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Research paper

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.

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

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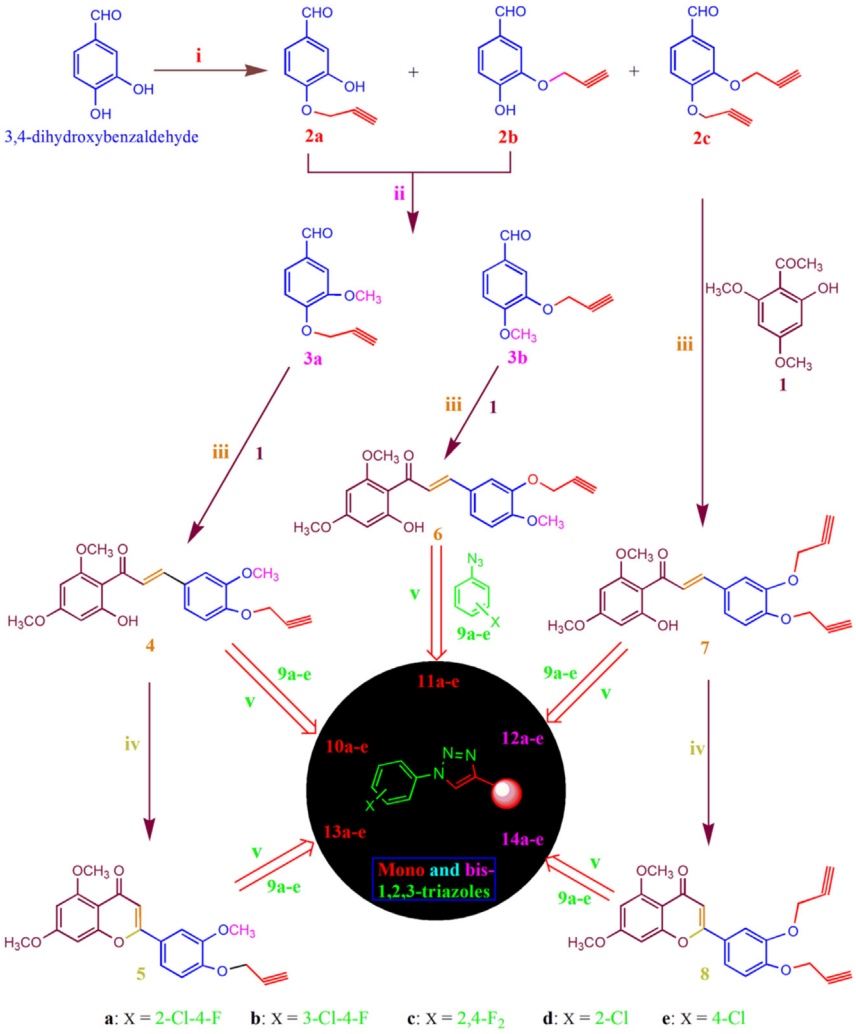
with varied biological activities by the combination of 1,2,3-triazoles with other pharmacophores via click chemistry. For example, a series of 1,2,3-triazole bearing chalcone showed notable antimalarial activity against the D10, Dd2 and W2 strains of *Plasmodium falciparum* [34], a family of 1,2,3-triazole 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)**



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).