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Short communication

Design, synthesis and antiproliferative activity of functionalized flavone-triazole-tetrahydropyran conjugates against human cancer cell lines

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ABSTRACT

Under optimized reaction conditions, an efficient synthetic method has been developed to afford the functionalized flavone-triazole-tetrahydropyran conjugates *via* click reactions. The Cu-catalyzed 1,3-dipolar cycloaddition reaction gave the pure products, 5-iodo- and 5-*H*-1-(tetrahydropyran)-1,2,3-triazol-4-(3-methoxylflavone) derivatives in excellent yield (90–98%) within 1–3 h. Further, Pd-catalyzed Suzuki coupling of 5-iodo-1,2,3-triazoles with phenylboronic acids afforded 5-phenyl-1-(tetrahydropyran)-1,2,3-triazol-4-(3-methoxylflavone) derivatives in excellent yield (93–95%) in 4–5 h. Products (**3a**–**l**, **4a**–**j**) were screened *in vitro* for their anti-proliferative activity against three human cancer cell lines (MDA-MB 231, KCL22 and Hela). Compounds **3c**, **3g**, **3i**, **3j**, **4c** and **4h** have shown better cytotoxicity (IC_{50} 0.61–1.68 μM) than the reference drugs. Compounds **4e** (IC_{50} 0.70 μM), **3j** (IC_{50} 0.61 μM) and **4d** (IC_{50} 0.65 μM) exhibited anti-proliferative activity better than the reference drugs against the MDA-MB 231 cells, KCL22 cells and HeLa cells respectively.

1. Introduction

1,2,3-Triazole and 1,2,4-triazole scaffolds possess immense importance in the medicinal chemistry due to their use as precursors in the synthesis of various biologically active heterocyclic compounds [1]. They are used as antifungal, antibacterial, antiviral, anti-HIV and antitumor activities against Gram positive and negative bacteria, selective β3-adrenergic receptor agonist [2–4], herbicidal, antituberculosis, tyrosinase inhibitors, antiallergic and glycosidase inhibitors [5–7]. 1,2,3-Triazole tethered β-lactam-chalcone bifunctional hybrid **1**, showed a potent anticancer agents [8] and thiolactone-chalcone scaffold containing triazole **2** as excellent antiplasmodial activity against W2 strain *Plasmodium falciparum* (IC_{50} 0.68–0.81 μM) [9]. 8-Triazolylflavone derivative **3** have shown antifungal and antibacterial activities [10], while compounds **MA-6**, **MA-8** and **MA-21** exhibited estrogen receptor alpha-positive breast cancer inhibitors (Fig. 1) [11]. More recently, these moieties are also used as pharmacophores in a number of pharmaceutical and agrochemical products [12,13].

Molecular hybridization is a new concept in the drug design and development based on the combination of pharmacophores of different bioactive substances to produce a novel hybrid molecule with improved affinity and efficacy [14]. The flavonoids have shown many biological applications [15,16] and when conjugated with other biologically active molecules further enhanced their biological activity [17]. For example, triazole based chalcone-pyrrolo [2,1-c] [1,4] benzodiazepine (PBD) hybrids resulted in G1 cell-cycle arrest and exhibited inhibitory effects on the NF-kB and Bcl-XL proteins which are vital for the breast cancer cell proliferation [18]. Similarly, the flavonoid based pyran derivatives like epicalyxin F, epicalyxin G, epicalyxin K, calyxin K, and calyxin I were isolated from the seeds of *Alpinia blepharocalyx* Sp. are commonly used in traditional medicine for the treatment of various stomach disorders in China and Japan. Most of these natural products have shown excellent hepatoprotective and antiproliferative activities against cancer cells. Exclusively, epicalyxin F is the most potent member of this class and has shown anti-cancer activity (approx.1 μM) against

Abbreviations: μg, (microgram); μL, (microliter); μM, (micromole); mL, (milliliter); mg, (milligram); nm, (nanometre); mmol, (millimole); MTT, ((3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide); TFA, (trifluoroacetic acid); $CHCl_3$, (chloroform); DCM, (dichloromethane); DMSO, (dimethyl sulfoxide); MS 4 Å, (molecular sieves 4 Å).

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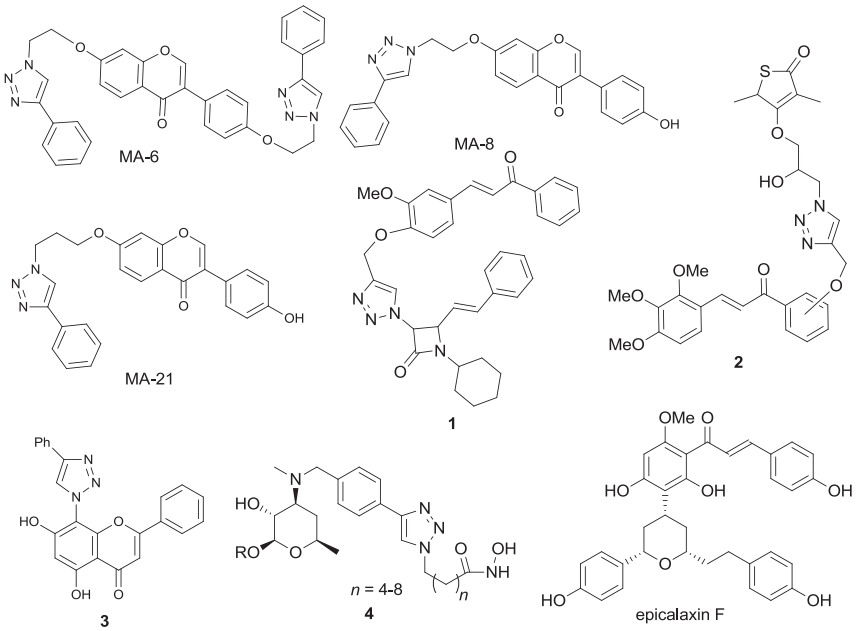

Fig. 1. Flavonoid-tetrahdropyran-triazole conjugates as potential drug entities.

the human HT-1080 fibrosarcoma and the murine 26-L5 carcinoma [19]. The structure–activity relationship (SAR) studies revealed that compound **4** displayed both linker length and macrolide type dependent HDAC inhibition activities (IC_{50}- μM range) [20].

Because of the remarkable biological importance of triazole containing derivatives, various methods were explored for their convenient synthesis [21,22]. Among them, the most attractive method is the thermal Huisgen 1,3-dipolar cycloaddition reaction of azides with alkynes. The synthesis of 1,2,3-triazoles *via* Huisgen 1,3-dipolar cycloaddition got developed in modern synthetic concept by Sharpless and co-workers and has become a paradigm of the click chemistry [23,24]. In this concept, the copper(I) catalyzed azide–alkyne cycloaddition (CuAAC) reaction termed as the 'cream of the crop' of the click reactions is a modular synthetic approach towards the assembly of new molecular entities [4,25]. Wu et al. first time reported a regio-specific synthesis of 5-iodo-1,4-disubstituted-1,2,3-triazoles using ICl as iodinating agent [26]. Zhang et al. reported for the same synthesis using NBS-CuI as iodinating agent [27] and Zhu et al. also reported for the same synthesis using copper(II) perchlorate-NaI [28]. Similarly, Hein et al. reported the synthesis of 5-iodotriazole using CuI-catalyzed cycloaddition of 1-iodoalkyne and organic azide in the presence of an assisting ligand such as tris((1-benzyl-1H-1,2,3-triazolyl)-methyl)amine (TBTA) and tris((1-tert-butyl-1H-1,2,3-triazolyl)-methyl)amine (TTTA) [29]. However, 1-iodoalkyne is unstable and difficult to handle and ICl reagent is corrosive in nature therefore these methods got less synthetic importance due to the environmental concerns. And Zhu et al. method failed to give the desired product. However, Zhang et al. method gave a mixture of 5-iodotriazole and 5-prototriazole derivatives. Therefore, we considered to develop the click reaction as an efficient method to synthesize flavone-triazole-tetrahydropyran conjugates.

Flavone, tetrahydropyran and triazole moieties are known for their beneficial effects in human health and therefore the therapeutic potential of these molecules have been explored [30]. Based on useful applications as well as our research interest in the synthesis of pharmacologically active flavonoid and tetrahydropyran molecules [31–34] herein, we designed for the synthesis of the novel flavone-triazole-tetrahydropyran conjugates (i) 5-iodo-1-(tetrahydropyran)-1,2,3-triazol-4-(3-methoxyl flavone) and (ii) 5-H-1-(tetrahydropyran)-1,2,3-triazol-4-(3-methoxylflavone) using 4-azido tetrahydropyran and 3-(2-propynyloxy)flavone derivatives under two different copper-catalyzed reaction conditions.

2. Results and discussion

2.1. Chemistry

2.1.1. Synthesis of 5-iodo-1-(tetrahydropyran)-1,2,3-triazol-4-(3-methoxylflavone) derivatives

Initially, the reaction was performed with 4-azido tetrahydropyran (**1a**) and alkyne (**2a**) in the presence of copper (I) iodide (1 equiv.) and *N*-bromosuccinamide (NBS, 1.1 equiv.). The reactants were remained intact even after prolonging the reaction time. However, on addition of base like DIPEA (diisopropylethylamine, 0.5 equiv.) gave 5-iodo-1,2,3-triazole (**3a**) along with 5-prototriazoles (**4**) in 10:1 ratio in 75% overall yield (Table 1, entry 9). Further, we varied the quantity of DIPEA from 0.5 to 3.0 equiv. At 2.5 equiv. of DIPEA, the reaction gave maximum yield of 5-iodo substituted triazole as a single product (Table 1, entry 13). In search of more efficient base, we screened other bases such as TEA, 2,6-lutidine, DBU, DABCO, Na_2CO_3 and 1,10-phenanthroline under the same reaction condition (varying ratio from 0.5 to 3.0 equiv.). However, DIPEA was found to be the most suitable base in the reaction (Table 1).

Furthermore, we observed the solvent effects using ACN, MeOH, THF, THF:H_2O, EtOAc, acetone, toluene, DMF, water, ACN:H_2O. These solvents have no significant effects on the product **3**:**4** ratio, but gave less yield in a longer reaction time (Table 2). Therefore, THF was found as a suitable solvent.

To prove its general applicability, an array of flavone based terminal alkynes and 4-azido tetrahydropyrans were subjected under optimized reaction conditions as CuI (1.2 equiv. as copper source), DIPEA (2.5 equiv. as base), NBS (1.1 equiv) and THF as the solvent (Table 3). The reaction proceeded smoothly in all the cases, where 5-iodo-1,2,3-triazoles (**3**) were obtained as exclusive product. A