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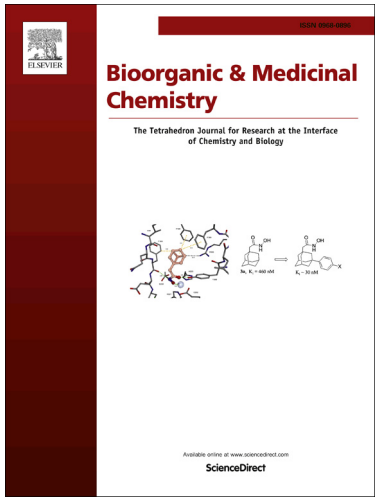

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Graphical Abstract

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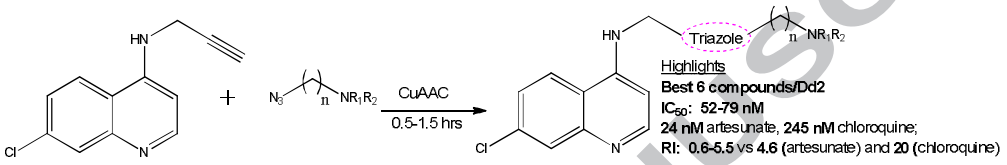

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Lebusetsa Taleli,[a] Carmen de Kock,[b] Peter J. Smith,[b] Stephen C. Pelly,[a] Margaret A. L. Blackie[a] and Willem. A. L. van Otterlo[a*]

[a] *Department of Chemistry and Polymer Science, University of Stellenbosch, Private Bag X1, Matieland 7602, South Africa*
[b] *Division of Pharmacology, Department of Medicine, University of Cape Town, Observatory 7925, South Africa*

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ABSTRACT

The synthesis and *in vitro* evaluation of novel triazole-linked chloroquinoline derivatives as potential antiplasmodial agents against *Plasmodium falciparum* is reported. The 15 synthesized target compounds were obtained by means of a copper(I)-mediated click reaction between a variety of 1,2- and 1,3-azidoamines and 7-chloro-*N*-(prop-2-yn-1-yl)quinolin-4-amine in moderate to good yields (53–85%). The compounds were screened for antiplasmodial activity against NF54 chloroquine-sensitive and Dd2 chloroquine-resistant strains, alongside chloroquine and artesunate as reference compounds. Six of the test compounds revealed a 3–5 fold increase in antiplasmodial activity against chloroquine-resistant strain Dd2 compared to chloroquine. Among the six compounds with good antiplasmodial activity, a reduced cross-resistance relative to artesunate (>3 fold in comparison to chloroquine) was observed, mainly in derivatives that incorporated chloroquine-resistance reversing pharmacophores. A general trend for reduced chloroquine cross-resistance was also detected among 12 out of the 15 compounds tested.

* Corresponding author. Tel.: +27-021-808-3344; fax: +27-021-808-3360; e-mail: wvo@sun.ac.za

1. Introduction

For several decades, the challenge of emerging multidrug resistant strains of *Plasmodium falciparum* and its mosquito vector has been partially managed by the provision of chemotherapeutic regimens and insecticide-treated nets to the people at risk of endemic malaria. Despite significant progress, there are still ~109 countries where malaria is endemic, of which 99 have on-going malaria transmission challenges.[1] Because of the rapid emergence of resistance the use of combinations of existing antimalarial drugs is almost ubiquitous. Nonetheless, systematic research efforts to identify the next generation of antimalarial drugs remain a pressing need.

In this regard, researchers have demonstrated that the 4-aminoquinoline core can be used as a template for the discovery of novel agents.[2, 3] Compounds such as chloroquine (CQ) have thus remained inspirational for alternative malaria chemotherapies [**Fig. 1 (a)**].[4, 5] Of importance is that this class of compound derives its popularity from decent safety profiles, efficacy and cost effective syntheses.[5, 6] In terms of compounds from this class, clinical candidates such AQ-13 **(b)**,[7] amodiaquine **(c)**,[8] and GSK369796 **(d)**,[8] and many more have been demonstrated as effective antimalarial agents against numerous CQ-resistant *P. falciparum* strains.[8, 9a]

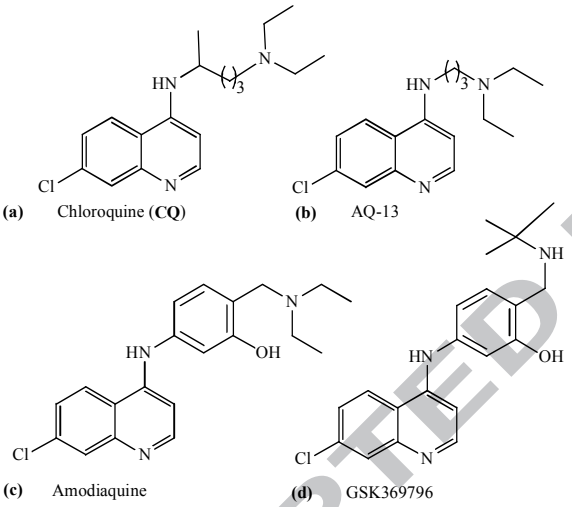


Figure 1: Quinoline-based antimalarial agents

A number of investigations aimed at the reversal of CQ-resistance in *P. falciparum* isolates have involved the covalent linking of privileged 4-aminoquinoline scaffolds with CQ modulating agents.[10-12] In this area, several hybridized CQ molecules (see **Fig. 2**) that act as chemosensitizers for *P. falciparum*, have been investigated; however, only a few of these compounds have reached clinical trials.[13-14] Among these compounds, hybrids that are composed of the chloroquinoline scaffold and dibenzyl or bulky distal aryl amine groups have been shown to be promising sensitizers and resistance reversing agents.[15, 16] In some instances, hybrids with distal amine functional groups have also been associated with the ability to induce sensitivity and increase drug accumulation in CQ-resistant parasite to levels similar, or close to those of CQ-sensitive strains.[11] Earlier studies have however shown that short chain *N,N*-dialkylamine analogues tend to undergo *in vivo* dealkylation which also affects their activity and cross-resistance properties.[9b, 17] While the bulkier distal amine groups have proven to enhance *in vivo* efficacy, small heterocyclic rings have been demonstrated to possess metabolic stability and significantly improve antimalarial activity.[18]

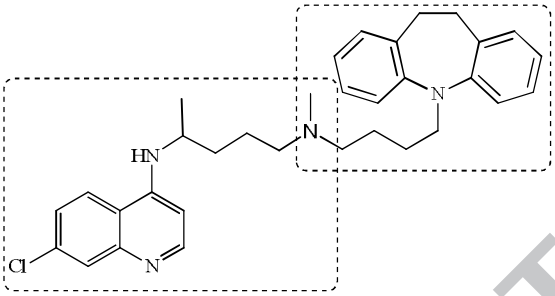


Figure 2 A hybridized CQ compound with chemosensitizing effects in CQ-resistant *P. falciparum* strains.[13]

With these points in mind, we proposed the synthesis of short-chain chloroquinoline derivatives, coupled to various small heterocyclic and/or aryl amine functionalities through a triazole linker. We have recently explored triazole-linked quinoline derivatives against *P. falciparum* and found these compounds to have moderate activity.[19, 20] It was thus decided to re-examine the 7-chloro-4-aminoquinoline nucleus, a haematin-binding core recognized for potent antiplasmodial activity, due to its association with haem and the prevention of toxic haematin sequestration.[3, 21]

The use of a triazole-linker, a privileged pharmacophore in a large number of bioactive agents,[22] afforded an opportunity to link various functional groups by way of click chemistry. Moreover, triazoles have been shown to possess metabolic stability which makes them ideal lipophilic-linkers.[22] It should be noted that several synthetic approaches to triazole-linked 7-chloroquinoline antimalarials have been documented.[23-27] The synthesis of the largest set of triazole-quinoline prototypes have been carried out by click reactions between 4-azido-7-chloroquinoline and alkyne moieties, resulting in structures with the generic structure **(e)** [as in Figure 3].[24, 25, 28-30] Alternatively, small libraries of molecules have been generated with the triazole portion on a side chain originating from the 4-amino-7-chloroquinoline scaffold. This is exemplified by the generic structure **(f)** [**Fig. 3**] and this template has been recently utilized by the groups of Egan,[26] Andrews and Poulsen[27] Unfortunately, the bioactivities of compounds with the general structure **(e)** have to date been rather modest, most probably because there is no 4-amino functionality on the quinoline nucleus, which appears to strongly influence the haematin binding ability of these compounds, as well as their ability to accumulate in the food vacuole of the parasite.[2, 25, 31] On the other hand, a number of compounds with the general structure **(f)** have shown improved antimalarial activity against drug resistant *P. falciparum* parasite strains.[26, 27] In view of the influence of the side chain amino groups on antiplasmodial activity,[2, 26] together with the above discussed factors; we prepared 7-chloro-*N*-(prop-2-yn-1-yl)quinolin-4-amine **1** (**Scheme 1**) and generated a small library of compounds by click chemistry of this compound and varied 1,2- and 1,3-azidoamines. Subsequently, their antimalarial activity against *P. falciparum* was determined.

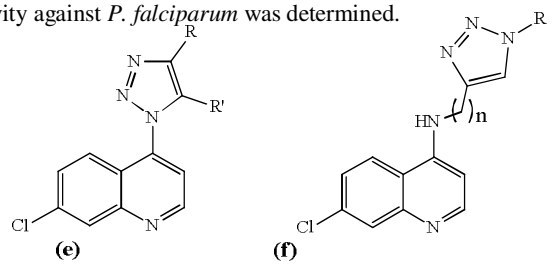
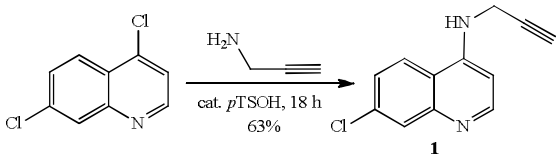


Figure 3 Triazole-linked choroquinoline antiplasmodial agents.

2. Results and discussion

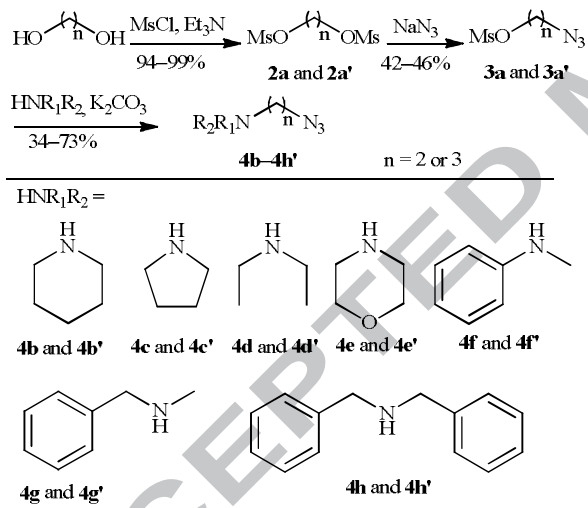
2.1. Chemistry

Starting from a commercially available 4,7-dichloroquinoline, nucleophilic substitution at the C(4)-position was carried out under inert conditions using propargyl amine and catalytic *p*-toluene sulfonic acid in dioxane, to afford 7-chloro-*N*-(prop-2-yn-1-yl)quinolin-4-amine (**1**) in 63% yield as depicted in **Scheme 1**.



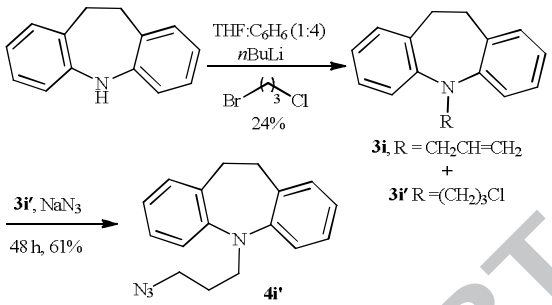
Scheme 1 Synthesis of 4-aminoquinoline alkyne precursor **1**.

The aliphatic azides connected to variable carbon spacers were then synthesized from propane-1,3-diol and ethane-1,2-diol (see reaction **Scheme 2**). The diols were firstly converted into their corresponding *bis*-mesylate compounds using mesyl chloride and trimethylamine to obtain compounds **2a** and **2a′** (94% and 99%, respectively).[32] The *bis*-mesylate compounds were then treated with sodium azide in acetonitrile to obtain azidoamine mesylates **3a** and **3a′** in moderate yields (42% and 46%, respectively). Finally, selected secondary amines were coupled to compounds **3a** and **3a′** in an S_N2 reaction to afford the desired amino azides (**4b–4h′**) in yields of 34–73%.



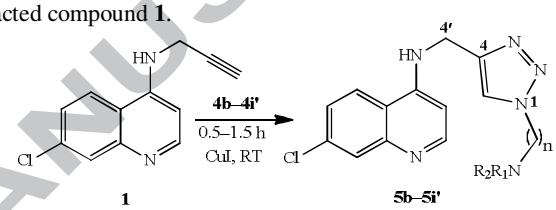
Scheme 2 Preparation of amine azide building blocks (see experimental section for more details).

Following unsuccessful attempts to prepare sterically hindered dibenzo-fused amine azide analogues from **3a** and **3a′**, amino azide **4i′** was prepared from commercially available 10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine and 1-bromo-3-chloropropane starting materials by consecutive nucleophilic displacement of the halogens (shown on **Scheme 3**). The first step of the reaction sequence[33] afforded intermediate **3i′**, which was separated from the 5-allyl byproduct (**3i**) by means of chromatography. In the second step, azidation was carried out on **3i′** with excess sodium azide in a 1:1 DMSO-C_6H_6 solvent mixture to afford compound **4i′** in a reasonable 61% yield.



Scheme 3 Preparation of dibenzo-fused amino azide building block.

In terms of the click reactions, compounds (**5b–5i′**) were obtained in moderate to good yields (53–85%) using anhydrous Cu(I) in THF for 0.5–1.5 h (see **Scheme 4**). The desired products were highly polar and often their extraction from aqueous saturated ammonium chloride solution resulted in low yields. Therefore, removal of excess CuI was achieved by filtration through celite after dilution of the reaction mixture with dichloromethane. Silica gel column purifications were then performed to separate desired compounds (**5b–5i′**) from any unreacted compound **1**.



Scheme 4 Click synthesis of 7-chloroquinoline derivatives.

All the compounds (**5b–5i′**) were characterized by NMR, IR and high resolution mass spectroscopy, providing spectral data in agreement with the postulated structures. In addition, the regioselective formation of the triazoles was unambiguously confirmed by the application of gHSQCAD and gHMBC NMR spectroscopic experiments.[34]

2.2. In vitro antiplasmodial activity

The antiplasmodial activity of compounds **5b–5i'** was evaluated against strains of *P. falciparum* NF54 (CQ susceptible) and Dd2 (CQ resistant), using CQ and artesunate as positive controls (see **Table 1** and **Figure 4**). The resistance factor (RI) for each compound was subsequently calculated (see **Table 1** **Table 1** and **Figure 4**).[18]

Among the 15 triazole-linked chloroquinoline derivatives under study, 10 compounds displayed a moderate to good 50% growth inhibition of CQ-resistant Dd2 at a concentration range of 51–261 nM (refer to **Table 1** and **Figure 4**). Of these, six compounds (**5b**, **5c**, **5d**, **5g'**, **5h** and **5i'**) possessed increased antiplasmodial activity at 100 nM (50.8–78.6 nM range) against Dd2, when compared to CQ (245 nM). It must be noted that these compounds were 3–5 fold more active than CQ; however, they were still 2–3 fold less active compared to the gold standard artesunate. It is noteworthy that this activity was more or less equivalent to the CQ reference drug against CQ-susceptible NF54 *P. falciparum* strain.

Table 1 Antimalarial activity of test compounds **5b–5i'** [see **Figure 4** below] against NF54 and Dd2 *P. falciparum* strains.

5b–5i'

Figure 4 General structure of triazole-based test compounds*

		IC_{50} (nM)		RI
Compound*	**n†**	**NF54**	**Dd2**	**Dd2/NF54**
CQ	n/a	12.1 ± 0.4	245 ± 5	20
Artesunate	n/a	< 5.2 ± 0.5	24.2 ± 3.1	4.6
5b	2	10.2 ± 2.4	51.6 ± 6.8	5.1
5b′	3	8.9 ± 1.6	123 ± 1	14
5c	2	16.2 ± 5.1	69.3 ± 22.7	4.3
5c′	3	18.4 ± 3.0	149 ± 28	8.1
5d	2	9.8 ± 1.1	53.5 ± 3.3	5.5
5d′	3	1977 ± 142	5330 ± 268	2.7
5e	2	1303± 217	1763 ± 121	1.4
5e′	3	77.7 ± 4.7	261 ± 13	3.3
5f	2	380 ± 66	492 ± 82	1.3
5f′	3	165 ± 42	305 ± 15	1.8
5g	2	151 ± 4	216 ± 42	1.4
5g′	3	15.0 ± 3.1	50.8 ± 4.5	3.4
5h	2	140 ± 11	78.6 ± 26.9	0.6
5h′	3	114 ± 4	2241 ± 158	20
5i′	3	64.3 ± 5.0	74.1 ± 6.1	1.2

* The NR_1R_2 portions of the chemical structures shown in **Figure 4** are graphically shown in **Scheme 2**. In addition, the full structures are provided in the supporting information as **Table S1**; †ethyl/propyl side chain spacer.

Interestingly, antiplasmodial activity was observed for triazole-linked chloroquinoline analogues that contained small *N*-heterocyclic (**5b**, **5c** and **5d**) and bulky *N*-aryl amine (**5g'**, **5h** and **5i'**) side chain groups. In general, analogues with smaller amines on the lateral side chain demonstrated an overall increase in activity towards the CQ sensitive NF54 strain, when compared to their bulkier *N*-aryl amine counterparts. However, there was no evident trend against the CQ resistant Dd2 strain in this regard.

Twelve of the compounds tested showed reduced cross-resistance, with a resistance index factor in the range 0.6–8.1 compared to 20 for CQ. Chloroquinoline derivatives incorporating known CQ resistance reversing pharmacophores[35-37] (**5f–5i'**) generally had improved resistance factors when compared to artesunate (4.6), with the exception of **5h'**. The observed resistance index of the three most active compounds (compound **5g'**, **5h** and **5i'**) was between 0.6–3.4.

In line with our earlier investigations,[19, 20] this study has illustrated that another class of triazole-linked 7-chloroquinoline compounds based on the 7-chloro-*N*-(prop-2-yn-1-yl)quinolin-4-amine scaffold, was able to overcome a CQ resistant *P. falciparum* strain. It should be noted that Kumar and co-workers reported a marginal improvement of antimalarial profile between mono- and bis-1,2,3-triazole tethered 7-chloroquinolines against CQ resistant W2.[28] This slight increase in antiplasmodial activity was thought to be a result of the bis-triazole linker motif or enhanced binding of haem to the bis-7-chloroquinoline compounds.[28] Recently, studies on triazole-chloroquinoline hybrids have, however, strongly highlighted the dependence of activity upon the alkyl side chain rather than a triazole linker.[25-27] The latter developments support proposals that quinoline scaffolds and variations in chain length are the core features responsible for activity, while the triazole-linker provides structural variations which could be responsible for circumventing CQ resistance. Although a direct comparison between the antiplasmodial activities of various triazole-chloroquinoline derivatives is impractical due to variations in study approaches (different *P. falciparum* strains and assay methods), it appears that in the cases where a triazole group is tethered directly to the 4-position of quinolone core, it is the loss of the amino functionality on the quinoline which appears to affect basicity, haem interactions and subsequent potency.[2, 25, 31] The side chain amino group also impacts the effect of resistance reversing activity as reflected in previously published work.[26, 35] Keeping in mind that the 4-aminoquinoline core is a known privileged antimalarial scaffold with potent haemozoin inhibition properties,[2] the scaffold used in this manuscript maintains these favorable properties while affording the opportunity to vary the side chains in a divergent manner with a variety of amino azides.

3. Conclusion

Fifteen *N*-[(1*H*-1,2,3-triazol-4-yl)methyl]-7-chloroquinolin-4-amine derivatives have been synthesized by applying a copper-mediated click strategy to the 7-chloro-*N*-(prop-2-yn-1-yl)quinolin-4-amine scaffold and a variety of 1,2- and 1,3-aminoazides. The compounds were tested in terms of their ability to *in vitro* inhibit NF54 and Dd2 *P. falciparum* strains and preliminary evaluations indicate that some members of this novel class of compounds (**5b**, **5c**, **5d**, **5g'**, **5h** and **5i'**) have the ability (3–5 fold) to overcome CQ resistance when compared to CQ. We believe that these new CQ derivatives offer a fresh approach for the synthesis and identification of novel compounds with activity against CQ resistant *P. falciparum* strains. Our future work intends to explore other isomeric triazole linkers, and to perform additional biological assessment of these lead compounds.

4. Experimental

4.1. General

Unless otherwise indicated, air- and moisture-sensitive reactions were carried out in oven dried glassware with anhydrous solvents distilled prior to use under a positive pressure of nitrogen gas. Organic solvents were evaporated on Büchi rotary evaporator equipped with diaphragm vacuum pump.

Analytical grade reagents were used as received from commercial sources. Preparative column chromatography was carried out on a silica gel 60 (70–230 mesh ASTM), Fluka. Thin layer chromatography (TLC) was performed using pre-coated 60F aluminium silica gel plates with 254 nm fluorescent indicator from Merck. Developed TLC plates were viewed under ultra violet light or by treatment with an appropriate stain such as iodine, $KMnO_4$, while aliphatic azides were visualized after a contrast Rehumann's purple colour was developed with ninhydrin following a TLC Staudinger azide reduction protocol.[38]

The melting points were determined on a variable heat Gallenkamp apparatus (temperature range 20–350 °C) equipped with a laboratory thermometer, and are uncorrected. NMR

spectra were obtained from Varian Unity Inova spectrometers with ^{1}H frequency of 300 MHz or 400 MHz, and ^{13}C frequency of 75 MHz or 150 MHz. All spectra were obtained on a 5 mm dual broad band PFG probe with a probe temperature of 25 °C and the solvents that were used are indicated in the text. Data for ^{1}H NMR spectra are reported as follows: chemical shifts (δ, ppm) relative to internal solvent peaks, integration, multiplicity abbreviation were as singlet (s), (doublet), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplet (dt), multiplet (m), and coupling constants (*J,* Hz). Data for ^{13}C NMR spectra are reported in chemical shifts (δ, ppm) relative to residual solvent peak. High resolution mass spectra were recorded on electrospray ionisation in positive mode (ESI^{+}) using a quadrupole MALDI-TOF LC-MS instrument. The recorded mass values are within ± 5 ppm. Fingerprint identification of functional groups was achieved using wavenumbers (υ, cm^{-1}) on Nexus infra-red Pc spectrometer equipped with a DTGS KBr detector.

4.2. Synthesis

4.2.1. 7-Chloro-N-(prop-2-yn-1-yl)quinolin-4-amine (1)

In a Schlenk reaction tube, a solution of 4,7-dichloroquinoline (0.50 g, 2.5 mmol) and a catalytic amount of anhydrous *p*TsOH (43 mg, 0.25 mmol) in 1,4-dioxane (0.5 mL) was stirred at 50 °C for 30 min. To this emulsion, propargyl amine (0.38 mL, 5.5 mmol) was added and the reaction was continued for 18–24 h at 85 °C. The reaction was then cooled to RT and was diluted with CH_2Cl_2 (20 mL) and washed with 10% aqueous $NaHCO_3$ (3 × 20 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to obtain a pale yellow solid. Purification of crude was performed on a silica gel column (Hex/EtOAc; 6:4) giving **1** (0.33 g, 63% yield) as off-white solid (mp: 186–190 °C). IR υ_{max} 3461, 3089, 2947, 2161, 1573; ^{1}H NMR (300 MHz, DMSO) δ 8.49 (d, *J* = 5.4 Hz, 1H), 8.19 (d, *J* = 9.0 Hz, 1H), 7.83 (d, *J* = 2.2 Hz, 1H), 7.80–7.72 (m, 1H), 7.49 (dd, *J* = 9.0, 2.3 Hz, 1H), 6.59 (d, *J* = 5.4 Hz, 1H), 4.14 (dd, *J* = 5.7, 2.3 Hz, 2H), 3.19 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (75 MHz, DMSO) δ 152.3, 149.7, 149.4, 134.0, 128.0, 125.0, 124.3, 118.0, 100.3, 80.9, 74.2, 32.0; HRMS $[M + H]^{+}$ calculated for $C_{12}H_9ClN_2$ was 217.0533, found 217.0529.

*4.2.2. Representative procedure for the synthesis of sulfonyl esters (**2a** and **2a′**)*

Synthesis **2a** and **2a′** was carried out using a previously described literature method using THF solvent.[32] Starting with ethane-1,2-diol (4.5 mL, 80 mmol) solution in THF (200 mL), mesyl chloride (7.6 mL, 96 mmol) was added in a drop-wise manner over *ca.* 15 min. The reaction was stirred in an ice bath for 1 h, warmed to RT and stirring was continued for another 3 h. A white precipitate formed which was removed by filtration and the solvent removed by evaporation under reduced pressure, to afford **2a** as a colourless oil (16.6 g, 94% yield) following a silica gel column purification using 20% EtOAc/Hex eluent. ^{1}H NMR and ^{13}C NMR spectra data for **2a** were found to match the values reported in the literature.[32] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (s, 4H), 3.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.6 (2C), 37.9 (2C).

In a similar manner, compound **2a′** was obtained as a colourless oil (14.7 g, 99% yield) and spectroscopic data was found to be consistent with the literature values.[39] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (t, *J* = 7.2 Hz, 4H), 3.04 (s, 6H), 2.19 (p, *J* = 7.6, 4.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.5 (2C), 37.7 (2C), 29.2.

4.2.3. Preparation of azido mesylate spacers (3a and 3a′)

Both compounds **3a** and **3a′** were prepared according to a published method.[32] Starting with **2a** (10 g, 46 mmol), **3a** was obtained as a colourless oil (3.2 g, 42% yield) and the NMR spectra data obtained matched the literature values.[32] ^{1}H and ^{13}C NMR (300 MHz, $CDCl_3$) δ 4.28 (br t, *J* = 7.7 Hz, 2H), 3.53 (br t, *J* = 6.5 Hz, 2H), 3.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.4, 48.9, 36.8.

In a similar manner, compound **3a′** was obtained as a colourless oil (5.0 g, 46% yield) from **2a′** (14 g, 60 mmol). ^{1}H and ^{13}C NMR spectroscopic data was found to be in agreement with literature data.[40] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (t, *J* = 6.0 Hz, 2H), 3.50 (t, *J* = 6.5 Hz, 2H), 3.05 (s, 3H), 2.07–1.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.5, 47.4, 37.4, 28.7.

It should be noted that during the synthesis of **3a** and **3a'** the corresponding bis-azide-containing by-products were also observed on TLC (as less polar spots) [see reference 39 for the staining procedure utilized]. However, after chromatoraphic isolation of a desired product, no attempt was made to concentrate or characterise these byproducts due to their potential hazardous nature.

4.2.4. Preparation of amine azides (4b–4e′)

Compounds **4b–4e′** were synthesized using the same literature procedure,[32] with the exception of **4c** and **4c′** which were prepared using an alternative literature procedure.[41] The former reactions were performed using the **3a** or **3a′** intermediates at 0.5 g scale. In brief, to **3a** (3.0 mmol) and K_2CO_3 (1.3 g, 9.1 mmol) in MeCN (15 mL) was added the corresponding amine (HNR_2, 2.6 mmol). The resulting mixture was then heated at reflux overnight. After filtration and chromatographic separation on a silica gel column (Hex/EtOAc; 2:3), the desired products were obtained as colourless to yellow oils (characterizations follow).

4.2.4.1. 1-(2-Azidoethyl)piperidine (4b)

Compound **4b** was obtained as a pale yellow oil (0.27 g, 72% yield). The NMR spectroscopic data for **4b** was found to be in agreement with the data reported in the literature.[42] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.34 (t, *J* = 6.3 Hz, 2H), 2.55 (t, *J* = 6.3 Hz, 2H), 2.43 (br t, *J* = 6.2 Hz, 4H), 1.64–1.54 (m, 4H), 1.48-1.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.8, 54.6 (2C), 48.4, 25.7 (2C), 24.3.

4.2.4.2. 1-(3-Azidopropyl)piperidine (4b′)

Compound **4b′** was obtained as a pale yellow oil (0.27 g, 70% yield). The NMR spectroscopic data was found to match that of reported data.[43] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.33 (t, *J* = 6.8 Hz, 2H), 2.56–2.47 (m, 6H), 1.84–1.73 (m, 2H), 1.64–1.53 (m, 4H), 1.48–1.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.2, 54.6 (2C), 49.8, 26.4, 26.0 (2C), 24.4.

4.2.4.3. 1-(2-Azidoethyl)pyrrolidine (4c)

Compounds **4c** and **4c′** were synthesized by adapting the literature method.[41] Compound **4c** was obtained as a pale yellow oil (0.20 g, 64%). The NMR spectroscopic data for **4c** was consistent with the same compound previously reported.[44] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.38 (t, *J* = 6.4 Hz, 2H), 2.67 (t, *J* = 6.4 Hz, 2H), 2.56–2.52 (m, 4H), 1.81–1.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.9, 54.2 (2C), 50.2, 23.5 (2C).

4.2.4.4. 1-(3-Azidopropyl)pyrrolidine (4c')

Compound **4c′** was afforded as pale yellow oil (0.26 g, 73% yield). IR υ_{max} 2961, 2789, 2093, 1456, 1276, 1147; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.31 (t, *J* = 6.6 Hz, 2H), 2.51–2.42 (m, 6H), 1.80–1.70 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.8 (2C), 55.9, 52.4, 31.0, 26.1(2C); HRMS $[M + H]^+$ calculated for $C_7H_{14}N_4$ was 155.1297, found 155.1297.

4.2.4.5. 2-Azido-N,N-diethylenamine (4d)

Compound **4d** was obtained as colourless oil (0.19 g, 48%). The NMR spectrum was found to be similar to one reported in the literature.[45] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.29 (t, *J* = 6.4 Hz, 2H), 2.65 (t, *J* = 6.4 Hz, 2H), 2.56 (q, *J* = 7.2 Hz, 4H), 1.04 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.4, 49.7, 47.5 (2C), 12.0 (2C).

4.2.4.6. 3-Azido-N,N-diethylpropan-1-amine (4d')

Compound **4d′** was afforded as a colourless oil (0.13 g, 36% yield). IR υ_{max} 2942, 2097, 1343, 1169; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.34 (t, *J* = 6.8 Hz, 2H), 2.58–2.47 (m, 6H), 1.79–1.67 (m, 2H), 1.03 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.8 (2C), 46.9 (2C), 26.7, 11.8 (2C); HRMS $[M + H]^+$ calculated for $C_7H_{16}N_4$ was 157.1454, found 157.1446.

4.2.4.7. 4-(2-Azidoethyl)morpholine (4e)

Compound **4e** was obtained as a colourless oil (0.27 g, 69% yield) and the ^{1}H and ^{13}C NMR spectrum corresponded to published data.[46] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78–3.69 (m, 4H), 3.35 (br t, *J* = 6.4 Hz, 2H), 2.63–2.57 (m, 2H), 2.55–2.47 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.9 (2C), 57.6, 53.6 (2C), 47.9.

4.2.4.8. 4-(3-Azidopropyl)morpholine (4e')

Compound **4e′** was obtained as a colourless oil (0.27 g, 68% yield). The ^{1}H and ^{13}C NMR spectrum was in agreement with the published data.[43] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76–3.67 (m, 4H), 3.35 (t, *J* = 6.7 Hz, 2H), 2.50–2.32 (m, 6H), 1.82–1.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.9 (2C), 55.6, 53.6 (2C), 47.5, 25.9.

4.2.5. Preparation of azido phenyl/benzylamine moieties (4f–4h')

Azido phenylamines **4f** and **4f′** were prepared from **3a** and **3a′** by adapting a previously described literature procedure and a representative procedure is described below.[47] In a round-bottomed flask, a catalytic amount of KI (38 mg, 0.23 mmol) was added to a mixture of **3a** (0.50 g, 3.0 mmol) and K_2CO_3 (1.3 g, 9.1 mol) in MeCN (15 mL). *N*-Methylaniline (0.20 g, 1.9 mmol) was then added and the reaction was heated at reflux for 72 h. The K_2CO_3 was then filtered off, the filtrate washed with saturated brine (20 mL) and the product was extracted into CH_2Cl_2 (3 × 20 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to obtain the following products after purification as described below:

4.2.5.1. N-(2-Azidoethyl)-N-methylaniline (4f)

Compound **4f** was obtained as a pale yellow oil (0.12 g, 34% yield) following purification on a silica gel column using hexane eluant. IR υ_{max} 2947, 2791, 2092, 1453, 1253; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.23 (m, 2H), 6.81–6.71 (m, 3H), 3.60–3.54 (m, 2H), 3.51–3.44 (m, 2H), 3.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 129.3 (2C), 116.3, 111.9 (2C), 52.0, 49.8, 38.7; HRMS $[M + H]^+$ calculated for $C_9H_{12}N_4$ was 177.1142, found 177.1142.

4.2.5.2. N-(3-Azidopropyl)-N-methylaniline (4f')

Compound **4f′** was obtained as a pale yellow oil (0.13 g, 37% yield) and purified as in **4f** above. IR υ_{max} 3056, 2945, 2875, 2092, 1588, 1492, 1243; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.21 (m, 2H), 6.79–6.71 (m, 3H), 3.45 (t, *J* = 6.5 Hz, 2H), 3.40 (t, *J* = 6.5 Hz, 2H), 2.97 (s, 3H), 1.95–1.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 129.3 (2C), 116.5, 112.2 (2C), 49.8, 49.2, 38.5, 26.3; HRMS $[M + H]^+$ was 191.1294 calculated for $C_{10}H_{14}N_4$, found 191.1294.

4.2.5.3. 2-Azido-N-benzyl-N-methylethanamine (4g).

Benzylamine azide compounds **4g–4h′** were synthesized using a literature procedure.[48] Compound **4g** was obtained as a colourless oil (0.16 g, 41% yield). IR υ_{max} 2947, 2791, 2092, 1453, 1253; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.23 (m, 5H), 3.59 (s, 2H), 3.36 (t, *J* = 6.1 Hz, 2H), 2.67 (t, *J* = 6.1 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 128.9 (2C), 128.3 (2C), 127.1, 62.5, 56.2, 48.9, 42.2; HRMS $[M + H]^+$ calculated for $C_{10}H_{14}N_4$ was 191.1297, found 191.1300.

4.2.5.4. 3-Azido-N-benzyl-N-methylpropan-1-amine (4g').

Compound **4g′** was obtained as a colourless oil (0.18 g, 47% yield). IR υ_{max} 3096, 3059, 2937, 2873, 2090, 1598, 1503, 1258; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.22 (m, 5H), 3.51 (s, 2H), 3.37 (t, *J* = 6.9 Hz, 2H), 2.48 (t, *J* = 6.9 Hz, 2H), 2.21 (s, 3H), 1.86–1.75 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.0, 128.9 (2C), 128.2 (2C), 126.9, 62.4, 54.2, 49.5, 42.0, 25.5; HRMS $[M + H]^+$ calculated for $C_{11}H_{16}N_4$ was 205.1454, found 205.1457.

4.2.5.5. 2-Azido-N,N-dibenzylethanamine (4h)

Compound **4h** was obtained as a colourless oil that slowly solidified into an off-white solid at room temperature (0.33 g, 61% yield, mp: 36–38 °C). IR υ_{max} 3021, 2947, 2796, 2089, 1493, 1449, 1294; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.25 (m, 10H), 3.67 (s, 4H), 3.28 (t, *J* = 6.1 Hz, 2H), 2.74 (t, *J* = 6.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0 (2C), 128.8 (4C), 128.4 (4C), 127.1 (2C), 58.9 (2C), 53.0, 49.3; HRMS $[M + H]^+$ calculated for $C_{16}H_{18}N_4$ was 267.1610, found 267.1610.

4.2.5.6. 3-Azido-N,N-dibenzylpropan-1-amine (4h')

Compound **4h′** was obtained as a pale yellow oil (0.30 g, 57% yield). IR υ_{max} 3021, 2947, 2796, 2089, 1490, 1449, 1294; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.22 (m, 10H), 3.58 (s, 3H), 3.31 (t, *J* = 7.0 Hz, 2H), 2.53 (t, *J* = 6.8 Hz, 2H), 1.82–1.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4 (2C), 128.5 (4C), 128.3 (4C), 127.1 (2C), 58.5 (2C), 50.6, 49.6, 26.6; HRMS $[M + H]^+$ calculated for $C_{17}H_{20}N_4$ was 281.1767, found 281.1775.

4.2.6. Synthesis of 5-(3-Azidopropyl)-10,11-dihydro-5H-dibenzo[b,f]azepine (4i')

Synthesis of compound **4i′** was carried out in two separate steps, starting from commercially available 10,11-dihydro-5*H*-dibenzo[*b,f*]azepine that was coupled with 1-bromo-3-chloropropane using a modified procedure reported by DePue,[33] followed by azidation to afford the desired product. Under inert conditions, 10,11-dihydro-5*H*-dibenzo[*b,f*]azepine (0.25 g, 1.3 mmol) was dissolved in a mixture of benzene-THF (1:4, 10 mL) in a Schlenk vessel and then *n*BuLi (1.7 M in hexane, 0.76 mL, 1.3 mmol) was added in a drop-wise fashion over 30 min at 0 °C. The reaction mixture was allowed to warm to RT and 1-bromo-3-chloropropane (0.16 mL, 55 mmol) was added, and the reaction was stirred for an additional 3.5 h. The light brown solution was then concentrated *in vacuo* to obtain a crude product (0.15 g)

from which an intermediate **3i′** was isolated from **3i** on a silica gel column using hexane mobile phase (see characterization below).

4.2.6.1. 5-allyl-10,11-dihydro-5H-dibenzo[b,f]azepine (3i)

Compound **3i** was obtained as a colourless oil (70 mg, 23% yield. The NMR data was in agreement with the published data.[49] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21–7.03 (m, 6H), 7.00–6.89 (m, 2H), 5.82 (tdd, *J* = 5.7Hz, 17.3, 10.3 Hz, 1H), 5.28 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.12 (dd, *J* = 10.3, 1.5 Hz, 1H), 4.45–4.41 (m, 2H), 3.20 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0 (2C), 135.6, 134.1, 129.7 (2), 126.2(2), 122.4 (2C), 120.4 (2C), 117.1 (2C), 54.4, 32.4 (2C).

4.2.6.2. 5-(3-Chloropropyl)-10,11-dihydro-5H-dibenzo[b,f]azepine (3i')

Compound **3i′** was obtained as a pale yellow solid (84 mg, 24% yield, mp: 43–45 °C). IR υ_{max} 3056, 2953, 1587, 1492, 1364, 1265, 747, 693; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.05 (m, 6H), 7.01–6.94 (m, 2H), 3.94 (t, *J* = 6.5 Hz, 2H), 3.60 (t, *J* = 6.5 Hz, 2H), 3.20 (s, 4H), 2.13–203 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0 (2C), 133.3 (2C), 128.9 (2C), 125.4 (2C), 121.7 (2), 118.8 (2C), 46.5, 41.9, 31.1 (2C), 29.6; HRMS $[M + H]^+$ calculated for $C_{17}H_{18}ClN$ was 272.1207, found 272.1215.

4.2.6.3. 5-(3-Azidopropyl)-10,11-dihydro-5H-dibenzo[b,f]azepine (4i')

In a round-bottomed flask, compound **3i′** (70 mg, 0.26 mmol) was dissolved in benzene (2.5 mL) and a solution of NaN_3 (25 mg, 0.39 mmol) in DMSO (2.5 mL) was transferred into the reaction flask *via* a syringe. The reaction was then stirred at 100 °C for 48 h until TLC showed the starting material had been consumed. The reaction mixture was then diluted with distilled water (15 mL) and product was extracted into CH_2Cl_2 (3 × 15 mL). The organic solvent was dried over $MgSO_4$ and the evaporated *in vacuo* to afford **4i′** (61%, 44 mg) as a pale yellow oil. IR υ_{max} 2921, 2843, 2091, 1592, 1485, 1229; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.06 (m, 6H), 7.02–6.92 (m, 2H), 3.86 (t, *J* = 6.7 Hz, 2H), 3.36 (t, *J* = 6.7 Hz, 2H), 3.19 (s, 4H), 1.94–184 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0 (2C), 134.3 (2C), 130.0 (2C), 126.5 (2C), 122.8 (2C), 119.8 (2C), 49.6, 47.5, 32.2 (2C), 27.2; HRMS $[M + H]^+$ calculated for $C_{17}H_{18}N_4$ was 272.1610, found 279.1619.

4.2.7. General procedure for the preparation of triazole-linked chloroquinoline derivatives (5b–5i')

Triazole-linked compounds were synthesized using a CuAAC click reaction adapted from the literature.[50] In a 2.5 mL round-bottomed flask, compound **1** (20 mg, 0.092 mmol) and CuI (17 mg, 0.089 mmol) were mixed in anhydrous THF (0.5 mL). The appropriate amino alkyl azide (0.11 mmol) was then added and the reaction mixture was stirred for 30–90 min. at RT, until the starting material was consumed. The reaction mixture was then diluted with CH_2Cl_2 (3 mL), filtered through celite and purified on a silica gel column by means of a gradient elution with 50% EtOAc:Hex to 10% MeOH:Me_2CO mobile phase.

4.2.7.1. 7-Chloro-N-({1-[2-(piperidin-1-yl)ethyl]-1H-1,2,3-triazol-4-yl}methyl)quinolin-4-amine (5b)

Compound **5b** was obtained as a pale yellow solid (22 mg, 76% yield, mp: 132–134 °C). IR υ_{max} 3145, 2925, 1576, 1451, 1370; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 5.2 Hz, 1H), 7.96 (d, *J* = 2.1 Hz, 1H), 7.77 (s, 1H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.38 (dd, *J* = 6.8, 2.0 Hz, 1H), 6.52 (d, *J* = 5.4 Hz, 1H), 5.95 (br s, 1H), 4.63 (2s, 2H overlapping), 4.45 (t, *J* = 6.2 Hz, 2H), 2.75 (t, *J* = 6.2 Hz, 2H), 2.48–2.36 (m, 4H), 1.57–1.45 (m, 4H), 1.46–1.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 148.4, 147.7, 143.0, 134.2, 127.4, 124.6, 121.2, 120.4, 116.2, 98.4, 54.0, 53.3 (2C), 47.3, 38.0, 26.1, 24.6 (2C); HRMS $[M + H]^+$ calculated for $C_{19}H_{23}ClN_6$ was 371.1752, found 371.1751.

4.2.7.2. 7-Chloro-N-({1-[3-(piperidin-1-yl)propyl]-1H-1,2,3-triazol-4-yl}methyl)quinolin-4-amine (5b')

Compound **5b′** was obtained as a pale yellow solid (23 mg, 79% yield, mp: 133–135 °C). IR υ_{max} 3489, 2922, 1461, 1260, 1022; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, *J* = 5.4 Hz, 1H), 7.94 (d, *J* = 2.1 Hz, 1H), 7.78 (d, *J* = 9.0 Hz, 1H), 7.57 (s, 1H), 7.33 (dd, *J* = 8.9, 2.1 Hz, 1H), 6.48 (d, *J* = 5.4 Hz, 1H), 6.08 (br s, 1H), 4.64 (2s, 2H overlapping), 4.42 (t, *J* = 6.9 Hz, 2H), 2.35–2.14 (m, 6H), 2.11–2.00 (m, 2H), 1.58–1.47 (m, 4H), 1.46–1.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 149.6, 149.1, 144.0, 135.3, 128.7, 125.7, 122.4, 121.6, 117.5, 99.6, 55.3, 54.6 (2C), 48.6, 39.1, 27.6, 26.2 (2C), 24.5; HRMS $[M + H]^+$ calculated for $C_{20}H_{25}ClN_6$ was 385.1876, found 385.1895.

4.2.7.3. 7-Chloro-N-({1-[2-(pyrrolidin-1-yl)ethyl]-1H-1,2,3-triazol-4-yl}methyl)quinolin-4-amine (5c)

Compound **5c** was obtained as a pale yellow solid (18 mg, 67% yield, mp: 117–119 °C). IR υ_{max} 3409, 2923, 1699, 1518, 1451; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (br s, 1H), 7.95 (s, 1H), 7.81 (d, *J* = 9.0 Hz, 1H), 7.75 (s, 1H), 7.35 (dd, *J* = 8.9, 2.1 Hz, 1H), 6.54 (d, *J* = 5.4 Hz, 1H), 6.17 (s, 1H), 4.65 (s, 2H), 4.50 (t, *J* = 6.4 Hz, 2H), 2.98 (t, *J* = 6.4 Hz, 2H), 2.60–2.51 (m, 4H), 1.83–1.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 149.3, 148.2, 143.5, 135.4, 128.0, 125.8, 122.5, 121.7, 117.1, 99.5, 55.7, 54.1 (2C), 49.7, 39.0, 23.6 (2C); HRMS $[M + H]^+$ calculated for $C_{18}H_{21}ClN_6$ was 357.1595, found 357.1581.

4.2.7.4. 7-Chloro-N-({1-[3-(pyrrolidin-1-yl)propyl]-1H-1,2,3-triazol-4-yl}methyl)quinolin-4-amine (5c')

Compound **5c′** was obtained as a pale yellow solid (18 mg, 63% yield, mp: 115–117 °C). IR υ_{max} 3493, 2977, 1740, 1388, 1217; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, *J* = 5.3 Hz, 1H), 7.97 (d, *J* = 2.1 Hz, 1H), 7.80 (d, *J* = 9.0 Hz, 1H), 7.60 (s, 1H), 7.37 (dd, *J* = 8.9, 1.6 Hz, 1H), 6.51 (d, *J* = 5.2 Hz, 1H), 6.02 (br s, 1H), 4.65 (2s, 2H overlapping), 4.44 (t, *J* = 6.4 Hz, 2H), 2.39–2.26 (m, 4H), 2.18–2.01 (m, 2H), 1.64–1.41 (m, 4H), 1.49–1.41 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 149.3, 149.1, 143.8, 135.1, 128.8, 125.6, 122.0, 121.2, 116.5, 99.5, 54.0 (2C), 52.3, 48.5, 39.2, 29.4, 23.5 (2C); HRMS $[M + H]^+$ calculated for $C_{19}H_{23}ClN_6$ was 371.1752, found 371.1751.

4.2.7.5. 7-Chloro-N-({1-[2-(diethylamino)ethyl]-1H-1,2,3-triazol-4-yl}methyl)quinolin-4-amine (5d)

Compound **5d** was obtained as a pale yellow solid (19 mg, 70% yield, mp: 83–85 °C). IR υ_{max} 3493, 3054, 2976, 1581, 1495, 1365, 1265; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (br s, 1H), 7.94 (s, 1H), 7.75 (d, *J* = 8.9 Hz, 1H), 7.70 (s, 1H), 7.34 (d, *J* = 9.0 Hz, 1H), 6.50 (d, *J* = 5.2 Hz, 1H), 5.95 (br s, 1H), 4.63 (s, 2H), 4.39 (t, *J* = 6.2 Hz, 2H), 2.85 (t, *J* = 6.1 Hz, 2H), 2.52 (q, *J* = 6.9 Hz, 4H), 0.92 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 149.4, 148.8, 143.2, 135.4, 128.4, 125.7, 122.6, 121.3, 117.3, 99.5, 52.9, 49.2, 47.3 (2C), 39.0, 11.8 (2C); HRMS $[M + H]^+$ calculated for $C_{18}H_{23}ClN_6$ was 359.1752, found 359.1758.

4.2.7.6. 7-Chloro-N-({1-[3-(diethylamino)propyl]-1H-1,2,3-triazol-4-yl}methyl)quinolin-4-amine (5d')

Compound **5d′** was obtained as a pale yellow solid (17 mg, 61% yield, mp: 82–84 °C). IR υ_{max} 3493, 3080, 2852, 1513,

1459,1336, 1216; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, *J* = 5.4 Hz, 1H), 7.98 (d, *J* = 2.1 Hz, 1H), 7.79 (d, *J* = 9.0 Hz, 1H), 7.61 (s, 1H), 7.39 (dd, *J* = 8.9, 2.2 Hz, 1H), 6.52 (d, *J* = 5.4 Hz, 1H), 5.92 (s, 1H), 4.66 (s, 2H), 4.45 (t, *J* = 6.9 Hz, 2H), 2.55 (q, *J* = 7.2 Hz, 4H), 2.47 (t, *J* = 6.9 Hz, 2H), 2.15–2.06 (m, 2H), 1.00 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 149.7, 149.5, 144.2, 135.6, 129.1, 126.2, 122.6, 121.8, 117.8, 100.2, 50.2, 49.4, 47.7 (2C), 40.1, 28.9, 12.5 (2C). HRMS $[M + H]^+$ calculated for $C_{19}H_{25}ClN_6$ was 373.1908, found 373.1904.

4.2.7.7. 7-Chloro-N-{[1-(2-morpholinoethyl)-1H-1,2,3-triazol-4-yl]methyl}quinolin-4-amine (5e)

Compound **5e** was obtained as a pale yellow solid (21 mg, 74% yield, mp: 158–160 °C). IR υ_{max} 3485, 2921, 2849, 1581, 1460, 1374, 1260; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (br s, 1H), 7.95 (d, *J* = 2.0 Hz, 1H), 7.78 (d, *J* = 9.0 Hz, 1H), 7.71 (s, 1H), 7.32 (dd, *J* = 8.9, 2.0 Hz, 1H), 6.51 (d, *J* = 5.3 Hz, 1H), 6.07 (br s, 1H), 4.64 (2s, 2H), 4.46 (t, *J* = 6.9 Hz, 2H), 3.66 (t, *J* = 4.8 Hz, 4H), 2.81 (t, *J* = 4.6 Hz, 4H), 2.50–2.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 149.5, 148.7, 143.7, 135.3, 128.3, 125.7, 122.3, 121.4, 117.2, 99.6, 66.8 (2C), 57.8, 53.5 (2C), 47.4, 39.0; HRMS $[M + H]^+$ calculated for $C_{18}H_{21}ClN_6O$ was 373.1544, found 373.1537.

4.2.7.8. 7-Chloro-N-{[1-(3-morpholinopropyl)-1H-1,2,3-triazol-4-yl]methyl}quinolin-4-amine (5e')

Compound **5e′** was obtained as a pale yellow solid (25 mg, 85% yield, mp: 153–155 °C). IR υ_{max} 3338, 2929, 1576, 1450, 1370; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (br s, 1H), 7.97 (d, *J* = 2.0 Hz, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.55 (s, 1H), 7.37 (dd, *J* = 8.9, 2.0 Hz, 1H), 6.51 (d, *J* = 5.3 Hz, 1H), 5.97 (s, 1H), 4.66 (2s, 2H overlapping), 4.45 (t, *J* = 6.9 Hz, 2H), 3.70–3.63 (m, 4H), 2.40–2.36 (m, 4H), 2.40 (t, *J* = 6.8 Hz, 2H overlapping), 2.13–2.04 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 149.5, 147.5, 142.8, 134.2, 127.2, 124.6, 121.5, 120.5, 116.3, 98.8, 65.9 (2C), 53.8 (2C), 52.5, 47.2, 37.9, 25.9; HRMS $[M + H]^+$ calculated for $C_{19}H_{23}ClN_6O$ was 387.1701, found 387.1707.

4.2.7.9. 7-Chloro-N-[(1-{2-[phenyl(methyl)amino]ethyl}-1H-1,2,3-triazol-4-yl)methyl]quinolin-4-amine (5f)

Compound **5f** was obtained as an off-white solid (25 mg, 85% yield, mp: 167–169 °C). IR υ_{max} 3493, 2970, 1740, 1368, 1217; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, *J* = 5.3 Hz, 1H), 7.99 (d, *J* = 2.1 Hz, 1H), 7.68 (d, *J* = 8.9 Hz, 1H), 7.40 (s, 1H overlapping), 7.39 (dd, *J* = 8.7, 2.2 Hz, 1H ovelapping), 7.26–7.12 (m, 2H), 6.81–6.70 (m, 1H), 6.59–6.54 (m, 2H), 6.46 (d, *J* = 5.4 Hz, 1H), 5.65 (br s, 1H), 4.63–4.52 (m, 4H), 3.84 (t, *J* = 5.9 Hz, 2H), 2.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0, 149.1, 148.2, 144.1, 135.1, 129.4 (2C) , 128.8 (2C), 125.6, 122.8, 121.1, 117.6, 117.2, 112.3 (2C), 99.5, 53.1, 48.0, 38.9, 38.6; HRMS $[M + H]^+$ calculated for $C_{21}H_{21}ClN_6$ was 393.1595, found 393.1595.

4.2.7.10. 7-Chloro-N-[(1-{3-[phenyl(methyl)amino]propyl}-1H-1,2,3-triazol-4-yl)methyl]quinolin-4-amine (5f')

Compound **5f′** was obtained as an off-white solid (17 mg, 53% yield, mp: 163–165 °C). IR υ_{max} 3452, 2932, 1576, 1450, 1366, 1220; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 5.4 Hz, 1H), 7.94 (d, *J* = 2.1 Hz, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.47 (s, 1H), 7.33 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.24–7.15 (m, 2H), 6.78–6.67 (m, 1H), 6.65 (d, *J* = 8.0 Hz, 2H), 6.49 (d, *J* = 5.4 Hz, 1H), 6.09 (br s, 1H) 4.63 (br s, 2H), 4.38 (t, *J* = 7.0 Hz, 2H), 3.37 (t, *J* = 6.9 Hz, 2H), 2.89 (s, 3H), 2.28–2.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 150.3, 149.8, 149.2, 144.7, 136.0, 130.0 (2C), 128.9 (2C), 126.4, 122.5, 122.2, 117.8, 113.4 (2C), 100.2, 50.2, 49.0, 39.7, 39.3, 30.4; HRMS $[M + H]^+$ calculated for $C_{22}H_{23}ClN_6$ was 407.1752, found 407.1743.

4.2.7.11. 7-Chloro-N-[(1-{2-[benzyl(methyl)amino]ethyl}-1H-1,2,3-triazol-4-yl)methyl] quinolin-4-amine (5g)

Compound **5g** was obtained as an off-white solid (22 mg, 69% yield, mp: 133–135 °C). IR υ_{max} 3444, 3317, 3144, 2932, 2847, 1579, 1448, 1367, 1220; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (br s, 1H), 7.88 (s, 1H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.53 (s, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.26–7.02 (m, 5H), 6.44 (d, *J* = 5.2 Hz, 1H), 5.92 (br s, 1H), 4.56 (2s, 2H overlapping), 4.37 (t, *J* = 6.1 Hz, 2H), 3.45 (s, 2H), 2.78 (t, *J* = 6.1 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 149.6, 148.6, 143.6, 138.2 (2C), 135.2, 128.8 (2C), 128.3(2C), 127.3, 125.7, 122.3, 122.4, 117.2, 99.4, 62.4, 56.4, 48.4, 42.2, 39.0; HRMS $[M + H]^+$ calculated for $C_{22}H_{23}ClN_6$ was 407.1752, found 407.1744.

4.2.7.12. 7-Chloro-N-[(1-{3-[benzyl(methyl)amino]propyl}-1H-1,2,3-triazol-4-yl)methyl]quinolin-4-amine (5g')

Compound **5g′** was obtained as an off-white solid (21 mg, 65% yield, mp: 132–134 °C). IR υ_{max} 3444, 3317, 2932, 1579, 1448, 1367, 1220, 1137; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (br s, 1H), 7.98 (s, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.42–7.18 (m, 7H), 6.51 (s, 1H), 5.95 (br s, 1H), 4.58 (s, 2H), 4.43 (t, *J* = 6.8 Hz, 2H), 3.46 (s, 2H), 2.35 (t, *J* = 6.4 Hz, 2H), 2.22 (s, 3H), 2.09–2.04 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 149.8, 148.0, 143.4, 138.8, 135.5, 129.1 (2C), 128.3 (2C), 127.9, 127.2, 125.8, 122.2, 121.5, 117.1, 99.4, 62.7, 53.0, 48.1, 42.2, 38.9, 27.8; HRMS $[M + H]^+$ calculated for $C_{23}H_{25}ClN_6$ was 421.1908, found 421.1905.

4.2.7.13. 7-Chloro-N-({1-[2-(dibenzylamino)ethyl]-1H-1,2,3-triazol-4-yl}methyl)quinolin-4-amine (5h)

Compound **5h** was obtained as a yellow solid (20 mg, 54% yield, mp: 115–118 °C). IR υ_{max} 3493, 3004, 2970, 1740, 1368, 1217, 1054; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (br s, 1H), 7.98 (s, 1H), 7.78 (d, *J* = 9.0 Hz, 1H), 7.41–7.17 (m, 10H), 6.89 (s, 1H), 6.48 (d, *J* = 5.4 Hz, 1H), 5.98 (br s, 2H), 4.50 (s, 2H), 4.35 (t, *J* = 6.1 Hz, 2H), 3.57 (s, 4H), 2.46 (t, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 150.1, 149.2, 143.8, 140.1 (2C), 136.1, 129.8 (4C), 129.1 (2C), 128.9 (4C), 127.9, 126.4, 122.8, 122.1, 117.7, 100.0, 59.5 (2C), 50.4, 48.7, 39.5; HRMS $[M + H]^+$ calculated for $C_{28}H_{27}ClN_6$ was 483.2065, found 483.2063.

4.2.7.14. 7-Chloro-N-({1-[3-(dibenzylamino)propyl]-1H-1,2,3-triazol-4-yl}methyl)quinolin-4-amine (5h')

Compound **5h′** was obtained as a yellow solid (24 mg, 63% yield, mp: 114–115 °C). IR υ_{max} 3484, 3206, 2994, 2931, 1580, 1543, 1431, 1365; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.8 Hz, 1H), 7.98 (d, *J* = 1.8 Hz, 1H), 7.76 (d, *J* = 9.0 Hz, 1H), 7.39–7.22 (m, 11H), 6.79 (s, 1H), 6.47 (d, *J* = 5.4 Hz, 1H), 5.96 (br s, 1H), 4.49 (2s, 2H overlapping), 4.35 (t, *J* = 6.8 Hz, 2H), 3.56 (s, 4H), 2.46 (t, *J* = 6.2 Hz, 2H), 2.10–2.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 149.3, 148.9, 143.2, 139.4 (2C), 135.2, 129.1 (4C), 128.7 (2C), 128.4 (4C), 127.2, 125.7, 121.9, 121.2, 117.2, 99.4, 58.8 (2C), 49.7, 48.0, 38.9, 28.1; HRMS $[M + H]^+$ calculated for $C_{29}H_{29}ClN_6$ was 497.2221, found 497.2214.

4.2.7.15. 7-Chloro-N-({1-[2-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)ethyl]-1H-1,2,3-triazol-4-yl}methyl)quinolin-4-amine (5i')

Compound **5i′** was obtained as a pale yellow solid (24 mg, 64% yield, mp: 67–69 °C). IR υ_{max} 3484, 3371, 3147, 2927, 2851, 1576, 1544, 1258, 1058; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, *J* = 5.4 Hz, 1H), 7.97 (d, *J* = 2.1 Hz, 1H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.38 (d, *J* = 2.1 Hz, 1H), 7.35 (s, 1H) 7.16–6.90 (m, 8H), 6.44 (d, *J* = 5.5 Hz, 1H), 5.98 (br s, 1H) 4.57 (2s, 2H overlapping), 4.35 (t, *J* = 6.9 Hz, 2H), 3.77 (t, *J* = 6.4 Hz, 2H), 3.18 (s, 4H), 2.26–2.16 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 150.6, 147.6, 143.8, 135.4, 134.1 (2C), 130.1(2C), 129.5, 128.0, 126.6 (2C), 125.7, 123.1 (2C), 121.9, 121.4, 121.0, 119.7 (2C), 117.0, 99.3, 48.1, 46.9, 38.9, 32.1 (2C), 28.3; HRMS $[M + H]^+$ calculated for $C_{29}H_{27}ClN_6$ was 495.2065, found 495.2067.

4.3. Cell culture and antiplasmodial activity measurements

The antimalarial activity of compounds ***5b–5i′*** was tested and determined in triplicate on two separate occasions against chloroquine-sensitive (NF54) and chloroquine-resistant (Dd2) strains of *P. falciparum*. Continuous *in vitro* cultures of asexual erythrocyte stages of *P. falciparum* were maintained using a modified method of Trager and Jensen.[51] Quantitative assessment of antiplasmodial activity *in vitro* was determined via the parasite lactate dehydrogenase assay (pLDH) using a modified method essentially described by Makler *et al*.[52]

The test samples were prepared to a 20 mg/mL stock solution in 100% DMSO. Stock solutions were stored at -20 °C. Further dilutions were prepared on the day of the experiment. CQ diphosphate (Sigma) and artesunate (Sigma) were used as the reference drugs in all experiments. The concentration inhibiting 50% of parasite growth (IC_{50} value) for each compound was determined from a full-dose response curve. The test samples were tested at a starting concentration of 100 µg/mL, which was then serially diluted 2-fold in complete medium to give 10 concentrations, with the lowest concentration being 0.20 µg/mL. Reference drugs were tested at 100 ng/mL starting concentration of 100 ng/mL. Several compounds were also tested at a starting concentration of 1000 µg/mL. The highest concentration of solvent to which the parasites were exposed to had no measurable effect on the parasite viability (data not included). The IC_{50} values were obtained using non-linear dose-response curve fitting analysis via Graph Pad Prism v.4.0 software.

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