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Synthesis and biological evaluation of some 4-aminoquinoline derivatives as potential antitubercular agents

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Abstract

Background: Based on bioisosteric similarities with thiacetazone, a series of 7-chloro-4-aminoquinoline derivatives have been designed and synthesized. The target compounds were elucidated by NMR, mass, and FTIR spectral data. All synthesized compounds were evaluated for their in vitro antitubercular activity against *Mycobacterium tuberculosis* H_{37}Rv (MTB), and human dermal fibroblast cell lines were used to assess toxicity of selected ligands.

Results: All of the designed compounds showed inhibition of MTB with MIC of 1.56–50 μM. Among the tested compounds, **7c** and **7g** proved to be most potent MTB inhibitors (MIC = 1.56 μM).

Conclusions: The outcome of present study suggests that most of the synthesized compounds are sensitive to *Mycobacterium tuberculosis* and showed acceptable range for molecular parameters. Thus, 7-chloro-4-aminoquinolines could be a useful lead for the development of new MTB inhibitory agents.

Keywords: Thiosemicarbazones, Semicarbazones, Quinoline, Antitubercular, Cytotoxicity

Background

Tuberculosis (TB) is considered to be the most widespread and lethal communicable disease in the world. TB is caused by an infection with the slow-growing *Mycobacterium tuberculosis* (MTB). According to the World Health Organization, there were an estimated 10.0 million new TB cases in 2017 with 1.3 million TB deaths. In addition, more than 65% of the world's TB cases occur in Southeast Asia, the West Pacific, and Africa [1]. Commonly used TB treatment regimen DOTS (directly observed therapy short-course) requires taking INH, PZA, and RIF for 60 days followed by an additional 120 days of treatment with INH and RIF [2, 3]. Due to the resistance acquired by the *Mycobacterium tuberculosis* against various first-line drugs [4], there is a need to find new and better drug candidates for the treatment. Quinoline and analogs have always attracted the attention of industrial and academic personnel. It is being reported as having many interesting biological properties such as antimalarial [5, 6], cytotoxic [7, 8], anti-inflammatory [9, 10], antiviral [11, 12], antimicrobial [13, 14], antifungal [15], anti-Alzheimer [16], antiprotozoal [17], and antitubercular [18] activities. Quinoline is a basic pharmacophore used for the design of antitubercular agents, like mefloquine, ciprofloxacin, moxifloxacin, and bedaquiline which are already in the market [18]. Furthermore, thiosemicarbazone and semicarbazone derivatives are frequently used scaffolds in biology-orientated synthesis which possess a huge variety of pharmacological activities including an antibacterial, antifungal, antitubercular, and anticancer activity [19, 20].

In view of the above observations, the diverse pharmacological activities of these pharmacophores prompted us to synthesize the target compounds, presuming that their hybrid in a one-structural entity could potentially yield new heterocyclic compounds with significant synergistic antitubercular properties. Hence, with an aim to develop promising antitubercular agents, a series of novel 7-chloro-N-phenylquinolin-4-amine derivatives

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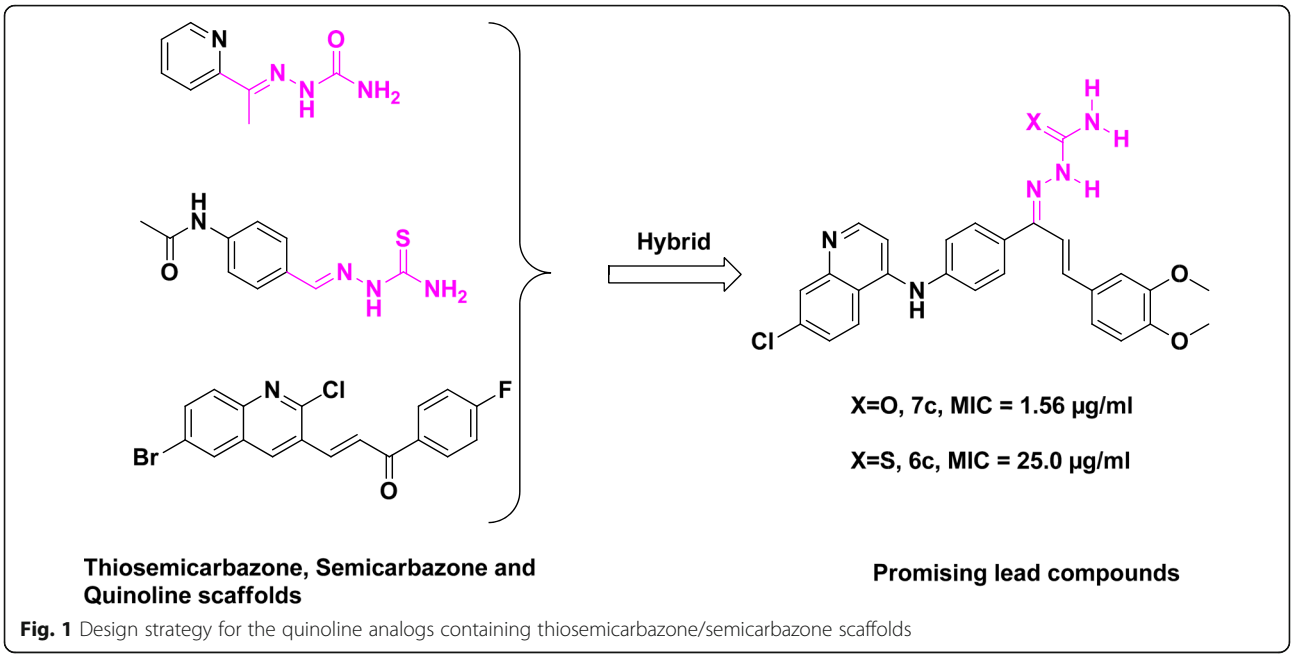


Fig. 1 Design strategy for the quinoline analogs containing thiosemicarbazone/semicarbazone scaffolds

containing thiosemicarbazone and semicarbazone [19, 20], scaffolds were designed and synthesized (Fig. 1). In the present study, all target ligands are screened for their in vitro antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ (MTB), and human dermal fibroblast cell line were used for toxicity study.

Method

Synthesis of thiosemicarbazide and semicarbazide derivatives

An equimolar amount of thiosemicarbazide or semicarbazide hydrochloride (20 mmol) and substituted α,β-unsaturated ketones (**4a-i, and 5a-i**) (20 mmol) [21] were dissolved in isopropyl alcohol, and glacial acetic acid (0.1 ml) was used as a catalyst. The mixture was stirred at 85 °C for 36 h. On completion of the reaction, as monitored by TLC, the reaction mixture was cooled. Precipitate was filtered by suction and washed with cooled isopropyl alcohol and solvent ether. The structures of target compounds were established by using different spectroscopic techniques.

Antitubercular activity assay

Microplate alamar blue assay (MABA) method [22, 23] was adopted to evaluate antitubercular activities (Additional file 1).

Cytotoxic assay

MTT (3-(4, 5-dimethylthiazo-2-yl)-2,5-diphenyl-tetrazolium bromide) [24] assay protocol was used to assess the toxicity studies of selected analogs.

Results

Synthesis and spectral data

((E)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)-3-(p-tolyl)allylidene)hydrazinecarbothioamide(6a)

Yield: 55%; m.p.: 196–198 °C; IR (KBr cm^{-1}): 3362 (NH_2), 1593 (C=C), 1351 (C=S), 1170 (OCH_3); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 2.62 (s, 3H, CH_3), 7.05 (s, 1H, ArH), 7.37 (d, 2H, J = 8.4 Hz, ArH), 7.56 (m, 4H, ArH), 7.72–7.69 (m, 3H, ArH, -C=HC-), 7.83 (d, 1H, J = 15.6 Hz, -C=HC-), 7.85 (s, 1H, NH_2), 7.88 (s, 1H, NH_2), 7.91 (s, 1H, ArH), 8.18 (s, 1H, ArH), 8.42 (s, 1H, ArH), 8.55 (s, 1H, ArH), 9.95 (s, 1H, NH), 10.83 (s, 1H, =N-NH-C); LC-MS *M/Z*: 473 $[M + H]^+$.

2-((E)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)-3-(4-methoxyphenyl)allylidene)hydrazinecarbothioamide(6b)

Yield: 53%; m.p.: 190–192 °C; IR (KBr cm^{-1}): 3367 (NH_2), 1593 (C=C), 1350 (C=S), 1172 (OCH_3); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) 3.82 (s, 3H, OCH_3), 7.02 (s, 1H, ArH), 7.34 (d, 2H, J = 8.4 Hz, ArH), 7.53 (m, 4H, ArH), 7.70–7.63 (m, 3H, ArH, -C=HC-), 7.85 (d, 1H, J = 15.6 Hz, -C=HC-), 7.87 (s, 1H, NH_2), 7.89 (s, 1H, NH_2), 7.88 (s, 1H, ArH), 8.18 (s, 1H, ArH), 8.40 (s, 1H, ArH), 8.58 (s, 1H, ArH), 9.93 (s, 1H, NH), 10.81 (s, 1H, =N-NH-C); LC-MS *M/Z*: 489 $[M + H]^+$.

2-((E)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)-3-(3,4-dimethoxyphenyl)allylidene)hydrazinecarbothioamide(6c)

Yield: 56%; m.p.: 148–150 °C; IR (KBr cm^{-1}): 3367 (NH_2), 1265 (OCH_3), 1350 (C=S); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 3.81 (s, 3H, OCH_3), 3.86 (s, 3H, $-OCH_3$), 7.02 (s, 1H, ArH), 7.45 (s, 1H, ArH), 7.38 (s,

1H, ArH), 7.53 (m, 3H, ArH), 7.72–7.69 (m, 3H, ArH, -C=HC-), 7.85 (d, 1H, J = 15.6 Hz, -C=HC-), 7.91 (s, 1H, NH_2), 7.96 (s, 1H, NH_2), 7.98 (s, 1H, ArH), 8.23 (s, 1H, ArH), 8.47 (s, 1H, ArH), 8.61 (s,1H, ArH), 9.91 (s, 1H, NH), 10.82 (s, 1H, =N-NH-C); LC-MS *M/Z*: 519 $[M + H]^+$.

2-((E)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)-3-(3,4,5-trimethoxyphenyl)allylidene)hydrazinecarbothioamide(6d)

Yield: 66%; m.p.: 138–140 °C; IR (KBr cm^{-1}): 3343 (NH_2), 1593 (C=C), 1352 (C=S), 1128 (OCH_3), 1128 (OCH_3); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 3.76 (s, 3H, OCH_3), 3.86 (s, 6H, -OCH_3), 6.42 (s, 1H, ArH), 7.27 (d, 2H, J = 8.4 Hz ArH), 7.42 (s, 1H, ArH), 7.52 (s, 1H, ArH), 7.71–7.64 (m, 3H, ArH, -C=HC-), 7.89 (d, 1H, J = 15.6 Hz, -C=HC-), 7.92 (s, 1H, NH_2), 7.95 (s, 1H, NH_2), 7.98(s, 1H, ArH), 8.23 (s, 1H, ArH), 8.40 (s, 1H, ArH), 8.59 (s, 1H, ArH), 9.68 (s, 1H, NH), 10.72 (s, 1H, =N-NH-C); LC-MS *M/Z*: 549 $[M + H]^+$.

2-((E)-3-(4-chlorophenyl)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)allylidene)hydrazinecarbothioamide(6e)

Yield: 73%; m.p.: 142–144 °C; IR (KBr cm^{-1}): 3365 (NH_2), 1554 (C=C), 1350 (C=S); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.08 (s, 1H, ArH), 7.51–7.749 (m, 3H, ArH, -C=HC-), 7.62 (d, 2H, J = 8.8 Hz, ArH), 7.70 (d,1H, J = 15.6 Hz -C=HC-), 7.78 (s, 1H, ArH), 7.89 (s, 1H, NH_2), 7.91 (s, 1H, NH_2), 7.95 (s, 1H, ArH), 8.01 (d, 2H, J = 8.4 Hz, ArH), 8.20 (d, 2H, J = 8.8 Hz, ArH), 8.41 (s, 1H, ArH), 8.62 (s, 1H, ArH), 10.08 (s, 1H, NH), 11.06 (s, 1H, =N-NH-C); LC-MS *M/Z*: 494 $[M + H]^+$.

2-((E)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)-3-(4-fluorophenyl)allylidene)hydrazinecarbothioamide(6f)

Yield: 58%; m.p.: 178–180 °C; IR (KBr cm^{-1}): 3354 (NH_2), 1575 (C=C), 1351 (C=S); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.01 (s, 1H, ArH), 7.32–7.24 (m, 3H, ArH, -C=HC-), 7.52 (d, 2H, J = 8.8 Hz, ArH), 7.64 (d,1H, J = 15.6 Hz -C=HC-), 7.66 (s, 1H, NH_2), 7.75 (s, 1H, NH_2), 7.98 (s, 1H, ArH), 7.98–7.95 (m, 3H, ArH), 8.23–8.20 (m, 2H, ArH), 8.46 (s, 1H, ArH), 8.60 (s, 1H, ArH), 10.02 (s, 1H, NH), 11.03 (s, 1H, =N-NH-C); LC-MS *M/Z*: 477 $[M + H]^+$.

2-((E)-3-(4-bromophenyl)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)allylidene)hydrazinecarbothioamide(6 g)

Yield: 66%; m.p.: 186–188 °C; IR (KBr cm^{-1}): 3375 (NH_2), 1580 (C=C), 1352 (C=S); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 6.53 (s, 1H, ArH), 6.86 (d, 1H, J = 15.6 Hz, -C=HC-), 6.99 (d, 1H, J = 12.6 Hz, -C=HC-), 7.07 (s, 1H, ArH), 7.30 (s, 1H, ArH), 7.47 (s, 1H, ArH), 7.62 (s, 1H, NH_2), 7.77–7.70 (m, 4H, ArH,), 7.81 (s, 1H, NH_2) 7.85 (d, 2H, J = 8.4 Hz, ArH), 8.20 (s, 1H, ArH), 8.30 (s, 1H, ArH), 8.51 (s, 1H, ArH), 10.10 (s, 1H, NH), 11.07 (s, 1H, =N-NH-C); LC-MS *M/Z*: 538 $[M + H]^+$.

2-((E)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)-3-(4-nitrophenyl)allylidene)hydrazinecarbothioamide(6 h)

Yield: 47%; m.p.: 216–218 °C; IR (KBr cm^{-1}): 3361 (NH_2), 1540 (C=C), 1350 (C=S); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.20 (d, 1H, J = 5.6 Hz, ArH), 7.23–7.10 (m, 4H, ArH, NH_2), 7.47 (d, 2H, J = 8.8 Hz, ArH), 7.71–7.60 (m, 3H, ArH, -C=HC-), 7.96 (s, 1H, NH_2), 8.13 (s, 1H, ArH), 8.26 (s, 1H, ArH), 8.44–8.38 (m, 4H, ArH), 9.87 (s, 1H, NH), 11.69 (s, 1H, =N-NH-C); LC-MS *M/Z*: 504 $[M + H]^+$.

2-((E)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)-3-(4-hydroxyphenyl)allylidene)hydrazinecarbothioamide(6i)

Yield: 50%; m.p.: 230–232 °C; IR (KBr cm^{-1}): 3365 (NH_2), 1567 (C=C), 1353 (C=S); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.20 (s, 1H, ArH), 7.27 (d, 2H, J = 8.8 Hz, ArH), 7.45–7.40 (m, 3H, ArH, CH=C), 7.73–7.61 (m, 3H, ArH, -C=HC-), 7.93 (s, 1H, NH_2), 7.96 (s, 1H, NH_2), 8.13 (s, 1H, ArH), 8.25 (d, 1H, ArH), 8.44–8.38 (m, 4H, ArH), 9.86 (s, 1H, NH), 9.88 (s, 1H, OH), 11.55 (s, 1H, =N-NH-C); LC-MS *M/Z*: 475 $[M + H]^+$.

2-((E)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)-3-(p-tolyl)allylidene)hydrazinecarboxamide(7a)

Yield: 72%; m.p.: 148–150 °C; IR (KBr cm^{-1}): 3425 (NH_2), 1693 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) 2.88 (s, 3H, CH_3), 6.51 (s, 2H, NH_2), 6.83–6.81 (d, 2H, J = 8.8 Hz, ArH), 6.86 (s, 1H, ArH), 6.90 (s, 1H, ArH), 7.60 (d, 2H, J = 8.8, ArH), 7.73 (d, 1H,, J = 15.6 Hz, -C=HC-), 7.83 (d, 1H, J = 15.6 Hz, -C=HC-), 7.85 (s, 1H, ArH), 7.93 (d, 2H, J = 8.4 Hz, ArH), 8.06 (d, 2H, J = 8.4 Hz, ArH), 8.57 (s, 1H, ArH), 8.69 (s, 1H, ArH), 9.41 (s, 1H, NH), 10.91(s, 1H, =N-NH-C); LC-MS *M/Z*: 457 $[M + H]^+$.

2-((E)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)-3-(4-methoxyphenyl)allylidene)hydrazinecarboxamide(7b)

Yield: 65%; m.p.: 238–240 °C; FTIR (KBr) cm^{-1}: 3450 (NH_2), 1685 (C=O), 1251 (OCH_3); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 3.72 (s, 3H, OCH_3), 6.48 (s, 2H, NH_2), 6.88 (d, 2H, J = 8.8 Hz, ArH), 6.96 (s, 1H, ArH), 7.13 (d, 2H, J = 8.8, ArH), 7.51 (d, 2H, J = 8.4 Hz, ArH), 7.75 (d, 1H, J = 15.6 Hz, -C=HC-), 7.78 (d, 1H, J = 15.6 Hz, -C=HC-), 7.85 (s, 1H, ArH), 7.93 (d, 2H, J = 8.8 Hz, ArH), 8.0 (s, 1H, ArH), 8.54 (s, 1H, ArH), 8.72 (s, 1H, ArH), 9.38 (s, 1H, NH), 10.76 (s, 1H, =N-NH-C); LC-MS *M/Z*: 473 $[M + H]^+$.

2-((E)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)-3-(3,4-dimethoxyphenyl)allylidene)hydrazinecarboxamide(7c)
Yield: 56%; m.p.: 214–216 °C; IR (KBr cm^{-1}): 3442 (NH_2), 1681 (C=O), 1255 (OCH_3); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 3.72 (s, 3H, OCH_3), 3.81 (s, 3H, -OCH_3), 6.50 (s, 2H, NH_2), 6.81 (s, 1H, ArH), 7.20–6.96 (m, 3H, *J* = 8.4, ArH), 7.53 (d, 2H, *J* = 8.8 Hz, ArH), 7.79 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.81 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.85 (s, 1H, ArH), 7.95 (d, 2H, *J* = 8.4 Hz, ArH), 8.07 (s, 1H, ArH), 8.56 (s, 1H, ArH), 8.72 (s, 1H, ArH), 10.20 (s, 1H, NH), 10.81 (s, 1H, =N-NH-C); LC-MS *M/Z*: 503 $[M + H]^+$.

2-((E)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)-3-(3,4,5-trimethoxyphenyl)allylidene)hydrazinecarboxamide(7d)
Yield: 52%; m.p.: 238–240 °C; IR (KBr cm^{-1}): 3442 (NH_2), 1671 (C=O), 1251 (OCH_3); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 3.82 (s, 6H, OCH_3), 3.87 (s, 3H, OCH_3), 6.49 (s, 2H, NH_2), 6.76 (s, 1H, ArH), 6.88 (s, 1H, ArH), 7.54 (d, 2H, *J* = 8.8 Hz, ArH), 7.71 (s, 1H, ArH), 7.81 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.83 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.93 (d, 2H, *J* = 8.8, ArH), 8.02 (s, 2H, ArH), 8.54 (s, 1H, ArH), 8.76 (s, 1H, ArH), 10.09 (s, 1H, NH), 11.02 (s, 1H, =N-NH-C); LC-MS *M/Z*: 533 $[M + H]^+$.

2-((E)-3-(4-chlorophenyl)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)allylidene)hydrazinecarboxamide(7e)
Yield: 45%; m.p.: 174–176 °C; IR (KBr cm^{-1}): 3335 (NH_2,), 1680 (C=O), 1226 (C-N); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 6.48 (s, 2H, NH_2), 7.22 (s, 1H, Ar-H), 7.54 (d, 2H, *J* = 8.4, Ar-H), 7.62 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.76 (s, 1H, Ar-H), 7.87 (d, 1H, *J* = 15.6 Hz, –CH=C), 7.89 (d, 1H, *J* = 15.6 Hz, –CH=C), 7.95 (d, 2H, *J* = 8.8, Ar-H), 7.99 (s, 1H, Ar-H), 8.05 (s, 1H, Ar-H), 8.29 (d, 2H, *J* = 8.8 Hz, Ar-H), 8.62 (s, 1H, Ar-H), 10.17 (s, 1H, NH), 10.76 (s, 1H, =N-NH-C); LC-MS *M/Z*: 477 $[M + H]^+$.

2-((E)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)-3-(4-fluorophenyl)allylidene)hydrazinecarboxamide(7f)
Yield: 70%; m.p.: 230–232 °C; IR (KBr cm^{-1}): 3433 (NH_2), 1686 (C=O), 1370 (C-N); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 6.54 (s, 2H, NH_2), 7.22 (s, 1H, ArH), 7.44 (d, 2H, *J* = 8.4, ArH), 7.52 (d, 2H, *J* = 8.8 Hz, ArH), 7.73 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.76 (s, 1H, A-H), 7.83 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.91 (d, 2H, *J* = 8.8, ArH), 7.7 (s, 1H, ArH), 7.80–7.85 (m, 3H, ArH), 8.01 (s, 1H, ArH), 10.11 (s, 1H, –NH), 10.41 (s, 1H, =N-NH-C); LC-MS *M/Z*: 461 $[M + H]^+$.

2-((E)-3-(4-bromophenyl)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)allylidene)hydrazinecarboxamide(7 g)
Yield: 51%; m.p.: 244–246 °C; IR (KBr cm^{-1}): 3452 (NH_2,), 1680 (C=O), 1251 (C-N); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 6.52 (s, 2H, NH_2), 7.16 (s, 1H, ArH), 7.61(d, 2H, *J* = 8.4, ArH), 7.68 (d, 2H, *J* = 8.4 Hz, ArH), 7.74 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.78 (s, 1H, ArH), 7.81 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.90 (d, 2H, *J* = 8.0, ArH), 8.00 (s, 1H, ArH), 8.06 (s, 1H, ArH), 8.27 (d, 2H, *J* = 8.8 Hz, ArH), 8.62 (s, 1H, ArH), 10.18 (s, 1H, NH), 10.83 (s, 1H, =N-NH-C); LC-MS *M/Z*: 522 $[M + H]^+$.

2-((E)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)-3-(4-nitrophenyl)allylidene)hydrazinecarboxamide(7 h)
Yield: 70%; m.p.: 196–198 °C; IR (KBr cm^{-1}): 3398 (NH_2), 1675 (C=O), 1585 (NO_2), 1371 (C- N); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 6.50 (s, 2H, NH_2), 7.20 (s, 1H, ArH), 7.42 (d, 2H, *J* = 8.8 Hz, ArH), 7.62 (d, 2H, *J* = 8.8 Hz, ArH), 7.80 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.83 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.9 (s, 1H, ArH), 8.02 (d, 2H, *J* = 8.4, ArH), 8.16 (s, 1H, ArH), 8.29 (d, 2H, *J* = 8.4 Hz, ArH), 8.53 (s, 1H, ArH), 8.62 (s, 1H, ArH), 10.30 (s, 1H, NH), 10.76 (s, 1H, =N-NH-C); LC-MS *M/Z*: 488 $[M + H]^+$.

2-((E)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)-3-(4-hydroxyphenyl)allylidene)hydrazinecarboxamide(7i)
Yield: 45%; m.p.: 240–242 °C; IR (KBr cm^{-1}): 3360 (NH_2), 1680 (C=O), 1251 (C-N); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 6.53 (s, 2H, NH_2), 7.23 (s, 1H, ArH), 7.56 (d, 2H, *J* = 8.8 Hz, ArH), 7.68 (d, 2H, *J* = 8.8 Hz, ArH), 7.78 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.81 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.7 (s, 1H, ArH), 8.0 (d, 2H, *J* = 8.2, ArH), 8.16 (s, 1H, ArH), 8.26 (d, 2H, *J* = 8.4 Hz, ArH), 8.51 (s, 1H, ArH), 8.60 (s, 1H, ArH), 9.89 (s, 1H, OH), 10.32 (s, 1H, NH), 10.71 (s, 1H, =N-NH-C); LC-MS *M/Z*: 459 $[M + H]^+$.

2-((E)-1-(3-((7-chloroquinolin-4-yl)amino)phenyl)-3-(p-tolyl)allylidene)hydrazinecarbothioamide(8a)
Yield: 50%; m.p.: 238–240 °C; IR (KBr cm^{-1}): 3350 (NH_2), 1575 (C=C), 1352 (C=S), 1261 (C-N); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 2.62 (s, 3H, CH_3), 6.99 (s, 1H, ArH), 7.20–7.15 (m, 4H, ArH), 7.25 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.37 (d, 2H, *J* = 8.4 Hz, ArH), 7.50 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.59 (d, 2H, *J* = 8.4 Hz, ArH), 7.76 (s, 1H, ArH), 7.85 (s, 1H, NH_2), 7.88 (s, 1H, NH_2), 7.92 (s, 1H, ArH), 8.26 (s, 1H, ArH), 8.46 (s, 1H, ArH), 9.25 (s, 1H, NH), 11.25 (s, 1H, =N-NH-C); LC-MS *M/Z*: 473 $[M + H]^+$.

2-((E)-1-(3-((7-chloroquinolin-4-yl)amino)phenyl)-3-(4-Methoxyphenyl)allylidene)hydrazinecarbothioamide(8b)
Yield: 43%; m.p.: 210–212 °C; IR (KBr cm^{-1}): 3365 (NH_2), 1568 (C=C), 1350 (C=S), 1255 (OCH_3); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 3.81 (s, 3H, OCH_3), 7.42–7.35 (m, 4H, ArH), 7.67–7.58 (m, 3H, ArH, –NH_2), 7.71 (s, 1H, NH_2), 7.72 (s, 1H, ArH), 7.73 (d, 1H, *J* =

15.6 Hz, -C=HC-), 7.76 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.84 (d, 2H, *J* = 8.8 Hz, ArH), 7.93 (s, 1H, ArH), 8.04 (s, 1H, ArH), 8.43 (s, 1H, ArH), 8.50 (s, 1H, ArH), 9.26 (s, 1H, NH), 11.75 (s, 1H, =N-NH-C); LC-MS *M/Z*: 489 $[M + H]^+$.

2-((E)-1-(3-((7-chloroquinolin-4-yl)amino)phenyl)-3-(3,4-dimethoxyphenyl)allylidene)hydrazinecarbothioamide(8c)

Yield: 41%; m.p.: 120–122 °C; IR (KBr cm^{-1}): 3655 (NH_2), 1516 (C=C), 1313 (C=S), 1267 (C-N), 1560 (C=C), 1183 (OCH_3); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 3.81 (s, 3H, OCH_3), 3.84 (s, 3H, $-OCH_3$), 7.39 (s, 1H, ArH), 7.41 (s, 1H, ArH), 7.65 (s, 1H, $-NH_2$), 7.70–7.66 (m, 3H, ArH), 7.73 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.80 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.92–7.85 (m, 3H, ArH), 7.94 (s, 1H, ArH), 8.01 (s, 1H, ArH), 8.1 (s, 1H, $-NH_2$), 8.14 (s, 1H, ArH), 8.49 (s, 1H, ArH), 9.71 (s, 1H, NH), 11.95 (s, 1H, =N-NH-C); LC-MS *M/Z*: 519 $[M + H]^+$.

2-((E)-1-(3-((7-chloroquinolin-4-yl)amino)phenyl)-3-(3,4,5-trimethoxyphenyl)allylidene)hydrazinecarbothioamide(8d)

Yield: 60%; m.p.: 240–242 °C; IR (KBr cm^{-1}): 3352 (NH_2), 1560 (C=C), 1352 (C=S), 1246 (C-N), 1182 (OCH_3); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 3.70 (s, 3H, OCH_3), 3.84 (s, 6H, OCH_3), 7.22 (s, 1H, ArH), 7.64–7.58 (m, 4H, ArH), 7.67 (s, 1H, ArH), 7.71(d, 1H, *J* = 15.6, -C=HC-), 7.84 (s, 1H, NH_2), 7.85 (d, 1H, *J* = 15.6, -C=HC-), 7.91 (s, 1H, NH_2), 7.97 (s 2H, ArH), 8.02 (s, 1H, ArH), 8.43 (s, 1H, ArH), 8.51 (s, 1H, ArH), 9.28 (s, 1H, NH), 10.96 (s, 1H, =N-NH-C); LC-MS *M/Z*: 549 $[M + H]^+$.

2-((E)-3-(4-chlorophenyl)-1-(3-((7-chloroquinolin-4-yl)amino)phenyl)allylidene)hydrazinecarbothioamide(8e)

Yield: 66%; m.p.: 212–214 °C; IR (KBr cm^{-1}): 3338 (NH_2), 1597 (C=C), 1350 (C=S), 1261 (C-N); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.21 (s, 1H, ArH), 7.46 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.52 (d, 2H, *J* = 8.4 Hz, ArH), 7.59 (d,1H, *J* = 15.6 Hz, -C=HC-), 7.61 (d, 2H, *J* = 8.4 Hz, ArH), 7.79–7.63 (m, 4H, ArH), 7.81 (s, 1H, NH_2), 7.85 (s, 1H, ArH), 7.93 (s, 1H, NH_2), 8.20 (s, 1H, ArH), 8.24 (s, 1H, ArH), 8.47(s, 1H, ArH), 9.29 (s, 1H, NH), 11.12 (s, 1H, =N-NH-C); LC-MS *M/Z*: 494 $[M + H]^+$.

2-((E)-1-(3-((7-chloroquinolin-4-yl)amino)phenyl)-3-(4-fluorophenyl)allylidene)hydrazinecarbothioamide(8f)

Yield: 60%; m.p.: 234–236 °C; IR (KBr cm^{-1}): 3358 (NH_2), 1591 (C=C), 1350 (C=S); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.21 (s, 1H, ArH), 7.41–7.34 (m, 4H, ArH), 7.48 (d,1H, *J* = 15.6 Hz, -C=HC-), 7.57 (d, 2H, *J* = 8.4 Hz, ArH), 7.63 (d, 2H, *J* = 8.4 Hz, ArH), 7.76 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.88 (s, 1H, NH_2), 7.83 (s, 1H, ArH), 7.95 (s, 1H, NH_2), 8.22 (s, 1H, ArH), 8.31 (s, 1H, ArH), 8.45 (s, 1H, ArH), 9.25 (s, 1H, NH), 11.22 (s, 1H, =N-NH-C); LC-MS *M/Z*: 477 $[M + H]^+$.

2-((E)-3-(4-bromophenyl)-1-(3-((7-chloroquinolin-4-yl)amino)phenyl)allylidene)hydrazinecarbothioamide(8 g)

Yield: 55%; m.p.: 238–240 °C; IR (KBr cm^{-1}): 3364 (NH_2), 1575 (C=C), 1355 (C=S); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.21 (s, 1H, ArH), 7.45–7.37 (m, 4H, ArH), 7.48 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.53 (d, 2H, *J* = 8.4 Hz, ArH), 7.68 (d, 2H, *J* = 8.4 Hz, ArH), 7.75 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.83 (s, 1H, NH_2), 7.91 (s, 1H, ArH), 7.96 (s, 1H, NH_2), 8.14 (s, 1H, ArH), 8.23 (s, 1H, ArH), 8.46 (s, 1H, ArH), 9.23 (s, 1H, NH), 11.21 (s, 1H, =N-NH-C); LC-MS *M/Z*: 538 $[M + H]^+$.

2-((E)-1-(3-((7-chloroquinolin-4-yl)amino)phenyl)-3-(4-nitrophenyl)allylidene)hydrazinecarbothioamide(8 h)

Yield: 47%; m.p.: 218–220 °C; IR (KBr cm^{-1}): 3356 (NH_2), 1593 (NO_2), 1550 (C=C), 1350 (C=S); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.20 (s, 1H, ArH), 7.52–7.43 (m, 4H, ArH), 7.56 (d, 2H, *J* = 8.4 Hz, ArH), 7.61 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.64 (d, 2H, *J* = 7.6 Hz, ArH), 7.69 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.72 (s, 1H, NH_2), 7.96 (s, 1H, NH_2), 8.16 (s, 1H, ArH), 8.31 (s, 1H, ArH), 8.36 (s, 1H, ArH), 8.48 (s, 1H, ArH), 9.68 (s, 1H, NH), 11.23 (s, 1H, =N-NH-C); LC-MS *M/Z*: 504 $[M + H]^+$.

2-((E)-1-(3-((7-chloroquinolin-4-yl)amino)phenyl)-3-(4-hydroxyphenyl)allylidene)hydrazinecarbothioamide(8i)

Yield: 57%; m.p.: 250–242 °C; IR (KBr cm^{-1}): 3478 (OH), 3360 (NH_2), 1590 (C=C), 1361 (C=S), 1265 (C-N); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.2 (s, 1H, ArH), 7.20–7.15 (m, 4H, ArH), 7.25 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.38 (d, 2H, *J* = 8.4 Hz, ArH), 7.50 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.61 (d, 2H, *J* = 8.4 Hz, ArH), 7.76 (s, 1H, ArH), 7.87 (s, 1H, NH_2), 7.93 (s, 1H, NH_2), 7.97 (s, 1H, ArH), 8.31 (s, 1H, ArH), 8.43 (s, 1H, ArH), 9.35 (s, 1H, NH), 9.98 (s, 1H, OH), 11.22 (s, 1H, =N-NH-C); LC-MS *M/Z*: 475 $[M + H]^+$.

2-((E)-1-(3-((7-chloroquinolin-4-yl)amino)phenyl)-3-(p-tolyl)allylidene)hydrazinecarboxamide(9a)

Yield: 55%; m.p.: 192–194 °C; IR (KBr cm^{-1}): 3365 (NH_2), 1690 (C=O), 1575 (C=C), 1261(C-N); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 2.61 (s, 3H, CH_3), 6.73 (s, 2H, NH_2), 7.16 (s, 1H, ArH), 7.33–7.21 (m, 4H, ArH), 7.36 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.41 (d, 2H, *J* = 8.4 Hz, ArH), 7.53 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.61 (d, 2H, *J* = 8.4 Hz, ArH), 7.82 (s, 1H, ArH), 7.91 (s, 1H, ArH), 8.32 (s, 1H, ArH), 8.41 (s, 1H, ArH), 9.33 (s, 1H, NH), 10.93 (s, 1H, =N-NH-C); LC-MS *M/Z*: 457 $[M + H]^+$.

2-((E)-1-(3-((7-chloroquinolin-4-yl)amino)phenyl)-3-(4-methoxyphenyl) allylidene)hydrazinecarboxamide(9b)
Yield: 40%; m.p.: 188–190 °C; IR (KBr cm^{-1}): 3365 (NH_2), 1685 (C=O), 1590 (C=C), 1235 (OCH_3); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 3.83 (s, 3H, OCH_3), 6.69 (s, 2H, NH_2), 7.52–7.43 (m, 4H, ArH), 7.65 (d, 2H, ArH), 7.68 (s, 1H, ArH), 7.71 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.75 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.81 (d, 2H, *J* = 8.8 Hz, ArH), 7.93 (s, 1H, ArH), 8.01 (s, 1H, ArH), 8.42 (s, 1H, ArH), 8.47 (s, 1H, ArH), 9.34 (s, 1H, NH), 11.10 (s, 1H, =N-NH-C); LC-MS *M/Z*: 473 $[M + H]^+$.

2-((E)-1-(3-((7-chloroquinolin-4-yl)amino)phenyl)-3-(3,4-dimethoxyphenyl)allylidene)hydrazinecarboxamide(9c)
Yield: 51%; m.p.: 254–256 °C; IR (KBr cm^{-1}): 3648 (NH_2), 1680 (C=O), 1580 (C=C), 1215 (OCH_3); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 3.86 (s, 3H, OCH_3), 3.89 (s, 3H, $-OCH_3$), 6.69 (s, 2H, $-NH_2$), 7.53 (s, 1H, ArH), 7.68–7.59 (m, 3H, ArH), 7.71 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.79 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.91–7.83 (m, 3H, ArH), 7.94 (s, 1H, ArH), 8.10 (s, 1H, ArH), 8.23 (s, 1H, ArH), 8.49 (s, 1H, ArH), 8.51(s, H, ArH), 9.36 (s, 1H, NH), 11.13 (s, 1H, =N-NH-C); LC-MS *M/Z*: 503 $[M + H]^+$.

2-((E)-1-(3-((7-chloroquinolin-4-yl)amino)phenyl)-3-(3,4,5-trimethoxyphenyl) allylidene)hydrazinecarboxamide(9d)
Yield: 60%; m.p.: 258–260 °C; IR (KBr cm^{-1}): 3363 (NH_2), 1690 (C=O), 1565 (C=C), 1248 (C-N), 1189 (OCH_3); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 3.76 (s, 3H, OCH_3), 3.85 (s, 6H, -OCH_3), 6.79 (s, 2H, NH_2), 7.41 (s, 1H, ArH), 7.81–7.7 (m, 4H, ArH), 7.92 (s, 1H, ArH), 7.83 (d, 1H, *J* = 15.6, -C=HC-), 7.87 (d, 1H, *J* = 15.6, -C=HC-), 7.96 (s 2H, ArH), 8.13 (s, 1H, ArH), 8.41 (s, 1H, ArH), 8.48 (s, 1H, ArH), 9.33 (s, 1H, NH), 10.83 (s, 1H, =N-NH-C); LC-MS *M/Z*: 533 $[M + H]^+$.

2-((E)-3-(4-chlorophenyl)-1-(3-((7-chloroquinolin-4-yl)amino)phenyl)allylidene)hydrazinecarboxamide(9e)
Yield: 50%; m.p.: 226–228 °C; IR (KBr cm^{-1}): 3354 (NH_2), 1686 (C=O), 1583 (C=C), 1270 (C-N); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 6.73 (s, 2H, NH_2), 7.13 (s, 1H, ArH), 7.48 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.53 (d, 2H, *J* = 8.4 Hz, ArH), 7.58 (d,1H, *J* = 15.6 Hz, -C=HC-), 7.65 (d, 2H, *J* = 8.4 Hz, ArH), 7.81–7.75 (m, 4H, ArH), 7.83 (s, 1H, ArH), 8.22 (s, 1H, ArH), 8.35 (s, 1H, ArH), 8.43 (s, 1H, ArH), 9.31 (s, 1H, NH), 10.86 (s, 1H, =N-NH-C); LC-MS *M/Z*: 477 $[M + H]^+$.

2-((E)-1-(3-((7-chloroquinolin-4-yl)amino)phenyl)-3-(4-fluorophenyl)allylidene)hydrazinecarboxamide(9f)
Yield: 55%; m.p.: 198–200 °C; IR (KBr cm^{-1}): 3360 (NH_2), 1685 (C=O), 1595 (C=C); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 6.73 (s, 2H, NH_2), 7.28 (s, 1H, ArH), 7.45–7.36 (m, 4H, ArH), 7.49 (d,1H, *J* = 15.6 Hz, -C=HC-), 7.53 (d, 2H, *J* = 8.4 Hz, ArH), 7.59 (d, 2H, *J* = 8.4 Hz, ArH), 7.75 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.95 (s, 1H, ArH), 8.26 (s, 1H, ArH), 8.35 (s, 1H, ArH), 8.46 (s, 1H, ArH), 9.29 (s, 1H, NH), 10.98 (s, 1H, =N-NH-C); LC-MS *M/Z*: 461 $[M + H]^+$.

2-((E)-3-(4-bromophenyl)-1-(3-((7-chloroquinolin-4-yl)amino)phenyl)allylidene)hydrazinecarboxamide(9 g)
Yield: 60%; m.p.: 306–308 °C; IR (KBr cm^{-1}): 3360 (NH_2), 1686 (C=O), 1570 (C=C); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 6.75 (s, 2H, NH_2), 7.14 (s, 1H, ArH), 7.49–7.38 (m, 4H, ArH), 7.52 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.63 (d, 2H, *J* = 8.4 Hz, ArH), 7.71 (d, 2H, *J* = 8.4 Hz, ArH), 7.79 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.93 (s, 1H, ArH), 8.22 (s, 1H, ArH), 8.29 (s, 1H, ArH), 8.45 (s, 1H, ArH), 9.27 (s, 1H, NH), 10.96 (s, 1H, =N-NH-C); LC-MS *M/Z*: 522 $[M + H]^+$.

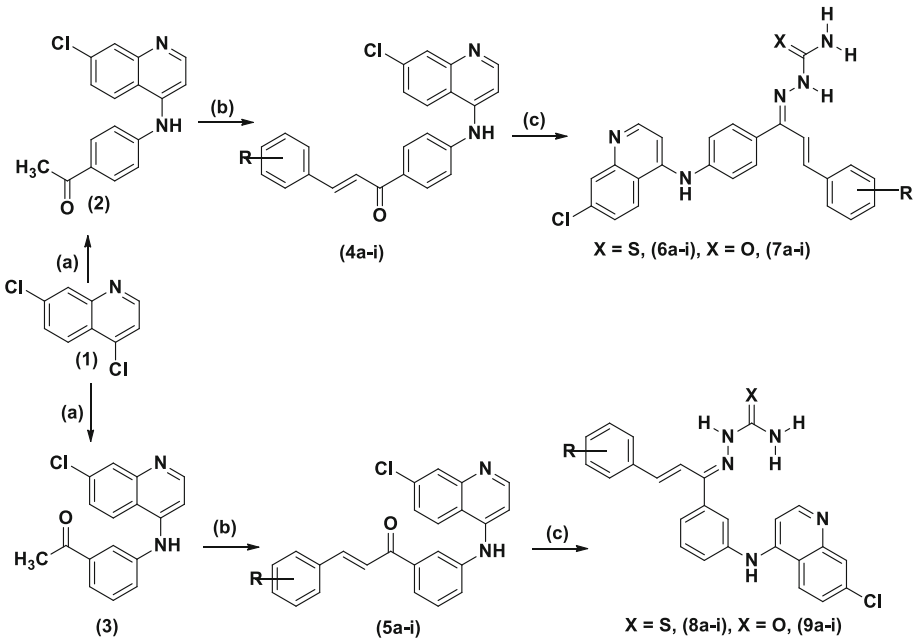
2-((E)-1-(3-((7-chloroquinolin-4-yl)amino)phenyl)-3-(4-nitrophenyl)allylidene)hydrazinecarboxamide(9 h)
Yield: 43%; m.p.: 246–248 °C; IR (KBr cm^{-1}): 3360 (NH_2), 1690 (C=O), 1595 (NO_2), 1565 (C=C); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 6.72 (s, 2H, NH_2), 7.20 (s, 1H, ArH), 7.53–7.48 (m, 4H, ArH), 7.56 (d 2H, *J* = 8.4 Hz, ArH), 7.65 (d, 2H, *J* = 7.6 Hz, ArH), 7.73 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.96 (d, 1H, *J* = 15.6 Hz, -C=HC-), 8.13 (s, 1H, ArH), 8.26 (s, 1H, ArH), 8.33 (s, 1H, ArH), 8.47 (s, 1H, ArH), 9.36 (s, 1H, NH), 10.87 (s, 1H, =N-NH-C); LC-MS *M/Z*: 488 $[M + H]^+$.

2-((E)-1-(3-((7-chloroquinolin-4-yl)amino)phenyl)-3-(4-hydroxyphenyl)allylidene)hydrazinecarboxamide(9i)
Yield: 43%; m.p.: 234–236 °C; IR (KBr cm^{-1}): 3362 (NH_2), 1685 (C=O), 1593 (C=C), 1265(C-N); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 6.67 (s, 2H, NH_2), 7.10 (s, 1H, ArH), 7.23–7.14 (m, 4H, ArH), 7.27 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.49 (d, 2H, *J* = 8.4 Hz, ArH), 7.62 (d, 1H, *J* = 15.6 Hz, -C=HC-), 7.73 (d, 2H, *J* = 8.4 Hz, ArH), 7.98 (s, 1H, ArH), 8.15 (s, 1H, ArH), 8.36 (s, 1H, ArH), 8.46 (s, 1H, ArH), 9.29 (s, 1H, NH), 9.85 (s, 1H, OH), 10.93 (s, 1H, =N-NH-C); LC-MS *M/Z*: 459 $[M + H]^+$.

Discussions

Chemistry

The reaction sequence employed for synthesis of the title compounds (**6a-i**), (**7a-i**), (**8a-i**), and (**9a-i**) are illustrated in Scheme 1. Initially, compounds 1-(4-((7-chloroquinolin-4-yl) amino)phenyl)ethanone (**2**) and 1-(3-((7-chloroquinolin-4-yl)amino) phenyl)ethanone (**3**) were prepared with slight modification on the basis of the previously reported methods [21]. Their IR spectra showed the appearance of characteristic band at around 3564–3651 cm^{-1} attributed to amino (NH) group and



Scheme 1 Reagents and conditions: (a) dry methanol, reflux 9–10 h; (b) methanol, NaOH, THF, RT; (c) thiosemicarbazide or semicarbazide hydrochloride, dry isopropyl alcohol, and glacial acetic acid, reflux 36 h

carbonyl (C=O) stretching frequency at around 1684 cm^{-1}, while their ^1H NMR spectrum indicated singlet signal at around δ 11.16 and 11.33 ppm for amine (NH) protons. Further, these compounds were confirmed by D_2O exchange experiment. The key intermediate α, β-unsaturated ketones (chalcones) (**4a-i**) and (**5a-i**) were synthesized by reacting 1-(4-((7-chloroquinolin-4-yl)amino)phenyl)ethanone (**2**) or 1-(3-((7-chloroquinolin-4-yl)amino)phenyl)ethanone (**3**) with appropriate aldehydes by conventional base-catalyzed Claisen-Schmidt condensation. The IR spectra of the compounds (**4a-i**) and (**5a-i**) showed new band at 1530 cm^{-1} attributed to an alkene (C=C) group of α, β-unsaturated ketones. In addition, two sets of protons with a trans coupling constant (J = 16 Hz) were present at δ 7.72 and 8.05 ppm which confirms the completion of Claisen-Schmidt condensation reactions. Reaction of chalcones (**4a-i**) and (**5a-i**) with thiosemicarbazide and semicarbazide hydrochloride in dry isopropyl alcohol and the presence of glacial acetic acid for 36 h afforded the target thiosemicarbazone (**6a-i**) and (**8a-i**) and semicarbazone (**7a-i**) and (**9a-i**) derivatives respectively.

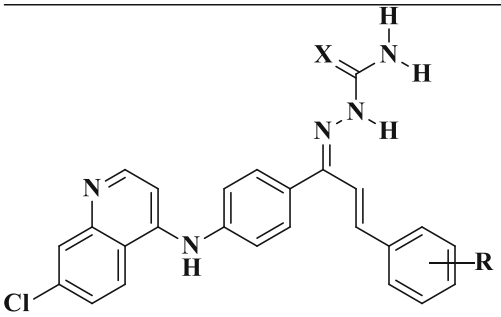
The structures of target compounds were established by using different spectroscopic techniques, including FTIR, NMR, and mass spectroscopy. The FTIR spectra of these compounds showed a medium to strong band for C=N stretch which appeared in the range 1620 to 1560 cm^{-1}, C=S absorption band appeared at 1341 to 1356 cm^{-1}, and semicarbazone derivatives showed C=O absorption band at 1661 to 1690 cm^{-1}. In addition, FTIR spectra showed the appearance of characteristic bands at 3350 and 3290 cm^{-1} assignable for amino (NH) group, while their proton NMR spectrum indicated singlet at around δ 11.69–11.82 ppm for =N-N**H**-C- proton. The two amino (-NH_2) protons appeared as two singlets in the range at 7.67 and 8.2 ppm. Finally, formation of these compounds was also evidenced by mass spectral data.

Biological activities

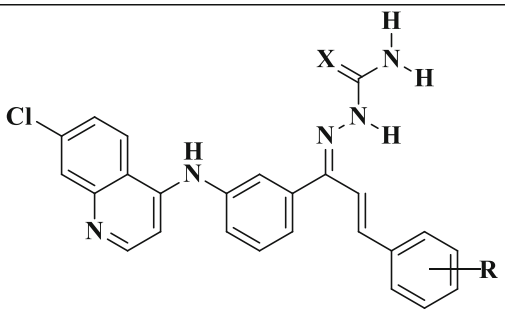
Antitubercular activity

The new thiosemicarbazone derivatives (**6a-i**) and (**8a-i**) and semicarbazide compounds (**7a-i**) and (**9a-i**) were evaluated against *Mycobacterium tuberculosis* (MTB) $H_{37}Rv$ (ATCC 27294) by using the microplate alamar blue assay (MABA) [22, 23]. The minimum inhibitory concentration (MIC) was determined for each derivative which was measured as the minimum concentration of the compound required to completely inhibit the bacterial growth. Isoniazid, pyrazinamide, and ciprofloxacin were used as standard drugs for comparison. Antitubercular activity results are summarized in Table 1. From the results, it was observed that among the tested compounds, the most active compounds **7c** and **7 g** exhibited *Mycobacterium tuberculosis* inhibition at 1.56 μM as compared to standard isoniazid (MIC = 1.56 μM). Three compounds **7a**, **7i**, and **9a** inhibited MTB with MIC value of 6.25 μM, when compared to ciprofloxacin (MIC = 12.5 μM) and pyrazinamide (MIC = 50 μM). Nine compounds **6a**, **6b**, **6d**, **6e**, **7d**, **7e**, **8a**, **8b**, **9b**, and **9c** are

Table 1 Physical data and antimycobacterial activities of compound (**6a-i**), (**7a-i**), (**8a-i**), and (**9a-i**) against MTB $H_{37}Rv$



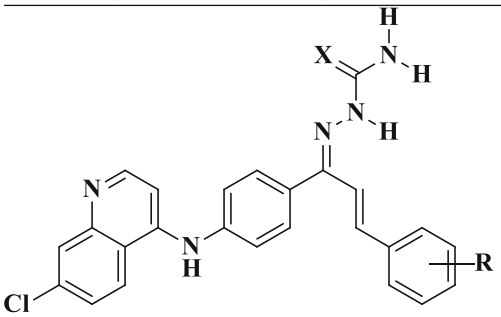
((X = S, 6a-i), (X = O, 7a-i))



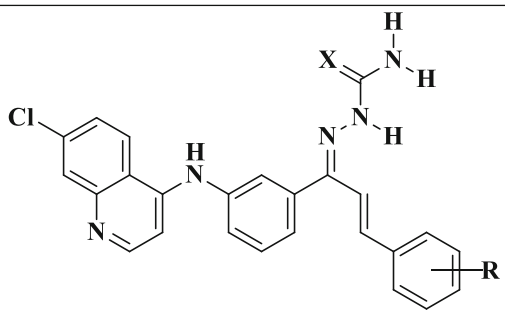
((X = S, 8a-i), (X = O, 9a-i))

Comp.	*R*	Mol. formula	Melting point (°C)[a]	MIC (μM)[b]	Drug score[c]
6a	4-CH_3	$C_{26}H_{22}ClN_5S$	196–198	12.5	0.69
6b	4-OCH_3	$C_{26}H_{22}ClN_5OS$	190–192	12.5	1.02
6c	3,4-OCH_3	$C_{27}H_{24}ClN_5O_2S$	148–150	25.0	1.09
6d	3,4,5-OCH_3	$C_{28}H_{26}ClN_5O_3S$	138–140	12.5	0.98
6e	4-Cl	$C_{25}H_{19}Cl_2N_5S$	142–143	12.5	0.78
6f	4-F	$C_{25}H_{19}ClFN_5S$	178–180	50.0	0.75
6 g	4-Br	$C_{25}H_{19}BrClN_5S$	186–188	50.0	0.58
6 h	4-NO_2	$C_{25}H_{19}ClN_6O_2S$	216–218	50.0	0.24
6i	4-OH	$C_{25}H_{20}ClN_5OS$	230–232	50.0	0.88
7a	4-CH_3	$C_{26}H_{22}ClN_5O$	148–150	6.25	0.87
7b	4-OCH_3	$C_{26}H_{22}ClN_5O_2$	238–240	25.0	1.12
7c	3,4-OCH_3	$C_{27}H_{24}ClN_5O_3$	214–216	1.56	1.18
7d	3,4,5-OCH_3	$C_{28}H_{26}ClN_5O_4$	238–240	12.5	1.07
7e	4-Cl	$C_{25}H_{19}Cl_2N_5O$	174–186	12.5	0.96
7f	4-F	$C_{25}H_{19}ClFN_5O$	230–232	25.0	0.94
7 g	4-Br	$C_{25}H_{19}BrClN_5O$	244–246	1.56	0.76
7 h	4-NO_2	$C_{25}H_{19}ClN_6O_3$	196–198	12.5	0.35
7i	4-OH	$C_{25}H_{20}ClN_5O_2$	240–242	6.25	1.07
8a	4-CH_3	$C_{26}H_{22}ClN_5S$	238–240	12.5	0.55
8b	4-OCH_3	$C_{26}H_{22}ClN_5OS$	210–212	25.0	0.86
8c	3,4-OCH_3	$C_{27}H_{24}ClN_5O_2S$	120–122	25.0	0.94
8d	3,4,5-OCH_3	$C_{28}H_{26}ClN_5O_3S$	240–242	25.0	0.85
8e	4-Cl	$C_{25}H_{19}Cl_2N_5S$	212–214	25.0	0.62
8f	4-F	$C_{25}H_{19}ClFN_5S$	234–236	50.0	0.60
8 g	4-Br	$C_{25}H_{19}BrClN_5S$	238–240	25.0	0.43
8 h	4-NO_2	$C_{25}H_{19}ClN_6O_2S$	218–220	25.0	0.13
8i	4-OH	$C_{25}H_{20}ClN_5OS$	250–252	50.0	0.71
9a	4-CH_3	$C_{26}H_{22}ClN_5O$	192–194	6.25	0.73
9b	4-OCH_3	$C_{26}H_{22}ClN_5O_2$	188–190	12.5	0.96
9c	3,4-OCH_3	$C_{27}H_{24}ClN_5O_3$	254–256	12.5	1.03
9d	3,4,5-OCH_3	$C_{28}H_{26}ClN_5O_4$	258–260	25.0	0.94
9e	4-Cl	$C_{25}H_{19}Cl_2N_5O$	226–228	25.0	0.80
9f	4-F	$C_{25}H_{19}ClFN_5O$	198–200	25.0	0.78
9 g	4-Br	$C_{25}H_{19}BrClN_5O$	306–308	25.0	0.61

Table 1 Physical data and antimycobacterial activities of compound (**6a-i**), (**7a-i**), (**8a-i**), and (**9a-i**) against MTB $H_{37}Rv$ *(Continued)*



((X = S, 6a-i), (X = O, 7a-i))



((X = S, 8a-i), (X = O, 9a-i))

Comp.	*R*	Mol. formula	Melting point (°C)[a]	MIC (μM)[b]	Drug score[c]
9 h	4-NO_2	$C_{25}H_{19}ClN_6O_3$	246–248	25.0	0.25
9i	4-OH	$C_{25}H_{20}ClN_5O_2$	234–236	25.0	0.90
INH[d]	–	$C_6H_7N_3O$	–	1.56	0.53
Pyra[e]	–	$C_5H_5N_3O$	–	50.0	− 0.15
Cipro[f]	–	$C_{17}H_{18}FN_3O_3$	–	12.5	0.93

[a]The melting points were determined in open capillary tubes and are uncorrected
[b]Minimum inhibitory concentration against *Mycobacterium tuberculosis* $H_{37}Rv$
[c]Calculated using molsoft (http://molsoft.com/mprop/)
[d]Isoniazid
[e]Pyrazinamide
[f]Ciprofloxacin

found to be equally active as ciprofloxacin (12.5 μM). When compared to pyrazinamide (50.0 μM), most of the compounds were found to be more active, though 34 compounds were less potent than the first-line antitubercular drug isoniazid. Further, the following features of structure-activity relationship (SAR) of 7-chloro-N-phenylquinolin-4-amine derivatives (**6a-i**), (**7a-i**), (**8a-i**), and (**9a-i**) have been drawn against the inhibition of *Mycobacterium tuberculosis*. The thiosemicarbazide (**6a-i**) compounds with electron donating groups like 4-CH_3 (**6a**), 4-OCH_3 (**6b**), and 3,4,5-OCH_3 (**6d**) have shown activity at 12.5 μM. When the same methoxy group was substituted at C-3 and C-4 positions (3,4-OCH_3), the activity decreased to 25 μM as shown by compound **6c**. Substitution of the C-4 position by a hydroxyl group (**6i**) further decreased the activity to 50 μM. Compounds **6f**, **6g**, and **6h** with electron withdrawing groups like F, Br, and NO_2 substituted at the C-4 position showed very weak activity (50 μM). However, the 4-chloro substituted compound **6e** showed moderate activity (12.5 μM).

Among the semicarbazones (**6a-i**), compounds **7c** and **7g** displayed very promising activity at 1.56 μM, which was higher than the activities shown by their thiosemicarbazone counterparts. Compound **7a** with an alkyl substituent (4-CH_3) showed better activity at 6.25 μM as compared to **6a**, whereas compound **7b** with an alkoxy (4-OCH_3) substituent displayed decreased activity as compared to **6b**. Compounds with 3,4,5-$(OCH_3)_3$ group (**7d**) and 4-Cl group (**7e**) showed activities at 12.5 μM, similar to **6d** and **6e**. Compound **7g** with an electronegative group at position C-4 proved to be the next most potent molecule by exhibiting inhibitory activity at 1.56 μM. Compounds **7h** (4-NO_2) and **7i** (4-OH) displayed better inhibitory activities (12.5 μM and 6.25 μM) as compared to compounds **6h** and **6i** (50 μM). In the next series, the compound **8a** with an electron donating 4-CH_3 group has shown inhibitory activity at 12.5 μM. Other compounds **8b**, **8c**, and **8d** with electron donating groups like 4-OCH_3, 3,4-$(OCH_3)_2$, and 3,4,5-$(OCH_3)_3$ have shown inhibitory activity at 25 μM. Compounds with electron accepting substituents at the C-4 position like Cl (**8e**), Br (**8 g**), and NO_2 (**8 h**) also showed activity at 25 μM, whereas compounds **8f** (with substituent 4-F) and **8i** (with substituent 4-OH) showed inhibitory activity at 50 μM. In these meta-substituted compounds, the most potent compound was **9a** with a 4-methyl substituent exhibiting activity at 6.25 μM, which was better than that exhibited by **8a**. Compounds **9b** and **9c** with electropositive substituents like 4-OCH_3 and 3,4-OCH_3 showed inhibitory activities at 12.5 μM, both being better than compound **8b** and **8c** with activity at 25 μM. Compounds **9d**, **9e**, **9g**, and **9h** displayed activities at 25 μM, which was similar to activities shown by **8d**, **8e**, **8g**, and **8h**. Compounds **9f** and **9i** with electronegative substituents 4-F and 4-OH showed better activities at 25 μM when compared with **8f** and **8i**. With respect to structure-activity relationship, the study revealed that the nature of carbazide and substituent(s) on the phenyl

Table 2 Molecular parameters of 7-chloro-4-aminoquinoline based semicarbazones and thiosemicarbazones (**6a-i**), (**7a-i**), (**8a-i**), and (**9a-i**)

Compounds	TPSA	n-rotb	nON	nOHNH	miLog*p*	MW
Rule of 5	–	–	≤ 10	≤ 5	≤ 5	≤ 500
6a	75.33	7	5	4	7.101	472
6b	84.567	8	6	4	6.71	488
6c	93.801	9	7	4	6.299	518
6d	103.035	10	8	4	6.284	548
6e	75.333	7	5	4	7.331	492
6f	75.333	7	5	4	6.817	475
6 g	75.333	7	5	4	7.462	536
6 h	121.157	8	8	4	6.612	502
6i	95.561	7	6	5	6.174	473
7a	92.404	6	6	4	6.561	455
7b	101.638	7	7	4	6.169	471
7c	110.872	8	8	4	5.759	501
7d	120.106	9	9	4	5.743	532
7e	92.404	6	6	4	6.79	476
7f	92.404	6	6	4	6.276	459
7 g	92.404	6	6	4	6.921	520
7 h	138.228	7	9	4	6.071	486
7i	112.632	6	7	5	5.633	457
8a	75.333	7	5	4	7.077	472
8b	84.567	8	6	4	6.686	488
8c	93.801	9	7	4	6.275	518
8d	103.035	10	8	4	6.26	548
8e	75.333	7	5	4	7.307	492
8f	75.333	7	5	4	6.793	475
8 g	75.333	7	5	4	7.438	536
8 h	121.157	8	8	4	6.588	502
8i	95.561	7	6	5	6.15	473
9a	92.404	6	6	4	6.537	455
9b	101.638	7	7	4	6.145	471
9c	110.872	8	8	4	5.735	501
9d	120.106	9	9	4	5.719	532
9e	92.404	6	6	4	6.766	476
9f	92.404	6	6	4	6.252	459
9 g	92.404	6	6	4	6.897	520
9 h	138.228	7	9	4	6.047	486
9i	112.632	6	7	5	5.609	457
INH	68.013	1	4	3	− 0.969	137
Pyra	68.878	1	4	2	− 0.711	123
Cipro	74.569	3	6	2	− 0.701	331

TPSA topological polar surface area, *n-rotb* number of rotatable bonds, *nON* number of hydrogen bond acceptors, *nOHNH* number of hydrogen bond donors, *miLogP* logarithm of compound partition coefficient between n-octanol and water, *MW* molecular weight, *INH* isoniazid, *Pyra* pyrazinamide, *Cipro* ciprofloxacin

ring greatly affects the antitubercular activity. Thus, the comparative study of thiosemicarbazones and semicarbazones revealed that in general, semicarbazone compounds exhibited better inhibitory activity against *Mycobacterium tuberculosis*.

In recent years, drug likeness and rule of five models [25–27] are a novel approach for better understanding molecular parameters. The obtained results are showing that most of the synthesized compounds have better predicted value of hydrogen bond acceptor, polar surface area, and hydrogen bond donor. According to Lipinski's rule of five, a biological therapeutic ligand should have number of hydrogen bond accepter atoms of 10 or less (N or O), number of hydrogen bond donor atoms of 5 or less, log *p* not more than 5, and molecular weight (MW) of 500 or less. The values of calculated drug scores revealed that most of the synthesized analogs have positive drug likeness score; interestingly, compound **7c** exhibited promising inhibitory activity against *Mycobacterium tuberculosis* and highest drug likeness score Table 2.

Cytotoxicity activity assay

The in vitro cytotoxicity of the active compounds (MIC ≤ 12.5 μM *Mycobacterium tuberculosis*) was evaluated against normal HDF cell line using 3-(4, 5-dimethylthiazo-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) cell proliferation assay. The graphical representation of the cell growth inhibition by the active compounds at a concentration of 50 μM is shown in Table 3. The assay data revealed that none of the active compounds are toxic to the normal cells thus proving the lack of general toxicity.

Table 3 Cytotoxicity of compounds against HDF (human dermal fibroblast) cell line

Compound	% cell viability[a] (50 μM)
6a	23.87
6b	20.81
6d	23.18
6e	25.83
7a	20.18
7c	26.39
7d	19.40
7e	19.57
7 g	24.35
7 h	27.83
7i	23.28
8a	23.87
9a	20.81
9b	23.18
9c	25.83

[a]Each experiment was independently performed three times, and data are shown as means SD

Conclusion

In conclusion, a series of 7-chloro-N-phenylquinolin-4-amine derivatives (**6a-i**), (**7a-i**), (**8a-i**), and (**9a-i**) have been designed and synthesized. All synthesized derivatives underwent in vitro antitubercular evaluation against *Mycobacterium tuberculosis* $H_{37}Rv$ (MTB), and selected analogs were screened for cytotoxicity against normal HDF cell line by MTT cell proliferation assay. The results displayed that among the tested compounds, the most potent antitubercular activity was displayed by **7c** and **7g** with MIC = 1.56 μM and with low cytotoxicity. Thus, it can be concluded that 7-chloro-N-phenylquinolin-4-amines could be a promising approach for the design of new MTB inhibitory agents.

Additional file

Additional file 1. Supplementary material.

Abbreviations

DOTS: Directly observed therapy short-course; INH: Isoniazid; MIC: Minimum inhibitory concentration; MTB: *Mycobacterium tuberculosis*; MTT: 3-(4, 5-dimethylthiazo-2-yl)-2,5-diphenyl-tetrazolium bromide; PZA: Pyrazinamide; RIF: Rifampicin; TB: Tuberculosis

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Authors' contributions

All authors have read and approved the manuscript. SA designed and outlined and contributed to the characterization of the study. KK, SK, RK, and PS managed the synthetic application. MP, SA, and SS contributed to the analytical work.

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Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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