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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and evaluation of antioxidant activity of 2-styrylchromones

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Abstract Antioxidants are emerging as potential prophylactic and therapeutic agents which scavenge free radicals otherwise reactive oxygen species and prevent the damage caused by them. Free radicals have been associated with pathogenesis of various disorders like cancer, diabetes, cardiovascular diseases, autoimmune diseases, neurodegenerative disorders and are implicated in aging. Chromones and their derivatives display important biological activities such as anti-tumor, anti-hepatotoxic, anti-inflammatory, anti-spasmolytic, oestrogenic and antibacterial activities, in particular the antioxidant behavior of these compounds continue to draw attention of researchers. In the present communication a series of halo substituted 2-styrylchromones **4a**–**4k** were prepared and tested for the antioxidant activity by using DPPH (1, 1 diphenyl 2, picryl hydrazyl) method, and among the synthesized compounds **4e** and **4h** shows strong antioxidant activity while remaining compounds show antioxidant activity in the normal range.

Keywords Antioxidants · Pathogenesis · Synthesis · 2-Styrylchromones · Halo substituted

Introduction

In the recent years antioxidants have gained a lot of importance because of their potential as prophylactic and therapeutic agents in many diseases. The discovery of the role of free radicals in cancer, diabetes cardiovascular diseases, autoimmune diseases neurodegenerative disorders aging and other diseases has led to medical revolution that is a promising a new paradigm of healthcare. Traditionally, herbal medicines with antioxidant properties have been used for various purposes and epidemiological data also points at widespread acceptance and use of these agents. The global market of antioxidants is increasing rapidly, because of the increased health risk in a constantly polluting environment. Further application of these agents in cosmetics has fuelled extensive research in search for novel anti oxidants of therapeutic significance. Free radicals are highly reactive molecules or chemical species containing unpaired electrons that cause oxidative stress, which is defined as "an imbalance between oxidants and antioxidants in favor of the oxidants, potentially leading to damage" (Sies, 1997). Oxidative stress can damage lipids, proteins, enzymes, carbohydrates and DNA in cells and tissues, resulting in membrane damage, fragmentation or random cross linking of molecules like DNA, enzymes and structural proteins and even lead to cell death induced by DNA fragmentation and lipid peroxidation (Beckman and Ames, 1998). The consequences of oxidative stress is the molecular basis in the development of cancer, neurodegenerative disorders, cardiovascular diseases, diabetes and autoimmune disorders.

Chromones and their derivatives of different oxidation level are well known naturally occurring oxygen-containing heterocyclic compounds which perform important biological functions in nature. It is known that certain natural and synthetic derivatives possess important biological activities, such as anti-tumor, anti-hepatotoxic, anti-inflammatory, anti-spasmolytic, oestrogenic and antibacterial activities and in particular the antioxidant behavior of these compounds is the matter of immense interest (McClure,

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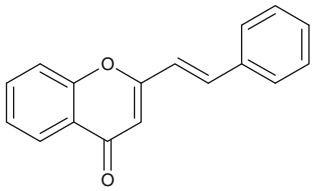
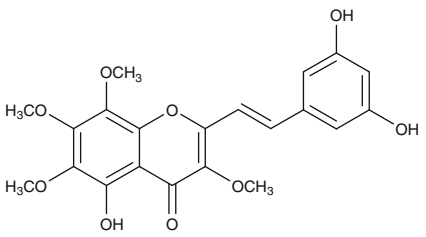


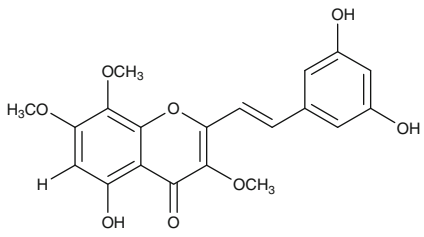
Fig. 1 Molecular scaffold of 2-styrylchromone

1975; Atassi *et al*., 1985; Middleton and Kandaswami, 1994; Bruneton, 1999; Harborne and Williams, 2000). 2-Styrylchromones are one of the scarcest classes of natural chromones. Hormothamnione **1** and 6-desmethoxyhormothamnione **2** are the first and to the best of our knowledge the only naturally occurring styrylchromones isolated from the marine crytophyte *Chrysophaeum taylori*. (Gerwick *et al*., 1986; Gerwick, 1989). Hormathamnione **1** is exceptionally cytotoxic to P388 lymphocytic leukemia and HL-60 promyelocytic leukemia cell lines in vitro and appears to be a selective inhibitor of RNA synthesis. (Gerwick *et al*., 1986) while 6-Desmethoxyhormothamnione **2** showed cytotoxicity to 9 KB cell lines (Gerwick, 1989). The pharmacological profile and their presence in low concentration in natural sources prompted us to synthesise these compounds and study their antioxidant activity (Fig. 1).



1

Hormothamnione



2

6-Desmethoxyhormothamnione

Results and discussion

Chemistry

The synthetic route of the desired 2-styrylchromones is summarized in Scheme 1. This two-step approach involves an Aldol reaction followed by an oxidative cyclization. The Base-catalyzed Aldol reaction of cinnamaldehydes with 2′-hydroxyacetophenones in ethanolic solution afforded (*E*, *E*)-2′-hydroxycinnamylidene-acetophenones. Second step involves oxidative cyclization of (*E*, *E*)-2′-hydroxycinnamylidene-acetophenones into (*E*)-2-styrylchromones. In DMSO usning catalytic amount of Iodine. The reaction proceeds smoothly to afford the corresponding flavones in good yield.

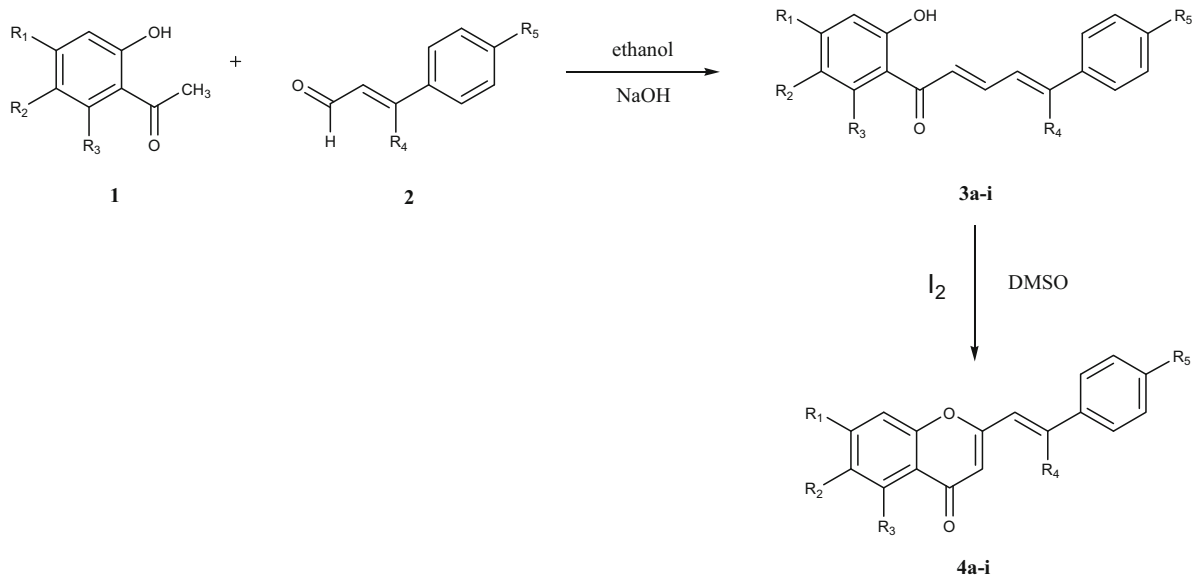
Antioxidant activity

The newly synthesized 2-styrylchromones **4a**–**4k** have been tested for the antioxidant activity by DPPH method and ascorbic acid was used as standard for comparison of antioxidant activity. The results are presented in Table 1. The antioxidant values are taken in the term of % RSA (Radical scavenging activity). The synthesized compounds show antioxidant activity in the range of 60–71 %. The compounds **4e** and **4h** shows significant antioxidant activity 71.40 and 71.11 % respectively, while remaining compounds show normal antioxidant behavior, from these results it is apparent that introduction of functional groups such as iodo/chloro/OH/OCH_3/CH_3 significantly increased antioxidant activity in comparison to unsubstituted styryl chromone.

In conclusion the present paper describes facile synthesis of substituted styryl chromones from easily available starting material using molecular iodine as catalyst. The study clearly indicates that substitution with halogens on aromatic nucleus enhance antioxidant activity.

Experimental section

All melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini Spectrometer 300 MHz. IR spectra were recorded on Nicolet Fourier Transform spectrometer. Mass spectra were obtained on a 7070H or VG Auto spec Mass spectrometer using LSIMS technique. Thin-layer chromatography (TLC) was performed on GF-25U (Anal. Tech) plates and silica gel glass-backed plates. Routine column chromatography was conducted using silica gel 60–120 mesh.



4a: R_1 = I, R_2 = Cl, R_3, R_4, R_5 = H; **4b:** R_1 = I, R_2 = Cl, R_3, R_4 = H, R_5 = OCH_3; **4c:** R_1, R_4 = H, R_2 = Br, R_5 = OCH_3, **4d:** R_1 = I, R_2, R_3, R_4, R_5 = H; **4e:** R_1 = I, R_2 = Cl, R_4 = CH_3, R_3, R_5 = H; **4f:** R_1 = I, R_2, R_3, R_4 = H, R_5 = OCH_3; **4g:** R_1 = I, R_2, R_3, R_5 = H, R_4 = CH_3; **4h:** R_1, R_2, R_4 = H, R_3 = OH, R_5 = OCH_3; **4i:** R_1, R_2, R_3, R_5 = H R_4 = CH_3 ; **4j:** R_1, R_2, R_3, R_4, R_5 = H; **4k:** R_1 = I, R_2 = Cl, R_3, R_4, R_5 = H.

Scheme 1 Synthesis of studied 2-Styrylchromones

Table 1 Antioxidant activity of synthesized 2-styrylchromones

Compounds	Antioxidant activity Mean % RSA
4a	67.18
4b	69.12
4c	60.94
4d	64.96
4e	71.40
4f	66.75
4g	69.59
4h	71.11
4i	65.81
4j	64.43
4k	67.48

Synthesis of halogenated 2-styrylchromones

General procedure

To the aqueous solution of NaOH (2.5 equiv.) in ethanol at 0–5 °C, halogenated 2-hydroxyacetophenone (1 mmol) **1** was added and stirred for 10 min. After 10 min substituted cinnamaldehyde (1 mmol) **2** was added and the resulting mixture was stirred for 12-h at room temperature. The reaction progress was monitored by TLC. After completion of reaction it was poured into water and acidified with dil. HCl, and was filtered to obtain the product. The product was washed with cold water, and recrystallized using ethanol.

The above product in DMSO was refluxed in the presence of catalytic amount of iodine for 0.5 h; progress of reaction was monitored by TLC. After completion of reaction, workup with water followed by sodium thiosulphate wash afforded the desired Styrylchromone in good yield. The product was purified by recrystallisation from ethanol.

*(E)-6-chloro-7-iodo-2-styryl-4H-chromen-4-one (**4a**)*

Yield: 65 %; mp 175–177 °C. IR (KBr cm^{-1}): 3072, 3035, 3000, 1710, 1680, 1591, 1515, 1442, 1427, 1365, 1332, 1280, 972, 686, 600. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 6.32 (1H, s, =CH), 6.68 (1H, d, J = 16.0 Hz, =CH), 7.26–7.61 (5H, m, Ar), 7.76 (1H, d, J = 16 Hz, =CH), δ 8.07 (1H, s), δ 8.13 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 85.7, 109.3, 114.5, 116.9, 125.1, 125.5, 127.4, 129.6, 132.4, 135.7, 138.4, 153.2, 161.5, 162.9, 175.6. EI MS: *m/z* (rel.abund. %) 408 (M^+, 100), 410 (M^{2+}, 33).

*(E)-2-(4-methoxystyryl)-6-chloro-7-iodo-4H-chromen-4-one (**4b**)*

Yield: 59 %; mp 188–190 °C. IR (KBr cm^{-1}) 3070, 3065, 3030, 2810, 1721, 1717, 1689, 1650, 1600, 1548, 1508, 1442, 1425, 1363, 1250, 1172, 1100, 1031, 670, 550. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.86$ (3H, s, OCH_3), 6.27 (1H, s, =CH), 6.62 (1H, d, $J = 16.0$ Hz, =CH), 6.94 (2H, d, $J = 7.6$ Hz), 7.54 (2H, d, $J = 8.0$ Hz), 7.75 (1H, d, $J = 16.0$ Hz), 8.05 (1H, s), 8.11 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.4$, 85.6, 109.2, 114.4, 116.8, 125.0, 125.5, 127.4, 129.6, 131.4, 138.7, 142.4, 153.2, 161.4, 162.8, 176.6. EI MS: *m/z* (rel.abund. %) 438 (M^+, 100), 440 (M^{2+}, 33).

*(E)-2-(4-methoxystyryl)-6-bromo-4H-chromen-4-one (**4c**)*

Yield: 66 %; mp 168–170 °C. IR (KBr cm^{-1}): 3076, 3043, 3030, 3003, 2966, 2947, 2935, 2908, 2835, 1700, 1650, 1633, 1600, 1553, 1505, 1458, 1445, 1369, 1284, 1255, 1238, 1166, 1128, 1024, 968, 835, 825, 804, 601. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.86$ (3H, s, OCH_3), 6.29 (1H, s, =CH), 6.64 (1H, d, $J = 16.4$ Hz, =CH), 6.94 (2H, d, $J = 8.8$ Hz, Ar), 7.41(1H, d, $J = 8.8$ Hz, Ar), 7.52–7.58 (3H, m, Ar), 7.74 (1H, dd, $J = 2.2$ Hz, 9.0 Hz, Ar), 8.31 (1H, d, $J = 2.0$ Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.4$, 109.7, 114.4, 117.3, 118.2, 119.7, 125.4, 127.5, 128.2, 129.3, 136.4, 137.1, 154.6, 161.2, 162.4, 176.8. EI MS: *m/z* (rel.abund. %) 357 (M^+, 100), 359 (M^{2+}, 97).

*(E)-7-iodo-2-styryl-4H-chromen-4-one (**4d**)*

Yield: 69 %; mp 173–175 °C. IR (KBr cm^{-1}): 3061, 3055, 3020, 2996, 2972, 2941, 2912, 2861, 1625, 1539, 1438, 1361, 1271, 1199, 1091, 977, 860, 750, 650. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.33$ (1H, s, =CH), 6.76 (1H, d, $J = 16.0$ Hz, =CH), 7.15–7.24 (2H, m, Ar), 7.38–7.46 (2H, m, Ar), 7.60–7.61 (2H, m, Ar), 7.80 (1H, d, $J = 16.0$ Hz, =CH), 8.38 (1H, d, $J = 2.0$ Hz, Ar), 8.45 (1H, d, $J = 1.6$ Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 85.3$, 107.6, 124.7, 125.3, 127.8, 128.5, 128.1, 129.7, 131.3, 135.6, 136.2, 140.5, 153.4, 165.1, 176.7. EI MS: *m/z* (rel.abund. %) 375 (M^+, 100).

*(E)-6-chloro-7-iodo-2-(2-phenylprop-1-enyl)-4H-chromen-4-one (**4e**)*

Yield: 64 %; mp 178–180 °C. IR (KBr cm^{-1}): 3076, 3049, 3018, 2974, 1675, 2941, 1622, 1589, 1548, 1448, 1431, 1367, 1332, 1309, 1130, 1068, 987, 933, 881, 862, 736, 696. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.21$ (3H, s, $–CH_3$), 6.52 (1H, s, =CH), 7.35–7.46 (4H, m, Ar), 7.93 (1H, s, =CH), 8.08 (1H, S, Ar), 8.11 (1H, s, Ar), 8.18 (1H, s, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.1$, 85.7, 107.6, 124.5, 125.4, 127.7, 128.4, 128.5, 129.7, 131.5, 135.8, 135.9, 142.6, 153.4, 164.9, 176.9. EI MS: *m/z* (rel.abund. %) 422 (M^+, 100), 424 (M^{2+}, 33).

*(E)-2-(4-methoxystyryl)-7-iodo-4H-chromen-4-one (**4f**)*

Yield: 60 %; mp 174-176 °C. IR (KBr cm^{-1}): 3052, 2995, 2966, 2952, 2812, 1648, 1598, 1541, 1512, 1436, 1419, 1357, 1253, 1174, 1031, 974, 833, 813. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.86$ (3H, s, $–OCH_3$), 6.28 (1H, s, =CH), 6.62 (1H, d, $J = 16.0$ Hz, =CH), 6.90–6.96 (3H, m, Ar), 7.55 (2H, d, $J = 8.8$ Hz, Ar), 7.75 (1H, d, $J = 15.6$ Hz, =CH), 8.36–8.37 (1H, m, Ar), 8.44–8.46 (1H, m, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.4$, 86.3, 89.2, 109.4, 114.4, 116.8, 124.7, 125.9, 129.5, 134.9, 138.8, 150.2, 154.3, 161.4, 162.7, 176.3. EI MS: *m/z* (rel.abund. %) 405 (M^+, 100).

*(E)-7-iodo-2-(2-phenylprop-1-enyl)-4H-chromen-4-one (**4g**)*

Yield: 61 %, mp 150–152 °C. IR (KBr cm^{-1}): 3052, 2995, 2966, 2952, 2812, 1648, 1598, 1541, 1512, 1436, 1419, 1357, 1253, 1174, 1031, 974, 833, 813. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.20$ (3H, s, $–CH_3$), 6.51 (1H, s, =CH), 7.14–7.23 (2H, m, Ar), 7.39–7.46 (2H, m, Ar), 7.59–7.61 (2H, m, Ar), 7.91 (1H, s, =CH), 8.39 (1H, d, $J = 2.0$ Hz, Ar), 8.44 (1H, d, $J = 1.6$ Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.1$, 85.5, 107.7, 124.6, 125.5, 127.8, 128.3, 128.4, 129.6, 131.0, 135.8, 136.1, 140.6, 153.4, 164.9, 176.9. EI MS: *m/z* (rel.abund. %) 389 (M^+, 100).

*(E)-2-(4-methoxystyryl)-5-hydroxy-4H-chromen-4-one (**4h**)*

Yield: 57 %; mp 190–192 °C (191–193 °C (Pinto *et al.*, 2000)). IR (KBr cm^{-1}): 3620, 3065, 3058, 3000, 2952, 2920, 2900, 1647, 1629, 1602, 1548, 1508, 1442, 1425, 1363, 1250, 1195, 1172, 1031, 974, 833, 815. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.85$ (3H, s, $–OCH_3$), 6.90–7.06 (5H, m, =CH, Ar), 7.17 (1H, d, $J = 14.8$ Hz, =CH), 7.45–7.49 (2H, m, Ar), 7.69–7.75 (1H, m, Ar), 7.84 (1H, dd, $J = 1.4$ Hz, $J = 8.0$ Hz, Ar), 12.98 (1H, s, OH). EI MS: *m/z* (rel.abund. %) 295 (M^+, 100).

*(E)-2-(2-phenylprop-1-enyl)-4H-chromen-4-one (**4i**)*

Yield: 58 %; mp 151–153 °C. IR (KBr cm^{-1}): 3059, 3022, 2968, 2950, 1650, 1631, 1624, 1548, 1465, 1427, 1388, 1328, 1201, 1172, 1095, 1058, 971, 966, 754, 682. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.21$ (3H, s, $–CH_3$), 6.50

(1H, s, =CH), 7.14–7.23 (3H, m, Ar), 7.48–7.61 (4H, m, Ar), 7.91 (1H, s, =CH), 8.01–8.22 (2H, m, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.2$, 85.4, 107.8, 124.5, 125.4, 127.7, 128.4, 128.6, 129.5, 131.2, 135.9, 136.4, 140.5, 148.4, 165.0, 176.7. EI MS: *m/z* (rel.abund. %) 263 (M^+, 100).

*(E)-2-styryl-4H-chromen-4-one (**4j**)*

Yield: 64 %; mp 139–141 °C (140 °C (Pinto *et al*., 1996)). IR (KBr cm^{-1}): 3060, 3053, 3022, 2996, 2974, 2939, 2868, 1635, 1530, 1441, 1359, 1273, 1188, 1089, 968, 859. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.50$ (1H, s, =CH), 6.77 (1H, d, $J = 16.0$ Hz, =CH), 7.14–7.23 (3H, m, Ar), 7.50–7.61 (4H, m, Ar), 7.81 (1H, d, $J = 16.0$ Hz, =CH), 8.01–8.22 (2H, m, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 85.6$, 107.7, 124.7, 125.6, 127.5, 128.2, 128.5, 129.7, 131.1, 136.0, 136.3, 140.7, 148.2, 165.0, 175.7. EI MS: *m/z* (rel.abund. %) 249 (M^+, 100).

*(E)-6-chloro-7-iodo-2-styryl-4H-chromen-4-one (**4k**)*

Yield: 64 %; mp 177–180 °C. IR (KBr cm^{-1}): 3069, 3053, 3001, 2981, 1672, 2939, 1629, 1589, 1544, 1436, 1371, 1329, 1322, 1125, 1072, 980, 938, 850, 732, 670. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.32$ (1H, s, =CH), 6.77 (1H, d, $J = 16.0$ Hz, =CH), 7.42–7.44 (3H, m, Ar), 7.61 (2H, d, $J = 6.8$ Hz, Ar), 7.81 (1H, d, $J = 16.0$ Hz, =CH), 8.07 (1H, S, Ar), 8.13 (1H, s, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 85.6$, 109.9, 119.3, 125.0, 125.6, 127.9, 129.0, 130.2, 131.6, 134.7, 139.1, 142.6, 153.3, 162.3, 176.6. EI MS: *m/z* (rel.abund. %) 408 (M^+, 100), 410 (M^{2+}, 33).

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