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Research Paper

Green synthesis and anticancer potential of chalcone linked-1,2,3-triazoles

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ABSTRACT

A series of chalcone linked-1,2,3-triazoles was synthesized *via* cellulose supported copper nanoparticle catalyzed click reaction in water. The structures of all the compounds were analyzed by IR, NMR and Mass spectral techniques. All the synthesized products were subjected to 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cytotoxicity assay against a panel of four human cancer cell lines (MCF-7, MIA-Pa-Ca-2, A549, HepG2) to check their anticancer potential. Compound **6h** was found to be most active against all the tested cancer cell lines with IC_{50} values in the range of 4–11 μM and showed better or comparable activity to the reference drug against all the tested cell lines. Cell cycle analysis revealed that compound **6h** induces apoptosis and G2/S arrest in MIA-Pa-Ca-2 cells. Compound **6h** triggers mitochondrial potential loss in pancreatic cancer MIA-Pa-Ca-2 cells. Further, Compound **6h** also triggers caspase-3 and PARP-1 cleavage, which increases in dose dependent manner.

1. Introduction

Cancer is basically a group of dreadful diseases recognized by uncontrolled cell growth. Despite enormous progress in the treatment of cancer, it remains the second most common cause of death globally because of ineffective chemotherapy, which is caused by drug resistance as well as the inability of many drugs to differentiate between normal cells and the cancerous cells [1]. The number of cancer patients is increasing significantly worldwide, especially in developed countries. According to the global oncology trend report (2015), global spending on cancer medications rose 10.3% in 2014 to $ 100 billion from $ 75 billion in 2009 [2]. Therefore, there is an urgent need of systematic approach to the development of new chemotherapeutic agents with superior efficacy, lower toxicity as well as better selectivity.

Chalcones (1,3-diaryl-2-propenones) are of paramount interest of the synthetic and medicinal chemists because they are the important precursors for various synthetic and naturally available heterocycles like isoxazolines, pyrazolines, pyrimidines, quinoxalines, aurones, benzalcoumaranones, aurones, anthocynins, flavones, flavanones etc. [3]. Chalcones are the open-chain flavonoids in which the two aromatic rings are joined through a three-carbon α,β-unsaturated carbonyl system [4,5]. Conventionally, chalcones are synthesized by base catalyzed Claisen-Schmidt condensation between benzaldehyde and acetophenone. Chalcones and their synthetic analogues have been reported to possess a wide range of pharmacological activities including antitumor [6], antiplatelet [7], antiviral [8], antitubercular [9], antifungal [10], cytotoxic [11] and enzyme inhibitory properties [12]. A recent review article highlighted the structural features of chalcones and their analogues inhibiting various molecular targets [13].

1,2,3-triazoles, a class of five membered nitrogen heterocycles represent a privileged structural component in a variety of bioactive molecules. 1,4-disubstituted 1,2,3-triazoles have attracted great deal of attraction because they are endowed with numerous biological activities such as antiviral [14], antiepileptic [15], antimicrobial [16–19], antimalarial [20,21], antitubercular [22,23],

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antidiabetic [24], antiallergic [25,26], anti-HIV [27,28] etc. Moreover, a large number of 1,2,3-triazoles have also been reported with significant anticancer activities [29–32]. In view of their remarkable synthetic utility by click chemistry, they have been studied extensively by the medicinal chemists for the development of novel lead molecules [33].

Cellulose is one of the most abundant organic compounds available in nature which serve as a synthetic template for metal nanoparticles. It contains microfibrils which act as a nanoreactor for the stabilization of metal nanoparticles through metal-oxygen electrostatic interactions [34]. The cellulose supported metal nanoparticles have been extensively explored as a heterogeneous catalytic system because of its advantages over homogeneous catalysts [35]. For instance, cellulose supported copper (0) nanoparicles act as a chemoselective catalyst for the Aza-Michael Addition Reaction [36], protodecarboxylation and oxidative decarboxylation of aromatic acids [37], N-arylation of nitrogen heterocycles with different aryl halides and arylboronic acids [38]. Moreover, cellulose supported cuprous iodide nanoparticles have also been reported as highly efficient and reusable catalyst for the click synthesis of 1,2,3-triazoles under environmentally benign conditions [39]. The significance of copper nanoparticles as heterogeneous catalytic system for the synthesis of 1,2,3-triazoles has also been described in the literature [40,41].

Now a day, molecular hybridization approach that combines two pharmacophores to yield a single molecule with additive biological properties has gained special attention from medicinal chemists [42]. There are few reports in literature on chalcone-triazole hybrids exhibiting synergistic biological activities (Fig. 1). For instance, a new class of chalcone-pyrrolo[2,1-c] [1,4]benzodiazepine conjugates (**I**) containing a 1,2,3-triazole moiety exhibited broad spectrum anticancer activity ranging from <0.1–2.9 μM against selected human cancer cell lines of lung, breast, oral, colon, prostate, ovarian and cervix [43]. A novel series of 1,2,3-triazole tethered-β lactam-chalcone hybrids (**II**) have shown promising anticancer activity against A-549 and Caco-2 cell lines [44]. Pingaew et al. prepared some chalcone-triazole-coumarin hybrids with anticancer and antimalarial properties [45]. Kant et al. reported some 1,2,3-triazole linked chalcone and flavone hybrids (**III**) as antimicrobial, antiplasmodial agents [46]. Very recently, Chinthala and his co-workers investigated the novel chalcone-triazole derivatives as anticancer agents [47]. Some triazole-chalconyl allied organosilatranes are also reported as antigiardicidal and antitrichomonacidal agents [48]. Keeping in view of the biological importance of chalcone and triazole moieties, herein, we report the synthesis and anticancer evaluation of some chalcone-1,2,3-triazole hybrids. All these hybrids were synthesized in environmentally benign conditions utilizing water as a green solvent.

2. Results and discussion

2.1. Chemistry

The synthetic outlines for the synthesis of starting and title compounds are presented in Schemes 1 and 2. First, 4-hydroxybenzaldehyde (**1**) was treated with propargyl bromide in the presence of anhydrous potassium carbonate in dry acetone under reflux to yield 4-*O*-propargylated benzaldehyde (**2**) *via* reported procedure [16]. In the next step, 4-*O*-propargylated benzaldehyde (**2**) was reacted with appropriately substituted acetophenones (**3a-3c**) *via* base catalyzed Claisen-Schmidt condensation to yield the corresponding chalcones (**4a-4c**). All the chalcones obtained were *E* isomers, as confirmed on the basis of their ^{1}H NMR spectra.

In the last step, click chemistry approach involving the cycloaddition of terminal alkynes with organic azides has been taken up for the regioselective synthesis of 1,2,3-triazoles. 4-*O*-propargylated chalcones (**4a-4c**) were reacted with sodium azide and various benzyl bromides in presence of cellulose supported copper nanoparticles in water at 70 °C to afford the chalcone linked-1,2,3-triazoles in very high yields. The copper nanoparticles were synthesized following the reported method [39]. This reaction proceeded *via in situ* formation of organic azides from corresponding bromides; thereby circumvent the problem of isolation of azides. To the best of our knowledge, this is the first report on chalcone-triazole hybrids synthesized using water.

To check the reusability and catalytic activity of the catalyst, we performed an experiment carrying model reaction between propargylated chalcone and benzyl bromide by recycling the catalyst. Propargylated chalcone (**3a)** (2 mmol) was reacted with benzyl bromide (2 mmol), and sodium azide (2.4 mmol) in water (4 mL) in the presence of cellulose supported CuI nanoparticles (0.2 gm) and the reaction mixture was heated at 70 °C. After complete conversion, the catalyst was filtered and washed with ethyl acetate, acetone, dried in air and used in next turn. It was observed that the recovered catalyst could be used directly upto four run without significant loss in efficiency (Table 1).

The structures of all the synthesized products were established on the basis of their FTIR, ^{1}H NMR, ^{13}C NMR and HRMS data.

2.1.1. IR analysis

In the IR spectra of propargyl chalcones (**4a-4c**), peaks appeared in the range 3199–3287 and 2110-2132 cm^{-1} due to alkyne ≡C–H stretching and C≡C stretching, respectively and were absent in the spectra of all the title compounds (**6a-6u**). The presence of characteristic peak in the region 3128-3148 cm^{-1} in the IR spectra of all the triazoles (**6a-6u**) evidenced the formation of triazole ring. The synthesized triazoles exhibited two moderate absorption bands in the range 1568–1602 cm^{-1} and 1649-1658 cm^{-1}, which were attributed to the stretching vibrations of C=C and C=O, respectively.

2.1.2. ^{1}H NMR analysis

The ^{1}H NMR spectra of all the synthesized chalcones exihibited two doublets in the region δ 7.37–7.45 and δ 7.76–7.83 with a characteristic coupling constant (*J*) of 15.6 Hz, which confirms the formation of chalcones. The higher value of coupling constant confirmed the *E*-geometry of double bond in chalcones and also assigned the purity of all the synthesized chalcones (**4a-4c**). In addition, two sharp singlets of methylene protons (OCH_2 and NCH_2) appeared in the range δ 5.23–5.28 and δ 5.51–5.70 respectively. A characteristic sharp singlet in the region δ 7.57–7.70 was assigned to triazolyl proton in all the synthesized triazoles (**6a-6u**).

2.1.3. ^{13}C NMR analysis

In the ^{13}C NMR spectra, the peaks of C-4 and C-5 carbon atoms of triazole appeared in the region δ 143.54–144.29 and δ 122.61–123.15, respectively. The C_α and C_β carbon atoms of the α,β-unsaturated carbonyl system resonated at δ 119.26–119.99 and δ 143.37–146.45, respectively. The peak in the region δ 188.68–189.37 was attributed to the carbonyl carbon atom.

2.1.4. HRMS analysis

The HRMS data of all the synthesized products was in good agreement with their calculated values.

2.2. Anticancer activity

All the synthesized compounds (**4a-4c; 6a-6c**) were evaluated for their cytotoxicity towards the panel of four human cancer cell