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Structural Characterization of Chrysin Derivatives

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ABSTRACT

New series of chrysin derivatives were synthesized from 2,4,6-trihydroxyacetophenone using modified Baker-Venkataraman transformation. The chemical structures of the synthesized derivatives were confirmed by spectral and elemental data analysis.

Keywords: Synthesis; Chrysin; MS; IR

INTRODUCTION

Structurally, flavonoids belong to the class of polyphenolic compounds that are universally found among various plants kingdom and are largely consumed for the therapeutic purposes [1,2]. Flavones are secondary metabolites and represent the major subclass of flavonoids. They have basic carbon skeleton consisting of two benzene rings A and B, linked by a three carbon chain that forms a closed pyran ring C. Therefore, their structure is also denoted as C6-C3-C6. The distinctive features of flavone is the presence of double bond between position 2 and 3 and a ketone group at position 4 of the ring C [3]. A natural flavone Chrysin (5,7-dihydroxyflavone), commonly found in several plant extracts, has been reported to exhibit various biological activities such as anti-cancer [4,5], anxiolytic [6,7], anti-inflammatory [8,9], anti-virus [10], anti-oxidant [11,12], anti-bacterial [13], anti-diabetic [14], and hepatoprotective [15] effects. Owing to numerous bioactivities, chrysin has gained particular interest as a beneficial and health promoting agent. However, its therapeutic potential has been significantly restricted due to its low solubility, poor absorption, and the rapid metabolism [16]. Molecular modification is one of the approach through which we can enhance ADME properties of drug moeities. To overcome the drawbacks, we planned to synthesize several derivatives of chrysin in view to obtain compounds with improved efficacy and selectivity that can be used clinically. The synthetic method involves Baker-Venkataraman rearrangement as a key step. Different substituents are added to B ring of chrysin, and all the synthezised compounds were characterized by their spectral data.

EXPERIMENTAL SECTION

All the chemicals and reagents were purchased commercially and used without further purification, unless otherwise stated. Thermo ink precision melting point apparatus was used to determine melting point and are uncorrected. Thin Layer Chromatography (TLC) was performed to ascertain the purity of the compounds. The samples were prepared in methanol and the solvent system used as mobile phase was petroleum ether: ethyl acetate (2:3). The solutions of the compounds were spotted on glass plate coated with silica gel G and the spots were visualized in the UV chamber at 254 nm. IR spectra were recorded in the region of 400-4000 cm^{-1} using KBr pellets on Shimadzu Fourier Transform Infrared Spectrophotometer (FTIR-8400s). All compounds were sent to Diya Labs Analytical Services, Airoli, Mumbai for ^{1}H NMR and Mass spectral study. The 1H NMR spectra were recorded on Bruker Avance 300 spectrometer at 300 MHz in DMSO using tetramethylsilane (TMS) as internal standard (chemical shift in δ ppm). Mass spectra were acquired using Pe-Sciex API 2000 in Q1MSQ1 mode and scanned in 110-500 m/z range.

General method for preparation of 2-substituted benzoyloxy-4,6-dihydroxy acetophenone 3a-e

In a stoppered conical flask, 0.25 mol of 2,4,6-trihydroxy acetophenone and 0.35 mol of substituted benzoyl chloride were taken. To it 50 mL of dry redistilled pyridine was added. The contents in the flask were mixed thoroughly. After 20 minutes, the reaction mixture was poured with stirring into 1200 mL of 1 M hydrochloric acid containing 500 g of crushed ice. The crude product was filtered and washed with 50 mL ice-cold methanol followed by 50 mL of water. The product was recrystallized from methanol [17].

General method for preparation of 1-(substituted phenyl)-3-(2,4,6-trihydroxyphenyl) propane-1,3-dione 4a-e

In a stoppered conical flask, 0.2 mol of 2-substituted benzoyloxy-4,6-dihydroxy acetophenone was dissolved in 180 mL of dry pyridine and the solution was heated upto 50°C. To it 0.3 mol of potassium hydroxide was added with the mechanical stirring. The contents were continued to stir for about 15 minutes. The mixture was cooled to room temperature and acidified with stirring by adding 10% aqueous acetic acid. The pale yellow coloured precipitate was collected and dried in oven at 50°C. The product was recrystallized from methanol [17].

General method for preparation of 5,7-dihydroxy-2-(substituted phenyl) -4H-chromen-4-one 5a-e

In a round conical flask, 0.15 mol of substituted 2,4,6-trihydroxydibenzoyl methane was dissolved in 200 mL of glacial acetic acid. To it 8 mL of concentrated sulphuric acid was added. The reaction mixture was refluxed on water bath with intermittent shaking for 1 hour. The content was poured with stirring onto crushed ice. The crude product was filtered, washed with water and dried in an oven at 50°C. The product was recrystallized from light petroleum [17].

5,7-dihydroxy-2-(phenyl)-4H-chromen-4-one (5a)

5,7-dihydroxy-2-(phenyl)-4H-chromen-4-one (5a) mp 284-288°C; Rf: 0.80 (petroleum ether: ethyl acetate 2:3); IR (potassium bromide): 3151.69 cm^{-1} (Ar-CH stretch), 1628.36 cm^{-1} (C-O-C stretch), 1400 cm^{-1} (C=C stretch); 1H NMR (DMSO-d6): δ 10.374 (m, 1H, 7-OH), 12.232 (s, 1H, 5-OH), 6.523 (d, 1H, H-8), 6.94 (s, 1H, H-3), 8.06 (d, 2H, H-2'-6'), 7.59 (m, 3H, H-3'4',5'); MS: m/z: 255 (M+); Anal. Calcd. for $C_{15}H_{10}O_4$: C, 70.86; H, 3.96; O, 25.17; Found: C, 71.61; H, 3.52; O, 24.76.

5,7-dihydroxy-2-(4'-chlorophenyl)-4H-chromen-4-one (5b)

5,7-dihydroxy-2-(4'-chlorophenyl)-4H-chromen-4-one (5b) mp 214-218°C; Rf: 0.82 (petroleum ether: ethylacetate 2:3); IR (potassium bromide): 3151.69 cm^{-1} (Ar-CH stretch), 1628.36 cm^{-1} (C-O-C stretch), 1400 cm^{-1} (C=C stretch), 750 cm^{-1} (Ar-Cl); ^1H NMR (DMSO-d6): δ 10.3676 (s, 1H, 5-OH), 12.236 (s, 1H, 7-OH), 6.351 (d, 1H, H-8), 6.228 (s, 1H, H-3), 8.066 (d, 2H, H-2'-6'), 7.56 (m, 3H, H-3'4',5'); MS: m/z: 289 (M+); Anal. Calcd. for $C_{15}H_9C_{lO4}$: C, 62.41; H, 3.14; O, 22.17; Found: C, 62.16; H, 3.28; O, 22.35.

5,7-dihydroxy-2-(4'-methoxyphenyl)-4H-chromen-4-one (5c)

5,7-dihydroxy-2-(4'-chlorophenyl)-4H-chromen-4-one (5b) mp 106-110°C; Rf: 0.84 (petroleum ether: ethyl acetate 2:3); IR (potassium bromide): 3363.86 cm^{-1} (Ar-CH), 3531.66 cm^{-1} (Ar-OH), 1665.30 cm^{-1} (C-O-C), 1427 cm^{-1} (C=C Aromatic), 2800 cm^{-1} (Ar-CH); 1H NMR (DMSO-d6): δ 10.367 (s, 1H, 5-OH), 12.323 (s, 1H, 7-OH), 6.314 (d, 1H, H-8), 6.211 (s, 1H, H-3), 8.046 (d, 2H, H-2'-6'), 7.111 (m, 3H, H-3',4',5'); MS: m/z: 284 (M+); Anal. Calcd. for $C_{16}H_{12}O_5$: C, 67.6; H, 4.25; O, 28.14; Found: C, 67.38; H, 4.65; O, 28.99.

5,7-dihydroxy-2-(2'-fluorophenyl)-4H-chromen-4-one (5d)

5,7-dihydroxy-2-(2'-fluorophenyl)-4H-chromen-4-one (5d) mp 158-160°C; Rf: 0.81 (petroleum ether:ethyl acetate 2:3); IR (potassium bromide): 3203.76 cm^{-1} (Ar-OH), 3400 cm^{-1} (Ar-CH), 1467.83 cm^{-1} (C=C Aromatic), 1679.72 cm^{-1} (C-O-C), 1138.00 cm^{-1} (Ar-F); 1H NMR (DMSO-d6): δ 10.369 (s, 1H, 5-OH), 12.231 (s, 1H, 7-OH), 6.346 (d, 1H, H-8), 6.232 (s, 1H, H-3), 8.006 (d, 2H, H-6'), 7.421 (m, 3H, H-4',5'); MS: m/z: 274 (M+); Anal. Calcd. for $C_{15}H_9FO_4$: C, 66.18; H, 3.33; O, 23.51; Found: C, 66.23; H, 3.25; O, 23.38.

5,7-dihydroxy-2-(4'-nitrophenyl)-4H-chromen-4-one (5e)

5,7-dihydroxy-2-(4'-nitrophenyl)-4H-chromen-4-one (5e) mp 118-120°C; Rf: 0.72 (petroleum ether: ethyl acetate 2:3); IR (potassium bromide): 3151.69 cm^{-1} (Ar-CH), 1628.36 cm^{-1} (C-O-C), 1400 cm^{-1} (C=C Aromatic), 2320.37 cm^{-1} (Ar-$_{NO2}$); 1H NMR (DMSO-d6): δ 10.369 (s, 1H, 5-OH), 12.236 (s, 1H, 5-OH), 6.401 (d, 1H, H-8), 6.276 (s, 1H, H-3), 8.162 (d, 2H, H-2'-6'), 7.421 (m, 3H, H-3',4',5'); MS: m/z: 294.3 (M+); Anal. Calcd. for $C_{15}H_9NO_6$: C, 60.21; H, 3.03; O, 32.08; Found: C, 60.99; H, 3.43; O, 32.80.

RESULT AND DISCUSSION

Compounds 5a-e were synthesized according to the general procedure illustrated in Scheme 1. Commercially available benzoyl chloride/substituted benzoyl chloride 2a-e were reacted with 2,4,6-trihydroxyacetophenone 1a in the presence of pyridine, potassium hydroxide to give the corresponding 1,3 diketones 4a-e. Treatment of 4a-e with acetic acid followed by the flavone ring formation gave 5,7-dihydroxy flavone derivatives 5a-e. The analytical and spectral data of all the synthesized compounds were in conformity with the structure assigned, and detailed spectra are given in the Experimental section.

CONCLUSION

Chrysin derivatives were synthesized and the structures were confirmed by spectral and elemental data.

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