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Synthesis and Evaluation of Antioxidant Activity of 6-Methoxy-2*H*-chromenes

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3-(6-Methoxy-2*H*-chromen-3-yl)-1-phenyl prop-2-en-1-one and 1-(6-methoxy-2*H*-chromen-3-yl)-3-phenyl prop-2-en-1-one were synthesized by condensation of 6-methoxy-2*H*-chromen-3-carbaldehyde or 1-(6-methoxy-2*H*-chromen-3-yl)ethanone with acetophenone or benzaldehyde, respectively. The synthesized chalcones were evaluated for their antioxidant activity using ferric reducing antioxidant power (FRAP) and DPPH free radical scavenging methods. Both compounds showed antioxidant activity, in comparison with trolox.

Key Words: Synthesis, Antioxidant, Chromene, DPPH & Ferric reducing antioxidant power assay.

INTRODUCTION

Reactive oxygen species (ROS) is a term which encompasses all highly reactive, oxygen-containing molecules, including free radicals. Types of ROS include the hydroxyl radical, the superoxide anion radical, hydrogen peroxide, single oxygen, nitric oxide radical, hypochlorite radical and various lipid peroxides[1-3]. ROS have been recognized to play an important role in the initiation and/or propagation of various diseases[4]. All are capable of reacting with membrane lipids, nucleic acids, proteins and enzymes and other small molecules, resulting in cellular damage[1-3].

Free radicals play an important role in the toxicity of pesticides and environmental chemicals. Pesticides may induce oxidative stress, leading to generation of free radicals and alteration in antioxidants, oxygen free radicals, the scavenging enzyme system and lipid peroxidation[5].

Seeking stability, radicals attack nearby molecules to obtain another electron and this damage the structure and function of the molecule. If free radicals are not inactivated, their chemical reactivity can damage all cellular macromolecules, including proteins, carbohydrates, lipid and nucleic acids[6].

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Free radicals and other reactive species are derived either from normal essential metabolism in the human body or from external sources, such as exposure to rays, ozone, cigarette smoking, certain drugs, pesticides, air pollutants and industrial chemicals[6,7].

The human body has several mechanisms to counteract the damage caused by free radicals. The basic and the most important defense mechanism of the human body are antioxidant agents. The term antioxidant has been defined as any substance that delays or inhibits oxidative damage to target molecule. These molecules are stable enough to neutralize free radicals have been found to have antioxidant activity, but in the human body, they can be categorized in two main systems. The main system of defense against damage from free radicals is the enzymatic system that opposes oxidation[8]. The body maintains pools of the antioxidant vitamins, such as vitamin E, vitamin C, β-carotene and vitamin A precursor. This first defence system tries to handle all free radicals, but if the oxidative stress is far greater than the capacity of the system, the second line of defense (vitamins) may come into play. Vitamins scavenge and quench free radicals, but are oxidized and in activated in the process. Each of these antioxidant nutrients has specific activities and they often work synergistically to enhance the overall antioxidant capacity of the body[9].

Recently, 6-hydroxy-7-methoxy-4-chromanone and chroman-2-carbox--amides have been reported as antioxidant[10]. Furtheremore, some similar chalcones have shown antitumor, antiinflammatory, antiplasmodial, immunosuppression, antioxidant and cytotoxic effects[11].

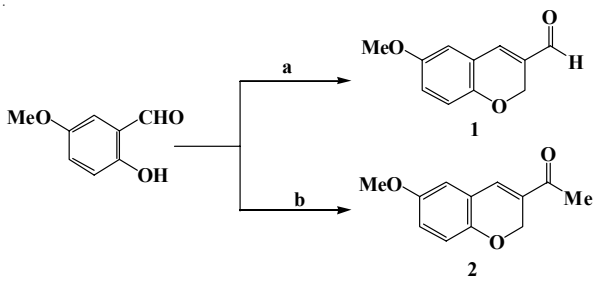
In this study, we reported the synthesis of two substituted chalcones bearing a chromene ring and evaluation of the antioxidant activity of the synthesized compounds in comparison with trolox.

EXPERIMENTAL

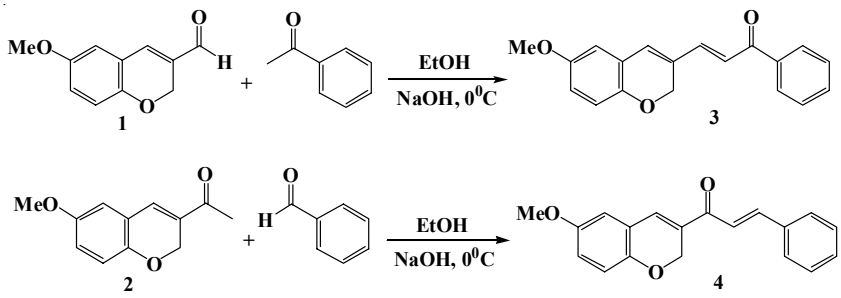
The synthesis of 6-methoxy-2*H*-chromanene derivatives (**1** and **2**) was achieved through the route outlined in **Scheme-I**. The reaction of 5-methoxy-2-hydroxybenzaldehyde with acrolein or methyl vinyl ketone using potassium carbonate in refluxing dioxane gave the corresponding chromenes **1** and **2**, respectively[12].

Base catalyzed condensation of **1** with acetophenone in ethanol afforded 3-(6-methoxy-2*H*-chromen-3-yl)-1-phenylprop-2-en-1-one (**3**). Similarly, condensation of **2** with benzaldehyde afforded 1-(6-methoxy-2*H*-chromen-3-yl)-3-phenylprop-2-en-1-one (**4**) (**Scheme-II**). The synthesized compounds were characterized by ^{1}H NMR, IR and mass spectral data.

Compounds **3** and **4** were evaluated for their antioxidant activity using ferric reducing antioxidant power (FRAP) and DPPH free radical scavenging methods.



Scheme-I. Reagents and condition: (a) acrolein, K_2CO_3, 1,4-dioxane, reflux; (b) methyl vinyl ketone, K_2CO_3, 1,4-dioxane, reflux



Scheme-II

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker FT-80 and chemical shifts are expressed as δ (ppm) with tetramethylsilane as internal standard. The IR spectra were obtained on a Shimadzu 470 spectrophotometer (KBr disks). The electron impact mass (EIMS) spectra were run on a Finigan TSQ-70 spectrometer (Finigan, USA) at 70 eV. Merck silica gel 60 F254 plates were used for analytical TLC. Yields of purified product were not optimized.

Synthesis of 6-methoxy-2*H*-chromen-3-carbaldehyde (1): 5-Methoxy-2-hydroxybenzaldehyde (7 mmol) and potassium carbonate (7 mmol) were taken in 12.5 mL of 1,4-dioxane and treated with acrolein (0.5 mL). The mixture was heated at 100 ºC for 8 h and allowed to cool. The mixture was diluted with water and extracted several times with ether. The combined ether extracts were dried (Na_2SO_4) and evaporated to give **1** as a yellow solid which was crystallized from ethyl acetate-hexane mixture[12].

Yield: 89 % (lit.[12] Yield: 72 %); m.p. 48-49 ºC; ^{1}H NMR (80 MHz, $CDCl_3$) δ: 9.58 (s, 1H, CHO), 7.20 (s, 1H, H_4), 6.94-6.68 (m, 3H, H_5, H_7 and H_8), 4.96 (d, 2H, CH_2), 3.78 (s, 3H, 6-OMe). IR (KBr, cm^{-1}) ν_{max}: 2847

(C-H, aldehyde), 1664 (C=O). Ms (m/z, %): 190 (M^+, 100), 161 (60), 147 (18), 118 (26), 91 (26), 89 (19), 63 (10).

Synthesis of 1-(6-methoxy-2*H*-chromen-3-yl)ethanone (2): 5-Methoxy-2-hydroxybenzaldehyde (6 mmol) and potassium carbonate (6 mmol) were taken in 6 mL of 1,4-dioxane and treated with methyl vinyl ketone (0.4 mL). The mixture was heated at 100 ºC for 4 h and allowed to cool. The mixture was diluted with water and extracted several times with ether. The combined ether extracts were dried (Na_2SO_4) and evaporated to give **2** as a yellow solid. The compound was crystallized from ethyl acetate-hexane mixture.

Yield: 96 %; m.p. 56-58 ºC; ^{1}H NMR (80 MHz, $CDCl_3$) δ: 7.26 (s, 1H, H_4), 6.89-6.64 (m, 3H, H_5, H_7 and H_8), 4.94 (d, 2H, J = 1.19Hz, CH_2), 3.77 (s, 3H, 6-OMe), 2.40 (s, 3H, Me). IR (KBr, cm^{-1}) ν_{max}: 1649 (C=O). Ms (m/z, %): 204 (M^+, 100), 203 (18), 162 (10), 161 (60), 147 (10), 118 (24), 89 (10), 43 (25).

Synthesis of 3-(6-methoxy-2*H*-chromen-3-yl)-1-phenyl prop-2-en-1-one (3): Compound **1** (0.5 mmol), acetophenone (0.5 mmol) and a solution of 3.5 M NaOH (2mL) in absolute ethanol (5 mL), was stirred in an ice bath for 24 h. Water was added and the precipitate was collected and crystallized from ethanol to give **3** as yellow shiny crystals.

Yield: 55 %; m.p. 56-58 ºC; ^{1}H NMR (80 MHz, $CDCl_3$) δ: 8.10-7.40 (m, 5H, aromatic), 7.26 (s, 1H, H_4), 6.98-6.62 (m, 5H, CH-2, CH-3, H_5, H_7 and H_8), 5.02 (s, 2H, CH_2), 3.78 (s, 3H, 6-MeO). IR (KBr, cm^{-1}) ν_{max}: 1649 (C=O). Ms (m/z, %): 292 (M^+, 60), 277 (28), 227 (16), 187 (38), 142 (23), 113 (30), 105 (75), 76 (86), 45 (100).

Synthesis of 1-(6-methoxy-2*H*-chromen-3-yl)-3-phenyl prop-2-en-1-one (4): Compound **4** was synthesized by condensation of **2** (0.5 mmol) with benzaldehyde (0.5 mmol) using the same procedure for **3**.

Yield: 76 %; m.p. 73-75 ºC; ^{1}H NMR (80 MHz, $CDCl_3$) δ: 7.80-7.15 (m, 8H, H_4, CH-2, CH-3 and aromatic), 6.95-6.66 (m, 3H, H_5, H_7 and H_8), 5.12 (d, 2H, CH_2), 3.79 (s, 3H, 6-OMe). IR (KBr, cm^{-1}) ν_{max}: 1649 (C=O). Ms (m/z, %): 293 ([M^++1], 38), 291 (60), 273 (38), 270 (16), 159 (38), 130 (50), 100 (100), 74 (100).

RESULTS AND DISCUSSION

Antioxidants may be classified according to their mode of action as being free radical scavenger, chelators of metal ions involved in catalyzing lipid oxidation or oxygen scavengers that react with oxygen in closed systems[13]. Several different methods are available to assess the total antioxidant capacity of numerous molecules. In the present study, two commonly used antioxidant evaluation methods, the DPPH and FRAP methods were chosen to determine the antioxidant potential of the target compounds in comparison with trolox and they have been reported in our previous study[14].

DPPH radical scavenging activity: The DPPH radical scavenging model is extensively used to evaluate antioxidant activities in less time than other methods. DPPH is a stable free radical that can accept an electron or hydrogen radical and thus be converted into a stable, diamagnetic molecule. DPPH has an odd electron and so has a strong absorption band at 517 nm. When this electron becomes paired, the absorption decreases with respect to the number of electrons taken up.

The scavenging effect of the synthesized compounds on the DPPH radical was evaluated according to the reported method[15]. The IC_{50} values of 69 ± 0.38 and 67 ± 0.44 μM were obtained for compounds **3** and **4**, respectively. Both compounds showed a good DPPH free radical scavenging activity with respect to trolox (36.4 ± 0.53 μM).

Ferric reducing antioxidant power (FRAP) activity: The FRAP assay measures the ability of a compound to reduce the ferric 2,4,6-tripyridyl-*s*-triazine complex to the coloured ferrous complex. FRAP values are obtained by comparing the absorbance change at 593 nm in test reaction mixtures with those containing Fe^{2+} ions in known concentration[16]. According to the data, compound **3** (89 ± 0.37 μM Fe^{2+}) showed better antioxidant power in comparison with compound **4** (102 ± 0.41 μM Fe^{2+}). Generally, both compounds exhibited less potent antioxidant potential in FRAP assay with respect to reference drug trolox (49.3 ± 0.27 μM Fe^{2+}).

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