Practical and Green Protocol for the Synthesis of Substituted 4*H*-Chromenes Using Room Temperature Ionic Liquid Choline Chloride–Urea

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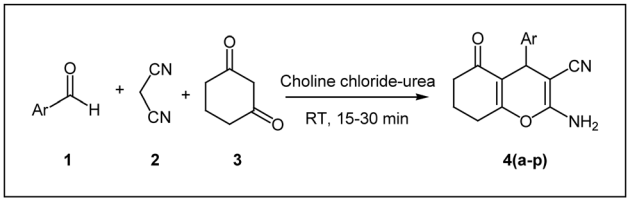

An efficient and convenient synthesis of substituted 4*H*-chromenes is described using room temperature ionic liquid (RTIL) choline chloride–urea in one pot under solvent free conditions. Three-component Knoevenagel condensation of an aromatic aldehyde, with an active methylene compound, and a cyclohexane dione is reported. This new approach has advantage of excellent yields (82–96%), clean reaction, and short reaction time (15–30 min) at room temperature.

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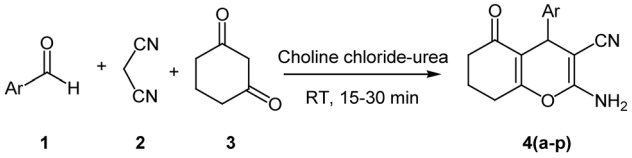
INTRODUCTION

The development of multicomponent reactions (MCRs) has attracted much attention from the advantage point of combinatorial and medicinal chemistry [1]. In general, the MCR strategy affords savings in synthetic time and effort, and has significant advantages over conventional two-component reactions in several ways, such as variable and high bond forming efficiency. Many important heterocyclic syntheses are MCRs. Recently, the synthesis of 4*H*-chromene and quinoline derivatives has attracted great interest because of biological and pharmacological activities. The 4*H*-chomene derivatives show various pharmacological properties such as spasmolytic diuretics, anticoagulant, anticancer, antianaphylactic, antibacterial, and antimalarial activities [2,3]. 4*H*-Pyrans also constitute the structural unit of a series of natural products [4]. Several 2-amino-4*H*-pyrans are useful as photoactive materials [5(a)]. The present 4*H*-chromene derivatives bearing a nitrile functionality arises from their potential application in the treatment of human neurodegenerative disorders [5(b)]. In the conventional reported syntheses of 4*H*-chromenes, the use of organic solvents such as DMF or acetic acid [6,7] but these solvents make the work-up procedure complicated and lead to poor yields of products. The known procedure for the synthesis of 4*H*-chromene derivatives use a three-component condensation of cyclic 1,3-diketones, aryl aldehydes, and malononitrile under various reaction conditions. Other methods of synthesis of 4*H*-chromene derivatives use microwave [8], electro generated base [9], and ultrasound irradiations [10]. Recently two- and three-component reactions have been catalyzed by using alkyl ammonium salts [11], $Re(PFO)_3$ [12], $KF–Al_2O_3$ [13], proline [14], NH_4HPO_4, and tetra-*n*-butyl ammonium fluoride (TBAF) [15(a)]. Wang *et al*. reported the synthesis of *N*-arylquinoline derivatives in ionic liquid [bmim+]BF at reflux condition and required 5–6 h [15(b)]. Very recently and Fang *et al*. synthesized 4*H*-benzopyrans catalyzed by acyclic acidic ionic liquids at high temperature [16]. Several general synthetic methods have also been reported [17]. However, they were poor yields, long reaction times, harsh reaction conditions, and tedious work-up procedures and organic solvents were used during all the reactions. To overcome such obstacles, chemists are challenged to develop clean procedures that avoid harmful organic solvents or completely eliminate the latter. This prompted us to search for improved and more efficient condition for the synthesis of 4*H*-chromenes. Room temperature ionic liquids (RTILs), especially those based on the choline chloride–urea have shown great promise as attractive alternatives to conventional solvents. The distinctive property of RTILs is that, they have essentially no vapor pressure, which makes them optimal replacements for the volatile organic solvents traditionally used as industrial solvents. Because of these advantages, ionic liquid choline chloride–urea has made significant contributions to green

Scheme 1



chemistry and it can be widely used as a reaction medium in organic chemistry. Herein, we report a series of substituted 4*H*-chromene derivatives by three-component reactions of aryl aldehyde, malanonitrile, and 1,3-cyclohexane dione in ionic liquid (Scheme 1).

RESULTS AND DISCUSSION

Choline chloride and urea are commercially available cheap chemicals; using these, ionic liquid was prepared easily at 50°C and the reaction mixture was brought to room temperature. We used RTILs in the three-component reaction as green medium. When the reaction of arylaldehyde, cyclic 1,3-diketone, and malononitrile was performed in ionic liquid choline chloride–urea at room temperature, the excellent yields (82–96%) of 4*H*-chromene derivatives were obtained within a short period of time (15–30 min), which are shown in Table 1 on the basis of optimization of reaction conditions. The scope of these ionic liquid catalyzed MCRs was explored. Not only electron-rich aryl aldehyde but also electron-deficient aryl aldehyde and heterocyclic aldehyde in the reactions afforded substituted 4*H*-chromenes. The 4*H*-chromene derivatives thus formed can be obtained in pure form by recrystallizing or passing the crude through a short plug of silica. The structure of the products was confirmed from physical and spectroscopic (IR, LC–MS, ^{1}H NMR, and elementary analysis) data. ^{1}H NMR spectra of 4*H*-chromenes **4**(**a**–**p**) show characteristic peaks at d 4.14–4.70 ppm.

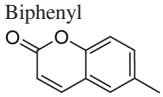
The proposed mechanism for the synthesis of chromene is outlined in Scheme 2. The reaction occurs *via* initial formation of the cyano olefin **A** from the condensation of aryl aldehyde **1** and malanonitrile **3** which reacts with 1,3-cyclohexanedione **2** to give the intermediate **B** which subsequently cyclizes to afford the desired compound **4**.

The three-component reaction of benzaldehyde, 1,3-cyclohexanedione, and malanonitrile at 50°C in a mixture of water and ethanol (1:1) as solvent for 10 h in the absence of ionic liquid yields alkene **A**, and no chromene **4a** was formed. Prolonging the reaction to 30 h in the same condition results in the formation of a trace amount of chromene **4a**. This proves the essential effect of ionic liquid as promoter.

In conclusion, we have developed an efficient procedure for the synthesis of 4*H*-chromene derivatives, which are often encountered in molecules of biologically active compounds. The procedure described here is simple, mild, and rapid. The use of ionic liquid as promoter has the advantages of being economically viable, mild reaction conditions, and operational simplicity for MCRs in aqueous media. The reaction system can successfully applied to a variety of aryl aldehydes as well

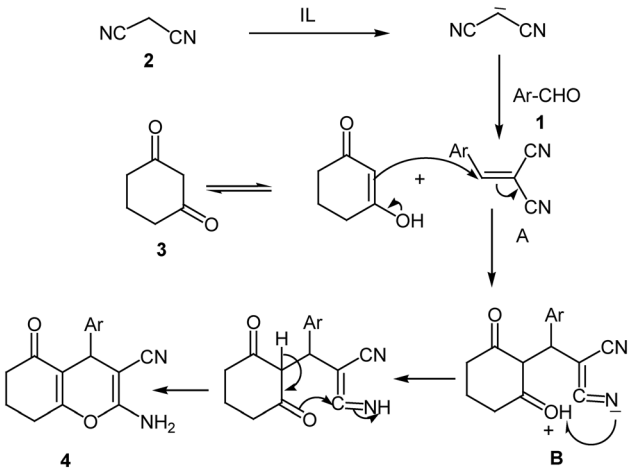
Table 1

Ionic liquid catalyzed one-pot synthesis of 4*H*-chromene derivatives.

Entry	Ar	Time (min)	Product	Yield[a] (%)	mp (°C)	Reported[b] (°C)
1.	C_6H_5	30	**4a**	96	224–226	227 [18]
2.	3-C_6H_5N	25	**4b**	94	221–223	
3.	2CN C_6H_5	30	**4c**	95	238–242	
4.	4-Isobutyl-C_6H_5	20	**4d**	80%	190–192	
5.	2Cl C_6H_5	25	**4e**	92	203–205	
6.	3-NO_2 C_6H_5	30	**4f**	86	221–222	
7.	Biphenyl	30	**4g**	92	232–234	
8.		25	**4h**	88	99–201	
9.	Thiazole	30	**4i**	94	220–222	
10.	4CN Ph	25	**4j**	88	215–218	
11.	4-(NMe_2)C_6H_4	30	**4k**	85	223–224	
12.	4-CH_3 C_6H_5	30	**4l**	90	220–221	221–222 [18]
13.	2-F-Phenyl	25	**4m**	94	224–225	
14.	4-Cl 1-CH_3 1*H*-pyrazole-3-yl	30	**4n**	86	245–245	
15.	Isoquinolin-8-yl	30	**4o**	88	232–234	
16.	1-Napthyl	30	**4p**	82	223–225	

[a]Yields refer to those of pure isolated products.
[b]Products were characterized by comparison of their spectroscopic data with those reported.

Scheme 2. The proposed mechanism for ionic liquid choline chloride–urea catalyzed synthesis of substituted chromenes **4**(**a**–**p**).



as heterocyclic aldehydes to synthesize a wide variety of heterocycles in excellent yields. In addition, it is possible to apply the tenets of green chemistry to the generation of biologically interesting products using ionic liquid approaches that are less expensive and less toxic than those with organic solvents.

EXPERIMENTAL

All analytical thin layer chromatography was performed with E. Merck silica gel $60F_{254}$ aluminum sheets and was visualized with UV light. The following mobile phases were used for TLC: chloroform, methanol and hexane, and ethyl acetate in different ratios.

The instrumental techniques used for the characterization of the newly synthesized compounds include ^{1}H NMR and mass spectroscopy. The details of instrumentation are briefly given below.

^{1}H (400 MHz) spectra were recorded on DMSO-d_6 solution in a 5-mm tube on a BRUKER amx 400 and 300 Fourier transform spectrophotometer (at SIF, Indian Institute of Science, Bangalore, India) with tetramethylsilane (TMS) as an internal standard. The spectrophotometer was internally locked to the deuterium frequency of the solvent. Chemical shifts were recorded in ppm relative to TMS. Mass and purity were recorded on a LC–MSD-Trap-XCT.

Preparation of ionic liquid. A mixture of anhydrous choline chloride (5 g, 35.8 mmol) and anhydrous urea (4.29 g, 71.61 mmol) under nitrogen atmosphere was heated to 50°C for 5–10 min with stirring. After the formation of clear viscous liquid (ionic liquid), the reaction mixture was brought to room temperature, this was analytically characterized and this RTIL was used for the reaction.

In a typical experimental procedure. The mixture of malanonitrile (0.324g, 4.9 mmol) and benzaldehyde (0.52 g, 4.908 mmol) was taken in the above-prepared ionic liquid and stirred for 5 min under nitrogen atmosphere and then 1,3-cyclohexane dione (0.5 g, 4.46 mmol) was added and the reaction mixture was stirred at room temperature for 30 min under nitrogen atmosphere. After the reaction, water was added and solid formed was filtered. The resulting solid formed was triturated with hexane:ethyl acetate (10–30%), filtered and dried to get light brown colored solid with good yield.

2-Amino-5,6,7,8-tetrhydro-5-oxo-4-phenyl-4*H*-chromene-3-carbonitrile (4a). White solid. Yield 1.13 g (96%). mp 224–226°C. IR (KBr): 3308.8, 3160.0, 2188.5, 1681.5, 1643.5, 1414.3, 1204.4. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30–2.41 (m, 2H, CH_2), 2.03–2.10 (m, 2H, CH_2), 2.61 (m, 2H, CH_2), 4.45 (s, 1H, CH), 4.55 (s, 2H, NH_2), 7.19–7.32 (m, 5H, Ar-H). MS (ESI + ion): *m*/*z* = 267.2. Anal. Cacld for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.17; H, 5.30; N, 10.52.

2-Amino-5,6,7,8-tetrahydro-5-oxo-4-(pyridine-3-yl)-4*H*-chromene-3-carbonitrile (4b). White solid. Yield 1.15 g (97%). mp 221–223°C. IR (KBr): 3349.2, 3035, 2187.5, 1658.0, 1608, 1359.8, 1359. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.05 (m, 2H, CH_2), 2.40 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 4.49 (s, 1H, CH), 4.72 (s, 2H, NH_2), 7.35 (dd, $^3J_{H,H}$ = 7.7 Hz, 1H, Ar-H), 7.77 (d, $^3J_{H,H}$ = 7.8 Hz, 1H, Ar-H), 8.50 (t, $^3J_{H,H}$ = 8.5 Hz, 2H, Ar-H). MS (ESI + ion): *m*/*z* = 268.2. Anal. Cacld for $C_{15}H_{13}N_3O_2$: C, 67.41; H, 4.90; N, 15.72. Found: C, 67.48; H, 4.86; N, 15.68.

2-Amino-4-(2-cyanophenyl)-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile (4c). White solid. Yield 1.25 g (97%). mp 238–242°C. IR (KBr): 3391.1, 3327.3, 3211.7, 2188.3, 1684.8, 1661.0, 1359.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.08 (m, 2H, CH_2), 2.58 (m, 2H, CH_2), 2.71 (m, 2H, CH_2), 4.61 (s, 1H, CH), 4.68 (s, 2H, NH_2), 7.35 (m, 1H, Ar-H), 7.56 (m, 2H, Ar-H), 7.65 (d, $^3J_{H,H}$ = 1.0 Hz, 1H, Ar-H). MS (ESI + ion): *m*/*z* = 292.0 Anal. Cacld for $C_{17}H_{13}N_3O_2$: C, 70.09%; H, 4.50; N, 14.42. Found: C, 70.18; H, 4.54; N, 14.38.

2-Amino-5,6,7,8-tetrahydro-4-(4-isobutylphenyl)-5-oxo-4*H*-chromene-3-carbonitrile (4d). White solid. Yield 1.34 g (93%). mp 190–192°C. IR (KBr): 3448.2, 3307.4, 3257.8, 3201.7, 2951.2, 2199.2, 1685.4, 1659.4, 1359. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.85 (d, $^3J_{H,H}$ = 6.6 Hz, 6H, $(CH_3)_2$), 1.79 (m, 1H, CH), 1.95 (m, 2H, CH_2), 2.28 (m, 2H, CH_2), 2.38 (d, $^3J_{H,H}$ = 7.2 Hz, 2H, CH_2), 2.60 (m, 2H, CH_2), 4.14 (s, 1H, CH), 6.98 (s, 2H, NH_2), 6.97 (d, $^3J_{H,H}$ = 9.1 Hz, 2H, Ar-H), 7.07 (d, $^3J_{H,H}$ = 9.1 Hz, 2H, Ar-H). MS (ESI + ion): *m*/*z* = 323.2. Anal. Cacld for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88%; H, 4.50; N, 8.69. Found: C, 74.54; H, 6.78; N, 8.73.

2-Amino-2-(chlorophenyl)-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile (4e). White solid. Yield 1.20 g (90%). mp 203–205°C. IR (KBr): 3471.1, 3309, 3175.1, 2190.5, 1680.7, 1651.5, 1593.5, 1404.5, 1357.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.91–2.00 (m, 2H, CH_2), 2.17–2.34 (m, 2H, CH_2), 2.63 (m, 2H, CH_2), 4.70 (s, 1H, CH), 7.03 (s, 2H, NH_2), 7.20 (m, 2H, Ar-H), 7.35 (d, $^3J_{H,H}$ = 8.0 Hz, 1H, Ar-H), 7.36 (d, $^3J_{H,H}$ = 7.4 Hz, 1H, Ar-H). MS (ESI + ion): *m*/*z* = 301. Anal. Cacld for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; H, 4.50; N, 14.42. Found: C, 63.86; H, 4.46; N, 14.42.

2-Amino-5,6,7,8-tetrahydro-4-(3-nitrophenyl)-5-oxo-4*H*-chromene-3-carbonitrile (4f). White solid. Yield 1.19 g (86%). mp 221–222.8°C. IR (KBr): 3416.5, 3392.3, 3200.4, 2191.5, 1679.4, 1523.6, 1344.7, 1203.6. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.94 (m, 2H, CH_2), 2.28 (m, 2H, CH_2), 2.64 (m, 2H, CH_2), 4.40 (s, 1H, CH), 7.17 (s, 2H, NH_2), 7.59 (t, $^3J_{H,H}$ = 7.9 Hz, 1H, Ar-H), 7.65 (d, $^3J_{H,H}$ = 7.2 Hz, 1H, Ar-H), 7.98 (d, $^3J_{H,H}$ = 1.5 Hz, 1H, Ar-H), 8.08 (d, $^3J_{H,H}$ = 8.0 Hz, 1H, Ar-H). MS (ESI + ion): *m*/*z* = 312. Anal. Cacld for

$C_{16}H_{13}ClN_3O_4$: C, 61.73; H, 4.21; H, 4.50; N, 13.50. Found: C, 61.68; H, 4.25; H, 4.50; N, 13.45.

2-Amino-5,6,7,8-tetrahydro-5-oxo-4-biphenyl-4*H*-chromene-3-carbonitrile (4g). White solid. Yield 1.46 g (96%). mp 232–234°C. IR (KBr): 3434.5, 3324.4, 2067.2, 1679.0, 1649.6, 1363.7, 1200.4. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.89–2.00 (m, 2H, CH_2), 2.23–2.32 (m, 2H, CH_2), 2.61 (m, 2H, CH_2), 4.22 (s, 1H, CH), 7.03 (d, 2H, NH_2), 7.24 (d, $^3J_{H,H}$ = 8.2 Hz, 1H, Ar-H), 7.35 (t, $^3J_{H,H}$ = 7.2 Hz, 2H, Ar-H), 7.44 (t, $^3J_{H,H}$ = 7.6Hz, 2H, Ar-H), 7.57 (d, $^3J_{H,H}$ = 8.2 Hz, 2H, Ar-H), 7.62 (d, $^3J_{H,H}$ = 7.8 Hz, 2H, Ar-H). MS (ESI + ion): *m/z* = 343.2. Anal. Cacld for $C_{22}H_{18}N_2O_2$: C, 61.73; H, 4.21; H, 4.50; N, 13.50. Found: C, 61.73; H, 4.21; H, 4.50; N, 13.50.

Amino-5,6,7,8-tetrahydro-5-oxo-4-(2-oxo-2*H*-chromen-8-yl)-4-chromen-3-carbonitrile (4h). White solid. Yield 1.34 g (90%). mp 198–200°C. IR (KBr): 3323.1, 3205.9, 2187.3, 1729.2, 1643.4, 1365.5. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.85–1.94 (m, 2H, CH_2), 2.20–2.30 (m, 2H, CH_2), 2.61 (m, 2H, CH_2), 4.27 (s, 1H, CH), 6.45 (d, $^3J_{H,H}$ = 9.6 Hz, 1H, Ar-H), 7.08 (s, 2H, NH_2), 7.32 (d, $^3J_{H,H}$ = 8.5 Hz, 1H, Ar-H), 7.41 (d, 1H, Ar-H), 7.51 (s, 1H, Ar-H), 8.08 (d, $^3J_{H,H}$ = 9.6 Hz, 1H, Ar-H). MS (ESI + ion): *m/z* =335.2.2. Anal. Cacld for $C_{19}H_{14}N_2O_4S$: C, 68.26; H, 4.22; N, 8.38. Found: C, 68.29; H, 4.18; N, 8.43.

2-Amino-5,6,7,8-tetrahydro-5-oxo-4-(thiazol-4-yl)-4*H*-chromene-3-carbonitrile (4i). White solid. Yield 1.17 g (96%). mp 220–223°C. IR (KBr): 3395.4, 3310.5, 3203.1, 2175.4, 1674.2, 1643.5, 1358.8, 1259.4. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.8–1.98 (m, 2H, CH_2), 2.2–2.35 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 4.43 (s, 1H, CH), 7.00 (s, 2H, NH_2), 7.36 (s, 1H, Ar-H), 8.94 (s, 1H, Ar-H). MS (ESI + ion): *m/z* = 274.2. Anal. Cacld for $C_{13}H_{11}N_3O_2S$: C, 57.13; H, .4.06; N, 15.37. Found: C, 57.13; H, 4.06; N, 15.37.

2-Amino-4-(4-cyanophenyl)-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile (4j). White solid. Yield 1.26 g (97%). mp 215–217°C. IR (KBr): 3324.5, 3173.2, 3211.7, 2925.3, 2186.5, 1679.5, 1364.5, 1208. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87–1.98 (m, 2H, CH_2), 2.24–2.34 (m, 2H, CH_2), 2.61 (m, 2H, CH_2), 4.28 (s, 1, CH), 7.14 (s, 2H, NH_2), 7.36 (d, $^3J_{H,H}$ = 8.3 Hz, 2H, Ar-H), 7.75 (d, $^3J_{H,,H}$ = 8.3 Hz, 2H, Ar-H). MS (ESI + ion): *m/z* = 292.2. Anal. Cacld for $C_{17}H_{13}N_3O_2$: C, 70.09%; H, 4.50; N, 14.42. Found: C, 70.18; H, 4.54; N, 14.38.

2-Amino-4-(4-(dimethylamino)phenyl)-5-oxo-5,6,7,8-tetrahydro-5-4*H*-chromene-3-carbonitrile (4k). White solid. Yield 1.16 g (84%). mp 222–225°C. IR (KBr): 3324.5, 3173.2, 3211.7, 2925.3, 2186.5, 1679.5, 1364.5, 1208. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.81–1.96 (m, 2H, CH_2), 2.19–2.29 (m, 2H, CH_2), 2.50 (m, 2H, CH_2), 4.05 (s, 1H, CH), 6.63 (d, $^3J_{H,H}$ = 8.7 Hz, 2H, Ar-H), 6.87 (s, 2H, NH_2), 6.94 (d, $^3J_{H,H}$ = 8.7 Hz, 2H, Ar-H). MS (ESI + ion): *m/z* = 310.2. Anal. Cacld for $C_{18}H_{19}N_3O_2$: C, 69.88%; H, 6.19; N, 13.58. Found: C, 69.83; H, 6.16; N, 13.61.

2-Amino-5,6,7,8-tetrahydro-5-oxo-4-*p*-tolyl-4-chromene-3-carbonitrile (4l). White solid. Yield 1.05 g (84%). mp 219–221°C. IR (KBr): 3408.9, 3332.1, 3257.8, 2195.8, 1683.0, 1659.2, 1366.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.83–1.97 (m, 2H, CH_2), 2.24–2.33 (m, 5H, CH_2, Ar-CH_3), 2.58 (m, 2H, CH_2), 4.13 (s, 1H, CH), 6.94 (s, 2H, NH_2), 7.02 (d, $^3J_{H,H}$ = 8.0 Hz, 2H, Ar-H), 7.08 (d, $^3J_{H,H}$ = 8.0 Hz, 2H, Ar-H). MS (ESI + ion): *m/z* = 281.2. Anal. Cacld for $C_{17}H_{16}N_2O_2$: C, 72.84%; H, 5.75; N, 9.99. Found: C, 72.87; H, 5.79; N, 10.05.

2-Amino-4-(2-fluorophenyl)-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile (4m). White solid. Yield 1.04 g (82%). mp 224–225°C. IR (KBr): 3325.5, 3175.8, 2190.9, 1684.2, 1647.1, 1370.1, 1211.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88–1.20 (m, 2H, CH_2), 2.19–2.34 (m, 2H, CH_2), 2.63 (m, 2H, CH_2), 4.46 (s, 1H, CH), 7.02 (s, 2H, NH_2), 7.07–7.25 (m, 4H, Ar-H). MS (ESI + ion): *m/z* = 285.2. Anal. Cacld for $C_{16}H_{13}FN_2O_2$: C, 67.60%; H, 4.61; N, 9.85. Found: C, 67.67; H, 4.65; N, 9.88.

2-Amino-4-(1,4-dihloro-1*H*-pyrazol-3-yl)-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile (4n). White solid. Yield 1.11 g (82%). mp 245–247°C. IR (KBr): 3387.4, 3293.6, 2196.1, 1678.9, 1657.1, 1363.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.83–1.99 (m, 2H, CH_2), 2.21–2.30 (m, 2H, CH_2), 2.56 (m, 2H, CH_2), 3.71 (s, 3H, N CH_3), 4.33 (s, 1H, CH), 6.97 (s, 2H, NH_2), 7.75 (s, 1H, Ar-H). MS (ESI + ion): *m/z* = 305.0. Anal. Cacld for $C_{14}H_{13}ClN_4O_2$: C, 55.18; H, 4.30; N, 18.39. Found: C, 55.23; H, 4.32; N, 18.88.

2-Amino-5,6,7,8-tetrahydro-4-(isoquinolin-8-yl)-5-oxo-4*H*-chromene-3-carbonitrile (4o). White solid. Yield 1.15 g (82%). mp 232–235°C. IR (KBr): 3815.8, 3576.5, 3298.8, 2958.1, 2175.1, 1598.7, 1359.1, 1210.9. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.94–2.00 (m, 2H, CH_2), 2.16–2.32 (m, 2H, CH_2), 2.65–2.74 (m, 2H, CH_2), 5.11 (s, 1H, CH), 7.03 (s, 2H, NH_2), 7.54 (d, $^3J_{H,H}$ = 7.3 Hz, 1H, Ar-H), 7.62 (t, $^3J_{H,H}$ = 8.0 Hz, 1H, Ar-H), 7.98 (d, $^3J_{H,H}$ = 8.0 Hz, 1H, Ar-H), 8.21 (d, $^3J_{H,H}$ = 6.1 Hz, 1H, Ar-H), 8.53 (d, $^3J_{H,H}$ = 6.1 Hz, 1H, Ar-H), 9.30 (s, 1H, Ar-H). MS (ESI + ion): *m/z* = 318.2. Anal. Cacld for $C_{19}H_{15}N_3O_2$: C, 71.91%; H, 4.76; N, 13.24. Found: C, 71.95; H, 4.79; N, 13.28.

2-Amino-5,6,7,8-tetrahydro-4-(napthalen-1-yl)-5-oxo-4*H*-chromene-3-carbonitrile (4p). White solid. Yield 1.15 g (82%). mp 223–225°C. IR (KBr): 3452.5, 3327.2, 2197.3, 1663.8, 1598.1, 1357.6. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.91–2.02 (m, 2H, CH_2), 2.16–2.33 (m, 2H, CH_2), 2.48–2.74 (m, 2H, CH_2), 5.14 (s, 1H, CH), 6.93 (s, 2H, NH_2), 7.24 (d, $^3J_{H,H}$ = 6.8 Hz, 1H, Ar-H), 7.43 (t, $^3J_{H,H}$ = 8.0 Hz, 1H, Ar-H), 7.49–7.58 (m, 2H, Ar-H), 7.76 (d, $^3J_{H,H}$ = 8.1 Hz, 1H, Ar-H), 7.91 (d, $^3J_{H,H}$ = 7.9 Hz, 1H, Ar-H), 8.37 (d, $^3J_{H,H}$ = 8.4 Hz, 1H, Ar-H). MS (ESI + ion): *m/z* = 316.0. Anal. Cacld for $C_{20}H_{16}N_2O_2$: C, 75.93%; H, 5.10; N, 8.85. Found: C, 75.95; H, 5.18; N, 8.88.

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