Chapter 2

SYNTHESIS OF 4-AMINOQUINOLINE-TRIAZOLE AND 4-AMINOQUINOLINE-TRIAZOLE-TRIAZINE HYBRIDS VIA CLICK CHEMISTRY AND EVALUATION OF THEIR ANTIMALARIAL ACTIVITY

Research Article

Synthesis of 4-aminoquinoline-1,2,3-triazole and 4-aminoquinoline-1,2,3-triazole-1,3,5-triazine Hybrids as Potential Antimalarial Agents

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2.1 Introduction

Click chemistry has played a vital role in all aspects of drug discovery including pharmaceutical polymers,\textsuperscript{1} bioconjugation strategies for proteomics,\textsuperscript{2} lead optimization through combinatorial screenings,\textsuperscript{2} generation of natural product derivatives\textsuperscript{3} and many others.\textsuperscript{4,5} The click chemistry is not limited only to drug discovery but also extended to other fields of chemistry such as nanotechnology,\textsuperscript{6} biochemistry,\textsuperscript{7} surface chemistry,\textsuperscript{8} material sciences,\textsuperscript{9} colloidal sciences\textsuperscript{10} and supramolecular chemistry\textsuperscript{11} etc. The concept of click chemistry was introduced by Sharpless and co-workers in 2001 with an aim of giving a chemical philosophy which can mimic nature’s ability of generating substances by a much easier way of joining small modular units.\textsuperscript{12} The term ‘click’ refers to reliable, facile, efficient, selective and versatile chemical transformations, which lead to a single reaction product and uses readily available insensitive starting materials. According to its inventor Dr. K. Barry Sharpless, “A click reaction must be modular, wide in scope, high yielding, create only inoffensive by-products (that can be removed without chromatography), are stereospecific, simple to perform and that require benign or easily removed solvent.”\textsuperscript{12} So, click chemistry can be defined as a bunch of powerful, virtually 100% reliable reactions for the rapid synthesis of new compounds via carbon-heteroatom (C-X-C) bond formation.

2.2 Classes of Click Reactions

Any reaction which fulfils the above given criteria of click chemistry can be considered as ‘click’ reaction. However, it is highly unlikely that any reaction can be
considered as perfect for every situation and applications. To date, four major classes of click reactions have been identified which fit the concept of ‘click’ better than others.\textsuperscript{2,12,13}

\section*{2.2.1 Nucleophilic Ring-Opening Reactions}

These include the opening of highly strained rings and heterocyclic electrophiles such as aziridines, epoxides, cyclic sulfates, cyclic sulfamidates, aziridinium ions and episulfonium ions by $S_N^2$ mechanism.\textsuperscript{12} Of these heterocycles, epoxides and aziridines are the most commonly used starting materials for click reactions and in particular, their regioselective ring opening is highly useful for the formation of diverse compound libraries.

\begin{center}
\begin{tikzpicture}
\node at (0,0) [circle, draw] (A) {$\cdot$Nu};
\node at (1,0) [circle, draw] (B) {$\cdot$H};
\node at (2,0) [circle, draw] (C) {$\cdot$Nu$_2$};
\node at (3,0) [circle, draw] (D) {$\cdot$XH};
\draw (A) edge[<->] node[above] {$X$} (B);
\draw (B) edge[<->] node[above] {$\text{Nu}$} (C);
\draw (C) edge[<->] node[above] {$\text{Nu}_2$} (D);
\end{tikzpicture}
\end{center}

$x = O, NR, SR, NR_2$

$\text{Nu} = \text{Nucleophile}$

\section*{2.2.2 ‘Non-Aldol’ Type Reactions}

Non-aldol type reactions in carbonyl compounds such as formations of ureas, thioureas, hydrazones, oxime ethers and aromatic heterocycles are considered as click reactions as they are efficient, facile and high yielding reactions.\textsuperscript{12} On the other hand, due to low thermodynamic driving force of aldol-type reactions, they are quite sluggish and give side products, and hence cannot fulfil the requirement of click reactions.

\begin{center}
\begin{tikzpicture}
\node at (0,0) [circle, draw] (A) {$\cdot$O};
\node at (1,0) [circle, draw] (B) {$R_1$};
\node at (2,0) [circle, draw] (C) {$R_2$};
\node at (3,0) [circle, draw] (D) {$\cdot$NR};
\node at (4,0) [circle, draw] (E) {$\cdot$XR$_3$};
\node at (5,0) [circle, draw] (F) {$\cdot$R$_1$};
\node at (6,0) [circle, draw] (G) {$R_2$};
\draw (A) edge[<->] node[above] {$R_3X-NH_2$} (B);
\draw (B) edge[<->] node[above] {$-\text{H}_2\text{O}$} (C);
\draw (C) edge[<->] node[above] {$\text{Nu}$} (D);
\draw (D) edge[<->] node[above] {$\text{XR}_3$} (E);
\end{tikzpicture}
\end{center}

Hydrazone/oxime ether formation
2.2.3 Carbon-Carbon Multiple Bond Addition Reactions

Oxidation reactions such as nitrosyl and sulfenyl halide additions, aziridination, epoxidation, dihydroxylation and certain Michael addition reactions of Nu-H reactants comes under this category of click reactions.

Michael addition reaction

2.2.4 Cycloaddition Reactions

1,3-Dipolar cycloadditions including hetero-Diels-Alder reactions primarily constitutes this class of click reactions. Efficient and quantitative formations of biologically relevant triazoles and tetrazoles via 1,3-dipolar cycloaddition reactions are examples of ideal click chemical reactions.

Tetrazole formation through 1,3-dipolar cycloaddition

Among the four major classifications, cycloaddition reactions, in particular, the most popular Cu (I) catalyzed intermolecular Huisgen [3+2] cycloaddition between a terminal alkyne and an azide to generate substituted 1,2,3-triazoles is of great interest as it has found tremendous applications in various facets of drug discovery. This reaction is so interesting that it has been termed as ‘cream of the crop’ of click reactions.
Copper (I) catalysed Huisgen $[3+2]$ cycloaddition

It has been found that high amount of regioselectivity$^{23,24}$ and functional group tolerance$^{21}$ is achieved in this reaction. As alkyne and azide components can be incorporated into a wide range of substituents,$^{16}$ this reaction can serve as a linking reaction to combine two distinct moieties. The formation of triazole is especially relevant for drug discovery as it has favourable physicochemical properties.$^2$ Triazoles serve as rigid linking units that are almost impossible to oxidise or reduce, cannot be easily cleaved hydrolytically; possess a large dipole moment of $\sim$5 Debye and nitrogen atoms at position 2 and 3 functions as weak hydrogen bond acceptors. These topological and electronic features are even better than nature’s ubiquitous amide connectors which are susceptible to hydrolytic cleavage.

2.3 **Mechanism of Copper (I) Catalysed Huisgen $[3+2]$ Cycloaddition Reactions**

Based on the experimental evidences, copper(I)-catalysed Huisgen $[3+2]$ cycloaddition reaction involving azide and terminal alkynes as reaction substrates is believed to proceed in a stepwise manner as shown in figure 2.1.$^{25,26}$ It is in contrary to the general cycloaddition reactions which proceed through a concerted mechanism.

Density functional theory calculations,$^{27}$ experimental kinetic data$^{28}$ and molecular modelling$^{25}$ performed on this reaction shows a preference for the stepwise addition ($A \rightarrow B \rightarrow C \rightarrow D$) rather than a concerted cycloaddition ($A \rightarrow D$) by approximately 11-15 kcal/mol (figure 2.1).$^{23}$ In the first step, Cu (I) inserts itself into
terminal alkyne in a Sonagashira type of coupling and subsequently deprotonation of terminal alkyne occurs to yield copper (I) acetylide (A). In the following step (Step 2), N(1) of azide attaches itself to the Cu of Cu-acetylide complex to form B which in-turn ‘activates’ the azide for nucleophilic attack. Now, due to close proximity and electronic factors, N(3) of azide can easily attack C(4) of alkyne to yield intriguing six-membered metallocycle C (Step 3). The metallocycle subsequently contracts to form respective 1,2,3-triazole D (Step 4) and finally protonation releases the Cu (I) catalyst from triazole D to form E (Step 5). The free Cu (I) catalyst at this stage can undergo a second catalytic cycle with different alkyne to form respective triazoles again.

![Proposed catalytic cycle of Huisgen [3 + 2] cycloaddition reaction](image)

**Figure 2.1: Proposed catalytic cycle of Huisgen [3 + 2] cycloaddition reaction**

A variety of Cu (I) catalyst like CuI, CuBr, CuOTf(C₆H₆), [Cu(NCCH₃)₄][PF₆] etc. can be used directly in this reaction but the *in-situ* generation of Cu (I) by
reducing Cu (II) salts like CuSO₄·5H₂O is generally more preferred due to cheapness and environmentally safety purposes (figure 2.1). Reducing agents like sodium ascorbate, hydrazine and tris(2-carboxyethyl)phosphine are generally used to activate Cu (II) to Cu (I).

2.4 Pharmaceutical Application of 1,2,3-Triazoles

Click chemistry has been used extensively in drug discovery and this ligation process by which two entities are linked through formation of 1,2,3-triazoles came out like a dream for medicinal chemists all over the world. Chimeric drugs bearing two distinct activities like linezolid and a macrolide or vancomycin and a cephalosporin have been synthesised successfully by this approach (figure 2.2).

Figure 2.2: Chimeric drugs containing 1,2,3-triazole moiety

Click chemistry was also used exhaustively in synthesising a range of potent drugs and agents including antifungal (1), antibacterial (2), anti-tubercular (3) and inhibitors of protein tyrosine phosphatase (4), HIV-1 proteases (5) and fucosyltransferase (6) (figure 2.3). Pharmaceutically it has been used as an efficient
reaction step for stepwise synthesis of drugs, drug modifications and drug conjugations.40-46

![Figure 2.3: Examples of potent drugs prepared via copper-catalyzed in situ click cycloaddition of azides and alkynes](image)

**2.5 Present Investigation**

During the synthesis of 4-aminoquinoline based hybrids, we screened a library of hybrids bearing 4-aminoquinoline and triazine or pyrimidine as a biologically active pharmacophores. This study resulted a unique observation which is summarized below.
Encouraged by these observations, our next goal was to synthesize 4-aminoquinoline based hybrids by keeping 4-aminoquinoline portion of the hybrids intact and modify the triazine portion by keeping three nitrogen of triazine intact but reduce the ring size from six to five. In another scheme, triazole was introduced between 4-aminoquinoline and triazine moiety. These hybrids which contain two different chemical entities in a single domain can act as a ‘dual drug’ interfering with two different targets simultaneously. The resulted 4-aminoquinoline-triazole (11-28) and 4-aminoquinoline-triazole-triazine (47-62) hybrids are further evaluated for their biological response (figure 2.4).

**Figure 2.4: Prototype structure of the compounds under present study**
2.6 Results and Discussion

The synthetic strategy consists of two parts, first was the synthesis of hybrid 4-aminoquinoline-1,2,3-triazole conjugates and the second was the synthesis of 4-aminoquinoline-1,2,3-triazole-1,3,5-triazine conjugates. The 4-aminoquinoline-1,2,3-triazole hybrids were synthesised using azides (10a-b) and alkynes as depicted in scheme 2.2. The synthesis started with the preparation of azides (10a-b) as shown in scheme 2.1. Commercially available 4,7-dichloroquinoline (7) was reacted with aminoalcohols under neat conditions that led to the formation of 4-aminoquinolines with free hydroxyl group at terminal position (8a-b) in excellent yield. The free hydroxyl group was then chemoselectively O-mesylated by literature method using mesyl chloride and triethylamine as base to yield mesylated 4-aminoquinolines (9a-b). The azidation of these mesylated products (9a-b) were then carried out using sodium azide as nucleophile and DMF as solvent at 50 °C to obtain the corresponding azides (10a-b).

![Scheme 2.1](image-url)
Finally, these azides (10a-b) were reacted with commercially available and substituted terminal alkynes to generate 1,2,3-triazoles by click chemistry using standard protocol of sodium ascorbate and copper sulfate as catalyst and an equimolar ratio of water and t-butanol as solvents to yield the final target compounds 11-28 in moderate to good yield (scheme 2.2). All of these compounds (11-28) were purified and characterized spectroscopically. FT-IR spectrum of compound 11 (figure 2.5) showed a broad absorption at 3428 cm\(^{-1}\) and a sharp absorption at 3287 cm\(^{-1}\) due to the presence of OH and NH functional groups respectively, present in the molecule. The \(^1\)H NMR spectrum of the compound 11 (figure 2.6) showed a multiplet of two protons at \(\delta\) 3.84-3.86 due to the presence of a methylene group attached to NH of quinoline moiety. A sharp singlet of two protons at \(\delta\) 4.52 showed the presence of methylene group present between the triazole ring and hydroxyl group while the methylene group attached to nitrogen of triazole ring was confirmed by the presence of a triplet of two protons at \(\delta\) 4.69. Six aromatic protons consisting of five quinoline ring protons and one triazole ring proton appeared in the aromatic region of \(\delta\) 6.51-8.31. The two broad peaks at \(\delta\) 5.15 and 8.42 were assigned to OH and NH groups respectively. The appearance of a molecular ion peak at m/z 303.5206 (M+H)\(^+\) further confirms the structure of the molecule (figure 2.7).
Figure 2.5: FT-IR spectrum of compound 11
Figure 2.6: $^1$H NMR spectrum of compound 11

Figure 2.7: Mass spectrum of compound 11
In order to draw a systematic structure activity relationship (SAR) study, our next target was to mix up three pharmacophoric groups viz aminoquinoline, triazole and triazine. So in order to achieve this goal, we started our work with the synthesis of substituted triazines (40-46). Triazole ring was chosen as a linker because of its favourable basicity and physiochemical properties and it can help in increasing the bioavailability of the drug as the improved basicity is needed for these molecules to accumulate more in the acidic food vacuole of the parasite to exhibit enhanced antimalarial activity. The synthesis of substituted triazines (40-46) started with the nucleophilic substitution of three chlorine atom of the cyanuric chloride (29) in a temperature controlled stepwise manner as shown in scheme 2.3. Nucleophilic substitution by various aromatic and aliphatic amines on cyanuric chloride at 0 °C in the presence of a base afforded mono-substituted 1,3,5-triazines (30-34) in major yields which were purified and characterized spectroscopically. In the FT-IR spectrum of compound 32 (figure 2.8), absorption at around 3291 cm\(^{-1}\) shows the presence of NH functionality. Due to symmetrical structure of the molecule, \(^1\)H NMR of compound 32 (figure 2.9) shows four signals in all. A sharp singlet of six protons at \(\delta\) 3.83 showed the presence of two methoxy groups attached to phenyl ring. Two symmetrical aromatic protons attached at ortho position of NH group appeared as a singlet at \(\delta\) 6.77 while the aromatic proton flanked by two methoxy groups appears as a singlet at \(\delta\) 6.32. The NH proton appeared as a broad peak at \(\delta\) 7.47. The \(^{13}\)C NMR (figure 2.10) shows seven peaks in all. Two methoxy carbons appeared at \(\delta\) 55.4 while all the aromatic carbon of phenyl ring and triazine ring appeared at \(\delta\) 97.5, 99.4, 99.5, 137.3, 161.1 and 163.9 respectively.
Figure 2.8: FT-IR spectrum of compound 32
Figure 2.9: $^1$H NMR spectrum of compound 32

Figure 2.10: $^{13}$C NMR spectrum of compound 32
These mono-substituted 1,3,5-triazines (30-34) were further subjected to nucleophilic substitution by propargyl alcohol at room temperature to give di-substituted 1,3,5-triazines (35-39; scheme 2.3), which were purified by column chromatography. The structures of these compounds (35-39) were further confirmed by IR, $^1$H and $^{13}$C NMR spectroscopy. FT-IR spectrum of compound 37 (figure 2.11) shows an absorption at 3307 cm$^{-1}$ due to the presence of NH group in the molecule. $^1$H NMR of compound 37 (figure 2.12) shows six signals in all. A triplet of one proton at $\delta$ 2.54 was assigned to acetyllinic proton while singlet of six protons at $\delta$ 3.81 was assigned to two methoxy groups attached to phenyl ring. A doublet of two protons appearing at $\delta$ 5.03 was assigned to methylene group attached to triple bond. Aromatic proton, para to NH group appeared as a triplet at $\delta$ 6.29 while the other two symmetrical aromatic protons, ortho to NH group appeared as a singlet at $\delta$ 6.80. The NH proton appeared as a broad peak at $\delta$ 7.41. In the $^{13}$C NMR of compound 37 (figure 2.13), two methoxy carbons appeared as a single peak at $\delta$ 55.4 while the methylene carbon attached to triple bond appeared at $\delta$ 55.6. The peak at $\delta$ 76.6 was assigned to terminal acetyllinic carbon while the peak at $\delta$ 78.0 was assigned to triple bond carbon attached to methylene group. Seven aromatic carbons appeared at $\delta$ 96.9, 99.2, 99.3, 138.2, 161.0, 165.0 and 165.1 respectively.
Figure 2.11: FT-IR spectrum of compound 37

Figure 2.12: $^1$H NMR spectrum of compound 37
Finally, the di-substituted 1,3,5-triazines (35-39) were subjected to third round of nucleophilic substitution by different primary and secondary aliphatic amines at room temperature in THF as solvent to afford tri-substituted triazines 40-46 (scheme 2.3). All the compounds were purified over silica gel column and characterized by FT-IR, $^1$H and $^{13}$C NMR spectroscopy. FT-IR spectrum of compound 40 shows absorption at 3304 cm$^{-1}$ (figure 2.14) due to presence of NH functionality in the molecule. In the $^1$H NMR of compound 40 (figure 2.15), acetyllinic proton appears as a triplet at $\delta$ 2.47 while methylene protons attached to acetyllinic carbon comes as a doublet at $\delta$ 4.95. Two triplets at $\delta$ 3.72 and $\delta$ 3.85 of four protons each were assigned to methylene groups attached to ‘N’ and ‘O’ of morpholine ring respectively. Aromatic proton para to NH group appeared as a triplet at $\delta$ 6.20 while the other two symmetrical aromatic protons ortho to NH group appeared as a singlet at $\delta$ 6.81. The
NH proton appeared as a broad peak at δ 7.04. $^{13}$C NMR showed twelve peaks in all (figure 2.16). Two peaks at δ 43.8 and δ 66.5 of two carbons each were assigned to methylene groups attached to ‘N’ and ‘O’ of morpholine ring respectively while the methylene carbon attached to acetyllinic carbon appeared at δ 54.1. Two methoxy carbons attached to phenyl ring appeared at δ 55.2. Peak appearing at δ 74.7 and δ 78.2 were assigned to carbon of triple bond. All the aromatic protons of phenyl ring and triazine ring appeared at δ 95.4, 98.3, 140.1, 160.8, 165.0 and 165.8.

Figure 2.14: FT-IR spectrum of compound 40
Figure 2.15: $^1$H NMR spectrum of compound 40

Figure 2.16: $^{13}$C NMR spectrum of compound 40
The 4-aminoquinoline-triazole-triazine hybrids were synthesised by the click reaction of azides (10a-b) and alkynes (35, 36, 38, 40-46) (scheme 2.4) using standard protocol as discussed in scheme 2.2. All of these compounds (47-62) were characterized spectroscopically. FT-IR spectrum of compound 47 (figure 2.17) showed an absorption at 3393 cm\(^{-1}\) which was assigned to the NH group present in the molecule. In the \(^1\)H NMR spectrum of compound 47 (figure 2.18), 16 aliphatic protons consisting four methylene groups of morpholine ring, one methylene group attached to NH of quinoline ring and two methoxy groups appeared as a multiplet between \(\delta\) 3.40-3.82. Two \(CH_2\) protons attached to nitrogen of triazole ring appeared at \(\delta\) 4.66 as a triplet while two \(CH_2\) protons attached between oxygen and triazole ring appeared as a singlet at \(\delta\) 5.35. Peaks between \(\delta\) 6.12-8.23 were assigned for aromatic protons of quinoline and phenyl ring. This region also includes peak of two NH protons present in the molecule. The peak arising at \(\delta\) 9.50 as a singlet was assigned to triazolyl proton. The appearance of a molecular ion peak at m/z 619.2375 (M+H\(^+\)) further confirms the structure of the molecule (figure 2.19).
Figure 2.17: FT-IR spectrum of compound 47

Figure 2.18: $^1$H NMR spectrum of compound 47
2.7 Antimalarial Activity Evaluation

The antimalarial activity was determined by measuring plasmodial LDH activity as described earlier. A suspension of red blood cells infected with D6 or W2 strain of *P. falciparum* (200 µL, with 2% parasitemia and 2% hematocrit in RPMI 1640 medium supplemented with 10% human serum and 60 µg/mL amikacin) was added to the wells of a 96-well plate containing 10 µL of serially diluted test samples. The plate was flushed with a gas mixture of 90% N₂, 5% O₂, and 5% CO₂ and incubated at 37 °C for 72 h in a modular incubation chamber (Billups-Rothenberg Inc., Del Mar, CA, USA). Parasitic LDH activity was determined according to the procedure of Makler and Hinrichs. Briefly, 20 µL of the incubation mixture was mixed with 100 µL of the Malstat™ reagent (Flow Inc., Portland, OR, USA) and incubated at room temperature for 30 min. Twenty microliters of a 1:1 mixture of...
NBT / PES (Sigma, St Louis, MO, USA) was then added, and the plate is further incubated in the dark for 1 h. The reaction was then stopped by the addition of 100 µL of a 5% acetic acid solution. The plate was read at 650 nm. Artemisinin and chloroquine were included in each assay as antimalarial drug controls. IC₅₀ values were computed from the dose–response curves. To determine the selectivity index of antimalarial activity of compounds, their *in vitro* cytotoxicity to mammalian cells was also determined. The assay was performed in 96-well tissue culture–treated plates as described earlier.⁴⁹ Vero cells (monkey kidney fibroblasts) were seeded to the wells of 96-well plate at a density of 25000 cells/well and incubated for 24 h. Samples at different concentrations were added and plates were again incubated for 48 h. The number of viable cells was determined by Neutral Red assay. IC₅₀ values were obtained from dose-response curves. Doxorubicin was used as a positive control for cytotoxicity.

*In-vitro* antimalarial activity of compounds **11-28** (table 2.1) and **47-62** (table 2.2) was determined against chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of *P. falciparum*, while the cytotoxicity was determined against Vero cell line. Among the series of eighteen 4-aminoquinoline-triazole hybrids **11-28**, simple aliphatic analogues containing polar hydroxy group (**11, 12, 25, 26**) displayed mild to moderate activity against both strains of *P. falciparum*. The protection of hydroxyl group by THP group (**13**) did not enhance the activity, but incorporation of aryl groups (**13-24, 27, 28**) gave a clear drift toward rise in activity. Among these compounds, with aryl groups having halogen (**14-17, IC₅₀ ranging from 1.28 to 1.55 µM**) and alkyl (**18-21, IC₅₀ ranging from 1.39 to 2.63 µM**) side chains at different positions of the aromatic ring exhibited similar activity profile. Interestingly,
introduction of COCH$_3$ functionality at para position of aromatic ring (23 and 27) improved antimalarial activity against both CQ-sensitive and CQ-resistant strains with IC$_{50}$ values of 0.91-0.65 µM and 1.12-1.25 µM, respectively, with an increase in selectivity index. Changing the phenyl ring to biphenyl moiety (24 and 28) also improves antimalarial activity. The antimalarial activity profile of these compounds clearly demonstrates that compounds with C-3 spacer (25-28) showed better antimalarial activity than their C-2 counterparts (11-24). This trend may be due to the increase in lipophilicity as we move from C-2 spacer to C-3 spacer. Another set of compounds having three pharmacophore together (47-62) showed a similar trend of increase in activity with increasing length of carbon spacer. Introduction of basic moieties like piperidine, morpholine and dimethylamine (47-59) in place of chloro group (60-62) boosts up the activity. This is in accordance with the fact that basic side chain at the terminal position of 4-aminoquinolines is important for better activity. Among this series of analogues, compound 56 (having 2,6-dimethyl anilino and dimethyl amino moiety attached at 4 and 6 position of triazine nucleus) was the most active analogue exhibiting IC$_{50}$ of 0.58 µM against D6 strain and 0.73 µM against W2 strain of *P. falciparum*. The substitution of 2,6-dimethyl anilino group at 4 position (56) with less lipophilic 3,5-dimethoxy anilino group (55) leads to a decrease in activity. Substitution of both the position of triazine nucleus with aliphatic moieties (51, 52, 58, 60) also leads to further decrease in activity with an exception of compound 63 that showed moderate activity. All the compounds (11-28 and 47-62) were found to be non-cytotoxic up to 12 µM concentration to Vero cells, indicating their safety toward mammalian cells.
Table 2.1: *In-vitro* antimalarial activity and cytotoxicity of 4-aminoquinoline-triazole hybrids (11-28)

<table>
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<tr>
<th>Comp.</th>
<th>cLogP*</th>
<th>P. falciparum (D6 Clone)</th>
<th>P. falciparum (W2 Clone)</th>
</tr>
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<tr>
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<td>IC&lt;sub&gt;50&lt;/sub&gt;&lt;sup&gt;1&lt;/sup&gt;/IC&lt;sub&gt;50&lt;/sub&gt;&lt;sup&gt;2&lt;/sup&gt; (µM)</td>
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<td>S.I.§</td>
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<td>1.77</td>
<td>6.58/7.90 7.24/9.69</td>
<td>&gt;2.4</td>
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<td>3.79</td>
<td>6.45/6.72 6.58/7.65</td>
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<td>5.50</td>
<td>1.39/1.41 1.40/1.45</td>
<td>&gt;7.4</td>
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<td>Comp.</td>
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<td>P. falciparum (D6 Clone)</td>
<td>P. falciparum (W2 Clone)</td>
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Chloroquine  
0.04  >300  0.42  >30  
Artemisinin  
0.03  >500  0.025 >670

<sup>a</sup>cLogP: Calculated by ChemBioDraw 11 Software, Cambridge, MA, USA.  
<sup>1</sup>Mean: Mean of IC<sub>50</sub><sup>1</sup> and IC<sub>50</sub><sup>2</sup>  
<sup>§</sup>S.I.: Selectivity index (IC<sub>50</sub> for cytotoxicity/IC<sub>50</sub> for antimalarial activity).  
All the compounds did not showed any toxicity against Vero cells upto 12 µM.
### Table 2.2: *In-vitro* antimalarial activity and cytotoxicity of 4-aminoquinoline-triazole-triazine hybrids (52-67)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>cLogP&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P. falciparum (D6 Clone)</th>
<th>P. falciparum (W2 Clone)</th>
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<tr>
<td></td>
<td>IC50&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Mean&lt;sup&gt;1&lt;/sup&gt; + SEM</td>
<td>IC50&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>n</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;</td>
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<td>Chloroquine</td>
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<td>Artemisinin</td>
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</tbody>
</table>

<sup>a</sup>cLogP: Calculated by ChemBioDraw 11 Software, Cambridge, MA, USA.

<sup>1</sup>Mean: Mean of IC<sub>50</sub><sup>1</sup> and IC<sub>50</sub><sup>2</sup>

<sup>3</sup>S.I.: Selectivity index (IC<sub>50</sub> for cytotoxicity / IC<sub>50</sub> for antimalarial activity)

All the compounds did not showed any toxicity against Vero cells upto 12 µM
The activity pattern clearly indicate that lipophilicity plays an important role in driving the activity profile of these conjugates (figure 2.20) which is in agreement with the literature observation that higher cLogP values are essential for better antimalarial activity.\textsuperscript{50}

![Graph showing cLogP vs Plasmodium falciparum activity](image.png)

**Figure 2.20:** cLogP vs *P. falciparum* activity plot showing the dependence of lipophillic character

The structure activity relationship (SAR) inferred from the activity pattern of synthesised 4-aminoquinoline-triazole and 4-aminoquinoline-triazine-triazole hybrids are summarized in figure 2.21. The SAR clearly indicates that 4-aminoquinoline on attachment with triazine results in improvement of activity while activity drops when three nitrogen and aromaticity of triazine ring is kept intact but size of the ring is decreased to five membered (4-aminoquinoline-triazole hybrids). On attaching these 4-aminoquinoline-triazoles to triazines, the activity improves marginally. To our surprise,
when one nitrogen of triazine from 4-aminoquinoline-triazine was removed by CH₃, the resulting 4-aminoquinoline-pyrimidine hybrids demonstrated 2-25 fold better in vitro activity than CQ, without any toxicity. In vivo results were more encouraging as two of the compounds showed much better activity that standard drug CQ (chapter 1).

Figure 2.21: Structure activity relationship (SAR) of synthesised 4-aminoquinoline-triazole and 4-aminoquinoline-triazine-triazole hybrids

2.8 Experimental Section

2.8.1 Instrumentation and chemicals

All of the chemicals used in the synthesis were purchased from Sigma-Aldrich and were used as such. Thin layer chromatography was used to monitor the progress of the reactions and checked by precoated TLC plates (E. Merck Kieselgel 60 F$_{254}$) with spots being visualized by iodine vapours. Compounds were purified over silica gel (60-120 mesh) column or crystallized with suitable solvents. Solvents were distilled before using for purification purposes. Melting points were recorded on an
ERS automated melting point apparatus and are uncorrected. IR spectra were recorded using Perkin-Elmer spectrophotometer and the values are expressed as $\lambda_{\text{max}}$ cm$^{-1}$. Mass spectral data were recorded on a Jeol-AccuTOF JMS-T100LC and micromass LCT Mass Spectrometer/Data system. Elemental analyses were performed on Carlo Erba Model EA-1108 elemental analyser and data of C, H and N is within ± 0.4 of calculated values. $^1$H NMR spectra were recorded on Bruker and Jeol Spectrospin spectrometer at 300 MHz and 400 MHz respectively as indicated while $^{13}$C NMR spectra were recorded on Bruker and Jeol Spectrospin spectrometer at 75.5 and 100 MHz respectively using TMS as an internal standard. The chemical shift values are recorded on $\delta$ scale and the coupling constants ($J$) are in Hz.

**2.8.2 Synthesis and Characterization of Compounds**

**Typical procedure: Synthesis of 2-((7-chloroquinolin-4-yl)amino)ethanol (8a) and related compound (8b)**

In a round bottom flask, a mixture of 4,7-dichloroquinoline (5.0 g, 25.2 mmol) (7) and ethanolamine (7.71 g, 126.2 mmol) was slowly heated to 130-150 °C under N$_2$ atmosphere for 10-12 h (scheme 2.1). After completion, ice was added to the reaction mixture and it was stored in the refrigerator for 1 h. The precipitate thus formed was filtered, washed with cold water (500 mL) and dried. The crude product thus obtained was recrystallized by hot ethyl acetate to get pale brown solid of compound 8a. Yield: 90%; mp: 219-221 °C [Lit. 220-222 °C].

3-((7-Chloroquinolin-4-yl)amino)propan-1-ol (8b): Yield: 80%; mp: 215-216 °C [Lit. 214 °C].
Typical procedure: Synthesis of 2-((7-chloroquinolin-4-yl)amino)ethyl methanesulfonate (9a) and related compound (9b)

In a round bottom flask, a mixture of compound 8a (2.0 g, 8.9 mmol) (7) and triethylamine (1.81 g, 17.8 mmol) in 50 ml dry THF was stirred for 10-15 min at 0 °C. After that, methane sulphonyl chloride (2.05 g, 17.8 mmol) in THF (10 mL) was added to the reaction mixture slowly by dropping funnel. Once addition was complete, reaction mixture was allowed to stir at 0 °C for 30 mins followed by stirring at room temperature for 1 h (scheme 2.1). After completion of reaction as evident by TLC, a saturated solution of NaHCO$_3$ (50 mL) was added to reaction mixture and it was extracted with CHCl$_3$ (2 × 25 mL). The combined organic layer was washed with water (3 × 200 mL) and finally with brine. The organic layer was dried on Na$_2$SO$_4$, filtered and excess of solvent was removed under vacuum. The crude residue thus obtained was purified over SiO$_2$ column using MeOH/CHCl$_3$ as eluent to afford light brown solid compound 9a. Yield: 75%; mp: 135-137 °C [Lit. 138-140 °C].$^{53}$

3-((7-Chloroquinolin-4-yl)amino)propyl methanesulfonate (9b): Yield: 80%; mp: 123-125 °C [Lit. 124-126 °C].$^{54}$

Typical procedure: Synthesis of N-(2-azidoethyl)-7-chloroquinolin-4-amine (10a) and related compound (10b)

Compound 9a (1.0 g, 3.3 mmol) was dissolved in 10 ml DMF and NaN$_3$ (1.08 g, 16.6 mmol) was added. The reaction mixture was allowed to stir at 50-60 °C for 4-5 h (scheme 2.1). After completion of reaction as evident by TLC, 50 ml of ice cold water was added to reaction mixture. The precipitate thus formed was filtered, washed, dried and finally recrystallized with ethanol to get white crystalline solid of compound 10a. Yield: 90%; mp: 143-145 °C [Lit. 145-147 °C].$^{51}$
N-(3-Azidopropyl)-7-chloroquinolin-4-amine (10b): Yield: 80%; mp: 148-151 °C; IR (KBr, cm⁻¹): 3220 (NH), 3065, 2960, 2100 (N³), 1578, 1451, 1370, 1283, 1140, 1079; ¹H NMR (400 MHz, DMSO-d₆) δ: 1.94-2.00 (m, 2H, CH₂CH₂CH₂), 3.40 (q, J = 8.0 Hz, 2H, CH₂N₃), 4.86 (t, J = 8.0 Hz, 2H, CH₂N₃), 5.47 (brs, 1H, NH), 6.37 (d, J = 4.0 Hz, 1H, ArH), 7.30 (d, J = 8.0 Hz, 1H, ArH), 7.66 (d, J = 8.0 Hz, 1H, ArH), 7.91 (s, 1H, ArH), 8.48 (d, J = 4.0 Hz, 1H, ArH); ¹³C NMR (100 MHz, DMSO-d₆) δ: 27.75, 40.85, 49.51, 98.91, 117.14, 121.06, 125.39, 128.51, 134.92, 148.91, 149.61, 151.82; ESI-MS (m/z): 261.82 (M+H)⁺, 263.77 (M+2)⁺; Anal. Calcd for C₁₂H₁₂ClN₅: C, 55.07; H, 4.62; N, 26.76. Found: C, 55.17; H, 4.65; N, 26.78.

Typical procedure: Synthesis of {1-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-1H-[1,2,3]triazol-4-yl}-methanol (11) and related compounds (12-28)

To a stirred solution of compound 10a (0.25 g, 1 mmol) and propargyl alcohol (0.06 g, 1.07 mmol) in t-BuOH (8 mL), a solution of sodium ascorbate (0.08 g, 0.40 mmol) and CuSO₄·5H₂O (0.05 g, 0.20 mmol) in water (8 mL) was added. Reaction mixture was heated at 40 °C for 3 h (scheme 2.2). After the completion of reaction, CHCl₃ (20 mL) was added, and organic layer was washed with water (2 × 100 mL). The organic layer was dried over Na₂SO₄, and excess of solvent was evaporated to dryness, and the crude material thus obtained was purified by SiO₂ column using MeOH/CHCl₃ as eluent. The title compound 11 was obtained in 70% yield. mp: 200-202 °C; IR (KBr, cm⁻¹): 3428 (OH), 3287 (NH), 3114, 2841, 1591, 1384, 1040, 806; ¹H NMR (300 MHz, DMSO-d₆) δ: 3.84-3.86 (m, 2H, NHCH₂CH₂), 4.52 (s, 2H, CH₂OH), 4.69 (t, J = 6.0 Hz, 2H, NHCH₂CH₂), 5.15 (brs, 1H, OH), 6.58 (d, J = 5.7 Hz, 1H, ArH), 7.46 (d, J = 9.0 Hz, 1H, ArH), 7.84 (s, 1H, ArH), 7.65-7.98 (m, 2H, ArH), 8.29 (d, J = 9.0 Hz, 1H, ArH), 8.42 (brs, 1H, NH); ESI-HRMS (m/z): 303.5206
1-{1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1H-[1,2,3]triazol-4-yl}-cyclohexanol (12): Yield: 65%; mp: 188-190 °C; IR (KBr, cm⁻¹): 3400 (OH), 3254 (NH); ¹H NMR (300 MHz, DMSO-d₆) δ: 1.24-1.83 (m, 10H, 5 × cyclohexyl-CH₂), 3.78-3.83 (m, 2H, NH-CH₂-CH₂), 4.64 (t, J = 6.0 Hz, 2H, NH-CH₂-CH₂), 4.80 (brs, 1H, OH), 6.46 (d, J = 5.7 Hz, 1H, ArH), 7.38-7.52 (m, 2H, ArH), 7.77-7.82 (m, 2H, ArH), 8.16-8.19 (m, 1H, ArH), 8.39 (brs, 1H, NH); ¹³C NMR (100 MHz, DMSO-d₆) δ: 21.7, 25.3, 37.8, 42.7, 47.8, 67.9, 98.6, 116.8, 121.8, 124.7, 124.8, 125.1, 134.9, 145.7, 148.9, 151.7, 155.6; ESI-MS (m/z): 372.44 (M+H)⁺, 374.40 (M+2)⁺; Anal. Calcd for C₁₉H₂₂ClN₅O: C, 61.37; H, 5.96; N, 18.83. Found: C, 61.32; H, 6.18; N, 18.96.

(7-Chloro-quinolin-4-yl)-{2-[4-(tetrahydro-pyran-2-ylloxymethyl)-[1,2,3]triazol-1-yl]-ethyl}-amine (13): Yield: 68%; mp: 162-165 °C; IR (KBr, cm⁻¹): 3246 (NH), 2941, 2870, 1578, 1451, 1331, 1032, 873; ¹H NMR (400 MHz, DMSO-d₆) δ: 1.40-1.64 (m, 6H), 3.70-3.77 (m, 4H), 4.44-4.64 (m, 5H), 6.54 (d, J = 5.7 Hz, 1H, ArH), 7.43-7.45 (m, 2H, ArH), 7.79 (s, 1H, ArH), 8.07 (s, 1H, ArH), 8.14 (d, J = 9.0 Hz, 1H, ArH), 8.40 (brs, 1H, NH); ¹³C NMR (100 MHz, DMSO-d₆) δ: 18.9, 24.9, 29.9, 42.4, 47.7, 59.4, 61.2, 96.8, 99.1, 117.6, 123.9, 124.3, 124.5, 127.6, 133.5, 143.8, 149.1, 149.6, 151.8; ESI-MS (m/z): 388.22, (M+H)⁺, 390.13 (M+2)⁺; Anal. Calcd for C₁₉H₂₂ClN₅O₂: C, 58.84; H, 5.72; N, 18.06. Found: C, 58.88; H, 5.76; N, 18.20.

{2-[4-(4-Bromo-phenoxymethyl)-[1,2,3]triazol-1-yl]-ethyl}-(7-chloro-quinolin-4-yl)-amine (14): Yield: 75%; mp: 155-157 °C; IR (KBr, cm⁻¹): 3228 (NH), 3069, 2924, 1579, 1488, 1244, 1140, 823; ¹H NMR (300 MHz, DMSO-d₆) δ: 3.76-3.78 (m, 2H,
NHCH₂(CH₂)₂, 4.65 (t, J = 6.0 Hz, 2H, NHCH₂CH₂), 5.09 (s, 2H, CH₂OAr), 6.54 (d, J = 5.7 Hz, 1H, ArH), 6.95 (d, J = 9.0 Hz, 2H, ArH), 7.39-7.46 (m, 4H, ArH), 7.80 (d, J = 5.7 Hz, 1H, ArH), 8.15 (d, J = 9.0 Hz, 1H, ArH), 8.23 (s, 1H, ArH), 8.40 (brs, 1H, NH); ESI-MS (m/z): 460.25 (M+H)⁺, 462.31 (M+2)⁺; Anal. Calcd for C₂₀H₁₇BrClN₅O: C, 52.36; H, 3.74; N, 15.27. Found: C, 52.72; H, 3.84; N, 15.39.

{2-[4-(4-Chloro-phenoxymethyl)-[1,2,3]triazol-1-yl]-ethyl}-(7-chloro-quinolin-4-yl)-amine (15): Yield: 71%; mp: 154-156 °C; IR (KBr, cm⁻¹): 3241 (NH), 3063, 2928, 1578, 1491, 1239, 1006, 826; ¹H NMR (300 MHz, DMSO-δ₆) δ: 3.78-3.80 (m, 2H, NHCH₂(CH₂)₂), 4.65 (t, J = 6.0 Hz, 2H, NHCH₂CH₂), 5.09 (s, 2H, CH₂OAr), 6.55 (d, J = 5.7 Hz, 1H, ArH), 7.01 (d, J = 9.0 Hz, 2H, ArH), 7.28 (d, J = 9.0 Hz, 2H, ArH), 7.44-7.57 (m, 2H, ArH), 7.80 (d, J = 5.7 Hz, 1H, ArH), 8.17 (d, J = 9.0 Hz, 1H, ArH), 8.23 (s, 1H, ArH), 8.42 (brs, 1H, NH); ¹³C NMR (100 MHz, DMSO-δ₆) δ: 42.4, 47.9, 61.3, 99.9, 116.4, 120.5, 124.1, 124.5, 125.2, 127.1, 128.8, 129.2, 133.8, 142.3, 150.1, 151.3, 156.8; ESI-MS (m/z): 414.99 (M+H)⁺, 416.37 (M+2)⁺; Anal. Calcd for C₂₀H₁₇Cl₂N₅O: C, 57.98; H, 4.14; N, 16.90. Found: C, 58.05; H, 4.19; N, 16.98.

(7-Chloro-quinolin-4-yl){2-[4-(2,6-dichlorophenoxymethyl)-[1,2,3]triazol-1-yl]-ethyl}-amine (16): Yield: 65%; mp: 198-201 °C; IR (KBr, cm⁻¹): 3237 (NH), 3036, 2928, 1584, 1446, 12449, 1060, 788; ¹H NMR (300 MHz, DMSO-δ₆) δ: 3.77-3.78 (m, 2H, NHCH₂(CH₂)₂), 4.67 (t, J = 6.0 Hz, 2H, NHCH₂CH₂), 5.07 (s, 2H, CH₂OAr), 6.58 (d, J = 5.7 Hz, 1H, ArH), 7.11-7.17 (m, 1H, ArH), 7.42-7.46 (m, 4H, ArH), 7.79 (d, J = 5.7 Hz, 1H, ArH), 8.15 (d, J = 9.0 Hz, 1H, ArH), 8.32 (s, 1H, ArH), 8.42 (brs, 1H, NH); ¹³C NMR (100 MHz, DMSO-δ₆) δ: 42.5, 47.8, 66.1, 99.2, 117.7, 124.1, 124.4, 125.6, 126.3, 127.5, 128.8, 129.3, 133.6, 142.1, 148.83, 149.76, 150.12, 151.76; ESI-
MS (m/z): 448.27 (M+H)+, 450.28 (M+2)+, 452.28 (M+4)+; Anal. Calcd for C20H16Cl3N5O: C, 53.53; H, 3.59; N, 15.61. Found: C, 53.65; H, 3.47; N, 15.74.

{2-[4-(4-Chloro-3-methyl-phenoxymethyl)-[1,2,3]triazol-1-yl]-ethyl}-(7-chloroquinolin-4-yl)-amine (17): Yield: 58%; mp: 170-172 °C; IR (KBr, cm⁻¹): 3252 (NH), 3064, 2963, 1578, 1479, 1245, 1172, 1043, 801; ¹H NMR (300 MHz, DMSO-d₆) δ: 2.25 (s, 3H, CH₃), 3.76-3.78 (m, 2H, NHCH₂CH₂), 4.64 (t, J = 6.0 Hz, 2H, NHCH₂CH₂), 5.07 (s, 2H, NHCH₂OAr), 6.54 (d, J = 5.7 Hz, 1H, ArH), 6.82-6.85 (m, 1H, ArH), 7.25 (d, J = 9.0 Hz, 1H, ArH), 7.43-7.45 (m, 2H, ArH), 7.78 (d, J = 5.7 Hz, 1H, ArH), 8.13 (d, J = 9.0 Hz, 1H, ArH), 8.22 (s, 1H, ArH), 8.40 (brs, 1H, NH); ¹³C NMR (100 MHz, DMSO-d₆) δ: 19.8, 42.4, 47.9, 61.3, 98.9, 113.8, 117.4, 123.9, 124.4, 124.8, 125.1, 127.6, 129.5, 133.5, 136.5, 142.4, 149.1, 149.7, 151.8, 156.8; ESI-MS (m/z): 428.88 (M+H)+, 430.86 (M+2)+; Anal. Calcd for C21H19Cl2N5O: C, 58.89; H, 4.47; N, 16.35. Found: C, 58.93; H, 4.55; N, 16.68.

(7-Chloro-quinolin-4-yl)-[2-(4-p-tolyloxymethyl-[1,2,3]triazol-1-yl)-ethyl]-amine (18): Yield: 75%; mp: 172-174 °C; IR (KBr, cm⁻¹): 3245 (NH), 3137, 2927, 1577, 1511, 1236, 1014, 806; ¹H NMR (300 MHz, DMSO-d₆) δ: 2.18 (s, 3H, CH₃), 3.76-3.78 (m, 2H, NHCH₂CH₂), 4.64 (t, J = 6.0 Hz, 2H, NHCH₂CH₂), 5.03 (s, 2H, CH₂OAr), 6.54 (d, J = 5.7 Hz, 1H, ArH), 6.85 (d, J = 9.0 Hz, 2H, ArH), 7.03 (d, J = 9.0 Hz, 2H, ArH), 7.43-7.53 (m, 2H, ArH), 7.79 (d, J = 5.7 Hz, 1H, ArH), 8.15 (d, J = 9.0 Hz, 1H, ArH), 8.21 (s, 1H, ArH), 8.40 (brs, 1H, NH); ¹³C NMR (100 MHz, DMSO-d₆) δ: 20.1, 42.8, 47.9, 61.1, 98.8, 114.5, 124.1, 124.5, 124.9, 127.3, 129.5, 129.8, 133.7, 142.9, 148.6, 148.8, 149.9, 151.6, 155.9; ESI-MS (m/z): 428.88 (M+H)+, 430.86 (M+2)+; Anal. Calcd for C21H20ClN5O: C, 58.04; H, 5.12; N, 17.78. Found: C, 64.10; H, 5.21; N, 17.99.
(7-Chloro-quinolin-4-yl)-[2-(4-m-tolyloxymethyl-[1,2,3]triazol-1-yl)-ethyl]-amine (19): Yield: 72%; mp: 140-142 °C; IR (KBr, cm\(^{-1}\)): 3235 (NH), 3058, 2924, 1579, 1542, 1243, 1160, 1046, 805; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\): 2.23 (s, 3H, CH\(_3\)), 3.77-3.79 (m, 2H, NHCH\(_2\)CH\(_2\)), 4.65 (t, \(J = 6.0\) Hz, 2H, NHCH\(_2\)CH\(_2\)), 5.06 (s, 2H, CH\(_2\)OAr), 6.54 (d, \(J = 5.7\) Hz, 1H, ArH), 6.71-7.14 (m, 4H, ArH), 7.43-7.45 (m, 2H, ArH), 7.79 (d, \(J = 5.7\) Hz, 1H, ArH), 8.15 (d, \(J = 9.0\) Hz, 1H, ArH), 8.22 (s, 1H, ArH), 8.39 (brs, 1H, NH); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\): 21.1, 42.4, 47.9, 60.9, 99.1, 111.6, 114.5, 115.3, 121.6, 123.9, 124.4, 124.9, 127.6, 129.2, 129.8, 135.6, 139.1, 142.8, 149.7, 151.9, 158.1; ESI-MS (m/z): 394.54 (M+H\(^+\)), 396.22 (M+2\(^+\)); Anal. Calcd for C\(_{21}\)H\(_{20}\)ClN\(_5\)O: C, 64.04; H, 5.12; N, 17.78. Found: C, 63.95; H, 5.23; N, 17.86.

(7-Chloro-quinolin-4-yl)-{2-[4-(3,4-dimethylphenoxymethyl)-[1,2,3]triazol-1-yl]-ethyl}-amine (20): Yield: 75%; mp: 168-170 °C; IR (KBr, cm\(^{-1}\)): 3237 (NH), 2970, 1578, 1544, 1625, 1167, 1047, 800; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\): 2.12 (s, 3H, CH\(_3\)), 2.16 (s, 3H, CH\(_3\)), 3.76-3.82 (m, 2H, NHCH\(_2\)CH\(_2\)), 4.66 (t, \(J = 6.0\) Hz, 2H, NHCH\(_2\)CH\(_2\)), 5.04 (s, 2H, CH\(_2\)OAr), 6.56 (d, \(J = 5.7\) Hz, 1H, ArH), 6.68-6.78 (m, 2H, ArH), 6.99 (d, \(J = 9.0\) Hz, 1H, ArH), 7.44-7.49 (m, 2H, ArH), 7.81 (d, \(J = 5.7\) Hz, 1H, ArH), 8.16 (d, \(J = 9.0\) Hz, 1H, ArH), 8.22 (s, 1H, ArH), 8.41 (brs, 1H, NH); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\): 18.4, 19.6, 42.4, 47.8, 61.0, 98.8, 111.5, 116.0, 120.2, 123.9, 124.4, 124.9, 127.5, 128.3, 130.1, 133.6, 137.3, 142.9, 148.9, 149.7, 151.8, 158.1; ESI-MS (m/z): 408.11 (M+H\(^+\)), 410.02 (M+2\(^+\)); Anal. Calcd for C\(_{22}\)H\(_{22}\)ClN\(_5\)O: C, 64.04; H, 5.12; N, 17.17. Found: C, 63.95; H, 5.81; N, 17.24.

(7-Chloro-quinolin-4-yl)-{2-[4-(4-isopropylphenoxymethyl)-[1,2,3]triazol-1-yl]-ethyl}-amine (21): Yield: 69%; mp: 196-198 °C; IR (KBr, cm\(^{-1}\)): 3228 (NH), 2970, 1580, 1546, 1241, 1013, 837; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\): 1.11 (d, 6H, 2 ×...
(7-Chloro-quinolin-4-yl)-{2-[4-(4-nitrophenoxymethyl)-[1,2,3]triazol-1-yl]-ethyl}-amine (22): Yield: 65%; mp: 112-114 °C; IR (KBr, cm\(^{-1}\)): 3348 (NH), 3109, 2924, 1588, 1496, 1342, 1258, 1112, 848; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\): 3.79-3.81 (m, 2H, NHCH\(_2\)CH\(_2\)), 4.67 (t, \(J = 6.0\) Hz, 2H, NHCH\(_2\)CH\(_2\)), 5.27 (s, 2H, CH\(_2\)OAr), 6.54 (d, \(J = 5.7\) Hz, 1H, ArH), 7.19 (d, \(J = 8.0\) Hz, 2H, ArH), 7.48-7.50 (m, 2H, ArH), 7.78-7.81 (m, 2H, ArH), 8.15-8.27 (m, 4H, ArH, NH); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\): 42.6, 47.9, 61.8, 79.0, 114.9, 115.3, 124.7, 124.6, 125.0, 125.6, 125.8, 126.9, 134.2, 140.9, 141.7, 150.3, 163.2; ESI-MS (m/z): 426.11 (M+H), 458.32 (M+2); Anal. Calcd for C\(_{20}\)H\(_{17}\)ClN\(_6\)O\(_3\): C, 56.54; H, 4.03; N, 19.78. Found: C, 56.91; H, 4.22; N, 19.85.

1-(4-{1-[(2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-phenyl)-ethanone (23): Yield: 63%; mp: 194-196 °C; IR (KBr, cm\(^{-1}\)): 3225 (NH), 3066, 2923, 1669 (C=O), 1578, 1249, 1179, 841; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\): 2.51 (s, 3H, COCH\(_3\)), 3.77-3.78 (m, 2H, NHCH\(_2\)CH\(_2\)), 4.65 (t, \(J = 6.0\) Hz, 2H, NHCH\(_2\)CH\(_2\)), 5.20 (s, 2H, CH\(_2\)OAr), 6.53 (d, \(J = 5.7\) Hz, 1H, ArH), 7.09 (d, \(J = 9.0\) Hz, 2H, ArH), 7.43-7.60 (m, 2H, ArH), 7.79 (s, 1H, ArH), 7.90 (d, \(J = 9.0\) Hz, 2H,
\[(7\text{-Chloro-quinolin-4-yl})\{2-[4-(naphthalen-2-yloxymethyl)-[1,2,3]\text{triazol-1-yl]-ethyl\}\-amine (24): \text{Yield}: 55\%; \text{mp}: 90-92^\circ C; \text{IR (KBr, cm}^{-1}\text{)}: 3253 (\text{NH}), 3057, 2925, 1578, 1451, 1367, 1214, 1009, 809; ^1\text{H NMR (300 MHz, DMSO-}d_6\text{)} \delta: 3.78-3.79 \text{ (m, 2H, }NH\text{CH}_2\text{CH}_2\text{CH}_2\text{)}, 4.65 (t, J = 6.0 Hz, 2H, NHCH}_2\text{CH}_2\text{)}, 5.19 (s, 2H, }CH_2\text{OAr), 6.56 (d, J = 5.7 Hz, 1H, ArH), 7.10-7.12 \text{ (m, 1H, ArH), 7.29-7.32 \text{ (m, 1H, ArH), 7.39-7.44 \text{ (m, 3H, ArH), 7.68-7.79 \text{ (m, 5H, ArH), 8.17 \text{ (d, J = 9.0 Hz, 1H, ArH), 8.29 \text{ (s, 1H, ArH), 8.40 \text{ (brs, 1H, NH); ESI-MS (m/z): 430.20 (M+H)}^+\text{, 432.24 (M+2)}^+; Anal. Calcd for C_{24}H_{20}ClN_5O: C, 67.05; H, 4.69; N, 16.29. Found: C, 67.15; H, 4.70; N, 16.31.}\]

\{1-[3-(7-Chloro-quinolin-4-ylamino)-propyl]-[1H]-[1,2,3]\text{triazol-4-yl}-methanol (25): \text{Yield}: 72\%; \text{mp}: 152-154^\circ C; \text{IR (KBr, cm}^{-1}\text{)}: 3350 (\text{OH and NH merging}), 3067, 2923, 1586, 1372, 1141, 1051, 797; ^1\text{H NMR (400 MHz, DMSO-}d_6\text{)} \delta: 2.20-2.22 \text{ (m, 2H, CH}_2\text{CH}_2\text{CH}_2\text{)}, 3.40-3.56 \text{ (m, 2H, NHCH}_2\text{CH}_2\text{)}, 4.48-4.60 \text{ (m, 4H), 5.17 \text{ (brs, 1H, OH), 6.51 \text{ (d, J = 5.7 Hz, 1H, ArH), 7.50-7.52 \text{ (m, 1H, ArH), 7.78-7.82 \text{ (m, 2H, ArH), 8.02 \text{ (s, 1H, ArH), 8.32-8.42 \text{ (m, 2H, ArH, NH); ESI-MS (m/z): 318.26 (M+H)}^+\text{, 320.13 (M+2)}^+; Anal. Calcd for C_{15}H_{16}ClN_5O: C, 56.69; H, 5.08; N, 22.04. Found: C, 56.82; H, 4.92; N, 22.25.}\]

1-[1-[3-(7-Chloro-quinolin-4-ylamino)-propyl]-[1H]-[1,2,3]\text{triazol-4-yl}-cyclohexanol (26): \text{Yield}: 70\%; \text{mp}: 158-160^\circ C; \text{IR (KBr, cm}^{-1}\text{)}: 3309, 2932, 1582, 1450, 1332, 1138, 807; ^1\text{H NMR (400 MHz, DMSO-}d_6\text{)} \delta: 1.11-1.83 \text{ (m, 10H, cyclohexyl-CH}_2\text{),
2.21-2.23 (m, 2H, CH$_2$CH$_2$CH$_2$), 3.31-3.38 (m, 2H, NHCH$_2$CH$_2$), 4.48 (t, $J = 6.0$ Hz, 2H, NHCH$_2$CH$_2$), 4.82 (brs, 1H, O$H$), 6.53 (d, $J = 5.7$ Hz, 1H, Ar$H$), 7.52-7.54 (m, 1H, Ar$H$), 7.82-8.05 (m, 4H, Ar$H$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 21.7, 25.3, 28.5, 31.3, 37.8, 47.1, 67.9, 98.6, 117.2, 121.2, 14.1, 124.7, 125.5, 134.5, 146.6, 149.5, 151.2, 155.7; ESI-MS (m/z): 386.55 (M+H)$^+$, 388.40 (M+2)$^+$. Anal. Calcd for C$_{20}$H$_{24}$ClN$_5$O: C, 62.25; H, 6.27; N, 18.15. Found: C, 62.41; H, 6.36; N, 18.10.

1-(4-{1-[3-(7-Chloro-quinolin-4-ylamino)-propyl]-1H-[1,2,3]triazol-4-ylmethoxy}phenyl)-ethanone (27): Yield: 67%; mp: 160-162 $^\circ$C; IR (KBr, cm$^{-1}$): 3213 (NH), 3063, 2956, 1674 (C=O), 1580, 1573, 1356, 1261, 1176, 836; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 2.51 (s, 3H, COCH$_3$), 2.21-2.26 (m, 2H, CH$_2$CH$_2$CH$_2$), 3.30-3.34 (m, 2H, NHCH$_2$CH$_2$), 4.54 (t, $J = 6.0$ Hz, 2H, NHCH$_2$CH$_2$), 5.25 (s, 2H, CH$_2$OAr), 6.47 (d, $J = 5.7$ Hz, 1H, Ar$H$), 7.15 (d, $J = 9.0$ Hz, 2H, Ar$H$), 7.49-7.56 (m, 2H, Ar$H$), 7.81 (d, $J = 5.7$ Hz, 1H, Ar$H$), 7.94 (d, $J = 9.0$ Hz, 2H, Ar$H$), 8.29-8.33 (m, 2H, Ar$H$), 8.45 (brs, 1H, N$H$); ESI-MS (m/z): 436.37 (M+H)$^+$, 438.11 (M+2)$^+$. Anal. Calcd for C$_{23}$H$_{22}$ClN$_5$O$_2$: C, 63.37; H, 5.09; N, 16.07. Found: C, 63.35; H, 5.11; N, 16.20.

(7-Chloro-quinolin-4-yl)-{3-[4-(naphthalen-2-yloxymethyl)-[1,2,3]triazol-4-ylmethoxy]propyl}-amine (28): Yield: 70%; mp: 164-166 $^\circ$C; IR (KBr, cm$^{-1}$): 3258 (NH), 3063, 2956, 1674 (C=O), 1580, 1567, 1368, 1214, 1179, 808; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 2.23-2.31 (m, 2H, CH$_2$CH$_2$CH$_2$), 3.31-3.39 (m, 2H, NHCH$_2$CH$_2$), 4.57 (t, $J = 6.0$ Hz, 2H, NHCH$_2$CH$_2$), 5.28 (s, 2H, CH$_2$OAr), 6.48 (d, $J = 5.7$ Hz, 1H, Ar$H$), 7.19-7.22 (m, 1H, Ar$H$), 7.35-7.39 (m, 1H, Ar$H$), 7.46-7.57 (m, 4H, Ar$H$), 7.80-7.86 (m, 4H, Ar$H$), 8.31 (d, $J = 9.0$ Hz, 1H, Ar$H$), 8.37 (s, 1H, Ar$H$), 8.41 (brs, 1H, N$H$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 42.5, 47.9, 61.2, 99.1, 107.1, 118.7, 123.7, 124.2, 124.7, 125.2, 126.5,
Typical procedure: Synthesis of (4,6-dichloro-[1,3,5]triazin-2-yl)-phenyl-amine (30) and related compounds (31-34)

To a stirred suspension of cyanuric chloride (29; 5 g, 27.1 mmol) and K$_2$CO$_3$ (6.83 g, 81.3 mmol) in 30 mL THF, aniline (2.52 g, 27 mmol) was added slowly at 0 °C. The reaction mixture was stirred at 0-5 °C for 2-3 h (scheme 2.3). After completion of reaction, K$_2$CO$_3$ was removed by filtration and excess of solvent was removed under vacuum. The crude product thus obtained was dissolved in 100 mL CHCl$_3$ and washed with water (2 x 200 mL) and finally with brine. The CHCl$_3$ layer was dried over Na$_2$SO$_4$, and after removal of solvent, residue was purified over SiO$_2$ column using EtOAc:Hexane as an eluent to yield compound 30 as white solid. Yield: 82%; mp: 193-195 °C [Lit 196 °C].

(4,6-Dichloro-[1,3,5]triazin-2-yl)-(2,6-dimethylphenyl)-amine (31): Yield: 85%; mp: 192-194 °C; IR (KBr, cm$^{-1}$): 3221 (NH), 2958, 1609, 1556, 1518, 1398, 1201, 1017; $^1$H NMR (300 MHz, CDCl$_3$) δ: 2.23 (s, 6H, 2 × CH$_3$), 7.12-7.23 (m, 3H, Ar H), 7.63 (brs, 1H, NH); ESI-MS (m/z): 240.10 (M+H)$^+$, 242.28 (M+2)$^+$; Anal. Calcd for C$_{11}$H$_{10}$Cl$_2$N$_4$: C, 49.09; H, 3.75; N, 20.82 Found: C, 49.11; H, 3.81; N, 20.84.

(4,6-Dichloro-[1,3,5]triazin-2-yl)-(3,5-dimethoxyphenyl)-amine (32): Yield: 85%; mp: 188-190 °C; IR (KBr, cm$^{-1}$): 3291 (NH), 2926, 1631, 1548, 1391, 1175, 1071; $^1$H NMR (300 MHz, CDCl$_3$) δ: 2.38 (s, 6H, 2 × CH$_3$), 6.32 (s, 1H, Ar H), 6.77 (s, 2H, Ar H), 7.47 (brs, 1H, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): 55.4, 97.5, 99.4, 99.5, 137.38, 161.18, 163.99; ESI-MS (m/z): 302.56 (M+H)$^+$, 304.54 (M+2)$^+$, 306.55
Cyclopropyl-(4,6-dichloro-[1,3,5]triazin-2-yl)-amine (33): Yield: 80%; mp: 111-112 °C; IR (KBr, cm\(^{-1}\)): 3257 (NH), 2918, 1744, 1594, 1555, 1500, 1351, 1163, 850; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 0.52-1.00 (m, 4H, CH\(_2\)CH\(_2\)), 2.70-3.00 (m, 1H, CH); 5.25 (brs, 1H, NH); ESI-MS (m/z): 204.66 (M+H\(^+\)), 206.68 (M+2); Anal. Calcd for C\(_6\)H\(_6\)Cl\(_2\)N\(_4\): C, 35.15; H, 2.95; N, 27.32. Found: C, 35.37; H, 3.05; N, 27.28.

4-(4,6-Dichloro-1,3,5-triazin-2-yl)morpholine (34): Yield: 80%; mp: 156-158 °C [Lit. 154-156 °C].\(^{56}\)

Typical procedure: Synthesis of (4-chloro-6-prop-2-ynyloxy-[1,3,5]triazin-2-yl)-phenyl-amine (35) and related compounds (36-39)

Propargyl alcohol (0.46 g, 8.2 mmol) was added slowly to a suspension of (4,6-dichloro-[1,3,5]triazin-2-yl)-phenyl-amine (30; 2 g, 8.2 mmol) in 20 mL THF at room temperature followed by K\(_2\)CO\(_3\) (3.43 g, 24.8 mmol). Reaction mixture was allowed to stir at room temperature for 3-4 h (scheme 2.3). The progress of reaction was monitored by thin layer chromatography. After completion, the reaction mixture was filtered and excess of solvent was evaporated under vacuum. The residue was dissolved in 50 mL CHCl\(_3\), and organic layer was washed with water (2 \times 200 mL). The chloroform layer was dried over anhydrous Na\(_2\)SO\(_4\), and excess of solvent was removed under vacuum to give crude product that was purified over SiO\(_2\) column using EtOAc:Hexane as eluent. The title compound 35 was obtained as a white solid. Yield: 51%; mp: 115-118 °C; IR (KBr, cm\(^{-1}\)): 3350 (NH), 3277, 1607, 1572, 1547, 1436, 1333, 1019; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 2.54 (s, 1H, CH), 5.00 (d, \(J = 2.5\) Hz, 2H, CH\(_2\)), 7.15-7.59 (m, 5H, ArH), 7.65 (brs, 1H, NH); ESI-MS (m/z): 260.95
4-aminoquinoline-triazole antimalarial activity

Chapter 2

(M+H)$^+$, 262.30 (M+2)$^+$; Anal. Calcd for C$_{12}$H$_9$ClN$_4$O: C, 55.29; H, 3.48; N, 21.49. Found: C, 54.98; H, 3.44; N, 21.52.

(4-Chloro-6-prop-2-ynyloxy-[1,3,5]triazin-2-yl)-(2,6-dimethyl-phenyl)-amine (36): Yield: 54%; mp: 126-128 °C; IR (KBr, cm$^{-1}$): 3304 (NH), 3226, 2956, 1601, 1576, 1457, 1337, 1017; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 2.23 (s, 6H, 2 × CH$_3$), 2.52 (t, $J = 6.0$ Hz, 1H, CH), 4.99 (d, $J = 2.5$ Hz, 2H, CH$_2$), 7.10-7.16 (m, 3H, ArH), 7.46 (brs, 1H, NH); ESI-MS (m/z): 288.89 (M+H)$^+$, 290.22 (M+2)$^+$; Anal. Calcd for C$_{14}$H$_{13}$ClN$_4$O: C, 58.24; H, 4.54; N, 19.40. Found: C, 58.34; H, 4.60; N, 19.38.

(4-Chloro-6-prop-2-ynyloxy-[1,3,5]triazin-2-yl)-(3,5-dimethoxy-phenyl)-amine (37): Yield: 58%; mp: 130-133 °C; IR (KBr, cm$^{-1}$): 3307 (NH), 2925, 1634, 1576, 1456, 1335, 1164; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 2.54 (t, $J = 6.0$ Hz, 1H, CH), 3.81 (s, 6H, 2 × OCH$_3$), 5.03 (d, $J = 2.5$ Hz, 2H, CH$_2$), 6.29 (d, $J = 6.0$ Hz, 2H, ArH), 6.80 (s, 1H, ArH), 7.41 (brs, 1H, NH); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 55.4, 55.6, 76.6, 78.0, 96.9, 99.2, 99.3, 138.2, 161.0, 165.0, 165.1; ESI-MS (m/z): 320.78 (M+H)$^+$, 322.18 (M+2)$^+$; Anal. Calcd for C$_{14}$H$_{13}$ClN$_4$O$_3$: C, 52.43; H, 4.09; N, 17.47. Found: C, 52.38; H, 4.10; N, 17.55.

(4-Chloro-6-prop-2-ynyloxy-[1,3,5]triazin-2-yl)-cyclopropyl-amine (38): Yield: 50%; mp: 120-122 °C; IR (KBr, cm$^{-1}$): 3258 (NH), 3142, 2940, 1625, 1570, 1519, 1335, 1011; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 0.53-0.64 (m, 2H), 0.85-0.89 (m, 2H), 2.51 (t, $J = 6.0$ Hz, 1H, CH), 2.79-2.89 (m, 1H, CH/NNH), 5.02 (d, $J = 2.5$ Hz, 2H, CH$_2$O), 5.97 (brs, 1H, NH); ESI-MS (m/z): 224.32 (M+H)$^+$, 226.11 (M+2)$^+$; Anal. Calcd for C$_9$H$_9$ClN$_4$O: C, 48.12; H, 4.04; N, 24.94. Found: C, 48.22; H, 4.21; N, 24.99.

4-(4-Chloro-6-(prop-2-ynyloxy)-1,3,5-triazin-2-yl)morpholine (39): Yield: 55%; mp: 130-132 °C; IR (KBr, cm$^{-1}$): 3300 (NH), 2963, 2867, 1585, 1502, 1343, 11283,
Typical procedure: Synthesis of N-(3,5-dimethoxyphenyl)-4-morpholino-6-(prop-2-ynyloxy)-1,3,5-triazin-2-amine (40) and related compounds (41-46)

To a solution of compound 37 (0.5 g, 1.5 mmol) in THF (20 mL), morpholine (0.40 g, 4.5 mmol) was added. Reaction mixture was stirred at room temperature for 4 h (scheme 2.3). After the completion of reaction, CHCl₃ (20 mL) was added and organic layer was washed with water (2 × 100 mL). The organic layer was dried over Na₂SO₄, and excess of solvent was evaporated to dryness, and the crude material thus obtained was purified by SiO₂ column using EtOAc / Hexane as eluent. The title compound 40 was obtained in 86% yield. mp: 139-142 °C; IR (KBr, cm⁻¹): 3306 (NH), 2938, 1595, 1563, 1412, 1203, 1151, 807; ¹H NMR (400 MHz, CDCl₃) δ: 2.47 (t, J = 6.0 Hz, 1H, CH), 3.72 (t, 4H, CH₂OCH₂), 3.78 (s, 6H, 2 × OCH₃), 3.85 (t, 4H, CH₂NCH₂), 4.94 (d, J = 2.5 Hz, 2H, CH₂OAr); 6.19-6.20 (m, 1H, ArH), 6.80-6.82 (m, 2H, ArH), 7.12 (brs, 1H, NH); ¹³C NMR (100 MHz, CDCl₃) δ: 43.8, 54.1, 55.2, 66.5, 74.7, 78.2, 95.4, 98.3, 98.4, 140.1, 160.8, 165.0, 165.8; ESI-MS (m/z): 370.85 (M+H)⁺; Anal. Calcd for C₁₈H₂₁N₅O₄: C, 58.15; H, 5.76; N, 18.92. Found: C, 58.21; H, 5.70; N, 18.86.

N₂-(3,5-Dimethoxyphenyl)-N₄,N₄-dimethyl-6-(prop-2-ynyloxy)-1,3,5-triazine-2,4-diamine (41): Yield: 88%; mp: 148-150 ⁰C; IR (KBr, cm⁻¹): 3281 (NH), 3127, 2934, 1598, 1548, 1410, 1151, 831; ¹H NMR (400 MHz, CDCl₃) δ: 2.47 (t, J = 6.0 Hz, 1H, CH), 3.17-3.19 (m, 6H, 2 × CH₃), 3.77 (s, 6H, 2 × OCH₃), 4.95 (d, J = 2.5 Hz, 2H,
N-(2,6-Dimethylphenyl)-4-morpholino-6-(prop-2-ynloxy)-1,3,5-triazin-2-amine (42): Yield: 90%; mp: 158-161 °C; IR (KBr, cm\(^{-1}\)): 3227 (NH), 2920, 2852, 1552, 1501, 1409, 1114, 808; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 2.32 (s, 6H, \(2 \times CH_3\)), 2.32-2.46 (m, 1H, CH), 3.49-3.81 (m, 8H), 4.93 (d, \(J = 2.5\) Hz, 2H, \(CH_2OAr\)), 6.76 (brs, 1H, NH), 7.07-7.10 (m, 3H, ArH); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 18.6, 43.7, 54.0, 66.6, 74.6, 78.3, 126.7, 127.9, 134.6, 135.8, 136.2, 165.6, 165.8, 169.5; ESI-MS (m/z): 340.86 (M+H)\(^+\); Anal. Calcd for C\(_{18}\)H\(_{21}\)N\(_5\)O\(_2\): C, 63.70; H, 6.24; N, 20.64. Found: C, 63.98; H, 6.26; N, 20.44.

N2-(2,6-Dimethylphenyl)-N4,N4-dimethyl-6-(prop-2-ynloxy)-1,3,5-triazine-2,4-diamine (43): Yield: 85%; mp: 166-168 °C; IR (KBr, cm\(^{-1}\)): 3184 (NH), 2928, 1581, 1502, 1406, 1111, 807; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 2.23 (s, 6H, \(2 \times CH_3\)), 2.36-2.45 (m, 1H, CH), 3.09-3.15 (m, 6H, \(2 \times OCH_3\)), 4.95 (d, \(J = 2.5\) Hz, 2H, \(CH_2OAr\)), 6.29 (brs, 1H, NH), 7.05-7.11 (m, 3H, ArH); ESI-MS (m/z): 298.58 (M+H)\(^+\); Anal. Calcd for C\(_{16}\)H\(_{19}\)N\(_5\)O: C, 64.63; H, 6.44; N, 23.55. Found: C, 64.60; H, 6.21; N, 23.58.

N-Butyl-4-morpholino-6-(prop-2-yn-1-yloxy)-1,3,5-triazin-2-amine (44): Yield: 88%; mp: 135-137 °C; IR (KBr, cm\(^{-1}\)): 3246 (NH), 2957, 1581, 1508, 1334, 1110, 808; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 0.91 (t, 3H, \(CH_3\)), 1.31-1.40 (m, 2H, \(CH_2CH_3\)), 1.48-1.57 (m, 2H, \(CH_2CH_2CH_3\)), 2.40 (t, \(J = 6.0\) Hz, 1H, CH), 3.34-3.36 (m, 2H, \(NHCH_2CH_2CH_3\)), 3.68-3.79 (m, 8H, \(CH_2OCH_2, CH_2NHCH_2CH_2CH_3\)), 4.87 (d, \(J = 2.5\) Hz, 2H,
N-Cyclopropyl-4-morpholino-6-(prop-2-ynyloxy)-1,3,5-triazin-2-amine (45): Yield: 92%; mp: 167-170 °C; IR (KBr, cm⁻¹): 3258 (NH), 2959, 1572, 1502, 1332, 1109, 1022, 808; ¹H NMR (400 MHz, CDCl₃) δ: 0.42-0.52 (m, 2H), 0.64-0.76 (m, 2H), 2.39 (t, J = 6.0 Hz, 1H, CH₂), 2.67-2.85 (m, 1H, CHNH), 3.65-3.74 (m, 8H, CH₂O, CH₂, CH₂NCH₂), 4.84 (d, J = 2.5 Hz, 2H, CH₂OAr), 5.26-5.60 (m, 1H, NH); ¹³C NMR (100 MHz, CDCl₃) δ: 6.9, 23.3, 43.6, 53.8, 66.6, 74.3, 78.5, 165.8, 168.4, 169.9; ESI-MS (m/z): 274.88 (M+H)⁺; Anal. Calcd for C₁₃H₁₇N₅O: C, 56.71; H, 6.22; N, 25.44. Found: C, 56.80; H, 6.16; N, 25.40.

N-Cyclopropyl-4-(piperidin-1-yl)-6-(prop-2-ynyloxy)-1,3,5-triazin-2-amine (46): Yield: 90%; mp: 144-146 °C; IR (KBr, cm⁻¹): 3249 (NH), 2941, 2856, 1581, 1542, 1329, 1296, 1100, 809; ¹H NMR (400 MHz, CDCl₃) δ: 0.44-0.47 (m, 2H), 0.62-0.76 (m, 2H), 1.50-1.60 (m, 6H), 2.38 (t, J = 6.0 Hz, 1H, CH₂), 2.71-2.72 (m, 1H, CHNH), 3.62-3.82 (m, 4H), 4.85 (d, J = 2.5 Hz, 2H, CH₂OAr), 5.32 (brs, 1H, NH); ¹³C NMR (100 MHz, CDCl₃) δ: 6.9, 23.4, 24.7, 25.7, 44.3, 53.7, 74.1, 78.7, 165.3, 168.3, 169.7; ESI-MS (m/z): 274.62 (M+H)⁺; Anal. Calcd for C₁₄H₁₉N₅O: C, 61.52; H, 7.01; N, 25.62. Found: C, 61.48; H, 7.08; N, 25.71.

Typical procedure: Synthesis of (7-chloro-quinolin-4-yl)-(2-{4-[4-(3,5-dimethoxy-phenylamino)-6-morpholin-4-yl-[1,3,5]triazin-2-yloxymethyl]-[1,2,3]triazol-1-yl}-ethyl)-amine (47) and related compounds (48-62)

To a stirred solution of compound 10a (0.1 g, 0.40 mmol) and alkyne 40 (0.16 g, 0.44 mmol) in t-BuOH (8 mL), a solution of sodium ascorbate (0.03 g, 0.16 mmol) and CuSO₄·5H₂O (0.02 g, 0.08 mmol) in water (8 mL) was added. Reaction mixture was
heated at 40 °C for 3 h (scheme 2.4). After the completion of reaction, CHCl₃ (20 mL) was added to the reaction mixture, and organic layer was washed with water (2 × 100 mL), and dried over Na₂SO₄. The excess of solvent was evaporated to dryness, and the crude material obtained was purified by SiO₂ column using MeOH/CHCl₃ as eluent. Compound 47 was isolated in 58% yield. mp: 201-203 °C; IR (KBr, cm⁻¹): 3393 (NH), 2925, 2854, 1585, 1540, 1420, 1151, 808; ¹H NMR (300 MHz, DMSO-d₆) δ: 3.60-3.82 (m, 16H), 4.66 (t, J = 6.0 Hz, 2H, CH₂CH₂), 5.35 (s, 2H, OCH₂), 6.12 (s, 1H, ArH), 6.57 (d, J = 5.7 Hz, 1H, ArH), 6.97 (s, 2H, ArH), 7.47 (d, J = 9.0 Hz, 1H, ArH), 7.80 (s, 1H, ArH), 7.90 (brs, 1H, NH), 8.18-8.23 (m, 2H, ArH), 8.23 (brs, 1H, NH), 9.50 (s, 1H, ArH); ¹³C NMR (100 MHz, DMSO-d₆) δ: 42.6, 43.6, 47.8, 55.0, 59.2, 65.8, 94.4, 98.1, 98.8, 116.9, 124.3, 124.9, 125.4, 125.6, 134.6, 141.3, 142.3, 146.5, 149.8, 151.1, 160.3, 164.9, 165.5, 169.8; ESI-HRMS (m/z): 619.2375 (M+H)⁺, 621.2584 (M+2)⁺; Anal. Calcd for C₂₉H₃₁ClN₁₀O₄: C, 56.26; H, 5.05; N, 22.63. Found: C, 56.05; H, 5.08; N, 22.69.

6-((1-(2-(7-Chloroquinolin-4-ylamino)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-N₂-(3,5-dimethoxyphenyl)-N₄,N₄-dimethyl-1,3,5-triazine-2,4-diamine (48): Yield: 60%; mp: 200-202 °C; IR (KBr, cm⁻¹): 3316 (NH), 2926, 2851, 1597, 1550, 1412, 1315, 1149, 809; ¹H NMR (300 MHz, DMSO-d₆) δ: 3.03 (s, 3H, NCH₃), 3.10 (s, 3H, NCH₃), 3.68 (s, 6H, 2 × OCH₃), 3.80-3.81 (m, 2H, NHCH₂CH₂), 4.67 (t, J = 6.0 Hz, 2H, CH₂CH₂), 5.35 (s, 2H, OCH₂Ar), 6.11 (s, 1H, ArH), 6.56 (d, J = 5.7 Hz, 1H, ArH), 7.05 (s, 2H, ArH), 7.45 (d, J = 9.0 Hz, 1H, ArH), 7.80-7.88 (m, 2H, ArH, NH), 8.18-8.23 (m, 2H, ArH, NH), 8.40 (d, J = 5.7 Hz, 1H, ArH), 9.40 (s, 1H, ArH); ¹³C NMR (100 MHz, DMSO-d₆) δ: 35.9, 36.2, 47.8, 54.9, 59.1, 94.2, 97.9, 98.8, 117.0, 124.2, 124.8, 125.3, 125.8, 134.4, 141.6, 142.5, 146.9, 150.1, 150.9, 160.3, 164.7, 166.0, 169.5; ESI-MS (m/z): 576.82 (M+H)⁺, 578.76 (M+2)⁺; Anal. Calcd for C₂₇H₂₉ClN₁₀O₃: C, 56.20; H, 5.07; N, 24.27. Found: C, 56.15; H, 5.16; N, 24.21.
6-((1-(2-(7-Chloroquinolin-4-ylamino)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-N2-(2,6-dimethylphenyl)-N4,N4-dimethyl-1,3,5-triazine-2,4-diamine (49): Yield: 68%; mp: 140-142 °C; IR (KBr, cm\(^{-1}\)): 3392 (\(\text{NH}\)), 2951, 1581, 1534, 1406, 1239, 1214, 1093, 811; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\): 2.09 (s, 3H, CH\(_3\)), 2.13 (s, 3H, CH\(_3\)), 3.05 (s, 3H, CH\(_3\)), 3.16 (s, 3H, CH\(_3\)), 3.77-3.83 (m, 2H, NHCH\(_2\)CH\(_2\)), 4.62 (t, \(J = 6.0\) Hz, 2H, CH\(_2\)CH\(_2\)-triazole), 5.25 (s, 2H, CH\(_2\)OAr), 6.58 (d, \(J = 5.7\) Hz, 1H, Ar\(H\)), 6.99-7.05 (m, 3H, Ar\(H\)), 7.48 (d, \(J = 9.0\) Hz, 1H, Ar\(H\)), 7.68-7.83 (m, 2H, Ar\(H\), NH); 13C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\): 18.3, 18.4, 35.8, 35.9, 42.6, 47.9, 58.9, 99.3, 124.3, 124.7, 125.4, 126.6, 127.6, 134.1, 135.5, 136.0, 142.5, 142.7, 150.4, 150.8, 165.7, 166.2, 166.3, 169.9; ESI-MS (m/z): 576.95 (M+H)\(^+\), 578.82 (M+2)\(^+\); Anal. Calcd for C\(_{27}\)H\(_{29}\)ClN\(_{10}\)O\(_3\): C, 56.20; H, 5.07; N, 24.27. Found: C, 56.28; H, 5.19; N, 24.23.

(7-Chloro-quinolin-4-yl)-(2-{4-[4-(2,6-dimethylphenylamino)-6-morpholin-4-yl-[1,3,5]triazin-2-yloxymethyl]-[1,2,3]triazol-1-yl}-ethyl)-amine (50): Yield: 56%; mp: 218-220 °C; IR (KBr, cm\(^{-1}\)): 3246 (\(\text{NH}\)), 2957, 2854, 1581, 1534, 1446, 1272, 1112, 811; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\): 2.08 (s, 3H, CH\(_3\)), 2.10 (s, 3H, CH\(_3\)), 3.37-3.69 (m, 10H), 4.61 (t, \(J = 6.0\) Hz, 2H, CH\(_2\)CH\(_2\)-triazole), 5.25 (s, 2H, CH\(_2\)OAr), 6.54 (d, \(J = 5.7\) Hz, 1H, Ar\(H\)), 7.03 (s, 3H, Ar\(H\)), 7.45 (d, \(J = 9.0\) Hz, 1H, Ar\(H\)), 7.65-7.81 (m, 2H, Ar\(H\), NH); 13C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\): 18.3, 18.4, 43.2, 43.3, 47.8, 58.9, 59.0, 65.8, 65.9, 98.8, 124.2, 124.6, 125.3, 126.7, 127.6, 134.0, 135.6, 136.0, 142.3, 142.5, 150.2, 151.0, 165.6, 165.7, 166.4, 169.9; ESI-MS (m/z): 588.26 (M+H)\(^+\), 590.21 (M+2)\(^+\); Anal. Calcd for C\(_{29}\)H\(_{32}\)ClN\(_{10}\)O\(_2\): C, 59.33; H, 5.32; N, 23.86. Found: C, 59.27; H, 5.31; N, 23.94.
(7-Chloro-quinolin-4-yl)-{2-[4-(4-cyclopropylamino-6-morpholin-4-yl-[1,3,5]triazin-2-yloxymethyl)-[1,2,3]triazol-1-yl]-ethyl}-amine (52): Yield: 65%; mp: 104-106 °C; IR (KBr, cm⁻¹): 3293 (NH), 2924, 2854, 1581, 1534, 1362, 1112, 810; ¹H NMR (300 MHz, DMSO-­d₆) δ: 0.43-0.59 (m, 4H, 2 × CH₂), 2.65-2.78 (m, 1H, CHNH), 3.56-3.80 (m, 10H), 4.65 (t, J = 6.0 Hz, 2H, CH₂CH₂-triazole), 5.27 (s, 2H, CH₂OAr), 6.59 (d, J = 5.7 Hz, 1H, ArH), 7.45-7.48 (m, 2H, ArH), 7.78-7.90 (m, 2H, ArH), 8.18-8.29 (m, 2H, ArH), 8.50 (b.rs, 1H, NH); ¹³C NMR (100 MHz, DMSO-­d₆) δ: 6.0, 6.2, 23.4, 42.6, 43.3, 47.8, 58.8, 65.9, 98.9, 124.3, 124.8, 125.3, 126.2, 134.3, 142.6, 150.4, 150.7, 165.7, 167.6, 168.0, 169.5, 169.9; ESI-MS (m/z): 522.45 (M+H)+, 524.22 (M+2)+; Anal. Calc.d for C₂₄H₂₃ClN₁₀O₂: C, 55.70; H, 5.80; N, 25.98. Found: C, 55.16; H, 5.25; N, 26.99.

(7-Chloro-quinolin-4-yl)-{3-[4-(4-cyclopropylamino-6-morpholin-4-yl-[1,3,5]triazin-2-yloxymethyl)-[1,2,3]triazol-1-yl]-propyl}-amine (53): Yield: 62%; mp: 97-99 °C; IR (KBr, cm⁻¹): 3401 (NH), 2960, 2855, 1581, 1534, 1362, 1112, 810; ¹H NMR (300 MHz, DMSO-­d₆) δ: 0.44-0.61 (m, 4H, 2 × CH₂), 2.19-2.23 (m, 2H, CH₂CH₂CH₂), 2.68-2.80...
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(7-Chloro-quinolin-4-yl)-(3-{4-[4-(3,5-dimethoxyphenylamino)-6-morpholin-4-yl-[1,3,5] triazol-2-yloxyethyl]-[1,2,3]triazol-1-yl}-propyl)-amine (54): Yield: 57%; mp: 100-102 °C; IR (Nujol, cm⁻¹): 2921, 2854, 2723, 1612, 1585, 1463, 1377, 1150, 808; ¹H NMR (300 MHz, DMSO-d₆) δ: 2.20-2.24 (m, 2H, CH₂CH₂CH₂), 3.33-3.72 (m, 16H), 4.51 (t, J = 6.0 Hz, 2H, CH₂CH₂-triazole), 5.37 (s, 2H, CH₂OAr), 6.12 (s, 1H, ArH), 6.48 (d, J = 5.7 Hz, 1H, ArH), 6.98 (s, 2H, ArH), 7.50 (d, J = 9.0 Hz, 1H, ArH), 7.82 (s, 1H, ArH), 7.92 (s, 1H, NH), 8.25 (s, 1H, ArH), 8.33-8.40 (m, 2H, ArH), 9.50 (s, 1H, ArH); ¹³C NMR (100 MHz, DMSO-d₆) δ: 28.8, 40.2, 44.0, 47.8, 55.4, 59.8, 66.3, 94.9, 98.5, 99.1, 117.4, 125.1, 125.3, 125.5, 125.6, 135.1, 141.7, 142.8, 146.6, 149.8, 151.9, 160.7, 165.4, 166.0, 170.2; ESI-MS (m/z): 632.96 (M+H)+, 632.88 (M+2); Anal. Calcd for C₃₀H₃₃ClN₁₀O₄: C, 56.91; H, 5.25; N, 22.12. Found: C, 56.93; H, 5.57; N, 22.10.

6-((1-(3-(7-Chloroquinolin-4-ylamino)propyl)-1H-1,2,3-triazol-4-yl)methoxy)-N₂-(3,5-dimethoxyphenyl)-N₄,N₄-dimethyl-1,3,5-triazine-2,4-diamine (55): Yield: 73%; mp: 88-90 °C; IR (KBr, cm⁻¹): 3401 (NH), 2930, 1593, 1539, 1408, 1151, 807; ¹H NMR (300 MHz, DMSO-d₆) δ: 2.12-2.17 (m, 2H, CH₂CH₂CH₂), 3.01 (s, 3H, CH₃), 3.05 (s, 3H, CH₃), 3.36-3.43 (m, 2H, NHCH₂CH₂), 3.60 (s, 6H, 2 × OCH₃), 4.44 (t, J = 6.0 Hz, 2H, CH₂CH₂-triazole), 5.29 (s, 2H, CH₂OAr), 6.04 (s, 1H, ArH), 6.43 (d, J = 5.7 Hz, 1H, ArH), 6.99 (s, 2H, ArH), 7.45 (d, J = 9 Hz, 1H, ArH), 7.75 (s, 1H, ArH), 7.87 (s, 1H, ArH), 8.20 (s, 1H, ArH), 8.32 (d, J = 5.7 Hz, 1H, ArH), 8.41 (brs, 1H, NH); ESI-MS (m/z): 538.19 (M+H)+, 540.26 (M+2); Anal. Calcd for C₂₅H₂₉ClN₁₀O₂: C, 55.91; H, 5.44; N, 26.08. Found: C, 56.00; H, 5.41; N, 26.11.
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6-((1-(3-(7-Chloroquinolin-4-ylamino)propyl)-1H-1,2,3-triazol-4-yl)methoxy)-N2-(2,6-dimethylphenyl)-N4,N4-dimethyl-1,3,5-triazine-2,4-diamine (56): Yield: 49%; mp: 215-218 °C; IR (KBr, cm⁻¹): 3401 (NH), 2926, 1581, 1541, 1406, 1324, 1215, 811; ¹H NMR (300 MHz, DMSO-d₆) δ: 2.08-2.21 (m, 8H), 3.07 (s, 6H, 2 × CH₃); 3.35-3.55 (m, 2H, NHCH₂CH₂), 4.45 (t, J = 6.0 Hz, 2H, CH₂CH₂-triazole), 5.21 (s, 2H, CH₂OAr), 6.55 (d, J = 5.7 Hz, 1H, ArH), 7.02-7.05 (m, 3H, ArH), 7.47 (d, J = 9.0 Hz, 1H, ArH), 7.58-7.92 (m, 3H, ArH), 8.26-8.35 (m, 2H, ArH), 8.67 (s, 1H, ArH); ESI-MS (m/z): 560.78 (M+H)⁺, 562.79 (M+2)⁺; Anal. Calcd for C₂₈H₃₁ClN₁₀O: C, 60.15; H, 5.59; N, 25.05. Found: C, 60.10; H, 5.67; N, 24.88.

(7-Chloroquinolin-4-yl)-(3-{4-[4-(2,6-dimethylphenylamino)-6-morpholin-4-yl-[1,3,5]triazin-2-yloxymethyl]-[1,2,3]triazol-1-yl}-propyl)-amine (57): Yield: 72%; mp: 138-141 °C; IR (KBr, cm⁻¹): 3401 (NH), 2923, 2853, 1581, 1534, 1363, 1271, 1113, 811; ¹H NMR (300 MHz, DMSO-d₆) δ: 2.09-2.28 (m, 8H), 3.15-3.70 (m, 10H), 4.46 (t, J = 6.0 Hz, 2H, CH₂CH₂-triazole), 5.28 (s, 2H, CH₂OAr), 6.48 (d, J = 5.7 Hz, 1H, ArH), 7.02 (s, 3H, ArH), 7.47-7.58 (m, 2H, ArH), 7.76-7.81 (m, 2H, ArH), 8.30-8.32 (m, 2H, ArH), 8.72-8.78 (m, 1H); ¹³C NMR (100 MHz, DMSO-d₆) δ: 18.2, 18.3, 28.5, 43.1, 43.3, 47.3, 58.9, 59.0, 65.7, 65.9, 98.6, 124.6, 124.9, 125.9, 126.4, 127.6, 134.3, 135.4, 136.0, 142.3, 142.6, 150.1, 150.9, 165.6, 165.7, 166.3, 169.9, 170.1; ESI-MS (m/z):
600.57 (M+H)^+, 602.22 (M+2)^+; Anal. Calcd for C\textsubscript{30}H\textsubscript{33}ClN\textsubscript{10}O\textsubscript{2}: C, 59.94; H, 5.53; N, 23.30. Found: C, 60.15; H, 5.58; N, 23.40.

(7-Chloro-quinolin-4-yl)-{2-[4-(4-cyclopropylamino-6-piperidin-1-yl-[1,3,5]triazin-2-yloxymethyl)-[1,2,3]triazol-1-yl]-ethyl}-amine (58): Yield: 72%; mp: 174-176 °C; IR (KBr, cm\textsuperscript{-1}): 3297 (NH), 2935, 1582, 1532, 1447, 1358, 1138, 810; \textsuperscript{1}H NMR (300 MHz, DMSO-\textsubscript{d}\textsubscript{6}) \(\delta\): 0.40-0.55 (m, 4H), 1.39-1.52 (m, 6H), 2.62-2.75 (m, 1H, CH\textsubscript{2}NH), 3.40-3.76 (m, 6H), 4.63 (t, J = 6.0 Hz, 2H, CH\textsubscript{2}CH\textsubscript{2}-triazole), 5.25 (s, 2H, CH\textsubscript{2}OAr), 6.65 (d, J = 5.7 Hz, 1H, Ar\textsubscript{H}), 7.29 (s, 1H, Ar\textsubscript{H}), 7.43 (d, J = 9.0 Hz, 1H, Ar\textsubscript{H}), 7.68-7.92 (m, 3H, Ar\textsubscript{H}), 8.13-8.27 (m, 2H, Ar\textsubscript{H}); ESI-MS (m/z): 522.40 (M+H)^+, 524.30 (M+2)^+; Anal. Calcd for C\textsubscript{25}H\textsubscript{29}ClN\textsubscript{10}O: C, 57.63; H, 5.61; N, 26.88. Found: C, 57.64; H, 5.72; N, 26.89.

(7-Chloro-quinolin-4-yl)-{3-[4-(4-cyclopropylamino-6-piperidin-1-yl-[1,3,5]triazin-2-yloxymethyl)-[1,2,3]triazol-1-yl]-propyl}-amine (59): Yield: 52%; mp: 90-92 °C; IR (KBr, cm\textsuperscript{-1}): 3292 (NH), 2933, 2854, 1582, 1533, 1499, 1356, 1136, 810; \textsuperscript{1}H NMR (300 MHz, DMSO-\textsubscript{d}\textsubscript{6}) \(\delta\): 0.43-0.60 (m, 4H), 1.37-1.55 (m, 6H), 2.18-2.23 (m, 2H), 2.65-2.78 (m, 1H, CH\textsubscript{2}NH), 3.28-3.63 (m, 6H), 4.50 (t, J = 6.0 Hz, 2H, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-triazole), 5.27 (s, 2H, CH\textsubscript{2}OAr), 6.46 (d, J = 5.7 Hz, 1H, Ar\textsubscript{H}), 7.35 (s, 1H, Ar\textsubscript{H}), 7.48 (d, J = 9.0 Hz, 1H, Ar\textsubscript{H}), 7.58-7.80 (m, 2H, Ar\textsubscript{H}), 8.18 (s, 1H, Ar\textsubscript{H}), 8.44 (d, J = 5.7 Hz, 1H, Ar\textsubscript{H}), 8.51 (brs, 1H, NH), ESI-MS (m/z): 534.91 (M+H)^+, 536.55 (M+2)^+; Anal. Calcd for C\textsubscript{26}H\textsubscript{31}ClN\textsubscript{10}O: C, 58.36; H, 5.84; N, 26.18. Found: C, 58.40; H, 6.11; N, 26.23.

{3-[4-(4-Chloro-6-cyclopropylamino-[1,3,5]triazin-2-yloxymethyl)-[1,2,3]triazol-1-yl]-propyl}-(7-chloro-quinolin-4-yl)-amine (60): Yield: 65%; mp: 242-244 °C; IR (KBr, cm\textsuperscript{-1}): 3235 (NH), 3089, 2925, 1580, 1528, 1420, 1326, 1209, 1010, 807; \textsuperscript{1}H NMR (300 MHz, DMSO-\textsubscript{d}\textsubscript{6}) \(\delta\): 0.55-0.86 (m, 4H, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 2.26-2.33 (m, 2H, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 2.77-2.82 (m, 1H, CH\textsubscript{2}NH), 3.56-3.71 (m, 2H, NHCH\textsubscript{2}CH\textsubscript{2}), 4.56 (t, J = 6.0 Hz, 2H,
CH₂CH₂-triazole), 5.39 (s, 2H, CH₂OAr), 6.65 (d, J = 5.7 Hz, 1H, ArH), 7.10 (s, 1H, ArH), 7.58 (d, J = 9.0 Hz, 1H, ArH), 7.83-7.94 (m, 2H, ArH), 8.30-8.52 (m, 3H, ArH);

ESI-MS (m/z): 486.21 (M+H)\(^+\), 488.22 (M+2)\(^+\), 490.22 (M+4)\(^+\); Anal. Calcd for C\(_{21}\)H\(_{21}\)Cl\(_2\)N\(_9\)O: C, 51.86; H, 4.35; N, 25.92. Found: C, 51.93; H, 4.56; N, 125.95.

{3-[4-(4-Chloro-6-phenylamino-[1,3,5]triazin-2-yloxymethyl)-[1,2,3]triazol-1-yl]-propyl}-(7-chloro-quinolin-4-yl)-amine (61): Yield: 78%; mp: 236-238 °C; IR (KBr, cm\(^{-1}\)): 3241 (NH), 3095, 2926, 1558, 1428, 1364, 1207, 1003, 806; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\): 2.24-2.27 (m, 2H, CH₂CH₂CH₂), 3.70-3.82 (m, 2H, NHCH₂CH₂), 4.54 (t, J = 6.0 Hz, 2H, CH₂CH₂-triazole), 5.46 (s, 2H, CH₂OAr), 6.70 (d, J = 5.7 Hz, 1H, ArH), 6.97-7.37 (m, 4H, ArH), 7.61-7.68 (m, 4H, ArH), 7.90 (s, 1H, ArH), 8.42-8.54 (m, 3H, ArH); ESI-MS (m/z): 522.96 (M+H)\(^+\), 524.12 (M+2)\(^+\);

Anal. Calcd for C\(_{24}\)H\(_{21}\)Cl\(_2\)N\(_9\)O: C, 55.18; H, 4.05; N, 24.13. Found: C, 55.28; H, 4.18; N, 24.32.

(3-{4-[4-Chloro-6-(2,6-dimethyl-phenylamino)-[1,3,5]triazin-2-yloxymethyl]-[1,2,3]triazol-1-yl]-propyl}-(7-chloro-quinolin-4-yl)-amine (62): Yield: 63%; mp: 248-250 °C; IR (KBr, cm\(^{-1}\)): 3233 (NH), 3081, 2925, 1577, 1458, 1364, 1207, 999, 809; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\): 2.08-2.21 (m, 8H, CH₂CH₂CH₂, 2 × CH₃), 3.62-3.90 (m, 2H, NHCH₂CH₂), 4.49 (t, J = 6.0 Hz, 2H, CH₂CH₂-triazole), 5.24 (s, 2H, CH₂OAr), 6.70-7.13 (m, 5H, ArH), 7.48-7.73 (m, 2H, ArH), 8.18 (brs, 1H, NH), 8.45-8.93 (m, 3H); ESI-MS (m/z): 550.99 (M+H)\(^+\), 552.74 (M+2)\(^+\); Anal. Calcd for C\(_{26}\)H\(_{25}\)Cl\(_2\)N\(_9\)O: C, 56.73; H, 4.58; N, 22.90. Found: C, 56.75; H, 4.68; N, 22.96.
2.9 References


