

Search for new pharmacophores for antimalarial activity (Part I): Synthesis and antimalarial activity of new 2-methyl-6-ureido-4-quinolinamides

S. Madapa,^a Z. Tusi,^a D. Sridhar,^a A. Kumar,^b M.I. Siddiqi,^b K. Srivastava,^c A. Rizvi,^c R. Tripathi,^c S. K. Puri,^c G.B. Shiva Keshava,^d P. K. Shukla^d and S. Batra^{a,*}

^aMedicinal and Process Chemistry Division, Central Drug Research Institute, PO Box 173, Lucknow 226001

^bMolecular and Structural Biology Division, Central Drug Research Institute, PO Box 173, Lucknow 226001

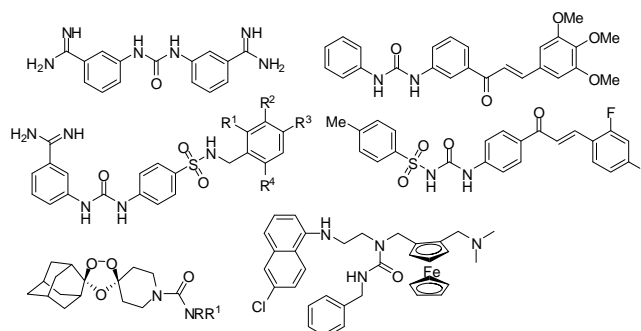
^cParasitology Division, Central Drug Research Institute, PO Box 173, Lucknow 226001

^dFermentation Division, Central Drug Research Institute, PO Box 173, Lucknow 226001

Abstract— A total of 80 new 2-methyl-6-ureido-4-quinolinamides were synthesized and evaluated for their antimalarial activity. Several analogs elicited the antimalarial effect at MIC of 0.25 mg/mL against the chloroquine-sensitive *P. falciparum* strain. The IC₅₀ values of the active compounds were observed to be in ng/mL range and two of the analogs have better IC₅₀ value than the standard chloroquine. In the in vivo assay against mdr CQ resistant *P. yoelii* N67/ *P. yoelii nigeriensis*, however, none of the compound showed complete suppression of parasitaemia on day 7. One of the compounds displayed significant antibacterial effect against several strains of bacteria and was many-fold better than the standard drug gentamicin.

Introduction

The health problem caused by malaria, one of the most lethal of the parasitic diseases, is now compounded due to the emergence of strains of *Plasmodium* which show resistance to the known chemotherapeutic agents. The artemisinin and its derivatives or their combinations have now replaced the chloroquine (CQ) and other quinoline antimalarials especially in the endemic areas. However lower abundance and high cost of artemisinin and related products motivate the medicinal chemists to search for new chemical pharmacophores which may prove effective as antimalarials. In this context Restelli et al. have earlier disclosed dihydrofolate reductase (DHFR) inhibitors belonging to several new unrelated chemical classes from the docking studies of the ACD database with the DHFR domain of DHFR-TS, a validated target of antimalarial



antifolates.¹ Amongst the several chemical classes having the potential to display the antimalarial activity disclosed in this report included the urea derivatives. Urea derivatives have been independently also well represented in the literature to elicit potent antimalarial activity.² Prototype structures of some of the ureides possessing significant *in vitro* antimalarial activity are presented in Figure 1. Although Restelli and co-workers proposed that the urea derivatives interact with the DHFR through hydrogen bonding, other workers have proposed that the urea derivatives accumulate in the food vacuole and inhibit the

Figure 1. A few urea derivatives which display antimalarial activity

* Corresponding author. Tel.: +91-522-2621411-18 Xtn. 4368; fax: +91-522-2623405; e-mail: batra_san@yahoo.co.uk

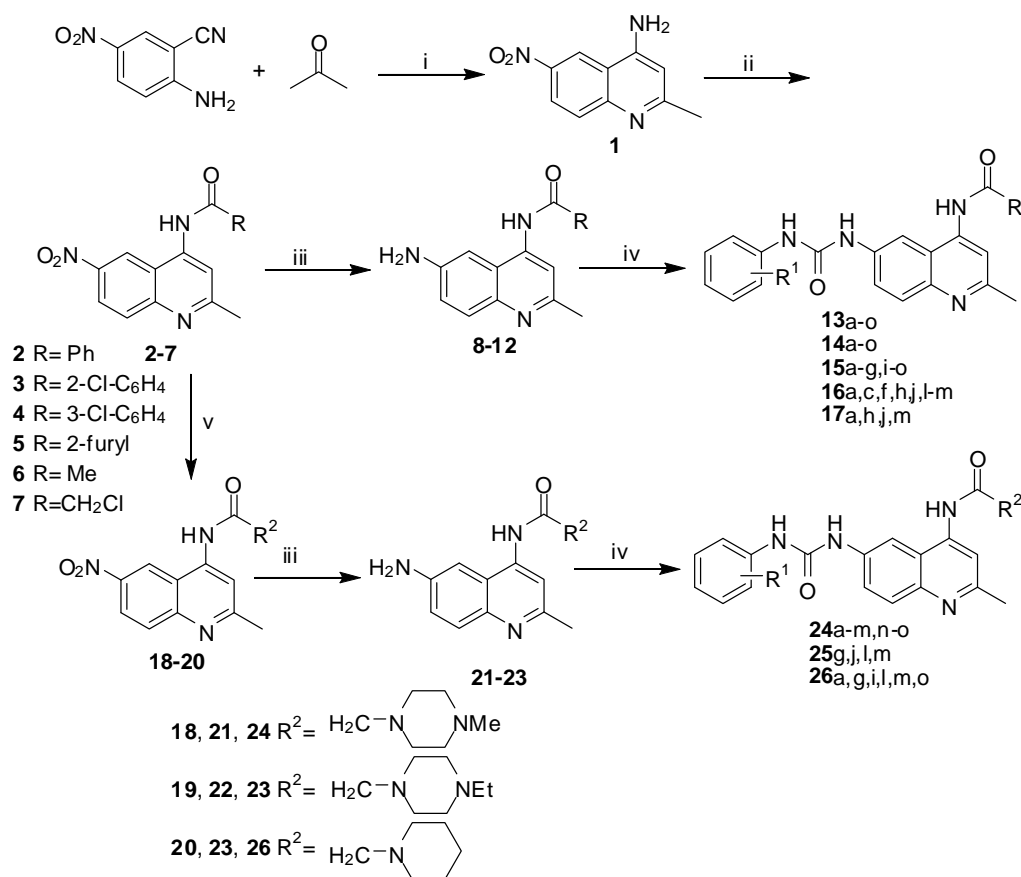
Keywords. Quinoline, Antimalarial, urea, in vitro, docking

plasmepsin of the parasite.^{2d} In our program aimed at discovery of antimalarial activity in new structural prototypes we carried out the synthesis of novel 2-methyl-6-ureido-4-quinolinamide derivatives and investigated the in vitro antimalarial efficacy of the generated compounds. Simultaneously the docking scores of these compounds with the PfDHFR were investigated. These studies resulted in discovery of several new compounds exhibiting potent in vitro antimalarial effect. Based on the literature³ precedence that aryl urea display significant antibacterial activity these compounds were also investigated for their antibacterial efficacy. Results of our study on synthesis and bioactivity of new urea derivatives are presented in this paper.

Results and Discussion

The synthesis of the 4-quinolinoacetamide and 4-quinolinobenzamide urea derivatives is outlined in scheme

1. The starting substrate 2-methyl-6-nitro-4-aminoquinoline (**1**) was prepared via a known strategy.⁴ The reaction of **1** with acetyl chloride, benzoyl chloride, substituted benzoyl chloride or chloroacetyl chloride furnished the required amides **2-7**. These amides were subjected to reduction either via hydrogenation in the presence of Pd-C for **2,5-6** to furnish **8,11-12** or in the presence of SnCl₂·2H₂O for **3-4** to yield **9-10** in good yields. The latter route was adopted to circumvent dehalogenation of the aromatic ring which generally takes place under catalytic-hydrogenation.⁵ With the required amines in hand two well known strategies were employed to obtain the urea derivatives **13-14a-o**, **15a-g,i-o**, **16a,c,f,h,j,l-o** and **17a,h,j,m**. The first route involved the reaction of amine with a commercially available isocyanate in acetonitrile whereas the second one involved the activation of an amine with p-nitrobenzylchloroformate and its treatment with the 6-amino-2-methyl-4-quinolinamide to afford the final compound in moderate to excellent yields. With the objective to introduce diversity at the 4-position compound



Scheme 1. Reagents and conditions. i) SnCl₄, toluene, reflux, 4 h. ii) RCOCl, Et₃N, DMAP, CH₂Cl₂, rt, 8-10 h. iii) Pd-C (10%), MeOH, rt, 1 h or SnCl₂, MeOH, reflux, 1 h. iv) R¹-C₆H₄-NCO, MeCN, rt, 2 min to 10 h. v) N-methyl piperazine or N-ethyl piperazine or piperidine, DMF, rt, 2-3 h.

7 was further treated with substituted piperazines and piperidine to furnish products **18-20**. Reduction of the nitro-group in **18-20** yielded the respective amino derivatives **21-23**. These amines were utilized to synthesize

the urea derivatives **24a-m,n-o**, **25g,j,l,m**, **26a,g,i,l,m,o** using the above mentioned procedures.

In-vitro Antimalarial activity

The results of the in vitro antimalarial assay of 80 analogs against 3D7 chloroquine-sensitive *P. falciparum* strain are shown in Table 1. As noted above the present study evolved as a consequence of the literature precedence that urea pharmacophore show hydrogen bonding with the aspartic acid 154 of the *Pf*/DHFR. The quinoline as the basic core was selected due to its presence in several compounds being used as antimalarial in clinics. The MICs ($\mu\text{g/mL}$) for all compounds were initially recorded and the analogs displaying an MIC of 0.5 $\mu\text{g/mL}$ or less were subjected to IC_{50} evaluation and cytotoxicity assay. Index of selectivity (SI) indicates comparative safety of compounds against the parasites. Finally several analogs were randomly selected for the in vivo evaluation against *mdr P. yoellii nigeriensis* or CQ-resistant *P. yoellii*. The MIC and IC_{50} of CQ that was used as standard in the bioassay were recorded as 15.0 ng/mL and 2.0 ng/mL , respectively. Notably, compounds **8-12** and **21-23** had MIC value of more than 50 ($\mu\text{g/mL}$) reflecting that the activity of these compounds is essentially due to the presence of urea unit. Broadly the urea derivatives described herein can be divided in two broad structural variant. The first being the 2-methyl-6-ureido-4-quinolinobenzamide derivatives (**13-16**) while the later being the 2-methyl-6-ureido-4-quinolinoacetamide derivatives (**17,24-26**). For compounds belonging to benzamide group it was observed that analogs (**13a-o**) bearing unsubstituted phenyl carbamoyl moiety at 4-position did not elicit good biological response. Only two compounds **13l** and **13o** carrying 3,4- Cl_2 and 4-Cl-3- CF_3 substitutions, respectively were found to show activity at 1.0 $\mu\text{g/mL}$ although **13l** had IC_{50} of 10.94 ng/mL as compared to 19.38 ng/mL for **13o**. The other two analogs to show modest effect included **13j** and **13m** with MIC value of 2.0 $\mu\text{g/mL}$. Analysis of the activity pattern of compounds within this group revealed that except for **13k** and **13n**, compounds having disubstitution on the phenyl ring of the aryl urea subunit displayed better antimalarial effect in comparison to compounds containing monosubstituted phenyl ring.

The introduction of a chloro-group at 2-position of the phenyl ring of the benzamide subunit resulting in **14** significantly improves upon the antimalarial effect. Out of **14a-o** except for **14b,14k** and **14n** all compounds displayed potent bioactivity with MIC of 2.0 $\mu\text{g/mL}$ or below. On the basis of MIC compound **14d** with a value of 0.5 $\mu\text{g/mL}$ displayed most significant activity. However calculation of the IC_{50} s of all compounds showing MIC of 1.0 $\mu\text{g/mL}$ delineated that **14m** containing 3,5- Cl_2 as the substitution on the phenyl ring of the urea unit was more potent with a value of 21.0 ng/mL . Compound **14f** bearing nitrile-group at 3-position was slightly less active with IC_{50} of 28.1 ng/mL whereas **14o** had a value of 35.6 ng/mL . However SI of **14f** was four fold better as compared to **14m**. Unfortunately **14d** which had better MIC seems to be less

potent on the basis of the IC_{50} with a value of 219.6 ng/mL . Even the SI of this compound was found to be low indicating it to be less safe as compared to **14f,m** or **o**.

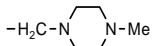
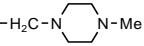
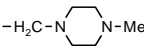
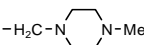
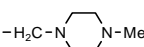
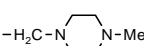
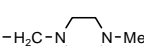
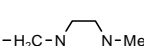
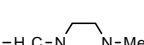
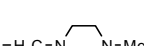
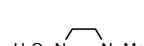
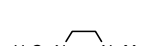
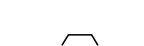
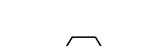
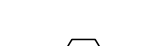

Next modifying the point of substitution of the chloro group in the phenyl ring of the benzamide subunit from 2 to 3-position in the next group of compounds (**15**) seems to have altering effect on the bioactivity. Although no clear pattern emerged, it was observed that compounds comprising of chloro-substitution on the phenyl ring of the urea unit display better activity. Compounds **15a,15k** and **15n** having 4-Cl, 3-Cl-4-Me and 3-Cl-4-F group, respectively had MIC of 1.0 $\mu\text{g/mL}$. Compound **15g** having 3- CF_3 too was found to have MIC of 1.0 $\mu\text{g/mL}$. However on the basis of IC_{50} value of these compounds, **15g** with a value of 9.9 ng/mL followed by **15a** with a value of 14.4 ng/mL were best amongst this series. The high SI of **15g** indicated it to be safe too.

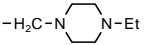
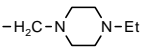
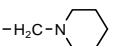
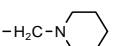
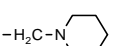
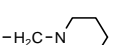
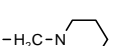
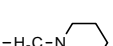
In subsequent set of compounds (**16**) the phenyl group of the benzamide moiety was replaced with a furyl ring. Interestingly for this prototype structure a set of only eight compounds were prepared incorporating only those substitutions in the phenyl ring of the urea group which have shown good activity for **13-15**. Out of these compounds, **16l** could not be evaluated as it was found to be insoluble while all other analogs displayed promising activity except for **16h**. On the basis of the MIC **16a,16f** and **16j** containing 4-Cl, 3-CN and 3-Cl-4-Me, respectively on the phenyl ring of urea subunit were observed to be equipotent with a value of 0.5 $\mu\text{g/mL}$ whereas **16o** with 4-Cl-3- CF_3 had MIC of 0.25 $\mu\text{g/mL}$. Examination of IC_{50} however resulted in a lower value for **16f** (0.4 ng/mL) than **16o** (9.9 ng/mL) or **16a** (13.9 ng/mL) or **16j** (134.6 ng/mL). Hence on the basis of these results it was evident that compound **16f** was five fold more potent as compared to the standard CQ used in the assay. The high SI value indicated that compounds belonging to this prototype would be less toxic.

In the next phase of the study the urea derivatives comprising of acetamide or substituted acetamide group at 4-position of the quinoline ring were investigated. The examination of four analogs (**17a,h,j,k**) comprising of unsubstituted acetamide group did not show any promising activity therefore no more compounds belonging to the prototype were pursued. As indicated in the preceding text the synthesis of substituted acetamide urea derivative was accomplished by introducing the chloroacetyl group and then replacing the chloro group with secondary amines including substituted piperazines and piperidine. This exercise ensued from the fact that several piperazine derivatives have been reported to display significant antimalarial effect.⁶ In the first set of compounds N-methylpiperazine was introduced to prepare **24a-o**. It was pleasing to note that except for compounds **24e** and **24k** all

Table 1. Results of in vitro and in vivo antimalarial assays of compounds

Com pd. No	R (13-17) / R ² (24-26)	R ¹	MIC (µg/mL)	IC ₅₀ (ng/mL)	Selectivity Index (SI)	<i>In vivo</i> (% Mean Parasitaemia± S.D. on day 4)	<i>In vivo</i> (% Mean Parasitaemia± S.D. on day 7)
13a	Ph	4-Cl	>50	-	-	-	-
13b	Ph	4-F	10	-	-	-	-
13c	Ph	4-Br	10	-	-	-	-
13d	Ph	3-Cl	50	-	-	-	-
13e	Ph	3-F	10	-	-	-	-
13f	Ph	3-CN	10	-	-	-	-
13g	Ph	3-CF ₃	10	-	-	-	-
13h	Ph	4-COMe	50	-	-	-	-
13i	Ph	3-COMe	10	-	-	-	-
13j	Ph	3-Cl-4-Me	2	-	-	-	-
13k	Ph	3-Cl-2-Me	50	-	-	-	-
13l	Ph	3,4-Cl ₂	1	10.9	-	-	-
13m	Ph	3,5-Cl ₂	2	-	-	-	-
13n	Ph	3-Cl-4-F	10	-	-	-	-
13o	Ph	4-Cl-3-CF ₃	1	19.4	-	-	-
14a	2-Cl-C ₆ H ₄	4-Cl	2	-	-	-	-
14b	2-Cl-C ₆ H ₄	4-F	50	-	-	-	-
14c	2-Cl-C ₆ H ₄	4-Br	2	-	-	1.90±0.55†	8.80±3.26
14d	2-Cl-C ₆ H ₄	3-Cl	0.5	219.6	32.1	4.23±3.31†	9.77±2.64
14e	2-Cl-C ₆ H ₄	3-F	2	-	-	-	-
14f	2-Cl-C ₆ H ₄	3-CN	1	28.4	2401.9	6.05±3.05†	12.11±9.35
14g	2-Cl-C ₆ H ₄	3-CF ₃	2	-	-	-	-
14h	2-Cl-C ₆ H ₄	4-COMe	2	-	-	3.03±0.67†	5.98±1.08
14i	2-Cl-C ₆ H ₄	3-COMe	2	-	-	-	-
14j	2-Cl-C ₆ H ₄	3-Cl-4-Me	1	44.5	205.1	2.15±0.47†	5.08±0.40
14k	2-Cl-C ₆ H ₄	3-Cl-2-Me	10	-	-	-	-
14l	2-Cl-C ₆ H ₄	3,4-Cl ₂	1	194.4	16.8	-	-
14m	2-Cl-C ₆ H ₄	3,5-Cl ₂	2	21.7	505.0	-	-
14n	2-Cl-C ₆ H ₄	3-Cl-4-F	10	-	-	57.6	-
14o	2-Cl-C ₆ H ₄	4-Cl-3-CF ₃	-	35.6	270.9	-	-
15a	3-Cl-C ₆ H ₄	4-Cl	1	14.4	-	-	-
15b	3-Cl-C ₆ H ₄	4-F	10	-	-	-	-
15c	3-Cl-C ₆ H ₄	4-Br	2	-	-	-	-
15d	3-Cl-C ₆ H ₄	3-Cl	50	-	-	-	-
15e	3-Cl-C ₆ H ₄	3-F	>50	-	-	-	-
15f	3-Cl-C ₆ H ₄	3-CN	1	-	-	-	-
15g	3-Cl-C ₆ H ₄	3-CF ₃	2	9.9	6014.2	-	-
15i	3-Cl-C ₆ H ₄	3-COMe	10	-	-	-	-
15j	3-Cl-C ₆ H ₄	3,5-Cl ₂	10	-	-	-	-
15k	3-Cl-C ₆ H ₄	3-Cl-4-Me	1	34.0	184.5	-	-
15l	3-Cl-C ₆ H ₄	3-Cl-2-Me	10	-	-	-	-
15m	3-Cl-C ₆ H ₄	3,4-Cl ₂	2	218.1	187.7	-	-
15n	3-Cl-C ₆ H ₄	3-Cl-4-F	0.5	68.2	125.6	3.76±2.85†	15.5±7.98

15o	3-Cl-C ₆ H ₄	4-Cl-3-CF ₃	>10	-	-	-	-
16a	2-furyl	4-Cl	0.5	13.9	3909.5	2.95±2.02†	13.2±11.7
16c	2-furyl	4-Br	1	57.1	1547.0	-	-
16f	2-furyl	3-CN	0.5	0.4	-	0.0±0.0*	1.84±3.67
16h	2-furyl	4-COMe	10	-	-	-	-
16j	2-furyl	3-Cl-4-Me	0.5	134.6	524.7	0.61±1.29†	21.1±7.75
16l	2-furyl	3,4-Cl ₂	insoluble	-	-	-	-
16m	2-furyl	3,5-Cl ₂	2	-	-	-	-
16o	2-furyl	4-Cl-3-CF ₃	-	9.9	713.3	-	-
17a	Me	4-Cl	10	-	-	-	-
17h	Me	4-COMe	10	-	-	-	-
17j	Me	3,5-Cl ₂	50	-	-	-	-
17m	Me	3-Cl-4-Me	2	-	-	-	-
24a		4-Cl	0.5	5.0	-	-	-
24b		4-F	2	-	-	-	-
24c		4-Br	1	-	-	-	-
24d		3-Cl	0.25	13.0	549.7	18.8±6.53*	50.0±0.0
24e		3-F	10	-	-	-	-
24f		3-CN	2	-	-	-	-
24g		3-CF ₃	0.25	0.8	2594.9	2.5±1.94†	21.9±10.9
24h		4-COMe	1	14.0	-	-	-
24i		3-COMe	0.5	146.3	524.5	-	-
24j		3-Cl-4-Me	0.25	3.3	-	1.67±1.76†	5.15±1.19
24k		3-Cl-2-Me	>10	-	-	-	-
24l		3,4-Cl ₂	0.25	2.2	-	2.55±1.53†	1.50±1.47
24m		3,5-Cl ₂	0.25	0.4	4404.8	4.78±2.30†	15.5±2.87
24o		4-Cl-3-CF ₃	0.5	18.2	53.4	2.28±2.02†	11.0±6.21
25g		3-CF ₃	0.5	28.0	-	-	-
25j		3-Cl-4-Me	0.5	3.5	-	-	-

25l		3,4-Cl ₂	2	-	-	-	-
25m		3,5-Cl ₂	2	-	-	-	-
26a		4-Cl	0.5	23.0	64.9	-	-
26g		3-CF ₃	0.25	33.5	214.3	-	-
26i		3-Cl-4-Me	10	365.1	214.4	-	-
26l		3,4-Cl ₂	0.25	75.8	524.2	-	-
26m		3,5-Cl ₂	0.5	28.8	396.9	-	-
26o		4-Cl-3-CF ₃	0.25	35.8	76.5	0.27±0.47*	13.83±19.2
CQ			0.015	2.0			

*Results at 100mg/kg x 4 days treatment against *P.yoelii nigeriensis* MDR parasites in swiss mice.

† Results at 50mg/kg x 4 days treatment against *P.yoelii* CQ-resistant parasites in swiss mice.

compounds had MIC of 2.0 µg/mL or less. The IC₅₀ evaluation of compounds revealed **24g** (0.79 ng/mL) and **24m** (0.42 ng/mL) to be even more potent than CQ (2.0 ng/mL) whereas **24l** (2.19 ng/mL) displayed almost similar antimalarial effect to that of CQ. Even compounds **24d** and **24h** were significantly potent with IC₅₀ of 13.0 ng/mL and 14.0 ng/mL whereas **24o** had IC₅₀ value of 18.2 ng/mL. The SI values for **24g** and **m** revealed them to be non-toxic.

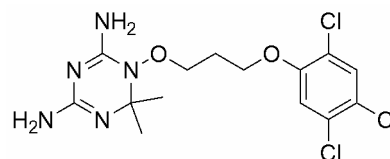
Replacing the methyl with ethyl as in compounds **25g,j,l,m** however, lowered the activity. Compared to the methyl analogs the corresponding ethyl analogs were twice less active. The IC₅₀s of two compounds **25l** (3,4-Cl₂) and **25m** (3,5-Cl₂) having MIC of 0.5 µg/mL were observed to be 28.0 ng/mL and 3.5 ng/mL, respectively.

In the last group of compounds (**26a,g,i,l,m,o**) the piperazine group was replaced by piperidine unit. Although only 6 compounds were synthesized and evaluated in this group, except **26i**, all compounds show promising activity with MIC of 0.5 µg/mL or less. This led to the IC₅₀ evaluation of all compounds from the group and based on it **26a**, bearing chloro at 4-position of the phenyl ring, with a value of 23.0 ng/mL was discovered to be the most active. The IC₅₀ value for **26m** and **26o** were observed to be 28.8 ng/mL and 35.8 ng/mL, respectively. However as compared to compounds belonging to type **24** these compounds had low SI indicating to be relatively more toxic as compared to **24**.

Docking Studies

Molecular docking studies of 2-methyl-6-ureido-4-quinolinamides into *P. falciparum* DHFR binding site

revealed very clear preference for the inhibitor binding pocket and all the compounds occupy the same spatial position as the co-crystallized *pf*DHFR inhibitor WR99210. Most of the 2-methyl-6-ureido-4-quinolinamides bind in more or less similar fashion with its 2-methyl quinoline ring occupying the interior of the deep cleft and its phenyl substitution towards urea is extended to the entrance of the hydrophobic binding cavity. The 2-methyl quinoline core of the compounds was held in the pocket by combination of van der Waals and hydrophobic interactions with the protein. The most important *pf*DHFR-ligand interactions involve residues Ile14, Leu40, Leu46, Trp48, Lys49, Phe58, Pro113, Phe116, Leu119, Arg122, Tyr170 and Phe223 (Fig. 1). In all cases, Leu46, Phe58, Ile164 and Phe223 are predicted to exhibit major hydrophobic contacts with the 2-methyl-quinoline core inside the inhibitor binding site. As seen from the docking studies, the 2-methyl-quinoline core act as possible basic and π-donor site and is involved in edge to face π - π stacking interaction with the nicotinamide ring of NADPH. This edge to face or T shaped aromatic stacking interaction is very important for *pf*DHFR inhibition and is responsible for the stability of the protein ligand complex.



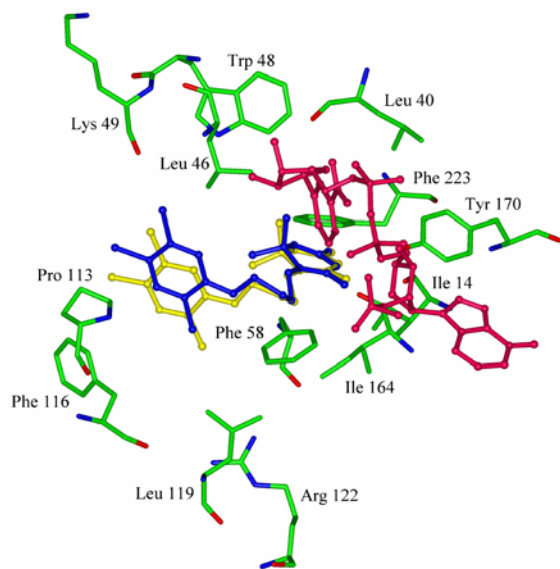


Figure 2. Structure of WR 99210 and its docked conformation of in yellow, Crystal structure conformation of WR99210 (blue) in the pDHFR

The phenyl moiety of the urea subunit make lipophilic interactions with Pro 113 and Phe 116 and it extends towards the solvent (as revealed from the docked conformations) so there is only small substituent effect on the inhibitory potency. Instead the substituents at 4-position of the 2-methyl quinoline ring have significant effect on the inhibitory potency. To facilitate the analysis of the biological data, 2-methyl-6-ureido-4-quinolinamides are classified according to the substitution at 4-position of the 2-methyl-quinoline ring and the nature of the substituent. As seen from our docking conformations bulkier substituents are preferred at this position due the hydrophobic environment provided by the side chains of Ile14, Leu46, Phe58, Ile164 and Phe223. Compounds of series **24**, **25** and **26** bearing methyl piperazine, ethyl piperazine and piperidine substituents, respectively displayed a binding mode as exemplified by representative compounds **24g**, **24l**, **25g** and **26g** in Fig. 2. These compounds show hydrophobic interactions with Ile 14, Leu 40, Leu 46, Phe 58, Ile 174, Tyr 170 and Phe 223.

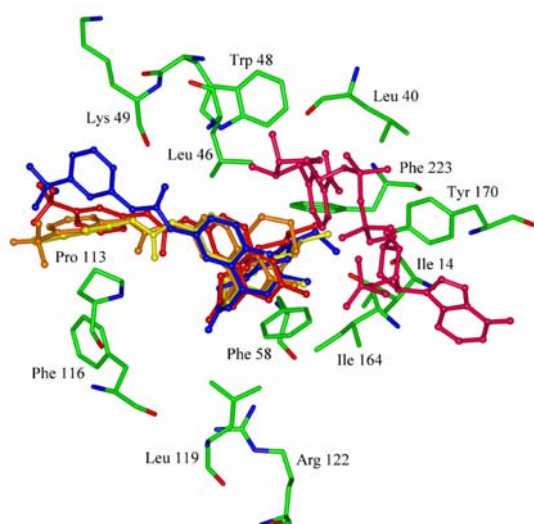


Figure 2. Docked conformation of **24g** (red) **24l** (yellow) **25g** (blue) **26g** (orange) in the pDHFR

In addition to these hydrophobic interactions, CH- π interactions are also found to occur between the π system of Phe58 and the CH in methyl piperazine, ethyl piperazine and piperidine ring. It is hypothesized that the presence of this particular CH- π interaction is responsible for the optimal orientation of the 2-methyl-quinoline core to make π -stacking interaction with the nicotinamide ring of NADPH. Any replacement of these groups with a smaller group led to decrease in the inhibitory activity. The displacement of this piperazine and piperidine moiety with phenyl, 2 and 3 chloro substituted phenyl ring in compounds **13a-o**, **14a-o** and **15a-o**, respectively led to decrease in the inhibitory activity where replacement causes the decrease in the hydrophobic interactions and thus decrease in the net hydrophobicity lower down the inhibitory potencies. In contrast although the series **16a,c,f,h,j,l-o** bearing furan ring show similar profile, they display better antimalarial effect. In case, compound **13i**, **14j**, **15a** and **16e** were not able to assume a conformation exactly similar to that of the active compounds because of their enhanced conformational rigidity due to the presence of planar substituents at 4-position (Fig. 3). However the docking studies performed in this study could not explain the pronounced activity of ureides with furan moiety.

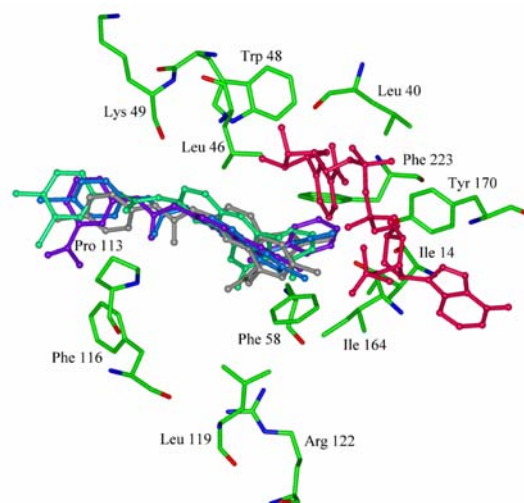


Figure 3. Docked conformation of **13i** (violet), **14j** (light green), **15a** (grey), **16e** (light blue) in the pDHFR

Further analysis of docking results revealed that compounds (**17a,h,j,m**) substituted with acetamide group at 4-position of the quinoline ring were devoid of any CH- π hydrogen bonds with Phe 58, hence 2-methyl quinoline ring was not able to attain proper conformation to make T shaped stacking (Fig. 4) and therefore the compounds were almost inactive.

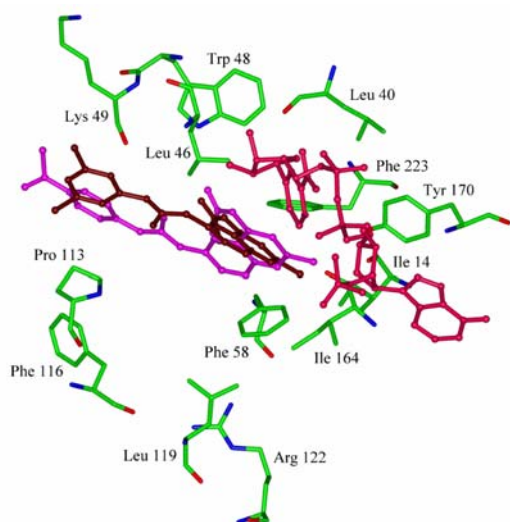


Figure 4. Docked conformation of **17h** (magenta), **17j** (brown) in the pfDHFR

In-vivo antimalarial activity

Three compounds namely **16f**, **24d** and **26o** were evaluated at an oral dose of 100mg/kg/day x 4 days against mdr *P. yoelli nigeriensis* whereas rests of evaluations were performed at 50mg/kg/day x 4 days against CQ-resistant *P. yoelli* N67. Only one group of animals treated with compound **16f**, no parasitaemia was observed on day 4 though low level of recrudescence occurred on day 7. However as compared to control group of untreated animals this activity was promising as indicated by 100 and 91.29% inhibition on day 4 and 7 respectively. Another group of animals treated with compound **26o** also showed marked effect on day 4 which diminished by day 7. Among the several sets of animals which were treated with the compounds at an oral dose of 50mg/kg/day x 4 days schedule elicited only modest suppression of parasitaemia. The group of animals treated with **16j** showed significant initial suppression but was almost inactive by day 7. On the other hand in the group of animals treated with **24i**, there was only a moderate increase in the levels of parasitemia even after day 7 illustrating its better antimalarial effect i.e. 92.9% inhibition on day 7. However since in most of the treated animals some level of parasitaemia was observed it was concluded that none of the compound had good in vivo antimalarial activity. Several reasons could be assigned for the low in vivo effect. The in vitro effect was investigated in the CQ-sensitive *P. falciparum* but the in vivo effect was examined in either mdr *P. yoelli nigeriensis* or CQ-resistant *P. yoelii*. Due to absence of CQ-resistant *P. falciparum* strain at this place we were unable to assess the activity of these compounds against it. Secondly poor solubility of these urea derivatives could have led to improper absorption and metabolism in the biosystem.

Antibacterial activity

Five strains of bacteria (*Streptococcus faecalis*, *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*

and *Staphylococcus aureus*), including Gram +ve and Gram –ve were included for the bioassay. Compounds which showed MIC of >50 µg/mL or above have not been included for the discussion. It was interesting to note that though several compounds show activity in different strains of bacteria only compounds **13m** and **15a** were found to be active against *P. aeruginosa* which is a Gram –ve strain of bacteria. Compounds **13m**, **15a**, **24j**, **24i**, **24m**, **24o**, **24c**, **25i**, and **25m** displayed MICs of 1.56 to 25 µg/mL against other four strains of bacteria (Table-2).

Based on the MIC values against different strains of bacteria compound **13m** was found to be a potent antibacterial. The values of 0.01 µg/mL against *S. faecalis*, 0.04 µg/mL against *K. pneumoniae*, 0.0025 µg/mL against *E. coli* and 0.09 µg/mL against *S. aureus* were best amongst all the compounds screened and were even better than the standard drug gentamicin by many folds. But its MIC against *P. aeruginosa* which was observed to be 12.5 µg/mL was only two fold better than gentamicin. Compound **24i** showed MIC of 1.56 µg/mL against the *S. faecalis* whereas compounds **24m** and **24o** were two fold less active against the same strain but these compounds were less active than the standard drug.

Table 2. Antibacterial activity of selected compounds only

Compd. No.	Bacteria ^a MIC (µg/mL)				
	1	2	3	4	5
13m	0.01	0.04	0.0025	12.5	0.09
15a	12.5	6.25	12.5	12.5	3.12
24c	6.25	6.25	6.25	>50	ND
24j	ND	12.5	6.25	>50	25
24i	1.56	1.56	1.56	>50	6.25
24m	3.125	1.56	1.56	>50	ND
24o	3.1	1.56	1.56	>50	6.25
25i	ND	12.5	ND	ND	6.25
25m	ND	6.25	ND	ND	3.12
Gentamicin	0.78	0.78	0.18	25	6.25

^a1. *S. faecalis*, 2. *K. pneumoniae*, 3. *E. coli*, 4. *P. Aeruginosa*, 5. *S. Aureus*

Other compounds were found to be active at MIC of 6.25 µg/mL or more. However against the *K. pneumoniae* compounds **24i**, **24m** and **24o** were equipotent with MIC of 1.56 µg/mL whereas **24c** showed modest activity with MIC of 6.25 µg/mL. Compounds **24i**, **24m** and **24o** had similar activity against *E. coli* with MIC of 1.56 µg/mL. Against the *S. aureus* though none of the compound showed comparable activity to the one elicited by **13m**, compound **14j** had the MIC of 3.12 µg/mL. On the other hand compounds **24i**, **24o** and **25i** were two fold less active with the MIC of 6.25 µg/mL. Analysis of the SAR of the active derivatives clearly demonstrate that a chloro group at 3-position of the phenyl ring of the aryl urea subunit is strongly required for compounds to show antibacterial activity.

Conclusions

In summary, we have disclosed the antimalarial activity of a new series of urea derivatives. On the basis of the compounds studied in the present study it is indicated that derivatives comprising of phenyl ring of the aryl urea subunit bearing disubstitutions at 3 and 4 positions elicit better biological activity. Amongst these di-substitutions the chloro group was the most favored. On the other hand the amido group present at the 4-position of the quinoline incorporating the *N*-methyl piperazine or the piperidine ring were best suited for the antimalarial activity. Introduction of benzamides generally leads to decrease in activity although the 2-chlorophenyl containing benzamides displayed better antimalarial activity as compared to unsubstituted phenyl group. In contrast the replacement of phenyl with furan moiety yielded compounds with good antimalarial effect. Although the docking studies of these compounds with the *pf*DHFR were accomplished, in the absence of investigation in a bioassay against DHFR it is premature to comment on the possible mode of action of these compounds. The lack of complete suppression of parasitaemia, however, reflects that the *in vivo* effect may have been influenced by the lower absorption of these compounds. Nevertheless, the compounds containing urea group does provide impetus to incorporate this group in other heterocyclic systems and evaluate their antimalarial effect.

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. ^1H 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 *N*-(2-methyl-6-nitroquinolin-4-yl)carbamides (2-7). To a mixture of Et_3N (22.2 mmol, 3.2 mL), DMAP (1.4 mmol, 0.17 g) and 2-methyl-6-nitroquinolin-4-amine (1) (14.8 mmol, 3.0 g) in anhydrous CH_2Cl_2 (50 mL), was added dropwise an appropriate acid chloride (22.16 mmol) under stirring at 0 °C. The reaction mixture was allowed to warm up to the room temperature and further stirred for 4 h. The precipitated solid was filtered, dried and crystallized from MeOH to furnish *N*-(2-methyl-6-nitroquinolin-4-yl)-carbamides (2-7) as crystalline solid in good yields.

***N*-(2-Methyl-6-nitroquinolin-4-yl)benzamide (2).** 87% as a yellow solid, mp 248–249 °C; ν_{max} (KBr) 1698 (CO), 3276 (NH) cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) δ = 2.83 (s,

3H, CH_3), 7.59–7.70 (m, 3H, ArH), 8.02 (dd, 2H, J_1 = 1.2 Hz, J_2 = 7.6 Hz, ArH), 8.18 (d, 1H, J = 9.2 Hz, ArH), 8.46–8.52 (m, 2H, ArH), 8.65 (s, 1H, NH), 8.86 (d, 1H, J = 2.2 Hz, ArH); mass (ES+) m/z = 308.0 (M^+ +1). Anal. Calcd. for $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}_3$ C, 66.44; H, 4.26; N, 13.67. Found C, 66.73; H, 4.06; N, 13.82.

2-Chloro-*N*-(2-methyl-6-nitroquinolin-4-yl)benzamide (3). 87% as a light yellow solid, mp 192–194 °C; ν_{max} (KBr) 1668 (CO), 3236 (NH) cm^{-1} ; ^1H NMR (DMSO-d_6 , 300 MHz) δ = 2.73 (s, 3H, CH_3), 7.54–7.67 (m, 3H, ArH), 7.73 (dd, 1H, J_1 = 1.7 Hz, J_2 = 7.1 Hz, ArH), 8.10 (d, 1H, J = 9.2 Hz, ArH), 8.26 (s, 1H, ArH), 8.43 (dd, 1H, J_1 = 2.5 Hz, J_2 = 9.2 Hz, ArH), 9.40 (d, 1H, J = 2.4 Hz, ArH), 11.26 (s, 1H, NH); mass (ES+) m/z = 342.1 (M^+ +1), 344.0 (M^+ +3). Anal. Calcd. for $\text{C}_{17}\text{H}_{12}\text{ClN}_3\text{O}_3$ C, 59.75; H, 3.54; N, 12.30. Found C, 59.98; H, 3.45; N, 12.62.

3-Chloro-*N*-(2-methyl-6-nitroquinolin-4-yl)benzamide (4). 89% as an off white solid, mp 201–203 °C; ν_{max} (KBr) 1685 (CO), 3219 (NH) cm^{-1} ; ^1H NMR (DMSO-d_6 , 300 MHz) δ = 2.71 (s, 3H, CH_3), 7.64 (t, 1H, J = 7.9 Hz, ArH), 7.75 (d, 1H, J = 8.6 Hz, ArH), 7.99 (d, 1H, J = 7.7 Hz, ArH), 8.04 (s, 1H, ArH), 8.09–8.12 (m, 2H, ArH), 8.44 (dd, 1H, J_1 = 2.4 Hz, J_2 = 9.2 Hz, ArH), 9.25 (d, 1H, J = 2.4 Hz, ArH), 11.00 (s, 1H, NH); ^{13}C NMR (DMSO-d_6 , 75 MHz) δ = 25.1, 116.7, 119.9, 121.3, 123.3, 127.5, 128.5, 131.0, 132.5, 133.7, 136.6, 144.1, 144.4, 151.0, 164.0, 166.2; mass (ES+) m/z = 342.2 (M^+ +1), 344.1 (M^+ +3). Anal. Calcd. for $\text{C}_{17}\text{H}_{12}\text{ClN}_3\text{O}_3$ C, 59.75; H, 3.54; N, 12.30. Found C, 59.51; H, 3.83; N, 12.17.

***N*-(2-Methyl-6-nitroquinolin-4-yl)-2-furamide (5).** 84% as a white solid, mp 232–234 °C; ν_{max} (KBr) 1672 (CO), 3325 (NH) cm^{-1} ; ^1H 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 = 298.2 (M^+ +1). Anal. Calcd. for $\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_4$ C, 60.61; H, 3.73; N, 14.14. Found C, 60.84; H, 4.01; N, 14.23.

***N*-(2-Methyl-6-nitroquinolin-4-yl)acetamide (6).** 91% as a light yellow solid, mp 210–215 °C; ν_{max} (KBr) 1680 (CO), 3263 (NH) cm^{-1} ; ^1H NMR (DMSO-d_6 , 300 MHz) δ = 2.42 (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 8.42 (d, 1H, J = 9.3 Hz, ArH), 8.56 (s, 1H, ArH), 8.69 (dd, 1H, J_1 = 2.1 Hz, J_2 = 9.3 Hz, ArH), 9.75 (d, 2H, J = 2.0 Hz, ArH), 11.19 (s, 1H, NH); mass (ES+) m/z = 246.0 (M^+ +1). Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_3$ C, 58.77; H, 4.52; N, 17.13. Found C, 59.06; H, 4.31; N, 17.40.

2-Chloro-*N*-(2-methyl-6-nitroquinolin-4-yl)acetamide (7). 80% as an off white solid, mp 153–155 °C; ν_{max} (KBr) 1676 (CO), 3255 (NH) cm^{-1} ; ^1H NMR (DMSO-d_6 , 300 MHz) δ = 2.68 (s, 3H, CH_3), 4.59 (s, 2H, CH_2), 8.07 (d, 1H, J = 9.2 Hz, ArH), 8.19 (s, 1H, ArH), 8.43 (dd, 1H, J_1 = 2.5 Hz, J_2 = 9.2 Hz, ArH), 9.38 (d, 2H, J = 2.3 Hz, ArH), 11.19 (s, 1H, NH); ^{13}C NMR (DMSO-d_6 , 75 MHz) δ = 25.0, 43.2, 112.6, 117.3, 119.1, 122.3, 130.0, 142.3, 143.5, 149.8, 163.2, 165.9; mass (ES+) m/z = 280.1 (M^+ +1), 282.1

($M^+ + 3$). Anal. Calcd. for $C_{12}H_{10}ClN_3O_3$ C, 51.53; H, 3.60; N, 15.02. Found C, 51.68; H, 3.92; N, 14.80.

General procedure for the preparation of *N*-(2-methyl-6-nitroquinolin-4-yl)-2-(substituted amino)acetamide (18–20). To a suspension of secondary amine (13.8 mmol) and NaH (28.6 mmol, 0.69 g) in 15 mL of anhydrous DMF was added a solution of 2-chloro-*N*-(2-methyl-6-nitroquinolin-4-yl)acetamide (7) (11.5 mmol, 3.2 g) in anhydrous DMF at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 6–10 h at room temperature. On completion, the reaction mixture was poured into ice cold water and allowed to warm up to ambient temperature. The mixture was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine (60 mL) and dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain a residue. The purification via silica gel column chromatography using hexanes:EtOAc (20:50:50–80, v/v) as the mobile phase yielded the desired carbamides (18–20).

***N*-(2-Methyl-6-nitroquinolin-4-yl)-2-(4-methylpiperazin-1-yl)acetamide (18).** 75% as a white solid, mp 245–247 °C; ν_{max} (KBr) 1691 (CO), 3405 (NH) cm^{-1} ; 1H NMR ($CDCl_3$, 300 MHz) δ = 2.46 (s, 3H, CH_3), 2.74–2.84 (m, 11H, CH_3 & 4 x CH_2), 3.34 (s, 2H, CH_2), 8.15 (d, 1H, J = 9.2 Hz, ArH), 8.47–8.51 (m, 2H, ArH), 8.93 (d, 2H, J = 2.3 Hz, ArH), 10.89 (s, 1H, NH); mass (ES+) m/z = 344.1 ($M^+ + 1$). Anal. Calcd. for $C_{17}H_{21}N_5O_3$: C, 59.46; H, 6.16; N, 20.40. Found C, 59.74; H, 5.97; N, 20.59.

2-(4-Ethylpiperazin-1-yl)-*N*-(2-methyl-6-nitroquinolin-4-yl)acetamide (19). 69% as a light yellow solid, mp 189–190 °C; ν_{max} (KBr) 1702 (CO), 3213 (NH) cm^{-1} ; 1H NMR ($CDCl_3$, 300 MHz) δ = 1.17 (t, 3H, J = 7.2 Hz, CH_2CH_3), 2.61 (q, 2H, J = 7.2 Hz, CH_2CH_3), 2.79–2.85 (m, 11H, CH_3 & 4 x CH_2), 3.34 (s, 2H, CH_2), 8.15 (d, 1H, J = 9.2 Hz, ArH), 8.47–8.51 (m, 2H, ArH), 8.92 (d, 1H, J = 2.3 Hz, ArH), 10.90 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 10.8, 24.9, 50.9, 51.9, 52.4, 60.7, 109.8, 115.2, 115.9, 121.6, 130.1, 140.1, 143.2, 149.4, 163.6, 168.0; mass (ES+) m/z = 358.2 ($M^+ + 1$). Anal. Calcd. for $C_{18}H_{23}N_5O_3$ C, 60.49; H, 6.49; N, 19.59. Found C, 60.77; H, 6.68; N, 19.41.

***N*-(2-Methyl-6-nitroquinolin-4-yl)-2-piperidin-1-ylacetamide (20).** 88% as a brown solid, mp 176–178 °C; ν_{max} (KBr) 1719 (CO), 3451 (NH) cm^{-1} ; 1H NMR ($CDCl_3$, 300 MHz) δ = 1.63–1.65 (m, 2H, CH_2), 1.83–1.90 (m, 4H, 2 x CH_2), 2.71–2.74 (m, 4H, 2 x CH_2), 2.79 (s, 3H, CH_3), 3.27 (s, 2H, CH_2), 8.14 (d, 1H, J = 9.3 Hz, ArH), 8.45–8.50 (m, 2H, ArH), 8.92 (d, 1H, J = 2.4 Hz, ArH), 11.01 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 23.9, 26.6, 27.1, 55.5, 63.3, 111.5, 117.0, 117.7, 123.2, 131.7, 141.9, 144.9, 151.0, 165.3, 170.3; mass (ES+) m/z = 329.1 ($M^+ + 1$). Anal. Calcd. for $C_{17}H_{20}N_4O_3$ C, 62.18; H, 6.14; N, 17.06. Found C, 62.33; H, 5.96; N, 17.26.

General procedure for the preparation of *N*-(6-amino-2-methylquinolin-4-yl)- carbamides (8, 11–12, 21–23). To a solution of appropriate *N*-(2-methyl-6-nitroquinolin-4-yl)carbamide (2, 5–6, 18–20) (4.1 mmol) was added 10%

Pd-C (0.20 g) under nitrogen atmosphere. Thereafter, the atmosphere of the vessel was replaced by hydrogen gas and reaction was carried out on the Parr assembly at 40 psi at room temperature for 1 h. The catalyst was then filtered over a celite bed and the filtrate was evaporated on rotavapour under reduced pressure to yield a residue. The residue was purified by recrystallization or column chromatography over silica gel using hexanes:EtOAc (65–55:35–45, v/v) as the eluent to yield compounds 8, 11–12, 21–23.

***N*-(6-Amino-2-methylquinolin-4-yl)benzamide (8).** 85% as a light yellow solid, mp 160–162 °C; ν_{max} (KBr) 1698 (CO), 3367 (NH & NH_2) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.81 (s, 3H, CH_3), 6.25 (brs, 2H, NH_2), 7.31 (d, 1H, J = 1.7 Hz, ArH), 7.45 (dd, 1H, J_1 = 1.8 Hz, J_2 = 9.0 Hz, ArH), 7.58–7.63 (m, 2H, ArH), 7.67–7.72 (m, 1H, ArH), 8.04–8.11 (m, 3H, ArH), 8.18 (s, 1H, ArH), 10.93 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 21.7, 100.0, 115.0, 121.9, 122.3, 127.3, 127.7, 128.4, 129.9, 131.4, 132.1, 133.1, 141.3, 146.4, 150.7, 165.4, 166.6; mass (ES+) m/z = 278.3 ($M^+ + 1$). Anal. Calcd. for $C_{17}H_{15}N_3O$ C, 73.63; H, 5.45; N, 15.15. Found C, 73.90; H, 5.69; N, 15.01.

***N*-(6-Amino-2-methylquinolin-4-yl)-2-furamide (11).** 87% as a light yellow solid, mp 195–197 °C; ν_{max} (KBr) 1665 (CO), 3327 (NH & NH_2) cm^{-1} ; 1H 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*-(6-Amino-2-methylquinolin-4-yl)acetamide (12).** 83% as a yellow solid, mp 280–282 °C; ν_{max} (KBr) 1680 (CO), 3456 (NH & NH_2) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.32 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 7.34–7.39 (m, 2H, ArH), 7.91 (d, 1H, J = 8.9 Hz, ArH), 8.17 (s, 1H, ArH), 10.51 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 19.9, 23.9, 99.7, 110.5, 120.2, 121.9, 123.5, 132.6, 144.4, 147.7, 150.1, 170.0; mass (ES+) m/z = 216.0 ($M^+ + 1$). Anal. Calcd. for $C_{12}H_{13}N_3O$ C, 66.96; H, 6.09; N, 19.52. Found C, 67.24; H, 6.28; N, 19.30.

***N*-(6-Amino-2-methylquinolin-4-yl)-2-(4-methylpiperazin-1-yl)acetamide (21).** 76% as a white solid, mp 225–227 °C; ν_{max} (KBr) 1718 (CO), 3453 (NH & NH_2) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.43 (s, 3H, CH_3), 2.74–2.77 (m, 7H, CH_3 & 2 x CH_2), 3.31 (s, 2H, CH_2), 3.34 (s, 4H, 2 x CH_2), 5.64 (brs, 2H, NH_2), 6.80 (s, 1H, ArH), 7.14 (dd, 1H, J_1 = 1.5 Hz, J_2 = 8.9 Hz, ArH), 7.61 (d, 1H, J = 8.9 Hz, ArH), 7.84 (s, 1H, ArH), 9.88 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 25.0, 44.8, 52.0, 54.3, 61.6, 98.8, 111.8, 120.9, 121.8, 130.1, 138.5, 142.6, 147.0, 153.3, 169.3; mass (ES+) m/z = 313.9 ($M^+ + 1$). Anal. Calcd. for $C_{17}H_{23}N_5O$ C, 65.15; H, 7.40; N, 22.35. Found C, 64.91; H, 7.62; N, 22.05.

***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 (NH₂), 3399 (NH) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ = 1.02 (t, 3H, J = 7.1 Hz, CH₂CH₃), 2.39 (q, 2H, J = 7.1 Hz, CH₂CH₃), 2.50 (s, 7H, CH₃ & 2 x CH₂), 2.62 (s, 4H, 2 x CH₂), 3.25 (s, 2H, CH₂), 5.55 (s, 2H, NH₂), 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); ¹³C NMR (DMSO-d₆, 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 C₁₈H₂₅N₅O C, 66.03; H, 7.70; N, 21.39. Found C, 66.31; H, 7.53; N, 21.47.

***N*-(6-Amino-2-methylquinolin-4-yl)-2-piperidin-1-ylacetamide (23)**. 82% as an off white solid, mp 208–210 °C; ν_{\max} (KBr) 1688 (CO), 3423 (NH & NH₂) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ = 1.58–1.60 (m, 2H, CH₂), 1.72–1.80 (m, 4H, 2 x CH₂), 2.68 (s, 7H, CH₃ & 2 x CH₂), 3.22 (s, 2H, CH₂), 3.96 (s, 2H, NH₂), 6.86 (d, 1H, J = 2.4 Hz, ArH), 7.15 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.9 Hz, ArH), 7.87 (d, 1H, J = 8.9 Hz, ArH), 8.19 (s, 1H, ArH), 10.18 (s, 1H, NH); ¹³C NMR (CDCl₃, 75 MHz) δ = 23.5, 25.2, 26.6, 99.8, 110.8, 119.6, 121.0, 130.8, 138.1, 143.5, 144.1, 156.0, 169.4; mass (ES+) m/z = 299.1 (M⁺+1). Anal. Calcd. for C₁₇H₂₂N₄O C, 68.43; H, 7.43; N, 18.78. Found C, 68.35; H, 7.68; N, 18.59.

General procedure for the preparation of *N*-(6-amino-2-methylquinolin-4-yl)-chlorobenzamides (9–10). A solution of chloro-*N*-(2-methyl-6-nitroquinolin-4-yl)benzamide **3-4** (5.86 mmol, 2.0 g) and anhydrous SnCl₂·2H₂O (29.32 mmol, 5.56 g) in MeOH (20 mL) was heated at reflux temperature for half an hour under nitrogen atmosphere. Thereafter excessive MeOH was evaporated and the residue was dissolved in EtOAc (100 mL) and basified with aqueous NaHCO₃ solution. The resulting mixture was filtered through a celite bed followed by separation of organic layer via partitioning. Organic layer was collected, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain the desired *N*-(6-amino-2-methylquinolin-4-yl)-chlorobenzamides (**9–10**) which were further purified by silica gel column chromatography with MeOH:CHCl₃ (2:98, v/v) as eluent and recrystallized from MeOH.

***N*-(6-Amino-2-methylquinolin-4-yl)-2-chlorobenzamide (9)**. 67% as a yellow solid, mp 191–193 °C; ν_{\max} (KBr) 1654 (CO), 3358 (NH & NH₂) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ = 2.69 (s, 3H, CH₃), 3.75 (brs, 2H, NH₂), 6.93 (s, 1H, ArH), 7.11 (d, 1H, J = 7.6 Hz, ArH), 7.50–7.67 (m, 3H, ArH), 7.85 (d, 1H, J = 7.0 Hz, ArH), 7.98 (d, 1H, J = 6.5 Hz, ArH), 8.20 (d, 1H, J = 6.3 Hz, ArH); mass (FAB+) m/z = 312 (M⁺+1). Anal. Calcd. for C₁₇H₁₄ClN₃O C, 65.49; H, 4.53; N, 13.48. Found C, 65.26; H, 4.46; N, 13.80.

***N*-(6-Amino-2-methylquinolin-4-yl)-3-chlorobenzamide (10)**. 62% as a yellow solid, mp 179–181 °C; ν_{\max} (KBr) 1697 (CO), 3313 (NH & NH₂) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ = 2.81 (s, 3H, CH₃), 7.30–7.33 (m, 1H, ArH), 7.46 (dd, 1H, J_1 = 2.1 Hz, J_2 = 9.1 Hz, ArH), 7.61–7.71 (m, 2H, ArH), 7.97–8.00 (m, 1H, ArH), 8.08–8.15 (m, 2H,

ArH), 8.20 (s, 1H, ArH), 10.89 (s, 1H, NH); mass (FAB+) m/z = 312 (M⁺+1). Anal. Calcd. for C₁₇H₁₄ClN₃O C, 65.49; H, 4.53; N, 13.48. Found C, 65.78; H, 4.73; N, 13.17.

General procedure for the preparation of compounds 13–14a-o, 15a-g,i-o, 16a,c,f,h, j,l-m,o, 17a,h,j,m, 24a-m,o, 25g,j,l-m, 26a,g,i,l-m,o. A mixture of appropriate amine from **8-12**, **21-23** (1.16 mmol) and aryl isocyanate or activated carbamate (1.28 mmol) in anhydrous MeCN or THF (10 mL) was stirred at room temperature for 2 min–6 h. Thereafter, the reaction mixture was adsorbed on silica gel or alumina and purified by column chromatography using hexanes:EtOAc (40–10:60–90, v/v) as the eluent to yield the desired compounds **13-14a-o**, **15a-g-i-o**, **16a,c,f,h, j,l-m,o**, **17a,h,j,m**, **24a-m,o**, **25g,j,l-m**, **26a,g,i,l-m,o**.

***N*-(6-[(4-Chloroanilino)carbonylamino]-2-methylquinolin-4-yl)benzamide (13a)**. 68% as a yellow solid, mp 263–264 °C; R_t= 21.73 min; ν_{\max} (KBr) 1644, 1665 (CO), 3254 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 200 MHz) δ = 2.62 (s, 3H, CH₃), 7.31 (d, 2H, J = 8.7 Hz, ArH), 7.48 (d, 2H, J = 8.8 Hz, ArH), 7.59–7.62 (m, 4H, ArH), 7.86 (s, 2H, ArH), 8.07 (d, 3H, J = 6.3 Hz, ArH), 8.89 (s, 1H, NH), 9.05 (s, 1H, NH), 10.56 (s, 1H, NH); mass (FAB+) m/z = 431 (M⁺+1). Anal. Calcd. for C₂₄H₁₉ClN₄O₂ C, 66.90; H, 4.44; N, 13.00. Found C, 66.61; H, 4.60; N, 13.23.

***N*-(6-[(4-Fluoroanilino)carbonylamino]-2-methylquinolin-4-yl)benzamide (13b)**. 77% as a white solid, mp 256–257 °C; ν_{\max} (KBr) 1651, 1698 (CO), 3369 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ = 2.61 (s, 3H, CH₃), 7.07–7.14 (m, 2H, ArH), 7.43–7.57 (m, 6H, ArH), 7.84 (d, 2H, J = 9.9 Hz, ArH), 8.05–8.09 (m, 3H, ArH), 8.79 (s, 1H, NH), 9.02 (s, 1H, NH), 10.62 (s, 1H, NH); ¹³C NMR (DMSO-d₆, 50 MHz) δ = 25.1, 109.5, 115.5, 155.9, 117.7, 120.5, 122.8, 123.3, 128.3, 128.9, 129.4, 132.4, 134.5, 136.2, 137.3, 141.6, 145.2, 153.1, 156.9, 166.5; mass (FAB+) m/z = 415 (M⁺+1). Anal. Calcd. for C₂₄H₁₉FN₄O₂ C, 69.55; H, 4.62; N, 13.52. Found C, 69.38; H, 4.82; N, 13.49.

***N*-(6-[(4-Bromoanilino)carbonylamino]-2-methylquinolin-4-yl)benzamide (13c)**. 71% as a white solid, mp 245–246 °C; R_t= 21.14 min; ν_{\max} (KBr), 1644, 1665 (CO), 3251 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 200 MHz) δ = 2.62 (s, 3H, CH₃), 7.43 (s, 3H, ArH), 7.59–7.66 (m, 5H, ArH), 7.85–7.86 (m, 2H, ArH), 8.08 (d, 3H, J = 6.9 Hz, ArH), 8.90 (s, 1H, NH), 9.05 (s, 1H, NH), 10.57 (s, 1H, NH); mass (FAB+) m/z = 475 (M⁺+1). Anal. Calcd. for C₂₄H₁₉BrN₄O₂ C, 60.64; H, 4.03; N, 11.79. Found C, 60.77; H, 4.21; N, 11.35.

***N*-(6-[(3-Chloroanilino)carbonylamino]-2-methylquinolin-4-yl)benzamide (13d)**. 81% as a white solid, mp 259–260 °C; R_t= 17.12 min; ν_{\max} (KBr) 1645, 1697 (CO), 3298 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ = 2.66 (s, 3H, CH₃), 7.02 (s, 1H, ArH), 7.29 (d, 2H, J = 4.2 Hz, ArH), 7.57–7.72 (m, 5H, ArH), 7.91 (s, 2H, ArH), 8.09 (d, 2H, J = 7.1 Hz, ArH), 8.17 (s, 1H, ArH), 9.11 (s, 1H, NH), 9.24 (s, 1H, NH), 10.67 (s, 1H, NH); mass (ES+) m/z = 431.0 (M⁺+1). Anal. Calcd. for

$C_{24}H_{19}ClN_4O_2$ C, 66.90; H, 4.44; N, 13.00. Found C, 66.81; H, 4.63; N, 12.74.

***N*-(6-[[3-(Fluoroanilino)carbonylamino]-2-methylquinolin-4-yl]benzamide (13e).** 80% as a white solid, mp 258–259 °C; v_{max} (KBr) 1651, 1693 (CO), 3350 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.72 (s, 3H, CH₃), 6.80 (t, 1H, J = 7.4 Hz, ArH), 7.16 (d, 1H, J = 8.1 Hz, ArH), 7.27–7.35 (m, 1H, ArH), 7.49–7.71 (m, 4H, ArH), 7.90 (s, 1H, ArH), 7.99 (s, 2H, ArH), 8.12 (d, 2H, J = 7.2 Hz, ArH), 8.31 (s, 1H, ArH), 9.50 (s, 1H, NH), 9.61 (s, 1H, NH), 10.85 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 22.3, 103.9, 104.2, 107.4, 107.6, 108.5, 113.1, 115.2, 120.9, 123.6, 125.3, 127.3, 127.8, 129.6, 131.6, 133.1, 136.8, 140.7, 143.1, 151.7, 155.0, 160.0, 163.2, 165.7; mass (ES+) m/z = 415.1 (M^+ +1). Anal. Calcd. for $C_{24}H_{19}FN_4O_2$ C, 69.55; H, 4.62; N, 13.52. Found C, 69.68; H, 4.94; N, 13.40.

***N*-(6-[[3-(Cyanoanilino)carbonylamino]-2-methylquinolin-4-yl]benzamide (13f).** 53% as a yellow solid, mp 272–273 °C; R_t = 17.70 min; v_{max} (KBr) 1656, 1703 (CO), 2230 (CN), 3280 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 200 MHz) δ = 2.71 (s, 3H, CH₃), 7.47–7.60 (m, 2H, ArH), 7.63–7.79 (m, 5H, ArH), 7.97–7.99 (m, 3H, ArH), 8.13 (d, 2H, J = 7.3 Hz, ArH), 8.23 (s, 1H, ArH), 9.31 (s, 1H, NH), 9.39 (s, 1H, NH), 10.74 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 23.2, 108.8, 110.8, 115.9, 118.0, 120.0, 121.2, 122.1, 122.9, 124.6, 127.2, 127.8, 129.4, 131.4, 133.2, 136.1, 139.7, 141.7, 151.8, 155.5, 165.5; mass (FAB+) m/z = 422 (M^+ +1). Anal. Calcd. for $C_{25}H_{19}N_5O_2$ C, 71.25; H, 4.54; N, 16.62. Found C, 71.03; H, 4.83; N, 16.39.

***N*-[2-Methyl-6-((3-(trifluoromethyl)anilino)carbonylamino)quinolin-4-yl]benzamide (13g).** 68% as a white solid, mp 252–254 °C; v_{max} (KBr) 1656, 1697 (CO), 3346 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.74 (s, 3H, CH₃), 7.32 (d, 1H, J = 5.9 Hz, ArH), 7.52–7.69 (m, 5H, ArH), 8.01–8.11 (m, 6H, ArH), 8.36 (s, 1H, ArH), 9.56 (s, 2H, 2 x NH), 10.90 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 23.3, 109.9, 114.5, 116.2, 118.7, 122.1, 122.2, 122.9, 125.1, 126.1, 128.7, 129.0, 129.8, 130.4, 132.9, 134.4, 138.1, 140.9, 144.7, 153.1, 156.2, 167.1; mass (ES+) m/z = 465.0 (M^+ +1). Anal. Calcd. for $C_{25}H_{19}F_3N_4O_2$ C, 64.65; H, 4.12; N, 12.06. Found C, 64.83; H, 3.98; N, 11.75.

***N*-(6-[[4-(Acetylanilino)carbonylamino]-2-methylquinolin-4-yl]benzamide (13h).** 59% as a white solid, mp 293–294 °C; R_t = 17.06 min; v_{max} (KBr) 1670, 1708 (CO), 3252 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.50 (s, 3H, CH₃), 2.86 (s, 3H, CH₃), 7.59–7.72 (m, 5H, ArH), 7.90 (d, 2H, J = 8.3 Hz, ArH), 8.08–8.20 (m, 4H, ArH), 8.33 (s, 1H, ArH), 8.62 (s, 1H, ArH), 10.03 (s, 1H, NH), 10.15 (s, 1H, NH), 11.26 (s, 1H, NH); mass (FAB+) m/z = 439 (M^+ +1). Anal. Calcd. for $C_{26}H_{22}N_4O_3$ C, 71.22; H, 5.06; N, 12.78. Found C, 71.39; H, 4.95; N, 12.56.

***N*-(6-[[3-(Acetylanilino)carbonylamino]-2-methylquinolin-4-yl]benzamide (13i).** 90% as a light yellow solid, mp 241–242 °C; R_t = 15.56 min; v_{max} (KBr) 1629, 1683 (CO), 3291 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 200 MHz) δ = 2.59 (s, 3H, CH₃), 2.66 (s, 3H, CH₃), 7.42–7.50 (m, 1H, ArH), 7.60–7.74 (m, 6H, ArH), 7.91 (s, 2H, ArH), 8.13 (d, 4H, J = 9.8 Hz, ArH), 9.01 (s, 1H, NH), 9.09 (s, 1H, NH), 10.59 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 50 MHz) δ = 25.1, 27.1, 109.7, 117.8, 122.5, 122.7, 123.3, 128.3, 128.9, 129.6, 132.4, 134.6, 137.1, 137.8, 140.4, 141.6, 145.2, 153.0, 157.0, 166.6, 198.1; mass (ES+) m/z = 439.1 (M^+ +1). Anal. Calcd. for $C_{26}H_{22}N_4O_3$ C, 71.22; H, 5.06; N, 12.78. Found C, 71.48; H, 5.00; N, 12.41.

***N*-(6-[[3-(Chloro-4-methylanilino)carbonylamino]-2-methylquinolin-4-yl]benzamide (13j).** 75% as a light yellow solid, mp 254–255 °C; R_t = 22.58 min; v_{max} (KBr) 1656, 1700 (CO), 3353 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.27 (s, 3H, CH₃), 2.88 (s, 3H, CH₃), 7.26 (s, 2H, ArH), 7.62–7.76 (m, 4H, ArH), 8.10–8.17 (m, 4H, ArH), 8.33 (s, 1H, ArH), 8.58 (s, 1H, ArH), 9.61 (s, 1H, NH), 9.92 (s, 1H, NH), 11.21 (s, 1H, NH); mass (FAB+) m/z = 445 (M^+ +1). Anal. Calcd. for $C_{25}H_{21}ClN_4O_2$ C, 67.49; H, 4.76; N, 12.59. Found C, 67.21; H, 4.75; N, 12.37.

***N*-(6-[[3-(Chloro-2-methylanilino)carbonylamino]-2-methylquinolin-4-yl]benzamide (13k).** 78% as a yellow solid, mp 242–244 °C; R_t = 20.89 min; v_{max} (KBr) 1640 (CO), 3285 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.29 (s, 3H, CH₃), 2.63 (s, 3H, CH₃), 7.15–7.18 (m, 2H, ArH), 7.57–7.66 (m, 4H, ArH), 7.72–7.75 (m, 1H, ArH), 7.89 (s, 2H, ArH), 8.07–8.10 (m, 3H, ArH), 8.24 (s, 1H, NH), 9.37 (s, 1H, NH), 10.60 (s, 1H, NH); mass (FAB+) m/z = 445 (M^+ +1). Anal. Calcd. for $C_{25}H_{21}ClN_4O_2$ C, 67.49; H, 4.76; N, 12.59. Found C, 67.16; H, 4.81; N, 12.36.

***N*-(6-[[3,4-Dichloroanilino)carbonylamino]-2-methylquinolin-4-yl]benzamide (13l).** 74% as an off white solid, mp 239–240 °C; R_t = 19.15 min; v_{max} (KBr) 1703 (CO), 3371 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.79 (s, 3H, CH₃), 7.38 (dd, 1H, J_1 = 3.0 Hz, J_2 = 9.0 Hz, ArH), 7.54 (d, 1H, J = 9.0 Hz, ArH), 7.60–7.64 (m, 2H, ArH), 7.70 (d, 1H, J = 9.0 Hz, ArH), 7.87 (s, 1H, ArH), 8.04–8.11 (m, 5H, ArH), 8.38 (s, 1H, ArH), 9.44 (s, 1H, NH), 9.53 (s, 1H, NH), 10.18 (s, 1H, NH); mass (FAB+) m/z = 464 (M^+ +1). Anal. Calcd. for $C_{24}H_{18}Cl_2N_4O_2$ C, 61.95; H, 3.90; N, 12.04. Found C, 61.63; H, 4.01; N, 11.86.

***N*-(6-[[3,5-Dichloroanilino)carbonylamino]-2-methylquinolin-4-yl]benzamide (13m).** 69% as a yellow solid, mp 274–275 °C; R_t = 19.47 min; v_{max} (KBr) 1711 (CO), 3424 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.76 (s, 3H, CH₃), 7.17 (s, 1H, ArH), 7.54–7.69 (m, 5H, ArH), 8.03–8.10 (m, 5H, ArH), 8.37 (s, 1H, ArH), 9.76 (s, 2H, 2 x NH), 10.98 (s, 1H, NH); mass (ES+) m/z = 465.1 (M^+ +1), 467.1 (M^+ +3). Anal. Calcd. for $C_{24}H_{18}Cl_2N_4O_2$ C, 61.95; H, 3.90; N, 12.04. Found C, 62.23; H, 3.68; N, 12.31.

***N*-(6-[[3-Chloro-4-fluoroanilino]carbonyl]amino)-2-methylquinolin-4-yl)benzamide (13n).** 79% as a white solid, mp 247–248 °C; ν_{\max} (KBr) 1657, 1699 (CO), 3328 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz) δ = 2.62 (s, 3H, CH₃), 7.11 (t, 2H, J = 8.8 Hz, ArH), 7.43–7.48 (m, 2H, ArH), 7.59–7.66 (m, 4H, ArH), 7.86 (d, 2H, J = 2.4 Hz, ArH), 8.07 (s, 2H, ArH), 8.10 (s, 1H, ArH), 8.79 (s, 1H, NH), 9.02 (s, 1H, NH), 10.62 (s, 1H, NH); mass (ES+) m/z = 449.1 (M^+ +1). Anal. Calcd. for C₂₄H₁₉ClFN₄O₂ C, 64.22; H, 4.04; N, 12.48. Found C, 64.33; H, 4.28; N, 12.51.

***N*-[6-([4-Chloro-3-(trifluoromethyl)anilino]carbonyl]amino)-2-methylquinolin-4-yl]acetamidebenzamide (13o).** 64% as a white solid, mp 205–208 °C; ν_{\max} (KBr) 1687 (CO), 3533 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz) δ = 2.65 (s, 3H, CH₃), 7.57–7.69 (m, 6H, ArH), 7.90 (s, 2H, ArH), 8.08–8.11 (m, 3H, ArH), 8.17 (s, 1H, ArH), 9.26 (s, 1H, NH), 9.32 (s, 1H, NH), 10.63 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 23.7, 108.9, 116.0, 116.3, 121.4, 121.6, 122.3, 122.5, 127.2, 127.7, 131.2, 131.3, 133.3, 135.7, 138.4, 140.9, 143.5, 151.7, 155.8, 165.4; mass (ES+) m/z = 499.2 (M^+ +1), 501.2 (M^+ +3). Anal. Calcd. for C₂₅H₁₈ClF₃N₄O₂ C, 60.19; H, 3.64; N, 11.23. Found C, 60.02; H, 3.91; N, 11.05.

2-Chloro-*N*-(6-[[4-chloroanilino]carbonyl]amino)-2-methylquinolin-4-yl)benzamide (14a). 91% as a white solid, mp 224–225 °C; ν_{\max} (KBr) 1653 (CO), 3282 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz) δ = 2.63 (s, 3H, CH₃), 7.32 (s, 1H, ArH), 7.36 (s, 1H, ArH), 7.49–7.60 (m, 5H, ArH), 7.70–7.76 (m, 2H, ArH), 7.86 (s, 2H, ArH), 8.20 (s, 1H, ArH), 9.07 (s, 1H, NH), 9.09 (s, 1H, NH), 10.78 (s, 1H, NH); mass (ES+) m/z = 465.1 (M^+ +1), 467.1 (M^+ +3). Anal. Calcd. for C₂₄H₁₈Cl₂N₄O₂ C, 61.95; H, 3.90; N, 12.04. Found C, 62.24; H, 3.99; N, 12.22.

2-Chloro-*N*-(6-[[4-fluoroanilino]carbonyl]amino)-2-methylquinolin-4-yl)benzamide (14b). 95% as a white solid, mp 264–266 °C; R_t = 16.80 min; ν_{\max} (KBr) 1645 (CO), 3273 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz) δ = 2.66 (s, 3H, CH₃), 7.16 (t, 2H, J = 8.8 Hz, ArH), 7.48–7.66 (m, 5H, ArH), 7.73–7.78 (m, 2H, ArH), 7.89 (s, 2H, ArH), 8.21 (s, 1H, ArH), 8.86 (s, 1H, NH), 8.95 (s, 1H, NH), 10.80 (s, 1H, NH); mass (FAB+) m/z = 449 (M^+ +1). Anal. Calcd. for C₂₄H₁₈ClFN₄O₂ C, 64.22; H, 4.04; N, 12.48. Found C, 63.97; H, 4.31; N, 12.61.

***N*-(6-[[4-Bromoanilino]carbonyl]amino)-2-methylquinolin-4-yl)-2-chlorobenzamide (14c).** 92% as a white solid, mp 136–138 °C; R_t = 21.38 min; ν_{\max} (KBr) 1645, 1689 (CO), 3356 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz) δ = 2.66 (s, 3H, CH₃), 7.47–7.50 (m, 3H, ArH), 7.53–7.66 (m, 3H, ArH), 7.73–7.80 (m, 2H, ArH), 7.90 (s, 2H, ArH), 8.13 (d, 1H, J = 6.9 Hz, ArH), 8.23 (s, 1H, ArH), 8.99 (s, 1H, NH), 9.01 (s, 1H, NH), 10.82 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 50 MHz) δ = 25.2, 109.7, 113.7, 116.0, 117.7, 120.5, 121.7, 122.8, 123.6, 127.6, 128.9, 129.6, 130.1, 130.5, 131.7, 136.9, 137.0, 139.4, 140.8, 141.6, 145.3, 152.8, 157.0, 166.4; mass (FAB+) m/z = 509 (M^+ +1).

Anal. Calcd. for C₂₄H₁₈BrClN₄O₂ C, 56.55; H, 3.56; N, 10.99. Found C, 56.79; H, 3.71; N, 10.78.

2-Chloro-*N*-(6-[[3-chloroanilino]carbonyl]amino)-2-methylquinolin-4-yl)benzamide (14d). 94% as a white solid, mp 242–243 °C; ν_{\max} (KBr) 1652, 1697 (CO), 3383 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz) δ = 2.66 (s, 3H, CH₃), 7.06 (d, 1H, J = 8.7 Hz, ArH), 7.32 (s, 2H, ArH), 7.50–7.66 (m, 3H, ArH), 7.73–7.83 (m, 3H, ArH), 7.89 (s, 2H, ArH), 8.24 (s, 1H, ArH), 9.07 (s, 2H, 2 x NH), 10.84 (s, 1H, NH); mass (FAB+) m/z = 465 (M^+ +1). Anal. Calcd. for C₂₄H₁₈Cl₂N₄O₂ C, 61.95; H, 3.90; N, 12.04. Found C, 62.04; H, 3.68; N, 12.29.

2-Chloro-*N*-(6-[[3-fluoroanilino]carbonyl]amino)-2-methylquinolin-4-yl)benzamide (14e). 94% as a white solid, mp 243–245 °C; ν_{\max} (KBr) 1641, 1697 (CO), 3288 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz) δ = 2.64 (s, 3H, CH₃), 6.80 (dt, 1H, J_1 = 2.3 Hz, J_2 = 8.4 Hz, ArH), 7.15 (dd, 1H, J_1 = 1.0 Hz, J_2 = 8.2 Hz, ArH), 7.28–7.36 (m, 1H, ArH), 7.49–7.64 (m, 4H, ArH), 7.71–7.77 (m, 2H, ArH), 7.83–7.91 (m, 2H, ArH), 8.21 (d, 1H, J = 1.1 Hz, ArH), 9.04 (s, 1H, NH), 9.07 (s, 1H, NH), 10.78 (s, 1H, NH); mass (FAB+) m/z = 449 (M^+ +1). Anal. Calcd. for C₂₄H₁₈ClFN₄O₂ C, 64.22; H, 4.04; N, 12.48. Found C, 64.51; H, 4.01; N, 12.73.

2-Chloro-*N*-(6-[[3-cyanoanilino]carbonyl]amino)-2-methylquinolin-4-yl)benzamide (14f). 92% as a white solid, mp 257–259 °C; R_t = 16.89 min; ν_{\max} (KBr) 1649, 1699 (CO), 2230 (CN), 3354 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz) δ = 2.67 (s, 3H, CH₃), 7.44–7.67 (m, 5H, ArH), 7.73–7.80 (m, 2H, ArH), 7.91 (s, 2H, ArH), 8.03 (s, 1H, ArH), 8.12 (d, 1H, J = 3.1 Hz, ArH), 8.24 (s, 1H, ArH), 9.14 (s, 1H, NH), 9.18 (s, 1H, NH), 10.83 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 50 MHz) δ = 25.2, 110.1, 112.0, 116.0, 119.2, 121.3, 121.7, 123.3, 123.7, 125.8, 127.6, 128.3, 128.9, 129.6, 130.1, 130.5, 131.7, 132.4, 136.8, 140.9, 145.4, 152.9, 157.2, 166.4; mass (FAB+) m/z = 456 (M^+ +1). Anal. Calcd. for C₂₅H₁₈ClN₅O₂ C, 65.86; H, 3.98; N, 15.36. Found C, 65.59; H, 4.13; N, 15.14.

2-Chloro-*N*-(2-methyl-6-([3-(trifluoromethyl)anilino]carbonyl]amino)quinolin-4-yl)benzamide (14g). 94% as a light yellow solid, mp 234–236 °C; ν_{\max} (KBr) 1692 (CO), 3312 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz) δ = 2.64 (s, 3H, CH₃), 7.33 (d, 1H, J = 7.4 Hz, ArH), 7.51–7.63 (m, 5H, ArH), 7.73–7.77 (m, 2H, ArH), 7.85–7.91 (m, 2H, ArH), 8.08 (s, 1H, ArH), 8.25 (s, 1H, ArH), 9.06 (s, 1H, NH), 9.18 (s, 1H, NH), 10.79 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 50 MHz) δ = 25.2, 110.0, 114.5, 116.1, 118.5, 121.7, 122.2, 123.7, 127.5, 129.0, 129.6, 130.0, 130.3, 130.5, 131.7, 136.9, 140.9, 145.4, 153.0, 157.1, 166.4; mass (FAB+) m/z = 499 (M^+ +1). Anal. Calcd. for C₂₅H₁₈ClF₃N₄O₂ C, 60.19; H, 3.64; N, 11.23. Found C, 60.53; H, 3.84; N, 11.02.

***N*-(6-[[4-Acetylanilino]carbonyl]amino)-2-methylquinolin-4-yl)-2-chlorobenzamide (14h).** 93% as a white solid, mp 221–223 °C; R_t = 22.15 min; ν_{\max} (KBr) 1641, 1699 (CO), 3353 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 ,

300 MHz) δ = 2.52 (s, 3H, CH₃), 2.64 (s, 3H, CH₃), 7.52–7.63 (m, 5H, ArH), 7.71–7.74 (m, 1H, ArH), 7.78 (s, 1H, ArH), 7.87–7.94 (m, 4H, ArH), 8.24 (s, 1H, ArH), 9.09 (s, 1H, NH), 9.25 (s, 1H, NH), 10.83 (s, 1H, NH); ¹³C NMR (DMSO-d₆, 75 MHz) δ = 25.3, 26.8, 110.0, 116.1, 117.7, 121.8, 123.7, 127.7, 128.4, 129.0, 129.7, 130.2, 130.6, 131.0, 131.8, 136.9, 137.0, 141.0, 144.7, 145.4, 152.7, 157.3, 166.5, 196.8; mass (ES+) m/z = 473.1 (M⁺+1), 475.1 (M⁺+3). Anal. Calcd. for C₂₆H₂₁ClN₄O₃ C, 66.03; H, 4.48; N, 11.85. Found C, 66.24; H, 4.55; N, 12.06.

***N*-(6-[[3-Acetylanilino]carbonyl]amino)-2-methylquinolin-4-yl)-2-chlorobenzamide (14i)**. 87% as a yellow solid, mp 245–247 °C; ν_{\max} (KBr) 1679, 1728 (CO), 3392 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 200 MHz) δ = 2.59 (s, 3H, COCH₃), 2.66 (s, 3H, CH₃), 7.44–7.83 (m, 8H, ArH), 7.88–7.95 (m, 2H, ArH), 8.14 (s, 1H, ArH), 8.29 (s, 1H, ArH), 9.05 (s, 1H, NH), 9.08 (s, 1H, NH), 10.86 (s, 1H, NH); ¹³C NMR (DMSO-d₆, 50 MHz) δ = 25.0, 27.1, 109.8, 116.1, 117.8, 121.8, 122.5, 123.3, 123.8, 127.6, 128.3, 129.6, 130.1, 130.5, 131.8, 136.8, 137.1, 137.7, 140.3, 141.1, 144.9, 153.0, 157.1, 166.5, 198.3; mass (FAB+) m/z = 473 (M⁺+1). Anal. Calcd. for C₂₆H₂₁ClN₄O₃ C, 66.03; H, 4.48; N, 11.85. Found C, 65.79; H, 4.77; N, 12.09.

2-Chloro-*N*-(6-[[3-chloro-4-methylanilino]carbonyl]amino)-2-methylquinolin-4-yl)benzamide (14j). 98% as a white solid, mp 137–139 °C; R_t = 22.15 min; ν_{\max} (KBr) 1658, 1685 (CO), 3353 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ = 2.25 (s, 3H, CH₃), 2.62 (s, 3H, CH₃), 7.23 (s, 2H, ArH), 7.50–7.62 (m, 3H, ArH), 7.72–7.74 (m, 3H, ArH), 7.85 (s, 2H, ArH), 8.20 (s, 1H, ArH), 9.12 (s, 1H, NH), 9.20 (s, 1H, NH), 10.78 (s, 1H, NH); ¹³C NMR (DMSO-d₆, 50 MHz) δ = 19.2, 25.1, 109.7, 116.0, 117.5, 118.6, 121.7, 123.4, 127.6, 128.3, 128.8, 129.5, 130.5, 131.6, 132.4, 133.5, 134.5, 137.1, 139.1, 140.8, 141.5, 145.3, 152.9, 157.0, 166.4; mass (FAB+) m/z = 479 (M⁺+1). Anal. Calcd. for C₂₅H₂₀Cl₂N₄O₂ C, 62.64; H, 4.21; N, 11.69. Found C, 62.92; H, 3.96; N, 11.47.

2-Chloro-*N*-(6-[[3-chloro-2-methylanilino]carbonyl]amino)-2-methylquinolin-4-yl)benzamide (14k). 90% as a white solid, mp 272–274 °C; ν_{\max} (KBr) 1649 (CO), 3288 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 200 MHz) δ = 2.29 (s, 3H, CH₃), 2.62 (s, 3H, CH₃), 7.16–7.19 (m, 2H, ArH), 7.48–7.61 (m, 3H, ArH), 7.66–7.77 (m, 3H, ArH), 7.86 (s, 2H, ArH), 8.17 (s, 1H, ArH), 8.27 (s, 1H, NH), 9.29 (s, 1H, NH), 10.60 (s, 1H, NH); ¹³C NMR (DMSO-d₆, 50 MHz) δ = 15.0, 25.1, 109.4, 115.9, 121.2, 121.7, 123.4, 124.1, 126.9, 127.2, 127.5, 139.3, 130.0, 130.4, 131.7, 133.9, 136.8, 137.2, 139.2, 140.7, 145.2, 153.0, 156.9, 166.3; mass (FAB+) m/z = 473 (M⁺+1). Anal. Calcd. for C₂₅H₂₀Cl₂N₄O₂ C, 62.64; H, 4.21; N, 11.69. Found C, 62.47; H, 4.40; N, 11.67.

2-Chloro-*N*-(6-[[3,4-dichloroanilino]carbonyl]amino)-2-methylquinolin-4-yl)benzamide (14l). 84% as a white solid, mp 223–224 °C; ν_{\max} (KBr) 1702 (CO), 3303 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ = 2.64 (s, 3H, CH₃), 7.36 (dd, 1H, J_1 = 2.1 Hz, J_2 = 8.7 Hz, ArH), 7.51–

7.63 (m, 4H, ArH), 7.71–7.77 (m, 2H, ArH), 7.83–7.92 (m, 3H, ArH), 8.22 (s, 1H, ArH), 9.10 (s, 1H, NH), 9.15 (s, 1H, NH), 10.79 (s, 1H, NH); ¹³C NMR (DMSO-d₆, 75 MHz) δ = 25.3, 110.2, 116.1, 118.8, 119.8, 121.8, 123.7, 123.8, 127.7, 129.7, 130.2, 130.6, 131.1, 131.5, 131.8, 136.9, 137.0, 140.4, 141.0, 145.5, 152.9, 157.3, 166.5; mass (ES+) m/z = 499.1 (M⁺+1), 501.1 (M⁺+3). Anal. Calcd. for C₂₄H₁₇Cl₃N₄O₂ C, 57.68; H, 3.43; N, 11.21. Found C, 58.01; H, 3.54; N, 11.47.

2-Chloro-*N*-(6-[[3,5-dichloroanilino]carbonyl]amino)-2-methylquinolin-4-yl)benzamide (14m). 87% as a off-white solid, mp >250 °C; ν_{\max} (KBr) 1696 (CO), 3324 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ = 2.63 (s, 3H, CH₃), 7.16 (t, 1H, J = 1.8 Hz, ArH), 7.49–7.62 (m, 5H, ArH), 7.71 (dd, 1H, J_1 = 1.4 Hz, J_2 = 7.1 Hz, ArH), 7.76 (s, 1H, ArH), 7.81–7.89 (m, 2H, ArH), 8.20 (d, 1H, J = 1.7 Hz, ArH), 9.12 (s, 1H, NH), 9.16 (s, 1H, NH), 10.77 (s, 1H, NH); mass (ES+) m/z = 499.2 (M⁺+1), 501.1 (M⁺+3). Anal. Calcd. for C₂₄H₁₇Cl₃N₄O₂ C, 57.68; H, 3.43; N, 11.21. Found C, 57.93; H, 3.61; N, 11.08.

2-Chloro-*N*-(6-[[3-chloro-4-fluoroanilino]carbonyl]amino)-2-methylquinolin-4-yl)benzamide (14n). 90% as a white solid, mp 256–258 °C; R_t = 18.24 min; ν_{\max} (KBr) 1673 (CO), 3414 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 200 MHz) δ = 2.68 (s, 3H, CH₃), 7.37 (d, 2H, J = 6.6 Hz, ArH), 7.44–7.68 (m, 3H, ArH), 7.75–7.91 (m, 5H, ArH), 8.25 (s, 1H, ArH), 9.05 (s, 1H, NH), 9.07 (s, 1H, NH), 10.82 (s, 1H, NH); mass (FAB+) m/z = 483 (M⁺+1). Anal. Calcd. for C₂₄H₁₇Cl₂FN₄O₂ C, 59.64; H, 3.55; N, 11.59. Found C, 59.92; H, 3.56; N, 11.74.

2-Chloro-*N*-(6-[[4-chloro-3-trifluoromethylanilino]carbonyl]amino)-2-methylquinolin-4-yl)benzamide (14o). 84% as a white solid, mp >250 °C; ν_{\max} (KBr) 1671 (CO), 3414 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ = 2.63 (s, 3H, CH₃), 7.49–7.63 (m, 5H, ArH), 7.70–7.75 (m, 2H, ArH), 7.83–7.89 (m, 2H, ArH), 8.15 (s, 1H, ArH), 8.24 (d, 1H, J = 1.6 Hz, ArH), 9.11 (s, 1H, NH), 9.28 (s, 1H, NH), 10.79 (s, 1H, NH); mass (ES+) m/z = 533.1 (M⁺+1), 535.1 (M⁺+3). Anal. Calcd. for C₂₅H₁₇Cl₂F₃N₄O₂ C, 56.30; H, 3.21; N, 10.51. Found C, 56.63; H, 3.17; N, 10.70.

3-Chloro-*N*-(6-[[4-chloroanilino]carbonyl]amino)-2-methylquinolin-4-yl)benzamide (15a). 86% as an off white solid, mp 238–239 °C; ν_{\max} (KBr) 1654, 1693 (CO), 3350 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ = 2.64 (s, 3H, CH₃), 7.33 (d, 2H, J = 8.8 Hz, ArH), 7.48–7.54 (m, 2H, ArH), 7.61–7.66 (m, 2H, ArH), 7.72–7.75 (m, 1H, ArH), 7.85–7.93 (m, 2H, ArH), 8.06 (d, 1H, J = 7.7 Hz, ArH), 8.11–8.18 (m, 2H, ArH), 8.92 (s, 1H, NH), 9.07 (s, 1H, NH), 10.71 (s, 1H, NH); ¹³C NMR (DMSO-d₆, 75 MHz) δ = 25.2, 109.7, 118.0, 120.3, 122.9, 123.5, 126.1, 127.2, 128.3, 128.5, 129.2, 129.6, 131.1, 132.4, 133.9, 136.7, 137.3, 139.1, 141.4, 145.4, 153.1, 157.1, 165.3, 166.7; mass (ES+) m/z = 465.1 (M⁺+1), 467.1 (M⁺+3). Anal. Calcd. for C₂₄H₁₈Cl₂N₄O₂ C, 61.95; H, 3.90; N, 12.04. Found C, 61.80; H, 4.08; N, 12.22.

3-Chloro-*N*-(6-((4-fluoroanilino)carbonylamino)-2-methylquinolin-4-yl)benzamide (15b). 95% as a white solid, mp 261–263 °C; ν_{\max} (KBr) 1647, 1698 (CO), 3356 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz) δ = 2.63 (s, 3H, CH₃), 7.11 (t, 2H, J = 8.8 Hz, ArH), 7.45–7.51 (m, 2H, ArH), 7.58–7.66 (m, 2H, ArH), 7.74 (d, 1H, J = 7.7 Hz, ArH), 7.85–7.95 (m, 2H, ArH), 8.02–8.05 (m, 1H, ArH), 8.12–8.19 (m, 2H, ArH), 8.84 (s, 1H, NH), 9.05 (s, 1H, NH), 9.80 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 50 MHz) δ = 25.1, 109.4, 115.5, 115.9, 117.7, 120.4, 120.5, 122.8, 123.3, 128.3, 128.9, 129.4, 132.4, 134.5, 136.3, 137.3, 141.5, 145.2, 153.1, 155.4, 156.8, 160.2, 166.5; mass (FAB+) m/z = 449 (M^+ +1). Anal. Calcd. for C₂₄H₁₈ClFN₄O₂ C, 64.22; H, 4.04; N, 12.48. Found C, 64.53; H, 3.96; N, 12.65.

***N*-(6-((4-Bromoanilino)carbonylamino)-2-methylquinolin-4-yl)-3-chlorobenzamide (15c).** 98% as a white solid, mp 214–216 °C; ν_{\max} (KBr) 1694, 1706 (CO), 3347 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz) δ = 2.62 (s, 3H, CH₃), 7.43–7.50 (m, 2H, ArH), 7.57–7.65 (m, 2H, ArH), 7.73 (d, 1H, J = 7.9 Hz, ArH), 7.82–7.90 (m, 2H, ArH), 8.03 (d, 1H, J = 7.6 Hz, ArH), 8.14 (d, 2H, J = 5.0 Hz, ArH), 8.89 (s, 2H, ArH), 8.95 (s, 1H, NH), 9.09 (s, 1H, NH), 10.69 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 25.2, 109.6, 113.8, 118.0, 120.7, 122.8, 123.5, 127.2, 128.2, 129.6, 131.1, 132.0, 132.3, 133.8, 136.6, 137.3, 139.4, 141.3, 145.3, 152.8, 153.0, 157.0, 165.2; mass (ES+) m/z = 508.0 (M^+ +1). Anal. Calcd. for C₂₄H₁₈BrClN₄O₂ C, 56.55; H, 3.56; N, 10.99. Found C, 56.39; H, 3.82; N, 10.94.

3-Chloro-*N*-(6-((3-chloroanilino)carbonylamino)-2-methylquinolin-4-yl)benzamide (15d). 89% as a white solid, mp 261–263 °C; ν_{\max} (KBr) 1651, 1695 (CO), 3354 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz) δ = 2.63 (s, 3H, CH₃), 7.01 (d, 1H, J = 3.1 Hz, ArH), 7.29 (d, 2H, J = 4.7 Hz, ArH), 7.56–7.74 (m, 4H, ArH), 7.84–7.90 (m, 2H, ArH), 7.98–8.16 (m, 3H, ArH), 8.98 (s, 1H, NH), 9.10 (s, 1H, NH), 10.58 (s, 1H, NH); mass (ES+) m/z = 465.2 (M^+ +1), 487.1 (M^+ +Na). Anal. Calcd. for C₂₄H₁₈Cl₂N₄O₂ C, 61.95; H, 3.90; N, 12.04. Found C, 62.28; H, 4.18; N, 11.79.

3-Chloro-*N*-(6-((3-fluoroanilino)carbonylamino)-2-methylquinolin-4-yl)benzamide (15e). 93% as a white solid, mp 232–234 °C; ν_{\max} (KBr) 1651, 1695 (CO), 3356 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz) δ = 2.64 (s, 3H, CH₃), 6.77 (dt, 1H, J_1 = 2.2 Hz, J_2 = 8.3 Hz, ArH), 7.13–7.16 (m, 1H, ArH), 7.26–7.32 (m, 1H, ArH), 7.48 (td, 1H, J_1 = 2.1 Hz, J_2 = 11.9 Hz, ArH), 7.57–7.67 (m, 3H, ArH), 7.82–7.91 (m, 2H, ArH), 8.09–8.12 (m, 2H, ArH), 8.16 (d, 1H, J = 1.8 Hz, ArH), 9.48 (s, 1H, NH), 9.52 (s, 1H, NH), 10.58 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 50 MHz) δ = 25.3, 105.0, 105.5, 108.5, 108.9, 109.6, 114.4, 118.0, 123.1, 123.5, 128.6, 129.2, 132.7, 134.8, 137.4, 141.8, 145.4, 153.3, 157.1, 165.4, 166.8; mass (FAB+) m/z = 473 (M^+ +1). Anal. Calcd. for C₂₄H₁₈ClFN₄O₂ C, 64.22; H, 4.04; N, 12.48. Found C, 64.04; H, 4.30; N, 12.34.

3-Chloro-*N*-(6-((3-cyanoanilino)carbonylamino)-2-methylquinolin-4-yl)benzamide (15f). 86% as a yellow solid, mp 221–223 °C; ν_{\max} (KBr) 1664, 1701 (CO), 2236

(CN), 3261 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz) δ = 2.68 (s, 3H, CH₃), 7.41–7.52 (m, 2H, ArH), 7.61–7.76 (m, 4H, ArH), 7.86–7.96 (m, 2H, ArH), 8.02 (s, 2H, ArH), 8.16 (s, 1H, ArH), 8.28 (s, 1H, ArH), 9.38 (s, 1H, NH), 9.41 (s, 1H, NH), 10.55 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 24.6, 109.8, 112.1, 117.4, 119.3, 121.2, 122.5, 123.3, 124.0, 125.9, 127.3, 128.3, 130.7, 131.0, 132.5, 133.8, 136.6, 137.4, 141.0, 142.5, 153.1, 156.8, 165.5; mass (ES+) m/z = 456.2 (M^+ +1). Anal. Calcd. for C₂₅H₁₈ClN₅O₂ C, 65.86; H, 3.98; N, 15.36. Found C, 65.73; H, 3.81; N, 15.60.

3-Chloro-*N*-(2-methyl-6-((3-(trifluoromethyl)anilino)carbonylamino)quinolin-4-yl)benzamide (15g). 92% as a yellow solid, mp 236–238 °C; ν_{\max} (KBr) 1683 (CO), 3392 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz) δ = 2.63 (s, 3H, CH₃), 7.30 (d, 1H, J = 7.2 Hz, ArH), 7.50–7.71 (m, 5H, ArH), 7.88 (s, 2H, ArH), 8.00–8.17 (m, 4H, ArH), 9.13 (s, 2H, 2 x NH), 10.57 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 50 MHz) δ = 30.3, 111.3, 115.2, 119.8, 122.9, 123.8, 127.5, 127.9, 128.7, 132.4, 133.6, 134.1, 134.7, 135.5, 136.1, 137.7, 139.8, 142.2, 146.1, 146.8, 150.5, 158.3, 162.3, 171.8; mass (FAB+) m/z = 499 (M^+ +1). Anal. Calcd. for C₂₅H₁₈ClF₃N₄O₂ C, 60.19; H, 3.64; N, 11.23. Found C, 60.38; H, 4.96; N, 11.02.

***N*-(6-((3-Acetylanilino)carbonylamino)-2-methylquinolin-4-yl)-3-chlorobenzamide (15i).** 86% as a yellow solid, mp 221–223 °C; ν_{\max} (KBr) 1661, 1699 (CO), 3336 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz) δ = 2.56 (s, 3H, COCH₃), 2.63 (s, 3H, CH₃), 7.43 (t, 1H, J = 7.8 Hz, ArH), 7.57–7.65 (m, 3H, ArH), 7.71 (d, 2H, J = 5.0 Hz, ArH), 7.87 (s, 2H, ArH), 8.04–8.09 (m, 2H, ArH), 8.17 (d, 2H, J = 7.0 Hz, ArH), 9.19 (s, 1H, NH), 9.25 (s, 1H, NH), 10.23 (s, 1H, NH); mass (FAB+) m/z = 473 (M^+ +1). Anal. Calcd. for C₂₆H₂₁ClN₄O₃ C, 66.03; H, 4.48; N, 11.85. Found C, 65.79; H, 4.63; N, 11.97.

3-Chloro-*N*-(6-((3-chloro-4-methylanilino)carbonylamino)-2-methylquinolin-4-yl)benzamide (15j). 83% as a white solid, mp 264–266 °C; ν_{\max} (KBr) 1689 (CO), 3288 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz) δ = 2.29 (s, 3H, CH₃), 2.62 (s, 3H, CH₃), 7.16–7.19 (m, 2H, ArH), 7.48–7.61 (m, 3H, ArH), 7.66–7.77 (m, 3H, ArH), 7.86 (s, 2H, ArH), 8.17 (s, 1H, ArH), 8.27 (s, 1H, NH), 9.29 (s, 1H, NH), 10.60 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 50 MHz) δ = 15.0, 25.1, 109.4, 115.9, 121.2, 121.7, 123.4, 124.1, 126.9, 127.2, 127.5, 139.3, 130.0, 130.4, 131.7, 133.9, 136.8, 137.2, 139.2, 140.7, 145.2, 153.0, 156.9, 166.3; mass (FAB+) m/z = 473 (M^+ +1). Anal. Calcd. for C₂₅H₂₀Cl₂N₄O₂ C, 62.64; H, 4.21; N, 11.69. Found C, 62.52; H, 4.45; N, 11.78.

3-Chloro-*N*-(6-((3-chloro-2-methylanilino)carbonylamino)-2-methylquinolin-4-yl)benzamide (15k). 97% as a white solid, mp >250 °C; ν_{\max} (KBr) 1721 (CO), 3260 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz) δ = 2.30 (s, 3H, CH₃), 2.62 (s, 3H, CH₃), 7.16–7.19 (m, 2H, ArH), 7.49–7.62 (m, 3H, ArH), 7.67–7.79 (m, 3H, ArH), 7.87 (s, 2H, ArH), 8.17 (s, 1H, ArH), 8.29

(s, 1H, NH), 9.32 (s, 1H, NH), 10.81 (s, 1H, NH); mass (ES+) m/z = 479.1 (M^+ +1), 481.1 (M^+ +3). Anal. Calcd. for $C_{25}H_{20}Cl_2N_4O_2$ C, 62.64; H, 4.21; N, 11.69. Found C, 62.90; H, 4.47; N, 11.52.

3-Chloro-*N*-(6-[(3,4-dichloroanilino)carbonylamino]-2-methylquinolin-4-yl)benzamide (15l). 80% as a white solid, mp 249–250 °C; ν_{\max} (KBr) 1683 (CO), 3310 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.64 (s, 3H, CH₃), 7.35 (dd, 1H, J_1 = 2.1 Hz, J_2 = 8.7 Hz, ArH), 7.52 (d, 1H, J = 8.8 Hz, ArH), 7.60–7.66 (m, 2H, ArH), 7.74 (d, 1H, J = 8.0 Hz, ArH), 7.82–7.91 (m, 3H, ArH), 8.03 (d, 1H, J = 7.4 Hz, ArH), 8.16 (s, 2H, ArH), 9.08 (s, 1H, NH), 9.15 (s, 1H, NH), 10.69 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 25.2, 110.0, 117.8, 118.9, 119.9, 122.7, 123.5, 123.8, 127.2, 128.2, 129.6, 131.0, 131.6, 132.3, 133.9, 136.7, 137.0, 140.3, 141.4, 145.4, 152.9, 157.2, 165.3; mass (ES+) m/z = 499.1 (M^+ +1), 501.1 (M^+ +3). Anal. Calcd. for $C_{24}H_{17}Cl_3N_4O_2$ C, 57.68; H, 3.43; N, 11.21. Found C, 57.85; H, 3.70; N, 11.27.

3-Chloro-*N*-(6-[(3,5-dichloroanilino)carbonylamino]-2-methylquinolin-4-yl)benzamide (15m). 91% as a white solid, mp >250 °C; ν_{\max} (KBr) 1691 (CO), 3307 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.62 (s, 3H, CH₃), 7.16 (d, 1H, J = 1.8 Hz, ArH), 7.49–7.61 (m, 6H, ArH), 7.69–7.72 (m, 2H, ArH), 7.80–7.89 (m, 2H, ArH), 8.20 (s, 1H, NH), 9.12 (s, 1H, NH), 9.16 (s, 1H, NH), 10.77 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 25.3, 110.2, 116.2, 116.6, 121.3, 121.7, 129.6, 129.7, 130.2, 130.6, 131.8, 134.6, 136.8, 137.0, 141.0, 142.8, 157.3, 161.1, 166.5; mass (ES+) m/z = 499.1 (M^+ +1), 501.1 (M^+ +3). Anal. Calcd. for $C_{24}H_{17}Cl_3N_4O_2$ C, 57.68; H, 3.43; N, 11.21. Found C, 57.85; H, 3.70; N, 11.27.

3-Chloro-*N*-(6-[(3-chloro-4-fluoroanilino)carbonylamino]-2-methylquinolin-4-yl)benzamide (15n). 92% as a white solid, mp 249–251 °C; ν_{\max} (KBr) 1705 (CO), 3277 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.67 (s, 3H, CH₃), 7.34 (s, 2H, ArH), 7.61–7.79 (m, 5H, ArH), 7.91 (s, 1H, ArH), 8.10–8.17 (m, 3H, ArH), 9.17 (s, 1H, NH), 9.29 (s, 1H, NH), 10.66 (s, 1H, NH); mass (FAB+) m/z = 483 (M^+ +1). Anal. Calcd. for $C_{24}H_{17}Cl_2FN_4O_2$ C, 59.64; H, 3.55; N, 11.59. Found C, 59.92; H, 3.80; N, 11.28.

3-Chloro-*N*-(6-[(4-chloro-3-trifluoromethylanilino)carbonylamino]-2-methylquinolin-4-yl)benzamide (15o). 90% as a white solid, mp >250 °C; ν_{\max} (KBr) 1688 (CO), 3404 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.63 (s, 3H, CH₃), 7.59–7.67 (m, 5H, ArH), 7.85–7.91 (m, 2H, ArH), 8.09–8.12 (m, 4H, ArH), 9.25 (s, 1H, NH), 9.31 (s, 1H, NH), 10.65 (s, 1H, NH); mass (ES+) m/z = 533.1 (M^+ +1), 535.1 (M^+ +3). Anal. Calcd. for $C_{25}H_{17}Cl_2F_3N_4O_2$ C, 56.30; H, 3.21; N, 10.51. Found C, 56.38; H, 3.52; N, 10.64.

***N*-(6-[(4-Chloroanilino)carbonylamino]-2-methylquinolin-4-yl)-2-furamide (16a).** 90% as a white solid, mp 246–248 °C; ν_{\max} (KBr) 1715 (CO), 3361 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.62 (s, 3H,

CH₃), 6.78 (s, 1H, ArH), 7.32–7.35 (m, 2H, ArH), 7.49–7.52 (m, 3H, ArH), 7.58 (s, 1H, ArH), 7.87 (s, 2H, ArH), 8.02 (s, 1H, ArH), 8.07 (s, 1H, ArH), 8.90 (s, 1H, NH), 9.09 (s, 1H, NH), 10.42 (s, 1H, NH); mass (FAB+) m/z = 421 (M^+ +1). Anal. Calcd. for $C_{22}H_{17}ClN_4O_3$ C, 62.79; H, 4.07; N, 13.31. Found C, 63.04; H, 4.19; N, 13.65.

***N*-(6-[(4-Bromoanilino)carbonylamino]-2-methylquinolin-4-yl)-2-furamide (16c).** 89% as a white solid, mp 220–222 °C; ν_{\max} (KBr) 1661 (CO), 3368 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.62 (s, 3H, CH₃), 6.77 (t, 1H, J = 1.6 Hz, ArH), 7.46–7.49 (m, 6H, ArH), 7.58 (s, 1H, ArH), 7.87 (d, 1H, J = 3.1 Hz, ArH), 8.02 (s, 1H, ArH), 8.08 (s, 1H, ArH), 8.95 (s, 1H, NH), 9.14 (s, 1H, NH), 10.41 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 50 MHz) δ = 30.3, 114.5, 118.0, 119.0, 121.2, 122.8, 125.9, 127.8, 128.6, 134.7, 137.2, 142.4, 144.7, 146.0, 150.4, 151.9, 152.7, 158.1, 162.1, 162.4; mass (FAB+) m/z = 465 (M^+ +1). Anal. Calcd. for $C_{22}H_{17}BrN_4O_3$ C, 56.79; H, 3.68; N, 12.04. Found C, 57.13; H, 3.64; N, 12.32.

***N*-(6-[(3-Cyanoanilino)carbonylamino]-2-methylquinolin-4-yl)-2-furamide (16f).** 87% as a white solid, mp 248–250 °C; ν_{\max} (KBr) 1659 (CO), 2231 (CN), 3380 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.61 (s, 3H, CH₃), 6.65–6.67 (m, 2H, ArH), 7.26 (d, 1H, J = 3.5 Hz, ArH), 7.40–7.51 (m, 3H, ArH), 7.63 (d, 1H, J = 8.3 Hz, ArH), 7.81 (dd, 1H, J_1 = 2.1 Hz, J_2 = 9.0 Hz, ArH), 7.93–7.98 (m, 3H, ArH & NH), 8.15 (d, 1H, J = 2.0 Hz, ArH), 9.05 (s, 1H, NH), 9.25 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 23.5, 107.0, 110.9, 112.0, 119.3, 120.2, 121.3, 122.1, 122.6, 124.7, 128.9, 129.4, 137.3, 139.6, 145.8, 147.4, 151.5, 156.5, 159.7; mass (ES+) m/z = 412.2 (M^+ +1). Anal. Calcd. for $C_{23}H_{17}N_5O_3$ C, 67.15; H, 4.16; N, 17.02. Found C, 67.10; H, 4.43; N, 17.22.

***N*-(6-[(4-Acetylanilino)carbonylamino]-2-methylquinolin-4-yl)-2-furamide (16h).** 88% as a white solid, mp 243–245 °C; ν_{\max} (KBr) 1664 (CO), 3340 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.52 (s, 3H, CH₃), 2.63 (s, 3H, CH₃), 6.78 (q, 1H, J = 1.71 Hz, ArH), 7.48 (d, 1H, J = 3.36 Hz, ArH), 7.59–7.62 (m, 3H, ArH), 7.84–7.93 (m, 4H, ArH), 8.02 (s, 1H, ArH), 8.09 (d, 1H, J = 1.4 Hz, ArH), 9.18 (s, 2H, 2 x NH), 10.44 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 50 MHz) δ = 25.1, 26.7, 109.6, 112.7, 115.9, 117.8, 122.5, 123.4, 129.6, 130.0, 130.9, 131.1, 136.9, 140.8, 144.3, 144.6, 145.3, 146.6, 147.5, 152.7, 157.0, 157.1, 196.7; mass (ES+) m/z = 429.2 (M^+ +1). Anal. Calcd. for $C_{24}H_{20}N_4O_4$ C, 67.28; H, 4.71; N, 13.08. Found C, 67.55; H, 4.96; N, 13.34.

***N*-(6-[(3-Chloro-4-methylanilino)carbonylamino]-2-methylquinolin-4-yl)-2-furamide (16j).** 92% as a white solid, mp 241–243 °C; ν_{\max} (KBr) 1705 (CO), 3277 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.25 (s, 3H, CH₃), 2.61 (s, 3H, CH₃), 6.75–6.77 (m, 1H, ArH), 7.20–7.24 (m, 2H, ArH), 7.47 (d, 1H, J = 3.4 Hz, ArH), 7.57 (s, 1H, ArH), 7.67 (s, 1H, ArH), 7.86 (s, 2H, ArH), 8.01–8.03 (m, 2H, ArH), 8.82 (s, 1H, NH), 9.07 (s, 1H, NH), 10.41 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 19.3, 25.2, 109.5, 112.8, 116.0, 117.6, 118.7, 122.7, 123.5, 128.9, 129.6,

131.7, 133.6, 137.3, 139.2, 140.8, 145.3, 146.7, 147.6, 153.0, 157.0, 157.2; mass (ES+) m/z = 435.2 (M^+ +1), 437.2 (M^+ +3). Anal. Calcd. for $C_{23}H_{19}ClN_4O_3$ C, 63.52; H, 4.40; N, 12.88. Found C, 63.76; H, 4.73; N, 12.65.

***N*-(6-[[3,4-Dichloroanilino]carbonylamino]-2-methylquinolin-4-yl)-2-furamide (16l)**. 93% as a white solid, mp 247–249 °C; ν_{\max} (KBr) 1678 (CO), 3347 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz) δ = 2.61 (s, 3H, CH_3), 6.66 (m, 1H, ArH), 7.16 (d, 1H, J = 1.7 Hz, ArH), 7.26 (d, 2H, J = 3.5 Hz, ArH), 7.40 (s, 1H, ArH), 7.49 (d, 2H, J = 1.7 Hz, ArH), 7.80 (dd, 1H, J_1 = 2.1 Hz, J_2 = 9.0 Hz, ArH), 7.92–7.98 (m, 2H, ArH & NH), 8.15 (d, 1H, J = 2.0 Hz, ArH), 9.07 (s, 1H, NH), 9.28 (s, 1H, NH); mass (ES+) m/z = 455.3 (M^+ +1), 457.2 (M^+ +3). Anal. Calcd. for $C_{22}H_{16}Cl_2N_4O_3$ C, 58.04; H, 3.54; N, 12.31. Found C, 57.79; H, 3.81; N, 12.50.

***N*-(6-[[3,5-Dichloroanilino]carbonylamino]-2-methylquinolin-4-yl)-2-furamide (16m)**. 91% as a white solid, mp 246–248 °C; ν_{\max} (KBr) 1715 (CO), 3362 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz) δ = 2.59 (s, 3H, CH_3), 6.65 (t, 1H, J = 1.6 Hz, ArH), 7.15 (d, 1H, J = 1.1 Hz, ArH), 7.24 (d, 1H, J = 3.2 Hz, ArH), 7.39 (s, 1H, ArH), 7.48 (s, 2H, ArH), 7.78 (d, 1H, J = 9.3 Hz, ArH), 7.91–7.97 (m, 3H, ArH), 8.14 (s, 1H, NH), 9.08 (s, 1H, NH), 9.30 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 50 MHz) δ = 30.0, 113.6, 118.5, 122.0, 125.8, 126.7, 127.7, 129.1, 129.4, 135.2, 139.7, 143.6, 147.6, 148.8, 150.8, 152.1, 153.7, 157.7, 162.9, 166.1; mass (ES+) m/z = 455.2 (M^+ +1), 457.2 (M^+ +3). Anal. Calcd. for $C_{22}H_{16}Cl_2N_4O_3$ C, 58.04; H, 3.54; N, 12.31. Found C, 58.29; H, 3.46; N, 12.67.

***N*-(6-[[4-Chloro-3-trifluoromethylanilino]carbonylamino]-2-methylquinolin-4-yl)-2-furamide (16o)**. 88% as a white solid, mp 217–218 °C; ν_{\max} (KBr) 1709 (CO), 3392 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz) δ = 2.59 (s, 3H, CH_3), 6.63–6.65 (m, 2H, ArH), 7.24 (d, 2H, J = 3.6 Hz, ArH), 7.39 (s, 1H, ArH), 7.54–7.61 (m, 2H, ArH), 7.78 (dd, 1H, J_1 = 2.3 Hz, J_2 = 9.2 Hz, ArH), 7.91 (d, 1H, J = 0.8 Hz, ArH), 8.08 (s, 1H, NH), 8.17 (d, 1H, J = 2.0 Hz, ArH), 9.18 (s, 1H, NH), 9.26 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 24.8, 108.3, 113.3, 120.5, 122.5, 123.0, 123.6, 123.9, 124.3, 125.1, 127.0, 127.4, 130.1, 132.4, 138.5, 139.6, 143.6, 145.7, 147.0, 148.5, 152.7, 157.7, 160.9; mass (ES+) m/z = 489.1 (M^+ +1), 491.1 (M^+ +3). Anal. Calcd. for $C_{23}H_{16}ClF_3N_4O_3$ C, 58.51; H, 3.30; N, 11.46. Found C, 58.29; H, 3.46; N, 12.67.

***N*-(6-[[4-Chloroanilino]carbonylamino]-2-methylquinolin-4-yl)acetamide (17a)**. 92% as a white solid, mp 225–226 °C; R_t = 20.50 min; ν_{\max} (KBr) 1631, 1685 (CO), 3298 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz) δ = 2.22 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 7.30–7.35 (m, 2H, ArH), 7.45–7.54 (m, 2H, ArH), 7.80–7.85 (m, 2H, ArH), 8.18 (s, 1H, ArH), 8.86 (s, 1H, ArH), 8.96 (s, 1H, NH), 8.99 (s, 1H, NH), 10.16 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 24.4, 25.3, 109.5, 114.4, 120.3, 120.9, 123.6, 126.0, 129.1, 129.7, 136.9, 139.0, 139.1, 141.2, 145.3, 152.8, 153.1, 157.1, 169.9; mass (ES+) m/z =

369.1 (M^+ +1), 371.1 (M^+ +3). Anal. Calcd. for $C_{19}H_{17}ClN_4O_2$ C, 61.87; H, 4.65; N, 15.19. Found C, 61.55; H, 4.98; N, 14.86.

***N*-(6-[[3-Chloro-4-methylanilino]carbonylamino]-2-methylquinolin-4-yl)acetamide (17j)**. 68% as a white solid, mp 213–214 °C; R_t = 15.52 min; ν_{\max} (KBr) 1645, 1676 (CO), 3285 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz) δ = 2.24 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 7.25 (s, 2H, ArH), 7.75–7.85 (m, 4H, ArH), 8.18 (s, 1H, ArH), 8.91 (s, 1H, NH), 8.98 (s, 1H, NH), 10.15 (s, 1H, NH); mass (ES+) m/z = 383.2 (M^+ +1). Anal. Calcd. for $C_{20}H_{19}ClN_4O_2$ C, 62.74; H, 5.00; N, 14.63. Found C, 62.54; H, 4.89; N, 14.80.

***N*-(6-[[4-Acetylanilino]carbonylamino]-2-methylquinolin-4-yl)acetamide (17h)**. 78% as a white solid, mp 230–231 °C; R_t = 13.79 min; ν_{\max} (KBr) 1663, 1708 (CO), 3339 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz) δ = 2.09 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 7.62 (t, 2H, J = 7.1 Hz, ArH), 7.80–7.95 (m, 4H, ArH), 8.22 (s, 1H, ArH), 9.10 (s, 1H, ArH), 9.26 (s, 2H, 2 x NH), 10.20 (s, 1H, NH); mass (ES+) m/z = 377.1 (M^+ +1). Anal. Calcd. for $C_{21}H_{20}N_4O_3$ C, 67.01; H, 5.36; N, 14.88. Found C, 66.73; H, 5.52; N, 14.57.

***N*-(6-[[3,5-Dichloroanilino]carbonylamino]-2-methylquinolin-4-yl)acetamide (17m)**. 75% as a yellow solid, mp 219–220 °C; R_t = 14.57 min; ν_{\max} (KBr) 1682 (CO), 3265 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz) δ = 2.24 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 7.17 (s, 1H, ArH), 7.58 (s, 2H, ArH), 7.78–7.83 (m, 3H, ArH), 8.19 (s, 1H, ArH), 9.12 (s, 1H, NH), 9.16 (s, 1H, NH), 10.14 (s, 1H, NH); mass (FAB+) m/z = 403 (M^+ +1). Anal. Calcd. for $C_{19}H_{16}Cl_2N_4O_2$ C, 56.59; H, 4.00; N, 13.89. Found C, 56.72; H, 4.31; N, 13.62.

***N*-(6-[[4-Chloroanilino]carbonylamino]-2-methylquinolin-4-yl)-2-(4-methylpiperazin-1-yl)acetamide (24a)**. 90% as a white solid, mp 220–221 °C; R_t = 20.49 min; ν_{\max} (KBr) 1698, 1705 (CO), 3295 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz) δ = 2.16 (s, 3H, CH_3), 2.58 (brs, 7H, CH_3 & 2 x CH_2), 3.28 (m, 6H, 3 x CH_2), 7.33 (d, 2H, J = 8.0 Hz, ArH), 7.41–7.49 (m, 2H, ArH), 7.60 (d, 2H, J = 8.0 Hz, ArH), 7.85 (d, 1H, J = 8.0 Hz, ArH), 8.54 (s, 1H, ArH), 8.99 (s, 1H, NH), 9.10 (s, 1H, NH), 10.27 (s, 1H, NH); mass (ES+) m/z = 467.2 (M^+ +1). Anal. Calcd. for $C_{24}H_{27}ClN_6O_2$ C, 61.73; H, 5.83; N, 18.00. Found C, 61.97; H, 6.06; N, 17.85.

***N*-(6-[[4-Fluoromethylanilino]carbonylamino]-2-methylquinolin-4-yl)-2-(4-methylpiperazin-1-yl)acetamide (24b)**. 90% as a white solid, mp 216–217 °C; R_t = 7.27 min; ν_{\max} (KBr) 1635, 1708 (CO), 3305 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz) δ = 2.16 (s, 3H, CH_3), 2.58 (brs, 11H, CH_3 & 4 x CH_2), 3.27 (s, 2H, CH_2), 7.13 (t, 2H, J = 8.8 Hz, ArH), 7.44 (d, 1H, J = 9.0 Hz, ArH), 7.55–7.60 (m, 2H, ArH), 7.85 (d, 1H, J = 9.0 Hz, ArH), 8.16 (s, 1H, ArH), 8.55 (s, 1H, ArH), 8.87 (s, 1H, NH), 9.05 (s, 1H, NH), 10.26 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 24.2, 44.4, 52.2, 53.4, 60.9, 104.9, 109.4, 114.2, 114.5,

117.7, 119.3, 122.0, 129.0, 135.1, 136.3, 138.7, 143.6, 151.8, 155.9, 168.6; mass (ES+) m/z = 451.2 (M^+ +1). Anal. Calcd. for $C_{24}H_{27}FN_6O_2$ C, 63.98; H, 6.04; N, 18.65. Found C, 63.72; H, 6.31; N, 18.51.

***N*-(6-[[4-Bromoanilino]carbonyl]amino)-2-methylquinolin-4-yl)-2-(4-methylpiperazin-1-yl)acetamide (24c).**

61% as a white solid, mp 225–227 °C; R_t = 11.27 min; ν_{\max} (KBr) 1684, 1698 (CO), 3300 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.42 (s, 3H, CH₃), 2.58 (s, 3H, CH₃), 2.76 (brs, 4H, 2 x CH₂), 2.95 (brs, 4H, 2 x CH₂), 3.33 (s, 2H, CH₂), 7.46–7.55 (m, 5H, ArH), 7.85 (d, 1H, J = 9.0 Hz, ArH), 8.15 (s, 1H, ArH), 8.46 (s, 1H, ArH), 9.53 (s, 1H, NH), 9.71 (s, 1H, NH), 10.23 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 24.2, 43.3, 51.0, 52.8, 60.6, 104.4, 109.3, 112.4, 117.8, 119.3, 121.7, 128.9, 130.7, 136.4, 138.3, 138.6, 143.5, 151.9, 155.8, 168.3; mass (ES+) m/z = 511.2 (M^+ +1), 513.1 (M^+ +3). Anal. Calcd. for $C_{24}H_{27}BrN_6O_2$ C, 56.36; H, 5.32; N, 16.43. Found C, 56.04; H, 5.66; N, 16.09.

***N*-(6-[[3-Chloromethylanilino]carbonyl]amino)-2-methylquinolin-4-yl)-2-(4-methylpiperazin-1-yl)acetamide (24d).**

81% as a white solid, mp 196–198 °C; ν_{\max} (KBr) 1702 (CO), 3303 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.20 (s, 3H, CH₃), 2.58 (brs, 11H, 2 x CH₃ & 4 x CH₂), 3.28 (s, 2H, CH₂), 7.04 (dd, 1H, J_1 = 1.8 Hz, J_2 = 6.9 Hz, ArH), 7.26–7.34 (m, 2H, ArH), 7.43 (dd, 1H, J_1 = 1.8 Hz, J_2 = 8.9 Hz, ArH), 7.86 (d, 1H, J = 8.9 Hz, ArH), 7.94 (s, 1H, ArH), 8.18 (s, 1H, ArH), 8.59 (d, 1H, J = 1.5 Hz, ArH), 9.06 (s, 1H, NH), 9.15 (s, 1H, NH), 10.29 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 50 MHz) δ = 25.9, 45.9, 53.6, 55.0, 62.5, 106.5, 110.9, 117.6, 118.6, 119.3, 122.5, 123.6, 130.7, 131.2, 134.2, 137.8, 140.4, 142.0, 145.3, 153.3, 157.7, 170.2; mass (ES+) m/z = 467.2 (M^+ +1), 469.1 (M^+ +3). Anal. Calcd. for $C_{24}H_{27}ClN_6O_2$ C, 61.73; H, 5.83; N, 18.00. Found C, 61.68; H, 6.15; N, 17.78.

***N*-(6-[[3-Fluoromethylanilino]carbonyl]amino)-2-methylquinolin-4-yl)-2-(4-methylpiperazin-1-yl)acetamide (24e).**

84% as a light green solid, mp 170–172 °C; ν_{\max} (KBr) 1651, 1707 (CO), 3366 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.18 (s, 3H, CH₃), 2.58–2.62 (m, 11H, CH₃ & 4 x CH₂), 3.27 (s, 2H, CH₂), 6.77 (dt, 1H, J_1 = 1.8 Hz, J_2 = 8.2 Hz, ArH), 7.20–7.33 (m, 2H, ArH), 7.49 (dd, 1H, J_1 = 1.7 Hz, J_2 = 9.0 Hz, ArH), 7.71–7.75 (m, 1H, ArH), 7.84 (d, 1H, J = 8.9 Hz, ArH), 8.18 (s, 1H, ArH), 8.60 (d, 1H, J = 1.5 Hz, ArH), 9.84 (s, 1H, NH), 9.91 (s, 1H, NH), 10.26 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 50 MHz) δ = 25.5, 27.2, 45.7, 53.9, 54.7, 62.2, 69.7, 106.4, 110.6, 118.0, 119.0, 122.5, 123.4, 129.5, 130.3, 137.4, 137.9, 140.0, 144.9, 153.0, 157.3, 169.8, 198.1; mass (ES+) m/z = 451.2 (M^+ +1). Anal. Calcd. for $C_{24}H_{27}FN_6O_2$ C, 63.98; H, 6.04; N, 18.65. Found C, 63.72; H, 6.30; N, 18.68.

***N*-(6-[[3-Cyanoanilino]carbonyl]amino)-2-methylquinolin-4-yl)-2-(4-methylpiperazin-1-yl)acetamide (24f).**

57% as a white solid, mp 169–170 °C; R_t = 7.69 min; ν_{\max} (KBr) 1695 (CO), 2230 (CN), 3397 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 200 MHz) δ = 2.25 (s, 3H, CH₃), 2.64 (s, 3H, CH₃), 2.69 (s, 8H, 4 x CH₂), 3.34 (s, 2H,

CH₂), 7.47–7.61 (m, 3H, ArH), 7.70 (d, 1H, J = 7.6 Hz, ArH), 7.93 (d, 1H, J = 9.0 Hz, ArH), 8.26–8.37 (m, 2H, ArH), 8.67 (s, 1H, ArH), 9.28 (s, 1H, NH), 9.32 (s, 1H, NH), 10.35 (s, 1H, NH); mass (ES+) m/z = 458.2 (M^+ +1). Anal. Calcd. for $C_{25}H_{27}N_7O_2$ C, 65.63; H, 5.95; N, 21.43. Found C, 65.42; H, 6.06; N, 21.22.

***N*-(2-Methyl-6-[[3-(trifluoromethyl)anilino]carbonyl]amino)quinolin-4-yl]-2-(4-methylpiperazin-1-yl)acetamide (24g).**

76% as an off white solid, mp 148–149 °C; R_t = 11.32 min; ν_{\max} (KBr) 1710 (CO), 3301 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.08 (s, 3H, CH₃), 2.57–2.61 (m, 7H, CH₃ & 2 x CH₂), 3.26 (s, 2H, CH₂), 3.45 (s, 4H, 2 x CH₂), 7.32 (d, 1H, J = 7.5 Hz, ArH), 7.43–7.61 (m, 3H, ArH), 7.86 (d, 1H, J = 8.9 Hz, ArH), 8.18 (d, 2H, J = 9.6 Hz, ArH), 8.56 (d, 1H, J = 1.7 Hz, ArH), 9.19 (s, 1H, NH), 9.21 (s, 1H, NH), 10.29 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 24.1, 44.2, 52.0, 53.3, 60.8, 105.0, 109.2, 113.5, 117.6, 121.1, 122.1, 128.6, 129.0, 136.0, 138.7, 139.6, 143.6, 151.6, 156.1, 168.6; mass (ES+) m/z = 501.2 (M^+ +1). Anal. Calcd. for $C_{25}H_{27}F_3N_6O_2$ C, 59.99; H, 5.44; N, 16.79. Found C, 59.98; H, 5.73; N, 16.83.

***N*-(6-[[4-Acetylanilino]carbonyl]amino)-2-methylquinolin-4-yl)-2-(4-methylpiperazin-1-yl)acetamide (24h).**

75% as a white solid, mp 226–228 °C; ν_{\max} (KBr) 1658, 1707 (CO), 3338 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.19 (s, 3H, CH₃), 2.51 (s, 3H, CH₃), 2.59–2.62 (m, 11H, CH₃ & 4 x CH₂), 3.29 (s, 2H, CH₂), 7.47 (dd, 1H, J_1 = 1.9 Hz, J_2 = 8.9 Hz, ArH), 7.70 (d, 2H, J = 8.7 Hz, ArH), 7.85–7.93 (m, 3H, ArH), 8.17 (s, 1H, ArH), 8.56 (d, 1H, J = 1.9 Hz, ArH), 9.20 (s, 1H, NH), 9.28 (s, 1H, NH), 10.28 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 24.2, 25.5, 44.5, 52.2, 53.4, 61.0, 105.2, 109.4, 116.5, 117.7, 122.0, 128.7, 129.0, 129.8, 135.9, 138.8, 143.4, 143.7, 151.3, 156.1, 168.5, 195.5; mass (ES+) m/z = 475.2 (M^+ +1). Anal. Calcd. for $C_{26}H_{30}N_6O_3$ C, 65.80; H, 6.37; N, 17.71. Found C, 65.57; H, 6.52; N, 17.43.

***N*-(6-[[3-Acetylanilino]carbonyl]amino)-2-methylquinolin-4-yl)-2-(4-methylpiperazin-1-yl)acetamide (24i).**

81% as a white solid, mp 235–237 °C; ν_{\max} (KBr) 1676, 1709 (CO), 3247 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 2.08 (s, 3H, CH₃), 2.58 (brs, 14H, 2 x CH₃ & 4 x CH₂), 3.28 (s, 2H, CH₂), 7.42–7.49 (m, 2H, ArH), 7.61 (d, 1H, J = 7.7 Hz, ArH), 7.82–7.88 (m, 2H, ArH), 8.11 (s, 1H, ArH), 8.16 (s, 1H, ArH), 8.55 (d, 1H, J = 1.1 Hz, ArH), 9.04 (s, 1H, NH), 9.07 (s, 1H, NH), 10.29 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ = 25.5, 27.2, 45.7, 53.5, 54.7, 62.2, 69.7, 106.4, 110.6, 118.0, 119.0, 122.5, 123.4, 129.5, 130.3, 137.4, 137.9, 140.0, 140.5, 144.9, 153.0, 157.3, 169.8, 198.1; mass (ES+) m/z = 475.2 (M^+ +1). Anal. Calcd. for $C_{26}H_{30}N_6O_3$ C, 65.80; H, 6.37; N, 17.71. Found C, 65.97; H, 6.51; N, 17.73.

***N*-(6-[[3-Chloro-4-methylanilino]carbonyl]amino)-2-methylquinolin-4-yl)-2-(4-methylpiperazin-1-yl)acetamide (24j).**

98% as a white solid, mp 217–219 °C; R_t = 22.65 min; ν_{\max} (KBr) 1685 (CO), 3293 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 200 MHz) δ = 2.20 (s, 3H, CH₃), 2.28 (s,

3H, CH₃), 2.60 (s, 3H, CH₃), 2.64 (brs, 4H, 2 x CH₂), 3.28–3.30 (m, 4H, 2 x CH₂), 3.48 (s, 2H, CH₂), 7.24 (d, 1H, *J* = 4.2 Hz, ArH), 7.44 (d, 1H, *J* = 7.3 Hz, ArH), 7.70 (d, 1H, *J* = 1.4 Hz, ArH), 7.88 (d, 1H, *J* = 8.9 Hz, ArH), 7.97 (s, 1H, ArH), 8.21 (s, 1H, ArH), 8.62 (s, 1H, ArH), 8.94 (s, 1H, NH), 9.11 (s, 1H, NH), 10.32 (s, 1H, NH); ¹³C NMR (DMSO-d₆, 75 MHz) δ = 18.0, 24.2, 44.6, 52.2, 53.4, 61.0, 104.7, 109.2, 116.1, 116.3, 117.5, 117.6, 122.0, 127.6, 129.0, 130.2, 132.3, 132.4, 136.2, 137.9, 138.7, 143.6, 151.5, 156.0, 168.6; mass (FAB+) *m/z* = 481 (M⁺+1). Anal. Calcd. for C₂₅H₂₉ClN₆O₂ C, 62.43; H, 6.08; N, 17.47. Found C, 62.79; H, 6.10; N, 17.64.

***N*-(6-[[3-Chloro-2-methylanilino]carbonylamino]-2-methylquinolin-4-yl)-2-(4-methylpiperazin-1-yl)acetamide (24k)**. 74% as a white solid, mp 238–240 °C; *v*_{max} (KBr) 1638, 1714 (CO), 3284 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ = 2.09 (s, 3H, CH₃), 2.34 (s, 3H, CH₃), 2.54–2.58 (m, 11H, 4 x CH₂ & CH₃), 3.26 (s, 2H, CH₂), 7.17 (d, 2H, *J* = 4.5 Hz, ArH), 7.44 (dd, 1H, *J*₁ = 1.4 Hz, *J*₂ = 8.9 Hz, ArH), 7.85–7.92 (m, 2H, ArH), 8.17 (s, 1H, ArH), 8.28 (s, 1H, ArH), 8.58 (s, 1H, NH), 9.40 (s, 1H, NH), 10.24 (s, 1H, NH); ¹³C NMR (DMSO-d₆, 50 MHz) δ = 14.1, 25.5, 45.6, 53.5, 54.6, 62.3, 113.2, 116.7, 121.7, 124.3, 127.3, 127.4, 128.3, 128.7, 130.7, 134.0, 134.7, 134.9, 139.3, 140.0, 148.1, 153.3, 169.9; mass (ES+) *m/z* = 481.2 (M⁺+1), 483.2 (M⁺+3). Anal. Calcd. for C₂₅H₂₉ClN₆O₂ C, 62.43; H, 6.08; N, 17.47. Found C, 62.75; H, 6.10; N, 17.69.

***N*-(6-[[3,4-Dichloroanilino]carbonylamino]-2-methylquinolin-4-yl)-2-(4-isopropylpiperazin-1-yl)acetamide (24l)**. 74% as a white solid, mp 227–229 °C; *v*_{max} (KBr) 1686, 1709 (CO), 3291 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ = 2.17 (s, 3H, CH₃), 2.58 (s, 3H, CH₃), 2.61 (s, 8H, 4 x CH₂), 3.28 (s, 2H, CH₂), 7.32 (dd, 1H, *J*₁ = 3.0 Hz, *J*₂ = 9.0 Hz, ArH), 7.44 (dd, 1H, *J*₁ = 3.0 Hz, *J*₂ = 9.0 Hz, ArH), 7.53 (d, 1H, *J* = 9.0 Hz, ArH), 7.87 (d, 1H, *J* = 9.0 Hz, ArH), 8.12 (d, 1H, *J* = 3.0 Hz, ArH), 8.18 (s, 1H, ArH), 8.57 (d, 1H, *J* = 3.0 Hz, ArH), 9.12 (s, 1H, NH), 9.15 (s, 1H, NH), 10.28 (s, 1H, NH); mass (ES+) *m/z* = 501.2 (M⁺+1), 503.1 (M⁺+3). Anal. Calcd. for C₂₄H₂₆Cl₂N₆O₂ C, 57.49; H, 5.23; N, 16.76. Found C, 57.19; H, 5.50; N, 16.51.

***N*-(6-[[3,5-Dichloroanilino]carbonylamino]-2-methylquinolin-4-yl)-2-(4-methylpiperazin-1-yl)acetamide (24m)**. 65% as a white solid, mp 160–162 °C; *R*_f = 15.46 min; *v*_{max} (KBr) 1698, 1719 (CO), 3353 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ = 2.19 (s, 3H, CH₃), 2.57 (s, 3H, CH₃), 2.63 (s, 8H, 4 x CH₂), 3.26 (s, 2H, CH₂), 7.15 (s, 1H, ArH), 7.43 (d, 1H, *J* = 6.0 Hz, ArH), 7.64 (s, 2H, ArH), 7.86 (d, 1H, *J* = 9.0 Hz, ArH), 8.18 (s, 1H, ArH), 8.56 (s, 1H, ArH), 9.20 (s, 1H, NH), 9.24 (s, 1H, NH), 10.26 (s, 1H, NH); ¹³C NMR (DMSO-d₆, 75 MHz) δ = 24.2, 44.4, 52.1, 53.4, 60.9, 78.3, 105.0, 109.1, 115.6, 117.5, 120.2, 122.0, 129.0, 133.3, 135.8, 138.7, 141.3, 143.7, 151.3, 156.2, 168.5; mass (ES+) *m/z* = 501.2 (M⁺+1), 503.1 (M⁺+3). Anal. Calcd. for C₂₄H₂₆Cl₂N₆O₂ C, 57.49; H, 5.23; N, 16.76. Found C, 57.31; H, 5.16; N, 16.83.

***N*-(6-[[4-Chloro-3-trifluoromethylanilino]carbonylamino]-2-methylquinolin-4-yl)-2-(4-methylpiperazin-1-yl)acetamide (24o)**. 62% as a white solid, mp 185–186 °C; *v*_{max} (KBr) 1684, 1718 (CO), 3281 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 200 MHz) δ = 2.06 (s, 3H, CH₃), 2.59 (brs, 7H, CH₃ & 2 x CH₂), 3.28–3.31 (m, 4H, 2 x CH₂), 3.46 (s, 2H, CH₂), 7.46 (d, 1H, *J* = 9.0 Hz, ArH), 7.60–7.63 (m, 2H, ArH), 7.87 (d, 1H, *J* = 9.0 Hz, ArH), 8.20 (s, 1H, ArH), 8.32 (d, 1H, *J* = 1.3 Hz, ArH), 8.57 (s, 1H, ArH), 9.28 (s, 1H, NH), 9.35 (s, 1H, NH), 10.32 (s, 1H, NH); mass (ES+) *m/z* = 535.1 (M⁺+1), 537.1 (M⁺+3). Anal. Calcd. for C₂₅H₂₆ClF₃N₆O₂ C, 56.13; H, 4.90; N, 15.71. Found C, 56.05; H, 4.77; N, 15.79.

***N*-(2-Methyl-6-[[3-(trifluoromethyl)anilino]carbonylamino]quinolin-4-yl)-2-(4-ethylpiperazin-1-yl)acetamide (25g)**. 79% as a white solid, mp 139–141 °C; *v*_{max} (KBr) 1684, 1717 (CO), 3338 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ = 0.84 (t, 3H, *J* = 7.2 Hz, CH₂CH₃), 2.21 (q, 2H, *J* = 7.2 Hz, CH₂CH₃), 2.54–2.58 (m, 11H, CH₃ & 4 x CH₂), 3.27 (s, 2H, CH₂), 7.32 (d, 1H, *J* = 7.7 Hz, ArH), 7.44–7.54 (m, 2H, ArH), 7.64 (d, 1H, *J* = 8.3 Hz, ArH), 7.86 (d, 1H, *J* = 9.0 Hz, ArH), 8.15 (d, 2H, *J* = 10.7 Hz, ArH), 8.56 (d, 1H, *J* = 1.8 Hz, ArH), 9.22 (s, 1H, NH), 9.23 (s, 1H, NH), 10.32 (s, 1H, NH); ¹³C NMR (DMSO-d₆, 75 MHz) δ = 11.1, 24.2, 50.3, 51.2, 52.2, 60.9, 98.7, 109.2, 117.6, 122.1, 129.0, 136.0, 138.7, 139.6, 143.7, 151.7, 156.1, 168.5; mass (ES+) *m/z* = 515.3 (M⁺+1). Anal. Calcd. for C₂₆H₂₉F₃N₆O₂ C, 60.69; H, 5.68; N, 16.33. Found C, 60.93; H, 5.54; N, 16.48.

***N*-(6-[[3-Chloro-4-methylanilino]carbonylamino]-2-methylquinolin-4-yl)-2-(4-ethylpiperazin-1-yl)acetamide (25j)**. 88% as a white solid, mp 213–215 °C; *v*_{max} (KBr) 1674, 1710 (CO), 3283 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ = 0.91 (t, 3H, *J* = 7.1 Hz, CH₂CH₃), 2.26–2.35 (m, 5H, CH₃, & CH₂CH₃), 2.58 (s, 3H, CH₃), 2.64 (brs, 8H, 4 x CH₂), 3.27 (s, 2H, CH₂), 7.22 (s, 2H, ArH), 7.42 (dd, 1H, *J*₁ = 1.9 Hz, *J*₂ = 9.0 Hz, ArH), 7.85 (d, 2H, *J* = 8.6 Hz, ArH), 8.17 (s, 1H, ArH), 8.56 (s, 1H, *J* = 1.8 Hz, ArH), 8.92 (s, 1H, NH), 9.09 (s, 1H, NH), 10.29 (s, 1H, NH); ¹³C NMR (DMSO-d₆, 75 MHz) δ = 11.3, 18.0, 24.2, 29.8, 50.4, 51.2, 52.3, 61.0, 104.8, 109.1, 116.3, 117.5, 117.6, 122.0, 127.6, 129.0, 130.2, 132.4, 136.1, 137.9, 138.7, 143.6, 151.6, 156.0, 168.5; mass (ES+) *m/z* = 495.4 (M⁺+1), 497.2 (M⁺+3). Anal. Calcd. for C₂₆H₃₁ClN₅O₂ C, 63.08; H, 6.31; N, 16.98. Found C, 59.97; H, 6.64; N, 16.92.

***N*-(6-[[3,4-Dichloroanilino]carbonylamino]-2-methylquinolin-4-yl)-2-(4-ethylpiperazin-1-yl)acetamide (25i)**. 61% as a white solid, mp 190–192 °C; *R*_f = 12.35 min; *v*_{max} (KBr) 1710 (CO), 3353 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ = 0.90 (t, 3H, *J* = 7.1 Hz, CH₂CH₃), 2.29 (q, 2H, *J* = 7.1 Hz, CH₂CH₃), 2.58 (s, 3H, CH₃), 2.64 (brs, 4H, 4 x CH₂), 3.17 (s, 4H, 4 x CH₂), 3.27 (s, 2H, CH₂), 7.33 (dd, 1H, *J*₁ = 2.4 Hz, *J*₂ = 8.8 Hz, ArH), 7.44 (dd, 1H, *J*₁ = 1.7 Hz, *J*₂ = 9.0 Hz, ArH), 7.51 (d, 1H, *J* = 8.7 Hz, ArH), 7.86 (d, 1H, *J* = 8.9 Hz, ArH), 8.05 (d, 1H, *J* = 2.3 Hz, ArH), 8.17 (s, 1H, ArH), 8.54 (d, 1H, *J* = 1.5 Hz, ArH), 9.17 (s, 1H, NH), 9.21 (s, 1H, NH), 10.30 (s, 1H, NH); ¹³C NMR

(DMSO- d_6 , 50 MHz) δ = 12.4, 25.4, 51.6, 52.4, 53.4, 62.1, 110.3, 119.0, 120.0, 123.3, 123.7, 130.2, 130.8, 131.5, 137.1, 139.9, 140.1, 144.8, 152.7, 157.4, 169.7; mass (ES+) m/z = 515.4 (M^+ +1), 517.2 (M^+ +3). Anal. Calcd. for $C_{25}H_{28}Cl_2N_6O_2$ C, 58.26; H, 5.48; N, 16.30. Found C, 58.31; H, 5.53; N, 16.47.

***N*-(6-[[3,5-Dichloroanilino]carbonyl]amino)-2-methylquinolin-4-yl)-2-(4-ethylpiperazin-1-yl)acetamide (25m).** 64% as a white solid, mp 186–188 °C; ν_{\max} (KBr) 1699, 1705 (CO), 3282 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 0.91 (t, 3H, J = 6.9 Hz, CH_2CH_3), 2.31 (q, 2H, J = 7.0 Hz, CH_2CH_3), 2.58 (s, 3H, CH_3), 2.64 (brs, 8H, 4 x CH_2), 3.27 (s, 2H, CH_2), 7.17 (s, 1H, ArH), 7.44 (d, 1H, J = 8.6 Hz, ArH), 7.63 (s, 2H, ArH), 7.86 (d, 1H, J = 8.8 Hz, ArH), 8.18 (s, 1H, ArH), 8.55 (s, 1H, ArH), 9.25 (s, 1H, NH), 9.31 (s, 1H, NH), 10.30 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 50 MHz) δ = 12.5, 25.4, 51.6, 52.4, 53.3, 62.1, 106.4, 110.3, 116.9, 118.7, 121.4, 123.3, 130.2, 134.5, 137.0, 139.9, 142.5, 152.6, 157.4, 169.7; mass (ES+) m/z = 515.3 (M^+ +1), 517.2 (M^+ +3). Anal. Calcd. for $C_{25}H_{28}Cl_2N_6O_2$ C, 58.26; H, 5.48; N, 16.30. Found C, 58.40; H, 5.61; N, 16.24.

***N*-(6-[[4-Chloroanilino]carbonyl]amino)-2-methylquinolin-4-yl)-2-piperidin-1-ylacetamide (26a).** 83% as a white solid, mp 249–250 °C; ν_{\max} (KBr) 1672, 1716 (CO), 3361 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 1.46 (brs, 2H, CH_2), 1.82 (brs, 4H, 2 x CH_2), 2.58 (s, 7H, CH_3 & 2 x CH_2), 3.22 (s, 2H, CH_2), 7.34 (d, 2H, J = 8.8 Hz, ArH), 7.44 (dd, 1H, J_1 = 1.9 Hz, J_2 = 9.0 Hz, ArH), 7.57 (d, 2H, J = 8.9 Hz, ArH), 7.85 (d, 1H, J = 9.0 Hz, ArH), 8.22 (s, 1H, ArH), 8.63 (d, 1H, J = 1.7 Hz, ArH), 8.96 (s, 1H, NH), 9.08 (s, 1H, NH), 10.46 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 50 MHz) δ = 22.8, 25.8, 45.9, 53.7, 54.9, 62.7, 105.5, 106.0, 110.8, 114.7, 119.3, 123.8, 130.4, 130.7, 130.9, 138.9, 140.3, 145.1, 154.0, 157.3, 160.9, 167.8, 170.3; mass (ES+) m/z = 452.2 (M^+ +1), 454.1 (M^+ +3). Anal. Calcd. for $C_{24}H_{26}ClN_5O_2$ C, 63.78; H, 5.80; N, 15.50. Found C, 63.72; H, 6.04; N, 15.82.

***N*-[2-Methyl-6-((3-(trifluoromethyl)anilino]carbonyl)amino)quinolin-4-yl)-2-piperidin-1-ylacetamide (26g).** 91% as a white solid, mp 219–220 °C; R_t = 17.26 min; ν_{\max} (KBr) 1668, 1718 (CO), 3367 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 1.42 (brs, 2H, CH_2), 1.80 (brs, 4H, 2 x CH_2), 2.57 (s, 7H, CH_3 & 2 x CH_2), 3.21 (s, 2H, CH_2), 7.32 (d, 1H, J = 6.6 Hz, ArH), 7.40 (dd, 1H, J_1 = 2.0 Hz, J_2 = 9.0 Hz, ArH), 7.50–7.52 (m, 2H, ArH), 7.85 (d, 1H, J = 9.0 Hz, ArH), 8.24 (s, 2H, ArH), 8.66 (d, 1H, J = 1.9 Hz, ArH), 9.18 (s, 1H, NH), 9.19 (s, 1H, NH), 10.48 (s, 1H, NH); mass (ES+) m/z = 486.3 (M^+ +1). Anal. Calcd. for $C_{25}H_{26}F_3N_5O_2$ C, 61.85; H, 5.40; N, 14.42. Found C, 61.59; H, 5.64; N, 14.57.

***N*-(6-[[3-Chloro-4-methylanilino]carbonyl]amino)-2-methylquinolin-4-yl)-2-piperidin-1-ylacetamide (26i).** 82% as a white solid, mp 265–266 °C; ν_{\max} (KBr) 1682 (CO), 3287 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 1.51 (brs, 2H, CH_2), 1.85 (brs, 4H, 2 x CH_2), 2.27 (s, 3H, CH_3), 2.58 (s, 7H, CH_3 & 2 x CH_2), 3.22 (s, 2H, CH_2), 7.13

(dd, 1H, J_1 = 1.8 Hz, J_2 = 8.3 Hz, ArH), 7.25 (d, 1H, J = 8.2 Hz, ArH), 7.38–7.41 (m, 1H, ArH), 7.85 (d, 1H, J = 8.9 Hz, ArH), 7.95 (d, 1H, J = 1.7 Hz, ArH), 8.25 (s, 1H, ArH), 8.70 (s, 1H, ArH), 8.91 (s, 1H, NH), 9.08 (s, 1H, NH), 10.48 (s, 1H, NH); mass (ES+) m/z = 466.1 (M^+ +1), 468.1 (M^+ +3). Anal. Calcd. for $C_{25}H_{28}ClN_5O_2$ C, 64.44; H, 6.06; N, 15.03. Found C, 64.19; H, 6.33; N, 14.97.

***N*-(6-[[3,4-Dichloroanilino]carbonyl]amino)-2-methylquinolin-4-yl)-2-piperidin-1-ylacetamide (26l).** 89% as a white solid, mp 215–216 °C; ν_{\max} (KBr) 1670, 1716 (CO), 3361 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 1.49 (brs, 2H, CH_2), 1.83 (brs, 4H, 2 x CH_2), 2.57 (s, 7H, CH_3 & 2 x CH_2), 3.21 (s, 2H, CH_2), 7.22 (dd, 1H, J_1 = 2.5 Hz, J_2 = 8.8 Hz, ArH), 7.40 (dd, 1H, J_1 = 2.0 Hz, J_2 = 9.0 Hz, ArH), 7.52 (d, 1H, J = 8.7 Hz, ArH), 7.84 (d, 1H, J = 8.9 Hz, ArH), 8.16 (d, 1H, J = 2.4 Hz, ArH), 8.24 (s, 1H, ArH), 8.68 (d, 1H, J = 1.9 Hz, ArH), 9.16 (s, 1H, NH), 9.20 (s, 1H, NH), 10.48 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 50 MHz) δ = 22.7, 24.2, 24.5, 53.6, 61.8, 104.5, 108.4, 117.2, 117.4, 118.2, 121.8, 122.4, 129.1, 129.7, 130.4, 136.0, 138.6, 139.0, 143.6, 151.5, 156.2, 168.9; mass (ES+) m/z = 486.4 (M^+ +1), 488.1 (M^+ +3). Anal. Calcd. for $C_{24}H_{25}Cl_2N_5O_2$ C, 59.26; H, 5.18; N, 14.40. Found C, 59.04; H, 5.35; N, 14.72.

***N*-(6-[[3,5-Dichloroanilino]carbonyl]amino)-2-methylquinolin-4-yl)-2-piperidin-1-ylacetamide (26m).** 89% as a white solid, mp 218–219 °C; ν_{\max} (KBr) 1680, 1720 (CO), 3255 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 1.52 (s, 2H, CH_2), 1.85 (s, 4H, 2 x CH_2), 2.59 (s, 7H, CH_3 & 2 x CH_2), 3.35 (s, 2H, CH_2), 7.19 (s, 1H, ArH), 7.42 (dd, 1H, J_1 = 1.6 Hz, J_2 = 9.0 Hz, ArH), 7.64 (d, 2H, J = 1.5 Hz, ArH), 7.86 (d, 1H, J = 9.0 Hz, ArH), 8.26 (s, 1H, ArH), 8.71 (s, 1H, ArH), 9.21 (s, 1H, NH), 9.29 (s, 1H, NH), 10.49 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 50 MHz) δ = 24.4, 25.9, 26.2, 55.3, 63.5, 99.0, 104.8, 106.3, 110.1, 117.0, 118.8, 121.9, 123.6, 130.8, 135.0, 137.6, 140.4, 143.1, 145.3, 153.1, 157.9, 170.6; mass (ES+) m/z = 486.1 (M^+ +1), 488.1 (M^+ +3). Anal. Calcd. for $C_{24}H_{25}Cl_2N_5O_2$ C, 59.26; H, 5.18; N, 14.40. Found C, 59.12; H, 5.07; N, 14.61.

***N*-(6-[[3-Chloro-4-(trifluoromethyl)anilino]carbonyl]amino)-2-methylquinolin-4-yl)-2-piperidin-1-ylacetamide (26o).** 86% as a white solid, mp 225–226 °C; ν_{\max} (KBr) 1682, 1728 (CO), 3353 (NH) cm^{-1} ; 1H NMR (DMSO- d_6 , 300 MHz) δ = 1.41 (brs, 2H, CH_2), 1.77 (brs, 4H, 2 x CH_2), 2.59 (s, 7H, CH_3 & 2 x CH_2), 3.37 (s, 2H, CH_2), 7.45 (dd, 1H, J_1 = 1.5 Hz, J_2 = 9.0 Hz, ArH), 7.58–7.65 (m, 2H, ArH), 7.87 (d, 2H, J = 9.0 Hz, ArH), 8.23 (s, 1H, ArH), 8.30 (t, 1H, J = 3.1 Hz, ArH), 9.23 (s, 1H, NH), 9.30 (s, 1H, NH), 10.47 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 50 MHz) δ = 24.3, 25.9, 26.0, 26.1, 55.3, 63.4, 67.9, 106.4, 110.4, 117.4, 119.0, 123.4, 123.7, 123.9, 130.8, 132.8, 137.6, 140.1, 140.4, 145.3, 153.3, 157.9, 170.6; mass (ES+) m/z = 520.1 (M^+ +1), 522.1 (M^+ +3). Anal. Calcd. for $C_{25}H_{25}ClF_3N_5O_2$ C, 57.75; H, 4.85; N, 13.47. Found C, 57.94; H, 5.02; N, 13.30.

Materials and Methods

In vitro antimalarial assay

The *in 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 (IC₅₀) 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 CO₂ 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 CO₂ 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 = $CS - TS \times 100 / CS$

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

For evaluation of IC₅₀ 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 IC₅₀ 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 (CC₅₀) 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 1×10^6 *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 three *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 28days or until animals survived.

Docking studies

LigandFit, a modern docking program within Cerius2 version 4.10 (Cerius2 Version 4.10 (2005), Accelrys Inc., San Diego, USA), was used for docking runs.¹² Reference protein coordinates for docking were taken from the X-ray structure of *Plasmodium falciparum* TS-DHFR in complex with the pfDHFR inhibitor WR99210. The site search was performed in the shape-based mode based on the crystal structure of the compound WR99210. All calculations were performed with the CFF 1.01 force field. Conformations were generated with Monte Carlo simulations (10 000 trials) and Flexible fit was selected. A grid resolution was set to 0.5 Å. Electrostatic energy was included in the calculation of the ligand internal energy. In order to avoid identical conformations, root mean square deviation threshold of 1.5 Å and a score threshold of 20 kcal/mol were used while saving the final conformations. The top 10 conformations were saved after rigid body minimizations of 1000 steps. Scoring was performed for each of the 10 saved ligand conformations using a set of scoring functions as implemented in Cerius2, including LigScore1, LigScore2,¹³ PLP1, PLP2,¹⁴ JAIN,¹⁵ PMF¹⁶ and LUDI.¹⁷ Consensus scoring function was also used to evaluate and rank the ligand binding affinities.

In-vitro antibacterial assay

The bacterial strains were grown on nutrient agar at 37 °C. After 24 h of incubation, bacterial cells were suspended in normal saline containing Tween 20 at 0.05% at a concentration of approximately $1.0\text{--}2.0 \times 10^7$ cells/mL by matching with 0.5 McFarland standards. The activity of compounds was determined by the NCCLS method using Mueller Hinton broth (Sigma Chemical Co.). The 96-well tissue culture plates were used with two fold serial dilution. Proper growth control, drug control and the blank were adjusted onto the plate. Compounds were dissolved in DMSO at a concentration of 1 mg/mL and 20 μ L of this was added to each well of 96-well tissue culture plate having 180 μ L Mueller Hinton broth. From here the solution was serially diluted resulting in two-fold serial dilution of the test compounds in subsequent wells. 100 μ L of Mc Farland matched inoculum was diluted in 10 ml of meida and then inoculum was added and kept for incubation. The drug was tested at a maximum conc. of 50 mg/mL. Micro-titer plates were incubated at 35 °C in a moist, dark chamber and MICs were recorded spectrophotometrically after 24 h incubation. For antibacterial screening, compounds were tested against both gram negative and gram positive bacterial strains and Gentamicin was used as standard drug.

Acknowledgments

Four authors (SM, AK, AR, SK) acknowledge the financial support from CSIR, New Delhi in the form of fellowships. This work was supported by the DST grant to ZT under WOS program.

References

- This is CDRI communication number **7625**.
- Rastelli, G.; Pacchioni, S.; Sirawaraporn, W.; Sirawaraporn, R.; Parenti, M. D.; Ferrari, A. M. *J. Med. Chem.* **2003**, *46*, 2834-2845.
 - (a) Dominguez, J. N.; Leon, C.; Rodrigues, J.; de Dominguez, N. G.; Gut, J.; Rosenthal, P. J. *J. Med. Chem.* **2005**, *48*, 3654-3658. (b) Leon, C.; Rodrigues, J.; de Dominguez, N. G.; Charris, J.; Gut, J.; Rosenthal, P. J.; Dominguez, J. N. *Eur. J. Med. Chem.* **2007**, *42*, 735-742. (c) Blackie, M. A. L.; Beagley, P.; Croft, S. L.; Kendrick, H.; Moss, J. R.; Chibale, K. *Bioorg. Med. Chem.* **2007**, *15*, 6510-6516. (d) Leban, J.; Pegoraro, S.; Dormeyer, M.; Lanzer, M.; Aschenbrenner, A.; Kramer, B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1979-1982. (e) Padmanilayam, M.; Scorneaux, B.; Dong, Y.; Chollet, J.; Matile, H.; Charman, S. A.; Creek, D. J.; Charman, W. N.; Tomas, J. S.; Scheurer, C.; Wittlin, S.; Brun, R.; Vennerstrom, J. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5542-5545.
 - Batra, S.; Tusi, Z.; Madapa, S. *Curr. Med. Chem.-AIA* **2006**, *135-160 and references cited therein*.
 - Sestili, I.; Borioni, A.; Mustazza, C.; Rodomonte, A.; Turchetto, L.; Sbraccia, M.; Riitano, D.; Giudice, M. R. D. *Eur. J. Med. Chem.* **2004**, *39*, 1047-1057.
 - Monguchi, Y.; Kume, A.; Hattori, K.; Maegawa, T.; Sajiki, H. *Tetrahedron* **2006**, *62*, 7926-7933.
 - A few examples only (a) Cunico, W.; Gomes, C. R. B.; Moreth, M.; Manhanini, D. P.; Figueiredo, I. H.; Penido, C.; Henriques, M. G. M. O.; Varotti, F. P.; Krettli, A. U. *Eur. J. Med. Chem.* **2008**, doi:10.1016/j.ejmech.2008.04.009. (b) Gemma, S.; Kukreja, G.; Campiani, G.; Butini, S.; Bernetti, M.; Joshi, B. P.; Savini, L.; Basilico, N.; Taramelli, D.; Yardley, V.; Bertamino, A.; Novellino, E.; Persico, M.; Catalanotti, B.; Fattorusso, C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3535-3539. (c) Gnoatto, S. C. B.; Susplugas, S.; Vecchia, L. D.; Ferreira, T. B.; Dassonville-Klimpt, A.; Zimmer, K. R.; Demailly, C.; Nascimento, S. D.; Guillon, J.; Grellier, P.; Verli, H.; Gosmann, G.; Sonnet, P. *Bioorg. Med. Chem.* **2008**, *16*, 771-782. (d) Ryckebusch, A.; Debreu-Fontaine, M.-A.; Mouray, E.; Grellier, P.; Sergheraert, C.; Melnyk, P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 297-302. (e) Ryckebusch, A.; Deprez-Poulain, R.; Debreu-Fontaine, M.-A.; Vandaele, R.; Mouray, E.; Grellier, P.; Sergheraert, C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3783-3787. (f) Osa, Y., Kobayashi, S., Sato, Y., Suzuki, Y., Takino, K., Takeuchi, T., Miyata, Y., Sakaguchi, M., and Takayanagi, H. *J. Med. Chem.* **2003**, *46*, 1948-1956.
 - Rieckmann, K.H.; Sax, L. H.; Campbell, G. H.; Mrema, J. E. *Lancet* **1978**; *1 (8054)*, 22-23.
 - Smilkstein M.; Sriwilajaroen N.; Kelly J. X.; Wilairat P.; Riscoe M. *Antimicrob. Agents Chemother.* **2004**, *48*, 1803-1806.
 - Srivastava, K.; Puri, S. K. *Exp. Parasitol.* **2004**, *108*, 74-75
 - Lambros C.; Vanderberg J. P. *J. Parasitol.* **1979**, *65*, 418-420.
 - Mosmann T. *J Immunol Methods* **1983**, *65*, 55-63.
 - Venkatachalam, C. M.; Jiang, X.; Oldfield, T.; Waldman, M. *J. Mol. Graph. Model* **2003**, *21*, 289-307.
 - Krammer, A.; Kirchhoff, P. D.; Jiang, X.; Venkatachalam, C. M.; Waldman, M. *J Mol Graph Model* **2005**, *23*, 395-407.
 - Gehlhaar, D. K.; Verkhivker, G. M.; Rejto, P. A.; Sherman, C. J.; Fogel, D. B.; Fogel, L. J. *Chem. Biol.* **1995**, *2*, 317-324.
 - Jain, A. N. *J. Comput. Aided Mol. Des.* **1996**, *20*, 427-440.
 - Muegge, I.; Martin, Y. C. *J. Med. Chem.* **1999**, *42*, 791-804.
 - Bohm, H. J. *J. Comput. Aided Mol. Des.* **1992**, *6*, 593-606.