Med Chem Res (2011) 20:838–846
DOI 10.1007/s00044-010-9395-1

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and cytotoxicity of novel chrysin derivatives

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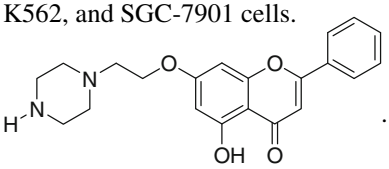
Received: 22 January 2010 / Accepted: 22 July 2010 / Published online: 15 August 2010

Abstract A series of chrysin derivatives 8a–8v were prepared and tested in vitro against HCT-116 (human colon cancer cell line), Hela (human cervical carcinoma cell line), DU-145 (human prostate cell line), K562 (human leukemia cell line), and SGC-7901 (human gastric cancer cell line). The chemical structures of these compounds were confirmed by means of MS, IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. Among these derivatives, 7-(2-(piperazin-1-yl)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one, 8n, had the strongest activity against HCT-116, Hela, DU-145, K562, and SGC-7901 cells.



8n

Keywords Synthesis · Chrysin · Cytotoxicity · MTT assay

Introduction

A significant part of drug discovery in the past few years has been focused on agents to prevent or treat cancer. This is not surprising because, in most developed countries and, to an increasing extent, cancer is among the three most common causes of death and morbidity. Cancer treatments may involve surgery, radiotherapy, and chemotherapy and often a combination of two or all three is employed. Natural compounds from plants play a significant role in cancer chemotherapy but in spite of successes there is still much activity directed to finding novel anticancer agents (Farnsworth *et al*., 1985; Cragg *et al*., 1997; Da Rocha *et al*., 2001).

Chrysin (5,7-dihydroxyflavone, shown in Scheme 1), a polyphenolic compound available in foods of plant origin, belongs to the flavone subclass of flavonoids usually occurring as glycosylated forms in plants. It has been reported to have many different biological activities such as a antibacterial (Qais *et al*., 1996), antioxidant (Hecker *et al*., 1996), anti-inflammatory (Fishkin and Winslow, 1997), antiallergic (Pearce *et al*., 1984), anti-virus (Cardenas *et al*., 2006), and anxiolytic activities (Wolfman *et al*., 1994). Chrysin can also display anticancer effect, and inhibit a series of human cancer cell lines (Habtemariam, 1997). However, few reports have been dedicated to the improvement of the anticancer activities and the structure–activity relationships of chrysin derivatives (Li *et al*., 2009; Babu *et al*., 2006). Our research interest now is focused on the modification of chrysin. In this article, chrysin was total synthesized by Baker–Venkataraman rearrangement. To increase the anticancer properties of chrysin, we prepared chrysin derivatives in which chrysin ring system linked to the different amines separated by 2 carbon spacers at C-7 position (Li *et al*., 2009; Babu *et al*., 2006). These derivatives, compared with their parent compound, displayed significant anticancer activities against HCT-116 (human colon cancer cell line), Hela (human cervical carcinoma cell line), DU-145 (human prostate cell line), K562 (human leukemia cell line), and SGC-7901 (human gastric cancer cell line), and all the synthetic compounds were well characterized by their spectral characteristics.

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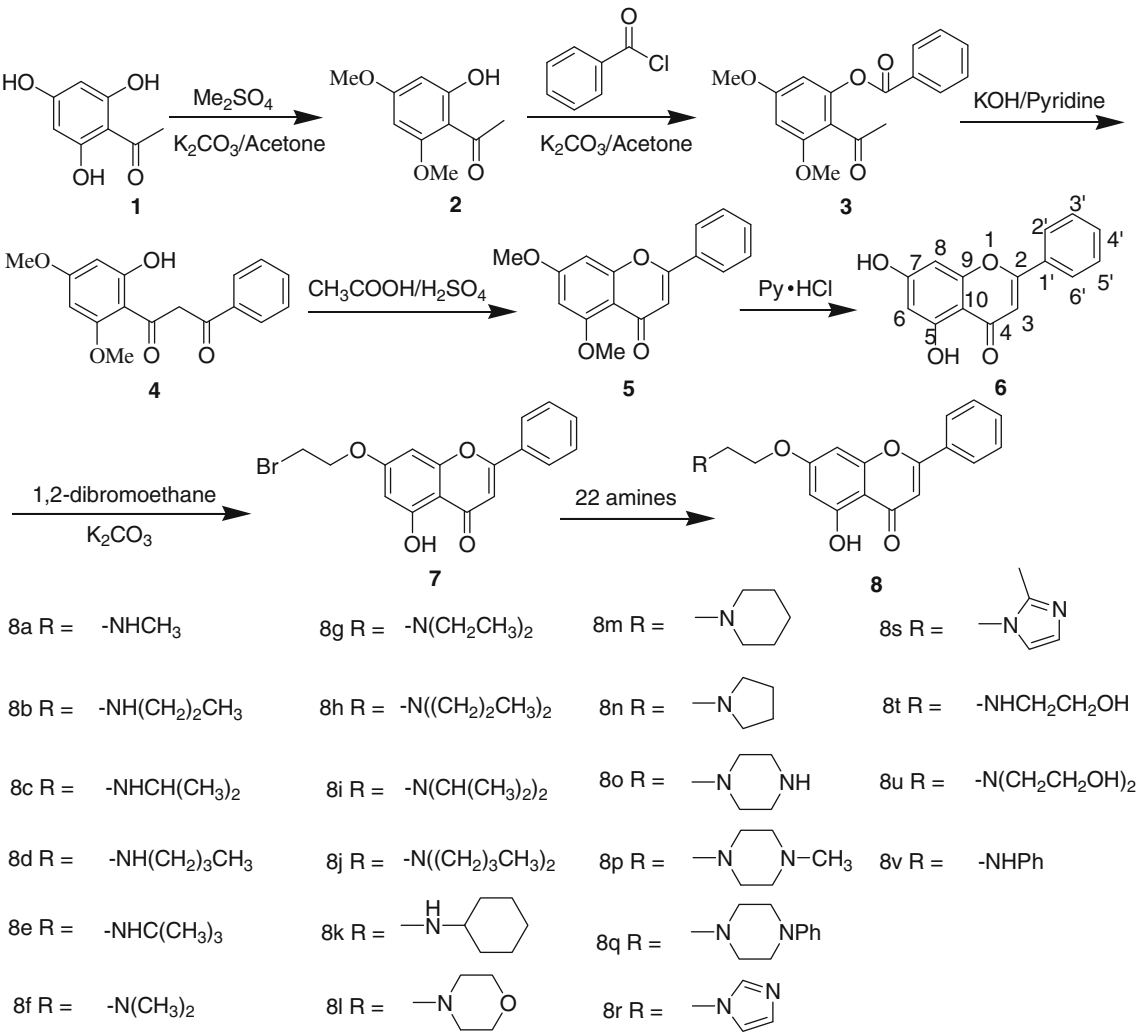

Scheme 1 General synthesis of 8a–8v

Chemistry and biological activity

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 500(500-MHz) or AM 300(300-MHz) spectrometer with Me_4Si as internal standard. All the chemical shifts (δ) are expressed as parts per million, and coupling constants (J) are given as hertz. Mass Spectra (MS) were recorded on a Mariner System 5304 Mass spectrometer. IR spectra were recorded on a Nicolet IR-460 spectrometer. Elemental analysis was performed on a CHN-O-Rapid instrument and was within ±0.4% of the theoretical values. All the reagents were commercial materials used without further purification.

2-hydroxy-4,6-dimethoxyacetophenone (2)

A mixture of 1 (0.01 mmol, 1.68 g), K_2CO_3 (3.03 g, 0.02 mol), Me_2SO_4 (2 ml, 0.02 mol), and 30 ml acetone was stirred at room temperature for 4 h, and then the mixture was poured into water (100 ml). The precipitated solid was filtered, washed with water, and crystallized from ethanol to give 2 as white powders. Yield, 90%. FAB-MS, *m/z*: 197(M + 1). IR νmax(cm^{-1}, KBr): 1619 (C=O), 2944(OH). ^{1}H NMR($CDCl_3$, 300 MHz): 2.61(3H, s,$COCH_3$), 3.83(3H, s,CH_3O-6), 3.87(3H,s,CH_3O-4), 5.92(1H, d, J = 2.6 Hz, H-5), 6.06(1H, d, J = 2.7 Hz, H-3), 14.03(1H, s, OH). ^{13}C NMR($CDCl_3$, 300 MHz): 32.8($CO\underline{C}H_3$), 55.5(2× OCH_3), 90.7(C-5), 93.5(C-3), 106.0(C-1), 162.9(C-6), 166.1(C-2), 167.6(C-4), 203.1(C=O). Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.22, H, 6.16. Found: C, 61.35, H, 6.27.

2-acetyl-3,5-dimethoxyphenyl benzoate(3)

A mixture of 2 (392 mg, 2 mmol), K_2CO_3 (414 mg, 3 mmol), benzoyl chloride (552 mg, 2.4 mmol), and 15 ml acetone was stirred at room temperature for 8 h, and then the mixture was poured into ice-cooled water (100 ml). The precipitated solid was filtered, washed with water, and

crystallized from ethanol to give 3 as white powders. Yield, 84%. FAB-MS, *m/z* : 301(M + 1). IR *v*max(cm^{-1}, KBr): 1678(C=O), 3 118(OH). ^{1}H NMR($CDCl_3$, 300 MHz): 2.47(3H, s, $COCH_3$), 3.82(3H, s, CH_3O-3), 3.86(3H, s, CH_3O-5), 6.37(1H, d, $J = 2.3$ Hz, H-6), 6.41(1H, d, $J = 2.1$ Hz, H-4), 7.47–7.63 (3H, m, H-4′,5′,6′), 8.13(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 300 MHz): 31.9($CO\underline{C}H_3$), 55.6($O\underline{C}H_3$), 55.9($O\underline{C}H_3$), 96.7(C-4), 100.2(C-6), 117.4(C-2), 128.4(C-2′,6′), 129.3(C-4′), 130.1(C-3′,5′), 133.6(C-1′), 149.8(C-1), 159.1(C-3), 162.2(COO), 165.0(C-5), 199.2(C=O). Anal. Calcd. for $C_{17}H_{16}O_5$: C, 67.99, H, 5.37. Found: C, 68.05, H, 5.42.

1-(2-hydroxy-4,6-dimethoxyphenyl)-3-phenylpropane-1,3-dione (4)

A solution of 3 (100 mg, 0.26 mmol) in 5 ml of anhydrous pyridine was prepared and warmed to 50°C. To the solution was added hot pulverized potassium hydroxide(35 mg, 0.63 mmol), followed by heating at 50°C for 1 h, and then the mixture was cooled to room temperature and acidified with 5% hydrochloric acid (20 ml). The precipitated solid was filtered, washed with water, and purified by column chromatography (petroleum ether/EtOAc) to give 4 as yellow powder. Yield, 71%. FAB-MS, *m/z* : 301(M + 1). IR *v*max(cm^{-1}, KBr): 1665(C=O), 3 165(OH). ^{1}H NMR ($CDCl_3$, 300 MHz): 3.85(3H, s, CH_3O-6), 3.88(3H, s, CH_3 O-4), 3.92(2H, s, –$COCH_2CO$–), 6.39(1H, d, $J = 2.8$ Hz, H-2), 6.43(1H, d, $J = 2.7$ Hz, H-5), 7.42–7.61(3H, m, H-4′,5′,6′), 8.17(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 300 MHz): 52.9($CO\underline{C}H_2CO$), 55.9(2× $O\underline{C}H_3$), 93.2(C-5), 95.6(C-3), 102.9(C-1), 128.8(C-2′,6′), 129.7(C-3′,5′), 132.3(C-4′), 136.5(C-1′), 161.7(C-6), 162.4(C-2), 167.8(C-4), 195.7(2× C=O). Anal. Calcd. for $C_{17}H_{16}O_5$: C, 67.99, H, 5.37. Found: C, 68.11, H, 5.49.

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

A solution of 4 (100 mg, 0.26 mmol) in 5 ml of glacial acetic acid was prepared and warmed to 90°C. To the solution was added 98% concentrated sulfuric acid (0.05 ml), followed by heating at 90°C for 1 h and then the mixture was cooled to room temperature and poured into ice-cooled water (100 ml). The precipitated solid was filtered, washed with water, and crystallized from ethanol to give 5 as white solid. Yield, 72%. FAB-MS, *m/z* : 283(M + 1). IR *v*max(cm^{-1}, KBr): 1647(C=O). ^{1}H NMR($CDCl_3$, 300 MHz): 3.91(3H, s, CH_3O-7), 3.96 (3H, s, CH_3O-5), 6.38(1H, d, $J = 2.6$ Hz, H-8), 6.58(1H, d, $J = 2.7$ Hz, H-6), 6.68(1H, s, H-3), 7.49(3H, m, H-4′,5′, 6′), 7.87(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 300 MHz): 55.7(OCH_3), 56.4(OCH_3), 92.8(C-6), 96.2(C-8), 109.0(C-10), 109.3(C-3), 125.9(C-2′,6′), 128.9(C-3′,5′), 131.1(C-4′), 131.5(C-1′), 159.9(C-9), 160.6(C-5), 160.9(C-2), 164.0(C-7), 177.6(C-4). Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.33, H, 5.00. Found: C, 72.21, H, 4.92.

5,7-dihydroxy-2-phenyl-4H-chromen-4-one (6)

A mixture of 5 (100 mg, 0.33 mmol) and Pyridine Hydrochloride (1 g, 8.69 mmol) was warmed to 220°C for 15 min and then the mixture was cooled to room temperature, acidified with 5% hydrochloric acid (20 ml) and followed by extraction with EtOAc (2× 30 ml). The organic phase was dried ($MgSO_4$) for 10 min, and the mixture was filtered and evaporated. The residue was purified by column chromatography (petroleum ether/EtOAc) to give 6 as yellow powder. Yield, 68%. FAB-MS *m/z*: 255(M + 1). IR *v*max(cm^{-1}, KBr): 1652 (C=O). ^{1}H NMR(DMSO-d_6, 500 MHz) : 6.23(1H, d, $J = 1.8$ Hz, H-6), 6.53(1H, d, $J = 1.7$ Hz, H-8), 6.98(1H, s, H-3), 7.56–7.63(3H, m, H-4′,5′,6′), 8.08(2H, m, H-2′,3′), 10.92(1H, s, OH-5), 12.83(1H, s, OH-7). ^{13}C NMR (DMSO-*d*, 500 MHz): 94.4(C-8), 99.3(C-6), 104.3(C-3), 105.5(C-10), 126.7(C-2′,6′), 129.4(C-3′,5′), 131.0(C-4′), 132.3(C-1′), 157.8(C-9), 161.8(C-2), 163.5($_6$C-5), 164.7(C-7), 182.1(C-4). Anal. Calcd. for $C_{15}H_{10}O_4$: C, 70.86, H, 3.96. Found: C, 70.91, H, 3.99.

7-(2-bromoethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (7)

To a solution of 6 (500 mg, 1.96 mmol) in 45 ml of anhydrous acetone was added 1,2-dibromoethane (3 ml, 0.035 mol) and potassium carbonate(544 mg, 3.93 mmol), followed by heating at reflux temperature for 24 h until the starting material 6 disappeared. To the reaction mixture was added ice water, dropwise. The mixture was distilled to form yellow solid. Recrystallization of the solid from 30 ml acetone gave the key intermediate 7 as yellow powder. Yield, 87.2%. FAB-MS *m/z*: 362(M + 1). IR *v*max(cm^{-1}, KBr): 1660 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 3.84–3.86(2H, t, $J = 10.5$ Hz, $OCH_2C\underline{H_2}$), 4.46–4.48(2H, t, $J = 10.5$ Hz, OCH_2), 6.43(1H, s, H-6), 6.88(1H, s, H-8), 7.06(1H, s, H-3), 7.58–7.65(3H, m, H-4′,5′,6′), 8.10–8.12(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 30.7($OCH_2\underline{C}H_2$), 68.4(CH_2), 93.4(C-8), 98.5(C-6), 105.1(C-3), 105.3(C-10), 126.4(C-2′, 6′), 129.0(C-3′,5′), 130.5(C-4′), 132.1(C-1′), 157.2(C-9), 161.2(C-5), 163.5(C-2), 163.8(C-7), 182.0(C-4). Anal. Calcd. for $C_{17}H_{13}BrO_4$: C, 56.53, H, 3.63. Found: C, 56.67, H, 3.75.

General procedures for preparation of 8a–8v

To a solution of 7 (100 mg, 0.277 mmol) in 15 ml of CH_3CN was added different amines (0.415 mmol) and

potassium carbonate (57 mg, 0.415 mmol), followed by heating at reflux temperature for 8–24 h until the starting material disappeared. To the reaction mixture was added ice water, dropwise. The precipitated solid was filtered, washed with water. The residue was purified with a silica gel column and was eluted with dichloromethane: methanol = 40:1 to afford corresponding products.

7-(2-(methylamino)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8a)

Yield, 74.1%. FAB-MS *m/z*: 312(M + 1). IR *v*max(cm^{-1}, KBr): 1657 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 2.53(3H, s, CH_3), 3.00–3.02(2H, t, J = 10 Hz, OCH_2CH_2),4.14–4.16-(2H, t, J = 10 Hz, OCH_2), 6.38(1H, s, H-6), 6.52(1H, s, H-8), 6.67(1H, s, H-3), 7.49–7.56(3H, m, H-4′,5′,6′), 7.88–7.89(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 36.3(CH_3), 50.4($OCH_2\underline{C}H_2$), 67.8(OCH_2), 93.2(C-8), 98.6(C-6), 105.7(C-3), 105.8(C-10), 126.2(C-2′, 6′), 129.0(C-3′,5′), 131.2(C-4′), 132.8(C-1′), 157.7(C-9), 161.2(C-2), 163.9(C-5), 164.8(C-7), 182.4(C-4). Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44, H, 5.50. Found: C, 69.37, H, 5.45.

7-(2-(propylamino)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8b)

Yield, 81.2%. FAB-MS *m/z*: 340(M + 1). IR *v*max(cm^{-1}, KBr): 1660 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 0.94–0.97(3H, t, J = 14.5 Hz, $NHCH_2CH_2\underline{CH_3}$), 1.54–1.59(2H, m, $NHCH_2\underline{CH_2}CH_3$), 2.66–2.69(2H, t, J = 14.5 Hz, $NH\underline{CH_2}CH_2CH_3$), 3.04–3.06(2H, t, J = 10 Hz, $OCH_2\underline{CH_2}$), 4.12–4.15(2H, t, J = 10 Hz, OCH_2), 6.38(1H, s, H-6), 6.52(1H, s, H-8), 6.67(1H, s, H-3), 7.49–7.55(3H, m, H-4′,5′,6′), 7.88–7.89(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 11.7($NCH_2\underline{C}H_2CH_3$), 23.1($N\underline{C}H_2CH_2CH_3$), 48.4($OCH_2\underline{C}H_2$), 51.7($\underline{C}H_2CH_2CH_3$), 68.1($OCH_2$), 93.1(C-8), 98.7(C-6), 105.8(C-3), 105.9(C-10), 126.3(C-2′,6′), 129.1(C-3′,5′), 131.4(C-4′), 131.8(C-1′), 157.8(C-9), 162.2(C-5), 164.0(C-2), 164.9(C-7), 182.5(C-4). Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78, H, 6.24. Found: C, 70.86, H, 6.34.

7-(2-(isopropylamino)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8c)

Yield, 62%. FAB-MS *m/z*: 340(M + 1). IR *v*max(cm^{-1}, KBr): 1658 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 1.11(6H, d, J = 6 Hz, $NHCH(\underline{CH_3})_2$), 2.89(1H, m, $NH\underline{CH}(CH_3)_2$), 3.02–3.04(2H, t, J = 10.5 Hz, $OCH_2\underline{CH_2}$), 4.14–4.16(2H, t, J = 10.5 Hz, OCH_2), 6.38(1H, s, H-6), 6.52(1H, s, H-8), 6.67(1H, s, H-3), 7.51–7.55(3H, m, H-4′,5′,6′), 7.87–7.89(2H, m, H-2′, 3′). ^{13}C NMR($CDCl_3$, 500 MHz): 22.9($CH(\underline{C}H_3)_2$), 46.0($OCH_2\underline{C}H_2$), 48.6(CH), 68.5(OCH_2), 93.1(C-8), 98.7(C-6), 105.8(C-3), 105.9(C-10), 126.3(C-2′, 6′), 129.1(C-3′,5′), 131.4(C-4′), 131.8(C-1′), 157.8(C-9), 162.2(C-5), 164.0(C-2), 164.9(C-7), 182.5(C-4). Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78, H, 6.24. Found: C, 70.89, H, 6.31.

7-(2-(butylamino)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8d)

Yield, 71.5%. FAB-MS *m/z*: 354(M + 1). IR *v*max(cm^{-1}, KBr): 1660 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 0.94–0.95(3H, t, J = 7 Hz, $NH(CH_2)_3\underline{CH_3}$), 1.36–1.37(2H, m, $NH(CH_2)_2\underline{CH_2}CH_3$), 1.39–1.40(2H, m, $NHCH_2\underline{CH_2}CH_2CH_3$), 2.69–2.72(2H, t, J = 14.5 Hz, $NH\underline{CH_2}(CH_2)_2CH_3$), 3.04–3.06(2H, t, J = 9.5 Hz, $OCH_2\underline{CH_2}$), 4.13–4.16(2H, t, J = 9.5 Hz, OCH_2), 6.38(1H, s, H-6), 6.52(1H, s, H-8), 6.68(1H, s, H-3), 7.51–7.54(3H, m, H-4′,5′,6′), 7.87–7.89(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 13.9($N(CH_2)_3\underline{C}H_3$), 20.4($N(CH_2)_2\underline{C}H_2CH_3$), 32.1($NCH_2\underline{C}H_2CH_2CH_3$), 48.4($N\underline{C}H_2(CH_2)_2CH_3$), 49.5($OCH_2\underline{C}H_2$), 68.1($OCH_2$), 93.1(C-8), 98.7(C-6), 105.8(C-3), 105.9(C-10), 126.3(C-2′,6′), 129.1(C-3′,5′), 131.4(C-4′), 131.8(C-1′), 157.8(C-9), 162.2(C-5), 164.0(C-2), 164.9(C-7), 182.5(C-4). Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37, H, 6.56. Found: C, 71.29, H, 6.48.

7-(2-(tert-butylamino)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8e)

Yield, 57.3%. FAB-MS *m/z*: 354(M + 1). IR *v*max(cm^{-1}, KBr): 1659 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 1.16(9H, s, $NHC(\underline{CH_3})_3$), 2.98–3.00(2H, t, J = 9.8 Hz, $OCH_2\underline{CH_2}$), 4.14–4.16(2H, t, J = 9.8 Hz, OCH_2), 6.38(1H, s, H-6), 6.52(1H, s, H-8), 6.67(1H, s, H-3), 7.52–7.55(3H, m, H-4′,5′,6′), 7.87–7.89(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 29.0($NHC(\underline{C}H_3)_3$), 41.5($OCH_2\underline{C}H_2$), 50.3($NH\underline{C}(CH_3)_3$), 69.2(OCH_2), 93.1(C-8), 98.7(C-6), 105.8(C-3), 105.9(C-10), 126.3(C-2′,6′), 129.0(C-3′,5′), 131.4(C-4′), 131.8(C-1′), 157.8(C-9), 162.2(C-5), 164.9(C-2), 164.9(C-7), 182.5(C-4). Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37, H, 6.56. Found: C, 71.31, H, 6.46.

7-(2-(dimethylamino)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8f)

Yield, 82.2%. FAB-MS *m/z*: 326(M + 1). IR *v*max(cm^{-1}, KBr): 1659 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 2.35(6H, s, $NH(C\underline{H_3})_2$), 2.78–2.79(2H, t, J = 7.5 Hz, $OCH_2\underline{CH_2}$), 4.01–4.03(2H, t, J = 7.5 Hz, OCH_2), 6.39(1H, s, H-6), 6.53(1H, s, H-8), 6.67(1H, s, H-3), 7.52–7.56(3H, m, H-4′,5′,6′), 7.88–7.89(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz):46.0($2CH_3$), 58.0($OCH_2\underline{C}H_2$), 66.9(OCH_2), 93.4(C-8), 98.7(C-6), 106.0(C-3), 106.2(C-10), 126.4(C-2′,

6′), 129.1(C-3′,5′), 131.2(C-4′), 131.8(C-1′), 157.8(C-9), 162.3(C-5), 164.1(C-2), 164.9(C-7), 182.5(C-4). Anal. Calcd. for $C_{19}H_{19}NO_4$: C, 70.14, H, 5.89. Found: C, 70.25, H, 5.97.

7-(2-(diethylamino)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8g)

Yield, 76.7%. FAB-MS *m/z*: 354(M + 1). IR *v*max(cm^{-1}, KBr): 1661 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 1.07–1.09(6H, t, J = 14 Hz, $N(CH_2C\underline{H_3})_2$), 2.62–2.67(4H, q, J = 21.5 Hz, $N(C\underline{H_2}CH_3)_2$), 2.88–2.91(2H, t, J = 12 Hz, $OCH_2C\underline{H_2}$), 4.11–4.13(2H, t, J = 12 Hz, OCH_2), 6.38(1H, s, H-6), 6.51(1H, s, H-8), 6.67(1H, s, H-3), 7.52–7.56(3H, m, H-4′,5′,6′), 7.88–7.89(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 12.0($N(CH_2\underline{C}H_3)_2$), 47.9($N(\underline{C}H_2CH_3)_2$), 51.5($OCH_2\underline{C}H_2$), 67.5($OCH_2$), 93.2(C-8), 98.7(C-6), 105.7(C-3), 105.9(C-10), 126.3(C-2′,6′), 129.1(C-3′,5′), 131.4(C-4′), 131.8(C-1′), 157.8(C-9), 162.2(C-5), 164.0(C-2), 165.0(C-7), 182.5(C-4). Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37, H, 6.56. Found: C, 71.52, H, 5.71.

7-(2-(dipropylamino)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8h)

Yield, 73.9%. FAB-MS *m/z*: 382(M + 1). IR *v*max(cm^{-1}, KBr): 1658 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 0.90(6H, t, J = 13.5 Hz, $N(CH_2CH_2C\underline{H_3})_2$), 1.49–1.50(4H, m, $N(CH_2C\underline{H_2}CH_3)_2$), 2.39–2.41(4H, t, J = 13.5 Hz, $N(C\underline{H_2}CH_2CH_3)_2$), 6.37(1H, s, H-6), 6.50(1H, s, H-8), 6.66(1H, s, H-3), 7.51–7.55(3H, m, H-4′,5′,6′), 7.88–7.90(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 11.8($N(CH_2CH_2\underline{C}H_3)_2$), 20.5($N(CH_2\underline{C}H_2CH_3)_2$), 52.7($OCH_2\underline{C}H_2$), 57.1($N(\underline{C}H_2CH_2CH_3)_2$), 67.5($OCH_2$), 93.2(C-8), 98.7(C-6), 105.7(C-3), 105.9(C-10), 126.3(C-2′,6′), 129.1(C-3′,5′), 131.4(C-4′), 131.8(C-1′), 157.8(C-9), 162.2(C-5), 163.9(C-2), 165.0(C-7), 182.5(C-4). Anal. Calcd. for $C_{23}H_{27}NO_4$: C, 72.42, H, 7.13. Found: C, 72.36, H, 7.03.

7-(2-(diisopropylamino)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8i)

Yield, 54.8%. FAB-MS *m/z*: 382(M + 1). IR *v*max(cm^{-1}, KBr): 1644 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 1.06(2H, d, J = 6.5 Hz, $4CH_3$), 2.84–2.87(2H, t, J = 14.2 Hz, $OCH_2C\underline{H_2}$), 3.03–3.08(2H, m, $N(CH)_2$), 3.95–3.97(2H, t, J = 14.2 Hz, OCH_2), 6.36(1H, s, H-6), 6.50(1H, s, H-8), 6.68(1H, s, H-3), 7.51–7.53(3H, m, H-4′,5′,6′), 7.88–7.89(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 20.4($4CH_3$), 44.1($OCH_2\underline{C}H_2$), 49.6(2CH), 69.9(OCH_2), 93.1(C-8), 98.7(C-6), 105.8(C-3), 105.9(C-10), 126.3(C-2′,6′), 129.0(C-3′,5′), 131.4(C-4′), 131.7(C-1′), 157.8(C-9), 162.2(C-5), 163.9(C-2), 165.1(C-7), 182.4(C-4). Anal. Calcd. for $C_{23}H_{27}NO_4$: C, 72.42, H, 7.13. Found: C, 72.25, H, 6.98.

7-(2-(dibutylamino)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8j)

Yield, 71.6%. FAB-MS *m/z*: 410(M + 1). IR *v*max(cm^{-1}, KBr): 1659 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 0.91–0.94(6H, t, J = 14.5 Hz, $N((CH2)_3C\underline{H_3})_2$), 1.32–1.36(4H, m, $N((CH2)_2C\underline{H_2}CH_3)_2$), 1.43–1.46(4H, m, $N(CH_2C\underline{H_2}CH_2CH_3)_2$), 2.50–2.53(4H, t, J = 14.8 Hz, $N(C\underline{H_2}(CH_2)_2CH_3)_2$), 2.87–2.90(2H, t, J = 12.1 Hz, $OCH_2C\underline{H_2}$), 4.08–4.10(2H, t, J = 12.1 Hz, OCH_2), 6.37(1H, s, H-6), 6.52(1H, s, H-8), 6.66(1H, s, H-3), 7.52–7.55(3H, m, H-4′,5′,6′), 7.88–7.89(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 14.0($N((CH2)_3\underline{C}H_3)_2$), 20.6($N((CH2)_2\underline{C}H_2CH_3)_2$), 29.5($N(CH_2\underline{C}H_2CH_2CH_3)_2$), 52.6($OCH_2\underline{C}H_2$), 54.8($N(\underline{C}H_2(CH_2)_2CH_3)_2$), 67.5($OCH_2$), 93.1(C-8), 98.7(C-6), 105.7(C-3), 105.9(C-10), 126.3(C-2′,6′), 129.1(C-3′,5′), 131.4(C-4′), 131.8(C-1′), 157.8(C-9), 162.1(C-5), 163.9(C-2), 165.0(C-7), 182.4(C-4). Anal. Calcd. for $C_{25}H_{31}NO_4$: C, 73.32, H, 7.63. Found: C, 73.49, H, 7.75.

7-(2-(cyclohexylamino)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8k)

Yield, 83.1%. FAB-MS, *m/z*: 380(M + 1). IR *v*max(cm^{-1}, KBr): 1652 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 1.07–1.30 (6H, m, $(C\underline{H_2})_3$), 1.63–1.77(6H, m, $(C\underline{H_2})_2$), 2.48–2.52(1H, m, CH), 3.05–3.07(2H, t, J = 10.3 Hz, $OCH_2C\underline{H_2}$), 4.13–4.16(2H, t, J = 10.4 Hz, OCH_2), 6.38(1H, s, H-6), 6.53(1H, s, H-8), 6.68(1H, s, H-3), 7.50–7.57(3H, m, H-4′,5′,6′), 7.88–7.89(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 25.0($(CH_2\underline{C}H_2)_2CH_2$), 26.1($(CH_2CH_2)_2\underline{C}H_2$), 33.6($(\underline{C}H_2CH_2)_2CH_2$), 45.5($OCH_2\underline{C}H_2$), 56.6(CH), 68.6 ($OCH_2$), 93.1(C-8), 98.7(C-6), 105.8(C-3), 105.9(C-10), 126.3(C-2′,6′), 129.1(C-3′,5′), 131.3(C-4′), 131.8(C-1′), 157.8(C-3), 162.1(C-5), 164.0(C-2), 164.9(C-7), 182.5(C-4). Anal. Calcd. for $C_{23}H_{25}NO_4$: C, 72.80, H, 6.64. Found: C, 72.69, H, 6.55.

7-(2-morpholinoethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8l)

Yield, 84%. FAB-MS, *m/z*: 368(M + 1). IR *v*max(cm^{-1}, KBr): 1663 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 2.59(4H, s, $N(CH_2)_2$), 2.84–2.87(2H, t, J = 11.5 Hz, $OCH_2C\underline{H_2}$), 3.74(4H, s, $O(CH_2)_2$), 4.19–4.22(2H, t, J = 11.5 Hz, OCH_2), 6.38(1H, s, H-6), 6.52(1H, s, H-8), 6.67(1H, s, H-3), 7.53–7.60(3H, m, H-4′,5′,6′), 7.88–7.90(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 54.1($N(CH_2)_2$), 57.3($OCH_2\underline{C}H_2$), 66.6(OCH_2), 66.9($O(CH_2)_2$), 93.3(C-8), 98.6(C-6), 105.8(C-3), 105.9(C-10), 126.3(C-2′,6′), 129.1(C-3′,5′),

131.4(C-4′), 131.8(C-1′), 157.8(C-9), 162.3(C-5), 164.0(C-2), 164.7(C-7), 182.5(C-4). Anal. Calcd. for $C_{21}H_{21}NO_5$: C, 68.65, H, 5.76. Found: C, 68.71, H, 5.88.

7-(2-(piperidin-1-yl)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8m)

Yield, 88.3%. FAB-MS, *m/z*: 366(M + 1). IR *v*max(cm^{-1}, KBr): 1661 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 1.60–1.64(6H, m, $N(CH_2)_2(CH_2)_3$), 2.52(4H, s, $N(CH_2)_2$), 2.79–2.82(2H, t, $J = 12$ Hz, $OCH_2C\underline{H_2}$), 4.17–4.19(2H, t, $J = 12$ Hz, OCH_2), 6.38(1H, s, H-6), 6.57(1H, s, H-8), 6.67(1H, s, H-3), 7.51–7.55(3H, m, H-4′,5′,6′), 7.88–7.89(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 24.1($N(CH_2CH_2)_2\underline{C}H_2$), 25.9($N(CH_2\underline{C}H_2)_2$), 55.1($N(\underline{C}H_2CH_2)_2$), 57.5($OCH_2C\underline{H_2}$), 66.8($OCH_2$), 93.2(C-8), 98.7(C-6), 105.7(C-3), 105.9(C-10), 126.3(C-2′,6′), 129.1(C-3′,5′), 131.4(C-4′), 131.8(C-1′), 157.8(C-9), 162.2(C-5), 164.0(C-2), 164.9(C-7), 182.5(C-4). Anal. Calcd. for $C_{22}H_{23}NO_4$: C, 72.31, H, 6.34. Found: C, 72.37, H, 6.42.

7-(2-(piperazin-1-yl)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8n)

Yield, 73.2%. FAB-MS, *m/z*: 367(M + 1). IR *v*max(cm^{-1}, KBr): 1660 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 2.56–2.66(4H, m, $N(C\underline{H_2}CH_2)_2$), 2.82–2.88(4H, m, $N(CH_2C\underline{H_2})_2$), 2.92–2.93(2H, t, $J = 9.5$ Hz, $OCH_2C\underline{H_2}$), 4.18–4.20(2H, t, $J = 11.2$ Hz, OCH_2), 6.38(1H, s, H-6), 6.52(1H, s, H-8), 6.67(1H, s, H-3), 7.51–7.55(3H, m, H-4′,5′,6′), 7.88–7.89(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 46.0($N(CH_2\underline{C}H_2)_2$), 55.0($N(\underline{C}H_2CH_2)_2$), 57.4($OCH_2\underline{C}H_2$), 66.5($OCH_2$), 93.2(C-8), 98.7(C-6), 105.8(C-3), 105.9(C-10), 126.3(C-2′,6′), 129.1(C-3′,5′), 131.3(C-4′), 131.8(C-1′), 157.7(C-9), 162.2(C-5), 164.0(C-2), 164.9(C-7), 182.5(C-4). Anal. Calcd. for $C_{21}H_{22}N_2O_4$: C, 68.84, H, 6.05. Found: C, 68.96, H, 6.13.

7-(2-(4-methylpiperazin-1-yl)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8o)

Yield, 68.2%. FAB-MS, *m/z*: 381(M + 1). IR *v*max(cm^{-1}, KBr): 1638 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 2.30(3H, s, NCH_3), 2.42–2.48(8H, m, $2N(CH_2)_2$), 2.84–2.86(2H, t, $J = 11.3$ Hz, $OCH_2C\underline{H_2}$), 4.17–4.19(2H, t, $J = 11.3$ Hz, OCH_2), 6.38(1H, s, H-6), 6.52(1H, s, H-8), 6.67(1H, s, H-3), 7.51–7.54(3H, m, H-4′,5′,6′), 7.88–7.89(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 46.0(CH_3), 53.6($N(\underline{C}H_2CH_2)_2$), 55.0($N(CH_2\underline{C}H_2)_2$), 56.8($OCH_2\underline{C}H_2$), 66.7($OCH_2$), 93.3(C-8), 98.7(C-6), 105.8(C-3), 105.9(C-10), 126.3(C-2′,6′), 129.1(C-3′,5′), 131.3(C-4′), 131.8(C-1′), 157.7(C-9), 162.1(C-5), 163.9(C-2), 164.9(C-7), 182.4(C-4). Anal. Calcd. for $C_{22}H_{24}N_2O_4$: C, 69.46, H, 6.36. Found: C, 69.23, H, 6.28.

7-(2-(4-benzylpiperazin-1-yl)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8p)

Yield, 58.4%. FAB-MS, *m/z*: 457(M + 1). IR *v*max(cm^{-1}, KBr): 1658 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 2.52(8H, s, $N(CH_2CH_2)_2$), 2.84–2.86(2H, t, $J = 11.5$ Hz, $OCH_2C\underline{H_2}$), 3.52(2H, s, CH_2), 4.16–4.18(2H, t, $J = 11.5$ Hz, OCH_2), 6.36(1H, s, H-6), 6.50(1H, s, H-8), 6.68(1H, s, H-3), 7.31–7.32(5H, m, $CH_2C_6\underline{H_5}$), 7.50–7.56(3H, m, H-4′,5′,6′), 7.87–7.88(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 52.9($N(CH_2\underline{C}H_2)_2$), 53.6($N(\underline{C}H_2CH_2)_2$), 56.7($OCH_2\underline{C}H_2$), 63.0($CH_2$), 66.5($OCH_2$), 93.2(C-8), 98.6(C-6), 105.7(C-3), 105.9(C-10), 126.2(C-2′,6′), 127.0(C-4″), 128.2(C-3″,5″), 129.0(C-2″,6″), 129.2(C-2′,6′), 131.2(C-4′), 131.8(C-1′), 137.9(C-1″), 157.7(C-9), 162.1(C-5), 163.9(C-2), 164.7(C-7), 182.4(C-4). Anal. Calcd. for $C_{28}H_{28}N_2O_4$: C, 73.66, H, 6.18. Found: C, 73.58, H, 6.11.

7-(2-(pyrrolidin-1-yl)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8q)

Yield, 81.6%. FAB-MS, *m/z*: 352(M + 1). IR *v*max(cm^{-1}, KBr): 1660 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz):1.81–1.83(4H, m, $N(CH_2C\underline{H_2})_2$), 2.64(4H, s, $N(C\underline{H_2}CH_2)_2$), 2.92–2.95(2H, t, $J = 11.5$ Hz, $OCH_2C\underline{H_2}$), 4.17–4.20(2H, t, $J = 11.5$ Hz, OCH_2), 6.39(1H, s, H-6), 6.53(1H, s, H-8), 6.67(1H, s, H-3), 7.51–7.55(3H, m, H-4′,5′,6′), 7.87–7.89(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 23.5($N(CH_2\underline{C}H_2)_2$), 54.7($N(\underline{C}H_2CH_2)_2$, $OCH_2\underline{C}H_2$), 67.9(OCH_2), 93.2(C-8), 98.7(C-6), 105.8(C-3), 105.9(C-10), 126.3(C-2′,6′), 129.1(C-3′,5′), 131.4(C-4′), 131.8(C-1′), 157.8(C-9), 162.2(C-5), 164.0(C-2), 164.9(C-7), 182.5(C-4). Anal. Calcd. for $C_{21}H_{21}NO_4$: C, 71.78, H, 6.02. Found: C, 71.57, H, 5.94.

7-(2-(1H-imidazol-1-yl)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8r)

Yield, 73.8%. FAB-MS, *m/z*: 349(M + 1). IR *v*max(cm^{-1}, KBr): 1657 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 4.28–4.30(2H, t, $J = 10$ Hz, $OCH_2C\underline{H_2}$), 4.38–4.4.(2H, t, $J = 10$ Hz, OCH_2), 6.34(1H, s, H-6), 6.48(1H, s, H-8), 6.66(1H, s, H-3), 7.05(1H, s, $\underline{H}C{=}CH$), 7.09(1H, s, $HC{=}C\underline{H}$), 7.51–7.56(3H, m, H-4′,5′,6′), 7.60(1H, s, N=CH), 7.86–7.88(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 46.1($OCH_2\underline{C}H_2$), 67.6(OCH_2), 93.4(C-8), 98.2(C-6), 106.0(C-3), 106.1(C-10), 119.2(HC=CH), 126.3(C-2′,6′), 129.1(C-3′,5′), 131.1(C-4′), 131.9(C-1′), 137.5(N=C), 157.7(C-9), 162.1(C-5), 163.6(C-2), 164.1(C-7), 182.4(C-4).

Anal. Calcd. for $C_{20}H_{16}N_2O_4$: C, 68.96, H, 4.63. Found: C, 69.15, H, 4.81.

7-(2-(2-methyl-1H-imidazol-1-yl)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8s)

Yield, 78.1%. FAB-MS, *m/z*: 363(M + 1). IR *v*max(cm^{-1}, KBr): 1658 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 2.49(3H, s, CH3), 4.27–4.29(2H, t, J = 8.5 Hz, $OCH_2C\underline{H_2}$), 4.34–4.37(2H, t, J = 8.5 Hz, OCH_2), 6.31(1H, s, H-6), 6.51(1H, s, H-8), 6.67(1H, s, H-3), 6.96(2H, s, H$\underline{C}$=CH), 7.51–7.57(3H, m, H-4′,5′,6′), 7.87–7.88(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 13.1(CH3), 45.1($OCH_2\underline{C}H_2$), 67.5(OCH_2), 93.2(C-8), 98.2(C-6), 105.9(C-3), 106.1(C-10), 119.3(H$\underline{C}$=CH), 126.3(C-2′,6′), 127.7(HC=$\underline{C}$H), 129.1(C-3′,5′), 131.1(C-4′), 131.9(C-1′), 144.9(N=C), 157.7(C-9), 162.1(C-5), 163.7(C-2), 164.1(C-7), 182.4(C-4). Anal. Calcd. for $C_{21}H_{18}N_2O_4$: C, 69.60, H, 5.01. Found: C, 69.78, H, 5.19.

7-(2-(2′-hydroxyethylamino)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8t)

Yield, 82.6%. FAB-MS, *m/z*: 342(M + 1). IR *v*max(cm^{-1}, KBr): 1664 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 2.63–2.65(2H, t, J = 11 Hz, $NC\underline{H_2}CH_2$), 2.90–2.92(2H, t, J = 10.6 Hz, $OCH_2C\underline{H_2}$), 3.46–3.48(2H, t, J = 11 Hz, $NCH_2C\underline{H_2}$), 4.14–4.16(2H, t, J = 10.6 Hz, OCH_2), 6.41(1H, s, H-6), 6.84(1H, s, H-8), 7.06(1H, s, H-3), 7.59–7.65(3H, m, H-4′,5′,6′), 8.10–8.12(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 47.7($OCH_2\underline{C}H_2$), 51.5($N\underline{C}H_2CH_2$), 60.4($NCH_2\underline{C}H_2$), 68.5(OCH_2), 93.1(C-8), 98.4(C-6), 104.8(C-3), 105.2(C-10), 126.3(C-2′,6′), 129.0(C-3′,5′), 130.5(C-4′), 132.0(C-1′), 157.2(C-9), 161.1(C-5), 163.3(C-2), 164.6(C-7), 181.9(C-4). Anal. Calcd. for $C_{19}H_{19}NO_5$: C, 66.85, H, 5.61. Found: C, 66.73, H, 5.54.

7-(2-(2′,2″-dihydroxydiethylamino)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8u)

Yield, 73.6%. FAB-MS, *m/z*: 386(M + 1). IR *v*max(cm^{-1}, KBr): 1660 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 2.64–2.66(4H, t, J = 12 Hz, $N(C\underline{H_2}CH_2)_2$), 2.93–2.95(2H, t, J = 10.8 Hz, $OCH_2C\underline{H_2}$), 3.44–3.46(4H, t, J = 11.3 Hz, $N(CH_2C\underline{H_2})_2$), 4.38–4.40(2H, t, J = 10.3 Hz, OCH_2), 6.39(1H, s, H-6), 6.83(1H, s, H-8), 7.05(1H, s, H-3), 7.55–7.63(3H, m, H-4′,5′,6′), 8.10–8.12(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 53.2($OCH_2\underline{C}H_2$), 57.0($N(\underline{C}H_2CH_2)_2$), 59.4($N(CH_2\underline{C}H_2)_2$), 67.3($OCH_2$), 93.1(C-8), 98.4(C-6), 104.8(C-3), 105.2(C-10), 126.3(C-2′,6′), 129.0(C-3′,5′), 130.5(C-4′), 132.0(C-1′), 157.2(C-9), 161.1(C-5), 163.3(C-2), 164.5(C-7), 181.9(C-4). Anal. Calcd. for $C_{21}H_{23}NO_6$: C, 65.44, H, 6.02. Found: C, 65.56, H, 6.18.

7-(2-(benzylamino)ethoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (8v)

Yield, 62.1%. FAB-MS, *m/z*: 388(M + 1). IR *v*max(cm^{-1}, KBr): 1658 (C=O). ^{1}H NMR($CDCl_3$, 500 MHz): 3.06–3.08(2H, t, J = 11.5 Hz, $OCH_2C\underline{H_2}$), 3.89(2H, s, NCH_2), 4.15–4,17(2H, t, J = 11.5 Hz, OCH_2), 6.37(1H, s, H-6), 6.52(1H, s, H-8), 6.69(1H, s, H-3), 7.33–7.36(5H, m, $CH_2C_6\underline{H_5}$), 7.49–7.55(3H, m, H-4′,5′,6′), 7.88–7.89(2H, m, H-2′,3′). ^{13}C NMR($CDCl_3$, 500 MHz): 47.8($OCH_2\underline{C}H_2$), 53.8(CH_2), 68.3(OCH_2), 93.1(C-8), 98.5(C-6), 105.8(C-3), 105.9(C-10), 126.3(C-2′,6′), 127.1(C-4″), 128.1(C-2″,6″), 128.5(C-3″,5″), 129.1(C-3′,5′), 131.1(C-4′), 131.8(C-1′), 140.0(C-1″), 157.8(C-9), 162.2(C-5), 164.0(C-2), 164.8(C-7), 181.4(C-4). Anal. Calcd. for $C_{24}H_{21}NO_4$: C, 74.40, H, 5.46. Found: C, 74, 33, H, 5.39.

Biological activity

HCT-116, Hela, DU-145, K562, and SGC-7901 cell lines were cultured and passaged in RPMI-1640 medium, supplemented with 10% (v/v) inactive calf bovine serum, in a humidified incubator at 37°C under an atmosphere of 5% CO_2. Stock solutions of tested compounds were prepared in DMSO and were used for serial dilutions in culture medium. The cytotoxicity assay was performed by a modification of the MTT method (Mosmann, 1983).

Results and discussion

Chrysin was total synthesized by Baker–Venkataraman rearrangement in five steps (Scheme 1). Compound 4 was the key intermediate for synthesis of chrysin, and it was prepared by the action of benzoyl chloride on a pyridine solution of Compound 3. The cyclization was effected by use of glacial acetic acid containing hydrogen chloride or sulfuric acid.

The synthesis of compounds 8a–8v was accomplished according to the general pathway illustrated in Scheme 1. Compound 7 was the key intermediate for synthesis of the compounds investigated. It was usually prepared from alkylation of 7-OH group by using 1,2-dibromoethane in the presence of bases such as NaOH or K_2CO_3 (Reinholz *et al*., 1990). To increase the anticancer properties of chrysin derivatives, chrysin derivatives in which the chrysin ring system is linked to the different amines were investigated.

All of the synthetic compounds gave satisfactory analytical and spectroscopic data, which were in full accordance with their depicted structures.

Assays were performed in 96-well plates essentially as described by Mosmann (1983). Pharmacological results are

Table 1 Human cancer cell line growth inhibition values (μM) for the synthesized compounds

Compoud	IC_{50}/(μM)				
	HCT-116	Hela	DU-145	K562	SGC-7901
8a	2.5	3.72	2.95	7.8	4.8
8b	1.5	56.6	1.4	12.9	11.1
8c	8.1	>100	>100	>100	>100
8d	2.7	40.9	1.85	14.9	1.88
8e	1.87	4.92	2.75	>100	3.15
8f	6.2	17.7	17.7	17.9	10.99
8g	9.8	18.82	3.17	12.9	13.9
8h	38	1.56	8.4	>100	23.6
8i	4.6	24.2	18.1	27.8	7.98
8j	9.7	13.3	44.2	43.4	53.3
8k	2.95	6.97	4.98	1.76	6.18
8l	>100	>100	>100	>100	42.99
8m	>100	1.7	3.17	16.9	3.1
8n	0.19	0.46	1.08	4.9	0.78
8o	32.3	>100	32.5	>100	>100
8p	18.7	47.4	28.7	23.9	55.7
8q	>100	>100	>100	>100	>100
8r	4.2	10.8	7.3	27.2	5.55
8s	3.2	9.7	8.2	10.8	7.83
8t	2.3	4.46	5.5	8.31	5.05
8u	22.2	86.5	>100	104.7	59.2
8v	35.5	>100	68.2	31.2	69.8
Chrysin	>100	43	9.81	>100	>100
5-FU	1.93	9.7	2.95	45.4	2.19

5-FU fluorouracil (positive reference drug)

summarized in Table 1. It appears that these closely related molecules display remarkable differences in cytotoxicity. As reported in Table 1, we discovered that compounds 8b, 8e, and 8n show stronger cytotoxicity toward HCT-116 cells, compounds 8a, 8h, 8m, and 8n have stronger cytotoxicity against Hela cells, compounds 8b, 8d, and 8n have stronger cytotoxicity against DU-145 cells, compounds 8a, 8k, 8n, and 8t have stronger cytotoxicity against K562 cells, and compounds 8d, 8m, and 8n possess stronger cytotoxicity toward SGC-7901 cells than chrysin. Among the chrysin derivatives, 7-(2-(piperazin-1-yl)ethoxy)-5-hydroxy-2- phenyl-4H-chromen-4-one (8n) revealed to be the most active of the synthesized compounds tested with IC_{50} values ranging from 0.19 to 1.08 μM against all tumor cell lines, except against K562 ($IC_{50} = 4.9$ μM). Compound 8c showed selective cytotoxic activity against HCT-116 (human colon cancer cell line, $IC_{50} = 8.1$ μM), and Compound 8l showed selective cytotoxic activity against SGC-7901 (human gastric cancer cell line, $IC_{50} = 42.99$ μM). Moreover, apart from 8c, 8e, and 8i, the activity against HCT-116, K562, and SGC-7901 was enhanced with a shorter alkyl chain on N. In addition, the different alkylated substituents on N had little effect against Hela and DU-145 cells.

In summary, a series of novel C(7) modified chrysin derivatives were prepared. Our results supported published data about flavones as interesting cytotoxic secondary metabolites. Certainly, the presence of hydroxy in position 5 appears to play a non-negligible part in the antitumor potency of tested compounds. However, the highest potency is obtained when a piperazin-1-yl-ethoxy group is present in position 7. These results contribute to further understanding the critical molecular requirements that lead to antitumor properties in the flavones series. Further in vivo studies are warranted to confirm the biological activity of the newly synthesized flavones and to investigate the molecular mechanisms responsible for the antitumor activity of the most active compounds with a potential pharmaceutical use.

Acknowledgments This research was supported by Jiangsu Provincial Natural Science Foundation (No. BK2009549).

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