

# Substituted quinolinyl chalcones and quinolinyl pyrimidines

## as a new class of anti-infective agents

Moni Sharma,<sup>a</sup> Vinita Chaturvedi,<sup>b</sup> Y.K. Manju,<sup>b</sup> Shalini Bhatnagar,<sup>b</sup> Kumkum Srivastava,<sup>c</sup> S. K. Puri,<sup>c</sup> and Prem M. S. Chauhan\*<sup>a</sup>

<sup>a</sup>Division of Medicinal Chemistry, Central Drug Research Institute, Lucknow 226001, India

<sup>b</sup>Anti- TB Screening Unit, <sup>c</sup>DTDDD, Central Drug Research Institute, Lucknow-226001, India

<sup>c</sup>Division of Parasitology, Central Drug Research Institute, Lucknow 226001, India

**Abstract-** Frequency of tuberculosis and malaria is progressively increasing worldwide. New emerging strain of bacterium and resistance to currently available drugs make this field more conscientious and alarming. In this connection a series of substituted quinolinyl chalcones and substituted quinolinyl pyrimidines were synthesised and evaluated for their in vitro antitubercular activity against *Mycobacterium tuberculosis* H<sub>37</sub>R<sub>V</sub> and antimalarial activity against NF-54 strain of *Plasmodium falciparum*. A comparison of structure-activity relationship reveals that different physicochemical and structural requirements exist for these two activities. Out of synthesized compounds, compound No. **18, 19** have shown antitubercular activity of MIC **3.12** µg/ml and were non toxic against VERO, MBMDM cell lines and compounds **49, 50, 51** have shown antimalarial activity of MIC **1.0** µg/ml.

Keywords: Tuberculosis, Malaria, Chalcones, Pyrimidines.

CDRI communication No. 7510

\*Corresponding author E-mail: prem\_chauhan\_2000@yahoo.com; premsc58@hotmail.com

Fax: +91 522 2623405.

### 1. Introduction

Tuberculosis (TB) caused by *Mycobacterium tuberculosis*, a facultative intracellular bacterium, is the leading single agent killer in the world among the infectious diseases [1-5]. The incidence of the tuberculosis has been progressively increasing worldwide with an elevated mortality rate. One third of the world's human civilization is thought to be infected with *Mycobacterium tuberculosis*, rising eight million new cases of the tuberculosis each year [6-8]. WHO estimates that 24000 people develop active disease and close to 5000 people die from the tuberculosis everyday [9-10]. Two developments make the resurgence in TB specifically alarming. The first is pathogenic synergy with HIV. The second is the emergence of drug resistant and multi-drug resistant TB (MDRTB) [11]. Although existing first line antitubercular drugs; Pyrazinamide, Isoniazid, Rifampin, Streptomycin and Ethambutol can achieve more than 99% efficacy but this is often reduced because of the above facts. So in this vision a search for the new antitubercular substances has ranked among the priority areas of chemotherapeutic researches, further accelerated after the WHO declaration of tuberculosis as a "Global health emergency" [12].

In conjunction with the spread of tuberculosis, malaria is also a devastating, parasitic infectious disease having high mortality rate [13-14]. The global picture of malaria is such that 300-500 million people are infected and atleast one million die each year including children under the age of five [15,16]. Widespread use of currently available drugs can profoundly influence the evolution of the human malaria parasite and the impact of these drugs on parasite genomes worldwide has been difficult to evaluate [17].

The development of new drugs will be greatly facilitated by a complete understanding of the molecular mechanism underlying previously successful antitubercular and antimalarial drugs [18]. For

structurally simple group of compounds, chalcones have displayed an impressive array of pharmacological activities like anti-protozoal [19-20], anti-inflammatory [21] immunomodulatory [22], nitric oxide inhibition [23], anticancer [24], activities. On the other hand Pyrimidine scaffold was the base of many bioactive molecule as antimalarial such as Pyrimethamine (**1**), Cycloguanil (DHFR inhibitor) [25], antibacterial (Trimethoprim, Iclaprim) [26], antitubercular (**2**) [27], Pyrazinamide (**3**).

Compounds act on more than one target site were liable to be more active. In our ongoing research, devoted to the synthesis of diverse heterocycles as anti-infective agents, we identified the pyrimidine and quinoline (separately) as good anti-infectious agents [28-38]. In this communication we described the synthesis of hybrid molecules consisting of chalcones and pyrimidines along with quinoline moiety and highlighted their in vitro antitubercular and antimalarial activities.

## 2. Chemistry

To synthesize Oxo linked pyrimidines (**32-43**) and amino linked pyrimidines (**44-59**), oxo linked chalcones (**4-15**) and amino linked chalcones (**16-31**) were reacted with guanidine hydrochloride in the presence of NaH in DMF. Chalcones (**4-15**) Oxo linked and (**16-31**) Amino linked were prepared by standard claisen Schmidt aldol condensation reaction of intermediates (**2**) and (**3**) with different aldehydes in 10% NaOH and MeOH. Intermediate (**2**) was synthesized by nucleophilic *ipso* substitution of 4-chloro of 4,7-dichloroquinoline with 4-hydroxy acetophenone in DMF in the presence of potassium hydroxide at 120 °C and intermediate (**3**) was synthesized by nucleophilic substitution of 4-chloro of 4,7-dichloroquinoline with 4-amino acetophenone in MeOH (Scheme 1). All the synthesized compounds were well characterized by spectroscopic methods such as IR, mass, NMR and elemental analysis.

## 3. Biological activity

Evaluation of in vitro antitubercular activity against *M. tuberculosis* H<sub>37</sub>Rv was carried out with a recommended protocol [39] using Middlebrook (MB) 7H10 agar medium. A 100 µl of serial two fold dilutions of the stock (1.0 mg /ml in DMSO, Dimethyl Sulphoxide) of test compounds and standard antitubercular drugs {isoniazid (INH) and rifampicin (RFM)} were incorporated in the medium (final volume, 2 ml/ tube) supplemented with OADC (oleic acid, albumin fraction IV, dextrose and catalase). Compounds/ drugs containing tubes were kept in slanting position till the medium solidified. Culture of *M. tuberculosis* H<sub>37</sub>RV grown on Lowenstein-Jensen (L-J) was harvested in N-saline containing 0.05% Tween-80. The culture was vigorously agitated with glass beads to make a single cell suspension. A working inoculum (2x 10<sup>7</sup> cfu/ ml; 10 µl/ tube) of mycobacterium was spread on the surface of the medium and the tubes were kept at 37°C for 4 weeks for the appearance of colonies. Tubes containing no drug served as control. The minimum concentration of the drugs (INH and RFM) / compounds that completely inhibited the growth of mycobacterium was recorded as Minimum Inhibitory Concentration (MIC) with respect to the used inoculums.

### Cytotoxic evaluation

(i) In VERO:<sup>14</sup> VERO cells (10<sup>4</sup> cells/well/0.1ml MEM containing antibiotics and 10% FBS) were seeded in 96 wells tissue culture plate. After 24 hrs incubation (37 °C, 5% CO<sub>2</sub>) medium was replaced with fresh medium (5% FBS and no antibiotic) containing different concentrations of test compound/ known toxic compound/DMSO. After 24 hrs incubation (37 °C, 5 % CO<sub>2</sub>) 20 ul MTS reagent (Promega Kit) is added and absorbance is read after 2 hrs at 490nm. Absorbance shown by DMSO containing wells is taken as 100% survivors. A compound is considered toxic if it causes 50% inhibition at concentration 10 fold higher than its MIC.

(ii) In Mouse Bone Marrow Macrophages: Plated 10<sup>5</sup> cells/0.1 ml/ well in Dulbecco,s Minimum Essential Medium (DMEM) (supplemented with antibiotics, 10% FBS, 15% (v/v) L-929 fibroblast conditioned supernatant and non-essential amino acids) in 96 wells tissue culture plate. After 5 days

incubation (37°C 5% CO<sub>2</sub>) 20µl MTS reagent (Promega Kit) was added and absorbance read after 2 hrs at 490 nm. Absorbance shown by DMSO containing wells is taken as 100% survivors. A compound is considered toxic if it causes 50% inhibition at concentration 10 fold higher than its MIC. The in vitro antimalarial assay was carried out in 96-well microtitre plates according to the microassay of Rieckmann et al [40]. The culture of *P. falciparum* NF-54 strain is routinely being maintained in medium RPMI-1640 supplemented with 25mM HEPES, 1% D-glucose 0.23% sodium bicarbonate and 10% heat inactivated human serum [41]. The asynchronous parasite of *P. falciparum* was synchronized after 5% D-sorbitol treatment to obtain parasitized cells harboring only the ring stage. For carrying out the assay, an initial ring stage parasitemia of ≈1% at 3% haematocrit in a total volume of 200µL of medium RPMI-1640 was uniformly maintained. The test compound in 20µL volume at required concentration (ranging between 0.25 µg/ml and 50 µg/ml) in duplicate wells was incubated with parasitized cell preparation at 37°C in a candle jar. After 36-40h incubation, the blood smears from each well were prepared and stained with giemsa stain. The slides were microscopically observed to record maturation of ring stage parasites into trophozoites and schizonts in the presence of different concentrations of compounds. The test concentration that inhibits the complete maturation into schizonts was recorded as the minimum inhibitory concentration (MIC).

#### 4. Results and Discussion

All the 56 synthesized compounds were screened against H<sub>37</sub>Rv strains of the *Mycobacterium tuberculosis* and NF-54 strains of *P. falciparum*. Among all, compounds of the first series where 4-oxo linkage between quinoline and chalcone **4-15** and pyrimidine **32-43** were found to be inactive, while their 4-amino linked analogues **16-31** and **44-59** showed promising activity against *Mycobacterium tuberculosis* and *P. falciparum* strains. These results immediately suggested the straightforward structure activity relationship of 4-amino linker over the 4-oxo linked compounds. Activity of the resulting hybrid chalcones and pyrimidines reveal that different physicochemical and structural requirements exist for these two activities. The 2,3-dimethoxyphenyl **18** and 2,5-dimethoxyphenyl **19** substituted derivative of chalcones were found to be active against Mtb showed MIC of 3.12 µg/ml and are non toxic against VERO and MBMDM cell lines, while their pyrimidine analogues were found to be inactive against the same strain. Compound **20** having chloro substitution at para position of phenyl ring showed MIC of 6.25 µg/ml. The 3,4,5-trimethoxy substituted phenyl system **48** was found to be active against Mtb have shown MIC of 12.5 µg/ml as compared to dimethoxy substituted phenyl systems **56** and **57** in pyrimidines, it is because of the analogy of resulting compound with antibacterial drug trimethoprim. Substitution with heterocyclic ring system did not alter the activity of pyrimidines to any greater extent, however oxygen containing heterocycle **47** is found to be moderately active showed MIC of 12.5 µg/ml against Mtb over the nitrogen containing heterocycle, 3-pyridyl substitution **50**. Contrarily nitrogen containing heterocycle compound **50** has shown significantly activity against *P. falciparum* showed MIC of 1.0 µg/ml compared to their oxygen containing heterocyclic analogue compound **47**. While compound **48** having isopropyl substitution at para position have shown activity against Mtb, showed MIC of 12.5 µg/ml. None of the chalcones have shown activity in malaria while their pyrimidine scaffolds were significantly active showed MIC in the range of 1-2 µg/ml. 4-Isopropyl and thiomethyl substituted phenyl ring systems were found inactive against Mtb, on the other hand same compounds **49** and **51** were found to be active in malaria and showed MIC of 1.0 µg/ml. Substitution of phenyl ring with 4-methoxy group reduced the activity of compound **46** to MIC of 2.0 µg/ml. All the results shown in Table 1.

#### 5. Conclusion

In conclusion, we have reported the systematic evaluation of the structure-activity relationships of the synthesized quinolinyl chalcones and quinolinyl pyrimidines. The in vitro screening of these synthesized compounds against *Mycobacterium tuberculosis* and *Plasmodium falciparum* have

shown promising activity. Out of the synthesized compounds, six compounds have shown antitubercular activity with MIC in the range of 3.12-12.5  $\mu\text{g/ml}$  and are nontoxic against VERO and MBMDM cell lines. Four compounds have shown antimalarial activity with MIC ranging from 1-2  $\mu\text{g/ml}$ . The SAR of these compounds showed that quinolinyl chalcones are antitubercular agents while their pyrimidine analogues were inactive against the same strain. On the other hand the pyrimidine analogues of these compounds were found to be active against malaria. On the basis of above observations, we will further modify to improve the anti-infective activity of chalcones and pyrimidines.

## 6. Experimental

IR spectra was recorded on Beckman Aculab-10, Perkin Elmer 881 and FTIR 8210 PC, Shimadzu spectrophotometers either on KBr discs or in neat. Nuclear magnetic resonance spectra were recorded on either Bruker Avance DRX-300 MHz or Bruker DPX 200 FT spectrometers using TMS as an internal reference. FAB mass spectra were recorded on JEOL SX 102/DA 6000 mass spectrometer using Argon/Xenon (6 Kv, 10mA) as the FAB gas. Chemical analysis was carried out on Carlo-Erba-1108 instrument. The melting points were recorded on an electrically heated melting point apparatus and are uncorrected.

### *Synthesis of 1-(4-(7-chloroquinolin-4-yloxy)phenyl)ethanone (2)*

The mixture of 4,7-dichloroquinoline (1.0 equiv), 4-hydroxyacetophenone (1.5 equiv) and KOH (1.5 equiv) in DMF was refluxed for 6h. Water was added into the reaction mixture, a solid started separating out. The solid was filtered out and purified by column chromatography to obtain compound **2** as a white crystals.

Yield: 60%; m.p. Yield: 65%; mp 165-168  $^{\circ}\text{C}$ ; MS: 298 (M+1), IR (KBr): 3073, 2350, 1648, 1610, 1573, 1526, 1430, 1354, 1210, 1072, 776, 670  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ):  $\delta$  9.01 (d, 1H,  $J = 8.7$  Hz, Ar-Qn), 8.41 (d, 1H,  $J = 9.0$  Hz, Ar-Qn), 8.03 (d, 2H,  $J = 8.4$  Hz, Ar), 7.83 (d, 1H,  $J = 9.0$  Hz, Ar-Qn), 7.71 (d, 1H,  $J = 1.8$  Hz, Ar-Qn), 7.19 (d, 2H,  $J = 8.7$  Hz, Ar), 6.49 (d, 1H,  $J = 8.4$  Hz, Ar-Qn), 2.68 (s, 3H,  $-\text{COCH}_3$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  189.91, 160.64, 159.87, 155.21, 147.38, 135.83, 133.08, 130.21, 129.13, 128.91, 124.67, 120.91, 118.17, 107.32, 30.18; Anal. Calcd. for  $\text{C}_{17}\text{H}_{12}\text{ClNO}_2$ : C 70.19, H 4.76, N 6.30; Found: C 70.0, H 4.90, N 6.78%.

### *1-(4-(7-chloroquinolin-4-ylamino)phenyl)ethanone (3)*

The mixture of 4,7-dichloroquinoline (1.00 equiv) and 4-amino-acetophenone (1.5 equiv) in MeOH was refluxed for 6h. The solvent was evaporated under vacuum and solid mass was obtained. The solid was recrystallised by methanol to obtain compound **3** as a yellow solid.

Yield: 85%; m.p. 160-162  $^{\circ}\text{C}$ ; MS: 297 (M+1), IR (KBr) 3435, 3021, 2361, 1670, 1623, 1473, 1215, 1093, 761, 669  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3 + \text{CD}_3\text{OD}$ ):  $\delta$  8.69 (d, 1H,  $J = 9.1$  Hz, Ar-Qn), 8.37 (d, 1H,  $J = 9.0$  Hz, Ar-Qn), 8.19-8.12 (m, 3H, Ar, NH), 7.66 (d, 1H,  $J = 8.6$  Hz, Ar-Qn), 7.62 (d, 1H,  $J = 2.1$  Hz, Ar-Qn), 7.47 (d, 2H,  $J = 8.4$  Hz, Ar), 7.06 (d, 1H,  $J = 8.3$  Hz, Ar-Qn), 2.71 (s, 3H,  $-\text{COCH}_3$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3 + \text{CD}_3\text{OD}$ ):  $\delta$  191.03, 152.38, 150.79, 148.36, 148.13, 135.63, 132.67, 130.16, 129.78, 125.13, 123.62, 120.62, 114.62, 110.07, 31.07; Anal. Calcd. for  $\text{C}_{17}\text{H}_{13}\text{ClN}_2\text{O}$ : C 68.81, H 4.42, N 9.44; Found: C 68.78, H 4.60, N 9.68%.

### *6.1. General procedure for synthesis of compounds 4-31*

Method a: 1 equiv of substituted quinoline was added dropwise to a cooled solution of 10% NaOH, 1.5 equiv of liquid aldehydes over a period of 30 min. The solution was maintained at  $0^{\circ}\text{C}$  for an hour then was allowed to stir at room temperature. After some time, a solid started separating out. The solution was further stirred for about 1 h. The solid was filtered out and recrystallised from methanol or ethanol to afford crystals of the chalcone having yield in the range 60-79%.

Method B: In case of solid aldehydes, the aldehydes (1.3 equiv) were first dissolved in a minimum quantity of methanol and then 10% NaOH solution was added to it to give a clear solution. The solution was cooled up to 0°C and 1 equiv of substituted quinoline was added dropwise to it, in around 30 min. The solution was maintained at 0°C for an hour then was allowed to stir at room temperature. After some time, a solid started separating out. The solution was further stirred for about 1h. The solid was filtered out and recrystallised from methanol or ethanol to afford crystals of the chalcone having yield in the range 60-79%.

#### 6.1.1. 1-(4-(7-chloroquinolin-4-yloxy)phenyl)-3-phenylprop-2-en-1-one (4)

Yield: 65%; m.p. 172-174 °C; MS: 386 (M+1), IR (KBr) 3061, 2362, 1663, 1567, 1492, 1376, 1215, 1097, 979, 833, 749, 670 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 8.74 (d, 1H, *J* = 5.34 Hz, Ar-Qn), 8.26 (d, 1H, *J* = 9.0 Hz, Ar), 8.16 (d, 2H, *J* = 8.7 Hz, Ar), 8.12 (d, 1H, *J* = 1.8 Hz, Ar-Qn), 7.86 (d, 1H, *J* = 15.6 Hz, -CH=CH-), 7.49-7.55 (m, 4H), 7.66-7.69 (m, 2H, Ar), 7.52-7.58 (m, 2H, Ar-Qn, -CH=CH-), 7.41-7.45 (m, 2H, Ar), 7.26 (d, 2H, *J* = 9.0 Hz, Ar), 7.16 (d, 1H, Ar), 6.69 (d, 1H, *J* = 5.4 Hz, Ar-Q); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 188.23, 160.71, 158.08, 152.06, 150.47, 145.21, 136.46, 135.55, 134.76, 131.03, 128.98, 128.47, 128.37, 127.48, 123.13, 121.34, 120.48, 119.92, 105.53, 96.15. Anal. Calcd. for C<sub>24</sub>H<sub>16</sub>ClNO<sub>2</sub>: C 74.71, H 4.18, N 3.63; Found: C 74.69, H 4.36, N 3.38%.

#### 6.1.2. 1-(4-(7-chloroquinolin-4-yloxy)phenyl)-3-*p*-tolylprop-2-en-1-one (5)

Yield: 60%; m.p. 160-162 °C; MS: 400 (M + 1), IR (KBr): 3045, 2918, 2362, 1658, 1597, 1492, 1376, 1216, 1092, 982, 809, 770 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.71 (d, 1H, *J* = 5.46 Hz, Ar-Qn), 8.31 (d, 1H, *J* = 9.0 Hz, Ar-Qn), 8.26 (d, 2H, *J* = 8.7 Hz, Ar), 8.17 (d, 2H, *J* = 8.6 Hz, Ar), 7.81 (d, 1H, *J* = 15.6 Hz, -CH=CH-), 7.73 (d, 1H, *J* = 2.1 Hz, Ar-Qn), 7.51-7.46 (m, 3H, Ar, -CH=CH-), 7.39 (d, 1H, *J* = 9.0 Hz, Ar-Qn), 6.79 (d, 2H, *J* = 8.7 Hz, Ar), 6.91 (d, 1H, *J* = 5.6 Hz, Ar-Qn), 2.19 (s, 3H, -CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 189.38, 161.72, 158.92, 153.08, 146.68, 137.82, 136.81, 133.62, 129.06, 127.68, 126.48, 125.38, 123.16, 122.38, 121.64, 120.69, 119.49, 119.32, 105.38, 98.13, 21.56; Anal. Calcd. for C<sub>25</sub>H<sub>18</sub>ClNO<sub>2</sub>: C 75.09, H 4.54, N 3.50; Found: C 75.28, H 4.78, N 3.70%.

#### 6.1.3. 1-(4-(7-chloroquinolin-4-yloxy)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (6)

Yield: 65%; m.p. 158-160 °C; MS: 416 (M + 1); IR (KBr): 3045, 2918, 2362, 1658, 1597, 1480, 1367, 1206, 1198, 980, 823, 770 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.73 (d, 1H, *J* = 5.4 Hz, Ar-Qn), 8.30 (d, 1H, *J* = 9.0 Hz, Ar-Qn), 8.16 (d, 2H, *J* = 8.6 Hz, Ar), 8.07 (d, 1H, *J* = 1.8 Hz, Ar-Qn), 7.93 (d, 2H, *J* = 8.7 Hz, Ar), 7.63 (d, 1H, *J* = 15.6 Hz, -CH=CH-), 7.59-7.55 (q, 1H, *J* = 2.1 Hz), 7.41 (d, 1H, *J* = 15.6 Hz, -CH=CH-), 6.97 (d, 2H, *J* = 8.7 Hz, Ar), 6.94 (d, 2H, *J* = 9.0 Hz, Ar), 6.37 (d, 1H, *J* = 5.3 Hz, Ar-Qn), 3.93 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>+ CD<sub>3</sub>OD): δ 190.32, 160.38, 158.91, 157.26, 152.37, 151.78, 147.28, 136.76, 134.98, 134.23, 131.67, 128.32, 126.27, 125.91, 125.48, 124.02, 122.38, 121.36, 119.05, 98.31, 23.38; Anal. Calcd. for C<sub>25</sub>H<sub>18</sub>ClNO<sub>3</sub>: C 72.20, H 4.36, N 3.37; Found: C 72.36, H 4.17, N 3.08%.

#### 6.1.4. 1-(4-(7-chloroquinolin-4-yloxy)phenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (7)

Yield: 78%; m.p. 168-170 °C; MS: 476 (M + 1); IR (KBr): 3063, 2999, 2832, 2362, 1658, 1590, 1452, 1377, 1211, 1130, 1032, 826, 768, 696 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.74 (d, 1H, *J* = 5.46 Hz, Ar-Qn), 8.28 (d, 1H, *J* = 9.0 Hz, Ar-Qn), 8.17 (d, 2H, *J* = 8.7 Hz, Ar), 8.14 (d, 1H, *J* = 2.1 Hz, Ar-Qn), 7.80 (d, 1H, *J* = 15.3 Hz, -CH=CH-), 7.59-7.55 (dd, 1H, *J* = 8.4 Hz, *J* = 2.1 Hz, Ar-Qn), 7.43 (d, 1H, *J* = 15.6 Hz, -CH=CH-), 7.32 (d, 2H, *J* = 9.0 Hz, Ar), 6.90 (s, 2H, Ar), 6.70 (d, 1H, *J* = 5.34 Hz, Ar-Qn), 3.95 (s, 6H, OCH<sub>3</sub>), 3.93 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 188.81, 160.78, 158.08, 153.53, 152.24, 150.41, 145.45, 140.68, 136.44, 135.57, 131.06, 130.18, 128.24, 127.49, 123.24, 120.79, 120.53, 119.98, 105.80, 105.62, 61.02, 56.26. Anal. Calcd. for C<sub>27</sub>H<sub>22</sub>ClNO<sub>5</sub>: C 68.14, H 4.66, N 2.94; Found: C 68.39, H 4.46, N 2.78%.

#### 6.1.5. 1-(4-(7-chloroquinolin-4-yloxy)phenyl)-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one (8)

Yield: 78%; m.p. 160-162<sup>0</sup>C; MS: 476 (M + 1); IR (KBr): 3061, 2998, 2867, 2364, 1655, 1592, 1479, 1379, 1210, 1136, 1038, 830, 756, 730, 690 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.71 (d, 1H, J = 5.34 Hz, Ar-Qn), 8.28 (d, 1H, J = 9.0 Hz, Ar-Qn), 8.11 (d, 2H, J = 8.46 Hz, Ar), 8.07 (d, 1H, J = 2.1 Hz, Ar-Qn), 7.81 (d, 1H, J = 15.6 Hz, -CH=CH-), 7.63 (d, 1H, J = 8.47 Hz, Ar-Qn), 7.55-7.51 (dd, 1H, J = 8.7 Hz, J = 1.8 Hz, Ar-Qn), 7.45 (d, 1H, J = 15.3 Hz, -CH=CH-), 7.37 (d, 2H, J = 9.0 Hz, Ar), 7.21 (d, 1H, J = 8.34 Hz, Ar), 6.67 (d, 1H, J = 5.34 Hz, Ar-Qn), 4.01 (s, 3H, OCH<sub>3</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 3.91 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 189.26, 161.71, 159.23, 155.72, 153.23, 151.64, 147.72, 141.12, 140.62, 138.71, 136.47, 135.62, 132.06, 131.13, 128.71, 127.57, 123.49, 121.83, 120.68, 119.34, 105.83, 105.61, 63.26, 62.71, 58.19; Anal. Calcd. for C<sub>27</sub>H<sub>22</sub>ClNO<sub>5</sub>: C 68.14, H 4.66, N 2.94; Found: C 68.29, H 4.56, N 2.78%.

**6.1.6. 1-(4-(7-chloroquinolin-4-yloxy)phenyl)-3-(furan-2-yl)prop-2-en-1-one (9)**

Yield: 72%; m.p. 165-167<sup>0</sup>C; MS: 376 (M + 1); IR (KBr): 3092, 2926, 2361, 1662, 1603, 1495, 1378, 1223, 1168, 1018, 968, 833, 755 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.73 (d, 1H, J = 5.46 Hz, Ar-Qn), 8.26 (d, 1H, J = 9.0 Hz, Ar-Qn), 8.18 (d, 2H, J = 8.76 Hz, Ar), 8.13 (d, 1H, J = 2.1 Hz, Ar-Qn), 7.65 (d, 1H, J = 15.6 Hz, -CH=CH-), 7.57-7.54 (m, 2H, Ar-Qn, Furan), 7.47 (d, 1H, J = 15.3 Hz, -CH=CH-), 7.28 (d, 2H, J = 8.4 Hz, Ar), 6.76 (d, 1H, J = 3.3 Hz, Furan), 6.67 (d, 1H, J = 5.13 Hz, Ar-Qn), 6.57-6.54 (m, 1H, Furan); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + CD<sub>3</sub>OD): δ 182.23, 154.77, 151.32, 145.41, 144.89, 143.19, 138.81, 130.31, 129.02, 124.80, 124.51, 121.16, 120.80, 116.83, 114.14, 113.40, 112.01, 110.47, 106.30, 98.87. Anal. Calcd for C<sub>22</sub>H<sub>14</sub>ClNO<sub>3</sub>: C 70.31, H 3.75, N 3.73; Found: C 70.29, H 3.66, N 3.78%.

**6.1.7. 1-(4-(7-chloroquinolin-4-yloxy)phenyl)-3-(2,3-dimethoxyphenyl)prop-2-en-1-one (10)**

Yield: 70%; m.p. 158-160<sup>0</sup>C; MS: 446 (M + 1); IR (KBr): 3067, 2953, 2361, 1666, 1604, 1481, 1383, 1266, 1171, 1080, 776, 696 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.73 (d, 1H, J = 5.4 Hz, Ar-Qn), 8.47 (d, 1H, J = 9.0 Hz, Ar-Qn), 8.17 (d, 2H, J = 8.6 Hz, Ar), 7.88-7.83 (m, 2H, Ar-Qn, -CH=CH-), 7.55-7.46 (m, 4H, -CH=CH-, Ar), 7.43 (d, 1H, J = 9.0 Hz, Ar-Qn), 7.17-7.13 (m, 2H, Ar), 6.97 (d, 1H, J = 5.3 Hz, Ar-Qn), 4.01 (s, 3H, OCH<sub>3</sub>), 3.91 (s, 3H, OCH<sub>3</sub>). <sup>13</sup>C (75 MHz CDCl<sub>3</sub> + CD<sub>3</sub>OD): δ 187.67, 160.72, 158.67, 155.37, 151.63, 148.31, 142.67, 141.37, 140.78, 138.23, 136.83, 135.31, 132.81, 131.62, 128.81, 127.56, 124.49, 121.26, 119.68, 119.12, 105.71, 105.31, 64.58, 62.63; Anal. Calcd. for C<sub>26</sub>H<sub>20</sub>ClNO<sub>4</sub>: C 70.03, H 4.52, N 3.14; Found: C 70.22, H: 4.76, N 3.31%.

**6.1.8. 1-(4-(7-chloroquinolin-4-yloxy)phenyl)-3-(2,5-dimethoxyphenyl)prop-2-en-1-one (11)**

Yield: 75%; m.p. 160-162<sup>0</sup>C; MS: 444 (M + 1); IR (KBr): 3071, 2998, 2367, 1655, 1610, 1521, 1479, 1377, 1280, 1078, 786, 776, 696 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.74 (d, 1H, J = 5.13 Hz, Ar-Qn), 8.43 (d, 1H, J = 8.7 Hz, Ar-Qn), 8.37 (d, 2H, J = 8.3 Hz, Ar), 7.97 (d, 1H, J = 1.8 Hz, Ar-Qn), 7.83 (d, 1H, J = 15.6 Hz, -CH=CH-), 7.67-7.63 (m, 3H, Ar), 7.61 (d, 1H, J = 9.0 Hz, Ar-Qn), 7.53-7.47 (m, 2H, -CH=CH-, Ar) 7.27 (d, 1H, J = 8.7 Hz, Ar), 6.91 (d, 1H, J = 5.34 Hz, Ar-Qn) 3.97 (s, 3H, OCH<sub>3</sub>), 3.89 (s, 3H, OCH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + CD<sub>3</sub>OD): 188.23, 160.32, 157.36, 154.72, 151.67, 147.23, 142.87, 141.39, 141.03, 137.71, 137.31, 135.82, 133.06, 131.32, 128.83, 127.58, 123.48, 120.71, 118.93, 118.17, 104.61, 103.93, 63.37, 61.81; Anal. Calcd. for C<sub>26</sub>H<sub>20</sub>ClNO<sub>4</sub>: C 70.03, H 4.52, N 3.14; Found: C 70.12, H 4.76, N 3.35%.

**6.1.9. 3-(4-chlorophenyl)-1-(4-(7-chloroquinolin-4-yloxy)phenyl)prop-2-en-1-one (12)**

Yield: 72%; m.p. 172-174<sup>0</sup>C; MS: 420 (M + 1); IR (KBr): 3063, 2918, 2362, 1666, 1606, 1496, 1379, 1266, 1218, 1030, 976, 831, 752 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.74 (d, 1H, J = 5.6 Hz, Ar-Qn), 8.26-8.21 (m, 3H, Ar-Qn, Ar), 8.17 (d, 1H, J = 1.8 Hz, Ar-Qn), 8.10 (d, 2H, J = 8.7 Hz, Ar), 7.79 (d, 1H, J = 15.6 Hz, -CH=CH-), 7.52-7.43 (m, 4H, Ar, Ar-Qn, -CH=CH-), 7.13 (d, 2H, J = 9.0 Hz, Ar), 6.87 (d, 1H, J = 5.1 Hz, Ar-Qn). <sup>13</sup>C (75 MHz, CDCl<sub>3</sub> + CD<sub>3</sub>OD): δ 187.38, 161.41, 152.38, 151.67, 151.06, 150.23, 147.68, 137.71, 135.08, 134.76, 132.61, 129.11, 125.21, 124.81, 124.08, 123.71, 122.39, 121.68, 118.73, 96.38; Anal. Calcd. for C<sub>24</sub>H<sub>15</sub>Cl<sub>2</sub>NO<sub>2</sub>: C 68.59 H 3.60, N 3.33; Found: C 68.52, H 3.76, N 3.25%.

**6.1.10. 3-(2-chlorophenyl)-1-(4-(7-chloroquinolin-4-yloxy)phenyl)prop-2-en-1-one (13)**

Yield: 70%; m.p. 178-180<sup>0</sup>C; MS: 420 (M + 1); IR (KBr): 3061, 2909, 2367, 1655, 1610, 1570, 1479, 1428, 1377, 1268, 1210, 1023, 831, 756 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.76 (d, 1H, *J* = 5.6 Hz, Ar-Qn), 8.21 (d, 1H, *J* = 8.7 Hz, Ar-Qn), 8.11-8.06 (m, 2H, Ar-Qn, Ar), 7.97 (d, 2H, *J* = 8.6 Hz, Ar), 7.81 (d, 1H, *J* = 15.3 Hz, -CH=CH-), 7.67 (d, 1H, *J* = 8.7 Hz, Ar), 7.59-7.51 (m, 6H, Ar, Ar-Qn, -CH=CH-), 6.89 (d, 1H, *J* = 5.4 Hz, Ar-Qn). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + CD<sub>3</sub>OD): δ 187.61, 159.91, 158.31, 156.12, 151.63, 144.23, 141.32, 140.68, 138.27, 137.57, 136.81, 135.13, 132.67, 131.17, 129.06, 127.67, 124.51, 121.13, 119.13, 118.78, 105.56, 104.93; Anal. Calcd. for C<sub>24</sub>H<sub>15</sub>Cl<sub>2</sub>NO<sub>2</sub>: C 68.59, H 3.60, N 3.33; Found: C 68.22, H 3.46, N 3.25%.

**6.1.11. 1-(4-(7-chloroquinolin-4-yloxy)phenyl)-3-(4-(methylthio)phenyl)prop-2-en-1-one (14)**

Yield: 68%; m.p. 180-182<sup>0</sup>C; MS: 432 (M + 1); IR (KBr): 3042, 2928, 2367, 1655, 1592, 1490, 1377, 1218, 1096, 980, 801, 756 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.67 (d, 1H, *J* = 5.4 Hz, Ar-Qn), 8.27 (d, 1H, *J* = 9.0 Hz, Ar-Qn), 8.19 (d, 2H, *J* = 8.7 Hz, Ar), 8.03 (d, 2H, *J* = 8.6 Hz, Ar), 7.73 (d, 1H, *J* = 15.6 Hz, -CH=CH-), 7.53 (d, 1H, *J* = 15.6 Hz, -CH=CH-), 7.47-7.43 (m, 3H, Ar, Ar-Qn), 7.31 (d, 1H, *J* = 9.0 Hz, Ar-Qn), 7.02 (d, 2H, *J* = 8.6 Hz, Ar), 6.47 (d, 1H, *J* = 5.1 Hz, Ar-Qn), 3.81 (s, 3H, -S-CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + CD<sub>3</sub>OD): δ 181.27, 161.75, 159.03, 152.38, 151.68, 146.38, 137.67, 135.91, 134.81, 132.08, 126.71, 126.27, 126.01, 125.61, 123.17, 122.67, 121.08, 118.68, 103.56, 97.91, 32.08; Anal. Calcd. for C<sub>25</sub>H<sub>18</sub>ClNO<sub>2</sub>S: C 69.52, H 4.20, N 3.24; Found: C 69.43, H 4.36, N 3.35%.

**6.1.12. 1-(4-(7-chloroquinolin-4-yloxy)phenyl)-3-(pyridin-3-yl)prop-2-en-1-one (15)**

Yield: 68%; m.p. 168-170<sup>0</sup>C; MS: 387 (M + 1); IR (KBr): 3031, 2938, 2357, 1645, 1580, 1479, 1387, 1210, 1013, 836, 779 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.13 (s, 1H, Ar-Py), 8.68 (d, 1H, *J* = 5.1 Hz, Ar-Qn), 8.61 (d, 1H, *J* = 6.38 Hz, Ar-Py), 8.33-8.27 (m, 2H, Ar-Qn, Ar-Py), 8.16 (d, 2H, *J* = 8.6 Hz, Ar), 7.87 (d, 1H, *J* = 2.1 Hz, Ar-Qn), 7.83 (d, 1H, *J* = 15.6 Hz, -CH=CH-), 7.61 (d, 1H, *J* = 15.6 Hz, -CH=CH-), 7.43 (d, 1H, *J* = 9.0 Hz, Ar-Qn), 7.37-7.31 (m, 3H, Ar-Py), 6.87 (d, 1H, *J* = 5.6 Hz, Ar-Qn). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 197.79, 157.03, 154.67, 153.83, 154.03, 152.38, 144.38, 141.23, 140.38, 139.67, 136.37, 136.07, 135.81, 135.23, 133.09, 130.61, 128.23, 124.91, 124.67, 124.19, 110.08; Anal. Calcd. for C<sub>23</sub>H<sub>15</sub>ClNO<sub>2</sub>: C 71.41, H 3.91, N 7.24; Found: C 71.53, H 3.76, N 7.45%.

**6.1.13. 1-(4-(7-chloroquinolin-4-ylamino)phenyl)-3-phenylprop-2-en-1-one (16)**

Yield: 68%; m.p. 190-192<sup>0</sup>C; MS: 385 (M + 1); IR (KBr): 3331, 2998, 2967, 2364, 1655, 1610, 1570, 1521, 1479, 1428, 1377, 1210, 756 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.61 (d, 1H, *J* = 5.1 Hz, Ar-Qn), 8.13-8.07 (m, 3H, Ar-Qn, Ar), 7.87-7.83 (m, 2H, Ar-Qn, -CH=CH), 7.73 (d, 1H, *J* = 15.3 Hz, -CH=CH), 7.56 (d, 2H, *J* = 9.0 Hz, Ar), 7.39-7.33 (m, 3H, Ar-Qn, Ar), 7.29-7.23 (m, 2H, Ar), 7.19-7.13 (m, 2H, Ar-Qn, Ar) 6.67 (s, 1H, NH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, DMSO-d<sub>6</sub>): δ 190.63, 152.22, 151.44, 149.10, 148.64, 141.23, 139.41, 134.66, 131.03, 129.14, 128.52, 127.57, 124.23, 122.16, 121.92, 119.64, 114.26, 112.87, 61.30, 55.82. Anal. Calcd. for C<sub>24</sub>H<sub>17</sub>ClN<sub>2</sub>O: C 74.90, H 4.45, N 7.28; Found: C 74.89, H 4.26, N 7.48%.

**6.1.14. 1-(4-(7-chloroquinolin-4-ylamino)phenyl)-3-p-tolylprop-2-en-1-one (17)**

Yield: 65%; m.p. 170-172<sup>0</sup>C; MS: 399 (M + 1); IR (KBr): 3349, 3020, 2360, 1729, 1640, 1578, 1522, 1480, 1324, 1216, 1031, 851, 771, 669 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, DMSO-d<sub>6</sub>): δ (ppm) 8.47 (d, 1H, *J* = 5.7 Hz, Ar-Qn), 8.13 (d, 1H, *J* = 9.0 Hz, Ar-Qn), 8.01 (d, 2H, *J* = 8.7 Hz, Ar), 7.87 (d, 1H, *J* = 2.1 Hz, Ar-Qn), 7.70 (d, 1H, *J* = 15.0 Hz, -CH=CH), 7.53 (d, 2H, *J* = 9.0 Hz, Ar), 7.43-7.37 (m, 4H, Ar-Qn, Ar, -CH=CH), 7.29-7.23 (m, 3H, Ar-Qn, Ar), 6.91 (s, 1H, NH), 2.98 (s, 3H, -CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, DMSO-d<sub>6</sub>): δ 192.02, 157.38, 148.07, 145.46, 145.03, 138.93, 136.71, 135.67, 135.12, 134.71, 134.21, 133.07, 132.81, 132.0, 131.06, 130.93, 130.78, 128.69, 125.04, 123.76, 23.38. Anal. Calcd. for C<sub>25</sub>H<sub>19</sub>ClN<sub>2</sub>O: C 75.28, H 4.80, N 7.02; Found: C 75.30, H 4.54, N 7.15%.

**6.1.15. 1-(4-(7-chloroquinolin-4-ylamino)phenyl)-3-(2,3-dimethoxyphenyl)prop-2-en-1-one (18)**

Yield: 78%; m.p. 160-162<sup>0</sup>C; MS: 445 (M + 1); IR (KBr): 3333, 3073, 2931, 2362, 1651, 1610, 1573, 1526, 1476, 1428, 1374, 1267, 1229, 1178, 1072, 817, 776, 710, 683 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 8.69 (d, 1H, *J* = 5.1 Hz, Ar-Qn), 8.09-8.16 (m, 3H, -CH=CH-, Ar), 7.90-7.97 (m, 2H, Ar-Qn, Ar), 7.64 (d, 1H, *J* = 15.6 Hz, -CH=CH-), 7.51 (d, 1H, *J* = 8.7 Hz, Ar-Qn), 7.37 (d, 1H, *J* = 8.7 Hz, Ar), 7.25-7.31 (m, 3H, Ar, Ar-Qn), 7.11 (d, 1H, *J* = 5.1 Hz, Ar-Qn), 6.99 (d, 1H, *J* = 7.8 Hz, Ar), 6.90 (s, 1H, NH), 3.92 (s, 3H, OMe), 3.86 (s, 3H, OMe); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 190.61, 152.22, 151.40, 149.15, 148.60, 141.28, 139.46, 134.64, 131.04, 129.15, 128.58, 127.52, 124.23, 122.14, 121.92, 119.64, 114.22, 112.84, 61.30, 55.81. Anal. Calcd. for C<sub>26</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>3</sub>: C 70.19, H 4.76, N 6.30; Found: C 70.23, H 4.90, N 6.68%.

**6.1.16. 1-(4-(7-chloroquinolin-4-ylamino)phenyl)-3-(2,5-dimethoxyphenyl)prop-2-en-1-one (19)**

Yield: 78%; m.p. 172-174<sup>0</sup>C; MS: 445 (M + 1); IR (KBr): 3366, 2939, 2834, 2362, 1652, 1610, 1570, 1528, 1458, 1429, 1375, 1322, 1258, 1220, 1178, 1029, 984, 836, 775, 670 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.70 (d, 1H, *J* = 5.1 Hz, Ar-Qn), 8.09-8.15 (m, 4H, , Ar, -CH=CH-), 7.94 (d, 1H, *J* = 9 Hz, Ar-Qn), 7.63 (d, 1H, *J* = 15.6 Hz, -CH=CH-), 7.51 (d, 1H, *J* = 8.7 Hz), 7.36 (d, 1H, *J* = 8.4 Hz, Ar), 7.28 (d, 2H, Ar, *J* = 8.7), 7.19 (d, 1H, *J* = 2.7 Hz, Ar-Qn), 6.95 (d, 1H, *J* = 2.7 Hz, Ar), 6.91 (s, 1H, NH), 6.90 (d, 1H, *J* = 5.1 Hz, Ar-Qn), 3.90 (s, 3H, OMe), 3.84 (s, 3H, OMe); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, DMSO-d<sub>6</sub>): δ 191.70, 156.77, 152.38, 151.12, 150.84, 143.33, 135.34, 135.16, 132.92, 129.33, 127.12, 124.54, 120.11, 122.56, 118.01, 117.55, 116.59, 115.72, 113.42, 109.81, 61.12, 60.69; Anal. Calcd. for C<sub>26</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>3</sub>: C 70.19, H 4.76, N 6.30; Found: C 70.56, H 4.55, N 6.12%.

**6.1.17. 3-(4-chlorophenyl)-1-(4-(7-chloroquinolin-4-ylamino)phenyl)prop-2-en-1-one (20)**

Yield: 78%; m.p. 175-177<sup>0</sup>C; MS: 419 (M + 1); IR (KBr): 3392, 3020, 2973, 2361, 1653, 1611, 1573, 1528, 1491, 1429, 1376, 1335, 1216, 1182, 1031, 867, 759, 669 cm<sup>-1</sup>; <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>, DMSO-d<sub>6</sub>): δ 8.71 (d, 1H, *J* = 5.1 Hz, Ar-Qn), 8.10-8.13 (m, 2H, *J* = 9 Hz, Ar), 7.94 (d, 1H, *J* = 8.7 Hz, Ar-Qn), 7.81 (d, 1H, *J* = 15.6 Hz, -CH=CH-), 7.57-7.62 (m, 3H, Ar, -CH=CH-), 7.46 (d, 1H, *J* = 9 Hz, Ar-Qn), 7.42 (d, 2H, *J* = 8.4 Hz, Ar), 7.37 (d, 2H, *J* = 8.7 Hz, Ar), 7.26-7.30 (m, 2H, Ar-Qn), 6.88 (s, 1H, NH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 192.11, 154.9, 151.2, 151.0, 146.78, 140.26, 135.46, 135.24, 133.96, 132.99, 130.51, 129.76, 127.73, 124.55, 124.18, 118.2, 113.2, 110.14, 100.76; Anal. Calcd. for. C<sub>24</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>2</sub>O: C 68.75, H 3.85, N 6.68, Found: C 68.56, H 3.98, N 6.42%.

**6.1.18. 1-(4-(7-chloroquinolin-4-ylamino)phenyl)-3-(4-isopropylphenyl)prop-2-en-1-one (21)**

Yield: 60%; m.p. 190-192<sup>0</sup>C; MS: 427 (M + 1); IR (KBr) 3362, 3010, 2953, 2334, 1650, 1609, 1545, 1500, 1429, 1376, 1324, 1210, 1082, 867, 759 cm<sup>-1</sup>; <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>, DMSO-d<sub>6</sub>): δ 8.67 (d, 1H, *J* = 5.1 Hz, Ar-Qn), 8.23-8.17 (m, 3H, Ar-Qn, Ar), 8.14 (d, 2H, *J* = 8.7 Hz, Ar), 7.93 (d, 1H, *J* = 2.1 Hz, Ar-Qn), 7.71 (d, 1H, *J* = 15.1 Hz, -CH=CH), 7.63-7.55 (m, 4H, Ar-Qn, Ar, -CH=CH), 7.39 (d, 2H *J* = 8.6 Hz, Ar), 7.13 (d, 1H, *J* = 5.3 Hz, Ar-Qn), 6.93 (s, 1H, NH), 2.96-2.94 (m, 1H, -CH), 1.27 (d, 6H, *J* = 6.0 Hz, -CH(CH<sub>3</sub>)<sub>2</sub>) ; <sup>13</sup>C NMR (75 MHz CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 190.37, 166.23, 165.71, 165.12, 156.45, 155.23, 152.67, 149.08, 140.73, 139.81, 137.70, 133.72, 133.32, 132.57, 130.75, 130.14, 126.51, 124.43, 106.64, 36.01, 26.34; Anal. Calcd. for. C<sub>27</sub>H<sub>23</sub>ClN<sub>2</sub>O: C 75.96, H 5.43, N 6.56, Found: C 75.66, H 5.18, N 6.22%.

**6.1.19. 1-(4-(7-chloroquinolin-4-ylamino)phenyl)-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one (22)**

Yield: 78%; m.p. 175-177<sup>0</sup>C; MS: 475 (M + 1); IR (KBr): 3392, 3020, 2973, 2361, 1653, 1611, 1573, 1528, 1491, 1429, 1335, 1258, 1216, 1182, 1031, 850, 775, 759, 669 cm<sup>-1</sup>; <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 8.53 (d, 1H, *J* = 5.34 Hz, Ar-Qn), 8.27-8.22 (m, 3H, Ar-Qn, Ar), 7.87-7.83 (m, 2H, Ar-Qn, -CH=CH), 7.71 (d, 1H, *J* = 15.3 Hz, -CH=CH), 7.65 (d, 1H, *J* = 8.4 Hz, Ar), 7.53 (d, 2H *J* = 8.7 Hz, Ar), 7.19 (d, 1H, *J* = 8.4 Hz, Ar), 7.03 (d, 1H, *J* = 5.1 Hz, Ar-Qn), 6.93 (s, 1H, NH), 3.97 (s, 3H, -OCH<sub>3</sub>), 3.95 (s, 3H, -OCH<sub>3</sub>), 3.87 (s, 3H, -OCH<sub>3</sub>) ; <sup>13</sup>C NMR (300MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 189.69, 157.59, 155.26, 151.84, 148.37, 144.03, 140.45, 136.64, 134.24, 132.34, 132.04, 131.85, 129.96, 127.43, 126.38, 125.40, 123.49, 122.45, 121.29, 121.12, 109.93, 106.77, 63.30, 62.53, 57.93; Anal. Calcd. for C<sub>27</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>4</sub>: C 68.28, H 4.88, N 5.90; Found: C 68.36, H 4.98, N 5.92%.

**6.1.20. 1-(4-(7-chloroquinolin-4-ylamino)phenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (23)**

Yield: 72%; m.p. 187-189<sup>0</sup>C; MS: 475 (M + 1); IR (KBr): 3382, 3025, 2973, 2361, 1653, 1611, 1573, 1528, 1429, 1335, 1216, 1182, 1031, 847, 759, 669 cm<sup>-1</sup>; <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 8.59 (d, 1H, *J* = 5.1 Hz, Ar-Qn), 8.33-8.27 (m, 3H, Ar-Qn, Ar), 7.97 (d, 1H, *J* = 2.1 Hz, Ar-Qn), 7.89 (d, 1H, *J* = 15.3 Hz, -CH=CH), 7.71 (d, 1H, *J* = 15.1 Hz, -CH=CH), 7.59-7.53 (m, 5H, Ar-Qn, Ar), 7.19 (d, 1H, *J* = 5.3 Hz, Ar-Qn), 6.93 (s, 1H, NH), 3.93 (s, 6H, -OCH<sub>3</sub>), 3.87 (s, 3H, -OCH<sub>3</sub>); <sup>13</sup>C NMR (300MHz, CDCl<sub>3</sub>, DMSO-d<sub>6</sub>): δ 188.81, 160.78, 158.08, 153.53, 152.24, 150.41, 145.45, 140.68, 136.44, 135.57, 131.06, 130.19, 128.29, 127.49, 123.24, 120.79, 120.53, 119.98, 105.80, 105.62, 61.02, 56.26; Anal. Calcd for. C<sub>27</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>4</sub> C 68.28, H 4.88, N 5.90; Found: C 68.37, H 4.89, N 5.89%.

**6.1.21. 3-(2-chlorophenyl)-1-(4-(7-chloroquinolin-4-ylamino)phenyl)prop-2-en-1-one (24)**

Yield: 70%; m.p. 172-175<sup>0</sup>C; MS: 419 (M + 1); IR (KBr): 3390, 3022, 2973, 2361, 1653, 1619, 1573, 1528, 1493, 1429, 1376, 1335, 1216, 1182, 1031, 867, 770, 759 cm<sup>-1</sup>; <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 8.57 (d, 1H, *J* = 5.13 Hz, Ar-Qn), 8.19-8.13 (m, 4H, Ar-Qn, Ar), 7.93 (d, 1H, *J* = 2.1Hz, Ar-Qn), 7.86 (d, 1H, *J* = 15.3 Hz, -CH=CH), 7.59-7.53 (m, 4H, Ar-Qn, Ar, -CH=CH), 7.41 (d, 1H, *J* = 8.3 Hz, Ar), 7.38-7.31 (m, 2H, Ar), 7.10 (d, 1H, *J* = 5.13Hz, Ar-Qn) 6.76 (s, 1H, NH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 187.88, 156.32, 152.18, 148.31, 148.12, 143.67, 139.38, 138.21, 135.12, 134.16, 133.06, 133.41, 128.62, 127.91, 125.34, 124.69, 122.68, 121.98, 121.67, 111.03, 108.71; Anal. Calcd. for C<sub>24</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>2</sub>O: C 68.75, H 3.85, N 6.68; Found: C 68.76, H 3.84, N 6.79%.

**6.1.22. 3-(3-bromophenyl)-1-(4-(7-chloroquinolin-4-ylamino)phenyl)prop-2-en-1-one (25)**

Yield: 68%; m.p. 180-182<sup>0</sup>C; MS: 476 (M + 1); IR (KBr): 3392, 3020, 2963, 2354, 1655, 1621, 1575, 1526, 1489, 1427, 1370, 1325, 1206, 1172, 1031, 867, 759, 555 cm<sup>-1</sup>; <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 8.71 (d, 1H, *J* = 5.3 Hz, Ar-Qn), 8.13-8.09 (m, 3H, Ar-Qn, Ar), 7.95 (d, 1H, *J* = 2.1 Hz, Ar-Qn), 7.81 (d, 1H, *J* = 15.3 Hz, -CH=CH), 7.59-7.50 (m, 3H, Ar-Qn), 7.38-6.93 (m, 6H, Ar-Qn, Ar, -CH=CH), 6.89 (s, 1H, NH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, DMSO-d<sub>6</sub>): δ 189.12, 153.73, 151.86, 148.12, 148.07, 143.49, 139.27, 136.63, 134.77, 133.53, 132.60, 132.45, 127.50, 127.46, 126.50, 125.34, 124.62, 121.50, 121.32, 121.09, 110.05, 109.87; Anal. Calcd. for C<sub>24</sub>H<sub>16</sub>BrClN<sub>2</sub>O: C 62.16, H 3.48, N 6.04; Found: C 62.35, H 3.54, N 6.39%.

**6.1.23. 3-(2-bromophenyl)-1-(4-(7-chloroquinolin-4-ylamino)phenyl)prop-2-en-1-one (26)**

Yield: 65%; m.p. 175-177<sup>0</sup>C; MS: 463 (M + 1); IR (KBr): 3392, 3020, 2973, 2361, 1653, 1611, 1573, 1528, 1491, 1429, 1376, 1335, 1216, 1182, 1031, 759, 569 cm<sup>-1</sup>; <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 8.61 (d, 1H, *J* = 5.3 Hz, Ar-Qn), 8.17-8.10 (m, 4H, Ar-Qn, Ar), 7.89 (d, 1H, *J* = 2.1 Hz, Ar-Qn), 7.81 (d, 1H, *J* = 15.3 Hz, -CH=CH), 7.55-7.49 (m, 4H, Ar-Qn, Ar, -CH=CH), 7.43-7.35 (m, 3H, Ar), 7.08 (d, 1H, *J* = 5.3Hz, Ar-Qn), 6.65 (s, 1H, NH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 181.23, 158.13, 155.03, 144.84, 142.64, 136.60, 131.93, 131.64, 131.21, 130.87, 130.68, 130.13, 129.02, 126.87, 120.61, 120.14, 116.24, 115.87, 115.21, 113.57, 112.85, 98.43; Anal. Calcd. for C<sub>24</sub>H<sub>16</sub>BrClN<sub>2</sub>O: C 62.16, H 3.48, N 6.04; Found: C 62.18, H 3.67, N 6.20%.

**6.1.24. 1-(4-(7-chloroquinolin-4-ylamino)phenyl)-3-(3-nitrophenyl)prop-2-en-1-one (27)**

Yield: 60%; m.p. 178-180<sup>0</sup>C; MS: 430 (M + 1); IR (KBr): 3389, 3022, 2963, 2351, 1655, 1621, 1563, 1530, 1491, 1429, 1376, 1355, 1219, 1082, 776, 759 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 8.97 (d, 1H, *J* = 2.3 Hz, Ar), 8.84 (d, 1H, *J* = 8.7 Hz, Ar), 8.69 (d, 1H, *J* = 5.3 Hz, Ar-Qn), 8.12 (d, 1H, *J* = 9 Hz, Ar), 8.02-8.09 (m, 3H, Ar-Qn, Ar), 7.62-7.71 (m, 3H, Ar-Qn, Ar, -CH=CH-), 7.65 (d, 1H, *J* = 15.6 Hz, -CH=CH-) 7.43 (d, 1H, *J* = 8.6 Hz, Ar-Qn), 7.23 (d, 2H, *J* = 8.6 Hz, Ar), 6.83 (d, 1H, *J* = 5.4 Hz, Ar-Qn), 6.31 (s, 1H, NH); <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 189.03, 153.51, 150.68, 148.67, 142.61, 139.13, 138.32, 137.03, 136.89, 134.32, 133.33, 132.89, 130.31, 129.21, 128.67, 127.89, 127.23, 125.37, 124.31, 122.03, 121.93, 108.11; Anal. Calcd. for C<sub>24</sub>H<sub>16</sub>ClN<sub>3</sub>O<sub>3</sub>: C 67.06, H 3.75, N 9.78; Found: C 67.15, H 3.79, N 9.89%.

**6.1.25. 1-(4-(7-chloroquinolin-4-ylamino)phenyl)-3-(pyridin-3-yl)prop-2-en-1-one (28)**

Yield: 65%; m.p. 174-176 °C; MS: 386 (M + 1); IR (KBr): 3450, 3360, 3025, 2945, 2362, 1637, 1570, 1522, 1489, 1377, 1244, 773, 669 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, DMSO-d<sub>6</sub>): δ 9.23 (s, 1H, Py), 8.65 (d, 1H, *J* = 7.7 Hz, Py), 8.51 (d, 1H, *J* = 5.38 Hz, Ar-Qn), 8.41-8.33 (m, 2H, Ar-Qn, Py), 8.17 (d, 2H, *J* = 8.3 Hz, Ar), 7.93 (d, 1H, *J* = 1.8 Hz, Ar-Qn), 7.89 (d, 1H, *J* = 15.3 Hz, -CH=CH), 7.76 (d, 1H, *J* = 15.1 Hz, -CH=CH), 7.49-7.43 (m, 4H, Ar-Qn, Ar, Py), 7.13 (d, 1H, *J* = 5.2 Hz, Ar-Qn) 6.91 (s, 1H, NH); <sup>13</sup>C (75 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 197.79, 153.64, 151.72, 151.66, 151.26, 149.27, 141.72, 137.41, 136.83, 136.22, 132.62, 132.62, 132.31, 131.72, 131.42, 129.90, 125.73, 125.08, 121.42, 121.12, 120.91, 106.99; Anal. Calcd. for C<sub>23</sub>H<sub>16</sub>ClN<sub>3</sub>O: C: 71.59, H 4.18, N 10.89; Found: C 71.82, H 4.39, N 10.99%.

**6.1.26. 1-(4-(7-chloroquinolin-4-ylamino)phenyl)-3-(furan-2-yl)prop-2-en-1-one (29)**

Yield: 78%; m.p. 188-190 °C; MS: 375 (M + 1); IR (KBr): 3386, 3065, 3021, 2932, 2361, 1656, 1520, 1427, 1312, 1215, 1033, 760, 690 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, DMSO-d<sub>6</sub>): δ 8.61 (d, 1H, *J* = 5.34 Hz, Ar-Qn), 8.23-8.17 (m, 3H, Ar-Qn, Ar), 7.93 (d, 1H, *J* = 2.1 Hz, Ar-Qn), 7.81 (d, 1H, *J* = 15.3 Hz, -CH=CH-), 7.73 (d, 1H, *J* = 8.4 Hz, Ar-Qn), 7.55-7.49 (m, 4H, Ar, Furan, -CH=CH), 7.21-7.17 (m, 2H, Ar-Qn, Furan), 6.67-6.63 (m, 2H, NH, Furan). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>+ DMSO-d<sub>6</sub>): δ 192.93, 155.50, 155.02, 153.08, 151.30, 149.19, 148.71, 139.85, 136.45, 134.63, 134.31, 131.07, 130.25, 127.36, 123.76, 123.35, 122.65, 120.51, 116.63, 108.56; Anal. Calcd. for C<sub>22</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>2</sub>: C 70.50, H 4.03, N 7.47; Found: C 70.32, H 4.34, N 7.59%.

**6.1.27. 1-(4-(7-chloroquinolin-4-ylamino)phenyl)-3-(4-(methylthio)phenyl)prop-2-en-1-one (30)**

Yield: 68%; m.p. 176-179 °C; MS: 431 (M + 1); IR (KBr): 3315, 3025, 2922, 2369, 1580, 1531, 1428, 1375, 1344, 1239, 813, 775, 669 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.53 (d, 1H, *J* = 5.1 Hz, Ar-Qn), 8.07 (d, 1H, *J* = 9.0 Hz, Ar-Qn), 7.98-7.91 (m, 3H, Ar-Qn, Ar), 7.69 (d, 1H, *J* = 15.6 Hz, -CH=CH), 7.37 (d, 2H, *J* = 8.1 Hz, Ar), 7.29 (d, 1H, *J* = 15.3 Hz, -CH=CH), 7.06-6.97 (m, 6H, Ar-Qn, Ar, NH), 6.29 (d, 1H, *J* = 5.1 Hz, Ar-Qn), 3.81 (s, 3H, SCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>+ DMSO-d<sub>6</sub>): δ 188.27, 160.75, 157.99, 152.09, 150.44, 144.72, 142.77, 136.45, 135.67, 131.16, 130.98, 128.84, 128.33, 127.47, 125.93, 123.16, 120.49, 120.36, 120.18, 105.49, 23.71; Anal. Calcd. for C<sub>25</sub>H<sub>19</sub>ClN<sub>2</sub>OS: C 69.68, H 4.44, N 6.50; Found: C 69.65, H 4.26, N 6.32%.

**6.1.28. 1-(4-(7-chloroquinolin-4-ylamino)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (31)**

Yield: 60%; m.p. 172-174 °C; MS: 415 (M + 1); IR (KBr): 3343, 3023, 2921, 2372, 1651, 1610, 1573, 1526, 1476, 1428, 1374, 1267, 1229, 1178, 1072, 1002, 827, 776 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 8.67 (d, 1H, *J* = 5.1 Hz, Ar-Qn), 8.13 (d, 1H, *J* = 9.0 Ar-Qn Hz), 8.08 (d, 2H, *J* = 8.3 Hz, Ar), 7.95 (d, 1H, *J* = 2.1 Hz, Ar-Qn), 7.94 (d, 2H, *J* = 9.0 Hz, Ar), 7.83 (d, 1H, *J* = 15.3 Hz, -CH=CH), 7.53 (d, 1H, *J* = 8.4 Hz, Ar-Qn), 7.31-7.23 (m, 3H, Ar, -CH=CH), 7.06 (d, 2H, *J* = 8.6 Hz, Ar-Qn) 6.71 (d, 1H, *J* = 5.1 Hz, Ar-Qn), 6.37 (s, 1H, NH), 3.87 (s, 3H, -OCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 188.87, 160.71, 158.07, 152.23, 150.38, 146.41, 139.91, 137.13, 136.06, 132.17, 131.09, 128.68, 127.43, 126.31, 124.11, 120.68, 120.31, 118.91, 106.08, 105.32, 56.79; Anal. Calcd. for C<sub>25</sub>H<sub>19</sub>ClN<sub>2</sub>O<sub>2</sub>: C 72.37, H 4.62, N 6.75; Found: C 72.35, H 4.72, N 6.58%.

**6.2. General procedure for the synthesis of compounds 32-59**

To a solution of guanidine hydrochloride (1.5 equiv) in DMF, NaH (3.0 equiv), and chalcones (1.0 equiv) were added. The reaction mixture was refluxed for 8h. Water was added to the reaction mixture, a solid started to separating out. The solid was filtered out and purified by column chromatography to afford the pure compound **32-59**.

**6.2.1. 4-(4-(7-chloroquinolin-4-yloxy)phenyl)-6-phenylpyrimidin-2-amine (32)**

Yield: 55%; m.p. 189-190 °C; MS: 425 (M + 1); IR (KBr): 3419, 3021, 2361, 1725, 1593, 1484, 1424, 1216, 1084, 767, 670 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.74 (d, 1H, *J* = 5.13 Hz, Ar-Qn), 8.27 (d, 1H, *J* = 9.0 Hz, Ar-Qn), 8.16 (d, 2H, *J* = 8.7 Hz, Ar), 8.14 (d, 1H, *J* = 1.8 Hz, Ar-Qn), 7.84 (s, 1H, Ar-Pym), 7.69-7.66 (m, 2H, Ar), 7.55 (d, 1H, *J* = 8.7 Hz, Ar-Qn), 7.28 (d, 2H, *J* = 8.34 Hz,

Ar), 7.16 (d, 1H,  $J = 8.7$  Hz, Ar), .696 (d, 1H,  $J = 5.1$  Hz, Ar-Qn), 5.37 (s, 2H, NH<sub>2</sub>) ; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>+ DMSO-d<sub>6</sub>): δ 162.41, 160.37, 147.72, 145.38, 143.67, 143.67, 143.08, 134.91, 130.26, 127.64, 127.13, 125.23, 124.53, 122.67, 119.92, 119.33, 116.72, 114.26, 111.67, 98.23, 97.56; Anal. Calcd. for C<sub>25</sub>H<sub>17</sub>ClN<sub>4</sub>O: C 70.67, H 4.03, N 13.19; Found: C 70.89, H 4.26, N 13.28%.

**6.2.2. 4-(4-(7-chloroquinolin-4-yloxy)phenyl)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-amine (33)**

Yield: 58%; m.p. 195-197 °C; MS: 515 (M + 1); IR (KBr): 3423, 3020, 2930, 2361, 1726, 1572, 1421, 1369, 1215, 1128, 1428, 760, 669, 480 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.73 (d, 1H,  $J = 5.13$  Hz, Ar-Qn), 8.46 (d, 1H,  $J = 8.7$  Hz, Ar-Qn), 8.13 (d, 2H,  $J = 8.7$  Hz, Ar), 8.01 (d, 1H,  $J = 1.8$  Hz, Ar-Qn), 7.90 (s, 1H, Ar-Pym), 7.63 (d, 2H,  $J = 8.4$  Hz, Ar), 7.56 (s, 2H, Ar), 7.51 (d, 1H,  $J = 9.0$  Hz, Ar-Qn), 7.01 (d, 1H,  $J = 5.34$  Hz, Ar-Qn), 5.67 (s, 2H, NH<sub>2</sub>), 4.07 (s, 6H, OCH<sub>3</sub>), 3.93 (s, 3H, OCH<sub>3</sub>) ; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + CD<sub>3</sub>OD): δ 161.87, 159.01, 158.12, 155.07, 148.85, 146.37, 144.81, 142.36, 133.23, 129.90, 128.73, 128.26, 125.79, 122.51, 120.60, 119.88, 116.49, 114.20, 112.85, 97.76, 97.52, 96.80, 53.79, 49.14; Anal. Calcd. for C<sub>28</sub>H<sub>23</sub>ClN<sub>4</sub>O<sub>4</sub>: C 65.31, H 4.50, N 10.88, Found: C 65.43, H 4.46, N 10.78%.

**6.2.3. 4-(4-(7-chloroquinolin-4-yloxy)phenyl)-6-(2,3,4-trimethoxyphenyl)pyrimidin-2-amine (34)**

Yield: 65%; m.p. 185-187 °C; MS: 515 (M + 1); IR (KBr): 3422, 3025, 2930, 2356, 1726, 1562, 1428, 1367, 1205, 1028, 1430, 760, 669, 486 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) : δ 8.53 (d, 1H,  $J = 5.34$  Hz, Ar-Qn), 8.27-8.21 (m, 3H, Ar-Qn, Ar), 7.87 (d, 1H,  $J = 2.1$  Hz, Ar-Qn), 7.81 (s, 1H, Ar-Pym), 7.73 (d, 1H,  $J = 9.0$  Hz, Ar-Qn), 7.61 (d, 1H,  $J = 8.7$  Hz, Ar), 7.53 (d, 2H,  $J = 8.3$  Hz, Ar), 7.21 (d, 1H,  $J = 8.71$  Hz, Ar), 6.97 (d, 1H,  $J = 5.13$  Hz, Ar-Qn), 6.12 (s, 2H,  $J = 5.34$  Hz, NH<sub>2</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 3.87 (s, 3H, OCH<sub>3</sub>) ; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + CD<sub>3</sub>OD): δ 161.68, 159.23, 158.67, 154.98, 149.03, 148.03, 148.31, 146.71, 144.45, 142.39, 133.37, 129.87, 129.07, 125.23, 122.81, 119.93, 119.08, 116.78, 115.20, 113.87, 111.92, 101.72, 100.98, 98.20, 54.71, 54.23, 48.78; Anal. Calcd. for C<sub>28</sub>H<sub>23</sub>ClN<sub>4</sub>O<sub>4</sub>: C 65.31, H 4.50, N 10.88, Found: C 65.23, H 4.46, N 10.58%.

**6.2.4. 4-(4-(7-chloroquinolin-4-yloxy)phenyl)-6-(4-methoxyphenyl)pyrimidin-2-amine (35)**

Yield: 50%; m.p. 162-164 °C; MS: 454 (M + 1); IR (KBr): 3421, 3029, 2830, 2346, 1722, 1568, 1430, 1345, 1225, 1127, 1420, 776, 669, 486 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.72 (d, 1H,  $J = 5.34$  Hz, Ar-Qn), 8.33 (d, 1H,  $J = 9.0$  Hz, Ar-Qn), 8.19 (d, 2H,  $J = 8.7$  Hz, Ar), 8.13 (d, 1H,  $J = 2.13$  Hz, Ar-Q), 8.07 (d, 2H,  $J = 8.4$  Hz, Ar), 7.59-7.55 (dd, 1H,  $J = 8.4$  Hz,  $J = 1.8$  Hz, Ar-Qn), 7.45 (s, 1H, Ar-Pym), 7.31 (d, 2H,  $J = 8.71$  Hz, Ar), 7.04 (d, 2H,  $J = 9.0$  Hz, Ar), 6.65 (d, 1H,  $J = 5.34$  Hz, Ar-Qn), 5.21 (s, 2H, NH<sub>2</sub>), 3.90 (s, 3H, OCH<sub>3</sub>) ; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 162.34, 160.0, 154.32, 149.37, 147.32, 145.87, 143.62, 134.37, 130.08, 129.62, 128.67, 126.13, 123.57, 121.62, 120.08, 116.92, 114.78, 113.09, 98.23, 97.25, 97.02, 51.63. Anal. Calcd. for C<sub>26</sub>H<sub>19</sub>ClN<sub>4</sub>O<sub>2</sub>: C 68.65, H 4.21, N 12.32; Found: C 68.72, H 4.66, N 12.58%.

**6.2.5. 4-(4-(7-chloroquinolin-4-yloxy)phenyl)-6-(2,3-dimethoxyphenyl)pyrimidin-2-amine (36)**

Yield: 60%; m.p. 162-164 °C; MS: 485 (M + 1); IR (KBr): 3419, 3020, 2361, 1725, 1576, 1492, 1367, 1261, 1216, 1084, 762, 670 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.69 (d, 1H,  $J = 5.13$  Hz, Ar-Qn), 8.41 (d, 1H,  $J = 9.0$  Hz, Ar-Qn), 8.11 (d, 2H,  $J = 8.7$  Hz, Ar), 7.86 (d, 1H,  $J = 2.1$  Hz, Ar-Q), 7.47-7.41 (m, 3H, Ar), 7.51 (s, 1H, Ar-Qn), 7.36 (d, 1H,  $J = 9.0$  Hz, Ar-Qn), 7.16-7.10 (m, 2H, Ar), 6.97 (d, 1H,  $J = 5.1$  Hz, Ar-Qn), 5.37 (s, 2H, NH<sub>2</sub>), 3.89 (s, 2H, OCH<sub>3</sub>), 3.94 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + CD<sub>3</sub>OD): δ 163.34, 161.10, 159.81, 149.75, 147.32, 146.89, 144.02, 142.37, 135.38, 134.27, 131.19, 130.27, 127.28, 124.58, 122.68, 121.37, 117.42, 115.23, 113.28, 111.87, 108.29, 107.93, 102.89, 53.28, 50.37; Anal. Calcd. for C<sub>27</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>3</sub>: C 66.87, H 4.36, N 11.55; Found: C 66.72, H 4.46, N 11.68%.

**6.2.6. 4-(4-(7-chloroquinolin-4-yloxy)phenyl)-6-(2,5-dimethoxyphenyl)pyrimidin-2-amine (37)**

Yield: 60%; m.p. 160-162 °C; MS: 485 (M + 1); IR (KBr): 3419, 3023, 2361, 1730, 1572, 1482, 1365, 1263, 1206, 1089, 762, 670 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.73 (d, 1H,  $J = 5.34$  Hz, Ar-Qn),

8.47 (d, 1H,  $J = 8.7$  Hz, Ar-Qn), 8.27 (d, 2H,  $J = 8.3$  Hz, Ar), 8.03 (d, 1H,  $J = 1.8$  Hz, Ar-Qn), 7.77-7.69 (m, 4H, Ar, Ar-Pym), 7.59 (d, 1H,  $J = 9.0$  Hz, Ar-Qn), 7.41 (d, 1H,  $J = 9.0$  Hz, Ar), 7.37 (d, 1H,  $J = 8.34$ , Ar), 6.93 (d, 1H,  $J = 5.13$  Hz, Ar-Qn), 5.18 (s, 2H, NH<sub>2</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 3.93 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + CD<sub>3</sub>OD):  $\delta$  165.36, 163.13, 161.87, 151.25, 149.38, 148.71, 146.0, 144.38, 136.29, 136.21, 133.18, 132.81, 129.25, 126.57, 124.69, 123.32, 119.67, 117.62, 115.23, 113.89, 110.26, 109.34, 105.67, 58.36. Anal. Calcd. for C<sub>27</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>3</sub>: C 66.87, H 4.36, N 11.55; Found: C 66.92, H 4.56, N 11.58%.

#### 6.2.7. 4-(4-(7-chloroquinolin-4-yloxy)phenyl)-6-(furan-2-yl)pyrimidin-2-amine (38)

Yield: 65%; m.p. 180-182 °C; MS: 414 (M + 1); IR (KBr): 3420, 3020, 2361, 1725, 1598, 1492, 1422, 1301, 1216, 1017, 761, 670 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  8.72 (d, 1H, Ar-Qn,  $J = 5.1$  Hz), 8.33 (d, 1H, Ar-Qn,  $J = 9$  Hz), 8.21 (d, 2H, Ar,  $J = 8.7$  Hz), 8.14 (d, 1H, Ar-Qn,  $J = 2.1$  Hz), 7.61 (d, 1H, Furan,  $J = 3.0$  Hz), 7.57 (dd, 1H, Ar-Qn,  $J = 8.7, 2.13$  Hz), 7.45 (s, 1H, Ar-Pym), 7.31 (d, 2H, Ar,  $J = 8.4$  Hz), 7.24 (d, 1H, Furan,  $J = 3.3$  Hz), 6.65 (d, 1H,  $J = 5.4$  Hz), 6.59-6.61 (m, 1H, Furan), 5.19 (s, 2H, NH<sub>2</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  166.02, 165.57, 158.28, 157.23, 156.98, 153.38, 152.0, 149.48, 144.68, 136.91, 133.82, 131.23, 129.84, 129.68, 127.08, 123.0, 126.87, 121.0, 115.92, 113.82, 111.0, 101.38, 99.65; Anal. Calcd. for C<sub>23</sub>H<sub>15</sub>ClN<sub>4</sub>O<sub>2</sub>: C 66.59, H 3.64, N 13.51; Found: C 66.79, H 3.86, N 13.68%.

#### 6.2.8. 4-(4-(7-chloroquinolin-4-yloxy)phenyl)-6-(pyridin-3-yl)pyrimidin-2-amine (39)

Yield: 62%; m.p. 178-180 °C; MS: 426 (M + 1); IR (KBr): 3486, 3156, 2931, 2364, 1720, 1568, 1456, 1355, 1214, 1164, 1098, 762, 681 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  9.21 (s, 1H, Ar-Py), 8.73 (d, 1H,  $J = 5.3$  Hz, Ar-Qn), 8.64 (d, 1H,  $J = 6.0$  Hz, Ar-Py), 8.43-8.37 (m, 2H, Ar-Qn, Ar-Py), 8.17 (d, 2H,  $J = 8.6$  Hz, Ar), 7.87 (d, 1H,  $J = 2.1$  Hz, Ar-Qn), 7.57 (s, 1H, Ar-Py), 7.43-7.38 (m, 4H, Ar-Qn, Ar, Ar-Py), 6.93 (d, 1H,  $J = 5.28$  Hz, Ar-Qn), 5.73 (s, 2H, NH<sub>2</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  159.46, 157.53, 157.33, 155.71, 150.05, 145.90, 144.61, 144.12, 143.62, 141.88, 130.66, 129.08, 128.89, 123.38, 121.46, 121.31, 121.21, 117.33, 115.12, 113.82, 98.81, 97.69; Anal. Calcd. for C<sub>24</sub>H<sub>16</sub>ClN<sub>5</sub>O: C 67.69, H 3.79, N 16.44; Found: C 67.53, H 3.86, N 16.65%.

#### 6.2.9. 4-(2-chlorophenyl)-6-(4-(7-chloroquinolin-4-yloxy)phenyl)pyrimidin-2-amine (40)

Yield: 55%; m.p. 172-174 °C; MS: 459 (M + 1); IR (KBr): 3420, 3020, 2361, 1725, 1598, 1492, 1422, 1301, 1216, 1017, 761, 670 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  8.72 (d, 1H,  $J = 5.3$  Hz, Ar-Qn), 8.26 (d, 1H,  $J = 9.0$  Hz, Ar-Qn), 8.19 (d, 1H,  $J = 8.7$  Hz, Ar), 8.16 (d, 1H,  $J = 1.8$  Hz, Ar-Qn), 7.98 (d, 2H,  $J = 8.7$  Hz, Ar), 7.87 (s, 1H, Ar-Pym), 7.63 (d, 1H,  $J = 8.4$ , Ar), 7.55-7.45 (m, 5H, Ar, Ar-Qn), 6.87 (d, 1H,  $J = 5.4$  Hz, Ar-Qn), 5.71 (s, 2H, NH<sub>2</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  162.12, 159.83, 145.64, 141.23, 132.32, 131.32, 128.68, 125.34, 125.03, 123.67, 122.07, 121.67, 121.08, 120.73, 119.23, 118.93, 118.78, 117.32, 117.13, 116.82, 115.06, 110.32, 100.29; Anal. Calcd. for C<sub>25</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>4</sub>O: C 65.37, H 3.51, N 12.20; Found: C 65.59, H 3.78, N 12.47%.

#### 6.2.10. 4-(4-chlorophenyl)-6-(4-(7-chloroquinolin-4-yloxy)phenyl)pyrimidin-2-amine (41)

Yield: 52%; m.p. 174-176 °C; MS: 459 (M + 1); IR (KBr): 3420, 3020, 2361, 1725, 1598, 1492, 1422, 1301, 1216, 1017, 761, 670 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  8.73 (d, 1H,  $J = 5.1$  Hz, Ar-Qn), 8.27 (d, 1H,  $J = 9$  Hz, Ar-Qn), 8.22 (d, 2H,  $J = 8.7$  Hz, Ar), 8.12 (d, 1H,  $J = 2.1$  Hz, Ar-Qn), 8.03 (d, 2H,  $J = 8.7$  Hz, Ar), 7.83 (s, 1H, Ar-Pym), 7.57 (d, 1H,  $J = 8.7$ , Ar-Qn), 7.48 (d, 2H,  $J = 8.4$  Hz, Ar), 7.07 (d, 2H,  $J = 9.0$  Hz, Ar), 6.83 (d, 1H,  $J = 5.4$  Hz, Ar-Qn), 5.39 (s, 2H, NH<sub>2</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  161.91, 159.28, 152.37, 148.39, 146.42, 144.83, 142.91, 133.21, 131.67, 130.09, 127.71, 125.67, 122.71, 120.78, 119.09, 115.71, 113.23, 112.21, 97.21, 96.38, 95.98; Anal. Calcd. for C<sub>25</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>4</sub>O: C 65.37, H 3.51, N 12.20; Found: C 65.49, H 3.26, N 12.39%.

#### 6.2.11. 4-(4-(7-chloroquinolin-4-yloxy)phenyl)-6-(4-(methylthio)phenyl)pyrimidin-2-amine (42)

Yield: 60%; m.p. 180-182 °C; MS: 471 (M + 1); IR (KBr): 3420, 3020, 2361, 1725, 1598, 1492, 1422, 1301, 1216, 1017, 761, 670 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  8.71 (d, 1H,  $J = 5.1$  Hz, Ar-Qn), 8.37 (d, 1H,  $J = 9$  Hz, Ar-Qn), 8.21 (d, 2H,  $J = 8.7$  Hz, Ar), 8.09 (d, 2H,  $J = 8.4$  Hz, Ar), 7.83 (s, 1H,

Ar-Pym), 7.51-7.47 (m, 3H, Ar-Qn, Ar), 7.23 (d, 1H,  $J = 9.0$  Hz, Ar-Qn), 6.89 (d, 2H,  $J = 8.7$  Hz, Ar), 6.37 (d, 1H,  $J = 5.3$  Hz, Ar-Qn), 5.72 (s, 2H, NH<sub>2</sub>), 3.83 (s, 3H, -S-CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  167.39, 167.10, 165.71, 162.98, 161.34, 159.75, 154.64, 145.46, 136.83, 134.27, 131.69, 130.16, 129.75, 129.57, 127.90, 126.29, 123.65, 125.68, 115.57, 111.83, 100.13, 57.18. Anal. Calcd. for C<sub>26</sub>H<sub>19</sub>ClN<sub>4</sub>O: C 66.30, H 4.07, N 11.90; Found: C 66.49, H 4.26, N 11.89%.

**6.2.12. 4-(4-(7-chloroquinolin-4-yloxy)phenyl)-6-p-tolylpyrimidin-2-amine (43)**

Yield: 50%; m.p. 178-180 °C; MS: 439 (M + 1); IR (KBr): 3420, 3020, 2361, 1725, 1598, 1492, 1422, 1301, 1216, 1017, 761, 670 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  8.73 (d, 1H,  $J = 5.3$  Hz, Ar-Qn), 8.39 (d, 1H,  $J = 9$  Hz, Ar-Qn), 8.27 (d, 2H,  $J = 8.4$  Hz, Ar), 8.12 (d, 2H,  $J = 8.4$  Hz, Ar), 7.86 (s, 1H, Ar-Pym), 7.51 (d, 1H,  $J = 1.8$  Hz, Ar-Qn), 7.46 (d, 2H,  $J = 8.6$  Hz, Ar), 7.36 (d, 1H,  $J = 9.0$  Hz, Ar-Qn), 6.97 (d, 2H,  $J = 8.4$  Hz, Ar), 6.83 (d, 1H,  $J = 5.4$  Hz, Ar-Qn), 5.86 (s, 2H, NH<sub>2</sub>), 2.63 (s, 3H, -CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  162.34, 160.0, 154.32, 149.37, 147.32, 145.87, 143.62, 134.37, 130.08, 129.62, 128.67, 126.13, 123.57, 121.62, 120.08, 116.92, 114.78, 113.09, 98.23, 97.25, 97.02, 51.63; Anal. Calcd. for C<sub>26</sub>H<sub>19</sub>ClN<sub>4</sub>O: C 71.15, H 4.36, N 12.77; Found: C 71.34, H 4.34, N 12.49%.

**6.2.13. N-(4-(2-amino-6-phenylpyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (44)**

Yield: 52%; m.p. 198-200 °C; MS: 424 (M + 1); IR (KBr): 3421, 3329, 2936, 2362, 1621, 1572, 1530, 1438, 1335, 1216, 1161, 774 cm<sup>-1</sup>; IR (KBr); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  9.26 (s, 1H, NH), 8.51 (d, 1H,  $J = 5.7$  Hz, Ar-Qn), 8.11 (d, 1H,  $J = 9.0$  Hz, Ar-Qn), 8.03 (d, 2H,  $J = 8.6$  Hz, Ar), 7.87 (d, 1H,  $J = 2.1$  Hz, Ar), 7.77 (s, 1H, Ar-Pym), 7.58 (d, 2H,  $J = 9.0$  Hz, Ar), 7.37-7.42 (m, 3H, Ar-Qn, Ar), 7.28-7.33 (m, 2H, Ar) 7.21-7.26 (m, 2H, Ar-Qn, Ar), 6.65 (s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub> + DMSO-d<sub>6</sub>, 75 MHz):  $\delta$  160.13, 157.87, 143.93, 141.89, 135.88, 132.40, 128.74, 126.33, 123.57, 123.43, 121.69, 121.49, 121.40, 120.53, 120.02, 119.04, 116.06, 114.58, 114.02, 100.70; Anal. Calcd. for C<sub>25</sub>H<sub>18</sub>ClN<sub>5</sub>: C 70.84, H 4.28, N 16.52; Found: C 70.51, H 4.46, N 16.35%.

**6.2.14. N-(4-(2-amino-6-p-tolylpyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (45)**

Yield: 48%; m.p. 170-172 °C; MS: 438 (M + 1); IR (KBr): 3433, 3382, 2973, 2362, 1653, 1618, 1573, 1530, 1494, 1429, 1367, 1335, 1231, 1182, 835, 759, cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>):  $\delta$  9.27 (s, 1H, NH), 8.42 (d, 1H,  $J = 6.0$  Hz, Ar-Qn), 8.10 (d, 1H,  $J = 9.0$  Hz, Ar), 7.98 (d, 2H,  $J = 8.7$  Hz, Ar), 7.85 (d, 1H,  $J = 2.1$  Hz, Ar-Qn), 7.71 (s, 1H, Ar-Pym), 7.51 (d, 2H,  $J = 9.0$  Hz, Ar), 7.33-7.38 (m, 3H, Ar-Q, Ar), 7.20-7.25 (m, 3H, Ar-Q, Ar) 6.65 (s, 2H, NH<sub>2</sub>), 3.23 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>):  $\delta$  160.11, 156.93, 143.91, 140.98, 135.88, 132.40, 128.75, 127.03, 123.73, 123.56, 121.63, 121.53, 121.33, 120.33, 120.06, 119.12, 117.03, 114.75, 114.06, 100.70, 95.15; Anal. Calcd. for C<sub>26</sub>H<sub>20</sub>ClN<sub>5</sub>: C 71.31, H 4.60, N 15.99; Found: C 71.21, H 4.46, N 15.65%.

**6.2.15. N-(4-(2-amino-6-(4-methoxyphenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (46)**

Yield: 50%; m.p. 162-164 °C; MS: 455 (M + 1); IR (KBr): 3544, 3421, 3020, 2936, 2361, 1572, 1516, 1438, 1325, 1216, 1113, 838, 760 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>):  $\delta$  9.23 (s, 1H, NH), 8.71 (d, 1H,  $J = 5.3$  Hz, Ar-Q), 8.33 (d, 1H,  $J = 9$  Hz, Ar-Q), 8.19 (d, 2H,  $J = 8.7$  Hz, Ar), 8.13 (d, 1H,  $J = 1.8$  Hz, Ar-Q), 8.08 (d, 2H,  $J = 9.0$  Hz, Ar), 7.57 (dd, 1H,  $J = 8.4$  Hz,  $J = 2.1$  Hz, Ar-Q), 7.45 (s, 1H, Ar-Pym), 7.32 (d, 2H,  $J = 8.4$  Hz, Ar), 7.08 (d, 2H,  $J = 8.7$  Hz, Ar), 6.65 (d, 1H,  $J = 5.3$  Hz, Ar-Q), 5.18 (s, 2H, NH<sub>2</sub>), 3.91 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>):  $\delta$  169.91, 166.72, 157.13, 155.15, 152.85, 148.12, 139.83, 137.85, 135.32, 133.90, 130.63, 129.90, 126.53, 124.32, 119.33, 108.60, 106.31, 60.77. Anal. Calcd. for C<sub>26</sub>H<sub>20</sub>ClN<sub>5</sub>O: C 68.80, H 4.44, N 15.43; Found: C 68.65, H 4.29, N 15.39%.

**6.2.16. N-(4-(2-amino-6-(furan-2-yl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (47)**

Yield: 60%; m.p. 176-178 °C; MS: 414 (M + 1); IR (KBr): 3586, 3322, 2989, 2361, 1556, 1520, 1427, 1312, 1215, 1033, 929, 760 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>):  $\delta$  9.27 (s, 1H, NH), 8.49 (d, 1H,  $J = 5.1$  Hz, Ar-Q), 8.38 (d, 1H,  $J = 9$  Hz, Ar-Q), 8.11 (d, 2H,  $J = 8.4$  Hz, Ar), 7.86 (d, 1H,  $J = 1.2$  Hz, Ar-Q), 7.75 (dd, 1H,  $J = 8.4$  Hz, 2.1 Hz, Ar-Q), 7.43-7.45 (m, 3H, Ar, Furan), 7.37

(s, 1H, Ar-Pym), 7.17-7.11 (m, 2H, Ar-Qn, Furan), 6.58 (m, 1H, Furan), 6.39 (s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 166.02, 165.50, 158.22, 154.10, 153.32, 151.23, 149.12, 146.40, 144.61, 136.12, 133.72, 129.70, 129.41, 126.90, 126.22, 122.72, 120.63, 113.90, 112.81, 104.90, 101.31; Anal. Calcd. for C<sub>23</sub>H<sub>16</sub>ClN<sub>5</sub>O: C 66.75, H 3.90, N 16.92; Found: C 66.56, H 3.78, N 16.72%.

6.2.17. *N*-(4-(2-amino-6-(3,4,5-trimethoxyphenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (48)

Yield: 65%; m.p. 170-172 °C; MS: 524 (M + 1); IR (KBr): 3544, 3207, 2932, 2362, 1566, 1526, 1446, 1371, 1312, 1226, 1126, 997, 817, 776, 713 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 9.27 (s, 1H, NH), 8.51 (d, 1H, *J* = 5.4 Hz, Ar-Q), 8.36 (d, 1H, *J* = 9 Hz), 8.23 (d, 2H, *J* = 8.6 Hz, Ar), 7.93 (d, 1H, *J* = 2.1 Hz, Ar-Q), 7.89 (s, 1H, Ar-Py), 7.54-7.50 (m, 5H, Ar-Q, Ar), 7.43 (s, 2H, NH<sub>2</sub>), 7.16 (d, 1H, *J* = 5.34 Hz, Ar-Q), 3.98 (s, 6H, OCH<sub>3</sub>), 3.86 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 165.5, 164.35, 157.77, 155.30, 148, 137.69, 132.8, 131.04, 130.31, 129.8, 128.33, 126.25, 115.4, 108.9, Anal. Calcd. for C<sub>28</sub>H<sub>24</sub>ClN<sub>5</sub>O<sub>3</sub>: C 65.43, H 4.71, N 13.63. Found: C 65.56, H 4.68, N 13.76%.

6.2.18. *N*-(4-(2-amino-6-(4-isopropylphenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (49)

Yield: 50%; m.p. 200-205 °C; MS: 466 (M + 1); IR (KBr): 3455, 3323, 3020, 2967, 2360, 1572, 1518, 1430, 1386, 838, 761 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 9.34 (s, 1H, NH), 8.56 (d, 1H, *J* = 5.1 Hz, Ar-Qn), 8.45 (d, 1H, *J* = 9 Hz, Ar-Qn), 8.27 (d, 2H, *J* = 9 Hz, Ar), 8.14 (d, 2H, *J* = 6.6 Hz, Ar), 7.94 (d, 1H, *J* = 2.1 Hz, Ar-Qn), 7.68 (s, 1H, Pym), 7.61 (d, 1H, *J* = 9 Hz, Ar-Qn), 7.50 (d, 2H, *J* = 8.4 Hz, Ar), 7.37 (d, 2H, *J* = 6.0 Hz, Ar), 7.18 (d, 1H, *J* = 5.4 Hz, Ar-Qn), 6.69 (s, 2H, NH<sub>2</sub>), 2.98-2.93 (m, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.24 (d, 6H, *J* = 6 Hz, CH(CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 169.40, 165.82, 156.42, 155.24, 154.95, 152.60, 149.42, 147.84, 137.45, 133.72, 132.31, 131.73, 130.42, 129.82, 123.43, 123.03, 116.86, 112.40, 108.56, 104.12, 39.01, 29.30; Anal. Calcd. for C<sub>28</sub>H<sub>24</sub>ClN<sub>5</sub>: C 72.17, H 5.19, N 15.03; Found: C, 72.34, H 5.46, N 15.26%.

6.2.19. *N*-(4-(2-amino-6-(pyridin-3-yl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (50)

Yield: 55%; m.p. 170-172 °C; MS: 450 (M + 1); IR (KBr): 3460, 3308, 3194, 2362, 1637, 1570, 1522, 1426, 1327, 1244, 773, 669 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 9.27 (s, 1H, Py), 9.10 (s, 1H, NH), 8.62 (d, 1H, *J* = 5.7 Hz, Py), 8.47 (d, 1H, *J* = 5.4 Hz, Ar-Qn), 8.33-8.41 (m, 2H, Py, Ar-Qn), 8.15 (d, 2H, *J* = 8.1 Hz, Ar), 7.84 (d, 1H, *J* = 1.8 Hz, Ar-Qn), 7.54 (s, 1H, Pym), 7.39-7.43 (m, 4H, Ar, Py, Ar-Qn), 7.11 (d, 1H, *J* = 5.28 Hz, Ar-Qn), 6.24 (s, 2H, NH<sub>2</sub>); 9.27 (s, 1H), 9.10 (s, 1H, NH), 8.62 (d, 1H, *J* = 1.2 Hz), 8.47 (d, 1H, *J* = 5.4 Hz), 8.41-8.33 (m, 2H), 8.15 (d, 2H, *J* = 8.1 Hz), 7.84 (d, 1H, *J* = 1.8 Hz), 7.54 (s, 1H), 7.43-7.39 (m, 4H), 7.11 (d, 1H, *J* = 5.28 Hz), 6.24 (s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 166.50, 164.52, 153.21, 152.40, 151.36, 149.91, 146.52, 147.21, 136.29, 134.81, 133.62, 129.82, 128.30, 126.82, 124.51, 122.63, 120.60, 115.72, 112.60, 103.67; Anal. Calcd. for C<sub>24</sub>H<sub>17</sub>ClN<sub>6</sub>: C 67.84, H 4.03, N 19.78; Found: C 67.61, H 4.24, N 19.63%.

6.2.20. *N*-(4-(2-amino-6-(4-(methylthio)phenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (51)

Yield: 55%; m.p. 190-192 °C; MS: 470 (M + 1); IR (KBr): 3315, 3195, 2922, 2361, 1570, 1521, 1427, 1365, 1324, 1234, 813, 775, 669 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 9.10 (s, 1H, NH), 8.46 (d, 1H, *J* = 5.1 Hz, Ar-Qn), 8.34 (d, 1H, *J* = 9 Hz, Ar-Qn), 8.11 (d, 2H, *J* = 8.4 Hz, Ar), 8.05 (d, 2H, *J* = 8.7 Hz, Ar), 7.85 (s, 1H, Ar-Qn), 7.40-7.45 (m, 4H, Ar, Ar-Qn), 7.08 (d, 1H, *J* = 5.4 Hz, Ar-Qn), 6.93 (d, 2H, *J* = 8.7 Hz, Ar), 6.09 (s, 2H, NH<sub>2</sub>), 3.79 (s, 3H, -SCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 165.56, 163.01, 153.31, 151.30, 149.28, 144.40, 136.21, 134.12, 131.65, 130.12, 129.71, 129.54, 126.01, 124.70, 122.92, 120.61, 115.52, 104.82, 102.80, 32.56; Anal. Calcd. for C<sub>26</sub>H<sub>20</sub>ClN<sub>5</sub>S: C 66.44, H 4.29, N 14.90; Found: C 66.20, H 4.56, N 14.66%.

6.2.21. *N*-(4-(2-amino-6-(2,3,4-trimethoxyphenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (52)

Yield: 58%; m.p. 164-166 °C; MS: 524 (M + 1); IR (KBr): 3344, 3207, 2932, 2362, 1566, 1526, 1446, 1371, 1312, 1226, 1126, 817, 776, 713, cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 9.24

(s, 1H), 8.47 (d, 1H,  $J = 5.34$  Hz, Ar-Qn), 8.47 (d, 1H,  $J = 5.34$  Hz, Ar-Qn), 8.31 (d, 1H,  $J = 8.7$  Hz, Ar-Qn), 8.19 (d, 2H,  $J = 8.34$  Hz, Ar), 7.87 (d, 1H,  $J = 2.13$ , Ar-Qn), 7.76 (s, 1H, Ar-Pym), 7.65 (d, 1H,  $J = 8.4$  Hz, Ar), 7.51 (d, 2H,  $J = 8.3$  Hz, Ar), 7.39 (s, 2H, NH<sub>2</sub>), 7.23 (d, 1H,  $J = 8.4$  Hz, Ar), 7.11 (d, 1H,  $J = 5.34$  Hz, Ar-Qn), 3.94 (s, 3H, OCH<sub>3</sub>), 3.91 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>):  $\delta$  167.19, 166.93, 166.63, 162.87, 162.53, 157.37, 153.38, 153.06, 151.37, 148.87, 135.89, 133.32, 131.93, 129.62, 128.97, 128.63, 127.72, 125.37, 123.32, 122.21, 120.49, 104.83, 102.19, 59.34, 59.27, 53.71; Anal. Calcd. for C<sub>28</sub>H<sub>24</sub>ClN<sub>5</sub>O<sub>3</sub>: C 65.43, H 4.71, N 13.63. Found: C 65.66, H 4.59, N 13.74%.

**6.2.22. *N*-(4-(2-amino-6-(3-nitrophenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (53)**

Yield: 48%; m.p. 175-178 °C; MS: 469 (M + 1); IR (KBr): 3434, 3207, 2932, 2363, 1651, 1572, 1531, 1442, 1353, 1242, 1126, 776, 670, cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>):  $\delta$  9.27 (s, 1H, NH), 8.92 (d, 1H,  $J = 2.3$  Hz, Ar), 8.79 (d, 1H,  $J = 8.7$  Hz, Ar), 8.72 (d, 1H,  $J = 5.3$  Hz, Ar-Qn), 8.13-8.20 (m, 4H, Ar-Qn, Ar), 7.77-7.83 (m, 2H, Ar-Qn, Ar), 7.51 (s, 1H, Pym), 7.43 (d, 1H,  $J = 9$  Hz, Ar-Qn), 7.32 (d, 2H,  $J = 8.7$  Hz, Ar), 6.91 (d, 1H,  $J = 5.4$  Hz, Ar-Qn), 6.52 (s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>):  $\delta$  163.23, 161.67, 159.54, 153.32, 149.78, 148.13, 139.55, 138.65, 137.67, 137.09, 134.23, 133.13, 132.32, 129.87, 129.34, 128.35, 127.67, 127.43, 125.07, 124.45, 121.04, 107.89, 103.91; Anal. Calcd. for C<sub>25</sub>H<sub>17</sub>ClN<sub>6</sub>O<sub>2</sub>: C 64.04, H 3.65, N 17.92; Found: C 64.26, H 3.78, N 17.81%.

**6.2.23. *N*-(4-(2-amino-6-(2-bromophenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (54)**

Yield: 52%; m.p. 179-181 °C; MS: 502 (M + 1); IR (KBr): 3413, 3197, 2926, 2362, 1572, 1439, 1368, 1328, 1257, 1187, 776, 768, 636 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>):  $\delta$  9.17 (s, 1H, NH), 8.46 (d, 1H,  $J = 5.4$  Hz, Ar-Qn), 8.21 (d, 1H,  $J = 9.0$ , Ar-Qn), 8.07 (d, 2H,  $J = 8.58$  Hz, Ar), 7.93 (d, 1H,  $J = 2.1$  Hz, Ar-Qn), 7.72 (d, 1H,  $J = 7.92$  Hz, Ar-Qn), 7.54-7.44 (m, 5H, Ar), 7.34 (m, 1H, Ar), 7.28 (s, 1H, Ar-Pym), 7.17 (d, 1H,  $J = 5.4$  Hz, Ar-Qn), 6.79 (s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>):  $\delta$  160.11, 157.85, 143.91, 141.87, 135.86, 132.38, 128.72, 126.31, 125.20, 123.55, 123.41, 121.67, 121.47, 121.38, 120.51, 120.51, 120.0, 119.02, 116.04, 114.56, 114.0, 100.68, 96.12; Anal. Calcd. for C<sub>25</sub>H<sub>17</sub>BrClN<sub>5</sub>: C 59.72, H 3.41, N 13.93; Found: C 59.86, H 3.58, N 13.67%.

**6.2.24. *N*-(4-(2-amino-6-(3-bromophenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (55)**

Yield: 50%; m.p. 186-188 °C; MS: 502 (M + 1); IR (KBr): 3434, 3187, 2932, 2362, 1566, 1446, 1371, 1322, 1246, 1176, 760, 776, 636 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>):  $\delta$  9.23 (s, 1H, NH), 8.51 (d, 1H,  $J = 5.4$  Hz, Ar-Qn), 8.29 (d, 1H,  $J = 9.0$ , Ar-Qn), 8.02 (d, 1H,  $J = 2.13$  Hz, Ar-Qn), 8.16 (d, 2H,  $J = 8.34$  Hz, Ar), 8.02 (d, 1H,  $J = 2.1$  Hz, Ar-Qn), 7.85 (d, 1H,  $J = 9.0$  Hz), 7.62-7.54 (m, 5H, Ar), 7.44 (m, 1H, Ar-Qn), 7.36 (s, 1H, Ar-Pym), 7.27 (d, 1H,  $J = 5.4$  Hz, Ar-Qn), 6.87 (s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>):  $\delta$  163.12, 160.87, 145.29, 144.34, 138.87, 135.39, 131.62, 129.34, 128.62, 126.51, 126.37, 123.87, 123.71, 123.65, 122.57, 122.07, 121.13, 119.08, 117.68, 117.58, 117.17, 103.12, 97.69; Anal. Calcd. for C<sub>25</sub>H<sub>17</sub>BrClN<sub>5</sub>: C 59.72, H 3.41, N 13.93; Found: C 59.86, H 3.58, N 13.75%.

**6.2.25. *N*-(4-(2-amino-6-(2,3-dimethoxyphenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (56)**

Yield: 55%; m.p. 160-162 °C; MS: 484 (M + 1); IR (KBr): 3327, 3205, 2932, 2362, 1649, 1571, 1528, 1438, 1356, 1331, 1234, 1190, 1121, 1028, 869, 774, 670, cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>):  $\delta$  9.22 (s, 1H, NH), 8.45 (d, 1H,  $J = 5.1$  Hz, Ar-Qn), 8.39 (d, 1H,  $J = 9.0$  Hz, Ar-Q), 8.10 (d, 2H,  $J = 8.4$  Hz, Ar), 7.88 (s, 1H, Ar-Qn), 7.53-7.38 (m, 4H, Ar, Pym), 7.32 (d, 1H,  $J = 9.0$  Hz, Ar-Qn), 7.13-7.07 (m, 3H, Ar-Qn, Ar), 6.34 (s, 2H, NH<sub>2</sub>), 3.85 (s, OCH<sub>3</sub>), 3.76 (s, OCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>):  $\delta$  168.03, 167.71, 167.13, 162.87, 158.31, 154.09, 152.87, 151.13, 148.73, 135.95, 133.38, 132.03, 129.87, 128.67, 128.17, 127.75, 125.21, 123.37, 122.71, 121.13, 120.79, 105.03, 101.98, 59.37, 53.79; Anal. Calcd. for C<sub>27</sub>H<sub>22</sub>ClN<sub>5</sub>O<sub>2</sub>: C 67.01, H 4.58, N 14.47; Found: C 67.26, H 4.78, N 14.67%.

6.2.26. *N*-(4-(2-amino-6-(2,5-dimethoxyphenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (**57**)  
Yield: 55%; m.p. 178-180 °C; MS: 484 (M + 1); IR (KBr): 3344, 3207, 2932, 2362, 1568, 1526, 1446, 1351, 1332, 1226, 1126, 1025, 870, 776, 667, cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 9.23 (s, 1H, NH), 8.73 (d, 1H, *J* = 5.1 Hz, Ar-Q), 8.43 (d, 1H, *J* = 9.0 Hz, Ar-Q), 8.12 (d, 2H, *J* = 8.1 Hz, Ar), 7.96 (s, 1H, Ar-Q), 7.63-7.52 (m, 4H, Ar, Ar-Py), 7.49 (d, 1H, *J* = 9.0 Hz, Ar-Q), 7.37 (d, 1H, *J* = 8.4 Hz, Ar), 7.32 (d, 1H, *J* = 8.4 Hz, Ar-Q), 7.13 (d, 1H, *J* = 5.1 Hz, Ar-Q), 6.37 (s, 2H, NH<sub>2</sub>), 3.90 (s, 3H, OCH<sub>3</sub>), 3.84 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 167.89, 166.93, 166.37, 162.13, 158.17, 153.53, 152.37, 151.31, 148.87, 135.39, 133.20, 132.17, 129.67, 128.31, 128.06, 127.57, 125.68, 124.06, 123.13, 121.26, 120.69, 104.86, 100.67, 58.97; Anal. Calcd. for: C 67.01, H 4.58, N 14.47; Found: C 67.36, H 4.38; N, 14.14%.

6.2.27. *N*-(4-(2-amino-6-(4-chlorophenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (**58**)  
Yield: 62%; m.p. 182-184 °C; MS: 458 (M + 1); IR (KBr): 3329, 3207, 2925, 2362, 1618, 1573, 1530, 1432, 1367, 1332, 1231, 1089, 865, 774, 713 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 9.39 (s, 1H, NH), 8.55 (d, 1H, *J* = 5.34 Hz, Ar-Qn), 8.45 (d, 1H, *J* = 9.0 Hz, Ar-Qn), 8.28 (d, 2H, *J* = 8.70 Hz, Ar-Qn), 8.25 (d, 2H, *J* = 8.64 Hz, Ar), 7.94 (d, 1H, *J* = 2.13 Hz, Ar-Qn), 7.74 (s, 1H, Ar-Pym), 7.62-7.56 (m, 3H, Ar, Ar-Qn), 7.50 (d, 2H, *J* = 8.64 Hz, Ar), 7.17 (d, 1H, *J* = 5.34 Hz, Ar-Qn), 6.79 (s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 163.37, 157.89, 147.53, 143.71, 132.87, 131.37, 126.91, 126.69, 125.67, 122.57, 122.12, 121.71, 121.13, 120.89, 120.12, 119.83, 119.34, 118.97, 118.10, 114.67, 114.03, 103.21, 100.67; Anal. Calcd. for C<sub>25</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>5</sub>: C 65.51, H 3.74, N 15.28; Found: C 65.76, H 3.82, N 15.37%.

6.2.28. *N*-(4-(2-amino-6-(2-chlorophenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (**59**)  
Yield: 68%; m.p. 178-180 °C; MS: 458 (M + 1); IR (KBr): 3475, 3327, 2923, 2363, 1618, 1571, 1525, 1454, 1367, 1236, 1195, 1080, 866, 776, 702 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 9.32 (s, 1H, NH), 8.49 (d, 1H, *J* = 5.27 Hz, Ar-Q), 8.47 (d, 1H, *J* = 9.0 Hz, Ar-Q), 8.25 (d, 2H, *J* = 8.70 Hz, Ar-Qn), 8.19 (dd, 2H, *J* = 8.64 Hz, *J* = 2.1 Hz, Ar), 7.91 (d, 1H, *J* = 2.13 Hz, Ar-Qn), 7.67 (s, 1H, Ar-Pym), 7.52-7.43 (m, 3H, Ar, Ar-Qn), 7.39 (dd, 1H, *J* = 8.37 Hz, 2.1 Hz), 7.36-7.26 (m, 2H, Ar), 7.11 (d, 1H, *J* = 5.27 Hz), 6.68 (s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 161.12, 158.87, 144.58, 141.97, 133.86, 131.38, 127.67, 126.87, 125.37, 122.53, 121.98, 121.34, 121.03, 120.93, 120.87, 120.31, 119.98, 119.06, 117.41, 114.53, 114.07, 102.67, 98.13; Anal. Calcd. for C<sub>25</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>5</sub>: C 65.51, H 3.74, N 15.28. Found: C 65.36, H 3.52, N 15.47%.

## Aknowledgments


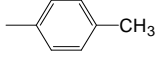
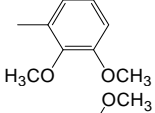
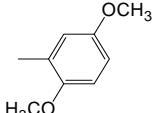
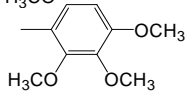
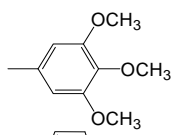

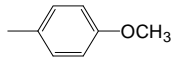
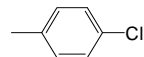
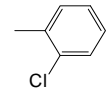
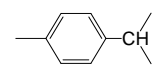

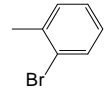
M. S. thanks to Indian Council of Medical Research (ICMR) for providing financial support. We are also thankful to S.A.I.F. Division, CDRI, Lucknow for providing spectroscopic data. CDRI communication No 7510.

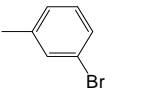
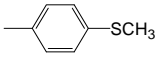
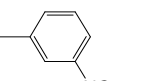
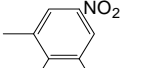
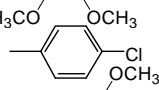
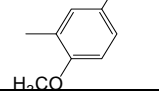
## References

- [1] E. Bogatkheva, C. Hanrahan, B. Nikonenko, R. Samala, P. Chen, J. Gearhart, F. Barbosa, L. Einck, C. A. Nancy, M. Protopopova, J. Med. Chem. 49 (2006) 3045-3048.
- [2] C. Dye, S. Scheele, P. Dolin, V. Pathania, M. C. Ravigilione, J. Am. Med. Assoc. 282 (1999) 677-686.
- [3] P. Farmer, J. Bayona, M. Becerra, J. Furin, C. Henry, H. Hiatt, J. Y. Kim, C. Mitnick, E. Nardell, S. Shin, Int. J. Tuberc. Lung Dis. 2 (1998) 869-876.
- [4] L. Qian, R. Paul, O. D. Montellano, Chem. Res. Toxicol. 19 (2006) 443-449.
- [5] J. F. Murray, Am. J. Respir. Crit. Care Med. 169 (2004) 1181-1186.
- [6] D. Gessler, C. Dye, P. Farmer, M. Murray, T. Navin, R. Reves, T. Shinnick, P. M. Small, T. Yates, G. Simpson, Science 311 (2006) 1245-1246.
- [7] S. Velaparthy, M. Brunsteiner, R. Uddin, B. Wan, G. S. Franzblau, P. A. Petukhov, J. Med. Chem. XXXX, xxx, 000-000. Published on Web 03/13/2008.
- [8] E. L. Corbett, C. G. Watt, N. Walker, D. Maher, B. G. Williams, M. C. Ravigilione, C. Dye, Arch. Intern. Med. 163 (2003) 1009-21.

- [9] L. Ballell, R. A. Field, K. Duncan, R. J. Young, *Antimicrobial Agents and Chemotherapy* (2005) 2153–2163.
- [10] World Health Organisation on fact sheet no. 104, WHO information, Geneva, Switzerland.
- [11] P.B. Jones, N. M. Parish, T.A. Houston, A. Stapon, N.P. Bansal, D.D. James, C.A. Townsend, *J. Med. Chem.* 43 (2003) 3304-3314.
- [12] P.M. Sivakumar, S.K.G. Babu, D. Mukesh, *Chem. Pharm. Bull.* 55 (2007) 44-49.
- [13] T. K. Dianne, S. A. Tina, K.J. Malcolm, M.B. Ian, W.G. Luke, D.J. John, *J. Med. Chem.* 49 (2006) 7479-7486.
- [14] D. Carucci, *Nature* 430 (2004) 944-945.
- [15] Y. Susan, J.S. Peter, C. Kelly, *Biochemical Pharmacology.* 72 (2006) 156-165.
- [16] World Health Organisation on fact sheet no. 94, WHO information, 2004.
- [17] J.C. Wootton, X. Feng, M.T. Ferdig, R.A. Cooper, J. Mu, D.I. Baruch, A.J. Magill, X. Su, *J. Nature.* 418 (2002) 320-323.
- [18] K. Zhang, P.K. Rathod, *Science*, 296 (2002) 482-483.
- [19] S.F. Nielsen, S.B. Christensen, G. Cruciani, A. Kharazmi, T. Liljefors, *J. Med. Chem.* 41 (1998) 4819-4832.
- [20] M. Liu, P. Wilairat, M.L. Go, *J. Med. Chem.* 44 (2001) 4443-4452.
- [21] H.K. Hsieh, T.H. Lee, J.J. Wang, C.N. Lin, *Pharm. Res.* 15 (1998) 39-46.
- [22] L. Barford, K. Kemp, M. Hansen, A. Kharazmi, *Int. Immunopharm.* 2 (2002) 545.
- [23] J. Rojas, M. Paya, J.N. Dominguez, M.L. Ferrandiz, *Bioorg. Med. Chem. Lett.* 12 (2002) 1951-1954.
- [24] S. Ducki, R. Forrest, J.A. Hadfield, A. Kendall, N.J. Lawrence, A.T. McGown, D. Renninson, *Bioorg. Med. Chem. Lett.* 8 (1998) 1051-1056.
- [25] A. Agarwal, K. Srivastava, S.K. Puri, P.M.S. Chauhan, 15 (2005) 531-533
- [26] H. Stephen, L. Sergio, I. Khalid, *Biochem. Pharmacology.* 71 (2006) 941-948.
- [27] W.H. Miller, M.A. Seefeld, K.A. Newlander, I.N. Uzinskas, W.J. Burgess, D.A. Heerding, C.C. Yuan, M.S. Head, D.J. Payne, S.F. Rittenhouse, T.D. Moore, S.C. Pearson, V. Berry, W.E DeWolf, P.M. Keller, B.J. Polizzi, X. Qiu, C.A. Janson, W.F. Huffman, *J. Med. Chem.* 45 (2002) 3246-3256.
- [28] A. Agarwal, K. Srivastava, S.K. Puri, P.M.S. Chauhan, P. M. S. *Bioorg. Med. Chem. Lett.* 15 (2005) 3133-3136.
- [29] S. Srivastava, S. Tiwari, P.M.S. Chauhan, S.K. Puri, A.P. Bhaduri, V.C. Pandey, *Bioorg. Med. Chem. Lett.* 9 (1999) 653-658.
- [30] A. Agarwal, K. Srivastava, S.K. Puri, P.M.S. Chauhan, *Bioorg. Med. Chem. Lett.* 15 (2005) 1881-1883.
- [31] A. Agarwal, K. Srivastava, S.K. Puri, S. Sinha, P.M.S. Chauhan, *Bioorg. Med. Chem. Lett.* 15 (2005) 5218-5221.
- [32] A. Agarwal, Ramesh, Ashutosh, N. Goyal, S. Gupta, P.M.S. Chauhan, *Bioorg. Med. Chem.* 13 (2005), 6678-6684.
- [33] A. Agarwal, K. Srivastava, S.K. Puri, P.M.S. Chauhan, *Bioorg. Med. Chem.* 13 (2005) 6226-6232.
- [34] A. Agarwal, K. Srivastava, S.K. Puri, S. Sinha, P.M.S. Chauhan, *Bioorg. Med. Chem. Lett.* 15 (2005) 4923-4926.
- [35] A. Agarwal, K. Srivastava, S.K. Puri, P.M.S. Chauhan, *Bioorg. Med. Chem.* 13 (2005) 4645-4650.
- [36] A. Agarwal, K. Srivastava, S.K. Puri, P.M.S. Chauhan, *Bioorg. Med. Chem. Lett.* 15 (2005) 3130-3132.
- [37] N. Sunduru, A. Agarwal, S.B. Katiyar, Nishi, N. Goyal, S. Gupta, P.M.S. Chauhan, *Bioorg. Med. Chem.* 14 (2006) 7706-7715.
- [38] L. Gupta, K. Srivastava, S. Singh, S.K. Puri, P.M.S. Chauhan, *Bioorg. Med. Chem. Lett.* 18 (2008) 3306-3309.
- [39] A.H. Cory, T.C. Owen, J.A. Barltrop, J.G. Cory, *Cancer Commu.* 3 (1991) 207-212.
- [40] K.H. Rieckmann, L.J. Sax, G.H. Campbell, J.E. Mrema, *Lancet* 311 (1978) 22-23.
- [41] C. Trager, J.P. Vanderberg, *J. Parasitol.* 193 (1979) 673-675.

Table1. Biological activity of chalcones and trisubstituted pyrimidines.

S.No.	R	<i>M. tuberculosis</i> MIC ( $\mu\text{g/ml}$ )	<i>P. falciparum</i> MIC ( $\mu\text{g/ml}$ )
44		NA	10
45		NA	10
56		NA	>10
57		NA	10
52		NA	10
48		12.5	>10
47		12.5	10
46		NA	2.0
58		NA	-
59		NA	-
49		6.25	1.0
50		NA	1.0
54		NA	10

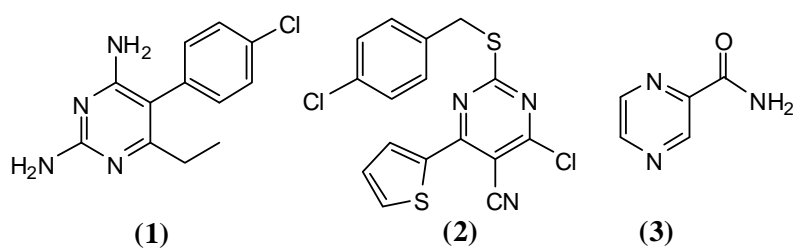
55		NA	10
51		NA	1.0
53		NA	>10
18		3.12	-
20		6.25	-
19		3.12	-

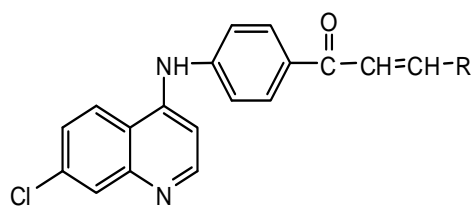
Pyrimethamine: Standard antimalarial drug (MIC 10µg/ml). Pyrazinamide: Anti-TB drug (MIC 50µg/ml).

Table 2  
Cytotoxicity against in VERO, MBMDM cell lines

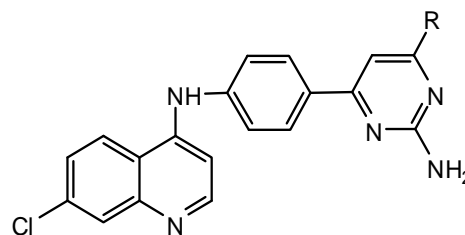
Compound No.	MIC (µg/ml)	VERO	MBMDM*
31	3.12	NT	NT
32	3.12	NT	NT
Pyrazinamide	50	NT	NT

\*MBMDM: mouse bone marrow derived macrophages; NT: non toxic

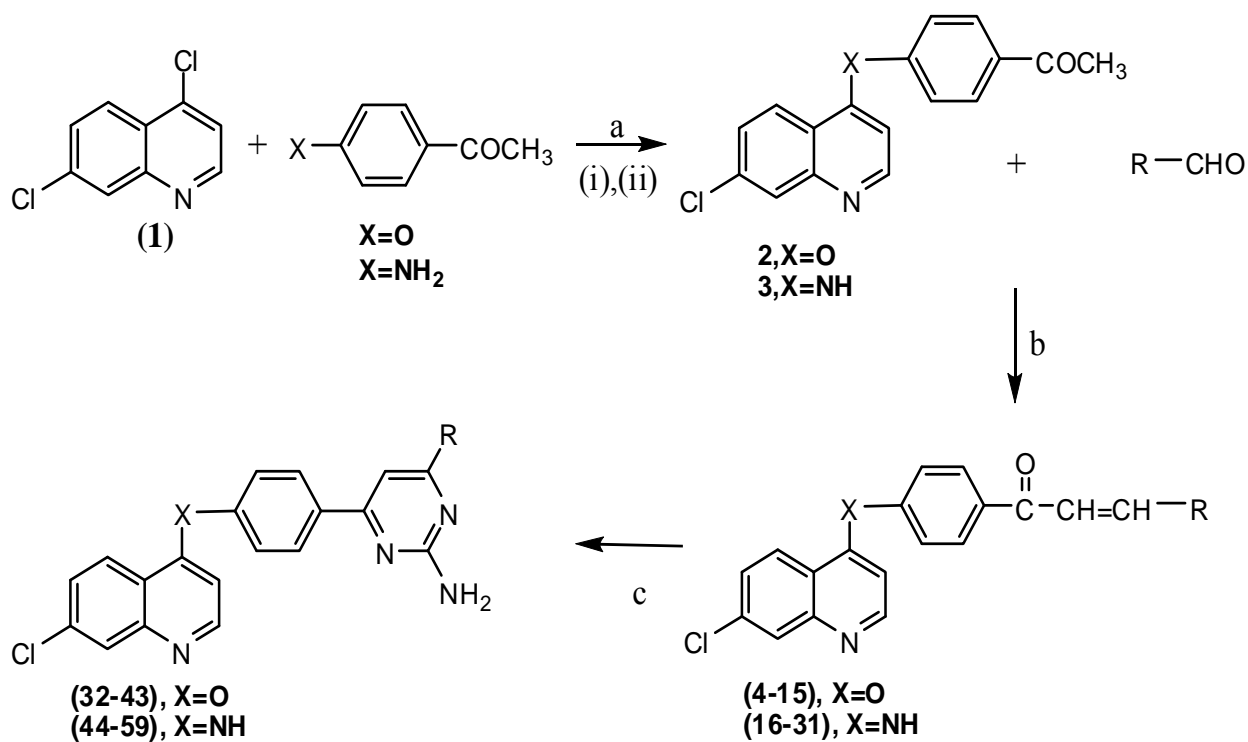




16-31



44-59



**Scheme 1** .Reagents and conditions: (a) (i) DMF, KOH, 120 °C, 8h; (ii) MeOH, 80°C, 8h; (b) 10% NaOH, MeOH, 0°C, r.t. 5h; (c) Guanidinehydrochloride, DMF, NaH, 120 °C, 10 h.