Bioorganic & Medicinal Chemistry 17 (2009) 222–234

Search for new pharmacophores for antimalarial activity (Part II): Synthesis and antimalarial activity of new 6-ureido-4-anilinoquinazolines

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Abstract— Synthesis of new 6-ureido-4-anilinoquinazolines have been accomplished and their in vitro antimalarial activity against chloroquine-sensitive *P. falciparum* have been examined. Out of 64 compounds evaluated, the IC_{50} of 16 compounds which have displayed MIC of 0.25 μg/mL were also recorded. One of the compounds **(24g)** had IC_{50} value of 2.27 ng/mL which was equipotent to the standard drug chloroquine used in the bioassay. The in vivo evaluation of a few compounds among the series led to discovey of one analog **(30g)** displaying 40% curative activity (28 days) against mdr *P. yoeilli nigeriensis* at an oral dose of 100mg/kg x 4days

Introduction

Quinazoline is an important scaffold due to variety of pharmacological properties associated with the derivatives bearing this heterocycle.[1] Especially their importance in the cancer chemotherapy is unparallel.[2] One of the prominent antimalarial the febrifugine also belongs to quinazoline class of compounds.[3] In our efforts to discover new chemical pharmacophores which may be responsible for the antimalarial activity, we have described our studies on the synthesis and evaluation of 6-ureido-2-methyl-4-quinolinamides as antimalarials.[4] Notably the urea subunit was discovered to be responsible for the antimalarial effect in these compounds which was in line with the observation of Restelli et al.[5] Driven by the success of discovering prominent activity in the ureido-derivatives it was desired to incorporate this pharmacophore in another pharmacologically privileged core so as to explore its potential further for antimalarial effect. As a result it was decided to undertake the synthesis and antimalarial evaluation of 6-ureido-4-anilinoquinazolines. During this study we discovered that several compounds display promising in vitro antimalarial activity against CQ-sensitive *P. falciparum*. The in vivo screening of a few compounds against mdr *P. yoeilli nigeriensis* led to identification of one of the analogs displaying curative activity. These results prompted us to present and discuss the details of the study in this paper.

Results and Discussion

The synthesis of compounds investigated in the present study is outlined in scheme 1. The required 6-nitro-4-anilino quinazoline **(1-10)** were generated following the reported procedure wherein the 5-nitoanthranonitrile was treated with dimethylformamide dimethyl acetal to produce an intermediate which reacted with anilines to furnish **1-10**.[6] The nitro group of **1-10** was reduced to amine either via hydrogenation in the presence of 10% Pd-C in a Parr assembly or with $SnCl_2.2H_2O$ to yield products **11-20** in good yields. Treatment of amine **11-20** with the aryl isocyanates in THF at room temperature gave the required ureides **(21-30)** in good to excellent yields.

In-vitro Antimalarial activity

In total sixty four compounds were investigated during the present study. Results of antimalarial evaluation of the compounds against CQ-sensitive *P. falciparum* are displayed in Table 1. It may be noted that none of the compounds from **11-20** displayed any antimalarial effect

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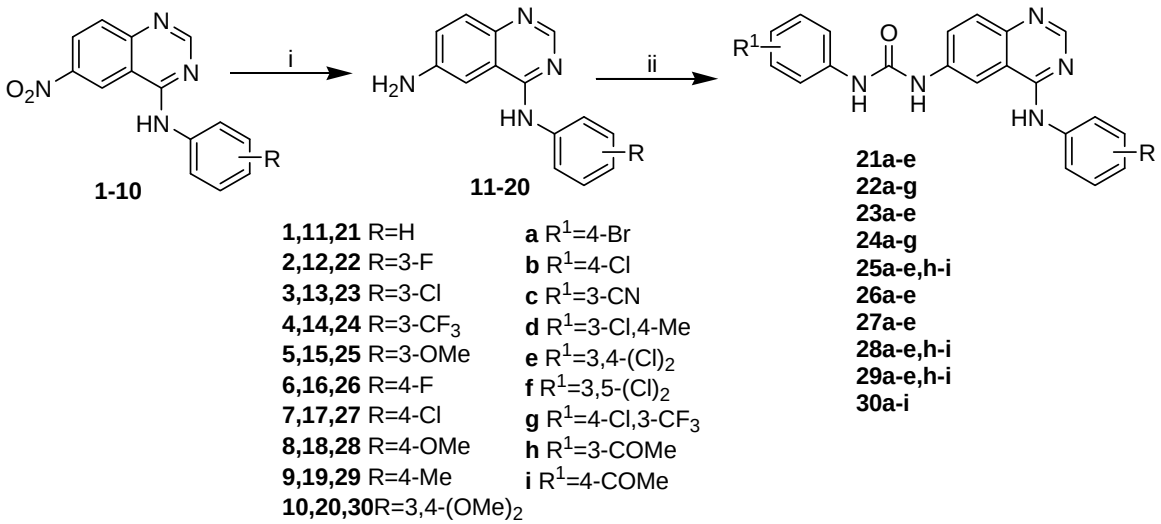
Keywords. Quinazoline, Antimalarial, urea, in vitro, in vivo, P. falciparum

indicating that the observed activity was due to the presence of urea sub-unit.

In order to generate a meaningful SAR, changes were introduced in the two aryl rings A and B which were part of the 4-anilino and the urea sub-units, respectively. Five functional groups in ring B namely 4-Br, 4-Cl, 3-CN, 3-Cl-4-Me and 3,4-Cl_2 were common to all prototypes. For **22,24,28-30** a few more analogs were prepared. Amongst the analogs of **21** wherein the anilino phenyl ring A did not carry any substitution, compound **21a** bearing 4-bromo-group on the B-ring of the aryl urea sub-unit was found to be the most active analog with MIC of 0.25 μg/mL. Compound **21c** containing 3-cyano group on the B-ring had MIC of 0.5 μg/mL whereas **21b** (4-Cl) and **21d** (3-Cl-4-Me) were equipotent with MIC of 1.0 μg/mL. Compound **21e** bearing 3,4-Cl_2 substitution in the B-ring had the MIC of 10.0 μg/mL. The IC_{50} of the most active analog **21a** was calculated to be 173.2 ng/mL while the SI was found to be 132.5. Introduction of 3-F group on the A-ring afforded compounds belonging to series **22** which except for **22a**, generally displayed higher MIC values indicating increased antimalarial effect. Compounds **22d** and **22e** incorporating 3-Cl-4-Me and 3,4-Cl_2 substitutions, respectively in B-ring had the MIC value of 0.25 μg/mL which were 4 and 40 times better than the corresponding compounds in **21**. Amongst them on the basis of the IC_{50} values, **22e** (22.5 ng/mL) was approximately 5 times more potent than **22d** (147.0 ng/mL). Even the SI value of 221.5 for **22e** was better than 76.6 of **22d**. Compounds **22a-c** with MIC of 0.5 μg/mL was equipotent. Better activity profile of **22e** led us to examine the activity of another analog incorporating dichloro substitution ot 3,5-position of B-ring. Unfortunately, this compound **22f** had MIC value of more than 10 μg/mL indicating loss of activity. On the contrary a new compound **22g** bearing 4-Cl-3-CF_3 was found to possess MIC of 0.5 μg/mL. Replacing the 3-F group at 3-position of the A-ring with 3-Cl resulted in the compounds belonging to the series **23**. Unfortunately the compounds **23 a-e** had higher MIC values as compared to the corresponding analogs belonging to **22**. Amongst this series, **23c** and **23e** incorporating 3-CN and 3,4-Cl_2 groups, respectively were the best with MIC values of 0.5 μg/mL.



Scheme 1. *Reagents and conditions*. i) 10% Pd-C, H_2, 40psi, rt, 2 h or $SnCl_2.2H_2O$, MeOH, reflux, 4 h. ii) $R^1C_6H_4NCO$, THF, rt, 5min-6 h.

In the next step of the study CF_3 group was introduced at 3-position of A-ring to produce another set of compounds **24**. Fortunately this alteration led to compounds with better antimalarial effect. Compounds **24b**, **24e** and **24g** bearing 4-Cl group in the B-ring which displayed MIC of 0.25 μg/mL were the best among this set of compounds. However IC_{50} value of **24g** (2.3 ng/mL) with SI of 1194 indicated it to be better than **24e** (13.0 ng/mL) and **24b** (67.4 ng/mL). This implied that **24g** was equipotent to the standard CQ. The MIC value of other analogs among the series ranged from 1-10 μg/mL. Replacement of the CF_3 with OMe in A-ring, however, in general led to loss of antimalarial effect. Except for compound **25b** which displayed an MIC of 0.25 μg/mL all other compounds had higher MIC values. This implied that analogs comprising of disubstitutions on the aryl ring of the urea sub-unit with at least chloro at 4-position were more relevant for antimalarial activity.

Next in the study the position of the substitution was

Table 1. Results of the in vitro activity against 3D7 *P.falciparum* and in vivo antimalarial activity against mdr *P.yoelii nigeriensis* in swiss mice

Compd. No	R	R^1	MIC (μg/mL)	IC_{50} (ng/mL)	Selectivity Index	*In vivo* (% Mean Parasitaemia± S.D. on day 4)	*In vivo* (% Mean Parasitaemia± S.D. on day 7)
21a	H	4-Br	0.25	173.2	132.5	-	-
21b	H	4-Cl	1	-	-	-	-
21c	H	3-CN	0.5	-	-	-	-
21d	H	3-Cl-4-Me	1	-	-	-	-
21e	H	3,4-Cl_2	10	-	-	-	-
22a	3-F	4-Br	0.5	-	-	-	-
22b	3-F	4-Cl	0.5	-	-	0.0 ±0.0	0.03 ±0.04
22c	3-F	3-CN	0.5	-	-	46.4±11.2	died
22d	3-F	3-Cl-4-Me	0.25	147.0	76.6	-	-
22e	3-F	3,4-Cl_2	0.25	24.5	221.5	-	-
22f	3-F	3,5-Cl_2	>10			-	-
22g	3-F	4-Cl-3-CF_3	0.5	-	-	22.0±4.30	14.5±2.12
23a	3-Cl	4-Br	1	-	-	-	-
23b	3-Cl	4-Cl	>10	-	-	-	-
23c	3-Cl	3-CN	0.5	-	-	-	-
23d	3-Cl	3-Cl-4-Me	10	-	-	-	-
23e	3-Cl	3,4-Cl_2	0.5	-	-	-	-
24a	3-CF_3	4-Br	2.0	-	-	50.4±6.80	died
24b	3-CF_3	4-Cl	0.25	67.4	35.9	-	-
24c	3-CF_3	3-CN	1	-	-	-	-
24d	3-CF_3	3-Cl-4-Me	10	-	-	-	-
24e	3-CF_3	3,4-Cl_2	0.25	13.0	69.0	-	-
24f	3-CF_3	3,5-Cl_2	10	-	-	-	-
24g	3-CF_3	4-Cl-3-CF_3	0.25	2.3	1194.0	10.0±5.03	30.5±6.36
25a	3-OMe	4-Br	2	-	-	-	-
25b	3-OMe	4-Cl	0.25	158.5	378.9	-	-
25c	3-OMe	3-CN	10	-	-		-
25d	3-OMe	3-Cl-4-Me	0.5	-	-	-	-
25e	3-OMe	3,4-Cl_2	2	-	-	-	-
25h	3-OMe	3-COMe	10	-	-	-	-
25i	3-OMe	4-COMe	>10	-	-	-	-
26a	4-F	4-Br	10	-	-	-	-
26b	4-F	4-Cl	0.5	-	-	1.18±0.77*	9.38±4.81
26c	4-F	3-CN	insoluble	-	-	-	-
26d	4-F	3-Cl-4-Me	0.5	-	-	2.8±1.8*	4.06±1.49
26e	4-F	3,4-Cl_2	10	-	-	-	-
27a	4-Cl	4-Br	1	-	-	-	-
27b	4-Cl	4-Cl	0.5	-	-	-	-
27c	4-Cl	3-CN	insoluble	-	-	-	-
27d	4-Cl	3-Cl-4-Me	1	-	-	-	-
27e	4-Cl	3,4-Cl_2	0.5	-	-	-	-
28a	4-OMe	4-Br	1	-	-	-	-
28b	4-OMe	4-Cl	0.25	94.0	435.1	-	-

28c	4-OMe	3-CN	2	-	-	-	-
28d	4-OMe	3-Cl-4-Me	0.25	50.0	114.9	-	-
28e	4-OMe	3,4-Cl_2	2	-	-	-	-
28h	4-OMe	3-COMe	10	--	-	-	-
28i	4-OMe	4-COMe	2.0	-	-	-	-
29a	4-Me	4-Br	1	-	-	-	-
29b	4-Me	4-Cl	1	77.1	126.3	-	-
29c	4-Me	3-CN	10	-	-	-	-
29d	4-Me	3-Cl-4-Me	0.5	-	-	3.38 ±1.5*	10.82±5.30
29e	4-Me	3,4-Cl_2	1	-	-	-	-
29h	4-Me	3-COMe	2	-	-	-	-
29i	4-Me	4-COMe	2	-	-	-	-
30a	3,4-$(OMe)_2$	4-Br	0.5	-	-	26.3±12.4	26.5±1.0
30b	3,4-$(OMe)_2$	4-Cl	0.5	-	-	-	-
30c	3,4-$(OMe)_2$	3-CN	0.5	-	-	13.9±5.7	23.2±6.4
30d	3,4-$(OMe)_2$	3-Cl-4-Me	0.25	22.3	449.0	-	-
30e	3,4-$(OMe)_2$	3,4-Cl_2	0.25	80.7	74.5	41±6.08	14.0±0.0
30f	3,4-$(OMe)_2$	3,4-Cl_2	0.25	83.2	36.1	23.7±12.9	10.75±1.06
30g	3,4-$(OMe)_2$	4-Cl-3-CF_3	0.25	18.2	345.8	0.0±0.0	0.49±0.28
30h	3,4-$(OMe)_2$	3-COMe	10	-	-	-	-
30i	3,4-$(OMe)_2$	4-COMe	10	-	-	-	-
Chloroquine			0.125	2.0	-	-	-
Control (MDR *P .yoelii nigeriensis*)			-	-	-	55.7±4.64	died
Control (CQ-resistant *P .yoelii N-67)*			-	-	-	8.88±4.27	16.12±3.73

*Screened against CQ-resistant *P .yoelii N67*.

changed from 3 to 4 in the phenyl ring (A-ring) of the aniline unit. The placement of fluorine at 4-position resulted in compounds **26a-e**. Though compound **26c** having 3-cyano group on the aryl of the urea group was found to be insoluble and could not be screened. Relatively these compounds were less active than the compounds of series **22** which had 3-F group in A-ring. Two compounds **26b** and **26d** comprising of 4-Cl and 3-Cl-4-Me groups, respectively showed MIC of 0.5 μg/mL each whereas others (**26a** and **26e**) had MIC of 10 μg/mL. Changing the fluoro to chloro substitution at 4-position in A-ring led to compounds **27a-e**. Here too the 3-cyano analog **27c** was found to be insoluble and was not evaluated. Although these compounds have slightly better profile than compounds of series **26**, they showed similar pattern to that of compounds of series **23** bearing 3-Cl in A-ring. Compounds **27b** and **27e** with 4-Cl and 3,4-Cl_2 substitutions, respectively had MIC of 0.5 μg/mL whereas **27a** and **27d** displayed MIC value of 1.0 μg/mL.

Following, a new series **28a-e,h-i** containing 4-methoxy group at 4-position of the aryl ring of the aniline moiety was evaluated. Amongst them **28b** and **28d** with 4-Cl and 3-Cl-4-Me were the most active with MIC value of 0.25 μg/mL, whereas all other compounds had MIC value of 1.0 μg/mL or above. Fortunately, this group of compounds was relatively more active than compounds of series **25**. Examination of the IC_{50} values revealed compound **28d** (50 ng/mL) to be twice more active than **28b** (94 ng/mL), but the SI for **28b** (435.1) was better than **28d** (114.9). Increasing the hydrophobicity by the introduction of a methyl group in place of the methoxy group at 4-position led to compounds **(29a-e,h-i)** with lower activity profile. Only one compound **29d** bearing the 3-Cl-4-Me substitution on the aryl ring of the urea sub-unit displayed the MIC of 0.5 μg/mL while all other analogs in the series had activity of 1.0 μg/mL or higher. In another variation 3,4-dimethoxy group was introduced in A-ring to produce compounds **30a-i**. Interestingly all compounds in this series possessing disubstitution in B-ring showed pronounced antimalarial effect. Compounds **30d-g** bearing 3-Cl-4-Me, 3,4-Cl_2, 3,5-Cl_2 and 4-Cl-3-CF_3 groups displayed an MIC of 0.25 μg/mL whereas **30a-c** comprising of 4-Br, 4-Cl and 3-CN substitution on the B-ring showed MIC value of 0.5 μg/mL. However **30h** and **i** were observed to relatively less potent. An IC_{50} evaluation of compounds **30d-g** indicated compound **30g** to be the most active with IC_{50} value of 18.2 and SI of 345.8. On the other hand the IC_{50} values calculated for **30d-f** were 22.3, 80.7 and 83.2 with corresponding SI of 449.0, 74.5 and 36.1.

On the basis of SAR of the compounds studied herein it could be concluded that disubstitutions on both the phenyl rings results in compounds with better antimalarial effect. Compounds bearing 4-Cl substitution on B-ring scores over other derivatives in terms of bioactivity.

In-vivo antimalarial activity

Several of the analogs which displayed MIC of 0.5 μg/mL or below were investigated for antimalarial activity in the in vivo assay either against mdr *P. yoellii nigeriensis* or CQ-resistant N67 *P. yoelli* at an oral dose of 100mg/kg x 4 days. The two best compounds amongst this series were **22b** and **30g** as they displayed complete suppression of parasitaemia on day 4 and 99% suppression on day 7. However further monitoring indicated that animals which received **22b** showed significant amount of parasitemia on day 10 onwards. In contrast the group of 5 animals which have received compound **30g** displayed promising results. The mean levels of parsitemia on day 14 were observed to be 0.49±0.28 whereas on day 21 it was observed to be 13.0±15.3. Fortunately out of the group, 2 animals which survived till day 28 were found to be completely cured. All other compounds which were investigated for their in vivo efficacy did not diplay any promising activity. Even compound **24g** which was equipotent to the standard CQ in terms of IC_{50} and had high SI failed to translate the effect in the in vivo system.

Conclusions

In summary, we have disclosed the antimalarial efficacy of another series of urea derivatives. Significantly though compounds displayed better in vitro effect, like quinoline derivatives reported earlier, no correaltion could be drawn between their in vitro and the in vivo effect. Nevertheless the potential of compound **30g** to cure the animals reflects the potential of the urea derivatives. It would be interesting to study the effect of thiourea and guanidino pharmacophore instead of urea due to their better compatibility with the biological systems. Further work in this direction is underway and the results would be reported shortly.

Experimental

General

Melting points are uncorrected and were determined in capillary tubes on an apparatus containing silicon oil. IR spectra were recorded using a Perkin Elmer's Spectrum RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker DPX-200 FT or Bruker Avance DRX-300 spectrometer, using TMS as an internal standard (chemical shifts in δ). The ESMS and FABMS were recorded on MICROMASS Quadro-II LCMS and JEOL SX/102/DA 6000 system, respectively. Elemental analyses were performed on a Carlo Erba's 108 or an Elementar's Vario EL *III* microanalyzer.

General procedure for the preparation of 6-nitro-4-arylaminoquinazoline (1-10). A mixture of *N*'-(2-cyano-4-nitrophenyl)-*N*, *N*-dimethylformamide (13.7 mmol, 3.0 g) and appropriate aniline (15.1 mmol) in AcOH was heated at reflux for 1-8 h. On completion, the reaction was cooled to ambient temperature. The separated solid was filtered and washed with ether to obtain the compounds **2-3, 10**. Some of the reaction mixtures did not give the solid products. In such cases excess AcOH was evaporated from reaction mixtures to obtain the residue which upon trituration with the mixture of hexanes and EtOAc afforded desired compounds **1, 4-9**.

6-Nitro-*N*-phenylquinazolin-4-amine (1). 98% as a yellow solid, mp 242-243 °C; ν_{max} (KBr) 3449 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.21 (t, 1H, *J*= 7.3 Hz, ArH), 7.39-7.46 (m, 2H, ArH), 7.82 (d, 2H, *J*= 7.9 Hz, ArH), 7.92 (d, 1H, *J*= 9.1 Hz, ArH), 8.52 (dd, 1H, J_1= 1.8 Hz, J_2= 9.1 Hz, ArH), 8.76 (s, 1H, ArH), 9.70 (d, 1H, *J*= 1.7 Hz, ArH), 10.15 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 114.7, 121.1, 123.2, 124.8, 126.8, 128.8, 129.7, 138.7, 144.7, 153.4, 158.0, 159.1; mass (ES+) *m/z*= 267.1 (M^++1). Anal. Calcd. for $C_{14}H_{10}N_4O_2$ C, 63.15; H, 3.79; N, 12.02. Found C, 63.01; H, 3.51; N, 12.33.

***N*-(3-Fluorophenyl)-6-nitroquinazolin-4-amine (2).** 73% as a light yellow solid, mp 227-229 °C; ν_{max} (KBr) 3272 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 6.99 (dt, 1H, J_1= 2.1 Hz, J_2= 8.4 Hz, ArH), 7.44 (q, 1H, *J*= 7.0 Hz, ArH), 7.67 (d, 1H, *J*= 8.1 Hz, ArH), 7.86-7.95 (m, 2H, ArH), 8.54 (dd, 1H, J_1= 2.3 Hz, J_2= 9.2 Hz, ArH), 8.76 (s, 1H, NH), 9.63 (d, 2H, *J*= 1.8 Hz, ArH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 114.7, 118.4, 118.5, 121.1, 126.9, 129.9, 130.3, 130.4, 144.9, 153.3, 157.7, 158.9, 159.9, 164.6; mass (ES+) *m/z*= 285.3 (M^++1). Anal. Calcd. for $C_{14}H_9FN_4O_2$ C, 59.16; H, 3.19; N, 19.71. Found C, 58.96; H, 3.34; N, 20.03.

***N*-(3-Chlorophenyl)-6-nitroquinazolin-4-amine (3).** 96% as a yellow solid, mp >250 °C; ν_{max} (KBr) 3295 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.21-7.24 (m, 1H, ArH), 7.44 (t, 1H, *J*= 8.1 Hz, ArH), 7.83 (d, 1H, *J*= 8.0 Hz, ArH), 7.94 (d, 1H, *J*= 9.2 Hz, ArH), 8.06 (s, 1H, ArH), 8.55 (dd, 1H, J_1= 2.4 Hz, J_2= 9.1 Hz, ArH), 8.77 (s, 1H, ArH), 9.64 (d, 1H, *J*= 2.1 Hz, ArH), 10.47 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 114.7, 121.1, 124.6, 127.0, 128.5, 128.8, 129.9, 137.8, 144.9, 153.3, 157.8, 158.9, 172.4; mass (ES+) *m/z*= 301.2 (M^++1), 303.2 (M^++3). Anal. Calcd. for $C_{14}H_9ClN_4O_2$ C, 55.92; H, 3.02; N, 18.63. Found C, 56.22; H, 3.28; N, 18.50.

6-Nitro-*N*-[3-(trifluoromethyl)phenyl]quinazolin-4-amine (4). 67% as a yellow solid, mp 203-205 °C; ν_{max} (KBr) 3397 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz) δ= 7.27 (s, 1H, ArH), 7.48-7.63 (m, 2H, ArH), 8.03 (d, 2H, *J*= 8.9 Hz, ArH), 8.17 (s, 1H, NH), 8.55 (dd, 1H, J_1= 1.7 Hz, J_2= 9.1 Hz, ArH), 8.86 (s, 1H, ArH), 9.05 (s, 1H, ArH); mass (ES+) *m/z*= 335.1 (M^++1). Anal. Calcd. for $C_{15}H_9F_3N_4O_2$ C, 53.90; H, 2.71; N, 16.76. Found C, 54.21; H, 2.99; N, 16.58.

***N*-(3-Methoxyphenyl)-6-nitroquinazolin-4-amine (5).** 71% as a yellow solid, mp 216-218 °C; ν_{max} (KBr) 3021 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.77 (s, 3H, CH_3), 6.73 (d, 1H, *J*= 7.3 Hz, ArH), 7.28 (t, 1H, *J*= 8.1 Hz, ArH), 7.44 (d, 2H, *J*= 12.2 Hz, ArH), 7.72-7.83 (m, 1H,

ArH), 8.44 (d, 1H, *J*= 7.2 Hz, ArH), 8.64-8.68 (m, 1H, ArH), 9.53 (s, 1H, ArH), 10.25 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 55.5, 109.0, 110.1, 114.7, 115.3, 121.1, 126.8, 129.6, 129.8, 140.0, 144.8, 149.4, 153.3, 159.7, 160.6; mass (ES+) *m/z*= 297.2 (M^++1). Anal. Calcd. for $C_{15}H_{12}N_4O_3$ C, 60.81; H, 4.08; N, 18.91. Found C, 61.13; H, 4.02; N, 19.20.

***N*-(4-Fluorophenyl)-6-nitroquinazolin-4-amine (6).** 88% as a light yellow solid, mp >250 °C; ν_{max} (KBr) 3369 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.28 (t, 2H, *J*= 8.8 Hz, ArH), 7.81-7.86 (m, 2H, ArH), 7.93 (d, 1H, *J*= 8.8 Hz, ArH), 8.56 (dd, 1H, J_1= 2.3 Hz, J_2= 9.2 Hz, ArH), 8.69 (s, 1H, ArH), 9.63 (d, 1H, *J*= 8.8 Hz, ArH), 10.48 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 114.7, 115.5, 115.8, 121.2, 125.4, 127.1, 129.9, 135.1, 144.9, 153.5, 158.1, 159.3; mass (ES+) *m/z*= 285.3 (M^++1). Anal. Calcd. for $C_{14}H_9FN_4O_2$ C, 59.16; H, 3.19; N, 19.71. Found C, 59.27; H, 3.51; N, 19.95.

***N*-(4-Chlorophenyl)-6-nitroquinazolin-4-amine (7).** 87% as a yellow solid, mp >250 °C; ν_{max} (KBr) 3302 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.10 (td, 1H, J_1= 0.6 Hz, J_2= 7.9 Hz, ArH), 7.27 (dd, 1H, J_1= 2.3 Hz, J_2= 8.8 Hz, ArH), 7.34-7.41 (m, 2H, ArH), 7.55 (d, 1H, *J*= 8.8 Hz, ArH), 7.83 (dd, 1H, J_1= 1.1 Hz, J_2= 8.2 Hz, ArH), 8.11 (t, 1H, *J*= 1.9 Hz, ArH), 8.39 (s, 1H, ArH), 9.60 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 101.8, 117.4, 120.6, 121.6, 123.1, 124.7, 129.1, 130.7, 133.4, 142.3, 142.8, 148.3, 150.1, 156.6; mass (ES+) *m/z*= 301.1 (M^++1), 303.1 (M^++3). Anal. Calcd. for $C_{14}H_9ClN_4O_2$ C, 55.92; H, 3.02; N, 18.63. Found C, 55.97; H, 3.34; N, 18.64.

***N*-(4-Methoxyphenyl)-6-nitroquinazolin-4-amine (8).** 75% as a yellow solid, mp 202-204 °C; ν_{max} (KBr) 3415 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.85 (s, 3H, CH_3), 6.95-7.00 (m, 2H, ArH), 7.56-7.62 (m, 2H, ArH), 7.98 (d, 2H, *J*= 9.0 Hz, ArH), 8.52 (dd, 1H, J_1= 2.4 Hz, J_2= 9.2 Hz, ArH), 8.77 (s, 1H, ArH), 8.94 (d, 1H, *J*= 2.3 Hz, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 54.4, 112.9, 113.4, 119.9, 123.8, 125.5, 128.4, 130.3, 143.4, 152.2, 155.5, 157.0, 157.9, 171.2; mass (ES+) *m/z*= 297.2 (M^++1). Anal. Calcd. for $C_{15}H_{12}N_4O_3$ C, 60.81; H, 4.08; N, 18.91. Found C, 60.94; H, 4.39; N, 19.32.

***N*-(4-Methylphenyl)-6-nitroquinazolin-4-amine (9).** 75% as a yellow solid, mp 163-165 °C; ν_{max} (KBr) 3418 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ= 2.40 (s, 3H, CH_3), 7.27 (d, 2H, *J*= 8.0, ArH), 7.61 (d, 2H, *J*= 8.4 Hz, ArH), 7.89 (s, 1H, NH), 8.02 (d, 1H, *J*= 9.2 Hz, ArH), 8.57 (dd, 1H, J_1= 2.4 Hz, J_2= 9.2 Hz, ArH), 8.85 (s, 1H, ArH), 8.96 (d, 1H, *J*= 2.3 Hz, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 19.8, 113.5, 120.0, 122.1, 125.6, 128.1, 128.5, 132.9, 134.9, 143.5, 152.2, 156.9, 157.9; mass (ES+) *m/z*= 281.2 (M^++1). Anal. Calcd. for $C_{15}H_{12}N_4O_2$ C, 64.28; H, 4.32; N, 19.99. Found C, 64.14; H, 4.40; N, 19.91.

***N*-(3,4-Dimethoxyphenyl)-6-nitroquinazolin-4-amine (10).** 69% as a red solid, mp 195-198 °C; ν_{max} (KBr) 3409 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.78 (s, 6H, 2 x OCH_3), 7.00 (d, 1H, *J*= 8.5 Hz, ArH), 7.38-7.42 (m, 2H, ArH), 7.90 (d, 1H, *J*= 9.2 Hz, ArH), 8.53 (dd, 1H, J_1= 2.3 Hz, J_2= 9.1 Hz, ArH), 8.66 (s, 1H, ArH), 9.62 (d, 1H, *J*= 2.1 Hz, ArH), 10.32 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 55.9, 56.1, 108.4, 112.0, 114.7, 115.6, 121.0, 126.8, 129.7, 131.9, 144.7, 146.4, 148.8, 153.4, 158.1, 159.0; mass (ES+) *m/z*= 327.1 (M^++1). Anal. Calcd. for $C_{16}H_{14}N_4O_4$ C, 58.89; H, 4.32; N, 17.17. Found C, 58.67; H, 4.59; N, 17.08.

General procedure for the preparation of compounds 11-12, 14-16, 18-20. To a methanolic solution of appropriate compound from **1-2, 4-6, 8-10** (3.0 mmol), 10% Pd-C (0.125 g) was added under nitrogen atmosphere. The atmosphere of the vessel was replaced by hydrogen gas and the reaction was hydrogenated on the Parr assembly at 40 psi at room temperature for 1 h. Thereafter, the catalyst was filtered over a celite bed and the filtrate was evaporated to yield a solid residue. The residue was recrystellized from MeOH to offord the pure compounds **11-12, 14-16, 18-20** as yellow solids in good yields.

***N*^{4}-Phenylquinazoline-4,6-diamine (11).** 84% as a yellow solid, mp 197-199 °C; ν_{max} (KBr) 3297 (NH), 3363 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz,) δ= 5.58 (brs, 2H, NH_2), 7.06 (t, 1H, *J*= 7.4 Hz, ArH), 7.23 (dd, 1H, J_1= 2.3 Hz, J_2= 8.6 Hz, ArH), 7.32 (s, 1H, ArH), 7.35-7.37 (m, 2H, ArH), 7.52 (d, 1H, *J*= 8.8 Hz, ArH), 7.84 (d, 2H, *J*= 7.8 Hz, ArH), 8.32 (s, 1H, ArH), 9.37 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 101.5, 117.0, 122.2, 123.3, 124.0, 128.7, 128.8, 140.2, 142.6, 147.7, 150.1, 156.5; mass (ES+) *m/z*= 237.3 (M^++1). Anal. Calcd. for $C_{14}H_{12}N_4$ C, 71.17; H, 5.12; N, 23.71. Found C, 70.85; H, 5.33; N, 23.96.

***N*^{4}-(3-Fluorophenyl)quinazoline-4,6-diamine (12).** 75% as a yellow solid, mp 122-124 °C; ν_{max} (KBr) 3437 (NH & NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 6.88 (dt, 1H, J_1= 2.2 Hz, J_2= 8.4 Hz, ArH), 7.28 (dd, 1H, J_1= 2.2 Hz, J_2= 8.9 Hz, ArH), 7.34-7.42 (m, 3H, ArH & NH), 7.56 (d, 1H, *J*= 8.8 Hz, ArH), 7.68 (d, 1H, *J*= 8.2 Hz, ArH), 7.92 (d, 1H, *J*= 12.1 Hz, ArH), 8.41 (s, 1H, ArH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 101.3, 117.0, 117.5, 124.3, 128.6, 130.1, 130.3, 142.0, 142.2, 147.9, 149.7, 156.2, 160.0, 164.8; mass (ES+) *m/z*= 255.4 (M^++1). Anal. Calcd. for $C_{14}H_{11}FN_4$ C, 66.13; H, 4.36; N, 22.04. Found C, 65.82; H, 4.69; N, 22.18.

***N*^{4}-[3-(Trifluoromethyl)phenyl]quinazoline-4,6-diamine (14).** 73% as a yellow solid, mp >250 °C; ν_{max} (KBr) 3300 (NH), 3412 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 5.70 (s, 2H, NH_2), 7.29-7.41 (m, 3H, ArH), 7.55-7.61 (m, 2H, ArH), 8.25 (d, 1H, *J*= 7.5 Hz, ArH), 8.41 (d, 2H, *J*= 17.2 Hz, ArH), 9.66 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 200 MHz) δ= 101.3, 117.2, 117.7, 119.2, 123.0, 124.4, 125.2, 126.6, 129.4, 129.9, 141.4, 143.2, 147.9, 150.0, 156.2; mass (ES+) *m/z*= 305.4 (M^++1). Anal. Calcd. for $C_{15}H_{11}F_3N_4$ C, 59.21; H, 3.64; N, 18.41. Found C, 59.52; H, 3.71; N, 18.56.

***N*^{4}-(3-Methoxyphenyl)quinazoline-4,6-diamine (15).** 71% as a yellow solid, mp 216-218 °C; ν_{max} (KBr) 3352 (NH & NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.77

(s, 3H, CH_3), 5.58 (brs, 2H, NH_2), 6.64-6.66 (m, 1H, ArH), 7.23-7.28 (m, 2H, ArH), 7.39 (s, 1H, ArH), 7.50-7.59 (m, 3H, ArH), 8.36 (s, 1H, ArH), 9.30 (s, 1H, NH); mass (ES+) *m/z*= 267.2 (M^++1). Anal. Calcd. for $C_{15}H_{14}N_4O$ C, 67.65; H, 5.30; N, 21.04. Found C, 67.83; H, 5.51; N, 21.10.

***N*^{4}-(4-Fluorophenyl)quinazoline-4,6-diamine (16).** 92% as a light yellow solid, mp 169-171 °C; ν_{max} (KBr) 3333 (NH & NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz) δ= 5.55 (brs, 2H, NH_2), 7.11-7.28 (m, 2H, ArH), 7.35 (d, 1H, *J*= 1.8 Hz, ArH), 7.52 (d, 1H, *J*= 8.8 Hz, ArH), 7.80-7.87 (m, 2H, ArH), 8.24 (s, 1H, ArH), 8.32 (s, 1H, ArH), 9.47 (s, 1H, NH); mass (ES+) *m/z*= 255.3 (M^++1). Anal. Calcd. for $C_{14}H_{11}FN_4$ C, 66.13; H, 4.36; N, 22.04. Found C, 66.41; H, 4.54; N, 22.03.

***N*^{4}-(4-Methoxyphenyl)quinazoline-4,6-diamine (18).** 81% as a light yellow solid, mp 125-128 °C; ν_{max} (KBr) 3332 (NH & NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.75 (s, 3H, CH_3), 5.55 (brs, 2H, NH_2), 6.93 (d, 2H, *J*= 9.0 Hz, ArH), 7.20 (dd, 1H, J_1= 2.2 Hz, J_2= 8.8 Hz, ArH), 7.32 (d, 1H, *J*= 2.2 Hz, ArH), 7.48 (d, 1H, *J*= 8.8 Hz, ArH), 7.68 (d, 2H, *J*= 9.0 Hz, ArH), 8.24 (s, 1H, ArH), 9.23 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 55.6, 101.6, 113.9, 116.9, 123.8, 124.2, 128.8, 133.1, 142.6, 147.5, 150.4, 155.7, 156.1; mass (ES+) *m/z*= 267.2 (M^++1). Anal. Calcd. for $C_{15}H_{14}N_4O$ C, 67.65; H, 5.30; N, 21.04. Found C, 67.46; H, 5.34; N, 20.87.

***N*^{4}-(4-Methylphenyl)quinazoline-4,6-diamine (19).** 89% as a light yellow solid, mp 181-183 °C; ν_{max} (KBr) 3337 (NH & NH_2) cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz) δ= 2.37 (s, 3H, CH_3), 7.22 (d, 2H, *J*= 8.2 Hz, ArH), 7.29-7.33 (m, 2H, ArH), 7.54-7.58 (m, 2H, ArH), 8.25 (s, 1H, ArH); ^{13}C NMR (CD_3OD, 75 MHz) δ= 19.0, 101.1, 115.5, 122.6, 123.6, 124.7, 128.3, 134.0, 134.9, 137.8, 147.4, 148.2, 156.8; mass (ES+) *m/z*= 251.3 (M^++1). Anal. Calcd. for $C_{15}H_{14}N_4$ C, 71.98; H, 5.64; N, 22.38. Found C, 71.91; H, 5.59; N, 22.21.

***N*^{4}-(3,4-Dimethoxyphenyl)quinazoline-4,6-diamine (20).** 79% as a light yellow solid, mp 198-200 °C; ν_{max} (KBr) 3334 (NH), 3499 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 5.51 (s, 2H, NH_2), 6.94 (d, 1H, *J*= 8.7 Hz, ArH), 7.22 (dd, 1H, J_1= 2.2 Hz, J_2= 8.9 Hz, ArH), 7.34 (d, 1H, *J*= 2.1 Hz, ArH), 7.43 (dd, 1H, J_1= 2.4 Hz, J_2= 8.7 Hz, ArH), 7.48-7.52 (m, 2H, ArH), 8.28 (s, 1H, ArH), 9.18 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 56.0, 56.2, 101.5, 107.7, 112.3, 114.6, 116.9, 123.8, 128.9, 133.6, 142.7, 145.3, 147.5, 148.8, 150.4, 156.5; mass (ES+) *m/z*= 297.2 (M^++1). Anal. Calcd. for $C_{16}H_{16}N_4O_2$ C, 64.85; H, 5.44; N, 18.91. Found C, 64.93; H, 5.19; N, 19.25.

General procedure for the preparation of compounds 13, 17. A solution of *N*-(chlorophenyl)-6-nitroquinazolin-4-amine **(3, 7)** (5.86 mmol) and anhydrous $SnCl_2 \cdot 2H_2O$ (29.32 mmol, 5.56 g) in MeOH (20 mL) was heated at reflux for 30 min under nitrogen atmosphere. Thereafter excessive MeOH was evaporated and the residue was dissolved in EtOAc (100 mL) and basified with aqueous $NaHCO_3$ solution. The resulting mixture was filtered through a celite bed followed by separation of organic layer and water layer was extracted with EtOAc (2 x 20 mL), these organic fractions were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the desired *N*^{4}-chlorophenylquinazoline-4, 6-diamine **(13, 17)**. The crude products were recrystallized from MeOH.

***N*^{4}-(3-Chlorophenyl)quinazoline-4,6-diamine (13).** 90 % as a light yellow solid, mp 180-182 °C; ν_{max} (KBr) 3384 (NH & NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 5.63 (s, 2H, NH_2), 7.08 (dd, 1H, J_1= 1.2 Hz, J_2= 7.9 Hz, ArH), 7.26 (dd, 1H, J_1= 1.9 Hz, J_2= 8.8 Hz, ArH), 7.32-7.38 (m, 2H, ArH), 7.54 (d, 1H, *J*= 8.9 Hz, ArH), 7.80 (d, 1H, *J*= 8.9 Hz, ArH), 8.09 (s, 1H, ArH), 8.36 (s, 1H, ArH), 9.48 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 101.3, 117.1, 120.2, 121.2, 122.8, 124.3, 129.1, 130.4, 133.2, 141.9, 143.0, 147.9, 150.0, 156.2; mass (ES+) *m/z*= 271.3 (M^++1), 273.3 (M^++3). Anal. Calcd. for $C_{14}H_{11}ClN_4$ C, 62.11; H, 4.10; N, 20.70. Found C, 62.29; H, 4.18; N, 20.53.

***N*^{4}-(4-Chlorophenyl)quinazoline-4,6-diamine (17).** 88% as a yellow solid, mp 237-239 °C; ν_{max} (KBr) 3295 (NH), 3425 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz) δ= 7.15 (t, 1H, *J*= 7.1 Hz, ArH), 7.27-7.44 (m, 3H, ArH), 7.57 (d, 1H, *J*= 8.8 Hz, ArH), 7.75 (d, 1H, *J*= 8.3 Hz, ArH), 7.85 (d, 1H, *J*= 8.7 Hz, ArH), 7.73-7.87 (m, 2H, ArH), 8.44 (d, 1H, *J*= 6.1 Hz, ArH), 10.00 (s, 1H, NH); mass (ES+) *m/z*= 271.3 (M^++1), 273.2 (M^++1). Anal. Calcd. for $C_{14}H_{11}ClN_4$ C, 62.11; H, 4.10; N, 20.70. Found C, 62.35; H, 4.03; N, 20.58.

General procedure for the preparation of compounds 169-173a-j, 174-175d,f,j,176-177g-i. A mixture of appropriate amine from **168a-j** (1.06 mmol) and aryl isocyanate (1.16 mmol) in anhydrous THF (10 mL) was stirred at room temperature for 5 min-6 h. Thereafter the reaction mixture was slurried and purified by column chromatography over silica gel or alumina using hexanes:EtOAc (30-10:70-90, v/v) as the eluent to yield the desired compounds **169-173a-j, 174-175d,f,j,176-177g-i**.

***N*-(4-Anilinoquinazolin-6-yl)-*N*'-(4-bromophenyl)urea (21a).** 76% as a white solid, mp >250 °C; R_t= 21.30 min; ν_{max} (KBr) 1658 (CO), 3429 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.12 (t, 1H, *J*= 7.2 Hz, ArH), 7.39 (t, 2H, *J*= 8.1 Hz, ArH), 7.47-7.52 (m, 4H, ArH), 7.74-7.91 (m, 4H, ArH), 8.48-8.49 (m, 2H, ArH), 9.00 (s, 1H, NH), 9.05 (s, 1H, NH), 9.76 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 116.2, 118.7, 119.1, 121.2, 125.9, 128.1, 128.7, 129.1, 131.1, 132.1, 134.0, 137.2, 142.9, 143.8, 144.6, 145.0, 151.6, 158.0, 158.2, 158.5, 162.9; mass (ES+) *m/z*= 434.2 (M^++1), 436.1 (M^++3). Anal. Calcd. for $C_{21}H_{16}BrN_5O$ C, 58.08; H, 3.71; N, 16.13. Found C, 58.21; H, 3.49; N, 16.07.

***N*-(4-Anilinoquinazolin-6-yl)-*N*'-(4-chlorophenyl)urea (21b).** 84% as a white solid, mp 250-251 °C; R_t= 20.13 min; ν_{max} (KBr) 1657 (CO), 3295 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.11 (t, 1H, *J*= 7.4 Hz, ArH),

7.33-7.40 (m, 4H, ArH), 7.54 (d, 2H, *J*= 8.8 Hz, ArH), 7.72-7.90 (m, 4H, ArH), 8.47 (d, 2H, *J*= 3.7 Hz, ArH), 9.02 (s, 1H, NH), 9.08 (s, 1H, NH), 9.74 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 109.3, 114.3, 118.6, 121.1, 122.2, 124.3, 125.2, 127.1, 127.4, 136.0, 137.3, 138.1, 144.6, 151.3, 151.5, 156.0; mass (ES+) *m/z*= 390.1 (M^++1), 392.1 (M^++3). Anal. Calcd. for $C_{21}H_{16}ClN_5O$ C, 64.70; H, 4.14; N, 17.96. Found C, 64.41; H, 5.34; N, 18.19.

***N*-(4-Anilinoquinazolin-6-yl)-*N*'-(3-cyanophenyl)urea (21c).** 98% as a white solid, mp 230-232 °C; R_t= 17.85 min; ν_{max} (KBr) 1706 (CO), 2220 (CN), 3344 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.11 (t, 1H, *J*= 7.4 Hz, ArH), 7.35-7.54 (m, 4H, ArH), 7.70-7.90 (m, 5H, ArH), 8.04-8.05 (m, 1H, ArH), 8.49 (d, 2H, *J*=4.0 Hz, ArH), 9.15 (s, 1H, NH), 9.28 (s, 1H, NH), 9.74 (s, 1H, NH); mass (ES+) *m/z*= 381.2 (M^++1). Anal. Calcd. for $C_{22}H_{16}N_6O$ C, 69.46; H, 4.24; N, 22.09. Found C, 69.23; H, 4.51; N, 22.37.

***N*-(4-Anilinoquinazolin-6-yl)-*N*'-(3-chloro-4-methylphenyl)urea (21d).** 76% as a white solid, mp >250 °C; R_t= 21.86 min; ν_{max} (KBr) 1705 (CO), 3442 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 2.26 (s, 3H, CH_3), 7.11 (t, 1H, *J*= 7.2 Hz, ArH), 7.24-7.27 (m, 2H, ArH), 7.37 (t, 2H, *J*= 7.6 Hz, ArH), 7.72-7.87 (m, 5H, ArH), 8.48 (s, 2H, ArH), 8.99 (s, 2H, 2 x NH), 9.73 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 17.5, 109.2, 114.3, 115.8, 117.0, 121.1, 122.2, 125.2, 127.0, 129.9, 131.9, 136.0, 137.4, 138.1, 144.6, 151.2, 151.5, 156.0; mass (ES+) *m/z*= 404.2 (M^++1), 406.1 (M^++3). Anal. Calcd. for $C_{22}H_{18}ClN_5O$ C, 65.43; H, 4.49; N, 17.34. Found C, 65.19; H, 4.25; N, 17.61.

***N*-(4-Anilinoquinazolin-6-yl)-*N*'-(3,4-dichlorophenyl)urea (21e).** 90% as a light green solid, mp >250 °C; R_t= 21.42 min; ν_{max} (KBr) 1662 (CO), 3426 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.13 (t, 1H, *J*= 7.3 Hz, ArH), 7.39-7.42 (m, 3H, ArH), 7.55 (d, 1H, *J*= 8.8 Hz, ArH), 7.74-7.82 (m, 3H, ArH), 7.88 (dd, 1H, J_1= 1.9 Hz, J_2= 9.0 Hz, ArH), 7.97 (d, 1H, *J*= 2.3 Hz, ArH), 8.50-8.53 (m, 2H, ArH), 9.31 (s, 1H, NH), 9.49 (s, 1H, NH), 9.86 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 111.0, 115.8, 118.7, 119.6, 123.2, 123.6, 124.3, 127.1, 127.7, 128.8, 131.0, 131.4, 137.9, 139.5, 140.3, 144.8, 152.7, 152.9, 157.9; mass (ES+) *m/z*= 424.2 (M^++1), 426.1 (M^++3). Anal. Calcd. for $C_{21}H_{15}Cl_2N_5O$ C, 59.45; H, 3.56; N, 16.51. Found C, 59.32; H, 3.72; N, 16.42.

***N*-(6-Amino-2-methylquinolin-4-yl)-2-furamide (11).** 87% as a light yellow silod, mp 195-197 °C; ν_{max} (KBr) 1665 (CO), 3327 (NH & NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 2.82 (s, 3H, CH_3), 6.70 (q, 1H, *J*= 1.7 Hz, ArH), 7.43 (d, 1H, *J*= 3.6 Hz, ArH), 7.73 (d, 1H, *J*= 1.1 Hz, ArH), 8.18 (d, 1H, *J*= 9.2 Hz, ArH), 8.49-8.53 (m, 2H, ArH), 8.88-8.91 (m, 2H, ArH & NH); mass (ES+) *m/z*= 268.2 (M^++1). Anal. Calcd. for $C_{15}H_{13}N_3O_2$ C, 67.40; H, 4.90; N, 15.72. Found C, 67.04; H, 4.96; N, 15.65.

***N*-(4-Bromophenyl)-*N*'-[4-(3-fluoroanilino)quinazolin-6-yl]urea (22a).** 91% as a white solid, mp >250 °C; ν_{max} (KBr) 1655 (CO), 3284 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.14 (d, 1H, *J*= 7.6 Hz, ArH), 7.36-7.48 (m, 5H, ArH), 7.74-7.91 (m, 3H, ArH), 8.06 (s, 1H, ArH), 8.53 (d, 2H, *J*= 7.6 Hz, ArH), 9.56 (s, 1H, NH), 9.68 (s, 1H, NH), 9.91 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 108.6, 112.0, 114.4, 118.7, 119.1, 120.1, 121.6, 125.2, 127.2, 128.7, 130.3, 131.4, 136.5, 138.0, 140.0, 144.6, 151.2, 151.4, 155.8; mass (ES+) *m/z*= 452.2 (M^++1). Anal. Calcd. for $C_{21}H_{15}BrFN_5O$ C, 55.77; H, 3.34; N, 15.48. Found C, 55.68; H, 3.53; N, 15.31.

***N*-(4-Chlorophenyl)-*N*'-[4-(3-fluoroanilino)quinazolin-6-yl]urea (22b).** 78% as a brown solid, mp 228-230 °C; R_t= 17.96 min; ν_{max} (KBr) 1703 (CO), 3296 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 6.92 (dt, 1H, J_1= 2.0 Hz, J_2= 8.4 Hz, ArH), 7.33-7.45 (m, 3H, ArH), 7.57 (d, 2H, *J*= 8.8 Hz, ArH), 7.68 (d, 1H, *J*= 8.2 Hz, ArH), 7.74-7.79 (m, 1H, ArH), 7.88-7.93 (m, 2H, ArH), 8.51 (s, 1H, ArH), 8.56 (s, 1H, ArH), 9.43 (s, 1H, NH), 9.45 (s, 1H, NH), 9.84 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 108.7, 109.2, 110.5, 116.1, 118.0, 120.2, 124.1, 125.8, 127.0, 128.6, 128.8, 129.0, 130.1, 138.2, 138.9, 141.7, 146.3, 152.8, 157.4, 160.1, 164.7; mass (ES+) *m/z*= 408.2 (M^++1). Anal. Calcd. for $C_{21}H_{15}ClFN_5O$ C, 61.85; H, 3.71; N, 17.17. Found C, 61.81; H, 3.94; N, 17.36.

***N*-(6-Amino-2-methylquinolin-4-yl)-2-(4-ethylpiperazin-1-yl)acetamide (22).** 83% as an off white solid, mp 201-202 °C; ν_{max} (KBr) 1694 (CO), 3186 (NH_2), 3399 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ= 1.02 (t, 3H, *J*= 7.1 Hz, CH_2CH_3), 2.39 (q, 2H, *J*= 7.1 Hz, CH_2CH_3), 2.50 (s, 7H, CH_3 & 2 x CH_2), 2.62 (s, 4H, 2 x CH_2), 3.25 (s, 2H, CH_2), 5.55 (s, 2H, NH_2), 6.75 (d, 1H, *J*= 1.7 Hz, ArH), 7.14 (dd, 1H, J_1= 1.9 Hz, J_2= 8.9 Hz, ArH), 7.62 (d, 1H, *J*= 8.9 Hz, ArH), 7.87 (s, 1H, ArH), 9.91 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 12.5, 25.0, 51.8, 52.8, 53.3, 62.0, 98.4, 111.3, 120.6, 121.7, 130.2, 138.3, 142.6, 146.8, 153.3, 169.4; mass (ES+) *m/z*= 328.1 (M^++1). Anal. Calcd. for $C_{18}H_{25}N_5O$ C, 66.03; H, 7.70; N, 21.39. Found C, 66.31; H, 7.53; N, 21.47.

***N*-(3-Cyanophenyl)-*N*'-[4-(3-fluoroanilino)quinazolin-6-yl]urea (22c).** 72% as a brown solid, mp 233-234 °C; R_t= 15.52 min; ν_{max} (KBr) 1702 (CO), 2231 (CN), 3318 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 6.95 (dt, 1H, J_1= 2.0 Hz, J_2= 8.4 Hz, ArH), 7.38-7.55 (m, 3H, ArH), 7.65-7.94 (m, 6H, ArH), 8.05 (s, 1H, ArH), 8.55 (s, 1H, ArH), 8.60 (s, 1H, NH), 9.27 (s, 1H, NH), 9.38 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 111.0, 112.0, 115.9, 118.3, 119.2, 121.2, 123.3, 125.9, 127.3, 128.1, 130.1, 130.3, 130.6, 137.9, 140.9, 141.4, 141.6, 145.2, 152.9, 157.6, 159.9, 164.7; mass (ES+) *m/z*= 399.1 (M^++1). Anal. Calcd. for $C_{22}H_{15}FN_6O$ C, 66.33; H, 3.80; N, 21.09. Found C, 59.98; H, 4.01; N, 21.18.

***N*-(3-Chloro-4-methylphenyl)-*N*'-[4-(3-fluoroanilino)quinazolin-6-yl]urea (22d).** 74% as an off white solid, mp 221-222 °C; R_t= 20.50 min; ν_{max} (KBr) 1704 (CO), 3331 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 2.27 (s, 3H, CH_3), 6.93 (dt, 1H, J_1= 2.1 Hz, J_2= 8.3 Hz, ArH), 7.22-7.28 (m, 2H, ArH), 7.41 (m, 1H, ArH),

7.67 (d, 1H, *J*= 8.1 Hz, ArH), 7.76-7.79 (m, 2H, ArH), 7.87-7.92 (m, 2H, ArH), 8.53 (s, 1H, ArH), 8.57 (s, 1H, ArH), 9.03 (s, 1H, NH), 9.07 (s, 1H, NH), 9.93 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 22.7, 112.5, 112.8, 113.4, 113.7, 114.3, 119.6, 121.0, 121.6, 122.2, 130.6, 132.3, 132.4, 133.7, 133.8, 135.1, 137.1, 141.5, 142.7, 156.5, 161.0, 167.5; mass (ES+) *m/z*= 422.2 (M^++1), 424.1 (M^++3). Anal. Calcd. for $C_{22}H_{17}ClFN_5O$ C, 62.64; H, 4.06; N, 16.60; Found C, 62.79; H, 3.98; N, 16.27.

***N*-(3,4-Dichlorophenyl)-*N*'-[4-(3-fluoroanilino)quinazolin-6-yl]urea (22e).** 72% as a yellow solid, mp 233-234 °C; R_t= 22.25 min; ν_{max} (KBr) 1703 (CO), 3326 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 6.92 (t, 1H, *J*= 7.4 Hz, ArH), 7.36-7.44 (m, 3H, ArH), 7.53 (d, 1H, *J*= 8.7 Hz, ArH), 7.66 (d, 1H, *J*= 7.7 Hz, ArH), 7.77 (d, 1H, *J*= 8.9 Hz, ArH), 7.86-7.95 (m, 3H, ArH & NH), 8.52 (s, 1H, ArH), 8.57 (s, 1H, ArH), 9.13 (s, 1H, NH), 9.23 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 107.8, 108.1, 108.8, 109.1, 109.9, 114.8, 116.9, 117.6, 118.6, 122.5, 126.0, 127.4, 128.9, 129.7, 130.3, 136.6, 139.0, 144.7, 156.3, 159.6, 162.8; mass (ES+) *m/z*= 442.2 (M^++1), 444.1 (M^++3). Anal. Calcd. for $C_{21}H_{14}Cl_2FN_5O$ C, 57.03; H, 3.19; N, 15.83. Found C, 57.13; H, 3.35; N, 16.02.

***N*-(3,5-Dichlorophenyl)-*N*'-[4-(3-fluoroanilino)quinazolin-6-yl]urea (22f).** 65% as a brown solid, mp >250 °C; R_t= 21.51 min; ν_{max} (KBr) 1708 (CO), 3351 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 6.94 (t, 1H, *J*= 7.4 Hz, ArH), 7.19 (s, 1H, NH), 7.38-7.45 (m, 1H, *J*= 7.4 Hz, ArH), 7.60-7.68 (m, 4H, ArH), 7.77-7.90 (m, 3H, ArH), 8.56 (s, 1H, ArH), 8.59 (s, 1H, ArH), 9.25 (s, 1H, NH), 9.34 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 109.0, 109.5, 110.4, 111.2, 115.9, 116.8, 118.2, 121.4, 127.3, 128.3, 130.1, 130.3, 134.5, 137.7, 141.5, 142.5, 145.7, 152.7, 157.5, 159.9, 164.7; mass (ES+) *m/z*= 442.2 (M^++1), 444.1 (M^++3). Anal. Calcd. for $C_{21}H_{14}Cl_2FN_5O$ C, 57.03; H, 3.19; N, 15.83. Found C, 59.86; H, 3.23; N, 15.46.

***N*-[4-Chloro-3-(trifluoromethyl)phenyl]-*N*'-[4-(3-fluoroanilino)quinazolin-6-yl]urea (22g).** 65% as a brown solid, mp 138-140 °C; ν_{max} (KBr) 1710 (CO), 3331 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 6.92 (dt, 1H, J_1= 2.1 Hz, J_2= 8.4 Hz, ArH), 7.40 (q, 1H, *J*= 8.1 Hz, ArH), 7.62-7.71 (m, 3H, ArH), 7.78 (d, 1H, *J*= 8.9 Hz, ArH), 7.86-7.90 (m, 2H, ArH), 8.18 (d, 1H, *J*= 2.0 Hz, ArH), 8.52 (d, 1H, *J*= 1.5 Hz, ArH), 8.57 (s, 1H, ArH), 9.13 (s, 1H, NH), 9.35 (s, 1H, NH), 9.87 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 108.8, 109.8, 111.2, 116.0, 117.3, 118.1, 122.9, 123.5, 126.8, 127.2, 128.9, 130.3, 132.4, 137.5, 139.6, 141.8, 146.5, 152.9, 153.1, 157.4, 160.0, 164.8; mass (ES+) *m/z*= 476.2 (M^++1), 478.1 (M^++3). Anal. Calcd. for $C_{22}H_{14}ClF_4N_5O$ C, 55.53; H, 2.97; N, 14.72. Found C, 55.91; H, 3.02; N, 14.71.

***N*-(4-Bromophenyl)-*N*'-[4-(3-chloroanilino)quinazolin-6-yl]urea (23a).** 97% as a white solid, mp 250-251 °C; R_t= 22.09 min; ν_{max} (KBr) 1655 (CO), 3284 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.14 (d, 1H, *J*= 7.6 Hz, ArH), 7.36-7.48 (m, 5H, ArH), 7.74-7.91 (m, 3H, ArH), 8.06 (s, 1H, ArH), 8.53 (d, 2H, *J*= 7.6 Hz, ArH), 9.56 (s, 1H, NH), 9.68 (s, 1H, NH), 9.91 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 108.6, 112.0, 114.4, 118.7, 119.1, 120.1, 121.6, 125.2, 127.2, 128.7, 130.3, 131.4, 136.5, 138.0, 140.0, 144.6, 151.2, 151.4, 155.8; mass (ES+) *m/z*= 468.2 (M^++1), 470.1 (M^++3). Anal. Calcd. for $C_{21}H_{15}BrClN_5O$ C, 53.81; H, 3.23; N, 14.94. Found C, 54.08; H, 3.76; N, 15.31.

***N*-[4-(3-Chloroanilino)quinazolin-6-yl]-*N*'-(4-chlorophenyl)urea (23b).** 96% as an off white solid, mp >250 °C; ν_{max} (KBr) 1703 (CO), 3501 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.16 (dd, 1H, J_1= 1.3 Hz, J_2= 7.9 Hz, ArH), 7.34-7.43 (m, 3H, ArH), 7.55 (dd, 2H, J_1= 2.0 Hz, J_2= 7.0 Hz, ArH), 7.76-7.90 (m, 3H, ArH), 8.07 (t, 1H, *J*= 1.9 Hz, ArH), 8.51 (d, 1H, *J*= 1.8 Hz, ArH), 8.56 (s, 1H, ArH), 9.04 (s, 1H, NH), 9.06 (s, 1H, NH), 9.87 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 110.7, 116.0, 120.3, 120.7, 121.8, 123.3, 126.0, 127.0, 128.9, 129.0, 130.3, 133.1, 137.9, 138.9, 141.5, 146.3, 152.9, 157.4; mass (ES+) *m/z*= 424.3 (M^++1), 426.3 (M^++3). Anal. Calcd. for $C_{21}H_{15}Cl_2N_5O$ C, 59.45; H, 3.56; N, 16.51. Found C, 59.79; H, 3.89; N, 16.70.

***N*-[4-(3-Chloroanilino)quinazolin-6-yl]-*N*'-(3-cyanophenyl)urea (23c).** 91% as a light yellow solid, mp 239-240 °C; R_t= 20.35 min; ν_{max} (KBr) 1690 (CO), 2226 (CN), 3334 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.15 (dd, 1H, J_1= 1.4 Hz, J_2= 7.9 Hz, ArH), 7.37-7.54 (m, 3H, ArH), 7.71-7.89 (m, 4H, ArH), 8.04-8.07 (m, 2H, ArH), 8.52-8.56 (m, 2H, ArH), 9.15 (s, 1H, NH), 9.24 (s, 1H, NH), 9.86 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 109.1, 110.4, 114.1, 117.6, 119.3, 119.9, 121.0, 121.4, 122.5, 124.1, 125.3, 125.8, 128.8, 129.0, 131.4, 136.8, 139.2, 139.3, 150.4, 151.4, 156.4; mass (ES+) *m/z*= 415.4 (M^++1), 417.5 (M^++3). Anal. Calcd. for $C_{22}H_{15}ClN_6O$ C, 63.69; H, 3.64; N, 20.26. Found C, 63.52; H, 3.79; N, 20.42.

***N*-[4-(3-Chloroanilino)quinazolin-6-yl]-*N*'-(3,4-dichlorophenyl)urea (23e).** 95% as an off white solid, mp >250 °C; R_t= 21.12 min; ν_{max} (KBr) 1708 (CO), 3334 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.15 (dd, 1H, J_1= 1.3 Hz, J_2= 8.0 Hz, ArH), 7.35-7.43 (m, 2H, ArH), 7.54 (d, 1H, *J*= 8.8 Hz, ArH), 7.76-7.87 (m, 3H, ArH), 7.95 (d, 1H, *J*= 2.4 Hz, ArH), 8.05 (s, 1H, ArH), 8.52-8.56 (m, 2H, ArH), 9.13 (s, 1H, NH), 9.23 (s, 1H, NH), 9.87 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 109.3, 114.3, 117.2, 118.2, 119.2, 120.2, 121.7, 122.1, 125.5, 127.2, 128.7, 129.3, 129.8, 131.4, 136.0, 138.5, 139.8, 144.6, 151.1, 151.3, 155.8; mass (ES+) *m/z*= 458.2 (M^++1), 460.1 (M^++3). Anal. Calcd. for $C_{21}H_{14}Cl_3N_5O$ C, 54.89; H, 3.08; N, 15.27. Found C, 54.72; H, 3.15; N, 15.42.

***N*-(4-Bromophenyl)-*N*'-{4-[3-(trifluoromethyl)anilino]quinazolin-6-yl}urea (24a).** 89% as a white solid, mp 245-247 °C; ν_{max} (KBr) 1707 (CO), 3454 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.44-7.56 (m, 3H, ArH), 7.63 (t, 1H, *J*= 7.9 Hz, ArH), 7.72-7.89 (m, 3H, ArH), 8.06 (s, 1H, ArH), 8.22 (d, 1H, *J*=

8.2 Hz, ArH), 8.31 (d, 1H, *J*= 6.3 Hz, ArH), 8.58 (s, 2H, ArH), 9.20 (s, 1H, NH), 9.26 (s, 1H, NH), 10.01 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 300MHz) δ= 109.2, 110.1, 113.2, 113.7, 113.9, 117.3, 119.4, 121.5, 122.9, 123.1, 124.0, 125.1, 126.8, 128.7, 134.0, 135.5, 138.9, 144.3, 151.0, 154.5, 155.8, 159.3; mass (ES+) *m/z*= 502.1 (M^++1), 504.1 (M^++3). Anal. Calcd. for $C_{22}H_{15}BrF_3N_5O$ C, 52.61; H, 3.01; N, 13.94. Found C, 52.56; H, 2.89; N, 13.72.

***N*-(4-Chlorophenyl)-*N*'-{4-[3-(trifluoromethyl)anilino]quinazolin-6-yl}urea (24b).** 68% as a brown solid, mp 246-248 °C; ν_{max} (KBr) 1705 (CO), 3319 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.30-7.36 (m, 2H, ArH), 7.42-7.44 (m, 1H, ArH), 7.49-7.64 (m, 3H, ArH), 7.79 (d, 1H, *J*= 8.9 Hz, ArH), 7.86-7.90 (m, 1H, ArH), 8.23 (d, 1H, *J*= 8.2 Hz, ArH), 8.30 (s, 1H, ArH), 8.55-8.58 (m, 2H, ArH), 9.04 (s, 2H, 2 x NH), 9.99 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 109.7, 115.1, 117.3, 117.5, 119.4, 119.5, 125.1, 125.2, 126.2, 128.0, 128.1, 128.5, 129.0, 131.2, 137.1, 138.0, 139.9, 145.5, 151.9, 152.0, 156.6; mass (ES+) *m/z*= 458.1 (M^++1), 460.1 (M^++3). Anal. Calcd. for $C_{22}H_{15}ClF_3N_5O$ C, 57.71; H, 3.30; N, 15.30. Found C, 57.42; H, 3.38; N, 15.61.

***N*-(3-Cyanophenyl)-*N*'-{4-[3-(trifluoromethyl)anilino]quinazolin-6-yl}urea (24c).** 89% as a white solid, mp 245-247 °C; ν_{max} (KBr) 1707 (CO), 2244 (CN), 3454 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.44-7.56 (m, 3H, ArH), 7.63 (t, 1H, *J*= 8.0 Hz, ArH), 7.72-7.89 (m, 3H, ArH), 8.06 (s, 1H, ArH), 8.22 (d, 1H, *J*= 8.2 Hz, ArH), 8.31 (d, 1H, *J*= 6.3 Hz, ArH), 8.58 (s, 2H, ArH), 9.20 (s, 1H, NH), 9.26 (s, 1H, NH), 10.01 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 300 MHz) δ= 109.2, 110.1, 113.2, 113.7, 113.9, 117.3, 119.4, 121.5, 122.9, 123.1, 124.0, 125.1, 126.8, 128.7, 134.0, 135.5, 138.9, 144.3, 151.0, 154.5, 155.8, 159.3; mass (ES+) *m/z*= 449.3 (M^++1). Anal. Calcd. for $C_{23}H_{15}F_3N_6O$ C, 61.61; H, 3.37; N, 18.74. Found C, 61.34; H, 3.39; N, 18.92.

***N*-(3-Chloro-4-methylphenyl)-*N*'-{4-[3-(trifluoromethyl)anilino]quinazolin-6-yl}urea (24d).** 71% as a white solid, mp >250 °C; ν_{max} (KBr) 1705 (CO), 3326 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 2.27 (s, 3H, CH_3), 7.25 (s, 2H, ArH), 7.44 (d, 1H, *J*= 7.6 Hz, ArH), 7.86 (t, 1H, *J*= 7.9 Hz, ArH), 7.77-7.88 (m, 3H, ArH), 8.22 (d, 1H, *J*= 8.2 Hz, ArH), 8.30 (d, 1H, *J*= 1.6 Hz, ArH), 8.57 (s, 2H, ArH), 8.98 (s, 1H, NH), 9.04 (s, 1H, NH), 9.98 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 18.0, 109.4, 114.8, 116.3, 117.5, 118.7, 124.8, 125.3, 125.9, 126.3, 127.6, 127.7, 127.9, 128.7, 130.4, 132.3, 136.8, 137.9, 139.6, 145.2, 149.2, 151.7, 156.3; mass (ES+) *m/z*= 472.1 (M^++1), 474.1 (M^++3). Anal. Calcd. for $C_{23}H_{17}ClF_3N_5O$ C, 58.54; H, 3.63; N, 14.84. Found C, 58.37; H, 3.79; N, 14.53.

***N*-(3,4-Dichlorophenyl)-*N*'-{4-[3-(trifluoromethyl)anilino]quinazolin-6-yl}urea (24e).** 87% as a white solid, mp >250 °C; ν_{max} (KBr) 1699 (CO), 3324 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.16 (t, 1H, *J*= 1.6 Hz, ArH), 7.43 (d, 1H, *J*= 7.6 Hz, ArH), 7.58-7.63 (m, 3H, ArH), 7.77-7.86 (m, 2H, ArH), 8.20 (d, 1H, *J*= 8.2 Hz, ArH), 8.28 (s, 1H, ArH), 8.57 (s, 2H, ArH), 9.19 (s, 1H, ArH), 9.25 (s, 1H, NH), 9.97 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 109.9, 114.7, 115.7, 116.0, 117.4, 118.7, 120.3, 121.6, 124.9, 125.8, 126.1, 127.8, 128.2, 128.7, 133.3, 136.4, 139.5, 141.3, 145.4, 151.5, 151.8, 156.3; mass (ES+) *m/z*= 492.1 (M^++1), 494.0 (M^++3). Anal. Calcd. for $C_{22}H_{14}Cl_2F_3N_5O$ C, 53.68; H, 2.87; N, 14.23. Found C, 53.44; H, 3.14; N, 14.07.

***N*-(3,5-Dichlorophenyl)-*N*'-{4-[3-(trifluoromethyl)anilino]quinazolin-6-yl}urea (24f).** 83% as a white solid, mp >250 °C; R_t= 20.90 min; ν_{max} (KBr) 1708 (CO), 3338 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.14 (d, 1H, *J*= 1.5 Hz, ArH), 7.42 (d, 1H, *J*= 7.6 Hz, ArH), 7.57-7.62 (m, 3H, ArH), 7.75 (d, 1H, *J*= 8.9 Hz, ArH), 7.84 (dd, 1H, J_1= 1.7 Hz, J_2= 9.0 Hz, ArH), 8.19 (d, 1H, *J*= 8.0 Hz, ArH), 8.28 (s, 1H, ArH), 8.29 (s, 1H, NH), 8.55-8.57 (m, 2H, ArH), 9.70 (brs, 2H, 2 x NH); mass (ES+) *m/z*= 492.1 (M^++1), 494.1 (M^++3). Anal. Calcd. for $C_{22}H_{14}Cl_2F_3N_5O$ C, 53.68; H, 2.87; N, 14.23. Found C, 53.51; H, 2.88; N, 14.54.

***N*-[4-Chloro-3-(trifluoromethyl)phenyl]-*N*'-{4-[3-trifluoromethyl)anilino]quinazolin-6-yl}urea (24g).** 78% as an off white solid, mp >250 °C; ν_{max} (KBr) 1699 (CO), 3324 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.42 (d, 1H, *J*= 7.7 Hz, ArH), 7.57-7.70 (m, 3H, ArH), 7.77-7.88 (m, 2H, ArH), 8.17-8.21 (m, 2H, ArH), 8.28 (s, 1H, ArH), 8.57 (s, 2H, ArH), 9.15 (s, 1H, NH), 9.36 (s, 1H, NH), 9.98 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 109.9, 114.8, 116.0, 117.3, 121.6, 122.4, 124.9, 125.8, 126.1, 127.8, 128.2, 128.6, 128.7, 131.2, 136.4, 138.4, 139.5, 145.4, 151.7, 151.8, 156.3; mass (ES+) *m/z*= 526.1 (M^++1), 528.1 (M^++3). Anal. Calcd. for $C_{23}H_{14}ClF_6N_5O$ C, 52.53; H, 2.68; N, 13.32. Found C, 52.73; H, 2.89; N, 13.17.

***N*-(4-Bromophenyl)-*N*'-[4-(3-methoxyanilino)quinazolin-6-yl]urea (25a).** 91% as a white solid, mp 230-231 °C; ν_{max} (KBr) 1655 (CO), 3296 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.76 (s, 3H, OCH_3), 6.69 (dd, 1H, J_1= 2.1 Hz, J_2= 8.1 Hz, ArH), 7.27 (t, 1H, *J*= 8.2 Hz, ArH), 7.44-7.50 (m, 6H, ArH), 7.74 (d, 1H, *J*= 8.9 Hz, ArH), 7.87 (dd, 1H, J_1= 1.9 Hz, J_2= 9.0 Hz, ArH), 8.46 (d, 1H, *J*= 1.8 Hz, ArH), 8.50 (s, 1H, ArH), 9.00 (s, 1H, NH), 9.04 (s, 1H, NH), 9.69 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 55.4, 108.5, 109.1, 110.8, 113.8, 114.9, 116.0, 120.7, 126.9, 128.7, 129.5, 131.9, 137.8, 139.5, 141.0, 146.2, 153.0, 153.1, 157.6, 159.7; mass (ES+) *m/z*= 464.1 (M^++1), 466.1 (M^++3). Anal. Calcd. for $C_{22}H_{18}BrN_5O_2$ C, 56.91; H, 3.91; N, 15.08. Found C, 56.83; H, 4.23; N, 15.36.

***N*-(4-Chlorophenyl)-*N*'-[4-(3-methoxyanilino)quinazolin-6-yl]urea (25b).** 88% as an off white solid, mp 222-224 °C, ν_{max} (KBr) 1655 (CO), 3291 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.77 (s, 3H, OCH_3), 6.69 (dd, 1H, J_1= 1.9 Hz, J_2= 8.0 Hz, ArH), 7.24-7.36 (m, 3H, ArH), 7.44-7.55 (m, 4H, ArH), 7.74 (d, 1H, *J*= 8.9 Hz, ArH), 7.88 (dd, 1H, J_1= 1.9 Hz, J_2= 9.0 Hz, ArH), 8.46 (d, 1H, *J*= 1.6 Hz, ArH), 8.51 (s, 1H, ArH), 8.99 (s, 1H, NH), 9.04 (s, 1H, NH), 9.69 (s, 1H, NH); ^{13}C

NMR (DMSO-d_6, 50 MHz) δ= 55.4, 108.5, 109.1, 110.9, 114.9, 116.0, 120.3, 126.0, 126.9, 128.8, 129.0, 129.5, 137.7, 138.9, 141.0, 146.3, 153.0, 153.1, 157.6, 159.7; mass (ES+) *m/z*= 420.1 (M^++1), 422.0 (M^++3). Anal. Calcd. for $C_{22}H_{18}ClN_5O_2$ C, 62.93; H, 4.32; N, 16.68. Found C, 63.20; H, 4.23; N, 17.01.

***N*-(3-Cyanophenyl)-*N*'-[4-(3-methoxyanilino)quinazolin-6-yl]urea (25c).** 97% as an off white solid, mp 243-244 °C; ν_{max} (KBr) 1696 (CO), 2227 (CN), 3353 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 3.78 (s, 3H, OCH_3), 6.70 (dd, 1H, J_1= 2.0 Hz, J_2= 8.0 Hz, ArH), 7.29 (t, 1H, *J*= 8.2 Hz, ArH), 7.45-7.55 (m, 4H, ArH), 7.72-7.78 (m, 2H, ArH), 7.89 (dd, 1H, J_1= 2.0 Hz, J_2= 9.0 Hz, ArH), 8.06 (s, 1H, ArH), 8.50 (d, 1H, *J*= 1.9 Hz, ArH), 8.53 (s, 1H, ArH), 9.14 (s, 1H, NH), 9.26 (s, 1H, NH), 9.71 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 54.2, 107.3, 108.0, 110.1, 110.9, 113.8, 114.8, 118.0, 120.2, 122.2, 124.7, 125.8, 127.6, 128.3, 129.4, 136.3, 139.7, 139.8, 145.3, 151.8, 152.1, 156.5, 158.6; mass (ES+) *m/z*= 411.2 (M^++1). Anal. Calcd. for $C_{23}H_{18}N_6O_2$ C, 67.31; H, 4.42; N, 20.48. Found C, 67.57; H, 4.66; N, 20.69.

***N*-(3-Chloro-4-methylphenyl)-*N*'-[4-(3-methoxyanilino)quinazolin-6-yl]urea (25d).** 90% as a light yellow solid, mp >250 °C; ν_{max} (KBr) 1703 (CO), 3427 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 2.27 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.70 (dd, 1H, J_1= 2.0 Hz, J_2= 8.1 Hz, ArH), 7.22-7.31 (m, 3H, ArH), 7.45-7.53 (m, 2H, ArH), 7.74-7.78 (m, 2H, ArH), 7.87 (dd, 1H, J_1= 2.1 Hz, J_2= 9.0 Hz, ArH), 8.49 (d, 1H, *J*= 2.1 Hz, ArH), 8.52 (s, 1H, ArH), 9.00 (s, 1H, NH), 9.01 (s, 1H, NH), 9.70 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 18.0, 54.2, 107.3, 107.9, 109.7, 113.8, 114.9, 116.3, 117.5, 125.7, 127.6, 128.2, 130.4, 132.4, 136.5, 137.9, 139.8, 145.1, 151.7, 151.9, 156.4, 158.5; mass (ES+) *m/z*= 434.2 (M^++1), 436.1 (M^++3). Anal. Calcd. for $C_{23}H_{20}ClN_5O_2$ C, 63.67; H, 4.65; N, 16.14. Found C, 63.44; H, 4.63; N, 16.29.

***N*-(3,4-Dichlorophenyl)-*N*'-[4-(3-methoxyanilino)quinazolin-6-yl]urea (25e).** 93% as a yellow solid, mp >250 °C; ν_{max} (KBr) 1711 (CO), 3394 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 3.78 (s, 3H, OCH_3), 6.69-6.72 (m, 1H, ArH), 7.29 (t, 1H, *J*= 8.2 Hz, ArH), 7.38 (dd, 1H, J_1= 2.4 Hz, J_2= 8.8 Hz, ArH), 7.45-7.48 (m, 1H, ArH), 7.51-7.56 (m, 2H, ArH), 7.76 (d, 1H, *J*= 8.9 Hz, ArH), 7.87 (dd, 1H, J_1= 2.1 Hz, J_2= 9.0 Hz, ArH), 7.97 (d, 1H, *J*= 2.4 Hz, ArH), 8.51 (d, 1H, *J*= 2.0 Hz, ArH), 8.53 (s, 1H, ArH), 9.11 (s, 1H, NH), 9.22 (s, 1H, NH), 9.71 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 54.2, 107.3, 107.9, 110.1, 113.8, 114.8, 117.6, 118.7, 122.5, 125.8, 127.6, 128.2, 129.8, 130.3, 136.2, 139.0, 139.8, 145.3, 151.6, 152.1, 156.4, 158.5; mass (ES+) *m/z*= 454.1 (M^++1), 456.2 (M^++3). Anal. Calcd. for $C_{22}H_{17}ClN_5O_2$ C, 58.16; H, 3.77; N, 15.42. Found C, 57.94; H, 4.96; N, 15.65.

***N*-(3-Acetylphenyl)-*N*'-[4-(3-methoxyanilino)quinazolin-6-yl]urea (25h).** 91% as a light yellow solid, mp 238-239 °C; ν_{max} (KBr) 1703 (CO), 3427 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 2.57 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 6.69 (dd, 1H, J_1= 1.9 Hz, J_2= 8.1 Hz, ArH), 7.27 (t, 1H, *J*= 8.2 Hz, ArH), 7.44-7.51 (m, 3H, ArH), 7.61 (d, 1H, *J*= 7.7 Hz, ArH), 7.73 (t, 2H, *J*= 9.2 Hz, ArH), 7.89 (dd, 1H, J_1= 1.9 Hz, J_2= 9.0 Hz, ArH), 8.14 (s, 1H, ArH), 8.47-8.51 (m, 2H, ArH), 9.00 (s, 1H, NH), 9.13 (s, 1H, NH), 9.71 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 27.2, 55.5, 108.6, 109.2, 111.0, 115.0, 116.1, 117.9, 122.7, 123.4, 127.0, 128.9, 129.6, 129.7, 137.8, 137.9, 140.5, 141.1, 146.4, 153.1, 157.7, 159.8, 198.2; mass (ES+) *m/z*= 428.2 (M^++1). Anal. Calcd. for $C_{24}H_{21}N_5O_3$ C, 67.44; H, 4.95; N, 16.38. Found C, 67.70; H, 4.72; N, 16.53.

***N*-(4-Acetylphenyl)-*N*'-[4-(3-methoxyanilino)quinazolin-6-yl]urea (25i).** 90% as an off white solid, mp 243-244 °C; ν_{max} (KBr) 1720 (CO), 3351 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 2.53 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.70 (dd, 1H, J_1= 2.0 Hz, J_2= 8.0 Hz, ArH), 7.29 (t, 1H, *J*= 8.1 Hz, ArH), 7.47 (d, 1H, *J*= 8.1 Hz, ArH), 7.52 (d, 1H, *J*= 2.0 Hz, ArH), 7.65 (d, 2H, *J*= 8.7 Hz, ArH), 7.77 (d, 1H, *J*= 8.9 Hz, ArH), 7.88-7.95 (m, 3H, ArH), 8.51-8.53 (m, 2H, ArH), 9.10 (s, 1H, NH), 9.34 (s, 1H, NH), 9.73 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 26.8, 55.5, 108.6, 109.2, 111.2, 115.0, 116.1, 117.7, 127.0, 128.9, 129.6, 130.2, 131.1, 137.6, 141.1, 144.7, 146.5, 152.8, 153.3, 157.7, 159.8, 196.8; mass (ES+) *m/z*= 428.2 (M^++1). Anal. Calcd. for $C_{24}H_{21}N_5O_3$ C, 67.44; H, 4.95; N, 16.38. Found C, 67.69; H, 5.03; N, 16.41.

***N*-(4-Bromophenyl)-*N*'-[4-(4-fluoroanilino)quinazolin-6-yl]urea (26a).** 85% as a white solid, mp >250 °C; ν_{max} (KBr) 1706 (CO), 3328 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 7.23 (t, 2H, *J*= 8.8 Hz, ArH), 7.49 (s, 4H, ArH), 7.73-7.88 (m, 4H, ArH), 8.47 (s, 2H, ArH), 9.01 (s, 1H, NH), 9.05 (s, 1H, NH), 9.80 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 110.8, 113.9, 115.1, 115.6, 115.9, 120.7, 124.8, 124.9, 126.9, 128.8, 131.9, 136.0, 137.7, 139.4, 146.2, 152.9, 153.2, 156.4, 157.7, 161.1; mass (ES+) *m/z*= 452.2 (M^++1), 454.1 (M^++3). Anal. Calcd. for $C_{21}H_{15}BrFN_5O$ C, 55.77; H, 3.34; N, 17.67. Found C, 55.53; H, 3.62; N, 17.36.

***N*-(4-Chlorophenyl)-*N*'-[4-(4-fluoroanilino)quinazolin-6-yl]urea (26b).** 81% as a yellow solid, mp 274-276 °C; ν_{max} (KBr) 1594 (CO), 3425 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ= 7.17-7.26 (m, 2H, ArH), 7.34 (d, 2H, *J*= 8.7 Hz, ArH), 7.53 (d, 2H, *J*= 8.7 Hz, ArH), 7.71-7.88 (m, 4H, ArH), 8.47 (s, 2H, ArH), 9.00 (s, 1H, NH), 9.03 (s, 1H, NH), 9.89 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 110.8, 115.1, 115.6, 115.8, 120.3, 124.9, 125.1, 126.1, 127.0, 128.2, 129.0, 135.9, 137.9, 138.9, 145.4, 152.9, 156.5, 157.8, 161.3; mass (FAB+) *m/z*= 408 (M^++1). Anal. Calcd. for $C_{21}H_{15}ClFN_5O$ C, 61.85; H, 3.71; N, 17.17. Found C, 62.07; H, 3.72; N, 17.42.

***N*-(3-Cyanophenyl)-*N*'-[4-(4-fluoroanilino)quinazolin-6-yl]urea (26c).** 81% as a white solid, mp 215-217 °C; R_t= 22.50 min; ν_{max} (KBr) 1708 (CO), 2234 (CN), 3365 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 7.22 (t, 2H, *J*= 8.9 Hz, ArH), 7.44-7.55 (m, 2H, ArH), 7.71-7.88 (m, 5H, ArH), 8.05 (s, 1H, ArH), 8.47-8.50 (m, 2H, ArH), 9.14 (s, 1H, NH), 9.25 (s, 1H, NH), 9.80 (s, 1H, NH); ^{13}C NMR

(DMSO-d_6, 50 MHz) δ= 109.2, 110.1, 113.2, 113.7, 117.3, 119.4, 121.5, 122.9, 123.1, 124.0, 125.1, 126.8, 128.7, 134.0, 135.5, 138.9, 144.3, 151.0, 151.3, 154.5, 155.8, 159.3; mass (ES+) *m/z*= 399.2 (M^++1). Anal. Calcd. for $C_{22}H_{15}FN_6O$ C, 66.33; H, 3.80; N, 21.09. Found C, 66.57; H, 3.89; N, 21.02.

***N*-(3-Chloro-4-methylphenyl)-*N*'-[4-(4-fluoroanilino)quinazolin-6-yl]urea (26d).** 72% as a yellow solid, mp 278-280 °C; ν_{max} (KBr) 1655 (CO), 3304 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ= 2.29 (s, 3H, CH_3), 7.21-7.30 (m, 4H, ArH), 7.75-7.86 (m, 5H, ArH), 8.50-8.52 (m, 2H, ArH), 9.01 (s, 1H, NH), 9.03 (s, 1H, NH), 9.89 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 19.2, 110.7, 115.1, 115.6, 115.8, 117.5, 118.7, 125.0, 125.1, 127.0, 128.3, 128.9, 131.6, 133.5, 135.9, 137.8, 139.0, 145.5, 152.9, 157.8, 161.3; mass (FAB+) *m/z*= 422 (M^++1). Anal. Calcd. for $C_{22}H_{17}ClFN_5O$ C, 62.64; H, 4.06; N, 16.60. Found C, 62.41; H, 3.85; N, 16.53.

***N*-(3,4-Dichlorophenyl)-*N*'-[4-(4-fluoroanilino)quinazolin-6-yl]urea (26e).** 81% as an off white solid, mp >250 °C; ν_{max} (KBr) 1706 (CO), 3345 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 7.22 (t, 2H, *J*= 8.1 Hz, ArH), 7.38 (d, 1H, *J*= 7.7 Hz, ArH), 7.55 (d, 1H, *J*= 8.3 Hz, ArH), 7.74-7.83 (m, 4H, ArH), 7.97 (s, 1H, ArH), 8.49 (d, 1H, *J*= 7.4 Hz, ArH), 9.11 (s, 1H, NH), 9.22 (s, 1H, NH), 9.80 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 111.1, 115.1, 115.5, 115.8, 118.8, 119.8, 123.7, 124.8, 125.0, 126.9, 128.8, 130.9, 131.5, 136.0, 137.4, 140.2, 146.3, 152.8, 153.3, 156.4, 157.7, 161.2; mass (ES+) *m/z*= 442.2 (M^++1), 444.1 (M^++3). Anal. Calcd. for $C_{21}H_{14}Cl_2FN_5O$ C, 57.03; H, 3.19; N, 15.83. Found C, 66.85; H, 4.13; N, 15.52.

***N*-(4-Bromophenyl)-*N*'-[4-(4-chloroanilino)quinazolin-6-yl]urea (27a).** 82% as a brown solid, mp >250 °C; ν_{max} (KBr) 1707 (CO), 3302 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 7.41-7.48 (m, 6H, ArH), 7.75 (d, 1H, *J*= 9.0 Hz, ArH), 7.85-7.90 (m, 3H, ArH), 8.48-8.50 (m, 2H, ArH), 9.01 (s, 1H, NH), 9.05 (s, 1H, NH), 9.83 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 109.1, 112.2, 114.3, 119.0, 122.4, 125.3, 125.7, 126.9, 127.2, 130.3, 136.1, 137.2, 137.7, 144.6, 151.0, 151.2, 151.3, 155.8; mass (ES+) *m/z*= 468.2 (M^++1), 470.0 (M^++3). Anal. Calcd. for $C_{21}H_{15}BrClN_5O$ C, 53.81; H, 3.23; N, 14.94. Found C, 53.49; H, 3.51; N, 15.27.

***N*-[4-(4-Chloroanilino)quinazolin-6-yl]-*N*'-(4-chlorophenyl)urea (27b).** 87% as a yellow solid, mp >250 °C; R_t= 22.02 min; ν_{max} (KBr) 1706 (CO), 3332 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 7.34 (d, 2H, *J*= 8.8 Hz, ArH), 7.42 (d, 2H, *J*= 8.9 Hz, ArH), 7.53 (d, 2H, *J*= 8.9 Hz, ArH), 7.75 (d, 1H, *J*= 8.9 Hz, ArH), 7.85-7.90 (m, 3H, ArH), 8.48-8.51 (m, 2H, ArH), 9.00 (s, 1H, NH), 9.04 (s, 1H, NH), 9.83 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 109.1, 114.3, 118.6, 122.4, 124.3, 125.3, 125.7, 126.9, 127.2, 127.4, 136.2, 137.2, 144.6, 151.2, 151.3, 155.8; mass (ES+) *m/z*= 424.2 (M^++1), 426.2 (M^++3). Anal. Calcd. for $C_{21}H_{15}Cl_2N_5O$ C, 59.45; H, 3.56; N, 16.51. Found C, 59.76; H, 3.91; N, 16.85.

***N*-[4-(4-Chloroanilino)quinazolin-6-yl]-*N*'-(3-cyanophenyl)urea (27c).** 80% as a white solid, mp 223-224 °C; ν_{max} (KBr) 1708 (CO), 2221 (CN), 3320 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 7.41-7.54 (m, 4H, ArH), 7.70-7.78 (m, 2H, ArH), 7.85-7.89 (m, 3H, ArH), 8.04 (s, 1H, ArH), 8.51 (s, 2H, ArH), 9.14 (s, 1H, NH), 9.24 (s, 1H, NH), 9.83 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 111.0, 112.0, 115.9, 119.2, 121.3, 123.4, 124.2, 125.9, 127.1, 127.4, 128.6, 128.9, 130.6, 137.6, 138.8, 140.8, 146.4, 152.9, 153.1, 157.5; mass (ES+) *m/z*= 415.1 (M^++1), 417.1 (M^++3). Anal. Calcd. for $C_{22}H_{15}ClN_6O$ C, 63.69; H, 3.64; N, 20.26. Found C, 63.45; H, 3.87; N, 20.02.

***N*-[4-(4-Chloroanilino)quinazolin-6-yl]-*N*'-(3-chloro-4-methylphenyl)urea (27d).** 86% as a yellow solid, mp >250 °C; R_t= 22.50 min; ν_{max} (KBr) 1701 (CO), 3399 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 2.27 (s, 3H, CH_3), 7.22-7.29 (m, 2H, ArH), 7.44 (d, 2H, *J*= 8.8 Hz, ArH), 7.76 (d, 2H, *J*= 8.6 Hz, ArH), 7.85-7.91 (m, 3H, ArH), 8.50-8.52 (m, 2H, ArH), 8.99 (s, 1H, NH), 9.02 (s, 1H, NH), 9.82 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 19.2, 110.6, 115.9, 117.5, 118.7, 124.2, 127.0, 127.5, 128.6, 128.8, 128.9, 131.6, 133.5, 137.8, 138.8, 139.0, 146.2, 152.9, 153.0, 157.5; mass (ES+) *m/z*= 438.2 (M^++1), 440.1 (M^++3). Anal. Calcd. for $C_{22}H_{17}Cl_2N_5O$ C, 60.29; H, 3.91; N, 15.98. Found C, 59.93; H, 3.86; N, 16.37.

***N*-[4-(4-Chloroanilino)quinazolin-6-yl]-*N*'-(3,4-dichlorophenyl)urea (27e).** 86% as a yellow solid, mp >250 °C; R_t= 22.95 min; ν_{max} (KBr) 1705 (CO), 3332 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 7.38-7.44 (m, 3H, ArH), 7.54 (d, 1H, *J*= 8.8 Hz, ArH), 7.76 (d, 1H, *J*= 8.9 Hz, ArH), 7.83-7.89 (m, 3H, ArH), 7.95 (d, 1H, *J*= 2.4 Hz, ArH), 8.51 (s, 2H, ArH), 9.11 (s, 1H, NH), 9.22 (s, 1H, NH), 9.83 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 109.4, 114.3, 117.2, 118.2, 122.1, 122.5, 125.4, 125.7, 126.9, 127.2, 129.3, 129.8, 135.9, 137.1, 138.5, 144.7, 151.1, 151.4, 155.8; mass (ES+) *m/z*= 458.2 (M^++1), 460.2 (M^++3). Anal. Calcd. for $C_{21}H_{14}Cl_3N_5O$ C, 54.98; H, 3.08; N, 15.27. Found C, 54.62; H, 3.39; N, 15.53.

***N*-(4-Bromophenyl)-*N*'-[4-(4-methoxyanilino)quinazolin-6-yl]urea (28a).** 82% as a white solid, mp 237-238 °C; R_t= 24.69 min; ν_{max} (KBr) 1658 (CO), 3290 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 3.76 (s, 3H, OCH_3), 6.95 (d, 2H, *J*= 9.0 Hz, ArH), 7.44-7.51 (m, 4H, ArH), 7.64-7.72 (m, 3H, ArH), 7.85 (dd, 1H, J_1= 1.9 Hz, J_2= 9.0 Hz, ArH), 8.41-8.43 (m, 2H, ArH), 8.94 (s, 1H, NH), 9.02 (s, 1H, NH), 9.64 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 54.7, 110.1, 113.0, 113.1, 115.0, 119.8, 124.0, 125.9, 127.9, 131.1, 131.7, 136.7, 138.6, 145.3, 152.1, 152.6, 155.2, 157.0; mass (ES+) *m/z*= 464.2 (M^++1), 466.2 (M^++3). Anal. Calcd. for $C_{22}H_{18}BrN_5O_2$ C, 56.91; H, 3.91; N, 15.08. Found C, 56.65; H, 4.13; N, 15.37.

***N*-(4-Chlorophenyl)-*N*'-[4-(4-methoxyanilino)quinazolin-6-yl]urea (28b).** 69% as a white solid, mp 244-246 °C; R_t= 20.53 min; ν_{max} (KBr) 1704 (CO), 3325 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300

MHz) δ= 3.78 (s, 3H, OCH_3), 6.97 (d, 2H, *J*= 8.8 Hz, ArH), 7.35 (d, 2H, *J*= 8.7 Hz, ArH), 7.55 (d, 2H, *J*= 8.7 Hz, ArH), 7.66-7.73 (m, 3H, ArH), 7.87 (d, 1H, *J*= 8.8 Hz, ArH), 8.43 (d, 2H, *J*= 1.4 Hz, ArH), 8.94 (s, 1H, NH), 9.03 (s, 1H, NH), 9.63 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 55.6, 110.9, 114.0, 115.9, 120.2, 124.8, 125.8, 126.7, 128.6, 129.0, 132.6, 137.7, 139.1, 146.1, 153.0, 153.3, 156.1, 157.8; mass (ES+) *m/z*= 420.2 (M^++1), 422.1 (M^++3). Anal. Calcd. for $C_{22}H_{18}ClN_5O_2$ C, 62.93; H, 4.32; N, 16.68. Found C, 63.20; H, 4.23; N, 17.01.

***N*-(3-Cyanophenyl)-*N*'-[4-(4-methoxyanilino)quinazolin-6-yl]urea (28c).** 73% as a light yellow solid, mp 215-216 °C; R_t= 21.11 min; ν_{max} (KBr) 1711 (CO), 2229 (CN), 3338 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.76 (s, 3H, OCH_3), 6.96 (d, 2H, *J*= 9.0 Hz, ArH), 7.43-7.54 (m, 2H, ArH), 7.64-7.73 (m, 4H, ArH), 7.85 (dd, 1H, J_1= 1.9 Hz, J_2= 9.0 Hz, ArH), 8.04 (s, 1H, ArH), 8.42-8.46 (m, 2H, ArH), 9.07 (s, 1H, NH), 9.22 (s, 1H, NH), 9.64 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 54.7, 110.4, 111.2, 113.1, 115.0, 118.4, 120.5, 122.5, 124.0, 125.0, 126.0, 127.9, 129.8, 131.7, 136.4, 140.1, 145.4, 152.1, 152.7, 155.3, 157.0; mass (ES+) *m/z*= 411.1 (M^++1). Anal. Calcd. for $C_{23}H_{18}N_6O_2$ C, 67.31; H, 4.42; N, 20.48. Found C, 67.45; H, 4.48; N, 20.79.

***N*-(3-Chloro-4-methylphenyl)-*N*'-[4-(4-methoxyanilino)quinazolin-6-yl]urea (28d).** 85% as a yellow solid, mp >250 °C; ν_{max} (KBr) 1700 (CO), 3321 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 2.27 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.97 (d, 2H, *J*= 8.8 Hz, ArH), 7.25-7.28 (m, 2H, ArH), 7.65-7.86 (m, 5H, ArH), 8.44 (d, 2H, *J*= 9.7 Hz, ArH), 8.94 (s, 1H, NH), 8.96 (s, 1H, NH), 9.64 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 18.0, 54.4, 109.7, 112.8, 114.6, 116.2, 117.4, 123.7, 124.1, 125.5, 127.5, 127.6, 130.4, 131.4, 132.4, 136.3, 137.9, 144.9, 151.7, 152.2, 154.9; mass (ES+) *m/z*= 434.2 (M^++1), 436.1 (M^++3). Anal. Calcd. for $C_{23}H_{20}ClN_5O_2$ C, 63.67; H, 4.65; N, 16.14. Found C, 64.01; H, 4.23; N, 16.37.

***N*-(3,4-Dichlorophenyl)-*N*'-[4-(4-methoxyanilino)quinazolin-6-yl]urea (28e).** 82% as a yellow solid, mp 245-246 °C; R_t= 23.67 min; ν_{max} (KBr) 1706 (CO), 3450 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.76 (s, 3H, CH_3), 6.95 (d, 2H, *J*= 8.9 Hz, ArH), 7.36 (dd, 1H, J_1= 2.4 Hz, J_2= 8.8 Hz, ArH), 7.53 (d, 1H, *J*= 8.8 Hz, ArH), 7.63-7.72 (m, 3H, ArH), 7.83 (dd, 1H, J_1= 1.7 Hz, J_2= 8.9 Hz, ArH), 7.96 (d, 1H, *J*= 2.4 Hz, ArH), 8.41-8.46 (m, 2H, ArH), 9.04 (s, 1H, NH), 9.19 (s, 1H, NH), 9.64 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 54.4, 110.1, 112.8, 114.7, 117.6, 118.6, 122.5, 123.7, 125.6, 127.5, 129.8, 130.3, 131.4, 136.1, 139.1, 145.1, 151.7, 152.3, 154.9, 156.7; mass (ES+) *m/z*= 454.2 (M^++1), 456.1 (M^++3). Anal. Calcd. for $C_{22}H_{17}Cl_2N_5O_2$ C, 58.16; H, 3.77; N, 15.42. Found C, 58.32; H, 3.71; N, 15.19.

***N*-(3-Acetylphenyl)-*N*'-[4-(4-methoxyanilino)quinazolin-6-yl]urea (28h).** 85% as a yellow solid, mp 221-223 °C; R_t= 24.96 min; ν_{max} (KBr) 1685 (CO), 3345 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 2.57 (s, 3H, $COCH_3$), 3.76 (s, 3H, OCH_3), 6.95 (d, 2H, *J*= 8.9 Hz, ArH), 7.45 (t, 1H, *J*= 7.9 Hz, ArH), 7.59-7.73 (m, 5H, ArH), 7.86 (dd, 1H, J_1= 1.6 Hz, J_2= 8.9 Hz, ArH), 8.14 (s, 1H, ArH), 8.41-8.46 (m, 2H, ArH), 8.95 (s, 1H, NH), 9.12 (s, 1H, NH), 9.66 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 26.3, 54.7, 110.1, 113.1, 115.0, 116.9, 121.7, 122.4, 124.0, 125.9, 127.8, 128.7, 131.7, 136.7, 136.9, 137.0, 145.2, 152.2, 152.5, 155.3, 157.0, 197.3, mass (ES+) *m/z*= 428.2 (M^++1). Anal. Calcd. for $C_{24}H_{21}N_5O_3$ C, 67.44; H, 4.95; N, 16.38. Found C, 67.57; H, 5.05; N, 16.25.

***N*-(4-Acetylphenyl)-*N*'-[4-(4-methoxyanilino)quinazolin-6-yl]urea (28i).** 81% as a light yellow solid, mp 233-235 °C; R_t= 24.48 min; ν_{max} (KBr) 1678 (CO), 3297 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 2.52 (s, 3H, $COCH_3$), 3.76 (s, 3H, OCH_3), 6.94-6.97 (d, 2H, *J*= 7.0 Hz, ArH), 7.62-7.74 (m, 5H, ArH), 7.84-7.94 (m, 3H, ArH), 8.42-8.46 (m, 2H, ArH), 9.04 (s, 1H, NH), 9.31 (s, 1H, NH), 9.67 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 25.9, 54.7, 110.3, 113.1, 115.0, 116.8, 124.0, 125.9, 127.9, 129.2, 130.1, 131.7, 136.4, 143.8, 145.4, 151.8, 152.6, 155.3, 157.0, 195.9; mass (ES+) *m/z*= 428.2 (M^++1). Anal. Calcd. for $C_{24}H_{21}N_5O_3$ C, 67.44; H, 4.95; N, 16.38. Found C, 67.57; H, 5.05; N, 16.25.

***N*-(4-Bromophenyl)-*N*'-[4-(4-toluidino)quinazolin-6-yl]urea (29a).** 85% as a white solid, mp >250 °C; R_t= 20.48 min; ν_{max} (KBr) 1655 (CO), 3304 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 2.31 (s, 3H, CH_3), 7.19 (d, 2H, *J*= 8.3 Hz, ArH), 7.46-7.52 (m, 4H, ArH), 7.67-7.75 (m, 3H, ArH), 7.87 (dd, 1H, J_1= 2.0 Hz, J_2= 9.0 Hz, ArH), 8.46 (s, 2H, ArH), 8.99 (s, 1H, NH), 9.07 (s, 1H, NH), 9.70 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 19.7, 109.8, 112.6, 114.8, 119.4, 121.7, 125.6, 127.5, 128.0, 130.8; 131.7, 136.0, 136.4, 138.2, 145.0, 151.7, 152.1, 156.5; mass (ES+) *m/z*= 448.2 (M^++1), 450.2 (M^++3). Anal. Calcd. for $C_{22}H_{18}BrN_5O$ C, 58.94; H, 4.05; N, 15.62. Found C, 58.82; H, 4.21; N, 15.68.

***N*-(4-Chlorophenyl)-*N*'-[4-(4-toluidino)quinazolin-6-yl]urea (29b).** 69% as a light yellow solid, mp >250 °C; R_t= 20.41 min; ν_{max} (KBr) 1655 (CO), 3295 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 2.31 (s, 3H, CH_3), 7.19 (d, 2H, *J*= 7.9 Hz, ArH), 7.35 (d, 2H, *J*= 8.5 Hz, ArH), 7.55 (d, 2H, *J*= 8.6 Hz, ArH), 7.68-7.75 (m, 3H, ArH), 7.88 (d, 1H, *J*= 8.7 Hz, ArH), 8.46 (s, 2H, ArH), 8.94 (s, 1H, NH), 9.02 (s, 1H, NH), 9.65 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 20.9, 111.0, 116.0, 120.2, 122.9, 126.0, 126.8, 128.7, 129.0, 129.2, 132.9, 137.2, 137.6, 139.0, 146.2, 152.9, 153.3, 157.7; mass (ES+) *m/z*= 404.2 (M^++1), 406.1 (M^++3). Anal. Calcd. for $C_{22}H_{18}ClN_5O$ C, 65.43; H, 4.49; N, 17.34. Found C, 65.07; H, 4.72; N, 17.42.

***N*-(3-Cyanophenyl)-*N*'-[4-(4-toluidino)quinazolin-6-yl]urea (29c).** 83% as a light green solid, mp 233-235 °C; R_t= 17.97 min; ν_{max} (KBr) 1703 (CO), 2232 (CN), 3352 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 2.31 (s, 3H, CH_3), 7.19 (d, 2H, *J*= 8.3 Hz, ArH), 7.44-7.55 (m, 2H, ArH), 7.67-7.76 (m, 4H, ArH), 7.87 (dd, 1H, J_1= 2.1 Hz, J_2= 9.0 Hz, ArH), 8.06 (s, 1H, ArH), 8.47-8.49 (m, 2H, ArH), 9.12 (s, 1H, NH), 9.26 (s, 1H, NH), 9.70 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 19.7, 110.1,

110.8, 114.7, 118.0, 120.1, 121.8, 122.2, 124.7, 125.7, 127.5, 128.0, 129.4, 131.8, 135.9, 136.2, 139.7, 145.1, 151.7, 152.2, 156.5; mass (ES+) *m/z*= 395.1 (M^++1). Anal. Calcd. for $C_{23}H_{18}N_6O$ C, 70.04; H, 4.60; N, 21.31. Found C, 70.21; H, 4.69; N, 21.18.

***N*-(3-Chloro-4-methylphenyl)-*N*'-[4-(4-toluidino)quinazolin-6-yl]urea (29d).** 94% as an off white solid, mp >250 °C; R_t= 19.98 min; ν_{max} (KBr) 1705 (CO), 3332 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ= 2.31 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 7.21-7.33 (m, 4H, ArH), 7.70-7.91 (m, 5H, ArH), 8.49 (s, 2H, ArH), 9.01 (s, 2H, NH), 9.71 (s, 1H, NH); mass (FAB+) *m/z*= 418 (M^++1). Anal. Calcd. for $C_{23}H_{20}ClN_5O$ C, 66.10; H, 4.82; N, 16.76. Found C, 66.36; H, 5.03; N, 16.95.

***N*-(3,4-Dichlorophenyl)-*N*'-[4-(4-toluidino)quinazolin-6-yl]urea (29e).** 74% as a light green solid, mp >250 °C; R_t= 20.89 min; ν_{max} (KBr) 1707 (CO), 3349 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 2.31 (s, 3H, CH_3), 7.19 (d, 2H, *J*= 8.2 Hz, ArH), 7.38 (dd, 1H, J_1= 2.3 Hz, J_2= 8.8 Hz, ArH), 7.55 (d, 1H, *J*= 8.8 Hz, ArH), 7.67-7.75 (m, 3H, ArH), 7.85 (dd, 1H, J_1= 1.7 Hz, J_2= 9.0 Hz, ArH), 7.97 (d, 1H, *J*= 2.2 Hz, ArH), 8.48 (d, 2H, *J*= 8.1 Hz, ArH), 9.09 (s, 1H, NH), 9.23 (s, 1H, NH), 9.69 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 19.7, 110.1, 114.7, 117.6, 118.6, 121.8, 122.5, 125.7, 127.6, 128.0, 129.8, 130.3; 131.8, 135.9, 136.1, 139.0, 145.2, 151.6, 152.2, 156.5; mass (ES+) *m/z*= 438.2 (M^++1), 440.1 (M^++3). Anal. Calcd. for $C_{22}H_{17}Cl_2N_5O$ C, 60.29; H, 3.91; N, 15.98. Found C, 60.32; H, 4.01; N, 16.03.

***N*-(3-Acetylphenyl)-*N*'-[4-(4-toluidino)quinazolin-6-yl]urea (29h).** 78% as an off white solid, mp 235-237 °C; R_t= 20.84 min; ν_{max} (KBr) 1685 (CO), 3275 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 2.30 (s, 3H, CH_3), 2.56 (s, 3H, $COCH_3$), 7.18 (d, 2H, *J*= 8.2 Hz, ArH), 7.45 (t, 1H, *J*= 7.8 Hz, ArH), 7.59-7.74 (m, 5H, ArH), 7.87 (dd, 1H, J_1= 1.7 Hz, J_2= 8.9 Hz, ArH), 8.14 (s, 1H, ArH), 8.45-8.48 (m, 2H, ArH), 8.98 (s, 1H, NH), 9.13 (s, 1H, NH), 9.70 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 20.1, 26.3, 110.2, 115.1, 117.0, 121.8, 122.2, 122.5, 126.0, 127.8, 128.4, 128.8, 132.2, 136.3, 136.8, 137.0, 139.6, 145.2, 152.2, 152.4, 156.9, 197.4; mass (ES+) *m/z*= 412.2 (M^++1). Anal. Calcd. for $C_{24}H_{21}N_5O_2$ C, 70.06; H, 5.14; N, 17.02. Found C, 69.85; H, 5.33; N, 17.24.

***N*-(4-Acetylphenyl)-*N*'-[4-(4-toluidino)quinazolin-6-yl]urea (29i).** 75% as a white solid, mp >250 °C; R_t= 21.45 min; ν_{max} (KBr) 1679 (CO), 3329 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 2.30 (s, 3H, CH_3), 2.52 (s, 3H, $COCH_3$), 7.18 (d, 2H, *J*= 8.3 Hz, ArH), 7.62-7.75 (m, 5H, ArH), 7.86-7.94 (m, 3H, ArH), 8.46-8.48 (m, 2H, ArH), 9.06 (s, 1H, NH), 9.32 (s, 1H, NH), 9.71 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 20.1, 25.9, 110.4, 115.1, 116.8, 122.1, 126.0, 127.9, 128.4, 129.2, 130.1, 132.2, 136.3, 136.5, 143.7, 145.4, 151.8, 152.5, 156.9, 195.8; mass (ES+) *m/z*= 412.2 (M^++1). Anal. Calcd. for $C_{24}H_{21}N_5O_2$ C, 70.06; H, 5.14; N, 17.02. Found C, 69.93; H, 5.02; N, 17.31.

***N*-(4-Bromophenyl)-*N*'-[4-(3,4-dimethoxyanilino)quinazolin-6-yl]urea (30a).** 79% as a yellow solid, mp 246-248 °C; ν_{max} (KBr) 1705 (CO), 3317 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.96 (d, 1H, *J*= 8.7 Hz, ArH), 7.36-7.47 (m, 6H, ArH), 7.71 (d, 1H, *J*= 8.9 Hz, ArH), 7.84 (d, 1H, *J*= 8.8 Hz, ArH), 8.44 (s, 2H, ArH), 8.93 (s, 1H, NH), 9.01 (s, 1H, NH), 9.58 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 55.9, 56.1, 108.3, 111.0, 112.1, 112.1, 113.8, 115.3, 115.9, 120.7, 126.8, 128.7, 131.9, 133.1, 137.5, 139.4, 145.7, 146.2, 148.8, 152.9, 153.4, 157.8; mass (ES+) *m/z*= 494.2 (M^++1), 496.1 (M^++3). Anal. Calcd. for $C_{23}H_{20}BrN_5O_3$ C, 55.88; H, 4.08; N, 14.17. Found C, 55.61; H, 3.86; N, 14.15.

***N*-(4-Chlorophenyl)-*N*'-[4-(3,4-dimethoxyanilino)quinazolin-6-yl]urea (30b).** 76% as a yellow solid, mp 233-235 °C; ν_{max} (KBr) 1705 (CO), 3338 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 3.78 (s, 6H, 2 x OCH_3), 6.97 (d, 1H, *J*= 8.5 Hz, ArH), 7.34-7.45 (m, 4H, ArH), 7.55 (d, 2H, *J*= 8.4 Hz, ArH), 7.72 (d, 1H, *J*= 8.8 Hz, ArH), 7.86 (d, 1H, *J*= 8.7 Hz, ArH), 8.45 (s, 2H, ArH), 8.96 (s, 1H, NH), 9.04 (s, 1H, NH), 9.60 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 55.9, 56.1, 108.3, 111.0, 112.2, 115.3, 115.9, 120.2, 125.9, 126.7, 128.7, 129.0, 133.1, 137.6, 140.0, 145.7, 146.2, 148.8, 153.0, 153.4, 157.7; mass (ES+) *m/z*= 450.2 (M^++1), 452.2 (M^++3). Anal. Calcd. for $C_{23}H_{20}ClN_5O_3$ C, 61.40; H, 4.48; N, 15.57. Found C, 61.17; H, 4.63; N, 15.31.

***N*-(3-Cyanophenyl)-*N*'-[4-(3,4-dimethoxyanilino)quinazolin-6-yl]urea (30c).** 77% as a brown solid, mp 185-187 °C; ν_{max} (KBr) 1707 (CO), 2233 (CN), 3323 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 3.76 (s, 6H, 2 x OCH_3), 6.96 (d, 1H, *J*= 8.5 Hz, ArH), 7.35-7.51 (m, 4H, ArH), 7.72 (d, 2H, *J*= 8.5 Hz, ArH), 7.83 (d, 1H, *J*= 8.0 Hz, ArH), 8.04 (s, 1H, ArH), 8.44 (s, 1H, ArH), 8.46 (s, 1H, ArH), 9.12 (s, 1H, NH), 9.26 (s, 1H, NH), 9.59 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 55.9, 56.1, 108.3, 111.3, 112.0, 112.2, 115.3, 115.9, 119.2, 121.3, 123.4, 125.8, 126.9, 128.7, 130.6, 133.0, 137.3, 140.9, 145.7, 146.3, 148.8, 153.0, 153.4, 157.8; mass (ES+) *m/z*= 441.2 (M^++1). Anal. Calcd. for $C_{24}H_{20}N_6O_3$ C, 65.45; H, 4.58; N, 19.08. Found C, 65.21; H, 4.39; N, 18.84.

***N*-(3-Chloro-4-methylphenyl)-*N*'-[4-(3,4-dimethoxyanilino)quinazolin-6-yl]urea (30d).** 70% as a yellow solid, mp 235-236 °C; ν_{max} (KBr) 1705 (CO), 3319 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 2.27 (s, 3H, CH_3), 3.77 (s, 6H, 2 x OCH_3), 6.97 (d, 1H, *J*= 8.6 Hz, ArH), 7.25 (s, 2H, ArH), 7.37-7.42 (m, 2H, ArH), 7.71-7.85 (m, 3H, ArH), 8.45 (d, 1H, *J*= 4.1 Hz, ArH), 9.03 (s, 2H, 2 x NH), 9.60 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 19.2, 55.9, 56.1, 108.3, 110.9, 112.1, 115.3, 115.9, 117.4, 118.7, 126.7, 128.7, 128.8, 131.6, 133.1, 133.5, 137.6, 139.2, 145.7, 146.1, 148.8, 153.0, 153.3, 157.8; mass (ES+) *m/z*= 464.2 (M^++1), 466.1 (M^++3). Anal. Calcd. for $C_{24}H_{22}ClN_5O_3$ C, 62.14; H, 4.78; N, 15.10. Found C, 62.21; H, 4.67; N, 14.98.

***N*-(3,4-Dichlorophenyl)-*N*'-[4-(3,4-dimethoxyanilino)quinazolin-6-yl]urea (30e).** 77% as a yellow solid, mp >250 °C; ν_{max} (KBr) 1707 (CO), 3365 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 3.78 (s, 6H, 2 x OCH_3), 6.97 (d, 1H, *J*= 8.7 Hz, ArH), 7.37-7.43 (m, 3H, ArH), 7.55 (d, 1H, *J*= 8.8 Hz, ArH), 7.73 (d, 1H, *J*= 8.9 Hz, ArH), 7.83 (d, 1H, *J*= 8.8 Hz, ArH), 7.97 (d, 1H, *J*= 1.8 Hz, ArH), 8.47 (d, 1H, *J*= 5.8 Hz, ArH), 9.06 (s, 1H, NH), 9.20 (s, 1H, NH), 9.59 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 55.9, 56.1, 108.3, 111.3, 112.1, 115.3, 115.9, 118.8, 119.8, 123.7, 126.9, 128.7, 131.0, 131.5, 133.0, 137.3, 140.2, 145.7, 146.3, 148.8, 152.8, 153.5, 157.8; mass (ES+) *m/z*= 484.2 (M^++1), 486.1 (M^++3). Anal. Calcd. for $C_{23}H_{19}Cl_2N_5O_3$ C, 57.04; H, 3.95; N, 14.46. Found C, 56.79; H, 3.65; N, 14.17.

***N*-(3,5-Dichlorophenyl)-*N*'-[4-(3,4-dimethoxyanilino)quinazolin-6-yl]urea (30f).** 73% as a white solid, mp 250-251 °C; ν_{max} (KBr) 1716 (CO), 3312 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 3.78 (s, 6H, 2 x OCH_3), 6.97 (d, 1H, *J*= 8.7 Hz, ArH), 7.19 (s, 1H, NH), 7.37-7.43 (m, 2H, ArH), 7.54 (d, 1H, *J*= 1.3 Hz, ArH), 7.61 (d, 2H, *J*= 1.0 Hz, ArH), 7.73 (d, 1H, *J*= 8.9 Hz, ArH), 7.82 (d, 1H, *J*= 8.9 Hz, ArH), 8.46 (s, 1H, ArH), 8.49 (s, 1H, ArH), 9.23 (brs, 2H, 2 x NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 55.9, 56.1, 108.3, 111.5, 112.1, 115.4, 115.8, 116.8, 117.1, 121.4, 126.9, 128.7, 133.0, 134.5, 137.1, 142.2, 142.6, 145.7, 146.4, 148.8, 152.8, 153.5, 157.8; mass (ES+) *m/z*= 484.2 (M^++1), 486.1 (M^++3). Anal. Calcd. for $C_{23}H_{19}Cl_2N_5O_3$ C, 57.04; H, 3.95; N, 14.46. Found C, 57.24; H, 3.91; N, 14.38.

***N*-[4-Chloro-3-(trifluoromethyl)phenyl]-*N*'-[4-(3,4-dimethoxyanilino)quinazolin-6-yl]urea (30g).** 71% as a yellow solid, mp 240-242 °C; ν_{max} (KBr) 1709 (CO), 3340 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 3.76 (s, 6H, 2 x OCH_3), 6.96 (d, 1H, *J*= 8.4 Hz, ArH), 7.34-7.41 (m, 2H, ArH), 7.61-7.73 (m, 3H, ArH), 7.81-7.84 (m, 1H, ArH), 8.18 (s, 1H, ArH), 8.46 (d, 2H, *J*= 7.4 Hz, ArH), 9.08 (s, 1H, NH), 9.36 (s, 1H, NH), 9.60 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 55.9, 56.1, 108.4, 111.5, 112.2, 115.4, 115.9, 117.3, 122.9, 123.6, 127.0, 128.8, 132.4, 133.0, 137.2, 139.7, 145.8, 146.4, 148.8, 152.9, 153.5, 157.8; mass (ES+) *m/z*= 518.2 (M^++1), 520.1 (M^++3). Anal. Calcd. for $C_{24}H_{19}ClF_3N_5O_3$ C, 55.66; H, 3.70; N, 13.52. Found C, 55.37; H, 3.78; N, 13.81.

***N*-(3-Acetylphenyl)-*N*'-[4-(3,4-dimethoxyanilino)quinazolin-6-yl]urea (30h).** 67% as a yellow solid, mp 181-183 °C; ν_{max} (KBr) 1707 (CO), 3323 (NH) cm^{-1}, ^1H NMR (DMSO-d_6, 300 MHz) δ= 2.58 (s, 3H, CH_3), 3.78 (s, 6H, 2 x OCH_3), 6.97 (d, 1H, *J*= 6.9 Hz, ArH), 7.40-7.44 (m, 3H, ArH), 7.61-7.86 (m, 4H, ArH), 8.15 (s, 1H, ArH), 8.46 (s, 2H, ArH), 8.98 (s, 1H, NH), 9.13 (s, 1H, NH), 9.62 (s, 1H, NH); mass (ES+) *m/z*= 458.2 (M^++1). Anal. Calcd. for $C_{25}H_{23}N_5O_4$ C, 65.63; H, 5.07; N, 15.31. Found C, 65.66; H, 5.38; N, 15.54.

***N*-(3-Acetylphenyl)-*N*'-[4-(3,4-dimethoxyanilino)quinazolin-6-yl]urea (30i).** 71% as a yellow solid, mp 165-167 °C; ν_{max} (KBr) 1701 (CO), 3315 (NH) cm^{-1}, ^1H NMR (DMSO-d_6, 300 MHz) δ= 2.59 (s, 3H, CH_3), 3.78 (s, 6H, 2 x OCH_3), 6.97 (d, 1H, *J*= 8.5 Hz, ArH), 7.34-7.45 (m, 4H, ArH), 7.55 (d, 2H, *J*= 8.4 Hz, ArH), 7.72 (d, 1H, *J*= 8.8 Hz, ArH), 7.86 (d, 1H, *J*= 8.7 Hz, ArH), 8.45 (s, 2H, ArH), 8.96 (s, 1H, NH), 9.04 (s, 1H, NH), 9.60 (s, 1H, NH); mass (ES+) *m/z*= 458.2 (M^++1). Anal. Calcd. for $C_{25}H_{23}N_5O_4$ C, 65.63; H, 5.07; N, 15.31. Found C, 65.66; H, 5.38; N, 15.54.

Materials and Methods

In vitro antimalarial assay

The i*n vitro* antimalarial activity of the compounds was assessed against CQ-sensitive 3D7 strain of *P. falciparum* and compared with that of chloroquine. The schizontocidal activities (MIC) as well as 50% Inhibitory concentration (IC_{50}) were obtained following techniques of Rickman's et al. and Smilkstein et al., respectively.[7-8] In brief the parasites were maintained *in vitro* in RPNI medium (Srivastava and Puri)[9] supplemented with gentamycin at 40 µg/mL; (Sigma), Fungizone at 0.25 µg/mL; (GIBCO) and 10% foetal bovine serum (pH 7.2), at 37°C in a CO_2 incubator.

The compounds were dissolved in DMSO at 5mg/ml and required dilutions were made in a template plate with RPMI medium. 20 µl from each dilution was transferred, in duplicate, in the test plate and two wells receiving 20 µl of vehicle were kept as untreated control. For evaluation of schizontocidal activity parasite culture was synchronized using 5% D-sorbitol to obtain ring stages only and 180 µl of 3% cell suspension containing 1% parasitized cells was added to each well containing test compounds.[10] The plates were incubated at 37°C in CO_2 incubator for more than 40 h. after which thin smears were prepared from each well on grease-free glass slides. These were fixed in methanol, stained with Giemsa's stain and examined under light microscope, 100x oil immersion. The minimum inhibitory concentration (MIC) of test compound was designated as the minimum concentration required producing 100% inhibition of schizont maturation.

Percent inhibition of maturation = CS -TS X 100/CS

CS- No. of schizonts in untreated culture; TS- No. of schizonts in treated culture

For evaluation of IC_{50} of the compounds, SYBR Green I-based fluorescence (MSF) assay was used. For the assays, fresh dilutions of all compounds in screening medium were prepared and 50 µl of highest starting concentration (10-500 ng/ml) was dispensed in duplicate wells in row 'B' of 96 well tissue culture plate. The highest starting concentration for chloroquine was 25ng/ml. Subsequently two fold serial dilutions were prepared up to row 'H' (seven concentrations) and finally 50 µl of 2.5% parasitized cell suspension containing 0.5% parasitaemia was added to each well except 4wells in row 'A' received non infected cell suspension. These wells containing non infected erythrocytes in the absence of compound served as negative

control, while parasitized erythrocytes in the presence of CQ served as positive control. After incubating the plates for 72 h, 100 µl of lysis buffer [20 mM Tris (pH 7.5), 5 mM EDTA, 0.008% (wt/vol) saponin, and 0.08% (vol/vol) Triton X-100] containing 1x concentration of SYBR Green-I was added to each well and incubated for one hour at room temperature. The plates were examined for the relative fluorescence units (RFUs) per well using the fluorescence plate reader (FLUOstar, BMG labtechnologies). The IC_{50} was determined using Logit regression analysis of dose-response curves.

Cytotoxicity assay

Cytotoxicity of the compounds was carried out with Vero cell line (C1008; Monkey kidney fibroblast) following the method of Mosmann with certain modifications.[11] The cells were incubated with serially diluted compounds for 72h. The highest concentration of compounds was remained to be 100µg/ml. MTT was used as reagent for the detection of cytotoxicity. 50% cytotoxic concentration (CC_{50}) values represented the concentration of compound required to kill 50% of the fibroblast cells.

Selectivity Index (SI): It was calculated as-

SI= CC_{50}/IC_{50}

In-vivo antimalarial assay

Swiss mice (25±1 g) of either sex were inoculated with $1x10^6$ *P. yoelii nigeriensis* MDR / *P. yoelii* N67 chloroquine resistant parasitized cells on day zero. A group of five mice was administered aqueous suspension of the test compounds at 50 mg/kg or 100 mg/kg dose from day zero to four *via* oral route; while another five mice were administered the vehicle alone. Thin blood smears from the tail vein of treated as well as control mice were observed on day 4, 7, 14, 21 and 28 days to record the degree of parasitaemia till 28 days or until animals survived.

Acknowledgments

Three authors (SM, AM, SKP) acknowledge the financial support from CSIR, New Delhi nad ICMR, New Delhi in the form of fellowships. This work was supported by the DST grant to ZT under WOS program.

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This is CDRI communication number **7626**.

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