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Pd-Mediated Synthesis of Substituted Benzenes Fused with Carbocycle/Heterocycle

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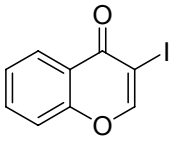
Experimental Section:

General methods

Unless stated otherwise, reactions were performed under a 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 $CDCl_3$ or DMSO-d_6 solution on 400 and 50 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.00$) 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. All the terminal alkynes used are commercially available. All the halides used are either commercially available or prepared according to the following procedure.

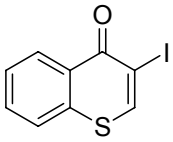
General procedure for the preparation of 3-Iodo-chromen-4-one (1d) and 3-Iodo-thiochromen-4-one (1e): A mixture of chromen-4-one or thiochromen-4-one (0.93 mmol), ceric ammonium nitrate (23.29 mmol) and iodine (23.29 mmol) in acetonitrile (70 mL) was refluxed for 15 h. After completion of the reaction, the mixture was cooled to room temperature, poured into water (300 mL) with stirring, treated with saturated aqueous solution of sodium thiosulphate (20 ml) and extracted with EtOAc (3 x 150 mL). The organic layers were collected, combined, washed with brine solution followed by cold water (2 x 100 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether-EtOAc) to afford the desired product in 50-60% yields.

3-Iodo-chromen-4-one[1] **(1d)**



Pale yellow solid; mp: 96-98 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.25 (dd, *J* = 8.3 & 1.6 Hz, 1H), 7.76-7.61 (m, 1H), 7.50-7.42 (m, 2H); IR (KBr, cm^{-1}) 1646 (C=O), 1608, 1462, 1065, 762, 684; MS (ES, i-Butane) 273.0 (M+1, 65%); HPLC 98.77%, column: ODS3V (150 x 4.6 mm), mobile phase 0.01M KH_2PO_4: CH_3CN, gradient (T/%B) 0/20, 2/20, 14/80 24/80, 25/20, 26/20, UV 210 nm, flow rate 1.5 mL / min retention time 12.10 min.

3-Iodo-thiochromen-4-one (1e)

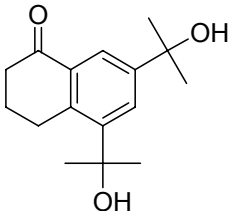


Pale brown solid; mp 130-132 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61-8.57 (m, 1H), 8.51 (s, 1H), 7.67-7.58 (m, 3H); IR (KBr, cm^{-1}) 1623 (C=O), 1589, 1337, 739; MS (ES, i-Butane) 288.9 (M+1, 100%); HPLC 98.33 %, column: ODS3V (150 x 4.6 mm), mobile phase 0.01M KH_2PO_4: CH_3CN, gradient (T/%B) 0/40, 2/40, 12/80 22/80, 23/40, 24/40, UV 260 nm, flow rate 1.5 mL / min, retention time 7.69 min.

General procedure for the preparation of compound 3: A mixture of **1** (0.9 mmol), $(PPh_3)_2PdCl_2$ (0.036 mmol) and triethylamine (7.2 mmol) in DMF or 1,4-dioxane (6 mL) was stirred at room temperature for 5 minutes under a nitrogen atmosphere and acetylenic compound **2** (0.27 mmol) was added slowly with stirring. The reaction mixture was then stirred at 80 ºC for 3-5 h. After completion of the reaction (as indicated by TLC), the mixture was cooled to room temperature, poured in cold water (30 mL), stirred for 15 min and extracted with EtOAc (3 x 30 mL). The organic layers were collected, combined, washed with brine solution followed by cold water (2 x 100 mL), dried over anhydrous

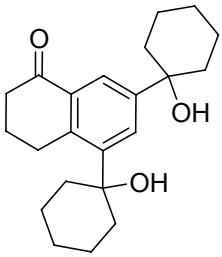
Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether-EtOAc) to afford the desired product.

5,7-Bis-(1-hydroxy-1-methyl-ethyl)-3,4-dihydro-2H-naphthalen-1-one (3a)



Light brown solid; mp 108-110 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 2.6 Hz, 1H), 7.91 (d, *J* = 2.6 Hz, 1H), 3.33 (t, *J* = 6.8 Hz, 2H), 2.65 (t, *J* = 6.8 Hz, 2H), 2.10-2.07 (m, 2H), 1.72 (s, 6H, 2Me), 1.59 (s, 6H, 2Me); IR (KBr, cm^{-1}) 3416 (bs, OH), 2926, 1662 (C=O), 1374, 1184, 911, 757; MS (ES, i-Butane) 263.0 (M+1, 100%); ^{13}C NMR (50 MHz, DMSO-*d*$_6$) 198.4 (C=O), 147.7, 146.8, 141.3, 133.4, 127.2, 121.5, 72.1, 70.7, 38.9, 32.0 (2C), 31.4 (2C), 27.9, 23.3; HPLC 99.04 %, column: Inertsil ODS3V (150 x 4.6 mm), mobile phase 0.01M KH_2PO_4: CH_3CN, gradient (T/%B) 0/20, 2/20, 14/80 24/80, 25/20, 26/20, UV 210 nm, retention time 8.27 min; Elemental analysis found C, 73.41; H, 8.39; $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45.

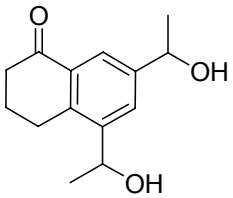
5,7-Bis-(1-hydroxy-cyclohexyl)-3,4-dihydro-2H-naphthalen-1-one (3b)



Light brown solid; DSC 174-176 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 2.6 Hz, 1H), 7.90 (d, *J* = 2.6 Hz, 1H), 3.39 (t, *J* = 6.0 Hz, 2H), 2.65 (t, *J* = 6.2 Hz, 2H), 2.10-1.59 (m, 20H), 1.34-1.25 (m, 2H); IR (KBr, cm^{-1}) 3482 (bs, OH), 2936, 1653 (C=O), 1598, 1177, 983, 887; MS (ES, i-Butane) 343.2 (M+1, 100%); ^{13}C NMR (50 MHz, $CDCl_3$) 199.1 (C=O), 146.9, 145.9, 142.5, 134.3, 127.0, 122.6, 74.5, 73.1, 39.1 (2C), 38.7 (2C), 37.8 (2C), 28.5, 25.39, 25.33, 23.3 (2C), 22.06 (2C); HPLC 99.95%, column: Inertsil

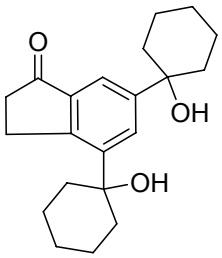
ODS3V (150 x 4.6 mm), mobile phase 0.01M KH_2PO_4: CH_3CN, gradient (T/%B) 0/40, 4/40, 14/80 20/80, 24/40, 25/40, UV 210 nm, flow rate 1.5 mL / min retention time 10.74 min.; Elemental analysis found C, 77.52; H, 8.80; $C_{22}H_{30}O_3$ requires C, 77.16; H, 8.83.

5,7-Bis-(1-hydroxy-ethyl)-3,4-dihydro-2H-naphthalen-1-one (3c)



Brown gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.82 (s, 1H), 5.21-5.18 (m, 1H), 4.96-4.94 (m, 1H), 3.05-2.99 (m, 1H), 2.91-2.86 (m, 1H), 2.66 (t, *J* = 6.0 Hz, 2H), 2.17 (t, *J* = 6.5 Hz, 2H), 1.53 (d, *J* = 1.9 Hz 3H), 1.51 (d, *J* = 1.9 Hz 3H); IR (Neat, cm^{-1}) 3382.9 (bs, OH), 2970, 1674 (C=O), 1605, 1075, 903, 756; MS (ES-MS, i-Butane) 235.1 (M+1, 100%); ^{13}C NMR (50 MHz, $CDCl_3$) 198.7 (C=O), 144.2, 139.6, 127.3, 127.0, 123.3, 123.1, 69.8, 66.2, 25.3, 25.0, 24.8, 24.1, 22.7; HPLC 96.59%, column: Inertsil ODS3V (250 x 4.6 mm), mobile phase 0.01M KH_2PO_4: CH_3CN, gradient (T/%B) 0/30, 2/30, 16/80 26/80, 28/30, 30/30, UV 210 nm, flow rate 1.0 mL / min, retention time 6.06 min.; Elemental analysis found C, 71.56; H, 7.87; $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74.

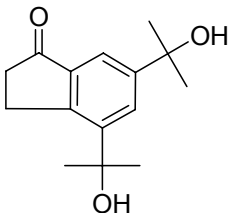
4,6-Bis-(1-hydroxy-cyclohexyl)-indan-1-one (3d)



Pale brown solid; mp: 164-166 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 1.9 Hz, 1H), 7.75 (d, *J* = 1.6 Hz, 1H), 3.43 (t, *J* = 6.0 Hz, 2H), 2.67 (t, *J* = 6.0 Hz, 2H), 1.96-1.26 (m, 20H); IR (KBr, cm^{-1}) 3420 (bs, OH), 2931, 1694 (C=O), 1608, 1152, 977, 886; MS

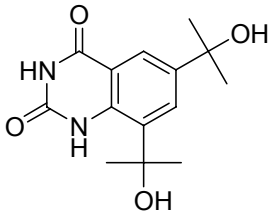
(ES, i-Butane) 329.3 (M+1, 100%); Elemental analysis found C, 76.85; H, 8.50; $C_{21}H_{28}O_3$ requires C, 76.79; H, 8.59.

4,6-Bis-(1-hydroxy-1-methyl-ethyl)-indan-1-one (3e)



Pale yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 1.9 Hz, 1H), 7.73 (d, *J* = 1.9 Hz, 1H), 3.39 (t, *J* = 6.0 Hz, 2H), 2.70 (t, *J* = 6.0 Hz, 2H), 1.70 (s, 6H, 2Me), 1.61 (s, 6H, 2Me); IR (Neat, cm^{-1}) 3410 (bs, OH), 2974, 1694 (C=O), 1611, 1169, 966, 755; MS (ES, i-Butane) 249.4 (M+1, 100%); Elemental analysis found C, 72.59; H, 8.11; $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12.

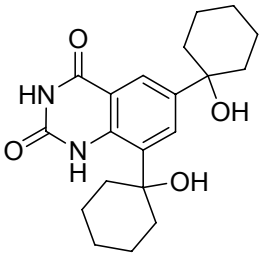
6,8-Bis-(1-hydroxy-1-methyl)-1H-quinazoline-2,4-dione (3f)



Off white solid; mp: 252-254 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.35 (bs, D_2O exchangeable, 1H, NH), 10.56 (bs, D_2O exchangeable, 1H, NH), 7.92 (d, *J* = 2.6 Hz, 1H), 7.66 (d, *J* = 2.6 Hz, 1H), 6.35 (s, D_2O exchangeable, 1H, OH), 5.14 (s, D_2O exchangeable, 1H, OH), 1.59 (s, 6H, 2Me), 1.43 (s, 6H, 2Me); IR (KBr, cm^{-1}) 3416 (bs, OH), 2985, 1694 (C=O), 1615, 1147, 907, 761; MS (ES-MS, i-Butane) 279 (M+1, 60%), 261.2 (100%); ^{13}C NMR (50 MHz, DMSO-d_6) 163.0 (C=O), 149.2 (C=O), 144.4, 136.8, 132.5, 128.2, 121.3, 114.6, 73.6, 70.3, 31.7 (2C), 30.5 (2C); HPLC 99.05%, column: Inertsil ODS3V (150 x 4.6 mm), mobile phase 0.01M KH_2PO_4: CH_3CN, gradient (T/%B)

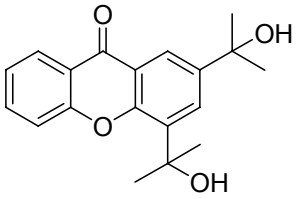
0/20, 4/20, 14/70 20/70, 21/20, 22/20, UV 210 nm, flow rate 1.0 mL / min, retention time 5.55 min.; Elemental analysis found C, 60.13; H, 6.57; N, 10.11; $C_{14}H_{18}N_2O_4$ requires C, 60.42; H, 6.52; N, 10.07.

6,8-Bis-(1-hydroxy-cyclohexyl)-1H-quinazoline-2,4-dione (3g)



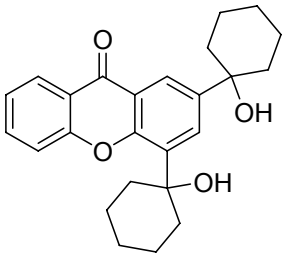
Off white solid; mp: 286-288 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.35 (bs, D_2O exchangeable, 1H, NH), 10.56 (bs, D_2O exchangeable, 1H, NH), 7.94 (d, J = 2.2 Hz, 1H), 7.73 (d, J = 2.2 Hz, 1H), 6.06 (s, D_2O exchangeable, 1H, OH), 4.83 (s, D_2O exchangeable, 1H, OH), 1.95-1.24 (m, 20H); IR (KBr, cm^{-1}) 3391 (bs, OH), 2930, 1692 (C=O), 1675 (C=O), 1500, 1151, 966, 765; MS (ES-MS, i-Butane) 359 (M+1, 70%), 341 (M^+–OH, 100%); ^{13}C NMR (50 MHz, DMSO-d_6) 163.1 (C=O), 149.2 (C=O), 145.0, 137.2, 133.4, 128.2, 121.5, 114.6, 73.9, 71.2 , 38.2 (2C), 36.6 (2C), 24.9 (2C), 21.6 (2C), 21.1 (2C); HPLC 99.05%, column: Inertsil ODS3V (150 x 4.6 mm), mobile phase 0.01M KH_2PO_4: CH_3CN, gradient (T/%B) 0/20, 4/20, 14/70 20/70, 21/20, 22/20, UV 210 nm, flow rate 1.0 mL / min, retention time 5.55 min.; Elemental analysis found C, 67.82; H, 7.30; N, 7.52; $C_{20}H_{26}N_2O_4$ requires C, 67.02; H, 7.31; N, 7.82.

2,4-Bis-(1-hydroxy-1-methyl-ethyl)-xanthen-9-one (3h)



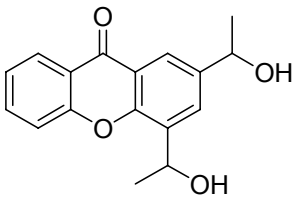
Pale brown solid; mp: 218-220 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, J = 2.4 Hz, 1H), 8.22 (d, J = 7.7 Hz, 1H), 8.20 (d, J = 2.4 Hz, 1H), 7.90-7.85 (m, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.51-7.47 (m, 1H), 5.44 (s, D_2O exchangeable, 1H, OH), 5.23 (s, D_2O exchangeable, 1H, OH), 1.72 (s, 6H), 1.51 (s, 6H); IR (KBr, cm^{-1}) 3333 (bs, OH), 2963, 1663 (C=O), 1609, 1470, 1320, 1135, 960, 754; MS (ES-MS, i-Butane) 312.9 (M+1, 100%); ^{13}C NMR (50 MHz, DMSO-d_6) 176.1 (C=O), 154.9, 150.7, 145.5, 138.1, 135.2, 129.2, 125.7, 124.2, 120.6, 120.5, 119.6, 118.0, 70.5, 70.4, 31.8 (2C), 30.0 (2C); HPLC 96.17%, column: Inertsil ODS3V (150 x 4.6 mm), mobile phase 0.01M KH_2PO_4: CH_3CN, gradient (T/%B) 0/30, 3/30, 12/80 18/80, 19/30, 22/30, UV 210 nm, flow rate 1.5 mL / min, retention time 5.55 min.; Elemental analysis found C, 73.11; H, 6.43; $C_{19}H_{20}O_4$ requires C, 73.06; H, 6.45.

2,4-Bis-(1-hydroxy-cyclohexyl)-xanthen-9-one (3i)



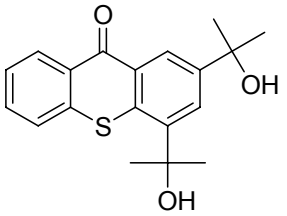
Pale brown solid; mp: 174-176 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 7.9 Hz, 1H), 8.35 (d, J = 2.4 Hz, 1H), 8.24 (d, J = 2.4 Hz, 1H), 7.77-7.30 (m, 1H), 7.53-7.43 (m, 1H), 7.43-7.39 (m, 1H), 2.55 (s, D_2O exchangeable, 1H, OH), 2.40-1.14 (m, 20H); IR (KBr, cm^{-1}) 3454 (bs, OH), 2929, 1658 (C=O), 1603, 1471, 1167, 960, 749, 637; MS (ES-MS, i-Butane) 393.3 (M+1, 100%); ^{13}C NMR (50 MHz, DMSO-d_6) 176.3 (C=O), 154.9, 151.1, 146.2, 138.4, 135.2, 130.0, 125.8, 124.2, 120.9, 120.5, 120.1, 118.0, 72.1, 71.4, 38.3 (2C), 35.3 (2C), 28.9 (2C), 25.1 (2C), 21.6 (2C); HPLC 99.74%, column: Inertsil ODS 3V (250 x 4.6 mm), mobile phase A:0.01M KH_2PO_4: B:CH_3CN, gradient (T/%B) 0/30, 4/30, 24/80 34/80, 35/30, 36/30, UV 224 nm, flow rate 1.0 mL/min, retention time 15.97 min.; Elemental analysis found C, 76.44; H, 7.20; $C_{25}H_{28}O_4$ requires C, 76.50; H, 7.19.

2,4-Bis-(1-hydroxy-ethyl)-xanthen-9-one (3j)



Light brown solid; mp: 154-156 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 7.8 & 1.6 Hz, 1H), 8.24 (d, *J* = 2.1 Hz, 1H), 8.01 (d, *J* = 1.9 Hz, 1H), 7.76-7.72 (m, 1H), 7.43-7.39 (m, 1H), 7.15 (d, *J* = 8.6 Hz, 1H), 5.61-5.60 (m, 1H), 5.08-5.04 (m, 1H), 2.13 (s, D_2O exchangeable, 1H, OH), 1.93 (s, D_2O exchangeable, 1H, OH), 1.67 (d, *J* = 1.4 Hz, 3H), 1.66 (d, *J* = 1.4 Hz, 3H); IR (KBr, cm^{-1}) 3421 (bs, OH), 1643 (C=O), 1612, 1470, 1163, 759; MS (ES-MS, i-Butane) 285.2 (M+1, 100%); HPLC 98.81%, column: Inertsil ODS3V (250 x 4.6 mm), mobile phase 0.01M KH_2PO_4: CH_3CN, gradient (T/%B) 0/30, 2/30, 16/80 26/80, 28/30, 30/30, UV 243 nm, flow rate 1.0 mL / min, retention time 9.84 min.; Elemental analysis found C, 71.70; H, 5.69; $C_{17}H_{16}O_4$ requires C, 71.82; H, 5.67.

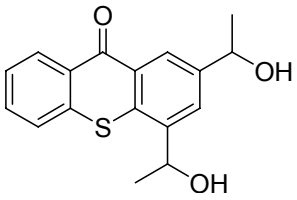
2,4-Bis-(1-hydroxy-1-methyl-ethyl)-thioxanthen-9-one (3k)



Pale yellow solid; mp: 198-200 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 2.6 Hz, 1H), 8.53-8.51 (m, 1H), 7.94 (d, *J* = 2.6 Hz, 1H), 7.63-7.61 (m, 2H), 7.48-7.44 (m, 2H), 2.33 (s, D_2O exchangeable, 1H, OH), 1.85 (s, 6H), 1.64 (s, 6H); IR (KBr, cm^{-1}): 3323 (bs, OH), 2978, 1618 (C=O), 1585, 1330, 1142, 750; MS (ES-MS, i-Butane): 329.1 (M+1, 100%); ^{13}C-NMR (50 MHz, DMSO-d_6) 180 (C=O), 147.8, 145.1, 138.7, 133.0, 132.6, 129.7, 128.2, 127.5, 126.7, 126.4, 126.2, 123.6, 72.7, 70.5, 31.7 (2C), 30.1 (2C); HPLC

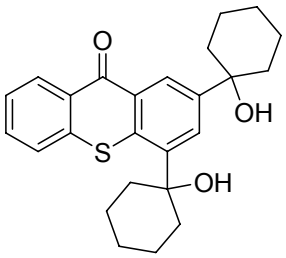
98.83%, column: Inertsil ODS3V (150 x 4.6 mm), mobile phase 0.01M KH_2PO_4: CH_3CN, gradient (T/%B) 0/40, 4/40, 14/80 20/80, 24/40, 25/40, UV 262 nm, flow rate 1.5 mL / min retention time 6.72 min.; Elemental analysis found C, 69.39; H, 6.21; $C_{19}H_{20}O_3S$ requires C, 69.48; H, 6.14.

2,4-Bis-(1-hydroxy-ethyl)-thioxanthen-9-one (3l)



Brown gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 8.1 Hz, 1H), 8.53-8.51 (m, 1H), 8.00 (t, *J* = 1.6 Hz, 1H) 7.65-7.48 (m, 3H), 5.43-5.40 (m, 1H), 5.06-5.03 (m, 1H), 2.21 (s, D_2O exchangeable, 1H, OH), 1.64 (d, *J* = 1.6 Hz, 3H), 1.63 (d, *J* = 1.6 Hz, 3H); IR (KBr, cm^{-1}) 3422 (bs, OH), 2920, 1632 (C=O), 1592, 1436, 1112, 741; MS (ES-MS, i-Butane) 301.1 (M+1, 100%); ^{13}C-NMR (50 MHz, $CDCl_3$) 180.3 (C=O), 144.0, 132.8, 132.3, 132.0, 129.5, 129.2, 128.6, 128.3, 126.5, 126.2, 125.8, 125.5, 69.8, 66.4, 25.2, 23.6; Elemental analysis found C, 67.92; H, 5.40; $C_{17}H_{16}O_3S$ requires C, 67.98; H, 5.37.

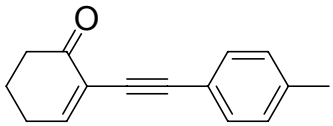
2,4-Bis-(1-hydroxy-cyclohexyl)-thioxanthen-9-one (3m)



Yellow solid; mp: 246-248 ºC; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.58 (d, *J* = 2.2 Hz, 1H) 8.38 (dd, *J* = 8.1 & 1.1 Hz, 1H), 7.95 (d, *J* = 1.9 Hz 1H), 7.84 (d, *J* = 8.1 Hz 1H), 7.75-7.71 (m, 1H), 7.55-7.51 (m, 1H), 5.41 (s, D_2O exchangeable, 1H, OH), 4.97 (s, D_2O

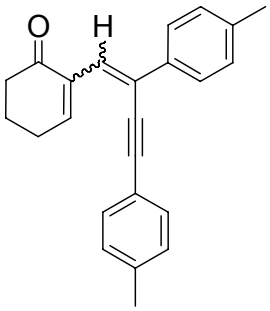
exchangeable, 1H, OH), 2.20-1.16 (m, 20H); IR (KBr, cm^{-1}) 3452 (bs, OH), 2929, 1621 (C=O), 1588, 1327, 1145, 746, 640; MS (ES-MS, i-Butane) 409.2 (M+1, 50%); ^{13}C-NMR (50 MHz, DMSO-d_6) 180.1 (C=O), 148.3, 145.9, 139.1, 133.5, 132.6, 129.8, 128.1, 127.4, 126.8, 126.5, 126.1, 124.0, 73.5, 71.4, 38.6 (2C), 38.2 (2C), 36.4 (2C), 25.3, 25.0, 21.6 (2C); HPLC 99.93%, column: ODS3V (150 x 4.6 mm), mobile phase 0.01M KH_2PO_4: CH_3CN, gradient (T/%B) 0/40, 2/40, 12/80 22/80, 23/40, 24/40, UV 262 nm, flow rate 1.5 mL / min, retention time 12.99 min.; Elemental analysis found C, 73.42; H, 6.96; $C_{25}H_{28}O_3S$ requires C, 73.50; H, 6.91.

2-*p*-tolylethynyl cyclohex-2-enone (3n)



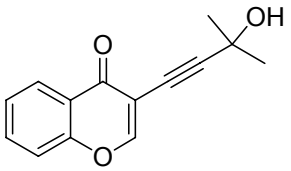
Colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38 (d, J = 8.1 Hz, 2H), 7.32 (t, J = 4.4 Hz, 1H), 7.11 (d, J = 8.1 Hz, 2H), 2.55-2.49 (m, 4H), 2.34 (s, 3H), 2.09-2.04 (m, 2H); IR (KBr, cm^{-1}) 2923, 1688 (C=O), 1508, 1363; MS (ES-MS, i-Butane) 211.1 (M^+, 100%).

2-(2,4-Di-p-tolyl but-1-en-3-ynyl)cyclohex-2-enone (3nn)



Light brown oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, J = 8.0 Hz, 2H), 7.27-7.25 (m, 4H), 7.19 (d, J = 7.8 Hz, 2H), 6.90 (t, J = 4.8 Hz, 1H), 6.60 (s, 1H), 2.83 (t, J = 5.3 Hz, 2H), 2.74-2.69 (m, 2H), 2.40 (s, 3H), 2.38 (s, 3H), 2.09-2.04 (m, 2H); IR (KBr, cm^{-1}) 2929, 1647 (C=O), 1624, 1504, 1465; MS (ES-MS, i-Butane) 327.1 (M^+, 100%).

3-(3-Hydroxy-3-methyl but-1-ynyl) chromen-4-one (3hh)



Low melting solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, J = 8.1 & 1.5 Hz, 1H), 7.70-7.66 (m, 1H), 7.45-7.40 (m, 2H), 6.12 (s, 1H), 1.57 (s, 1H, OH), 1.52 (s, 3H), 1.43 (s, 3H); IR (KBr, cm^{-1}) 3364 (bs, OH), 1647, 1628, 1609, 1574, 1455; MS (ES, i-Butane) 228.9 (M^+, 100%); Elemental analysis found C, 73.41; H, 5.39; $C_{14}H_{12}O_3$ requires C, 73.67; H, 5.30.

X-ray crystal structure of 3b:

Single crystals of **3b** suitable for X-ray diffraction have been grown from "chloroform". The compound crystallizes as monoclinic in $P2_1/C$ space group with cell dimensions a = 12.653(6) Å, b = 16.148(7) Å, c = 11.478(5) Å, β=93.125(6) °, V = 2341(1) $Å^3$ with Z=4. The intensity data have been collected on Rigaku AFC-7S diffractometer with Mercury CCD area detector using graphite monochromated Mo-Kα radiation. The structure has been solved with direct methods and refined using least squares procedure using the Crystal structure software. The present R factors are R = 0.090 for the 2930 "observed" reflections and the wR2 = 0.167 for all 5278 unique reflections.

The molecular structure (ORTEP diagram) of **3b** is shown in the Figure 1. Both the hydroxy cyclohexyl groups are in chair conformation and the tetralone ring is in sofa conformation. The carbonyl oxygen (O1) of the tetralone moiety is involved in a bifurcated hydrogen bonding interaction with the hydroxy oxygens of the glide related (O3) and center of symmetry related (O2) molecule. The chloroform molecule in the lattice is stabilized by the C---H…O interaction with one of the hydroxy oxygen atoms (O2).

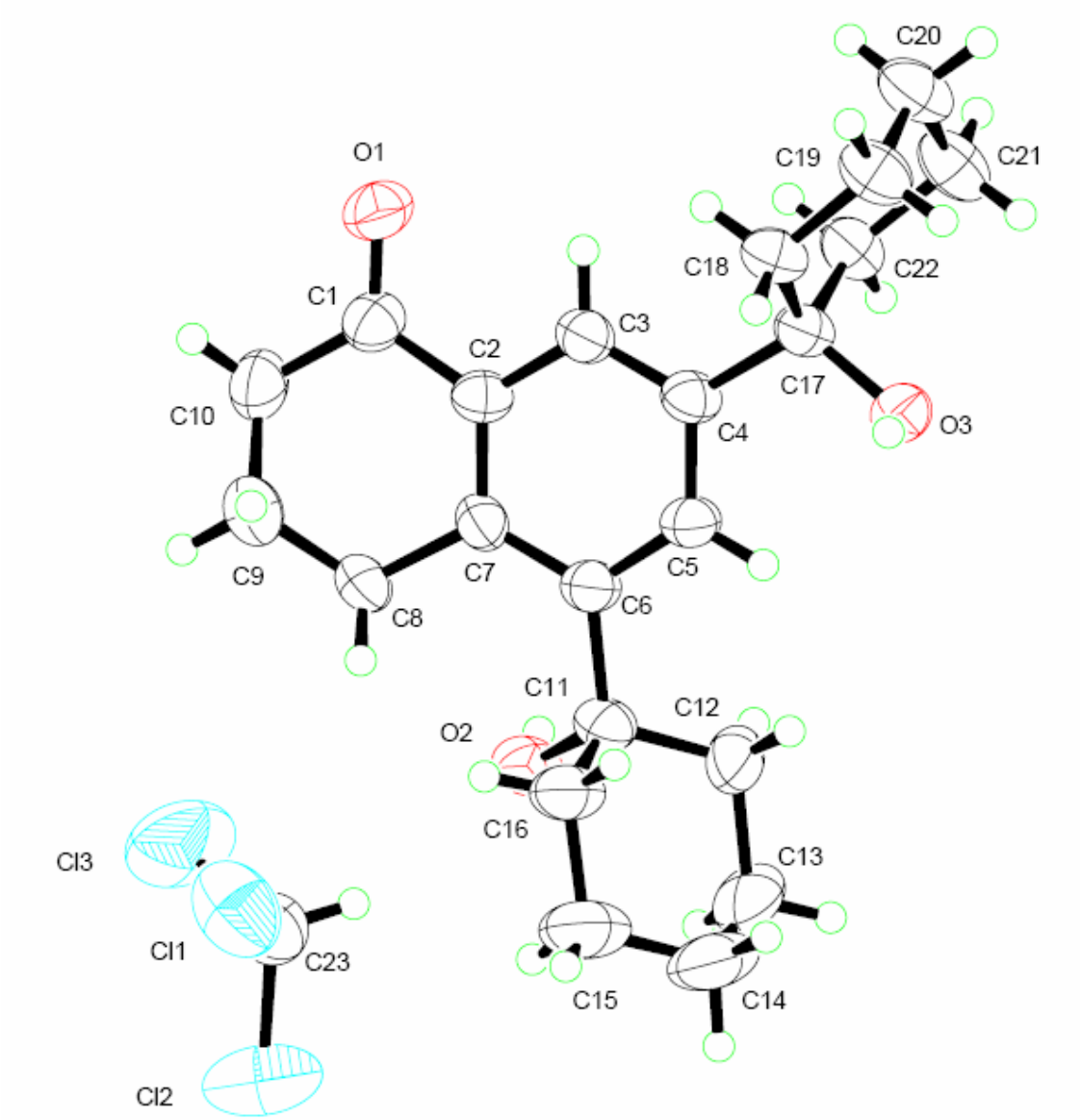


Figure S1 X-ray crystal structure of **3b** (ORTEP diagram). Displacement ellipsoids are drawn at 50% probability level for non-hydrogen atoms.

In vitro anticancer activity: we evaluated some of the compounds synthesized for in vitro anticancer activity. Selected compounds were tested on a panel of cancer cell lines e.g. HT-29 (colon), NCI-H460 (lung) and LoVo (colon) using the NCI standard protocol for screening anticancer molecules.[2] After treating the cells with compounds at 100 μM

concentration initially the percentage growth of cells was measured. Based on the result obtained for all these compounds we tested them further at lower concentrations such as 10, 1.0, 0.1 & 0.01 μM against the same cancer cell line and the percentage growth was noted. The GI_{50} values (the concentration that causes 50% inhibition of cancer cell growth against a cell line is expressed as GI_{50}) for all these compounds are listed in Table 1. Additionally, the respective average LC_{50} values (LC_{50} or Lethal Concentration 50 is the concentration of a compound that kills 50% of cells treated) are also shown in Table 1. Thus compounds **3i** and **3m** showed promising anticancer activity with an average GI_{50} of 14.6 and 7.1 μM respectively with an average LC_{50} of 80. The present study thus indicates that compounds **3i** and **3m** could be new and potential candidates for the development of novel anticancer agents.

Table S1. In vitro anti cancer activities of polyfunctionalized benzenes

Compound	GI_{50} in μM			Average GI_{50} in μM	Average LC_{50} in μM
	LoVo	H460	HT-29		
3a	100	100	100	100	100
3b	19.7	40.9	39.6	33.4	100
3g	84.8	100	100	94.9	100
3i	2.99	21.5	19.3	14.6	80
3k	15.1	36.6	38.9	30.2	98
3m	2.0	14.7	4.7	7.1	80

Protocol for In Vitro Cell growth assay: Anticancer activity of selected compounds has been tested in HT-29 (ATCC NO# HTB-38 Colon adenocarcinoma), NCI-H460 (ATCC NO# HTB-177 Large cell lung cancer) and LoVo (ATCC NO# CCL-229 Colon adenocarcinoma) cell lines by using Sulphorhodamine B (SRB) assay.[2] Cells were maintained in RPMI 1640 with 10% FBS (Fatal Bovine Serum) and Penicillin (50 μg/mL), Streptomycin (100 μg/mL). Cells were seeded in a 96-well cell culture plates at a concentration of 10000 cells per well and incubated at 37 ºC in CO_2 incubator. Twenty-four hours later cells were treated with different concentrations (100, 10, 1, 0.1 & 0.01 μM) of compound dissolved in DMSO and incubated for 48 h. Cells were fixed by adding ice-cold 50% trichloroacetic acid (TCA) and incubating for 1 h at 4 ºC. The plates

were washed with distilled water, air-dried and stained with SRB solution (0.4% wt/vol in 1% acetic acid) for 30 minutes at room temperature. Unbound SRB was removed by washing thoroughly with 1% acetic acid and the plates were air-dried. The bound SRB stain was solubilized with 10 mM Tris buffer, and the optical densities were read on a spectrophotometric plate reader at 515 nm. At the time of drug addition separate reference plate for cell growth at time 0 h (the time at which drugs were added) was also terminated as described above. From the optical densities the percentage growths were calculated using the following formulae, If T is greater than or equal to T_0, percentage growth = 100 x $[(T-T_0)/(C-T_0)]$ and if T is less than T_0, percentage growth = 100 x $[(T-T_0)/T_0)]$, Where T is optical density of test, C is the optical density of control and T_0 is the optical density at time zero. From the percentage growths a dose response curve was generated and GI_{50} values were interpolated from the growth curves.

Reference

1. G.-q. Lin, R. J. Hong, *J. Org. Chem.* 2001, **66**, 2877.
2. A. Monks, D. Scudiero, P. Skehan, R. Shoemaker, K. Paull, D. Vistica, C. Hose, J. Langley, P. Cronise, A. Vaigro-Wolff, M. Gray-Goodrich, H. Campbell, J. Mayo, M. Boyd, *Journal of the National Cancer Institute* 1991, **83**, 757.