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Original article

1,2,3-Triazole tethered acetophenones: Synthesis, bioevaluation and molecular docking study

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ABSTRACT

A small focused library of eighteen new 1,2,3-triazole tethered acetophenones has been efficiently prepared *via* click chemistry approach and evaluated for their antifungal and antioxidant activity. The antifungal activity was evaluated against five human pathogenic fungal strains: *Candida albicans*, *Fusarium oxysporum*, *Aspergillus flavus*, *Aspergillus niger*, and *Cryptococcus neoformans*. Among the synthesized compounds, **9c**, **9i**, and **9p** found to be more potent antifungal agents that the reference standard. These 1,2,3-triazole based derivatives were also evaluated for antioxidant activity, and compound **9h** was found to be the most potent antioxidant as compared to the standard drug. Furthermore, molecular docking study of the newly synthesized compounds was performed and results showed good binding mode in the active site of fungal *C. albicans* enzyme P450 cytochrome lanosterol 14α-demethylase. Moreover, the synthesized compounds were also analyzed for ADME properties and showed potential as good oral drug candidates.

1. Introduction

In recent years, the incidence of systemic fungal infection has increased significantly due to an increase in the numbers of patients undergoing organ transplants, anticancer chemotherapy patients, and patients with AIDS. The commonly used azole antifungal agents fluconazole, itraconazole, miconazole, and voriconazole display broad spectrum antifungal activity [1]. Azoles have broad spectrum activities against most yeasts and filamentous fungi and are the drug of choice for antifungal chemotherapy [2]. These antifungal drugs inhibit CYP51 in the process of biosynthesis of ergosterol through a mechanism in which the heterocyclic nitrogen atom (N-4 of triazole) binds to the heme iron atom [3]. However, increasing use of these antifungal drugs has led to the increase in resistance to these drugs [4].

Recently, click chemistry has emerged as a fast and powerful approach for the synthesis of novel compounds with biological importance. The copper-catalyzed 1,3-dipolar azide–alkyne cycloaddition (CuAAC) reaction [5] is the premier example of "click chemistry" as it is virtually quantitative and easy to perform. The formed triazole is essentially inert to reactive conditions such as oxidation, reduction, and hydrolysis. CuAAC is particularly useful for the synthesis of a variety of molecules ranging from enzyme inhibitors to molecular materials [6]. 1,2,3-Triazole based compounds are reported to possess a wide range of biological activities such as antifungal [7], antitubercular [8], antiallergic, antibacterial, anti-HIV activity [9], α-glycosidase inhibition [10], antimicrobial [11], anticoccidiostats [12], anticonvulsant [13], antimalarial [14], antiviral [15] and antimycobacterial activity [16]. Triazole has been used to improve the pharmacokinetic properties of desired drugs [17].

Acetophenones exhibit a wide range of biological activities like antagonist activity (Fig. 1A) [18], anesthetics, pain control [19], and they are used as oral hypoglycemic agents [20] (Fig. 1B) for the treatment of non insulin dependent diabetes mellitus. Some of the marketed drugs containing acetophenone moiety are used for the treatment of schizophrenia [20] (Fig. 1C). Drugs containing acetophenone moiety also exhibit antidiabetic, sedative, antipsychotic [20] (Fig. 1D), psychoactive (Fig. 1E), anti-inflammatory [21], and antimicrobial [22] (Fig. 1F)

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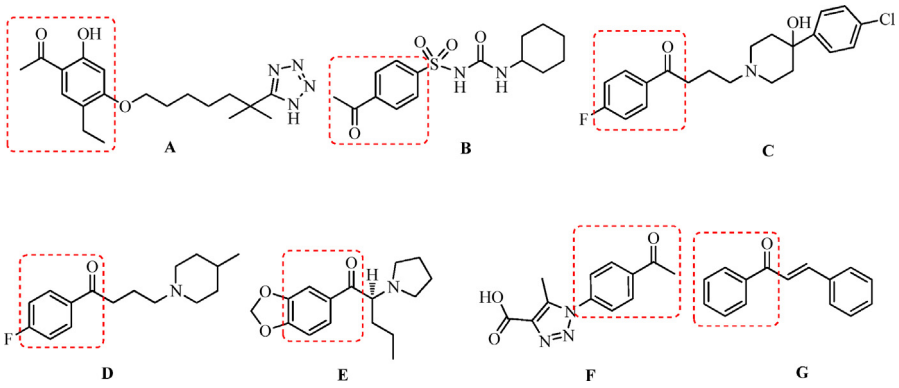

Fig. 1. Some bioactive compounds having acetophenone core.

activity. Benzylidene acetophenone or chalcone (Fig. 1G) shows antibacterial, antifungal, anti-inflammatory [21a], antitumor [20,21b], and other activities.

Considering the importance of 1,2,3-triazole and acetophenone moieties as a single molecular scaffold, and in continuation of our recent reports on 1,2,3-triazole derivatives as antitubercular and antifungal agents and other bioactive heterocyclic compounds [23], we planned to synthesize some new synthetic 1,2,3-triazole tethered acetophenone derivatives to evaluate their antifungal and antioxidant activity. Computational characterizations included a docking study for antifungal activity and ADME prediction of synthesized 1,2,3-triazole-acetophenone conjugates **9a**–**r**.

2. Experimental

2.1. Chemistry

Synthesis of compounds **2a**–**c** and **3a**–**c** are given in the Supporting information.

General procedure for the synthesis of 2-(prop-2-yn-1-yloxy)phenylethanone (**4a**–**c**): K_2CO_3 (18 mmol) was added to a stirred solution of hydroxyacetophenone (15 mmol) in *N,N*-dimethylformamide (DMF) (8 mL). The reaction mixture was stirred at room temperature for 30 min, which results in the corresponding oxyanion. To this, propargyl bromide (15 mmol) was added and stirred for 2 h at room temperature. The progress of the reaction was monitored by TLC using ethyl acetate:hexane as a solvent system. The reaction mixture was quenched by crushed ice. If the product was solid (**4b** and **4c**), it was filtered and crystallized using aq. ethanol. When the product (**4a**) was liquid, it was extracted in ethyl acetate (20 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under a reduced pressure and the product was used in further steps without purification.

General experimental procedure for the synthesis of substituted 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxyphenylethanone (**9a**–**r**): A mixture of 2-(prop-2-yn-1-yloxy)phenylethanones **4a**–**c** (2 mmol), substituted benzyl azide **8a**–**f** (2 mmol) and copper diacetate [$Cu(OAc)_2$] (20 mole%) in *t*-BuOH–H_2O (3:1, 8 mL) was stirred at room temperature for 19–27 h. The progress of the reaction was monitored by TLC using ethyl acetate:hexane as a solvent system. The reaction mixture was quenched with crushed ice and extracted with ethyl acetate (2 × 25 mL). The organic extracts were washed with brine solution (2 × 15 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to afford the corresponding crude compounds (**9a**–**r**). The obtained crude compounds were recrystallized using ethanol.

2.2. Biological activity

Antifungal activity: The antifungal activity was evaluated against five human pathogenic fungal strains, such as *Candida albicans* (NCIM 3471), *Fusarium oxysporum* (NCIM 1332), *Aspergillus flavus* (NCIM 539), *Aspergillus niger* (NCIM 1196), and *Cryptococcus neoformans* (NCIM 576), which are often encountered clinically. For each compound, antifungal activity was compared with standard drugs miconazole and fluconazole. Miconazole and fluconazole were purchased from TCI chemicals at 98% purity. Minimum inhibitory concentration (MIC) values were determined using the standard agar method [24].

Antioxidant activity: Antioxidant activity of the synthesized compounds has been assessed *in vitro* by the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay [25] and the results were compared with standard synthetic antioxidant BHT (Butylated Hydroxy Toluene). The hydrogen atom or electron donation ability of the compounds was measured from the bleaching of the purple colored methanol solution of DPPH. 1 mL of various concentrations of the test compounds (5, 10, 25, 50 and 100 μg/mL) in methanol was added to 4 mL of 0.004% (w/v) methanol solution of DPPH. After a 30 min incubation period at room temperature, the absorbance was measured against blank at 517 nm. The percent inhibition (I%) of free radical production from DPPH was calculated by the following equation.

$$\%\ \text{of scavenging} = \left[\frac{(\text{A control} - \text{A sample})}{\text{A blank}}\right] \times 100$$

where 'A control' is the absorbance of the control reaction (containing all reagents except the test compound) and 'A sample' is the absorbance of the test compound. Tests were carried out in triplicate.

2.3. Computational study

Molecular docking: Glide (Grid-Based Ligand Docking with Energetics) program integrated in the Schrodinger molecular modeling software [26] was used to study the binding mode of the title compounds into the active site of sterol 14α-demethylase (CYP51).

ADME properties: The success of a drug is determined not only by good efficacy but also by an acceptable ADME (absorption, distribution, metabolism and excretion) profile. In this study, molecular volume (MV), molecular weight (MW), logarithm of partition coefficient (miLog *P*), number of hydrogen bond acceptors (*n*-ON), number of hydrogen bonds donors (*n*-OHNH), topological polar surface area (TPSA), and number of rotatable bonds (*n*-ROTB) were calculated using Lipinski's rule of five [27a] and the