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Synthesis of aryl pyrazole via Suzuki coupling reaction, *in vitro* mushroom tyrosinase enzyme inhibition assay and *in silico* comparative molecular docking analysis with Kojic acid

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ABSTRACT

Aryl pyrazoles are well recognized class of heterocyclic compounds found in several commercially available drugs. Owing to their significance in medicinal chemistry, in this current account we have synthesized a series of suitably substituted aryl pyrazole by employing Suzuki cross-coupling reaction. All compounds were evaluated for inhibition of mushroom tyrosinase enzyme both *in vitro* and *in silico*. Compound 3f (IC_{50} = 1.568 ± 0.01 μM) showed relatively better potential compared to reference kojic acid (IC_{50} = 16.051 ± 1.27 μM). A comparative docking studies showed that compound **3f** have maximum binding affinity against mushroom tyrosinase (PDBID: 2Y9X) with binding energy value (−6.90 kcal/mol) as compared to Kojic acid. The 4-methoxy group in compound **3f** shows 100% interaction with Cu. Compound 3f displayed hydrogen binding interaction with His61 and His94 at distance of 1.71 and 1.74 Å which might be responsible for higher activity compared to Kojic acid.

1. Introduction

Tyrosinase (EC 1.14.18.1) is a multifunctional, glycosylated copper containing metallic enzyme. It is widely distributed in fungi, bacteria, plants and mammals. Tyrosinase isolated from champignon mushroom, *Agaricus bisporus* resembles with enzyme obtained from mammals [1,2]. Ease of availability makes mushroom tyrosinase a suitable model to carry out investigations on Melanogenesis [3]. Tyrosinase in involved in the catalysis of tyrosine to produced l-DOPA (monophenolase activity) and on further treatment l-DOPA is converted into dopaquinone (diphenolase activity) [4]. Through a series of oxidation reaction, a macromolecule pigment is formed which is known as melanin. Besides involved in the production of melanin, tyrosinase enzyme is attributed to have role in the detoxification for symbiotic bacteria, and sclerotisation of insect cuticles [5]. Moreover, tyrosinase can be employed to remove phenol from wastewater [6]. Cells of basal layer, melanocytes produce melanin which acts as protective barrier by absorbing harmful ultraviolet radiation and thus preventing skin cells from radiation induced damage [7]. The quantity of melanin present in skin cells determines the color of human skin, owing to the presence of excessive quantity of melanin results in the loss of white color and mainly damages the aesthetics of human being [8,9]. In addition, injured fruits and vegetables are prone towards browning, particularly post harvesting is the stage where agricultural products tend to lose freshness. The development of tyrosinase inhibitors could possibly be an alternative to prevent food quality, protect skin cells and treat hyperpigmentation disorders. Tyrosinase inhibitors have been widely employed by dermatologists and also used in cosmetic industry [10]. There are four classes of tyrosinase inhibitor based upon their mode of inhibition competitive inhibitors, uncompetitive inhibitors, mixed-type inhibitors, and noncompetitive inhibitors. Fig. 1 depicts the various inhibitors of tyrosinase enzyme [11].

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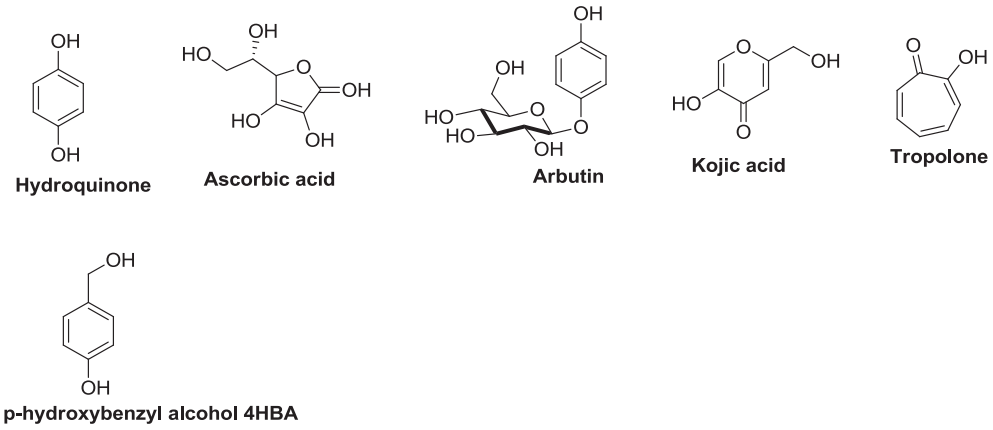

Fig. 1. Potent inhibitors of mushroom tyrosinase.

Among the above mentioned numerous tyrosinase inhibitors, kojic acid has received great attention as an effective dual mode competitive/mixed inhibitor of tyrosinase and it also scavenges free radicals. However, kojic acid displays chemical instability and also it also shows cytotoxicity which sometimes results in the irritation in skin cells [12–14].

This necessitates the drive to develop improved and safe inhibitors of tyrosinase enzyme in order to curb food browning and prevent skin cells from harmful effects of melanin which results in hyperpigmentation disorders.

The reactivity and stability of heterocyclic compounds has enjoyed voluminous success in the field of medicinal chemistry and almost more than half of organic compounds comprised of heterocyclic ring. Moreover nitrogen containing heterocyclic compounds exhibit water solubility and show ability to forms salts thus making these compounds suitably for designing oral drugs. Pyrazoles are well recognized aromatic five membered di nitrogen containing heterocyclic compounds and display numerous biological, agrochemical and pharmaceutical properties [15–20]. Pyrazoles possess broad spectrum of biological activities and recently several drugs have been designed based on pyrazole nucleus (Fig. 2) [21–24].

Besides on massive biological importance, pyrazoles display utility in material chemistry and can be used in semiconductor and other organic molecules based electronic devices [25]. Moreover, pyrazoles can be used for the extraction of metal ions because they acts as chelating agents. Pyrazoles possess reactive sites where synthetic modification could render new derivatives which can be used for developing potent and selective drugs. The derivatization of aryl pyrazoles is an interesting subjects for synthetic chemists. To hook up carbon−carbon bond with each other, several organometallic name reactions are available and among them Suzuki reaction has received great attention to construct C−C linkages. Suzuki together with Heck and Negishi was jointly awarded Noble prize in 2010 in chemistry for “palladium-catalyzed cross couplings in organic synthesis”. Suzuki coupling has been employed in various fields such as natural products synthesis, pharmaceutically active molecules and polymer compounds, such an extensive utility of this reaction stems from the numerous advantages such as mild reaction conditions; (ii) ready availability of organoboron reagents, which also are inert to water and related solvents, as well as oxygen, and generally thermally stable; (iii) tolerant toward various functional groups; and (iv) low toxicity of starting materials and by-products.

In this account, we employed Suzuki coupling reaction to construct aryl pyrazoles and explored their potential as mushroom tyrosinase inhibitors.

2. Experimental

2.1. General procedure for the preparation of pyrazoles (1a-1e),

2.1.1. General procedure for the synthesis of N-substituted pyrazole (1a-1e)

Substituted aromatic hydrazides (150 mg, 1 mmole), were treated with 3-chloropentane-2,4-dione (135 mg, 1 mmole) and acetic acid (1.0 ml) was refluxed in ethanol (10 ml) for 5 h. The precipitate which formed after cooling was collected by filtration and recrystallized from ethanol to give compound.

2.1.2. Procedure of Suzuki cross-coupling reactions (3a-j)

For a typical reaction, a Schlenk tube was charged with aryl halide (0.5 mmol), phenylboronic acid (0.6 mmol), KOH (2 equiv), Pd catalyst precursor (2.0 mol%), TBAB (1 g), and H_2O (5 ml). The reaction mixture was stirred at 80 °C for 2–12 h. After cooling to room temperature, the reaction mixture was extracted with diethyl ether (3–10 ml). The organic solvent was evaporated to dryness under vacuum to give the

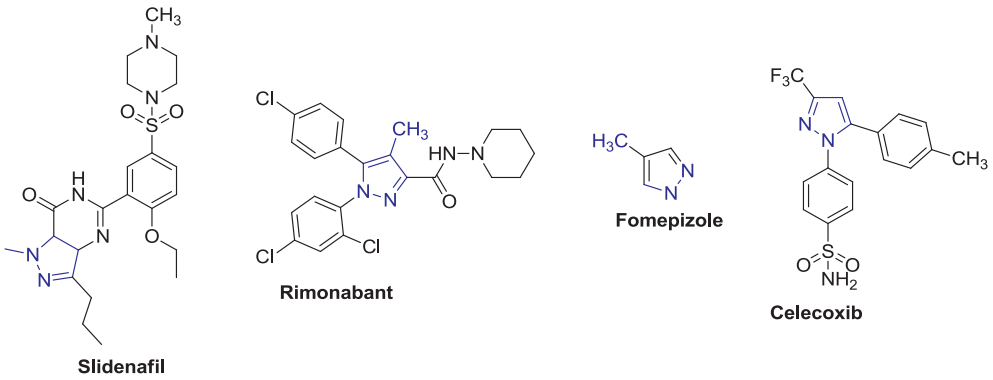

Fig. 2. Pyrazole containing commercial drugs.

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