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**ARTICLE** *in* BIOORGANIC & MEDICINAL CHEMISTRY · JULY 2009

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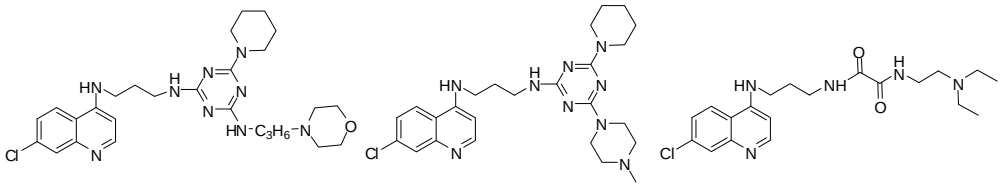

**48, $IC_{50}$ = 5.23 ng/mL** **41, $IC_{50}$ = 7.88 ng/mL** **13, $IC_{50}$ = 15.58 ng/mL**

In search of novel 4–aminoquinolines to counteract the problem of resistance, side chain incorporated oxalamide and triazine derivatives were synthesized and screened for their antimalarial activities. Compounds **48, 41** showed potent activity of $IC_{50}$ 5.23, 7.88 ng/mL respectively and compound **12** showed above moderate activity of $IC_{50}$ 15.58 ng/mL against 3D7 strain of *Plasmodium falciparum*.

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# Synthesis of oxalamide and triazine derivatives as a novel class of hybrid 4–aminoquinoline with potent antiplasmodial activity

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Abstract— Frequency of malaria and its resistance to chemotherapeutic options are emerging rapidly. To counter this problem, a series of 4–aminoquinolines having oxalamide and triazine functionalities in the side chain were synthesized and screened for their antimalarial activities. Triazine derivative **48** found to be the most active against CQ sensitive strain 3D7 of *plasmodium falciparum* in an *in vitro* assay with an $IC_{50}$ of 5.23 ng/mL and oxalamide derivative **13** showed an *in vivo* suppression of 70.45% on day 4 against CQ resistant strain N–67 of *plasmodium yoelii*.

## 1. Introduction

Among more than 100 species of *Plasmodium*; *falciparum* is the most severe and main causative agent of malaria worldwide.[1] Despite decades of research and the successful development of combination therapy, malaria remains one of the most serious health problem to the developing world specially the countries where it is endemic.[2] It is estimated that approximately 500 million people are infected in subtropical countries with a mortal rate of 2.5 million death annually and about a million of these being children under the age of five.[3] Chloroquine (CQ), a frontline antimalarial developed as substitute for quinine during World war II was approved as a safe, effective, easily available, affordable and economic treatment against malaria.[1] For understanding the action of chloroquine, it is relevant that the actual disease malaria is caused by multiplication of the parasites in human red blood cells. During digestion of host cell hemoglobin by the parasite, large amounts of free heme are produced in the food vacuole. Most of this is polymerized to inert hemozoin, while the residual heme diffuses into the parasite's cytosol where it is detoxified by interaction with glutathione (GSH). The CQ–induced heme accumulation in cytosol and

Keywords: Antimalarial, 4–aminoquinoline, triazine, oxalamide.
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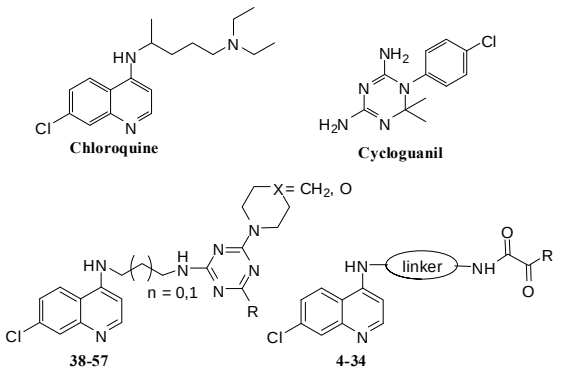



**Figure 1.** Structure of Chloroquine, Cycloguanil and synthesised compounds.

membranes of the parasite causes or at least contributes to cell death.[4] The molecular basis for CQ resistance is not fully understood. However, it is clear that the resistance is a consequence of decreased accumulation of the drug in the parasite, due to enhanced efflux, reduced uptake or a combination of the both. Several studies indicate that point mutations in the multidrug resistance 1 (*pfmdr1*), candidate (*cg2*) and CQ resistance transporter (*pfcrt*) gene are involved in the mechanism of resistance.[5] The other antimalarial drugs cycloguanil and pyrimethamine are specific inhibitor of plasmodial DHFR which is one of the important target for drugs against malaria, are also become resistant.[6] Therefore, the metabolic functions related to hemoglobin digestion, heme detoxification and DHFR inhibitor pathways still represent a valid target for the discovery of new antimalarial drugs.

In chemotherapeutic point of view, the search for a molecule having multiple targets has always been a very

attractive strategy for medicinal chemists. In search of such molecules, trioxaneaminoquinoline chimeras ("trioxaquines"),[7] artemisinin–quinine,[8] 4–aminoquinoline based isatin derivatives,[9] ferrocene–chloroquine analogues[10] and the 4–aminoquinoline based inhibitors of neutral zinc aminopeptidase,[11] possess improved antimalarial activity in comparison to parent drugs are reported to counter the problem of drug resistance. Additionally, a new hybrid chloroquine reversal agents have also been developed through coupling of imipramine (reversal agent) with 4–aminoquinoline.[12] Our group has synthesized the novel heterocylces as anti–malarial agents such as substituted triazines, pyrimidines[13] and also established the synthesis of hybrid molecules by the introduction of diverse functionalities in the lateral side chain of 4–aminoquinoline, which led to the identification of new 4–aminoquinoline based antimalarials, effective against both chloroquine sensitive and chloroquine resistant strains of *P. falciparum.*[14] The role of carbon chain length in aminoalkyl side chain is also investigated by many research groups, introducing the side chain modified derivatives with potent antimalarial activity.[15–17] A wealth of information accumulated during the past decade, introduced urea derivatives with potent antimalarial activity targeting DHFR[18] and β–hematin formation inhibition.[19] Urea derivatives interact with aspartic/glutamic acid corresponding to D54 in *Pf*DHFR via hydrogen bonding ability of these derivatives through urea linkage.[18] More recently it was observed that the urea derivatives also accumulate in the food vacuole and inhibit the plasmepsin of the parasite.[20]

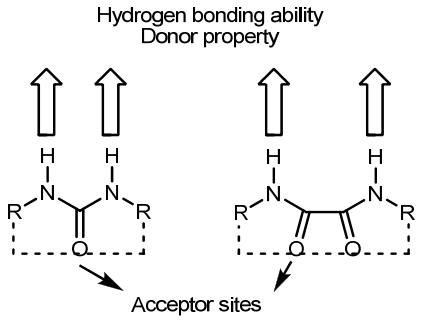



**Figure 2.** Hydrogen bonding ability of oxalamide group

The advantages of the chloroquine are seems to be simply too strong to abandon, therefore identification of hybrid 4–aminoquinolines having multiple targets is a hope of generating effective antimalarial chemotherapy. In this perception we introduced the oxalamide functionality in the side chain of 4–aminoquinoline which is based on; its greater stability towards enzyme degradation [21] and retained H–bonding ability [22] (Fig 2). Our another approach is to synthesise the hybrid of 4–aminoquinoline 1,3,5–triazines to enhance the antimalarial activity by inducing DHFR inhibitor on the side chain of 4–aminoquinoline.

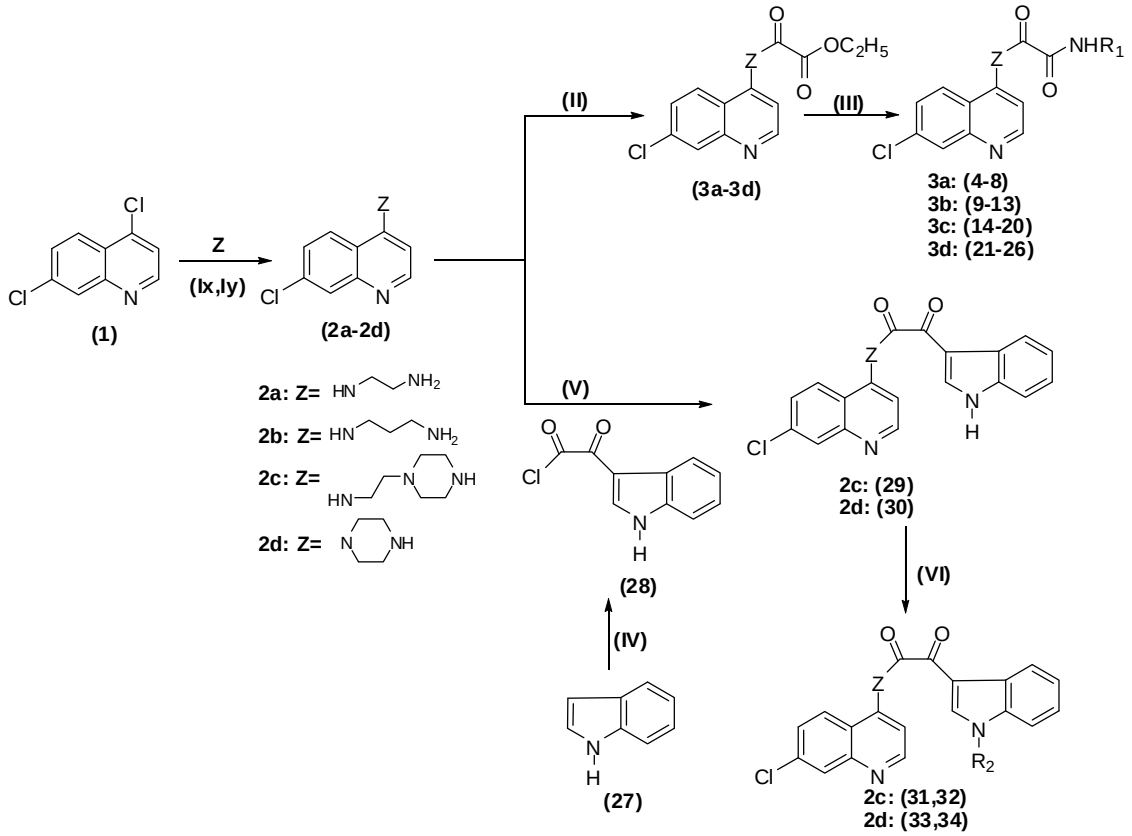
## 2. Chemistry

The desired compounds **4–26, 29–34** and **38–57** were synthesised by the synthetic protocols as outlined in **scheme–1** and **scheme–2** respectively. Synthesis of compounds **2a–2d** was achieved by the *ipso* nucleophilic substitution of the 4–Cl atom of 4,7–dichloroquinoline **(1)** with various cyclic and acyclic amines. The so formed compounds then reacted with ethylchlorooxoacetate to afford the corresponding oxaloacetates **3a–3d**. Chemoselectivity of these compounds arises due to the greater electrophilicity of carbonyl carbon to which Cl is directly attached. These compounds further undergo the nucleophilic substitution reaction with different amines (Table 1) at acetate group to furnish the final product **4–26** in good to moderate yield. In another route compounds **2c** and **2d** were reacted with 2–(indol–3–yl)–2–oxoacetyl chloride (**28**), which was prepared by the reaction of indole with oxalylchloride to yield the hybrid of quinoline and indole (**29**, **30**)**.** In these hybrid molecules, NH of indole was protected with alkyl or aryl halides to yield the compounds (**31**–**34**)**.**

The synthesis of monosubstituted [1,3,5]–triazines (**36, 37**) were accomplished by the *ipso* nucleophilic substitution of the Cl atom of the cynauric chloride (**35**). The sequence of addition of amines to cyanuric chloride depends upon the strength and structure of nucleophile. Subsequently the monosubstituted triazines were reacted initially with compounds **2a** and **2b**, followed by the treatment with more nucleophilic amine (Table 2) to obtain the respective targeted compounds (**38–57**)**.** All the synthesized compounds were well characterized by IR, Mass, NMR and the purity is established with elemental analysis.

## 3. Results and discussion

All the compounds having modification at the lateral side chain of 4–aminoquinoline with oxalamide linker **(4–26)**, α–ketoamide linker coupled with indole **(29–34)** and hybrid derivatives of aminoquinoline–triazine **(38–57)** were evaluated for their *in vitro* antimalarial activities against CQ sensitive 3D7 strain of *Plasmodium falciparum*. The *in vitro* antimalarial activity, inhibition of β–hematin formation and selectivity index (SI) of above synthesised compounds are given in Table 1 and 2. Compounds with potent *in vitro* antimalarial activity and good SI values were also

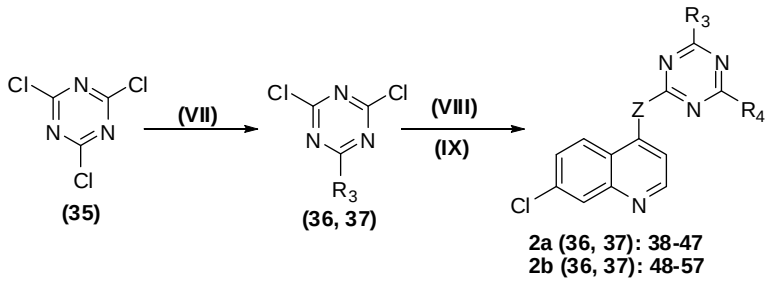



**Scheme 1.** Reagents and conditions: (I) (x) α,γ–diamines, reflux, 7h; (y) N–aminoethylpiperazine/piperazine, MeOH, reflux, 5h; (II) $ClCOCO_2Et$, DCM, rt, 1h; (III) primary amines, *n*–BuOH, reflux under pressure, 8h; (IV) $(COCl)_2$, dry $Et_2O$, 0 °C, 1h; (V) **2c**/**2d**, $Et_3N$, *n*–BuOH, reflux, 9h; (VI) MeI/ PTSC, NaOH, PTC, DCM, 0 °C–rt, 2h.

evaluated for their *in vivo* potency against the CQ resistant N–67 strain of *P. yoelii* in swiss mice at 50mg/kg/day for 4 days by intraperitoneal route (i.p).

Among all the synthesised side chain modified derivatives, compounds having oxalamide linker joining two alkyl amine side chains with high degree of flexibility and H–bonding capability, showed moderate antimalarial activity with $IC_{50}$ in the range of 15.58–233.38 ng/mL. Compound **12** consisting of aminopropyl chain linked to the 7–chloroquinoline and N,N–diethylethylenediamine as $\mathbf{R_1}$ showed potent antimalarial activity of $IC_{50}$ 15.58 ng/mL with inhibitory activity of β–hematin formation $IC_{50}$ 7.99 µg/ml. On replacing $\mathbf{R_1}$ with N,N–dimethylethylenediamine **(13)** the activity decreases to 26.41 ng/mL, though its β–hematin inhibitory activity remains same. Compound **10** having aminopropylmorpholine as $\mathbf{R_1}$ have shown $IC_{50}$ of 25.42 ng/mL with β–hematin formation inhibition of $IC_{50}$ 8.74 µg/ml, while replacing $\mathbf{R_1}$ with aminoethylmorpholine **(9)** the activity reduced to 82.21 ng/mL due to its decreased inhibition of β–hematin formation of $IC_{50}$ 10.67 µg/mL. Similarly,compound **11** consisting of *n*–butyl chain as $\mathbf{R_1}$ showed decrease in activity with $IC_{50}$ 233.38 ng/mL due to reduced β–hematin formation inhibitory activity of 15.6 µg/mL. Reducing the methylene group at the lateral side chain significantly increased the β–hematin inhibitory activity but reduced the antimalarial activity of the compounds **(4–8)**. Compound **4** having aminopropylmorpholine as $\mathbf{R_1}$ showed $IC_{50}$ of 31.32 ng/mL with β–hematin formation inhibition of $IC_{50}$ 7.18 µg/ml and compound **8** having N,N–dimethylethylenediamine as $\mathbf{R_1}$ showed equal potency of $IC_{50}$ 31.59 ng/mL even though β–hematin formation inhibition decreased to 11.09 µg/mL. Contrarily compounds **4**, **6** and **7** showed decrease in antimalarial activity, though the β–hematin formation inhibition is increased to 6.87, 6.76 and 7.01 µg/mL respectively. Compounds with cyclic diamine i.e. aminoethyl piprazine **(14–20)**, piprazine **(21–26)** were found to be less active compared to their acyclic analogues which may be due to the inflexible nature of the side chain and the loss of secondary amide character. Compounds **15**, **24** having

aminopropylmorpholine and N,N–diethylethylenediamine as $\mathbf{R_1}$ showed better




**Scheme 2.** (VII) piperidine/morpholine, 0 °C, THF, 1h; (VIII) **2a**/**2b**, $K_2CO_3$, THF, 4h; (IX) different amines, $K_2CO_3$, 80 °C, reflux, 6h.

**Table 1.** Biological activity of the Scheme 1 compounds.

| Compound | Z | $\mathbf{R_1}$/$\mathbf{R_2}$ | In vitro antimalarial activity $IC_{50}$ (ng/mL)[a] | SI[b] | Inhibition of β-hematin formation $IC_{50}$ (μg/mL)[c] | In vivo % suppression on day 4[d] |
|---|---|---|---|---|---|---|
| **4** | 1,2-ethylenediamine | 2-aminoethylmorpholine | 90.83 | 567.43 | 6.87 (5.71–8.26) | |
| **5** | 1,2-ethylenediamine | 3-aminopropylmorpholine | 31.32 | 1567.05 | 7.18 (6.01–8.58) | 43.64 |
| **6** | 1,2-ethylenediamine | *n*-butylamine | 233.07 | 18.88 | 6.76 (5.60–8.16) | |
| **7** | 1,2-ethylenediamine | N,N-diethylethylenediamine | 50.28 | 605.61 | 7.01 (5.80–8.47) | |
| **8** | 1,2-ethylenediamine | N,N-dimethylethylenediamine | 31.59 | 383.03 | 11.09 (8.70–14.14) | |
| **9** | 1,3-propanediamine | 2-aminoethylmorpholine | 82.21 | 191.82 | 10.67 (8.38–13.59) | |
| **10** | 1,3-propanediamine | 3-aminopropylmorpholine | 25.42 | 1625.52 | 8.74 (6.91–11.08) | 21.36 |
| **11** | 1,3-propanediamine | *n*-butylamine | 233.38 | 38.13 | 15.66 (9.99–24.55) | |
| **12** | 1,3-propanediamine | N,N-diethylethylenediamine | 15.58 | 232.99 | 7.99 (6.84–9.33) | |
| **13** | 1,3-propanediamine | N,N-dimethylethylenediamine | 26.41 | 2527.65 | 7.98 (6.80–9.39) | 70.45 |
| **14** | aminoethylpiperazine | 2-aminoethylmorpholine | 261.84 | 183.05 | 14.17 (10.86–16.13) | |
| **15** | aminoethylpiperazine | 3-aminopropylmorpholine | 40.84 | 1221.84 | NI | |
| **16** | aminoethylpiperazine | *n*-butylamine | NA | ND | ND | |
| **17** | aminoethylpiperazine | N,N-diethylethylenediamine | 79.78 | 194.0 | NI | |
| **18** | aminoethylpiperazine | N,N-dimethylethylenediamine | 84.45 | 65.0 | <20 | |
| **19** | aminoethylpiperazine | *t*-butylamine | NA | ND | ND | |
| **20** | aminoethylpiperazine | 1-aminopropylimidazole | 135.01 | 233.09 | <20 | |
| **21** | piperazine | 2-aminoethylmorpholine | NA | ND | ND | |
| **22** | piperazine | 3-aminopropylmorpholine | NA | ND | ND | |
| **23** | piperazine | *n*-butylamine | NA | ND | ND | |
| **24** | piperazine | N,N-diethylethylenediamine | 41.98 | 1183.41 | <20 | |
| **25** | piperazine | N,N-dimethylethylenediamine | NA | ND | ND | |
| **26** | piperazine | *t*-butylamine | NA | ND | ND | |
| **29** | aminoethylpiperazine | hydrogen | NA | ND | ND | |
| **30** | piperazine | hydrogen | NA | ND | ND | |
| **31** | aminoethylpiperazine | methyl | NA | ND | ND | |
| **32** | aminoethylpiperazine | *p*-tolylsulphonyl | NA | ND | ND | |
| **33** | piperazine | methyl | NA | ND | ND | |
| **34** | piperazine | *p*-tolylsulphonyl | NA | ND | ND | |

antimalarial activity of $IC_{50}$ 40.84, 41.98 ng/mL respectively, compared to the other substituents of $\mathbf{R_1}$. Hybridization of the aminoquinoline with indole derivatives by α–ketoamide linkage (**26**–**34**) diminishes the antimalarial activity and β–hematin formation inhibition of these compounds. All these foregoing results suggest that the oxalamide derivatives having secondary amide and acyclic lateral side chain on 4–aminoquinoline were most active. So, the retaining of secondary amide character of the oxalamide entity is the necessary criteria for antimalarial activity.

On the other hand, incorporation of 1,3,5–triazine on the lateral side chain of 4–aminoquinoline led to the significant increase of antimalarial potency which is comparable to the chloroquine. Among all the hybrid derivatives (**38**–**57**), compounds **41, 46, 48, 49, 51** showed potent antimalarial activity in the range of $IC_{50}$ 5.23–10.02 ng/mL and the β–hematin inhibition of these compounds is also in good agreement with their antimalarial activity having $IC_{50}$ in the range of 6.19–9.10 μg/mL. Compounds **39, 40** and **50** also showed the moderate antiplasmodial activity with $IC_{50}$ of 14.70, 15.89 and 15.63 ng/mL respectively compared to CQ. These compounds have piperidine ring as $\mathbf{R_3}$ and N, N–dialkylethylenediamines as $\mathbf{R_4}$ and showed moderate β–hematin inhibitory activity in the range of $IC_{50}$ 8.19–13.34 μg/mL compared to previous ones. The compounds having morpholine substitution as $\mathbf{R_3}$ on the triazine ring system (**47, 53–56**) or aminoalkylmorpholines as $\mathbf{R_4}$ **(38, 47, 53)** have shown a great fall in the antiplasmodial activity, however the compounds **43, 44** showed better activity

compared to above molecules with an $IC_{50}$ of 22.20 and 29.74 ng/mL respectively. As discussed above, we find that the morpholine substitution on the triazine ring system reduces the activity of the compounds while piperidine

**Table 2**. Biological activity of the Scheme 2 compounds

| Compound | Z | $R_3$ | $R_4$ | In vitro antimalarial activity $IC_{50}$ (ng/mL)[a] | SI[b] | Inhibition of β-hematin formation $IC_{50}$ (μg/mL)[C] | In vivo % suppression on day 4[d] |
|---|---|---|---|---|---|---|---|
| **38** | 1,2-ethylenediamine | piperidine | 3-aminopropylmorpholine | 65.63 | 65.21 | 7.79 (6.71–9.04) | |
| **39** | 1,2-ethylenediamine | piperidine | N,N-diethylethylenediamine | 14.70 | 223.13 | 10.15 (8.86–11.62) | |
| **40** | 1,2-ethylenediamine | piperidine | N,N-dimethylethylenediamine | 15.89 | 1062.30 | 13.34 (11.15–15.96) | |
| **41** | 1,2-ethylenediamine | piperidine | N-methylpiperazine | 7.88 | 958.12 | 9.10 (7.34–11.28) | Toxic |
| **42** | 1,2-ethylenediamine | piperidine | 2-aminoethylmorpholine | NA | ND | ND | |
| **43** | 1,2-ethylenediamine | morpholine | 3-aminopropylmorpholine | 22.20 | 2405.86 | 8.58 (6.93–10.61) | |
| **44** | 1,2-ethylenediamine | morpholine | N,N-diethylethylenediamine | 29.74 | 1663.75 | 9.42 (7.33–12.11) | |
| **45** | 1,2-ethylenediamine | morpholine | N,N-dimethylethylenediamine | 39.39 | 1291.71 | 8.10 (6.59–9.96) | |
| **46** | 1,2-ethylenediamine | morpholine | N-methylpiperazine | 10.02 | 4692.08 | 6.19 (5.13–7.46) | Toxic |
| **47** | 1,2-ethylenediamine | morpholine | 2-aminoethylmorpholine | 48.18 | 1176.40 | 17.16 (11.05–26.63) | |
| **48** | 1,3-propanediamine | piperidine | 3-aminopropylmorpholine | 5.23 | 860.41 | 7.54 (6.50–8.76) | Toxic |
| **49** | 1,3-propanediamine | piperidine | N,N-diethylethylenediamine | 8.97 | 1011.15 | 7.45 (6.44–8.63) | |
| **50** | 1,3-propanediamine | piperidine | N,N-dimethylethylenediamine | 15.63 | 330.11 | 8.19 (7.07–9.49) | |
| **51** | 1,3-propanediamine | piperidine | N-methylpiperazine | 9.13 | 530.20 | 7.45 (6.19–8.97) | |
| **52** | 1,3-propanediamine | piperidine | 2-aminoethylmorpholine | NA | ND | ND | |
| **53** | 1,3-propanediamine | morpholine | 3-aminopropylmorpholine | 52.06 | 706.15 | 8.60 (7.52–9.84) | |
| **54** | 1,3-propanediamine | morpholine | N,N-diethylethylenediamine | 40.27 | 1068.32 | 10.64 (8.01–14.14) | |
| **55** | 1,3-propanediamine | morpholine | N,N-dimethylethylenediamine | 163.99 | 219.77 | 7.94 (6.85–9.19) | |
| **56** | 1,3-propanediamine | morpholine | N-methylpiperazine | 40.08 | 704.25 | 8.55 (7.46–9.81) | |
| **57** | 1,3-propanediamine | morpholine | 2-aminoethylmorpholine | 17.87 | 1017.32 | 8.72 (7.39–10.72) | |
| **CQ**[e] | | | | 5.2 | 8983 | 4.87 | 99.05 |

[a] $IC_{50}$: concentration corresponding to 50% growth inhibition of chloroquine sensitive strain 3D7 of *P. falciparum*; [b] SI= $IC_{50}$ values of toxicity against VERO cell line/ $IC_{50}$ values of antimlarial activity; [C] The 50% inhibitory concentration ($IC_{50}$) was determined using non-linear regression analysis dose-response curves, Confidence interval is of 95%; [d] In vivo antimalarial activity against chloroquine resistant strain N-67 of *P. yoelii* in swiss mice at dose 50 mg/Kg/day by intraperitoneal route; [e] chloroquine at a dose of 10mg/Kg, oral for 4 days; NA: not active; ND: not done; NI: no inhibition; Toxic: Mice died.

substitution enhances the antimalarial potency. It has also been conjectured that to further increase the antiplasmodial activity the N–methylpiperazine, N,N dimethylethylenediamine and N,N–diethylethylenediamine plays a critical role due to the basic nature of terminal nitrogen atom of these molecules.

These compounds were also tested for their cytotoxicity against VERO cells. Among all, aminoquinoline–triazine derivatives have good selectivity index (Table 2) in comparison with oxalamide derivatives (Table 1). Compound **46** having an $IC_{50}$ of 10.02 ng/mL showed highest selectivity index of 4692.08, while most potent compound **48** having an $IC_{50}$ of 5.23 ng/mL showed selectivity index of 860.41. Similarly compound **41** having an $IC_{50}$ of 7.88 ng/mL showed SI of 958.12, thus illustrating the good activity profile. On the other hand oxalamide derivatives (**5**, **10** and **13**) having an $IC_{50}$ of 31.32, 25.42 and 26.41 ng/mL showed selectivity index of 1567.05, 1625.52 and 2527.65 respectively. Considering the *in vitro* antimalarial activity and selectivity index, compounds (**5, 10, 13, 41, 46** and **48**) were also screened in an *in vivo* model against chloroquine resistant N–67 strain of *P.yoelii* in swiss mice at 50mg/Kg/day for 4 days by intraperitoneal route (i.p) (Table 1) and (Table 2). Out of six evaluated compounds, oxalamide derivative **13** found to be the most active against chloroquine resistant strain with 70.45 % suppression on day 4. Where as hybrid derivatives of aminoquinoline–triazine found to be toxic against this strain, but their in vitro results prove these new hybrids as promising model for further optimization.

## 4. Conclusion

Malaria is progressively increasing worldwide and developing its virulent forms. In order to overcome the problem of drug resistance in malaria, it appears wise to concentrate on drug discovery efforts towards new structural classes. In this connection we designed, synthesised the hybrid of 4–aminoquinolines having oxalamide and triazine functionalities in the side chain and studied their structure activity relationship. In oxalamide derivatives the presence of secondary amide functionality increases the antimalarial activity, while the presence of tertiary amide and α–ketoamide decreases the activity due to less binding ability sites for H– bonding. On the other hand triazine derivatives substituted with amines which have terminal basic nitrogen like chloroquine increases the antiplasmodial potency.

## 5. Experimental

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

### 5.1. General procedure for the synthesis of compounds 2a, 2b

A mixture of 4,7–dichloroquinoline (1 equiv) and 1,2–diaminoethane/1,3–diaminopropane (5 equiv) was heated slowly from room temperature to 80 °C over 1 h with stirring and subsequently at 120–130 °C for 6h with continued stirring to drive the reaction to completion. The reaction mixture was cooled to room temp and taken up in dichloromethane. The organic layer was successively washed with 5% aq $NaHCO_3$ followed by water wash and then finally with brine. The organic layer was dried over anhydrous $Na_2SO_4$ and solvent was removed under reduced pressure and the residue was precipitated by the addition of 80:20 hexane–chloroform to obtain compounds **2a**, **2b** respectively.

**5.1.1. *N*$^1$–(7–chloroquinolin–4–yl) ethane–1,2–diamine (2a).** yield: 87%; mp 131–132 °C; ESMS: 222 (M+1); IR (KBr) 3356, 2973, 1585, 1216, 763 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.51 (d, 1H, *J* = 5.37 Hz), 7.94 (d, 1H, *J* = 2.02 Hz), 7.75 (d, 1H, *J* = 8.92 Hz), 7.34 (dd, 1H, *J* = 1.86, 8.89 Hz), 6.39 (d, 1H, *J* = 5.35 Hz), 5.82 (br–s, 1H), 3.27 (br–s, 2H), 3.11–3.18 (m, 4H); $^{13}$C NMR (50 MHz, DMSO–$d_6$): 156.13, 144.71, 140.52, 138.43, 127.41, 126.55, 120.74, 117.06, 99.39, 42.94, 38.12; Anal. Calcd for $C_{11}H_{12}ClN_3$: C, 59.60; H, 5.46; N, 18.95; found: C, 59.62; H, 5.51; N, 18.91.

**5.1.2. *N*$^1$–(7–chloroquinolin–4–yl) propane–1,3–diamine (2b).** yield: 88%; mp 96–98 °C; ESMS: 236 (M+1); IR (KBr) 3379, 3019, 1587, 1216, 762 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.47 (d, 1H, *J* = 5.32 Hz), 7.92 (d, 1H, *J* = 1.98 Hz), 7.71 (d, 1H, *J* = 8.89 Hz), 7.37 (br–s, 1H), 7.28 (dd, 1H, *J* = 1.92, 8.84 Hz), 6.34 (d, 1H, *J* = 5.37 Hz), 3.47–3.28 (m, 2H), 3.11–3.02 (m, 2H), 2.74 (br–s, 2H), 1.97–1.93 (m, 2H); $^{13}$C NMR (50 MHz, DMSO–$d_6$): 155.96, 144.38, 140.26, 138.17, 127.21, 126.37, 120.43, 117.13, 98.87, 42.19, 40.63. 30.65; Anal. Calcd for $C_{12}H_{14}ClN_3$: C, 61.15; H, 5.99; N, 17.83; found: C, 61.19; H, 5.94; N, 17.89.

### 5.2. General procedure for the synthesis of compounds 2c, 2d

A mixture of 4,7–dichloroquinoline (1 equiv) and N–aminoethyl piperazine/piperazine (5 equiv) in MeOH were refluxed for 5 h. After completion of reaction the solvent was evaporated under vacuum and solid mass was extracted with water and ethylacetate. The organic layer was evaporated under vacuum and the solid was purified with column chromatography to obtain compounds **2c, 2d** respectively.

**5.2.1. 7–chloro–N–(2–(piperazin–1–yl)ethyl)quinolin–4–amine (2c).** yield: 85%; mp 140–142 °C; ESMS: 291 (M+1); IR (KBr) 3450, 3022, 2950, 1652, 1217, 762 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.67 (d, 1H, *J* = 5.05 Hz), 8.15–7.94 (m, 3H), 7.51 (dd, 1H, *J* = 2.11, 8.65 Hz), 6.86 (d, 1H, *J* = 5.12 Hz), 3.52–3.39 (m, 4H), 2.99 (t, 2H, *J* = 6.02 Hz), 2.91–2.83 (m, 4H), 2.72 (t, 2H, *J* = 5.71 Hz), 2.16 (br–s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): 161.41, 155.22, 153.13, 139.32, 131.42, 130.21, 129.32, 125.61, 112.81, 61.32, 56.71, 55.70, 40.91; Anal. Calcd for $C_{15}H_{19}ClN_4$: C, 61.96; H, 6.59; N, 19.27; Found: C, 61.94; H, 6.65; N, 19.28.

**5.2.2. 7–chloro–4–(piperazin–1–yl)quinoline (2d).** yield: 80%; mp 160–162 °C; ESMS: 248 (M+1); IR (KBr) 3433, 3026, 2967, 1642, 1216, 760; $^1$H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.71 (d, 1H, *J* = 5.12 Hz), 8.07–7.97 (m, 2H), 7.59 (dd, 1H, *J* = 2.08, 8.73 Hz), 6.89 (d, 1H, *J* = 5.07 Hz), 4.01 (t, 2H, *J* = 6.62 Hz), 3.96 (t, 2H, *J* = 6.58 Hz), 2.94–2.87 (m, 4H), 2.42 (br–s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): 158.01, 151.62, 149.50, 135.62, 127.81, 126.62, 125.52, 122.01, 109.21, 53.01, 45.52; Anal. Calcd for $C_{13}H_{14}ClN_3$: C, 63.03; H, 5.70; N, 16.96; Found: C, 63.07; H, 5.75; N, 16.92.

### 5.3. General procedure for the synthesis of compounds (3a–3d)

A mixture of **2a**–**2d** (1.0 equiv) and ethylchlorooxoacetate (1.5 equiv) in DCM were stirred for 1 h at room temperature. The solvent was evaporated under vacuum and the solid was purified directly with column chromatography to obtain the respective compounds **3a–3d**.

**5.3.1. Ethyl 2–(2–(7–chloroquinolin–4–ylamino) ethylamino)–2–oxoacetate (3a).** yield: 71%; mp 194–196 °C; ESMS: 322 (M+1); IR (KBr) 3296, 3019,1754, 1615, 1450, 1215, 749 cm$^{-1}$; $^1$H NMR

(200 MHz, DMSO–$d_6$): δ (ppm) 9.16–9.11 (m, 2H), 8.56 (d, 1H, *J* = 4.58 Hz), 8.49 (d, 1H, *J* = 6.06 Hz), 8.01 (d, 1H, *J* = 1.34 Hz), 7.74 (dd, 1H, *J* = 1.32, 6.08 Hz), 6.91 (d, 1H, *J* = 4.62 Hz), 4.22 (q, 2H, *J* = 4.72 Hz), 3.65–3.61 (m, 2H), 3.47–3.45 (m, 2H), 1.27 (t, 3H, *J* = 4.47); $^{13}$C NMR (50 MHz, DMSO–$d_6$): 161.19, 158.20, 156.04, 144.67, 140.51, 138.38, 127.45, 126.51, 120.81, 116.65, 99.47, 62.95, 42.78, 38.33, 14.70; Anal. Calcd for $C_{15}H_{16}ClN_3O_3$: C, 55.99; H, 5.01; N, 13.06; found: C, 56.03; H, 4.98; N, 13.11.

**5.3.2. Ethyl 2–(3–(7–chloroquinolin–4–ylamino)propylamino)–2–oxoacetate (3b).** yield: 72%; mp 140–142 °C; ESMS: 336 (M+1); IR (KBr) 3402, 3020,1751, 1615, 1447, 1216, 762 cm$^{-1}$; $^1$H NMR (200 MHz, DMSO–$d_6$): δ (ppm) 9.31–9.27 (m, 1H), 9.17–9.02 (m, 1H), 8.59–8.51 (m, 2H), 8.02 (d, 1H, *J* = 2.03 Hz), 7.73 (dd, 1H, *J* = 1.94, 8.98 Hz), 6.82 (d, 1H, *J* = 6.98 Hz), 4.19 (q, 2H, *J* = 7.09 Hz), 3.49–3.37 (m, 2H), 3.31–3.21 (m, 2H), 1.91–1.84 (m, 2H), 1.27 (t, 3H, *J* = 4.82); $^{13}$C NMR (50 MHz, DMSO–$d_6$): 161.11, 158.17, 156.02, 144.65, 140.52, 138.33, 127.46, 126.47, 120.84, 116.59, 99.43, 62.87, 42.83, 39.13, 28.14, 14.91; Anal. Calcd for $C_{16}H_{18}ClN_3O_3$: C, 57.23; H, 5.40; N, 12.51; found: C, 57.27; H, 5.37; N, 12.53.

**5.3.3. Ethyl 2–(4–(2–(7–chloroquinolin–4–ylamino)ethyl)piperazin–1–yl)–2–oxoacetate (3c)** yield: 75%; mp 178–180 °C; ESMS: 391 (M+1); IR (KBr) 3450, 3022, 2950, 1754, 1652, 1562, 1423, 1216, 762 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.69 (d, 1H, *J* = 5.13 Hz), 8.09 (d, 1H, *J* = 2.11 Hz), 7.86–7.79 (m, 2H), 7.53 (dd, 1H, *J* = 2.06, 8.83 Hz), 6.87 (d, 1H, *J* = 5.09 Hz), 4.08 (q, 2H, *J* = 8.11 Hz), 3.48 (t, 2H, *J* = 6.02 Hz), 3.51–3.39 (m, 4H), 2.93–2.81 (m, 4H), 2.71 (t, 2H, *J* = 6.59 Hz), 1.13 (t, 3H, *J* = 6.71 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$): 161.02, 160.72, 156.33, 151.22, 149.91, 135.02, 128.91, 125.91, 124.72, 123.32, 110.12, 63.72, 61.31, 56.72, 55.73, 40.93, 16.72; Anal. Calcd for $C_{19}H_{23}ClN_4O_3$: C, 58.38, H, 5.93; N, 14.33; Found: C, 58.34; H, 5.98; N, 14.31.

**5.3.4. Ethyl 2–(4–(7–chloroquinolin–4–yl)piperazin–1–yl)–2–oxoacetate (3d)** yield: 73%; mp 190–192 °C; ESMS: 348 (M+1); IR (KBr) 3432, 3019, 2962, 1754, 1652, 1570, 1438, 1216, 762 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.72 (d, 1H, *J* = 5.05 Hz), 8.07 (d, 1H, *J* = 1.79 Hz), 7.86 (d, 1H, *J* = 9.01 Hz), 7.57 (dd, 1H, *J* = 2.11, 8.65 Hz), 6.83 (d, 1H, *J* = 5.05 Hz), 4.11 (q, 2H, *J* = 8.11Hz), 4.03 (t, 2H, *J* = 6.78 Hz), 3.99 (t, 2H, *J* = 6.71 Hz), 3.47–3.31 (m, 4H), 1.19 (t, 3H, *J* = 6.58 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$): 161.31, 160.42, 156.73, 152.01, 150.53, 135.42, 129.32, 126.64, 125.14, 123.72, 111.14, 63.92, 53.73, 45.82, 17.33; Anal. Calcd for $C_{17}H_{18}ClN_3O_3$: C, 58.71; H,5.22; N,12.08 ; Found: C, 58.76; H, 5.26; N, 12.13.

**5.4. General procedure for the synthesis of compounds (4–26)**

A mixture of **3a**–**3d** and different amines (1.5 equiv) listed in Table 1 were refluxed in *n*–BuOH at 120 °C in the steal bomb for 8h. The solvent was removed under reduced pressure and the solid mass was purified by column chromatography over silica gel using $CHCl_3$/MeOH as the eluent to yield the compounds **4–26.**

**5.4.1. $N^1$–(2–(7–chloroquinolin–4–ylamino)ethyl)–$N^2$–(2–morpholinoethyl)oxalamide (4).** yield: 76%; mp 173–175 °C; ESMS: 406 (M+1); IR (KBr) 3297, 2924, 1657, 1584, 1529, 1226, 773 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.52 (d, 1H, *J* = 5.36 Hz), 8.03 (br–s, 1H), 7.94 (d, 1H, *J* = 2.12 Hz), 7.86 (br–s, 1H), 7.73 (d, 1H, *J* = 8.96 Hz), 7.36 (dd, 1H, *J* = 2.14, 8.94 Hz), 6.35 (d, 1H, *J* = 5.42 Hz), 6.18 (br–s, 1H), 3.82–3.71 (m, 6H), 3.53–3.37 (m, 4H), 2.56–2.44 (m, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$): 161.18, 160.86, 152.51, 151.12, 149.65, 134.57, 128.17, 125.09, 124.96, 118.41, 99.63, 67.15, 57.71, 53.89, 41.02, 37.76, 36.91; Anal. Calcd for $C_{19}H_{24}ClN_5O_3$: C, 56.22; H, 5.96; N, 17.25; found: C, 56.25; H, 6.01; N, 17.22.

**5.4.2. $N^1$–(2–(7–chloroquinolin–4–ylamino)ethyl)–$N^2$–(3–morpholinopropyl)oxalamide (5).** yield: 73%; mp 158–160 °C; ESMS: 420 (M+1); IR (KBr) 3344, 2924, 1668, 1580, 1495, 1205, 767 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.21 (br–s, 1H), 8.51 (d, 1H, *J* = 5.36 Hz), 8.09 (br–s, 1H), 7.94 (d, 1H, *J* = 2.06 Hz), 7.75 (d, 1H, *J* = 8.96 Hz), 7.37 (dd, 1H, *J* = 2.12, 8.93 Hz), 6.42 (br–s, 1H), 6.32 (d, 1H, *J* = 5.41 Hz), 3.88–3.72 (m, 6H), 3.51–3.39 (m, 4H), 2.55–2.48 (m, 6H) 1.76–1.67 (m, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$): 161.19, 158.20, 156.04, 144.67, 140.50, 138.38, 127.45, 126.51, 120.80, 116.65, 99.47, 67.18, 62.95, 60.64, 42.78, 39.17, 38.33, 29.87; Anal. Calcd for $C_{20}H_{26}ClN_5O_3$: C, 57.21; H, 6.24; N, 16.68; found: C, 57.19; H, 6.21; N, 16.71.

**5.4.3. $N^1$–butyl–$N^2$–(2–(7–chloroquinolin–4–ylamino)ethyl)oxalamide (6).** yield: 71%; mp 178–180 °C; ESMS: 349 (M+1); IR (KBr) 3312, 3020, 1666, 1578, 1518, 1216, 762 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.51 (d, 1H, *J* = 5.34 Hz), 8.08 (br–s, 1H), 7.94 (d, 1H, *J* = 2.06 Hz), 7.71 (d, 1H, *J* = 8.96 Hz), 7.49 (br–s, 1H), 7.36 (dd, 1H, *J* = 2.08, 8.92 Hz), 6.33 (d, 1H, *J* = 5.41 Hz), 6.18 (br–s, 1H), 3.80–3.72 (m, 2H), 3.52–3.44 (m, 2H), 3.37–3.27 (m, 2H), 1.60–1.49 (m, 2H) 1.33–1.28 (m, 2H), 0.92 (t, 3H, *J* =

7.17 Hz); $^{13}$C NMR (50 MHz, $CDCl_3$): 161.17, 160.74, 152.56, 151.08, 149.62, 134.53, 128.09, 125.17, 124.86, 118.52, 96.78, 46.26, 42.13, 39.91, 33.14, 21.76, 14.07; Anal. Calcd for $C_{17}H_{21}ClN_4O_2$: C, 58.53; H, 6.07; N, 16.06; found: C, 58.56; H, 6.11; N, 16.03.

**5.4.4. $N^1$–(2–(7–chloroquinolin–4–ylamino)ethyl)–$N^2$–(2–(diethylamino)ethyl)oxalamide (7).** yield: 68%; mp 92–94 °C; ESMS: 392 (M+1); IR (KBr) 3340, 2970, 1672, 1585, 1506, 1207, 766 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.51 (d, 1H, *J* = 5.36 Hz), 8.08 (br–s, 2H), 7.93 (d, 1H, *J* = 2.08 Hz), 7.74 (d, 1H, *J* = 8.96 Hz), 7.33 (dd, 1H, *J* = 2.12, 8.93 Hz), 6.33 (d, 1H, *J* = 5.42 Hz), 6.26 (br–s, 1H), 3.81–3.72 (m, 2H), 3.52–3.44 (m, 2H), 3.39–3.30 (m, 2H), 2.64–2.52 (m, 6H) 1.04 (t, 6H, *J* = 7.12 Hz); $^{13}$C NMR (50 MHz, $CDCl_3$): 161.26, 160.06, 151.84, 150.37, 149.12, 135.62, 128.42, 125.86, 121.96, 118.03, 99.04, 51.61, 47.52, 44.68, 39.76, 37.92, 13.83; Anal. Calcd for $C_{19}H_{26}ClN_5O_2$: C, 58.23; H, 6.69; N, 17.87; found: C, 58.19; H, 6.72; N, 17.91.

**5.4.5. $N^1$–(2–(7–chloroquinolin–4–ylamino)ethyl)–$N^2$–(2–(dimethylamino)ethyl)oxalamide (8).** yield: 71%; mp 112–114 °C; ESMS: 364 (M+1); IR (KBr) 3306, 2943, 1656, 1582, 1525, 1222, 769 cm$^{-1}$; $^1$H NMR (200 MHz, DMSO–$d_6$): δ (ppm) 9.01 (br–s, 1H), 8.58 (t, 1H, *J* = 5.82 Hz), 8.39 (d, 1H, *J* = 5.41 Hz), 8.19 (d, 1H, *J* = 9.14 Hz), 7.77 (d, 1H, *J* = 2.18 Hz), 7.45 (dd, 1H, *J* = 2.18, 8.86 Hz), 7.42 (br–s, 1H), 6.61 (d, 1H, *J* = 5.48 Hz), 3.39–3.33 (m, 4H), 3.27–3.17 (m, 2H), 2.36 (t, 2H, *J* = 6.47 Hz), 2.15 (s, 6H); $^{13}$C NMR (50 MHz, DMSO–$d_6$): 161.28, 160.58, 152.67, 151.01, 149.74, 134.40, 128.23, 125.10, 124.81, 118.28, 99.62, 58.22, 45.73, 42.47, 38.31, 37.54; Anal. Calcd for $C_{17}H_{22}ClN_5O_2$: C, 56.12; H, 6.09; N, 19.25; found: C, 58.15; H, 6.11; N, 19.23.

**5.4.6. $N^1$–(3–(7–chloroquinolin–4–ylamino)propyl)–$N^2$–(2–morpholinoethyl)oxalamide (9).** yield: 74%; mp 166–168 °C; ESMS: 420 (M+1); IR (KBr) 3422, 3020, 1658, 1583, 1519, 1216, 762 cm$^{-1}$; $^1$H NMR (200 MHz, DMSO–$d_6$): δ (ppm) 8.91 (t, 1H, *J* = 6.02 Hz), 8.58 (t, 1H, *J* = 5.99 Hz), 8.37 (d, 1H, *J* = 5.44 Hz), 8.22 (d, 1H, *J* = 9.02 Hz), 7.77 (d, 1H, *J* = 2.21 Hz), 7.45 (dd, 1H, *J* = 2.24, 8.98 Hz), 7.37 (t, 1H, *J* = 5.07 Hz), 6.46 (d, 1H, *J* = 5.54 Hz), 3.53 (t, 4H, *J* = 4.63 Hz), 3.32–3.19 (m, 6H), 2.50–2.46 (m, 2H), 2.41–2.33 (m, 4H), 1.89–1.78 (m, 2H); $^{13}$C NMR (50 MHz, DMSO–$d_6$): 161.01, 160.73, 152.42, 151.02, 149.55, 134.44, 128.06, 125.04, 124.91, 118.28, 99.49, 67.05, 57.62, 53.99, 40.72, 37.62, 36.79, 28.15; Anal. Calcd for $C_{20}H_{26}ClN_5O_3$: C, 57.21; H, 6.24; N, 16.68; found: C, 57.18; H, 6.21; N, 16.71.

**5.4.7. $N^1$–(3–(7–chloroquinolin–4–ylamino)propyl)–$N^2$–(3–morpholinopropyl)oxalamide (10).** yield: 72%; mp 195–197 °C; ESMS: 434 (M+1); IR (KBr) 3392, 3020, 1664, 1582, 1516, 1216, 764 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.31 (br–s, 1H), 8.51 (d, 1H, *J* = 5.41 Hz), 7.95–7.86 (m, 2H), 7.74 (br–s, 1H), 7.42 (dd, 1H, *J* = 2.17, 8.94 Hz), 6.41 (d, 1H, *J* = 5.46 Hz), 6.34 (br–s, 1H), 3.87 (t, 4H, *J* = 4.62 Hz), 3.52–3.36 (m, 6H), 2.58–2.52 (m, 6H), 1.92–1.86 (m, 2H), 1.81–1.72 (m, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$+DMSO–$d_6$): 165.90, 165.06, 157.03, 155.48, 154.42, 139.45, 133.06, 129.63, 128.60, 122.97, 103.74, 71.80, 62.67, 58.90, 44.75, 44.31, 41.85, 32.40, 30.10; Anal. Calcd for $C_{21}H_{28}ClN_5O_3$: C, 58.13; H, 6.50; N, 16.14; found: C, 58.09; H, 6.48; N, 16.21.

**5.4.8. $N^1$–butyl–$N^2$–(3–(7–chloroquinolin–4–ylamino)propyl)oxalamide (11).** yield: 71%; mp 146–148 °C; ESMS: 363 (M+1); IR (KBr) 3384, 3016, 1668, 1582, 1520, 1222, 762 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.26 (br–s, 1H), 8.52 (d, 1H, *J* = 5.36 Hz), 7.94 (d, 1H, *J* = 2.14 Hz), 7.89 (d, 1H, *J* = 8.97 Hz), 7.51 (br–s, 1H), 7.39 (dd, 1H, *J* = 2.14, 8.86 Hz), 6.39–6.29 (m, 2H), 3.51–3.44 (m, 2H), 3.38–3.19 (m, 6H), 1.89–1.77 (m, 2H), 1.35–1.28 (m, 2H), 0.93 (t, 3H, *J* = 7.13 Hz); $^{13}$C NMR (50 MHz, $CDCl_3$): 161.21, 160.82, 152.61, 151.03, 149.63, 135.02, 128.16, 125.27, 124.88, 117.76, 99.43, 43.19, 40.86, 39.13, 35.28, 28.16, 22.03, 14.11; Anal. Calcd for $C_{18}H_{23}ClN_4O_2$: C, 59.58; H, 6.39; N, 15.44; found: C, 59.62; H, 6.37; N, 15.47.

**5.4.9. $N^1$–(3–(7–chloroquinolin–4–ylamino)propyl)–$N^2$–(2–(diethylamino)ethyl)oxalamide (12).** yield: 70%; mp 127–129 °C; ESMS: 406 (M+1); IR (KBr) 3298, 3060, 1652, 1580, 1516, 1213, 769 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.51 (d, 1H, *J* = 5.44 Hz), 7.98 (br–s, 1H), 7.95 (d, 1H, *J* = 2.12 Hz), 7.88 (d, 1H, *J* = 8.98 Hz), 7.76 (br–s, 1H), 7.38 (dd, 1H, *J* = 2.15, 8.95 Hz), 6.39 (d, 1H, *J* = 5.51 Hz), 6.21 (br–s, 1H), 3.53–3.33 (m, 6H), 2.70–2.53 (m, 6H), 1.99–1.89 (m, 2H), 1.04 (t, 6H, *J* = 7.12 Hz), 1.89–1.78 (m, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$): 161.38, 159.89, 151.81, 150.46, 149.09, 135.54, 128.47, 125.82, 122.19, 117.79, 98.97, 51.54, 47.30, 39.78, 37.89, 37.13, 28.25, 12.16; Anal. Calcd for $C_{20}H_{28}ClN_5O_2$: C, 59.18; H, 6.95; N, 17.25; found: C, 59.14; H, 6.93; N, 17.31.

**5.4.10. $N^1$–(3–(7–chloroquinolin–4–ylamino)propyl)–$N^2$–(2–(dimethylamino)ethyl)oxalamide (13).** yield: 72%; mp 167–169 °C; ESMS: 478 (M+1); IR (KBr) 3400, 3020, 1664, 1582, 1518, 1216, 762 cm$^{-1}$; $^1$H NMR (200 MHz, DMSO–$d_6$): δ (ppm) 8.91 (t, 1H, *J* = 5.74 Hz), 8.54 (t, 1H, *J* = 5.79 Hz), 8.37 (d, 1H, *J* = 5.41

Hz), 8.22 (d, 1H, *J* = 9.04 Hz), 7.76 (d, 1H, *J* = 2.16 Hz), 7.44 (dd, 1H, *J* = 2.17, 8.97 Hz), 7.35 (br–s, 1H), 6.45 (d, 1H, *J* = 5.48 Hz), 3.31–3.18 (m, 6H), 2.38 (t, 2H, *J* = 6.47 Hz), 2.17 (s, 6H), 1.81–1.79 (m, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$+ DMSO–$d_6$): 160.98, 160.73, 152.62, 150.91, 149.79, 134.32, 128.24, 124.97, 124.92, 118.33, 99.49, 58.22, 45.72, 40.09, 37.89, 37.62, 37.48, 28.15; Anal. Calcd for $C_{18}H_{24}ClN_5O_2$: C, 57.21; H, 6.40; N, 18.53; found: C, 57.24; H, 6.39; N, 18.59.

**5.4.11. 2–(4–(2–(7–chloroquinolin–4–ylamino)ethyl)piperazin–1–yl)–N–(2–morpholinoethyl)–2–oxoacetamide (14).** yield: 72%; mp 84–88 °C; ESMS: 475 (M+1); IR (KBr) 3421, 3019, 2959, 1669, 1576, 1510, 1454, 1216, 1116, 762 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.74 (d, 1H, *J* = 5.05 Hz), 8.66 (br–s, 1H), 8.07 (d, 1H, *J* = 2.11 Hz), 7.96 (d, 1H, *J* = 9.24 Hz), 7.86 (br–s, 1H), 7.45 (dd, 1H, *J* = 1.83, 8.68 Hz), 6.86 (d, 1H, *J* = 5.05 Hz), 3.84–3.81 (m, 4H), 3.53–3.42 (m, 4H), 3.37–3.29 (m, 4H), 2.87–2.79 (m, 4H), 2.72 (t, 2H, *J* = 5.71 Hz), 2.63–2.48 (m, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$): 160.32, 160.21, 157.33, 152.21, 150.42, 135.32, 129.22, 126.62, 125.53, 122.32, 109.41, 58.12, 56.73, 53.22, 52.42, 39.91, 36.64, 30.12, 25.12; Anal. Calcd for $C_{23}H_{31}ClN_6O_3$: C,58.16; H,6.58; N,17.69; Found: C, 58.21; H, 6.57; N, 17.73.

**5.4.12. 2–(4–(2–(7–chloroquinolin–4–ylamino)ethyl)piperazin–1–yl)–N–(3–morpholinopropyl)–2–oxoacetamide (15).** yield: 74%; mp 180–182 °C; ESMS: 489 (M+1); IR (KBr) 3402, 3019, 2968, 1669, 1509, 1454, 1216, 1116, 761 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.72 (d, 1H, *J* = 5.05 Hz), 8.63 (br–s, 1H), 8.07 (d, 1H, *J* = 2.11 Hz), 7.95 (d, 1H, *J* = 9.12 Hz), 7.84 (br–s, 1H), 7.42 (dd, 1H, *J* = 1.82, 8.69 Hz), 6.85 (d, 1H, *J* = 5.11 Hz), 3.81–3.78 (m, 4H) 3.51–3.39 (m, 4H), 3.38–3.29 (m, 4H), 2.83–2.77 (m, 4H), 2.69 (t, 2H, *J* = 5.69 Hz), 2.62–2.54 (m, 6H), 1.81–1.77 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): 160.32, 160.23, 157.32, 152.24, 150.43, 135.32, 129.21, 126.63, 125.52, 122.32, 109.42, 58.13, 56.72, 53.23, 52.43, 39.91, 36.62, 30.11, 25.12, 25.01; Anal. Calcd for $C_{24}H_{33}ClN_6O_3$: C, 58.95; H, 6.80; N,17.19; Found: C, 58.91; H, 6.77; N,17.22.

**5.4.13. N–butyl–2–(4–(2–(7–chloroquinolin–4–ylamino)ethyl)piperazin–1–yl)–2–oxoacetamide (16).** yield 71%; mp 100–104 °C; ESMS: 418 (M+1); IR (KBr) 3394, 3293, 2955, 1663, 1575,1513, 1429, 1218, 1143, 762 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.73 (d, 1H, *J* = 5.18 Hz), 8.11 (d, 1H, *J* = 2.09 Hz), 7.95–7.90 (m, 2H), 7.52–7.42 (m, 2H), 6.87 (d, 1H, *J* = 5.06 Hz), 3.53–3.47 (m, 2H), 3.37–3.30 (m, 6H), 2.93–2.81 (m, 4H,), 2.72 (t, 2H, *J* = 6.01 Hz), 1.81–1.74 (m, 2H), 1.51–1.26 (m, 2H), 0.91 (t, 3H, *J* = 7.26 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$): 159.92, 159.71, 156.91, 151.72, 149.93, 135.02, 128.73, 126.13, 125.12, 121.82, 108.92, 56.24, 52.72, 52.01, 39.43, 36.24, 31.23, 19.91, 13.62; Anal. Calcd for $C_{21}H_{28}ClN_5O_2$: C, 60.35; H, 6.75; N, 16.76; Found: C, 60.38; H, 6.72; N, 16.79.

**5.4.14. 2–(4–(2–(7–chloroquinolin–4–ylamino)ethyl)piperazin–1–yl)–N–(2–(diethylamino)ethyl)–2–oxoacetamide (17).** yield: 71%; mp 150–152 °C; ESMS: 461 (M+1); IR (KBr) 3392, 3019, 2966, 1673, 1572, 1509, 1457, 1216, 756 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.74 (d, 1H, *J* = 5.09 Hz), 8.56 (br–s, 1H), 8.06 (d, 1H, *J* = 1.82 Hz), 7.96 (d, 1H, *J* = 9.01 Hz), 7.85 (br–s, 1H), 7.45 (dd, 1H, *J* = 1.97, 8.85 Hz), 6.86 (d, 1H, *J* = 5.14 Hz), 3.51–3.41 (m, 4H), 3.38–3.27 (m, 4H), 2.86–2.79 (m, 4H), 2.28–1.97 (m, 8H ), 1.10 (t, 6H, *J* = 6.89 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$): 159.82, 159.33, 156.52, 151.92, 149.81, 134.94, 128.82, 126.14, 125.13, 121.72, 109.02, 56.33, 52.81, 52.03, 51.13, 46.92, 37.12, 36.24, 29.63, 11.52, 11.42; Anal. Calcd for $C_{23}H_{33}ClN_6O_2$: C, 59.92; H, 7.22; N, 18.23; Found: C, 59.87; H, 7.27; N,18.19.

**5.4.15. 2–(4–(2–(7–chloroquinolin–4–ylamino)ethyl)piperazin–1–yl)–N–(2–(dimethylamino)ethyl)–2–oxoacetamide (18).** Yield: 68%; mp 130–134 °C ESMS: 433 (M+1); IR (KBr) 3415, 3020, 2971, 1674, 1572, 1511, 1459, 1216, 763 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.83 (d, 1H, *J* = 5.17 Hz), 8.61 (br–s, 1H), 8.15 (d, 1H, *J* = 1.81 Hz), 8.05 (d, 1H, *J* = 8.69 Hz), 7.96 (br–s, 1H), 7.54 (dd, 1H, *J* = 1.81, 8.68 Hz), 6.95 (d, 1H, *J* = 4.68 Hz), 3.60–3.50 (m, 4H), 3.42–3.35 (m, 4H), 2.91–2.84 (m, 4H), 2.79 (t, 2H, *J* = 6.11 Hz), 2.61 (t, 2H, *J* = 6.02 Hz), 2.36 (s, 6H,); $^{13}$C NMR (75 MHz, $CDCl_3$): 159.81, 159.32, 156.81, 151.94, 150.12, 134.93, 128.82, 126.14, 125.13, 121.92, 109.04, 57.54, 56.31, 52.83, 52.04, 45.14, 37.12, 36.22, 29.61; Anal. Calcd for $C_{21}H_{29}ClN_6O_2$: C, 58.26; H, 6.75; N, 19.41; Found: C, 58.29; H, 6.76; N, 19.43.

**5.4.16. N–tert–butyl–2–(4–(2–(7–chloroquinolin–4–ylamino)ethyl)piperazin–1–yl)–2 oxoacetamide (19).** yield 74%; mp 98–100 °C ESMS: 418 (M+1); IR (KBr) 3424, 3021, 2970, 1641, 1521, 1430, 1216, 760 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$+$CD_3OD$): δ (ppm) 8.74 (d, 1H, *J* = 5.12 Hz), 8.08 (d, 1H, *J* = 2.11 Hz), 8.02 (d, 1H, *J* = 9.01 Hz), 7.60 (dd, 1H, *J* = 1.81, 9.02 Hz), 7.04 (d, 1H, *J* = 5.06 Hz), 3.76–3.63 (m, 8H), 3.47–3.41 (m, 4H), 1.39 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$): 168.12, 167.43, 159.34, 154.53, 152.32, 139.34, 131.22, 130.50, 127.91, 124.62, 112.93, 59.62,

55.21, 53.15, 51.42, 36.93, 32.90; Anal. Calcd for $C_{21}H_{28}ClN_5O_2$: Calculated C, 60.35; H, 6.75; N,16.76; Found: C, 60.32, H, 6.81, N, 16.79.

**5.4.17. N–(3–(1H–imidazol–2–yl)propyl)–2–(4–(2–(7–chloroquinolin–4–ylamino)ethyl)piperazin–1–yl)–2–oxoacetamide (20).** yield: 72%; mp 142–144 °C ESMS: 470 (M+1); IR (KBr): 3437, 3020, 2980, 1635, 1520, 1437, 1216, 1124, 768 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$+$CD_3OD$): δ (ppm) 8.62 (d, 1H, *J* = 5.16 Hz), 8.01–7.97 (m, 1H), 7.91 (d, 1H, *J* = 9.02 Hz), 7.61–7.53 (m, 1H), 7.42 (dd, 1H, *J* = 2.11, 9.01 Hz), 7.03–6.99 (m, 1H), 6.98–6.94 (m, 1H), 6.84 (d, 1H, *J* = 5.19 Hz), 3.98 (t, 4H, *J* = 5.98 Hz), 3.47 (t, 2H, *J* = 5.62 Hz), 3.34–3.24 (m, 6H), 2.83–2.74 (m, 2H), 2.68 (m, 2H, *J* = 5.91 Hz), 2.07–1.95 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$): 157.02, 151.61, 149.81, 136.92, 135.13, 128.33, 126.32, 126.25, 125.13, 121.81, 119.54, 119.23, 109.02, 56.21, 52.74, 51.91, 44.34, 36.71, 30.61, 29.62; Anal. Calcd for $C_{23}H_{28}ClN_7O_2$: C, 58.78; H, 6.01; N, 20.86; Found: C, 58.81; H, 6.04; N, 20.83.

**5.4.18. 2–(4–(7–chloroquinolin–4–yl)piperazin–1–yl)–N–(2–morpholinoethyl)–2–oxoacetamide (21).** yield 68%; mp 118–120 °C; ESMS: 432 (M+1); IR (KBr) 3430, 3020, 2972, 1637, 1523, 1430, 1216, 1118, 761 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ (ppm) 8.67 (d, 1H, *J* = 5.23 Hz), 8.01–7.94 (m, 3H), 7.51 (dd, 1H, *J* = 1.81, 9.02 Hz), 6.94 (d, 1H, *J* = 5.17 Hz), 4.21–4.09 (m, 8H), 3.68–333 (m, 4H), 2.99 (t, 2H, *J* = 6.01 Hz), 2.89–2.81 (m, 4H), 2.59 (t, 2H, *J* = 6.34 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$): 161.42, 161.12, 155.23, 153.12, 150.61, 139.32, 131.43, 130.21, 129.32, 125.62, 112.83, 61.32, 57.31, 56.74, 55.72, 40.92; Anal. Calcd for $C_{21}H_{26}ClN_5O_3$: C, 58.40; H, 6.07; N, 16.21; Found: C, 58.45; H, 6.09; N, 16.24.

**5.4.19. 2–(4–(7–chloroquinolin–4–yl)piperazin–1–yl)–N–(3–morpholinopropyl)–2–oxoacetamide (22).** yield: 73%; mp 194–196 °C; ESMS: 446 (M+1); IR (KBr) 3454, 3067, 2980, 1643, 1529, 1427, 1206, 1115, 761 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ (ppm) 8.75 (d, 1H, *J* = 5.16 Hz), 8.49 (br–s, 1H), 8.07 (d, 1H, *J* = 2.11 Hz), 7.97 (d, 1H, *J* = 9.01 Hz), 7.48 (dd, 1H, *J* = 2.11, 9.02 Hz), 6.85 (d, 1H, *J* = 5.05 Hz), 4.45 (t, 2H, *J* = 4.82 Hz), 3.96 (t, 2H, *J* = 4.81 Hz), 3.78 (t, 4H, *J* = 4.52 Hz), 3.44–3.37 (m, 2H), 3.31–3.26 (m, 4H), 2.52–2.48 (m, 6H), 1.84–1.71 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$):160.99, 160.96, 156.32, 151.82, 150.02, 135.23, 128.90, 126.71, 124.72, 121.71, 109.32, 66.82, 56.71, 53.32, 52.52, 52.01, 46.22, 43.03, 35.71; Anal. Calcd for $C_{22}H_{28}ClN_5O_3$: C, 59.25; H, 6.33; N, 15.70; Found: C, 59.21; H, 6.34; N, 15.67.

**5.4.20. N–butyl–2–(4–(7–chloroquinolin–4–yl)piperazin–1–yl)–2–oxoacetamide (23).** yield: 70%; mp 110–112 °C; ESMS: 375 (M+1); IR (KBr) 3338, 3075, 2955, 1673, 1642, 1570, 1427, 1381, 1210, 1160, 771 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ (ppm) 8.75 (d, 1H, *J* = 5.05 Hz), 8.09 (d, 1H, *J* = 1.82 Hz), 7.96 (d, 1H, *J* = 9.01 Hz), 7.49 (dd, 1H, *J* = 2.11, 9.02 Hz), 7.32 (br–s, 1H), 6.85 (d, 1H, *J* = 5.16 Hz), 4.50 (t, 2H, *J* = 4.82 Hz), 3.96 (t, 2H, *J* = 4.81 Hz), 3.35–3.26 (m, 6H), 1.61–1.51 (m, 2H), 1.45–1.32 (m, 2H), 0.97 (t, 3H, *J* = 6.92 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$): 160.91, 160.72, 156.32, 151.72, 150.01, 135.21, 128.90, 126.61, 124.72, 121.71, 109.32, 57.32, 52.62, 52.01, 46.32, 43.12, 39.21, 31.22, 20.02, 13.61; Anal. Calcd for $C_{19}H_{23}ClN_4O_2$: C, 60.88; H, 6.18; N, 14.95; Found: C, 60.86; H, 6.21; N, 14.98.

**5.4.21. 2–(4–(7–chloroquinolin–4–yl)piperazin–1–yl)–N–(2–(diethylamino)ethyl)–2–oxoacetamide (24).** yield: 73%; mp 168–170 °C ESMS: 418 (M+1); IR (KBr) 3452, 3020, 2973, 1629, 1500, 1426, 1216, 1046, 761 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ (ppm) 8.75 (d, 1H, *J* = 4.81 Hz), 8.07 (d, 1H, *J* = 1.81 Hz), 7.97 (d, 1H, *J* = 9.02 Hz), 7.83 (br–s, 1H) 7.48 (dd, 1H, *J* = 1.81, 8.69 Hz), 6.85 (d, 1H, *J* = 4.81 Hz), 4.38 (m, 2H), 3.94 (m, 2H), 3.41–3.39 (m, 2H), 3.25 (m, 4H), 2.69–2.59 (m, 6H), 1.13 (t, 6H, *J* = 6.89 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$): 161.22, 161.12, 156.32, 151.91, 150.02, 135.23, 128.90, 126.61, 124.72, 121.71, 109.32, 52.52, 52.02, 51.13, 46.24, 42.92, 36.91, 11.51; Anal. Calcd for $C_{21}H_{28}ClN_5O_2$: C, 60.35; H, 6.75; N, 16.76;. Found: C, 60.31; H, 6.78; N, 16.73.

**5.4.22. 2–(4–(7–chloroquinolin–4–yl)piperazin–1–yl)–N–(2–(dimethylamino)ethyl)–2–oxoacetamide(25).** yield: 72%; mp158–160 °C; ESMS: 390 (M+1); IR (KBr) 3236, 3195, 2988, 1676, 1574, 1426, 1379, 1230, 1189, 775 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ (ppm) 8.75 (d, 1H, *J* = 5.21 Hz), 8.07 (d, 1H, *J* = 2.11 Hz), 7.97 (d, 1H, *J* = 9.01 Hz), 7.68 (br–s, 1H) 7.49 (dd, 1H, *J* = 2.02, 9.02 Hz), 6.86 (d, 1H, *J* = 5.19 Hz), 4.41 (t, 2H, *J* = 4.81 Hz), 3.46–3.40 (m, 2H), 3.37–3.29 (m, 6H), 2.56 (t, 2H, *J* = 6.02 Hz), 2.31 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$): 161.19, 161.02, 156.31, 151.92, 150.12, 135.12, 129.02, 126.62, 124.73, 121.82, 109.32, 57.32, 52.52, 52.02, 46.22, 45.13, 42.91, 36.81; Anal. Calcd for $C_{19}H_{24}ClN_5O_2$: C, 58.53; H, 6.20; N, 17.96; Found: C, 58.57; H, 6.21; N, 17.93.

**5.4.23. N–tert–butyl–2–(4–(7–chloroquinolin–4–yl)piperazin–1–yl)–2–oxoacetamide (26).** yield 74%; mp 100–104 °C; ESMS: 375 (M+1); IR (KBr) 3441, 3020, 2968, 1659, 1579, 1426, 1215, 1035, 761 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$+ $CD_3OD$): δ (ppm) 8.74 (d, 1H, *J* = 5.05 Hz), 8.08 (d, 1H, *J* = 2.11 Hz), 8.02

(d, 1H, *J* = 9.01 Hz), 7.60 (dd, 1H, *J* = 1.81, 9.02 Hz), 7.04 (d, 1H, *J* = 5.05 Hz), 4.14–3.92 (m, 2H), 3.94–3.87 (m, 2H), 3.50 (m, 4H), 1.37 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$): 168.11, 167.42, 159.32, 154.52, 152.31, 139.32, 131.24, 130.52, 127.91, 124.63, 112.91, 59.61, 55.21, 53.13, 51.41, 36.91, 32.91; Anal. Calcd for $C_{19}H_{23}ClN_4O_2$: Calculated C: 60.88; H, 6.18; N, 14.95; Found: C, 60.84; H, 6.22, N, 14.98.

### 5.5. General procedure for the synthesis of compounds (29–30)

A mixure of 2–(1H–indol–3–yl)–2–oxoacetyl chloride **28** (prepared by the reaction of indole with oxalylchloride in dry ether at 0 °C for 1h, a yellow colour precipitate formed is filtered and immediately used for further reaction), **2c/2d** and $Et_3N$ were reflux at 120 °C in steal bomb for 9h. The Solvent was removed under reduced pressure to yield a residue. The solid mass was purified by column chromatography over silica gel using $CHCl_3$/MeOH as the eluent to yield compounds **29** and **30.**

**5.5.1. 1–(4–(2–(7–chloroquinolin–4–ylamino)ethyl)piperazin–1–yl)–2–(1H–indol–3–yl)ethane–1,2–dione. (29)** yield: 75%; mp 182–184 °C; ESMS: 462 (M+1); IR (KBr) 3371, 3061, 2943, 1681, 1620, 1573, 1492, 1239, 786 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$+$CD_3OD$): δ (ppm) 8.97 (s, 1H), 8.66 (d, 1H, *J* = 5.12 Hz), 8.41–8.38 (m, 1H), 8.01–7.95 (m, 2H), 7.49–7.44 (m, 2H), 7.36–7.28 (m, 3H), 6.91 (d, 1H, *J* = 5.09 Hz), 3.59 (t, 2H, *J* = 6.01 Hz), 3.38–3.33 (m, 4H), 2.85–2.75 (m, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$): 184.52, 167.41, 161.53, 155.11, 153.03, 142.90, 140.32, 139.32, 131.32, 130.61, 130.23, 129.43, 127.72, 126.93, 125.81, 125.62, 116.71, 116.02, 112.81, 60.32, 56.62, 55.71, 39.82; Anal. Calcd for $C_{25}H_{24}ClN_5O_2$: C, 65.00; H, 5.24; N, 15.16; Found: C, 65.04; H, 5.29; N, 15.13.

**5.5.2. 1–(4–(7–chloroquinolin–4–yl)piperazin–1–yl)–2–(1H–indol–3–yl)ethane–1,2–dione (30).** yield: 77% mp 190–194 °C; ESMS: 419 (M+1); IR (KBr): 3420, 3020, 2926, 1643, 1577, 1530, 1442, 1216, 762 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$+$CD_3OD$): δ (ppm) 8.97 (s, 1H), 8.66 (d, 1H, *J* = 5.18 Hz), 8.41–8.38 (m, 1H), 8.01–7.95 (m, 2H), 7.49–7.44 (m, 2H), 7.36–7.28 (m, 2H), 6.91 (d, 1H, *J* = 5.12 Hz), 3.97 (t, 2H, *J* = 4.81 Hz), 3.79 (t, 2H, *J* = 5.05 Hz), 3.39 (t, 2H, *J* = 4.82 Hz) 3.22 (t, 2H, *J* = 4.82 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$): 188.11, 169.32, 159.52, 154.01, 151.72, 140.02, 138.32, 130.11, 129.41, 127.62, 127.22, 126.32, 125.42, 124.11, 124.05, 116.31, 114.72, 112.01, 54.91, 54.41, 48.72, 44.22; Anal. Calcd for $C_{23}H_{19}ClN_4O_2$: C, 65.95; H, 4.57; N, 13.38; Found: C, 65.97; H, 4.53; N, 13.41.

### 5.6. General procedure for the synthesis of compounds (31–34)

The solution of methyl iodide/p–toluenesulphonyl chloride (1.5 equiv) in DCM was added dropwise to an ice–cold mixture of hybrid quinoline–indoles (**29**, **30**), NaOH and phasetransfer catalyst in DCM during 30 min. The reaction mixture was stirred at 0 °C for 1 h and consequently at room temperature for 1h. Solvent was removed under reduced pressure and solid was extracted with water and DCM. Organic layer was separated and dried over anhydrous $Na_2SO_4$, concentrated. The residue was purified by column chromatography over silica gel using $CHCl_3$/MeOH as the eluent to yield the desired compounds **31–34**.

**5.6.1. 1–(4–(2–(7–chloroquinolin–4–ylamino) ethyl)piperazin–1–yl)–2–(1–methyl–1H–indol–3–yl)ethane–1,2–dione (31).** yield: 73%; mp 164–166 °C; ESMS: 476 (M+1); IR (KBr): 3397, 3020, 2974, 1672, 1623, 1504, 1466, 1426, 1216, 761 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.98 (s, 1H), 8.73 (d, 1H, *J* = 4.82 Hz), 8.44–8.41 (m, 1H), 8.06 (d, 1H, *J* = 2.11 Hz), 7.96–7.93 (m, 2H), 7.44–7.33 (m, 4H), 6.87 (d, 1H, *J* = 5.02 Hz), 3.92 (s, 3H), 3.60–3.54 (m, 2H), 3.31–3.29 (m, 4H), 2.84–2.73 (m, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$): 179.81, 162.62, 156.81, 151.72, 50.02, 141.91, 137.02, 134.91, 128.90, 127.61, 126.12, 125.02, 123.81, 123.42, 122.61, 121.81, 112.02, 109.73, 109.02, 56.53, 52.81, 52.12, 35.92, 33.71; Anal. Calcd for $C_{26}H_{26}ClN_5O_2$: C, 65.61; H, 5.51; N, 14.71; Found: C, 65.65; H, 5.54; N, 14.67.

**5.6.2. 1–(4–(2–(7–chloroquinolin–4–ylamino)ethyl)piperazin–1–yl)–2–(1–tosyl–1H–indol–3–yl)ethane–1,2–dione (32).** yield 71%; mp 144–148 °C ESMS: 616 (M+1); IR (KBr): 3380, 3022, 2978, 1675, 1620, 1500, 1465, 1420, 1216, 765 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): δ (ppm), 9.35 (s, 1H), 8.65 (d, 1H, *J* = 4.52 Hz), 8.31 (d, 1H, *J* = 6.91 Hz), 8.01–7.85 (m, 6H), 7.43–7.25 (m, 5H), 6.85 (d, 1H, *J* = 4.81), 3.93–3.89 (m, 2H), 3.54–3.30 (m, 4H), 2.77–2.62 (m, 6H), 2.24 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): 179.72, 162.22, 157.02, 151.51, 150.02, 141.32, 139.03, 136.51, 134.42, 134.01, 131.92, 128.41, 127.12, 126.52, 125.32, 124.31, 123.3, 123.0, 122.12, 121.51, 112.02, 109.71, 109.12, 56.23, 52.63, 51.71, 35.24, 23.71; Anal. Calcd for $C_{32}H_{30}ClN_5O_4S$: C, 62.38; H, 4.91; N, 11.37; Found: C, 62.34; H, 4.97; N, 11.35.

**5.6.3. 1–(4–(7–chloroquinolin–4–yl)piperazin–1–yl)–2–(1–methyl–1H–indol–3–yl)ethane–1,2–dione (33).** Yield: 71%; mp 178–180 °C; ESMS: 433 (M+1); IR (KBr) 3432, 3027, 2928, 1650, 1579, 1543, 1445,

1216, 765 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$+$CD_3OD$): δ (ppm) 8.67 (d, 1H, *J* = 5.12 Hz), 8.29–8.26 (m, 1H), 8.02–7.99 (m, 3H), 7.52–7.48 (m, 2H), 7.34–7.31 (m, 2H), 6.96 (d, 1H, *J* = 5.05 Hz), 4.08–4.05 (m, 2H), 3.84–3.81 (m, 2H), 3.41 (t, 2H, *J* = 4.79 Hz), 3.35 (s, 3H) 3.29 (t, 2H, *J* = 4.81 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$): 188.51, 169.91, 160.02, 154.31, 152.21, 140.21, 138.72, 130.71, 129.82, 128.21, 127.90, 127.12, 126.14, 124.62, 124.52, 116.92, 115.21, 112.43, 55.11, 54.82, 49.12, 44.34, 33.61; Anal. Calcd for $C_{24}H_{21}ClN_4O_2$: C, 66.59; H, 4.89; N, 12.94; Found: C, 66.57; H, 4.93; N, 12.91.

**5.6.4. 1–(4–(7–chloroquinolin–4–yl)piperazin–1–yl)–2–(1–tosyl–1H–indol–3–yl)ethane–1,2–dione (34).** yield: 69%; mp 150–152 °C; ESMS: 573 (M+1); IR (KBr) 3423, 3020, 2926, 1643, 1577, 1530, 1442, 1216, 762 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm), 8.74 (d, 1H, *J* = 4.94 Hz), 8.41 (s, 1H), 8.38–8.27 (m, 1H), 8.06 (d, 1H, *J* = 2.02 Hz), 7.94–7.85 (m, 4H), 7.47–7.25 (m, 5H), 6.86 (d, 1H, *J* = 4.95 Hz), 4.08–4.04 (m, 2H), 3.84–3.79 (m, 2H), 3.36–3.24 (m, 4H), 2.38 (s, 3H); $^{13}C$ NMR (50 MHz, $CDCl_3$): 179.72, 162.21, 157.03, 151.53, 150.01, 141.32, 139.04, 136.52, 134.41, 134.04, 131.92, 128.40, 127.12, 126.52, 125.33, 124.31, 123.33, 123.01, 122.13, 121.52, 112.01, 109.71, 109.10, 54.91, 54.31, 48.64, 44.03, 33.25; Anal. Calcd for $C_{30}H_{25}ClN_4O_4S$: C, 62.88; H, 4.40; N, 9.78; Found: C, 62.84; H, 4.43; N, 9.76.

### 5.7. General procedure for the synthesis of compounds 36, 37

The solution of piperidine/morpholine (1 equiv) in dry THF was added dropwise to an ice–cold mixture of cyanuric chloride (1.5 equiv) and $K_2CO_3$ (1 equiv) in dry THF during 30 min. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was filtered and solvent was evaporated under vacuum to dryness. The solid mass was dissolved in $CHCl_3$, washed with water and dried over anhydrous $Na_2SO_4$, concentrated, and purified with column chromatography to afford respective compounds **36** and **37**.

**5.7.1. 2,4–dichloro–6–(piperidin–1–yl)–1,3,5–triazine (36).** yield: 84%; mp 176–178 °C; ESMS: 233 (M+1); IR (KBr) 2945, 1574, 1472, 1217, 765 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm) 3.81 (t, 4H, *J* = 5.18 Hz), 1.68–1.59 (m, 6H); $^{13}C$ NMR (50 MHz, $CDCl_3$): 170.54, 164.43, 45.74, 26.06, 24.63; Anal. Calcd for $C_8H_{10}Cl_2N_4$: C, 41.22; H, 4.32; N, 24.04; found: C, 41.26; H, 4.29; N, 24.11.

**5.7.2. 4–(4,6–dichloro–1,3,5–triazin–2–yl)morpholine (37).** yield: 82%; mp 154–156 °C; ESMS: 235 (M+1); IR (KBr) 2968, 1576, 1477, 1219, 763 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm) 3.91 (t, 4H, *J* = 3.21 Hz), 3.76(t, 4H, *J* = 3.18 Hz); $^{13}C$ NMR (50 MHz, $CDCl_3$): 170.83, 164.50, 66.77, 44.88; Anal. Calcd for $C_7H_8Cl_2N_4O$: C, 35.77; H, 3.43; N, 23.83; found: C, 35.69; H, 3.37; N, 23.85.

### 5.8. General procedure for the synthesis of compounds 38–57

The mixture of compounds **36**/**37** (1 equiv) and **2a**/**2b** (1 equiv) and $K_2CO_3$ (1 equiv) in dry THF was stirred at room temperature for 4 h. Subsequently the different amines (1.5 equiv) listed in Table 2 and $K_2CO_3$ (1 equiv) were added to the reaction and stirred at 80 °C for 6 h additionally. The reaction mixture was filtered and the solvent was evaporated under vacuum. The solid residue was purified with column chromatography using silica–gel as adsorbent to obtain respective compounds **38–57**.

**5.8.1. $N^2$–(2–(7–chloroquinolin–4–ylamino)ethyl)–$N^4$–(3–morpholinopropyl)–6–(piperidin–1–yl)–1,3,5–triazine–2,4–diamine (38).** yield: 70%; mp 163–165 °C; ESMS: 526 (M+1); IR (KBr) 3366, 2927, 1611, 1562, 1455, 1370, 1214, 1109, 808, 762 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm) 8.44 (d, 1H, *J* = 5.48 Hz), 7.92 (d, 1H, *J* = 2.01 Hz), 7.58–7.56 (m, 1H), 7.34–7.21 (m, 2H), 6.26 (d, 1H, *J* = 5.42 Hz), 5.42 (br–s, 1H), 5.34 (br–s, 1H), 3.93–3.69 (m, 10H), 3.52–3.29 (m, 4H), 2.59–2.42 (m, 6H), 1.93–1.71 (m, 8H); $^{13}C$ NMR (50 MHz, $CDCl_3$): 167.81, 165.05, 151.67, 151.17, 149.14, 135.34, 128.34, 125.37, 122.88, 117.49, 98.50, 67.38, 63.07, 57.76, 54.11, 51.33, 44.71, 39.47, 34.67, 26.23, 25.21; Anal. Calcd for $C_{26}H_{36}ClN_9O$: C, 59.36; H, 6.90; N, 23.96; found: C, 59.33; H, 6.94; N, 23.91.

**5.8.2. $N^2$–(2–(7–chloroquinolin–4–ylamino)ethyl)–$N^4$–(2–(diethylamino)ethyl)–6–(piperidin–1–yl)–1,3,5–triazine–2,4–diamine (39).** yield: 68%; mp 81–83 °C; ESMS: 498 (M+1); IR (KBr) 3424, 3020, 1582, 1540, 1445, 1367, 1216, 1141, 806, 768 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm) 8.45 (d, 1H, *J* = 5.34 Hz), 7.91 (d, 1H, *J* = 1.84 Hz), 7.63–7.59 (m, 1H), 7.25–7.21 (m, 2H), 6.27 (d, 1H, *J* = 5.41 Hz), 5.59 (br–s, 2H), 3.83–3.77 (m, 6H), 3.51–3.42 (m, 4H), 2.66–2.49 (m, 6H), 1.69–1.52 (m, 6H), 1.05 (t, 6H, *J* = 7.11 Hz); $^{13}C$ NMR (50 MHz, $CDCl_3$): 167.92, 164.97, 151.47, 151.26, 148.83, 135.41, 127.95, 125.44, 122.94, 117.51, 98.52, 52.25, 47.31, 44.84, 39.41, 38.52, 30.09, 26.23, 25.19, 11.48; Anal. Calcd for $C_{25}H_{36}ClN_9$: C, 60.29; H, 7.29; N, 25.31; found: C, 60.26; H, 7.34; N, 25.27.

**5.8.3. $N^2$–(2–(7–chloroquinolin–4–ylamino)ethyl)–$N^4$–(2–(dimethylamino)ethyl)–6–(piperidin–1–yl)–1,3,5–triazine–2,4–diamine (40).** yield: 71%; mp 127–129 °C; ESMS: 470 (M+1); IR (KBr) 3417, 3020, 1580, 1535, 1450, 1216, 1112, 806, 762 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm) 8.46 (d, 1H, *J* = 5.46 Hz), 7.92 (d, 1H, *J* = 2.11 Hz), 7.57–7.51 (m, 1H), 7.35–7.22 (m, 2H), 6.28 (d, 1H, *J* = 5.52 Hz), 5.49 (br–s, 2H), 3.77–3.68 (m, 6H), 3.48–3.41 (m, 4H), 2.51–2.42 (m, 2H), 2.28 (s, 6H), 1.71–1.59 (m, 6H); $^{13}C$ NMR (50 MHz, $CDCl_3$+$CD_3OD$): 172.44, 164.73, 151.56, 151.02, 147.96, 135.75, 127.14, 125.57, 122.85, 117.37, 98.51, 58.77, 45.34, 44.84, 39.14, 38.28, 30.01, 26.12, 25.05; Anal. Calcd for $C_{23}H_{32}ClN_9$: C, 58.77; H, 6.86; N, 26.82; found: C, 58.75; H, 6.91; N, 26.85.

**5.8.4. $N^1$–(7–chloroquinolin–4–yl)–$N^2$–(4–(4–methylpiperazin–1–yl)–6–(piperidin–1–yl)–1,3,5–triazin–2–yl)ethane–1,2–diamine (41).** yield: 74%; mp 139–141 °C; ESMS: 482 (M+1); IR (KBr) 3265, 2931, 2850, 1585, 1528, 1443, 1364, 1279, 1141, 806, 771 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm) 8.47 (d, 1H, *J* = 5.41 Hz), 7.91 (d, 1H, *J* = 2.04 Hz), 7.47 (d, 1H, *J* = 8.92 Hz), 7.26–7.21 (m, 1H), 7.09 (br–s, 1H), 6.28 (d, 1H, *J* = 5.44 Hz), 5.21 (t, 1H, *J* = 6.65 Hz), 3.87–3.72 (m, 10H), 3.43–3.38 (m, 2H), 2.49–2.36 (m, 4H), 2.31 (s, 3H), 1.71–1.53 (m, 6H); $^{13}C$ NMR (50 MHz, $CDCl_3$): 167.91, 165.48, 152.07, 150.96, 149.08, 135.22, 128.55, 125.51, 122.58, 117.56, 98.55, 55.33, 47.09, 46.62, 44.81, 43.58, 39.42, 26.22, 25.22; Anal. Calcd for $C_{24}H_{32}ClN_9$: C, 59.80; H, 6.69; N, 26.15; found: C, 59.84; H, 6.72; N, 26.11.

**5.8.5. $N^2$–(2–(7–chloroquinolin–4–ylamino)ethyl)–$N^4$–(2–morpholinoethyl)–6–(piperidin–1–yl)–1,3,5–triazine–2,4–diamine (42).** yield: 70%; mp 147–149 °C; ESMS: 512 (M+1); IR (KBr) 3375, 2937, 1588, 1537, 1357, 1218, 1115, 806, 767 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm) 8.47 (d, 1H, *J* = 5.42 Hz), 7.91 (d, 1H, *J* = 2.06 Hz), 7.54–7.51 (m, 1H), 7.21 (dd, 1H, *J* = 1.91, 8.91 Hz), 7.12 (br–s, 1H), 6.28 (d, 1H, *J* = 5.51 Hz), 5.41 (br–s, 1H), 5.27 (br–s, 1H), 3.84–3.68 (m, 10H), 3.51–3.39 (m, 4H), 2.58–2.47 (m, 6H), 1.67–1.54 (m, 6H); $^{13}C$ NMR (50 MHz, $CDCl_3$): 167.89, 165.08, 151.91, 151.02, 149.68, 135.24, 128.39, 125.32, 122.59, 117.53, 98.56, 57.91, 53.85, 46.87, 44.83, 39.47, 37.53, 26.25, 25.19; Anal. Calcd for $C_{25}H_{34}ClN_9O$: C, 58.64; H, 6.69; N, 24.62; found: C, 58.62; H, 6.73; N, 24.59.

**5.8.6. $N^2$–(2–(7–chloroquinolin–4–ylamino)ethyl)–6–morpholino–$N^4$–(3–morpholinopropyl)–1,3,5–triazine–2,4–diamine (43).** yield: 73%; mp 165–167 °C; ESMS: 528 (M+1); IR (KBr) 3379, 3020, 1589, 1546, 1444, 1361, 1216, 1115, 811, 763 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm) 8.47 (d, 1H, *J* = 5.36 Hz), 7.91 (d, 1H, *J* = 2.11 Hz), 7.54–7.49 (m, 1H), 7.26–7.21 (m, 2H), 6.28 (d, 1H, *J* = 5.28 Hz), 5.37 (br–s, 1H), 5.31 (br–s, 1H), 3.72–3.66 (m, 16H), 3.41–3.32 (m, 2H), 2.45–2.36 (m, 6H), 1.86–1.67 (m, 2H); $^{13}C$ NMR (50 MHz, $CDCl_3$): 167.81, 165.54, 152.25, 150.76, 149.27, 135.06, 128.72, 125.25, 123.15, 117.59, 98.62, 67.37, 67.19, 58.03, 54.09, 46.58, 44.07, 40.67, 39.51, 30.08; Anal. Calcd for $C_{25}H_{34}ClN_9O_2$: C, 56.86; H, 6.49; N, 23.87; found: C, 56.83; H, 6.51; N, 23.84.

**5.8.7. $N^2$–(2–(7–chloroquinolin–4–ylamino)ethyl)–$N^4$–(2–(diethylamino)ethyl)–6–morpholino–1,3,5–triazine–2,4–diamine (44).** yield: 71%; mp 119–121 °C; ESMS: 500 (M+1); IR (KBr) 3280, 2971, 1587, 1544, 1434, 1276, 1113, 810, 767 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm) 8.48 (d, 1H, *J* = 5.41 Hz), 7.91 (d, 1H, *J* = 2.02 Hz), 7.54–7.51 (m, 1H), 7.25 (dd, 1H, *J* = 2.09, 8.41 Hz), 7.09 (br–s, 1H), 6.29 (d, 1H, *J* = 5.39 Hz), 5.56 (br–s, 1H), 5.29 (br–s, 1H), 3.79–3.72 (m, 10H), 3.62–3.41 (m, 4H), 2.64–2.54 (m, 6H), 1.02 (t, 6H, *J* = 7.11 Hz); $^{13}C$ NMR (50 MHz, $CDCl_3$): 167.61, 165.53, 152.09, 150.81, 149.12, 135.16, 128.56, 125.39, 122.42, 117.57, 98.61, 67.20, 52.20, 47.14, 46.48, 44.13, 39.47, 38.85, 11.85; Anal. Calcd for $C_{24}H_{34}ClN_9O$: C, 57.65; H, 6.85; N, 25.21; found: C, 57.63; H, 6.79; N, 25.18.

**5.8.8. $N^2$–(2–(7–chloroquinolin–4–ylamino)ethyl)–$N^4$–(2–(dimethylamino)ethyl)–6–morpholino–1,3,5–triazine–2,4–diamine (45).** yield: 74%; mp 137–139 °C; ESMS: 472 (M+1); IR (KBr) 3423, 3020, 1580, 1545, 1445, 1363, 1216, 1113, 809, 763 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm) 8.47 (d, 1H, *J* = 5.42 Hz), 7.91 (d, 1H, *J* = 2.08 Hz), 7.57–7.54 (m, 1H), 7.26 (dd, 1H, *J* = 1.86, 8.76 Hz), 6.93 (br–s, 1H), 6.29 (d, 1H, *J* = 5.46 Hz), 5.55 (br–s, 1H), 5.31 (br–s, 1H), 3.79–3.71 (m, 10H), 3.49–3.42 (m, 4H), 2.62–2.54 (m, 2H), 2.27 (s, 6H); $^{13}C$ NMR (50 MHz, $CDCl_3$): 167.76, 165.87, 152.52, 150.85, 149.06, 135.51, 128.82, 126.15, 122.15, 117.81, 99.12, 67.75, 59.07, 47.93, 46.72, 44.38, 40.05, 38.38; Anal. Calcd for $C_{22}H_{30}ClN_9O$: C, 55.98; H, 6.41; N, 26.71; found: C, 56.03; H, 6.39; N, 26.75.

**5.8.9. $N^1$–(7–chloroquinolin–4–yl)–$N^2$–(4–(4–methylpiperazin–1–yl)–6–morpholino–1,3,5–triazin–2–yl)ethane–1,2–diamine (46).** yield: 72%; mp 161–163 °C; ESMS: 484 (M+1); IR (KBr) 3399, 3020, 2852, 1586, 1525, 1442, 1363, 1216, 1039, 812, 762 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm) 8.49 (d, 1H, *J* = 5.38 Hz), 7.92 (d, 1H, *J* = 2.04 Hz), 7.46 (d, 1H, *J* = 8.91 Hz), 7.25 (dd, 1H, *J* = 2.14, 8.86 Hz),

6.87 (br–s, 1H), 6.31 (d, 1H, *J* = 5.46 Hz), 5.19 (br–s, 1H), 3.88–3.73 (m, 14H), 3.45–3.41 (m, 2H), 2.52–2.42 (m, 4H), 2.32 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): 167.84, 165.48, 152.26, 150.74, 149.21, 135.18, 128.85, 125.60, 122.24, 117.57, 98.68, 67.22, 55.31, 46.85, 46.62, 44.19, 42.78, 39.47; Anal. Calcd for $C_{23}H_{30}ClN_9O$: C, 57.08; H, 6.25; N, 26.05; found: C, 57.05; H, 6.22; N, 26.09.

**5.8.10. $N^2$–(2–(7–chloroquinolin–4–ylamino)ethyl)–6–morpholino–$N^4$–(2–morpholinoethyl)–1,3,5–triazine–2,4–diamine (47).** yield: 71%; mp 148–150 °C; ESMS: 513 (M+1); IR (KBr) 3292, 2970, 1583, 1543, 1438, 1356, 1212, 1114, 809, 768 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.48 (d, 1H, *J* = 5.38 Hz), 7.92 (d, 1H, *J* = 2.08 Hz), 7.53–7.51 (m, 1H), 7.26–7.21 (m, 2H), 6.31 (d, 1H, *J* = 5.44 Hz), 5.48 (br–s, 1H), 5.32 (br–s, 1H), 3.81–3.68 (m, 16H), 3.42–3.32 (m, 2H), 2.51–2.37 (m, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$): 167.73, 165.38, 152.15, 151.27, 149.69, 135.21, 128.82, 125.49, 122.48, 117.57, 98.68, 67.31, 67.22, 53.83, 47.05, 44.38, 41.27, 39.51, 37.04; Anal. Calcd for $C_{24}H_{32}ClN_9O_2$: C, 56.08; H, 6.27; N, 24.52; found: C, 56.11; H, 6.32; N, 24.49.

**5.8.11. $N^2$–(3–(7–chloroquinolin–4–ylamino)propyl)–$N^4$–(3–morpholinopropyl)–6–(piperidin–1–yl)–1,3,5–triazine–2,4–diamine (48).** yield: 71%; mp 127–129 °C; ESMS: 540 (M+1); IR (KBr) 3445, 3020, 1579, 1540, 1446, 1364, 1216, 1117, 810, 762 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.49 (d, 1H, *J* = 5.38 Hz), 7.93 (d, 1H, *J* = 2.09 Hz), 7.66 (d, 1H, *J* = 7.36 Hz), 7.29 (dd, 1H, *J* = 2.12, 9.04 Hz), 7.25 (br–s, 1H), 6.39 (d, 1H, *J* = 5.46 Hz), 5.51 (br–s, 1H), 5.11 (br–s, 1H), 3.69–3.52 (m, 10H), 3.48–3.36 (m, 4H), 2.43–2.36 (m, 6H), 2.08–1.94 (m, 2H), 1.76–1.51 (m, 8H); $^{13}$C NMR (50 MHz, $CDCl_3$): 167.13, 164.95, 151.99, 150.51, 149.14, 135.31, 128.65, 125.54, 121.95, 117.73, 99.29, 67.37, 57.52, 54.11, 44.52, 41.14, 40.12, 38.61, 29.13, 26.51, 26.20, 25.26; Anal. Calcd for $C_{27}H_{38}ClN_9O$: C, 60.04; H, 7.09; N, 23.34; found: C, 59.97; H, 7.06; N, 23.31.

**5.8.12. $N^2$–(3–(7–chloroquinolin–4–ylamino)propyl)–$N^4$–(2–(diethylamino)ethyl)–6–(piperidin–1–yl)–1,3,5–triazine–2,4–diamine (49).** yield: 68%; mp 80–82 °C; ESMS: 512 (M+1); IR (KBr) 3418, 3019, 1580, 1540, 1446, 1366, 1216, 1114, 813, 768 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.48 (d, 1H, *J* = 5.41 Hz), 7.92 (d, 1H, *J* = 2.01 Hz), 7.71–7.63 (m, 1H), 7.38–7.27 (m, 2H), 6.41 (d, 1H, *J* = 5.43 Hz), 5.53 (br–s, 2H), 3.76–3.67 (m, 4H), 3.58–3.47 (m, 6H), 2.68–2.54 (m, 6H), 2.05–1.98 (m, 2H), 1.61–1.51 (m, 6H), 1.08 (t, 6H, *J* = 7.09 Hz); $^{13}$C NMR (50 MHz, $CDCl_3$+$CD_3OD$): 169.33, 168.39, 157.57, 151.01, 147.97, 141.57, 130.51, 128.48, 127.52, 120.93, 102.93, 64.49, 52.15, 48.51, 44.93, 42.16, 33.93, 31.97, 30.02, 29.01, 13.54; Anal. Calcd for $C_{26}H_{38}ClN_9$: C, 60.98; H, 7.48; N, 24.62; found: C, 60.97; H, 7.44; N, 24.59.

**5.8.13. $N^2$–(3–(7–chloroquinolin–4–ylamino)propyl)–$N^4$–(2–(dimethylamino)ethyl)–6–(piperidin–1–yl)–1,3,5–triazine–2,4–diamine (50).** yield: 70%; mp 87–89 °C; ESMS: 484 (M+1); IR (KBr) 3432, 3021, 1583, 1542, 1446, 1365, 1216, 1084, 808, 762 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.49 (d, 1H, *J* = 5.37 Hz), 7.92 (d, 1H, *J* = 2.06 Hz), 7.59–7.51 (m, 1H), 7.36–7.28 (m, 2H), 6.39 (d, 1H, *J* = 5.39 Hz), 5.52 (br–s, 2H), 3.81–3.52 (m, 10H), 2.75–2.59 (m, 2H), 2.29 (s, 6H), 2.07–1.92 (m, 2H), 1.69–1.56 (m, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$+$CD_3OD$): 169.34, 168.23, 158.28, 149.77, 146.67, 142.21, 130.86, 128.76, 126.44, 120.67, 102.52, 62.66, 48.54, 48.26, 42.09, 41.33, 33.92, 31.87, 30.01, 28.99; Anal. Calcd for $C_{24}H_{34}ClN_9$: C, 59.55; H, 7.08; N, 26.04; found: C, 59.57; H, 7.11; N, 26.09.

**5.8.14. $N^1$–(7–chloroquinolin–4–yl)–$N^3$–(4–(4–methylpiperazin–1–yl)–6–(piperidin–1–yl)–1,3,5–triazin–2–yl)propane–1,3–diamine (51).** yield: 74%; mp 217–219 °C; ESMS: 484 (M+1); IR (KBr) 3440, 3067, 2850, 1579, 1546, 1443, 1365, 1218, 1138, 808, 765 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.51 (d, 1H, *J* = 5.06 Hz), 7.93 (d, 1H, *J* = 1.89 Hz), 7.53 (d, 1H, *J* = 8.86 Hz), 7.31–7.26 (m, 2H), 6.39 (d, 1H, *J* = 5.34 Hz), 5.42 (br–s, 1H), 3.75–3.53 (m, 10H), 3.49–3.42 (m, 2H), 2.59–2.35 (m, 4H), 2.31 (s, 3H), 2.03–1.96 (m, 2H), 1.67–1.53 (m, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$+$CD_3OD$): 168.37, 167.98, 154.46, 154.14, 151.42, 138.73, 130.08, 128.57, 125.66, 120.43, 101.93, 58.01, 49.05, 47.54, 45.93, 44.07, 41.63, 31.66, 29.04, 28.11; Anal. Calcd for $C_{25}H_{34}ClN_9$: C, 60.53; H, 6.91; N, 25.41; found: C, 60.49; H, 6.87; N, 25.47.

**5.8.15. $N^2$–(3–(7–chloroquinolin–4–ylamino)propyl)–$N^4$–(2–morpholinoethyl)–6–(piperidin–1–yl)–1,3,5–triazine–2,4–diamine (52).** yield: 70%; mp 102–104 °C; ESMS: 526 (M+1); IR (KBr) 3317, 2931, 1581, 1505, 1443, 1361, 1282, 1115, 806, 771 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.49 (d, 1H, *J* = 5.42 Hz), 7.95 (d, 1H, *J* = 1.92 Hz), 7.73–7.69 (m, 1H), 7.31 (dd, 1H, *J* = 2.14, 8.91 Hz), 7.28 (br–s, 1H), 6.41 (d, 1H, *J* = 5.48 Hz), 5.47 (br–s, 1H), 5.37 (br–s, 1H), 3.68–3.52 (m, 10H), 3.47–3.31 (m, 4H), 2.53–2.45 (m, 6H), 2.01–1.95 (m, 2H), 1.62–1.42 (m, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$): 166.37, 164.71, 151.01, 150.12, 148.21, 135.71, 127.83, 125.73, 122.38, 117.57, 99.13, 67.31, 57.82, 53.82, 44.59, 41.13, 38.58, 37.45, 28.96, 26.21, 25.22;

Anal. Calcd for $C_{26}H_{36}ClN_9O$: C, 59.36; H, 6.90; N, 23.96; found: C, 59.39; H, 6.87; N, 23.92.

**5.8.16. $N^2$–(3–(7–chloroquinolin–4–ylamino)propyl)–6–morpholino–$N^4$–(3–morpholinopropyl)–1,3,5–triazine–2,4–diamine (53).** yield: 73%; mp 109–111 °C; ESMS: 542 (M+1); IR (KBr) 3379, 3020, 1589, 1547, 1439, 1356, 1216, 1112, 809, 762 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm) 8.51 (d, 1H, *J* = 5.42 Hz), 7.89 (d, 1H, *J* = 1.93 Hz), 7.52 (d, 1H, *J* = 8.76 Hz), 7.39–7.28 (m, 2H), 6.41 (d, 1H, *J* = 5.39 Hz), 5.37 (br–s, 2H), 3.82–3.57 (m, 12H), 3.47–3.39 (m, 6H), 2.57–2.41 (m, 6H), 2.03–1.89 (m, 2H), 1.73–1.54 (m, 2H); $^{13}C$ NMR (50 MHz, $CDCl_3$): 166.97, 165.23, 151.54, 150.27, 149.16, 135.57, 128.46, 125.13, 122.36, 117.41, 98.89, 67.43, 67.19, 59.13, 54.72, 47.51, 44.03, 40.92, 38.97, 30.03, 26.76; Anal. Calcd for $C_{26}H_{36}ClN_9O_2$: C, 57.61; H, 6.69; N, 23.26; found: C, 57.64; H, 6.73; N, 23.21.

**5.8.17. $N^2$–(3–(7–chloroquinolin–4–ylamino)propyl)–$N^4$–(2–(diethylamino)ethyl)–6–morpholino–1,3,5–triazine–2,4–diamine (54).** yield: 71%; mp 134–136 °C; ESMS: 514 (M+1); IR (KBr) 3423, 3020, 1580, 1543, 1438, 1362, 1216, 1045, 806, 763 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm) 8.43 (d, 1H, *J* = 5.37 Hz), 7.89 (d, 1H, *J* = 2.03 Hz), 7.74 (d, 1H, *J* = 8.41 Hz), 7.42–7.26 (m, 2H), 6.32 (d, 1H, *J* = 5.43 Hz), 5.51 (br–s, 1H), 4.92 (br–s, 1H), 3.79–3.64 (m, 8H), 3.51–3.39 (m, 6H), 2.61–2.55 (m, 6H), 2.02–1.94 (m, 2H), 1.02 (d, 6H, *J* = 7.03 Hz); $^{13}C$ NMR (50 MHz, $CDCl_3$): 167.53, 165.47, 151.83, 150.69, 149.23, 135.39, 128.44, 125.32, 122.63, 118.03, 99.08, 67.32, 53.19, 47.18, 46.57, 43.92, 40.06, 38.19, 28.34, 12.15; Anal. Calcd for $C_{25}H_{36}ClN_9O$: C, 58.41; H, 7.06; N, 24.52; found: C, 58.39; H, 7.11; N, 24.54.

**5.8.18. $N^2$–(3–(7–chloroquinolin–4–ylamino)propyl)–$N^4$–(2–(dimethylamino)ethyl)–6–morpholino–1,3,5–triazine–2,4–diamine (55).** yield: 74%; mp 123–125 °C; ESMS: 486 (M+1); IR (KBr) 3383, 3020, 1586, 1541, 1444, 1356, 1216, 1117, 806, 764 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm) 8.28 (d, 1H, *J* = 5.44 Hz), 7.84 (d, 1H, *J* = 2.12 Hz), 7.74 (d, 1H, *J* = 8.73 Hz), 7.35–7.26 (m, 2H), 6.39 (d, 1H, *J* = 5.39 Hz), 5.56 (br–s, 2H), 3.82–3.62 (m, 8H), 3.54–3.32 (m, 6H), 2.71 (t, 2H, *J* = 5.61 Hz), 2.44 (s, 6H), 1.95–1.87 (m, 2H); $^{13}C$ NMR (50 MHz, $CDCl_3$): 167.19, 165.03, 151.52, 150.36, 148.97, 135.42, 128.15, 125.26, 121.91, 117.78, 98.73, 67.43, 58.97, 47.69, 46.53, 44.27, 41.49, 40.07, 30.14; Anal. Calcd for $C_{23}H_{32}ClN_9O$: C, 56.84; H, 6.64; N, 25.94; found: C, 56.81; H, 6.67; N, 25.92.

**5.8.19. $N^1$–(7–chloroquinolin–4–yl)–$N^3$–(4–(4–methylpiperazin–1–yl)–6–morpholino–1,3,5–triazin–2–yl)propane–1,3–diamine (56).** yield: 74%; mp 119–121 °C; ESMS: 498 (M+1); IR (KBr) 3442, 3020, 2855, 1613, 1536, 1441, 1364, 1216, 1093, 815, 763 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm) 8.53 (d, 1H, *J* = 5.39 Hz), 8.35–8.19 (m, 2H), 7.29–7.26 (m, 1H), 7.04 (br–s, 1H), 6.38 (d, 1H, *J* = 5.36 Hz), 5.41 (br–s, 1H), 3.94–3.55 (m, 16H), 2.47–2.39 (m, 4H), 2.32 (s, 3H), 2.04–1.92 (m, 2H); $^{13}C$ NMR (50 MHz, $CDCl_3$): 167.37, 165.24, 152.03, 150.84, 149.51, 135.42, 128.63, 125.31, 121.78, 117.82, 98.76, 67.15, 55.46, 46.81, 46.59, 44.26, 42.07, 40.11, 29.72; Anal. Calcd for $C_{24}H_{32}ClN_9O$: C, 57.88; H, 6.48; N, 25.31; found: C, 57.91; H, 6.47; N, 25.36.

**5.8.20. $N^2$–(3–(7–chloroquinolin–4–ylamino)propyl)–6–morpholino–$N^4$–(2–morpholinoethyl)–1,3,5–triazine–2,4–diamine (57).** yield: 71%; mp 124–126 °C; ESMS: 528 (M+1); IR (KBr) 3422, 3020, 1615, 1545, 1442, 1362, 1216, 1114, 817, 763 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm) 8.48 (d, 1H, *J* = 5.38 Hz), 7.91 (d, 1H, *J* = 2.11 Hz), 7.58–7.52 (m, 1H), 7.37–7.28 (m, 2H), 6.38 (d, 1H, *J* = 5.34 Hz), 5.3 (br–s, 2H), 3.81–3.53 (m, 12H), 3.47–3.41 (m, 6H), 2.54–2.38 (m, 6H), 2.03–1.85 (m, 2H); $^{13}C$ NMR (50 MHz, $CDCl_3$): 167.21, 165.74, 151.87, 150.47, 149.72, 135.32, 128.63, 125.44, 121.29, 117.56, 99.31, 67.54, 67.39, 54.02, 47.46, 44.27, 41.83, 40.27, 28.92; Anal. Calcd for $C_{25}H_{34}ClN_9O_2$: C, 56.86; H, 6.49; N, 23.87; found: C, 56.83; H, 6.47; N, 23.91.

## 6. Biological materials and methods

### 6.1. In vitro antimalarial assay

The compounds were dissolved in DMSO at 5 mg/mL. For the assays, fresh dilutions of all compounds in screening medium were prepared and 50 µL of highest starting concentration (500 ng/mL) was dispensed in duplicate wells in row B of 96 well tissue culture plate. The highest concentration for chloroquine was 25 ng/mL. Subsequently two fold serial dilutions were prepared up to row H (seven concentrations). Finally 50 µL of 2.5% parasitized cell suspension containing 0.5% parasitaemia was added to each well except four wells in row A which received non infected cell suspension. These wells containing non infected erythrocytes in the absence of drugs served as negative controls, while parasitized erythrocytes in the presence of CQ served as positive control. After 72 h of incubation, 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 1 x concentration of SYBER Green I (Invitrogen) was

added to each cell.[23] The plates were re–incubated for 1 h at room temperature and examined for the relative fluoroscence units (RFUs) per well using the FLUOstar, BMG lab technologies. The 50% inhibitory concentration ($IC_{50}$) was determined using non–linear regression analysis dose–response curves.

### 6.2. Inhibition of β–hematin formation assay

Male swiss mice, weighing 15–20 g were inoculated with 1 x $10^5$ *P. yoelii* infected RBCs. Blood of infected animal at ~50% parasitemia was collected by cardiac puncture in 2.0% citrate buffer and centrifuged at 5000 rpm for 10 min at 4 °C. The plasma was used in assay of β–hematin formation. The assay mixture contained 100 mM sodium acetate buffer pH (5.1), 50 µL plasma, 100 µM hemin as the substrate and 1–20 µg compound/drug in a total volume of 1.0 mL. The control tube contained all reagents except compound. The reaction mixture in triplicate was incubated at 37 °C for 16 h in a rotary shaker. The reaction was stopped by centrifugation at 10,000 rpm for 10 min at 30 °C. The pellet was suspended in 100 mM Tris–HCl buffer pH (7.4) containing 2.5% SDS. The pellet obtained after centrifugation was washed thrice with distilled water (TDW) to remove free hemin attached to β–hematin. The pellet was solubilized in 50 µL of 2N NaOH and volume was made up to 1.0 mL with TDW. Absorbance was measured at 400 nm.[24] The 50% inhibitory concentration ($IC_{50}$) was determined using non–linear regression analysis dose–response curves.

### 6.3. Cytotoxicity assay

Cytotoxicity of the compounds was determined against VERO cell lines (C–1008; Monkey kidney fibroblast cells). A total of 1 x $10^4$ cells/well were incubated with varying concentrations of compound for 72 h. The highest concentration of compound was 100 µg/mL. MTT was used as reagent for the detection of cytotoxicity.[25] 50% cytotoxic concentration ($CC_{50}$) values represented the concentration of compound required to kill 50% of the fibroblast cells.

Selectivity Index (SI): $CC_{50}/IC_{50}$.

### 6.4. In vivo antimalarial assay

The in vivo drug response was evaluated in Swiss mice infected with *P. yoelii* (N–67 strain) which is innately resistant to CQ. The mice (22 ± 2g) were inoculated with 1 x $10^6$ parasitized RBC on day 0 and treatment was administered to a group of five mice from day 0 to 3, once daily. The aqueous suspensions of compounds were prepared with a few drops of Tween 80. The efficacy of test compounds was evaluated at 50 mg/kg/day and required daily dose was administered in 0.2 mL volume via intraperitoneal route. Parasitaemia levels were recorded from thin blood smears on days 4. The mean value determined for a group of five mice was used to calculate the percent suppression of parasitaemia with respect to the untreated control group. Mice treated with CQ served as reference controls.[26]


### Acknowledgements

N.S thanks the Council of Scientific and Industrial Research, India, for the award of Senior Research Fellowship. We are also thankful to S.A.I.F. Division, CDRI, Lucknow, for providing spectroscopic data. Thanks are also due to Mr. M. P. S. Negi, Division of Biometry & Statistics, CDRI for data analysis. CDRI communication No.7760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