**Synthesis and *in vitro* antiproliferative effects of**

**new dihydropyrano[3,2-*b*]chromene derivatives**

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**Experimental Section**

Solvents and reagents were purchased from commercial sources and were used without further purification. Melting points were measured on an Electrothermal-9100 apparatus and are uncorrected. IR spectra were recorded on a Brucker FTIR Tensor 27 infrared spectrophotometer. 1H NMR spectra were recorded on a BruckerAvance III 300 MHz spectrometer. 13C NMR spectra were recorded on the same instruments at 75 MHz, using TMS as an internal standard. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. 3-Hydroxy-4*H*-chromen-4-one (**1**) was prepared according to literature procedures1.

**Preparation of Nanosized MgO**

The MgO nanoparticles were synthesized by precipitation of the magnesium hydroxide gels in aqueous solution using Mg(NO3)2 as salt and liquid ammonia as the precipitating agent. Initially, the pH of 200 mL of distilled water was adjusted to 10.5 by addition of liquid ammonia. To this solution, 0.1 M magnesium nitrate solution (0.0148 g/mL) was added dropwise with continuous stirring. The rate of addition of the salt solution was kept at 20 mL/h. During the addition, the pH of the mixture decreased due to hydrolysis of the salt. The pH was maintained at 10.5 by controlled addition of liquid ammonia solution. After completion of the precipitation procedure, the mixture was stirred at room temperature for 12 h, filtered, repeatedly washed with distilled water, dried at 120°C, and calcined at 500°C for 2 h2.

**General procedure for the preparation of dihydropyrano[3,2-*b*]chromene derivatives (4a-j)**

A mixture of 3-hydroxy-4*H*-chromen-4-one (**1**) (324 mg, 2 mmol), aromatic aldehydes (**2a-h**) (2 mmol), malononitrile (**3a**) (132 mg, 2 mmol) or ethyl cyanoacetate (**3b**) (0.21 mL, 2 mmol), and nanosized MgO (44 mg, 55 mol%) in ethanol (10 mL) was refluxed for in the reported time in Table 3 (the progress of the reaction was monitored by TLC and hexane/ethyl acetate was used as an eluent). After completion of the reaction, the mixture was cooled, nanosized MgO was removed by filtration and the obtained crude product was recrystallized from ethanol to give the pure solid sample for analysis.



*2-Amino-10-oxo-4-phenyl-4,10-dihydropyrano[3,2-b]chromene-3-carbonitrile (****4a****).*

Cream powders; yield: 91%; mp 268-269 ˚C (dec.); IR (KBr, νmax/cm-1): 3419, 3292 (NH2), 2193 (CN), 1657 (C=O), 1616, 1597 (C=C); 1H NMR (300 MHz, DMSO) δppm: 8.10 (dd, 1H, *J*=9Hz, *J*=3Hz, CH-Ar), 7.76-7.70 (m, 1H, CH-Ar), 7.50-7.30 (m, 9H, CH-Ar, NH2), 4.95 (s, 1H, CH); 13C NMR (75 MHz, DMSO) δppm: 169.02 (C=O), 159.79 (C2), 154.98 (C5a), 150.43, 141.45, 134.90, 133.75, 129.45, 128.39, 125.86, 125.74, 123.58, 119.84 (CN), 118.65, 56.10 (C3), 41.47 (C4); Anal. calcd. for C19H12N2O3: C, 72.15; H, 3.82; N, 8.86%. Found: C, 71.95; H, 3.65; N, 8.68%.



*2-Amino-4-(4-chlorophenyl)-10-oxo-4,10-dihydropyrano[3,2-b]chromene-3-carbonitrile (****4b****).*

White powders; yield: 92%; mp 261-262 ˚C (dec.); IR (KBr, *ν*max/cm-1): 3379, 3318 (NH2), 2198 (CN), 1662 (C=O), 1637, 1611 (C=C); 1H NMR (300 MHz, DMSO) δppm: 8.10 (dd, 1H, *J*=9Hz*, J*=3Hz, CH-Ar), 7.78-7.72 (m, 1H, CH-Ar), 7.52-7.34 (m, 8H, CH-Ar, NH2), 5.03 (s, 1H, CH); 13C NMR (75 MHz, DMSO) δppm: 169.04 (C=O), 159.78 (C2), 155.00 (C5a), 149.83, 140.37, 134.95, 133.83, 133.06, 130.39, 129.42, 125.90, 125.76, 123.60, 119.71 (CN), 118.66, 55.70 (C3), 40.81 (C4); Anal. calcd. for C19H11ClN2O3: C, 65.06; H, 3.16; N, 7.99%. Found: C, 64.88; H, 2.99; N, 7.79%.



*2-Amino-4-(2,4-dichlorophenyl)-10-oxo-4,10-dihydropyrano[3,2-b]chromene-3-carbonitrile(****4c****).*

White powders; yield: 94%; mp 257-258 ˚C (dec.); IR (KBr, *ν*max/cm-1): 3393, 3331 (NH2), 2189 (CN), 1651 (C=O), 1629, 1592 (C=C); 1H NMR (300 MHz, DMSO) δppm: 8.10 (d, 1H, *J*=9Hz, CH-Ar), 7.77-7.68 (m, 2H, CH-Ar), 7.54-7.39 (m, 6H, CH-Ar, NH2), 5.45 (s, 1H, CH); 13C NMR (75 MHz, DMSO) δppm: 168.93 (C=O), 160.03 (C2), 154.94, 148.87 (C5a), 137.19, 135.00, 134.35, 134.15, 133.98, 133.01, 129.89, 128.81, 125.94, 125.75, 123.61, 119.37 (CN), 118.68, 54.54 (C3), 38.80 (C4); Anal. calcd. for C19H10Cl2N2O3: C, 59.24; H, 2.62; N, 7.27%. Found: C, 59.06; H, 2.45; N, 7.08%.



*2-Amino-4-(4-bromophenyl)-10-oxo-4,10-dihydropyrano[3,2-b]chromene-3-carbonitrile (****4d****).*

White powders; yield: 91%; mp 261-262 ˚C (dec.); IR (KBr, *ν*max/cm-1): 3378, 3318 (NH2), 2198 (CN), 1663 (C=O), 1637, 1610 (C=C); 1H NMR (300 MHz, DMSO) δppm: 8.10 (d, 1H, *J*=9Hz, CH-Ar), 7.76 (t, 1H, *J*=9Hz, CH-Ar), 7.62-7.34 (m, 8H, CH-Ar, NH2), 5.02 (s, 1H, CH); 13C NMR (75 MHz, DMSO) δppm: 169.04 (C=O), 159.77 (C2), 155.00 (C5a), 149.77, 140.79, 134.96, 133.84, 132.34, 130.74, 125.91, 125.77, 123.60, 121.63, 119.71 (CN), 118.67, 55.63 (C3), 39.16 (C4); Anal. calcd. for C19H11BrN2O3: C, 57.74; H, 2.81; N, 7.09%. Found: C, 57.55; H, 2.64; N, 6.92%.



*2-Amino-10-oxo-4-(p-tolyl)-4,10-dihydropyrano[3,2-b]chromene-3-carbonitrile (****4e****).*

White powders; yield: 89%; mp 265-266 ˚C (dec.); IR (KBr, *ν*max/cm-1): 3387, 3308 (NH2), 2198 (CN), 1652 (C=O), 1637, 1598 (C=C); 1H NMR (300 MHz, DMSO) δppm: 8.10 (dd, 1H, *J*=6Hz*, J*=3Hz, CH-Ar), 7.76-7.70 (m, 1H, CH-Ar), 7.49-7.19 (m, 8H, CH-Ar, NH2), 4.89 (s, 1H, CH), 2.28 (s, 3H, CH3); 13C NMR (75 MHz, DMSO) δppm: 169.01 (C=O), 159.72 (C2), 154.97 (C5a), 150.62, 138.52, 137.65, 134.88, 133.64, 129.99, 128.28, 125.84, 125.73, 123.56, 119.86 (CN), 118.64, 56.21 (C3), 41.12 (C4), 21.12 (CH3); Anal. calcd. for C20H14N2O3: C, 72.72; H, 4.27; N, 8.48%. Found: C, 72.53; H, 4.09; N, 8.30%.



*2-Amino-4-(4-methoxyphenyl)-10-oxo-4,10-dihydropyrano[3,2-b]chromene-3-carbonitrile (****4f****).*



Cream powders; yield: 88%; mp 219-221 ˚C (dec.); IR (KBr, *ν*max/cm-1): 3367, 3307 (NH2), 2202 (CN), 1649 (C=O), 1639, 1600 (C=C); 1H NMR (300 MHz, DMSO) δppm: 8.10 (d, 1H, *J*=6Hz, CH-Ar), 7.75 (t, 1H, *J*=9Hz, CH-Ar), 7.51-7.25 (m, 6H, CH-Ar, NH2), 6.95 (d, 1H, *J*=3Hz, CH-Ar), 4.89 (s, 1H, CH), 3.75 (s, 3H, OCH3); 13C NMR (75 MHz, DMSO) δppm: 169.03 (C=O), 159.67 (C2), 159.34 (ArC-OMe), 154.99 (C5a), 150.74, 134.89, 133.54, 133.45, 129.53, 125.84, 125.75, 123.56, 119.90 (CN), 118.65, 114.78, 56.34 (C3), 55.57 (OCH3), 40.82 (C4); Anal. calcd. for C20H14N2O4: C, 69.36; H, 4.07; N, 8.09%. Found: C, 69.18; H, 3.90; N, 7.91%.

*Ethyl 2-amino-10-oxo-4-phenyl-4,10-dihydropyrano[3,2-b]chromene-3-carboxylate (****4g****).*

Brown powders; yield: 89%; mp 175-176 ˚C (dec.); IR (KBr, *ν*max/cm-1): 3453, 3402 (NH2), 1685 (COOEt), 1666 (C=O), 1614, 1575 (C=C); 1H NMR (300 MHz, DMSO) δppm: 8.10 (d, 1H, *J*=9Hz, CH-Ar), 7.89 (s, 1H, CH-Ar), 7.75 (t, 1H, *J*=6Hz, CH-Ar), 7.56-7.23 (m, 8H, CH-Ar, NH2), 4.95 (s, 1H, CH), 3.97 (q, 2H, *J*=6Hz, CH2), 1.04 (t, 3H, *J*=6Hz, CH3); 13C NMR (75 MHz, DMSO) δppm: 168.96 (C=O), 168.08 (COOEt), 160.18 (C2), 155.04 (C5a), 153.20, 143.61, 134.79, 133.27, 129.01, 128.20, 127.65, 125.79, 125.72, 123.67, 118.71, 75.49 (OCH2), 59.39, (C3), 41.04 (C4), 14.58 (CH3); Anal. calcd. for C21H17NO5: C, 69.41; H, 4.72; N, 3.85%. Found: C, 69.24; H, 4.56; N, 3.68%.



*Ethyl 2-amino-4-(4-fluorophenyl)-10-oxo-4,10-dihydropyrano[3,2-b]chromene-3-carboxylate (****4h****).*

Yellow powders; yield: 90%; mp 197-198 ˚C (dec.); IR (KBr, *ν*max/cm-1): 3451, 3398 (NH2), 1685 (COOEt), 1667 (C=O), 1615, 1576 (C=C); 1H NMR (300 MHz, DMSO) δppm: 8.105 (d, 1H, *J*=9Hz, CH-Ar), 7.90 (s, 1H, CH-Ar), 7.77 (t, 1H, *J*=9Hz, CH-Ar), 7.56-7.12 (m, 7H, CH-Ar, NH2), 4.98 (s, 1H, CH), 3.97 (q, 2H, *J*=6Hz, CH2), 1.04 (t, 3H, *J*=6Hz, CH3); 13C NMR (75 MHz, DMSO) δppm: 168.98 (C=O), 168.02 (COOEt), 163.31 (ArC-F), 160.11 (C2), 155.05 (C5a), 152.80, 139.81, 134.83, 133.24, 130.19, 125.82, 125.73, 123.66, 118.71, 115.90, 115.61, 75.36 (OCH2), 59.41 (C3), 40.82 (C4), 14.59 (CH3); Anal. calcd. for C21H16FNO5: C, 66.14; H, 4.23; N, 3.67%. Found: C, 65.97; H, 3.06; N, 3.50%.



*Ethyl 2-amino-10-oxo-4-(p-tolyl)-4,10-dihydropyrano[3,2-b]chromene-3-carboxylate (****4i****).*

Yellow powders; yield: 88%; mp 194-196 ˚C (dec.); IR (KBr, *ν*max/cm-1): 3394, 3290 (NH2), 1678 (COOEt), 1663 (C=O), 1615, 1576 (C=C); 1H NMR (300 MHz, DMSO) δppm: 8.10 (d, 1H, *J*=9Hz, CH-Ar), 7.86 (s, 1H, CH-Ar), 7.76 (t, 1H, *J*=9Hz, CH-Ar), 7.56-7.11 (m, 7H, CH-Ar, NH2), 4.90 (s, 1H, CH), 3.97 (q, 2H, *J*=6Hz, CH2), 2.24 (s, 3H, CH3), 1.07 (t, 3H, *J*=6Hz, CH3); 13C NMR (75 MHz, DMSO) δppm: 168.95 (C=O), 168.10 (COOEt), 160.14 (C2), 155.04 (C5a), 153.43, 140.66, 136.82, 134.77, 133.20, 129.58, 128.04, 125.78, 125.71, 123.66, 118.71, 75.57 (OCH2), 59.41 (C3), 40.82 (C4), 21.07 (Ar-CH3), 14.62 (CH3); Anal. calcd. for C22H19NO5: C, 70.02; H, 5.07; N, 3.71%. Found: C, 69.85; H, 4.89; N, 3.54%.



*Ethyl 2-amino-4-(4-methoxyphenyl)-10-oxo-4,10-dihydropyrano[3,2-b]chromene-3-carboxylate (****4j****).*

Brown powders; yield: 86%; mp 167-168 ˚C (dec.); IR (KBr, *ν*max/cm-1): 3397, 3293 (NH2), 1681 (COOEt), 1664 (C=O), 1614, 1509 (C=C); 1H NMR (300 MHz, DMSO) δppm: 8.10 (d, 1H, *J*=6Hz, CH-Ar), 7.86 (s, 1H, CH-Ar), 7.75 (t, 1H, *J*=6Hz, CH-Ar), 7.55-7.44 (m, 3H, CH-Ar, NH2), 7.22 (d, 2H, *J*=9Hz, CH-Ar), 6.88 (d, 2H, *J*=9Hz, CH-Ar), 4.88 (s, 1H, CH), 3.98 (q, 2H, *J*=6Hz, CH2), 3.70 (s, 3H, OCH3), 1.07 (t, 3H, *J*=6Hz, CH3); 13C NMR (75 MHz, DMSO) δppm: 168.94 (C=O), 168.13 (COOEt), 160.11 (C2), 158.81 (ArC-OMe), 155.04 (C5a), 153.50, 135.63, 134.74, 133.13, 129.19, 125.75, 125.71, 123.66, 118.69, 114.37, 75.72 (OCH2), 59.40 (C3), 55.47 (OCH3), 40.82 (C4), 14.64 (CH3); Anal. calcd. for C22H19NO6: C, 67.17; H, 4.87; N, 3.56%. Found: C, 66.99; H, 4.69; N, 3.38%.



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