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Synthesis of benzylidene dioxoaryl dihydrofuro [3,2-g] chromene-aminocarbonitrile: Aurone analogues

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Abstract: Novel series of Aurones coupled with chromene derivatives **5(a-f)** have been developed by using resorcinol as starting compound and by involving 2,4-dihydroxy acetophenone **(1)**, (2*E*)-1-(2,4-dihydroxyphenyl)-3-phenylprop-2-en-1-one **(2),** (2Z)-2-benzylidene-6-hydroxy-1-benzfuran-3(*2H*)-one **(3)** and (2Z)-7-amino-2-benzylidene-3-oxo-5-aryl-2, 3-dihydro-*5H*-furo*[3, 2-g]*-chromene-6-carbonitrile **4(a-f)** as intermediates. The synthesized compounds were confirmed by their IR, NMR and Mass spectral data.

Keywords: 2,4-Dihydroxyacetophenone, Aurones, Furochromenes, FT–IR, NMR chemical shifts.

Introduction

Benzopyran derivatives represent the major class of heterocycles. The pyran derivatives have more applications in biological and pharmacological properties such as anti-cancer [1], anti-coagulant, spasmolytic, diuretic, and anti-anapbhylactin [2-5]. They also act as modulators of potassium and calcium channels influencing the activity of heart and blood pressure, anti-neoplasmatic agents [6-7]. The limited methods of synthesis of aurones have been received and this class of compounds showed a range of pharmacological activities including anti-cancer and anti-parasitic activities, anti-microbial, antiviral and antioxidant activities [8-11]. Aurones can be used as potential cancer chemotherapy agents and as inhibitors of an enzyme involved in the metabolism of thyroid hormones [12-13].

They have also been reported to be anti-proliferative agents, tyrosine kinase inhibitors, anti-microbial agents and as potentially useful imaging agents for detecting beta-amyloid plaques in Alzheimer's disease [14-15].

Results and Discussion

The compound (2Z)-7-amino-2-benzylidene-3,7dioxo-5-aryl-2,3-dihydro-*5H*-furo *[3,2-g]*chromene-6-carbonitrile **5(a-f)** was obtained after multiple reaction steps starting with condensation of 3-acetyl resorcinol with benzaldehyde, followed by cyclization with iodine as a catalyst affording (2Z)-2-benzylidene-6-hydroxy-1-benzofuran-3(*2H*)-one **(3).** Cyclization of compound **3** with malononitrile and aromatic aldehydes **(a-f)** under basic conditions gave the corresponding (2Z)-7-amino-2-benzylidene-3-oxo-5-aryl-2,3-dihydro-*5H*-furo*[3,2-g]*chromene-6-carbonitriles **4(a-f)** and these compounds are treated with formic acid deamination takes place to produced corresponding (2Z)-7-amino-2-benzylidene-3,7-dioxo-5-aryl-2,3-dihydro-*5H*-furo*[3,2-g]*chromene-6-

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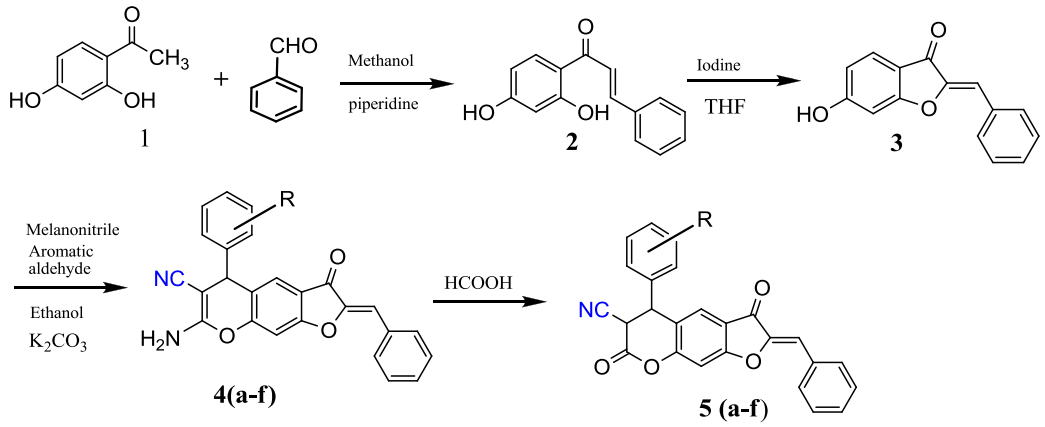
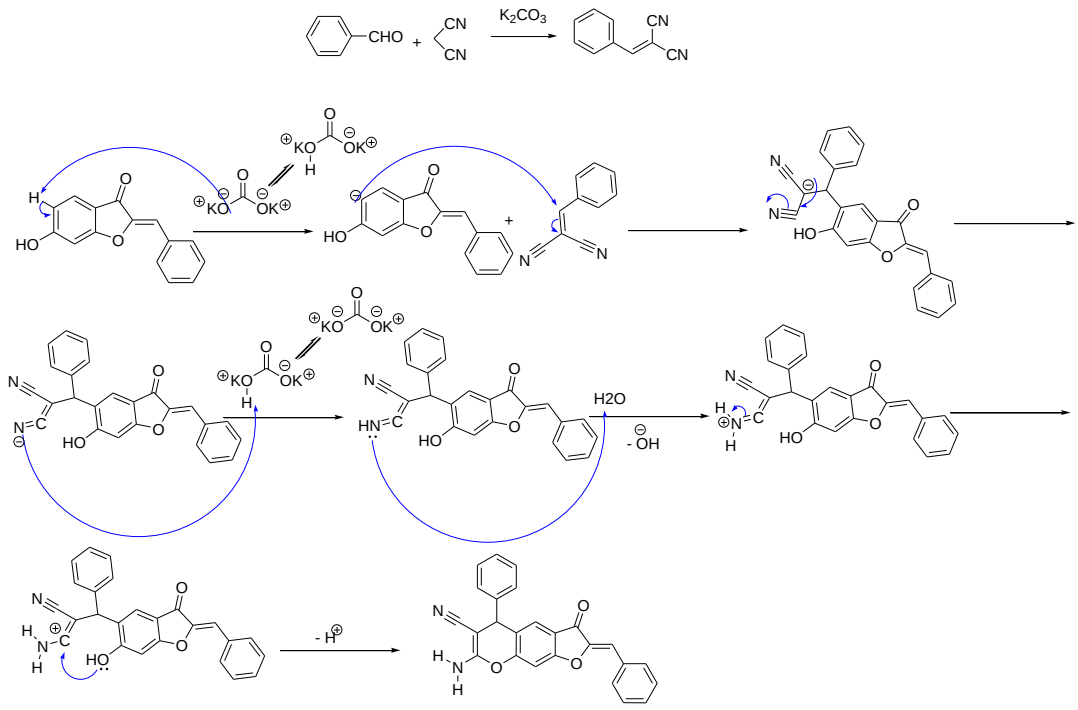
carbonitrile **5(a-f)** in good yields (Scheme **1**). The pure compounds were obtained by re-crystallization from an ethanol as solvent. All the synthesized compounds were confirmed based on elemental analyses, IR and NMR spectral data.

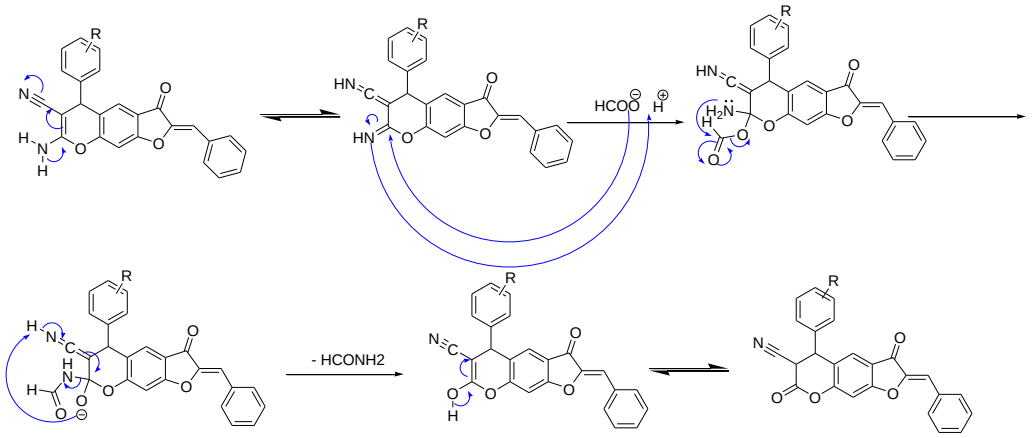


a) Benzaldehyde b) O-Salyciladehyde c) p-methoxy benzaldehyde d) dichloro benzaldehyde e) m-Nitro benzaldehyde f) Pyridine-2-carbaldehyde

Scheme 1: Synthesis of furo*[3,2-g]*chromenes



Scheme 2: proposed mechanism for compound **4**



Scheme 3: proposed mechanism for compound **5**

Experimental

Melting points were uncorrected. Infrared spectra were obtained by using a Bruker WM-4(X) spectrometer 577 model. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker WM-400 spectrophotometer in DMSO-d_6 with tetramethylsilane as reference. Mass spectra (ESI) were carried out on a JEOL SX-102 spectrophotometer. Elemental analysis was done on a Carlo Erba EA 1108 automatic elemental analyzer. The chemicals and solvents were commercial grade, used without further purification. Purification of the synthesized compounds by column chromatography and thin-layer chromatography (TLC) was carried out by using alumina sheets purchased from Merck.

General procedure for the synthesis of 2,4-dihydroxy acetophenone (1):

Anhydrous ferric chloride (16.5 g, 0.12 mol) was dissolved in 15.8 mL (0.27 mol) of acetic anhydride in 250 mL round bottomed flask and add resorcinol (11.0 g, 0. 1 mol) with constant stirring. The solution was heated on oil both at 140-150 ^{0}C. The hot mixture was cooled to room temperature and poured into 140 mL of 50% dilute HCl, orange precipitate was formed and increased with standing until 1 h. The orange crude product was obtained by filtration with suction pump, washed with water, orange needle crystals were obtained by crystallization using ethanol.

General procedure for the synthesis of (2E)-1-(2,4-dihydroxyphenyl)-3-phenylprop-2-en-1-one (2):

A mixture of 4-acetylresorcinol **(1)** (0.01mol) and benzaldehyde (0.015mol) in ethanol (20 mL) stirred at room temperature for 10 min. Then catalytic amount of piperidine was added into the reaction mixture and stirring was continued for 10 min at same temperature. Then the reaction mixture was refluxed for 4h at 40-50 ^{0}C. After completion of reaction, (monitored by TLC) the reaction mixture cooled to room temperature solid separated and washed with water.

Yield (75%): m p: 128-130 ^{0}C. IR spectrum, *v,* cm^{-1}: 3400-3500 (-OH), 1650 (m), 1620 (vs), 1200 (vs), 1150 (vs); ^{1}HNMR spectrum, δ, ppm: 5.1 (s, 2H, -OH), 6.3-6.7 (m, 2H, Ar-H), 7.5 (m, 3H, Ar-H), 7.6 (m, 3H, Ar-H), 7.8 (d, 1H,=CH), 7.9 (d,1H, =CH); ^{13}C NMR spectrum, δ, ppm: 103.2, 116.4, 119.1, 125.5, 118.3, 125.2, 128.9, 136.8, 138.6, 144.4, 149.5. $C_{15}H_{12}O_3$, **Calculated,** %: C 74.99; H 5.03; **Found, %;** C 73.83; H 4.99.

General procedure for the synthesis of (2Z)-2-benzylidene-6-hydroxy-1-benzfuran-3(2H)-one (3):

Compound **(2)** (0.01 mol) dissolved in THF (5 mL), than added catalytic amount of iodine with continuous stirring at room temperature for 12 h. After completion of the reaction (monitored by TLC), the mixture was poured into hypo solution. The product was extracted with ethyl acetate and dried over anhydrous sodiumsulphate, distilled under vaccum to get the crude which was purified by column chromatography (2:8 ratio of EA: Pet. ether).

Yield (70 %): m p: 142-144 ^{0}C; IR spectrum, *v,* cm^{-1}: 3350-3450, 1650 (C=O), 1615 (C=C), 1470, 1340, 1200, 1120; ^{1}HNMR spectrum, δ, ppm: 5.3 (s, 1H, -OH), 7.1 (s, 1H,-CH), 7.2 (s, 2H, Ar-H) 7.4 (s, 2H,

Ar-H) 7.6 (m, 3H, Ar-H), 7.9. (s, 1H, A r-H); ^{13}CNMR spectrum, δ, ppm: 102, 114, 118, 125, 126 128, 134, 146, 166, 169. **Calculated%,** $C_{15}H_{10}O_3$: C 75.62; H 4.23: **Found**: C 74.02; H 4.10.

General procedure for the synthesis of (2Z)-7-a mino-2-benzylidene-3-oxo-5-aryl-2, 3-dihydro-5H-furo[3, 2-g]-chromene-6-carbonitrile 4(a-f):

A mixture of compound **(3)** (0.01mol) substituted aromatic aldehydes **(a-f)** (0.01mol), and malononitrile (0.01mol) dissolved in ethanol added anhydrous K_2CO_3 with continuous stirring at 0^0C for 30 min and continued at room temperature for 4 h. After completion of the reaction (monitored by TLC), mixture poured into ice-cold water orange color solid separated, filtered and dried. The compounds were purified by column chromatography (mobile phase 2:8 EA; Pet. Ether).

(2Z)-7-Amino-2-benzylidene-3-oxo-5-phenyl-2,3-dihydro-5H-furo[3,2-g]chromene-6-carbonitrile(4a):

Yield (62 %): m p: 123-124 ^{0}C; IR spectrum, *ν,* cm^{-1}: 3280-3407 (-NH_2), 2170 (-CN), 1676 (-C=O),1630 (-C=C-), 1491, 1365, 1216, 1140; ^{1}HNMR ($CDCl_3$) δ 4.80 (s, 1H, pyran–H), 5.6 (s, 1H ,-CH), 6.9 (d, 2H, Ar-H), 7.1 (m, 3H, Ar-H), 7.2 (s, 2H, Ar-H), 7.5 (m, 4H, Ar-H), 7.6 (s, 1H, Ar-H), 7.8 (s, 1H, Ar-H), 6.6 (brs,-NH_2, D_2O exchangeable); ^{13} CNMR ($CDCl_3$): δ 28.1, 59.5, 113.2, 114.5, 117.0, 118.5, 125.4, 126.3, 128.9, 129.6, 131.2, 132.6, 146.7, 160.2, 164.1, 177.7, 180.5. **Calculated %,** $C_{25}H_{16}N_2O_3$: C 75.62; H 4.23; **Found:** C 75.59; H 4.21.

(Z)-7-Amino-2-benzylidene-5-(2-hydroxyphenyl)-3-oxo-3,5-dihydro-2H-furo[3,2-g]chromene-6-carbonitrile(4b):

Yield (69%): m.p: 138-140 ^{0}C; IR spectrum, *ν,* cm^{-1}: 3500 (-OH), 3200-3350 (-NH_2), 2200 (-CN), 1681 (-C=O), 1620 (-C=C-), 1480, 1210 ; ^{1}HNMR ($CDCl_3$): δ 4.35 (s, 1H, pyran–H), 5.8 (s, 1H ,-CH), 7.0 (s, 1H, Ar-H), 7.2 (m, 4H, Ar-H), 7.3 (m, 2H, Ar-H), 7.5 (m, 2H, Ar-H), 7.6 (s, 1H, Ar-H), 7.8 (s,1H, Ar-H), 6.8 (brs, -NH_2, D_2O exchangeable),; ^{13}CNMR ($CDCl_3$): 26.1, 56.4, 112.5, 115.2, 116.9, 122.3, 123.4, 125.7, 127.0, 128.5, 130.2, 131.1, 135.6, 143.3, 158.4, 172.8, 181.1. **Calculated %,** $C_{26}H_{16}N_2O_5$: C 71.56; H 3.70; **Found:** C 71.52; H 3.68.

(Z)-7-amino-2-benzylidene-5-(4-methoxyphenyl)-3-oxo-3,5-dihydro-2H-furo[3,2-g]chromene-6-carbonitrile (4c):

Yield (74%): m.p:116-118 ^{0}C; IR spectrum, *ν,* cm^{-1}: 3180-3340 (-NH_2), 2190 (-CN) , 1680 (-C=O), 1650 (-C=C-), 1480, 1312, 1240, 1130; ^{1}HNMR ($CDCl_3$): δ 3.91(s, 3H, -OCH_3), 4.9 (s,1H, pyran-H), 5.4 (s,1H, -CH), 6.9 (d, 2H), 6.98 (s, -NH_2), 7.1 (m, 2H, Ar-H), 7.3 (m, 1H, Ar-H), 7.4 (s. 1H, Ar-H), 7.5 (d, 1H, Ar-H), 7.6 (s, 1H, Ar-H), 7.8 (d, 2H, Ar-H); ^{13}CNMR ($CDCl_3$); 28.2, 58.3, 62.9, 113.6, 114.7, 117.5, 123.2, 124.5, 125.9, 126.0, 129.5, 131.2, 134.3, 142.2, 156.8, 163.5, 174.6, 179.9; **Calculated %,** $C_{26}H_{18}N_2O_4$; C 73.92; H 4.29; N 6.63; **Found:** C 73.05; H; 4.30; .N 6.02.

(Z)-7-Amino-2-benzylidene-5-(2, 3-dichlorophenyl)-3-oxo-3, 5-dihydro-2H-furo [3, 2-g] chromene-6-carbonitrile (4d):

Yield (78 %): m p:143-145 ^{0}C; IR spectrum, *ν,* cm^{-1}: 3200-3350 (-NH_2), 2200 (-CN), 1650 (-C=O), 1630 (-C=C-), 1500, 1350, 1180, 820, 630; ^{1}HNMR($CDCl_3$): δ 4.35 (pyran-H), 6.2 (s, 2H, -NH_2), 6.8 (s, 1H, Ar-H), 6.9 (m, 2H, Ar-H), 7.2 (d, 2H, Ar-H), 7.4 (m,1H, Ar-H), 7.5 (m, 1H, Ar-H), 7.6 (m,1H, Ar-H), 7.8 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 25.1, 56.5, 113.7, 114.2, 118.3, 125.4, 126.3, 128.7, 129.6, 130.4, 132.2, 142.1, 148.3, 156.4, 164.2, 177.3, 184.2. **Calculated %,** $C_{25}H_{14}Cl_2N_2O_3$; C 65.09; H 3.06; N 6.07: **Found:** C 64.93; H 3.02; N 5.97.

(Z)-7-Amino-2-benzylidene-5-(3-nitrophenyl)-3-oxo-3,5-dihydro-2H-furo[3,2-g] chromene-6-carbonitrile (4e):

Yield (62 %): m.p:126-128 ^{0}C; IR spectrum, *ν,* cm^{-1}: 3300-3350 (-NH_2), 2190 (-CN), 1690 (-C=O), 1630 (-C=C-), 1515 (-N-O), 1460, 1340, 1230, 1130. ^{1}HNMR ($CDCl_3$): δ 4.9 (pyran–H), 5.1 (s, 1H), 5.8 (s, 1H, -CH), 6.7 (s, 2H,-NH_2), 7.2 (m, 5H, Ar-H), 7.3 (s, 1H, Ar-H), 7.4 (s, 2H, Ar-H), 7.5 (m, 1H, Ar-H), 7.6 (s,1H, Ar-H), 7.8 (s, 1H, Ar-H),; ^{13}CNMR ($CDCl_3$): δ 27.0, 62.3, 110.2, 112.5, 114.2, 118.6, 121.7, 124.5, 126.3, 128.6, 129.7, 131.2, 132.3, 134.1, 143.6, 148.7, 149.4, 158.7, 165.9, 178.4,183.0; **Calculated %,** $C_{25}H_{15}N_3O_5$.C 68.65, H 3.46, N 9.61; **Found:** C 67.64, H 3.02, N 9.42.

(Z)-7-Amino-2-benzylidene-3-oxo-5-(pyridin-2-yl)-3,5-dihydro-2H-furo[3,2-g] chromene-6-carbonitrile (4f):

Yield (65 %); m. p: 146-148 ^{0}C; IR spectrum, *ν,* cm^{-1}: 3180-3250 (-NH_2), 2230 (-CN), 1700 (-C=O), 1640 (-C=C-), 1490, 1340, 1250, 1160; ^{1}HNMR ($CDCl_3$): δ 4.7 (s, 1H, pyran–H), 5.1 (s, 1H, -CH), 5.8 (s,1H, -=CH), 6.7 (s, 2H, -NH_2), 7.1(m, 3H, Ar-H), 7.2 (m,

5H, Ar-H), 7.5 (s, 1H, Ar-H), 7.6 (s, 2H, Ar-H), 7.8 (s, 2H, Ar-H); ^{13}CNMR ($CDCl_3$): δ 32.2, 58.5, 111.4, 112.8, 115.8, 117.3, 118.1, 121.4, 123.6, 127.2, 128.0, 132.3, 134.4, 137.7, 147.1, 148.2, 158.5, 159.7, 163.9, 175.0, 180.1. **Calculated %,** $C_{24}H_{15}N_3O_3$: C 73.27; H 3.84; N 10.68; **Found:** C 73.98; H 3.64; N 10.42.

General procedure for the synthesis of (2Z)-7-Amino-2-benzylidene-3,7-dioxo-5-aryl-2, 3-dihydro-5H-furo[3, 2-g]-chromene-6-carbonitrile 5(a-f):

To the compounds **4(a-f)**, (0.01 mol) added a solution of formic acid (0.02 mol) drop wise with stirring at room temperature for 10 min. Than continued the stirring at 50 ^{0}C for 40 min. After completion of the reaction (monitored by TLC), the mixture poured into ice-cold water, yellow colored solid separated, filtered, washed with water than re-crystallized from ethanol.

(Z)-2-Benzylidene-3,7-dioxo-5-phenyl-3,5,6,7-tetrahydro-2H-furo[3,2-g]chromene-6-carbonitrile(5a):

Yield (72 %); m p: 184-186 ^{0}C; IR spectrum, *ν,* cm^{-1}: 3200-3350 (-NH_2), 2190 (-CN), 1690, 1640 (-C=O), 1620 (-C=C-), 1470, 1350, 1230, 1120; ^{1}HNMR ($CDCl_3$): δ 2.8 (d, 2H), 4.80 (d, 1H, pyran-H), 5.4 (s, 1H, -=CH), 6.9-7.1 (m, 5H, Ar-H), 7.2 (d, 2H, Ar-H), 7.3 (m, 1H, Ar-H), 7.5 (m, 2H, Ar-H), 7.6 (s, 1H, Ar-H), 7.8 (s, 1H, Ar-H); ^{13}CNMR ($CDCl_3$): δ 36.4, 45.8, 113.2, 118.1, 121.3, 126.6, 127.7, 129.0, 131.0, 132.4, 134.1, 145.7, 146.3, 158.2, 164.6, 170.7, 182.0. **Calculated %,** $C_{25}H_{15}NO_4$: C 76.33; H 3.84; N 3.56: **Found:** C 72.98; H 3.64; N 3.45.

(Z)-2-Benzylidene-5-(2-hydroxyphenyl)-3,7-dioxo-3,5,6,7-tetrahydro-2H-furo[3,2-g] chromene-6-carbonitrile (5b):

Yield (83 %): m.p:168-170 ^{0}C; IR spectrum, *ν,* cm^{-1}: 3400 (brs,-OH), 3190-3250 (-NH_2), 2250 (-CN), 1680, 1650 (C=O), 1630 (-C=C-), 1440, 1250, 1160, 870, 820; ^{1}HNMR ($CDCl_3$): δ 2.7 (d, 2H, -CH), 4.35 (d, 1H, pyran-H), 5.7 (s, 1H,-=CH), 7.2 (m, 5H, Ar-H), 7.3 (d, 2H, Ar-H), 7.4 (m, 3H, Ar-H), 7.6 (s, 1H, Ar-H), 7.8 (s, 1H, Ar-H), 10.2 (s,1H,-OH); ^{13}CNMR ($CDCl_3$): δ 28.9, 44.4, 112.2, 117.5, 119.6, 121.7, 125.4, 129.6, 130.2, 132.1, 133.5, 146.7, 159.8, 166.2, 172.1, 184.0. **Calculated %,** $C_{25}H_{15}NO_5$; C 73.35; H 3.69; N 3.42; **Found:** C 73.25; H 3.36; N 3.06.

(z)-2-benzylidene-5-(4-methoxyphenyl)-3,7-dioxo-3,5,6,7-tetrahydro-2H-furo[3,2-g]chromene-6-carbonitrile(5c):

Yield(78%): m.p: 210-212 ^{0}C; IR spectrum, *ν,* cm^{-1}: 3250-3300 (-NH_2), 2200 (-CN) , 1670, 1660 (-C=O), 1630 (-C=C-), 1450, 1345, 1230, 1140, 1090, 860, 810; ^{1}HNMR ($CDCl_3$): δ 2.6 (d, 1H, -CH), 3.8 (s, 3H, -OMe), 5.0 (d, 1H, pyran-H), 5.8 (s, 1H, -=CH), 7.2 (m, 5H, Ar-H), 7.5 (m, 5H, Ar-H), 7.6 (s, 1H, Ar-H), 7.8 (s, 1H, Ar-H); ^{13}CNMR($CDCl_3$): δ 35.2, 46.5, 55.3, 115.1, 116.7, 119.8, 123.2, 128.5, 129.9, 132.1, 133.5, 138.6, 149.4, 155.7, 162.8, 166.6, 173.6, 183.1. **Calculated,** $C_{26}H_{17}NO_5$; C 73.75; H 4.05; N, 3.31; **Found:** C 72.96; H 3.86; N, 3.24.

(Z)-2-Benzylidene-5-(2, 3-dichlorophenyl)-3, 7-dioxo-3,5,6,7-tetrahydro-2H-furo[3,2-g] chromene-6-carbonitrile (5d)

Yield (76%): m. p: 194-196 ^{0}C; IR spectrum, *ν,* cm^{-1}: 3150-3300 (-NH_2), 2250 (-CN), 1660, 1650 (-C=O), 1620 (-C=C-), 1510, 1350, 1150, 820, 630; ^{1}HNMR ($CDCl_3$): δ 2.1(d, 1H, -CH), 4.6 (d, 1H, pyran-H), 5.8 (s, 1H, -=CH), 6.9 (d, 2H, Ar-H), 7.0 (m, 3H, Ar-H), 7.2 (m, 1H, Ar-H), 7.5 (d, 2H, Ar-H), 7.6 (s, 1H, Ar-H), 7.8 (s, 1H, Ar-H),; ^{13}CNMR ($CDCl_3$): δ 29.1, 43.5, 113.6, 117.4, 122.7, 128.5, 128.4, 129.8, 131.2, 134.3, 135.8, 138.6, 147.9, 155.4, 167.3, 171.2, 184.5. **Calculated %,** $C_{25}H_{13}Cl_2NO_3$: C 64.95; H 2.83; N 3.03; **Found:** C 63.98; H 2.64; N 2.86.

(Z)-2-Benzylidene-5-(3-nitrophenyl)-3,7-dioxo-3,5,6,7-tetrahydro-2H-furo[3,2-g] chromene-6-carbonitrile (5e)

Yield (69 %): m. p: 236-238 ^{0}C; IR spectrum, *ν,* cm^{-1}: 3250-3380 (-NH_2), 2210 (-CN), 1690 1670 (-C=O), 1640 (-C=C-), 1530 (-N-O), 1450, 1380, 1250, 1120, 860, 820; ^{1}HNMR ($CDCl_3$): δ 2.5 (d, 1H, -CH), 4.6 (d, 1H, pyran-H), 5.8 (s,1H,-=CH), 7.2 (m, 5H, Ar-H), 7.5 (m, 3H, Ar-H), 7.6 (s, 1H, Ar-H), 7.7 (s, 1H, Ar-H), 7.8 (s, 1H, Ar-H); ^{13}CNMR ($CDCl_3$): δ 33.2, 46.1, 114.0, 118.2, 121.5, 123.6, 125.9, 128.2, 129.1, 130.0, 133.2, 134.4, 135.4, 145.6, 148.4, 158.7, 162.3, 171.1, 182.0. **Calculated %,** $C_{25}H_{14}N_2O_6$: C 68.49; H 3.22; N 6.39. **Found %:** C; 67.98, H 3.03; N 5.42.

(Z)-2-benzylidene-3,7-dioxo-5-(pyridine-2-yl)-3,5,6,7-tetrahydro-2*H*-furo[*3,2-g]*chromene-6-carbonitrile (5f):

Yield (62%): m p: 223-225 ^{0}C; IR spectrum, *ν,* cm^{-1}: 3280-3350 (-NH_2), 2190 (-CN), 1670, 1650 (-C=O), 1620 (-C=C-), 1460, 1330, 1260, 1140; ^{1}HNMR ($CDCl_3$): δ 2.5 (d, 1H, -CH), 4.65 (d, 1H, pyran–H), 5.8 (s, 1H, -=CH), 7.2 (m, 5H, Ar-H), 7.3 (m, 1H, Ar-H), 7.5 (d, 2H, Ar-H), 7.8 (s, 1H, Ar-H), 7.9 (s, 1H, Ar-H); ^{13}CNMR ($CDCl_3$): δ 35.2, 44.4, 113.2, 117.7,

119.5, 121.0, 124.3, 128.2, 129.7, 132.5, 133.0, 138.2, 146.4, 149.1, 154.4, 163.7, 169.5, 182.2. **Calculated %,** $C_{24}H_{41}N_2O_4$ C 73.09; H 3.58; N 7.10: **Found**: C 72.98; H 3.24; N 6.42.

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