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THREE-COMPONENT SYNTHESIS OF TETRAHYDROBENZO[*b*]-PYRANS CATALYZED BY SODIUM CYCLAMATE

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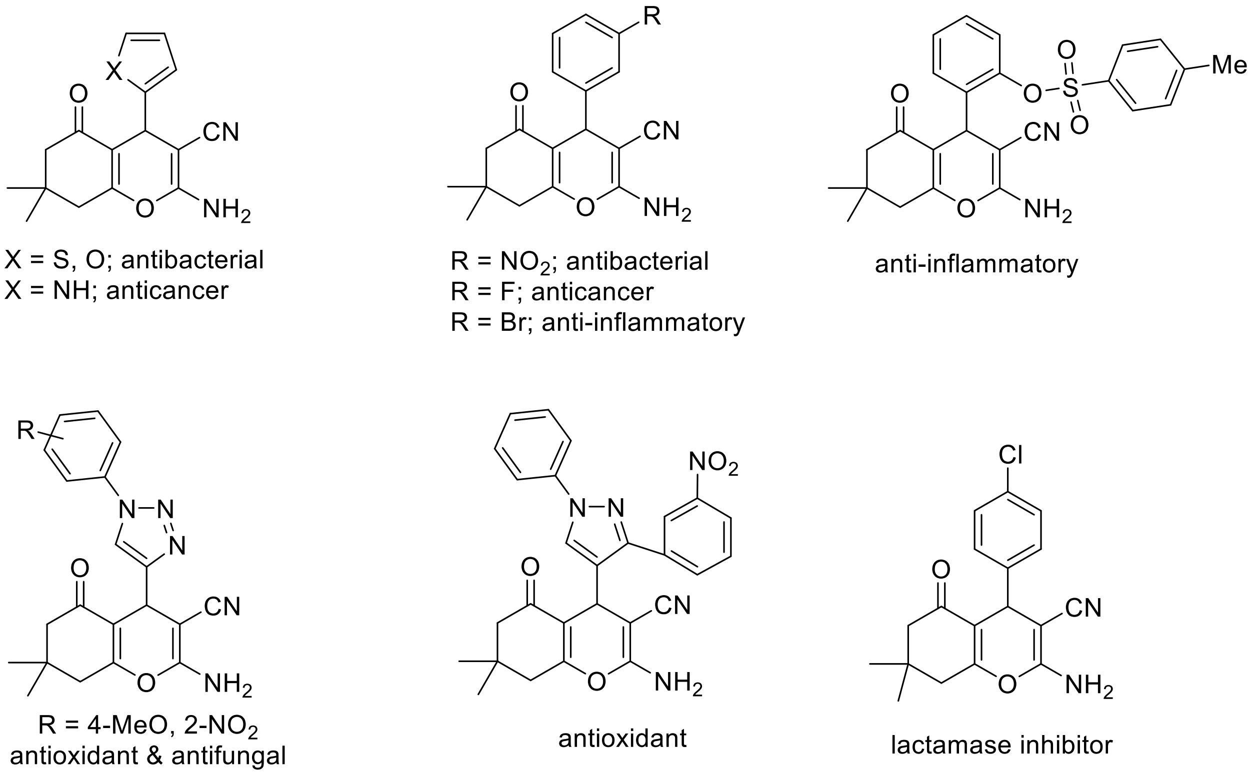
Abstract – The one-pot three-component cyclocondensation for the synthesis of tetrahydrobenzo[*b*]pyran derivatives in the presence of sodium cyclamate has been investigated. The three-component reaction was carried out in water medium under refluxing condition. Screening the reaction conditions revealed that 20 mol% sodium cyclamate refluxing water afforded the best results. Under green conditions, different substituted tetrahydrobenzo[*b*]pyrans were obtained from simple available starting materials, including malononitrile, functionalized benzaldehydes, and dimedone, *via* using an established efficient and straightforward approach.

Multicomponent reactions (MCRs) involve at least three reactants that reacted in one-pot approach to synthesize valuable organic compounds and pharmacologically active molecules with high complexity and diversity as well as minimum side reactions. Green bond-forming, atomic and structural economy, step economy, high bond-forming index, avoidance of complicated purification processes and separation of intermediates, time-saving, mild conditions, environmental friendliness, elimination of waste production, energy-saving, and excellent functional group compatibility are the merits of MCRs.[1] In this reason, MCRs have been used for the synthesis of various heterocyclic compounds.[2]

Tetrahydrobenzo[*b*]pyran derivatives are one of the biologically scaffolds owing to their applications in the synthetic and medicinal chemistry.[3] These important oxygen-containing heterocyclic compounds exhibit bioactivities, including anti-coagulant,[3] anti-anaphylactic,[3] calcium antagonist,[3] anticancer,[4] antibacterial,[5] anti-inflammatory,[6] lactamase inhibitor,[7] antifungal,[8] antioxidant,[8] anti-Huntington, anti-Alzheimer, anti-Schizophrenia, and anti-Parkinson.[3,9] The structures of some biologically active tetrahydrobenzo[*b*]pyrans are depicted in Figure 1. Besides, tetrahydrobenzo[*b*]pyrans were applied as starting materials to synthesize spirocyclopropylbarbiturates,[10] spirocyclopropylpyrazolones,[10] and 2-oxa-7-azabicyclo[4.1.0]hept-3-en-1-yl carboxylates.[11]



X = S, O; antibacterial
X = NH; anticancer

R = NO$_2$; antibacterial
R = F; anticancer
R = Br; anti-inflammatory

anti-inflammatory

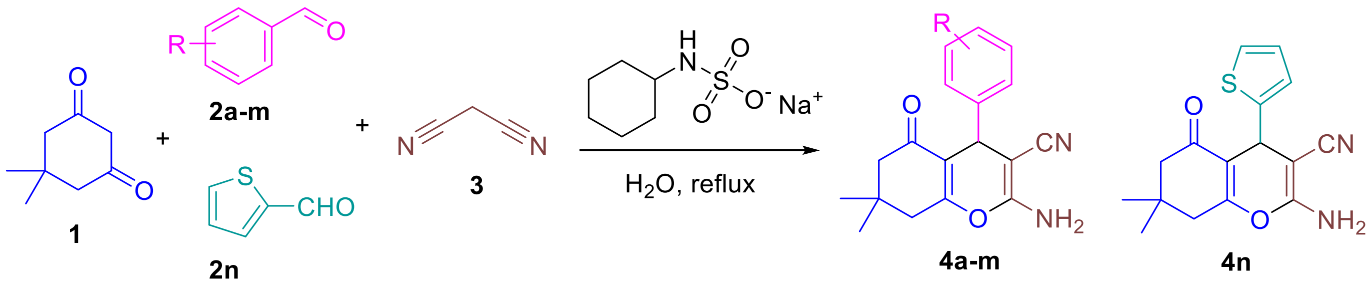
R = 4-MeO, 2-NO$_2$
antioxidant & antifungal

antioxidant

lactamase inhibitor

Figure 1. Some biologically active tetrahydrobenzo[*b*]pyrans

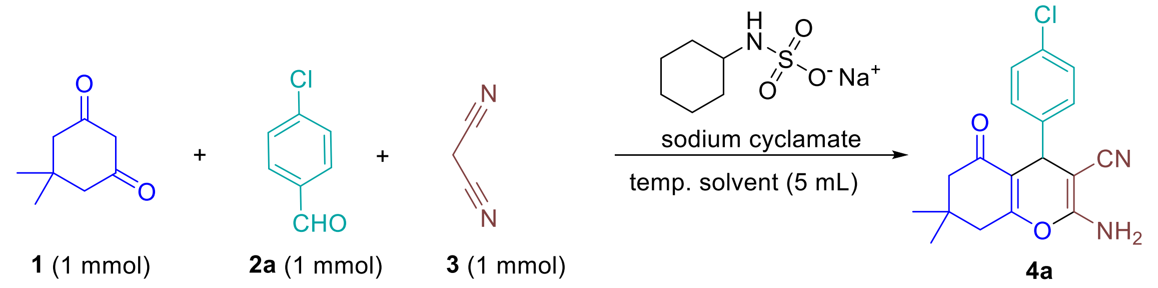
Due to the importance of these category of heterocycles, many research groups have tried to synthesize them using various catalytic methods. The synthesis of these compounds has been studied by employing catalysts such as L-ascorbic acid,[12] water extract of muskmelon fruit shell ash (WEMFSA),[13] cinchonine,[14] humic acid supported ionic liquid,[15] sodium malonate,[16] sodium citrate,[17] *N,N*-dimethylbenzylamine (DMBA),[18] potassium phthalimide,[19] potassium hydrogen phthalate,[20] 1-ethyl-3-methylimidazolium 2-hydroxybenzoate,[21] L-pyrrolidine-2-carboxylic acid sulfate,[22] 1,3-dihexylimidazolium 2-aminobenzoate,[23] choline taurinate,[24] artificial sweetener ionic liquid,[25] triethanolamine,[26] 1-methyl-3-(2-phenoxyethyl)-1*H*-imidazol-3-ium hydroxide,[27] choline chloride-pentaerythritol,[28] 1-ethyl-3-methylimidazolium acetate,[29] bovine serum albumin and NaCl (ball milling method),[30] lipase from *Thermomyces lanuginosus* immobilized on particle silica gel (TLIM),[31] tris-hydroxymethylaminomethane,[32] ammonium carbonate,[33] MgSO$_4$,[34] K$_2$CO$_3$/montmorillonite,[35] and free-ZnO nanoparticles.[36] Electrolysis using LiClO$_4$[37] or deep eutectic solvent,[38] catalyst-free using UV$_{365}$ light,[39] magnetized water,[40] aqueous ethylene glycol at 100 °C[41] as well as aqueous PEG-400[42] are among approaches for the synthesis of tetrahydrobenzo[*b*]pyrans.



Scheme 1. Three-component synthesis of tetrahydrobenzo[*b*]pyrans (**4a-n**) in the presence of sodium cyclamate

The three-component reaction of dimedone (**1**), *p*-chlorobenzaldehyde (**2a**), and malononitrile (**3**) was selected as the model reaction. The results are shown in Table 1.

Table 1. Screening the reaction conditions



Entry	Catalyst/mol%	Solvent	Temp./°C	Time/h/min	Isolated yields/%
1	-	H_2O	rt	6 h	15
2	5	H_2O	rt	6 h	30
3	10	H_2O	rt	3 h	35
4	15	H_2O	rt	2 h	40
5	20	H_2O	rt	1.5 h	50
6	20	H_2O	40	1.5 h	55
7	20	H_2O	50	1 h	62
8	20	H_2O	60	50 min	66
9	20	H_2O	70	50 min	70
10	20	H_2O	80	50 min	77
11	**20**	**H_2O**	**reflux**	**45 min**	**90**
12	20	EtOH	reflux	80 min	80
13	20	MeOH	reflux	2 h	25
14	20	$CHCl_3$	reflux	2 h	trace
15	20	CH_2Cl_2	reflux	2 h	trace
16	20	*n*-hexane	reflux	2 h	trace
17	20	solvent-free	80	2 h	60
18	-	H_2O	reflux	60 min	20

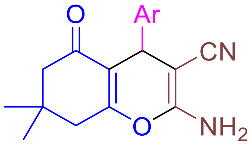
The reaction at room temperature for 6 h under the catalyst-free, furnished the expected heterocyclic product **4a** in only 15% yield (Table 1, Entry 1). On obtaining very low yield, we further investigated the

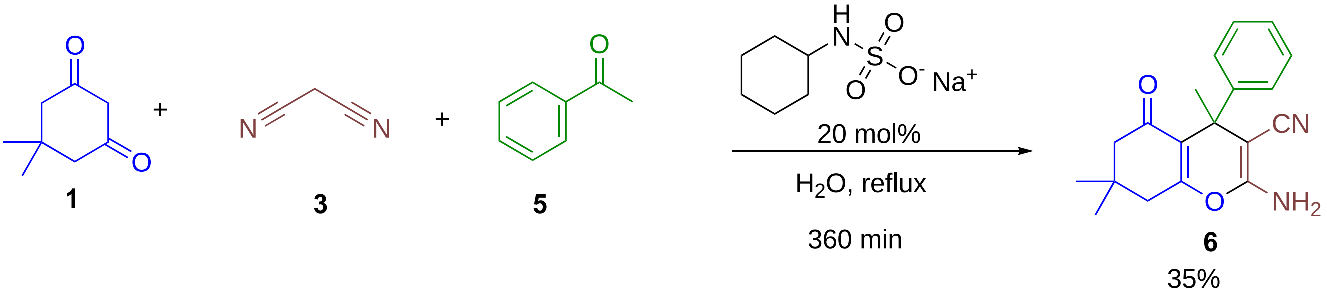
effect of catalyst on the model reaction in water at room temperature (rt). The reaction carried out using 5 mol% sodium cyclamate as the organo-catalyst at rt for 6 h in water, and the expected heterocyclic product (**4a**) was obtained in only 30% yield (Table 1, Entry 2). For the yield and reaction time to be improved, the catalyst loading was increased. When 10 mol% of an organo-catalyst was used, the product (**4a**) was achieved in 35% isolated yield for 3 h (Table 1, Entry 3). Moderate yields of the **4a** were reached as other catalyst loading (15 mol% and 20 mol%) were used (Table 1, Entries 4 and 5). The three-component reaction was also performed at various reaction temperatures (Table 1, Entries 6-11) in the presence of 20 mol% catalyst. Among them, refluxing water gave the best results (Table 1, Entry 11). Additionally, the reaction was performed in different solvents, including EtOH, MeOH, CH_2Cl_2, $CHCl_3$, and *n*-hexane using 20 mol% catalyst at reflux conditions (Table 1, Entries 12-16). A moderate yield of the corresponding heterocyclic product could be attained under solvent-free conditions (Table 1, Entry 17). The reaction was also examined under the catalyst-free conditions refluxing water. In these conditions, small amounts of the target product (**4a**) were obtained after 60 min (Table 1, Entry 18). It should be noted that a similar reaction has been reported using benzaldehyde, dimedone, and malononitrile in water under reflux conditions without using any catalyst. In that study, the reaction proceeds smoothly and only trace amounts of the corresponding heterocyclic product had been obtained.[43]
After the optimization, the scope of the aryl aldehydes was investigated (Table 2). Different substituted benzaldehydes were subjected to the optimized reaction conditions. Many substituted benzaldehydes successfully afforded the corresponding tetrahydrobenzo[*b*]pyrans in high yields.

Benzaldehydes containing electron-withdrawing groups (**2a**-**e**) reacted faster than those with electron-donating groups (**2g**-**k**) (Table 2, Entries 1-5 and 7-11). Various functional groups, including chloro-, nitro-, methyl-, and methoxy- groups, are compatible with the reaction conditions. Disubstituted benzaldehydes, such as 2,4-dichlorobenzaldehyde (**2f**) and 3,4-dimethoxybenzaldehyde (**2l**) also provided the corresponding pyrans (**4f** and **4l**) in good to excellent yields (Table 2, Entries 6 and 12). Moreover, heteroaryl aldehydes such as thiophene-2-caboxaldehyde (**2n**) can be employed under the optimized reaction conditions to generate the corresponding pyran (**4n**) (Table 2, Entry 14).

In addition to aryl/heteroaryl aldehydes, other carbonyl compounds were tried to be investigated in the three-component reaction. As an example, acetophenone (**5**) was used as a carbonyl precursor and reacted with dimedone (**1**) and malononitrile (**3**) under optimized conditions. The promising results were not obtained in terms of yield and reaction time. In this three-component reaction, 360 min after the start of the reaction, 2-amino-4,7,7-trimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**6**) was obtained in 35% yield (Scheme 2).

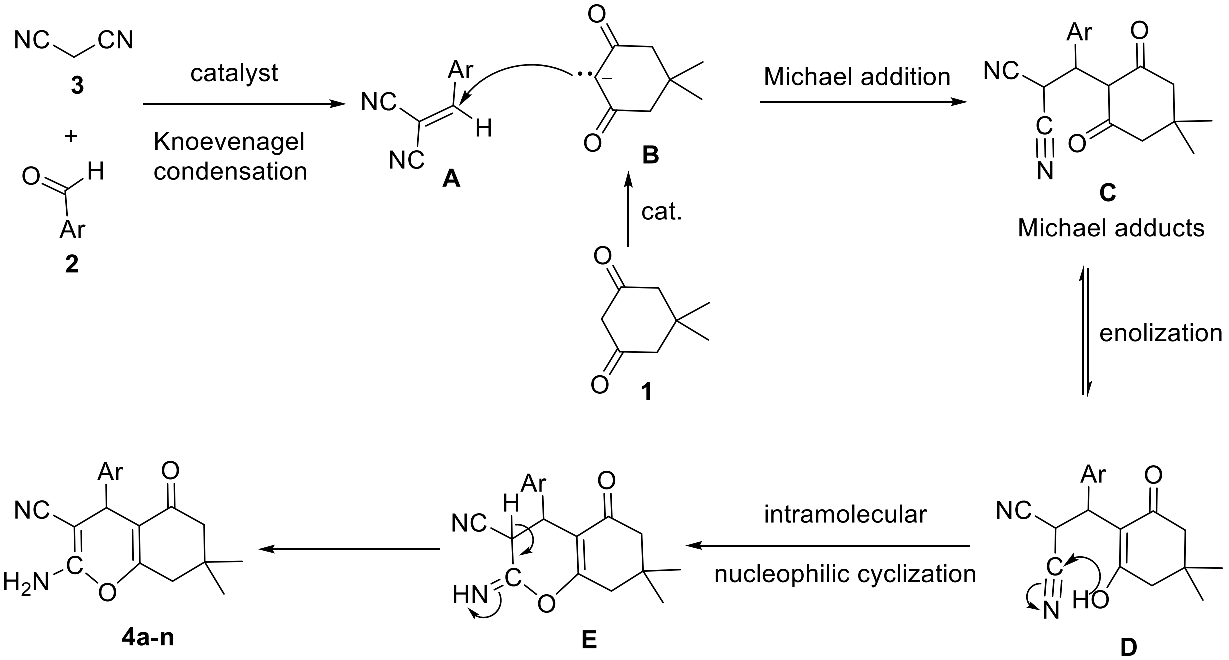
Table 2. Synthesis of tetrahydrobenzo[*b*]pyrans (**4a-n**) in the presence of 20 mol% sodium cyclamate under green conditions

Entry	Structure of heterocyclic targets  /Ar (Compound code)	Time/ min	Isolated yields/%	Mp/°C	
				Observed	Reported ref.
1	4-Cl-C_6H_4 (**4a**)	45	90	212-214	214-215[38]
2	2-Cl-C_6H_4 (**4b**)	48	89	211-214	212-214[12]
3	2-NO_2-C_6H_4 (**4c**)	35	90	215-217	222-223[38]
4	3-NO_2-C_6H_4 (**4d**)	25	92	209-211	208-210[38]
5	4-NO_2-C_6H_4 (**4e**)	20	98	185-187	183-185[18]
6	2,4-di-Cl-C_6H_3 (**4f**)	40	90	191-193	192-194[18]
7	3-HO-C_6H_4 (**4g**)	55	85	221-223	226-227[18]
8	4-HO-C_6H_4 (**4h**)	50	90	215-217	213-215[18]
9	4-Me-C_6H_4 (**4i**)	46	83	214-216	218-219[12]
10	4-MeO-C_6H_4 (**4j**)	45	80	198-199	200-202[12]
11	4-Me_2N-C_6H_4 (**4k**)	60	89	222-226	223-224[18]
12	3,4-di-MeO-C_6H_3 (**4l**)	65	78	177-179	174-176[18]
13	C_6H_5 (**4m**)	40	88	227-229	228-229[12]
14	2-Thienyl (**4n**)	50	89	217-220	215-218[18]



Scheme 2. Three-component synthesis of 2-amino-4,7,7-trimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**6**) under optimized conditions

Based on previous investigations,[19,32-34] a plausible reaction mechanism for the production of tetrahydrobenzo[*b*]pyrans (**4a-n**) is depicted in Scheme 3. Concisely, the reaction can proceeds *via* the Knoevenagel condensation between aryl/heteroaryl aldehydes (**2**) and malononitrile (**3**) to generation of the *α,β*-unsaturated nitrile compounds (**A**), which undergoes Michael attack of dimedone anion (**B**) to afford the Michael adducts (**C**). The enolization can then occur and the enol form **D** is formed. The intramolecular nucleophilic attack of enolized OH group to CN group and subsequent proton exchange lead to the formation of target compounds (**4a-n**).



Scheme 3. Possible reaction mechanism

In conclusion, the green, efficient, and simple synthesis of tetrahydrobenzo[*b*]pyrans utilizing variously aryl/heteroaryl aldehydes, dimedone, and malononitrile is described. The reactions were performed *via* treatment of reactants in the presence of sodium cyclamate as an organo-catalyst refluxing water. Good to excellent yields, no use of hazardous organic solvents for implementation of the three-component reaction, commercially available catalyst, environmentally benign, atom and pot economy, and no use of column chromatography for purification of oxygen-containing heterocyclic compounds are notable features of this process.

EXPERIMENTAL

All chemicals, unless otherwise specified, were purchased from commercial sources and were used without further purification, with the exception of liquid aldehydes, which were distilled before using. The well-known products were characterized by comparison of their physical data with those of known samples or by their spectral data. Melting points were measured on a Büchi 510 melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian-INOVA 500 MHz. FT-IR spectra were recorded on a Perkin Elmer RXI spectrometer at Damghan University using the KBr disk technique. High-resolution mass spectra (HRMS) were recorded with Agilent 6520 mass spectrometer. The development of reactions was monitored by analytical thin layer chromatography (TLC) on Merck pre-coated silica gel 60 F_{254} aluminum sheets, visualized by UV light.

General procedure for the synthesis of tetrahydrobenzo[*b*]pyrans (4a-n). A mixture of aryl/heteroaryl aldehyde (**2a-n**, 1 mmol), dimedone (**1**, 1 mmol), malononitrile (**3**, 1 mmol), and sodium cyclamate (20 mol%) in water (10 mL) was heated under reflux conditions. After completion of the reaction as indicated by TLC (*n*-hexane: EtOAc eluent system, 7:3), the mixture was cooled to rt. $CHCl_3$ was added, and the mixture was washed several times with water. The organic layers were combined, and the solvent was evaporated under reduced pressure. The precipitated products were recrystallized from EtOH to give the pure products **4a-n**.

2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4a). IR (KBr, cm^{-1}) υ 3385, 3195, 3020, 2982, 2185, 1675, 1638, 1658, 1605, 1380; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.93 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.08 (d, J = 16.2 Hz, 1H, CH_2), 2.23 (d, J = 16.3 Hz, 1H, CH_2), 2.47 (d, J = 17.5 Hz, 1H, CH_2), 2.53 (d, J = 17.5 Hz, 1H, CH_2), 4.19 (s, 1H, CH), 7.06 (s, 2H, NH_2), 7.17 (d, J = 8.4 Hz, 2H, Ar-H), 7.34 (d, J = 8.4 Hz, 2H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 27.3, 28.8, 32.2, 35.6, 50.4, 58.3, 112.8, 119.8, 128.7, 129.6, 131.6, 144.2, 158.9, 161.0, 196.1; HRMS *m/z*: [M^{+}] = 328.09.

2-Amino-4-(2-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4b). IR (KBr, cm^{-1}) υ 3390, 3330, 2985, 2195, 1665, 1658, 1375; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.98 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.09 (d, J = 16.0 Hz, 1H, CH_2), 2.24 (d, J = 16.0 Hz, 1H, CH_2), 2.47-2.57 (m, 2H, CH_2), 4.89 (s, 1H, CH), 7.19 (s, 2H, NH_2), 7.17-7.27 (m, 3H, Ar-H), 7.32-7.436 (m, 2H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 27.8, 28.8, 32.1, 33.9, 50.6, 57.4, 112.8, 118.4, 127.1, 128.5, 130.4, 130.6, 133.3, 139.5, 157.7, 163.2, 195.8; HRMS *m/z*: [M^{+}] = 328.11.

2-Amino-7,7-dimethyl-4-(2-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4c). IR (KBr, cm^{-1}) υ 3471, 3321, 3102, 2968, 1686, 1664, 1576, 1524, 1398, 1218; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.87 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 2.09 (d, J = 16.2 Hz, 1H, CH_2), 2.22 (d, J = 16.3, 1H, CH_2), 2.43-2.54 (m, 2H, CH_2), 4.92 (s, 1H, CH), 7.17 (s, 2H, NH_2), 7.34 (d, J = 7.9 Hz, 1H, Ar-H), 7.41 (t, J = 7.9 Hz, 1H, ArH), 7.65 (t, J = 7.7 Hz, 1H, ArH), 7.80 (d, J = 8.2 Hz, 1H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 27.2, 28.7, 30.4, 32.3, 50.0, 56.9, 112.8, 119.5, 124.2, 128.3, 130.7, 133.8, 139.4, 149.4, 159.6, 163.2, 196.2; HRMS *m/z*: [M^{+}] = 339.10.

2-Amino-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4d). IR (KBr, cm^{-1}) υ 3390, 3328, 3185, 2966, 2190, 1682, 1660, 1572, 1470, 1408, 1368, 1218; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.99 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.99 (d, J = 16.2 Hz, 1H, CH_2), 2.18 (d, J = 16.3, 1H, CH_2), 2.55 (m, 2H, CH_2), 4.29 (s, 1H, CH), 7.14 (s, 2H, NH_2), 7.58-7.69 (m, 2H, Ar-H), 7.97 (t, J = 2.1, 3.3 Hz, 1H, Ar-H), 8.06 (m, 1H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 27.2, 28.8, 32.3, 35.9, 50.3, 56.5, 112.3, 119.8, 122.1, 122.2, 130.4, 134.6, 147.4, 148.3, 159.1, 163.6, 196.2; HRMS *m/z*: [M^{+}] = 339.11.

2-Amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4e). IR (KBr, cm^{-1}) υ 3375, 3309, 3100, 2974, 2184, 1688, 1635, 1568, 1475, 1390, 1225; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.95 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.09 (d, J = 16.2 Hz, 1H, CH_2), 2.22 (d, J = 16.3, 1H, CH_2), 2.49-2.56 (m, 2H, CH_2), 4.32 (s, 1H, CH), 7.16 (s, 2H, NH_2), 7.43 (d, J = 8.7 Hz, 2H, Ar-H), 8.17 (d, J = 8.7 Hz, 2H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 27.4, 28.7, 32.3, 36.1, 50.3, 57.5, 112.2, 119.7, 124.1, 129.1, 146.7, 152.7, 159.0, 163.5, 196.1; HRMS *m/z*: [M$^+$] = 339.10.

2-Amino-4-(2,4-dichlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4f). IR (KBr, cm^{-1}) υ 3415, 3328, 3186, 2962, 2195, 1682, 1662, 1597, 1562, 1469, 1366, 1215; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.06 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 2.12 (d, J = 16.1 Hz, 1H, CH_2), 2.24 (d, J = 16.0, 1H, CH_2), 2.38-2.45 (m, 2H, CH_2), 4.65 (s, 1H, CH), 6.81 (s, 2H, NH_2), 7.07-7.09 (m, 1H, ArH), 7.19 (d, J = 7.8 Hz, 1H, Ar-H), 7.35 (d, J = 7.9 Hz, 1H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 27.8, 28.8, 31.9, 33.2, 40.6, 58.9, 111.4, 118.2, 128.6, 128.7, 130.1, 134.9, 135.4, 136.9, 158.5, 163.1, 196.1; HRMS *m/z*: [M$^+$] = 362.04.

2-Amino-4-(3-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4g). IR (KBr, cm^{-1}) υ 3454, 3311, 2963, 2198, 1675, 1598, 1396, 1211, 1151; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.96 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.12 (d, J = 15.9 Hz, 1H, CH_2), 2.26 (d, J = 15.9, 1H, CH_2), 2.51-2.54 (m, 2H, CH_2), 4.05 (s, 1H, CH), 6.56 (s, 2H, NH_2), 6.94 (s, 1H, ArH), 7.04-7.09 (m, 1H, Ar-H), 7.11-7.15 (m, 2H, Ar-H), 9.32 (s, OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.8, 28.9, 32.1, 35.4, 50.0, 58.4, 112.9, 113.5, 114.1, 119.8, 121.1, 129.2, 146.1, 157.3, 158.5, 162.3, 195.6; HRMS *m/z*: [M$^+$] = 310.12.

2-Amino-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4h). IR (KBr, cm^{-1}) υ 3425, 3321, 2962, 2220, 1675, 1598, 1396, 1216; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.96 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.11 (d, J = 15.9 Hz, 1H, CH_2), 2.26 (d, J = 15.9, 1H, CH_2), 2.50-2.53 (m, 2H, CH_2), 4.09 (s, 1H, CH), 6.68 (dd, J = 2.1, 7.8 Hz, 2H, Ar-H), 6.93-6.97 (m, 4H, Ar-H, NH_2), 9.29 (s, OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 27.2, 28.9, 32.13, 35.2, 50.5, 59.3, 113.7, 115.5, 120.4, 128.6, 135.7, 156.5, 158.9, 162.5, 196.2; HRMS *m/z*: [M$^+$] = 310.11.

2-Amino-7,7-dimethyl-5-oxo-4-(*p*-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4i). IR (KBr, cm^{-1}) υ 3425, 3321, 2962, 2220, 1675, 1598, 1396, 1216; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.94 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.06 (d, J = 16.2 Hz, 1H, CH_2), 2.16 (d, J = 16.3, 1H, CH_2), 2.21 (s, 3H, CH_3), 2.36 (m, 2H, CH_2), 4.20 (s, 1H, CH), 6.02 (s, 2H, NH_2), 6.98 (d, J = 7.8 Hz, 2H, Ar-H), 7.01 (d, J = 7.8 Hz, 2H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO-d_6): δ 21.0, 27.5, 28.5, 32.1, 35.4, 50.7, 60.5, 113.8, 119.8, 127.4, 129.1, 136.1, 141.4, 158.5, 161.9, 195.8; HRMS *m/z*: [M$^+$] = 308.13.

2-Amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4j). IR (KBr, cm^{-1}) υ 3375, 3350, 2965, 2198, 1715, 1640, 1505, 1381, 1252; ^{1}H NMR (500 MHz, DMSO-*d*6): δ 0.93 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.08 (d, *J* = 16.1 Hz, 1H, CH_2), 2.23 (d, *J* = 16.1, 1H, CH_2), 2.44-2.53 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 4.14 (s, 1H, CH), 6.83 (d, *J* = 8.1 Hz, 2H, Ar-H), 6.93 (s, 2H, NH_2), 7.05 (d, *J* = 8.3 Hz, 2H, Ar-H); ^{13}C NMR (125 MHz, DMSO-*d*6): δ 27.3, 28.9, 32.2, 35.2, 50.5, 55.5, 59.1, 113.5, 114.1, 120.2, 128.7, 137.3, 158.4, 158.9, 162.5, 196.0; HRMS *m/z*: [M^+] = 324.14.

2-Amino-4-(4-(dimethylamino)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4k). IR (KBr, cm^{-1}) υ 3378, 3332, 2960, 2196, 1645, 1510, 1381, 1249; ^{1}H NMR (500 MHz, DMSO-*d*6): δ 0.96 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.08 (d, *J* = 16.1 Hz, 1H, CH_2), 2.26 (d, *J* = 16.1, 1H, CH_2), 2.47-2.53 (m, 2H, CH_2), 2.88 (s, 6H, NMe_2), 4.05 (s, 1H, CH), 6.63 (s, 2H, NH_2), 6.86 (d, *J* = 8.3 Hz, 2H, Ar-H), 6.94 (d, *J* = 8.6 Hz, 2H, Ar-H); ^{13}C NMR (125 MHz, DMSO-*d*6): δ 27.2, 28.9, 32.3, 35.1, 39.4, 40.6, 50.5, 58.6, 112.2, 113.7, 119.2, 128.5, 133.6, 148.9, 156.5, 159.3, 196.2; HRMS *m/z*: [M^+] = 337.16.

2-Amino-4-(3,4-dimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4l). IR (KBr, cm^{-1}) υ 3383, 3322, 2962, 2192, 1654, 1565, 1325, 1245; ^{1}H NMR (500 MHz, DMSO-*d*6): δ 0.95 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.06 (d, *J* = 16.1 Hz, 1H, CH_2), 2.24 (d, *J* = 16.1, 1H, CH_2), 2.39-2.43 (m, 2H, CH_2), 3.75 (s, 3H, OMe), 3.82 (s, 3H, OMe), 4.65 (s, 1H, CH), 6.91 (s, 1H, Ar-H), 6.74-6.76 (m, 2H, Ar-H), 7.28 (s, 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-*d*6): δ 26.2, 28.2, 31.9, 35.1, 49.2, 53.6, 54.5, 59.2, 112.6, 113.8, 114.7, 119.7, 124.3, 136.7, 145.6, 151.8, 153.6, 167.5, 198.7; HRMS *m/z*: [M^+] = 354.14.

2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4m). IR (KBr, cm^{-1}) υ 3319, 3185, 2963, 2190, 1682, 1650, 1605, 1369, 1252, 1193; ^{1}H NMR (500 MHz, DMSO-*d*6): δ 0.96 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.11 (d, *J* = 16.2 Hz, 1H, CH_2), 2.26 (d, *J* = 16.2, 1H, CH_2), 2.49-2.52 (m, 2H, CH_2), 4.17 (s, 1H, CH), 7.01 (s, 2H, NH_2), 7.13-7.20 (m, 3H, Ar-H), 7.27-7.31 (m, 2H, Ar-H); ^{13}C NMR (125 MHz, DMSO-*d*6): δ 27.3, 28.9, 32.3, 36.0, 50.4, 58.8, 113.2, 120.2, 127.1, 127.6, 128.8, 145.2, 159.0, 163.0, 196.1; HRMS *m/z*: [M^+] = 394.13.

2-Amino-7,7-dimethyl-5-oxo-4-(thiophen-2-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4n). IR (KBr, cm^{-1}) υ 3384, 3242, 2172, 1681, 1218; ^{1}H NMR (500 MHz, DMSO-*d*6): δ 0.98 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.17 (d, *J* = 16.1 Hz, 1H, CH_2), 2.32 (d, *J* = 16.1, 1H, CH_2), 2.43-2.54 (m, 2H, CH_2), 4.53 (s, 1H, CH), 6.85 (s, 2H, NH_2), 6.92 (t, *J* = 3.5 Hz, 1H, Ar-H), 7.02 (d, *J* = 3.2 Hz, 1H, Ar-H), 7.31 (d, *J* = 5.4 Hz, 1H, Ar-H); ^{13}C NMR (125 MHz, DMSO-*d*6): δ 27.4, 28.7, 30.4, 31.9, 49.8, 58.1, 112.9, 119.7, 123.9, 124.4, 126.9, 149.3, 158.9, 162.4, 195.6; HRMS *m/z*: [M^+] = 300.08.

2-Amino-4,7,7-trimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6). This compound was synthesized using dimedone (**1**), malononitrile (**3**), and acetophenone (**5**), under optimized conditions. M.p. 215-217 ºC (Lit.[34] 216.2-216.8 ºC); IR (KBr, cm^{-1}) υ 3394, 3325, 3215, 2962, 2195, 1680, 1662, 1604, 1446, 1351, 1213; ^{1}H NMR (500 MHz, DMSO-*d*6): δ 1.00 (s, 3H, CH_3), 1.03 (s, 3H,

CH_3), 1.77 (s, 3H, CH_3), 2.09 (d, J = 15.7 Hz, 1H, CH_2), 2.19 (d, J = 15.7, 1H, CH_2), 2.51-2.55 (m, 2H, CH_2), 6.79 (s, 2H, NH_2), 7.13-7.16 (m, 1H, Ar-H), 7.25-7.29 (m, 4H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 25.9, 27.9, 28.0, 31.9, 38.2, 51.9, 55.5, 66.5, 116.5, 119.3, 126.1, 126.8, 128.2, 148.4, 156.9, 161.8, 196.2; HRMS *m/z*: [M^+] = 308.13.

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