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Original article

Substituted quinolinyl chalcones and quinolinyl pyrimidines as a new class of anti-infective agents

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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 synthesized and evaluated for their *in vitro* antitubercular activity against *Mycobacterium tuberculosis* $H_{37}R_V$ 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 nos. **22** and **23** have shown antitubercular activity of MIC 3.12 μg/mL and were nontoxic against VERO, MBMDM cell lines and compounds **54**, **55**, and **56** have shown antimalarial activity of MIC 1 μg/mL.

1. Introduction

Infectious diseases are influencing the world with their morbidity and mortality, out of which tuberculosis and malaria are major infectious diseases caused by *Mycobacterium tuberculosis* [1,2] and *Plasmodium falciparum* [3,4] respectively, have become more virulent now a days by claiming about three to four million lives and infecting over ten million people annually [5–8]. The current chemotherapy is based on age old drugs like Chloroquine (**Ia**), Pyrimethamine-sulfadoxine for malaria [3,4] and Pyrazinamide, Isoniazid and Rifampin for tuberculosis [9]. The efficacy of these drugs has been deteriorated by the emerging resistant strains. More over the pathogenic synergy of HIV to these diseases is alarming the world to develop new efficient chemotherapy for infectious diseases [10].

The development of new drugs will be greatly facilitated by a complete understanding of the molecular mechanism underlying previously successful antimalarial drugs [11]. For structurally simple group of compounds which act on more than one target site are liable to be more active. The chalcones have displayed an impressive array of pharmacological activities like anti-protozoal [12,13], anti-inflammatory [14] immunomodulatory [15]. On the other hand pyrimidine scaffold was the base of many bioactive molecule as antimalarial such as Pyrimethamine (**Ib**), Cycloguanil {DHFR (DiHydroFolate Reductase) inhibitor} [16], antibacterial (Trimethoprim, Iclaprim) [17], antitubercular agents (**II**) [18].

As our research is devoted to the synthesis of diverse heterocycles as anti-infective agents, we identified the pyrimidine and quinoline (separately) as good anti-infectious agents [19–29]. Keeping this in view we designed and synthesized new prototypes by combining both pyrimidine and quinoline. 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**) and (**16**–**31**) 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

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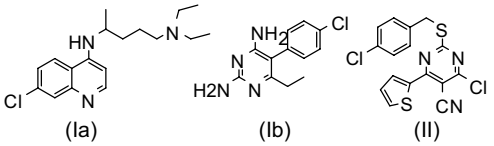
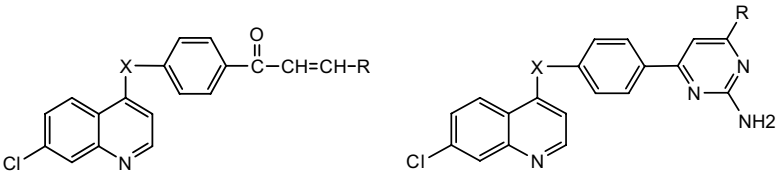
ipso-substitution of 4-chloro of 4,7-dichloroqinoline with 4-hydroxy acetophenone in DMF in the presence of potassium hydroxide at 120 °C and intermediate (**3**) was synthesized by nucleophilic substitution of 4-chloro of 4,7-dichloroquinoline with 4-amino acetophenone in MeOH (Scheme 1). All the synthesized compounds as mentioned in Table 1 were well characterized by spectroscopic methods such as IR, FAB, NMR and elemental analysis.





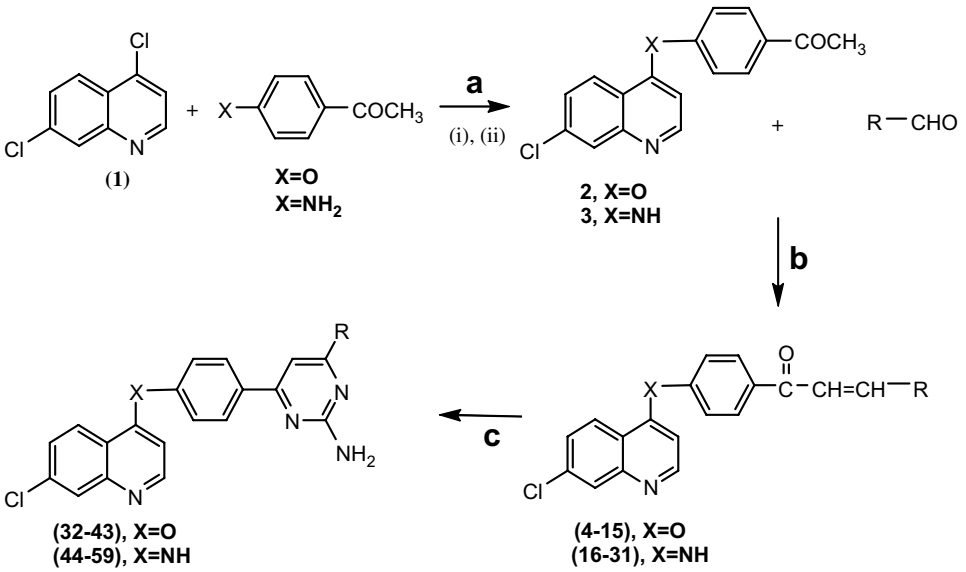
3. Biological activity

Evaluation of *in vitro* antitubercular activity against *M. tuberculosis* $H_{37}Rv$ strain was carried out with a recommended protocol [30] using Middle Brook (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* $H_{37}RV$ 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 (2×10^7 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.

3.1. Cytotoxic evaluation

(i) In VERO [31] cells {10^4 cells/well/0.1 mL MEM (Minimum Essential Medium) containing antibiotics and 10% FBS (Fetal Bovine Serum)} were seeded in 96 wells tissue culture plate. After 24 h incubation (37 °C, 5% CO_2) medium was replaced with fresh medium (5% FBS and no antibiotic) containing different concentrations of test compound/known toxic compound/DMSO. After 24 h incubation (37 °C, 5% CO_2) 20 μL MTS (Meyallothioneins) reagent (Promega Kit) is added and absorbance is read after 2 h 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.

(ii) In Mouse Bone Marrow Derived Macrophages (MBMDM): plated 10^5 cells/0.1 mL/well in DMEM (Dulbecco's Minimum



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

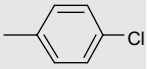
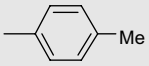
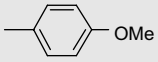
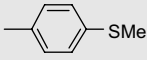
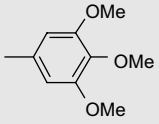
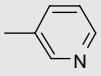
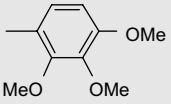
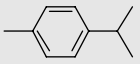
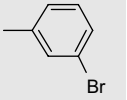
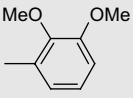
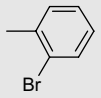
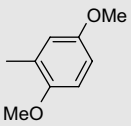
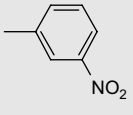
Essential Medium) (supplemented with antibiotics, 10% FBS, 15% (v/v) L-929 fibroblast conditioned supernatant and non-essential amino acids) in 96 wells tissue culture plate. After 5 days incubation (37 °C, 5% CO_2) 20 μL MTS reagent (Promega Kit) was added and absorbance read after 2 h at 490 nm. Absorbance 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. [32]. The culture of *P. falciparum* NF-54 strain is routinely being maintained in medium RPMI-1640 supplemented with 25 mM HEPES {4-(2-hydroxy ethyl)-1-piprazine ethane sulphonic acid}. 1% D-Glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum [33]. 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 200 μL of medium RPMI-1640 was uniformly maintained. The test compound in 20 μL 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 36–40 h 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 tested concentration, which inhibits the complete maturation into schizonts, was recorded as the minimum inhibitory concentration Table 2.

4. Results and discussion

All the 56 synthesized compounds were screened against $H_{37}Rv$ strains of the *M. tuberculosis* and NF-54 strains of *P. falciparum*. The compounds of the series which have shown significant activity are mentioned in Table 2. Among all, compounds of the first series where 4-oxo linkage between quinoline and chalcone **4**–**15** and

Table 1
All the synthesized compounds of the 4-oxo and 4- amino linked series.

[a]Chalcones (oxo linked, amino linked)	[a]Pyrimidines (oxo linked, amino linked)	*R* (oxo linked, amino linked)	Chalcones (oxo linked, amino linked)	Pyrimidines (oxo linked, amino linked)	*R* (oxo linked, amino linked)
4, **16**	**32**, **44**		**12**, **24**	**40**, **52**	
5, **17**	**33**, **45**		**13**, **25**	**41**, **53**	
6, **18**	**34**, **46**		**14**, **26**	**42**, **54**	
7, **19**	**35**, **47**		**15**, **27**	**43**, **55**	
8, **20**	**36**, **48**		**28**[b]	**56**	
9, **21**	**37**, **49**		**29**	**57**	
10, **22**	**38**, **50**		**30**	**58**	
11, **23**	**39**, **51**		**31**	**59**	

[a] First no. refers to oxo linked and second no. refers to amino linked compounds.
[b] single set of no. only refers to amino linked compounds.

pyrimidine **32**–**43** were found to be inactive, while their 4-amino linked analogues **16**–**31** and **44**–**59** showed promising activity against *M. 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 chalcones and hybrid of quinoline and pyrimidines reveals that different physiochemical and structural requirements exist for these two activities. The 2,3-dimethoxyphenyl **22** and 2,5-dimethoxyphenyl **23** substituted derivatives of chalcones were found to be active against Mtb having a MIC of 3.12 μg/mL and are nontoxic against VERO and MBMDM cell lines (Table 3), while their pyrimidine analogues were found to be inactive against the same strain. Compound **24** having chloro-substitution at *para*-position of phenyl ring showed MIC of 6.25 μg/mL. The 3,4,5-trimethoxy substituted phenyl system **47** was found to be active against Mtb have shown MIC of 12.5 μg/mL as compared to dimethoxy substituted phenyl systems **50** and **51** 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 **49** is found to be moderately active having MIC of 12.5 μg/mL against Mtb over the nitrogen containing heterocycle, 3-pyridyl substitution **55**. Contrarily nitrogen containing heterocycle compound **55** has shown significant activity against *P. falciparum* having a MIC of 1 μg/mL compared to oxygen containing heterocycle (furan) compound **49** having a MIC of 10 μg/mL. None of the chalcones have shown activity in malaria while their pyrimidine scaffolds were significantly active having MIC in the range of 1–2 μg/mL. 4-Isopropyl substituted phenyl ring system **56** was found to be moderately active having a MIC 6.25 μg/mL. On the other hand same compounds **56** and **54** having 4-thiomethyl substituted phenyl ring system were found to be active in malaria and having a MIC of 1 μg/mL. Substitution of phenyl ring with 4-methoxy group reduced the activity of compound **46** to MIC of 2 μg/mL. All the results of biological activity are shown in Table 2.

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* screenings of these compounds against *M. tuberculosis* and *P. falciparum* have shown their promising activity. Out of the synthesized compounds, six compounds have shown antitubercular activity with MIC in the range of 3.12–12.5 μg/mL and are nontoxic against VERO and MBMDM cell lines. Four compounds have shown antimalarial activity with MIC ranging from 1 to 2 μg/mL. The SAR of these compounds showed that quinolinyl chalcones are antitubercular agents while their pyrimidine analogues were moderately active 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.

Table 2
Biological activity of chalcones and trisubstituted pyrimidines.

Compound no.	*Mycobacterium tuberculosis* MIC (μg/mL)	*Plasmodium falciparum* MIC (μg/mL)
22	3.12	NA
23	3.12	NA
24	6.25	NA
46	NA	2
47	12.5	NA
49	12.5	NA
54	NA	1
55	NA	1
56	6.25	1
Chloroquine	–	0.125
Pyrazinamide	50	–

*Only active compounds are shown in table.

Table 3
Cytotoxicity against VERO and MBMDM cell lines.

Compound No.	MIC (μg/mL)	VERO	MBMDM[a]
22	3.12	NT	NT
23	3.12	NT	NT
Pyrazinamide	50	NT	NT

[a] MBMDM: mouse bone marrow derived macrophages; NT: nontoxic.

6. Experimental

IR spectra were recorded on Beckman Aculab-10, Perkin Elmer 881 and FTIR 8210 PC, Schimadzu 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, 10 mA) 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.

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

The mixture of 4,7-dichloroquinoline (1.0 equiv), 4-hydroxy acetophenone (1.5 equiv) and KOH (1.5 equiv) in DMF was refluxed for 6 h. 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 white crystals.

Yield: 65%; m.p. 165–168 °C; MS: 298 (M + 1); IR (KBr): 3073, 2350, 1648, 1610, 1573, 1526, 1430, 1354, 1210, 1072, 776, 670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 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, $-COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 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 $C_{17}H_{12}ClNO_2$: C 70.19, H 4.76, N 6.30; Found: C 70.0, H 4.90, N 6.78%.

6.2. 1-(4-(7-Chloroquinolin-4-ylamino)phenyl)ethanone (**3**)

The mixture of 4,7-dichloroquinoline (1.0 equiv) and 4-amino-acetophenone (1.5 equiv) in MeOH was refluxed for 6 h. The solvent was evaporated under vacuum and solid mass was obtained. The solid was recrystallised from methanol to obtain compound **3** as a yellow solid.

Yield: 85%; m.p 160–162 °C; MS: 297 (M + 1); IR (KBr) 3435, 3021, 2361, 1670, 1623, 1473, 1215, 1093, 761, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + CD_3OD$): δ: 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, $-COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3 + CD_3OD$): δ 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 $C_{17}H_{13}ClN_2O$: C 68.81, H 4.42, N 9.44; Found: C 68.78, H 4.60, N 9.68%.

6.3. 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, and 1.5 equiv of liquid aldehydes

over a period of 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 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 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%.

*6.3.1. 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^{-1}; ^1H NMR ($CDCl_3$, 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{24}H_{16}ClNO_2$: C 74.71, H 4.18, N 3.63; Found: C 74.69, H 4.36, N 3.38%.

*6.3.2. 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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{25}H_{18}ClNO_2$: C 75.09, H 4.54, N 3.50; Found: C 75.28, H 4.78, N 3.70%.

*6.3.3. 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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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_3); ^{13}C NMR (75 MHz, $CDCl_3 + CD_3OD$): 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 $C_{25}H_{18}ClNO_3$: C 72.20, H 4.36, N 3.37; Found: C 72.36, H 4.17, N 3.08%.

*6.3.4. 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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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_3), 3.93 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{27}H_{22}ClNO_5$: C 68.14, H 4.66, N 2.94; Found: C 68.39, H 4.46, N 2.78%.

*6.3.5. 1-(4-(7-Chloroquinolin-4-yloxy)phenyl)-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one (**8**)*

Yield: 78%; m.p 160–162 °C; MS: 476 (M + 1); IR (KBr): 3061, 2998, 2867, 2364, 1655, 1592, 1479, 1379, 1210, 1136, 1038, 830, 756, 730, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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_3), 3.99 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, CDCl): 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 $C_{27}H_{22}ClNO_5$: C 68.14, H 4.66, N 2.94; Found: C 68.29, H 4.56, N 2.78%.

*6.3.6. 1-(4-(7-Chloroquinolin-4-yloxy)phenyl)-3-(furan-2-yl)prop-2-en-1-one (**9**)*

Yield: 72%; m.p 165–167 °C; MS: 376 (M + 1); IR (KBr): 3092, 2926, 2361, 1662, 1603, 1495, 1378, 1223, 1168, 1018, 968, 833, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3 + CD_3OD$): 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 $C_{22}H_{14}ClNO_3$: C 70.31, H 3.75, N 3.73; Found: C 70.29, H 3.66, N 3.78%.

*6.3.7. 1-(4-(7-Chloroquinolin-4-yloxy)phenyl)-3-(2,3-dimethoxyphenyl)prop-2-en-1-one (**10**)*

Yield: 70%; m.p 158–160 °C; MS: 446 (M + 1); IR (KBr): 3067, 2953, 2361, 1666, 1604, 1481, 1383, 1266, 1171, 1080, 776, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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_3), 3.91 (s, 3H, OCH_3); ^{13}C (75 MHz $CDCl_3 + CD_3OD$): 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 $C_{26}H_{20}ClNO_4$: C 70.03, H 4.52, N 3.14; Found: C 70.22, H: 4.76, N 3.31%.

*6.3.8. 1-(4-(7-Chloroquinolin-4-yloxy)phenyl)-3-(2,5-dimethoxyphenyl)prop-2-en-1-one (**11**)*

Yield: 75%; m.p 160–162 °C; MS: 444 (M + 1); IR (KBr): 3071, 2998, 2367, 1655, 1610, 1521, 1479, 1377, 1280, 1078, 786, 776, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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_3), 3.89 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3 + CD_3OD$): 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 $C_{26}H_{20}ClNO_4$: C 70.03, H 4.52, N 3.14; Found: C 70.12, H 4.76, N 3.35%.

*6.3.9. 3-(4-Chlorophenyl)-1-(4-(7-chloroquinolin-4-yloxy)phenyl)prop-2-en-1-one (**12**)*

Yield: 72%; m.p 172–174 °C; MS: 420 (M + 1); IR (KBr): 3063, 2918, 2362, 1666, 1606, 1496, 1379, 1266, 1218, 1030, 976, 831, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C (75 MHz, $CDCl_3 + CD_3OD$): 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 $C_{24}H_{15}Cl_2NO_2$: C 68.59 H 3.60, N 3.33; Found: C 68.52, H 3.76, N 3.25%.

*6.3.10. 3-(2-Chlorophenyl)-1-(4-(7-chloroquinolin-4-yloxy)phenyl)prop-2-en-1-one (**13**)*

Yield: 70%; m.p 178–180 °C; MS: 420 (M + 1); IR (KBr): 3061, 2909, 2367, 1655, 1610, 1570, 1479, 1428, 1377, 1268, 1210, 1023, 831, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3 + CD_3OD$): 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 $C_{24}H_{15}Cl_2NO_2$: C 68.59, H 3.60, N 3.33; Found: C 68.22, H 3.46, N 3.25%.

*6.3.11. 1-(4-(7-Chloroquinolin-4-yloxy)phenyl)-3-(4-(methylthio)phenyl)prop-2-en-1-one (**14**)*

Yield: 68%; m.p 180–182 °C; MS: 432 (M + 1); IR (KBr): 3042, 2928, 2367, 1655, 1592, 1490, 1377, 1218, 1096, 980, 801, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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_3); ^{13}C NMR (75 MHz, $CDCl_3 + CD_3OD$): 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 $C_{25}H_{18}ClNO_2S$: C 69.52, H 4.20, N 3.24; Found: C 69.43, H 4.36, N 3.35%.

*6.3.12. 1-(4-(7-Chloroquinolin-4-yloxy)phenyl)-3-(pyridin-3-yl)prop-2-en-1-one (**15**)*

Yield: 68%; m.p 168–170 °C; MS: 387 (M + 1); IR (KBr): 3031, 2938, 2357, 1645, 1580, 1479, 1387, 1210, 1013, 836, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 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 $C_{23}H_{15}ClNO_2$: C 71.41, H 3.91, N 7.24; Found: C 71.53, H 3.76, N 7.45%.

*6.3.13. 1-(4-(7-Chloroquinolin-4-ylamino)phenyl)-3-phenylprop-2-en-1-one (**16**)*

Yield: 68%; m.p 190–192 °C; MS: 385 (M + 1); IR (KBr): 3331, 2998, 2967, 2364, 1655, 1610, 1570, 1521, 1479, 1428, 1377, 1210, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$, DMSO-d_6): 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 $C_{24}H_{17}ClN_2O$: C 74.90, H 4.45, N 7.28; Found: C 74.89, H 4.26, N 7.48%.

*6.3.14. 1-(4-(7-Chloroquinolin-4-ylamino)phenyl)-3-*p*-tolylprop-2-en-1-one (**17**)*

Yield: 65%; m.p 170–172 °C; MS: 399 (M + 1); IR (KBr): 3349, 3020, 2360, 1729, 1640, 1578, 1522, 1480, 1324, 1216, 1031, 851, 771, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, DMSO-d_6): 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_3); ^{13}C NMR (75 MHz, $CDCl_3$, DMSO-d_6): 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 $C_{25}H_{19}ClN_2O$: C 75.28, H 4.80, N 7.02; Found: C 75.30, H 4.54, N 7.15%.

*6.3.15. 1-(4-(7-Chloroquinolin-4-ylamino)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**18**)*

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): 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_3); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{25}H_{19}Cl–N_2O_2$: C 72.37, H 4.62, N 6.75; Found: C 72.35, H 4.72, N 6.58%.

*6.3.16. 1-(4-(7-Chloroquinolin-4-ylamino)phenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**19**)*

Yield: 72%; m.p 187–189 °C; MS: 475 (M + 1); IR (KBr): 3382, 3025, 2973, 2361, 1653, 1611, 1573, 1528, 1429, 1335, 1216, 1182, 1031, 847, 759, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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_3), 3.87 (s, 3H, –OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, DMSO-d_6): 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. $C_{27}H_{23}ClN_2O_4$ C 68.28, H 4.88, N 5.90; Found: C 68.37, H 4.89, N 5.89%.

*6.3.17. 1-(4-(7-Chloroquinolin-4-ylamino)phenyl)-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one (**20**)*

Yield: 78%; m.p 175–177 °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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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, $-OCH_3$), 3.95 (s, 3H, $-OCH_3$), 3.87 (s, 3H, $-OCH_3$); ^{13}C NMR (300 MHz, $CDCl_3$ + DMSO-d_6): 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 $C_{27}H_{23}ClN_2O_4$: C 68.28, H 4.88, N 5.90; Found: C 68.36, H 4.98, N 5.92%.

*6.3.18. 1-(4-(7-Chloroquinolin-4-ylamino)phenyl)-3-(furan-2-yl)prop-2-en-1-one (**21**)*

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$, DMSO-d_6): 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); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 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 $C_{22}H_{15}ClN_2O_2$: C 70.50, H 4.03, N 7.47; Found: C 70.32, H 4.34, N 7.59%.

*6.3.19. 1-(4-(7-Chloroquinolin-4-ylamino)phenyl)-3-(2,3-dimethoxyphenyl)prop-2-en-1-one (**22**)*

Yield: 78%; m.p 160–162 °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^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): 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); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 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 $C_{26}H_{21}ClN_2O_3$: C 70.19, H 4.76, N 6.30; Found: C 70.23, H 4.90, N 6.68%.

*6.3.20. 1-(4-(7-Chloroquinolin-4-ylamino)phenyl)-3-(2,5-dimethoxyphenyl)prop-2-en-1-one (**23**)*

Yield: 78%; m.p 172–174 °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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$, DMSO-d_6): 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 $C_{26}H_{21}ClN_2O_3$: C 70.19, H 4.76, N 6.30; Found: C 70.56, H 4.55, N 6.12%.

*6.3.21. 3-(4-Chlorophenyl)-1-(4-(7-chloroquinolin-4-ylamino)phenyl)prop-2-en-1-one (**24**)*

Yield: 78%; m.p 175–177 °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^{-1}; ^1H NMR (300 MHz, $CDCl_3$, DMSO-d_6): 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); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 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. $C_{24}H_{16}Cl_2N_2O$: C 68.75, H 3.85, N 6.68, Found: C 68.56, H 3.98, N 6.42%.

*6.3.22. 3-(2-Chlorophenyl)-1-(4-(7-chloroquinolin-4-ylamino)phenyl)prop-2-en-1-one (**25**)*

Yield: 70%; m.p 172–175 °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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.57 (d, 1H, $J = 5.13$ Hz, Ar-Qn), 8.19–8.13 (m, 4H, Ar-Qn, Ar), 7.93 (d, 1H, $J = 2.1$ Hz, 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, $J = 5.13$ Hz, Ar-Qn), 6.76 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 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 $C_{24}H_{16}Cl_2N_2O$: C 68.75, H 3.85, N 6.68; Found: C 68.76, H 3.84, N 6.79%.

*6.3.23. 1-(4-(7-Chloroquinolin-4-ylamino)phenyl)-3-(4-(methylthio)phenyl)prop-2-en-1-one (**26**)*

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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_3); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 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 $C_{25}H_{19}ClN_2OS$: C 69.68, H 4.44, N 6.50; Found: C 69.65, H 4.26, N 6.32%.

*6.3.24. 1-(4-(7-Chloroquinolin-4-ylamino)phenyl)-3-(pyridin-3-yl)prop-2-en-1-one (**27**)*

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$, DMSO-d_6): 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); ^{13}C (75 MHz, $CDCl_3$ + DMSO-d_6): 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 $C_{23}H_{16}ClN_3O$: C: 71.59, H 4.18, N 10.89; Found: C 71.82, H 4.39, N 10.99%.

*6.3.25. 1-(4-(7-Chloroquinolin-4-ylamino)phenyl)-3-(4-isopropylphenyl)prop-2-en-1-one (**28**)*

Yield: 60%; m.p 190–192 °C; MS: 427 (M + 1); IR (KBr) 3362, 3010, 2953, 2334, 1650, 1609, 1545, 1500, 1429, 1376, 1324, 1210, 1082, 867, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, DMSO-d_6): 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, $-CH(CH_3)_2$); ^{13}C NMR (75 MHz $CDCl_3$ + DMSO-d_6): 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. $C_{27}H_{23}ClN_2O$: C 75.96, H 5.43, N 6.56; Found: C 75.66, H 5.18, N 6.22%.

*6.3.26. 3-(3-Bromophenyl)-1-(4-(7-chloroquinolin-4-ylamino)phenyl)prop-2-en-1-one (**29**)*

Yield: 68%; m.p 180–182 °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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$, DMSO-d_6): 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 $C_{24}H_{16}BrClN_2O$: C 62.16, H 3.48, N 6.04; Found: C 62.35, H 3.54, N 6.39%.

*6.3.27. 3-(2-Bromophenyl)-1-(4-(7-chloroquinolin-4-ylamino)phenyl)prop-2-en-1-one (**30**)*

Yield: 65%; m.p 175–177 °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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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, $J = 5.3$ Hz, Ar-Qn), 6.65 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 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 $C_{24}H_{16}BrClN_2O$: C 62.16, H 3.48, N 6.04; Found: C 62.18, H 3.67, N 6.20%.

*6.3.28. 1-(4-(7-Chloroquinolin-4-ylamino)phenyl)-3-(3-nitrophenyl)prop-2-en-1-one (**31**)*

Yield: 60%; m.p 178–180 °C; MS: 430 (M + 1); IR (KBr): 3389, 3022, 2963, 2351, 1655, 1621, 1563, 1530, 1491, 1429, 1376, 1355, 1219, 1082, 776, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): 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); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 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 $C_{24}H_{16}ClN_3O_3$: C 67.06, H 3.75, N 9.78; Found: C 67.15, H 3.79, N 9.89%.

*6.4. 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 8 h. 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 compounds **32–59**.

*6.4.1. 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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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), .6.96 (d, 1H, $J = 5.1$ Hz, Ar-Qn), 5.37 (s, 2H, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 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 $C_{25}H_{17}ClN_4O$: C 70.67, H 4.03, N 13.19; Found: C 70.89, H 4.26, N 13.28%.

*6.4.2. 4-(4-(7-Chloroquinolin-4-yloxy)phenyl)-6-*p*-tolylpyrimidin-2-amine (**33**)*

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 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_2), 2.63 (s, 3H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{26}H_{19}ClN_4O$: C 71.15, H 4.36, N 12.77; Found: C 71.34, H 4.34, N 12.49%.

*6.4.3. 4-(4-(7-Chloroquinolin-4-yloxy)phenyl)-6-(4-methoxyphenyl)pyrimidin-2-amine (**34**)*

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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_2), 3.90 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{26}H_{19}ClN_4O_2$: C 68.65, H 4.21, N 12.32; Found: C 68.72, H 4.66, N 12.58%.

*6.4.4. 4-(4-(7-Chloroquinolin-4-yloxy)phenyl)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-amine (**35**)*

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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_2), 4.07 (s, 6H, OCH_3), 3.93 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): 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 $C_{28}H_{23}ClN_4O_4$: C 65.31, H 4.50, N 10.88; Found: C 65.43, H 4.46, N 10.78%.

*6.4.5. 4-(4-(7-Chloroquinolin-4-yloxy)phenyl)-6-(2,3,4-trimethoxyphenyl)pyrimidin-2-amine (**36**)*

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : 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_2), 4.01 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): 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 $C_{28}H_{23}ClN_4O_4$: C 65.31, H 4.50, N 10.88; Found: C 65.23, H 4.46, N 10.58%.

*6.4.6. 4-(4-(7-Chloroquinolin-4-yloxy)phenyl)-6-(furan-2-yl)pyrimidin-2-amine (**37**)*

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 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_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 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 $C_{23}H_{15}ClN_4O_2$: C 66.59, H 3.64, N 13.51; Found: C 66.79, H 3.86, N 13.68%.

6.4.7. 4-(4-(7-Chloroquinolin-4-yloxy)phenyl)-6-(2,3-dimethoxyphenyl)pyrimidin-2-amine (**38**)

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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_2), 3.89 (s, 2H, OCH_3), 3.94 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3 + CD_3OD$): 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 $C_{27}H_{21}ClN_4O_3$: C 66.87, H 4.36, N 11.55; Found: C 66.72, H 4.46, N 11.68%.

6.4.8. 4-(4-(7-Chloroquinolin-4-yloxy)phenyl)-6-(2,5-dimethoxyphenyl)pyrimidin-2-amine (**39**)

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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_2), 4.01 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3 + CD_3OD$) : δ 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 $C_{27}H_{21}ClN_4O_3$: C 66.87, H 4.36, N 11.55; Found: C 66.92, H 4.56, N 11.58%.

6.4.9. 4-(4-Chlorophenyl)-6-(4-(7-chloroquinolin-4-yloxy)phenyl)pyrimidin-2-amine (**40**)

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 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_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 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 $C_{25}H_{16}Cl_2N_4O$: C 65.37, H 3.51, N 12.20.; Found: C 65.49, H 3.26, N 12.39%.

6.4.10. 4-(2-Chlorophenyl)-6-(4-(7-chloroquinolin-4-yloxy)phenyl)pyrimidin-2-amine (**41**)

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 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_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 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 $C_{25}H_{16}Cl_2N_4O$: C 65.37, H 3.51, N 12.20, Found: C 65.59, H 3.78, N 12.47%.

6.4.11. 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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 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_2), 3.83 (s, 3H, –S–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 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 $C_{26}H_{19}ClN_4OS$: C 66.30, H 4.07, N 11.90; Found: C 66.49, H 4.26, N 11.89%.

6.4.12. 4-(4-(7-Chloroquinolin-4-yloxy)phenyl)-6-(pyridin-3-yl)pyrimidin-2-amine (**43**)

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 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_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 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 $C_{24}H_{16}ClN_5O$: C 67.69, H 3.79, N 16.44; Found: C 67.53, H 3.86, N 16.65%.

6.4.13. 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^{-1}; IR (KBr); ^1H NMR (300 MHz, $CDCl_3$): δ 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_2); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 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 $C_{25}H_{18}ClN_5$: C 70.84, H 4.28, N 16.52; Found: C 70.51, H 4.46, N 16.35%.

6.4.14. 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^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 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_2), 3.23 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 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 $C_{26}H_{20}ClN_5$: C 71.31, H 4.60, N 15.99; Found: C 71.21, H 4.46, N 15.65%.

6.4.15. 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^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 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_2), 3.91 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 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 $C_{26}H_{20}ClN_5O$: C 68.80, H 4.44, N 15.43; Found: C 68.65, H 4.29, N 15.39%.

6.4.16. N-*(4-(2-Amino-6-(3,4,5-trimethoxyphenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (**47**)*

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^{-1}, ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): 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_2), 7.16 (d, 1H, $J = 5.34$ Hz, Ar-Q), 3.98 (s, 6H, OCH_3), 3.86 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 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 $C_{28}H_{24}ClN_5O_3$: C 65.43, H 4.71, N 13.63. Found: C 65.56, H 4.68, N 13.76%.

6.4.17. N-*(4-(2-Amino-6-(2,3,4-trimethoxyphenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (**48**)*

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): 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_2), 7.23 (d, 1H, $J = 8.4$ Hz, Ar), 7.11 (d, 1H, $J = 5.34$ Hz, Ar-Qn), 3.94 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 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 $C_{28}H_{24}ClN_5O_3$: C 65.43, H 4.71, N 13.63. Found: C 65.66, H 4.59, N 13.74%.

6.4.18. N-*(4-(2-Amino-6-(furan-2-yl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (**49**)*

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 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_2); ^{13}C NMR (300 MHz, $CDCl_3$ + DMSO-d_6): 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 $C_{23}H_{16}ClN_5O$: C 66.75, H 3.90, N 16.92; Found: C 66.56, H 3.78, N 16.72%.

6.4.19. N-*(4-(2-amino-6-(2,3-dimethoxyphenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (**50**)*

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 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_2), 3.85 (s, OCH_3), 3.76 (s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 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 $C_{27}H_{22}ClN_5O_2$: C 67.01, H 4.58, N 14.47; Found: C 67.26, H 4.78, N 14.67%.

6.4.20. N-*(4-(2-Amino-6-(2,5-dimethoxyphenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (**51**)*

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): 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_2), 3.90 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 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%.

6.4.21. N-*(4-(2-Amino-6-(4-chlorophenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (**52**)*

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): 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_2); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 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 $C_{25}H_{17}Cl_2N_5$: C 65.51, H 3.74, N 15.28; Found: C 65.76, H 3.82, N 15.37%.

6.4.22. N-*(4-(2-Amino-6-(2-chlorophenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (**53**)*

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): 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_2); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 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 $C_{25}H_{17}Cl_2N_5$: C 65.51, H 3.74, N 15.28. Found: C 65.36, H 3.52, N 15.47%.

6.4.23. N-*(4-(2-Amino-6-(4-(methylthio)phenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (**54**)*

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): 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_2), 3.79 (s, 3H, $-SCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 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 $C_{26}H_{20}ClN_5S$: C 66.44, H 4.29, N: 14.90; Found: C 66.20, H 4.56, N 14.66%.

6.4.24. N-*(4-(2-Amino-6-(pyridin-3-yl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (**55**)*

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^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): 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_2); 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_2); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 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 $C_{24}H_{17}ClN_6$: C 67.84, H 4.03, N 19.78; Found: C 67.61, H 4.24, N 19.63%.

6.4.25. N-*(4-(2-Amino-6-(4-isopropylphenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (**56**)*

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^{-1}1; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): 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_2), 2.98–2.93 (m, 1H, $CH(CH_3)_2$), 1.24 (d, 6H, $J = 6$ Hz, $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 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 $C_{28}H_{24}ClN_5$: C 72.17, H 5.19, N 15.03; Found: C 72.34, H 5.46, N 15.26%.

6.4.26. N-*(4-(2-Amino-6-(3-bromophenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (**57**)*

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^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 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_2); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 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 $C_{25}H_{17}BrClN_5$: C 59.72, H 3.41, N 13.93; Found: C 59.86, H 3.58, N 13.75%.

6.4.27. N-*(4-(2-Amino-6-(2-bromophenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (**58**)*

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^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 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_2); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 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 $C_{25}H_{17}BrClN_5$: C 59.72, H 3.41, N 13.93; Found: C 59.86, H 3.58, N 13.67%.

6.4.28. N-*(4-(2-Amino-6-(3-nitrophenyl)pyrimidin-4-yl)phenyl)-7-chloroquinolin-4-amine (**59**)*

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^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 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_2); ^{13}C NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 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 $C_{25}H_{17}ClN_6O_2$: C 64.04, H 3.65, N 17.92; Found: C 64.26, H 3.78, N 17.81%.

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