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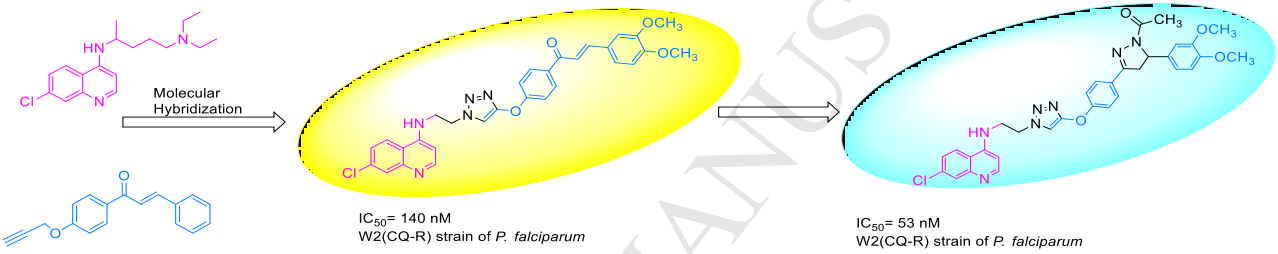

Synthesis and *in vitro* antiplasmodial evaluation of 4-aminoquinoline-chalcone/*N*-acetylpyrazoline conjugates against W2 (CQ-R) strain of *P. falciparum*

4-Aminoquinoline-Chalcone/-*N*-Acetylpyrazoline Conjugates: Synthesis and antiplasmodial Evaluation

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Abstract: 1*H*-1,2,3-triazole linked 4-aminoquinoline-chalcone/-*N*-acetylpyrazoline conjugates were synthesized and evaluated against cultured chloroquine (CQ) resistant strain. Antiplasmodial activities of the synthesized conjugates revealed dependence of activity on the length of the alkyl chain as well as on the presence of methoxy substituents on ring A/ring B of the chalcone. The most potent and non-cytotoxic conjugate showed comparable antiplasmodial activity with that of CQ, with an IC_{50} value of 53.7 nM.

Key Words: 4-Aminoquinoline - Chalcone - *N*-Acetylpyrazoline - Click Chemistry - Antiplasmodial

1. Introduction

Despite substantial progress since 2000 in the fight against malaria, the disease continues to be the most lethal parasitic infection. According to the latest World Health Organization (WHO) update, malaria was responsible for 212 million illnesses and 4,29,000 deaths in 2015, with children and pregnant women the most affected groups [1]. Among the five plasmodial species that infect humans, *P. falciparum* is most virulent and prevalent form, accounting for >90% of malarial deaths [2]. CQ was the mainstay for treatment of malaria [3-6], but it is no longer used to treat falciparum malaria in most areas due to widespread resistance. WHO now recommends fixed dose artemisinin-based combination therapies (ACTs) to treat uncomplicated malaria [7-10]. However, emergence of resistance to artemisinins and frequent failures after therapy with some ACTs in Cambodia and nearby countries has provided strong impetus to discover new antimalarial agents [1,10].

4-Aminoquinoline-hybridization involving covalent fusion of two or more pharmacophoric fragments to yield a single hybrid molecule with improved efficacy compared to the parent drugs has emerged as a promising strategy in antimalarial chemotherapy [11-14]. The potential of quinoline hybridization is well exemplified by

trioxaferroquines, artemisinin-quinine, and clotrimazole-quinoline conjugates, all of which demonstrate potent antimalarial activity [15].

Chalcones, belonging to the flavanoid family of natural products, have been a source of motivation to synthetic medicinal chemists because of their synthetic accessibility and diverse biological activities [16-18]. The antiplasmodial potential of chalcones has been attributed to their ability to inhibit plasmodial aspartic proteases, cysteine proteases, cyclin-dependent protein kinases and new permeation pathways [19], but mechanisms of action are uncertain. 4-Aminoquinoline-chalcone conjugates, prepared either *via* click chemistry or aromatic nucleophilic substitution, have shown good antimalarial activities against CQ-resistant strains of *P. falciparum* [20]. Pyrazoline is another well-known pharmacophore found in many natural products. It exhibits a wide range of biological activities, including antimicrobial, antitubercular, antitumor, anticancer and antiplasmodial actions [21-25].

Recent work from our lab described the synthesis and antiplasmodial activities of amide-tethered 4-aminoquinoline-chalcone/4-aminoquinoline-ferrocenyl chalcone conjugates [26]. Structure-activity relationship (SAR) studies revealed methoxy substituents on ring B of the chalcones along with longer alkyl chains, introduced as spacers between two pharmacophores, to be essential for good activities. Inspired by these results and in continuation [27], the present manuscript describes the synthesis and antiplasmodial evaluation of 1*H*-1,2,3-triazole-tethered 4-aminoquinoline-chalcone/ *N*-acetylpyrazoline conjugates (**Figure 1**) along with their antiplasmodial evaluation against *P. falciparum*. The insertion of a 1*H*-1,2,3-triazole core in the present series of conjugates is based on its well established stability under acidic, basic, reductive and oxidative conditions, along with additional favourable properties including capability of hydrogen bonding and rigidity in binding with biomolecular targets [28].

2. Result and Discussion

2.1 Synthetic Chemistry

The synthetic approach involved an initial treatment of 4,7-dichloroquinoline **1** with ethanolamine or 1-propanol amine at 120 °C to afford another precursor **2**. The treatment of **2** with methane sulphonyl chloride in dry DCM at 0 °C for 2 h, followed by its reaction with sodium azide at 120 °C in dry DMF for 12 h afforded **3**, as depicted in **Scheme 1** [29].

The precursors' acetylenic chalcones **6** and their corresponding pyrazolines **7** were prepared *via* an initial propargylation of substituted-4-hydroxy acetophenones **4** to yield the

corresponding *O*-propargylated acetophenones **5**. Aldol condensation of **5** with substituted benzaldehydes in the presence of KOH led to the formation of *O*-propargylated chalcones **6**. The treatment of **6** with hydrazine hydrate in acetic acid at 120°C led to the formation of corresponding pyrazolines **7** (**Scheme 2**).

Cu-promoted azide-alkyne cycloaddition reaction of **6** with (2-azido-ethyl/propyl)-(7-chloro-quinolin-4-yl)-amine **3** in the presence of sodium ascorbate at room temperature afforded the desired 1*H*-1,2,3-triazole tethered 4-aminoquinoline-chalcone conjugates **8** in good to excellent yields. A similar approach, involving the reaction between **3** and **7** in ethanol: water (85:15) mixture, was employed for the preparation of 1*H*-1,2,3-triazole-tethered 4-aminoquinoline-pyrazoline conjugates **9** (**Scheme 3**).

The structure to the synthesized conjugates was assigned on the basis of spectral data and analytical evidence. For example, **9p** showed a molecular ion peak $[M]^+$ at 699.2561 and [M+2] at 701.2579 in its high resolution mass spectrum (HRMS), while its ^{1}H NMR spectrum exhibited the presence of a singlet at δ 2.43 due to the presence of an acetyl group, a singlet at δ 5.19 due to presence of two methylene proton and a singlet at δ 8.94 corresponding to a triazole ring proton, along with characteristic absorptions due to quinoline ring protons. The presence of the required number of carbons in the ^{13}C NMR spectrum of **9p** along with characteristic absorption due to a carbonyl carbon at δ 167.9 further confirmed the assigned structure.

2.2 In vitro Antiplasmodial activity

The synthesized conjugates were assayed for their antiplasmodial efficacy against the chloroquine-resistant W2 strain of *P. falciparum* (**Table 1**). Although, the synthesized compounds were not as active as artemisinin (ART); some of the conjugates exhibited comparable or better activities than CQ. A careful analysis of **Table 1** revealed the dependence of activity on the length of the alkyl chain introduced as a spacer along with the nature of substituents at ring A/ ring B of the chalcones. Comparing the activity data among ethyl chain linked 4-aminoquinoline-chalcone conjugates *viz.* **8a-h** revealed a reduction in antiplasmodial efficacy with the introduction of a $–OCH_3$ substituent at ring A irrespective of the nature of substituents at ring B. The conjugates **8a-d** (R=H, ring A) exhibited IC_{50} values ranging from 114.4-172.1 nM. Increasing the chain length from ethyl to propyl (**8i-p**) resulted in considerable loss in antiplasmodial activities, except in the case **8o**, which displayed an

IC_{50} value of 357 nM. The introduction of a pyrazoline ring substantially improved the antiplasmodial activity of the synthesized conjugates. Comparing the activities among ethyl chain linked 4-aminoquinoline-pyrazoline conjugates, **9a-h** revealed improved activity with the introduction of a $–OCH_3$ substituent at ring A of the chalcone, as evident with conjugates **9f** and **9g,** exhibiting IC_{50} values of 58.7 nM and 53.7 nM, respectively. Similar comparison among conjugates **9i-p**, with a propyl linker, revealed reduction in antiplasmodial activities; except for **9m,** with an IC_{50} value of 77nM. Cytotoxicity of few of the most potent compounds *viz.* **8b**, **8c**, **9b**, **9f**, **9g** and **9m** were assessed against mammalian HeLa cells and the results are enlisted in **Table 2**. As evident the compounds were non-cytotoxic and exhibited a good selectivity index.

In conclusion, a series of 4-aminoquinoline-chalcones/*N*-acetyl-pyrazolines were synthesized *via* Cu-promoted azide-alkyne cycloaddition reaction and evaluated against chloroquine-resistant *P. falciparum.* SAR studies revealed the conjugates to have comparable antiplasmodial activities with that of chloroquine. 4-aminoquinoline-pyrazoline conjugate **9g,** with an optimum combination of a $–OCH_3$ substituent at ring A and 3,4-dimethoxy substituents at ring B proved to be most potent and non-cytotoxic, with an IC_{50} value of 53.7 nM.

3. Experimental Section

^{1}H NMR spectra were recorded in deuterochloroform and DMSO-d_6 with a Jeol 400 (400 MHz) and Bruker 500 (500 MHz) spectrometer using TMS as an internal standard. Chemical shift values are expressed as parts per million downfield from TMS and J values are in hertz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, m: multiplet, dd: double doublet, ddd: doublet of a doublet of a doublet, and br: broad peak. ^{13}C NMR spectra were recorded on a Bruker 400 (100 MHz) and Bruker 500 (125 MHz) spectrometer in dimethylsulfoxide using TMS as internal standard. High resolution mass spectra were recorded on a Bruker-micrOTOF-Q II spectrometer.

3.1 General procedure for the synthesis of conjugates **8** or **9**: To the stirred solution of (2-Azido-ethyl/propyl)-(7-chloro-quinolin-4-yl)-amine **3** (1 mmol) and propargylated substituted chalones **6** (1 mmol) or propargylated substituted pyrazolines **7** (1 mmol) in ethanol: water (85:15) mixture, was added $CuSO_4.5H_2O$ (0.055 mmol) and sodium ascorbate (0.143 mmol). The reaction mixture was allowed to stir at room temperature for 7-8 h, with progress monitored *via* TLC. After the usual workup in DCM and water, combined organic

layers were collected, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to yield crude product which was purified by column chromatography over 60-120 silica gel using 95:5 ($CHCl_3$: MeOH) mixture.

3.1.1 1-(4-{1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-phenyl)-3-phenyl-propenone (**8a**): Yield 85%; Light yellow Solid; m.p. 140-141 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.50-3.52 (m, 2H, -CH_2), 4.48-4.50 (m, 2H, -CH_2), 5.21 (s, 2H, -OCH_2), 6.42 (d, J = 5.6 Hz, 1H, H^2), 7.10 (m, 2H, ArH), 7.33 (d, J = 9.2 Hz, 1H, H^4), 7.42-7.46 (d, J = 8.8 Hz, 2H, ArH), 7.51 (d, J = 15.6 Hz, 1H, olefinic-H), 7.62 (m, 3H, ArH),7.76 (s, 1H, -NH exchangeable with D_2O), 7.81 (d, J = 15.6 Hz, 1H, olefinic-H), 7.89 (s, 1H, H^5), 7.95 (d, J = 9.2 Hz, 1H, H^3), 8.07 (d, J = 8.4 Hz, 2H, ArH), 8.22 (s, 1H, H^6), 8.42 (d, J = 5.6 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 100 MHz): 48.5, 62.0, 69.9, 99.2, 107.2, 115.4, 117.6, 120.9, 124.1, 125.2, 125.8, 126.4, 128.3, 130.7, 131.9, 134.6, 140.9, 142.6, 144.2, 146.5, 150.2, 151.6, 152.3, 162.1, 188.0; HRMS: Calcd for $C_{29}H_{24}ClN_5O_2$ $[M]^+$509.1619 and [M+2] 511.1619, found 509.1610 and 511.1605; Anal. Calcd (%) for: C, 68.30; H, 4.74; N, 13.73, found: C, 68.43; H, 4.67; N, 13.65.

3.1.2 1-(4-{1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-phenyl)-3-(4-methoxy-phenyl)-propenone (**8b**):Yield 82%; Light Yellow Solid; m.p. 179-180 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.65-3.67 (m, 2H, -CH_2-),3.70 (s, 3H, -OCH_3), 4.69-4.71 (m, 2H, -CH_2), 5.20 (s, 2H, -OCH_2), 6.45 (d, J = 5.6 Hz, 1H, H^2), 7.02 (d, J = 8.8 Hz, 2H, ArH), 7.32 (d, J = 9.2 Hz, 1H, H^4), 7.42 (d, J = 8.4 Hz, 2H, ArH), 7.54 (d, J = 15.6 Hz, 1H, olefinic-H), 7.69 (d, J = 8.4 Hz, 2H, ArH), 7.83 (d, J = 15.6 Hz, 1H, olefinic-H), 7.88 (s, 1H, H^5), 7.98 (s, 1H, -NH exchangeable with D_2O), 8.05 (d, J = 9.2 Hz, 1H, H^3), 8.17 (d, J = 8.8 Hz, 2H, ArH), 8.25 (s, 1H, H^6), 8.46 (d, J = 5.6 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 100 MHz): 48.8, 55.2, 62.0, 70.5, 99.0, 107.4, 115.7, 117.5, 121.0, 124.3, 125.4, 126.0, 126.8, 130.7, 131.4, 134.8, 140.6, 142.9, 144.4, 146.3, 150.1, 151.8, 152.2, 157.5, 162.0, 188.3; HRMS: Calcd for $C_{30}H_{26}ClN_5O_3$ $[M]^+$539.1724 and [M+2] 541.1724, found 539.1733 and 541.1720; Anal. Calcd (%) for: C, 66.72; H, 4.85; N, 12.97, found: C, 66.62; H, 4.77; N, 12.84.

3.1.3 1-(4-{1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-phenyl)-3-(3,4-dimethoxy-phenyl)-propenone (**8c**): Yield 90%; Light yellow Solid; m.p. 162-163 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.70 (s, 3H, -OCH_3), 3.77-3.79 (m, 2H, -CH_2),3.82 (s, 3H, -OCH_3), 4.52-4.55 (m, 2H, -CH_2), 5.19 (s, 2H, -OCH_2), 6.44 (d, J = 6.0 Hz, 1H, H^2), 6.49 (dd, J = 2.0, 8.0 Hz, 1H, ArH), 6.57 (d, J = 2.5 Hz, 1H, ArH), 6.80 (d, J = 8.5

Hz, 1H, ArH), 7.18 (d, *J* = 8.5 Hz, 2H, ArH),7.52 (d, *J* = 15.6 Hz, 1H, olefinic-H), 7.59 (dd, *J* = 1.5, 9.0 Hz, 1H, H^4), 7.73 (d, *J* = 8.5 Hz, 2H, ArH), 7.83 (d, *J* = 15.6 Hz, 1H, olefinic-H), 7.85 (s, 1H, -NH exchangeable with D_2O), 8.09 (s, 1H, H^5), 8.20 (d, *J* = 9.0 Hz, 1H, H^3), 8.34 (s, 1H, H^6), 8.46 (d, *J* = 4.5 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 48.0, 56.4, 60.6, 62.1, 79.3, 99.2, 107.1, 115.4, 117.5,121.2, 123.9, 124.8, 125.1, 126.0, 126.6, 129.8, 131.6, 135.0, 140.2, 142.7, 144.0, 147.4, 150.6, 151.1, 151.8, 152.9, 153.6, 162.5, 188.1; HRMS: Calcd for $C_{31}H_{28}ClN_5O_4$ $[M]^+$569.1830 and [M+2] 571.1830, found 569.1836 and 571.1842; Anal. Calcd (%) for: C, 65.32; H, 4.95; N, 12.29, found: C, 65.45; H, 5.09; N, 12.24.

3.1.4 1-(4-{1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-phenyl)-3-(3,4,5-trimethoxy-phenyl)-propenone (**8d**): Yield 87%; Light yellow Solid; m.p. 152-153 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.74 (s, 3H, -OCH_3), 3.77 (s, 6H, 2×-OCH_3), 3.81-3.83 (m, 2H, -CH_2), 4.74-4.76 (m, 2H, -CH_2), 5.20 (s, 2H, -OCH_2),6.40 (s, 2H, ArH), 6.46(d, *J* = 6.0 Hz, 1H, H^2), 6.99 (d, *J* = 9.2 Hz, 2H, ArH), 7.32 (dd, *J* = 2.0, 8.4 Hz, 1H, H^4), 7.51 (d, *J* = 15.6 Hz, 1H, olefinic-H), 7.58 (d, *J* = 8.8 Hz, 2H, ArH), 7.72 (s, 1H, H^5), 7.79 (d, *J* = 15.6 Hz, 1H, olefinic-H), 7.85 (m, 2H, H^3+ H^6), 8.33 (d, *J* = 5.6 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 100 MHz): 47.9, 55.1, 55.4, 60.3, 61.8, 68.8, 98.9, 104.6, 115.0, 117.2, 121.7, 123.5, 124.5, 125.3, 126.0, 126.6, 128.6, 134.9, 140.1, 142.5, 144.0, 147.5, 150.3, 154.8, 156.9, 159.7, 161.0, 187.2; HRMS: Calcd for $C_{32}H_{30}ClN_5O_5$ $[M]^+$599.1935 and [M+2] 601.1935, found 599.1928 and 601.1944; Anal. Calcd (%) for: C, 64.05; H, 5.04; N, 11.67, found: C, 63.95; H, 5.16; N, 11.59.

3.1.5 1-(4-{1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-3-methoxy-phenyl)-3-phenyl-propenone (**8e**): Yield 90%; Light yellow Solid; m.p. 143-144 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.71-3.74 (m, 5H, -CH_2+ -OCH_3), 4.76-4.78 (m, 2H, -CH_2), 5.17 (s, 2H, -OCH_2), 6.54 (d, *J* = 6.0 Hz, 1H, H^2), 6.93 (m, 2H, ArH), 7.18 (d, *J* = 8.0 Hz, 1H, ArH), 7.31 (d, *J* = 8.8 Hz, 1H, H^4), 7.53-7.61 (m, 6H, ArH+ olefinic-H), 7.82 (d, *J* = 15.6 Hz, 1H, olefinic-H), 7.85 (s, 1H, H^5), 8.01 (d, *J* = 8.8 Hz, 1H, H^3), 8.15 (s, 1H, H^6), 8.40 (d, *J* = 6.0 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 48.1, 55.1, 61.5, 79.0, 99.1, 106.8, 111.2, 112.5, 117.1, 120.5, 123.2, 124.3, 125.3, 125.7, 126.4, 128.0, 131.4, 135.0, 139.9, 142.2, 143.7, 147.5, 149.8, 150.1, 151.6, 152.8, 161.7, 188.6; HRMS: Calcd for $C_{30}H_{26}ClN_5O_3$ $[M]^+$539.1724 and [M+2] 541.1724, found 539.1731 and 541.1712; Anal. Calcd (%) for: C, 66.72; H, 4.85; N, 12.97, found: C, 66.62; H, 4.71; N, 12.90.

3.1.6 1-(4-{1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-3-methoxy-phenyl)-3-(4-methoxy-phenyl)-propenone (**8f**): Yield 83%; Light Yellow Solid; m.p. 182-183 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.71 (s, 3H, -OCH_3), 3.74 (s, 3H, -OCH_3), 3.81-3.84 (m, 2H, -CH_2), 4.59-4.61 (m, 2H, -CH_2), 5.20 (s, 2H, -OCH_2), 6.47 (d, *J* = 5.6 Hz, 1H, H^2), 6.80 (d, *J* = 8.8 Hz, 2H, ArH), 7.21 (d, *J* = 8.p Hz, 1H, ArH), 7.32 (d, *J* = 9.2 Hz, 1H, H^4), 7.54-7.62 (m, 5H, 4ArH+olefinic-H), 7.79 (d, *J* = 15.6 Hz, 1H, olefinic-H), 7.90 (s, 1H, H^5), 8.04 (d, *J* = 9.2 Hz, 1H, H^3), 8.20 (s, 1H, H^6), 8.42 (d, *J* = 5.6 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 48.4, 55.1, 55.6, 62.0, 79.1, 98.8, 106.2, 111.5, 112.7, 117.3, 120.6, 123.4, 124.2, 125.1, 125.7, 126.0, 128.9, 131.0, 135.3, 140.2, 142.4, 143.9, 147.6, 149.7, 150.2, 151.8, 157.4, 162.1, 188.2; HRMS: Calcd for $C_{31}H_{28}ClN_5O_3$ $[M]^+$569.1830 and [M+2] 571.1830, found 569.1840 and 571.1837; Anal. Calcd (%) for: C, 65.32; H, 4.95; N, 12.29, found: C, 65.46; H, 4.87; N, 12.43.

3.1.7 1-(4-{1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-3-methoxy-phenyl)-3-(3,4-dimethoxy-phenyl)-propenone (**8g**): Yield 79%; Light yellow Solid; m.p. 155-156 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.82-3.86 (m, 11H, -CH_2+3×-OCH_3), 4.70-4.72 (m, 2H, -CH_2), 5.25 (s, 2H, -OCH_2), 6.66 (d, *J* = 5.6 Hz, 1H, H^2), 7.02 (d, *J* = 8.5 Hz, 1H, ArH), 7.29 (d, *J* = 8.5 Hz, 1H, ArH), 7.40 (d, *J* = 9.0 Hz, 1H, H^4), 7.53-7.60 (m, 3H, ArH), 7.68 (d, *J* = 15.5 Hz, 1H, olefinic-H), 7.81-7.91 (m, 3H, olefinic-H+H^3+ArH), 8.02 (s, 1H, H^5), 8.27-8.33 (m, 2H, H^6+H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 48.3, 56.0, 56.1, 56.2, 62.1, 79.6, 99.7, 104.7, 111.3, 111.4, 112.0, 112.6, 119.9, 123.5, 124.1, 124.8, 125.5, 125.8, 128.1, 131.5, 135.1, 139.8, 142.6, 144.0, 149.3, 149.4, 151.5, 151.8, 152.1, 155.0, 162.7, 187.7; HRMS: Calcd for $C_{32}H_{30}ClN_5O_5$ $[M]^+$599.1935 and [M+2] 601.1935, found 599.1942 and 601.1948; Anal. Calcd (%) for: C, 64.05; H, 5.04; N, 11.67, found: C, 64.21; H, 5.11; N, 11.55.

3.1.8 1-(4-{1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-3-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-propenone (**8h**): Yield 90%; Light yellow Solid; m.p. 148-149 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.71-3.79 (m, 14H, 4×-OCH_3+ -CH_2), 4.83-4.85 (m, 2H, -CH_2), 5.22 (s, 2H, -OCH_2), 6.33 (s, 2H, ArH), 6.70 (d, *J* = 6.0 Hz, 1H, H^2), 7.12 (d, *J* = 8.0 Hz, 1H, ArH), 7.43 (d, *J* = 9.2 Hz, 1H, H^4), 7.47-7.52 (m, 2H, ArH), 7.65 (d, *J* = 15.6 Hz, 1H, olefinic-H), 7.82 (d, *J* = 15.6 Hz, 1H, olefinic-H), 7.85 (s, 1H, H^5), 7.99 (d, *J* = 9.2 Hz, 1H, H^3), 8.24 (s, 1H, H^6), 8.41 (d, *J* = 6.0 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 47.4, 55.2, 55.4, 55.5, 60.5, 61.0, 79.6, 99.1, 106.3, 111.4, 112.9, 116.8, 120.1, 124.0, 124.6, 125.4, 125.7, 126.3, 127.9, 131.4, 135.3, 139.7, 142.5, 143.6,

147.5, 150.3, 154.0, 156.4, 159.5, 162.6, 187.8; HRMS: Calcd for $C_{33}H_{32}ClN_5O_6$ $[M]^+$629.2041 and [M+2] 631.2041, found 629.2036 and 631.2049; Anal. Calcd (%) for: C, 62.90; H, 5.12; N, 11.11, found: C, 62.95; H, 5.01; N, 11.04.

3.1.9 1-(4-{1-[3-(7-Chloro-quinolin-4-ylamino)-propyl]-1H-[1,2,3]triazol-4-ylmethoxy}-phenyl)-3-phenyl-propenone (**8i**): Yield 89%; Light yellow Solid; m.p. 161-162 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.25-2.28 (m, 2H, -CH_2), 3.55-3.57 (m, 2H, -CH_2), 4.64-4.66 (m, 2H, -CH_2), 5.17 (s, 2H, -OCH_2), 6.39 (d, *J* = 5.2 Hz, 1H, H^2), 7.18 (m, 2H, 2ArH), 7.31 (d, *J* = 8.8 Hz, 1H, H^4), 7.49 (d, *J* = 8.8 Hz, 2H, ArH),7.57 (d, *J* = 15.6 Hz, 1H, olefinic-H), 7.68-7.70 (m, 3H, ArH), 7.85 (d, *J* = 15.6 Hz, 1H, olefinic-H), 7.93 (s, 1H, H^5), 7.97 (d, *J* = 8.8Hz, 1H, H^3), 8.06 (d, *J* = 8.8 Hz, 2H, ArH), 8.19 (s, 1H, H^6), 8.41 (d, *J* = 5.6 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 100 MHz): 28.6, 48.5, 61.7, 70.3, 99.0, 107.3, 114.9, 117.4, 121.1, 124.1, 125.3, 125.8, 126.5, 128.6, 130.7, 131.9, 134.3, 140.7, 142.5, 144.6, 146.4, 150.0, 151.5, 152.5, 162.3, 188.1; HRMS: Calcd for $C_{30}H_{26}ClN_5O_2$ $[M]^+$523.1775 and [M+2] 525.1775, found 523.1768 and 525.1784; Anal. Calcd (%) for: C, 68.76; H, 5.00; N, 13.36, found: C, 68.87; H, 5.08; N, 13.50.

3.1.10 1-(4-{1-[3-(7-Chloro-quinolin-4-ylamino)-propyl]-1H-[1,2,3]triazol-4-ylmethoxy}-phenyl)-3-(4-methoxy-phenyl)-propenone (**8j**): Yield 86%; Light Yellow Solid; m.p. 175-176 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.29-2.32 (m, 2H, -CH_2), 3.70-3.73 (m, 5H, -CH_2+-OCH_3), 4.75-4.77 (m, 2H, -CH_2), 5.21 (s, 2H, -OCH_2), 6.47 (d, *J* = 5.6 Hz, 1H, H^2), 7.07 (d, *J* = 8.8 Hz, 2H, ArH), 7.39 (d, *J* = 9.2 Hz, 1H, H^4), 7.51 (d, *J* = 8.8 Hz, 2H, ArH), 7.54 (d, *J* = 15.6 Hz, 1H, olefinic-H), 7.78 (d, *J* = 8.8 Hz, 2H, ArH), 7.83 (d, *J* = 15.6 Hz, 1H, olefinic-H),7.97 (s, 1H, H^5), 8.02 (s, 1H, -NH exchangeable with D_2O), 8.14 (d, *J* = 9.2 Hz, 1H, H^3), 8.22 (d, *J* = 8.8 Hz, 2H, ArH), 8.31(s, 1H, H^6), 8.44 (d, *J* = 5.6 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 100 MHz): 29.1, 48.1, 55.2, 61.5, 79.0, 99.0, 107.1, 115.6, 117.3, 121.0, 124.3, 125.7, 126.4, 126.7, 130.4, 131.4, 135.2, 140.8, 142.9, 145.1, 146.3, 150.4, 152.2, 152.6, 157.4, 162.3, 187.9; HRMS: Calcd for $C_{31}H_{28}ClN_5O_3$ $[M]^+$553.1881 and [M+2] 555.1881, found 553.1871 and 555.1887; Anal. Calcd (%) for: C, 67.20; H, 5.09; N, 12.64, found: C, 67.31; H, 4.97; N, 12.74.

3.1.11 1-(4-{1-[3-(7-Chloro-quinolin-4-ylamino)-propyl]-1H-[1,2,3]triazol-4-ylmethoxy}-phenyl)-3-(3,4-dimethoxy-phenyl)-propenone (**8k**): Yield 93%; Light yellow Solid; m.p. 146-147 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.25-2.28 (m, 2H, -CH_2), 3.69 (s, 3H, -OCH_3), 3.77-3.79 (m, 2H, -CH_2), 3.82 (s, 3H, -OCH_3), 4.52-4.55 (m, 2H, -CH_2), 5.19 (s, 2H, -OCH_2),

6.44 (d, *J* = 6.0 Hz, 1H, H^2), 6.49 (dd, *J* = 2.0, 8.0 Hz, 1H, ArH), 6.57 (d, *J* = 2.5 Hz, 1H, ArH), 6.80 (d, *J* = 8.5 Hz, 1H, ArH), 7.18 (d, *J* = 8.5 Hz, 2H, ArH), 7.59 (dd, *J* = 1.5, 9.0 Hz, 1H, H^4), 7.73 (d, *J* = 8.5 Hz, 2H, ArH), 7.85 (s, 1H, -NH exchangeable with D_2O), 8.20 (d, *J* = 9.0 Hz, 1H, H^3), 8.29 (s, 1H, H^5), 8.34 (s, 1H, H^6), 8.46 (d, *J* = 4.5 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 28.6, 48.2, 56.1, 60.1, 62.0, 78.7, 98.8, 107.0, 115.5, 117.7, 121.4, 124.0, 124.6, 125.1, 126.1, 126.8, 130.6, 131.8, 135.2, 140.4, 142.5, 144.3, 147.7, 150.4, 151.6, 152.0, 153.1, 153.9, 162.4, 188.0; HRMS: Calcd for $C_{32}H_{30}ClN_5O_4$ $[M]^+$583.1986 and [M+2] 585.1986, found 583.1976 and 585.1992; Anal. Calcd (%) for: C, 65.80; H, 5.18; N, 11.99, found: C, 65.89; H, 5.10; N, 12.05.

3.1.12 1-(4-{1-[3-(7-Chloro-quinolin-4-ylamino)-propyl]-1H-[1,2,3]triazol-4-ylmethoxy}-phenyl)-3-(3,4,5-trimethoxy-phenyl)-propenone (**8l**): Yield 86%; Light yellow Solid; m.p. 173-174 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): *δ* 2.24-2.27 (m, 2H, -CH_2), 3.62-3.64 (m, 2H, -CH_2), 3.72 (s, 3H, -OCH_3), 3.87 (s, 6H, 2×-OCH_3), 4.54-4.56 (m, 2H, -CH_2), 5.29 (s, 2H, -OCH_2), 6.53 (d, *J* = 6.0 Hz, 1H, H^2), 7.20-7.22 (m, 4H, ArH), 7.54 (dd, *J* = 2.0, 9.0 Hz, 1H, H^4), 7.67 (d, *J* = 15.5 Hz, 1H, olefinic-H), 7.82-7.83 (m, 2H, H^5+-NH exchangeable with D_2O), 7.89 (d, *J* = 15.5 Hz, 1H, olefinic-H), 7.93 (d, *J* = 8.5 Hz, 1H, H^3), 8.19 (d, *J* = 9.0 Hz, 2H, ArH), 8.33 (s, 1H, H^6), 8.43 (d, *J* = 4.5 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 28.8, 47.8, 56.1, 56.6, 60.6, 61.9, 70.2, 99.1, 106.9, 115.1, 117.4, 121.6, 124.9, 125.2, 125.3, 126.0, 130.8, 131.3, 134.9, 140.0, 142.6, 144.1, 147.0, 150.3, 151.6, 152.8, 153.5, 162.3, 187.7; HRMS: Calcd for $C_{33}H_{32}ClN_5O_5$ $[M]^+$613.2092 and [M+2] 615.2092, found 613.2085 and 615.2098; Anal. Calcd (%) for: C, 64.54; H, 5.25; N, 11.40, found: C, 64.64; H, 5.33; N, 11.47.

3.1.13 1-(4-{1-[3-(7-Chloro-quinolin-4-ylamino)-propyl]-1H-[1,2,3]triazol-4-ylmethoxy}-3-methoxy-phenyl)-3-phenyl-propenone (**8m**): Yield 79%; Light yellow Solid; m.p. 157-158 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): *δ* 2.35-2.38 (m, 2H, -CH_2), 3.72 (s, 3H, -OCH_3), 3.82-3.84 (m, 2H, -CH_2), 4.66-4.68 (m, 2H, -CH_2), 5.21 (s, 2H, -OCH_2), 6.38 (d, *J* = 5.6 Hz, 1H, H^2), 6.87 (m, 2H, ArH), 7.09 (d, *J* = 8.0 Hz, 1H, ArH), 7.40 (d, *J* = 9.2 Hz, 1H, H^4), 7.49-7.56 (m, 6H, 5ArH+olefinic-H), 7.82 (d, *J* = 15.6 Hz, 1H, olefinic-H), 7.93 (s, 1H, H^5), 7.98 (d, *J* = 9.2 Hz, 1H, H^3), 8.20 (s, 1H, H^6), 8.43 (d, *J* = 5.6 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 28.2, 48.5, 55.2, 62.0, 70.5, 99.1, 106.0, 111.2, 112.6, 118.1, 119.7, 123.4, 124.5, 125.2, 125.6, 126.8, 128.1, 131.3, 135.2, 139.7, 142.1, 143.6, 147.4, 149.9, 150.0, 151.7, 152.9, 161.8, 188.2; HRMS: Calcd for $C_{31}H_{28}ClN_5O_3$ $[M]^+$553.1881 and [M+2] 555.1881,

found 553.1872 and 555.1893; Anal. Calcd (%) for: C, 67.20; H, 5.09; N, 12.64, found: C, 67.30; H, 5.22; N, 12.57.

3.1.4 1-(4-{1-[3-(7-Chloro-quinolin-4-ylamino)-propyl]-1H-[1,2,3]triazol-4-ylmethoxy}-3-methoxy-phenyl)-3-(4-methoxy-phenyl)-propenone (**8n**): Yield 92%; Light Yellow Solid; m.p. 160-161 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.21-2.24 (m, 2H, -CH_2-), 3.70 (s, 3H, -OCH_3), 3.76 (s, 3H, -OCH_3), 3.83-3.85 (m, 2H, -CH_2), 4.72-4.75 (m, 2H, -CH_2), 5.18 (s, 2H, -OCH_2), 6.49 (d, J = 5.6 Hz, 1H, H^2), 7.09-7.12 (m, 3H, ArH), 7.41 (d, J = 9.2 Hz, 1H, H^4), 7.45-7.51 (m, 4H, ArH), 7.58 (d, J = 15.6 Hz, 1H, olefinic-H), 7.83 (d, J = 15.6 Hz, 1H, olefinic-H), 7.89 (s, 1H, H^5), 8.11 (d, J = 9.2 Hz, 1H, H^3), 8.17 (s, 1H, H^6), 8.41 (d, J = 5.6 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 28.0, 47.5, 55.2, 55.5, 62.1, 79.2, 98.9, 105.7, 111.3, 111.8, 118.3, 119.8, 123.1, 124.0, 125.4, 125.6, 126.2, 128.7, 131.1, 135.4, 140.6, 142.1, 143.7, 147.5, 149.8, 150.0, 152.4, 157.0, 161.8, 188.3; HRMS: Calcd for $C_{32}H_{30}ClN_5O_4$ $[M]^+$583.1986 and [M+2] 585.1986, found 583.1991 and 558.1979; Anal. Calcd (%) for: C, 65.80; H, 5.18; N, 11.99, found: C, 65.89; H, 5.27; N, 11.84.

3.1.15 1-(4-{1-[3-(7-Chloro-quinolin-4-ylamino)-propyl]-1H-[1,2,3]triazol-4-ylmethoxy}-3-methoxy-phenyl)-3-(3,4-dimethoxy-phenyl)-propenone (**8o**): Yield 89%; Light yellow Solid; m.p. 144-145 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.26-2.29 (m, 2H, -CH_2), 3.62-3.64 (m, 2H, -OCH_2), 3.71 (s, 3H, -OCH_3), 3.75 (s, 6H, 2×-OCH_3), 4.84-4.87 (m, 2H, -CH_2), 5.22 (s, 2H, -OCH_2), 6.39 (d, J = 8.0 Hz, 1H, ArH), 6.54 (d, J = 5.6 Hz, 1H, H^2), 6.91 (d, J = 8.4 Hz, 1H, ArH), 7.21 (d, J = 8.0 Hz, 1H, ArH), 7.42 (d, J = 9.0 Hz, 1H, H^4), 7.51-7.56 (m, 3H, ArH), 7.62 (d, J = 15.6 Hz, 1H, olefinic-H), 7.81 (d, J = 15.6 Hz, 1H, olefinic-H), 7.94 (s, 1H, H^5), 8.08 (d, J = 9.2 Hz, 1H, H^3), 8.19 (s, 1H, H^6), 8.29 (d, J = 5.6 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 27.8, 48.0, 55.1, 55.4, 60.2, 62.3, 79.1, 99.5, 104.4, 111.2, 111.5, 114.6, 120.5, 123.1, 124.0, 124.5, 125.3, 125.5, 125.1, 127.9, 131.2, 135.0, 139.6, 142.4, 143.7, 147.2, 149.0, 149.2, 151.2, 151.6, 154.4, 162.1, 188.0; HRMS: Calcd for $C_{33}H_{32}ClN_5O_5$ $[M]^+$ 613.2092 and [M+2] 615.2092, found 613.2085 and 615.2083; Anal. Calcd (%) for: C, 64.54; H, 5.25; N, 11.40, found: C, 64.61; H, 5.42; N, 11.33.

3.1.16 1-(4-{1-[3-(7-Chloro-quinolin-4-ylamino)-propyl]-1H-[1,2,3]triazol-4-ylmethoxy}-3-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-propenone (**8p**): Yield 86%; Light yellow Solid; m.p. 169-170 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.27-2.30 (m, 2H, -CH_2), 3.73-3.80 (m, 14H, 4×-OCH_3+ -CH_2), 4.59-4.61 (m, 2H, -CH_2), 5.16 (s, 2H, -OCH_2), 6.36 (s, 2H, ArH), 6.58 (d, J = 5.6 Hz, 1H, H^2), 7.15 (d, J = 8.0 Hz, 1H, ArH), 7.38 (d, J = 8.8 Hz, 1H,

H^4), 7.42-4.46 (m, 2H, ArH), 7.57 (d, *J* = 15.6 Hz, 1H, olefinic-H), 7.85 (d, *J* = 15.6 Hz, 1H, olefinic-H), 7.90 (s, 1H, H^5), 8.10 (d, *J* = 8.8 Hz, 1H, H^3), 8.22 (s, 1H, H^6), 8.46 (d, *J* = 5.6 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 100 MHz): 28.4, 47.5, 55.0, 55.1, 55.5, 60.9, 62.4, 78.6, 99.0, 105.1, 111.4, 112.6, 117.3, 119.1, 123.3, 124.2, 125.5, 125.9, 126.1, 128.2, 131.6, 135.7, 139.9, 142.4, 143.6, 147.5, 150.2, 153.6, 156.9, 159.3, 162.4, 187.7; HRMS: Calcd for $C_{34}H_{34}ClN_5O_6$ $[M]^+$643.2198 and [M+2] 645.2198, found 643.2187 and 645.2204; Anal. Calcd (%) for: C, 63.40; H, 5.32; N, 10.87, found: C, 63.45; H, 5.21; N, 10.98.

3.1.17 1-[3-(4-{1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-phenyl)-5-phenyl-4,5-dihydro-pyrazol-1-yl]-ethanone (**9a**): Yield 94%; Light yellow Solid; m.p. 181-182 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): *δ* 2.41 (s, 3H, -CH_3), 2.95 (dd, *J* = 4.0, 17.5 Hz, 1H, H^7), 3.51 (dd, *J* = 11.5, 17.5 Hz, 1H, H^8), 3.81-3.83 (m, 2H, -CH_2), 4.72-4.74 (m, 2H, -CH_2), 5.22 (s, 2H, -OCH_2), 5.59 (dd, *J* = 4.5, 11.5 Hz, 1H, H^9), 6.41 (d, *J* = 5.5 Hz, 1H, H^2), 7.13 (m, 2H, ArH), 7.37 (d, *J* = 9.0 Hz, 1H, H^4), 7.52-7.57 (m, 5H, ArH), 7.88 (s, 1H, H^5), 7.92 (d, *J* = 9.2 Hz, 1H, H^3), 8.11 (d, *J* = 8.5 Hz, 2H, ArH), 8.23 (s, 1H, H^6), 8.40 (d, *J* = 5.5 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125MHz): 21.6, 40.1, 42.5, 47.8,62.1, 79.0, 99.1, 107.7, 115.5, 117.4, 121.1, 123.5, 124.6, 125.4, 125.8, 126.0, 126.8, 128.4, 135.8, 139.7, 143.4, 146.9, 150.1, 151.6, 154.9, 160.5, 167.9; HRMS: Calcd for $C_{31}H_{28}ClN_7O_2$ $[M]^+$565.1993 and [M+2] 567.1993, found 565.2004 and 567.1987; Anal. Calcd (%) for: C, 65.78; H, 4.99; N, 17.32, found: C, 65.90; H, 4.94; N, 17.20.

3.1.18 1-[3-(4-{1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-phenyl)-5-(4-methoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-ethanone (**9b**):Yield 82%; Light Yellow Solid; m.p. 189-190 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 2.27 (s, 3H, -CH_3), 2.91 (dd, *J* = 4.0, 17.5 Hz, 1H, H^7), 3.48 (dd, *J* = 11.5, 17.5 Hz, 1H, H^8), 3.73 (s, 3H, -OCH_3), 3.76-3.79 (m, 2H, -CH_2), 4.78-4.80 (m, 2H, -CH_2), 5.19 (s, 2H, -OCH_2), 5.56 (dd, *J* = 4.5, 11.5 Hz, 1H, H^9), 6.45 (d, *J* = 5.5 Hz, 1H, H^2), 7.05 (d, *J* = 8.5 Hz, 2H, ArH), 7.31(d, *J* = 9.0 Hz, 1H, H^4), 7.41 (d, *J* = 8.5 Hz, 2H, ArH), 7.73 (d, *J* = 8.5 Hz, 2H, ArH), 7.92 (s, 1H, H^5), 8.00 (s, 1H, -NH exchangeable with D_2O), 8.09 (d, *J* = 9.0 Hz, 1H, H^3), 8.19 (d, *J* = 8.5 Hz, 2H, ArH), 8.30 (s, 1H, H^6), 8.41 (d, *J* = 5.5 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 22.1, 39.8, 42.0, 48.6, 55.1, 62.4, 78.5, 99.3, 107.7, 115.6, 117.8, 121.2, 123.9, 124.4, 125.2, 126.0, 126.5, 128.4, 134.8, 139.3, 143.1, 147.3, 150.2, 151.4, 154.8, 157.5, 160.0, 168.3; HRMS: Calcd for $C_{32}H_{30}ClN_7O_3$ $[M]^+$595.2099 and [M+2] 597.2099, found 595.2091 and 597.2086; Anal. Calcd (%) for: C, 64.48; H, 5.07; N, 16.45, found: C, 64.38; H, 5.19; N, 16.52.

3.1.19 1-[3-(4-{1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-phenyl)-5-(3,4-dimethoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-ethanone (**9c**): Yield 72%; Light yellow Solid; m.p. 183-184 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.30 (s, 3H, -CH_3), 2.91 (dd, J = 4.0, 17.5 Hz, 1H, H^7), 3.68-3.74 (m, 4H, -OCH_3+ H^8), 3.79 (s, 3H, -OCH_3), 3.83-3.85 (m, 2H, -CH_2), 4.67-4.70 (m, 2H, -CH_2), 5.17 (s, 2H, -OCH_2), 5.56 (dd, J = 4.5, 11.5 Hz, 1H, H^9), 6.43 (dd, J = 2.0, 8.0 Hz, 1H, ArH), 6.58 (d, J = 2.5 Hz, 1H, ArH), 6.60 (d, J = 5.5 Hz, 1H, H^2), 6.78 (d, J = 8.5 Hz, 1H, ArH), 7.05 (m, 2H, ArH), 7.53 (dd, J = 1.5, 9.0 Hz, 1H, H^4), 7.67 (d, J = 8.5 Hz, 2H, ArH), 7.88 (s, 1H, -NH exchangeable with D_2O), 8.21 (d, J = 9.0 Hz, 1H, H^3), 8.27 (s, 1H, H^5), 8.32 (s, 1H, H^6), 8.43 (d, J = 4.5 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 22.1, 41.7, 42.9, 48.3, 55.6, 56.0, 61.6, 79.6, 99.3, 104.9, 115.3, 117.5, 122.2, 124.6, 124.7, 125.3, 125.6, 126.5, 128.6, 131.0, 134.9, 138.3, 142.8, 147.3, 150.5, 151.4, 154.7, 157.2, 159.9, 160.2, 167.4; HRMS: Calcd for $C_{33}H_{32}ClN_7O_4$ $[M]^+$625.2204 and [M+2] 627.2204, found 625.2212 and 627.2208; Anal. Calcd (%) for: C, 63.30; H, 5.15; N, 15.66, found: C, 63.39; H, 5.28; N, 15.54.

3.1.20 1-[3-(4-{1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-phenyl)-5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-ethanone (**9d**): Yield 81%; Light yellow Solid; m.p. 166-167 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.41 (s, 3H, -CH_3), 3.07 (dd, J = 4.8, 17.6 Hz, 1H, H^7), 3.67 (dd, J = 12.0, 18.0 Hz, 1H, H^8), 3.76 (s, 3H, -OCH_3), 3.77 (s, 6H, 2×-OCH_3), 3.91-3.93 (m, 2H, -CH_2), 4.75-4.77 (m, 2H, -CH_2), 5.17 (s, 2H, -OCH_2), 5.47 (dd, J = 4.4, 11.6 Hz, 1H, H^9), 6.34 (d, J = 6.0 Hz, 1H, H^2), 6.38 (s, 2H, ArH), 6.94 (d, J = 9.2 Hz, 2H, ArH), 7.30 (dd, J = 2.0, 8.4 Hz, 1H, H^4), 7.62 (d, J = 8.8 Hz, 2H, ArH), 7.74 (s, 1H, H^5), 7.89 (m, 2H, H^3+ H^6), 8.36 (d, J = 5.6 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125MHz): 22.0, 42.7, 43.1, 48.7, 56.1, 60.2, 60.8, 61.8, 79.5, 98.5, 102.3, 114.9, 116.7, 122.4, 124.2, 124.6, 126.5, 128.3, 136.6, 137.8, 144.0, 147.0, 150.5, 151.5, 153.6, 153.8, 156.5, 159.8, 161.0, 169.0; HRMS: Calcd for $C_{34}H_{34}ClN_7O_5$ $[M]^+$655.2310 and [M+2] 657.2310, found 655.2318 and 657.2302; Anal. Calcd (%) for: C, 62.24; H, 5.22; N, 14.94, found: C, 62.36; H, 5.19; N, 15.24.

3.1.21 1-[3-(4-{1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-3-methoxy-phenyl)-5-phenyl-4,5-dihydro-pyrazol-1-yl]-ethanone (**9e**): Yield 90%; Light yellow Solid; m.p. 199-200 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.41 (s, 3H, -CH_3), 3.01 (dd, J = 4.0, 17.6 Hz, 1H, H^7), 3.51 (dd, J = 11.6, 18.0 Hz, 1H, H^8), 3.73 (s, 3H, -OCH_3), 3.79-3.81 (m, 2H, -CH_2), 4.81-4.83 (m, 2H, -CH_2), 5.25 (s, 2H, -OCH_2), 5.46 (dd, J = 4.0, 11.6 Hz, 1H, H^9), 6.45 (d, J = 5.6 Hz, 1H, H^2), 6.88-6.91 (m, 2H, ArH), 7.10 (d, J = 8.0 Hz,

1H, ArH), 7.33 (d, *J* = 9.2 Hz, 1H, H^4), 7.51-7.56 (m, 5H, ArH), 7.90 (s, 1H, H^5), 8.00 (d, *J* = 9.2 Hz, 1H, H^3), 8.07 (s, 1H, H^6), 8.29 (d, *J* = 5.6 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 21.4, 39.8, 41.8, 47.2, 55.2, 61.6, 79.1, 99.1, 105.4, 111.1, 112.2, 116.4, 121.0, 123.1, 124.2, 125.4, 125.8, 126.0, 126.4, 128.6, 135.8, 139.8, 143.2, 146.8, 149.7, 150.2, 151.2, 154.9, 160.4, 167.8; HRMS: Calcd for $C_{32}H_{30}ClN_7O_3$ $[M]^+$595.2099 and [M+2] 597.2099, found 595.2094 and 597.2110; Anal. Calcd (%) for: C, 64.48; H, 5.07; N, 16.45, found: C, 64.55; H, 5.21; N, 16.38.

3.1.22 1-[3-(4-{1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-3-methoxy-phenyl)-5-(4-methoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-ethanone (**9f**): Yield 83%; Light Yellow Solid; m.p. 190-191 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 2.37 (s, 3H, -CH_3), 2.96 (dd, *J* = 4.0, 17.6 Hz, 1H, H^7), 3.46 (dd, *J* = 11.6, 17.6 Hz, 1H, H^8), 3.71 (s, 3H, -OCH_3), 3.73 (s, 3H, -OCH_3), 3.78-3.81 (m, 2H, -CH_2), 4.68-4.71 (m, 2H, -CH_2), 5.16 (s, 2H, -OCH_2), 5.50 (dd, *J* = 4.0, 11.6 Hz, H^9), 6.61 (d, *J* = 5.6 Hz, 1H, H^2), 6.77 (d, *J* = 8.8 Hz, 2H, ArH), 7.03 (d, *J* = 8.0 Hz, 1H, ArH), 7.42 (d, *J* = 9.2 Hz, 1H, H^4), 7.49-7.53 (m, 4H, ArH), 7.95-7.98 (m, 2H, H^3+H^5), 8.06 (s, 1H, H^6), 8.22 (d, *J* = 5.6 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 21.6, 41.2, 42.3, 48.2, 55.2, 55.5, 62.5, 79.4, 99.1, 105.4, 111.0, 112.3, 115.9, 119.8, 123.3, 124.3, 125.4, 126.5, 126.8, 128.4, 135.1, 139.7, 142.9, 147.2, 149.6, 150.1, 151.4, 153.0, 157.5, 160.3, 168.0; HRMS: Calcd for $C_{33}H_{32}ClN_7O_4$ $[M]^+$625.2204 and [M+2] 627.2204, found 625.2216 and 627.2189; Anal. Calcd (%) for: C, 63.30; H, 5.15; N, 15.66, found: C, 63.20; H, 5.23; N, 15.63.

3.1.23 1-[3-(4-{1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-3-methoxy-phenyl)-5-(3,4-dimethoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-ethanone (**9g**): Yield 79%; Light yellow Solid; m.p. 197-198 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): *δ* 2.31 (s, 3H, -CH_3), 3.09 (dd, *J* = 4.0, 17.6 Hz, 1H, H^7), 3.42 (dd, *J* = 11.6, 17.6 Hz, 1H, H^8), 3.82-3.86 (m, 11H, -CH_2+3×-OCH_3), 4.70-4.72 (m, 2H, -CH_2), 5.24 (s, 2H, -OCH_2), 5.46 (dd, *J* = 4.0, 11.6 Hz, H^9), 6.64 (d, *J* = 5.6 Hz, 1H, H^2), 7.01 (d, *J* = 7.8 Hz, 1H, ArH), 7.15 (d, *J* = 8.4 Hz, 1H, ArH), 7.40 (d, *J* = 9.0 Hz, 1H, H^4), 7.50-7.54 (m, 3H, ArH), 7.76 (s, 1H, ArH), 8.02 (s, 1H, H^5), 8.09 (d, *J* = 9.2 Hz, 1H, H^3), 8.22 (s, 1H, H^6), 8.41 (d, *J* = 5.6 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 21.4, 40.5, 42.6, 48.0, 55.3, 55.6, 55.7, 62.3, 79.6, 99.0, 105.4, 110.9, 111.8, 112.3, 120.4, 123.1, 123.6, 124.5, 125.1, 125.3, 125.7, 128.0, 134.9, 139.6, 143.2, 147.3, 149.0, 149.9, 151.2, 151.6, 155.5, 158.8, 161.4, 168.4; HRMS: Calcd for $C_{34}H_{34}ClN_7O_5$ $[M]^+$655.2310 and [M+2] 657.2310, found 655.2317 and 657.2305; Anal. Calcd (%) for: C, 62.24; H, 5.22; N, 14.94, found: C, 62.16; H, 5.39; N, 14.90.

3.1.24 1-[3-(4-{1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-3-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-ethanone (**9h**): Yield 90%; Light yellow Solid; m.p. 184-185 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.36 (s, 3H, -CH_3), 2.89 (dd, J = 4.0, 17.6 Hz, 1H, H^7), 3.40 (dd, J = 11.6, 17.6 Hz, 1H, H^8), 3.74-3.77 (m, 14H, -CH_2+4×-OCH_3), 4.83-4.85 (m, 2H, -CH_2), 5.25 (s, 2H, -OCH_2), 5.58 (dd, J = 4.0, 11.6 Hz, H^9), 6.44 (s, 2H, ArH), 6.54 (d, J = 5.6 Hz, 1H, H^2), 7.00 (d, J = 8.0 Hz, 1H, ArH), 7.44 (d, J = 9.2 Hz, 1H, H^4), 7.46-7.48 (m, 2H, ArH), 7.89 (s, 1H, H^5), 7.96 (d, J = 9.2 Hz, 1H, H^3), 8.01 (s, 1H, H^6), 8.25 (d, J = 5.6 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 21.6, 41.1, 42.4, 48.8, 55.3, 55.5, 56.0, 60.7, 62.7, 79.6, 98.8, 106.2, 111.0, 112.4, 116.4, 120.5, 122.9, 124.2, 125.6, 126.4, 126.8, 128.0, 134.7, 139.7, 142.6, 146.8, 150.3, 151.4, 154.5, 156.3, 159.2, 161.6, 168.3; HRMS: Calcd for $C_{35}H_{36}ClN_7O_6$ $[M]^+$685.2416 and [M+2] 687.2416, found 685.2411 and 687.2408; Anal. Calcd (%) for: C, 61.27; H, 5.29; N, 13.99, found: C, 61.39; H, 5.21; N, 13.86.

3.1.25 1-[3-(4-{1-[3-(7-Chloro-quinolin-4-ylamino)-propyl]-1H-[1,2,3]triazol-4-ylmethoxy}-phenyl)-5-phenyl-4,5-dihydro-pyrazol-1-yl]-ethanone (**9i**): Yield 79%; Light yellow Solid; m.p. 204-205 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.27-2.30 (m, 2H, -CH_2), 2.40 (s, 3H, -CH_3), 2.95 (dd, J = 4.0, 17.5 Hz, 1H, H^7), 3.51 (dd, J = 11.5, 17.5 Hz, 1H, H^8), 3.81-3.83 (m, 2H, -CH_2), 4.72-4.74 (m, 2H, -CH_2), 5.22 (s, 2H, -OCH_2), 5.59 (dd, J = 4.5, 11.5 Hz, 1H, H^9), 6.41 (d, J = 5.5 Hz, 1H, H^2), 7.13 (d, J = 8.5 Hz, 2H, ArH), 7.37 (d, J = 9.0 Hz, 1H, H^4), 7.55-7.59 (m, 5H, ArH), 7.88 (s, 1H, H^5), 7.92 (d, J = 9.2 Hz, 1H, H^3), 8.11 (d, J = 8.5 Hz, 2H, ArH), 8.23(s, 1H, H^6), 8.40 (d, J = 5.5 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125MHz): 22.0, 28.6, 40.4, 42.7, 48.3, 62.5, 78.9, 98.9, 108.2, 115.4, 117.7, 121.4, 124.2,125.1, 125.9, 126.3, 126.7, 128.5, 129.0, 134.8, 139.0, 142.1, 147.6, 150.3, 151.7, 154.8,160.4, 168.5; HRMS: Calcd for $C_{32}H_{30}ClN_7O_2$ $[M]^+$579.2149 and [M+2] 581.2149, found 579.2155 and 581.2141; Anal. Calcd (%) for: C, 66.26; H, 5.21; N, 16.90, found: C, 66.41; H, 5.26; N, 17.01.

3.1.26 1-[3-(4-{1-[3-(7-Chloro-quinolin-4-ylamino)-propyl]-1H-[1,2,3]triazol-4-ylmethoxy}-phenyl)-5-(4-methoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-ethanone (**9j**):Yield 93%; Light Yellow Solid; m.p. 177-178 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.26-2.28 (m, 2H, -CH_2), 2.40 (s, 3H, -CH_3), 2.91 (dd, J = 4.0, 17.5 Hz, 1H, H^7), 3.48 (dd, J = 11.5, 17.5 Hz, 1H, H^8), 3.71 (s, 3H, -OCH_3), 3.76-3.79 (m, 2H, -CH_2), 4.78-4.80 (m, 2H, -CH_2), 5.19 (s, 2H, -OCH_2), 5.56 (dd, J = 4.5, 11.5 Hz, 1H, H^9), 6.45 (d, J = 5.5 Hz, 1H, H^2), 7.05 (d, J = 8.5 Hz, 2H, ArH), 7.31 (d, J = 9.0 Hz, 1H, H^4), 7.41 (d, J = 8.5 Hz, 2H, ArH), 7.73 (d, J = 8.5 Hz, 2H,

ArH), 7.92 (s, 1H, H^5), 8.00 (s, 1H, -NH- exchangeable with D_2O), 8.09 (d, *J* = 9.0 Hz, 1H, H^3), 8.19 (d, *J* = 8.5 Hz, 2H, ArH), 8.30 (s, 1H, H^6), 8.41 (d, *J* = 5.5 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125MHz): 21.5, 28.2, 40.0, 41.6, 48.6, 55.4, 61.9, 78.7, 99.0, 108.5, 115.4, 117.7, 121.0, 123.8, 124.2, 125.4, 126.3, 126.8, 128.5, 134.1, 139.0, 142.9, 147.6, 150.1, 151.5,154.3, 157.0, 160.2, 168.7; HRMS: Calcd for $C_{33}H_{32}ClN_7O_3$ $[M]^+$609.2255 and [M+2] 611.2255, found 609.2247 and 611.2252; Anal. Calcd (%) for: C, 64.96; H, 5.29; N, 16.07, found: C, 65.07; H, 5.21; N, 16.20.

3.1.27 1-[3-(4-{1-[3-(7-Chloro-quinolin-4-ylamino)-propyl]-1H-[1,2,3]triazol-4-ylmethoxy}-phenyl)-5-(3,4-dimethoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-ethanone (**9k**): Yield 76%; Light yellow Solid; m.p. 210-211 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.29-2.32 (m, 2H, -CH_2), 2.44 (s, 3H, -CH_3), 2.94 (dd, *J* = 4.0, 17.5 Hz, 1H, H^7), 3.33-3.35 (m, 2H, -CH_2), 3.59 (dd, *J* = 11.5, 18.0 Hz, 1H, H^8), 3.70 (s, 6H, 2×-OCH_3), 4.47-4.50 (m, 2H, -CH_2), 5.17 (s, 2H, -O-CH_2), 5.69 (dd, *J* = 4.0, 11.5 Hz, H^9), 6.30-6.32 (m, 2H, ArH), 6.35 (d, *J*= 2.0 Hz, 1H, ArH), 6.63 (d, *J* = 4.5 Hz, 1H, H^2), 6.86 (d, *J* = 8.5 Hz, 1H, H^4), 6.96 (d, *J* = 8.5 Hz, 2H, ArH), 7.63 (d, *J* = 8.5 Hz, 2H, ArH), 7.73 (s, 1H, H^5), 7.86 (s, 2H, H^6), 7.91 (d, *J* = 8.5 Hz, 1H, H^3), 8.38 (d, *J* = 4.5 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 22.0, 28.3, 40.0, 41.6, 48.0, 55.3, 55.4, 61.8, 65.8, 98.8, 104.0, 114.8, 117.1, 121.4, 122.5, 123.5, 124.7, 125.5, 126.2, 126.8, 128.2, 135.5, 139.2, 143.7, 147.4, 150.2, 150.6, 154.8, 156.9, 159.7, 160.2, 168.7; HRMS: Calcd for $C_{34}H_{34}ClN_7O_4$ $[M]^+$639.2361 and [M+2] 641.2361, found 639.2370 and 641.2375; Anal. Calcd (%) for: C, 63.79; H, 5.35; N, 15.32, found: C, 63.87; H, 5.46; N, 15.25.

3.1.28 1-[3-(4-{1-[3-(7-Chloro-quinolin-4-ylamino)-propyl]-1H-[1,2,3]triazol-4-ylmethoxy}-phenyl)-5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-ethanone (**9l**): Yield 86%; Light yellow Solid; m.p. 187-188 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.24-2.27 (m, 2H, -CH_2), 2.42 (s, 3H, -CH_3), 2.99 (dd, *J* = 4.0, 17.5 Hz, 1H, H^7), 3.47 (dd, *J* = 11.5, 18.0 Hz, 1H, H^8), 3.72 (s, 3H, -OCH_3), 3.78 (s, 6H, 2×-OCH_3), 3.86-3.89 (m, 2H, -CH_2), 4.79-4.81 (m, 2H, -CH_2), 5.18 (s, 2H, -OCH_2), 5.66 (dd, *J* = 4.0, 11.5 Hz, H^9), 6.38 (s, 2H, ArH), 6.48 (d, *J* = 6.0 Hz, 1H, H^2), 7.05 (d, *J* = 9.0 Hz, 2H, ArH), 7.30 (dd, *J* = 2.0, 8.5 Hz, 1H, H^4), 7.74 (s, 1H, H^5), 7.90 (d, *J* = 8.5 Hz, 2H, H^3), 8.11 (d, *J* = 9.0 Hz, 2H, ArH), 8.22 (s, 1H, H^6), 8.32 (d, *J* = 5.5 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 21.6, 28.0, 40.3, 42.6, 48.1, 56.1, 56.4, 61.4, 62.2, 79.0, 98.9, 107.1, 115.5, 117.4, 121.3, 124.4, 125.3, 125.7, 126.2, 135.0, 139.4, 143.6, 146.9, 150.0, 151.6, 152.8, 154.5, 157.6, 159.4, 160.3, 167.7; HRMS: Calcd for

$C_{35}H_{36}ClN_7O_5$ $[M]^+$669.2466 and [M+2] 671.2466, found 669.2472 and 671.2453; Anal. Calcd (%) for: C, 62.73; H, 5.41; N, 14.63, found: C, 62.68; H, 5.47; N, 14.51.

3.1.29 1-[3-(4-{1-[3-(7-Chloro-quinolin-4-ylamino)-propyl]-1H-[1,2,3]triazol-4-ylmethoxy}-3-methoxy-phenyl)-5-phenyl-4,5-dihydro-pyrazol-1-yl]-ethanone (**9m**): Yield 79%; Light yellow Solid; m.p. 201-202 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.38-2.41 (m, 2H, -CH_2), 2.44 (s, 3H, -CH_3), 3.00 (dd, J = 4.0, 17.6 Hz, 1H, H^7), 3.47 (dd, J = 11.6, 17.6 Hz, 1H, H^8), 3.72 (s, 3H, -OCH_3), 3.83-3.85 (m, 2H, -CH_2), 4.78-4.81 (m, 2H, -CH_2), 5.20 (s, 2H, -OCH_2), 5.55 (dd, J = 4.0, 11.6 Hz, H^9), 6.59 (d, J = 5.6 Hz, 1H, H^2), 6.89-6.93 (m, 2H, ArH), 7.06 (d, J = 8.0 Hz, 1H, ArH), 7.41 (d, J = 9.2 Hz, 1H, H^4), 7.52-7.56 (m, 5H, ArH), 7.90 (s, 1H, H^5), 7.96 (d, J = 9.2 Hz, 1H, H^3), 8.11 (s, 1H, H^6), 8.29 (d, J = 5.6 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 21.6, 28.5, 40.1, 42.0, 48.4, 55.3, 62.0, 79.5, 99.2, 105.6, 111.3, 112.5, 117.2, 120.7, 123.1, 124.0, 125.4, 125.7, 126.1, 126.5, 128.8, 135.7, 140.2, 142.9, 147.4, 149.6, 150.3, 151.3, 154.5, 160.9, 167.6; HRMS: Calcd for $C_{33}H_{32}ClN_7O_3$ $[M]^+$609.2255 and [M+2] 611.2255, found 609.2264 and 611.2249; Anal. Calcd (%) for: C, 64.96; H, 5.29; N, 16.07, found: C, 64.90; H, 5.21; N, 16.17.

3.1.30 1-[3-(4-{1-[3-(7-Chloro-quinolin-4-ylamino)-propyl]-1H-[1,2,3]triazol-4-ylmethoxy}-3-methoxy-phenyl)-5-(4-methoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-ethanone (**9n**): Yield 92%; Light Yellow Solid; m.p. 195-196 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.21-2.24 (m, 2H, -CH_2-), 2.32 (s, 3H, -CH_3), 2.88 (dd, J = 4.0, 17.6 Hz, 1H, H^7), 3.39 (dd, J = 11.6, 18.0 Hz, 1H, H^8), 3.70 (s, 3H, -OCH_3), 3.75 (s, 3H, -OCH_3), 3.81-3.84 (m, 2H, -CH_2), 4.72-4.75 (m, 2H, -CH_2), 5.15 (s, 2H, -OCH_2), 5.44 (dd, J = 4.0, 11.6 Hz, H^9), 6.63 (d, J = 5.6 Hz, 1H, H^2), 7.04-7.07 (m, 3H, ArH), 7.35 (d, J = 9.2 Hz, 1H, H^4), 7.52-7.57 (m, 4H, ArH), 7.80 (s, 1H, H^5), 8.15 (d, J = 9.2 Hz, 1H, H^3), 8.08 (s, 1H, H^6), 8.34 (d, J = 5.6 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 21.6, 27.8, 40.0, 41.9, 48.3, 55.1, 55.4, 62.5, 79.1, 98.6, 106.2, 111.2, 112.4, 116.4, 120.2, 123.5, 124.1, 125.3, 126.4, 126.7, 128.0, 135.5, 139.9, 143.2, 147.4, 149.4, 150.0, 151.6, 152.5, 157.7, 160.4, 167.7; HRMS: Calcd for $C_{34}H_{34}ClN_7O_4$ $[M]^+$639.2361 and [M+2] 641.2361, found 639.2367 and 641.2373; Anal. Calcd (%) for: C, 63.79; H, 5.35; N, 15.32, found: C, 63.92; H, 5.45; N, 15.27.

3.1.31 1-[3-(4-{1-[3-(7-Chloro-quinolin-4-ylamino)-propyl]-1H-[1,2,3]triazol-4-ylmethoxy}-3-methoxy-phenyl)-5-(3,4-dimethoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-ethanone (**9o**): Yield 89%; Light yellow Solid; m.p. 192-193 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.26-2.29 (m, 2H, -CH_2), 2.45 (s, 3H, -CH_3), 2.99 (dd, J = 4.0, 17.2 Hz, 1H, H^7), 3.40 (dd, J = 11.6, 17.2

Hz, 1H, H^8), 3.72-3.75 (m, 11H, 3×-OCH_3+-OCH_2), 4.77-4.81 (m, 2H, -CH_2), 5.17 (s, 2H, -OCH_2), 5.52 (dd, *J* = 4.0, 11.6 Hz, H^9), 6.49 (d, *J* = 8.0 Hz, 1H, ArH), 6.57 (d, *J* = 5.6 Hz, 1H, H^2), 7.01 (d, *J* = 8.4 Hz, 1H, ArH), 7.26 (d, *J* = 8.0 Hz, 1H, ArH), 7.33 (d, *J* = 9.0 Hz, 1H, H^4), 7.52-7.56 (m, 3H, ArH), 7.87 (s, 1H, H^5), 8.06 (d, *J* = 9.2 Hz, 1H, H^3), 8.22 (s, 1H, H^6), 8.36 (d, *J* = 5.6 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 125 MHz): 21.7, 27.8, 39.5, 42.1, 47.9, 55.2, 55.4, 55.7, 62.1, 79.2, 99.1, 104.6, 111.2, 111.9, 112.5, 118.9, 122.4, 123.2, 124.0, 125.1, 125.4, 125.4, 128.3, 135.0, 139.2, 143.1, 146.6, 149.3, 150.7, 151.4, 152.1, 156.4, 159.2, 162.3, 167.0; HRMS: Calcd for $C_{35}H_{36}ClN_7O_5$ $[M]^+$ 669.2466 and [M+2] 671.2466, found 669.2460 and 671.2479; Anal. Calcd (%) for: C, 62.73; H, 5.41; N, 14.63, found: C, 62.80; H, 5.49; N, 14.87.

3.1.32 1-[3-(4-{1-[3-(7-Chloro-quinolin-4-ylamino)-propyl]-1H-[1,2,3]triazol-4-ylmethoxy}-3-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-ethanone (**9p**): Yield 86%; Light yellow Solid; m.p. 159-160 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.27-2.30 (m, 2H, -CH_2), 2.43 (s, 3H, -CH_3), 2.86 (dd, *J* = 4.0, 18.0 Hz, 1H, H^7), 3.36 (dd, *J* = 11.6, 18.0 Hz, 1H, H^8), 3.71-3.76 (m, 14H, 4×-OCH_3+ -CH_2), 4.65-4.67 (m, 2H, -CH_2), 5.19 (s, 2H, -OCH_2), 5.48 (dd, *J* = 4.0, 11.6 Hz, H^9), 6.48 (d, *J* = 5.6 Hz, 1H, H^2), 6.53 (s, 2H, ArH), 7.09 (d, *J* = 8.0 Hz, 1H, ArH), 7.32 (d, *J* = 9.2 Hz, 1H, H^4), 7.49-7.53 (m, 2H, ArH), 7.93-7.96 (m, 2H, H^3+H^5), 8.12 (s, 1H, H^6), 8.30 (d, *J* = 5.6 Hz, 1H, H^1); ^{13}C NMR (DMSO-d_6, 100 MHz): 22.0, 28.4, 39.4, 42.3, 48.5, 55.0, 55.5, 55.8, 60.4, 61.9, 79.2, 98.8, 105.6, 111.1, 112.2, 116.8, 119.5, 123.5, 124.0, 125.2, 126.1, 126.7, 128.3, 135.2, 140.4, 142.5, 146.7, 149.7, 150.9, 154.6, 156.5, 159.0, 161.2, 167.9; HRMS: Calcd for $C_{36}H_{38}ClN_7O_6$ $[M]^+$699.2572 and [M+2] 701.2572, found 699.2561 and 701.2579; Anal. Calcd (%) for: C, 61.75; H, 5.47; N, 14.00, found: C, 61.64; H, 5.33; N, 14.10.

3.2 Biological evaluation:

3.2.1 Methods for assessment of antimalarial activity of test compounds:

The W2 strain of *P. falciparum* was cultured at 37 °C in human red blood cells at 2% hematocrit in medium RPMI-1640 supplemented with 0.5% Albumax®, 100 uM hypoxanthine, 2 μM L-glutamine and 25 μM HEPES pH 7.4 under atmosphere of 3% O_2, 5% CO_2 balance nitrogen. The parasites were synchronized with 5% D-sorbitol at ring stage [30] and incubated with different concentrations of compounds for 48 h. The compounds were added from DMSO stocks; the maximum concentration of DMSO used was 0.1 %. Controls without inhibitors included 0.1% DMSO. After 48 h when control cultures had progressed to new rings, the culture were fixed for 48 h by adding equal volume of 2% formaldehyde in

PBS, pH 7.4, at room temperature. Fixed parasites were then transferred to 0.1% Triton X-100 in PBS containing 100 μM ammonium chloride and 1 nM YOYO-1 dye (Molecular Probes). Parasitemia was determined from dot plots (forward scatter *vs.* fluorescence) acquired on a FACSort flow cytometer using Cell Quest software (Beckton Dickinson). IC_{50} values for growth inhibition were determined from plots of percent control parasitemia over inhibitor concentration using the Prism 3.0 program, (GraphPad Software), with data from duplicate experiments fitted by non linear regression [31].

3.2.2 In vitro analysis of cytotoxicity on HeLa cells

HeLa cells were cultured in 60mm × 15mm tissue culture dishes containing 5 mL of Dulbecco's Modified Eagle's Medium (DMEM) supplemented with penicillin and streptomycin. Compounds were dissolved in DMSO to 100 μM concentrations. Once cell cultures reached 70% confluency, 5 μL of compound was added to the DMEM in the tissue culture dish for a final concentration of 100 μM. Cells were incubated for 24 h in a 37 °C CO_2 incubator. After 24 h incubation, the media was removed from the HeLa cells and the cells were then washed with 5 mL of 1X PBS. The cells were then cleaved off of the bottom of the plate *via* 5-minute incubation with 0.5 mL of 0.25% trypsin. Cells were re-suspended in 1 mL of 1X PBS and transferred to a microcentrifuge tube. 100 μL of trypan blue solution were added to the re-suspended cells and allowed to incubate at room temperature for approximately 10 minutes. Viable and dead cells were visualized and counted with a hemacytometer. IC_{50} values were determined using GraphPad PRISM.

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Captions:

Table 1. Antimalarial activity of synthesized conjugates

Table 2. Cytotoxicity and Selective index of potent conjugates

Figure 1. General structure of lead compound and target hybrid compounds

Scheme 1: Synthesis of (2-Azido-ethyl/propyl)-(7-chloro-quinolin-4-yl)-amine **3**

Scheme 2: Synthesis of precursors acetylenic chalcones **6** and their corresponding pyrazolines **7**

Scheme 3: Synthesis of 4-aminoquinoline-chalcone conjugates **8** and 4-aminoquinoline-pyrazoline conjugates **9**

Table 1: Antimalarial activities of synthesized compounds

Compound	R	R^1	n	W2 (CQ-R)[a] IC_{50}(nM)±Std. deviation
8a	H	H	1	172.1± 3.4
8b	H	4-OCH_3	1	114.4± 2.6
8c	H	3,4-$(OCH_3)_2$	1	140.9± 6.6
8d	H	3,4,5-$(OCH_3)_3$	1	175.3± 28.1
8e	OCH_3	H	1	354.8± 0.6
8f	OCH_3	4-OCH_3	1	1909.0± 56.6
8g	OCH_3	3,4-$(OCH_3)_2$	1	830.1± 5.1
8h	OCH_3	3,4,5-$(OCH_3)_3$	1	355.4± 105.9
8i	H	H	2	>10000
8j	H	4-OCH_3	2	>10000
8k	H	3,4-$(OCH_3)_2$	2	>10000
8l	H	3,4,5-$(OCH_3)_3$	2	5275.5± 188
8m	OCH_3	H	2	6960.0± 425.7
8n	OCH_3	4-OCH_3	2	>10000
8o	OCH_3	3,4-$(OCH_3)_2$	2	337.1± 30.8
8p	OCH_3	3,4,5-$(OCH_3)_3$	2	831.4± 119.6
9a	H	H	1	237.4± 122.5
9b	H	4-OCH_3	1	130.7± 18.3
9c	H	3,4-$(OCH_3)_2$	1	151.7± 22.9
9d	H	3,4,5-$(OCH_3)_3$	1	425.8± 0.9
9e	OCH_3	H	1	285.5± 34.4
9f	OCH_3	4-OCH_3	1	58.7± 22.7
9g	OCH_3	3,4-$(OCH_3)_2$	1	53.7± 25.0
9h	OCH_3	3,4,5-$(OCH_3)_3$	1	139.0± 9.9
9i	H	H	2	3003.5± 68.6
9j	H	4-OCH_3	2	498.0± 49.2
9k	H	3,4-$(OCH_3)_2$	2	503.5± 119.1
9l	H	3,4,5-$(OCH_3)_3$	2	2424.0± 125.9
9m	OCH_3	H	2	77.0± 49.4
9n	OCH_3	4-OCH_3	2	1571.5± 72.8

9o	OCH_3	3,4-$(OCH_3)_2$	2	1684.0± 411.5
9p	OCH_3	3,4,5-$(OCH_3)_3$	2	1741± 79.2
CQ				150± 20.0
ART				32.1± 17.0

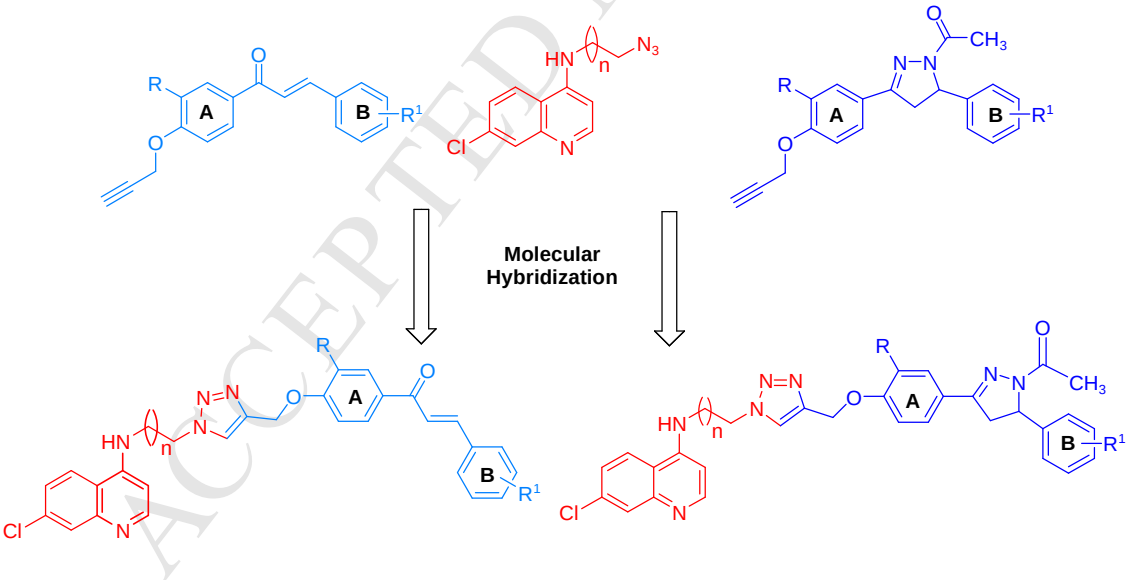
[a]CQ-R: Chloroquine-resistant strain

Table 2: Cytotoxicity and Selectivity index of potent conjugates

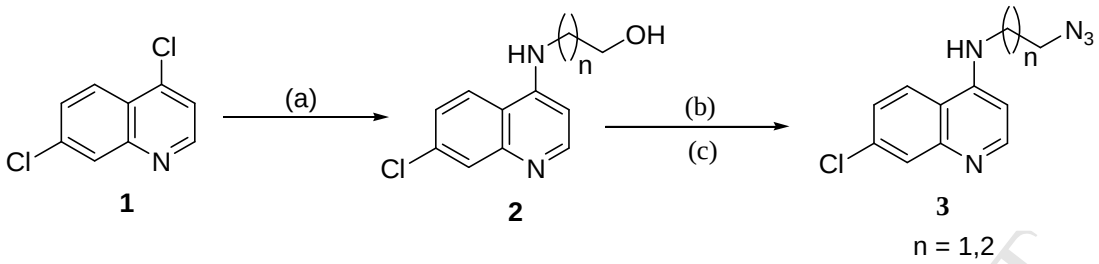
Compound	**Cytotoxicity[a] (μM)**	***P. falciparum* (CQ-R)[b] IC_{50} (nM)**	**SI[c]**
8b	35.6	114.4	311
8c	12.7	140.9	90
9b	29.2	130.7	223
9f	32.8	58.7	558
9g	42.7	53.7	795
9m	46.1	77.0	598
Doxorubicin	8.30		

[a] Cytotoxicity against HeLa cell line
[b] CQ-R: Chloroquine resistant strain
[c] SI: Selective index is ratio of IC_{50} value of HeLa cell line to that of W2 resistant strain

Figure 1. General structure of target hybrid compounds

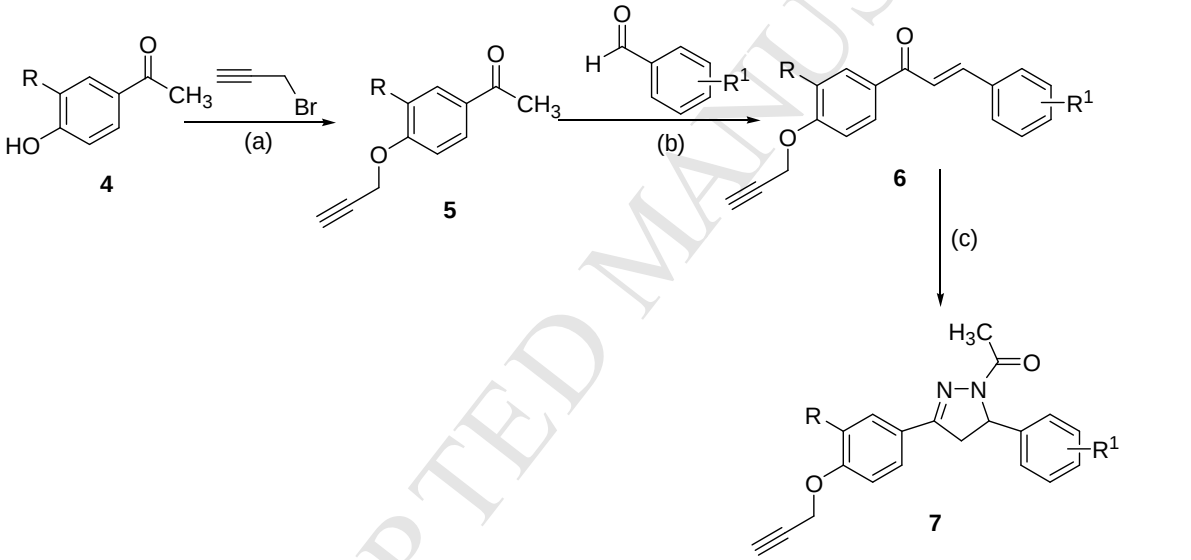


Scheme 1: Synthesis of (2-Azido-ethyl/propyl)-(7-chloro-quinolin-4-yl)-amine **3**



Reagents and conditions: (a) Ethanol/propanolamine, Et_3N, 120 °C, 12 h; (b) MsCl, Et_3N, dry $CHCl_3$, 0 °C-rt, 2-3 h; (c) NaN_3, DMF, 120 °C, 12 h

Scheme 2: Synthesis of precursors acetylenic chalcones **6** and their corresponding pyrazolines **7**

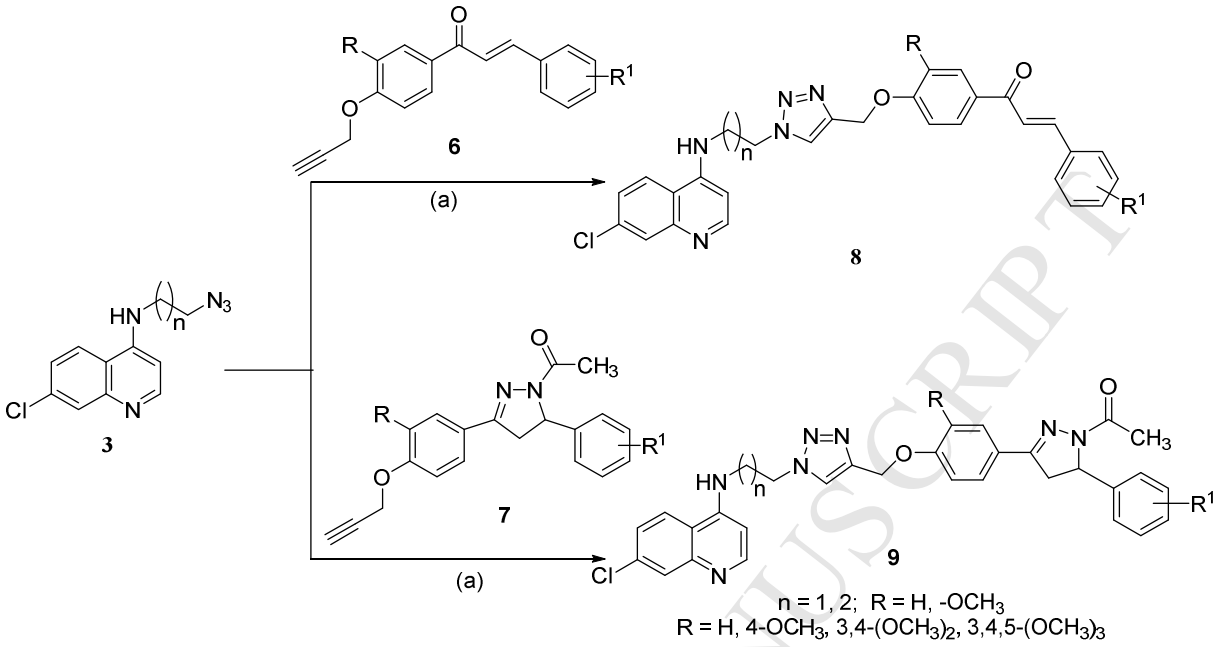


R = H, -OCH_3

R^1 = H, 4-OCH_3, 3,4-$(OCH_3)_2$, 3,4,5-$(OCH_3)_3$

Reagents and conditions: (a) K_2CO_3, DMF, rt, 2 h.; (b) KOH, EtOH, 30min.-2 h; (c) Hydrazine hydrate, Acetic acid, reflux, 2-3 h

Scheme 3: Synthesis of 4-aminoquinoline-chalcone conjugates **8** and 4-aminoquinoline-pyrazoline conjugates **9**



Reagents and conditions: (a) $CuSO_4.5H_2O$, Sodium ascorbate, EtOH:H_2O, rt, 7-8 h

- Synthesis and antiplasmodial evaluation of 4-aminoquinoline-chalcone/-pyrazoline conjugates
- Conjugates have comparable antiplasmodial activities with that of Chloroquine
- Most potent and non-cytotoxic conjugate exhibited an IC_{50} of 53.7 nM