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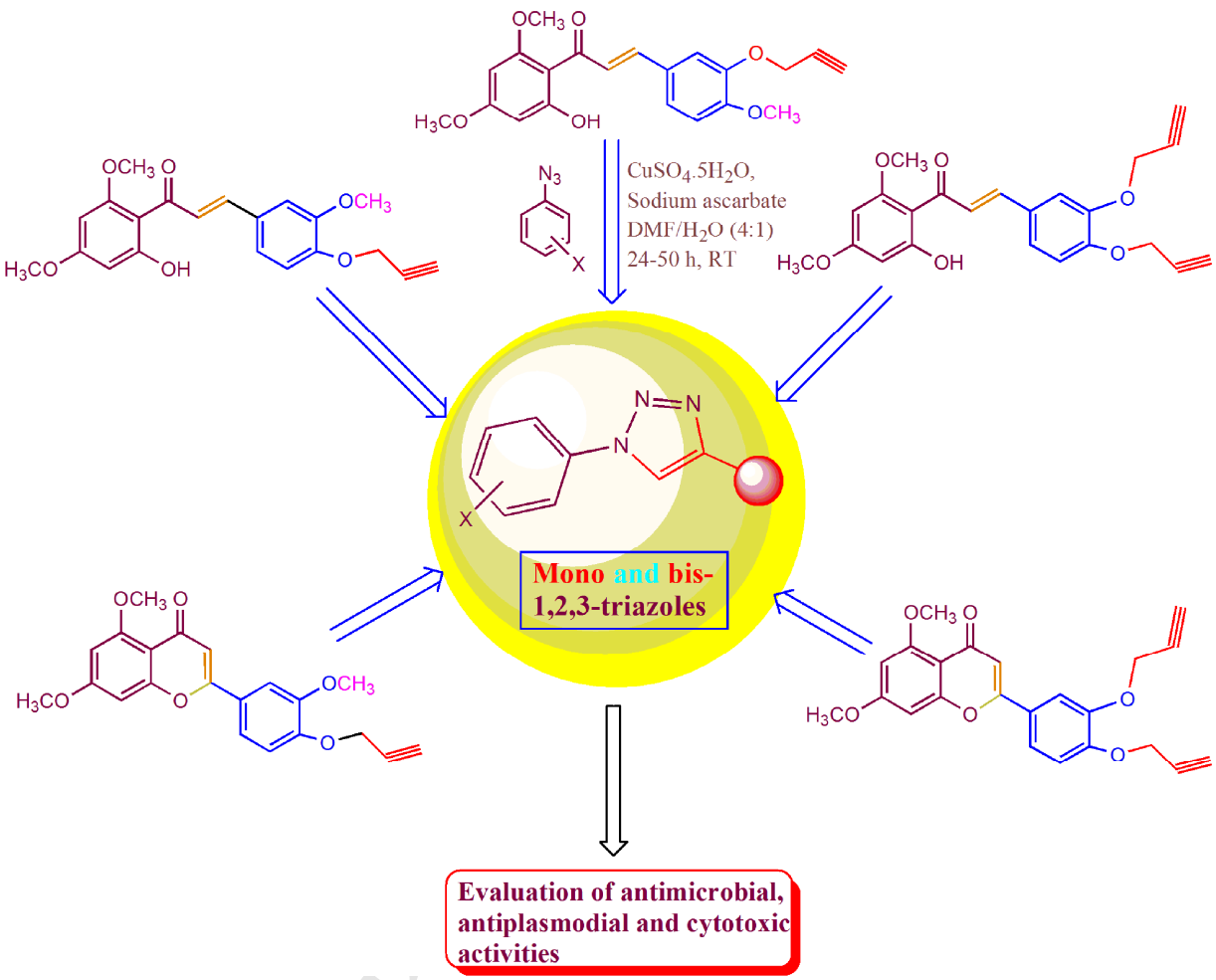
Graphical abstract



Synthesis of Newer 1,2,3-Triazole Linked Chalcone and Flavone Hybrid Compounds and Evaluation of their Antimicrobial and Cytotoxic Activities

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Abstract

The present study was carried out in an attempt to synthesize a new class of antimicrobial and antiplasmodial agents by copper catalyzed click chemistry to afford 25 compounds **10-14(a-e)** of 1,4-disubstituted-1,2,3-triazole derivatives of chalcones and flavones. The structures of the newly synthesized compounds were established by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and Mass spectral data. The newly synthesized compounds were evaluated for their antibacterial

activity against Gram positive bacteria (*Staphylococcus aureus, Enterococcus faecalis*), Gram negative bacteria (*Escherichia coli, Pseudomonas aeruginosa, Shigella boydii, Klebsiella pneumoniae*) and antifungal activity against (*Candida albicans, Candida tropicalis, Candida parapsilosis, Cryptococcus neoformans, Dermatophyte*) as well as molds (*Aspergillus niger, Aspergillus fumigatus*). The antiplasmodial and cytotoxic activities of these compounds were also evaluated against human malaria parasite *Plasmodium falciparum* strain 3D7 and human hepato-cellular carcinoma cells (Huh-7), respectively. Compounds **10a**, **10c**, **10d**, **12c** and **14e** showed promising antibacterial activity while compounds **10e**, **11d**, **11e**, **12c**, **13a**, **13b**, **13e**, **14a** and **14d** showed good antifungal activity as compared to the corresponding standard drugs. Compound **10b** was found to be the most active against *Plasmodium falciparum* while the remaining compounds showed moderate to weak antiplasmodial activity. However, cytotoxic activities of all compounds were found ineffective against Huh-7 cells.

Key words; 1,2,3-Triazole, Chalcone, Antibacterial activity, Antifungal activity, Antiplasmodial activity, Cytotoxicity

1. Introduction

The organic compounds containing chalcone and flavone scaffold as a core unit exhibit various biological and pharmaceutical activities [1-3]. They are important as structural motifs among biologically active molecules and also for combinatorial assembly of heterocyclic scaffolds [4-6]. Chalcones containing several functional groups showed a wide spectrum of biological activities such as antimicrobial [7,8], antimalarial [9,10], anticancer [11,12], anti-inflammatory [13], antileishmanial [10,14], antiprotozoal [15], anti-HIV [16], antioxidant [17] and antiulcer [18] activities. Flavones and their derivatives have also been found to display

antioxidant [19], antimicrobial [20], anticancer [21], antimalarial [22], anti-inflammatory [23], antiulcer [24], antileishmanial [25] and anti-HIV [26] properties. Due to its remarkable bioactivities and structural novelty, much more effort has been devoted to the synthesis of chalcone and flavone analogues [1,2].

1,2,3-Triazoles have received attention not only in organic chemistry but also in medicinal chemistry due to their easy synthesis by copper-catalyzed click reaction as well as numerous biological activities [27-33]. In recent years, 1,2,3-triazoles have gained special attention in the drug discovery because several drug molecules contain 1,2,3-triazole group such as Tazobactam, Cephalosporin and Cefatrizine. They are clinically used for the treatment of bacterial infections. A number of compounds were synthesized with varied biological activities by the combination of 1,2,3-triazoles with other pharmacophores via click chemistry. For example, a series of 1,2,3-triazole bearing chalcone showed notable antimalarial activity against the D10, Dd2 and W2 strains of *Plasmodium falciparum* [34], a family of 1,2,3-triazole tethered *β*-lactam-chalcone bifunctional hybrids exhibited moderate to good cytotoxic activity [35], 1,2,3-triazole analogues of flavone displayed antimicrobial activity [36] and estrogen receptor alpha-positive breast cancer inhibitors [37]. It is well known that the combination of two or more types of pharmacophores into one molecule could afford a new entity with increased bioactivities [38,39]. As part of ongoing research work aimed towards the development of small molecules as therapeutic agents [40-42], here we report the synthesis, antimicrobial, antiplasmodial and cytotoxic activities of 1,2,3-triazole linked chalcone and flavone hybrids.

2. Result and discussion

2.1. Chemistry

A synthetic strategy was followed for the synthesis of novel 1,2,3-triazole derivatives of chalcones and flavones as shown in Scheme 1. The series of triazole derivatives **10-14(a-e)** were synthesized in various steps. The compound **1** was prepared by the simple methylation of 2,4,6-trihydroxyacetophenone with $(CH_3)_2SO_4$ and K_2CO_3 in dry acetone at reflux. This compound was a common intermediate to all molecules being synthesized. In next step, 3,4-dihydroxybenzaldehyde was reacted with propargyl bromide in presence of NaH at 0 °C to room temperature to obtain mono and di-alkyne derivatives (**2a-c**). The mono-alkyne derivates (**2a** and **2b**) were again methylated with $(CH_3)_2SO_4$ to yield compound **3a** and **3b**. Then, the compound **1** was condensed with propargylated-benzaldehyde (**3a**, **3b** and **2c**) in the basic medium to give respective 2-hydroxychalcones (**4**, **6** and **7**). The mono and dipropargylated-2-hdroxychalcone (**4** and **7**) was enough to react with I_2 in DMSO to give corresponding flavones (**5** and **8**). In the final step, the chalcones (**4**, **6** and **7**) and flavones (**5** and **8**) were further reacted with substituted aromatic azides (**9a-e**) via copper catalyzed [3+2] azide-alkyne cycloaddition reaction to afford 25 compounds **10-14(a-e)** [Table 1]. The details of general synthetic procedure of all compounds are mentioned in the experimental section. The structure of all synthesized compounds **10-14(a-e)** were confirmed by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The structure of compound **10e** was also confirmed by X-ray crystallographic analysis (Fig. 1).

2.2. Biological activity

2.2.1. Antimicrobial activity

A small library of 25 compounds **10-14(a-e)** of 1,4-disubstituted-1,2,3-triazole containing either one or two triazole units linked with chalcone and flavone scaffolds by exploiting copper catalyzed [3+2] azide-alkyne cycloaddition [32] were synthesized. All the synthesized

compounds **10-14(a-e)** were screened for their antimicrobial activity (MIC) against various bacterial and fungal strains. The potentiality of the compounds as antibacterials was appraised for their antibacterial studies against various Gram positive such as *Staphylococcus aureus* (ATCC 25323), *Enterococcus faecalis* (ATCC 29212) and Gram negative such as *Escherichia coli* (ATCC 35218), *Pseudomonas aeruginosa* (ATCC 27893), *Shigella boydii* ((clinical isolate) and *Klebsiella pneumoniae* (ATCC 27736) strains. The activity result as MIC is summarized in Table 3. It is an interesting observation that the results of the antibacterial activity of these compounds appeared to be related to the nature and position of substituents on the phenyl ring and as well as on the structural variation and isomeric effects in the skeleton moieties. It is evident from Table 3 that seven compounds viz. **10a**, **10c**, **10d**, **11c**, **11d**, **12c** and **14e** were found more potent with either equal or more MIC as compared to control drug ciprofloxacin. DMSO was also taken in a control experiment which showed no effect in the experiment.

The compound **10a** containing 2-chloro-4-fluoro substituted benzene ring showed potent inhibitory activity against *S. aureus* and *E. faecalis* with MIC 6.25 µg/mL which is similar to the standard drug ciprofloxacin (MIC 6.25 µg/mL). Further, the same compound also exhibited good activity with MIC 12.5 µg/mL in *E. coli*, *P. aeruginosa* and *S. boydii* while in *K. pneumoniae*, it showed moderate activity with MIC 25 µg/mL. The compound **10b** having 3-chloro-4-fluoro substituted benzene ring was found to have moderate to weak activity against all the tested strains at a MIC range of 25-100 µg/mL. The compounds **10c** and **10d** having 2,4-difluoro and 2-chloro substituted benzene ring, respectively showed most potent activity against *E. coli* and *S. boydii* at MIC 6.25 µg/mL. Further, these compounds were also found active against *S. aureus* and *P. aeruginosa* with MIC 12.5 µg/mL. Again, the compound **10d** was found to be the most potent with MIC 6.25 µg/mL while the compound **10c** exhibited good activity with MIC 12.5

µg/mL against *E. faecalis*. Further, the compound **10c** showed MIC 12.5 µg/mL while compound **10d** showed MIC 25 µg/mL against strain *K. pneumoniae*. The compounds **11c** and **11d** were also found to possess good activity against *S. boydii* with MIC 12.5 µg/mL and showed moderate to weak activity in the range of 25-100 µg/mL or > 100 µg/mL against remaining strains. Furthermore, compound **12c** containing 2,4-difluoro substituted benzene showed excellent potency against *E. faecalis*, *E. coli* and *S. boydii* with MIC 6.25 µg/mL. It also exhibited potent antibacterial activity against *S. aureus*, *P. aeruginosa* and *K. pneumoniae* with MIC 12.5 µg/mL. Moreover, the compounds **12d** to **14d** were found weak or inactive with MIC 50-100 µg/mL or >100 µg/mL against all strains. The compound **14e** having 4-chloro substituted benzene ring was found most active against *E. coli* with MIC 6.25 µg/mL while remaining strains showed good to moderate susceptibility with MIC in the range of 12.5-25 µg/mL. In general, control drug ciprofloxacin showed MIC 6.25 µg/mL against all the tested microorganisms.

It is obvious from the analysis of activity results that electron withdrawing groups such as chloro, fluoro and also their combination has strong effects in rendering the antibacterial activity. This observation is supported by the highest activity shown by the five compounds **10a**, **10c**, **10d**, **12c** and **14e** against both the Gram positive and Gram negative bacterial strains while compound **10a** and **10d** showed MIC 25 µg/mL against *K. pneumoniae*. Further, the positions of these groups in benzene ring also play a critical role towards activity. For example, compound **10a** containing chloro and fluoro groups at position-2 and 4 in benzene ring, showed potency while the compound **10b** with chloro and fluoro groups at position-3 and 4 in benzene ring lost activity. Again, the compound **10d** with chloro group at 2-position in benzene ring showed best potency against all strains. While the compound **10e** containing chloro group at 4-position in

benzene ring lost the potency. However, it is reversed in triazole containing flavones. For example, the compound **14e** containing chloro group at position-4 in benzene ring has potential activity with MIC 6.25 µg/mL in *E. coli* while in other strains compound showed MIC 12.5-25 µg/mL. The compound **14d** with chloro group at 2-position lost the activity and exhibited MIC >100 µg/mL in all tested strains. Thus, it is hypothesized that the chloro group at position-2 is critical for antibacterial activity in chalcone triazoles while the chloro group at position-4 is important for antibacterial activity in flavone triazoles. The presence of fluoro group has significant effect on antibacterial activity in chalcone triazoles but in flavone triazoles, it lost the activity.

Another interesting observation is based on the isomeric effects and structural variation in the skeleton moieties. The compounds **10a-e** are structural isomers of compounds **11a-e** synthesized from isomeric skeleton moieties **4** and **6**, while compounds **10-14(a)** and **10-14(d)** are position isomers of compounds **10-14(b)** and **10-14(e)**, respectively. It is evident from the screening results shown in Table 3 that the triazole compounds **10a-e** synthesized from the skeleton moiety **4** showed most potent inhibitory activity as compare to the compounds **11a-e** synthesized from skeleton moiety **6.** Again the isomeric effects have been observed in other systems. For example, the compounds **10(a** and **d)**, **11(a** and **d)** and **13(a** and **d)** showed better potency against bacterial strains as compare to the compounds **10(b** and **e)**, **11(b** and **e)** and **13(b** and **e)**, respectively. Further, the structural variations in the skeleton moieties also play a critical role toward activity. For example, the triazole compounds **13-14(a-e)** synthesized from the flavones (**5** and **8**) showed negligible activity except **14e** as compare to the compounds synthesized from chalcones (**4** and **7**). In order to ascertain this hypothesis, more synthesis of diversified compounds using multifunctional substituted phenyl ring were needed. More

systematic structure activity relationship (SAR) study is needed involving large number of compounds to get molecule for *in vivo* studies which may be eventually a clinical candidate for future.

Further, these compounds **10-14(a-e)** were also screened for their antifungal activity against six fungal strains such as *Candida albicans* (ATCC 90028), *Candida albicans* (clinical), *Candida tropicalis* (ATCC 750), *Candida parapsilosis* (ATCC 22019), *Cryptococcus neoformans* (clinical), *Dermatophyte* (clinical) and two molds *Aspergillus niger* (clinical) and *Aspergillus fumigatus* (clinical). The results of antifungal activity of tested compounds were found to be somewhat different from their antibacterial activity as shown in Table 4. These compounds showed weak to moderate antifungal activity as compared to the standard drug fluconazole. It is evident from antifungal data that nine compounds viz. **10e**, **11d**, **11e**, **12c**, **13a**, **13b**, **13e**, **14a** and **14d** were found more potent as compared to the MIC of other compounds with standard drug.

The compound **10a** containing 2-chloro-4-fluoro substituted benzene ring showed moderate to weak activity with MIC range of 25-100 µg/mL and >100 µg/mL while fluconazole has MIC in the range of 0.50-4.00 µg/mL against all tested strains in the present study. The compound **10c** having 2,4-difluoro substituted benzene ring was found moderate potential against *C. parapsilosis* with MIC 25 µg/mL while in remaining strains, it showed weak activity with MIC 50 µg/mL or >100 µg/mL. The compound **10e** containing 4-chloro substituted benzene ring was found to be the most potential activity against *C. albicans* (clinical) and *C. tropicalis* with MIC 6.25 µg/mL. Again, the compound **10e** also showed good activity against four strains *C. albicans, C. parapsilosis, C. neoformans* and *Dermatophyte* with MIC 12.5 µg/mL, while in

A. niger and *A. fumigatus* strains, it showed moderate activity with MIC 25 µg/mL. The compounds **11d** and **11e** having 2-chloro and 4-chloro substituted benzene ring, respectively were found to be the most potent with MIC 6.25 µg/mL in *C. tropicalis*. Further, the same compounds also showed MIC 12.5 µg/mL in *C. albicans* (clinical), *C. parapsilosis, C. neoformans* and *Dermatophyte*. Again, the compound **11d** was found to be the most potential active with MIC 6.25 µg/mL in *C. albicans* while the compound **11e** exhibited good activity with MIC 12.5 µg/mL. Further, the compound **11d** showed MIC 12.5 µg/mL while compound **11e** showed MIC 25 µg/mL against *A. niger* and *A. fumigatus*. The compound **12c** containing 2,4-difluoro substituted benzene ring showed potent antifungal activity against both species of *C. albicans* and *C. neoformans* with MIC 6.25 µg/mL while moderate activity was observed with other strains in the range of 12.5-25 µg/mL.

The flavone compounds **13a** and **13b** having 2-chloro-4-fluoro and 3-chloro-4-fluoro substituted benzene ring respectively, showed good activity against four strains viz. *C. albicans, C. albicans* (clinical), *C. tropicalis* and *C. parapsilosis* with MIC 12.5 µg/mL while fluconazole showed MIC 0.50 µg/mL. Further, the compound **13a** showed good activity again *C. neoformans, A. niger* and *A. fumigates* with MIC 12.5 µg/mL except *Dermatophyte* with MIC 25 µg/mL. Again, the compound **13b** was found to be the most potent against *C. neoformans* with MIC 6.25 µg/mL while against *Dermatophyte, A. niger* and *A. fumigates*, it showed good to weak activity with MIC 12.5-50 µg/mL. The compound **13e** containing 4-chloro substituted benzene ring showed good antifungal activity against *C. albicans* (clinical), *C. neoformans* and *Dermatophyte* with MIC 12.5 µg/mL while against the remaining strains showed MIC 50 µg/mL. Further, the compound **14a** having 2-chloro-4-fluoro substituted benzene ring showed potent inhibitory activity with MIC 6.25 µg/mL against two strains *C. tropicalis* and

Dermatophyte while other remaining strains showed MIC 12.5 µg/mL. Again, the compound **14d** containing 2-chloro atom in benzene ring also showed reasonable good activity with MIC 6.25-12.5 µg/mL against all strains. The rest compounds were found to be weak or inactive against all strains with MIC 50-100 µg/mL or >100 µg/mL. Fluconazole was taken as a standard drug which showed MIC value in between 0.50-4.00 µg/mL against various strains.

It is obvious from the above antifungal screening results that presence of chloro group in phenyl ring of one triazole unit chalcones shows potent antifungal activity, while difluoro-compounds enhance antifungal activity in two triazole linked chalcones. Further, the combination of chloro and fluoro atoms in benzene ring has better antifungal activity than monohalogen compounds in one triazole linked flavones. But, the presence of 2-chloro or its combination with fluoro group in phenyl ring showed potent activity than other groups and their combinations in flavones contained two triazole units. Interestingly, the flavone compounds containing difluoro substituted phenyl rings were found to be inactive against antifungal as well as antibacterial activity. Further, the screening of these compounds will also help to predict structural variations, isomeric as well as position effect of functional groups on antimicrobial activity. Moreover, multifunctional substituted phenyl rings were used to generate large number of diverse compounds for *in vitro* antifungal activity. Thus, more systematic design and their synthesis of compounds with various functional groups are needed to establish a meaningful structure activity relationship (SAR). This relationship needs to be done on most potent molecule to find a lead molecule which can be evaluated for *in vivo* activity.

2.2.2. Antiplasmodial activity

1,2,3-Triazole derivatives of chalcones and flavones were evaluated *in vitro* against the erythrocytic stages of *P. falciparum* (3D7 strain). Results compiled in Table 5 show that many compounds exhibited moderate activities. The most potent compound was **10b** having 3-chloro-4-fluoro substituted benzene ring, with an IC_{50} of 2.74 µg/mL while artemisinin showed IC_{50} 1.117 ± 0.076 ng/mL. The compounds from chalcone series **10c** having 2,4-difluoro substituted phenyl ring and **10e** having 4-chloro substituted benzene showed IC_{50} of 3.58 µg/mL and 5.08 µg/mL, respectively. The compound **10d** containing 2-chloro substituted benzene ring in chalcone series showed IC_{50} 6.78 µg/mL. These compounds also showed promising antibacterial activity. Similarly, the compound **11a** containing 2-chloro-4-fluoro substituted benzene ring in chalcone series showed IC_{50} 4.92 µg/mL. The compounds of flavones series **13a** having 2-chloro-4-fluoro substituted benzene ring showed IC_{50} 3.85 µg/mL. Moreover, compound of same series **13b** having 3-chloro-4-fluoro substituted benzene ring and compound **13c** having 2,4-difluoro substituted benzene ring exhibited IC_{50} 4.48 µg/mL and 4.79 µg/mL, respectively. The compound **13e** having 4-chloro substituted benzene ring in flavone series showed IC_{50} 5.19 µg/mL. The standard drug artemisinin showed IC_{50} 1.117 ± 0.076 ng/mL. Rest of the compounds displayed moderate to weak antiplasmodial activities, as compared to the standard drug artemisinin.

2.2.3. Cytotoxicity

In order to validate the therapeutic value of compounds in the present study, toxicity on mammalian cells was assessed against Huh-7 cell line; a hepatocyte derived cellular carcinoma cell line (Table 5). All the compounds are devoid of any considerable cytotoxicity at the highest test concentration (100 µg/mL). These results further support the significance of this study.

3. Conclusion

The objective of the present study was to design, synthesis and screen the antimicrobial, antiplasmodial and cytotoxic activities of new triazole derivative of chalcone and flavone analogs with hope of discovering new structural entities. An efficient synthetic strategy was developed for synthesis of 1,2,3-triazole linked chalcone and flavone hybrid compounds. A small library of 25 compounds were synthesized with different functionalities by exploiting click chemistry and screened them against various Gram positive and Gram negative bacterial as well as fungal strains. In addition to this, antiplasmodial and cytotoxic activities of synthesized compounds were also carried out. The compound **10a**, **10c** and **10d** of chalcone series showed promising antibacterial activity with MIC 6.25 μg/mL against *S. auresus* (ATCC 25323), *E. faecalis* (ATCC 29212), *E. coli* (ATCC 35218) and *S. boydii* (clinical isolate) which is similar to ciprofloxacin MIC 6.25 μg/mL. The compound **12c** contain two triazole moieties in chalcone series showed promising antibacterial activity with MIC 6.25 μg/mL against *E. faecalis* (ATCC 29212), *E. coli* (ATCC 35218*) and S. boydii* (clinical isolate). Similarly, the compound **10e** exhibited promising antifungal activity with MIC 6.25 μg/mL against *C. albicans* (Clinical) *and C. tropicalis* (ATCC 750). The compounds **11d** and **12c** also showed potent antifungal activity with MIC 6.25 μg/mL against *C. albicans* (ATCC 90028). Other compounds showed moderate to weak activity against all tested fungal strains.

The compound **10b** showed IC_{50} 2.74 μg/mL *in vitro* against the erythrocytic stages of *P. falciparum* (3D7 strain). Rest of the compounds showed weak to moderate antiplamodial activity. These compounds were also evaluated for cytotoxicity *in vitro* against the Huh-7 cell line and exhibited no cytotoxic activity with CC_{50} values higher than 100 μg/mL.

Results obtained in this study clearly demonstrate compounds derived from chalcone and flavones moiety exhibited better antimicrobial activity. This is a preliminary result and to reach more appropriate conclusion 2nd and 3rd generation compounds should be synthesized in order to establish meaningful structure activity relationship (SAR).

This study, reporting the high yield of synthesis of novel compounds combining two types of pharmacophores into one molecule paves the way for further optimization aimed at lowering of their effective concentrations.

4. Experimental

All the chemicals and solvents were purchased from Sigma-Aldrich and E. Merck (India). The chemicals were used as received. The reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254 (mesh) and spots were visualized with UV light or iodine chamber. Merck silica gel (230-400 mesh) was used for column chromatography. Melting points of all synthesized compounds were determined by using open capillary method and may be uncorrected. NMR spectra were recorded on JEOL GS-400 model FT-NMR (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer and processed with Delta software. The chemical shifts were measured in parts per million (ppm) on the delta (δ) scale relative to the resonance of tetramethylsilane (TMS) as the internal reference. Infrared spectra were recorded in KBr pellets in the range of 4000-500 cm^{-1} at room temperature using Perkin-Elmer 400 FT-IR spectrometer. X-ray analysis was carried out on an Oxford Diffraction Xcalibur four-circle diffractometer with Eos CCD detector. Mass spectra were obtained on Agilent Technologies 6530 Accurate Mass Q-TOF LC/MS Mass spectrometer. Elemental analysis was done on a Perkin-Elmer Model 240B automatic analyzer.

4.1. *Synthesis of 1-(2-hydroxy-4,6-dimethoxyphenyl)ethan-1-one (**1**)*

A mixture of 1-(2,4,6-trihydroxyphenyl)ethan-1-one (2.50 g, 15 mmol), $(CH_3)_2SO_4$ (2.85 mL, 30 mmol) and anhydrous K_2CO_3 (4.56 g, 33 mmol) in dry acetone (60 mL) was refluxed for 10 h. The reaction mixture was concentrated and poured on to ice-water (100 mL). The resulting precipitate was filtered off and washed with cold water. The obtained residue was purified by silica gel column chromatography with hexane: ethyl acetate (95: 5) as eluent.

White solid, Yield: 54%, M.P: 78-80 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 14.03 (s, 1H,-OH), 6.06-6.05 (d, *J* = 2.20 Hz, 1H, Ar-H), 5.93-5.92 (d, *J* = 2.20 Hz, 1H, Ar-H), 3.86, 3.82 (s, each 3H, 2 × -OCH_3), 2.61 (s, 3H, -$COCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 203.17 (-C=O); 167.56; 166.06; 162.88; 105.97; 93.43; 90.72; 55.53 (-OCH_3); 50.86 (-OCH_3); 32.91 (-CH_3).

4.2. *Propargylation of 3,4-dihydroxybenzaldehyde*

In a dry two-neck flask with a nitrogen inlet, NaH (1.39 g, 57.91 mmol) was added into anhydrous DMSO (20 mL) in small portions under stirring. The solution was cooled to 0 °C. The anhydrous DMSO (25 mL) containing 3,4-dihydroxybenzaldehyde (4.0 g, 28.96 mmol) was added drop wise into the flask. The reaction mixture was then stirred at room temperature for 30 min. Propargyl bromide (3.87 mL, 43.44 mmol) was added drop wise and the mixture was stirred further 45 h at room temperature. The reaction was checked by TLC, showing the formation of three products due to visualization of spots on TLC plate. The reaction mixture was poured onto ice-water (300 mL) and neutralized by 1 M HCl solution. The products was extracted with dichloromethane, washed with brine solution (3 × 200 mL) and dried over Na_2SO_4. The solvent was removed under vacuum to afford a brownish crude product. The crude product was purified

by silica gel column with an eluent of hexane: ethyl acetate (95: 5) to give three products (**2a, 2b** and **2c**).

4.2.1. *3-hydroxy-4-(prop-2-yn-1-yloxy)benzaldehyde (**2a**)*

Colorless crystals, Yield: 29%, M.P: 66-68 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 9.86 (s, 1H, -CHO), 7.48-7.47 (d, *J* = 1.44 Hz, 1H, Ar-H), 7.46-7.43 (dd, *J* = 8.04, 1.48 Hz, 1H, Ar-H), 7.12-7.10 (d, *J* = 8.04 Hz, 1H, Ar-H), 5.83 (s, 1H, -OH), 4.87-4.86 (d, *J* = 2.20 Hz, 2H, -OCH_2), 2.62-2.61 (t, *J* = 2.20 Hz, 1H, -C≡CH); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 191.03 (-CHO); 149.60; 146.33; 131.31; 124.02; 114.80; 111.86; 56.81 (-OCH_2).

4.2.2. *4-hydroxy-3-(prop-2-yn-1-yloxy)benzaldehyde (**2b**)*

Colorless crystals, Yield: 9%, M.P: 93-95 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 9.84 (s, 1H, -CHO), 7.53-7.52 (d, *J* = 1.36 Hz, 1H, Ar-H), 7.49-7.47 (dd, *J* = 8.24, 1.36 Hz, 1H, Ar-H), 7.09-7.07 (d, *J* = 8.24 Hz, 1H, Ar-H), 6.29 (s, 1H, -OH), 4.85-4.84 (d, *J* = 2.28 Hz, 2H, -OCH_2), 2.61-2.60 (t, *J* = 2.28 Hz, 1H, -C≡CH); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 190.70 (-CHO); 151.87; 145.08; 129.75; 127.98; 115.06; 110.91; 56.97 (-OCH_2).

4.2.3. *3,4-bis(prop-2-yn-1-yloxy)benzaldehyde (**2c**)*

Colorless crystals, Yield: 21%, M.P: 99-101 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 9.89 (s, 1H, -CHO), 7.58-7.57 (d, *J* = 2.32 Hz, 1H, Ar-H), 7.55-7.52 (dd, *J* = 8.24, 1.84 Hz, 1H, Ar-H), 7.19-7.17 (d, *J* = 8.24 Hz, 1H, Ar-H), 4.87-4.86 (d, *J* = 2.76 Hz, 2H, -OCH_2), 4.84-4.83 (d, *J* = 2.28 Hz, 2H, -OCH_2), 2.58-2.57 (t, *J* = 2.28, Hz, 1H, -C≡CH), 2.56-2.55 (t, *J* = 2.72 Hz, 1H, -C≡CH); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 190.69 (-CHO); 152.59; 147.83; 130.70; 126.75; 113.07; 112.45; 77.63 (-C≡CH); 76.53 (-C≡CH); 56.71 (-OCH_2); 56.64 (-OCH_2).

4.3. *Methylation of 3-hydroxy-4-(prop-2-yn-1-yloxy)benzaldehyde (**2a**) and 4-hydroxy-3-(prop-2-yn-1-yloxy)benzaldehyde (**2b**).*

A mixture of benzaldehyde (**2a** or **2b,** 1.20 g, 6.81 mmol), anhydrous K_2CO_3 (2.82 g, 20.43 mmol) and $(CH_3)_2SO_4$ (0.97 mL, 10.33 mmol) in dry acetone (20 mL) was refluxed for 8 h. The reaction mixture was concentrated and then poured on to ice-water (50 mL). The resulting precipitate was filtered off and washed with cold water. The obtained product was sufficient pour for further reactions.

4.3.1. *3*-methoxy-*4-(prop-2-yn-1-yloxy)benzaldehyde (**3a**)*

White solid, Yield: 70%, M.P: 88-90 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 9.88 (s, 1H, -CHO), 7.48-7.46 (dd, *J* = 8.28, 1.80 Hz, 1H, Ar-H), 7.45-7.44 (d, *J* = 1.80 Hz, 1H, Ar-H), 7.16-7.14 (d, *J* = 8.28 Hz, 1H, Ar-H), 4.87-4.86 (d, *J* = 2.72 Hz, 2H, -OCH_2), 3.95 (s, 3H, -OCH_3), 2.57-2.56 (t, *J* = 2.28 Hz, 1H, -C≡CH); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 190.87 (-CHO); 152.11; 150.04; 130.94; 126.23; 112.60; 109.48; 56.61 (-OCH_2); 56.03 (-OCH_3).

4.3.2. *4*-methoxy-*3-(prop-2-yn-1-yloxy)benzaldehyde (**3b**)*

White solid, Yield: 75%, M.P: 68-70 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 9.87 (s, 1H, -CHO), 7.56-7.55 (d, *J* = 1.84 Hz, 1H, Ar-H), 7.54-52 (dd, *J* = 8.24, 1.84 Hz, 1H, Ar-H), 7.03-7.01 (d, *J* = 8.24 Hz, 1H, Ar-H), 4.84-4.83 (d, *J* = 2.28 Hz, 2H, -OCH_2), 3.97 (s, 3H, -OCH_3), 2.56-2.54 (t, *J* = 2.28 Hz, 1H, -C≡CH); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 190.06 (-CHO); 154.23; 146.61; 129.22; 126.66; 111.23; 110.23; 77.00 (-C≡CH); 75.79 (-C≡CH); 55.94 (-OCH_2); 55.52 (-OCH_3).

4.4. *General procedure for the synthesis of chalcones (**4**, **6** and **7**).*

A mixture of the 1-(2-hydroxy-4,6-dimethoxyphenyl)ethan-1-one (**1,** 1 eq) and the corresponding substituted benzaldehyde (**3a**, **3b** and **2c**, 1 eq) in ethanol (4.0 mL/mmol of acetophenone **1**) was stirred at room temperature during 10 min. Then, the aqueous solution of KOH (3 eq, 20% w/v) was added to reaction mixture. The reaction mixture was stirred at room temperature until benzaldehyde consumption as monitored by TLC. After completion of the reaction, HCl (10% v/v aqueous solution) was added until neutral. In all cases a yellow precipitate of chalcone was formed, which was filtered and dried. The products were purified using column chromatography with an eluent of chloroform : hexane (1 : 1).

4.4.1. *(2E)-1-(2-hydroxy-4,6-dimethoxyphenyl)-3-[3-methoxy-4-(prop-2-yn-1-yloxy)phenyl]prop-2-en-1-one (**4**)*

Yellow solid, Yield: 66%, M.P: 145-147 °C; IR (KBr) cm^{-1}: 3238, 2918, 2854, 2122, 1618, 1579, 1546, 1505, 1438, 1361, 1256, 1205, 1136, 1112, 1012, 980, 812, 757; ^{1}H NMR (DMSO-d_6, 400 MHz, ppm) δ: 13.35 (s, 1H, -OH), 7.67-7.63 (d, *J* = 15.36 Hz, 1H, -COC=CH), 7.61-7.57 (d, *J* = 15.40 Hz, 1H, -COCH=C), 7.32 (s, 1H, Ar-H), 7.30-7.28 (d, *J* = 8.08 Hz, 1H, Ar-H), 7.08-7.06 (d, *J* = 8.80 Hz, 1H, Ar-H), 6.14 (s, 1H, Ar-H), 6.11 (s, 1H, Ar-H), 4.85-4.84 (d, *J* = 2.20 Hz, 2H, -OCH_2), 3.87, 383, 3.80 (s, each 3H, 3 × -OCH_3), 3.61-3.59 (t, *J* = 2.20 Hz, 1H, -C≡CH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 192.24 (-CO); 165.23; 165.13; 161.69; 149.28; 148.63; 142.67; 128.51; 125.69; 122.14; 113.73; 111.30; 106.44; 93.85; 91.00; 78.93 (-C≡CH); 78.52 (-C≡CH); 56.10 (-OCH_2); 55.97 (-OCH_3); 55.58 (-OCH_3); 55.54 (-OCH_3).

4.4.2. *(2E)-1-(2-hydroxy-4,6-dimethoxyphenyl)-3-[4-methoxy-3-(prop-2-yn-1-yloxy)phenyl]prop-2-en-1-one (**6**)*

Yellow solid, Yield: 74%, M.P: 174-176 °C; IR (KBr) cm^{-1}: 3212, 2920, 2851, 2113, 1628, 1585, 1554, 1517, 1441, 1221, 1165, 1114, 1022, 983, 823, 766; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 14.37 (s, 1H, -OH), 7.82-7.78 (d, *J* = 15.60 Hz, 1H, -COC=CH), 7.76-7.72 (d, *J* = 15.60 Hz, 1H, -COCH=C), 7.33-7.32 (d, *J* = 1.84 Hz, 1H, Ar-H), 7.24-7.22 (d, *J* = 7.32 Hz, 1H, Ar-H), 6.91-6.89 (dd, *J* = 8.24, 2.20 Hz, 1H, Ar-H), 6.10-6.09 (d, *J* = 1.84 Hz 1H, Ar-H), 5.95-5.94 (d, *J* = 2.76 Hz, 1H, Ar-H), 4.81-4.80 (d, *J* = 1.80 Hz, 2H, $-OCH_2$), 3.90 (s, 6H, 2 × $-OCH_3$), 382 (s, 3H, $-OCH_3$), 2.54-2.53 (t, *J* = 2.76 Hz, 1H, -C≡CH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 192.17 (-CO); 165.42; 165.34; 161.76; 151.43; 146.60; 142.82; 127.33; 125.27; 124.17; 112.28; 112.05; 106.31; 93.87; 91.04; 79.13 (-C≡CH); 78.53 (-C≡CH); 56.13 ($-OCH_2$); 55.85 ($-OCH_3$); 55.66 ($-OCH_3$).

4.4.3. *(2E)-3-[3,4-bis(prop-2-yn-1-yloxy)phenyl]-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (**7**)*

Yellow solid, Yield: 50%, M.P: 169-171 °C; IR (KBr) cm^{-1}: 3277, 3219, 2918, 2849, 2111, 1626, 1582, 1557, 1508, 1212, 1139, 1015, 817, 761; ^{1}H NMR (DMSO-d_6, 400 MHz, ppm) δ: 13.45 (s, 1H, -OH), 7.70-7.66 (d, *J* = 14.68 Hz, 1H, -COC=CH), 7.61-7.57 (d, *J* = 15.64 Hz, 1H, -COCH=C), 7.44-7.43 (d, *J* = 1.96 Hz, 1H, Ar-H), 7.34-7.31 (dd, *J* = 8.80, 1.96 Hz, 1H, Ar-H), 7.12-7.10 (d, *J* = 7.84 Hz, 1H, Ar-H), 6.16-6.15 (d, *J* = 1.48 Hz, 1H, Ar-H), 6.12-6.11 (d, *J* = 1.96 Hz, 1H, Ar-H), 4.91-4.90 (d, *J* = 1.96 Hz, 2H, $-OCH_2$), 4.88-4.87 (d, *J* = 1.96 Hz, 2H, $-OCH_2$) 3.89, 381 (s, each 3H, 2 × $-OCH_3$), 3.64-3.63 (t, *J* = 1.96 Hz, 1H, -C≡CH), 3.62-3.61 (t, *J* = 1.96 Hz, 1H, -C≡CH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 192.14 (-CO); 165.37; 161.77;

148.99; 146.92; 142.45; 128.22; 125.76; 123.52; 113.88; 112.68; 106.32; 93.87; 91.02; 79.02 (-C≡CH); 78.84 (-C≡CH); 78.65 (-C≡CH); 78.57 (-C≡CH); 56.11 ($-OCH_2$); 55.99 ($-OCH_2$); 55.87 ($-OCH_3$); 55.62 ($-OCH_3$).

4.5. *General procedure for the synthesis of flavones (**5** and **8**).*

2-Hydroxychalcone (**4** or **7**, 1eq) was dissolved in DMSO (8.0 mL/mmol of 2-hydroxychalcone) and I_2 (0.05 eq) was added. The reaction mixture was refluxed for 1 h. Then, the mixture was cooled to room temperature and poured into water. The product was extracted with ethyl acetate, washed with brine solution until neutrality and dried with Na_2SO_4. The solvent was evaporated in vacuo and the product was purified by chromatographic column with ethyl acetate: hexane (1 : 1) as eluent.

4.5.1. *5,7-dimethoxy-2-[3-methoxy-4-(prop-2-yn-1-yloxy)phenyl]-4H-chromen-4-one (**5**)*

Brown solid, Yield: 65%, M.P: 148-150 °C; IR (KBr) cm^{-1}: 3305, 3015, 2918, 2848, 2148, 1638, 1602, 1215, 1159, 749, 665; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.49-7.47 (d, *J* = 8.56 Hz, 1H, Ar-H), 7.32 (s, 1H, Ar-H), 7.11-7.09 (d, *J* = 8.60 Hz, 1H, Ar-H), 6.59 (s, 1H, -COCH=C of flavone), 6.53 (s, 1H, Ar-H), 6.36 (s, 1H, Ar-H), 4.82 (s, 2H, $-OCH_2$), 3.94 (s, 6H, 2 × $-OCH_3$), 389 (s, 3H, $-OCH_3$), 2.53 (s, 1H, -C≡CH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 175.63 (-CO); 163.60; 160.20; 159.45; 159.11; 149.30; 149.14; 124.09; 118.92; 113.55; 109.43; 108.25; 107.29; 96.17; 93.39; 78.81 (-C≡CH); 78.63 (-C≡CH); 56.01 ($-OCH_2$); 55.92 ($-OCH_3$); 55.88 ($-OCH_3$).

4.5.2. *2-[3,4-bis(prop-2-yn-1-yloxy)phenyl]-5,7-dimethoxy-4H-chromen-4-one (**8**)*

White solid, Yield: 74%, M.P: 160-162 °C; IR (KBr) cm^{-1}: 3301, 3210, 3006, 2916, 2851, 2120, 1638, 1602, 1514, 1260, 1159, 1016, 749, 664; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.56-7.53 (dd, *J* = 8.56, 2.48 Hz, 1H, Ar-H), 7.52-7.51 (d, *J* = 2.44 Hz, 1H, Ar-H), 7.15-7.12 (d, *J* = 8.56 Hz, 1H, Ar-H), 6.59 (s, 1H, -COCH=C of flavone), 6.54-6.53 (d, *J* = 2.44 Hz, 1H, Ar-H), 6.37-6.36 (d, *J* = 2.44 Hz, 1H, Ar-H), 4.82-4.81 (d, *J* = 2.44 Hz, 4H, 2 × $-OCH_2$), 3.94, 390, (s, each 3H, 2 × $-OCH_3$), 2.56-2.54 (m, 2H, 2 × -C≡CH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 175.77 (-CO); 163.71; 160.27; 159.40; 159.17; 149.55; 146.96; 123.90; 119.89; 113.83; 111.49; 108.27; 107.36; 96.20; 93.40; 79.06 (-C≡CH); 78.88 (-C≡CH); 78.81 (-C≡CH); 78.71 (-C≡CH); 56.34 ($-OCH_2$); 56.09 ($-OCH_2$); 55.99 ($-OCH_3$).

4.6. *General procedure for the synthesis of azides (**9a-e**)*

The aniline (1 eq) was dissolved in 6 N HCl solution (10 mL/mmol of aniline) at room temperature and cooled up to 0 °C, followed by addition of $NaNO_2$ (1.2 eq) in small portions under stirring. After 10 min of stirring at same temperature, sodium azide (1.2 eq) was added to the reaction mixture. This mixture was further stirred at room temperature for 3 h. The reaction was worked up by extraction with chloroform. The organic layer was washed with brine solution and dried over Na_2SO_4. After evaporation of the solvent, the crude product **(9a-e)** was pure enough for further reactions. All azides were stored at -20 °C.

4.7. *General procedure for the synthesis of 1,2,3-triazole building blocks[**10-14(a-e)**]*

The alkyne (**4-8**, 1 eq) and various aromatic azide (**9a-e**, 1.2 eq for **4-6**, 2.4 eq for **7** and **8**) were dissolved in *N*,*N*-dimethylformamide (20 mL/mmol of alkyne). To this reaction mixture, the solution of sodium ascorbate (0.4 eq in minimum water) was added, followed by copper (II)

sulfate pentahydrate solution (0.2 eq in minimum water). The heterogeneous mixture was stirred vigorously at room temperature until alkyne consumption as monitored by TLC. After completion of the reaction, the mixture was poured onto ice-water and the precipitate was collected by filtration. The desired product was purified by column chromatography using an eluent of 2% methanol in chloroform.

4.7.1. *(2E)-3-(4-{[1-(2-chloro-4-fluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}-3-methoxyphenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (**10a**)*

IR (KBr) cm^{-1}: 3081, 3009, 2938, 2849, 1619, 1580, 1556, 1504, 1254, 1209, 1158, 1034, 818, 752; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 14.35 (s, 1H, -OH), 8.02 (s, 1H, -C=CH of triazole), 7.80-7.76 (d, *J* = 15.60 Hz, 1H, -COC=CH), 7.73-7.69 (d, *J* = 15.60 Hz, 1H, -COCH=C), 7.59-7.55 (dd, *J* = 9.16, 5.48 Hz, 1H, Ar-H), 7.31-7.29 (dd, *J* = 7.80, 2.76 Hz, 1H, Ar-H), 7.21-7.18 (dd, *J* = 8.24, 1.84 Hz, 1H, Ar-H), 7.17-7.14 (m, 1H, Ar-H), 7.13-7.10 (m, 2H, Ar-H), 6.08-6.07 (d, *J* = 2.28 Hz, 1H, Ar-H), 5.94-6.93 (d, *J* = 2.28 Hz, 1H, Ar-H), 5.41 (s, 2H, -OCH_2), 3.90, 389, 3.81 (s, each 3H, 3 × -OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 192.36 (-CO); 168.37; 166.07; 162.37; 149.60; 149.37; 143.78; 142.27; 129.55; 129.19; 129.10; 125.90; 125.23; 121.99; 118.22; 117.96; 115.41; 115.18; 113.98; 111.33; 106.26; 93.78; 91.23; 62.90 (-OCH_2); 55.88 (-OCH_3); 55.78 (-OCH_3); 55.55 (-OCH_3); Elemental analysis for $C_{27}H_{23}ClFN_3O_6$: Calculated: C 60.06, H 4.29, N 7.78; Found: C 59.95, H 4.31, N 7.82; LC-MS (m/z): 540.13 $[M+H]^+$.

4.7.2. *(2E)-3-(4-{[1-(3-chloro-4-fluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}-3-methoxyphenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (**10b**)*

IR (KBr) cm^{-1}: 3020, 1619, 1585, 1557, 1506, 1212, 741, 667; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 14.29 (s, 1H, -OH), 7.98 (s, 1H, -C=CH of triazole), 7.78-7.72 (m, 2H, Ar-H + -

COC=CH), 7.67-7.65 (d, *J* = 15.28 Hz, 1H, -COCH=C), 7.56-7.54 (m, 1H, Ar-H), 7.26-7.22 (t, *J* = 8.52 Hz, 1H, Ar-H), 7.17-7.14 (dd, *J* = 8.56, 1.84 Hz, 1H, Ar-H), 7.06-7.03 (m, 2H, Ar-H), 6.05-6.04 (d, *J* = 2.44 Hz, 1H, Ar-H), 5.90-5.89 (d, *J* = 2.44 Hz, 1H, Ar-H), 5.35 (s, 2H, $-OCH_2$), 3.87, 3.84, 3.77 (s, each 3H, 3 × $-OCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 192.22 (-CO); 165.23; 165.18; 161.70; 158.14; 149.55; 149.20; 143.66; 142.76; 133.48; 128.26; 125.53; 123.49; 122.49; 121.04; 120.96; 120.85; 120.66; 118.21; 117.98; 113.52; 111.25; 106.43; 93.90; 91.02; 61.48 ($-OCH_2$); 56.13 ($-OCH_3$); 55.62 ($-OCH_3$); 55.53 ($-OCH_3$); Elemental analysis for $C_{27}H_{23}ClFN_3O_6$: Calculated: C 60.06, H 4.29, N 7.78; Found: C 59.96, H 4.32, N 7.76; LC-MS (m/z): 540.13 $[M+H]^+$.

4.7.3. *(2E)-3-(4-{[1-(2,4-difluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}-3-methoxyphenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (**10c**)*

IR (KBr) cm^{-1}: 2961, 2917, 2849, 1621, 1583, 1556, 1509, 1458, 1258, 1213, 1030, 815, 750; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 14.36 (s, 1H, -OH), 8.14-8.13 (d, *J* = 2.04 Hz, 1H, -C=CH of triazole), 7.95-7.89 (m, 1H, Ar-H), 7.82-7.78 (d, *J* = 15.44 Hz, 1H, -COC=CH), 7.75-7.71 (d, *J* = 15.44 Hz, 1H, -COCH=C), 7.23-7.20 (dd, *J* = 8.72, 2.00 Hz, 1H, Ar-H), 7.14-7.11 (m, 2H, Ar-H), 7.09-7.03 (m, 2H, Ar-H), 6.11-6.10 (d, *J* = 2.00 Hz, 1H, Ar-H), 5.96-6.95 (d, *J* = 2.00 Hz, 1H, Ar-H), 5.42 (s, 2H, $-OCH_2$), 3.92, 390, 3.83 (s, each 3H, 3 × $-OCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 192.39 (-CO); 168.38; 166.08; 162.39; 149.57; 149.38; 144.32; 142.31; 129.55; 126.24; 126.14; 125.90; 124.34; 124.26; 122.02; 113.83; 112.77; 112.52; 111.32; 106.28; 105.66; 105.39; 105.13; 93.79; 91.25; 62.78 ($-OCH_2$); 55.89 ($-OCH_3$); 55.80 ($-OCH_3$); 55.58 ($-OCH_3$); Elemental analysis for $C_{27}H_{23}F_2N_3O_6$: Calculated: C 61.95, H 4.43, N 8.03; Found: C 61.91, H 4.46, N 8.11; LC-MS (m/z): 524.16 $[M+H]^+$.

4.7.4. *(2E)-3-(4-{[1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}-3-methoxyphenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (**10d**)*

IR (KBr) cm^{-1}: 3009, 2938, 2846, 1617, 1582, 1555, 1505, 1249, 1209, 1153, 1030, 750; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 14.38 (s, 1H, -OH), 8.09 (s, 1H, -C=CH of triazole), 7.83-7.79 (d, *J* = 15.28 Hz, 1H, -COC=CH), 7.76-7.72 (d, *J* = 15.28 Hz, 1H, -COCH=C), 7.63-7.60 (m, 1H, Ar-H), 7.58-7.56 (m, 1H, Ar-H), 7.47-7.44 (m, 2H, Ar-H), 7.24-7.21 (dd, *J* = 8.56, 2.44 Hz, 1H, Ar-H), 7.16-7.14 (d, *J* = 7.92 Hz, 1H, Ar-H), 7.12-7.11 (d, *J* = 1.8 Hz, 1H, Ar-H), 6.11-6.10 (d, *J* = 2.44 Hz, 1H, Ar-H), 5.96-5.95 (d, *J* = 2.44 Hz, 1H, Ar-H), 5.45 (s, 2H, $-OCH_2$), 3.92, 3.91, 3.83 (s, each 3H, 3 × $-OCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 192.40 (-CO); 168.38; 166.07; 162.40; 149.62; 149.44; 142.34; 134.77; 130.85; 130.77; 130.73; 129.54; 128.60; 127.93; 127.87; 127.76; 125.89; 125.63; 125.19; 122.02; 119.66; 114.04; 111.39; 106.30; 93.80; 91.25; 62.97 ($-OCH_2$); 55.91 ($-OCH_3$); 55.80 ($-OCH_3$); 55.57 ($-OCH_3$); Elemental analysis for $C_{27}H_{24}ClN_3O_6$: Calculated: C 62.13, H 4.63, N 8.05; Found: C 62.08, H 4.66, N 8.13; LC-MS (m/z): 522.14 $[M+H]^+$.

4.7.5. *(2E)-3-(4-{[1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}-3-methoxyphenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (**10e**)*

IR (KBr) cm^{-1}: 3020, 2919, 2852, 1617, 1582, 1551, 1505, 1255, 1215, 750; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 14.29 (s, 1H, -OH), 8.00 (s, 1H, -C=CH of triazole), 7.76-7.72 (d, *J* = 15.28 Hz, 1H, -COC=CH), 7.69-7.65 (d, *J* = 15.88 Hz, 1H, -COCH=C), 7.63-7.60 (d, *J* = 9.16 Hz, 2H, Ar-H), 7.44-7.42 (d, *J* = 7.92 Hz, 2H, Ar-H), 7.17-7.14 (dd, *J* = 8.56, 1.84 Hz, 1H, Ar-H), 7.07-7.05 (m, 2H, Ar-H), 6.05-6.04 (d, *J* = 2.44 Hz, 1H, Ar-H), 5.90-5.89 (d, *J* = 2.44 Hz, 1H, Ar-H), 5.35 (s, 2H, $-OCH_2$), 3.87, 3.84, 3.77 (s, each 3H, 3 × $-OCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 192.37 (-CO); 168.39; 166.09; 162.38; 149.49; 149.32; 142.26; 135.37;

134.73; 129.96; 129.53; 125.93; 121.98; 121.73; 121.14; 113.65; 111.31; 106.28; 93.80; 91.26; 62.83 (-OCH_2); 55.89 (-OCH_3); 55.79 (-OCH_3); 55.58 (-OCH_3); Elemental analysis for $C_{27}H_{24}ClN_3O_6$: Calculated: C 62.13, H 4.63, N 8.05; Found: C 62.10, H 4.65, N 8.09; LC-MS (m/z): 522.14 $[M+H]^+$.

4.7.6. *(2E)-3-(3-{[1-(2-chloro-4-fluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}-4-methoxyphenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (**11a**)*

IR (KBr) cm^{-1}: 3077, 3012, 2938, 2838, 1617, 1580, 1554, 1509, 1258, 1210, 1154, 1027, 821, 752; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 14.40 (s, 1H, -OH), 8.00 (s, 1H, -C=CH of triazole), 7.82-7.79 (d, *J* = 15.24 Hz, 1H, -COC=CH), 7.74-7.70 (d, *J* = 15.88 Hz, 1H, -COCH=C), 7.59-7.55 (dd, *J* = 9.16, 5.48 Hz, 1H, Ar-H), 7.40-7.39 (d, *J* = 1.84 Hz, 1H, Ar-H), 7.31-7.28 (dd, *J* = 7.92, 2.44 Hz, 1H, Ar-H), 7.20-7.18 (dd, *J* = 8.56, 1.84 Hz, 1H, Ar-H), 7.17-7.12 (m, 1H, Ar-H), 6.90-6.88 (d, *J* = 7.92 Hz, 1H, Ar-H), 6.08-6.07 (d, *J* = 2.44 Hz, 1H, Ar-H), 5.95-6.94 (d, *J* = 1.84 Hz, 1H, Ar-H), 5.44 (s, 2H, -OCH_2), 3.95, 390, 3.82 (s, each 3H, 3 × -OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 192.44 (-CO); 168.38; 166.09; 162.57; 151.68; 147.61; 142.34; 129.20; 129.11; 128.64; 125.56; 125.28; 124.49; 118.23; 117.96; 115.39; 115.17; 113.10; 111.58; 106.30; 93.74; 91.20; 63.11 (-OCH_2); 55.99 (-OCH_3); 5.96 (-OCH_3); 55.54 (-OCH_3); Elemental analysis for $C_{27}H_{23}ClFN_3O_6$: Calculated: C 60.06, H 4.29, N 7.78; Found: C 60.01, H 4.26, N 7.82; LC-MS (m/z): 540.13 $[M+H]^+$.

4.7.7. *(2E)-3-(3-{[1-(3-chloro-4-fluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}-4-methoxyphenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (**11b**)*

IR (KBr) cm^{-1}: 2922, 2846, 1624, 1582, 1552, 1509, 1440, 1265, 1210, 1157, 1033, 818, 763; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 14.33 (s, 1H, -OH), 7.99 (s, 1H, -C=CH of triazole), 7.78-7.73 (m, 2H, Ar-H + -COC=CH), 7.69-7.65 (d, *J* = 15.88 Hz, 1H, -COCH=C), 7.56-7.52

(m, 1H, Ar-H), 7.33-7.32 (d, *J* = 1.84 Hz, 1H, Ar-H), 7.26-7.21 (t, *J* = 8.56 Hz, 1H, Ar-H), 7.16-7.13 (dd, *J* = 8.52, 1.84 Hz, 1H, Ar-H), 6.86-6.84 (d, *J* = 8.56 Hz, 1H, Ar-H), 6.04-6.03 (d, *J* = 1.84 Hz, 1H, Ar-H), 5.91-5.90 (d, *J* = 2.44 Hz, 1H, Ar-H), 5.36 (s, 2H, -OCH_2), 3.91, 3.87, 3.77 (s, each 3H, 3 × -OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 192.44 (-CO); 168.40; 166.12; 162.57; 156.79; 151.55; 147.41; 142.28; 128.72; 125.67; 124.31; 123.15; 120.36; 120.29; 117.78; 117.55; 112.75; 111.63; 106.34; 93.79; 91.24; 62.97 (-OCH_2); 56.01 (-OCH_3); 55.95 (-OCH_3); 55.55 (-OCH_3); Elemental analysis for $C_{27}H_{23}ClFN_3O_6$: Calculated: C 60.06, H 4.29, N 7.78; Found: C 60.00, H 4.27, N 7.74; LC-MS (m/z): 540.13 $[M+H]^+$.

4.7.8. *(2E)-3-(3-{[1-(2,4-difluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}-4-methoxyphenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one ne (**11c**)*

IR (KBr) cm^{-1}: 2958, 2917, 2846, 1607, 1575, 1504, 1209, 1142, 1009, 822; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 14.32 (s, 1H, -OH), 8.08-8.07 (d, *J* = 2.72 Hz, 1H, -C=CH of triazole), 7.88-7.82 (m, 1H, Ar-H), 7.78-7.74 (d, *J* = 14.68 Hz, 1H, -COC=CH), 7.70-7.66 (d, *J* = 14.68 Hz, 1H, -COCH=C), 7.37 (s, 1H, Ar-H), 7.16-7.13 (dd, *J* = 8.24, 1.84 Hz, 1H, Ar-H), 7.02-6.97 (m, 2H, Ar-H), 6.86-6.84 (d, *J* = 8.28 Hz, 1H, Ar-H), 6.04-6.03 (d, *J* = 2.76 Hz, 1H, Ar-H), 5.91-6.90 (d, *J* = 1.80 Hz, 1H, Ar-H), 5.37 (s, 2H, -OCH_2), 3.91, 386, 3.77 (s, each 3H, 3 × -OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 192.17 (-CO); 168.50; 165.93; 162.20; 149.62; 149.29; 144.15; 142.10; 129.37; 126.21; 126.05; 125.73; 124.26; 121.81; 113.67; 112.62; 111.15; 106.15; 105.30; 93.91; 91.04; 62.62 (-OCH_2); 55.95 (-OCH_3); 55.73 (-OCH_3); 55.52 (-OCH_3); Elemental analysis for $C_{27}H_{23}F_2N_3O_6$: Calculated: C 61.95, H 4.43, N 8.03; Found: C 61.91, H 4.45, N 8.07; LC-MS (m/z): 524.16 $[M+H]^+$.

4.7.9. *(2E)-3-(3-{[1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}-4-methoxyphenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (**11d**)*

IR (KBr) cm^{-1}: 3015, 2917, 2852, 1617, 1582, 1557, 1510, 1260, 1215, 1153, 1031, 817, 750; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 14.39 (s, 1H, -OH), 8.06 (s, 1H, -C=CH of triazole), 7.83-7.79 (d, *J* = 15.28 Hz, 1H, -COC=CH), 7.75-7.71 (d, *J* = 15.88 Hz, 1H, -COCH=C), 7.61-7.58 (m, 1H, Ar-H), 7.56-7.53 (m, 1H, Ar-H), 7.44-7.42 (m, 3H, Ar-H), 7.20-7.18 (dd, *J* = 8.56, 1.84 Hz, 1H, Ar-H), 6.91-6.89 (d, *J* = 7.96 Hz, 1H, Ar-H), 6.09-6.08 (d, *J* = 1.84 Hz, 1H, Ar-H), 5.96-5.95 (d, *J* = 2.44 Hz, 1H, Ar-H), 5.45 (s, 2H, $-OCH_2$), 3.96, 3.91, 3.82 (s, each 3H, 3 × $-OCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 192.45 (-CO); 168.36; 166.06; 162.58; 151.70; 147.65; 142.37; 134.77; 130.84; 130.75; 128.67; 128.63; 127.90; 127.74; 125.53; 125.22; 124.53; 113.05; 111.55; 106.30; 93.72; 91.17; 63.16 ($-OCH_2$); 55.97 ($-OCH_3$); 55.52 ($-OCH_3$); Elemental analysis for $C_{27}H_{24}ClN_3O_6$: Calculated: C 62.13, H 4.63, N 8.05; Found: C 62.09, H 4.60, N 8.08; LC-MS (m/z): 522.14 $[M+H]^+$.

4.7.10. *(2E)-3-(3-{[1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}-4-methoxyphenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (**11e**)*

IR (KBr) cm^{-1}: 2958, 2917, 2846, 1611, 1575, 1544, 1504, 1264, 1198, 1142, 978, 815, 755; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 14.33 (s, 1H, -OH), 8.00 (s, 1H, -C=CH of triazole), 7.78-7.74 (d, *J* = 15.24 Hz, 1H, -COC=CH), 7.69-7.65 (d, *J* = 15.28 Hz, 1H, -COCH=C), 7.62-7.60 (d, *J* = 8.52 Hz, 2H, Ar-H), 7.44-7.42 (d, *J* = 9.16 Hz, 2H, Ar-H), 7.35-7.34 (d, *J* = 1.80 Hz, 1H, Ar-H), 7.16-7.13 (dd, *J* = 8.52, 2.44 Hz, 1H, Ar-H), 6.86-6.84 (d, *J* = 8.52 Hz, 1H, Ar-H), 6.04-6.03 (d, *J* = 2.44 Hz, 1H, Ar-H), 5.91-5.90 (d, *J* = 2.44 Hz, 1H, Ar-H), 5.37 (s, 2H, $-OCH_2$), 3.91, 3.86, 3.77 (s, each 3H, 3 × $-OCH_3$); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 192.23 (-CO); 165.22; 161.69; 149.61; 149.22; 142.79; 142.47; 131.20; 130.21; 128.24; 127.26; 125.51; 122.40; 118.01; 117.74; 115.75; 115.52; 113.62; 111.17; 106.44; 93.91; 91.05; 61.41 ($-OCH_2$); 56.05 ($-OCH_3$); 55.62 ($-OCH_3$); 55.53 ($-OCH_3$); Elemental analysis for $C_{27}H_{24}ClN_3O_6$:

Calculated: C 62.13, H 4.63, N 8.05; Found: C 62.15, H 4.60, N 8.10; LC-MS (m/z): 522.14 $[M+H]^+$.

4.7.11. *(2E)-3-[3,4-bis({[1-(2-chloro-4-fluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy})phenyl]-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (**12a**)*

IR (KBr) cm^{-1}: 3077, 3011, 2924, 2851, 1622, 1582, 1557, 1508, 1264, 1213, 1030, 816, 749; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 14.28 (s, 1H, -OH), 7.99, 7.95 (s, each 1H, 2 × -C=CH of triazole), 7.77-7.73 (d, *J* = 15.28 Hz, 1H, -COC=CH), 7.67-7.63 (d, *J* = 15.24 Hz, 1H, -COCH=C), 7.54-7.49 (m, 2H, Ar-H), 7.32-7.31 (d, *J* = 1.84 Hz, 1H, Ar-H), 7.25-7.21 (m, 2H, Ar-H), 7.18-7.15 (dd, *J* = 8.56, 1.84 Hz, 1H, Ar-H), 7.11-7.05 (m, 3H, Ar-H), 6.04-6.03 (d, *J* = 2.44 Hz, 1H, Ar-H), 5.90-5.89 (d, *J* = 2.44 Hz, 1H, Ar-H), 5.36, 5.35 (s, each 2H, 2 × $-OCH_2$), 3.89, 3.77 (s, each 3H, 2 × $-OCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 192.38 (-CO); 168.40; 166.17; 163.91; 162.54; 161.37; 150.28; 148.27; 141.92; 131.26; 131.22; 130.18; 130.15; 129.83; 129.19; 129.10; 126.17; 125.33; 125.30; 124.02; 118.23; 117.97; 115.41; 115.40; 115.18; 114.81; 114.69; 106.30; 93.78; 91.23; 63.39 ($-OCH_2$); 63.08 ($-OCH_2$); 55.96 ($-OCH_3$); 55.56 ($-OCH_3$); Elemental analysis for $C_{35}H_{26}Cl_2F_2N_6O_6$: Calculated: C 57.15, H 3.56, N 11.43; Found: C 57.11, H 3.58, N 11.46; LC-MS (m/z): 735.13 $[M+H]^+$.

4.7.12. *((2E)-3-[3,4-bis({[1-(3-chloro-4-fluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy})phenyl]-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-o (**12b**)*

IR (KBr) cm^{-1}: 2922, 2846, 1627, 1582, 1555, 1505, 1255, 1215, 1030, 817, 754; ^1H NMR (DMSO-d_6, 400 MHz, ppm) δ: 13.44 (s, 1H, -OH), 8.67, 8.65 (s, each 1H, 2 × -C=CH of triazole), 7.82-7.77 (m, 3H, Ar-H + -COCH=CH), 7.71-7.60 (m, 3H, Ar-H), 7.52-7.45 (m, 3H, Ar-H), 7.36-7.30 (m, 2H, Ar-H), 6.14 (s, 1H, Ar-H), 6.12 (s, 1H, Ar-H), 5.35, 5.32 (s, each 2H, 2 × $-OCH_2$), 3.89, 3.81 (s, each 3H, 2 × $-OCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 192.44 (-

CO); 168.28; 166.10; 163.91; 162.46; 161.37; 150.33; 148.20; 142.02; 131.22; 130.26; 130.07; 129.83; 129.19; 129.09; 126.29; 125.20; 123.93; 118.29; 118.06; 115.72; 115.29; 114.74; 114.55; 106.21; 93.90; 91.14; 63.51 (-OCH_2); 63.93 (-OCH_2); 55.96 (-OCH_3); 55.56 (-OCH_3); Elemental analysis for $C_{35}H_{26}Cl_2F_2N_6O_6$: Calculated: C 57.15, H 3.56, N 11.43; Found: C 57.11, H 3.58, N 11.40; LC-MS (m/z): 735.13 $[M+H]^+$.

4.7.13. *(2E)-3-[3,4-bis({[1-(2,4-difluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy})phenyl]-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (**12c**)*

IR (KBr) cm^{-1}: 3086, 3014, 2924, 2851, 1617, 1582, 1556, 1518, 1260, 1215, 753; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 14.33 (s, 1H, -OH), 8.14-8.13 (d, *J* = 2.44 Hz, 1H, -C=CH of triazole), 8.12 (s, 1H, -C=CH of triazole), 7.92-7.85 (m, 2H, Ar-H), 7.83-7.79 (d, *J* = 15.88 Hz, 1H, -COC=CH), 7.73-7.69 (d, *J* = 15.24 Hz, 1H, -COCH=C), 7.39 (s, 1H, Ar-H), 7.23-7.21 (dd, *J* = 8.56, 1.84 Hz, 1H, Ar-H), 7.13-7.11 (d, *J* = 8.56 Hz, 1H, Ar-H), 7.08-6.98 (m, 4H, Ar-H), 6.09-6.08 (d, *J* = 1.80 Hz, 1H, Ar-H), 5.96-6.95 (d, *J* = 2.44 Hz, 1H, Ar-H), 5.40 (s, 4H, 2 × -OCH_2), 3.95, 3.82 (s, each 3H, 2 × -OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 192.43 (-CO); 168.40; 166.18; 163.83; 163.73; 162.57; 150.25; 148.37; 141.95; 129.89; 126.27; 126.24; 126.17; 124.32; 124.26; 123.95; 114.73; 114.52; 112.73; 112.50; 106.37; 105.62; 105.37; 105.13; 93.82; 91.27; 63.37 (-OCH_2); 63.05 (-OCH_2); 55.94 (-OCH_3); 55.57 (-OCH_3); Elemental analysis for $C_{35}H_{26}F_4N_6O_6$: Calculated: C 59.83, H 3.73, N 11.96; Found: C 59.79, H 3.77, N 11.92; LC-MS (m/z): 703.19 $[M+H]^+$.

4.7.14. *(2E)-3-[3,4-bis({[1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl]methoxy})phenyl]-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (**12d**)*

IR (KBr) cm^{-1}: 3015, 2928, 2847, 1622, 1577, 1557, 1495, 1250, 1215, 1031, 745, 664; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 14.39 (s, 1H, -OH), 8.09, 8.06 (s, each 1H, 2 × -C=CH of

triazole), 7.84-7.80 (d, *J* = 15.28 Hz, 1H, -COC=CH), 7.75-7.71 (d, *J* = 15.88 Hz, 1H, -COCH=C), 7.61-7.52 (m, 4H, Ar-H), 7.47-7.40 (m, 5H, Ar-H), 7.24-7.22 (dd, *J* = 8.56, 1.24 Hz, 1H, Ar-H), 7.15-7.13 (d, *J* = 7.92 Hz, 1H, Ar-H), 6.10-6.09 (d, *J* = 1.84 Hz, 1H, Ar-H), 5.97-5.96 (d, *J* = 2.44 Hz, 1H, Ar-H), 5.44, 5.43 (s, each 2H, 2 × -OCH_2), 3.96, 3.83 (s, each 3H, 2 × -OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 192.42 (-CO); 168.38; 166.13; 162.56; 150.31 148.29; 142.03; 134.74; 130.82; 130.74; 129.74; 128.66; 128.58; 127.92; 127.90; 127.74; 126.08; 125.23; 124.09; 114.70; 114.49; 106.31; 93.75; 91.21; 63.41 (-OCH_2); 63.11 (-OCH_2); 55.97 (-OCH_3); 55.55 (-OCH_3); Elemental analysis for $C_{35}H_{28}Cl_2N_6O_6$: Calculated: C 60.09, H 4.03, N 12.01; Found: C 60.00, H 4.07, N 11.98; LC-MS (m/z): 699.15 $[M+H]^+$.

4.7.15. *(2E)-3-[3,4-bis({[1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl]methoxy})phenyl]-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (**12e**)*

IR (KBr) cm^{-1}: 2958, 2922, 2850, 1616, 1575, 1504, 1264, 1213, 1101, 1025, 810, 770; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 14.27 (s, 1H, -OH), 8.13, 8.09 (s, each 1H, 2 × -C=CH of triazole), 7.77-7.73 (d, *J* = 15.24 Hz, 1H, -COC=CH), 7.67-7.61 (m, 5H, -COCH=C + Ar-H), 7.44-7.41 (m, 4H, Ar-H), 7.32 (s, 1H, Ar-H), 7.18 (s, 1H, Ar-H), 7.07-7.05 (d, *J* = 7.96 Hz, 1H, Ar-H), 6.04-6.03 (d, *J* = 1.84 Hz, 1H, Ar-H), 5.91-5.90 (d, *J* = 2.44 Hz, 1H, Ar-H), 5.33 (s, 4H, 2 × -OCH_2), 3.89, 3.77 (s, each 3H, 2 × -OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 192.35 (-CO); 168.26; 166.22; 162.50; 150.24 148.18; 141.96; 134.67; 130.82; 129.64; 128.60; 127.91; 127.74; 125.99; 125.11; 123.93; 114.77; 114.49; 106.40; 93.64; 91.21; 63.54 (-OCH_2); 62.99 (-OCH_2); 55.83 (-OCH_3); 55.39 (-OCH_3); Elemental analysis for $C_{35}H_{28}Cl_2N_6O_6$: Calculated: C 60.09, H 4.03, N 12.01; Found: C 60.01, H 4.00, N 12.05; LC-MS (m/z): 699.15 $[M+H]^+$.

4.7.16. *2-(4-{[1-(2-chloro-4-fluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}-3-methoxyphenyl)-5,7-dimethoxy-4H-chromen-4-one (**13a**)*

IR (KBr) cm^{-1}: 3004, 2959, 2917, 2852, 1638, 1602, 1510, 1163, 1016, 821, 746; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.99 (s, 1H, -C=CH of triazole), 7.56-7.52 (dd, *J* = 9.16, 5.48 Hz, 1H, Ar-H), 7.46-7.44 (dd, *J* = 8.56, 1.84 Hz, 1H, Ar-H), 7.28-7.25 (m, 2H, Ar-H), 7.16-7.14 (d, *J* = 8.56 Hz, 1H, Ar-H), 7.13-7.08 (m, 1H, Ar-H), 7.55 (s, 1H, -COCH=C of flavone), 6.50-6.49 (d, *J* = 1.80 Hz, 1H, Ar-H), 6.32-6.31 (d, *J* = 2.44 Hz, 1H, Ar-H), 5.40 (s, 2H, $-OCH_2$), 3.90, 389, 3.85 (s, each 3H, 3 × $-OCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 177.60 (-CO); 163.99; 163.92; 161.38; 160.87; 160.41; 159.81; 150.13; 149.71; 143.59; 131.26; 130.20; 129.21; 129.12; 125.27; 125.01; 119.38; 118.25; 117.99; 115.42; 115.21; 113.77; 109.07; 108.14; 96.12; 92.82; 62.91 ($-OCH_2$); 56.41 ($-OCH_3$); 56.11 ($-OCH_3$); 55.76 ($-OCH_3$); Elemental analysis for $C_{27}H_{21}ClFN_3O6$: Calculated: C 60.29, H 3.93, N 7.81; Found: C 60.21, H 3.97, N 7.85; LC-MS (m/z): 538.12 $[M+H]^+$.

4.7.17. *2-(4-{[1-(3-chloro-4-fluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}-3-methoxyphenyl)-5,7-dimethoxy-4H-chromen-4-one (**13b**)*

IR (KBr) cm^{-1}: 3087, 3011, 2924, 2847, 1638, 1602, 1510, 1322, 1255, 1163, 1031, 821, 756; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 8.00 (s, 1H, -C=CH of triazole), 7.79-7.77 (dd, *J* = 6.12, 2.44 Hz, 1H, Ar-H), 7.58-7.54 (m, 1H, Ar-H), 7.46-7.43 (dd, *J* = 7.96, 1.84 Hz, 1H, Ar-H), 7.28-7.22 (m, 2H, Ar-H), 7.13-7.11 (d, *J* = 8.52 Hz, 1H, Ar-H), 6.54 (s, 1H, -COCH=C of flavone), 6.49-6.48 (d, *J* = 2.44 Hz, 1H, Ar-H), 6.32-6.31 (d, *J* = 1.84 Hz, 1H, Ar-H), 5.37 (s, 2H, $-OCH_2$), 3.90, 3.89, 3.85 (s, each 3H, 3 × $-OCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 177.58 (-CO); 163.99; 160.87; 160.35; 159.80; 156.79; 150.02; 149.62; 133.43; 125.07; 123.13; 122.53; 121.31; 120.35; 120.28; 119.37; 117.79; 117.57; 113.44; 109.02; 96.11; 92.82; 62.77 ($-OCH_2$); 56.40 ($-OCH_3$); 56.11 ($-OCH_3$); 55.74 ($-OCH_3$); Elemental analysis for $C_{27}H_{21}ClFN_3O6$:

Calculated: C 60.29, H 3.93, N 7.81; Found: C 60.22, H 3.97, N 7.78; LC-MS (m/z): 538.12 $[M+H]^+$.

4.7.18. *2-(4-{[1-(2,4-difluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}-3-methoxyphenyl)-5,7-dimethoxy-4H-chromen-4-one (**13c**)*

IR (KBr) cm^{-1}: 3014, 2922, 2850, 1636, 1600, 1515, 1213, 739, 663; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 8.09-8.08 (d, *J* = 2.76 Hz, 1H, -C=CH of triazole), 7.89-7.83 (m, 1H, Ar-H), 7.45-7.42 (dd, *J* = 8.28, 1.84 Hz, 1H, Ar-H), 7.27-7.26 (d, *J* = 1.80 Hz, 1H, Ar-H), 7.16-7.14 (d, *J* = 8.28 Hz, 1H, Ar-H), 7.02-6.97 (m, 2H, Ar-H), 6.54 (s, 1H, -COCH=C of flavone), 6.49-6.48 (d, *J* = 1.84 Hz, 1H, Ar-H), 6.32-6.31 (d, *J* = 1.80 Hz, 1H, Ar-H), 5.38 (s, 2H, $-OCH_2$), 3.89 (s, 6H, 2 × $-OCH_3$), 3.85 (s, 3H, $-OCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 177.64 (-CO); 163.97; 160.86; 159.81; 150.12; 149.68; 126.24; 126.13; 124.99; 124.38; 124.34; 124.29; 119.37; 113.65; 112.78; 112.74; 112.55; 112.52; 109.05; 105.66; 105.42; 105.39; 105.16; 96.11; 92.82; 62.77 ($-OCH_2$); 56.41 ($-OCH_3$); 56.10 ($-OCH_3$); 55.75 ($-OCH_3$); Elemental analysis for $C_{27}H_{21}F_2N_3O_6$: Calculated: C 62.19, H 4.06, N 8.06; Found: C 62.24, H 4.01, N 8.03; LC-MS (m/z): 522.15 $[M+H]^+$.

4.7.19. *2-(4-{[1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}-3-methoxyphenyl)-5,7-dimethoxy-4H-chromen-4-one (**13d**)*

IR (KBr) cm^{-1}: 3007, 2966, 2934, 2838, 1638, 1599, 1316, 1212, 1019, 745, 664; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 8.04 (s, 1H, -C=CH of triazole), 7.57-7.54 (m, 1H, Ar-H), 7.52-7.50 (m, 1H, Ar-H), 7.46-7.43 (dd, *J* = 8.56, 1.84 Hz, 1H, Ar-H), 7.42-7.36 (m, 2H, Ar-H), 7.27-7.26 (d, *J* = 1.84 Hz, 1H, Ar-H), 7.17-7.15 (d, *J* = 8.56 Hz, 1H, Ar-H), 6.54 (s, 1H, -COCH=C of flavone), 6.50-6.49 (d, *J* = 1.84 Hz, 1H, Ar-H), 6.32-6.31 (d, *J* = 1.84 Hz, 1H, Ar-H), 5.41 (s, 2H, $-OCH_2$), 3.89 (s, 6H, 2 × $-OCH_3$) 3.85 (s, 3H, $-OCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm)

δ: 177.65 (-CO); 163.99; 160.94; 160.47; 159.70; 150.13; 149.70; 143.59; 131.32; 130.16; 129.33; 129.11; 125.27; 125.00; 119.43; 118.20; 117.93; 115.38; 115.17; 113.71; 109.06; 108.04; 96.23; 92.69; 62.82 (-OCH_2); 56.49 (-OCH_3); 56.24 (-OCH_3); 55.60 (-OCH_3); Elemental analysis for $C_{27}H_{22}ClN_3O_6$: Calculated: C 62.37, H 4.26, N 8.08; Found: C 62.42, H 4.22, N 8.02; LC-MS (m/z): 520.13 $[M+H]^+$.

4.7.20. *2-(4-{[1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}-3-methoxyphenyl)-5,7-dimethoxy-4H-chromen-4-one (**13e**)*

IR (KBr) cm^{-1}: 3016, 2927, 2852, 1638, 1603, 1215, 741, 665; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 8.02 (s, 1H, -C=CH of triazole), 7.63-7.61 (d, *J* = 8.52 Hz, 2H, Ar-H), 7.45-7.43 (d, *J* = 8.56 Hz, 3H, Ar-H), 7.27 (s, 1H, Ar-H), 7.14-7.12 (d, *J* = 8.56 Hz, 1H, Ar-H), 6.54 (s, 1H, -COCH=C of flavone), 6.49 (s, 1H, Ar-H), 6.31 (s, 1H, Ar-H), 5.38 (s, 2H, -OCH_2), 3.90 (s, 6H, 2 × -OCH_3), 3.85 (s, 3H, -OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 177.61 (-CO); 163.99; 160.86; 160.40; 159.80; 150.07; 149.60; 135.34; 134.75; 129.96; 124.95; 121.73; 121.18; 119.39; 113.44; 109.00; 96.11; 92.82; 62.80 (-OCH_2); 56.41 (-OCH_3); 56.09 (-OCH_3); 55.75 (-OCH_3); Elemental analysis for $C_{27}H_{22}ClN_3O_6$: Calculated: C 62.37, H 4.26, N 8.08; Found: C 62.33, H 4.28, N 8.05; LC-MS (m/z): 520.13 $[M+H]^+$.

4.7.21. *2-[3,4-bis({[1-(2-chloro-4-fluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy})phenyl]-5,7-dimethoxy-4H-chromen-4-one (**14a**)*

IR (KBr) cm^{-1}: 3076, 2998, 2938, 1642, 1602, 1510, 1260, 1162, 821, 750; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 8.06, 8.04 (s, each 1H, 2 × -C=CH of triazole), 7.60-7.55 (m, 3H, Ar-H), 7.52-7.49 (dd, *J* = 8.56, 2.44 Hz, 1H, Ar-H), 7.30-7.27 (m, 2H, Ar-H), 7.21-7.19 (d, *J* = 8.52 Hz, 1H, Ar-H), 7.17-7.12 (m, 2H, Ar-H), 6.59 (s, 1H, -COCH=C of flavone), 6.58 (s, 1H, Ar-H), 6.37-6.36 (d, *J* = 2.20 Hz, 1H, Ar-H), 5.43 (s, 4H, 2 × -OCH_2), 3.94, 391 (s, each 3H, 2 × -

OCH_3); Elemental analysis for $C_{35}H_{24}Cl_2F_2N_6O_6$: Calculated: C 57.31, H 3.30, N 11.46; Found: C 57.28, H 3.31, N 11.45; LC-MS (m/z): 733.12 $[M+H]^+$.

4.7.22. *2-[3,4-bis({[1-(3-chloro-4-fluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy})phenyl]-5,7-dimethoxy-4H-chromen-4-one (**14b**)*

IR (KBr) cm^{-1}: 3076, 3020, 2922, 2852, 1647, 1607, 1510, 1215, 821, 754, 669; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 8.06, 8.04 (s, each 1H, 2 × -C=CH of triazole), 7.58-7.57 (d, *J* = 2.44 Hz, 1H, Ar-H), 7.55-7.52 (m, 2H, Ar-H), 7.50-7.47 (m, 2H, Ar-H), 7.40-7.36 (m, 3H, Ar-H), 7.17-7.15 (d, *J* = 8.56 Hz, 1H, Ar-H), 6.55 (s, 1H, -COCH=C of flavone), 6.54 (s, 1H, Ar-H), 6.32-6.31 (d, *J* = 2.44 Hz, 1H, Ar-H), 5.40, 5.39 (s, each 2H, 2 × $-OCH_2$), 3.89, 3.86 (s, each 3H, 2 × $-OCH_3$); Elemental analysis for $C_{35}H_{24}Cl_2F_2N_6O_6$: Calculated: C 57.31, H 3.30, N 11.46; Found: C 57.35, H 3.28, N 11.41; LC-MS (m/z): 733.12 $[M+H]^+$.

4.7.23. *2-[3,4-bis({[1-(2,4-difluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy})phenyl]-5,7-dimethoxy-4H-chromen-4-one (**14c**)*

IR (KBr) cm^{-1}: 3021, 1641, 1603, 1519, 1216, 734, 668; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 8.09, 8.06 (s, each 1H, 2 × -C=CH of triazole), 7.92-7.81 (m, 2H, Ar-H), 7.57-7.42 (m, 2H, Ar-H), 7.16-6.94 (m, 5H, Ar-H), 6.53 (s, 1H, -C=CH of flavone), 6.52 (s, 1H, Ar-H), 6.31 (s, 1H, Ar-H), 5.37, 5.36 (s, each 2H, 2 × $-OCH_2$), 3.89, 3.86 (s, each 3H, 2 × $-OCH_3$); Elemental analysis for $C_{35}H_{24}F_4N_6O_6$: Calculated: C 60.00, H 3.45, N 12.01; Found: C 60.06, H 3.42, N 11.96; LC-MS (m/z): 701.18 $[M+H]^+$.

4.7.24. *2-[3,4-bis({[1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl]methoxy})phenyl]-5,7-dimethoxy-4H-chromen-4-one (**14d**)*

IR (KBr) cm^{-1}: 3146, 3086, 3003, 2941, 1636, 1600, 1493, 1255, 1158, 1034, 823, 752; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 8.10, 8.08 (s, each 1H, 2 × -C=CH of triazole), 7.62-7.61 (d, *J*

= 1.84 Hz, 1H, Ar-H), 7.60-7.57 (m, 2H, Ar-H), 7.54-7.49 (m, 3H, Ar-H), 7.44-7.40 (m, 4H, Ar-H), 7.21-7.19 (d, *J* = 8.52 Hz, 1H, Ar-H), 6.60 (s, 1H, -COCH=C of flavone), 5.59 (s, 1H, Ar-H), 6.36-6.35 (d, *J* = 1.84 Hz, 1H, Ar-H), 5.44 (s, 4H, 2 × -OCH_2), 3.94, 3.91 (s, each 3H, 2 × -OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 177.50 (-CO); 164.05; 160.86; 159.82; 151.12; 148.41; 134.75; 130.83; 130.75; 128.62; 127.91; 127.74; 125.63; 125.31; 125.24; 120.74; 114.86; 113.54; 108.19; 96.27; 92.86; 63.78 (-OCH_2); 63.17 (-OCH_2); 56.38 (-OCH_3); 55.80 (-OCH_3); Elemental analysis for $C_{35}H_{26}Cl_2N_6O_6$: Calculated: C 60.27, H 3.76, N 12.05; Found: C 60.23, H 3.79, N 12.11; LC-MS (m/z): 697.13 $[M+H]^+$.

4.7.25. *2-[3,4-bis({[1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl]methoxy})phenyl]-5,7-dimethoxy-4H-chromen-4-one (**14e**)*

IR (KBr) cm^{-1}: 3141, 2928, 2846, 1647, 1607, 1505, 1260, 826; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 8.17, 8.13 (s, each 1H, 2 × -C=CH of triazole), 7.65-7.57 (m, 6H, Ar-H), 7.47-7.40 (m, 4H, Ar-H), 7.08-7.05 (d, *J* = 9.16 Hz, 1H, Ar-H), 6.54 (s, 1H, -COCH=C of flavone), 6.53 (s, 1H, Ar-H), 6.32-6.31 (d, *J* = 1.20 Hz, 1H, Ar-H), 5.36, 5.35 (s, each 2H, 2 × -OCH_2), 3.90, 3.87 (s, each 3H, 2 × -OCH_3); Elemental analysis for $C_{35}H_{26}Cl_2N_6O_6$: Calculated: C 60.27, H 3.76, N 12.05; Found: C 60.31, H 3.74, N 12.11; LC-MS (m/z): 697.13 $[M+H]^+$.

4.8. *X-ray crystallographic analysis*

The structure of the compound **10e** was determined by X-ray crystallographic analysis. A good quality single crystal of **10e** was obtained through the slow evaporation of its *N,N*-dimethylformamide solution at room temperature. The selected crystal was mounted on glass fiber and used for data collection. The data was collected at 293 K by the X-ray scan technique on an Oxford Diffraction Xcalibur four-circle diffractometer using graphite mono-chromatized Mo-*Ka* radiation (λ = 0.71073 Å). The data were corrected for Lorentz-polarization as well as for

absorption effects [43]. The crystal structure was solved by direct methods using the program SHELXS-97 [44] and refined by full-matrix least-squares technique on F^2 by SHELXL-97 [44]. All non-hydrogen atoms were refined anisotropically. Hydrogen atom bonded to oxygen atom in the compound was located in a difference Fourier map and refined isotropically, O–H = 0.820 Å with U_{iso}(H) = 1.5 U_{eq}(O). The other hydrogen atoms were positioned geometrically and refined as riding atoms with C–H = 0.930 Å (CH), C–H = 0.970 Å (CH_2), C–H = 0.960 Å (CH_3), and U_{iso}(H) = 1.2, 1.5 U_{eq} (C). The thermal ellipsoid plot was prepared by using ORTEP III [45]. The crystallographic data, data collection and structure refinement details are given in Table 2.

4.9. *Biological assays*

4.9.1. *Determination of antimicrobial activity*

The *in vitro* antimicrobial studies were carried out by using six bacterial strains viz. *S. aureus* (ATCC 25323), *E. faecalis* (ATCC 29212), *E. coli* (ATCC 35218), *P. aeruginosa* (ATCC 27893), *S. boydii* (clinical isolate) and *K. pneumoniae* (ATCC 27736) and eight fungal strains viz. *C. albicans* (ATCC 90028), *C. albicans* (clinical), *C. tropicalis* (ATCC 750), *C. parapsilosis* (ATCC 22019), *Cryptococcus neoformans* (clinical), *Dermatophyte* (clinical), *A. niger* (clinical) and *A. fumigatus* (clinical). All cultures were preserved at Department of Microbiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India. The cultures are used in the investigation, were obtained from American Type Culture Collection (ATCC) and clinical strain. The fresh microbial broth cultures were prepared in normal saline before the screening procedure. Ciprofloxacin and fluconazole were used as standard drug for antibacterial and antifungal activities, respectively. Minimum inhibitory concentration (MIC) of all compounds was determined by micro-dilution method [46] using a series of dilution at various

concentrations. Different concentrations of the compounds (100, 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78 µg/mL) were serially diluted in microtiter plate. Specifically, 0.01 mL of standardized inoculums (1-2 × 10^7 cfu/mL) was added in each tube of microtiter plate. The plates were incubated aerobically at 37 °C for 18-24 h. The lowest concentration of the compounds showed no visible bacterial growth and no turbidity in the solution when it was compared with the control regarded as the MIC. Mueller-Hinton agar and Luria broth (Hi-media, Mumbai, India), were used for antibacterial activity. Similar protocol was followed for evaluation of antifungal activity of the compounds except Sabouraud dextrose agar pH 7.3±0.2 (Hi-media) was used.

4.9.2. *Determination of antimalarial activity*

4.9.2.1. Malarial Parasite culture

Culture of erythrocytic stages of chloroquine sensitive *P. falciparum* strain 3D7 was procured from International Centre of Genetic Engineering and Biotechnology (ICGEB), New Delhi. It was continuously maintained as stocks in 25 cm^2 tissue culture flasks, on human O^+ red blood cells under low-oxygen concentration (3%) and high carbon dioxide atmosphere (4%) along with nitrogen (93%), at a temperature of 37 °C, in RPMI 1640 (Invitrogen) with 25 mM HEPES, 25 mM $NaHCO_3$, 200 mM L-glutamine, 50 mg/L gentamycin (Gibco), 5 g/L Albumax II (Life Technologies). The stock cultures were started with 5% hematocrit and parasitemia less than 1%. Subcultures were made at about 5% parasitemia.

4.9.2.2. Susceptibility of parasites to drugs

An asynchronous erythrocytic culture of *P. falciparum* at 1-1.5% parasitemia and 4% hematocrit in complete RPMI-1640 medium in multi-well plates were used to determine the sensitivity of the parasite strain to the various synthesized compounds. Inhibitory concentration

of individual drug needed to prevent the growth and multiplication of *P. falciparum* was determined *in vitro* using dose response assay in 24-well tissue culture plates in triplicates. Culture was challenged with graded concentration of drug solutions, covering a range from 0.10-100 µg/mL, for 48 hours at 37 °C in a CO_2 incubator. Medium was changed in each well after 24 hours with or without drug.

4.9.2.3. Slide preparation, staining and assessment

After 48-hour incubation, thin blood smear slides were prepared, air dried, methanol fixed, and stained in Giemsa solution. Stained slides were examined for counting the number of parasites in random adjacent microscopic fields, equivalent to about 4,000 erythrocytes at 1,000 X magnification. The percentage inhibition of parasitemia in relation to control was then calculated by examining thin smear Giemsa stained slides. The assay results were computed to determine the IC_{50} value of each drug. Reproducibility of counts was checked by two other readers to maintain the quality control.

4.9.3. *Cytotoxicity against Huh-7 cells*

Cytotoxicity of the compounds was evaluated in human hepato-cellular carcinoma cells (Huh-7) using MTT assay and CC50 values were calculated. Assays were performed in 96-well microtiter plates, each well containing 100 µL of DMEM medium supplemented with 1% penicillin-streptomycin-glutamine solution and 10% fetal bovine serum, and 4×10^3 Huh-7 cells. Serial drug dilutions of eight 2-fold dilution steps covering a range from 100-0.78 µg/mL were prepared. After 72 h of incubation the plates were inspected under an inverted microscope to assure growth of the controls and sterile conditions. 10 µL of MTT reagent (5 mg MTT dissolved

in 1 mL PBS) was then added to each well and the plates incubated for 2-4 h in the cell culture incubator. 100 μL of detergent reagent (90% isopropanol, 9.999% triton x-100, 0.001% conc. HCl) was then added to each well and the plates incubated for another 2 h in the dark at room temperature. The absorbance in each well was read with a Biotek Synergy HT microplate reader at a wavelength of 570 nm. Data were analyzed using the microplate reader software. Each CC_{50} value obtained is the mean of at least two separate experiments performed in duplicate.

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Supplementary data

The spectra of synthesized compounds are given in supplementary material for this article. CCDC No. 1434560 for compound **10e** contain the supplementary crystallographic data that can be obtained free of charge at http://www.ccdccam.ac.uk/const/retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44(0)1223-336033 or email:deposit@ccdc.cam.ac.uk.

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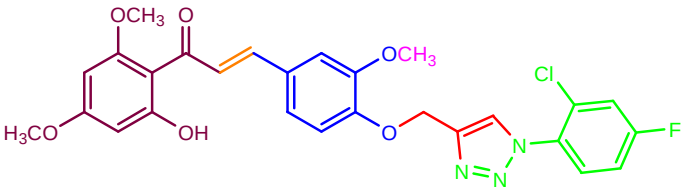
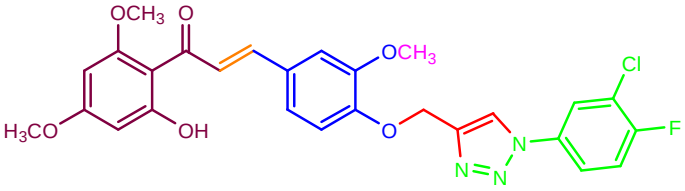
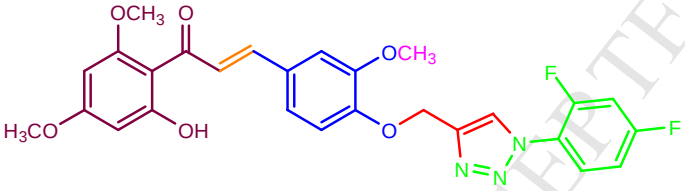
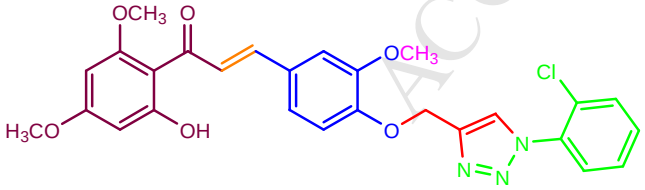
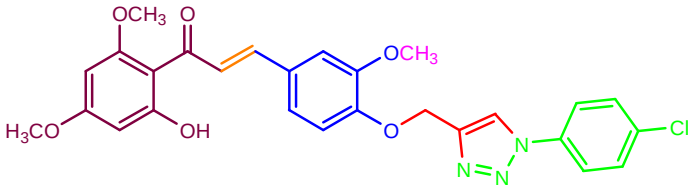
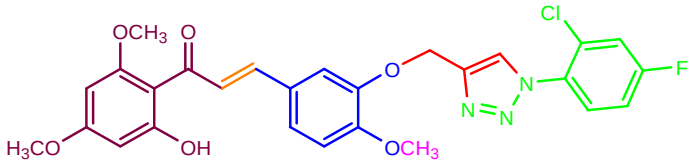
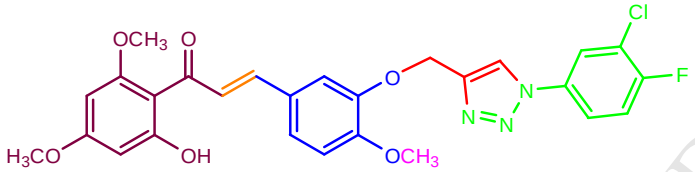
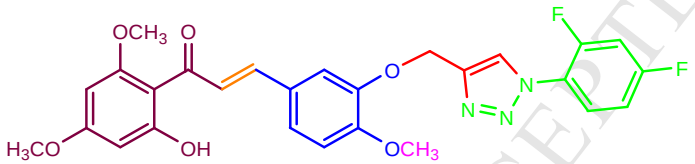
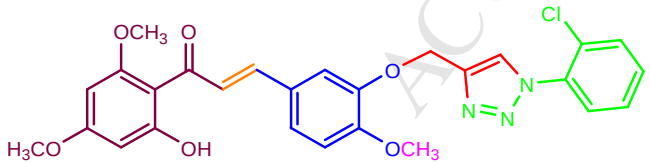
Figure captions

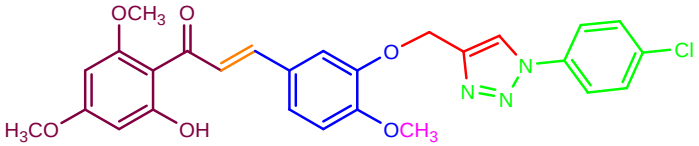
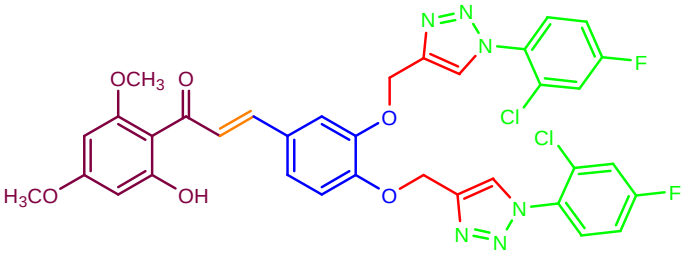
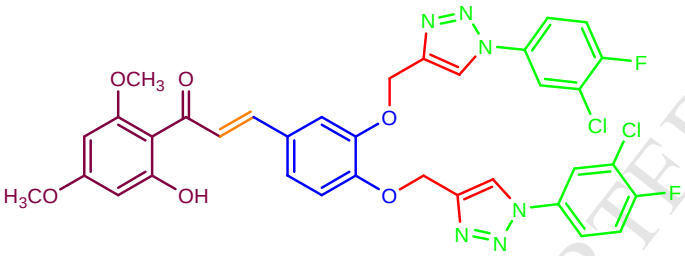
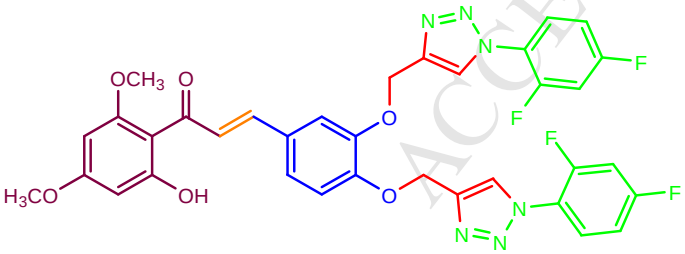
Scheme 1 A synthetic strategy for the synthesis of mono and bis-1,2,3-triazole derivatives of chalcones and flavones **10-14**(**a-e**).

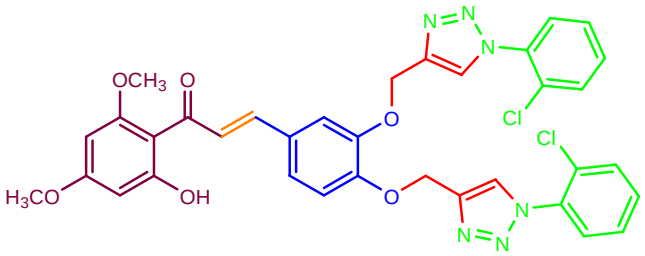
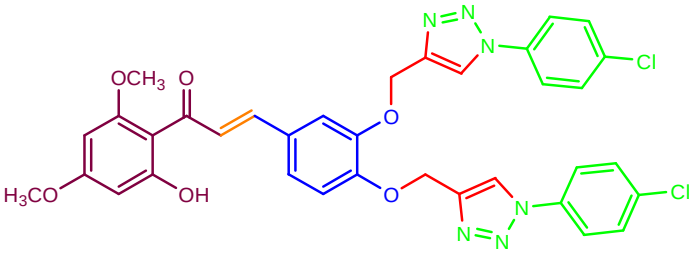
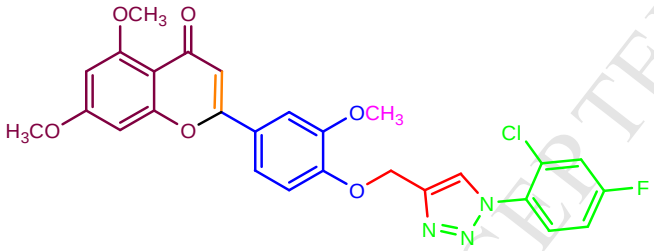
Fig. 1 X-ray structure (ORTEP view) of 1,2,3-triazole compound **10e**.

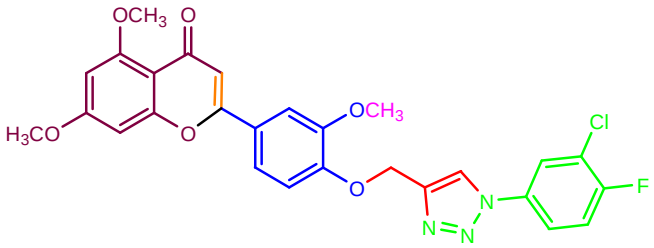
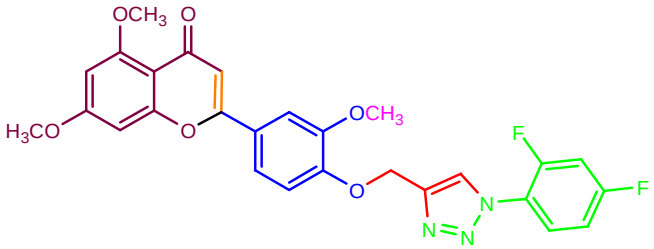
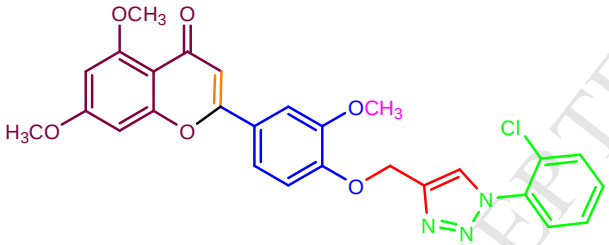
Table 1 Structure of mono and bis-1,2,3-triazole linked chalcone and flavone analogs.

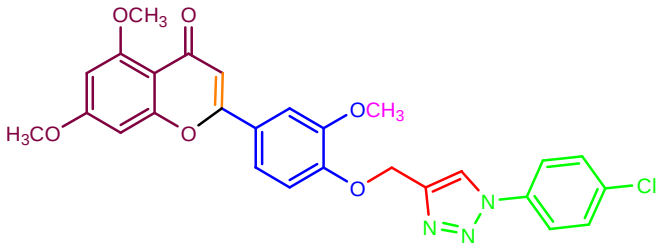
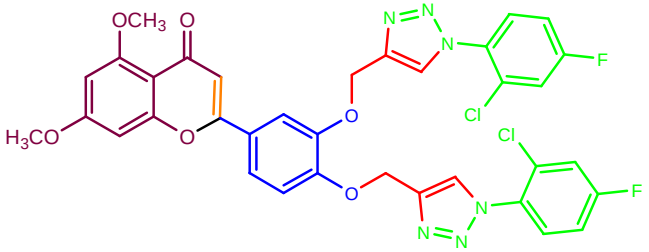
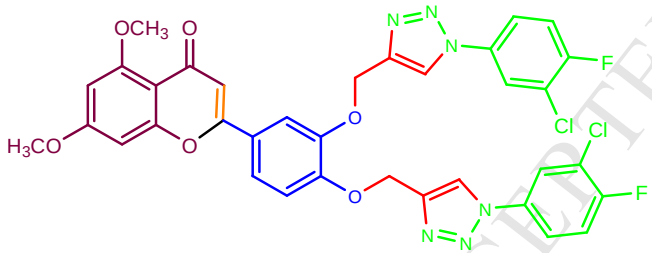
Compound	Structure of compound	Reaction time (h)	Yield %	Color/physical state	Melting point (°C)
10a		40	81	Yellow solid	148-150
10b		35	85	Yellow solid	135-137
10c		55	78	Yellow solid	140-142
10d		30	86	Yellow solid	138-140

10e		48	74	Yellow solid	180-182
11a		44	82	Yellow solid	145-147
11b		48	75	Yellow solid	170-172
11c		60	67	Yellow solid	198-200
11d		35	81	Yellow solid	165-167

11e		55	79	Yellow solid	203-205
12a		30	91	Yellow solid	152-154
12b		24	86	Yellow solid	182-184
12c		48	78	Yellow solid	195-197

12d		30	83	Yellow solid	128-130
12e		30	88	Yellow solid	188-190
13a		50	68	White solid	110-112

13b		60	77	White solid	193-195
13c		65	81	Brown solid	158-160
13d		50	78	White solid	138-140

13e		55	70	White solid	175-177
14a		30	63	Yellow solid	167-169
14b		48	78	Brown solid	242-244

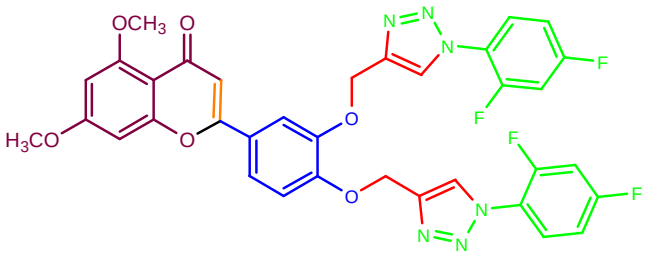
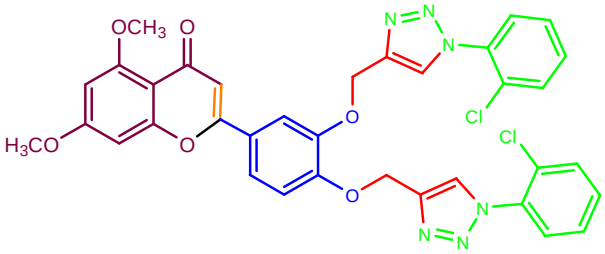
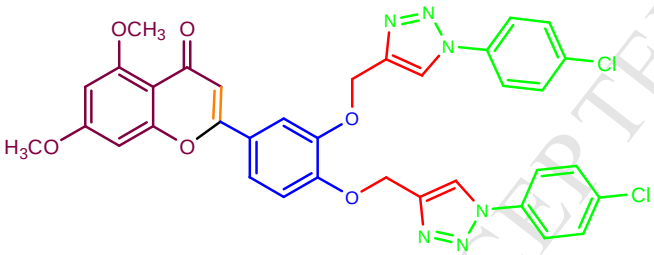
14c		50	84	Brown solid	213-215
14d		30	73	White solid	100-102
14e		35	78	Brown solid	265-267

Table 2 Crystal data, data collection and structure refinement details for 1,2,3-triazole compound **10e**

CCDC	1434560
Molecular Formula	$C_{27}H_{24}ClN_3O_6$
Molecular weight	521.95
Crystal system	Monoclinic
Space group	$P2_1/c$
Temperature (K)	293
a (Å)	13.2404 (18)
b (Å)	7.1418 (10)
c (Å)	26.947 (4)
V (Å^3)	2477.6 (6)
β (°)	103.513 (14)
Z	4
Dx (Mg m^{-3})	1.395
F(000)	1088
μ(mm^{-1})	0.20

Radiation λ (Å)	Mo *Ka* (0.71073)
Crystal dimensions (mm)	0.37 × 0.31 × 0.17
T_{min}/T_{max}	0.0.718/1.000
Θ_{max} (°)	289.3
Θ_{min} (°)	3.0
h	−16→18
k	−9→9
l	−36→35
Measured reflections	14787
Independent reflections	5395
Reflections with $I > 2\sigma(I)$	5230
R_{int}	0.110
Refinement on	F^2
$R[F^2 > 2\sigma(F^2)]$	0.054
$wR(F^2)$	0.129
S	0.81

Number of reflections	5395
Number of parameters	334
$(\Delta/\sigma)_{max}$	0.032
$\Delta\rho_{min}$, $\Delta\rho_{max}$ ($eÅ^{-3}$)	-0.18, 0.18

Table 3 Antibacterial activity (MIC µg/mL) of compounds **10-14(a-e)**.

Compound no.	Gram positive strains		Gram negative strains			
	S. aureus (ATCC 25323)	*E. faecalis* (ATCC 29212)	*E. coli* (ATCC 35218)	*P. aeruginosa* (ATCC 27893)	*S. boydii* (clinical isolate)	*K. pneumoniae* (ATCC 27736)
10a	6.25	6.25	12.5	12.5	12.5	25
10b	>100	50	50	100	25	>100
10c	12.5	12.5	6.25	12.5	6.25	12.5
10d	12.5	6.25	6.25	12.5	6.25	25
10e	>100	>100	>100	>100	>100	>100
11a	100	>100	>100	>100	>100	>100
11b	>100	100	100	>100	>100	>100
11c	100	25	50	>100	12.5	>100
11d	25	25	50	100	12.5	>100
11e	>100	100	100	>100	>100	>100
12a	>100	>100	>100	100	>100	>100
12b	>100	100	>100	>100	100	>100
12c	12.5	6.25	6.25	12.5	6.25	12.5

12d	>100	>100	>100	>100	>100	>100
12e	>100	>100	100	>100	>100	100
13a	50	>100	50	>100	50	>100
13b	>100	>100	>100	>100	>100	>100
13c	>100	>100	>100	>100	>100	>100
13d	50	50	100	50	>100	100
13e	>100	100	>100	>100	>100	>100
14a	>100	>100	>100	>100	>100	>100
14b	>100	>100	100	100	>100	>100
14c	>100	100	>100	>100	>100	>100
14d	>100	>100	>100	>100	>100	>100
14e	12.5	12.5	6.25	12.5	25	12.5
Ciprofloxacin	6.25	6.25	6.25	6.25	6.25	6.25

Table 4 Antifungal activity (MIC µg/mL) of compounds **10-14(a-e).**

Compound no.	Fungal species						Molds	
	C. albicans (ATCC 90028)	*C. albicans* (clinical)	*C. tropicalis* (ATCC 750)	*C. parapsilosis* (ATCC 22019)	*Cryptococcus neoformans* (clinical)	*Dermatophyte* (clinical)	*A. niger* (clinical)	*A. fumigatus* (clinical)
10a	50	>100	100	>100	>100	25	100	>100
10b	>100	>100	>100	>100	>100	>100	100	>100
10c	>100	50	>100	25	50	>100	>100	>100
10d	>100	>100	>100	>100	>100	>100	>100	>100
10e	12.5	6.25	6.25	12.5	12.5	12.5	25	25
11a	>100	>100	>100	>100	>100	>100	>100	>100
11b	>100	>100	100	>100	100	>100	>100	>100
11c	>100	>100	>100	>100	>100	>100	50	50
11d	6.25	12.5	6.25	12.5	12.5	12.5	12.5	12.5
11e	12.5	12.5	6.25	12.5	12.5	12.5	25	25
12a	>100	>100	>100	>100	>100	>100	>100	>100
12b	>100	>100	>100	>100	>100	>100	>100	>100
12c	6.25	6.25	12.5	12.5	6.25	12.5	25	25

12d	>100	>100	>100	>100	>100	>100	>100	>100
12e	>100	>100	>100	>100	>100	>100	>100	>100
13a	12.5	12.5	12.5	12.5	12.5	25	12.5	12.5
13b	12.5	12.5	12.5	12.5	6.25	12.5	50	50
13c	>100	>100	>100	>100	>100	>100	>100	>100
13d	>100	>100	>100	>100	>100	>100	>100	>100
13e	50	12.5	50	50	12.5	12.5	50	50
14a	12.5	12.5	6.25	12.5	12.5	6.25	12.5	12.5
14b	>100	>100	100	>100	>100	>100	100	>100
14c	50	>100	>100	100	>100	>100	>100	>100
14d	12.5	12.5	12.5	12.5	6.25	12.5	12.5	12.5
14e	>100	>100	>100	>100	>100	>100	>100	>100
Fluconazole	0.50	0.50	0.50	0.50	2.00	4.00	2.00	2.00

Table 5 Antiplasmodial activity (IC_{50} µg/mL) of compounds and cytotoxicity against Huh-7 cells.

Compound no.	IC_{50} ± SE[a] (µg/mL)	Mean CC_{50} ± SE[a] (µg/mL)
10a	6.27 ± 0.433	>100
10b	2.74 ± 0.317	>100
10c	3.58 ± 0.395	>100
10d	6.78 ± 0.459	>100
10e	5.08 ± 0.428	>100
11a	4.92 ± 0.384	>100
11b	7.52 ± 0.439	>100
11c	9.54 ± 0.498	>100
11d	8.03 ± 0.561	>100
11e	11.02 ± 0.526	>100
12a	8.55 ± 0.439	>100
12b	10.87 ± 0.437	>100
12c	8.86 ± 0.381	>100
12d	8.38 ± 0.495	>100

12e	12.76 ± 0.364	>100
13a	3.85 ± 0.306	>100
13b	4.48 ± 0.366	>100
13c	4.79 ± 0.302	>100
13d	12.07 ± 0.416	>100
13e	5.19 ± 0.338	>100
14a	14.48 ± 0.453	>100
14b	10.39 ± 0.386	>100
14c	9.25 ± 0.365	>100
14d	8.98 ± 0.492	>100
14e	11.32 ± 0.447	>100
Artemisinin	1.117 ± 0.076 ng/mL	>100

[a] Standard error

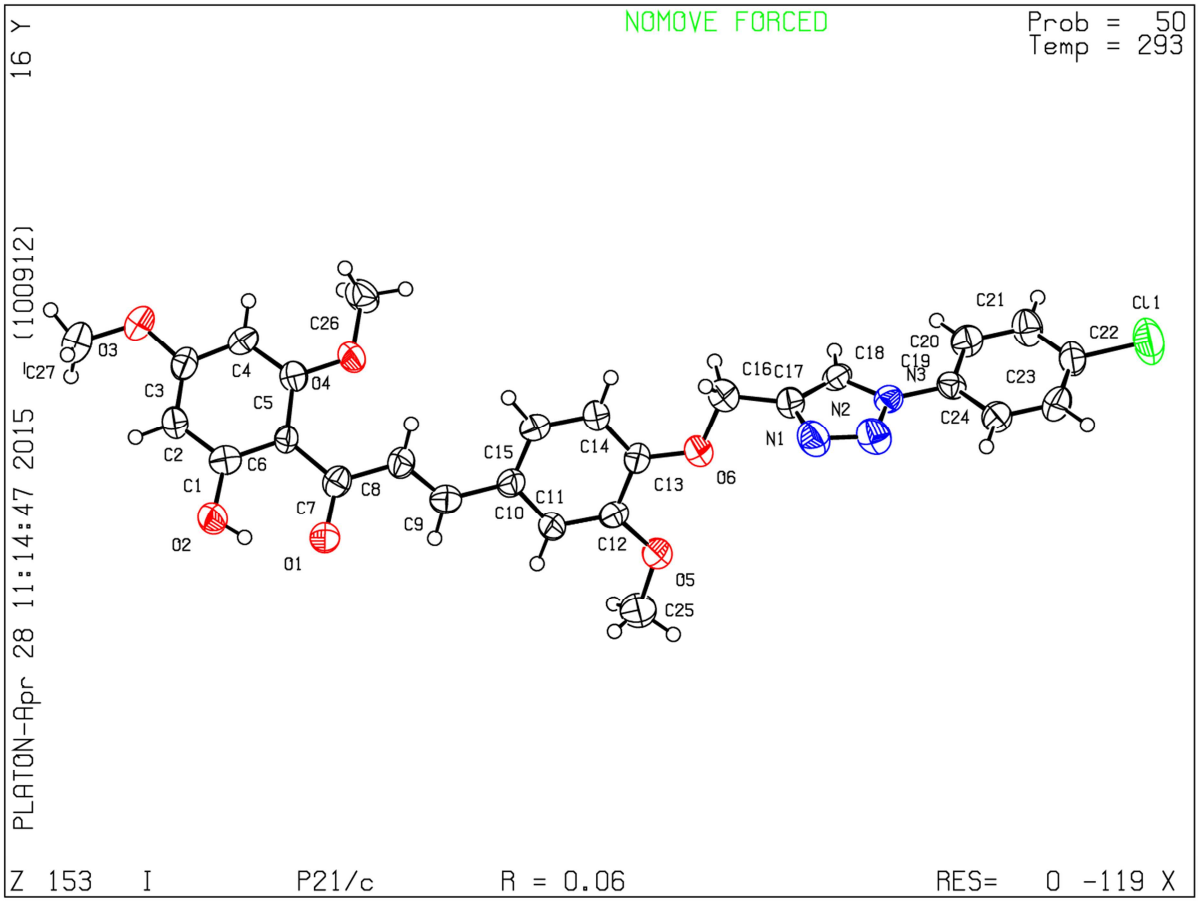
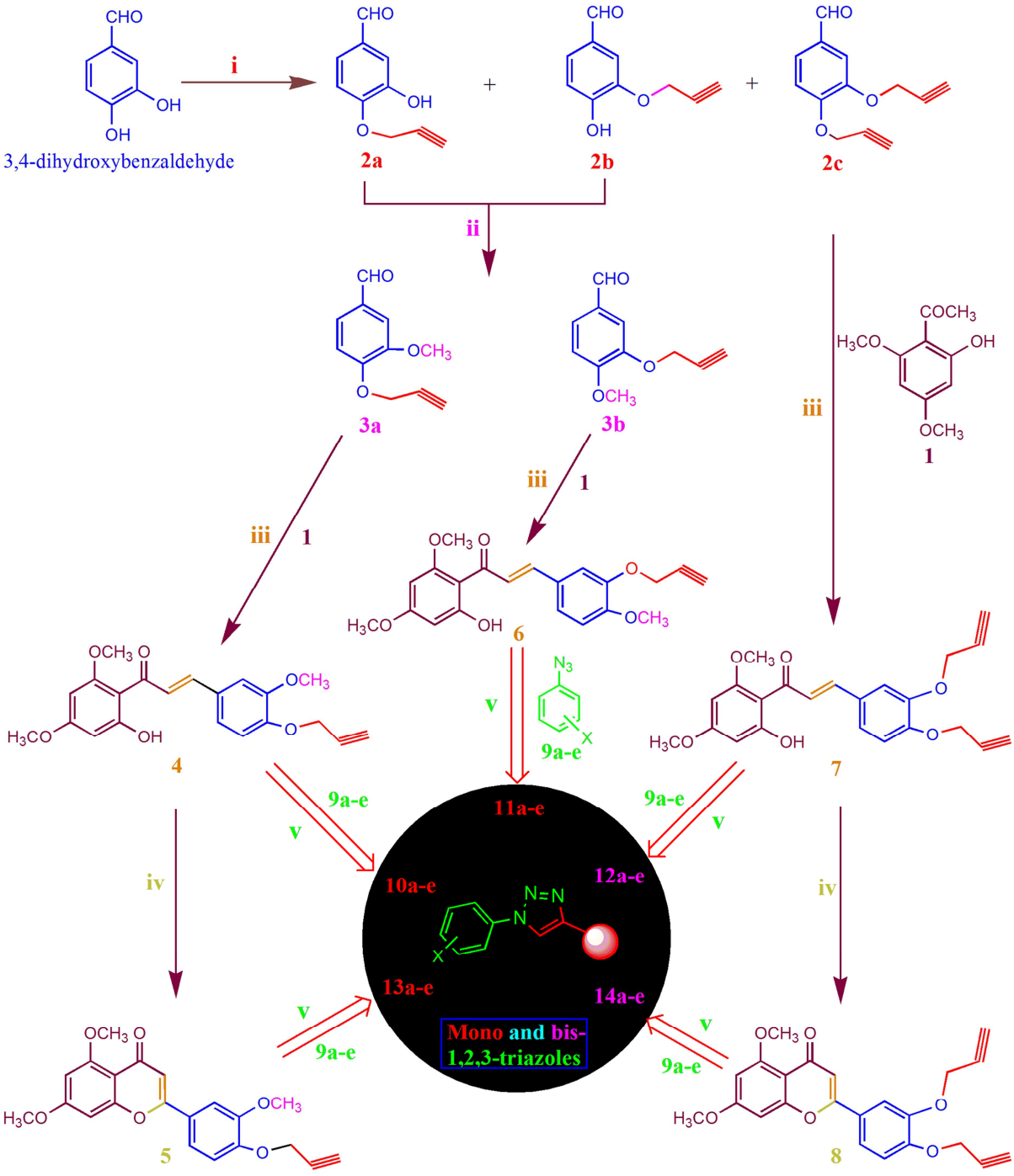


Fig.1



a: X = 2-Cl-4-F **b**: X = 3-Cl-4-F **c**: X = 2,4-F_2 **d**: X = 2-Cl **e**: X = 4-Cl

Reagents and Conditions: (**i**) Propargyl bromide, NaH, DMSO, RT; (**ii**) $(CH_3)_2SO_4$, K_2CO_3, Dry acetone, Reflux; (**iii**) Aq. KOH, Ethanol, RT; (**iv**) I_2, DMSO, Reflux; (**v**) $CuSO_4.5H_2O$, Sodium Ascorbate, DMF/H_2O, RT.

Scheme 1

Highlights

1. A series of newer 1,2,3-triazole linked chalcone and flavone hybrid compounds were synthesized.
2. The prepared compounds were evaluated for antibacterial, antifungal, antiplasmodial and cytotoxic activities.
3. Compound **12c** exhibited the most potent activity against bacterial as well as fungal strains.
4. Compound **10b** showed high effect against human malaria parasite *Plasmodium falciparum* strain 3D7.
5. The compound **10e** was substantiated by X-ray crystallographic studies.