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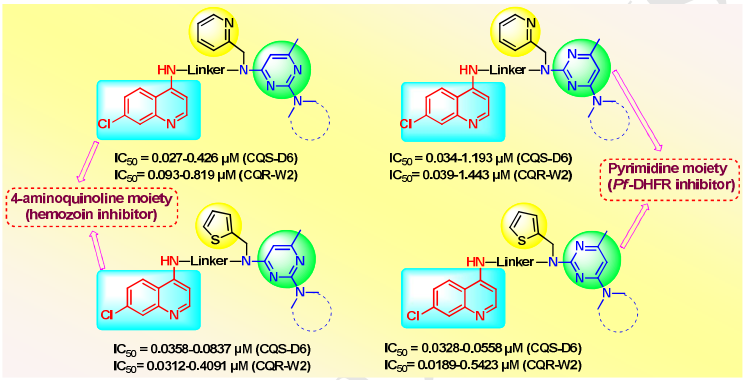
Graphical Abstract



N-Substituted aminoquinoline-pyrimidine hybrids: Synthesis, *in vitro* antimalarial activity evaluation and docking studies[#]

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[#]Dedicated to Dr PMS Chauhan, on the occasion of his 60th Birthday

Abstract: A series of novel molecular hybrids based on 4-aminoquinoline-pyrimidine were synthesized and examined for their antimalarial activity. Most of the compounds were found to have potent *in vitro* antimalarial activity against both CQ-sensitive D6 and CQ-resistant W2 strains of *P. falciparum*. The active compounds have no considerable cytotoxicity against the mammalian VERO cell lines. Twenty three compounds displayed better antimalarial activity against CQ-resistant strain W2 with IC_{50} values in the range 0.0189-0.945 µM, when compared with standard drug chloroquine. The best active compound **7d** was studied for heme binding so as to find the primary mode of action of these hybrid molecules. Compound **7d** was found to form a stable 1:1 complex with hematin as determined by its Job's plot which suggests that heme may be a probable target of these molecules. Docking studies performed with *Pf*-DHFR exhibited good binding interactions in the active site. The pharmacokinetic properties of some active compounds were also analysed using ADMET prediction.

Key Words: Aminoquinoline, pyrimidine, hybrid drugs, antimalarial Actvity, heme, docking study, ADMET properties.

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1. Introduction

Malaria still remains a global public health concern though there is a significant decrease in the mortality rate during the past few years. The recent WHO report says that malaria accounted 216 million new clinical cases and an estimated 4.5 lakh deaths worldwide in 2016 with children of age less than 5 years and the pregnant women amongst the most affected groups [1,2].Amongst the five plasmodial species that causes malaria in human beings, *P. falciparum* is the most common and virulent, responsible for more than 90% cases of malarial deaths [1]. The conventional aminoquinoline based antimalarial drugs such as chloroquine (CQ), amodiaquine, mefloquine and primaquine have long been used for treating the malaria however, the efficacy of many of these quinoline based drugs has been compromised to some extent by the spread of CQ-resistant strains of malarial parasites [3,4]. At present, the most effective treatment for the uncomplicated malaria due to *P. falciparum* is the artemisinin based combination therapy (ACT) [5]. The major advantages of ACTs are their high potency, fast action and the less chances of development of resistance.In ACT, the fast acting artemisinin based drugs are combined with a companion drug including amodiaquine, mefloquine, piperaquine, lumefantrine, sulfadoxine/pyrimethamine and chlorproguanil/dapsone [6]. Recently few cases of artemisinin resistance have been reported in five countries namely Myanmar, Cambodia, Thailand, Vietnam and the Lao People's Democratic Republic [7,8]. Therefore, it is a dire need to develop novel antimalarial agents which are safer, affordable, fast acting and effective against the resistant strains of *P. falciparum.*

In order to address the problems of drug-resistance, several strategies such as combination therapy, hybrid drug concept, development of analogues of already existing drugs, and incorporation of drug resistance reversers etc have been employed [9]. Of all these, the hybrid drugs concept has attracted much attention due to its many advantages over the others [10-12]. Hybrid drugs can exert dual mode of action and may solve the problems related to drug resistance, drug-drug interaction, drug delivery, poor solubility etc [13]. In molecular hybridisation two or more active pharmacophores are linked covalently resulting into one molecule which may act on multiple targets. Further in hybrid concept more structurally diversified compounds can be synthesized which may increase the chance of development of a new drug. Employing the concept of hybrid drugs, our research group has developed a variety of hybrid molecules which have shown potent antitubercular, antiamoebic, anticancer and antimalarial activities [14-23].

In continuation of our work on antimalarial agents, we thought to functionalize the *-NH* group of our previously reported aminoquinoline-pyrimidine hybrids with the aim to study the effect of substitution at the *-NH* of ethyl or propyl linker chain on the antimalarial activity. We introduced 2-formyl thiophene and 2-formyl pyridine ring at the *-NH* group through a simple reductive amination reaction (Fig. 1). These modifications may help in the accumulation of the compounds in acidic food vacuole of the malarial parasite and also increase the lipophilicity of the molecule which further may enhance the activity [24].Also, thiophene and pyridine rings have been found to be the part of many antimalarial compounds [25-28].The present article discuss the synthesis and antimalarial activity of 4-aminoquinoline-pyrimidine based molecular hybrids against D6, CQ-sensitive and W2, CQ-resistant strains of *P. falciparum*. All the compounds were also screened for their *in vitro* cytotoxicity against the mammalian Vero cell lines. The molecular docking studies with *Pf*-DHFR-TS and heme (monomeric and μ-oxodimeric) binding studies were also performed to determine the probable mode of action of these hybrids. To assess the pharmacokinetic behaviour, the ADME properties of the best active compounds were calculated.

<Insert Fig. 1 here>

2. Chemistry

The schemes 1 and 2 depict the synthesis of 4-aminoquinoline-pyrimidine hybrids. Firstly, 4,7-dichloroquinoline (**1**) was treated with the excess of 1,2-diaminoethane or 1,3-diaminopropane at 120 ^{o}C to yield compounds **2a** or **2b**, respectively [29].The intermediates **2a** or **2b** were then treated with 2-formylpyridine to give Schiff bases **3a** or **3b** which on reduction with $NaBH_4$ gave compounds **4a** or **4b** (Scheme 1). Compounds **4a** or **4b** were then treated with 2,4-dichloro-6-methylpyrimidine in the presence of Et_3N using THF as solvent at 60 ^{o}C to give two set of regio-isomers (**5a, 6a** and **5b, 6b**). The compounds **5a** and **5b** were obtained as major products while **6a** and **6b** were obtained as minor products. All the four compounds (**5a, 5b,6a** and **6b**) were finally reacted with various secondary amines at 120 °C to form the desired products (**7a-j** and **8a-i**) in 55-86% yield. A similar type of compounds, bearing thiophene moiety in place of pyridine ring, were also synthesized using the similar methodology (scheme 2). All the final compounds (**7a-j**, **8a-i, 13a-e** and **14a-e**) were purified using column chromatography and characterized through various spectroscopic techniques.

<Insert Scheme 1 here>

<Insert Scheme 2 here>

3. Results and Discussion

The antimalarial activity results shown in table 1 indicated that all the compounds displayed potent antimalarial activity with IC_{50} values in the range 0.027-.661 µM against CQ-sensitive (D6) strain and IC_{50} values in the range 0.0189-1.443 µM against CQ-resistant (W2) strain of *P. falciparum*. Compound **7d** was the most active compound against D6 strain with IC_{50} value 0.027 µM and selectivity index >351. Out of all compounds, 23 compounds (**5b, 7b, 7d, 7e, 7g, 7i, 7j, 8c-e, 8g-i**, **10a, 13a-e, 14a, 14b**, **14d** and **14e**) showed better activity than CQ against W2 strain. Among all the compounds, **14e** was found to be the best active compound (IC_{50} = 0.0189 µM) against W2 strain and exhibited 22-times better activity than CQ (IC_{50} = 0.4215 µM). When the activity of these compounds was compared with artemisinin (ART), two compounds **14d** and **14e** showed comparable activity to ART against the W2 strain. The regio-isomeric intermediates, **5a** and **6a** containing two carbon chain linker showed better activity against the sensitive strain (IC_{50}= 0.233 µM, 0.369 µM respectively) as compared to activity against resistant strain. In case of regio-isomeric intermediates **5b** and **6b,** containing three carbons linker exhibited better antimalarial activity against resistant strains as compared to the activity against the sensitive strain, whereas regio-isomers **11a** and **12a** showed better activity against the sensitive strain as compared to the resistant strain. Interestingly, when the chlorine atoms of the regio-isomers **5a** and **6a** were replaced by various cyclic amines, the activity of all the resulting aminoquinoline-thiophene-pyrimidine (**7a-7e** and **8a-8e**) hybrids against both sensitive and resistant strains got improved with the exception of two compounds, **7e** and **8a** which showed little decline in the activity against the resistant strain. Similarly compounds **7f-7j** and **8f-8i** showed improved activity as compared to their corresponding intermediate regio-isomers **5b** and **6b** against both the strains with the exception of three compounds **7f**, **7h** and **8f** which displayed weaker activity against CQ-resistant strain than their corresponding intermediates. Compounds **13a-13e** and **14a-14e** containing three carbons chain linker also showed enhanced activity against both the strains, D6 and W2, when compared the activity of their corresponding intermediate regio-isomers **11a** and **12a.**

Compounds having 4-methyl piperazine (**7d, 8d**) and 4-ethyl piperazine (**7e, 8e**) were found to show better activity than the compounds having piperidine (**7a, 8a**), pyrrolidine (**7b, 8b**) and morpholine (**7c, 8c**) moieties. No obvious trend of antimalarial activity was found on

comparison of the activity of regio-isomeric intermediates (**5a, 5b, 11a** and **6a, 6b, 12a**) and their derivatives (**7a-7j**, **8a-8i** and **13a-13e, 14a-14e**), differing in the point of attachment with pyrimidine ring. Compounds with two carbon chain linker (**7a-7e** and **8a-8d)** were found to be more active than the compounds with three carbon chain linker (**7f-7j** and **8f-8i**) against CQ-sensitive strains, whereas no particular trend was observed when compared activity against the resistant strain. Cytotoxicity of the compounds was also analysed using mammalian Vero cell lines (Table 1). All the compounds except four compounds **6a**, **13a**, **13c** and **14a** were found to be non-cytotoxic upto 10 µM, that is too high as compared to their corresponding IC_{50} values.

<Insert Table 1 here>

In order to determine the possible mode of action of the synthesized compounds, heme binding studies was performed with the most active compound **7d**. The binding stoichiometry was also determined using the literature reported method [30]. A band at 402 nm observed for a solution of hematin in 40% DMSO in water at pH 7.4 (20 mM HEPES buffer) and pH 5.6 (20 mM MES buffer) indicates the presence of monomeric heme at both the pH values. Compound **7d** when titrated with the monomeric heme solution at physiological pH (HEPES buffer, pH 7.4) and pH of parasite's food vacuole (MES buffer, pH 5.6) displayed a significant decrease in the absorbance of the band at 402 nm. (Fig. 2 and Fig. 3). Thus, indicating the interaction of compound **7d** with hematin. In the Job's plot, maxima at 0.5 mole fraction indicates 1:1 stoichiometry for the binding of monomeric heme with compound **7d** at pH 7.4 (Fig. 2) and pH 5.6 (Fig. 3). As chloroquine also binds to µ-oxodimericheme, therefore we studied the binding of compound **7d** with µ-oxo dimer of heme at pH 5.8. A peak at 362 nm of heme in aqueous NaOH indicates the presence of dimeric structure of heme as reported in literature. The intensity of absorbance at 362 nm decreases on titrating a solution of µ-oxo dimer heme at pH 5.8 (20 mM phosphate buffer) with compound **7d** (Fig. 4) indicating interaction between compound **7d** and µ-oxodimericheme. The Job's plot showed that the binding of compound **7d** with µ-oxodimericheme is in 1:1 stoichiometry (Fig. 4).

<Insert Fig. 2 here>

<Insert Fig. 3 here>

<Insert Fig. 4 here>

To explore the pharmacokinetics of the compounds under study, ADME predictions were done for the best active compounds using Qikprop v3.5 (Schrödinger, Inc., New York, NY, 2012) [31]. All the compounds prepared by LigPrep were used for the calculation of pharmacokinetic properties by QikProp. Table 2 shows the results of docking studies. The results indicate that the compounds with good antimalarial activity exhibited significant binding affinities as is evident from their Glide energies obtained on docking with the wild (Glide energy range -60.28 kcal mol^{-1} to -51.67 kcal mol^{-1}) as well as quadruple mutant (Glide energy range -59.11 kcal mol^{-1} to -52.74 kcal mol^{-1}). The Glide Scores (GScore) have also been shown in Table 2.

<Insert Table 2 here>

Fig. 5 and 6 show three dimensional binding pose compounds **7g, 7j** and **8e** with wild and mutant *Pf*-DHFR-TS. All the three selected compounds **(7g, 7j** and **8e)** showed hydrogen bonding pattern along with cation-pi interactions with the amino acid residues at the binding site. The protonated nitrogen of pyrimidine moiety of compound **7j**, displayed cation-pi interactions with Phe58 residue of both the mutant as well as the wild *Pf*-DHFR-TS and an additional hydrogen bond interaction with Ile164 residue of wild type *Pf*-DHFR-TS. In both the mutant and wild type *Pf*-DHFR-TS Asp54 formed a salt bridge with the nitrogen of piperazine ring of **7j** whereas Ser111 of the same compound formed a hydrogen bond with the protonablequinoline ring nitrogen atom of aminoquinoline moiety. An additional cation-pi interaction was also observed with protonable nitrogen of pyridine moiety of 39L and Phe116 residue of the wild type *Pf*-DHFR-TS. Compound **7g** showed slightly altered binding poses in the different parasitic DHFRs, and thus the interactions with both the DHFRs were different. The active site residues, Phe116 and Arg122 of mutant type *Pf*-DHFR-TS showed cation-pi interactions with the aminoquinoline moiety and Ser111 formed hydrogen bond with pyrimidine ring of compound **7g**. The same pyrimidine moiety formed hydrogen bond and a cation-pi interaction with Ile164 and Phe58 of the wild type *Pf*-DHFR-TS respectively whereas the pyridine moiety formed cation-pi interaction with Phe116. Although the binding poses adopted by compound **8e** were dissimilar for different DHFRs, the inhibitor showed similar interactions with both DHFRs.

<Insert Fig. 5 here>

<Insert Fig. 6 here>

In silico assessment of pharmacokinetics and ADME predictions of the best active compounds were carried out using Qikprop v3.5 [32].The most important of these properties and their permissible ranges are given in Table 3 and 4. The active compounds were tested for the Lipinski's rule of five (Ro5), which is a set of *in silico* guidelines applied to predict likelihood of high oral absorption [33]. An orally active compound must have less than 2 violations of Lipinski's Rule [32]. All the tested compounds passed the rule of five indicating their potential to become orally active drugs. The molecular weight of some compounds was higher than 500Da, thus violating one of the Ro5. In medicinalchemistry, an attempt to increase the selectivity and potency of hit compounds results in increase in molecular weight but several orally bio available drugs exist far beyond Ro5.

<Insert Table 3 here>

<Insert Table 4 here>

Results of *in silico* prediction of Percent Human Oral Absorption were within range (Table 4). Properties like size, polarity, lipophilicity and conformational dynamics affect the oral bioavailability which can be assessed by additional *in silico* properties, the number of rotatable bonds (<15) and polar surface area (70Å^2–200 Å^2) [34]. The test compounds displayed rotatable bonds less than 15 and the polar surface area in the permissible range (7-200 Å) (Table 4). The Caco-2 cells permeability (QPPCaco) which is a measure of intestinal drug absorption was found to be >500 for all the tested compounds. Trans cellular absorption occurs through passive diffusion through a cell membrane. This process is studied *in vitro* using human colorectal carcinoma (Caco-2) cells model. Prediction of human serum albumin binding (QPlogKhsa), brain/blood partition coefficient (QPlogBB) and the blood-brain barrier mimic MDCK cell permeability (QPPMDCK) for all the active compounds were in the permissible range.

4. Conclusions

In summary, we have reported the synthesis and antimalarial activity evaluation of 4-aminoquinoline pyrimidine based molecular hybrids. Most of the compounds displayed good antimalarial activity against CQ-sensitive D6 strain and CQ-resistant W2 strain of malarial parasite in the µM range with high selectivity index. Also, these hybrids exhibited no cytotoxicity towards the mammalian VERO cell lines up to 10 µM, the highest concentration tested. Among all the compounds, **7d** was found to be the most active compound against D6

strain (IC_{50} = 0.027 µM) and compound **14e** was found to be the most active compound against W2 strain (IC_{50} = 0.0189 µM). The primary mode of action of these hybrids was found to be through binding with heme as described by their heme binding studies. The molecular docking studies showed excellent binding interactions with *Pf*-DHFR. The Compounds showed good pharmacokinetic behaviour as predicted from their ADMET parameters.

5. Experimental Protocols

All the chemicals were purchased from Sigma-Aldrich and were used without further purification. Progress of the reactions was monitored by thin layer chromatography (Merck Kiesel 60 F254, 0.2 mm thickness) and the compounds were purified by silica gel column chromatography. IR spectra were recorded on Perkin-elmerFT-IR spectrophotometer using KBr pellets and the values were expressed in cm^{-1}. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Jeol ECX spectrospin instrument using $CDCl_3$ or DMSO-d_6 as solvent with TMS as internal reference. Thechemical shift values were expressed on d scale and the coupling constant (*J*) in Hz. Melting points were recorded on EZ-Melt automated melting point apparatus, Stanford Research Systems and are uncorrected. Mass data were recorded in Jeol-Accu TOF JMS-T100LC and micromass LCT mass spectrometer/Data system.

5.1. General procedure for the preparation of intermediates 2a-2b

A mixture of 4,7-dichloroquinoline (**1**, 10.0 g, 50.49 mmol) and 1,2-diaminoethane (10.2 mL, 151.47 mmol) was heated at 110-120 ^{o}C in neat condition for 5h (Scheme 1). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and ice-cold water was added. The solid product thus obtained was filtered and washed with excess water. Similarly, intermediate **2b** was prepared by using 1,3-diaminopropane. The crude products thus obtained were crystallized by using ethanol and all the intermediates were characterized and matched with previously reported data [29].

5.2. General procedure for the preparation of intermediates 3a-3b

Intermediate **2a** (5.0 g, 22.55 mmol) was dissolved in ethanol at room temperature, then pyridine-2-carboxaldehyde (2.4 g, 22.55 mmol) was added to it and the reaction mixture was stirred at room temperature for 12-16 h. After completion of the reaction, as monitored by TLC,

the reaction mixture was filtered and the solid product was used for the next step, without further purification. Similarly, intermediate **3b** was prepared and used for next step.

5.3. General procedure for the preparation of intermediates 4a-4b

Intermediate **3a** (7.0 g, 22.57 mmol) was dissolved in methanol and cooled to 0 ^{o}C then $NaBH_4$ (2.56 g, 67.72 mmol) was added to it in fractions and reaction mixture was allowed to stir at room temperature for 5-6 h. After completion of the reaction as monitored by TLC, the excess methanol was evaporated using rotatory evaporator and ice-cold water was added. The solid product thus obtained was filtered and washed with excess of water. Similarly, intermediate **4b** was obtained.

5.4. General procedure for the preparation of compounds 5a-5b and 6a-6b

Intermediate **(4a)** (6.0 g, 19.18 mmol) was dissolved in THF (70 mL) and triethylamine (8.02 mL, 57.54 mmol) was added followed by the addition of 2, 4-dichloro-6-methyl-pyrimidine (3.13 g, 19.18 mmol). The reaction mixture was allowed to stir at 60 ^{o}C for 12 h. The progress of reaction was monitored by TLC. On the completion of reaction, the excess THF was evaporated and the residue was diluted with water and extracted using ethyl acetate (3 x 500 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The crude product thus obtained was purified by silica gel column chromatography to obtain two regio-isomers **5a** and **6a** (**5a** as minor and **6a** as major). Similarly, regio-isomers **5b** and **6b** (**5b** as minor and **6b** as major) were obtained from the intermediate **4b**.

5.5. General procedure for the synthesis of compounds 7a-j and 8a-i

Compound **5a, 5b, 6a** or **6b** (1.0 mmol) was dissolved in 5-8 mL of DMF in aRB flask and then K_2CO_3 (3.0 mmol) was added to it. To this, a solution of respective amine (3.0 mmol) in DMF (1-2 mL) was added dropwise. The reaction mixture was allowed to stir at 100-120 ^{o}C for 10 h and progress of the reaction was monitored by TLC. After completion, water (20 mL) was added to reaction mixture and it was extracted with EtOAc (2 × 50 mL). The organic layer was then collected, washed with water (2 × 100 mL) and brine solution, dried over Na_2SO_4 and finally excess of solvent was evaporated under vacuum. The crude product thus obtained was purified by silica gel column chromatography to yield respective compounds **7a-j**and **8a-i**. Compounds **13a-13e** and **14a-14e** were synthesized by using the similar methodology.

5.5.1. N^1-(2-chloro-6-methylpyrimidin-4-yl)-N^2-(7-chloroquinolin-4-yl)-N^1-(pyridin-2-ylmethyl)ethane-1,2-diamine (5a): Off-white solid; yield 57%; mp 198–200 °C; IR (KBr, cm^{-1}): 3230, 3055, 2943, 2362, 1732, 1666, 1570, 1539, 1510, 1421, 1367, 1288, 1242, 1207, 1174, 1130, 1085, 1045, 968, 904, 846, 813, 775, 754, 696, 619, 584, 536, 495, 464;1H-NMR (400 MHz, $CDCl_3$): δ (ppm) 9.55 (brs, 1H), 8.54-8.49 (m, 3H), 8.05 (s, 1H), 7.70 (brs, 2H), 7.26-7.19 (m, 2H), 6.96 (brs, 1H), 6.55 (s, 1H), 4.83 (s, 2H), 3.89-3.81 (m, 4H), 2.13 (s, 3H); HRMS Calcd for $C_{22}H_{20}Cl_2N_6$: 438.112, Found: 439.1218 $(M + H)^+$, 441.1194 $(MH + 2)^+$.

5.5.2. N^1-(2-chloro-6-methylpyrimidin-4-yl)-N^3-(7-chloroquinolin-4-yl)-N^1-(pyridin-2-ylmethyl)propane-1,3-diamine (5b):Off-white solid; yield 52%; mp 118–120 °C; IR (KBr, cm^{-1}): 3238, 3061, 2932, 1586, 1531, 1503, 1472, 1422, 1373, 1322, 1284, 1230, 1211, 1186, 1155, 1044, 967, 915, 880, 847, 805, 762, 541; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.52 (d, J = 3.8 Hz, 1H), 8.45 (d, J = 5.3 Hz, 1H), 8.00 (brs, 1H), 7.90 (d, J = 1.5, Hz, 1H), 7.63 (t, J = 6.1 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.22-7.15 (m, 2H), 6.35 (d, J = 5.3 Hz, 2H), 6.11 (s, 1H), 4.69 (s, 2H), 3.81 (s, 2H), 3.39 (q, J = 5.3 Hz, 2H), 2.18 (s, 3H), 2.00-1.95 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 167.96, 159.97, 151.52, 149.94, 149.76, 149.61, 149.27, 148.80, 137.23, 135.07, 128.18, 125.21, 122.90, 121.97, 117.36, 100.23, 98.69, 53.80, 39.78, 29.67, 26.00, 23.94, HRMS Calcd for $C_{23}H_{22}Cl_2N_6$: 452.1289, Found: 453.1378 $(M + H)^+$,455.1354 $(MH + 2)^+$.

5.5.3. N^1-(4-chloro-6-methylpyrimidin-2-yl)-N^2-(7-chloroquinolin-4-yl)-N^1-(pyridin-2-ylmethyl)ethane-1,2-diamine (6a): Off-white solid; yield 43%; mp 198–200 °C; IR (KBr, cm^{-1}): 3230, 3055, 2943, 2362, 1732, 1666, 1570, 1539, 1510, 1421, 1367, 1288, 1242, 1207, 1174, 1130, 1085, 1045, 968, 904, 846, 813, 775, 754, 696, 619, 584, 536, 495, 464;^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.53-8.49 (m, 2H), 7.92 (d, J = 2.3 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.31 (br, 2H), 7.20-7.17 (m, 1H), 6.86 (brs, 1H), 6.52 (s, 1H), 6.39 (brs, 1H), 5.00 (s, 2H), 4.15 (t, J = 4.6 Hz, 2H), 3.56-3.55 (m, 2H), 2.31 (s, 3H); HRMS Calcd for $C_{22}H_{20}Cl_2N_6$: 438.1126, Found: 439.1193 $(M + H)^+$,441.1166 $(MH + 2)^+$.

5.5.4. N^1-(4-chloro-6-methylpyrimidin-2-yl)-N^3-(7-chloroquinolin-4-yl)-N^1-(pyridin-2-ylmethyl)propane-1,3-diamine (6b):Off-white solid; yield 71%; mp 126–128 °C ; IR (KBr, cm^{-1}): 3790, 3663, 3238, 3061, 2967, 1582, 1547, 1467, 1433, 1368, 1319, 1294, 1235, 1137, 1113, 1067, 994, 899, 879, 846, 806, 778, 753, 635; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 8.45 (d, J = 4.6 Hz, 1H), 8.41 (d, J = 5.3 Hz, 1H), 7.86 (d, J = 1.5 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.27-7.20 (m, 2H), 7.12 (t, J = 4.5 Hz, 1H), 6.41 (s, 1H), 6.29 (d, J = 5.3 Hz, 2H),

4.94 (s, 2H), 3.79 (brs, 2H), 3.32 (q, *J* = 5.3 Hz, 2H), 2.14 (s, 3H), 1.93-1.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.39, 161.82, 160.84, 158.16, 151.67, 150.12, 149.04, 148.90, 136.79, 134.79, 128.23, 124.90, 122.42, 122.27, 121.98, 117.39, 108.78, 98.69, 53.23, 40.37, 39.93, 26.10, 24.01; HRMS Calcd for $C_{23}H_{22}Cl_2N_6$: 452.1283, Found: 453.1362 $(M + H)^+$,455.1342 $(MH + 2)^+$.

5.5.5. N^1-(7-chloroquinolin-4-yl)-N^2-(6-methyl-2-(piperidin-1-yl)pyrimidin-4-yl)-N^2-(pyridin-2-ylmethyl)ethane-1,2-diamine (7a):Off-white solid; yield 60%; mp 162–164 °C; IR (KBr, cm^{-1}): 3323, 3052, 2933, 2852, 1578, 1570, 1477, 1420, 1364, 1327, 1244, 1136, 1046, 1022, 992, 983, 879, 838, 796, 758, 619, 591, 568; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.56 (d, *J* = 4.6 Hz, 1H), 8.49 (d, *J* = 5.3 Hz, 1H), 7.91 (d, *J* = 1.5 Hz, 1H), 7.54 (t, *J* = 6.9 Hz, 1H), 7.46 (d, *J* = 9.2 Hz, 1H), 7.31 (s, 1H), 7.26-7.05 (m, 3H), 6.29 (d, *J* = 5.3 Hz, 1H), 5.60 (s, 1H), 4.72 (s, 2H), 4.18 (s, 2H), 3.81 (s, 4H), 3.52 (d, *J* = 3.8 Hz, 2H), 2.14 (s, 3H), 1.60 (s, 6H), HRMS Calcd for $C_{27}H_{30}ClN_7$: 487.2251, Found: 488.2325$(M + H)^+$,490.2304 $(MH + 2)^+$.

5.5.6. N^1-(7-chloroquinolin-4-yl)-N^2-(6-methyl-2-(pyrrolidin-1-yl)pyrimidin-4-yl)-N^2-(pyridin-2-ylmethyl)ethane-1,2-diamine (7b):Off-white solid; yield 56%; mp 152–155 °C; IR (KBr, cm^{-1}): 3313, 2927, 2874, 2849,1578, 1457, 1331, 1243,1169, 1139, 944, 917, 876, 839, 801, 787, 592; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)8.48 (s, 1H), 8.37 (s, 1H), 8.07 (s, 1H), 7.77- 7.68(m, 2H), 7.48-7.42 (m, 2H), 7.20 (t, *J* = 8.4 Hz, 2H), 6.56 (s, 1H), 5.76 (brs, 1H), 4.75 (s, 2H), 3.85 (s, 2H), 3.56-3.35 (m, 6H), 2.49 (s, 3H), 1.98 (s, 4H), HRMS Calcd for $C_{26}H_{28}ClN_7$: 473.2111, Found: 474.2179 $(M + H)^+$,476.2158 $(MH + 2)^+$.

5.5.7. N^1-(7-chloroquinolin-4-yl)-N^2-(6-methyl-2-morpholinopyrimidin-4-yl)-N^2-(pyridin-2-ylmethyl)ethane-1,2-diamine (7c): Off-white solid; yield 43%; mp 178–180 °C; IR (KBr, cm^{-1}): 3226, 2943, 2360, 1705, 1635, 1577, 1512, 1462, 1423, 1365, 1325, 1286, 1232, 1207, 1165, 1139, 1112, 1076, 1018, 999, 945, 900, 854, 802, 788, 744, 702, 640, 615, 574, 526, 484, 420;^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.56 (d, *J* = 4.6 Hz, 1H), 8.51 (d, *J* = 5.3 Hz, 1H), 7.92 (s, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 9.2 Hz, 1H), 7.27 (t, *J* = 4.6 Hz, 1H), 7.20-7.13 (m, 3H), 6.32 (d, *J* = 5.3 Hz, 1H), 5.67 (s, 1H), 4.74 (s, 2H), 4.16 (s, 2H), 3.77-3.72 (m, 8H), 3.55 (d, *J* = 4.6 Hz, 2H), 2.13 (s, 3H); HRMS Calcd for $C_{26}H_{28}ClN_7O$: 489.2043, Found: 490.2112 $(M + H)^+$,492.2089 $(MH + 2)^+$.

5.5.8. N^1-(7-chloroquinolin-4-yl)-N^2-(6-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl)-N^2-(pyridin-2-ylmethyl)ethane-1,2-diamine (7d):Off-white solid; yield 40%; mp 154–156

°C; IR (KBr, cm^{-1}): 3199, 3062, 2917, 2787, 2373, 2345, 1578, 1449, 1381, 1325, 1297, 1270, 1234, 1188, 1139, 1009, 944, 901, 851, 767, 614; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.56 (d, *J* = 4.6 Hz, 1H), 8.51 (d, *J* = 5.3 Hz, 1H), 7.92 (s, 1H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.44 (d, *J* = 9.2 Hz, 1H), 7.26-7.12 (m, 4H), 6.31 (d, *J* = 4.6 Hz, 1H), 5.64 (s, 1H), 4.73 (s, 2H), 4.17 (s, 2H), 3.85 (s, 4H), 3.54 (d, *J* = 3.8 Hz, 2H), 2.44 (s, 4H), 2.31 (s, 3H), 2.14 (s, 3H); HRMS Calcd for $C_{27}H_{31}ClN_8$: 502.2360, Found: 503.2437 $(M + H)^+$,505.2410 $(MH + 2)^+$.

5.5.9. N^1-(7-chloroquinolin-4-yl)-N^2-(2-(4-ethylpiperazin-1-yl)-6-methylpyrimidin-4-yl)-N^2-(pyridin-2-ylmethyl)ethane-1,2-diamine(7e):Off-white solid; yield 57%; mp 106–108 °C; IR (KBr, cm^{-1}): 3309, 2931, 2849, 2801, 2372, 2345, 1578, 1420, 1364, 1331, 1272, 1237, 1203, 1165, 1150, 1127, 1079, 1027, 995, 875, 838, 802, 788, 763, 604; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.56 (d, *J* = 5.3 Hz, 1H), 8.50 (d, *J* = 5.3 Hz, 1H), 7.91 (d, *J* = 1.5 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 9.2 Hz, 1H), 7.27-7.12 (m, 4H), 6.31 (d, *J* = 5.3 Hz, 1H), 5.64 (s, 1H), 4.73 (s, 2H), 4.18 (s, 2H), 3.86 (s, 4H), 3.53 (d, *J* = 4.6 Hz, 2H), 2.49-2.40 (m, 6H), 2.14 (s, 3H), 1.10 (t, *J* = 7.2 Hz, 3H); HRMS Calcd for $C_{28}H_{33}ClN_8$: 516.2516, Found: 517.2601 $(M + H)^+$,519.2562 $(MH + 2)^+$.

5.5.10. N^1-(7-chloroquinolin-4-yl)-N^3-(6-methyl-2-(piperidin-1-yl)pyrimidin-4-yl)-N^3-(pyridin-2-ylmethyl)propane-1,3-diamine (7f):Off-white solid; yield 63%; mp 174–176 °C; IR (KBr, cm^{-1}): 3216, 3063, 2921, 2853, 1580, 1479, 1447, 1431, 1371, 1330, 1279, 1247, 1229, 1186, 1138, 1084, 1027, 995, 897, 846, 803, 782, 761, 640, 599, 465; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.42 (d, *J* = 5.3 Hz, 2H), 7.85 (s, 1H), 7.58-7.40 (m, 2H), 7.18-7.05 (m, 3H), 6.28 (d, *J* = 5.3 Hz, 1H), 5.77 (s, 1H), 5.51 (s, 1H), 4.70 (s, 2H), 3.72 (s, 2H), 3.60 (t, *J* = 5.0 Hz, 4H), 3.34 (q, *J* = 5.8 Hz, 2H), 2.02-1.98 (m, 5H), 1.52 (d, *J* = 3.8 Hz, 2H), 1.42 (d, *J* = 3.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 166.36, 162.62, 161.50, 158.35, 151.88, 149.84, 149.14, 149.07, 136.58, 134.66, 128.47, 124.96, 122.27, 121.38, 117.27, 98.72, 90.83, 53.65, 46.67, 44.75, 41.60, 26.59, 25.72, 24.90, 24.51,HRMS Calcd for $C_{28}H_{32}ClN_7$: 501.2407, Found: 502.2491 $(M + H)^+$,504.2471 $(MH + 2)^+$.

5.5.11. N^1-(7-chloroquinolin-4-yl)-N^3-(6-methyl-2-(pyrrolidin-1-yl)pyrimidin-4-yl)-N^3-(pyridin-2-ylmethyl)propane-1,3-diamine (7g):Off-white solid; yield 56%; mp 178–180 °C; IR (KBr, cm^{-1}): 3212, 3062, 2957, 2957, 2869, 1574, 1470, 1455, 1433, 1360, 1324, 1279, 1245, 1203, 1178, 1138, 1082, 1050, 996, 965, 898, 862, 847, 802, 784, 762, 696, 639, 603, 562, 464 ; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.45-8.41 (m, 2H), 7.85 (d, *J* = 1.9 Hz, 1H), 7.53-7.44 (m, 2H), 7.19-7.09 (m, 2H), 6.28 (d, *J* = 5.3 Hz, 1H), 5.79 (brs, 1H), 5.52 (s, 1H),

4.71 (s, 2H), 3.75 (brs, 2H), 3.38-3.34 (m, 6H), 2.04 (s, 3H), 1.78-1.74 (m, 6H);HRMS Calcd for $C_{27}H_{30}ClN_7$: 487.2251, Found: 488.2335 $(M + H)^+$,490.2316 $(MH + 2)^+$.

5.5.12. N^1-(7-chloroquinolin-4-yl)-N^3-(6-methyl-2-morpholinopyrimidin-4-yl)-N^3-(pyridin-2-ylmethyl)propane-1,3-diamine (7h): Off-white solid; yield 68%; mp 158–160 °C; IR (KBr, cm^{-1}): 3211, 3061, 2960, 2846, 2362, 1734, 1577, 1475, 1425, 1363, 1328, 1274, 1232, 1178, 1114, 1047, 995, 964, 896, 852, 790, 756, 634, 599, 555, 462; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.43 (d, *J* = 4.2 Hz, 2H), 7.85 (s, 1H), 7.55-7.48 (m, 2H), 7.19-7.12 (m, 3H), 6.27 (d, *J* = 4.6 Hz, 1H), 5.80 (s, 1H), 5.59 (s, 1H), 4.73 (s, 2H), 3.71 (s, 2H), 3.56 (s, 4H), 3.34-3.32 (m, 2H), 2.00 (s, 5H), 1.79 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 166.31, 162.53, 161.46, 158.16, 151.75, 149.89, 149.16, 148.91, 136.90, 134.72, 128.38, 124.97, 122.35, 121.38, 117.21, 98.70, 91.87, 66.77, 53.71, 46.83, 44.24, 41.64, 26.57, 24.34, HRMS Calcd for $C_{27}H_{30}ClN_7O$: 503.2197,Found: 504.2269 $(M + H)^+$,506.2254 $(MH + 2)^+$.

5.5.13. N^1-(7-chloroquinolin-4-yl)-N^3-(6-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl)-N^3-(pyridin-2-ylmethyl)propane-1,3-diamine(7i):Off-white solid; yield 52%; mp 144–146 °C; IR (KBr, cm^{-1}): 2914, 2788, 1578, 1485, 1426, 1366, 1325, 1250, 1139, 1008, 842, 768; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.42 (d, J = 5.3 Hz, 2H), 7.85 (d, *J* = 1.5 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 9.1 Hz, 1H), 7.19-7.09 (m, 3H), 6.27(d, *J* = 5.3 Hz, 1H), 5.76 (s, 1H), 5.55 (s, 1H), 4.72 (s, 2H), 3.72 (s, 2H), 3.62 (s, 4H), 3.34 (q, *J* = 5.3 Hz, 2H), 2.25 (t, *J* = 4.6 Hz, 2H), 2.20 (s, 3H), 2.01 (s, 3H), 1.88 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 166.37, 162.58, 161.43, 158.23, 151.93, 149.81, 149.19, 149.10, 136.89, 134.69, 128.56, 125.03, 122.33, 121.43, 121.31, 117.27, 98.76, 91.53, 54.92, 53.70, 46.73, 46.20, 43.66, 41.64, 26.61, 24.43 ; HRMS Calcd for $C_{28}H_{33}ClN_8$: 516.2516, Found: 517.2595 $(M + H)^+$,519.2572 $(MH + 2)^+$.

5.5.14. N^1-(7-chloroquinolin-4-yl)-N^3-(2-(4-ethylpiperazin-1-yl)-6-methylpyrimidin-4-yl)-N^3-(pyridin-2-ylmethyl)propane-1,3-diamine(7j):Off-white solid; yield 50%; mp 120–123 °C; IR (KBr, cm^{-1}): 3320, 2932, 2842, 2360, 1581, 1485, 1475, 1441, 1414, 1370, 1347, 1331, 1266, 1238, 1167, 1136, 996, 967, 873, 853, 790, 760, 620; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.42 (d, *J* = 4.6 Hz, 2H), 7.85 (d, *J* = 1.1 Hz, 1H), 7.54-7.46 (m, 2H), 7.19-7.09 (m, 3H), 6.27 (d, *J* = 5.3 Hz, 1H), 5.76 (s, 1H), 5.55 (s, 1H), 4.71 (s, 2H), 3.72 (brs, 2H), 3.63 (brs, 4H), 3.32 (t, *J* = 5.3 Hz, 2H), 2.34-2.28 (m, 6H), 2.01-1.92 (m, 6H), 1.02 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 166.32, 162.55, 161.39, 158.40, 151.86, 149.84, 149.15, 149.02, 136.88, 134.68, 128.46, 124.99, 122.31, 121.35, 117.25, 98.73,

91.46, 53.65, 52.67, 52.38, 46.69, 43.64, 41.58, 26.58, 24.40, 11.87;HRMS Calcd for $C_{29}H_{35}ClN_8$: 530.2673, Found: 531.2757 $(M + H)^+$,533.2735 $(MH + 2)^+$.

5.5.15. N^1-(7-chloroquinolin-4-yl)-N^2-(4-methyl-6-(piperidin-1-yl)pyrimidin-2-yl)-N^2-(pyridin-2-ylmethyl)ethane-1,2-diamine (8a):Off-white solid; yield 31%; mp 138–141 °C; IR (KBr, cm^{-1}):3290, 3005, 2931, 2850, 2362, 1573, 1541, 1475, 1415, 1367, 1321, 1249, 1219, 1130, 1076, 1031, 975, 916, 875, 840, 792, 758, 702, 642, 601, 534, 486, 428; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.52-8.50 (m, 1H), 8.47 (d, J = 5.0 Hz, 1H), 7.90 (d, J = 1.8 Hz, 1H), 7.57-7.46 (m, 3H), 7.24-7.21 (m, 2H), 7.13-7.10 (m, 1H), 6.26 (d, J = 5.5 Hz, 1H), 5.89 (s, 1H), 4.98 (s, 2H), 4.15 (t, J = 4.6 Hz, 2H), 3.49-3.43 (m, 6H), 2.36 (s, 3H), 1.61-1.49 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 162.57, 159.63, 152.11, 150.51, 149.07, 148.88, 136.53, 134.45, 128.38, 124.43, 122.28, 121.87, 121.35, 117.34, 98.12, 92.29, 53.32, 46.13, 45.11, 44.23, 25.41, 24.65, 24.55; HRMS Calcd for $C_{27}H_{30}ClN_7$: 487.2251, Found: 488.2324 $(M + H)^+$,490.2304 $(MH + 2)^+$.

5.5.16. N^1-(7-chloroquinolin-4-yl)-N^2-(4-methyl-6-(pyrrolidin-1-yl)pyrimidin-2-yl)-N^2-(pyridin-2-ylmethyl)ethane-1,2-diamine (8b):Off-white solid; yield 38%; mp 153–155 °C; IR (KBr, cm^{-1}):3325, 2951, 2866, 2362, 1730, 1587, 1546, 1479, 1417, 1363, 1327, 1296, 1246, 1213, 1170, 1136, 1083, 1043, 1002, 968, 902, 844, 794, 761, 698, 636, 596, 545, 486, 449, 414; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)8.52-8.50 (m, 1H), 8.46 (d, J = 5.5 Hz, 1H), 7.89 (d, J = 2.3 Hz, 1H), 7.59-7.53 (m, 1H), 7.50-7.45 (m,1H), 7.28-7.26 (m, 1H), 7.20 (d, J = 8.2 Hz, 1H), 7.13-7.10 (m, 1H), 6.25 (d, J = 5.0 Hz, 1H), 5.69 (s, 1H), 5.02 (s, 2H), 4.16 (t, J = 5.0 Hz, 2H), 3.45-3.37 (m, 6H), 2.36 (s, 3H), 2.00-1.91 (m, 4H);^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)162.47, 160.99, 159.74, 152.06, 150.55, 149.03, 148.84, 136.51, 134.45, 128.33, 124.35, 122.23, 121.87, 121.52, 117.35, 98.09, 93.14, 53.06, 46.16, 45.87, 44.21, 25.30, 24.36; HRMS Calcd for $C_{26}H_{28}ClN_7$: 473.2094, Found: 474.2161 $(M + H)^+$,476.2142 $(MH + 2)^+$.

5.5.17. N^1-(7-chloroquinolin-4-yl)-N^2-(4-methyl-6-morpholinopyrimidin-2-yl)-N^2-(pyridin-2-ylmethyl)ethane-1,2-diamine (8c): Off-white solid; yield 36%; mp 181–183 °C; IR (KBr, cm^{-1}): 3226, 2932, 1586, 1531, 1503, 1472, 1422, 1373, 1322, 1284, 1230, 1211, 1186, 1155, 1044, 967, 915, 880, 847, 805, 762, 541;^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.52-8.47 (m, 2H), 7.93 (d, J = 1.6 Hz, 1H), 7.58-7.48 (m, 3H), 7.26-7.19 (m, 2H), 7.14-7.11 (m, 1H), 6.30 (d, J = 5.5 Hz, 1H), 5.86 (s, 1H), 4.97 (s, 2H), 4.17 (t, J = 4.8 Hz, 2H), 3.65(brs, 4H), 3.47 (brs, 6H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 162.39, 159.36, 151.81, 150.58, 148.97, 148.74, 136.59, 134.66, 134.56, 128.47, 128.24, 124.85, 124.63,

122.09, 121.96, 117.25, 98.20, 92.30, 66.45, 53.27, 46.18, 44.23, 44.10, 24.55; HRMS Calcd for $C_{26}H_{28}ClN_7O$: 489.2043, Found: 490.2112 $(M + H)^+$,492.2089 $(MH + 2)^+$.

5.5.18. N^1-(7-chloroquinolin-4-yl)-N^2-(4-methyl-6-(4-methylpiperazin-1-yl)pyrimidin-2-yl)-N^2-(pyridin-2-ylmethyl)ethane-1,2-diamine (8d): Off-white solid; yield 41%; mp 89–90°C; IR (KBr, cm^{-1}): 3277, 3010, 2968, 2939, 2852, 2360, 1739, 1575, 1417, 1367, 1294, 1218, 1224, 1170,1082, 1045, 997, 887, 842, 821, 773, 696, 619, 586, 545, 482, 428; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.51 (d, J = 4.6 Hz, 1H), 8.46 (d, J = 5.1 Hz, 1H), 7.90 (d, J = 1.8 Hz, 1H), 7.56 (d, J = 7.3 Hz, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.27-7.22 (m, 2H), 7.13 (t, J = 5.5 Hz, 1H), 6.27 (d, J = 5.5 Hz, 1H), 5.88 (s, 1H), 4.98 (s, 2H), 4.15 (t, J = 4.8 Hz, 2H), 3.52 (brs, 4H), 3.46-3.45 (m, 2H), 2.36 (brs, 4H), 2.27 (s, 3H), 2.10 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 162.84, 162.43, 160.64, 159.44, 152.09, 150.43, 148.91, 136.56, 134.47, 128.40, 124.54, 122.15, 121.91, 121.28, 117.30, 98.16, 92.37, 54.55, 53.36, 46.09, 44.11, 43.80, 24.53;HRMS Calcd for $C_{27}H_{31}ClN_8$: 502.2360, Found: 503.2425 $(M + H)^+$,505.2378 $(MH + 2)^+$.

5.5.19. N^1-(7-chloroquinolin-4-yl)-N^2-(4-(4-ethylpiperazin-1-yl)-6-methylpyrimidin-2-yl)-N^2-(pyridin-2-ylmethyl)ethane-1,2-diamine (8e): Off-white solid; yield 31%; mp 92–94 °C; IR (KBr, cm^{-1}): 2914, 2788, 2362, 1739, 1575, 1417, 1367, 1222, 1139, 997, 889, 773; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.51 (d, J = 4.6 Hz, 1H), 8.46 (d, J = 4.6 Hz, 1H), 7.90 (s, 1H), 7.57 (d, J = 6.1 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.23 (d, J = 7.6 Hz, 3H), 7.13 (t, J = 6.1 Hz, 1H), 6.27 (d, J = 4.6 Hz, 1H), 5.88 (s, 1H), 4.98 (s, 2H), 4.15 (s, 2H), 3.53-3.46 (m, 6H), 2.40-2.37 (m, 8H), 1.07 (t, J = 7.6 Hz, 3H);HRMS Calcd for $C_{28}H_{33}ClN_8$: 516.2516, Found: 517.2587 $(M + H)^+$,519.2562 $(MH + 2)^+$.

5.5.20. N^1-(7-chloroquinolin-4-yl)-N^3-(4-methyl-6-(piperidin-1-yl)pyrimidin-2-yl)-N^3-(pyridin-2-ylmethyl)propane-1,3-diamine(8f): Off-white solid; yield 61%; mp 98–100 °C; IR (KBr, cm^{-1}): 3226, 2940, 2872, 1583, 1550, 1475, 1433, 1369, 1321, 1282, 1210, 1131, 1183, 1083, 973, 874, 853, 788, 754;^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.42 (d, J = 4.5 Hz, 1H), 8.39 (d, J = 5.3 Hz, 1H), 7.84 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.19-7.16 (m, 2H), 7.05 (t, J = 6.1 Hz, 1H), 6.64 (brs, 1H), 6.30 (d, J = 4.6 Hz, 1H), 5.66 (s, 1H), 4.86 (s, 2H), 3.79 (t, J = 5.3 Hz, 2H), 3.33 (s, 6H), 2.16 (s, 3H), 1.87-1.76 (m, 2H), 1.52-1.51 (m, 2H), 1.36 (brs, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)165.56, 162.47, 161.88, 159.92, 151.91, 150.27, 149.21, 148.76, 136.47, 134.55, 128.35, 124.57, 122.17, 121.75, 121.52, 117.69, 98.81, 91.73, 53.24, 44.91, 40.22, 26.59, 25.36, 24.84, 24.71;HRMS Calcd for $C_{28}H_{32}ClN_7$: 501.2389, Found: 502.2468 $(M + H)^+$,504.2458 $(MH + 2)^+$.

5.5.21. N^1-(7-chloroquinolin-4-yl)-N^3-(4-methyl-6-(pyrrolidin-1-yl)pyrimidin-2-yl)-N^3-(pyridin-2-ylmethyl)propane-1,3-diamine(8g): Off-white solid; yield 68%; mp 130–132 °C; IR (KBr, cm^{-1}): 3226, 2947, 2872, 1583, 1551, 1475, 1432, 1414, 1367, 1348, 1319, 1242, 1169, 1139, 974, 875, 853, 804, 789, 764;^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.43 (d, *J* = 4.6 Hz, 1H), 8.38 (d, *J* = 6.1 Hz, 1H), 7.83(d,*J* = 1.5 Hz, 1H), 7.73(d, *J* = 9.1Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.22-7.10 (m, 1H), 7.15 (dd*J* = 1.5, 2.6 Hz, 1H), 7.08-7.05(m, 1H), 6.67(brs, 1H) 6.29 (d, *J* = 5.3 Hz, 1H), 5.40 (s, 1H), 4.90 (s, 2H), 3.79 (t, *J* = 6.1 Hz, 2H), 3.34 (q, *J* = 5.3 Hz, 2H), 3.19 (s, 4H), 2.13 (s, 3H), 1.88-1.81 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 164.65, 161.72, 160.82, 160.06, 151.77, 150.36, 149.08, 148.71, 136.48, 134.53, 128.16, 124.48, 122.25, 121.78, 117.65, 98.75, 92.51, 53.04, 45.88, 44.95, 40.50, 26.52, 25.12, 24.57; HRMS Calcd for $C_{27}H_{30}ClN_7$: 487.2251, Found: 488.2348 $(M + H)^+$,490.2330 $(MH + 2)^+$.

5.5.22. N^1-(7-chloroquinolin-4-yl)-N^3-(4-methyl-6-morpholinopyrimidin-2-yl)-N^3-(pyridin-2-ylmethyl)propane-1,3-diamine(8h): Off-white solid; yield 50%; mp 120–122 °C; IR (KBr, cm^{-1}): 3226, 2932, 2853, 1582, 1557, 1503, 1472, 1409, 1367, 1321, 1245, 1187, 1122, 992, 873, 853, 791, 757, 594;^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.43 (d, *J* =4.5 Hz, 1H), 8.40 (d, *J* =5.5 Hz, 1H),7.84 (d, *J* =2.3, Hz, 1H), 7.74 (d, *J* = 9.1, Hz, 1H), 7.51 (t, *J* =7.8 Hz, 1H), 7.19-7.15 (m, 2H), 7.08 (t, *J* =5.0 Hz, 1H), 6.61 (brs, 1H), 6.30 (d, *J* = 5.5 Hz, 1H), 5.59 (s, 1H), 4.86 (s, 2H), 3.81 (t, *J* = 6.0 Hz, 2H), 3.54 (t, *J* = 5.0 Hz, 4H), 3.35-3.30 (m, 6H), 2.15 (s, 3H), 1.89 (q, *J* = 5.6 Hz, 2H);HRMS Calcd for $C_{27}H_{30}ClN_7O$: 503.2215, Found: 504.2293 $(M + H)^+$,506.2274 $(MH + 2)^+$.

5.5.23. N^1-(7-chloroquinolin-4-yl)-N^3-(4-methyl-6-(4-methylpiperazin-1-yl)pyrimidin-2-yl)-N^3-(pyridin-2-ylmethyl)propane-1,3-diamine(8i):Off-white solid; yield52%; mp 97–99°C; IR (KBr, cm^{-1}): 2940, 2797, 1583, 1553, 1473, 1410, 1368, 1322, 1284, 1252, 1232, 1199, 1169, 1138, 1000, 879, 853, 789, 751, 621;^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.48 (d, *J* = 8.4 Hz, 2H), 7.92 (s, 1H) 7.82 (d, *J*= 8.4, 1H), 7.57(s, 1H), 7.23-7.14 (m, 2H),6.76 (s, 1H), 6.37 (s, 1H), 5.69 (s, 1H), 4.94 (s, 2H), 3.87(s, 2H), 3.43 (brs, 6H), 2.31-2.12 (m, 10H), 1.96 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 165.92, 162.69, 161.69, 159.74, 151.59, 150.40, 148.74, 136.55, 134.67, 128.02, 124.65, 122.15, 121.85, 121.50, 117.56, 98.72, 91.76, 54.47, 53.27, 46.04, 45.21, 43.53, 40.41, 26.54, 24.76; HRMS Calcd for $C_{28}H_{33}ClN_8$: 516.2524, Found: 517.2600$(M + H)^+$,519.2575 $(MH + 2)^+$.

5.5.24. N^1-(7-Chloroquinolin-4-yl)-N^3-(thiophen-2-ylmethyl)propane-1,3-diamine (10a):White solid; yield: 89%; mp 112–114 °C; IR (KBr, cm^{-1}): 3199, 3061, 2937, 1573, 1442,

1363, 1211, 1076, 848, 705, 567, 478; ^{1}H NMR (400 MHz; $CDCl_3$):δ (ppm) 8.49 (d, *J* = 5.3 Hz, 1H), 7.91 (d, *J* = 2.2 Hz, 1H), 7.65 (d, *J* = 9.1 Hz, 1H), 7.44 (brs, 1H), 7.28-7.26 (m, 2H), 7.23 (dd, *J*= 9.1, 2.2 Hz, 1H), 7.01-6.96 (m, 2H), 6.31 (d, *J* = 5.3 Hz, 1H), 4.06 (s, 2H), 3.42-3.38 (m, 2H), 2.98 (t, *J* = 5.7 Hz, 2H), 1.97-1.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$):δ (ppm) 151.91, 150.40, 148.93, 142.74, 134.59, 128.36, 126.82, 125.56, 124.86, 124.77, 122.24, 117.43, 98.25, 48.83, 48.59, 43.76, 27.36; HRMS calcd for $C_{17}H_{18}ClN_3S$: 331.0910, found: 332.0984 $(M + H)^+$, 334.0956 $(MH + 2)^+$.

5.5.25. N^1-(2-Chloro-6-methylpyrimidin-4-yl)-N^3-(7-chloroquinolin-4-yl)-N^1-(thiophen-2-ylmethyl)propane-1,3-diamine (11a):White solid; yield: 60%; mp 117–119 ^{o}C; IR (KBr, cm^{-1}): 3236, 2956, 1735, 1583, 1500, 1423, 1365, 1220, 893, 696, 538, 470; ^{1}H NMR (400 MHz; $CDCl_3$):δ (ppm) 8.50 (d, *J* = 5.3 Hz, 1H), 8.01 (brs, 1H), 7.96-7.95 (m, 1H), 7.40-7.37 (m, 1H), 7.25-7.23 (m, 1H), 6.97-6.92 (m, 2H), 6.39 (d, *J*= 5.3 Hz, 1H), 6.30 (s, 1H), 5.98 (brs, 1H), 4.76 (s, 2H), 3.81-3.74 (m, 2H), 3.41-3.37 (m, 2H), 2.32 (s, 3H), 2.00-1.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$):δ (ppm) 172.09, 167.32, 162.38, 158.98, 151.57, 150.25, 148.98, 139.77, 133.64, 127.12, 126.64, 125.95, 124.26, 124.17, 117.43, 100.34, 98.92, 45.30, 25.27, 23.17, 21.12; HRMS calcd for $C_{22}H_{21}Cl_2N_5S$: 457.0895, found: 458.0936 $(M + H)^+$, 460.0910 $(MH + 2)^+$.

5.5.26. N^1-(4-Chloro-6-methylpyrimidin-2-yl)-N^3-(7-chloroquinolin-4-yl)-N^1-(thiophen-2-ylmethyl)propane-1,3-diamine (12a):White solid; yield: 26%; mp 154–156 ^{o}C; IR (KBr, cm^{-1}): 3242, 2929, 1737, 1571, 1431, 1363, 1286, 1220, 1116, 1068, 891,842, 702, 430;^{1}H NMR (400 MHz; $CDCl_3$) δ(ppm): 8.49 (d, *J* = 5.3 Hz, 1H), 7.96 (brs, 1H), 7.93 (d, *J* = 2.2 Hz, 1H), 7.35 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.20-7.18 (m, 1H), 7.01 (d, *J* = 3.81 Hz, 1H), 6.92 (dd, *J* = 5.3, 3.8 Hz, 1H), 6.51 (s, 1H), 6.38 (d, *J* = 5.3 Hz, 1H), 5.96-5.93 (m, 1H), 4.97 (s, 2H), 3.75 (t, *J* = 6.1 Hz, 2H), 3.36-3.32 (m, 2H), 2.37 (s, 3H), 1.97-1.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 169.45, 161.48, 160.90, 151.71, 149.77, 148.98, 140.28, 134.81, 128.33, 126.65, 126.21, 125.45, 124.91, 121.86, 117.36, 108.95, 98.72, 45.80, 43.63, 39.39, 26.13, 24.05; HRMS calcd for $C_{22}H_{21}Cl_2N_5S$: 457.0895, found: 458.0942 $(M + H)^+$, 460.0916 $(MH + 2)^+$.

5.5.27. N^1-(7-Chloroquinolin-4-yl)-N^3-(6-methyl-2-(piperidin-1-yl)pyrimidin-4-yl)-N^3-(thiophen-2-ylmethyl)propane-1,3-diamine (13a):Off white solid; yield: 89%; mp 194–196 ^{o}C; IR (KBr, cm^{-1}): 3226, 2924, 2858, 1571, 1469, 1433, 1367, 1236, 1141, 850, 796, 696, 464; ^{1}H NMR (400 MHz; $CDCl_3$) δ (ppm): 8.50 (d, *J* = 5.3 Hz, 1H), 7.94 (d, *J* = 2.2 Hz, 1H), 7.45 (d, *J* = 9.1 Hz, 1H), 7.31 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.18-7.17 (m, 1H), 6.90-6.89 (m, 2H),

6.34 (d, *J* = 5.3 Hz, 1H), 5.67 (s, 1H), 5.12 (brs, 1H), 4.78 (s, 2H), 3.76 (t, *J* = 5.3 Hz., 4H), 3.65 (t, *J* = 6.1 Hz, 2H), 3.37-3.33 (m, 2H), 2.17 (s, 3H), 2.06-1.99 (m, 2H), 1.65-1.59 (m, 2H), 1.57-1.51 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.06, 161.68, 160.68, 151.90, 149.94, 149.12, 141.63, 133.37, 127.52, 126.34, 126.18, 125.61, 125.50, 124.07, 117.53, 98.87, 90.58, 45.07, 44.07, 25.80, 25.37, 24.54, 24.04; HRMS calcd. for $C_{27}H_{31}ClN_6S$: 506.2019, found: 507.2053 $(M + H)^+$, 509.2024 $(MH + 2)^+$.

5.5.28. N^1-(7-Chloroquinolin-4-yl)-N^3-(6-methyl-2-(pyrrolidin-1-yl)pyrimidin-4-yl)-N^3-(thiophen-2-ylmethyl)propane-1,3-diamine (13b):Off white solid; yield: 82%; mp 217–219 ^{o}C; IR (KBr, cm^{-1}): 3207, 2954, 2858, 1564, 1462, 1327, 1242, 1139, 854, 769, 694, 559, 462; ^{1}H NMR (400 MHz; $CDCl_3$) δ (ppm): 8.49 (d, *J* = 5.3 Hz, 1H), 7.94 (d, *J* = 2.2 Hz, 1H), 7.45 (d, *J* = 9.1 Hz, 1H), 7.29 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.18-7.16 (m, 1H), 6.90-6.89 (m, 2H), 6.34 (d, *J* = 5.3 Hz, 1H), 5.70 (s, 1H), 5.21 (brs, 1H), 4.78 (s, 2H), 3.68 (t, *J* = 6.8 Hz, 2H), 3.55-3.52 (m, 4H), 3.39-3.34 (m, 2H), 2.19 (s, 3H), 2.06-2.00 (m, 2H), 1.90-1.87 (m, 4H); HRMS calcd. for $C_{26}H_{29}ClN_6S$: 492.1863, found: 493.1892 $(M + H)^+$, 495.1864 $(MH + 2)^+$.

5.5.29. N^1-(7-Chloroquinolin-4-yl)-N^3-(6-methyl-2-morpholinopyrimidin-4-yl)-N^3-(thiophen-2-ylmethyl)propane-1,3-diamine (13c):White solid; yield: 79%; mp 196–198 ^{o}C; ^{1}H NMR (400 MHz; $CDCl_3$) δ (ppm): 8.49 (d, *J* = 5.3 Hz, 1H), 7.95 (d, *J* = 2.2 Hz, 1H), 7.51 (d, *J* = 9.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.19-7.17 (m, 1H), 6.91-6.90 (m, 2H), 6.32 (d, *J* = 5.3 Hz, 1H), 5.74 (s, 1H), 5.17 (brs, 1H), 4.81 (s, 2H), 3.77-3.74 (m, 4H), 3.71-3.68 (m, 4H), 3.64 (t, *J* = 6.1 Hz, 2H), 3.37-3.32 (m, 2H), 2.16 (s, 3H), 2.07-2.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.50, 162.27, 161.56, 151.77, 149.51, 148.86, 141.02, 134.96, 128.62, 126.46, 125.79, 125.35, 125.32, 120.80, 117.04, 99.08, 91.76, 66.91, 46.34, 45.24, 44.38, 41.01, 26.69, 24.48; HRMS calcd. for $C_{26}H_{29}ClN_6OS$: 508.1812, found: 509.1920 $(M + H)^+$, 511.1900 $(MH + 2)^+$.

5.5.30. N^1-(7-Chloroquinolin-4-yl)-N^3-(6-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl)-N^3-(thiophen-2-ylmethyl)propane-1,3-diamine (13d): White solid; yield: 76%; mp 127–129 ^{o}C; IR (KBr, cm^{-1}): 3356, 3072, 2935, 1581, 1546, 1473, 1431, 1365, 1315, 1234, 999, 794, 599, 549; ^{1}H NMR (400 MHz; $CDCl_3$) δ (ppm): 8.50 (d, *J* = 5.3 Hz, 1H), 7.95 (d, *J* = 2.2 Hz, 1H), 7.48 (d, *J* = 9.1 Hz, 1H), 7.32 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.19-7.17 (m, 1H), 6.91-6.90 (m, 2H), 6.33 (d, *J* = 5.3 Hz, 1H), 5.72 (s, 1H), 5.07 (brs, 1H), 4.79 (s, 2H), 3.80 (t, *J* = 4.5 Hz, 4H), 3.64 (t, *J* = 6.1 Hz, 2H), 3.36-3.32 (m, 2H), 2.38 (t, *J* = 4.5 Hz, 4H), 2.29 (s, 3H), 2.16 (s, 3H), 2.06-1.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.46, 162.25, 161.45, 151.92, 149,43, 149.02, 141.07, 134.82, 128.69, 126.43, 125.73, 157.26, 120.83, 117.09, 98.99, 91.38, 55.00,

46.27, 46.21, 45.18, 43.72, 41.02, 26.65, 24.53; HRMS calcd. for $C_{27}H_{32}ClN_7S$: 521.2128, found: 522.2159 $(M + H)^+$, 524.2119 $(MH + 2)^+$.

5.5.31. N^1-(7-Chloroquinolin-4-yl)-N^3-(2-(4-ethylpiperazin-1-yl)-6-methylpyrimidin-4-yl)-N^3-(thiophen-2-ylmethyl)propane-1,3-diamine (13e): Off white solid; yield: 79 %; mp 114–116 ^oC; IR (KBr, cm^{-1}): 3215, 2958, 1564, 1431, 1365, 1238, 1134, 1004, 781, 702; ^1H NMR (400 MHz; $CDCl_3$) δ (ppm): 8.51 (d, J = 5.3 Hz, 1H), 7.96-7.94 (m, 1H), 7.47 (d, J = 9.1 Hz, 1H), 7.33-7.31 (m, 1H), 7.19-7.17 (m, 1H), 6.91-6.90 (m, 2H), 6.34 (d, J = 5.3 Hz, 1H), 5.72 (s, 1H), 5.06 (brs, 1H), 4.79 (s, 2H), 3.81 (t, J = 5.3 Hz, 4H), 3.65 (t, J = 6.10 Hz, 2H), 3.37-3.32 (m, 2H), 2.46-2.39 (m, 6H), 2.17 (s, 3H), 2.06-1.99 (m, 2H), 1.10 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.50, 162.31, 161.47, 151.90, 149.48, 149.00, 141.10, 134.88, 128.71, 126.46, 125.74, 125.32, 125.25, 120.80, 117.09, 99.08, 91.39, 52.79, 52.42, 46.34, 4524, 43.75, 41.09, 26.71, 24.54, 11.88; HRMS calcd. for $C_{28}H_{34}ClN_7S$: 535.2285; found: 536.2321 $(M + H)^+$, 538.2287 $(MH + 2)^+$.

5.5.32. N^1-(7-Chloroquinolin-4-yl)-N^3-(4-methyl-6-(piperidin-1-yl)pyrimidin-2-yl)-N^3-(thiophen-2-ylmethyl)propane-1,3-diamine (14a): White solid; yield: 89%; mp 142–144 ^oC; IR (KBr, cm^{-1}): 3215, 2927, 2854, 1564, 1463, 1423, 1361, 1238, 1207, 1126, 852, 692, 466 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ (ppm): 8.46 (d, J = 5.3 Hz, 1H), 7.92-7.91 (m, 1H), 7.81 (d, J = 9.1 Hz, 1H), 7.30-7.27 (m, 1H), 7.15-7.14 (m, 1H), 6.96-6.95 (m, 1H), 6.90-6.88 (m, 1H), 6.50 (brs, 1H), 6.38 (d, J = 5.3 Hz, 1H), 5.81 (s, 1H), 4.91 (s, 2H), 3.76 (t, J = 6.1 Hz, 2H), 3.58 (d, J = 5.3 Hz, 4H), 3.37-3.33 (m, 2H), 2.28 (s, 3H), 1.88 (t, J = 6.1 Hz, 2H), 1.66-1.65 (m, 2H), 1.57-1.56 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.60, 162.34, 161.65, 151.94, 150.11, 149.25, 142.21, 134.58, 128.42, 125.89, 125.86, 125.12, 124.59, 122.03, 117.69, 98.91, 91.80, 45.67, 45.02, 43.18, 39.51, 26.51, 25.57, 24.96, 24.76; HRMS calcd. for $C_{27}H_{31}ClN_6S$: 506.2019, found: 507.2042 $(M + H)^+$, 509.2019 $(MH + 2)^+$.

5.5.33. N^1-(7-Chloroquinolin-4-yl)-N^3-(4-methyl-6-(pyrrolidin-1-yl)pyrimidin-2-yl)-N^3-(thiophen-2-ylmethyl)propane-1,3-diamine (14b): Off white solid; yield: 86%; mp 140–142 ^oC; IR (KBr, cm^{-1}): 3217, 2960, 2856, 1570, 1463, 1419, 1352, 1234, 1138, 854, 769, 688, 460; ^1H NMR (400 MHz; $CDCl_3$) δ (ppm): 8.46 (d, J = 5.3 Hz, 1H), 7.93 (d, J = 2.2 Hz, 1H), 7.80 (d, J = 9.1 Hz, 1H), 7.28 (dd, J = 9.1, 2.2 Hz, 1H), 7.15-7.13 (m, 1H), 6.97 (d, J = 3.8 Hz, 1H), 6.89 (dd, J = 5.3, 3.8 Hz, 1H), 6.55 (brs, 1H), 6.38 (d, J = 5.3 Hz, 1H), 5.59 (s, 1H), 4.94 (s, 2H), 3.77 (t, J = 6.1 Hz, 2H), 3.58-3.34 (m, 6H), 2.28 (s, 3H), 1.94-1.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.74, 161.19, 160.99, 152.47, 150.58, 149.73, 143.05, 133.91,

128.10, 126.69, 126.63, 126.02, 124.65, 124.54, 118.15, 99.20, 92.56, 46.13, 45.64, 44.94, 40.80, 26.85, 25.26, 24.64; HRMS calcd. for $C_{26}H_{29}ClN_6S$: 492.1863, found: 493.1887 $(M + H)^+$, 495.1862 $(MH + 2)^+$.

5.5.34. N^1-(7-Chloroquinolin-4-yl)-N^3-(4-methyl-6-morpholinopyrimidin-2-yl)-N^3-(thiophen-2-ylmethyl)propane-1,3-diamine (14c): White solid; yield: 81%; mp 142–144 ^oC; IR (KBr, cm^{-1}): 3226, 2956, 2850, 1570, 1415, 1363, 1242, 1188, 1118, 993, 852, 794, 711, 636, 462 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ (ppm): 8.46 (d, J = 5.3 Hz, 1H),7.96-7.95 (m, 1H), 7.81 (d, J = 9.1 Hz, 1H), 7.31-7.29 (m, 1H), 7.16-7.15 (m, 1H), 6.96-6.95 (m, 1H), 6.91-6.88 (m, 1H), 6.53 (brs, 1H), 6.38 (d, J = 5.3 Hz, 1H), 5.79 (s, 1H), 4.91 (s, 2H), 3.78-3.72 (m, 6H), 3.59 (t, J = 5.3 Hz, 4H), 3.38-3.34 (m, 2H), 2.29 (s, 3H), 1.92-1.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.27, 162.95, 161.52, 151.71, 150.16, 148.98, 141.94, 134.79, 128.33, 125.98, 125.19, 124.77, 121.86, 117.57, 98.93, 91.83, 66.60, 43.83, 44.26, 43.39, 39.68, 26.59, 24.94; HRMS calcd. for $C_{26}H_{29}ClN_6OS$: 508.1812, found: 509.1924 $(M + H)^+$, 511.1906 $(MH + 2)^+$.

5.5.35. N^1-(7-Chloroquinolin-4-yl)-N^3-(4-methyl-6-(4-methylpiperazin-1-yl)pyrimidin-2-yl)-N^3-(thiophen-2-ylmethyl)propane-1,3-diamine (14d): White solid; yield: 76%; mp 108–110 ^oC; IR (KBr, cm^{-1}): 3228, 2924, 2787, 1570, 1458, 1417, 1363, 1207, 1138, 995, 788, 696, 462; ^1H NMR (400 MHz; $CDCl_3$) δ (ppm): 8.47 (d, J = 5.3 Hz, 1H), 7.92 (d, J = 2.2 Hz, 1H), 7.79 (d, J = 9.1 Hz, 1H), 7.29 (dd, J = 9.1, 2.2 Hz, 1H), 7.16-7.14 (m, 1H), 6.96-6.95 (m, 1H), 6.90-6.88 (m, 1H), 6.38-6.37 (m, 2H), 5.81 (s, 1H), 4.91 (s, 2H), 3.76 (t, J = 6.1 Hz, 2H), 3.65-3.61 (m, 4H), 3.37-3.32 (m, 2H), 2.43-2.29 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.05, 162.67, 161.58, 151.87, 150.13, 149.17, 142.08, 134.70, 128.43, 125.95, 125.17, 124.73, 121.89, 117.64, 98.94, 91.92, 54.70, 46.13, 45.80, 43.80, 43.40, 39.71, 26.60, 24.92; HRMS calcd. for $C_{27}H_{32}ClN_7S$: 521.2128, found: 522.2190 $(M + H)^+$, 524.2133 $(MH + 2)^+$.

5.5.36. N^1-(7-Chloroquinolin-4-yl)-N^3-(4-(4-ethylpiperazin-1-yl)-6-methylpyrimidin-2-yl)-N^3-(thiophen-2-ylmethyl)propane-1,3-diamine (14e): Off white solid; yield: 80%; mp 96–98 ^oC; IR (KBr, cm^{-1}): 3230, 2922, 1568, 1462, 1419, 1363, 1244, 1203, 1134, 997, 773, 696, 460; ^1H NMR (400 MHz; $CDCl_3$) δ (ppm): 8.47 (d, J = 5.3 Hz, 1H), 7.93-7.92 (m, 1H), 7.80 (d, J = 9.1 Hz, 1H), 7.30-7.28 (m, 1H), 7.15-7.14 (m, 1H), 6.97-6.96 (m, 1H), 6.90-6.88 (m, 1H), 6.46-6.32 (m, 2H), 5.81 (s, 1H), 4.91 (s, 2H), 3.76 (t, J = 6.1 Hz, 2H), 3.66-3.61 (m, 4H), 3.35-3.34 (m, 2H), 2.49-2.41 (m, 8H), 2.29 (s, 3H), 1.11 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.00, 162.67, 161.58, 151.81, 150.16, 149.11, 142.09, 134.74, 128.38, 125.95, 125.17, 124.74, 121.90, 117.63, 98.92, 91.92, 52.48, 52.34, 45.81, 43.83, 43.41, 39.71, 26.60,

24.92, 11.89; HRMS calcd. for $C_{28}H_{34}ClN_7S$: 535.2285; found: 536.2355 $(M + H)^+$, 538.2318 $(MH + 2)^+$.

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Table 1: *In vitro*antimalarial activity and cytotoxicity of the 4-aminoquinoline-pyrimidine molecular hybrids

Comp.	R	n	*P. falciparum* (D6 strain)		*P. falciparum* (W2 strain)		Cytotoxicity (VERO cells)
			IC_{50} (µM)	SI	IC_{50} (µM)	SI	IC_{50} (µM)
5a	Cl	2	0.233	>46.6	0.492	>22	NC
5b	Cl	3	1.391	>7.6	0.319	>33.5	NC
6a	Cl	2	0.369	23.2	1.006	8.5	3763.1
6b	Cl	3	1.661	>6.3	0.804	>13	NC
7a	Piperidin-1-yl	2	0.065	>150.9	0.494	>19.7	NC
7b	Pyrrolidin-1-yl	2	0.030	>331	0.143	>70	NC
7c	Morpholin-1-yl	2	0.152	>64.2	0.526	>18.5	NC
7d	4-Methyl-piperazin-1-yl	2	0.027	>351	0.142	>67	NC
7e	4-Ethyl-piperazin-1-yl	2	0.028	>326	0.093	>98	NC
7f	Piperidin-1-yl	3	0.093	>101.9	0.819	>11.6	NC
7g	Pyrrolidin-1-yl	3	0.036	>274	0.140	>69	NC
7h	Morpholin-1-yl	3	0.114	>82.5	0.511	>18.5	NC
7i	4-Methyl-piperazin-1-yl	3	0.426	>21.6	0.243	>37.8	NC
7j	4-Ethyl-piperazin-1-yl	3	0.028	>321	0.137	>66	NC
8a	Piperidin-1-yl	2	0.252	>38.6	1.443	>6.8	NC
8b	Pyrrolidin-1-yl	2	0.140	>71.7	0.855	>11.7	NC
8c	Morpholin-1-yl	2	0.311	>31.2	0.248	>39.1	NC
8d	4-Methyl-piperazin-1-yl	2	0.040	>238	0.139	>68	NC
8e	4-Ethyl-piperazin-1-yl	2	0.034	>270	0.039	>273	NC
8f	Piperidin-1-yl	3	1.193	>7.9	0.945	>10	NC
8g	Pyrrolidin-1-yl	3	1.039	>9.4	0.389	>25.1	NC
8h	Morpholin-1-yl	3	1.144	>8.3	0.334	>28.3	NC
8i	4-Methyl-piperazin-1-yl	3	0.551	>16.7	0.189	>48.5	NC
10a	-	3	0.4239	>33.8	0.0751	>19.1	NC
11a	Cl	3	0.2461	>42.2	0.6057	>17.1	NC
12a	Cl	3	0.1190	>87.2	0.4621	>22.5	NC
13a	Piperidin-1-yl	3	0.0837	109.4	0.2351	38.9	9.1549
13b	Pyrrolidin-1-yl	3	0.0420	>229.4	0.2023	>47.7	NC
13c	Morpholin-1-yl	3	0.0552	168.3	0.4091	22.7	9.2993
13d	4-Methyl-piperazin-1-yl	3	0.0370	>24.6	0.0387	>23.5	NC
13e	4-Ethyl-piperazin-1-yl	3	0.0358	>24.8	0.0312	>28.4	NC
14a	Piperidin-1-yl	3	0.0446	161.3	0.1852	38.9	7.1973
14b	Pyrrolidin-1-yl	3	0.0359	>26.8	0.0401	>24	NC
14c	Morpholin-1-yl	3	0.0558	>167.4	0.5423	>17.2	NC

14d	4-Methyl-piperazin-1-yl	3	0.0389	>23.4	0.0199	>45.8	NC
14e	4-Ethyl-piperazin-1-yl	3	0.0328	>27	0.0189	>46.8	NC
CQ	-	-	0.0204	>36.5	0.4215	>1.8	NC
ART	-	-	0.0171	>49.2	0.0162	>52	NC

IC_{50}: concentration of drug that results 50% growth inhibition; S.I. Selectivity index = (IC_{50} for cytotoxicity / IC_{50} for antimalarial activity); NC: No cytotoxicity up to 10 µM; Vero: Monkey kidney fibroblasts

Table 2:Glide docking scores (kcal mol^{-1}) and glide energies of best active compounds

Compounds	Docking results with wild *Pf*-DHFR		Docking results with mutant *Pf*-DHFR	
	XP GScore	Glide Energy	XP GScore	Glide Energy
7b	-8.27	-60.28	-6.96	-53.13
7d	-9.24	-51.67	-7.59	-55.95
7e	-8.00	-54.13	-7.10	-52.74
7g	-7.98	-52.11	-7.09	-55.84
7j	-7.74	-55.35	-7.56	-53.30
8d	-7.95	-56.41	-7.61	-53.84
8e	-7.40	-55.51	-7.77	-59.11
Pyrimethamine	-9.12	-40.42	-9.05	-40.38
Cycloguanil	-9.17	-40.67	-8.97	-40.24
WR99210	-9.48	-52.71	-9.62	-53.09
Dihydrofolate	-10.43	-57.71	-11.15	-67.66

Table 3: Prediction of Lipinski's rule of 5' for the most active compounds

Compounds	mol_MW (<500)	DonorHB (<5)	AccptHB (<10)	QPlogPo/w (<5)	RuleOfFive (<4)
7b	474.007	1	6	6.475	1
7d	503.048	1	8	5.494	2
7e	517.075	1	8	5.868	2
7g	488.034	1	6	6.633	1
7j	531.102	1	8	6.188	2
8d	503.048	1	8	5.289	2
8e	517.075	1	8	5.909	2
Pyrimethamine	248.71	4	3	1.82	0
Cycloguanil	251.72	4	3.5	1.63	0

Table 4: Calculated ADMET properties

Compounds	[a]Percent Human Oral Absorption (>80% high, <25% poor)	[a]QPPCaco nms^{-1} (<25 poor, >500 great)	[a]QPlogBB (-3.0-1.2)	[a]QPPMDC K(<25 poor, >500 great)	[a]QPlogKhs a(-1.5 to 1.5)	[a]PSA (7.0 – 200.0)	[a]#rotor (0 – 15)
7b	100	3065.592	-0.286	4095.553	1.184	58.60	7
7d	83.538	649.416	0.037	846.601	0.966	63.213	7
7e	86.295	699.001	0.003	916.682	1.072	62.744	8
7g	100	2893.763	-0.376	3849.357	1.237	58.62	8
7j	88.461	725.609	-0.062	954.472	1.164	62.134	9
8d	82.307	647.236	0.064	843.533	0.893	60.175	7
8e	87.42	782.858	0.047	1036.104	1.065	61.414	8
WR99210	91.09	396.41	-0.98	2171.83	-0.07	89.06	8
Pyrimethamine	84.39	412.17	-0.79	468.7	-0.24	73.73	4
Cycloguanil	84.92	507.32	-0.52	586.49	-0.22	73.49	2

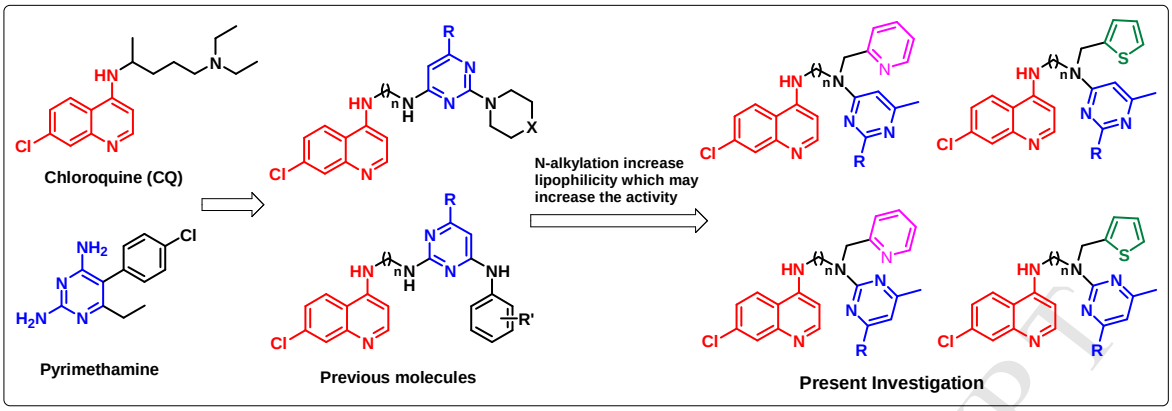


Fig. 1: Designing of 4-aminoquinoline-pyrimidine based molecular hybrids

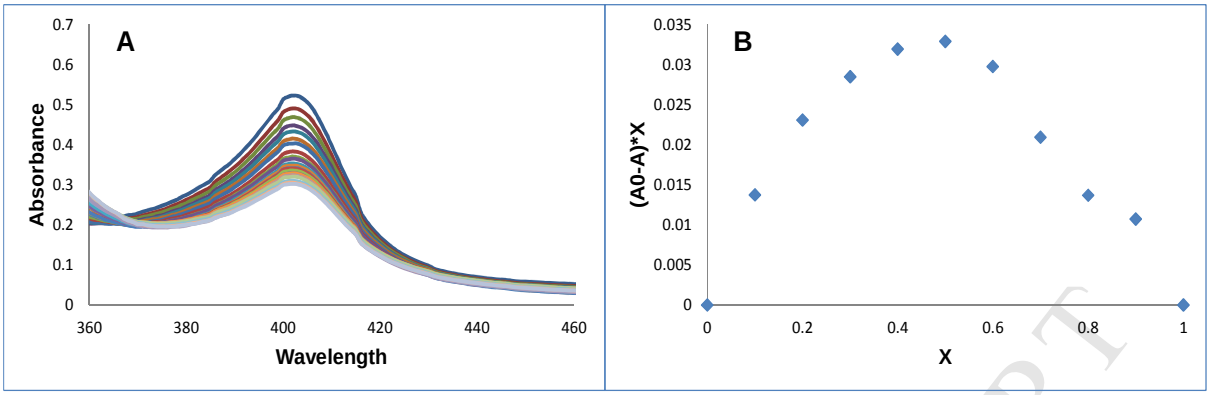


Fig. 2: A) Change in absorbance on titration of monomeric heme with compound **7d** at pH 7.4; **B)** Job's plot of monomeric heme complex formation with compound **7d** at pH 7.4; X (mole fraction of compound **7d**) = [compd. **7d**]/[compd. **7d**] + [heme]; A0 is the absorbance, when x = 1 and A is the absorbance at respective values of x**.**

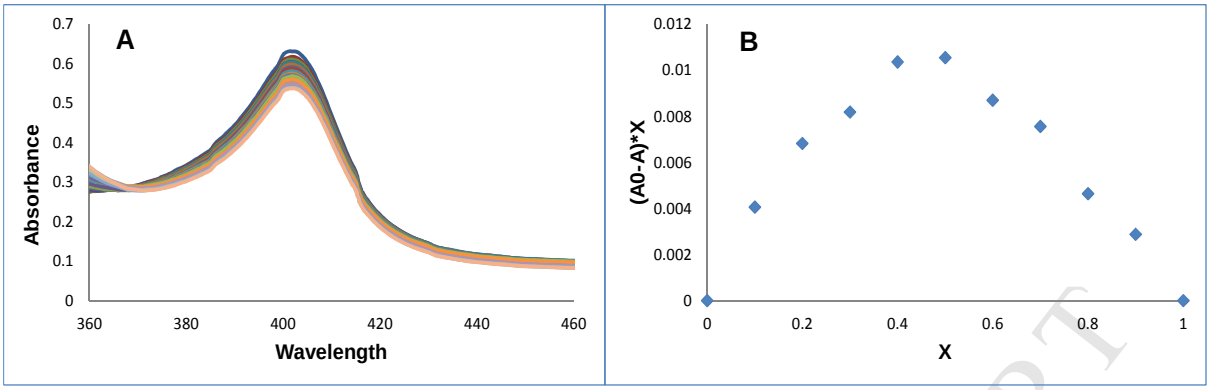


Fig. 3: A) Change in absorbance on titration of monomeric heme with compound **7d** at pH 5.6; **B)** Job's plot of monomeric heme complex formation with compound **7d** at pH 5.6.

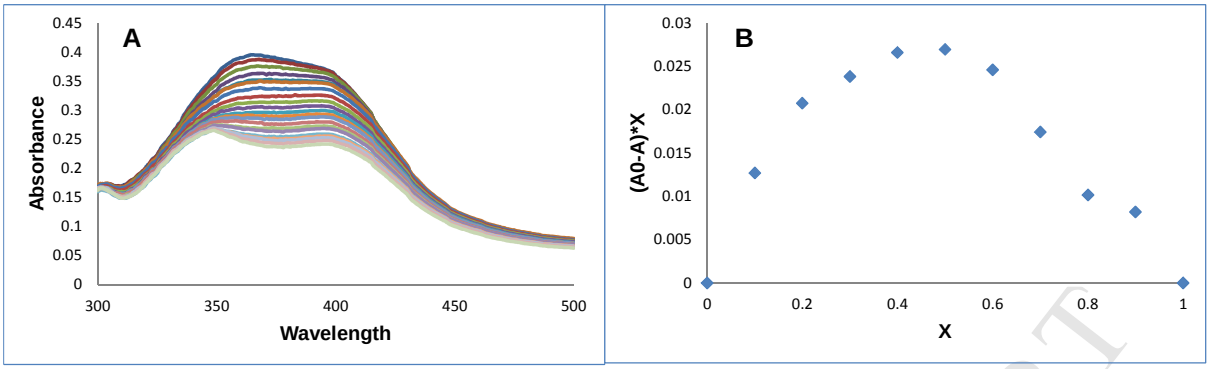


Fig. 4: A) Change in absorbance on titration of µ-oxodimericheme with compound **7d** at pH 5.8; **B)** Job's plot of µ-oxodimericheme complex formation with compound **7d** at pH 5.8.

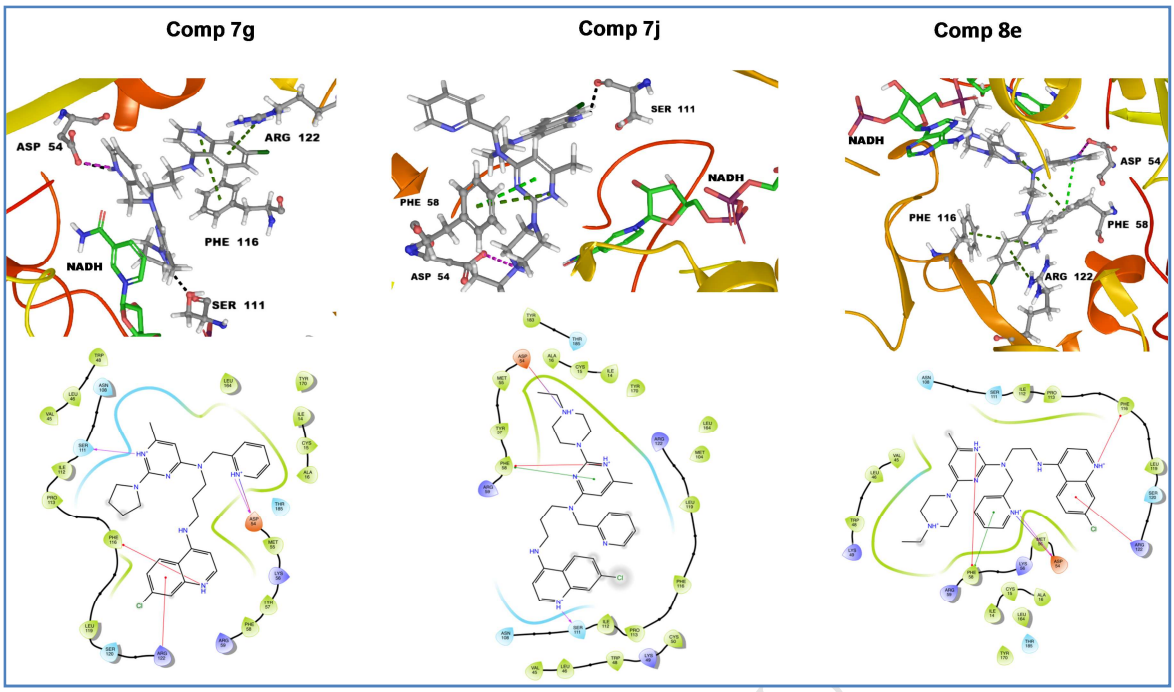


Fig. 5: 2D and 3D docking poses displaying interaction of compounds **7g**, **7j** and **8e** in the binding site of wild type *Pf*-DHFR-TS (PDB ID: 3QGT). Hydrogen bonds are shown by black dashed lines, π-π interactions by green dashed lines and salt-bridge formation by pink dashed lines.

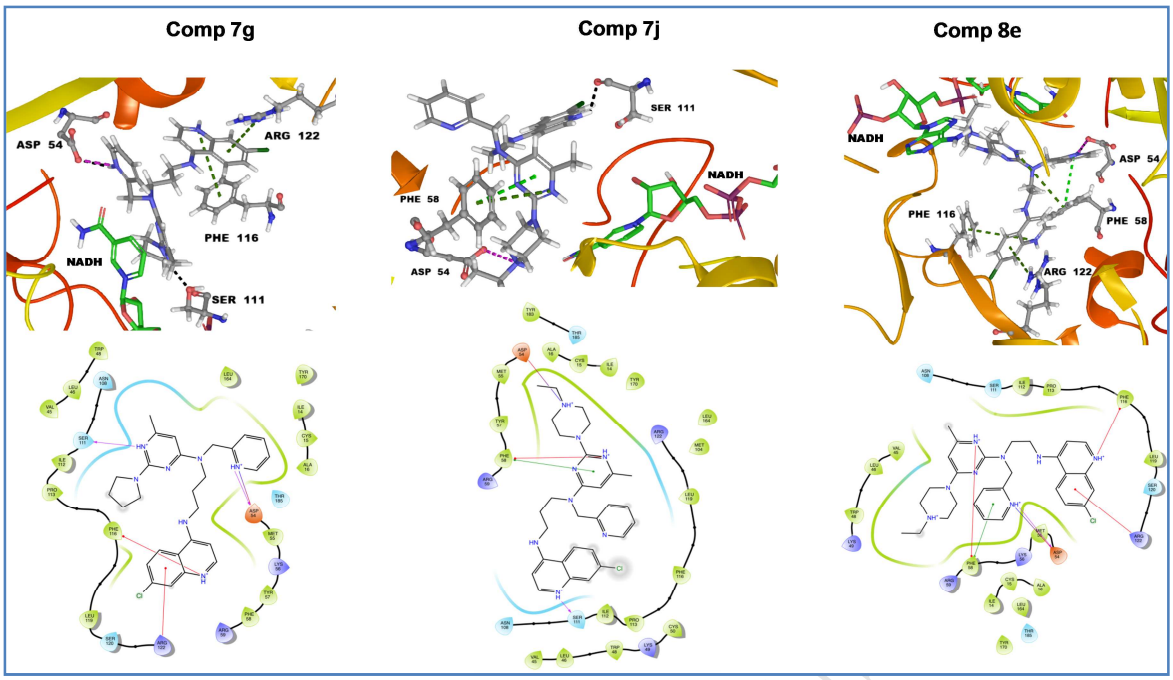
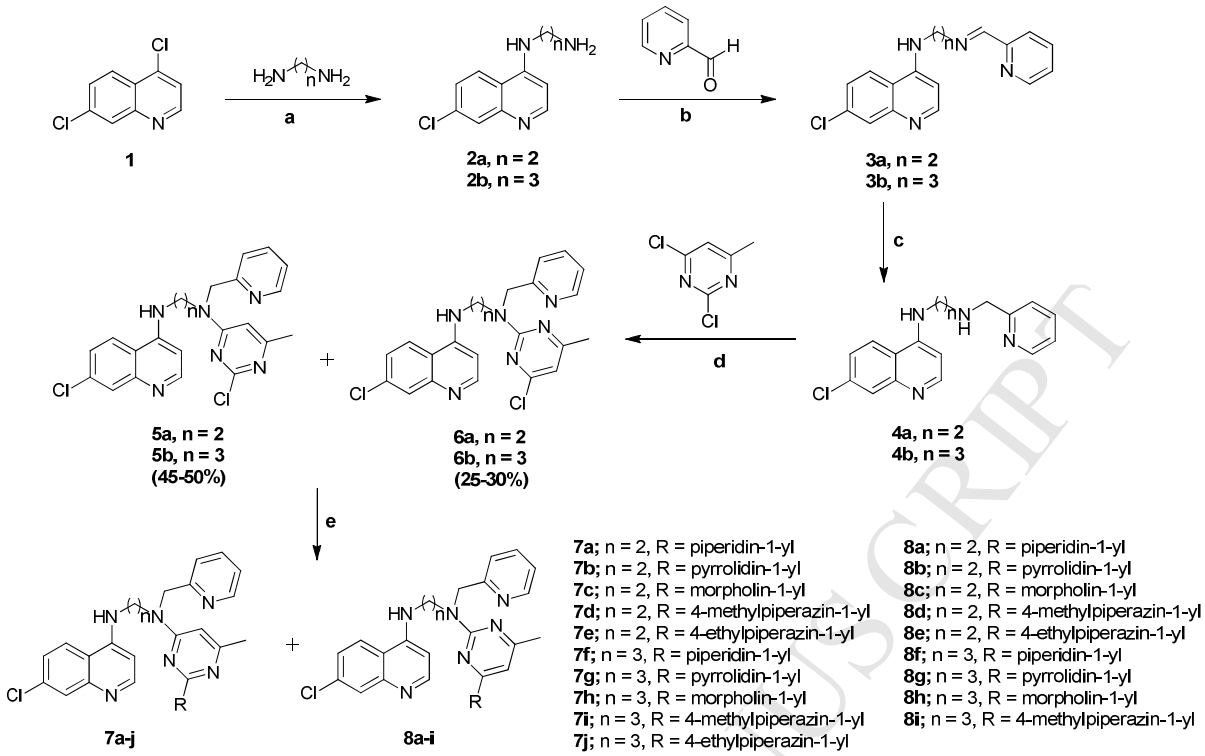
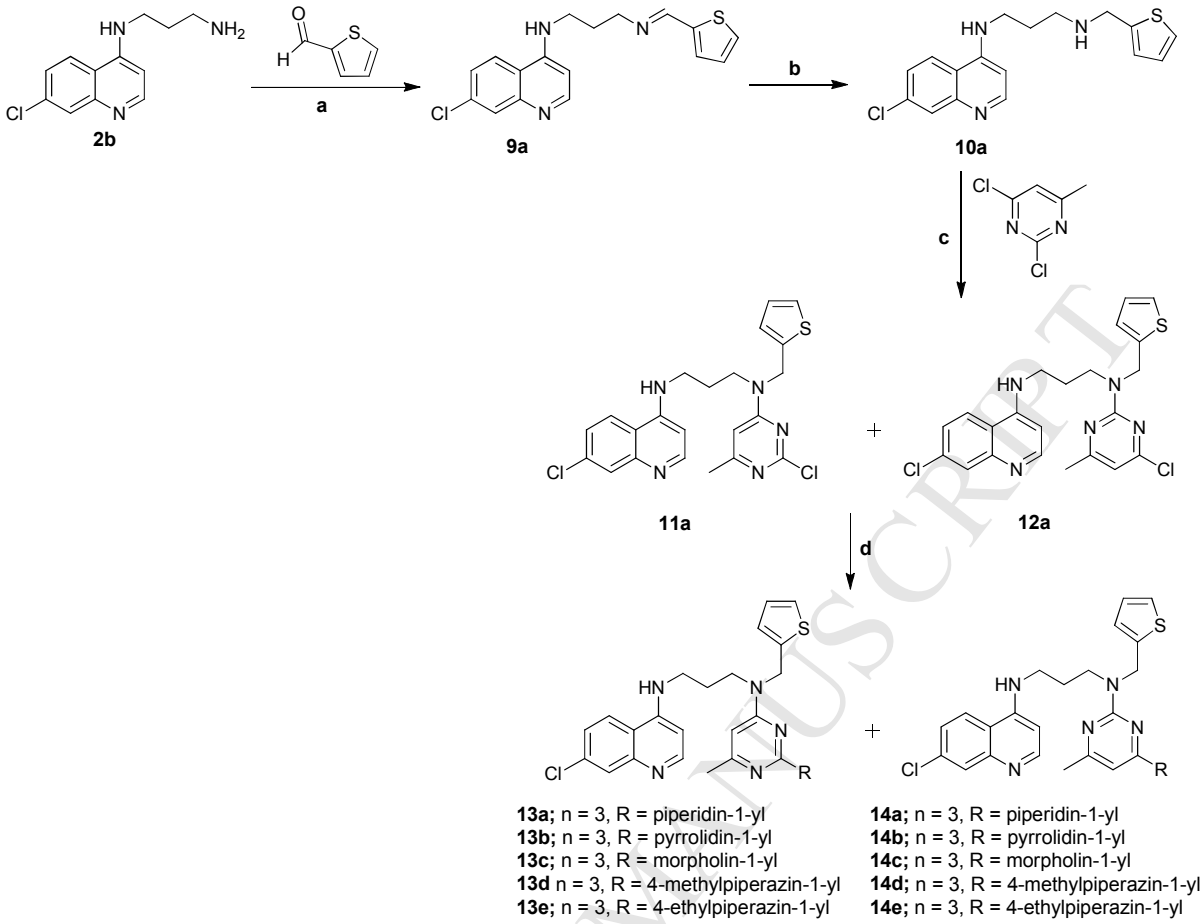


Fig. 6: 2D and 3D docking poses displaying interaction of compounds **7g**, **7j** and **8e** in the binding site of mutant type *Pf*-DHFR-TS (PDB ID: 3QG2). Hydrogen bonds are shown by black dashed lines, π-π interactions by green dashed lines and salt-bridge formation by pink dashed lines**.**



Scheme 1: (a) Neat, 110–120 ^{o}C, 5 h, 75–85%; (b) MeOH, RT, 12-16 h, 80-85%; (c) $NaBH_4$, MeOH, RT, 5-6 h, 85-88%; (d) Triethylamine, THF, 60 ^{o}C, 12 h, 70-80%; (e) Secondary amines, K_2CO_3, DMF, 120 ^{o}C, 10-12 h, 55-86%



13a; n = 3, R = piperidin-1-yl
13b; n = 3, R = pyrrolidin-1-yl
13c; n = 3, R = morpholin-1-yl
13d n = 3, R = 4-methylpiperazin-1-yl
13e; n = 3, R = 4-ethylpiperazin-1-yl

14a; n = 3, R = piperidin-1-yl
14b; n = 3, R = pyrrolidin-1-yl
14c; n = 3, R = morpholin-1-yl
14d; n = 3, R = 4-methylpiperazin-1-yl
14e; n = 3, R = 4-ethylpiperazin-1-yl

Scheme 2: (a) MeOH, RT, 12-16 h, 80 %; (b) $NaBH_4$, MeOH, RT, 5-6 h, 85 %; (c) Triethylamine, THF, 60 ^oC, 12 h, 70-80%; (d) Secondary amines, K_2CO_3, DMF, 120 ^oC, 10-12h, 55-86%.

Highlights

- A series of 4-aminoquinoline-pyrimidine based molecular hybrids was synthesized.
- Antimalarial activity against CQ-sensitive strain (D6) and CQ-resistant (W2) strain was evaluated.
- Performed heme binding and molecular docking studies.
- ADMET properties were calculated.