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Design, synthesis and in vitro antimalarial evaluation of triazole-linked chalcone and dienone hybrid compounds

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ABSTRACT

A targeted series of chalcone and dienone hybrid compounds containing aminoquinoline and nucleoside templates was synthesized and evaluated for in vitro antimalarial activity. The Cu(I)-catalyzed cycloaddition of azides and terminal alkynes was applied as the hybridization strategy. Several chalcone-chloroquinoline hybrid compounds were found to be notably active, with compound **8b** the most active, exhibiting submicromolar IC_{50} values against the D10, Dd2 and W2 strains of *Plasmodium falciparum*.

1. Introduction

Malaria remains one of the most widespread infectious diseases, and poses a great challenge to world health. This is underlined by staggering annual infection and mortality statistics. Estimates range from 300 to 500 million clinical cases of malaria each year, 90% of them in sub-Saharan Africa. The majority of these cases are caused by *P. falciparum*,[1,2] and result in about 1 million deaths annually, mostly in children under 5 years of age.[2,3]

Resistance of malaria parasites to available antimalarial drugs remains a main challenge to the effective control of the disease. Varying levels of resistance to available classes of antimalarials has been reported for *P. falciparum*, the predominant *Plasmodium* species in Africa and the most virulent of them.[1,4] This has led to the adoption of combination therapies for the routine treatment of uncomplicated malaria, with particular emphasis on artemisinin-based combination therapies (ACTs).[5–7] However, recent evidence of diminished activity of artemisinins in Southeast Asia threatens this strategy.[8,9]

With increasing resistance to available agents, intensive drug discovery efforts aimed at developing new antimalarial drugs or modifying existing agents are ongoing. Ideally, highly efficacious, novel antimalarial compounds will be developed to supplement available drugs.

Molecular hybridization as a drug discovery strategy involves the rational design of new chemical entities by the fusion (usually via a covalent linker) of two drugs, both active compounds and/or pharmacophoric units recognized and derived from known bioactive molecules.[10,11] The selection of the two principles in the dual drug is usually based on their observed (or anticipated) synergistic or additive pharmacological activities to enable the identification of highly active novel chemical entities. In the context of attempting to circumvent antimalarial drug resistance, hybridization is quite an attractive strategy, particularly when the pharmacophores/active molecules being merged possess independent modes of antimalarial action.

Another basis for hybridization is to exploit active transport mechanisms by linking bioactive units to moieties that are recognized and actively transported into mammalian cells, such as amino acids[12] and nucleosides.[13]

One of the potential disadvantages of molecular hybridization as a drug discovery strategy is the obvious possibility of transferring

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negative traits of any one of the hybrid components onto the target dual drugs. For example, the incorporation of the 7-chloroquinoline moiety could potentially result in cross-resistance, whereby hybrid compounds containing this sub-structure exhibit similar susceptibility patterns to chloroquine, specifically the reduced activity against chloroquine resistant strains of the malarial parasite. However, despite such potential liabilities, promising hybridization strategies need not be dismissed offhand as non-viable without preliminary experimental data confirming the existence of suspected shortcomings.

Although there are no examples of antimalarial dual drugs in clinical use, a number of active molecules have been identified using this approach. Highly active trioxaquines have been developed by covalently linking a 1,2,4-trioxane motif (derived from the highly active natural sesquiterpene artemisinin) to a 4-aminoquinoline moiety (borrowed from chloroquine and other aminoquinoline-based antimalarials) via an appropriate spacer.[14] Several chalcone-chloroquinoline hybrid compounds that showed inhibition of β-hematin formation comparable with that exhibited by chloroquine have also been identified.[15] These examples and others illustrate the potential of molecular hybridization as a strategy for the development of novel antimalarial agents.

We therefore sought to apply this approach in the design of hybrid compounds consisting of curcumin-related compounds linked to other rationally selected entities via a triazole linker. This hybridization strategy was to be facilitated by the robust and experimentally simple cycloaddition of azides and terminal alkynes to yield 1,2,3-triazoles.[16–20] This Cu(I)-catalyzed reaction has had wide application not just in mainstream organic chemistry, but also in medicinal chemistry/drug discovery for the synthesis of bioactive molecules and generation of libraries of drug-like scaffolds possessing the triazole ring.[21,22]

Chalcones and dienones are structurally related compounds. Chalcones can be readily synthesized, and both naturally occurring and synthetic chalcones have been shown to exhibit notable in vivo and in vitro antimalarial activity.[23–26] This has been proposed to be by the inhibition of either plasmodial aspartate proteases,[27] cysteine proteases[28] or new permeability pathways introduced into erythrocyte cell membranes by the malaria parasite.[29] However, no reports on the investigation of the potential antimalarial activity of dienones could be found in the literature.

AZT (Fig. 1), an antiretroviral agent approved for use in HIV infection, was selected as one of the entities for hybridization to the chalcones and dienones for several reasons. Firstly, AZT is relatively hydrophilic,[30] and the resulting hybrids would therefore have enhanced aqueous solubilities and possibly improved oral bioavailability. Secondly, AZT is a nucleoside (deoxythymidine) analogue; nucleosides are biological molecules that are known to be actively transported into mammalian cells,[13] and therefore we hypothesized that linking AZT to the chalcones or dienones (**7**, **9** and **13**, Fig. 1) could improve oral bioavailability and facilitate delivery to intracellular sites of action. Furthermore, hybridization of the potentially antimalarial chalcones and dienones to a molecule with intrinsic anti-HIV activity might lead to the identification of molecules that exhibit both antimalarial and anti-HIV activity. This is particularly interesting considering that in sub-Saharan Africa, the high burden of both malaria and HIV translates into high incidences of co-infection in many regions.[31] Synergism between antiretrovirals and established antimalarial drugs has also been reported.[32] Finally, AZT bears an azide functionality that could be conveniently exploited in its hybridization to other entities via click chemistry.

The 7-chloroquinoline moiety (Fig. 1), a pharmacophore present in several established antimalarials such as chloroquine and

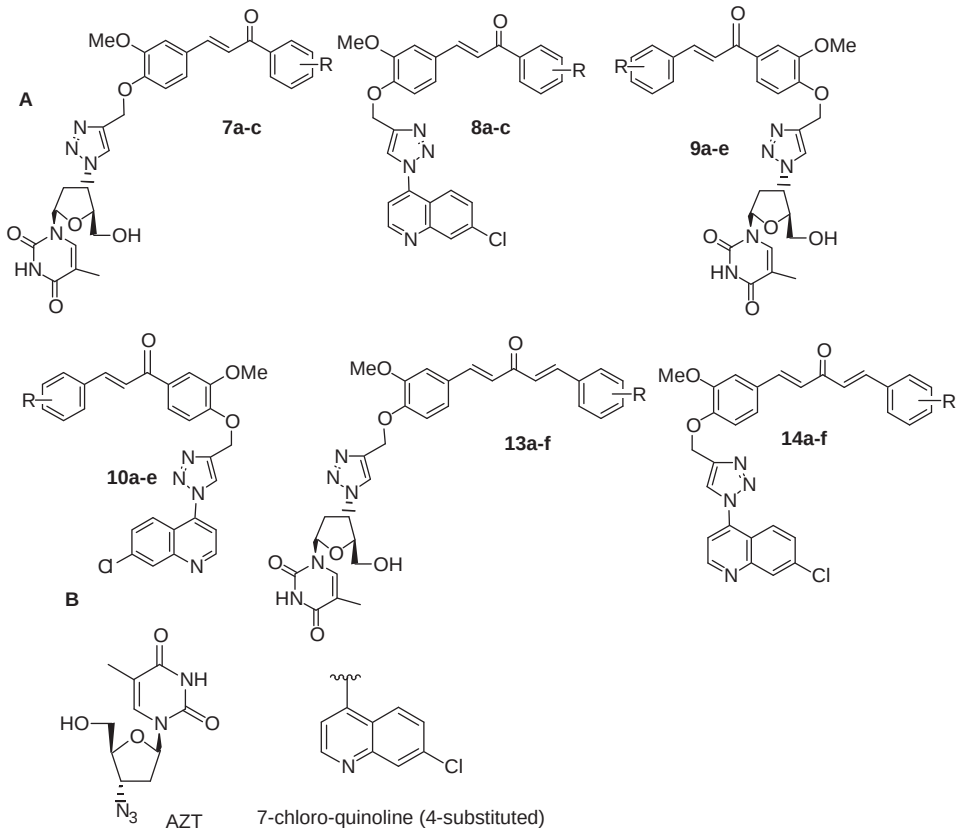


Figure 1. (A) General structures of the target chalcone and dienone hybrid compounds; (B) structures of AZT and 4-(substituted)-7-chloroquinoline.

amodiaquine, is thought to confer antimalarial potency to these compounds by facilitating binding to heme and consequently inhibiting hemozoin formation.[33] This study aimed at exploiting this feature by incorporating the 7-chloroquinoline moiety into hybrid molecules with chalcones and dienones (**8**, **10** and **14**, Fig. 1).

The synthesis and biological evaluation of the target hybrid compounds is reported and discussed herein.

2. Synthesis

The synthesis of the target triazole hybrid compounds involved the initial synthesis of the required precursors, that is, the acetylenic chalcones (**1a–c**, **2a–e**) and acetylenic dienones (**5a–f**), as well as 4-azido-7-chloroquinoline **6**. The synthesis and characterization of series **1** and **2** was carried out previously by our group and has already been reported.[34] The dienones selected for synthesis were to bear similar substitution patterns to these acetylenic chalcones.

The synthesis of the acetylenic dienones was a 3-step process as depicted in Scheme 1. The first step was an O-alkylation reaction, involving the reaction of vanillin with 1.5 equiv of propargyl bromide in anhydrous DMF in the presence of 1.5 equiv of anhydrous K_2CO_3. This reaction yielded the acetylenic intermediate **3** in good yield after purification by recrystallization from CH_2Cl_2/hexane mixtures. The synthesis of intermediate **4** involved the base-catalyzed Claisen–Schmidt condensation of **3** and acetone using the (modified) method reported by Ramachandra and Subbaraju.[35] Intermediate **3** was stirred in acetone (as reagent and solvent) in the presence of aqueous 2.5 M NaOH at room temperature for 6 h. The crude product of the reaction was purified by silica gel column chromatography to yield **4** in 84% yield.

A final condensation of intermediate **4** and the appropriately substituted benzaldehydes yielded the target acetylenic dienones **5a–e**. This condensation was successfully carried out by modifying a method reported for the synthesis of chalcones and which makes use of boron–trifluoride etherate (BF_3–Et_2O) as a Lewis-acid catalyst.[36] This involved the reaction of **4** with 1.1 equiv of the appropriate benzaldehyde in the presence of 1.5 equiv of BF_3–Et_2O; the reaction was carried out in anhydrous dioxane under a nitrogen atmosphere. The crude products were purified by silica gel column chromatography (EtOAc/hexane) to yield the target acetylenic dienone products in average yields.

Enantiomerically pure AZT (1-[(2*R*,4*S*,5*S*)-4-azido-5-(hydroxymethyl)oxolan-2-yl]-5-methyl-1,2,3,4-tetrahydro-pyrimidine-2,4-dione) was applied for the hybridization. It already bears the azide group, and as such was ready for hybridization to the acetylenic entities. 4-Azido-7-chloro-quinoline **6** was furnished by applying the (modified) method described by de Souza et al.,[37] whereby 4,7-dichloroquinoline was reacted with 2 equiv of NaN_3 in anhydrous DMF at 65 °C for 6 h. Crystallization of the product from CH_2Cl_2/hexane mixtures afforded **6** in 86% yield (Scheme 2).

The target chalcone hybrid compound series **7–10** were then accessed using the (modified) procedure reported by Fokin et al.[20] Equimolar amounts of AZT or **6** and the relevant acetylenic compound from series **1** or **2** were dissolved in DMF, after which 1 M sodium ascorbate (0.4 equiv) and 1 M $CuSO_4$ (20 mol %) were added sequentially, in that order (Scheme 3). The reaction mixture was then stirred vigorously at 65 °C for 24 h. Purification was by silica gel column chromatography.

The relatively low yields associated with the synthesis of the acetylenic dienones **5a–f** prompted a slightly different approach to the synthesis of the target dienone hybrid compounds (Scheme 4); these were synthesized by initially reacting acetylenic enone intermediate **4** with either AZT or **6** to generate the enone-triazole derivatives **11** and **12** in good yield. These intermediates were subsequently condensed with the appropriate benzaldehydes using boron–trifluoride etherate as catalyst as already described above to yield the target dienone hybrid derivatives **13a–f** and **14a–f**.

In order to investigate the role of the α,β-unsaturated carbonyl system of the enone intermediate **12**, 'control' hybrid compounds **16** and **17** were also synthesized. Compound **16** was the chloroquinoline triazole hybrid of phenoxyacetylene (**15**); **17** was the equivalent hybrid of **3**, an intermediate in the synthesis of the acetylenic chalcones and dienones. The chemistry applied was as described above for the other hybrid compounds (Scheme 5).

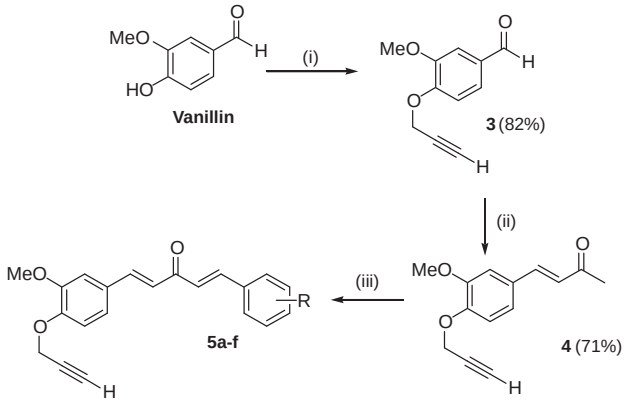
All compounds were characterized by ^{1}H NMR, ^{13}C NMR, Low Resolution Mass Spectrometry, IR Spectroscopy, Elemental analysis and melting point determination.

3. In vitro antimalarial assay results and discussion

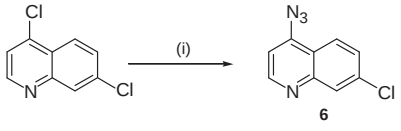
The target compounds were evaluated for their in vitro antimalarial activity against the chloroquine sensitive (CQS) strain D10 and chloroquine resistant (CQR) strains Dd2 and W2 of *P. falciparum*. Table 1 presents the in vitro antimalarial assay results for the intermediates **1–6**, **11** and **12**, the hybrid target compounds **7–10** and **13–14** as well as the control hybrid compounds **16** and **17**.

From Table 1 it can be seen that the target compounds generally exhibited moderate in vitro antimalarial activity across all three strains, with IC_{50} values generally falling in the lower micromolar to high nanomolar range. The dienone hybrid series **13** and **14** were noticeably less active against W2, with several of them showing no detectable antimalarial activity against this strain at the highest concentration tested (IC_{50} >20 μM).

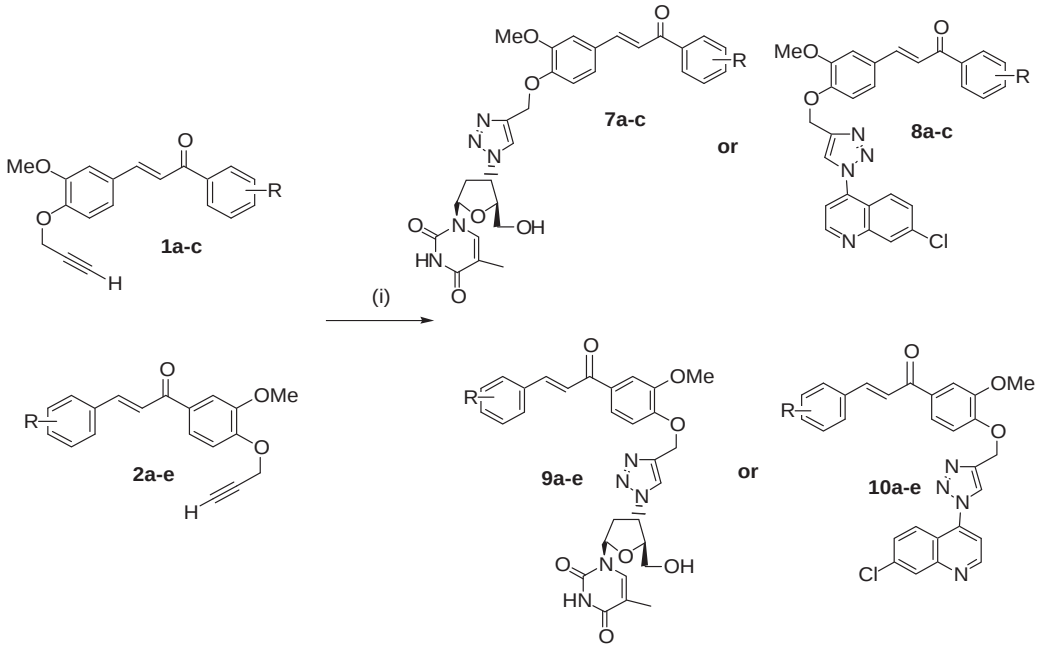
The acetylenic dienone series **5** showed in vitro antimalarial activity comparable to the acetylenic chalcones, though some of them showed negligible antimalarial activity against the D10 or W2 strains. The most active acetylenic compound was **5c**, the tri-methoxylated acetylenic dienone, which had an IC_{50} value of 0.9 and 1.4 μM against *P. falciparum* D10 and Dd2, respectively. Interestingly, the acetylenic enone intermediate **4** also showed



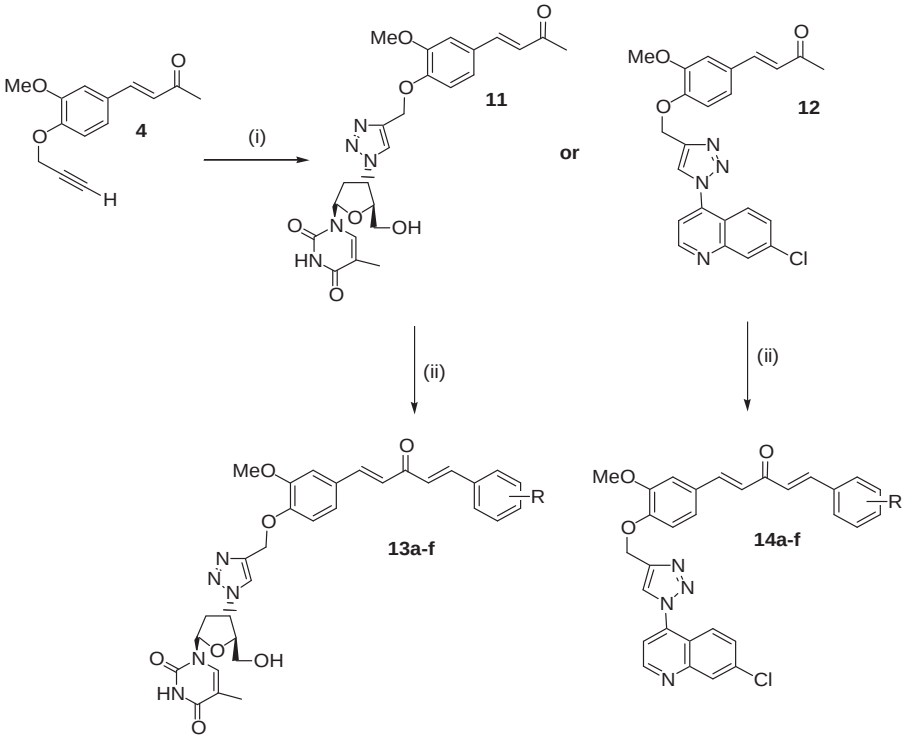
Scheme 1. Reagents and conditions: (i) Propargyl bromide, K_2CO_3, DMF, 30 °C, 18 h; (ii) acetone, 2.5 M NaOH, rt, 6 h; (iii) appropriate benzaldehydes, BF_3–Et_2O, dioxane, 50 °C, 16 h.



Scheme 2. Reagents and conditions: (i) NaN_3, DMF, 65 °C, 6 h.



Scheme 3. Reagents and conditions: (i) AZT (for **7a–c** and **9a–e**) or **6** (for **8a–c** and **10a–e**), 1 M Na ascorbate, 1 M $CuSO_4 \cdot 5H_2O$, DMF, 65 °C, 24 h.

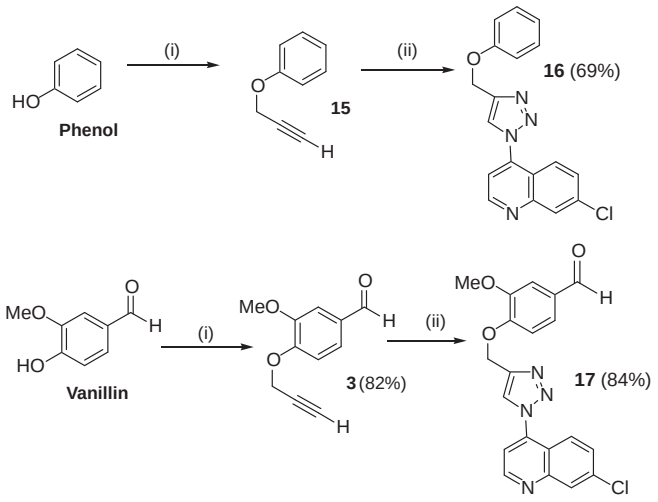


Scheme 4. Reagents and conditions: (i) AZT (for **11**) or **6** (for **12**), 1 M Na ascorbate, 1 M $CuSO_4 \cdot 5H_2O$, DMF, 65 °C, 24 h; (ii) appropriate benzaldehydes, BF_3–Et_2O, dioxane, 50 °C, 16 h.

moderate antimalarial activity, comparable to that of the acetylenic chalcones and dienones, with IC_{50}s of 9.7 and 7.5 μM against *P. falciparum* D10 and Dd2, respectively. This would suggest that for chalcones and dienones, the most basic structure/pharmacophore required to exhibit antimalarial activity could be the phenyl-propenone moiety.

The activities of the chalcone-AZT hybrid series **7** and **9** were comparable to that of the acetylenic chalcones, suggesting that the linking of the chalcones to AZT does not improve the in vitro antimalarial activity of the acetylenic chalcones. The same could be said for the dienone-AZT hybrid series **13**, which were only slightly more active than the acetylenic dienones **5**, particularly against D10 and Dd2.

Among the chalcone-chloroquinoline hybrid compounds (**8** and **10**), there were three compounds that were notably more potent; submicromolar IC_{50} values were observed for **8b**, **8c** and **10b**. Of



Scheme 5. Reagents and conditions: (i) Propargyl bromide, K_2CO_3, DMF, 30 °C, 18 h; (ii) **6**, 1 M Na ascorbate, 1 M $CuSO_4 \cdot 5H_2O$, DMF, 65 °C, 24 h.

these three, compound **8b** was the most active, having IC_{50} values of 0.04, 0.07 and 0.09 μM against the D10, Dd2 and W2 strains of *P. falciparum*, respectively. Notably, these three compounds were either di- or tri-methoxylated chalcone-chloroquinoline hybrids; none of the halogenated chalcone-chloroquinoline hybrid compounds exhibited submicromolar IC_{50} values. The presence of the chloroquinoline moiety on the three most active compounds is most likely contributing to the improved activity that these compounds exhibit; this is no surprise, since this sub-structure is present in several established antimalarial drugs such as the aminoquinolines chloroquine and amodiaquine. It is thought to confer antimalarial potency to these compounds by facilitating binding to intra-parasitic heme and consequently inhibiting hemozoin formation.[33] However, it was apparent that this significant improvement in activity was not universal, as shown by the fact that the other hybrid compounds in this class, as well as the corresponding dienone-chloroquinoline hybrid compounds **14**, did not have similarly improved in vitro antimalarial activities.

Also notable was that the enone-chloroquinoline triazole intermediate **12** showed notably high in vitro antimalarial activity, with submicromolar IC_{50} values against D10 and Dd2 *P. falciparum*; the control chloroquinoline hybrid compounds **16** and **17** were inactive against D10 and Dd2 *P. falciparum* at the highest concentration tested (IC_{50} >20 μM). The AZT triazole intermediate **11** showed moderate in vitro activity.

No obvious trends were observed as far as the influence of the different substitution patterns of the chalcones or dienones on antimalarial activity. The only consistent conclusion in this regard is that none of the compounds with submicromolar IC_{50} values were halogenated.

4. β-Hematin inhibition assay results and discussion

As alluded to earlier, the inhibition of hemozoin formation is one of the known mechanisms of antimalarial action, and quinoline-based antimalarials such as chloroquine and amodiaquine are proposed to exert their antimalarial activity via this mechanism.[38–40] On the strength of this, the chalcone-chloroquinoline hybrid compounds were investigated for their potential to inhibit hemozoin formation.

Assays have been designed to estimate the ability of compounds to inhibit hemozoin formation.[40] The assay described by Ncokazi and Egan[41] is one such assay, which colorimetrically quantifies the ability of a compound to inhibit the conversion of hematin to β-hematin, the synthetic equivalent of hemozoin. This particular assay was applied for the chalcone-chloroquinoline hybrid target molecules, and the IC_{50} values reported from this assay represent the number of molar equivalents of the test compound, relative to hematin, that are required to inhibit its conversion to β-hematin by 50%—the lower the IC_{50}, the more potent the compound is at inhibiting β-hematin formation.

The results from the β-hematin inhibition assays of some of the chalcone-chloroquinoline hybrid target molecules are shown in Table 2. With the exception of **10a** which was inactive at the highest concentration tested, the submitted compounds showed inhibition of β-hematin formation to varying degrees. The most potent compound was **8c**, with an IC_{50} of 0.2 equiv. Interestingly the acetylenic chalcone **1b** was also a more potent inhibitor of β-hematin formation than chloroquine, with an IC_{50} value of 0.5 equiv. Compound **8b**, the most potent compound in vitro, was only slightly more potent (IC_{50} 1.6 equiv) than chloroquine, as was

Table 1
In vitro antimalarial activities against the D10, Dd2 and W2 strains of *P. falciparum*[a]

Compound	R′	D10 IC_{50} (μM)	Dd2 IC_{50} (μM)	W2 IC_{50} (μM)
1a	4′-OMe	9.7	13.5	8.4
1b	2′,4′-diOMe	3.4	4.3	3.8
1c	2′,3′,4′-triOMe	7.7	2.8	7.0
2a	2,4-diOMe	>20	14.5	9.7
2b	2,3,4-triOMe	4.1	2.4	6.7
2c	2,4-diCl	3.3	2.8	5.0
2d	4-F	7.2	7.7	>20
2e	2,4-diF	>20	5.2	9.4
4	—	9.7	7.5	>20
5a	4′-OMe	11.8	10.7	>20
5b	2′,4′-diOMe	5.4	4.0	18.9
5c	2′,3′,4′-triOMe	0.9	1.4	9.2
5d	2,4-diCl	9.2	9.0	>20
5e	4-F	9.8	6.5	21.5
5f	2,4-diF	11.9	9.3	>20
6	—	>20	>20	>20
7a	4′-OMe	2.9	6.1	8.0
7b	2′,4′-diOMe	1.5	4.4	5.4
7c	2′,3′,4′-triOMe	3.3	3.7	5.4
8a	4′-OMe	0.6	2.2	5.0
8b	**2′,4′-diOMe**	**0.04**	**0.07**	**0.09**
8c	2′,3′,4′-triOMe	0.4	0.4	0.6
9a	2,4-diOMe	10.2	11.8	9.0
9b	2,3,4-triOMe	5.4	3.8	7.1
9c	2,4-diCl	3.7	1.9	8.4
9d	4-F	7.3	6.1	6.6
9e	2,4-diF	3.9	4.8	7.1
10a	2,4-diOMe	5.2	11.7	6.6
10b	2,3,4-triOMe	0.3	0.3	0.5
10c	2,4-diCl	6.0	1.9	11.5
10d	4-F	7.4	1.6	6.9
10e	2,4-diF	4.1	2.1	10.6
11	—	12.0	16.4	ND
12	—	0.8	0.7	ND
13a	4′-OMe	2.8	1.5	18.2
13b	2′,4′-diOMe	1.3	1.2	14.5
13c	2′,3′,4′-triOMe	1.3	2.4	8.3
13d	2,4-diCl	1.4	1.7	9.1
13e	4-F	1.7	2.6	ND
13f	2,4-diF	1.4	1.7	12.4
14a	4′-OMe	3.0	2.1	5.3
14b	2′,4′-diOMe	5.1	6.4	>20
14c	2′,3′,4′-triOMe	2.5	2.1	18.5
14d	2,4-diCl	19.0	16.8	>20
14e	4-F	9.4	9.3	>20
14f	2,4-diF	10.2	6.5	>20
16	—	>20	>20	ND
17	—	>20	>20	ND
AZT	—	>20	>20	>20
Chloroquine	—	0.017	0.097	0.069

ND: Not determined.
[a] Each compound was assayed in duplicate, on two separate occasions.

Table 2
Results from β-inhibition assay of selected chalcone-chloroquinoline hybrid compounds

Compound	R	β-Hematin inhibition (IC_{50} in equiv)[a]
1b	2′,4′-diOMe	0.5
8b	2′,4′-diOMe	1.6
8c	2′,3′,4′-triOMe	0.2
10a	2,4-diOMe	Inactive
10b	2,3,4-triOMe	4.1
10d	4-F	4.8
10e	2,4-diF	1.6
Chloroquine	—	1.91

[a] The IC_{50}s are averages of triplicate determinations and are reported in equivalents of the drug relative to hematin.

10e with a similar IC_{50}. Compounds **10b** and **10d** were less potent inhibitors of β-hematin formation than chloroquine. Though the chalcone component of the hybrid compounds could contribute to their potency as inhibitors of β-hematin formation (the chalcone **1b** was a potent β-hematin inhibitor, for example), no obvious structural features could be identified that could account for why some of the hybrid compounds were significantly more potent β-hematin inhibitors than others.

There was also no consistent correlation between β-hematin inhibition and in vitro antimalarial potency for this set of compounds, as the more potent inhibitors of β-hematin formation were not necessarily the more potent compounds in vitro. This implies the possible influence of other factors; one such factor could be the degree of accumulation within the parasite digestive vacuole, which is the definitive site of hemoglobin catabolism and therefore the site of action of hemozoin inhibitors. Chloroquine accumulates considerably within the parasite digestive vacuole by both saturable[42,43] and non-saturable (pH-dependent)[33,44,45] mechanisms, a factor that undoubtedly contributes to its antimalarial potency. The lower in vitro antimalarial activity (relative to chloroquine) of those target compounds showing comparable or superior β-hematin inhibition could therefore suggest the absence of equivalent accumulation mechanisms, resulting in lower concentrations at the site of action (digestive vacuole) and ultimately in relatively lower in vitro antimalarial efficacies. The target compounds were notably not as basic as the dibasic chloroquine, which would lessen the possibility of pH-dependent accumulation as a mechanism of accumulation for these compounds.

5. Discussion and conclusion

The moderate in vitro antimalarial activity observed for the acetylenic chalcones **1** and **2** is in line with the published results for alkoxylated chalcones, which have been reported as having IC_{50} values in the high nanomolar to low micromolar range;[23,24] this activity does not seem to be compromised by the presence of the acetylene substitution. Acetylenic dienones exhibit comparable antimalarial activity to the acetylenic chalcones. This is probably attributable to the presence of the common phenyl propenone sub-structure in both these series of compounds, as the acetylenic enone intermediate **4** also exhibits comparable in vitro antimalarial activity.

The AZT hybrid compounds of both the chalcones and dienones did not exhibit notably higher in vitro antimalarial activity relative to their acetylenic precursors, though the retention of activity in most cases is still noteworthy as AZT itself showed negligible in vitro antimalarial activity. It is therefore possible that the envisaged benefits of the AZT hybridization strategy, which were primarily the increased solubility and possibly enhanced oral bioavailability of these compounds, may only become apparent through pharmacokinetic profiling or in vivo antimalarial assays.

The chloroquinoline-hybridization strategy led to the identification of highly active hybrid compounds, that is, **8b**, **8c** and **10b**, as well as the enone-chloroquinoline intermediate **12**. Compound **8b** was the most active of these, with submicromolar IC_{50} values against all three tested *P. falciparum* strains.

Interestingly, both the chalcone-chloroquinoline hybrid compounds **8** and their dienone counterparts **14** can be considered as derivatives of intermediate **12** via modifications on its α-carbon. It is also intriguing to note that hybridization to chloroquinoline did not lead to a similarly potent activity in all these compounds; instead, only the three methoxylated chalcones mentioned previously had notably improved activity. This indicates that the group on the terminal α-carbon of **12** is likely to be crucial for the retention of activity, and some groups could actually negate any beneficial effects that the chloroquinoline moiety confers (as is the case with the halogenated chalcone-chloroquinoline and the dienone-chloroquinoline hybrid compounds).

Also noteworthy is the lack of activity of the control hybrid compounds **16** and **17**, both of which are structurally similar to **12** but don't possess the α,β-unsaturated carbonyl system. This would point to the importance of the α,β-unsaturated carbonyl system of **12** on its in vitro antimalarial activity.

The relatively lower activities of **13** and **14** against the CQR W2 *P. falciparum* (relative to the CQS D10 strain) may be interpreted as evidence of cross-resistance, though such an interpretation is somewhat blurred by the fact that the activities of these compounds against the CQS D10 and the CQR Dd2 strains appear to be comparable. This, along with the fact that the assay materials and techniques applied for all three strains were similar, suggests a lower intrinsic susceptibility of the W2 strain to these compounds, rather than the presence of overt cross-resistance.

The fact that some of the compounds were quite potent inhibitors of β-hematin formation (in several cases more active than chloroquine) would suggest that this is a primary mechanism by which these compounds exert their antimalarial activity, though the presence of other mechanisms of action is also quite possible.

In conclusion, chalcone and dienone hybrid compounds were successfully synthesized and tested for their in vitro antimalarial activity, and the chalcone chloroquinoline hybrid compound **8b** was the most promising compound identified from the study.

In anticipation of subsequent in vivo and pharmacokinetic profiling, compound **8b** was evaluated for its cytotoxicity against the Chinese Hamster Ovarian (mammalian) cell line. No cytotoxicity was observed at the highest concentration tested (100 μM).

6. Experimental data

To guide in the interpretation of the ^{1}H NMR data presented below, the complete (and numbered) structures of all the intermediates and target compounds can be found in the Supplementary data.

6.1. 3-Methoxy-4-prop-2-ynyloxy-benzaldehyde (3)

Vanillin (4-hydroxy-3-methoxybenzaldehyde) (13 mmol) was dissolved in 10 mL of anhydrous DMF. Anhydrous K_2CO_3 (2.7 g, 19.5 mmol) was then added to the solution, and the mixture stirred at 30 °C for 30 min. Propargyl bromide (3-bromopropyne, 2.2 mL, 19.5 mmol) was then added slowly to the reaction mixture, which was subsequently stirred at 30 °C for 6 h upon which TLC indicated completion of the reaction.

The reaction mixture was then diluted with 50 ml water and extracted with ethyl acetate (3 × 50 mL). These extracts were then

combined, washed with water (2 × 50 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to yield the product residue that was then recrystallized from CH_2Cl_2/Hexane mixtures to yield the pure **3** in 82% yield. Mp 86 °C (from CH_2Cl_2/Hex); R_f (EtOAc/CH_2Cl_2/Hex) 0.43; IR ν_{max} ($CHCl_3$)/cm^{-1} 3307 (Alkynyl C–H), 3021 (Ar C–H), 2127 (C═C), 1683 (C═O), 1590 (Ar C═C); δ_H (300 MHz, $CDCl_3$) 9.87 (1H, s, H-7), 7.45 (1H, dd, *J* 1.9 and 7.8, H-2), 7.43 (1H, d, *J* 1.9, H-1), 7.14 (1H, d, *J* 7.8, H-3), 4.85 (2H, d, *J* 2.4, H-5), 3.94 (3H, s, H-4), 2.55 (1H, t, *J* 2.4, H-6); δ_C (75 MHz, $CDCl_3$) 190.8, 152.1, 150.1, 131.0, 126.1, 112.7, 109.6, 77.4, 76.6, 56.6, 56.0; LRMS (EI) *m*/*z* 191.3 (M+H) M^+ $C_{11}H_{10}O_3$ requires 190.1. Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.5; H, 5.3. Found: C, 69.5; H 5.2.

6.2. 4-(3-Methoxy-4-prop-2-ynyloxy-phenyl)-but-3-en-2-one (4)

Compound (6.2 g, 32 mmol) **3** was dissolved in 30 mL acetone, after which 2.5 M aqueous NaOH (19 mL, 48 mmol) was added. The mixture was then stirred at room temperature for 6 h, after which TLC showed complete consumption of the benzaldehyde starting material. The reaction mixture was then gradually neutralized with 2.5 M HCl, during which the crude product precipitated out as an amorphous yellow solid. This crude product was then filtered, washed with water, air dried and purified by silica column chromatography (EtOAc/Hex) to yield a pale yellow, crystalline solid (5.3 g, 71%); mp 103–105 °C (from EtOAc/Hex); R_f (EtOAc/Hex 4:6) 0.33; IR ν_{max} (KBr)/cm^{-1} 3253 (Alkynyl C–H), 2985 (Ar C–H), 1671 (C═O), 1595 (Ar C═C); δ_H (400 MHz, $CDCl_3$) 7.49 (1H, d, *J* 16.2, H-a), 7.14 (1H, dd, *J* 2.0 and 8.3, H-2), 7.10 (1H, d, *J* 2.0, H-1), 7.05 (1H, d, *J* 8.3, H-3), 6.63 (1H, d, *J* 16.2, H-b), 4.81 (2H, d, *J* 2.4, H-5), 3.93 (3H, s, H-4), 2.43 (1H, t, *J* 2.4, H-6), 2.38 (3H, s, H-b′); δ_C (100 MHz, $CDCl_3$) 198.1, 149.9, 143.2, 128.6, 125.8, 122.4 (2C), 113.9, 110.4, 77.9, 76.2, 56.6, 55.9, 27.4; LRMS (EI) *m*/*z* 231.3 (M+H) M^+ $C_{14}H_{14}O_3$ requires 230.1. Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.0; H, 6.1. Found: C, 72.8; H, 6.2.

6.3. General method A for the preparation of compounds 5a–f

A mixture of 230 mg (1 mmol) of **4** and the appropriately substituted benzaldehyde (1.1 mmol) were dissolved in 10 mL anhydrous 1,4-dioxane under a nitrogen atmosphere. To the stirring mixture, BF_3–Et_2O (0.2 mL, 1.5 mmol) was added, and the mixture stirred overnight at 50 °C. The reaction mixture was then allowed to cool to ambient temperature, diluted with CH_2Cl_2 and washed twice with water. The organic layer was then collected, dried over anhydrous Na_2SO_4, concentrated in vacuo and the product residue purified by silica column chromatography (EtOAc/Hex).

6.3.1. 1-(4-Methoxy-phenyl)-5-(3-methoxy-4-prop-2-ynyloxy-phenyl)-penta-1,4-dien-3-one (5a)

Yellow solid (135 mg, 39%); mp 124–125 °C (from EtOAc/Hex); R_f (EtOAc/Hex 4:6) 0.30; IR ν_{max} (KBr)/cm^{-1} 3289 (Alkynyl C–H), 3035 (Ar C–H), 1643 (C═O), 1599 (Ar C═C); δ_H (300 MHz, $CDCl_3$) 7.70 (1H, d, *J* 16.0, H-a), 7.68 (1H, d, *J* 16.0, H-a′), 7.56 (2H, d, *J* 8.8, H-1′, 4′), 7.19 (1H, dd, *J* 2.0 and 8.3, H-2), 7.15 (1H, d, *J* 2.0, H-1), 7.05 (1H, d, *J* 8.3, H-3), 6.97 (1H, d, *J* 16.0, H-b), 6.94 (1H, d, *J* 16.0, H-b′), 6.92 (2H, d, *J* 8.8, H-2′, 3′), 4.81 (2H, d, *J* 2.4, H-5), 3.94 (3H, s, H-4), 3.85 (3H, s, H-4′), 2.54 (1H, t, *J* 2.4, H-6); δ_C (75 MHz, $CDCl_3$) 188.7, 161.6, 149.9, 148.9, 142.8, 142.6, 130.1 (2C), 129.1, 127.6, 124.4, 123.3, 122.4, 114.4 (2C), 113.9, 110.7, 78.0, 76.2, 56.7, 55.9, 55.4; LRMS (EI) *m*/*z* 348.9 (M+H) M^+ $C_{22}H_{20}O_4$ requires 348.1. Anal. Calcd for $C_{22}H_{20}O_4$: C, 75.8; H, 5.8. Found: C, 75.7; H, 5.7.

6.3.2. 1-(2,4-Dimethoxy-phenyl)-5-(3-methoxy-4-prop-2-ynyloxy-phenyl)-penta-1,4-dien-3-one (5b)

Yellow solid (185 mg, 49%); mp 57–59 °C (from EtOAc/Hex); R_f (EtOAc/Hex 4:6) 0.30; IR ν_{max} (KBr)/cm^{-1} 3260 (Alkynyl C–H), 2927 (Ar C–H), 1642 (C═O), 1595 (Ar C═C); δ_H (300 MHz, $CDCl_3$) 8.01 (1H, d, *J* 16.1, H-a′), 7.67 (1H, d, *J* 15.9, H-a), 7.55 (1H, d, *J* 8.6, H-3′), 7.19 (1H, dd, *J* 1.9 and 8.3, H-2), 7.15 (1H, d, *J* 1.9, H-1), 7.07 (1H, d, *J* 16.0, H-b′), 7.05 (1H, d, *J* 8.3, H-3), 6.98 (1H, d, *J* 15.8, H-b), 6.53 (1H, dd, *J* 2.3 and 8.6, H-2′), 6.46 (1H, d, *J* 2.2, H-1′), 4.81 (2H, d, *J* 2.4 H-5), 3.94 (3H, s, H-4′), 3.90 (3H, s, H-5′), 3.85 (3H, s, H-4), 2.54 (1H, t, *J* 2.4, H-6); δ_C (75 MHz, $CDCl_3$) 189.3, 163.0, 160.1, 149.8, 142.2, 138.5, 137.8, 130.4, 130.2, 129.4, 124.0, 122.2, 117.1, 113.9, 110.8, 105.5, 98.5, 77.4, 76.2, 56.7, 55.9, 55.5, 55.4; LRMS (EI) *m*/*z* 378.9 (M+H) M^+ $C_{23}H_{22}O_5$ requires 378.2. Anal. Calcd for $C_{23}H_{22}O_5 \cdot ½H_2O$: C, 71.2; H, 5.9. Found: C, 71.5; H, 5.9.

6.3.3. 1-(3-Methoxy-4-prop-2-ynyloxy-phenyl)-5-(2,3,4-trimethoxy-phenyl)-penta-1,4-dien-3-one (5c)

Yellow solid (191 mg, 47%); mp 67–69 °C (from EtOAc/Hex); R_f (EtOAc/Hex 4:6) 0.33; IR ν_{max} (KBr)/cm^{-1} 3260 (Alkynyl C–H), 2934 (Ar C–H), 1645 (C═O), 1588 (Ar C═C); δ_H (300 MHz, $CDCl_3$) 7.94 (1H, d, *J* 16.1, H-a′), 7.67 (1H, d, *J* 15.9, H-a), 7.36 (1H, d, *J* 8.8, H-2′), 7.20 (1H, dd, *J* 1.9 and 8.4, H-2), 7.15 (1H, d, *J* 1.9, H-1), 7.06 (1H, d, *J* 16.1, H-b′), 7.04 (1H, d, *J* 8.3, H-3), 6.97 (1H, d, *J* 15.8, H-b), 6.71 (1H, d, *J* 8.8, H-1′), 4.81 (2H, d, *J* 2.4 H-5), 3.95 (3H, s, H-3′), 3.94 (3H, s, H-5′), 3.91 (3H, s, H-4′), 3.89 (3H, s, H-4), 2.54 (1H, t, *J* 2.4, H-6); δ_C (100 MHz, $CDCl_3$) 189.1, 155.7, 149.8, 148.9, 142.6, 138.1 (2C), 129.2, 124.9, 124.3, 123.5, 122.3, 121.9, 113.9, 110.7 (2C), 107.7, 78.0, 76.2, 61.5, 60.9, 56.7, 56.1, 55.9; LRMS (EI) *m*/*z* 409.4 (M+H) M^+ $C_{24}H_{24}O_6$ requires 408.2. Anal. Calcd for $C_{24}H_{24}O_6 \cdot ½H_2O$: C, 69.0; H, 6.0. Found: C, 69.5; H, 6.1.

6.3.4. 1-(2,4-Dichloro-phenyl)-5-(3-methoxy-4-prop-2-ynyloxy-phenyl)-penta-1,4-dien-3-one (5d)

Yellow solid (251 mg, 65%); mp 74–76 °C (from EtOAc/Hex); R_f (EtOAc/Hex 4:6) 0.59; IR ν_{max} (KBr)/cm^{-1} 3239 (Alkynyl C–H), 2949 (Ar C–H), 1653 (C═O), 1588 (Ar C═C); δ_H (300 MHz, $CDCl_3$) 8.03 (1H, d, *J* 16.0, H-a′), 7.67 (1H, d, *J* 15.9, H-a), 7.64 (1H, d, *J* 8.5, H-3′), 7.46 (1H, d, *J* 2.1, H-1′), 7.29 (1H, dd, *J* 2.1 and 8.5, H-2′), 7.21 (1H, dd, *J* 2.0 and 8.4,, H-2), 7.14 (1H, d, *J* 2.0, H-1), 7.06 (1H, d, *J* 8.3, H-3), 7.04 (1H, d, *J* 16.0, H-b′), 6.96 (1H, d, *J* 15.9, H-b), 4.82 (2H, d, *J* 2.4 H-5), 3.94 (3H, s, H-4), 2.54 (1H, t, *J* 2.4, H-6); δ_C (75 MHz, $CDCl_3$) 188.5, 150.2, 149.2, 143.8, 137.4, 136.3, 135.9, 131.9, 130.1, 128.8, 128.4, 128.2, 127.6, 123.7, 122.6, 113.9, 110.8, 77.9, 76.3, 56.7, 56.0; LRMS (EI) *m*/*z* 387.2 (M+H) M^+ $C_{21}H_{16}Cl_2O_3$ requires 386.1. Anal. Calcd for $C_{21}H_{16}Cl_2O_3$: C, 65.1; H, 4.2. Found: C, 64.8; H, 4.2.

6.3.5. 1-(4-Fluoro-phenyl)-5-(3-methoxy-4-prop-2-ynyloxy-phenyl)-penta-1,4-dien-3-one (5e)

Yellow solid (151 mg, 45%); mp 106–108 °C (from EtOAc/Hex); R_f (EtOAc/Hex 4:6) 0.50; IR ν_{max} (KBr)/cm^{-1} 3231 (Alkynyl C–H), 2920 (Ar C–H), 1667 (C═O), 1591 (Ar C═C); δ_H (300 MHz, $CDCl_3$) 7.69 (1H, d, *J* 15.9, H-a′), 7.67 (1H, d, *J* 15.9, H-a), 7.61 (1H, d, *J* 8.7, H-4′), 7.60 (1H, d, *J* 8.7, H-1′), 7.20 (1H, dd, *J* 1.9 ad 8.3, H-2), 7.15 (1H, d, *J* 2.0, H-1), 7.13–7.04 (3H, m, H-2′, 3′, 3), 7.01 (1H, d, *J* 16.3, H-b′), 6.93 (1H, d, *J* 15.9, H-b), 4.81 (2H, d, *J* 2.4 H-5), 3.93 (3H, s, H-4), 2.54 (1H, t, *J* 2.4, H-6); δ_C (75 MHz, $CDCl_3$) 188.5, 165.7, 149.9, 149.1, 143.2, 141.7, 130.3, 130.1, 128.9, 125.0, 124.2, 122.6 (2C), 116.2, 115.9, 113.9, 110.7, 77.9, 76.2, 56.7, 55.9; LRMS (EI) *m*/*z* 336.9 (M+H) M^+ $C_{21}H_{17}FO_3$ requires 336.1. Anal. Calcd for $C_{21}H_{17}FO_3$: C, 74.9; H, 5.1. Found: C, 74.5; H, 5.1.

6.3.6. 1-(2,4-Difluoro-phenyl)-5-(3-methoxy-4-prop-2-ynyloxy-phenyl)-penta-1,4-dien-3-one (5f)

Yellow solid (153 mg, 43%); mp 99–101 °C (from EtOAc/Hex); R_f (EtOAc/Hex 4:6) 0.55; IR ν_{max} (KBr)/cm^{-1} 3224 (Alkynyl C–H), 2992 (Ar C–H), 1645 (C=O), 1584 (Ar C=C); δ_H (300 MHz, $CDCl_3$) 7.78 (1H, d, *J* 16.1, H-a′), 7.70 (1H, d, *J* 15.9, H-a), 7.62 (1H, d, *J* 8.5, H-3′), 7.21 (1H, dd, *J* 2.0 ad 8.3, H-2), 7.16–7.12 (2H, m, H-b′, 1), 7.07 (1H, d, *J* 8.3, H-3), 6.95 (1H, d, *J* 15.9, H-b), 6.90 (1H, dd, *J* 2.4 and 8.6, H-2′), 6.87 (1H, d, *J* 2.4, H-1′), 4.83 (2H, d, *J* 2.4 H-5), 3.94 (3H, s, H-4), 2.55 (1H, t, *J* 2.4, H-6); δ_C (75 MHz, $CDCl_3$) 188.5, 165.3, 160.7, 149.9, 149.0, 143.5, 134.5, 130.6, 128.9, 127.3, 124.1, 122.7, 113.9, 112.3, 112.0, 110.7, 104.9, 78.0, 76.3, 56.7, 56.0; LRMS (EI) *m*/*z* 355.0 (M+H) M$^+$ $C_{21}H_{16}F_2O_3$ requires 354.1. Anal. Calcd for $C_{21}H_{16}F_2O_3$: C, 71.2; H, 4.6. Found: C, 70.8; H, 5.0.

6.4. 4-Azido-7-chloro-quinoline (6)

4,7-Dichloroquinoline (2.0 g, 10 mmol) was dissolved in 5 mL anhydrous DMF. NaN_3 (1.3 g, 20 mmol) was then added in one portion, and the resulting mixture stirred at 65 °C for 6 h, whereupon TLC indicated reaction completion. The reaction mixture was then allowed to cool to ambient temperature, after which it was diluted with 100 mL CH_2Cl_2, washed with water (3 × 30 mL), dried over anhydrous Na_2SO_4, and evaporated to dryness. The resulting product residue was crystallised from a CH_2Cl_2/Hexane mixture to yield the final pure product as colorless, needle-like crystals (1.7 g, 86%); mp 115 °C (from CH_2Cl_2/Hex); R_f (EtOAc/Hex 3:7) 0.29; IR ν_{max} ($CHCl_3$)/cm^{-1} 3021 (Ar C–H), 1612 (Ar C=C); δ_H (300 MHz, $CDCl_3$) 8.83 (1H, d, *J* 4.9, H-2), 8.09 (1H, d, *J* 2.4, H-8), 8.01 (1H, d, *J* 9.3, H-5), 7.49 (1H, dd, *J* 2.4 and 9.3, H-6) 7.13 (1H, d, *J* 4.9, H-3); δ_C (100 MHz, $CDCl_3$) 150.9, 149.1, 146.8, 136.9, 127.9, 123.8, 119.9, 108.7; LRMS (EI) *m*/*z* 204.9 (M+H) M$^+$ $C_9H_5ClN_4$ requires 204.0. Anal. Calcd for $C_9H_5ClN_4$: C, 52.8; H, 2.5; N, 27.4. Found: C, 52.8; H, 2.4; N, 27.5.

6.5. General method B for the preparation of compounds 7, 8, 9 and 10

The appropriate acetylenic chalcone **1** or **2** (1 mmol) and the appropriate azide (**6** or enantiomerically pure (2*R*,4*S*,5*S*) AZT, 1 mmol) were dissolved in 5 mL DMF and, while stirring at 65 °C, 1 M sodium ascorbate (0.4 mL, 0.4 mmol) and 1 M $CuSO_4$ (0.2 mL, 20 mol %) were added sequentially, in that order. The reaction mixture was then stirred at 65 °C for 24 h. The crude product was then precipitated out by slowly adding cold water to the reaction mixture, after which it was filtered, washed with water, air dried and purified by silica column chromatography (eluents ranging in polarity from EtOAc/Hex 3:7 to 5%MeOH in EtOAc).

6.5.1. 1-[5-Hydroxymethyl-4-(4-{2-methoxy-4-[3-(4-methoxy-phenyl)-3-oxo-propenyl]-phenoxymethyl}-[1,2,3]triazol-1-yl)-tetrahydro-furan-2-yl]-5-methyl-1*H*-pyrimidine-2,4-dione (7a)

Yellow solid (294.4 mg, 50%); mp 121–122 °C (from MeOH/EtOAc); R_f (EtOAc/Hex 9:1) 0.11; IR ν_{max} ($CHCl_3$)/cm^{-1} 3385 (O–H), 3015 (Ar C–H), 1691 (C=O), 1599 (Ar C=C); δ_H (300 MHz, DMSO-d_6) 11.30 (1H, s, H-14), 8.41 (1H, s, H-6), 8.14 (2H, d, *J* 8.8, H-1′, 4′), 7.81 (1H, d, *J* 15.6, H-a), 7.80 (1H, s, H-12), 7.65 (1H, d, *J* 15.6, H-b), 7.52 (1H, d, *J* 1.7, H-1), 7.38 (1H, dd, *J* 1.7 and 8.3, H-2), 7.22 (1H, d, *J* 8.3, H-3), 7.07 (2H, d, *J* 8.9, H-2′, 3′), 6.42 (1H, t, *J* 6.6, H-9), 5.42–5.37 (1H, m, H-7), 5.20 (2H, s, H-5), 4.25–4.22 (1H, m, H-10), 3.86 (3H, s, H-5′), 3.84 (3H, s, H-4), 3.72–3.60 (2H, m, H-11), 2.78–2.62 (2H, m, H-8), 1.8 (3H, s, H-13); δ_C (100 MHz, DMSO-d_6) 187.9, 164.4, 163.8, 151.1, 150.5, 149.9, 144.2, 143.3, 136.9, 131.5, 130.9, 128.9, 125.2, 124.1, 120.6, 114.6, 113.9, 111.8, 110.3, 85.1, 84.6, 62.4, 61.5, 60.0, 56.4, 56.2, 37.9, 12.9; LRMS (EI) *m*/*z* 590.5 (M+H) M$^+$ $C_{30}H_{31}N_5O_8$ requires 589.2. Anal. Calcd for $C_{30}H_{31}N_5O_8{\cdot}H_2O$: C, 59.2; H, 5.4; N, 11.5. Found: C, 59.3; H, 5.4; N, 11.6.

6.5.2. 1-[4-(4-{4-[3-(2,4-Dimethoxy-phenyl)-3-oxo-propenyl]-2-methoxy-phenoxymethyl}-[1,2,3]triazol-1-yl)-5-hydroxymethyl-tetrahydro-furan-2-yl]-5-methyl-1*H*-pyrimidine-2,4-dione (7b)

Yellow solid (289.6 mg, 47%); mp: 133–134 °C (from MeOH/EtOAc); R_f (EtOAc/Hex 9:1) 0.11; IR ν_{max} ($CHCl_3$)/cm^{-1} 3385 (O–H), 3015 (Ar C–H), 1694 (C=O), 1602 (Ar C=C); δ_H (400 MHz, DMSO-d_6) 11.30 (1H, s, H-14), 8.41 (1H, s, H-6), 7.79 (1H, s, H-12), 7.56 (1H, d, *J* .5, H-3′), 7.47 (1H, d, *J* 15.8, H-a), 7.39 (1H, d, *J* 15.8, H-b), 7.31 (1H, d, *J* 1.9, H-1), 7.26 (1H, dd, *J* 1.9 and 8.3, H-2), 7.20 (1H, d, *J* 8.3 H-3), 6.66 (1H, d, *J* 2.4, H-1′), 6.62 (1H, dd, *J* 2.4 and 8.4, H-2′), 6.42 (1H, t, *J* 6.6, H-9), 5.41–5.36 (1H, m, H-7), 5.25 (1H, s, H-15), 5.19 (2H, s, H-5), 4.24–4.21 (1H, m, H-10), 3.87 (3H, s, H-4′), 3.83 (3H, s, H-5′), 3.79 (3H, s, H-4), 3.71–3.60 (2H, m, H-11), 2.77–2.61 (2H, m, H-8), 1.80 (3H, s, H-13); δ_C (100 MHz, DMSO-d_6) 190.3, 164.3, 160.6, 151.1, 150.2, 149.9, 143.3, 142.5, 136.9, 132.4, 128.9, 126.0, 125.2, 123.0, 122.4, 114.1, 111.8, 110.3, 106.6, 99.4, 92.2, 85.0, 84.6, 65.5, 62.4, 61.5, 60.0, 56.6, 56.1, 37.9, 12.9; LRMS (EI) *m*/*z* 620.5 (M+H) M$^+$ $C_{31}H_{33}N_5O_9$ requires 619.2. Anal. Calcd for $C_{31}H_{33}N_5O_9{\cdot}½H_2O$: C, 59.2; H, 5.4; N, 11.1. Found: C, 59.0; H, 5.1; N, 10.6.

6.5.3. 1-[5-Hydroxymethyl-4-(4-{2-methoxy-4-[3-oxo-3-(2,3,4-trimethoxy-phenyl)-propenyl]-phenoxymethyl}-[1,2,3]triazol-1-yl)-tetrahydro-furan-2-yl]-5-methyl-1*H*-pyrimidine-2,4-dione (7c)

Yellow solid (299.1 mg, 46%); mp 103–105 °C (from MeOH/EtOAc); R_f (EtOAc/Hex 9:1) 0.10; IR ν_{max} ($CHCl_3$)/cm^{-1} 3385 (O–H), 3015 (Ar C–H), 1694 (C=O), 1593 (Ar C=C); δ_H (400 MHz, DMSO-d_6) 11.29 (1H, s, H-14), 8.42 (1H, s, H-6), 7.80 (1H, s, H-12), 7.48 (1H, d, *J* 16.1, H-a), 7.32 (1H, d, *J* 16.1, H-b), 7.36–7.28 (3H, m, H-2′, 1, 2), 7.22 (1H, d, *J* 8.3, H-3), 6.93 (1H, d, *J* 8.8, H-1′), 6.43 (1H, t, *J* 6.3, H-9), 5.43–5.37 (1H, m, H-7), 5.24 (1H, s, H-15), 5.21 (2H, s, H-5), 4.27–4.23 (1H, m, H-10), 3.88 (3H, s, H-3′), 3.84 (3H, s, H-5′), 3.81 (3H, s, H-4′), 3.80 (3H, s, H-4), 3.75–3.63 (2H, m, H-11), 2.81–2.62 (2H, m, H-8), 1.82 (3H, s, H-13); δ_C (100 MHz, DMSO-d_6) 191.3, 164.4, 157.0, 153.3, 151.1, 150.4, 149.9, 143.8, 143.3, 142.4, 136.9, 128.6, 127.3, 125.5, 125.2, 123.3, 114.1, 111.8, 110.2, 108.5, 92.1, 85.1, 84.6, 62.3, 61.5, 61.2, 60.4, 60.0, 56.8, 56.3, 37.9, 12.9; LRMS (EI) *m*/*z* 650.7 (M+H) M$^+$ $C_{32}H_{35}N_5O_{10}$ requires 649.2. Anal. Calcd for $C_{32}H_{35}N_5O_{10}{\cdot}½H_2O$: C, 58.3; H, 5.3; N, 10.6. Found: C, 58.2; H, 5.4; N, 10.8.

6.5.4. 3-{4-[1-(7-Chloro-quinolin-4-yl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-3-methoxy-phenyl}-1-(4-methoxy-phenyl)-propenone (8a)

Yellow solid (303.4 mg, 58%); mp 178–180 °C (from EtOAc); R_f (EtOAc/Hex 6;4) 0.25; IR ν_{max} ($CHCl_3$)/cm^{-1} 3021 (Ar C–H), 1657 (C=O), 1599 (Ar C=C); δ_H (400 MHz, $CDCl_3$) 9.06 (1H, d, *J* 4.8, H-8), 8.27 (1H, d, *J* 2.0, H-9), 8.15 (1H, s, H-6), 8.01 (2H, d, *J* 9.0, H-1′, 4′), 7.98 (1H, d, *J* 9.0, H-11), 7.74 (1H, d, *J* 15.6, H-a), 7.59 (1H, dd, *J* 2.0 and 8.9, H-10), 7.51 (1H, d, *J* 4.8, H-7), 7.42 (1H, d, *J* 15.6, H-b), 7.23 (1H, d, *J* 1.8, H-1), 7.18–7.14 (2H, m, H-2, 3), 6.97 (2H, d, *J* 9.0, H-2′, 3′), 5.43 (2H, s, H-5), 3.94 (3H, s, H-5′), 3.88 (3H, s, H-4); δ_C (100 MHz, $CDCl_3$) 188.7, 163.3, 151.1, 149.8, 149.5, 144.8, 143.7, 141.1, 137.2, 131.2, 130.7, 129.6, 129.4, 128.8, 124.8, 124.5, 122.5, 120.6, 116.0, 114.1, 113.9, 111.1, 62.9, 56.1, 55.5; LRMS (EI) *m*/*z* 527.6 (M+H) M$^+$ $C_{29}H_{23}ClN_4O_4$ requires 526.1. Anal. Calcd for $C_{29}H_{23}ClN_4O_4{\cdot}½H_2O$: C, 64.9; H, 4.5; N, 10.4. Found: C, 65.1; H, 4.5; N, 10.7.

6.5.5. 3-{4-[1-(7-Chloro-quinolin-4-yl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-3-methoxy-phenyl}-1-(2,4-dimethoxy-phenyl)-propenone (8b)

Yellow solid (282.7 mg, 51%); mp: 122–124 °C (from EtOAc); R_f (EtOAc/Hex 6:4) 0.12; IR ν_{max} ($CHCl_3$)/$^{cm-1}$ 3020 (Ar C–H), 1653 (C=O), 1604 (Ar C=C); δ_H (400 MHz, $CDCl_3$) 9.05 (1H, d, *J* 4.8, H-8), 8.26 (1H, d, *J* 2.0, H-9), 8.13 (1H, s, H-6), 7.96 (1H, d, *J* 9.2, H-11), 7.74 (1H, d, *J* 8.6, H-3′), 7.60 (1H, d, *J* 15.6, H-a), 7.58 (1H, dd, *J* 2.0 and 9.2, H-10), 7.49 (1H, d, *J* 4.6, H-7), 7.38 (1H, d, *J* 15.6, H-b), 7.20 (1H, dd, *J* 2.0 and 8.4, H-2), 7.14–7.12 (2H, m, H-1, 3), 6.57 (1H, dd, *J* 2.2 and 8.6, H-2′), 6.50 (1H, d, *J* 2.2, H-1′), 5.48 (2H, s, H-5), 3.92 (3H, s, H-4′), 3.90 (3H, s, H-5′), 3.87 (3H, s, H-4); δ_C (100 MHz, $CDCl_3$) 190.5, 164.1, 160.2, 151.3, 150.2, 149.8, 149.2, 144.9, 141.9, 140.9, 137.0, 132.7, 129.8, 129.5, 129.0, 126.0, 124.8, 124.5, 122.4, 122.1, 120.6, 116.0, 114.2, 111.3, 105.2, 98.7, 63.0, 55.9, 55.9, 55.5; LRMS (EI) *m*/*z* 557.5 (M+H) M^+ $C_{30}H_{25}ClN_4O_5$ requires 556.2. Anal. Calcd for $C_{30}H_{25}ClN_4O_5$: C, 64.7; H, 4.5; N, 10.1. Found: C, 64.9; H, 4.4; N, 10.0. HPLC.

6.5.6. 3-{4-[1-(7-Chloro-quinolin-4-yl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-3-methoxy-phenyl}-1-(2,3,4-trimethoxy-phenyl)-propenone (8c)

Yellow solid (318.3 mg, 54%); mp: 124 °C (from EtOAc); R_f (EtOAc/Hex 6:4) 0.20; IR ν_{max} ($CHCl_3$)/cm^{-1} 3015 (Ar C–H), 1649 (C=O), 1593 (Ar C=C); δ_H (300 MHz, $CDCl_3$) 9.05 (1H, d, *J* 4.4, H-8), 8.27 (1H, d, *J* 1.9, H-9), 8.14 (1H, s, H-6), 7.99 (1H, d, *J* 9.3, H-11), 7.61 (1H, d, *J* 16.1, H-a), 7.59 (1H, dd, *J* 1.9 and 9.3, H-10), 7.50 (1H, d, *J* 4.4, H-7), 7.45 (1H, d, *J* 8.8, H-2′), 7.37 (1H, d, *J* 16.1, H-b), 7.21 (1H, dd, *J* 1.9, 8.3, H-2), 7.16–7.12 (2H, m, H-1, 3), 6.75 (1H, d, *J* 8.8, H-1′), 5.48 (2H, s, H-5), 3.92–3.90 (12H, m, H-3′, 5′, 4′, 4);δ_C (75 MHz, $CDCl_3$) 190.8, 156.9, 151.1, 149.8, 149.4, 144.9, 142.9, 142.2, 137.2, 129.6, 129.5, 128.8, 126.9, 125.6, 125.3, 124.8, 124.6, 122.5, 116.0, 114.0, 111.0, 107.4, 62.9, 62.1, 61.1, 56.1, 56.0; LRMS (EI) *m*/*z* 587.4 (M+H) M^+ $C_{31}H_{27}ClN_4O_6$ requires 586.2. Anal. Calcd for $C_{31}H_{27}ClN_4O_6$: C, 63.4; H, 4.6; N, 9.6. Found: C, 63.2; H, 4.5; N, 9.5.

6.5.7. 1-[4-(4-{4-[3-(2,4-Dimethoxy-phenyl)-acryloyl]-2-methoxy-phenoxymethyl}-[1,2,3]triazol-1-yl)-5-hydroxymethyl-tetrahydro-furan-2-yl]-5-methyl-1*H*-pyrimidine-2,4-dione (9a)

Yellow solid (272.6 mg, 44%); mp 135–136 °C (from MeOH/EtOAc); R_f (EtOAc/Hex 9:1) 0.15; IR ν_{max} ($CHCl_3$)/cm^{-1} 3021 (Ar C–H), 1691 (C=O), 1599 (Ar C=C); δ_H (400 MHz, DMSO-d_6) 8.43 (1H, s, H-6), 7.95 (1H, d, *J* 15.7, H-a), 7.90 (1H, d, *J* 8.6, H-2′), 7.81 (1H, dd, *J* 1.8 and 8.6, H-3), 7.78 (2H, m, H-1, 12), 7.74 (1H, d, *J* 15.6, H-b), 7.57 (1H, d, *J* 2.0, H-1′), 7.31 (1H, d, *J* 8.6, H-2), 6.61 (1H, dd, *J* 2.0 and 8.6, H-3′), 6.61 (1H, t, *J* 6.6, H-9), 5.42–5.37 (1H, m, H-7), 5.26 (2H, s, H-5), 4.24–4.21 (1H, m, H-10), 3.89 (3H, s, H-5′), 3.83 (6H, s, H-4, 4′), 3.74–3.63 (2H, m, H-11), 2.77–2.61 (2H, m, H-8), 1.79 (3H, s, H-13); δ_C (75 MHz, DMSO-d_6) 187.4, 163.6, 162.9, 159.8, 151.5, 150.3, 148.9, 142.4, 137.8, 136.1, 131.3, 129.9, 124.5, 122.6, 119.0, 116.0, 112.4, 110.9, 109.5, 106.3, 98.2, 84.4, 83.9, 61.7, 60.7, 59.3, 55.8, 55.5, 55.4, 37.1, 12.1; LRMS (EI) *m*/*z* 620.6 (M+H) M^+ $C_{31}H_{33}N_5O_9$ requires 619.2. Anal. Calcd for $C_{31}H_{33}N_5O_9{\cdot}½H_2O$: C, 59.2; H, 5.3; N, 11.1. Found: C, 59.0; H, 5.5; N, 11.0.

6.5.8. 1-[5-Hydroxymethyl-4-(4-{2-methoxy-4-[3-(2,3,4-trimethoxy-phenyl)-acryloyl]-phenoxymethyl}-[1,2,3]triazol-1-yl)-tetrahydro-furan-2-yl]-5-methyl-1*H*-pyrimidine-2,4-dione (9b)

Yellow solid (332.4 mg, 51%); mp 121–122 °C (from MeOH/EtOAc); R_f (EtOAc/Hex 9:1) 0.21; IR ν_{max} ($CHCl_3$)/cm^{-1} 3391 (O–H), 3015 (Ar C–H), 1694 (C=O), 1593 (Ar C=C); δ_H (400 MHz, DMSO-d_6) 11.28 (1H, s, H-14), 8.43 (1H, s, H-6), 7.87 (1H, d, *J* 15.6, H-a), 7.83 (1H, dd, *J* 2.0 and 8.6, H-3), 7.82 (1H, d, *J* 15.6, H-b), 7.79 (1H, s, H-12), 7.76 (1H, d, *J* 8.9, H-1′), 7.58 (1H, d, *J* 2.0, H-1), 7.32 (1H, d, *J* 8.6, H-2), 6.91 (1H, d, *J* 8.9, H-2′), 6.42 (1H, t, *J* 6.6, H-9), 5.42–5.37 (1H, m, H-7), 5.27 (2H, s, H-5), 5.24 (1H, s, H-15), 4.25–4.22 (1H, m, H-10), 3.86 (3H, s, H-5′), 3.85 (3H, s, H-3′), 3.83 (3H, s, H-4), 3.77 (3H, s, H-4′), 3.76–3.63 (2H, m, H-11), 2.77–2.62 (2H, m, H-8), 1.80 (3H, s, H-13); δ_C (75 MHz, DMSO-d_6) 187.4, 163.6, 155.5, 152.9, 151.6, 150.3, 148.9, 142.4, 141.8, 137.5, 136.1, 131.2, 124.5, 123.3, 122.7, 121.1, 120.4, 112.4, 111.0, 109.5, 108.4, 84.4, 83.9, 61.7, 61.4, 60.7, 60.4, 59.3, 56.0, 55.5, 37.1, 12.1; LRMS (EI) *m*/*z* 650.8 (M+H) M^+ $C_{32}H_{35}N_5O_{10}$ requires 649.2. Anal. Calcd for $C_{32}H_{35}N_5O_{10}{\cdot}1H_2O$: C, 57.5; H, 5.5; N, 10.5. Found: C, 57.3; H, 5.4; N, 10.4.

6.5.9. 1-[4-(4-{4-[3-(2,4-Dichloro-phenyl)-acryloyl]-2-methoxy-phenoxymethyl}-[1,2,3]triazol-1-yl)-5-hydroxymethyl-tetrahydro-furan-2-yl]-5-methyl-1*H*-pyrimidine-2,4-dione (9c)

Yellow solid (279.3 mg, 45%); mp 112–114 °C (from MeOH/EtOAc); R_f (EtOAc/Hex 8:2) 0.10; IR ν_{max} ($CHCl_3$)/cm^{-1} 3391 (O–H), 3018 (Ar C–H), 1692 (C=O), 1582 (Ar C=C); δ_H (400 MHz, DMSO-d_6) 11.30 (1H, s, H-14), 8.43 (1H, s, H-6), 8.23 (1H, d, *J* 8.6, H-2′), 8.02 (1H, d, *J* 15.6, H-a), 7.94–7.91 (2H, m, H-b, 3), 7.79 (1H, s, H-12), 7.73 (1H, d, *J* 2.0, H-1), 7.61 (1H, d, *J* 2.0, H-1′), 7.54 (1H, dd, *J* 2.0 and 8.6, H-3′), 7.33 (1H, d, *J* 8.6, H-2), 6.42 (1H, t, *J* 6.6, H-9), 5.42–5.37 (1H, m, H-7), 5.28 (2H, s, H-5), 4.25–4.22 (1H, m, H-10), 3.83 (3H, s, H-4), 3.73–3.60 (2H, m, H-11), 2.77–2.61 (2H, m, H-8), 1.80 (3H, s, H-13); δ_C (75 MHz, DMSO) 187.0, 163.6, 152.2, 150.4, 149.0, 142.3, 136.5, 136.1, 135.3, 134.9, 131.5, 130.5, 129.8, 129.4, 127.8, 125.3, 124.5, 123.4, 112.4, 111.1, 109.6, 84.4, 83.9, 61.7, 60.7, 59.3, 55.6, 37.1, 12.1; LRMS (EI) *m*/*z* 628.6 (M+H) M^+ $C_{29}H_{27}Cl_2N_5O_7$ requires 627.1. Anal. Calcd for $C_{29}H_{27}Cl_2N_5O_7{\cdot}½H_2O$: C, 54.7; H, 4.2; N, 11.0. Found: C, 54.4; H, 4.8; N, 10.8.

6.5.10. 1-[4-(4-{4-[3-(4-Fluoro-phenyl)-acryloyl]-2-methoxy-phenoxymethyl}-[1,2,3]triazol-1-yl)-5-hydroxymethyl-tetrahydro-furan-2-yl]-5-methyl-1*H*-pyrimidine-2,4-dione (9d)

Yellow solid (278.1 mg, 48%); mp 130–132 °C (from MeOH/EtOAc); R_f (EtOAc/Hex 9:1) 0.18; IR ν_{max} ($CHCl_3$)/cm^{-1} 3386 (O–H), 3018 (Ar C–H), 1689 (C=O), 1597 (Ar C=C); δ_H (300 MHz, DMSO-d_6) 11.28 (1H, s, H-14), 8.43 (1H, s, H-6), 7.85 (1H, d, *J* 15.6, H-a), 7.81 (1H, dd, *J* 1.9 and 8.8, H-3), 7.79 (1H, s, H-12), 7.78 (1H, d, *J* 15.6, H-b), 7.76 (2H, d, *J* 8.8, H-1′, 4′), 7.58 (1H, d, *J* 1.9, H-1), 7.31 (2H, d, *J* 8.8, H-2′, 3′), 6.89 (1H, d, *J* 8.8, H-2), 6.42 (1H, t, *J* 6.8, H-9), 5.43–5.36 (1H, m, H-7), 5.27 (2H, s, H-5), 4.26–4.22 (1H, m, H-10), 3.85 (3H, s, H-4), 3.70–3.59 (2H, m, H-11), 2.80–2.61 (2H, m, H-8), 1.80 (3H, s, H-13); δ_C (75 MHz, DMSO-d_6) 187.4, 163.6, 155.5, 152.9, 151.6, 150.3, 148.9, 142.4, 137.5, 136.1, 131.2, 124.5, 123.3, 122.8, 121.1, 120.4, 112.4, 111.0, 109.5, 108.4, 84.4, 83.9, 61.7, 60.7, 59.3, 55.5, 37.1, 12.1; LRMS (EI) *m*/*z* 578.6 (M+H) M^+ $C_{29}H_{28}FN_5O_7$ requires 577.2. Anal. Calcd for $C_{29}H_{28}FN_5O_7$: C, 60.3; H, 4.9; N, 12.1. Found: C, 60.1; H, 5.5; N, 11.9.

6.5.11. 1-[4-(4-{4-[3-(2,4-Difluoro-phenyl)-acryloyl]-2-methoxy-phenoxymethyl}-[1,2,3]triazol-1-yl)-5-hydroxymethyl-tetrahydro-furan-2-yl]-5-methyl-1*H*-pyrimidine-2,4-dione (9e)

Yellow solid (248.9 mg, 44%); mp 128–130 °C (from MeOH/EtOAc); R_f (EtOAc/Hex 9:1) 0.18; IR ν_{max} ($CHCl_3$)/cm^{-1} 3386 (O–H), 3018 (Ar C–H), 1692 (C=O), 1600 (Ar C=C); δ_H (300 MHz, DMSO-d_6) 11.30 (1H, s, H-14), 8.44 (1H, s, H-6), 7.97 (1H, d, *J* 15.6, H-a), 7.90 (1H, d, *J* 8.3, H-2′), 7.83–7.79 (2H, m, H-1, 3), 7.76 (1H, d, *J* 15.6, H-b), 7.59 (1H, d, *J* 1.9, H-1′), 7.34 (1H, dd, *J* 1.9 and 8.3, H-3′), 6.64 (1H, d, *J* 8.8, H-2), 6.44 (1H, t, *J* 6.3, H-9), 5.44–5.38 (1H, m, H-7), 5.28 (2H, s, H-5), 5.25 (1H, br s, H-15), 4.28–4.24 (1H, m, H-10), 3.85 (3H, s, H-4), 3.76–3.63 (2H, m, H-11), 2.81–2.62 (2H, m, H-8), 1.82 (3H, s, H-13); δ_C (75 MHz,

DMSO-d_6) 187.4, 163.6, 162.9, 159.8, 151.5, 150.3, 148.9, 142.4, 137.8, 136.1, 131.4, 129.9, 124.5, 122.6, 119.0, 116.0, 112.4, 110.9, 109.5, 106.3, 84.4, 83.9, 61.7, 60.7, 59.3, 55.4, 37.1, 12.1; LRMS (EI) *m*/*z* 596.4 (M+H) M^+ $C_{29}H_{27}F_2N_5O_7$ requires 595.2. Anal. Calcd for $C_{29}H_{27}F_2N_5O_7 \cdot ½H_2O$: C, 57.6; H, 4.6; N, 11.5. Found: C, 57.8; H, 4.6; N, 10.9.

6.5.12. 1-{4-[1-(7-Chloro-quinolin-4-yl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-3-methoxy-phenyl}-3-(2,4-dimethoxy-phenyl)-propenone (10a)

Yellow solid (228.3 mg, 41%); mp 157–158 °C (from MeOH/EtOAc); R_f (EtOAc/Hex 7:3) 0.25; IR ν_{max} ($CHCl_3$)/cm^{-1} 3020 (Ar C–H), 1649 (C=O), 1599 (Ar C=C); δ_H (400 MHz, $CDCl_3$) 9.09 (1H, br s, H-8), 8.26 (1H, s, H-9), 8.15 (1H, s, H-6), 8.04 (1H, d, *J* 15.7, H-a), 7.98 (1H, d, *J* 9.2, H-11), 7.68–7.65 (2H, m, H-1, 3), 7.59 (1H, d, *J* 9.2, H-10), 7.57 (1H, d, *J* 8.4, H-2′), 7.55 (1H, d, *J* 15.7, H-b), 7.51 (1H, br s, H-7), 7.18 (1H, d, *J* 8.6, H-2), 6,53 (1H, dd, *J* 2.2 and 8.4, H-3′), 6.48 (1H, d, *J* 2.2, H-1′), 5.53 (2H, s, H-5), 3.96 (3H, s, H-5′), 3.91 (3H, s, H-4′), 3.86 (3H, s, H-4); δ_C (75 MHz, $CDCl_3$) 189.3, 163.0, 160.4, 151.1, 149.6, 140.1, 137.2, 133.0, 131.0, 129.7, 124.6, 122.5, 119.9, 117.2, 112.6, 111.5, 105.4, 98.5, 62.8, 56.1, 55.6, 55.5; LRMS (EI) *m*/*z* 557.5 (M+H) M^+ $C_{30}H_{25}ClN_4O_5$ requires 556.2. Anal. Calcd for $C_{30}H_{25}ClN_4O_5 \cdot H_2O$: C, 62.6; H, 4.4; N, 9.7. Found: C, 62.7; H, 4.3; N, 9.4.

6.5.13. 1-{4-[1-(7-Chloro-quinolin-4-yl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-3-methoxy-phenyl}-3-(2,3,4-trimethoxy-phenyl)-propenone (10b)

Yellow solid (318.9 mg, 54%); mp 82–83 °C (from MeOH/EtOAc); R_f (EtOAc/Hex 6:4) 0.33; IR ν_{max} ($CHCl_3$)/cm^{-1} 3015 (Ar C–H), 1670 (C=O), 1596 (Ar C=C); δ_H (400 MHz, $CDCl_3$) 9,07 (1H, d, *J* 4.8, H-8), 8.27 (1H, d, *J* 2.0, H-9), 8.16 (1H, s, H-6), 7.98 (1H, d, *J* 9.2, H-11), 7.98 (1H, d, *J* 15.7, H-a), 7.68–7.66 (2H, m, H-1, 3), 7.60 (1H, dd, *J* 2.0 and 9.2, H-10), 7.57 (1H, d, *J* 15.7, H-b), 7.51 (1H, d, *J* 4.8, H-7), 7.36 (1H, d, *J* 8.8, H-1′), 7.20 (1H, d, *J* 8.6, H-2), 6.72 (1H, d, *J* 8.8, H-2′), 5.53 (2H, s, H-5), 3.96 (3H, s, H-5′), 3.95 (3H, s, H-3′), 3.91 (3H, s, H-4), 3.89 (3H, s, H-4′); δ_C (100 MHz, $CDCl_3$) 189.1, 155.8, 153.7, 151.1, 149.7, 144.7, 142.6, 141.1, 139.7, 137.3, 132.8, 129.7, 128.8, 124.9, 124.6, 123.9, 122.6, 122.1, 121.0, 116.0, 112.6, 111.5, 107.5, 62.9, 61.4, 60.9, 56.1; LRMS (EI) *m*/*z* 587.5 (M+H) M^+ $C_{31}H_{27}ClN_4O_6$ requires 586.2. Anal. Calcd for $C_{31}H_{27}ClN_4O_6 \cdot ½H_2O$: C, 62.5; H, 4.5; N, 9.4. Found: C, 62.1; H, 4.5; N, 9.2.

6.5.14. 1-{4-[1-(7-Chloro-quinolin-4-yl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-3-methoxy-phenyl}-3-(2,4-dichloro-phenyl)-propenone (10c)

Yellow solid (295.7 mg, 52%); mp 85–87 °C (from MeOH/EtOAc); R_f (EtOAc/Hex 1:1) 0.2; IR ν_{max} ($CHCl_3$)/cm^{-1} 3018 (Ar C–H), 1651 (C=O), 1595 (Ar C=C); δ_H (400 MHz, $CDCl_3$) 9.05 (1H, d, *J* 4.8, H-8), 8.27 (1H, d, *J* 2.2, H-9), 8.16 (1H, s, H-6), 8.01 (1H, d, *J* 15.6, H-a), 7.96 (1H, d, *J* 9.2, H-11), 7.67–7.65 (2H, m, H-1, 3), 7.59 (1H, dd, *J* 2.2 and 9.2, H-10), 7.56 (1H, d, *J* 8.4, H-2′), 7.55 (1H, d, *J* 15.7, H-b), 7.51 (1H, d, *J* 4.8, H-7), 7.19 (1H, d, *J* 8.6, H-2), 6.53 (1H, dd, *J* 2.4 and 8.4, H-3′), 6.48 (1H, d, *J* 2.4, H-1′), 5.53 (2H, s, H-5), 3.96 (3H, s, H-4); δ_C (100 MHz, $CDCl_3$) 189.3, 163.0, 160.3, 151.0, 149.6, 144.5, 141.0, 140.1, 137.1, 133.0, 131.1, 129.6, 128.8, 125.0, 124.5, 122.5, 120.1, 117.2, 115.9, 112.8, 111.6, 105.5, 98.6, 62.8, 55.5; LRMS (EI) *m*/*z* 565.3 (M+H) M^+ $C_{28}H_{19}Cl_3N_4O_3$ requires 564.1). Anal. Calcd for $C_{28}H_{19}Cl_3N_4O_3$: C, 59.4; H, 3.4; N, 9.9. Found: C, 59.7; H, 3.1; N, 9.5.

6.5.15. 1-{4-[1-(7-Chloro-quinolin-4-yl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-3-methoxy-phenyl}-3-(4-fluoro-phenyl)-propenone (10d)

Yellow solid (266.9 mg, 52%); mp 164–166 °C (from MeOH/EtOAc); R_f (EtOAc/Hex 6:4) 0.3; IR ν_{max} ($CHCl_3$)/cm^{-1} 3018 (Ar C–H), 1656 (C=O), 1595 (Ar C=C); δ_H (400 MHz, $CDCl_3$) 9.05 (1H, d, 4.6, H-8), 8.25 (1H, d, *J* 2.2, H-9), 8.16 (1H, s, H-6), 7.96 (1H, d, *J* 9.2, H-11), 7.80 (1H, d, *J* 15.6, H-a), 7.67 (1H, dd, *J* 1.8 and 8.4, H-3), 7.65 (1H, d, *J* 1.8, H-1), 7.61–7.58 (3H, m, H-1′, 2′, 10), 7.49 (1H, d, *J* 4.6, H-7), 7.42 (1H, d, *J* 15.6, H-b), 7.21 (1H, d, *H* 8.4, H-2), 6.94 (2H, d, *J* 8.9, H-3′, 4′), 5.53 (2H, s, H-5), 3.97 (3H, s, H-4); δ_C (100 MHz, $CDCl_3$) 188.6, 161.7, 151.3, 150.2, 149.8, 144.6, 144.2, 142.9, 140.9, 137.0, 132.7, 130.2, 129.6, 129.0, 127.7, 124.8, 124.5, 122.6, 119.3, 116.0, 114.5, 112.6, 111.5, 62.9, 56.1; LRMS (EI) *m*/*z* 515.4 (M+H) M^+ $C_{28}H_{20}ClFN_4O_3$ requires 514.2. Anal. Calcd for $C_{28}H_{20}ClFN_4O_3$: C, 65.3; H, 3.9; N, 10.9. Found: C, 64.9; H, 4.1; N, 10.6.

6.5.16. 1-{4-[1-(7-Chloro-quinolin-4-yl)-1*H*-[1,2,3]triazol-4-yl-methoxy]-3-methoxy-phenyl}-3-(2,4-difluoro-phenyl)-propenone (10e)

Yellow solid (202.5 mg, 38%); mp 106–108 °C (from MeOH/EtOAc); R_f (EtOAc/Hex 6:4) 0.3; IR ν_{max} ($CHCl_3$)/cm^{-1} 3000 (Ar C–H), 1657 (C=O), 1595 (Ar C=C); δ_H (300 MHz, $CDCl_3$) 9.06 (1H, d, *J* 4.4, H-8), 8.27 (1H, d, *J* 1.9, H-9), 8.16 (1H, s, H-6), 7.96 (1H, d, *J* 9.3, H-11), 7.85 (1H, d, *J* 15.6, H-a), 7.69–7.65 (2H, m, H-1, 3), 7.59 (1H, dd, *J* 1.9 and 9.3, H-10), 7.55 (1H, d, *J* 8.3, H-2′), 7.52 (1H, d, *J* 15.6, H-b), 7.51 (1H, d, *J* 4.4, H-7), 7.19 (1H, d, *J* 8.8, H-2), 6.73 (1H, dd, *J* 2.4 and 8.3, H-3′), 6.64 (1H, d, *J* 2.4, H-1′), 5.53 (2H, s, H-5), 3.96 (3H, s, H-4); δ_C (75 MHz, $CDCl_3$) 151.0, 149.8, 144.6, 137.2, 132.5, 130.9, 129.7, 128.8, 124.8, 124.6, 122.9, 122.7, 121.7, 116.0, 112.6, 111.4, 110.8, 102.2, 101.9, 98.5, 62.8, 56.1; LRMS (EI) *m*/*z* 533.4 (M+H) M^+ $C_{28}H_{19}ClF_2N_4O_3$ requires 532.1. Anal. Calcd for $C_{28}H_{19}ClF_2N_4O_3$: C, 63.1; H, 3.6; N, 10.5. Found: C, 63.4; H, 4.0; N, 10.2.

6.6. 1-(5-Hydroxymethyl-4-{4-[2-methoxy-4-(3-oxo-but-1-enyl)-phenoxymethyl]-[1,2,3]triazol-1-yl}-tetrahydro-furan-2-yl)-5-methyl-1*H*-pyrimidine-2,4-dione (11)

Synthesized from **4** and enantiomerically pure (2*R*,4*S*,5*S*) AZT by applying the General Method B. Fluffy white solid (3.9 g, 80%); mp 177–179 °C (from MeOH/EtOAc); R_f (MeOH/CH_2Cl_2 5:95) 0.42; IR ν_{max} (KBr)/cm^{-1} 3072 (Ar C–H), 1627 (C=O), 1595 (Ar C=C); δ_H (400 MHz, DMSO-d_6) 11.30 (1H, s, H-14), 8.41 (1H, s, H-6), 7.80 (1H, s, H-12), 7.56 (1H, d, *J* 16.3, H-a), 7.33 (1H, d, *J* 1.6, H-1), 7.25 (1H, dd, *J* 1.8 and 8.3, H-2), 7.21 (1H, d, *J* 8.4, H-3), 6.74 (1H, d, *J* 16.3, H-b), 6.42 (1H, t, *J* 6.5, H-9), 5.42–5.37 (1H, m, H-7), 5.19 (2H, s, H-5), 4.25–4.22 (1H, m, H-10), 3.80 (3H, s, H-4), 3.75–3.61 (2H, m, H-11), 2.78–2.62 (2H, m, H-8), 2.30 (3H, s, H-b′), 1.8 (3H, s, H-13); δ_C (100 MHz, DMSO-d_6) 197.8, 163.6, 150.4, 149.6, 149.1, 143.3, 142.5, 136.1, 127.6, 125.4, 124.4, 122.7, 113.2, 110.7, 109.5, 84.4, 83.9, 61.6, 60.7, 59.2, 55.5, 37.1, 27.1, 12.1; LRMS (EI) *m*/*z* 498.5 (M+H) M^+ $C_{24}H_{27}N_5O_7$ requires 497.2. Anal.Calcd for $C_{24}H_{27}N_5O_7 \cdot 1H_2O$: C, 55.9; H, 5.6; N, 13.6. Found: C, 55.6; H, 5.4; N, 14.0.

6.7. 4-{4-[1-(7-Chloro-quinolin-4-yl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-3-methoxy-phenyl}-but-3-en-2-one (12)

Synthesized from **4** and **6** by applying the General Method B. Off-white to pale brown solid (2.7 g, 62%); mp 82–84 °C (from EtOAc/Hex); R_f (EtOAc/Hex 8:2) 0.20; IR ν_{max} (KBr)/cm^{-1} 2927 (Ar C–H), 1663 (C=O), 1595 (Ar C=C); δ_H (300 MHz, $CDCl_3$) 9.05 (1H, d, 4.9, H-8), 8.24 (1H, d, *J* 2.0, H-9), 8.14 (1H, s, H-6), 7.94 (1H, d, *J* 9.3, H-11), 7.58 (1H, dd, *J* 2.0 and 9.3, H-10), 7.48 (1H, d, *J* 4.9, H-7), 7.46 (1H, d, *J* 15.6, H-a), 7.15–7.10 (3H, m, H-1, 2, 3), 6.62 (1H, d, *J* 15.6, H-b), 5.48 (2H, s, H-5), 3.91 (3H, s, H-4), 2.37 (3H, s, H-b′); δ_C (75 MHz, $CDCl_3$) 198.2, 151.4, 149.9, 149.7, 144.7, 143.0, 140.8, 137.0, 129.5, 129.1, 128.6, 125.9, 124.8, 124.5, 122.7, 120.5, 116.0 (2C), 113.9, 110.4, 62.9, 55.9, 27.4; LRMS (EI)

m/*z* 435.2 (M+H) M^+ $C_{23}H_{19}ClN_4O_3$ requires 434.1. Anal. Calcd for $C_{23}H_{19}ClN_4O_3{\cdot}2H_2O$: C, 58.6; H, 4.9; N, 11.9. Found: C, 58.4; H, 4.6; N, 11.6.

6.8. Preparation of compounds 13a–f and 14a–f

These compounds were synthesized by condensing either **11** or **12** with appropriately substituted benzaldehydes, applying the General Method A.

6.8.1. 1-[5-Hydroxymethyl-4-(4-{2-methoxy-4-[5-(4-methoxy-phenyl)-3-oxo-penta-1,4-dienyl]-phenoxymethyl}-[1,2,3]triazol-1-yl)-tetrahydro-furan-2-yl]-5-methyl-1*H*-pyrimidine-2,4-dione (13a)

Yellow solid (258 mg, 42%); mp: 192–194 °C (from MeOH/EtOAc); R_f (MeOH/EtOAc 5:95) 0.30; IR ν_{max} (KBr)/cm^{-1} 3340 (O–H), 3057 (Ar C–H), 1689 (C=O), 1584 (Ar C=C); δ_H (400 MHz, DMSO-d_6) 11.31 (1H, s, H-14), 8.43 (1H, s, H-6), 7.81 (1H, s, H-12), 7.75 (4H, m, H-a, a′, 1′, 4′), 7.41 (1H, d, *J* 1.7, H-1), 7.33 (1H, dd, *J* 1.8 and 8.3, H-2), 7.22 (1H, d, *J* 15.8, H-b′), 7.19 (1H, d, *J* 15.9, H-b), 7.02 (2H, d, *J* 8.7, H-2′, 3′), 6.43 (1H, t, *J* 6.4, H-9), 5.43–5.38 (1H, m, H-7), 5.21 (2H, s, H-5), 4.26–4.23 (1H, m, H-10), 3.83 (3H, s, H-5′), 3.82 (3H, s, H-4, 3.74–3.62 (2H, m, H-11), 2.79–2.63 (2H, m, H-8), 1.81 (3H, s, H-13); δ_C (100 MHz, DMSO-d_6) 188.0, 163.6, 161.1, 150.8, 150.4, 149.6, 149.2, 142.5, 142.4, 142.0, 136.1, 130.2, 128.1, 127.3, 124.4, 124.1, 123.4, 122.8, 114.4, 113.9, 113.2, 110.9, 109.5, 84.4, 83.9, 61.6, 60.7, 59.3, 55.6, 55.3, 37.1, 12.1; LRMS (EI) *m*/*z* 616.2 (M+H) M^+ $C_{32}H_{33}N_5O_8$ requires 615.2. Anal. Calcd for $C_{32}H_{33}N_5O_8{\cdot}1½H_2O$: C, 59.8; H, 5.6; N, 10.9. Found: C, 59.7; H, 5.6; N, 10.5.

6.8.2. 1-[4-(4-{4-[5-(2,4-Dimethoxy-phenyl)-3-oxo-penta-1,4-dienyl]-2-methoxy-phenoxymethyl}-[1,2,3]-triazol-1-yl)-5-hydroxymethyl-tetrahydro-furan-2-yl]-5-methyl-1*H*-pyrimidine-2,4-dione (13b)

Yellow solid (337 mg, 52%); mp 129–131 °C (from MeOH/EtOAc); R_f (MeOH/EtOAc 5:95) 0.30; IR ν_{max} (KBr)/cm^{-1} 3384 (O–H), 3057 (Ar C–H), 1692 (C=O), 1595 (Ar C=C); δ_H (300 MHz, DMSO-d_6) 11.20 (1H, s, H-14), 8.39 (1H, s, H-6), 7.87 (1H, d, *J* 16.0, H-a′), 7.78 (1H, s, H-12), 7.72 (1H, d, *J* 8.3, H-3′), 7.66 (1H, d, *J* 16.0, H-a), 7.56 (1H, dd, *J* 1.9 and 8.3, H-2), 7.43 (1H, d, *J* 1.9, H-1), 7.39 (1H, d, *J* 1.9, H-1′), 7.30 (1H, dd, *J* 1.9 and 8.4, H-2′), 7.23 (1H, d, *J* 8.4, H-3), 7.21 (1H, d, *J* 16.0, H-b′), 7.11 (1H, d, *J* 16.0, H-b), 6.42 (1H, t, *J* 6.5, H-9), 5.43–5.36 (1H, m, H-7), 5.22 (2H, s, H-5), 4.28–4.24 (1H, m, H-10), 3.90 (3H, s, H-4′), 3.84 (3H, s, H-5′), 3.82 (3H, s, H-4), 3.81–3.57 (2H, m, H-11), 2.82–2.62 (2H, m, H-8), 1.82 (3H, s, H-13); δ_C (75 MHz, DMSO-d_6) 191.0, 187.9, 163.4, 162.7, 159.7, 150.2, 149.5, 142.5, 141.9, 136.8, 135.9, 129.7, 128.1, 125.3, 124.7, 124.3, 124.1, 123.1, 122.5, 113.6, 111.1, 109.4, 106.2, 98.3, 84.3, 83.9, 61.7, 60.6, 59.2, 55.6, 55.3, 36.9, 11.9; LRMS (EI) *m*/*z* 646.2 (M+H) M^+ $C_{33}H_{35}N_5O_9$ requires 645.2. Anal. Calcd for $C_{33}H_{35}N_5O_9$: C, 61.4; H, 5.5; N, 10.9. Found: C, 61.7; H, 5.6; N, 10.6.

6.8.3. 1-[5-Hydroxymethyl-4-(4-{2-methoxy-4-[3-oxo-5-(2,3,4-trimethoxy-phenyl)-penta-1,4-dienyl]-phenoxymethyl}-[1,2,3]-triazol-1-yl)-tetrahydro-furan-2-yl]-5-methyl-1*H*-pyrimidine-2,4-dione (13c)

Yellow solid (263 mg, 40%); mp 144–146 °C (from MeOH/EtOAc); R_f (MeOH/EtOAc 5:95) 0.33; IR ν_{max} (KBr)/cm^{-1} 3391 (O–H), 2934 (Ar C–H), 1689 (C=O), 1584 (Ar C=C); δ_H (300 MHz, DMSO-d_6) 11.21 (1H, s, H-14), 8.38 (1H, s, H-6), 7.79 (1H, d, *J* 16.0, H-a′), 7.78 (1H, s, H-12), 7.69 (1H, d, *J* 16.0, H-a), 7.56 (1H, d, *J* 8.8, H-2′), 7.40 (1H, d, *J* 1.8 H-1), 7.32 (1H, dd, *J* 1.8 and 8.4, H-2), 7.24 (1H, d, *J* 16.0, H-b′), 7.23 (1H, d, *J* 8.4, H-3), 7.14 (1H, d, *J* 16.1, H-b), 6.91 (1H, d, *J* 8.9, H-1′), 6.42 (1H, t, *J* 6.6, H-9), 5.43–5.37 (1H, m, H-7), 5.22 (2H, s, H-5), 4.28–4.24 (1H, m, H-10), 3.87 (6H, s, H-3′, 5′), 3.84 (3H, s, H-4′), 3.79 (3H, s, H-4), 3.76–3.64 (2H, m, H-11), 2.82–2.63 (2H, m, H-8), 1.82 (3H, s, H-13); δ_C (75 MHz, DMSO-d_6) 187.9, 163.4, 155.3, 152.7, 150.2, 149.6, 149.2, 142.5, 142.3, 141.8, 136.5, 135.9, 128.1, 124.7, 124.2, 124.1, 122.9, 122.6, 120.9, 113.6, 111.2, 109.4, 108.4, 84.3, 83.9, 61.7, 61.1, 60.6, 60.2, 59.2, 55.9, 55.5, 36.9, 11.9; LRMS (EI) *m*/*z* 676.5 (M+H) M^+ $C_{34}H_{37}N_5O_{10}$ requires 675.3. Anal. Calcd for $C_{34}H_{37}N_5O_{10}{\cdot}1½H_2O$: C, 58.0; H, 5.7; N, 9.9. Found: C, 57.5; H, 5.7; N, 9.5.

6.8.4. 1-[4-(4-{4-[5-(2,4-Dichloro-phenyl)-3-oxo-penta-1,4-dienyl]-2-methoxy-phenoxymethyl}-[1,2,3] triazol-1-yl)-5-hydroxymethyl-tetrahydro-furan-2-yl]-5-methyl-1*H*-pyrimidine-2,4-dione (13d)

Yellow solid (379 mg, 58%); mp 239–241 °C (from MeOH/EtOAc); R_f (MeOH/EtOAc 5:95) 0.50; IR ν_{max} (KBr)/cm^{-1} 3442 (O–H), 3057 (Ar C–H), 1692 (C=O), 1580 (Ar C=C); δ_H (400 MHz, DMSO-d_6) 11.31 (1H, s, H-14), 8.43 (1H, s, H-6), 8.07 (1H, d, *J* 8.6, H-3′), 7.86 (1H, d, *J* 15.8, H-a′), 7.84 (1H, d, *J* 16.1, H-a), 7.81 (1H, s, H-12), 7.74 (1H, d, *J* 2.1, H-1), 7.55 (1H, d, *J* 15.5, H-b′), 7.54 (1H, dd, *J* 2.1 and 8.5, H-2), 7.41 (1H, d, *J* 1.7, H-1′), 7.33 (1H, dd, *J* 1.7 and 8.5, H-2′), 7.26 (1H, d, *J* 8.4, H-3), 7.13 (1H, d, *J* 16.1, H-b), 6.43 (1H, t, *J* 6.6, H-9), 5.43–5.38 (1H, m, H-7), 5.22 (2H, s, H-5), 4.26–4.23 (1H, m, H-10), 3.82 (3H, s, H-4), 3.78–3.61 (2H, m, H-11), 2.79–2.63 (2H, m, H-8), 1.81 (3H, s, H-13); δ_C (100 MHz, DMSO-d_6) 187.9, 164.6, 163.6, 150.4, 149.9, 149.2, 145.4, 144.1, 142.5, 140.9, 136.1, 134.8, 131.8, 131.6, 129.5, 128.0, 126.9, 124.5, 123.1, 114.7, 110.9, 109.5, 100.8, 84.4, 83.9, 61.6, 60.7, 59.3, 55.5, 37.1, 12.1; LRMS (EI) *m*/*z* 654.6 (M+H) M^+ $C_{31}H_{29}Cl_2N_5O_7$ requires 653.1. Anal. Calcd for $C_{31}H_{29}Cl_2N_5O_7{\cdot}½H_2O$: C, 56.1; H, 4.5; N, 10.6. Found: C, 56.0; H, 4.6; N, 10.7.

6.8.5. 1-[4-(4-{4-[5-(4-Fluoro-phenyl)-3-oxo-penta-1,4-dienyl]-2-methoxy-phenoxymethyl}-[1,2,3]-triazol-1-yl)-5-hydroxy-methyl-tetrahydro-furan-2-yl]-5-methyl-1*H*-pyrimidine-2,4-dione (13e)

Yellow solid (193 mg, 32%); mp °C (from MeOH/EtOAc); R_f (MeOH/EtOAc 5:95) 0.50; IR ν_{max} (KBr)/cm^{-1} 3387 (O–H), 3010 (Ar C–H), 1688 (C=O), 1602 (Ar C=C); δ_H (400 MHz, DMSO-d_6) 11.30 (1H, s, H-14), 8.43 (1H, s, H-6), 7.86 (1H, d, *J* 8.9, H-1′), 7.85 (1H, d, *J* 8.8, H-4′), 7.81 (1H, s, H-12), 7.75 (1H, d, *J* 16.0, H-a′), 7.72 (1H, d, *J* 16.0, H-a), 7.41 (1H, d, *J* 1.9, H-1), 7.34 (1H, dd, *J* 1.9 and 8.5, H-2), 7.32 (1H, d, *J* 16.1, H-b′), 7.30 (1H, d, *J* 8.9, H-2′), 7.29 (1H, d, *J* 8.9, H-3′), 7.25 (1H, d, *J* 8.4, H-3), 7,20 (1H, d, *J* 16.0, H-b), 6.43 (1H, t, *J* 6.5, H-9), 5.42–5.38 (1H, m, H-7), 5.21 (2H, s, H-5), 4.26–4.22 (1H, m, H-10), 3.83 (3H, s, H-4), 3.77–3.61 (2H, m, H-11), 2.78–2.63 (2H, m, H-8), 1.81 (3H, s, H-13); δ_C (100 MHz, DMSO-d_6 188.2, 163.6, 150.4, 149.8, 149.2, 145.4, 144.1, 143.1, 142.5, 137.6, 136.1, 131.4, 130.6, 127.9, 125.4, 124.4, 124.0, 122.9, 116.0, 113.2, 110.9, 109.5, 84.4, 83.9, 67.8, 61.6, 60.7, 59.3, 55.5, 37.1, 12.1; LRMS (EI) *m*/*z* 604.4 (M+H) M^+ $C_{31}H_{30}FN_5O_7$ requires 603.2. Anal. Calcd for $C_{31}H_{30}FN_5O_7$: C, 61.7; H, 5.0; N, 11.6. Found: C, 61.4; H, 5.2; N, 11.5.

6.8.6. 1-[4-(4-{4-[5-(2,4-Difluoro-phenyl)-3-oxo-penta-1,4-dienyl]-2-methoxy-phenoxymethyl}-[1,2,3]-triazol-1-yl)-5-hydroxy-methyl-tetrahydro-furan-2-yl]-5-methyl-1*H*-pyrimidine-2,4-dione (13f)

Yellow solid (191 mg, 31%); mp 197–199 °C (from MeOH/EtOAc); R_f (MeOH/EtOAc 5:95) 0.50; IR ν_{max} (KBr)/cm^{-1} 3434 (O–H), 3065 (Ar C–H), 1696 (C=O), 1609 (Ar C=C); δ_H (400 MHz, DMSO-d_6) 11.31 (1H, s, H-14), 8.43 (1H, s, H-6), 8.02 (1H, d, *J* 8.7, H-3′), 7.81 (1H, s, H-12), 7.77 (1H, d, *J* 16.0, H-a′), 7.70 (1H, d, *J* 16.1, H-a), 7.43 (1H, d, *J* 1.9, H-1), 7.42 (1H, d, *J* 16.1, H-b′), 7.37 (1H, d, *J* 2.1, H-1′), 7.35 (1H, dd, *J* 1.9 and 8.4, H-2), 7.25 (1H, d, *J*

8.5, H-3), 7.21 (1H, dd, *J* 2.1 and 8.5, H-2′), 7.19 (1H, d, *J* 16.1, H-b), 6.43 (1H, t, *J* 6.6, H-9), 5.42–5.38 (1H, m, H-7), 5.21 (2H, s, H-5), 4.26–4.22 (1H, m, H-10), 3.82 (3H, s, H-4), 3.77–3.61 (2H, m, H-11), 2.78–2.63 (2H, m, H-8), 1.81 (3H, s, H-13); δ_C (100 MHz, DMSO-d_6) 188.1, 163.6, 153.2, 150.4, 149.9, 149.2, 143.6, 140.9, 139.7, 136.1, 132.7, 130.8, 127.9, 127.4, 124.5, 124.2, 123.1, 113.2, 112.6, 112.4, 110.9, 109.5, 104.6, 84.4, 83.9, 61.6, 60.7, 59.3, 55.5, 37.1, 12.1; LRMS (EI) *m*/*z* 622.3 (M+H) M^+ $C_{31}H_{29}F_2N_5O_7$ requires 621.2. Anal. Calcd for $C_{31}H_{29}F_2N_5O_7.½H_2O$: C, 59.0; H, 4.8; N, 11.1. Found: C, 59.2; H, 5.0; N, 11.3.

6.8.7. 1-{4-[1-(7-Chloro-quinolin-4-yl)-1*H*-[1,2,3]triazol-4-yl-methoxy]-3-methoxy-phenyl}-5-(4-methoxy-phenyl)-penta-1,4-dien-3-one (14a)

Yellow solid (199 mg, 36%); mp: 173–175 °C (from EtOAc); R_f (EtOAc/Hex 7.3) 0.50; IR ν_{max} (KBr)/cm^{-1} 3036 (Ar C–H), 1642 (C=O), 1580 (Ar C=C); δ_H (400 MHz, $CDCl_3$) 9.08 (1H, d, *J* 4.6, H-8), 8.27 (1H, d, *J* 2.0, H-9), 8.13 (1H, s, H-6), 7.96 (1H, d, *J* 9.1, H-11), 7.71 (1H, d, *J* 15.6, H-a′), 7.68 (1H, d, *J* 15.8, H-a), 7.60 (1H, dd, *J* 2.0 and 9.1, H-10), 7.58 (2H, d, *J* 8.8, H-1′, 4′), 7.51 (1H, d, *J* 4.6, H-7), 7.23 (1H, dd, *J* 1.8 and 8.3, H-2), 7.19 (1H, d, *J* 1.7, H-1), 7.16 (1H, d, *J* 8.1, H-3), 6.97 (1H, d, *J* 15.8 H-b′), 6.96 (1H, d, *J* 15.8, H-b), 6.95 (2H, dd, *J* 2.1 and 8.8, H-2′, 3′), 5.50 (2H, s, H-5), 3.96 (3H, s, H-5′), 3.87 (3H, s, H-4); δ_C (100 MHz, $CDCl_3$) 161.7, 151.4, 150.3, 147.3, 144.8, 142.9, 142.5, 137.0, 136.8, 130.1, 129.5, 129.1, 128.6, 124.8, 124.5 (2C), 124.2, 123.2, 122.8, 122.6, 120.6, 116.1, 114.5, 114.0, 113.6, 111.3, 110.8, 110.4, 62.9, 56.0, 55.4; LRMS (EI) *m*/*z* 553.2 (M+H) M^+ $C_{31}H_{25}ClN_4O_4$ requires 552.1. Anal. Calcd for $C_{31}H_{25}ClN_4O_4.1H_2O$: C, 65.1; H, 4.7; N, 9.8. Found: C, 64.9; H, 4.7; N, 9.4.

6.8.8. 1-{4-[1-(7-Chloro-quinolin-4-yl)-1*H*-[1,2,3]triazol-4-yl-methoxy]-3-methoxy-phenyl}-5-(2,4-dimethoxy-phenyl)-penta-1,4-dien-3-one (14b)

Yellow solid (192 mg, 33%); mp: 103–105 °C (from EtOAc); R_f (EtOAc/Hex 8:2) 0.30; IR ν_{max} (KBr)/cm^{-1} 3079 (Ar C–H), 1656 (C=O), 1602 (Ar C=C); δ_H (300 MHz, $CDCl_3$) 9.07 (1H, d, *J* 4.6, H-8), 8.24 (1H, d, *J* 1.9, H-9), 8.14 (1H, s, H-6), 7.99 (1H, d, *J* 16.0, H-a′), 7.96 (1H, d, *J* 8.9, H-11), 7.65 (1H, d, *J* 15.8, H-a), 7.60 (1H, dd, *J* 2.1 and 9.1, H-10), 7.55 (1H, d, *J* 8.6, H-3′), 7.49 (1H, d, *J* 4.6, H-7), 7.21 (1H, dd, *J* 1.9 and 8.3, H-2), 7.16 (1H, d, *J* 1.9, H-1), 7.14 (1H, d, *J* 8.3, H-3), 7.05 (1H, d, *J* 16.0 H-b′), 6.98 (1H, d, *J* 15.8, H-b), 6.52 (1H, dd, *J* 2.3 and 8.6, H-2′), 6.47 (1H, d, *J* 2.3, H-1′), 5.49 (2H, s, H-5), 3.94 (3H, s, H-4′), 3.89 (3H, s, H-5′), 3.85 (3H, s, H-4); δ_C (75 MHz, $CDCl_3$) 183.9, 151.4, 142.0, 138.7, 137.1, 134.2, 132.6, 131.1, 130.4, 129.5, 129.1, 127.3, 124.8, 124.6, 123.9, 122.4, 120.6, 117.1, 116.5, 116.1, 114.8, 114.0, 112.8, 110.9, 109.6, 105.6, 103.6, 98.5, 63.0, 56.0, 55.6, 55.5; LRMS (EI) *m*/*z* 583.4 (M+H) M^+ $C_{32}H_{27}ClN_4O_5$ requires 582.2. Anal. Calcd for $C_{32}H_{27}ClN_4O_5.1½H_2O$: C, 63.0; H, 4.9; N, 9.2. Found: C, 62.9; H, 4.9; N, 9.8.

6.8.9. 1-{4-[1-(7-Chloro-quinolin-4-yl)-1*H*-[1,2,3]triazol-4-yl-methoxy]-3-methoxy-phenyl}-5-(2,3,4-trimethoxy-phenyl)-penta-1,4-dien-3-one (14c)

Yellow solid (202 mg, 33%); mp: 96–98 °C (from EtOAc); R_f (EtOAc/Hex 8:2) 0.30; IR ν_{max} (KBr)/cm^{-1} 3086 (Ar C–H), 1660 (C=O), 1588 (Ar C=C); δ_H (400 MHz, $CDCl_3$) 9.08 (1H, d, *J* 4.6, H-8), 8.27 (1H, d, *J* 1.9, H-9), 8.16 (1H, s, H-6), 7.99–7.93 (2H, m, H-11, a′), 7.66 (1H, d, *J* 15.8, H-a), 7.62 (1H, dd, *J* 2.0 and 9.1, H-10), 7.51 (1H, d, *J* 4.6, H-7), 7.38 (1H, d, *J* 8.8, H-2′), 7.23 (1H, dd, *J* 1.7 and 8.3, H-2), 7.18–7.16 (2H, m, H-1, 3), 7.09 (1H, d, *J* 16.0, H-b′), 6.97 (1H, d, *J* 15.9 H-b), 6.72 (1H, d, *J* 8.8, H-1′), 5.51 (2H, s, H-5), 3.97 (3H, s, H-3′), 3.96 (3H, s, H-5′), 3.92 (3H, s, H-4′), 3.90 (3H, s, H-4); δ_C (100 MHz, $CDCl_3$) 189.1, 151.4, 150.3, 149.9, 149.5, 144.8, 142.4, 140.9, 138.3, 129.5, 129.3, 129.1, 125.9, 124.9, 124.8, 124.5, 124.4, 123.5, 122.5, 121.9, 120.9, 116.1, 114.1, 111.6, 110.9, 110.5, 109.4, 107.7, 62.9, 61.5, 60.9, 56.1, 56.0; LRMS (EI) *m*/*z* 613.3 (M+H) M^+ $C_{33}H_{29}ClN_4O_6$ requires 612.2. Anal. Calcd for $C_{33}H_{29}ClN_4O_6.1H_2O$: C, 62.7; H, 4.9; N, 8.9. Found: C, 62.5; H, 4.9; N, 9.4.

6.8.10. 1-{4-[1-(7-Chloro-quinolin-4-yl)-1*H*-[1,2,3]triazol-4-yl-methoxy]-3-methoxy-phenyl}-5-(2,4-dichloro-phenyl)-penta-1,4-dien-3-one (14d)

Yellow solid (248 mg, 42%); mp: 159–161 °C (from EtOAc); R_f (EtOAc/Hex 8:2) 0.33; IR ν_{max} (KBr)/cm^{-1} 3050 (Ar C–H), 1653 (C=O), 1584 (Ar C=C); δ_H (400 MHz, $CDCl_3$) 9.08 (1H, d, *J* 4.6, H-8), 8.26 (1H, d, *J* 2.1, H-9), 8.16 (1H, s, H-6), 8.04 (1H, d, *J* 16.0, H-a′), 7.98 (1H, d, *J* 9.1, H-11), 7.71 (1H, d, *J* 15.9, H-a), 7.66 (1H, d, *J* 8.5, H-3′), 7.61 (1H, dd, *J* 2.1 and 9.1, H-10), 7.51 (1H, d, *J* 4.6, H-7), 7.48 (1H, d, *J* 2.0, H-1), 7.30 (1H, dd, *J* 2.1 and 8.5, H-2), 7.25 (1H, dd, *J* 1.9 and 8.4, H-2′), 7.20–7.18 (2H, m, H-1′, 3), 7.04 (1H, d, *J* 15.9, H-b′), 6.98 (1H, d, *J* 15.9, H-b), 5.51 (2H, s, H-5), 3.96 (3H, s, H-4); δ_C (100 MHz, $CDCl_3$) 188.3, 154.9, 153.2, 151.4, 150.3, 149.9, 144.7, 143.6, 140.9, 138.6, 137.5, 137.0, 136.4, 135.9, 131.8, 130.1, 129.5, 129.1, 128.4, 128.2 127.6, 124.8, 124.4, 123.8, 122.8, 120.6, 116.1, 110.9, 62.9, 56.1; LRMS (EI) *m*/*z* 591.1 (M+H) M^+ $C_{30}H_{21}Cl_3N_4O_3$ requires 590.1. Anal. Calcd for $C_{30}H_{21}Cl_3N_4O_3$.: C, 60.9; H, 3.6; N, 9.5. Found: C, 60.4; H, 3.7; N, 9.5.

6.8.11. 1-{4-[1-(7-Chloro-quinolin-4-yl)-1*H*-[1,2,3]triazol-4-yl-methoxy]-3-methoxy-phenyl}-5-(4-fluoro-phenyl)-penta-1,4-dien-3-one (14e)

Yellow solid (206 mg, 38%); mp: 107–109 °C (from EtOAc); R_f (EtOAc/Hex 7.3) 0.30; IR ν_{max} (KBr)/cm^{-1} 3036 (Ar C–H), 1653 (C=O), 1588 (Ar C=C); δ_H (400 MHz, $CDCl_3$) 9.08 (1H, d, *J* 4.6, H-8), 8.26 (1H, d, *J* 2.1, H-9), 8.16 (1H, s, H-6), 7.97 (1H, d, *J* 9.1, H-11), 7.78 (1H, d, *J* 16.1, H-a′), 7.70 (1H, d, *J* 15.9, H-a), 7.64 (1H, d, *J* 8.5, H-1′), 7.62 (1H, d, *J* 8.5, H-4′), 7.60 (1H, dd, *J* 2.2 and 9.1, H-10), 7.50 (1H, d, *J* 4.6, H-7), 7.24 (1H, dd, *J* 1.8 and 8.5, H-2), 7.18–7.16 (2H, m, H-1, 3), 7.14 (1H, d, *J* 16.1 H-b′), 6.95 (1H, d, *J* 15.9, H-b), 6.91 (1H, dd, *J* 2.1 and 8.6, H-2′), 6.88 (1H, dd, *J* 2.5 and 8.5, H-3′), 5.50 (2H, s, H-5), 3.95 (3H, s, H-4); δ_C (100 MHz, $CDCl_3$) 188.5, 151.4, 150.3, 149.9, 144.7, 143.4, 140.9, 138.5, 137.0, 135.3, 134.7, 130.7, 129.5, 129.1, 127.2, 124.8, 124.5, 124.2, 122.9, 120.6, 116.0, 113.9, 112.3, 112.1, 110.8, 104.9, 104.7, 104.5, 62.9, 56.0; LRMS (EI) *m*/*z* 541.4 (M+H) M^+ $C_{30}H_{22}ClFN_4O_3$ requires 540.1. Anal. Calcd for $C_{30}H_{22}ClFN_4O_3.½H_2O$: C, 65.5; H, 4.2; N, 10.2. Found: C, 65.9; H, 4.2; N, 10.0.

6.8.12. 1-{4-[1-(7-Chloro-quinolin-4-yl)-1*H*-[1,2,3]triazol-4-yl-methoxy]-3-methoxy-phenyl}-5-(2,4-difluoro-phenyl)-penta-1,4-dien-3-one (14f)

Yellow solid (173 mg, 31%); mp: 124–126 °C (from EtOAc); R_f (EtOAc/Hex 8:2) 0.30; IR ν_{max} (KBr)/cm^{-1} 3043 (Ar C–H), 1653 (C=O), 1580 (Ar C=C); δ_H (400 MHz, $CDCl_3$) 9.08 (1H, d, *J* 4.6, H-8), 8.26 (1H, d, *J* 2.1, H-9), 8.16 (1H, s, H-6), 7.97 (1H, d, *J* 9.1, H-11), 7.71 (1H, d, *J* 15.9, H-a′), 7.69 (1H, d, *J* 15.9, H-a), 7.62 (1H, d, *J* 8.5, H-3′), 7.60 (1H, dd, *J* 2.1 and 9.1, H-10), 7.50 (1H, d, *J* 4.6, H-7), 7.24 (1H, dd, *J* 1.9 and 8.3, H-2), 7.18 (1H, d, *J* 1.9, H-1), 7.17 (1H, d, *J* 8.3, H-3), 7.13 (1H, d, *J* 1.9, H-1′), 7.11 (1H, dd, *J* 1.8 and 8.5, H-2′), 7.03 (1H, d, *J* 15.9, H-b′), 6.95 (1H, d, *J* 15.9, H-b), 5.51 (2H, s, H-5), 3.95 (3H, s, H-4); δ_C (100 MHz, $CDCl_3$) 188.5, 151.4, 150.3, 149.9, 149.8, 146.5, 144.7, 143.7, 140.9, 137.0, 132.2, 131.1, 130.3, 129.5, 129.1, 125.0, 124.8, 124.5, 124.3, 122.8, 120.6, 118.6, 116.2, 116.0, 115.2, 114.0, 110.8, 105.9, 62.9, 56.0; LRMS (EI) *m*/*z* 559.3 (M+H) M^+ $C_{30}H_{21}ClF_2N_4O_3$ requires 558.1. Anal. Calcd for $C_{30}H_{21}ClF_2N_4O_3$: C, 64.5; H, 3.5; N, 10.0. Found: C, 64.6; H, 3.7; N, 10.2.

6.9. Prop-2-ynyloxy-benzene (15)

Phenol (10 mmol) was dissolved in 10 mL of anhydrous DMF. Anhydrous K_2CO_3 (20 mmol) was then added to the solution, and the mixture stirred at 30 °C for 30 min. Propargyl bromide (3-bromopropyne, 20 mmol) was then added slowly to the reaction mixture, which was subsequently stirred at 50 °C for 24 h.

The reaction mixture was then diluted with 100 ml ethyl acetate, washed with water (2 × 50 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to yield the product residue that was then purified by column chromatography (EtOAc/hexane) to yield **15**, the structure of which was confirmed by ^{1}H NMR, This intermediate was used for the synthesis of **16** without further purification or characterization. δ_H (400 MHz, $CDCl_3$) 7.32–7.36 (2H, m, H-1, 5), 7.02–7.06 (3H, m, H-2, 3, 4), 4.72 (2H, d, *J* 2.4, H-6), 2.55 (1H, t, *J* 2.4, H-7).

6.10. 7-Chloro-4-(4-phenoxymethyl-[1,2,3]triazol-1-yl)-quinoline (16)

Synthesized from **15** and **6** by applying the General Method B. Off-white solid (464 mg, 69%); mp: 116–117 °C (from EtOAc/hexane); R_f (EtOAc/Hex 7:3) 0.42; δ_H (400 MHz, $CDCl_3$) 9.08 (1H, d, *J* 4.6, H-9), 8.26 (1H, d, *J* 2.0, H-10), 8.10 (1H, s, H-7), 7.98 (1H, d, *J* 9.1, H-12), 7.61 (1H, dd, *J* 2.0 and 9.1, H-11), 7.51 (1H, d, *J* 4.6, H-8), 7.32–7.37 (2H, m, H-1, 5), 7.01–7.07 (3H, m, H-2, 3, 4), 5.40 (2H, s, H-6); δ_C (100 MHz, $CDCl_3$) 158.1, 151.2, 149.9, 145.3, 141.3, 137.1, 129.9 (2C), 129.6, 128.8, 124.6 (2C), 124.4, 121.6, 120.6, 116.0, 114.8, 61.9; LRMS (EI) *m*/*z* 336.0 M^+ $C_{18}H_{13}ClN_4O$ requires 336.1. Anal. Calcd for $C_{18}H_{13}ClN_4O$: C, 64.2; H, 3.9; N, 16.6. Found: C, 64.0; H, 3.5; N, 17.0.

6.11. 4-[1-(7-Chloro-quinolin-4-yl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-3-methoxy-benzaldehyde (17)

Synthesized from **3** and **6** by applying the General Method B. Off-white powder (990 mg, 84%); mp: 137–138 °C (from EtOAc/hexane); R_f (EtOAc/Hex 4:6) 0.22; δ_H (400 MHz, $CDCl_3$) 9.88 (1H, s, H-a), 9.06 (1H, d, *J* 4.6, H-8), 8.26 (1H, d, *J* 1.9, H-9), 8.17 (1H, s, H-6), 7.96 (1H, d, *J* 9.1, H-11), 7.60 (1H, dd, *J* 2.0 and 9.1, H-10), 7.51 (1H, d, *J* 4.5, H-7), 7.45–7.48 (2H, m, H-1, 2), 7.29 (1H, d, *J* 8.3, H-3), 5.54 (2H, s, H-5), 3.95 (3H, s, H-4); δ_C (100 MHz, $CDCl_3$) 190.7, 152.9, 151.3, 150.2 (2C), 144.3, 140.8, 136.9, 131.0, 129.7, 129.1, 126.7, 125.2, 124.4, 120.5, 116.0, 112.8, 109.8, 62.8, 56.2; LRMS (EI) *m*/*z* 394.0 M^+ $C_{20}H_{15}ClN_4O_3$ requires 394.1. Anal. Calcd for $C_{20}H_{15}ClN_4O_3$: C, 60.9; H, 3.8; N, 14.2. Found: C, 60.5; H, 3.7; N, 14.5.

6.12. Evaluation of in vitro antimalarial activity

The in vitro antimalarial activities of compounds were evaluated on CQS (D10) and CQR (Dd2 and W2) strains of *P. falciparum*.

The parasites were maintained in continuous in vitro culture by standard methods.[46] The cultured parasites were, whenever necessary, synchronized by treatment with 5% D-sorbitol (Sigma) at the ring stage.[47]

For studies with the D10 and Dd2 strains, the test compounds were tested in duplicate on two separate occasions. The compounds were dissolved in DMSO and serially diluted twofold with complete culture media (RPMI 1640 culture medium (Biowhittaker) supplemented with glucose, HEPES buffer, hypoxanthine, 5%w/v Albumax, sodium bicarbonate and gentamicin) to yield 100 μL solutions of varying concentration across a 96-well plate. The blank and negative control wells in each plate contained 100 μL of complete medium instead of the test compound. Chloroquine was also tested as a positive control. One-hundred microlitres of parasitized erythrocytes (2% parasitemia and 2% hematocrit) was then added to each of the test and control wells; 100 μL of unparasitized erythrocytes (2% hematocrit) was added to the blank wells. The assay plates were then incubated at 37 °C for 48 h in airtight gas chambers under a gas environment of 3% O_2, 4% CO_2 and 93% N_2. After the 48 h incubation period, the assay plates were retrieved from the gas chambers, and the contents of each well were re-suspended. Maintaining the same layout as the assay plate, 15 μL of the re-suspended mixtures were then transferred to a separate 96-well plate containing 100 μL of Malstat reagent (1 ml/L triton, 0.33 g/L APAD and 3.3 g/L TRIS buffer) in each well. Twenty-five microlitres of nitroblue tetrazolium (NBT)/phenazine ethosulphate (PES) solution was then added into each well, after which the plates were allowed to develop for 5–10 min in the dark. The absorbance of the blue formazan products in each well was then measured at 620 nm on a 7520 Microplate reader from Cambridge Technology Inc.

The absorbance data from the colorimetric determinations was then transformed to represent percentage viability by adjusting for the absorbance in the blank and control wells; this data was then analyzed using GraphPad Prism® Version 4 software to yield semi-logarithmic dose–response curves and the corresponding IC_{50} values for the compounds.

For studies with the W2 strain, assays were conducted as previously reported (Shenai et al. 2003[48]) with parasites cultured in standard medium including 10% human serum, except that parasite development was assessed with a FACS-based assay, as previously described (Sijwali and Rosenthal, 2004[49]).

6.13. β-Hematin inhibition assay

This assay was carried out as described by Ncokazi and Egan.[41]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2010.10.009.

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