Electronic supporting information

TFAA/H_3PO_4 mediated unprecedented *N*-acylation of carbazole leading to small molecules possessing anti-proliferative activities against cancer cells

Sunder Kumar Kolli,[a] Bagineni Prasad,[b] P. Vijaya Babu,[b] Mohd Ashraf Ashfaq,[b] Nasreen Z. Ehtesham,[b] R. Ramesh Raju,[a,]*and Manojit Pal[b,]*

[a]*Department of Chemistry, Acharya Nagarjuna University, Nagarjuna Nagar, Guntur-522510,A.P. India.*

[b]*Dr Reddy's Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad 500 046, India*

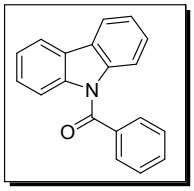
E-mail: manojitpal@rediffmail.com;

General method: Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$/DMSO-d_6 solution by using a 400 MHz spectrometer (VARIAN 400 MR). 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), dd (doublet of doublet), td (triplet of doublet) and m (multiplet) as well as bs (broad). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a FT-IR spectrometer (FT/IR-4200, JASCO). Melting points were determined by using melting point apparatus (Buchi melting point B-540) and are uncorrected. MS spectra were obtained on a mass spectrometer (AGILENT 6430 triple quardrupole LC-MS). Chromatographic purity by HPLC (Agilent 1200 series Chem Station software) 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 time.

General procedure for the preparation of compound 3:

A mixture of TFAA (2.093 mmol) and benzoic acid (0.598 mmol) was stirred for 20 min until the solid was dissolved. After stirring for additional 20 min, carbazole, **1** (0.598 mmol) was added in one portion. To this mixture was added 85% H_3PO_4 (0.059 mmol) drop wise for a duration of 20 min. The mixture was then stirred for 2h (monitored by TLC) and the excess of TFA/TFAA was distilled out at atmospheric pressure. The remaining liquid was partitioned between ethyl acetate (30 mL) and H_2O (15 mL). The organic layer was separated and washed with 5% NaOH (7 mL) and then brine (8 mL). The mixture was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography using EtOAc-n-hexane to give the desired product **3**.

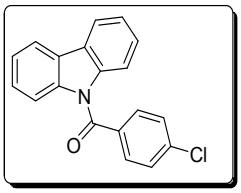
(9*H*-carbazol-9-yl)(phenyl)methanone (3a)[1]



3a was prepared according to the general procedure presented above by using **1** and **2a.**

White solid; yield: 75%; mp: 98-100 °C; R_f (1% EtOAc-*n*-Hexane) 0.36; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03-8.01 (m, 2H), 7.73-7.71 (m, 2H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.55-7.50 (m, 4H), 7.37-7.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6, 139.1, 135.7, 132.3, 129.0 (2C), 128.8 (2C), 126.7 (3C), 126.0, 123.3 (3C), 119.8 (3C), 115.7; HPLC: 99.6%, column: Symmetry C-18 75*4.6 mm, 3.5 µm, mobile phase A: 0.1 % Acetic acid in water mobile phase B: CH_3CN (gradient) T/%B: 0/50, 1.0/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 225 nm, retention time 6.19 min; IR (KBr, cm^{-1}): 2958, 2914, 1682, 1479, 1298; MS (ES mass): *m*/*z* 272.2 (M+1).

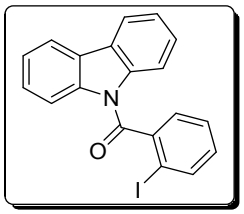
(9*H*-carbazol-9-yl)(4-chlorophenyl)methanone (3b)



3b was prepared according to the general procedure presented above by using **1** and **2b.**

White solid; yield: 55%; mp: 155-160 °C; R_f (Pure-*n*-Hexane) 0.27; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04-8.02 (m, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.55-7.51 (m, 4H), 7.41-7.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.4, 138.9, 138.8, 133.9, 130.6 (2C), 129.2 (3C), 126.8 (2C), 126.0, 123.5 (2C), 119.9 (2C), 115.6 (2C), 109.9; HPLC: 98.7%, column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Acetic acid in water mobile phase B: CH_3CN (gradient) T/%B: 0/50, 1.0/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 225 nm, retention time 6.80 min; IR (KBr, cm^{-1}): 2925, 2843, 1682, 1490, 1293; MS (ES mass): *m*/*z* 306.1 (M+1); Elemental analysis found C, 74.31; H, 3.95; N, 4.70; $C_{19}H_{12}ClNO$ requires C, 74.64; H, 3.96; N, 4.58.

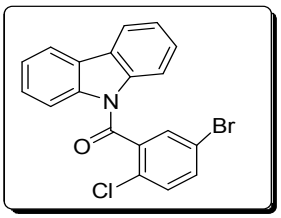
(9*H*-carbazol-9-yl)(2-iodophenyl)methanone (3c)[2]



3c was prepared according to the general procedure presented above by using **1** and **2c.**

Liquid; yield: 60%; R_f (2% EtOAc-*n*-Hexane) 0.36; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (t, *J* = 7.2 Hz, 4H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.47 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.38-7.24 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.6, 142.3, 139.9 (2C), 138.5, 131.8 (2C), 128.9, 128.4 (2C), 127.3 (2C), 126.6, 124.1 (2C), 119.7 (2C), 116.0, 92.6. HPLC: 99.0%, column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Acetic acid in water mobile phase B: CH_3CN (gradient) T/%B: 0/50, 1.0/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 225 nm retention time 6.26 min; IR (KBr, cm^{-1}): 2923, 2845, 1640, 1432, 1256; MS (ES mass): *m*/*z* 397.5 (M+1).

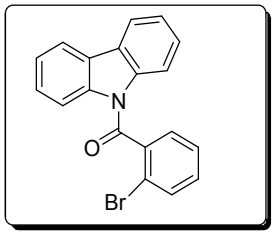
(5-Bromo-2-chlorophenyl)(9*H*-carbazol-9-yl)methanone (3d)



3d was prepared according to the general procedure presented above by using **1** and **2d.**

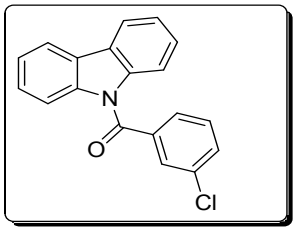
White solid; yield: 64%; mp: 98-100 °C; R_f (7% EtOAc-*n*-Hexane) 0.57; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, *J* = 7.2 Hz, 2H), 7.69-7.66 (m, 2H), 7.41-7.32 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.8, 138.2, 137.8, 134.9 (2C), 131.9 (2C), 131.5 (2C), 130.3, 127.4 (2C), 126.7, 124.4 (2C), 121.3, 119.9 (2C), 115.6; HPLC: 98.8%, column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Acetic acid in water mobile phase B: CH_3CN (gradient) T/%B: 0/50, 1.0/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 225 nm retention time 6.93 min; IR (KBr, cm^{-1}): 2920, 2841, 1687, 1446, 1391, 1298; MS (ES mass): *m*/*z* 385.5 (M+1); Elemental analysis found C, 59.21; H, 2.89; N, 3.77; $C_{19}H_{11}BrClNO$ requires C, 59.33; H, 2.88; N, 3.64.

(2-Bromophenyl)(9*H*-carbazol-9-yl)methanone (3e)[2]



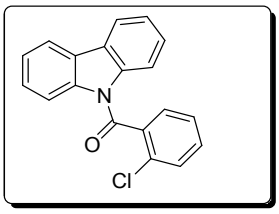
3e was prepared according to the general procedure presented above by using **1** and **2e.**
Semi solid; yield: 60%; R_f(5% EtOAc-*n*-Hexane) 0.46; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, *J* = 7.2 Hz, 2H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.52-7.48 (m, 4H), 7.38-7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2, 138.4, 138.3, 133.5 (2C), 131.9 (2C), 128.7 (2C), 128.2 (2C), 127.2 (2C), 126.6, 124.1 (2C), 119.7 (2C), 115.8; HPLC: 99.4%, column: Symmetry C-18 75*4.6 mm, 3.5µ, mobile phase A: 0.1 % Acetic acid in water mobile phase B: CH_3CN (gradient) T/%B: 0/50, 1.0/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 225 nm retention time 6.21 min; IR (KBr, cm^{-1}): 2920, 2849, 1676, 1594, 1446, 1210; MS (ES mass): *m*/*z* 349.5 (M+1).

(9*H*-carbazol-9-yl)(3-chlorophenyl)methanone (3f)



3f was prepared according to the general procedure presented above by using **1** and **2f.**
White solid; yield: 75%; mp: 105-110 °C; R_f(Pure-*n*-Hexane) 0.27; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, *J* = 8.0, 2H), 7.73 (s, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.39-7.32 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9, 138.8, 137.3, 135.0, 132.3, 130.2, 128.9, 127.0 (2C), 126.8 (2C), 126.1, 123.7 (2C), 119.9 (2C), 115.7 (2C), 109.9; HPLC: 99.5%, column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Acetic acid in water mobile phase B: CH_3CN (gradient) T/%B: 0/50, 1.0/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 225 nm retention time 6.77 min; IR (KBr, cm^{-1}): 2920, 2865, 2849, 1649, 1561, 1364; MS (ES mass): *m*/*z* 305.5 (M+1); Elemental analysis found C, 74.78; H, 3.97; N, 4.32; $C_{19}H_{12}ClNO$ requires C, 74.64; H, 3.96; N, 4.58.

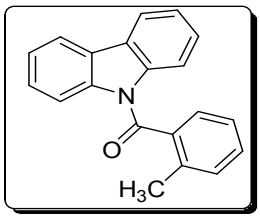
(9*H*-carbazol-9-yl)(2-chlorophenyl)methanone (3g)[2]



3g was prepared according to the general procedure presented above by using **1** and **2g.**

White solid; yield: 60%; mp: 110-115 °C; R_f (7% EtOAc-*n*-Hexane) 0.37; 8.00 (d, *J* = 7.6 Hz, 2H), 7.58-7.54 (m, 3H), 7.50-7.46 (m, 2H), 7.39-7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.5, 138.4, 136.2, 131.8 (2C), 131.3, 130.4 (2C), 128.7 (2C), 127.6, 127.2 (2C), 126.5, 124.1 (2C), 119.7 (2C), 115.7; HPLC: 99.6%, column: Symmetry C-18 75*4.6 mm, 3.5µ, mobile phase A: 0.1 % Acetic acid in water mobile phase B: CH_3CN (gradient) T/%B: 0/50, 1.0/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 225 nm retention time 6.19 min; IR (KBr, cm^{-1}): 2840, 2835, 1676, 1435, 1331, 1161; MS (ES mass): *m*/*z* 305.6 (M+1).

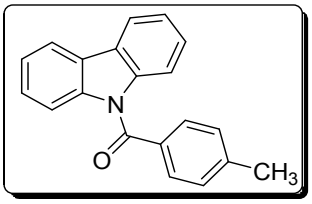
(9*H*-carbazol-9-yl)(o-tolyl)methanone (3h)



3h was prepared according to the general procedure presented above by using **1** and **2h.**

White solid; yield: 60%; mp: 75-80 °C; R_f (2% EtOAc-*n*-Hexane) 0.33; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.47-7.39 (t, *J* = 8.8 Hz, 3H), 7.37-7.26 (m, 6H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.8, 138.6, 136.5, 135.5, 131.1 (2C), 130.8 (2C), 127.3, 127.1 (2C), 126.5, 126.3, 123.7 (2C), 119.6 (2C), 115.8 (2C), 19.0; HPLC: 99.7%, column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Acetic acid in water mobile phase B: CH_3CN (gradient) T/%B: 0/50, 1.0/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm retention time 6.56 min; IR (KBr, cm^{-1}): 2834, 2367, 1649, 1331, 1062, 750; MS (ES mass): *m*/*z* 285.6 (M+1); Elemental analysis found C, 84.07; H, 5.30; N, 4.99; $C_{20}H_{15}NO$ requires C, 84.19; H, 5.30; N, 4.91.

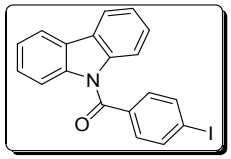
(9*H*-carbazol-9-yl)(p-tolyl)methanone (3i)



3i was prepared according to the general procedure presented above by using **1** and **2i.**

White solid; yield: 68%; mp: 135-140 °C; R_f (2% EtOAc-*n*-Hexane) 0.36; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03-8.01 (m, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.55-7.53 (m, 2H), 7.37-7.26 (m, 6H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6, 143.2, 139.1, 132.7, 129.4 (3C), 129.3 (3C), 126.5 (2C), 125.8, 123.1 (2C), 119.7 (2C), 115.6 (2C), 21.7; HPLC: 99.7%, column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Acetic acid in water mobile phase B: CH_3CN (gradient) T/%B: 0/50, 1.0/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 225 nm retention time 6.74 min; IR (KBr, cm^{-1}): 2914, 1676, 1605, 1435, 1293; MS (ES mass): *m*/*z* 285.6 (M+1); Elemental analysis found C, 84.27; H, 5.29; N, 4.70; $C_{20}H_{15}NO$ requires C, 84.19; H, 5.30; N, 4.91.

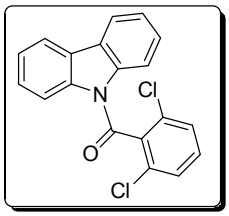
(9*H*-carbazol-9-yl)(4-iodophenyl)methanone (3j)[3]



3j was prepared according to the general procedure presented above by using **1** and **2j.**

Yellow; yield: 70%; mp: 145-147 °C; R_f (3% EtOAc-*n*-Hexane) 0.47; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (dd, *J* = 5.6, 2.4 Hz, 2H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.54-7.51 (m, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.38-7.34 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.6, 138.8 (2C), 138.1 (2C), 134.9, 130.5 (2C), 126.8 (2C), 126.0 (2C), 123.5 (2C), 119.8 (2C), 115.6 (2C), 99.6; HPLC: 96.9%, column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Acetic acid in water mobile phase B: CH_3CN (gradient) T/%B: 0/50, 1/50, 6/98, 12/98, 13/50, 15/50; flow rate: 1.0 mL/min; UV 225 nm retention time 7.16 min; IR (KBr, cm^{-1}): 2914, 1676, 1435, 1293; MS (ES mass): *m*/*z* 397.7 (M+1).

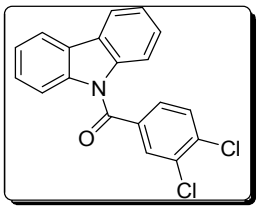
(9*H*-carbazol-9-yl)(2,6-dichlorophenyl)methanone (3k)



3k was prepared according to the general procedure presented above by using **1** and **2k.**

White soild; yield: 60%; mp: 130-132 °C; R_f (2% EtOAc-*n*-Hexane) 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.89 (d, *J* = 8.0 Hz, 1H), 8.02 (t, *J* = 8.0 Hz, 2H), 7.60-7.56 (m, 1H), 7.56-7.34 (m, 4H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.26 (s, 1H), 7.14 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3, 142.1, 138.8, 137.2, 135.9, 132.4, 131.6, 128.6 (2C), 128.0, 127.1 (2C), 126.5, 124.9, 124.0, 120.3, 119.4, 118.1, 112.9; HPLC: 97.5%, column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Acetic acid in water mobile phase B: CH_3CN (gradient) T/%B: 0/50, 1/50, 6/98, 12/98, 13/50, 15/50; flow rate: 1.0 mL/min; UV 225 nm retention time 6.53 min; IR (KBr, cm^{-1}): 2914, 1676, 1435, 1293; MS (ES mass): *m*/*z* 339.9 (M+1); Elemental analysis found C, 66.90; H, 3.19; N, 4.30; $C_{19}H_{11}Cl_2NO$ requires C, 67.08; H, 3.26; N, 4.12.

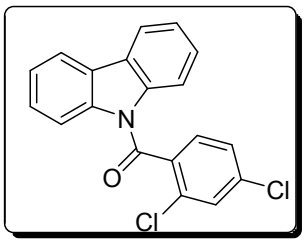
(9*H*-carbazol-9-yl)(3,4-dichlorophenyl)methanone (3l)



3l was prepared according to the general procedure presented above by using **1** and **2l.**

White soild; yield: 62%; mp: 128-130 °C; R_f (*n*-Hexane) 0.28; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, *J* = 1.6 Hz, 2H), 7.86 (d, *J* = 1.6 Hz, 1H), 7.59(d, *J* = 8.0 Hz, 1H), 7.53 (dd, *J* = 4.00, 1.6 Hz, 3H), 7.38 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.0, 138.7, 136.9, 135.2, 135.2, 133.5, 131.0, 130.9, 128.2, 126.9 (2C), 126.8, 126.1, 123.8 (2C), 120.0 (2C), 115.6 (2C); HPLC: 92.2%, column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Acetic acid in water mobile phase B: CH_3CN (gradient) T/%B: 0/50, 1/50, 6/98, 12/98, 13/50, 15/50; flow rate: 1.0 mL/min; UV 225 nm retention time 7.25 min; IR (KBr, cm^{-1}): 2934, 2843, 1676, 1435, 1293; MS (ES mass): *m*/*z* 339.9 (M+1); Elemental analysis found C, 66.85; H, 3.28; N, 4.26; $C_{19}H_{11}Cl_2NO$ requires C, 67.08; H, 3.26; N, 4.12.

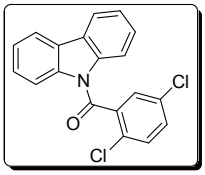
(9*H*-carbazol-9-yl)(2,4-dichlorophenyl)methanone (3m)



3m was prepared according to the general procedure presented above by using **1** and **2m.**

White soild; yield: 70%; mp: 134-136 °C; R_f (1% EtOAc-*n*-Hexane) 0.18; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, *J* = 6.8 Hz, 2H), 7.57 (d, *J* = 1.6 Hz, 1H), 7.51-7.48 (m, 3H), 7.41-7.26 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.5, 138.3, 137.4, 134.7, 132.4, 130.4 (2C), 129.8, 128.1 (2C), 127.3 (2C), 126.6, 124.3 (2C), 119.8 (2C), 115.6, 109.9; HPLC: 99.0%, column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Acetic acid in water mobile phase B: CH_3CN (gradient) T/%B: 0/50, 1/50, 6/98, 12/98, 13/50, 15/50; flow rate: 1.0 mL/min; UV 225 nm retention time 6.89 min; IR (KBr, cm^{-1}): 2924, 2860, 1662, 1421, 1163; MS (ES mass): *m*/*z* 339.8 (M+1); Elemental analysis found C, 67.01; H, 3.20; N, 4.30; $C_{19}H_{11}Cl_2NO$ requires C, 67.08; H, 3.26; N, 4.12.

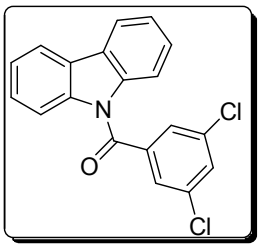
(9*H*-carbazol-9-yl)(2,5-dichlorophenyl)methanone (3n)



3n was prepared according to the general procedure presented above by using **1** and **2n.**

White soild; yield: 64%; mp: 115-118 °C; R_f (2% EtOAc-*n*-Hexane) 0.36; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, *J* = 7.2 Hz, 2H), 7.55-7.47 (m, 4H), 7.41-7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.8, 138.2, 137.6, 133.7, 131.9 (2C), 131.6 (2C), 128.6, 127.4 (2C), 126.6, 124.4 (2C), 119.9 (2C), 115.6, 115.6, 105.2; HPLC: 93.1%, column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Acetic acid in water mobile phase B: CH_3CN (gradient) T/%B: 0/50, 1/50, 6/98, 12/98, 13/50, 15/50; flow rate: 1.0 mL/min; UV 225 nm retention time 6.79 min; IR (KBr, cm^{-1}): 2954, 2856, 1675, 1469, 1245; MS (ES mass): *m*/*z* 339.8 (M+1); Elemental analysis found C, 67.29; H, 3.24; N, 4.01; $C_{19}H_{11}Cl_2NO$ requires C, 67.08; H, 3.26; N, 4.12.

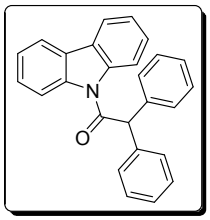
(9*H*-carbazol-9-yl)(3,5-dichlorophenyl)methanone (3o)



3o was prepared according to the general procedure presented above by using **1** and **2o.**

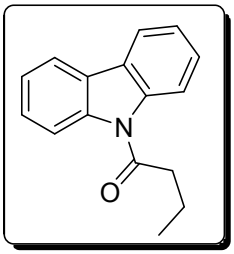
White soild; yield: 60%; mp: 158-160 °C; R_f(1% EtOAc-*n*-Hexane) 0.24; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, *J* = 6.4 Hz, 2H), 7.63 (s, 1H), 7.59 (d, *J* = 1.2 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.41-7.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.6, 148.1, 138.6 (2C), 138.3, 135.8 (2C), 132.1 (2C), 127.2, 127.0, 126.2 (2C), 124.0 (2C), 120.0 (2C), 115.6 (2C); HPLC: 97.7%, column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Acetic acid in water mobile phase B: CH_3CN (gradient) T/%B: 0/50, 1/50, 6/98, 12/98, 13/50, 15/50; flow rate: 1.0 mL/min; UV 225 nm retention time 7.40 min; IR (KBr, cm^{-1}): 2926, 2834, 1669, 1450, 1167. MS (ES mass): *m*/*z* 339.8 (M+1); Elemental analysis found C, 67.21; H, 3.27; N, 4.03; $C_{19}H_{11}Cl_2NO$ requires C, 67.08; H, 3.26; N, 4.12.

1-(9*H*-carbazol-9-yl)-2,2-diphenylethanone (3p)



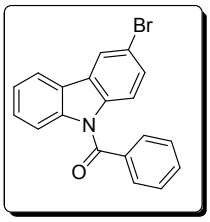
White solid; yield: 60%; mp: 178-180 °C; R_f(10% EtOAc-*n*-Hexane) 0.64; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (d, *J* = 7.5 Hz, 2H), 8.01-7.99 (m, 2H), 7.43-7.36 (m, 12H), 7.31 (q, *J* = 4.4 Hz, 2H), 6.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.3, 139.0, 138.4, 129.2, 128.8, 127.5, 127.4, 126.5, 123.8, 120.2, 119.8, 116.3, 58.5; MS (ES mass): *m*/*z* 362.0 (M+1); Elemental analysis found C, 86.62; H, 5.35; N, 3.59; $C_{26}H_{19}NO$ requires C, 86.40; H, 5.30; N, 3.88.

1-(9*H*-Carbazol-9-yl)butan-1-one (3q)



Semi solid; yield: 63%; R_f(10% EtOAc-*n*-Hexane) 0.66; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 (d, *J* = 8.4 Hz, 2H), 8.01 (d, *J* = 7.6 Hz, 2H), 7.49 (t, *J* = 8.4 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 3.14 (t, *J* = 7.6 Hz, 2H), 2.02-1.93 (m, 2H), 1.13 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.1, 138.6, 127.3, 126.4, 123.5, 119.8, 116.5, 41.1, 18.2, 13.9; MS (ES mass): *m*/*z* 238.0 (M+1); Elemental analysis found C, 80.75; H, 6.39; N, 6.03; $C_{16}H_{15}NO$ requires C, 80.98; H, 6.37; N, 5.90.

(3-Bromo-9*H*-carbazol-9-yl)(phenyl)methanone (3r)

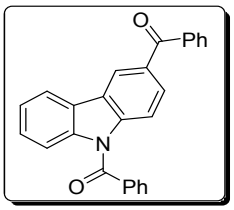


White solid; yield: 65%; mp: 120-122 °C; R_f(10% EtOAc-*n*-Hexane) 0.68; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (d, *J* = 0.8 Hz, 1H), 7.96-7.94 (m, 1H), 7.70-7.68 (m, 2H), 7.67-7.64 (m, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.45-7.40 (m, 3H), 7.37-7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.3, 139.4, 137.9, 135.3, 132.6, 129.4, 129.0, 128.9, 127.8, 127.4, 124.7, 123.6, 122.6, 120.0, 117.2, 116.5, 115.7; MS (ES mass): *m*/*z* 351.9 (M+1); Elemental analysis found C, 65.31; H, 3.57; N, 3.89; $C_{19}H_{12}BrNO$ requires C, 65.16; H, 3.45; N, 4.00.

Synthesis of (9*H*-carbazole-3,9-diyl)bis(phenylmethanone) (4a)[4]

A mixture of TFAA (1.291 mmol) and benzoic acid (0.369 mmol) was stirred for 20 min until the solid was dissolved. After stirring for additional 20 min, (9*H*-carbazol-9-yl)(phenyl)methanone **3a** (0.369 mmol) was added in one portion. To this mixture was added 85% H_3PO_4 (0.036 mmol) drop wise for a duration of 20 min. The mixture was then stirred for

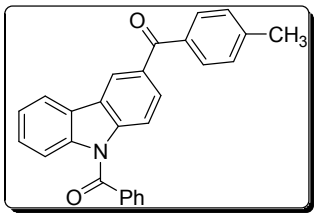
2h (monitored by TLC) and the excess of TFA/TFAA was distilled out at atmospheric pressure. The remaining liquid was partitioned between ethyl acetate (30 mL) and H_2O (15 mL). The organic layer was separated and washed with 5% NaOH (7 mL) and then brine (8 mL). The mixture was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography using EtOAc-n-hexane to give the desired product **4a**.



White solid; yield: 72%; mp: 162-165 °C (lit[4] 170 °C); R_f (8% EtOAc-*n*-Hexane) 0.8; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 (d, *J* = 1.3 Hz, 1H), 8.07 (dd, *J* = 6.9, 1.9 Hz, 1H), 7.88-7.82 (m, 3H), 7.79-7.75 (m, 2H), 7.70 (dd, *J* = 10.6, 4.3 Hz, 1H), 7.64-7.51 (m, 7H), 7.43-7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.2, 169.5, 141.6, 139.7, 138.0, 135.0, 132.9 (2C), 132.6, 132.2, 130.0 (2C), 129.2 (2C), 129.0 (2C), 128.3 (2C), 127.4, 125.8, 125.4, 123.8, 122.4, 120.2, 115.7, 115.1; HPLC: 95.39%, column: X BRIDGE C-18 150*4.6 mm, 5µm, mobile phase A: 0.1 % Formic acid in water mobile phase B: CH_3CN (gradient) T/%B: 0/20, 3/20, 6/98, 12/100, 18/100; flow rate: 1.0 mL/min; Diluent: CH_3CN UV 254 nm retention time 13.39 min; IR (KBr, cm^{-1}): 3073, 2915, 1698, 1649, 1309, 756; MS (ES mass): *m*/*z* 376.0 (M+1).

Synthesis of (9-benzoyl-9*H*-carbazol-3-yl)(p-tolyl)methanone (4b)

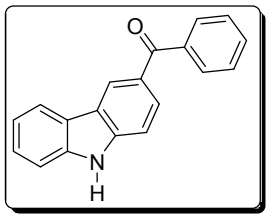
A mixture of TFAA (1.291 mmol) and 4-methyl benzoic acid (0.369 mmol) was stirred for 20 min until the solid was dissolved. After stirring for additional 20 min, (9*H*-carbazol-9-yl)(phenyl)methanone **3a** (0.369 mmol) was added in one portion. To this mixture was added 85% H_3PO_4 (0.036 mmol) drop wise for a duration of 20 min. The mixture was then stirred for 2h (monitored by TLC) and the excess of TFA/TFAA was distilled out at atmospheric pressure. The remaining liquid was partitioned between ethyl acetate (30 mL) and H_2O (15 mL). The organic layer was separated and washed with 5% NaOH (7 mL) and then brine (8 mL). The mixture was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography using EtOAc-n-hexane to give the desired product **4b**.



White solid; yield: 70%; mp: 152-155 °C; R_f (8% EtOAc-*n*-Hexane) 0.8; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (d, *J* = 1.2 Hz, 1H), 8.09-8.02 (m, 1H), 7.80 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.76 (dd, *J* = 7.5, 3.3 Hz, 4H), 7.69 (t, *J* = 7.4 Hz, 1H), 7.60-7.49 (m, 4H), 7.41-7.35 (m, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.0, 169.5, 143.1, 141.5, 139.7, 135.2, 135.1, 133.0, 132.9, 130.2 (2C), 129.2 (2C), 129.1, 129.0, 129.0, 128.9, 127.3, 125.8, 125.5, 123.7, 122.3 (2C), 120.2, 115.7, 115.1, 21.6; HPLC: 93.00%, column: X BRIDGE C-18 150*4.6 mm, 5µm, mobile phase A: 0.1 % Formic acid in water mobile phase B: CH_3CN (gradient) T/%B: 0/20, 3/20, 6/98, 12/100, 18/100; flow rate: 1.0 mL/min; Diluent: CH_3CN UV 254 nm retention time 13.80 min; IR (KBr, cm^{-1}): 2926, 2854, 1687, 1654, 1446, 1358, 1315; MS (ES mass): *m*/*z* 390.0 (M+1); Elemental analysis found C, 83.15; H, 4.91; N, 3.73; $C_{27}H_{19}NO_2$ requires C, 83.27; H, 4.92; N, 3.60.

Synthesis of (9*H*-carbazol-3-yl)(phenyl)methanone (5a)[5]

To the solution of amide, **4a** (0.256 mmol) in methanol (5 mL), DBU (0.512 mmol) was added and the reaction mixture was refluxed for 2 h. Then the reaction mixture was cooled to room temperature and solvent evaporated under vacuum.[6] Water added to this reaction mixture and the formed solid was filtered to give compound **5a** as Light yellow solid.

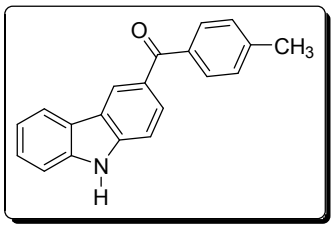


yield: 76%; mp: 200-202 °C (lit[5b] 203 - 205 °C); R_f (40% EtOAc-*n*-Hexane) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.60 (s, 1H), 8.46 (bs, 1H, NH), 8.10 (d, *J* = 7.5 Hz, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.86 (d, *J* = 7.2 Hz, 2H), 7.61 (t, *J* = 6.8 Hz, 1H), 7.54-7.48 (m, 5H), 7.29-7.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.7, 142.1, 140.1, 139.9, 138.8, 131.7, 129.9, 129.8, 129.0,

128.5, 128.1, 126.6, 126.5, 123.9, 122.9, 120.6, 120.3, 110.9, 110.2; MS (ES mass): *m*/*z* 272.0 (M+1).

Synthesis of 9*H*-carbazol-3-yl)(p-tolyl)methanone (5b)

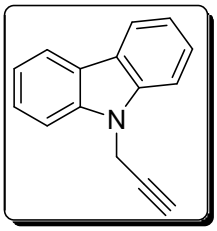
To the solution of amide, **4b** (0.256 mmol) in methanol (5 mL), DBU (0.512 mmol) was added and the reaction mixture was refluxed for 2 h. Then the reaction mixture was cooled to room temperature and solvent evaporated under vacuum.[6] Water added to this reaction mixture and the formed solid was filtered to give compound **5b** as off white solid.



Yield: 68%; mp: 222-224 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.64-8.54 (m, 1H), 8.47-8.36 (m, 1H), 8.15-8.05 (m, 1H), 8.03-7.94 (m, 1H), 7.83-7.72 (m, 2H), 7.48 (s, 3H), 7.31 (dd, *J* = 8.9, 7.8 Hz, 3H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.5, 130.2 (2C), 128.8 (2C), 128.5 (2C), 126.5, 126.5, 123.8 (2C), 123.4, 122.8, 120.6, 120.3 (2C), 110.9 (2C), 110.1, 21.6; MS (ES mass): *m*/*z* 285.0 (M+1); Elemental analysis found C, 84.41; H, 5.32; N, 4.67; $C_{20}H_{15}NO$ requires C, 84.19; H, 5.30; N, 4.91.

Synthesis of 9-(prop-2-ynyl)-9*H*-carbazole (7)[7]

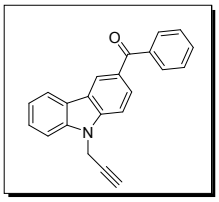
To a solution of carbazole **1** (10 mmol) in acetone (30 mL) was added K_2CO_2 (20 mmol). After stirring the mixture for 15 min, 3-bromopropyne (80 wt % solution in toluene, 15 mmol) was added drop wise for 30 min. Then the mixture was stirred for 3h at room temperature. The mixture was filtered and the filtrate was evaporated under reduced pressure. The crude product obtained was purified by chromatography on silica gel to give 9-(prop-2-ynyl)-9*H*-carbazole (**7**) as a white solid.



White solid; yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (d, *J* = 7.7 Hz, 2H), 7.64-7.44 (m, 4H), 7.41-7.17 (m, 2H), 5.06 (d, *J* = 2.3 Hz, 2H), 2.26 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.8, 125.9, 123.2, 120.4, 119.5, 108.7, 77.8, 72.2, 32.2. MS (ES mass): *m*/*z* 204.6 (M+1).

Synthesis of phenyl(9-(prop-2-ynyl)-9*H*-carbazol-3-yl)methanone (8)

A mixture of TFAA (1.704 mmol) and benzoic acid (0.487 mmol) was stirred for 20 min until the solid was dissolved. After stirring for additional 20 min the compound **7** (0.487 mmol) was added in one portion. To this mixture was added 85% H_3PO_4 (0.048 mmol) drop wise for a duration of 20 min. The mixture was then stirred for 2h (monitored by TLC) and the excess of TFA/TFAA was distilled out at atmospheric pressure. The remaining liquid was partitioned between ethyl acetate (30 ml) and H_2O (15 ml). The organic layer was separated and washed with 5% NaOH (7 ml) and then brine (8 ml). The mixture was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography using EtOAc-n-hexane to give the desired product **8**.



White soild; yield: 70%; mp: 168-170 °C; R_f(10% EtOAc-*n*-Hexane) 0.62; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63 (d, *J* = 1.2 Hz, 1H), 8.14 (d, *J* = 7.6 Hz, 1H), 8.08 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.87-7.85 (m, 2H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.57-7.52 (m, 5H), 7.36-7.32 (m, 1H), 5.11 (d, *J* = 2.4 Hz, 2H), 2.33 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.5, 142.3, 140.4, 138.8, 131.7, 129.9 (2C), 129.2, 128.6, 128.2 (2C), 126.7, 123.8, 123.3, 122.9, 120.8, 120.6, 109.2, 108.3, 77.3, 72.8, 32.5; MS (ES mass): *m*/*z* 310.2 (M+1); Elemental analysis found C, 85.60; H, 4.87; N, 4.41; $C_{22}H_{15}NO$ requires C, 85.41; H, 4.89; N, 4.53.

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Cell Proliferation Assay

The anti-proliferative activity and cancer cell selectivity of the synthesized compounds on normal and cancer cells was evaluated using the SRB (Sulforhodamine B) cell proliferation assay. This assay was chosen because of its sensitivity, large dynamic range and the ability to measure cell proliferation over three days with normalization to initial cell number as well as to vehicle-treated cells. Further, this assay is the standardized assay of choice for anticancer compound screening at the National Cancer Institute (NIH). The SRB assay provides a colorimetric readout which can be spectrophotometrically measured and does not involve antibodies or toxic reagents. The assay is based on detection of total protein content of cells, which increases or decreases in proportion with cell number.

In brief, the assay was performed as follows: Cancer(Cal 27(oral cancer cell line) and MDA-MB231(breast cancer cell line)) and non-cancer (Human Embryonic Kidney (HEK) 293T cell line) cells were seeded in 96-well plates and incubated overnight. The optimum cell numbers to be seeded were determined by a growth curve analysis for each cell line. In the initial (single dose) screen, compounds (dissolved in 100% DMSO to a stock concentration of 100mM) were added to the adhered cells at a final concentration of 10uM. After 72h of treatment, the cells were washed with phosphate-buffered saline and ice-cold 10% trichloroacetic acid added to the cells to precipitate all proteins for 1h at 4^0C. The cells were then washed with water and air-dried. Cellular proteins were then stained using 0.4% SRB solution in 1% acetic acid for 10 min at room temperature. The unbound dye was washed away by destaining with 1% acetic acid and

bound dye solubilized with 10mM Tris solution. Absorbance of solubilized dye was measured at a wavelength of 590 nm. Percentage growth was determined by the formula [(At-A0/Ac-A0)] X 100, where At=absorbance after 72h of test compound treatment, A0=Absorbance at time 0, Ac=Absorbance after 72h without treatment. (*Compounds which resulted in <50% growth of cancer cells were considered potentially anti-proliferative. Among such compounds, those which retained >75% growth of non-cancerous cells were considered potentially selective to cancer cells).* The Graphpad Prism 5 Demo software was used to generate the dose response curve using the sequence: select table and graph – enter data – analyze – transform data – nonlinear regression – inhibition vs response – results.

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