
13i			0
14a			1
14b			28
14c			21
14d			10
14e			10
14f			18
14g		$CH(CH_3)_2$	52
14h		CH_2CH_3	6
14i		C_6H_5	9
14j			30

*All compounds were tested at 6.25 μg/mL and (%) inhibition is given in the table.

Table I) show modest inhibition, and the most effective analog **11j** (R = 4-OCH_3-C_6H_4) exhibit 99% inhibition at 6.25 μg/mL, while **11g** [R = $CH(CH_3)_2$] produced 42% inhibition in the preliminary screen. All of the *n*-hexylamide derivatives (**12a-j**, **Table I**) exhibit low inhibition (≤42%) against *M. tuberculosis* at the tested dose of 6.25 μg/mL, while the morpholinomethanone derivatives (**13a-i**, **Table I**) were found to be totally inactive. Interestingly, some of the 4-methylpiperazinomethanone derivatives (**14a-j**, **Table I**) were found to show modest activity, and most active analog **14g** [R = $CH(CH_3)_2$] exhibit 52% inhibition at the MIC of 6.25 μg/mL. These observations clearly demonstrate that the anti-tuberculosis

activity of the 2,4-disubstituted quinoline derivatives is significantly affected by substitutions both on the C-4 position of the quinoline ring and the hydrazone substitution at the C-2 position. As far as substitution at the C-4 position of the quinolines nucleus is concerned phenylamide and benzylamide appear to be the most favourable groups, whereas at the C-2 position, a *p*-methoxyphenyl or an isopropyl group helps in the retention of the activity.

Two most active derivatives **10h** and **11j** were also evaluated for antimycobacterial activity against isoniazid resistant strain of *M. tuberculosis H37Rv*. Both analogs displayed promising activity (92 and 95% inhibition, respectively) at a test concentration of 12.5 μg/mL.

Experimental Section

Melting points were recorded on a Mettler DSC 851 instrument or a capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a 300 MHz Bruker FT-NMR (Avance DPX300) spectrometer using tetramethylsilane as internal standard and the chemical shifts are reported in δ units. Mass spectra were recorded on a HRMS (Finnigan Mat LCQ) spectrometer using ESI mode. Elemental analyses were carried out on an Elementar Vario EL spectrometer. Chromatographic purifications were carried out with silica gel 60 (230-400 mesh) and TLC (silica gel) was done on silica gel coated (Merck Kiesel 60 F_{254}, 0.2 mm thickness) sheets. All chemicals were purchased from Aldrich Chemical Ltd (Milwaukee, WI, USA). Solvents used for the chemical synthesis were acquired from commercial sources, were of analytical grade and used without further purification unless otherwise stated.

Synthesis of 1-acetyl-1*H*-indole-2,3-dione 5. A mixture of isatin (**4**, 25 g, 160 mmoles) and acetic anhydride (60 mL) was refluxed for 30 min at 160-170°C. The reaction mixture was allowed to stand at ambient temperature, and a yellow solid precipitated out. The precipitated solid was filtered and washed with acetic anhydride (20 mL). The combined filtrate was evaporated to yield additional amount of product. Combined product was suspended in toluene (100 mL), stirred for 10 min and filtered to afford 1-acetyl-1*H*-indole-2,3-dione **5** as crystalline yellow solid. Yield: 93%; m.p. 136°C; ^{1}H NMR ($CDCl_3$): δ 8.45 (d, 1H, *J* = 8.3 Hz), 7.80 (d, 1H, *J* = 7.5 Hz), 7.73 (m, 1H), 7.36 (m, 1H), 2.77 (s, 3H), ESIMS: *m/z* 190 (M+1); Analysis for $C_{10}H_7NO_3$ (189.2), Calcd, C, 63.49; H, 3.73; N, 7.40; Found, C, 63.77; H, 3.49; N, 7.65.

Synthesis of 2-hydroxy-4-quinolinecarboxylic acid 6. To a solution of NaOH (11.2 g, 0.28 mmole) in water (220 mL), 1-acetyl-1*H*-indole-2,3-dione (**5**, 24 g, 0.127 mmole) was added and reaction mixture was heated under reflux for 1 hr. The resulting mixture was cooled and added to acetone (100 mL). Mixture was stirred for 30 min at ambient temperature and separated solid filtered to afford 2-hydroxy-4-quinolinecarboxylic acid **6**. Yield: 60%; m.p. 124°C; ^{1}H NMR (CD_3OD): δ 7.58 (d, 1H, *J* = 7.8 Hz), 7.39 (d, 1H, *J* = 8.1 Hz), 7.32 (m, 1H), 7.29 (m, 1H), 7.05 (s, 1H); ESIMS: *m/z* 190 (M+1); Analysis for $C_{10}H_7NO_3$ (189.2), Calcd, C, 63.49; H, 3.73; N, 7.40; Found, C, 63.45; H, 3.70; N, 7.43.

Typical procedure for the synthesis of 2-chloro-quinoline-4-carboxylic acid alkylamides 8a-c and (2-chloro-quinolin-4-yl)alkyl-methanones 8d-e A mixture of 2-hydroxy-4-quinolinecarboxylic acid (**6**, 2 g, 10 mmoles) and thionyl chloride (3 mL, 37 mmoles) in anhydrous dichloroethane (15 mL) was heated at 80°C for 2 hr. Excess of $SOCl_2$ and all dichloroethane were removed under reduced pressure to afford intermediate acid chloride **7** *in situ*. The latter compound **7** was dissolved in anhydrous dichloromethane (15 mL) reacted with aliphatic or aromatic amine (aniline, benzylamine, *n*-hexylamine, morpholine, *N*-methylpiperazine, 12 mmoles) in the presence of triethylamine (1.6 mL, 12 mmoles) at 4°C for 2 hr. The reaction mixture was diluted with DCM (50 mL) and washed with water (2 × 25 mL) and finally with brine solution (25 mL). The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure to yield off-white residue that was purified by column chromatography using ethyl acetate/hexanes (10:90) as eluant to provide **8a-e**.

2-Chloro-quinoline-4-carboxylic acid phenyl-amide 8a. Yield: 55%; m.p. 198-200°C; IR (KBr): 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.21 (d, 1H, *J* = 8.3 Hz), 8.03 (d, 1H, *J* = 8.3 Hz), 7.95 (s, 1H), 7.74 (m, 3H), 7.59 (m, 1H), 7.46 (m, 2H), 7.21 (m, 1H), ESIMS: *m/z* 283 (M+1); Analysis for $C_{16}H_{11}ClN_2O$ (282.7), Calcd: C, 67.97; H, 3.92; N, 9.91; Found: C, 67.77; H, 3.92; N, 9.87.

2-Chloro-quinoline-4-carboxylic acid benzyl-amide 8b. Yield: 57%; m.p. 212-214°C; IR (KBr): 1722 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.20 (d, 1H, *J* = 8.3 Hz), 8.03 (d, 1H, *J* = 8.4 Hz), 7.77 (m, 1H), 7.61 (m, 1H), 7.35 (m, 6H), 4.72 (s, 2H); APCIMS: *m/z* 297 (M+1); Analysis for $C_{17}H_{13}ClN_2O$ (296.1), Calcd: C,

68.81; H, 4.42; N, 9.44; Found: C, 68.93; H, 4.57; N, 9.63.

2-Chloro-quinoline-4-carboxylic acid hexyl-amide 8c. Yield: 60%; m.p. 101-103°C; IR (KBr): 1638 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.14 (d, 1H, *J* = 8.3 Hz), 8.01 (d, 1H, *J* = 8.4 Hz), 7.75 (m, 1H), 7.59 (m, 1H), 7.32 (s, 1H), 6.15 (bs, 1H), 3.52 (m, 2H), 1.68-0.89 (m, 11H); ESIMS: *m/z* 292 (M+1); Analysis for $C_{16}H_{19}ClN_2O$ (291.0), Calcd: C, 66.09; H, 6.59; N, 9.63; Found: C, 65.79; H, 6.89; N, 9.87.

(2-Chloro-quinolin-4-yl)-morpholin-4-yl-methanone 8d. Yield: 56%; m.p. 146-148°C; IR (KBr): 1645 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.32 (d, 1H, *J* = 9.3 Hz), 7.79 (m, 2H), 7.64 (m, 1H), 7.33 (s, 1H), 4.03-3.18 (m, 8H); APCIMS : *m/z* 278 (M+1); Analysis for $C_{14}H_{13}ClN_2O_2$ (277.0), Calcd: C, 60.77; H, 4.74; N, 10.12; Found: C, 60.49; H, 4.56; N, 10.34.

(2-Chloro-quinolin-4-yl)-(4-methyl-piperazin-1-yl)methanone 8e. Yield: 54%; m.p. 101-103°C; IR (KBr): 1672 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.05 (d, 1H, *J* = 8.0 Hz), 7.78 (m, 2H), 7.61 (m, 1H), 7.31 (s, 1H), 3.90-2.27 (m, 8H), 2.30 (s, 3H); ESIMS: *m/z* 291 (M+1); Analysis for $C_{15}H_{16}ClN_3O$ (290.0), Calcd: C, 62.18; H, 5.57; N, 14.50; Found: C, 62.24; H, 5.62; N, 14.70.

General procedure for the synthesis of *N*-substituted-2-hydrazino-4-quinolinecarboxamides 9a-c and 2-hydrazino-4-quinolyl-substitutedmethanones 9d-e. A mixture of amide (**8a-e**, 3.5 mmoles) and hydrazine hydrate (20 mmoles) in 95% ethyl alcohol (20 mL) was heated at 80°C for 8 hr. The solvent was evaporated under reduced pressure and residue diluted with ethyl acetate (50 mL), washed with water (2 × 20 mL), brine solution (20 mL) and organic layer was dried over Na_2SO_4. Solvent was concentrated under reduced pressure to afford **9a-e**.

***N*-Phenyl-2-hydrazino-4-quinolinecarboxamide 9a.** Yield: 98%; semi-solid; IR (KBr): 3213, 1645 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.25 (bs, 1H), 7.98 (d, 1H, *J* = 8.5 Hz), 7.75 (m, 3H), 7.55 (m, 1H), 7.35 (m, 2H), 7.25 (m, 1H), 7.14 (m, 1H), 7.70 (s, 1H); ESIMS: *m/z* 279 (M+1); Analysis for $C_{16}H_{14}N_4O$, (278.1), Calcd: C, 69.05; H, 5.07; N, 20.13; Found: C, 69.06; H, 5.13; N, 20.18.

***N*-Benzyl-2-hydrazino-4-quinolinecarboxamide 9b.** Yield: 98%; semi-solid; IR (KBr): 3264, 1645 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.71 (bs, 1H), 8.01 (d, 1H, *J* = 7.4 Hz), 7.81 (m, 2H), 7.59 (m, 2H), 7.36 (m, 3H), 7.27 (m, 1H), 7.17 (m, 1H), 4.63 (s, 2H); ESIMS: *m/z* 293 (M+1); Analysis for $C_{17}H_{16}N_4O$ (292.3), Calcd: C, 69.85; H, 5.52; N, 19.17; Found: C, 69.89; H, 5.60; N, 19.21.

***N*-Hexyl-2-hydrazino-4-quinolinecarboxamide 9c.** Yield: 98%; semi-solid; IR (KBr): 3274, 1678 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.93 (d, 1H, *J* = 8.1 Hz), 7.72 (d, 1H, *J* = 8.3 Hz), 7.58 (m, 1H), 7.29 (m, 1H), 6.85 (s, 1H), 3.52 (m, 2H), 1.68-0.89 (m, 11H); ESIMS: *m/z* 287 (M+1); Analysis for $C_{16}H_{22}N_4O$ (286.4), Calcd: C, 67.11; H, 7.74; N, 19.56; Found: C, 65.79; H, 6.89; N, 9.87.

2-Hydrazino-4-quinolyl-morpholinomethanone 9d. Yield: 98%; semi-solid; IR (KBr): 3259, 1648 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.54 (m, 3H), 7.22 (m, 1H), 6.78 (s, 1H), 4.03-3.18 (m, 8H); APCIMS: *m/z* 273 (M+1); Analysis for $C_{14}H_{16}N_4O_2$ (272.1), Calcd: C, 61.75; H, 5.92; N, 20.58; Found: C, 61.83, H, 5.98, N, 20.65.

2-Hydrazino-4-quinolyl-4-methylpiperazinomethanone 9e. Yield: 94%; semi-solid; IR (KBr): 3312, 1698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.75 (d, 1H, *J* = 8.2 Hz), 7.56 (m, 2H), 7.29 (m, 1H), 6.76 (s, 1H), 3.98-2.20 (m, 8H), 2.31 (s, 3H); ESIMS: *m/z* 286 (M+1); Analysis for $C_{15}H_{19}N_5O$ (285.2), Calcd: C, 63.14; H, 6.71; N, 24.54; Found: C, 63.19; H, 6.85; N, 24.58.

General procedure for the synthesis of *N*4-substituted-2-(*N′*-substitutedhydrazino)-4-quinolinecarboxamides 10-12 and 2-substitutedhydrazino-4-quinolylmethanones 13-14.

To a mixture of **9a-e** (0.5 mmole) in abs. ethyl alcohol (10 mL) was added commercially available aliphatic, aromatic or heteroaromatic aldehydes (0.6 mmole). The reaction mixture was stirred at 80°C for 2 hr. Solvent was removed under reduced pressure. The resulting mixture was purified by column chromatography on neutral alumina using ethyl acetate/hexanes (15:85) as eluant to produce **10-14**.

***N*4-Phenyl-2-(*N′*-pyridin-4-ylmethylenehydrazino)-4-quinolinecarboxamide 10a.** Yield: 45%; m.p. 221-213°C; IR (KBr): 3283, 1647 cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.91 (bs, 1H), 10.81 (bs, 1H), 8.57 (d, 2H, *J* = 5.8 Hz), 8.08 (s, 1H), 7.91 (d, 1H, *J* = 8.1 Hz), 7.74 (m, 7H), 7.39 (m, 3H), 7.16 (m, 1H); ESIMS: *m/z* 368 (M+1); Analysis for $C_{22}H_{17}N_5O$ (367.4), Calcd: C, 71.92; H, 4.66; N, 19.06; Found: C, 71.85; H, 4.58; N, 19.02.

***N*4-Phenyl-2-(*N′*-pyridin-3-ylmethylenehydrazino)-4-quinolinecarboxamide 10b.** Yield: 60%; m.p. >250°C; IR (KBr): 3313, 1655 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.90 (bs, 1H), 9.05 (s, 1H), 8.63 (d, 1H, *J* = 4.4 Hz), 8.46 (d, 1H, *J* = 7.9 Hz), 8.28 (s, 1H), 7.83 (m, 5H), 7.60 (m, 1H), 7.43 (m, 3H), 7.18 (m, 1H); ESIMS: *m/z* 368 (M+1); Analysis for $C_{22}H_{17}N_5O$

(367.4), Calcd: C, 71.92; H, 4.66; N, 19.06; Found: C, 71.97; H, 4.65; N, 19.09.

***N*4-Phenyl-2-(*N′*-furan-2-ylmethylenehydrazino)-4-quinolinecarboxamide 10c.** Yield: 59%; m.p. >250°C; IR (KBr): 3291, 1654 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.32 (bs, 1H), 7.99 (m, 2H), 7.78 (m, 4H), 7.54 (s, 1H), 7.57 (m, 2H), 7.38 (m, 2H), 7.16 (m, 1H), 6.67 (m, 1H), 6.50 (m, 1H); ESIMS: *m/z* 357 (M+1); Analysis for $C_{21}H_{16}N_4O_2$ (356.4), Calcd: C, 70.77; H, 4.53; N, 15.72; Found: C, 70.65; H, 4.49; N, 15.67.

***N*4-Phenyl-2-(*N′*-thiophen-2-ylmethylenehydrazino)-4-quinolinecarboxamide 10d.** Yield: 59%; m.p. >250°C (dec.); IR (KBr): 3283, 1647 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.06 (m, 2H), 7.76 (m, 2H), 7.58 (m, 2H), 7.42 (m, 3H), 7.33 (m, 2H), 7.21 (m, 2H), 7.07 (s, 1H); ESIMS: *m/z* 373 (M+1); Analysis for $C_{21}H_{16}N_4OS$ (372.5), Calcd: C, 67.72; H, 4.33; N, 15.04; Found: C, 67.83; H, 4.37; N, 15.12.

***N*4-Phenyl-2-(*N′*-isobutylidenehydrazino)-4-quinolinecarboxamide 10e.** Yield: 63%; m.p. 195-197°C; IR (KBr): 3273, 1643 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.31 (bs, 1H), 7.99 (d, 1H, *J* = 8.2 Hz), 7.81 (m, 2H), 7.58 (m, 3H), 7.37 (m, 2H), 7.26 (m, 2H), 7.14 (m, 1H), 2.59 (m, 1H), 1.13 (d, 6H, *J* = 6.8 Hz); ESIMS: *m/z* 333 (M+1); Analysis for $C_{20}H_{20}N_4O$ (332.4), Calcd: C, 72.27; H, 6.06; N, 16.86; Found: C, 71.61; H, 5.84; N, 7.84.

***N*4-Phenyl-2-(*N′*-propylidenehydrazino)-4-quinolinecarboxamide 10f.** Yield: 64%; m.p. 201-203°C; IR (KBr): 3283, 1647 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.31 (bs, 1H), 7.99 (d, 1H, *J* = 8.2 Hz), 7.81 (m, 2H), 7.58 (m, 3H), 7.33 (m, 3H), 7.26 (m, 1H), 7.14 (m,1H), 2.35 (m, 2H), 1.16 (m, 3H); ESIMS: *m/z* 319 (M+1); Analysis for $C_{19}H_{18}N_4O$ (318.4), Calcd: C, 71.68; H, 5.70; N, 17.60; Found: C, 71.62; H, 5.65; N, 17.58.

***N*4-Phenyl-2-(*N′*-benzylidenehydrazino)-4-quinolinecarboxamide 10g.** Yield: 62%; m.p. 202-204°C; IR (KBr): 3283, 1647 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.39 (bs, 1H), 8.03 (m, 2H), 7.83 (m, 3H), 7.72 (m, 3H), 7.59 (m, 1H), 7.34 (m, 6H), 7.16 (m, 1H); ESIMS: *m/z* 367 (M+1); Analysis for $C_{23}H_{18}N_4O$ (366.4), Calcd: C, 75.39; H, 4.95; N, 15.29; Found: C, 65.79; H, 6.89; N, 9.87.

***N*4-Phenyl-2-(*N′*-4-methoxybenzylidenehydrazino)-4-quinolinecarboxamide 10h.** Yield: 66%; m.p. 205-208°C; IR (KBr): 3283, 1647 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.33 (bs, 1H), 8.01 (m, 2H), 7.82 (m, 3H), 7.70 (m, 3H), 7.56 (m, 2H), 7.38 (m, 1H), 7.30 (m, 1H), 7.16 (m, 1H), 6.92 (d, 2H, *J* = 8.4 Hz), 3.67 (s, 3H); ESIMS: *m/z* 397 (M+1); Analysis for $C_{24}H_{20}N_4O_2$ (396.4), Calcd: C, 72.71; H, 5.08; N, 14.13; Found: C, 72.65; H, 5.01; N, 14.01.

***N*4-Benzyl-2-(*N′*-pyridin-4-ylmethylenehydrazino)-4-quinolinecarboxamide 11a.** Yield: 69%; m.p. >250°C; IR (KBr): 3283, 1647 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.87 (bs, 1H), 8.60 (d, 2H, *J* = 5.0 Hz), 8.06 (s, 1H,), 7.92 (d, 1H, *J* = 7.8 Hz), 7.66 (m, 5H), 7.37 (m, 6H), 4.58 (s, 2H); APCIMS: *m/z* 382 (M+1); Analysis for $C_{23}H_{19}N_5O$ (381.4), Calcd: C, 72.42; H, 5.02; N, 18.36; Found: C, 72.65; H, 5.09; N, 18.45.

***N*4-Benzyl-2-(*N′*-pyridin-3-ylmethylenehydrazino)-4-quinolinecarboxamide 11b.** Yield: 63%; m.p. >250°C; IR (KBr): 3268, 1644 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.71 (bs, 1H), 8.87 (s, 1H), 8.54 (d, 1H, *J* = 4.7 Hz), 8.14 (m, 2H), 7.94 (m, 1H), 7.69 (m, 3H), 7.39 (m, 7H), 4.57 (s, 2H); APCIMS: *m/z* 382 (M+1); Analysis for $C_{23}H_{19}N_5O$ (381.4), Calcd: C, 72.42; H, 5.02; N, 18.36; Found: C, 72.55; H, 4.87; N, 18.59.

***N*4-Benzyl-2-(*N′*-furan-2-ylmethylenehydrazino)-4-quinolinecarboxamide 11c.** Yield: 30%; m.p. 232-234°C; IR (KBr): 3404, 1602 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.94 (bs, 1H), 7.90 (s, 1H), 7.63 (m, 5H), 7.35 (m, 6H), 6.65 (m, 1H), 6.51 (m, 1H), 4.65 (s, 2H); APCIMS: *m/z* 371 (M+1); Analysis for $C_{22}H_{18}N_4O_2$ (370.4), Calcd: C, 71.34; H, 4.90; N, 15.13; Found: C, 71.48; H, 4.73; N, 15.34.

***N*4-Benzyl-2-(*N′*-thiophen-2-ylmethylenehydrazino)-4-quinolinecarboxamide 11d.** Yield: 29%; m.p. 101-103°C; IR (KBr): 3272, 1642 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.50 (bs, 1H), 8.29 (s, 1H), 7.86 (d, 1H, *J* = 7.9 Hz), 7.55 (m, 3H), 7.42 (s, 1H), 7.35 (m, 7H), 7.10 (m, 1H), 4.56 (s, 2H); APCIMS: *m/z* 387 (M+1); Analysis for $C_{22}H_{18}N_4OS$ (386.5), Calcd: C, 68.37; H, 4.69; N, 14.50; Found: C, 68.47; H, 4.88; N, 14.63.

***N*4-Benzyl-2-(*N′*-anthracene-9-ylmethylenehydrazino)-4-quinolinecarboxamide 11e.** Yield: 47%; m.p. 226-227°C; IR (KBr): 3461, 1638 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.75 (m, 2H), 8.50 (m, 1H), 8.07 (m, 3H), 7.75 (m, 2H), 7.57 (m, 6H) 7.32 (m, 6H), 4.60 (s, 2H); ESIMS: *m/z* 481 (M+1); Analysis for $C_{32}H_{24}N_4O$ (480.6), Calcd: C, 79.98; H, 5.03; N, 11.66; Found: C, 79.93; H, 5.07; N, 11.63.

***N*4-Benzyl-2-(*N′*-2-methoxynaphthalen-1-ylmethylenehydrazino)-4-quinolinecarbox-amide 11f.** Yield: 49%; m.p. 220-222°C; IR (KBr): 3279, 1633

cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.80 (s, 1H), 8.03 (d, 1H, *J* = 8.4 Hz), 7.85 (m, 2H), 7.71 (m, 3H), 7.57 (m, 1H), 7.42 (m, 4H), 7.32 (m, 5H), 4.60 (s, 2H), 4.02 (s, 3H); APCIMS: *m/z* 461 (M+1); Analysis for $C_{29}H_{24}N_4O_2$ (460.5), Calcd: C, 75.63; H, 5.25; N, 12.17; Found: C, 75.50; H, 5.21; N, 12.10.

***N*4-Benzyl-2-(*N′*-isobutylidenehydrazino)-4-quinolinecarboxamide 11g.** Yield: 64%; m.p. 198-200°C; IR (KBr): 3255, 1643 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.33 (d, 1H, *J* = 8.1 Hz), 8.22 (d, 1H, *J* = 8.5 Hz), 7.73 (m, 2H), 7.57 (m, 2H), 7.36 (m, 5H), 4.68 (s, 2H), 2.61 (m, 1H), 1.13 (d, 6H, *J* = 6.8 Hz); APCIMS: *m/z* 347 (M+1); Analysis for $C_{21}H_{22}N_4O$ (346.4), Calcd: C, 72.81; H, 6.40; N, 16.17; Found: C, 73.06; H, 6.35; N, 16.20.

***N*4-Benzyl-2-(*N′*-propylidenehydrazino)-4-quinolinecarboxamide 11h.** Yield: 57%; m.p. 203-205°C; IR (KBr): 3461, 1631 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.94 (bs, 1H), 7.83 (d, 1H, *J* = 8.3 Hz), 7.59 (m, 2H), 7.41 (m, 6H), 7.29 (m, 2H), 4.53 (s, 2H), 2.28 (m, 2H), 1.07 (m, 3H); APCIMS: *m/z* 333 (M+1); Analysis for $C_{20}H_{20}N_4O$ (332.2), Calcd: C, 72.27; H, 6.06; N, 16.86; Found: C, 72.45; H, 6.34; N, 16.99.

***N*4-Benzyl-2-(*N′*-benzylidenehydrazino)-4-quinolinecarboxamide 11i.** Yield: 70%; m.p. 199-201°C; IR (KBr): 3273, 1651 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.10 (bs, 1H), 8.10 (s, 1H), 7.86 (d, 1H, *J* = 8.1 Hz), 7.65 (m, 6H), 7.41 (m, 6H), 7.31 (m, 2H), 4.56 (s, 2H); ESIMS: *m/z* 381 (M+1); Analysis for $C_{24}H_{20}N_4O$ (380.4), Calcd: C, 75.77; H, 5.30; N, 14.73; Found: C, 75.89; H, 5.45; N, 14.87.

***N*4-Benzyl-2-(*N′*-4-methoxybenzylidenehydrazino)-4-quinolinecarboxamide 11j.** Yield: 67%; m.p. 101-103°C; IR (KBr): 3287, 1657 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.38 (bs, 1H), 8.05 (s, 1H), 7.87 (m, 1H), 7.62 (m, 5H), 7.34 (m, 6H), 7.00 (d, 2H, *J* = 8.2 Hz), 4.56 (s, 2H), 3.80 (s, 3H); APCIMS: *m/z* 411 (M+1); Analysis for $C_{25}H_{22}N_4O_2$ (410.4), Calcd: C, 73.15; H, 5.40; N, 13.65; Found: C, 72.86; H, 5.34; N, 13.88.

***N*4-Hexyl-2-(*N′*-pyridin-4-ylmethylenehydrazino)-4-quinolinecarboxamide 12a.** Yield: 61%; m.p. 201-203°C; IR (KBr): 3296, 1642 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.97 (bs, 1H), 8.58 (d, 2H, *J* = 8.4 Hz), 8.05 (m, 3H), 7.56 (m, 5H), 3.52 (m, 2H), 1.68-0.7 (m, 11H); APCIMS: *m/z* 376 (M+1); Analysis for $C_{22}H_{25}N_5O$ (375.5), Calcd: C, 70.38; H, 6.71; N, 18.65; Found: C, 70.35; H, 6.65; N, 18.68.

***N*4-Hexyl-2-(*N′*-pyridin-3-ylmethylenehydrazino)-4-quinolinecarboxamide 12b.** Yield: 50%; m.p. 210-212°C; IR (KBr): 3230, 1634 cm^{-1}; ^1H NMR (CD_3OD): δ 10.94 (bs, 1H), 8.82 (s, 1H), 8.58 (d, 1H, *J* = 3.6 Hz), 8.05 (m, 2H), 7.71 (m, 4H), 7.33 (m, 2H), 3.57 (m, 2H), 1.88-0.91 (m, 11H); APCIMS: *m/z* 376 (M+1); Analysis for $C_{22}H_{25}N_5O$ (375.5), Calcd: C, 70.38; H, 6.71; N, 18.65; Found: C, 70.32; H, 6.63; N, 18.69.

***N*4-Hexyl-2-(*N′*-furan-2-ylmethylenehydrazino)-4-quinolinecarboxamide 12c.** Yield: 50%; m.p. 215-217°C; IR (KBr): 3230, 1634 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.62 (bs, 1H), 8.52 (d, 1H, *J* = 7.4 Hz), 8.04 (m, 3H), 7.70 (m, 3H), 6.90 (m, 1H), 6.65 (m, 1H), 3.50 (m, 2H), 1.68-0.89 (m, 11H); APCIMS: *m/z* 365 (M+1); Analysis for $C_{21}H_{24}N_4O_2$ (364.4), Calcd: C, 69.21; H, 6.64; N, 15.37; Found: C, 69.25; H, 6.62; N, 15.32.

***N*4-Hexyl-2-(*N′*-thiophen-2-ylmethylenehydrazino)-4-quinolinecarboxamide 12d.** Yield: 59%; m.p. 230-231°C; IR (KBr): 3230, 1634 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.67 (bs, 1H), 8.54 (d, 1H, *J* = 7.1 Hz), 8.09 (m, 3H), 7.58 (m, 3H), 6.92 (m, 1H), 6.70 (m, 1H), 3.50 (m, 2H), 1.68-0.89 (m, 11H); APCIMS: *m/z* 381 (M+1); Analysis for $C_{21}H_{24}N_4OS$ (380.5), Calcd: C, 66.29; H, 6.36; N, 14.72; Found: C, 66.39; H, 6.41; N, 14.78.

***N*4-Hexyl-2-(*N′*-anthracen-9-ylmethylenehydrazino)-4-quinolinecarboxamide 12e.** Yield: 66%; m.p. 201-203°C; IR (KBr): 3256, 1651 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.64 (m, 2H), 8.03 (s, 1H), 7.64 (m, 6H), 7.54 (m, 3H), 7.37 (m, 3H), 3.58 (m, 2H), 1.68-0.95 (m, 11H); APCIMS: *m/z* 475 (M+1); Analysis for $C_{31}H_{30}N_4O$ (474.6), Calcd: C, 78.45; H, 6.37; N, 11.81; Found: C, 78.49; H, 6.32; N, 11.75.

***N*4-Hexyl-2-(*N′*-2-methoxynaphthalen-1-ylmethylenehydrazino)-4-quinolinecarbox-amide 12f.** Yield: 63%; m.p. 199-201°C; IR (KBr): 3296, 1642 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.17 (m, 1H), 8.61 (s, 1H), 8.05 (m, 1H), 7.84 (m, 3H), 7.71 (m, 1H), 7.59 (m, 2H), 7.41 (m, 1H), 7.30 (m, 2H), 3.98 (s, 3H) 3.54 (m, 2H), 1.68-0.86 (m, 11H); APCIMS: *m/z* 455 (M+1); Analysis for $C_{28}H_{30}N_4O_2$ (454.5), Calcd: C, 73.98; H, 6.65; N, 12.33; Found: C, 73.84; H, 6.73; N, 12.33.

***N*4-Hexyl-2-(*N′*-isobutylidenehydrazino)-4-quinolinecarboxamide 12g.** Yield: 53%; m.p. 211-212°C; IR (KBr): 3294, 1643 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.99 (d, 1H, *J* = 8.2), 7.68 (m, 3H), 7.30 (m, 1H), 7.09 (m, 1H), 3.54 (m, 2H), 2.5 (m, 1H), 1.66-0.89 (m, 11H), 1.15 (d, 6H, *J* = 6.8 Hz); APCIMS: *m/z* 341 (M+1); Analysis for $C_{20}H_{28}N_4O$ (340.4), Calcd: C, 70.56; H, 8.29; N, 16.46; Found: C, 70.59; H, 8.25; N, 16.42.

***N*4-Hexyl-2-(*N′*-benzylidenehydrazino)-4-quinolinecarboxamide 12h.** Yield: 55%; m.p. 215-217°C;

IR (KBr): 3280, 1643 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.01 (d, 1H, *J* = 7.3 Hz), 7.83 (m, 1H), 7.68 (m, 5H), 7.39 (m, 4H), 3.57 (m, 2H,), 1.71-0.90 (m, 11H); APCIMS: *m/z* 375 (M+1); Analysis for $C_{23}H_{26}N_4O$ (374.4), Calcd: C, 73.77; H, 7.00; N, 14.96; Found: C, 73.74; H, 6.89; N, 14.89.

***N*4-Hexyl-2-(*N′*-4-methoxybenzylidenehydrazino)-4-quinolinecarboxamide 12i.** Yield: 43%; m.p. 101-103°C; IR (KBr): 3276, 1645 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.01 (d, 1H, *J* = 8.2 Hz), 7.78 (m, 1H), 7.65 (m, 5H), 7.31 (m, 1H), 6.95 (d, 2H, *J* = 8.5 Hz), 3.87 (s, 3H), 3.56 (m, 2H), 1.71-0.93 (m, 11H); APCIMS: *m/z* 405 (M+1); Analysis for $C_{24}H_{28}N_4O_2$ (404.50), Calcd: C, 71.26; H, 6.98; N, 13.85; Found: C, 71.22; H, 6.93; N: 13.81.

2-(*N′*-Pyridin-4-ylmethylenehydrazino)-4-quinolylmorpholinomethanone 13a. Yield: 65%; m.p. 120-122°C; IR (KBr): 3490, 1620 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.87 (bs, 1H), 8.59 (d, 2H, *J* = 4.7 Hz), 8.06 (s, 1H), 7.67 (m, 6H), 7.39 (m, 1H), 3.82-3.12 (m, 8H); ESIMS: *m/z* 362 (M+1); Analysis for $C_{20}H_{19}N_5O_2$ (361.4), Calcd: C, 66.47; H, 5.30; N, 19.38; Found: C, 66.44; H, 5.27; N, 19.45.

2-(*N′*-Pyridin-3-ylmethylenehydrazino)-4-quinolylmorpholinomethanone 13b. Yield: 61%; m.p. 125-127°C; IR (KBr): 3440, 1634 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.73 (bs, 1H), 8.89 (s, 1H), 8.54 (d, 1H, *J* = 4.0 Hz), 8.19 (d, 1H, *J* = 7.9 Hz), 8.12 (s, 1H), 7.64 (m, 4H), 7.40 (m, 2H), 3.92-3.16 (m, 8H); ESIMS: *m/z* 362 (M+1); Analysis for $C_{20}H_{19}N_5O_2$ (361.4), Calcd: C, 66.47; H, 5.30; N, 19.38; Found: C, 66.57; H, 5.30; N, 19.57.

2-(*N′*-Furan-2-ylmethylenehydrazino)-4-quinolylmorpholinomethanone 13c. Yield: 65%; m.p. 140-141°C; IR (KBr): 3312, 1688 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.52 (bs, 1H), 7.99 (s, 1H), 7.78 (s, 1H), 7.68 (m, 3H), 7.35 (m, 2H), 6.83 (m, 1H), 6.61 (m, 1H), 3.89-3.11 (m, 8H); ESIMS: *m/z* 351 (M+1); Analysis for $C_{19}H_{18}N_4O_3$ (350.4), Calcd: C, 65.13; H, 5.18; N, 15.99; Found: C, 65.05; H, 5.13; N, 15.90.

2-(*N′*-Thiophen-2-ylmethylenehydrazino)-4-quinolylmorpholinomethanone 13d. Yield: 58%; m.p. 130-132°C; IR (KBr): 3370, 1650 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.46 (bs, 1H), 8.22 (s, 1H), 7.54 (m, 4H), 7.27 (m, 3H), 7.04 (m, 1H), 3.70-3.06 (m, 8H); ESIMS: *m/z* 367 (M+1); Analysis for $C_{19}H_{18}N_4O_2S$ (366.4), Calcd: C, 62.28; H, 4.95; N, 15.29; Found: C, 62.40; H, 4.97; N, 15.35.

2-(*N′*-Anthracen-9-ylmethylenehydrazino)-4-quinolylmorpholinomethanone 13e. Yield: 29%; m.p. 150-152°C; IR (KBr): 3298, 1644 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.80 (bs, 1H), 9.32 (s, 1H), 8.67 (m, 3H), 8.16 (d, 2H, *J* = 8.1 Hz), 7.67 (m, 7H), 7.40 (m, 2H), 3.73-3.16 (m, 8H); ESIMS: *m/z* 461 (M+1); Analysis for $C_{29}H_{24}N_4O_2$ (460.5), Calcd: C, 75.63; H, 5.25; N, 12.17; Found: C, 75.57; H, 5.19; N, 12.10.

2-[*N′*-(2-Methoxynaphthalen-1-ylmethylene)hydrazino]-4-quinolylmorpholinomethan-one 13f. Yield: 27%; m.p. 145-147°C; IR (KBr): 3208, 1620 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.60 (bs, 1H), 9.15 (d, 1H, *J* = 8.6 Hz), 8.80 (s, 1H), 8.00 (d, 1H, *J* = 9.1 Hz), 7.92 (d, 1H, *J* = 8.1 Hz), 7.50 (m, 8H), 4.01 (s, 3H), 3.78-3.19 (m, 8H); ESIMS: *m/z* 441 (M+1); Analysis for $C_{26}H_{24}N_4O_3$ (440.5), Calcd: C, 70.89; H, 5.49; N, 12.72; Found: C, 70.95; H, 5.55; N, 12.76.

2-(*N′*-Isobutylidenehydrazino)-4-quinolylmorpholinomethanone 13g. Yield: 31%; m.p. 123-125°C; IR (KBr): 3379, 1667 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.54 (bs, 1H), 8.55 (s, 1H), 7.85 (m, 2H), 7.52 (s, 1H), 7.37 (m, 2H), 3.71-3.21 (m, 8H), 1.86 (m, 1H), 1.12 (d, 6H, *J* = 6.2 Hz); ESIMS: *m/z* 327 (M+1); Analysis for $C_{18}H_{22}N_4O_2$ (326.2), Calcd: C, 66.24; H, 6.79; N, 17.17; Found: C, 66.28; H, 6.73; N, 17.30.

2-(*N′*-Benzylidenehydrazino)-4-quinolylmorpholinomethanone 13h. Yield: 60%; m.p. 125-127°C; IR (KBr): 3431, 1646 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.54 (bs, 1H), 8.11 (s, 1H), 7.69 (m, 5H), 7.53 (s, 1H), 7.41 (m, 4H), 3.87-3.13 (m, 8H); ESIMS: *m/z* 361 (M+1); Analysis for $C_{21}H_{20}N_4O_2$ (360.4), Calcd: C, 69.98; H, 5.59; N, 15.55; Found: C, 69.76; H, 5.21; N, 14.96.

2-[*N*'-(4-Methoxybenzylidene)hydrazino]-4-quinolylmorpholinomethanone 13i. Yield: 66%; m.p. 127-129°C; IR (KBr): 3415, 1640 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.50 (bs, 1H), 8.05 (s, 1H), 7.64 (m, 5H), 7.50 (s, 1H), 7.32 (m, 1H), 6.99 (d, 2H, *J* = 8.46 Hz), 3.80 (s, 3H), 3.75-3.10 (m, 8H); ESIMS: *m/z* 391 (M+1); Analysis for $C_{22}H_{22}N_4O_3$ (390.4), Calcd: C, 67.68; H, 5.68; N, 14.35; Found: C, 67.75; H, 5.75; N, 14.40.

2-(*N*'-Pyridin-4-ylmethylenehydrazino)-4-quinolyl-4-methylpiperazinomethanone 14a. Yield: 53%; m.p. 170-175°C; IR (KBr): 3461, 1633 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.88 (bs, 1H), 8.58 (m, 2H), 8.13 (s, 1H), 7.70 (m, 4H), 7.58 (m, 2H), 7.26 (m, 1H), 3.94-2.20 (m, 8H), 2.28 (s, 3H); ESIMS: *m/z* 375 (M+1); Analysis for $C_{21}H_{22}N_6O$ (374.4), Calcd: C, 67.36; H, 5.92; N, 22.44; Found: C, 67.20; H, 5.85; N, 22.35.

2-(*N*'-Pyridin-3-ylmethylenehydrazino)-4-quinolyl-4-methylpiperazinomethanone 14b. Yield: 60%; m.p. 180-182°C; IR (KBr): 3466, 1690 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.72 (bs, 1H), 8.87 (s, 1H), 8.53 (d, 1H, *J* = 3.2 Hz), 8.17 (d, 1H, *J* = 7.7 Hz), 8.11 (s, 1H), 7.63 (m, 4H), 7.43 (m, 1H), 7.36 (m, 1H), 3.91-2.40 (m, 8H), 2.19 (s, 3H); ESIMS: *m/z* 375 (M+1); Analysis for $C_{21}H_{22}N_6O$ (374.4), Calcd: C, 67.36; H, 5.92; N, 22.44; Found: C, 62.32; H, 5.88; N, 22.40.

2-(*N*'-Furan-2-ylmethylenehydrazino)-4-quinolyl-4-methylpiperazinomethanone 14c. Yield: 64%; m.p. 177-180°C; IR (KBr): 3236, 1645 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.50 (bs, 1H), 8.0 (s, 1H), 7.63 (m, 3H), 7.36 (m, 3H), 6.82 (m, 1H), 6.62 (m, 1H), 3.85-2.42 (m, 8H), 2.20 (s, 3H); ESIMS: *m/z* 364 (M+1); Analysis for $C_{20}H_{21}N_5O_2$ (363.4), Calcd: C, 66.10; H, 5.82; N, 19.27; Found: C, 66.12; H, 5.87; N, 19.23.

2-(*N*'-Thiophen-2-ylmethylenehydrazino)-4-quinolyl-4-methylpiperazinomethanone 14d. Yield: 47%; m.p. 175-177°C; IR (KBr): 3446, 1633 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.58 (bs, 1H), 8.33 (s, 1H), 7.65 (m, 4H), 7.33 (m, 3H), 7.15 (m, 1H), 3.78-2.44 (m, 8H), 2.15 (s, 3H); ESIMS: *m/z* 380 (M+1); Analysis for $C_{20}H_{21}N_5OS$ (379.5), Calcd: C, 63.30; H, 5.58; N, 18.46; Found: C, 63.28; H, 5.55; N, 18.38.

2-(*N*'-Anthracen-9-ylmethylenehydrazino)-4-quinolyl-4-methylpiperazinomethanone 14e. Yield: 50%; m.p. 210-212°C; IR (KBr): 3450, 1627 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.89 (bs, 1H), 8.59 (m, 4H), 8.05 (s, 1H), 7.69 (m, 8H), 7.39 (m, 2H), 3.94-2.41 (m, 8H), 2.20 (s, 3H); ESIMS: *m/z* 474 (M+1); Analysis for $C_{29}H_{27}N_5O$, (473.2), Calcd: C, 76.09; H, 5.75; N, 14.79; Found: C, 76.21; H, 5.71; N, 14.73.

2-[*N*'-(2-Methoxynaphthalen-1-ylmethylene)hydrazino]-4-quinolyl-4-methylpiperazino-methanone 14f. Yield: 48%; m.p. 181-183°C; IR (KBr): 3434, 1627 cm^{-1}; ^1H NMR (CD_3OD): δ 8.60 (s, 1H), 7.84 (m, 2H), 7.66 (m, 5H), 7.42 (m, 2H), 7.34 (m, 2H), 3.99 (s, 3H), 3.8-2.35 (m, 8H), 2.31 (s, 3H); ESIMS: *m/z* 454 (M+1); Analysis for $C_{27}H_{27}N_5O_2$ (453.3), Calcd: C, 71.50; H, 6.00; N, 15.44; Found: C, 71.42; H, 5.95; N, 15.42.

2-(*N*'-Propylidenehydrazino)-4-quinolyl-4-methylpiperazinomethanone 14g. Yield: 33%; m.p. 185-187°C; IR (KBr): 3436, 1645 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.25 (d, 1H, *J* = 8.5 Hz), 7.80 (d, 1H, *J* = 7.6 Hz), 7.74 (m, 1H), 7.56 (m, 3H), 3.67-2.23 (m, 8H), 2.19 (s, 3H), 1.23 (m, 2H), 1.07 (d, 3H, *J* = 6.8 Hz); ESIMS: *m/z* 326 (M+1); Analysis for $C_{18}H_{23}N_5O$ (325.4), Calcd: C, 66.44; H, 7.42; N, 21.52; Found: C, 66.37; H, 7.44; N, 21.5.

2-(*N*'-Isopropylidenehydrazino)-4-quinolyl-4-methylpiperazinomethanone 14h. Yield: 26%; m.p. 101-103°C; IR (KBr): 3438, 1621 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.97 (bs, 1H), 8.34 (d, 1H, *J* = 8.6 Hz), 8.30 (s, 1H), 7.77 (d, 1H, *J* = 7.2 Hz), 7.43 (m, 3H), 3.73-2.20 (m, 8H), 2.21 (s, 3H), 2.10 (m, 1H), 1.23 (d, 6H, *J* = 6.8 Hz); ESIMS: *m/z* 340 (M+1); Analysis for $C_{19}H_{25}N_5O$ (339.4), Calcd: C, 67.23; H, 7.42; N, 20.63; Found: C, 67.18; H, 7.37; N, 20.80.

(*N*'-Benzylidenehydrazino)-4-quinolyl-4-methylpiperazinomethanone 14i. Yield: 38%; m.p. 227-229°C; IR (KBr): 3459, 1631 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.53 (bs, 1H), 8.10 (s,1H), 7.65 (m, 5H), 7.50 (m, 1H), 7.40 (m, 4H), 3.87-2.38 (m, 8H), 2.20 (s, 3H); ESIMS: *m/z* 374 (M+1); Analysis for $C_{22}H_{23}N_5O$ (373.4), Calcd: C, 70.76; H, 6.21; N, 18.75; Found: C, 70.73; H, 6.15; N, 18.65.

2-[*N*'-(4-Methoxybenzylidene)hydrazino]-4-quinolyl-4-methylpiperazinomethanone 14j. Yield: 66%; m.p. 230-232°C; IR (KBr): 3436, 1604 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.38 (bs, 1H), 8.04 (s, 1H), 7.64 (m, 4H), 7.54 (d, 1H, *J* = 8.0 Hz), 7.42 (s, 1H), 7.32 (m, 1H), 6.97 (d, 2H, *J* = 8.5 Hz), 3.79 (s, 3H), 3.91-2.47 (m, 8H), 2.19 (s, 3H); ESIMS: *m/z* 404 (M+1); Analysis for $C_{23}H_{25}N_5O_2$ (403.2), Calcd: C, 68.47; H, 6.25; N, 17.36; Found: C, 68.42; H, 6.13, N, 17.23.

Conclusions

A new series of 2,4-disubstituted quinolines starting from in-expensive isatin in six steps have been synthesized. Two of the synthesized analogs have been found to exhibit 99% inhibition at 6.25 μg/mL against drug-sensitive *M. tuberculosis H37Rv* and >90% inhibition at 12.5 μg/mL against isoniazid resitant *M. tuberculosis H37Rv* strain. The presence of aromatic amides at the C-4 position appears to be important in anti-TB activity, while placement of aliphatic and cyclic amide groups generally resulted in loss of anti-TB activity. In conclusion, 2,4-disubstituted quinolines are promising anti-TB compounds, and the structural optimization of this class may results in analogs with greater potency.

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