Journal of Molecular Structure 1148 (2017) 512–520

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

Synthesis, antihyperglycemic activity and computational studies of antioxidant chalcones and flavanones derived from 2,5 dihydroxyacetophenone

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ARTICLE INFO

Article history:
Received 16 January 2017
Received in revised form
29 June 2017
Accepted 19 July 2017
Available online 20 July 2017

Keywords:
Chalcones
Flavanones
Antioxidant
Diabetes
Antihyperglycemia

ABSTRACT

Chronic exposure of supraphysiologic glucose concentration to cells and tissues resulted in glucose toxicity which causes oxidative stress. Antioxidants have promising effect in suppressing the oxidative stress in the pathogenesis of diabetes mellitus (DM). Condensation of 2,5-dihydroxyacetophenone with different nitrobenzaldehydes was used to synthesize antioxidant nitro substituted chalcones along with nitro substituted flavanones in one step protocol. The compounds were characterized by IR, ^{1}H NMR and ^{13}C NMR and then screened for their *in vitro* antioxidant and *in vivo* antihyperglycemic activities. Postulated structures of the synthesized compounds were in agreement with their spectral data. The results indicated that the novel compound (2E)-1-(2,5-Dihydroxyphenyl)-3-(2-nitrophenyl) prop-2-en-1-one (2a) was potent antioxidant because of its lower IC_{50} value compared with trolox and ascorbic acid. Compound 2a also exhibited excellent antihyperglycemic activity in diabetic rats while the compound (E)-1-(2,5-Dihydroxyphenyl)-3-(4-nitrophenyl)prop-2-one (2c) suppressed the hyperglycemia more effectively in normal rats. The radical scavenging activity behavior was elucidated on the basis of hydrogen atom transfer and one-electron transfer mechanisms by density functional theory (DFT). The compound 2a showed the smallest ionization potential and bond dissociation enthalpy. Experimental and computational investigations concluded that compound 2a might be an effective antihyperglycemic agent because of its antioxidative nature and smallest ionization potential.

1. Introduction

Production of free radical is enhanced in the body due to oxidation of glucose, non-enzymatic glycation of proteins and the subsequent oxidative degradation of glycated proteins [1]. In diabetes mellitus (DM), erratically controlled hyperglycemia promotes free radicals accumulation and cause oxidative stress by enhancing the cascade of the oxidative reaction [2]. Antioxidants can be helpful in suppressing the oxidative stress and its related disorder including DM [3].

Chalcones and flavanones are well-known for their wide range of pharmacological activities including antimicrobial [4], anticancer, antioxidant [5], antiangiogenic [6], anti-inflammatory [7], antidiabetic, antihyperlipidemic [8], inhibition of tyrosinase activities [9] etc. Excellent antioxidant activity of chalcones and flavanones is due to the presence of hydroxyl groups on 'A' or 'B' ring of their structure. This antioxidant potential is involved in decreasing the oxidative stress in various diseases including cancer, atherosclerosis, DM, hypertension and heart diseases [10]. (see Fig. 1)

Both *in vitro* and *in vivo* studies have also demonstrated the effects of hydroxychalcones and hydroxyflavanones, originating from both natural and synthetic sources on the carbohydrate

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http://dx.doi.org/10.1016/j.molstruc.2017.07.042
0022-2860/

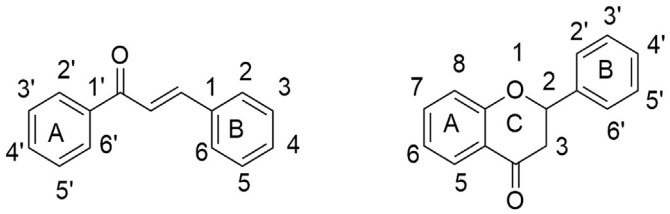

Fig. 1. Structure of chalcone and flavanone.

metabolism and regulation of insulin function [11], [8]. Antioxidant compounds are reported to have potential protective effects on diabetes by improving β-cells function. So enhancing antioxidant defense mechanisms in pancreatic islets may be a potential pharmacological approach to manage the diabetes [12].

Various drugs are on the horizon as well as there is a need to develop a new category of drug with lesser side effects and improve the variety of medications. In recent years, the high therapeutic properties of the chalcones and flavanones related drugs have brought attention of chemists to synthesize various kinds of their derivatives by improving the existing synthetic methodologies. Claisen-Schmidt condensation is usually used to synthesize the chalcones in the presence of basic catalysts such as NaOH/KOH [13], MgO, BaO, K_2O, Na_2O and ZaO [14]. It has been reported previously that the hydroxychalcones are difficult to synthesize in the presence of base due to formation of phenoxide anion. Acidic catalyst such as HCl, BF_3, B_2O_3 [15], para toluenesulfonic acid [16] and $SOCl_2$/EtOH [17] have been found to be more effective. It is therefore, the present work was designed to synthesize new chalcones and flavanones in the presence of acid without the protection of hydroxyl group. Furthermore, the main objective was to investigate *in vitro* and *in silico* antioxidant activities along with *in vivo* antihyperglycemic activities of synthesized compounds.

2. Experimental

2.1. Materials and methods

Chemicals were purchased from well reputed international suppliers. The chemicals were used mostly as such however when required purified by normal techniques i.e., distillation and recrystallization. Synthesis of 2, 5-dihydroxyacetophenone was done by already reported method [18]. Silica gel 60 F_{254} TLC plates were used to monitor the reaction. FT-IR, ^{1}H NMR and ^{13}C NMR spectra were recorded on Agilent Technologies 41630, AVANCE AV-400 MHz and AVANCE AV-500 MHz, and Bruker 125 MHz respectively while the EIMS data was taken on JEOL MS 600H-1.

2.2. General method for the synthesis of chalcones and flavanones

2,5-Dihydroxyacetophenone (50 mg, 0.3 mmol) and nitrobenzaldehyde (45 mg, 0.3 mmol) were dissolved in hot dry benzene (20 mL). Then p-Toluene sulfonic acid (5 mg, 0.03 mmol) was added. The resulting reaction mixture was refluxed for 48 h. The reaction was monitored with TLC. After completion of the reaction, benzene was removed under vacuum and residue was purified on silica gel column using hexane-ethyl acetate (4:1) as eluent. In case of 3-nitrobenzaldehyde and 4-nitrobenzaldehyde, corresponding flavanones were also isolated along with chalcones. Whereas with 2-nitrobenzaldehyde only a novel chalcone (2a) was obtained.

2.3. (2E)-1-(2,5-Dihydroxyphenyl)-3-(2-nitrophenyl) prop-2-en-1-one (2a)

Orange powder; yield 80%; IR (ν cm^{-1}): 3367; 1648; 1571; 1517.^{1}H NMR (500 MHz/DMSO-d_6): δ 11.34 (1H, s, 2′-OH), 9.28 (1H, s, 5′−OH), 8.12 (2H, m, 3-H, 6-H), 8.00 (1H, d, *J=15.5* Hz, β-H), 7.87−7.82 (2H, m, α-H, 5-H), 7.72 (1H, t, *J=7.2* Hz, 4-H), 7.41 (1H, d, *J=3* Hz, 6′-H), 7.05 (1H, dd, *J=8.8* Hz, 3.0 Hz, 4′-H), 6.87 (1H, d, *J=8.8 Hz*, 3′-H). ^{13}C NMR: δ 192.83, 154.56, 150.09, 149.22, 138.70, 134.33, 131.65, 130.11, 129.93, 127.67, 125.22, 125.00, 121.87, 118.92, 115.56. MS (EI$^+$): *m/z* 137 (100%), M$^+$ 285 (5), 27 (86), 238 (83).

2.4. (2E)-1-(2,5-Dihydroxyphenyl)-3-(3-nitrophenyl)prop-2-en-1-one (2b)

Orange powder; yield 53%; IR (ν cm^{-1}): 3430; 1643; 1561; 1530.^{1}H NMR (400 MHz/DMSO-d_6): δ 11.60 (1H, s, 2′-OH), 9.29 (1H, s, 5′-OH), 8.73 (1H, s, 2-H), 8.31 (1H, d, *j=7.8 Hz*, 4-H), 8.28 (1H, m, 4-H, 6-H), 8.10 (1H, d, *J=15.7 Hz*, β-H), 7.88 (1H, d, *J=15.6 Hz*, α-H), 7.75 (1H, t, *J=7.9 Hz*, 3-H), 7.54 (1H, d, *J=2.8 Hz*, 6′-H), 7.06 (1H, dd, *J=8.8, 2.8 Hz*, 4′-H), 6.87 (1H, d, *J=8.8 Hz*, 3′-H). ^{13}C NMR: δ 193.41, 154.98, 150.04, 148.89, 142.00, 136.84, 135.64, 130.93, 125.74, 125.30, 125.15, 123.49, 121.54, 118.84, 115.72.

2.5. 6-Hydroxy-2-(3-nitrophenyl)-2,3-dihydro-4H-chromen-4-one (3a)

Yellow crystals; yield 25%; IR (ν cm^{-1}): 3472, 1670; 1524; 1342.^{1}H NMR (500 MHz/DMSO-d_6): δ 9.57 (1H, s, 6-OH), 8.40 (1H, s, 2′-H), 8.24 (1H, dd, *J=8.2 Hz*, 2.0 Hz, 4′-H), 8.00 (1H, d, *J=7.8 Hz*, 6′-H), 7.74 (1H, t, *J=8 Hz*, 5′-H), 7.13 (1H, d, *J=3.0 Hz*, 5-H), 7.07 (1H, dd, *J=8.8, 3.0 Hz*, 7-H), 7.02 (1H, d, *J=8.8 Hz,* 8-H), 5.75 (1H, dd, *J=13.1, 2.7 Hz*, 2-H), 3.22 (1H, m, Ha), 2.88 (1H, dd, *J=16.9, 2.9 Hz*, Hb). ^{13}C NMR: δ 191.72, 154.47, 152.28, 148.35, 141.87, 133.56, 130.72, 125.14, 123.73, 121.63, 121.32, 119.54, 110.46.

2.6. (E)-1-(2,5-Dihydroxyphenyl)-3-(4-nitrophenyl)prop-2-one (2c)

Orange powder; yield 65%; IR (ν cm^{-1}): 3355; 1648; 1584; 1522.^{1}H NMR (500 MHz/DMSO-d_6): δ 11.44 (1H, s, 2′-H), 9.18 (1H, s, 5′-H), 8.28 (2H, d, *J=8.4 Hz*, 3-H, 5-H), 8.13 (2H, d, *J=8.8 Hz*, 2-H, 6-H), 8.07 (1H, d, *J=16 Hz*, β-H), 7.82 (1H, d, *J=15.6 Hz*, α-H), 7.48 (1H, d, *J=2.4 Hz*, 6′-H), 7.04 (1H, dd, *J=8.8, 2.8 Hz*, 4′-H), 6.85 (1H, d, *J=8.8 Hz*, 3′-H). MS (EI$^+$): *m/z* 136 (100%), M$^+$ 285 (91), 266 (9), 238 (8), 163 (45).

2.7. 6-Hydroxy-2-(4-nitrophenyl)-2,3-dihydro-4H-chromen-4-one (3b)

Light orange powder; yield 20%; IR (ν cm^{-1}): 3355; 1648; 1584; 1522.^{1}H NMR (400 MHz/DMSO-d_6): δ 9.57 (1H, s, 6-OH), 8.29 (2H, d, *J=8.7 Hz*, 3′-H, 5′-H), 7.82 (2H, d, *J=8.7 Hz*, 2′-H, 6′-H), 7.13 (1H, d, *J=3.0 Hz*, 5-H), 7.07 (1H, dd, *J=8.8, 3.0 Hz*, 7-H), 7.01 (1H, d, *J=8.8*, 8-H), 5.75 (1H, dd, *J=12.9, 2.9 Hz*, 2-H), 3.15 (1H, m, Ha), 2.89 (1H, dd, *J=16.9, 3.0 Hz*, Hb). ^{13}C NMR: δ 191.56, 154.42, 152.29, 147.78, 146.99, 128.08, 125.16, 124.18, 121.34, 119.54, 110.46, 78.14, 43.92.

2.8. In vitro antioxidant activities

The synthesized compounds were tested individually against five different *in vitro* antioxidant activities which include 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging, iron chelating, $FeCl_3$ reducing power, phosphomolybdenum (PM) and 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)