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Synthesis of Two Novel Flavonoid Derivatives with Extended π-System: Possible UV-B and UV-A Sunscreens

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Two novel flavonoid derivatives **5** and **6** were synthesized and characterized by IR, ^{1}H, ^{13}C NMR spectroscopy and mass spectrometry. The core structure of the two flavonoids was constructed by applying Baker-Venkataraman rearrangement on 2-acylphenyl ester intermediate. The two compounds exhibited remarkable UV-visible absorption activities compared to flavone. Flavonoid **5** showed a bathochromic shift of 75.6 nm when the size of the cinnamic acid was increased by phenylbutadienyl group and hence it is a good UVA sunscreen. The 4-nitrostyryl group introduced in the cinnamic acid subchromophore of flavonoid **6** causes the compound to absorb at 308.3 and at 345.8 nm which will make it a broad-spectrum sunscreen.

Keywords: Flavonoids, Baker-Venkataraman rearrangement, UV-visible absorption, Sunscreens, Bathochromic shit.

INTRODUCTION

Ultraviolet radiation (UVR) reaching the earth surface composed of about 95 % of UVA (aging rays, 320-400 nm) and 5 % of UVB (burning rays, 290-320 nm) [1]. This UV radiation causes a wide range of chronic types of skin damage such as sunburn, wrinkling, immunosuppression and photocarcinogenesis [2]. The shortest wavelength radiation, UVC (200-290 nm), is far more harmful to the skin than UVA and UVB, but fortunately, it is completely absorbed by ozone and molecular oxygen in the earth's atmosphere [3]. Prolong UVA exposure can cause significant damage in areas of the dermis layer and cause early aging, sagging and dry appearance of the skin [4]. Furthermore, chronic UVA exposure produces chemical alteration of DNA which leads to development of skin cancer [5]. It has been documented that about 67 % of malignant melanoma is attributed to UVA radiation [6,7]. UVA radiation triggers the release of melanin dye in the epidermis layer which causes the darkening of the skin [7]. Exposure to UVB radiation causes oxidative damage to the epidermal layer which leads to reddening and sunburn of the skin [8]. UVB radiation can harm the skin directly by inducing inflammation and proliferation or indirectly by depleting the antioxidants in the skin and producing reactive oxygen species (ROS) [9,10]. The most common type of human skin cancer, non-melanoma cancer (NMSC), is attributed to prolong exposure to UVB rays [11].

Given the adverse effect of UVR on the skin, several physical and chemical sunscreens have been developed and used to provide effective photoprotection against harmful UV radiation [12]. The principle of photoprotection in physical sunscreens such as titanium dioxide (TiO_2) is based on reflection of UVA and UVB rays away from the skin [13]. Chemical sunscreens, on the other hand, are organic aromatic compounds conjugated with carbonyl group capable of absorbing UVA and UVB radiations and hence protecting the skin from their harmful effects [14]. One of the earliest organic sunscreen developed was *p*-aminobenzoic acid. This synthetic sunscreen was found to cause photocontact allergies and degrades under sunlight into carcinogenic nitrosamine product [15]. Many other commercial synthetic organic compounds such as oxybenzone, octocrylene and avobenzone found their way into the market and became widely used as body sunscreens [16-18]. Unlike their physical counterparts, chemical sunscreens are invisible on the skin surface and therefore they are more commercially desired. However, several reports in the literature have shown that synthetic organic sunscreens, in general, cause skin irritation and phototoxic reactions. Moreover, under extensive UV irradiation, organic sunscreens tend to degrade into toxic radical species that can interact with biological molecules [19].

New trend has emerged of using naturally occurring substances to protect against UV radiation. Several natural compounds such as sulforaphane, ascorbic acid, β-carotene

and resveratrol have demonstrated their UV-shielding properties [20]. Curcumin, a yellow spice collected from *Curcuma longa* has been shown to provide effective photoprotection against UVB radiation [21]. Flavonoids are a class of secondary plant metabolites distributed widely in the leaves, seeds, bark and flowers [22]. They are responsible for the wonderful colours of flowers and provide protection for the plants against harmful UV radiation [23]. Flavonoids exhibit a wide range of pharmaceutical application such as antioxidant, anti-inflammatory, antitumor and cardioprotective properties [24-27]. Due to their highly conjugated aromatic structure, many flavonoids have been utilized to protect against UV radiation [28]. For instance, flavone showed an efficient pro-tection for zebrafish from UV induced damage [29]. Quercitrin, a common flavonoid in nature, functions as an antioxidant against UVB irradiation-induced oxidative damage to skin [30]. Flavonoids naringenin and rutin prevented the accumulation of DNA damage after irradiated with UVB light [31].

The basic structure of flavonoids can be viewed as a combination of two main fragments: the benzoyl sub-chromophore and the cinnamic acid sub-chromophore (Fig. 1). The absorption behaviour of flavonoids can be tuned according to particular needs by adjusting the substitution pattern on these two subchromofores. In this regard, when the cinnamic acid fragment in flavone **1** was extended by inserting a vinyl group, the absorption maximum has shifted from 289 to 330 nm in flavonoid **2** [32]. Such bathochromic shift makes flavonoid **2** a UVA sunscreen and hence can be used to protect against photoaging. In addition, when hydroxyl group (an electron-releasing) attached to the benzoyl subchromophore of flavone **1** a hypsochromic shift was observed from 289 to 265 nm in flavonoid **3** which will make it a good UVC sunscreen (Fig. 1) [33].

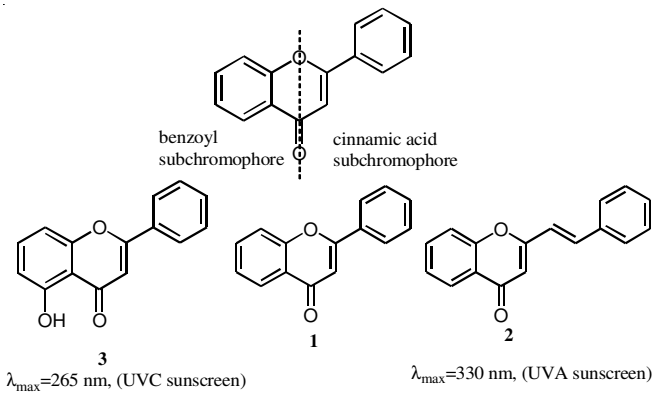


Fig. 1. Structure of flavonoids and UV absorptions of flavonoids derivative **2** and **3**

We have reported the synthesis of a novel flavonoid derivative **4** with extended π-system in the cinnamic acid sub-chromophore through the addition of a styryl group [34]. Flavonoid **4** showed a bathochromic shift from 294 to 320 nm compared to flavonoid **1**. This shift in the absorption maxima causes compound **4** to absorb at the borderline between UVB and UVA light regions. In continuation of our effort to explore the relationship between the structure of flavonoids and their UV absorption aptitudes we report herein the synthesis of two novel flavonoids **5** and **6** by extending the cinnamic acid fragments with *p*-nitrostyryl group in compound **5** and with 1-phenylbutadienyl group in compound **6** (Fig. 2) and to study their UV absorption activities.

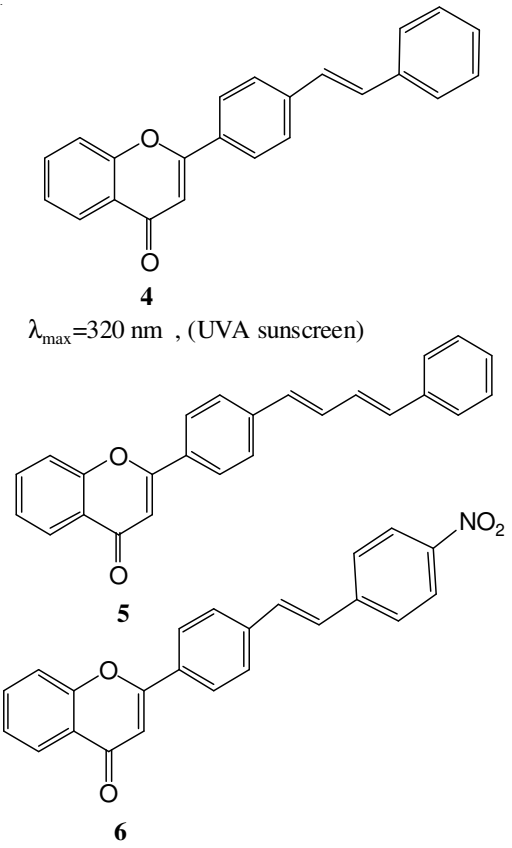


Fig. 2. UV absorption of flavonoid **4** and proposed flavonoid derivatives **5** and **6**

EXPERIMENTAL

All the reagents and solvents used in this study were obtained from Sigma-Aldrich Chemical Company (USA) and used without further purification. Melting points were determined using GallenKamp-MPA350 melting point apparatus (UK). Column chromatography was performed using Merck silica gel 60 (40-63 μm). IR spectra were determined on a Perkin-Elmer FTIR-881 spectrometer (Perkin Elmer, USA) using KBr pellets.

Proton magnetic resonance (^{1}H NMR) spectra were recorded using 400 or 700 MHz Bruker spectrometer (Bruker Corp., UK). Carbon Magnetic Resonance (^{13}C NMR) spectra were recorded at 100.4 or 176 MHz Bruker spectrometer (Bruker Corp., UK). Chemical shifts (δc) are quoted in parts per million (ppm) to the nearest 0.1 and 0.01 and are referenced to the solvent peaks ($CDCl_3$/DMSO-d_6). The NMR data have been processed using Topspin 3.2 software program.

Mass spectra were obtained using Quattro Ultima Pt tandem quadruple mass spectrometer (Waters Corp. MA, USA) instrument. High resolution mass spectra were obtained using Waters LCT Premier XE Mass Spectrometer instrument (determined at the University of Sheffield, UK). UV study was performed on a Shimadzu UV-visible spectrophotometer (multispec-1501, Shimadzu, Japan).

Ultraviolet-visible absorption study: A series of stock solutions were prepared by dissolving 1 mg of each flavone derivative (flavonoids **1**, **4**, **5** and **6**) in 10 mL acetonitrile. From each of the stock solutions, series of diluted solutions were formed by taking 0.3 mL of each stock solution and diluted by acetonitrile to 10 mL. UV-visible measurements were taken against acetonitrile as blank.

Synthesis of *E,E*-4-(4-phenylbuta-1,3-dienyl)benzoic acid (10): 4-Carboxybenzyltriphenylphosphonium bromide (18.06 g, 0.0378 mol) was suspended in dichloromethane (100 mL) in an Erlenmeyer flask. 75 mL of aqueous solution of sodium hydroxide (50 g) and *trans*-cinnamaldehyde (5 g, 0.0378 mol) were added to the reaction mixture. The neck of the flask was plugged with cotton wool and the yellow mixture stirred for 0.5 h. The organic layer was separated and the aqueous layer was extracted with (2 × 20 mL) dichloromethane. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Petroleum ether (50 mL) and few crystals of iodine were added to the residue and the mixture was refluxed for 3 h. The reaction mixture was washed with 25 % sodium metabisulfite and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give a yellow solid. The solid was recrystallized from ethanol to yield yellow needles (6.15 g. 65 %). m.p.: 152.2-153.5 °C; IR (KBr, ν_{max}, cm^{-1}): 3500-2496, 3051, 1670, 1608, 1556. ^1H NMR (400 MHz,$CDCl_3$): δ (ppm) 6.81 (d, 1H, *J* = 10.5 Hz), 6.83 (d, 1H, *J* = 10.5 Hz), 7.12 (dd, 1H, *J* = 10.5, *J* = 15.4 Hz) 7.25 (dd, 1H, *J* = 10.4, 15.4 Hz), 7.28 (m, 2H), 7.36 (m, 1H), 7.55 (m, 2H), 7.61 (d, 2H, *J* = 8.3 Hz), 7.93 (d, 2H, *J* = 8.3 Hz); ^{13}C NMR (100.4 MHz, $CDCl_3$): δ (ppm) 127.10 (2C), 128.59, 129.36 (2C), 129.54, 129.54, 130.38, 130.39, 132.14 (2C), 132.49 (2C), 134.71, 137.27, 168.08. ESI-MS (M^+) calcd. for $C_{17}H_{14}O_2$: 250.29, found: 250.55.

Synthesis of *E,E*-4-(4-phenylbuta-1,3-dienyl)benzoyl chloride: A mixture of *E,E*-4-(4-phenylbuta-1,3-dienyl)benzoic acid (**10**) (3.00 g, 11.99 mmol) and thionyl chloride (2.4 mL, 32.61 mmol) was heated under reflux for 1 h. Excess thionyl chloride was removed under reduced pressure and the crude solid was used for the next step.

Synthesis of *E,E*-2-acetylphenyl 4-(4-phenylbuta-1,3-dienyl)benzoate (12): To a solution of 2-hydroxyacetophenone (1.63 g, 11.99 mmol) in pyridine (2.3 mL) was added *E,E*-4-(4-phenylbuta-1,3-dienyl)benzoyl chloride (3.22 g, 11.99 mmol). The reaction mixture was stirred briefly at room temperature. After cooling, the reaction mixture was poured into a mixture of 60 mL HCl (3 %) and 30 g crushed ice. The product was extracted with chloroform (3 × 10 mL) and the combined organic layer was dried over $MgSO_4$ and evaporated to give yellowish solid. The product was purified by column chromatography on silica gel eluting with hexane: ethyl acetate (8:2) as eluting solvent to give light yellow solid (2.52 g, 56.7 %). m.p.: 124.2-125.4 °C; IR (KBr, ν_{max}, cm^{-1}): 3008, 2922, 1722, 1679, 1598, 1506. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm): 2.55 (3H, s), 6.74 (1H, d, *J* = 15.3 Hz), 6.79 (1H, d, *J* = 15.3 Hz), 6.99 (1H, dd, *J* = 15.3, *J* = 10.6 Hz), 7.11 (1H, dd, *J* = 15.3, *J* = 10.6 Hz), 7.23 (m, 1H)), 7.24 (1H, m), 7.28 (1H, m), 7.34 (m, 2H), 7.37 (2H, m), 7.47 (2H, d, *J* = 8.3 Hz), 7.56 (1H, m), 7.86 (1H, dd, *J* = 7.7, *J* = 1.4 Hz), 8.16 (2H, d, *J* = 8.3 Hz) ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm): 30.12, 124.30, 126.55 (2C), 126.84, 127.04, 128.04, 128.48 (2C), 129.09, 129.16, 129.87, 130.66 (2C), 131.17 (2C),131.78,132.78, 133.80, 135.37, 137.37, 143.27, 149.85, 165.30, 198.04. ESI-MS (M^+) calcd. for $C_{25}H_{20}O_3$: 368.14, found: 368.02.

Synthesis of flavonoid derivative (5): To a solution of *E,E*-2-acetylphenyl-4-(4-phenylbuta-1,3-dienyl)benzoate (**12**) (0.90 g, 2.44 mmol) in pyridine (2.8 mL) at 50 °C was added potassium hydroxide (0. 21 g, mmol) and the mixture was stirred for 15 min. Acetic acid solution (10 %, 4.3 mL) was added to the cooled mixture and the solid intermediate was collected by filtration. To a solution of the solid intermediate in acetic acid (15 mL) was added concentrated sulfuric acid (0.1 mL) and the mixture was refluxed for 1 h. The cooled mixture was poured into ice and the product was collected by suction filtration and washed with water. The product was recrystallized from ethanol to yield flavonoid derivative **5** as bright yellow crystals (0.46 g, 53.7 %). m.p.: 170-172 °C; IR (KBr, ν_{max}, cm^{-1}): 3062, 1641, 1642, 1597, 1506; λ_{max}, (nm) (log ε) 289.6 (4.29), 364.6 (4.77); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm): 6.69 (1H, d, *J* = 15.3 Hz), 6.75 (1H, d, *J* = 15.3 Hz), 6.84 (1H, s), 6.97 (1H, dd, *J* = 10.6, *J* = 15.3 Hz), 7.08 (1H, dd, *J* = 10.6, *J* = 15.3 Hz), 7.29 (1H, m), 7.35 (1H, m), 7.43 (2H, m), 7.46 (2H, m), 7.56 (2H, d, *J* = 8.3 Hz), 7.68 (1H, m), 7.71 (1H, m), 7.89 (2H, d, *J* = 8.3 Hz), 8.23 (1H, dd, *J* = 1.4, *J* = 7.9 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm): 107.56, 118.48, 124.40, 125.69, 125.63, 126.12, 127.00 (2C), 127.02 (2C), 127.22 (2C), 128.42 (2C), 129.15, 130.69, 131.51, 131.74, 132.04, 135.02, 137.41, 141.18, 156.63, 163.46, 178.9. ESI-MS ($M^+ + 1$) calcd. for $C_{25}H_{18}O_2$: 351.13, found: 351.06.

Synthesis of *E*-4-(*p*-nitrostyryl)benzoic acid (11): 4-Carboxybenzyltriphenylphosphonium bromide (9.0 g, 18.8 mmol) was suspended in dichloromethane (50 mL) in an Erlenmeyer flask. 75 mL of aqueous solution of sodium hydroxide (50 g) and 4-nitrobenzaldehyde (2.9 g, 18.8 mmol) were added to the reaction mixture. The neck of the flask was plugged with cotton wool and the yellow mixture stirred for 1 h. The reaction mixture was acidified to pH 1 using 1 M H_2SO_4. The organic layer was separated and the aqueous layer was extracted with (3 × 50 mL) dichloromethane. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude solid was recrystallized from ethanol to yield bright yellow solid (3.11 g, 61.7 %). m.p.: 120.2-125.4 C; IR (KBr, ν_{max}, cm^1): 3200-2400, 3061, 1701, 1592, 1506, 1337, 1156, 1116; ^1H NMR (700 MHz, DMSO-d_6): δ (ppm): 6.85 (d, 1H, *J* = 12.9 Hz), 6.92 (d, 1H, *J* = 12.9 Hz), 7.32 (d, 2H, *J* = 9.0 Hz), 7.45 (d, 2H, *J* = 9.0 Hz), 7.86 (d, 2H, *J* = 9.0 Hz), 8.12 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR (176 MHz, DMSO-d_6): δ (ppm): 124.16 (C), 129.19 (2C), 129.16 (2C), 130.07 (C), 130.31 (C), 131.93 (2C), 131.99 (2C), 140.92 (C), 144.00 (C), 146.77 (C), 167.42 (C=O). ES-MS (M^+): calcd. for $C_{15}H_{11}NO_4$: 269, found: 269.

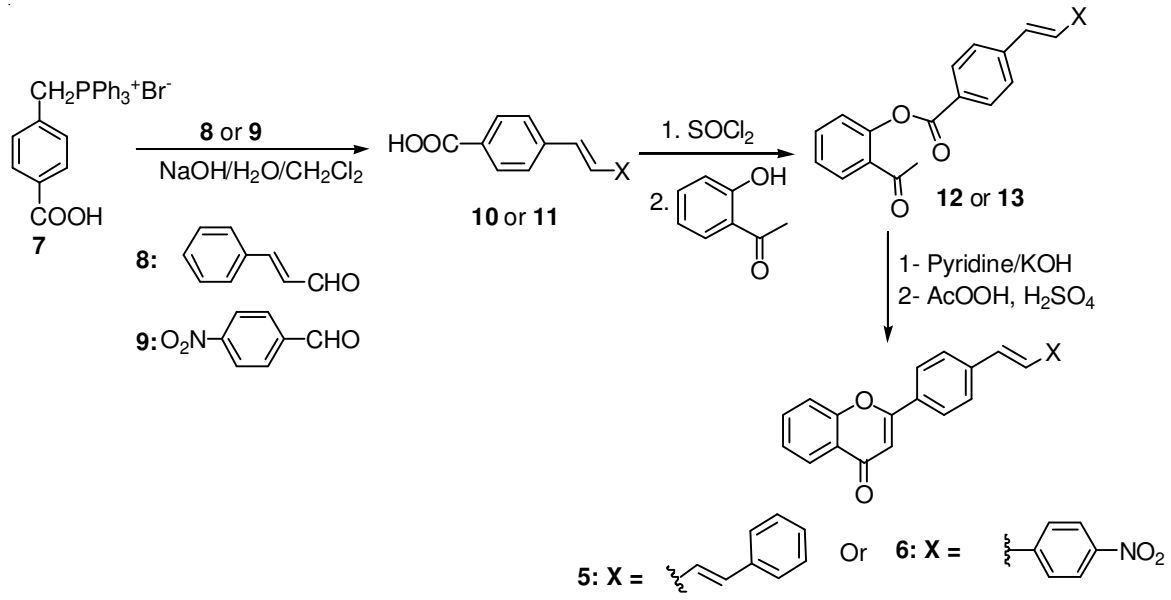
Synthesis of *E*-4-(*p*-nitrostyryl)benzoyl chloride: A mixture of *E*-4-(*p*-nitrostyryl)benzoic acid (**11**) (2.72 g, 10.10 mmol) and thionyl chloride (2.20 mL, 30.3 mmol) were heated under reflux for 1 h. Excess thionyl chloride was removed under reduced pressure and the crude solid was used for the next step.

Synthesis of 2-acetylphenyl *E*-4-(*p*-nitrostyryl)benzoate (13): To a solution of 2-hydroxy acetophenone (1.37 g, 10.10 mmol) in pyridine (15 mL) was added *E*-4-(*p*-nitrostyryl)-benzoyl chloride (2.90 g, 10.10 mmol). The reaction mixture was stirred briefly at room temperature. The temperature of the reaction increased spontaneously. After cooling, the reaction mixture was poured into a mixture of 20 mL HCl (3 %) and 30 g crushed ice. The product was extracted with chloroform (3 × 10 mL) and the combined organic layer was dried over $MgSO_4$ and evaporated to give yellow oil. The product was purified by column chromatography on silica gel eluting with petroleum ether : ethyl acetate (7 : 3) to yield light yellow solid (1.96 g, 50.6 %). m.p.: 175.3-177.5 °C; IR (KBr, ν_{max}, cm^{-1}): 3071, 2918, 1735, 1686, 1598, 1513, 1339, 1260, 1175, 856; ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm): 2.52 (s, 3H), 6.94 (d, 1H, *J* = 12.0 Hz), 6.99 (d, 1H, *J* = 12.0 Hz), 7.44 (d, 2H, *J* = 7.0 Hz), 7.47 (m, H), 7.51 (d, 2H, *J* = 8.0), 7.71 (m, H), 8.02 (d, 2H, *J* = 7.0 Hz), 8.07 (m, 1H), 8.17 (d, 2H, *J* = 8.0 Hz), 8.59 (m, 1H); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm): 29.87 (CH_3), 124.21 (C), 124.54 (C), 126.93 (C), 127.60 (2C),129.63 (2C),130.43 (2C), 130.67 (C), 130.96 (C),131.41 (C),132.73 (C),134.18 (C),142.63 (2C),143.93 (C),146.25 (C), 146.87 (C), 149.86 (C), 164.72 (C), 197.90 (CO). ES-MS (M^+):Calculated for $C_{23}H_{17}NO_5$: 387, found: 387.

Synthesis of flavonoid derivative (6): To a solution of 2-acetylphenyl *E*-4-(*p*-nitrostyryl)benzoate (0.70 g, 1.80 mmol) in pyridine (7 mL) at 70 °C was added potassium hydroxide (0.6 g, 1.33 mmol) and the mixture was stirred for 15 min. Acetic acid solution (10 %, 11 mL) was added to the cooled mixture and the solid intermediate was collected by filtration. To a solution of the solid intermediate in acetic acid (8 mL) was added concentrated sulfuric acid (0.25 mL) and the mixture was refluxed for 1 h. The cooled mixture was poured into ice and the product was collected by suction filtration and washed with water. The product was recrystallized from ethanol to give orange solid (0.37 g, 55.6 %); m.p.: 171.1-175.2 °C. IR (KBr, ν_{max}, cm^{-1}): 3022, 1637, 1618, 1590, 1503, 1463, 1333, 899; λ_{max}, (nm) (log ε) 308.3 (4.97), 345.8 (4.96); ^{1}H NMR (700 MHz, DMSO-d_6): δ (ppm): 6.90 (d, 1H, *J* = 12.0 Hz), 6.96 (d, 1H, *J* = 12.0 Hz), 7.13 (s, 1H), 7.53 (d, 2H, *J* = 9.0 Hz), 7.64 (m, 1H), 7.85 (m, 1H), 7.89 (d, 2H, *J* = 9.0 Hz), 7.93 (d, 2H, *J* = 9.0 Hz), 8.07 (m, 1H), 8.18 (m, 1H), 8.27 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR (176 MHz, DMSO-d_6): δ (ppm): 107.40 (C), 119.05 (C), 124.26 (C), 124.56 (2C), 125.26 (C), 124.44 (C), 126.04 (C), 127.34 (2C), 128.13 (C), 128.14 (2C), 130.77 (C), 132.82 (C), 134.84 (C), 140.13 (C), 144.05 (C), 146.97 (C), 156.15 (C), 162.54 (C), 177.59 (C=O). ES-MS (M^+): Calculated for $C_{23}H_{15}NO_4$: 369, found: 369.

RESULTS AND DISCUSSION

Different synthetic methods have been employed to furnish the structural skeleton of flavonoids such as cyclization of chalcones, intramolecular Wittig reaction and Allan-Robinson cyclization reaction [35]. Another favoured synthetic approach towards flavonoid structures is by applying the Baker-Venkataraman rearrangement reaction on substituted *ortho*-acetylphenyl benzoate ester [36]. Usually, the reaction commences from acylation of *ortho*-hydroxyacetophenone with substituted benzoyl chloride to form an ester which will undergo Baker-Venkataraman rearrangement reaction in basic condition to give 1,3-diketone intermediate. Cyclization of the diketone intermediate to the required flavonoid derivative is achieved by applying acid condition. In this regard, two new flavonoid derivatives **5** and **6** were synthesized using Baker-Venkataraman rearrangement starting from triphenylphosphonium bromide **7** (**Scheme-I**). The phophonium salt reacted *via* Wittig reaction with either *trans*-cinnamaldehyde **8** or with 4-nitrobenzal-dehyde **9** to give carboxylic acid **10** or **11**, respectively, in the presence of NaOH in H_2O/CH_2Cl_2 solvent system. Carboxylic acids (**10** and **11**) were purified by recrystallization from hot ethanol to give yields of 65 % and 61.7 % respectively. The coupling constants (*J*-values) of the two hydrogen atoms in the new constructed double bonds are 15.4 Hz in carboxylic acid **10** and 12.9 Hz in carboxylic acid **11** which indicate formation of *trans*-double bonds. Thionyl chloride was used to convert the carboxylic acids into their acid chloride counterparts



Scheme-I: Synthesis of flavonoid derivatives **5** and **6**

which were used without purification to react with 2-hydroxy acetophenone in pyridine to form esters (**12** and **13**) in 56.7 % and 50.6 %, respectively after recrystallization from ethanol. Flavonoid derivatives (**5** and **6**) were prepared by applying Baker-Venkataraman rearrangement reaction on esters **12** and **13** in a mixture of KOH and pyridine followed by acid treatment. The overall percent yields of the two derivatives were 20 % for flavonoid **5** and 17.4 % for flavonoid **6**.

The structures of all the synthesized compounds except acid chlorides were elucidated by combination of mass spectrometric and IR, NMR spectroscopic methods. The singlet at δ 6.84 ppm belongs to H-3 while the double bonds protons H-15 and H-18 show doublet signals due to the coupling with H-16 and H-17 at 6.75 ppm and 6.69 ppm, respectively. Protons H-16 and H-17 exhibit doublet-of-doublet signals at 7.08 ppm and 6.97 ppm because they couple with each other in addition to their coupling with H-15 and H-18. Other hydrogen atoms show their signals as predicted.

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