Supporting information

Regio- and Stereospecific Synthesis of Novel 3-Enynyl Substituted Thioflavones / Flavones Using a Copper free Palladium-Catalyzed Reaction

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Table of contents

Experimental Section:

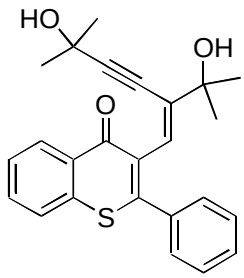
General methods

Unless stated otherwise, reactions were performed under nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230-400 mesh) using distilled petroleum ether, ethyl acetate, dichloromethane, chloroform and methanol. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$, DMSO-d_6 or MeOH-d_4 solution on 200 and 50 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on a FT- IR spectrometer. Melting points were determined by using melting point apparatus and are uncorrected. Thermal analysis data [Differential Scanning Calorimetry (DSC)] was generated with the help of DSC-50 detector. MS spectra were obtained on a mass spectrometer. Chromatographic purity by HPLC was determined by using area normalization method and the condition specified in each case: column, mobile phase (range used), flow rate, detection wavelength, and retention times. Microanalyses were performed using a C H N S/O analyzer.

General procedure for the preparation of IV:

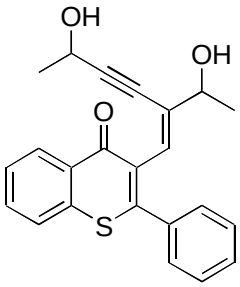
A mixture of **I** (2 mmol), $(PPh_3)_2PdCl_2$ (0.08-0.10 mmol) and triethylamine (16 mmol) in DMF (4 mL) was stirred at 80 ^{o}C for 1 h under a nitrogen atmosphere. The mixture was then cooled to room temperature and the acetylenic compound **II** (4 mmol) dissolved in DMF (1.0 mL) were added slowly with stirring. The reaction mixture was stirred at 25 ^{o}C for 2 h and then an additional quantity of acetylenic compound **II** (2 mmol) dissolved in DMF (1.0 mL) was added with stirring. Stirring was continued for 12-15 h under a nitrogen atmosphere and the mixture was poured into cold 2N HCl solution with stirring. The mixture was then extracted with EtOAc (3 x 200 mL), the combined organic layers were washed with cold water (2 x 100 mL), then dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether-EtOAc) to afford the desired product.

3-[(*E*)-5-Hydroxy-2-(1-hydroxy-1-methylethyl)-5-methyl-1-hexen-3-ynyl]-2-phenyl thiochromen-4-one (IVa)



IVa was isolated as brown solid; DSC: 180.8 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): 8.49 (d, *J* = 8.2 Hz, 1H), 7.63-7.59 (m, 2H), 7.58-7.48 (m, 3H), 7.39-7.36 (m, 3H), 6.83 (s, 1H), 3.11 (bs, D_2O exchangeable, 1H), 3.02 (bs, D_2O exchangeable, 1H), 1.36 (s, 6H), 1.15 (s, 6H); IR (KBr, cm^{-1}): 3384 (bs, OH), 3301, 2926, 1605 (C=O), 1580, 1526; MS (CI, i-Butane): 405.5 (M^{+}+1, 100%); ^{13}C-NMR (50 MHz, DMSO-d_6): 179.1, 149.6, 136.9 (2C), 135.3, 132.0, 131.8, 130.2, 129.4 (2C), 128.3 (2C), 128.1 (2C), 128.0, 126.8, 126.6, 101.7, 78.7, 71.9, 63.6, 31.5 (2C), 29.1 (2C); UV (MeOH, nm): 260, 206.5; HPLC: 98.5%, Hichrom RPB (250 x 4.6 mm), mobile phase 0.01M KH_2PO_4: CH_3CN, (T/%B) 0/20, 10/20 40/85, 50/85, 60/20, 65/20, 1.0 mL / min, 260 nm, retention time 30.53 min.; Elemental analysis found C, 74.33; H, 5.97; $C_{25}H_{24}O_3S$ requires C, 74.23; H, 5.98 %.

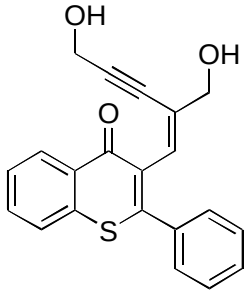
3-[(*E*)-5-Hydroxy-2-(1-hydroxyethyl)-1-hexen-3-ynyl]-2-phenyl thiochromen-4-one (IVb)



IVb was isolated as pale yellow solid; DSC: 146.39 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): 8.53 (d, *J* = 7.8 Hz, 1H), 7.62-7.53 (m, 4H), 7.49-7.46 (m, 2H), 7.42-7.38 (m, 2H), 6.74 (s, 1H), 4.49-4.44 (m, 1H), 4.30-4.26 (m, 1H), 1.78-1.58 (bs, D_2O exchangeable, 2H), 1.30-1.26 (m, 3H), 1.12-1.09 (m, 3H); IR (KBr, cm^{-1}): 3432 (bs, OH), 2927, 1608 (C=O), 1578, 1529, 1441; MS (CI, i-Butane): 377 (M^{+}+1, 100%); ^{13}C-NMR (50 MHz, DMSO-

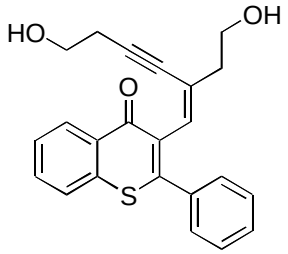
d_6): 178.9, 149.8, 136.8, 136.7, 131.9, 131.9, 130.8, 129.8, 129.3, 129.1 (2C), 128.1, 128.0 (2C), 127.9, 127.6, 126.4, 99.1, 79.6, 68.6, 56.6, 24.4, 22.5; UV (MeOH, nm) 349.4, 258.6, 212.4; HPLC: 99%. INERTSIL ODS 3V (250 x 4.6 mm), mobile phase 0.01M KH_2PO_4: CH_3CN (1:1), 1.0 mL / min, 255 nm, retention time 10.05 min.; Elemental analysis found C, 73.40; H, 5.34; $C_{23}H_{20}O_3S$ requires C, 73.38; H, 5.35 %.

3-[(*E*)-5-Hydroxy-2-hydroxymethyl-1-penten-3ynyl]-2-phenyl thiochromen-4-one (IVc)



IVc was isolated as brown solid; DSC: 182 ºC; ^{1}H NMR (200 MHz, DMSO-d_6): 8.37 (d, J = 7.5 Hz, 1H), 7.92-7.47 (m, 8H), 6.80 (s, 1H), 5.25 (bs, D_2O exchangeable, 1H), 5.09 (bs, D_2O exchangeable, 1H), 4.02-4.0 (m, 2H), 3.77 (m, 2H); IR (KBr, cm^{-1}): 3314 (bs, OH), 2924, 1608 (C=O), 1588; MS (CI, i-Butane): 349 (M^++1, 100 %); UV (MeOH, nm) 349, 259, 207.4; HPLC: 97%. INERTSIL ODS 3V (250 mm), 0.01M KH_2PO_4: CH_3CN (1:1), 1.0 mL / min, 260 nm, retention time 7.752 min; Elemental analysis found C, 72.35; H, 4.64; $C_{21}H_{16}O_3S$ requires C, 72.39; H, 4.63 %.

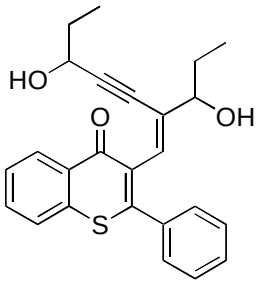
3-[(*Z*)-6-Hydroxy-2-(2-hydroxyethyl)-1-hexen-3-ynyl]-2-phenyl thiochromen-4-one (IVd)



IVd was isolated as brown gum; ^{1}H NMR (400 MHz, $CDCl_3$): 8.57 (d, J = 7.8 Hz, 1H), 7.69-7.43 (m, 8H), 6.35 (s, 1H), 3.67 (t, J = 5.9 Hz, 2H), 3.55 (t, J = 5.9 Hz, 2H), 2.43 (t,

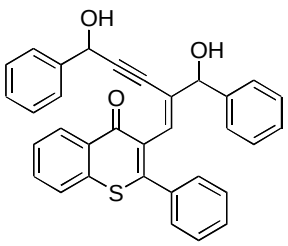
J = 6.4 Hz, 2H), 2.38 (t, *J* = 6.4 Hz, 2H), 2.33-2.04 (bs, D_2O exchangeable, 2H); IR (Neat, cm^{-1}): 3391 (bs, OH), 2926, 2231, 1606 (C=O), 1587; MS (CI, i-Butane): 377 (M^++1, 100%); ^{13}C NMR (50 MHz, DMSO-d_6): 178.9, 136.9, 136.6, 131.9, 131.6, 131.4, 130.8, 130.7, 129.9, 129.5, 128.9, 128.6, 128.2, 128.1, 127.9, 126.4, 124.1, 93.1, 80.1, 59.7 (2C), 40.8, 23.4; Elemental analysis found C, 73.41; H, 5.34; $C_{23}H_{20}O_3S$ requires C, 73.38; H, 5.35 %.

3-[(*E*)-5-Hydroxy-2-(1-hydroxypropyl)-1-hepten-3-ynyl]-2-phenyl thiochromen-4-one (IVe)



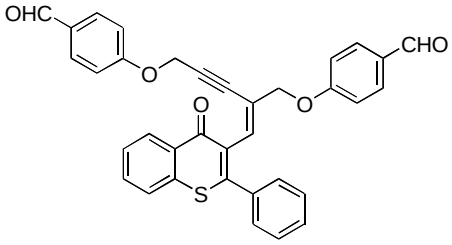
IVe was isolated as brown solid; DSC: 210.19 ºC; ^1H NMR (400 MHz, $CDCl_3$): 8.52 (d, *J* = 8.3 Hz, 1H), 7.61-7.51 (m, 3H), 7.48-7.38 (m, 5H), 6.66 (d, *J* = 2.9 Hz, 1H), 4.26 (t, *J* = 6.4 Hz, 1H), 4.02 (t, *J* = 6.4 Hz, 1H), 2.98-2.65 (bs, D_2O exchangeable, 2H), 1.59-1.45 (m, 4H), 0.81-0.70 (m, 3H), 0.69-0.65 (m, 3H); IR (KBr, cm^{-1}): 3384 (bs, OH), 2930, 1605 (C=O), 1585; MS (CI, i-Butane): 405 (M^++1, 100 %); ^{13}C NMR (50 MHz, $CDCl_3$): 178.9, 149.7, 136.8 (2C), 136.7, 131.9, 131.6, 131.3, 131.1, 130.0, 129.4, 128.9 (2C), 128.6, 128.2, 127.9, 126.3, 97.8, 80.6, 73.7, 62.1, 30.6, 28.5, 9.4, 9.1; Elemental analysis found C, 74.43; H, 5.97; $C_{25}H_{24}O_3S$ requires C, 74.23; H, 5.98 %.

3-[(*E*)-5-Hydroxy-2-(hydroxyphenylmethyl)-5-phenyl-1-penten-3-ynyl]-2-phenyl thiochromen-4-one (IVf)



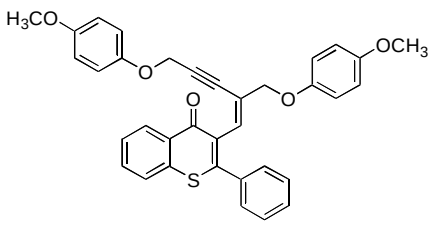
IVf was isolated as pale brown solid; DSC: 221.3 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): 8.50-8.48 (m, 1H), 7.65-7.52 (m, 3H), 7.33-7.29 (m, 3H), 7.26-7.1 (m, 8H), 7.09-7.04 (m, 4H), 6.93 (s, 1H), 5.29-5.25 (m, 2H), 3.45-2.62 (bs, D_2O exchangeable, 2H); IR (KBr, cm^{-1}): 3335 (bs, OH), 2925, 1616 (C=O), 1534, 1444; MS (CI, i-Butane): 501 (M^++1, 100%); ^{13}C-NMR (50 MHz, DMSO-*d_6*): 178.8, 150.1, 142.6, 141.7, 136.8, 136.6, 131.9, 130.8, 130.4, 130.0 (2C), 129.2, 128.8 (2C), 128.3 (2C), 127.9, 127.7 (5C), 127.2, 126.9 (2C), 126.9, 126.4, 126.3 (2C), 96.8, 82.1, 74.7, 62.7; Elemental analysis found C, 79.15; H, 4.85; $C_{33}H_{24}O_3S$ requires C, 79.17; H, 4.83 %.

3-[(*E*)-5-(4-Formylphenoxy)-2-(4-formylphenoxymethyl)pent-1-en-3-ynyl]-2-phenyl thiochromen-4-one (IVg)



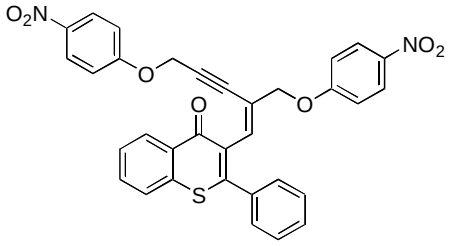
IVg was isolated as pale yellow solid; mp > 250 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): 9.89 (s, 1H, -CHO), 9.65 (s, 1H, -CHO), 8.48 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.63-7.26 (m, 14H), 6.91-6.86 (m, 1H), 4.75 (s, 2H), 4.55 (s, 2H); IR (KBr, cm^{-1}): 2926, 2120 (w, -C≡C-), 1690 (C=O), 1599, 1508, 1222; MS (CI, i-Butane): 557 (M^++1, 100%). ^{13}C-NMR (50 MHz, DMSO-*d_6*): 191.3, 190.9, 178.4, 162.7, 161.8, 151.0, 136.6, 136.3, 135.3, 132.1, 131.7 (2C), 131.2 (2C), 129.9, 129.8, 129.6, 129.3, 128.9, 128.7 (2C), 128.3 (2C), 128.1, 128.1, 126.5, 121.5, 115.2 (2C), 114.9 (2C), 89.8, 83.9, 69.5, 56.1; Elemental analysis found C, 75.50; H, 4.36; $C_{35}H_{24}O_5S$ requires C, 75.52; H, 4.35 %.

3-[(*E*)-5-(4-Methoxyphenoxy)-2-(4-methoxy phenoxymethyl)pent-1-en-3-ynyl]-2-phenyl thiochromen-4-one (IVh):



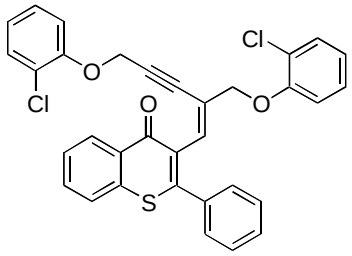
IVh was isolated as light brown low melting solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 6.7 Hz, 1H), 7.53 (d, *J* = 6.7 Hz, 2H), 7.4-7.32 (m, 7H), 6.90 (s, 1H), 6.79-6.68 (m, 4H), 6.58 (d, *J* = 4.6 Hz, 2H), 4.72 (s, 2H), 4.40 (s, 2H), 3.77 (s, 3H), 3.65 (s, 3H); IR (KBr, cm^{-1}) 1614 (C=O), 1591; m/z (CI, i-Butane) 561 (M+1, 100%); ^{13}C NMR (50 MHz, $CDCl_3$)δ 178.6, 153.5, 153.4, 151.7, 150.8, 136.6, 136.2, 131.9, 130.9, 129.7, 129.2, 128.9, 128.3, 128.1, 127.6, 127.5, 126.9, 125.3 (2C), 125.0, 122.4, 116.2 (2C), 115.3 (2C), 113.8 (2C), 113.6 (2C), 90.2, 82.9, 69.8, 56.4, 54.9, 54.7; HPLC: 98.5%, ACE 3C18 (150 x 4.6 mm), mobile phase 0.01M KH_2PO_4 (pH-5.5) : CH_3CN 70:30, (T/%B) 0/75, 5/75, 15/80, 40/80, 45/75, 50/75. 0.5 mL/min, retention time 11.42 min, VU: 210; Elemental analysis found C, 74.95; H, 5.04; $C_{35}H_{28}O_5S$ requires C, 74.98; H, 5.03 %.

3-[(*E*)-5-(4-Nitrophenoxy)-2-(4-nitrophenoxymethyl)pent-1-en-3-ynyl]-2-phenylthiochromen-4-one (IVi)



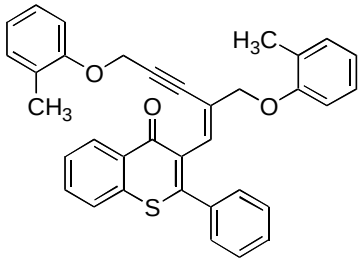
IVi was isolated as yellow solid, DSC 125.45 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, *J* = 7.5 Hz, 1H,), 8.14-8.11 (m, 2H), 7.86-7.84 (m, 2H), 7.77-7.58 (m, 2H), 7.62-7.58 (m, 2H), 7.45-7.36 (m, 6H), 7.02 (t, *J* = 9.2 Hz, 1H), 7.0 (s, 1H), 6.95 (d, *J* = 9.4 Hz, 1H), 4.99 (s, 2H), 4.68 (s, 2H); IR (KBr, cm^{-1}) 1606 (C=O), 1585; m/z (CI, i-Butane) 591 (M+1, 100%); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.8, 162.9, 162.0, 151.9, 141.7, 141.6, 136.9, 136.3, 134.7, 131.7 (2C), 130.1 (2C), 129.8, 129.4, 128.9, 128.7, 128.3 (2C), 127.8, 125.7, 125.6 (2C), 125.3, 121.5, 114.8 (2C), 114.5 (2C), 89.0, 84.7, 69.9, 56.7; HPLC: 97.1%, HICHROMR PB (250 x 4.6 mm), 0.01M KH_2PO_4: CH_3CN, 70:30, (T/%B) 0/60, 5/60, 15/80, 25/80, 30/60, 35/60, 1.0 mL/min, 210 nm, retention time 17.6 min; Eiemental analysis found C, 67.33; H, 3.73; N, 4.72; $C_{33}H_{22}N_2O_7S$ requires C, 67.11; H, 3.75; N, 4.74 %.

3-[(*E*)-5-(2-Chlorophenoxy)-2-(2-chlorophenoxymethyl)pent-1-en-3-ynyl]-2-phenyl thiochromen-4-one (IVj):



IVj was isolated as light brown solid, DSC 153.9 ºC; ^{1}H NMR (200 MHz, $CDCI_3$) δ 8.52 (d, *J* = 7.9 Hz, 1H), 7.62 (t, *J* = 6.7 Hz, 1H), 7.53 (d, *J* = 6.7 Hz, 2H), 7.4-7.32 (m, 7H), 6.90 (s, 1H), 6.79-6.68 (m, 4H), 6.58 (d, *J* = 4.6 Hz, 2H), 4.72 (s, 2H), 4.40 (s, 2H); IR (KBr, cm^{-1}) 1607 (C=O); m/z (CI, i-Butane) 570 (M+1, 100%); ^{13}C NMR (50 MHz, $CDCI_3$) δ 179.4, 153.7, 152.8, 151.8, 137.4, 136.6, 133.3, 131.3, 130.4, 130.2, 130.0, 129.6, 129.5, 129.0, 128.9, 128.2, 127.6 (2C), 127.5, 127.2 (2C), 125.7, 123.1, 122.7, 121.9, 121.9 (2C), 121.7, 114.1, 89.7, 84.3, 70.3, 57.1; HPLC: 98.1%, prevail C18, 0.01M KH_2PO_4 :CH_3CN, (T/%B) 0/50, 1/50, 10/85, 16/85, 18/50, 20/50, 2.5 mL/min, 210 nm, retention time 10.2 min; Elemental analysis found C, 69.69; H, 3.87; $C_{33}H_{22}Cl_2O_3S$ requires C, 69.60; H, 3.89 %.

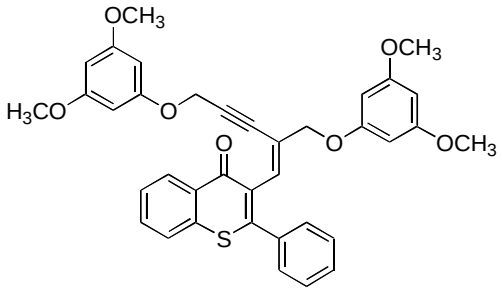
2-Phenyl-3-[(*E*)-5-*o*-tolyloxy-2-*o*-tolyloxymethylpent-1-en-3-ynyl]thiochromen-4-one (IVk):



IVk was isolated as light brown powder; DSC 146.03 ºC; ^{1}H NMR (400 MHz, $CDCI_3$) δ 8.52 (d, *J* = 4.3 Hz, 1H), 7.63 (t, *J* = 6.9 Hz, 1H), 7.60 (t, *J* = 5.4 Hz, 2H), 7.37-7.28 (m, 5H), 7.09 (d, *J* =7.3 Hz, 2H), 7.04 (t, *J* = 7.3 Hz, 1H), 6.94 (s, 1H), 6.86-6.78 (m, 2H),

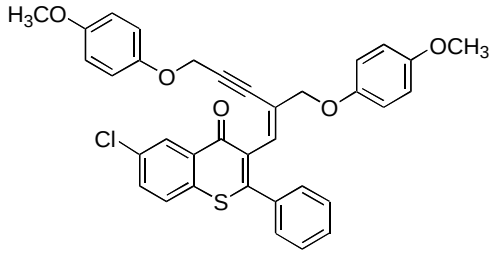
6.71 (t, *J* = 7.3 Hz, 2H), 6.63 (d, *J* = 8.1 Hz, 1H), 4.66 (s, 2H), 4.46 (s, 2H), 2.16 (s, 3H), 2.15 (s, 3H); IR (KBr, cm^{-1}) 1606 (C=O), 1587; m/z (CI, i-Butane) 529 (M+1, 100%); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.6, 156.4, 155.7, 151.5, 137.5, 136.8, 132.2, 131.3, 130.6, 130.0, 129.4, 129.1, 129.0, 128.7, 128.3, 128.2, 127.5, 127.0, 126.8 (2C), 126.6, 126.4 (2C), 125.7, 123.1, 120.9, 120.6, 111.6, 111.4, 90.5, 83.7, 69.5, 56.5, 16.3, 16.2; VU (MeOH, nm) 254.5, 225, 204; HPLC: 97.2%, symmetry shield RP18 (250 x 4.6 mm), mobile phase 0.01M KH_2PO_4 (pH =3.0): CH_3CN 70:30, (T/%B) 0/75, 5/75, 15/85, 40/85, 45/75, 50/75, 1.0 mL/min, 210 nm, retention time 18.73 min; Elemental analysis found C, 79.59; H, 5.32 ; N, ; $C_{35}H_{28}O_3S$ requires C, 79.52; H, 5.34 %.

3-[(*E*)-5-(3,5-Dimethoxyphenoxy)-2-(3,5-dimethoxyphenoxymethyl)pent-1-en-3-ynyl]-2-phenyl thiochromen-4-one (IVl):



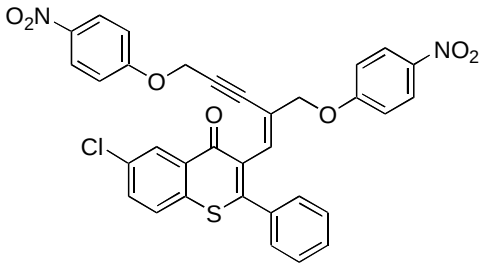
IVl was isolated as yellow solid; DSC 135.27 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 6.5 Hz, 1H), 7.54 (t, *J* = 6.4 Hz, 1H), 7.51 (t, *J* = 6.7 Hz, 2H), 7.37-7.28 (m, 5H), 6.96 (s, 1H), 6.09-6.08 (m, 1H), 6.03-6.01 (m, 4H), 5.97-5.95 (m, 1H), 4.59 (s, 2H), 4.42 (s, 2H), 3.75 (s, 6H), 3.65 (s, 6H); IR (KBr, cm^{-1}) 1606 (C=O); m/z (CI, i-Butane) 621 (M+1, 10%), 467 (100%); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.5, 161.3, 161.2 (2C), 160.1 (2C), 159.4, 152.0, 137.4, 136.8, 132.6, (2C), 131.2, 130.5, 129.7, 129.5, 129.0, 128.2, 127.4 (2C), 125.7, 122.4 (2C), 93.8 (2C), 93.6 (2C), 93.5, 93.5, 90.1, 83.9, 69.5, 56.5, 55.3 (2C), 55.2 (2C); HPLC: 98.0%, Alltima C18 (53 x 7 mm), mobile phase 0.01M KH_2PO_4 :CH_3CN 70:30, (T/%B) 0/60, 1/60, 14/85, 17/85, 19/60, 20/60, 2.5 mL/min, 225 nm, retention time 8.5 min, Elemental analysis found C, 71.70; H, 5.15; $C_{37}H_{32}O_7S$ requires C, 71.59 ; H, 5.20 %.

6-Chloro-3-[(*E*)-5-(4-methoxyphenoxy)-2-(4-methoxyphenoxymethyl)pent-1-en-3-ynyl]-2-phenyl thiochromen-4-one (IVm):



IVm was isolated as a light brown yield; mp 120 ºC; ^{1}H NMR (400 MHz, $CDCI_3$) δ 8.47 (d, J = 2.1 Hz, 1H), 7.58-7.55 (m, 1H), 7.47 (d, *J* =8.6 Hz, 1H), 7.41-7.29 (m, 5H), 6.85 (s, 1H), 6.79-6.72 (m, 6H), 6.57 (d, *J* = 4.3 Hz, 2H), 4.59 (s, 2H), 4.4 (s, 2H), 3.77 (s, 3H), 3.66 (s, 3H); IR (KBr, cm^{-1}) 1615 (C=O), 1586; m/z (CI, i-Butane) 595 (M^{+}, 100%); ^{13}C NMR (50 MHz, $CDCI_3$) δ 178.3, 154.0 (2C), 152.4, 151.5, 136.5, 135.5, 133.9, 131.7, 131.7, 130.0, 129.6 (2C), 129.0 (2C), 128.6 (2C), 128.2, 127.2 (2C), 123.6, 115.9 (2C), 115.8 (2C), 114.5 (2C), 114.2 (2C), 90.9, 83.8, 70.3, 57.1, 55.7, 55.5; HPLC: 97.2%, Alltima c18 (53 x 7 mm), mobile phase 0.01M KH_2PO_4 : CH_3CN (T/%B) 70:30, 0/60, 1/60, 3/80, 18/80, 19/60, 20/60, 2.5 mL/min, 210 nm, retention time 6.2 min.; Elemental analysis found C, 70.59; H, 4.59 $C_{35}H_{27}ClO_5S$ requires C, 70.64 ; H, 4.57 %.

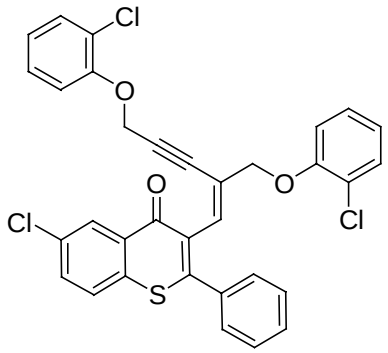
6-Chloro-3-[(*E*)-5-(4-nitrophenoxy)-2-(4-nitrophenoxymethyl)pent-1-en-3-ynyl]-2-phenyl thiochromen-4-one (IVn):



IVn was isolated as a light brown solid, mp 171.2 ºC; ^{1}H NMR (400 MHz, $CDCI_3$) δ 8.4 (s, 1H), 8.14 (d, *J* = 5.1 Hz, 2H), 7.9 (d, *J* = 4.8 Hz, 2H), 7.57 (d, *J* = 6.2 Hz, 1H), 7.45-7.4 (m, 2H), 7.36-7.27 (m, 4H), 6.86 -6.82 (m, 4H), 6.77 (s, 1H), 4.79 (s, 2H), 4.59 (s, 2H); IR (KBr, cm^{-1}) 1617 (C=O), 1589; m/z (CI, i-Butane) 625 (M^{+}, 100%); ^{13}C NMR (50 MHz, $CDCI_3$) δ 177.5, 162.9, 162.0, 152.0, 141.8, 141.6, 136.0, 135.0, 134.5, 134.0,

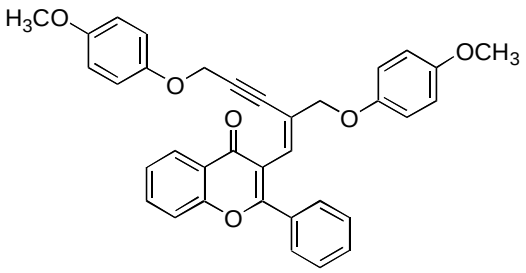
132.2, 131.3, 130.1, 129.4, 128.7, 128.6 (2C), 128.47 (2C), 127.1 (2C), 125.8, 125.4 (2C), 121.9, 114.8 (2C), 114.6 (2C), 89.4, 84.6, 69.9, 56.7; VU (MeOH, nm) 292.5, 205; HPLC: 98.9%, symmetry shield (250 x 4.6mm), mobile phase 0.01M KH_2PO_4 (pH =7.0): CH_3CN 70:30, (T/%B) 0/70, 5/70, 20/85, 30/85, 35/70, 40/70, 1.0 mL/min, 210 nm, retention time 17.9 min, Elemental analysis found C, 63.45; H, 3.40; N, 4.45; $C_{33}H_{21}ClN_2O_7S$ requires C, 63.41; H, 3.39; N, 4.48 %.

6-Chloro-3-[(*E*)-5-(2-Chlorophenoxy)-2-(2-chlorophenoxymethyl)pent-1-en-3-ynyl]-2-phenyl thiochromen-4-one (IVo):



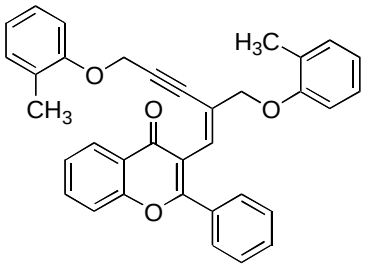
IVo was isolated as a light brown solid; mp 124 ºC; ^{1}H NMR (400 MHz, $CDCI_3$) δ 8.46 (s, 1H), 7.57 (d, *J* = 6.2 Hz, 1H), 7.48 (d, *J* =8.6 Hz, 1H), 7.37-7.22 (m, 6H), 7.14 (t, *J* = 6.5 Hz, 1H), 6.95 (s, 1H), 6.91 (t, *J* = 6.5 Hz, 1H), 6.89 -6.77 (m, 3H), 6.7 (t, *J* = 5.9 Hz, 2H), 4.74 (s, 2H), 4.52 (s, 2H); IR (KBr, cm^{-1}) 1615 (C=O); m/z (CI, i-Butane) 604 (M^+, 100%); VU (MeOH, nm) 356, 264, 204; HPLC: 97.2%, Prevail c18 (53 x 7 mm), mobile phase 0.01M KH_2PO_4: CH_3CN 70:30, (T/%B) 0/60, 2/60, 4/80, 18/80, 19/60, 20/60, 2.5 mL/min, 210 nm, retention time 7.3 min, Elemental analysis found C, 65.69; H, 3.49; $C_{33}H_{21}Cl_3O_3S$ requires C, 65.63; H, 3.50 %.

3-[(*E*)-5-(4-Methoxyphenoxy)-2-(4-methoxyphenoxymethyl)pent-1-en-3-ynyl]-2-phenylchromen-4-one (IVp):



IVp was isolated as a light brown low melting solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 6.2, 1.6 Hz, 1H), 7.69 (t, *J* = 6.9 Hz, 1H), 7.67 (d, *J* = 5.6 Hz, 2H), 7.46-7.41 (m, 3H), 7.36 (t, *J* = 7.5 Hz, 2H), 6.92 (s, 1H), 6.82 (s, 4H), 6.71 (d, *J* = 9.1 Hz, 2H), 6.58 (d, *J* = 9.1 Hz, 2H), 4.53 (s, 2H), 4.51 (s, 2H), 3.77 (s, 3H), 3.65 (s, 3H); IR (KBr, cm^{-1}) 1639 (C=O), 1616; m/z (CI, i-Butane) 545 (M^+, 100%); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.7, 161.9, 155.6, 153.9, 152.2, 151.4, 133.4, 133.3, 130.3, 128.8, 128.6, 128.1, 127.9, 125.7, 124.9 (2C), 123.7, 122.6, 117.8, 117.6, 115.9, 115.7 (2C), 115.5 (2C), 114.3 (2C), 114.1 (2C), 91.2, 83.4, 70.4, 66.7, 56.9 (2C); VU (MeOH, nm) 254, 225, 204; HPLC: 98.5%, Alltima c18 (53 x 7 mm), mobile phase 0.01M KH_2PO_4 : CH_3CN 70:30, (T/%B) 0/60, 1/60, 14/85, 17/85, 19/60, 20/60, 2.5 mL/min, 225 nm, retention time 6.9 min, Elemental analysis found C, 77.23; H, 5.15; $C_{35}H_{28}O_6$ requires C, 77.19; H, 5.18 %.

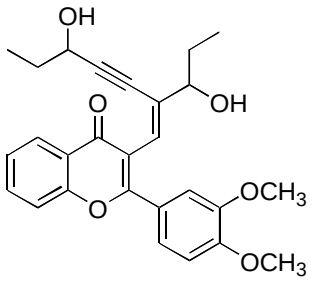
2-Phenyl-3-[(*E*)-5-o-tolyloxy-2-o-tolyloxymethylpent-1-en-3-ynyl]chromen-4-one (IVq):



IVq was isolated as a light brown solid; DSC 134.9 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 6.1, 1.7 Hz, 1H), 7.7 (t, *J* = 5.6 Hz, 1H), 7.54 (d, *J* = 5.1 Hz, 2H), 7.46 (s, 1H), 7.41 (d, *J* = 6.2 Hz, 2H), 7.32 (t, *J* = 6.2 Hz, 2H), 7.14 -7.12 (m, 2H), 7.02 (d, *J* = 6.5 Hz, 1H), 6.98 (s, 1H), 6.9 (t, *J* =7.5 Hz, 1H), 6.80-6.72 (m, 3H), 6.66 (d, *J* =8.1 Hz, 1H), 4.59 (s, 2H), 4.56 (s, 2H), 2.21 (s, 3H), 2.13 (s, 3H); IR (KBr, cm^{-1}) 1629 (C=O), 1564; m/z (CI, i-Butane) 513 (M+1, 100%); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.1, 162.1,

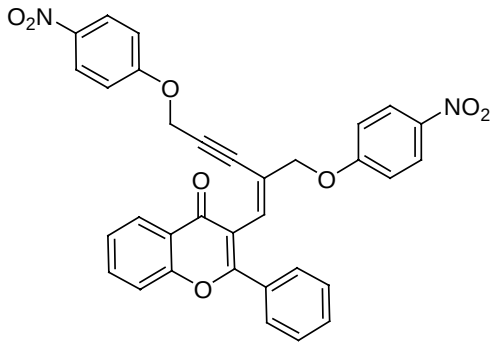
156.3, 155.9, 155.7, 133.5, 130.7, 130.5, 130.4, 128.9, 128.7, 128.2, 128.0 (2C), 127.1, 126.8, 126.6, 126.3, 126.0 (2C), 125.0, 123.6, 122.8, 120.9, 120.7, 117.9, 117.8, 111.7, 111.4, 91.1, 83.4, 69.6, 56.5, 16.3, 16.2; VU (MeOH, nm) 255, 204; HPLC: 97.5%, Alltima 3C18 (53 x 7 mm), mobile phase 0.01M KH_2PO_4 :CH_3CN, (T/%B) 0/60, 1/60, 10/85, 16/85, 18/60, 20/60, 2.5 mL/min, 215 nm, retention time 10.2 min, Elemental analysis found C, 82.15; H, 5.47; $C_{35}H_{28}O_4$ requires C, 82.01; H, 5.51 %.

2-(3,4-Dimethoxyphenyl)-3-[(*E*)-5-hydroxy-2-(1-hydroxypropyl)-1-hepten-3-ynyl] chromen-4-one (IVr)



IVr was isolated as yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.8 Hz, 1H), 7.87-7.81 (m, 2H), 7.6 (t, *J* = 6.8 Hz, 1H), 7.4 (d, *J* = 8.8 Hz, 1H), 7.44 (m, 1H), 7.1 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 2.9 Hz, 1H), 4.27 (t, *J* = 6.4 Hz, 1H), 4.03 (t, *J* = 6.4 Hz, 1H), 4.0 (s, 6H), 2.95-2.66 (bs, D_2O exchangeable, 2H), 1.58-1.44 (m, 4H), 0.81-0.70 (m, 3H), 0.68-0.64 (m, 3H); IR (KBr, cm^{-1}): 3384 (bs, OH), 2930, 2874, 1620 (C=O), 1585, 1538; MS (CI, i-Butane) 449 (M^+, 100 %); Elemental analysis found C, 72.36; H, 6.27; $C_{27}H_{28}O_6$ requires C, 72.30; H, 6.29 %.

3-[5-(4-Nitrophenoxy)-2-((*E*)-4-nitrophenoxymethyl)pent-1-en-3-ynyl]-2-phenyl chromen-4-one (IVs)

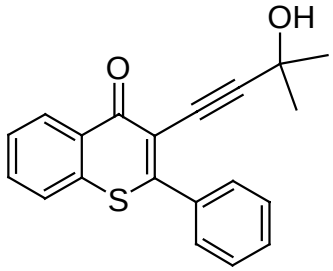


IVs was isolated a brown colored low melting solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (t, *J* = 6.9 Hz, 4H), 7.88 (d, *J* = 5.1 Hz, 2H), 7.57-7.55 (m, 2H), 7.48 (d, *J* = 6.2 Hz, 2H) 7.4-7.37 (m, 3H), 6.94 (t, *J* = 4.8 Hz, 2H), 6.89 (s, 1H), 6.81 (d, *J* = 4.8 Hz, 2H), 4.73 (s, 2H), 4.68 (s, 2H); IR (KBr, cm^{-1}) 1644 (C=O); m/z (CI, i-Butane) 574 (M^+, 100%); HPLC: 97.1%, Alltima c18 (53 x 7 mm), mobile phase 0.01M KH_2PO_4: CH_3CN 70:30, (T/%B) 0/60, 1/60, 14/85, 17/85, 19/60, 20/60, 2.5 mL/min, 220 nm, retention time 6.2 min; Elemental analysis found C, 68.94; H, 3.88; N, 4.50; $C_{33}H_{22}N_2O_8$ requires C, 68.99; H, 3.86; N, 4.88 %.

General procedure for the preparation of III:

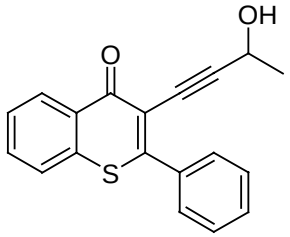
A mixture of **I** (2 mmol), $(PPh_3)_2PdCl_2$ (0.08 mmol), CuI (0.10 mmol) and triethylamine (16 mmol) in DMF (4 mL) was stirred at 25 ºC for 10 min under a nitrogen atmosphere. The acetylenic compound **II** (4 mmol) was added slowly to the mixture with with stirring. The reaction mixture was stirred at 25 ºC for 10-15 h The mixture was poured into cold 2N HCl solution with stirring and filtered (if solid was separated) or extracted with EtOAc (3 x 200 mL). Combined organic layers were washed with cold water (2 x 100 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether-EtOAc) to afford the desired product.

3-(3-Hydroxy-3-methyl-1-butynyl)-2-phenyl thiochromen-4-one (IIIa)



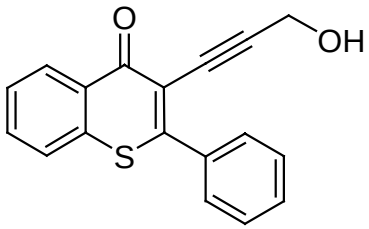
IIIa was isolated as brown gum; ^{1}H NMR (200 MHz, $CDCl_3$): 8.56 (d, *J* = 7.3 Hz, 1H), 7.69-7.47 (m, 8H), 3.09-2.83 (bs, D_2O exchangeable, 1H), 1.43 (s, 6H); IR (Neat, cm^{-1}): 3378 (bs, OH), 2980, 1614 (C=O); MS (CI, i-Butane): 321 (M^+, 30 %), 303 (100 %); Elemental analysis found C, 74.67; H, 5.00; $C_{20}H_{16}O_2S$ requires C, 74.97; H, 5.03 %.

3-(Hydroxy-1-butynyl)-2-phenyl thiochromen-4-one (IIIb)



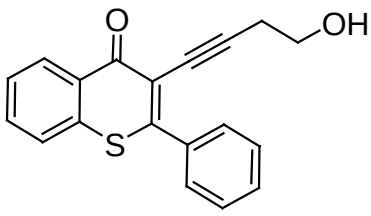
IIIb was isolated as semi solid; ^{1}H NMR (200 MHz, $CDCl_3$): 8.57 (d, *J* = 7.3 Hz, 1H), 7.70-7.45 (m, 8H), 4.48 (m, 1H), 2.87 (bs, D_2O exchangeable, 1H), 1.40 (d, *J* = 6.4 Hz, 3H); IR (Neat, cm^{-1}): 3378 (bs, OH), 2980, 1614 (C=O); MS (CI, i-Butane): 307 (M+1, 100 %); Elemental analysis found C, 74.53; H, 4.60; $C_{19}H_{14}O_2S$ requires C, 74.48; H, 4.61 %.

3-(3-Hydroxy-1-propynyl)-2-phenyl thiochromen-4-one (IIIc)



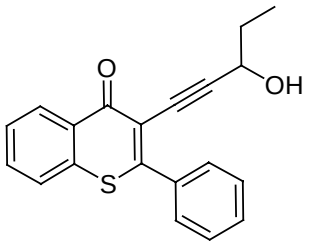
IIIc was isolated as brown semi solid; ^{1}H NMR (200 MHz, $CDCl_3$): 8.58 (d, *J* = 7.8Hz, 1H), 7.71-7.45 (m, 8H), 4.36 (s, 2H), 2.06 (bs, D_2O exchangeable, 1H); IR (Neat, cm^{-1}): 3384 (bs, OH), 2925, 2223 (w, -C≡C-), 1612 (C=O); MS (CI, i-Butane): 293 (M+1, 100%); Elemental analysis found C, 73.99; H, 4.13; $C_{18}H_{12}O_2S$ requires C, 73.95; H, 4.14 %.

3-(4-Hydroxy-1-butynyl)-2-phenyl thiochromen-4-one (IIId)



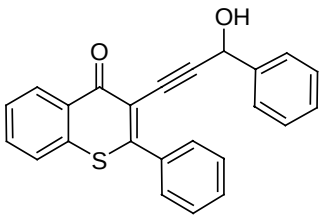
IIId was isolated as light brown solid, DSC: 277.8 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): 8.59 (d, *J* = 7.3 Hz, 1H), 7.70-7.52 (m, 8H), 3.78-8.71 (m, 2H), 2.62-2.5 (m, 2H), 2.31 (bs, D_2O exchangeable, 1H); IR (Neat, cm^{-1}): 3385 (bs, OH), 2929, 2225 (w, -C≡C-), 1612 (C=O); MS (CI, i-Butane): 307 (M+1, 100%); Elemental analysis found C, 74.58; H, 4.60; $C_{19}H_{14}O_2S$ requires C, 74.48; H, 4.61 %.

3-(3-Hydroxy-1-pentynyl)-2-phenyl thiochromen-4-one (IIIe)



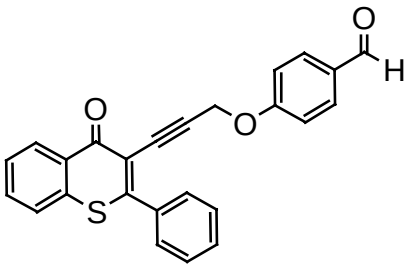
IIIe was isolated as light brown solid; ^{1}H NMR (200 MHz, $CDCl_3$) 8.59 (d, *J* = 7.3 Hz, 1H), 7.70-7.52 (m, 8H), 4.6 (m, 1H), 2.49 (bs, D_2O exchangeable, 1H), 1.85 (m, 2H), 1.1 (t, *J* = 7.0 Hz, 3H); IR (KBr, cm^{-1}) 3410 (bs, OH), 2223 (w, -C≡C-), 1612 (C=O); MS (CI, i-Butane) 320 (M^+, 100); Elemental analysis found C, 74.91; H, 5.05; $C_{20}H_{16}O_2S$ requires C, 74.97; H, 5.03 %.

3-(3-Hydroxy-3-phenyl-1-propynyl)-2-phenyl thiochromen-4-one (IIIf)



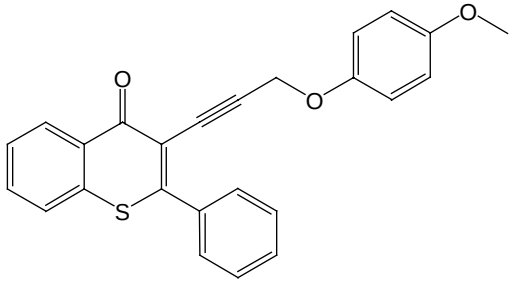
IIIf was isolated as brown solid; DSC 229.9 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): 8.55 (d, *J* = 7.8 Hz, 1H), 7.63-7.02 (m, 13H), 5.56 (s, 1H), 2.23-1.89 (bs, D_2O exchangeable, 1H); IR (KBr, cm^{-1}): 3405 (bs, OH), 2924, 2186 (w, -C≡C-), 1608 (C=O), 1587; MS (CI, i-Butane): 369 (M+1, 100 %); Elemental analysis found C, 78.35; H, 4.37; $C_{24}H_{16}O_2S$ requires C, 78.24; H, 4.38 %.

4-[3-(4-Oxo-2-phenyl-4*H*-thiochromen-3-yl)-2-propynyloxy] benzaldehyde (IIIg)



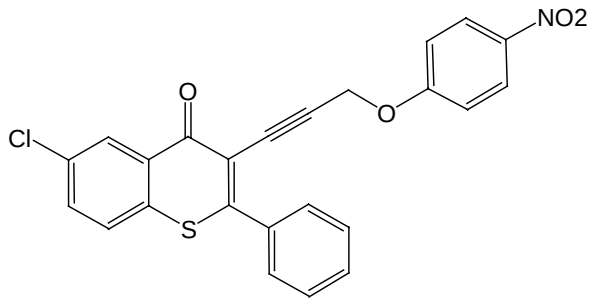
IIIg was isolated as pale yellow solid; DSC: 181.4 ºC, ^{1}H NMR (200 MHz, $CDCl_3$): 9.91 (s, 1H), 8.58 (d, *J* = 8.1 Hz, 1H), 7.79-7.75 (m, 3H), 7.66-7.49 (m, 3H), 7.40-7.31 (m, 3H), 7.04-6.94 (m, 3H), 4.85 (s, 2H); IR (Neat, cm^{-1}): 2739, 2223 (-C≡C-), 1690 (H-C=O); MS (CI, i-Butane): 397.0 (M+1, 100%); Elemental analysis found C, 75.70; H, 4.10; $C_{25}H_{16}O_3S$ requires C, 75.74; H, 4.07 %.

3-[3-(4-Methoxy phenoxy)prop-1-ynyl]-2-phenyl thiochromen-4-one (IIIh):



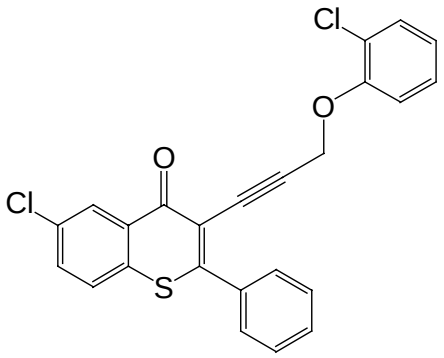
IIIh was isolated as a light brown color solid, mp155-157 ºC, DSC 156.5 ºC; ^{1}H NMR (200 MHz, $CDCI_3$) δ 8.57 (d, *J* = 6.9 Hz, 1H), 7.63-7.52 (m, 5H), 7.47-7.30 (m, 3H), 6.83-6.73 (m, 4H,), 4.78 (s, 2H), 3.77 (s, 3H); IR (KBr, cm^{-1}) 1621 (C=O); m/z (CI, i-Butane) 398 (M^{+}, 100%); ^{13}C NMR (50 MHz, $CDCI_3$) δ 178.6, 156.7, 154.1, 151.9, 136.1, 135.9, 131.7, 130.3, 129.9, 129.2, 128.7 (2C), 128.3, 127.9, 125.8 (2C), 117.9, 115.9 (2C), 114.4 (2C), 92.2, 81.5, 57.2, 55.6; VU (MeOH, nm) 356, 279.5, 228, 204; HPLC: 98.8%, Alltima 3C18 (53 x 7 mm), mobile phase 0.01M KH_2PO_4: CH_3CN 70:30, (T/%B) 0/50, 1/50, 7/80, 16/80, 18/50, 20/50, 2.5 mL/min, 210 nm, retention time 6.2 min, Elemental analysis found C, 75.41; H, 4.53; $C_{25}H_{18}O_3S$ requires C, 75.35; H, 4.55 %.

6-Chloro-3-[3-(4-nitro phenoxy)prop-1-ynyl]-2-phenyl thiochromen-4-one (IIIi)



IIIi was isolated as light brown solid, mp 211-213 ºC; ^{1}H NMR (400 MHz, $CDCI_3$) δ 8.53 (s, 1H), 8.10 (d, *J* = 3.5 Hz, 2H), 7.61 (d, *J* = 6.5 Hz, 1H), 7.53 (t, *J* = 4.6 Hz, 3H), 7.42 (t, *J* = 3.5 Hz, 1H), 7.33 (t, *J* = 6.2 Hz, 2H), 6.86 (d, *J* = 3.5 Hz, 2H), 4.92 (s, 2H); IR (KBr, cm^{-1}) 1625 (C=O); m/z (CI, i-Butane) 448 (M^+, 100%); VU (MeOH, nm) 356.5, 287.5; HPLC: 99.8%, Alltima C18 (53 x 7 mm), mobile phase 0.01M KH_2PO_4: CH_3CN 70:30, (T/%B) 0/40, 1/40, 12/80, 16/80, 18/40, 20/40, 2.5 mL/min, 284 nm, retention time 11.8 min.; Elemental analysis found C, 64.46; H, 3.14; N, 3.10; $C_{24}H_{14}ClO_4S$ requires C, 64.36; H, 3.15; N, 3.13 %.

7-Chloro-3-[3-(2-chloro phenoxy)prop-1-ynyl]-2-phenyl thiochromen-4-one (IIIj):



IIIo was isolated as light brown solid, mp 147-149 ºC, ^{1}H NMR (400 MHz, $CDCI_3$) δ 8.54 (s, 1H), 7.60 (d, *J* = 6.2 Hz, 1H), 7.54 (t, *J* = 5.9 Hz, 3H), 7.41 (t, *J* = 4.0 Hz, IH), 7.33-7.29 (m, 3H), 7.11 (t, *J* = 5.9 Hz, 1H), 6.94-6.88 (m, 2H), 4.91 (s, 2H); IR (KBr, cm^{-1}) 1616 (C=O); m/z (CI, i-Butane) 437 (M^+, 100%); ^{13}C NMR (200 MHz, $CDCI_3$) δ 177.6, 157.1, 153.2, 135.5, 134.6, 134.4, 132.3, 131.1, 130.7, 130.2, 128.8, 128.6 (2C), 128.5, 127.5 (2C), 127.4, 122.9, 121.9, 117.9, 114.1, 91.6, 82.1, 57.3; VU (MeOH, nm) 349.54, 255, 216.5; HPLC: 98.4%, symmetry shield (250 x 4.6 mm), mobile phase 0.01M KH_2PO_4 (pH-7.0): CH_3CN (70:30), (T/%B) 0/75, 5/75, 20/85, 30/85, 35/70, 40/70, 1.0

mL/min, 210 nm, retention time 19.4 min, Elemental analysis found C, 65.71; H, 3.25; $C_{24}H_{14}Cl_2O_2S$ requires C, 65.91; H, 3.23 %.

Biological assay:

Compounds synthesized above were screened against 9 cell line panel for their in vitro anticancer activity using cell growth assay.

Cell growth assay: Exponentially growing cells were seeded (10000 cells / well) in 96-well. Cell culture plates were incubated with different concentrations of test compounds at 37 °C in a 5 % CO_2 incubator. After 48 hours, cell were fixed by adding ice-cold 50 % tri chloro acetic acid (TCA), washed with distilled water and stained with SRB solution. The plates were washed with 1 % acetic acid, the bound SRB stain was solubilized with 10 mM tris buffer, and the optical densities were read on a spectro photometric plate read at a single wavelength of 515 nm. The percentage growths were calculated and the GI_{50} values were interpolated from the growth curves.

*Cytotoxicity GI_{50} values are the concentrations corresponding to 50 % growth inhibition.