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Simplified Approach to the Uncatalyzed Knoevenagel Condensation and Michael Addition Reactions in Water using Microwave Irradiation

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Abstract: Use of microwave irradiation in the synthesis of arylidenemalononitrile and benzopyran derivatives in water without catalyst is a clean method with high yield.

Keywords: arylidinemalononitrile, microwave, reaction in water, tetrahydrobenzo[b] pyrans

The use of microwave radiation to enhance organic reactions in environmentally benign solvents such as water, which is inexpensive and not dangerous, represents very powerful green chemical technology both from economic and synthetic points of view. This not only reduces the burden of organic solvent disposal but also enhances the rate of the reaction.

In recent years, the synthesis of compounds having benzopyran rings has attracted great interest, because they have diverse pharmacological activities.[1] In addition, a large number of benzopyran derivatives possess potent relaxant activity on blood vessels, cardiac muscle, and other smooth muscles.[2,3] On the other hand, the pyran pharmacophore is an important

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core structure of many natural products showing antibacterial, antitumor, antiallergic, antibiotic, hypolipidemic, and immunomodulating activites.[4]

Generally, the conventional synthesis of benzopyran derivatives involves acid- as well as base-catalyzed condensation of the aldehydes with the active methylene compounds in refluxing organic solvent and are plagued by the limitation of prolonged reaction times, poor yields, and side reactions of aldehydes.[5]

Knoevenagel condensation and Michael addition reactions are frequently performed in solution or without solvent under base, acid or Lewis acid catalysis.[5–9] Other methods such as dry solid supports and microwave heating were also applied.[10]

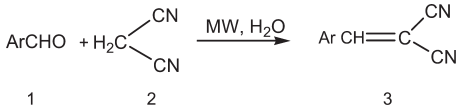
In continuation of our interest in heterocyclic compounds,[11,12] herein we describe a simple and highly efficient method for the synthesis of 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-1-benzopyran-3-carbonitrile derivatives under microwave irradiation using water as a solvent.

First, we have examined this method in the Knoevenagel condensation for the preparation of different arylidene derivatives. An equimolar quantity of the aromatic aldehyde **1** and malononitrile **2** were mixed together in water in a tightly closed tube and subjected to microwave irradiation from 0.5 to 2 min, and pure arylidenes **3** were obtained in excellent yields (Scheme 1). The results are shown in Table 1.

This encouraged us to apply these simple reaction conditions in the synthesis of benzopyran-5-one derivatives. When a mixture of arylidene **3** and dimedone **4** in water was subjected to microwave irradiation for a suitable time (2–5 min) in a tightly closed tube, the corresponding chromene derivatives **5** were produced efficiently without any catalyst in excellent yield via cyclization of intermediate A (Scheme 2). The results are shown in Table 2.

The structures of the newly synthesized products were characterized by IR, ^{1}H NMR, and mass spectroscopy. The IR spectra of compounds **5** show the NH_2 stretching vibrations in the region 3500–3200, the CN group around 2200 and the carbonyl group at 1715–1672 cm^{-1}. The ^{1}H NMR spectra of compound **5** show D_2O-exchangeable signal at δ 4.6–6.1 ppm due to NH_2 proton absorption. The proton on C-4 gives a singlet at 4.1–4.5 ppm. The methylene groups at C-6 and C-8 appear as singlet and multiplet at 2.44 and 2.28 respectively. The two methyl groups on C-7 appear as two sharp singlets at 0.96 and 1.1 ppm, indicating that protons of these two groups are not equivalent.

These results promoted us to study the one-pot, three-component reaction under the same conditions. Thus, when equimolar amounts of benzaldehyde,



Scheme 1.

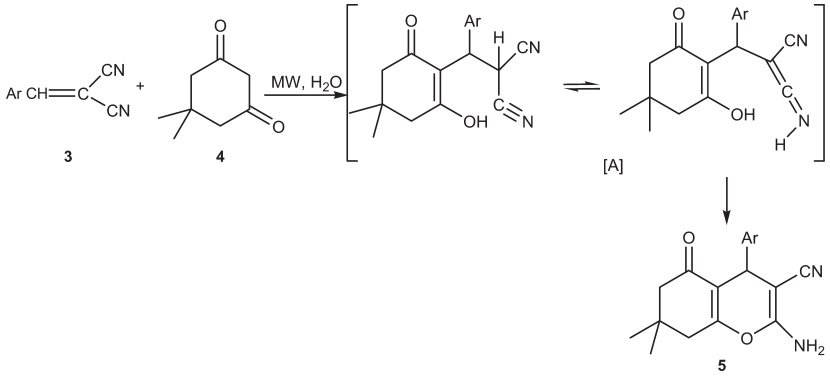
Table 1. Knoevenagel condensation between aldehydes **1** and malononitrile **2** in water using microwave irradiation

Entry	Ar	Reaction time (min)	Isolated yield (%)	Mp (°C)	Mp (°C) [Ref.]
3a	C_6H_5	2	89	82–83	83.5–84[13]
3b	2-BrC_6H_4	1	90	92–93	93–94[14]
3c	4-BrC_6H_4	1	92	159–161	159–160[14]
3d	2-ClC_6H_4	1	93	89–90	90.5–91[15]
3e	4-ClC_6H_4	1	92	161–163	162–163[16]
3f	4-FC_6H_4	2	90	125–126	126.8–127.2[15]
3g	4-$CH_3C_6H_4$	1.5	90	134–135	134–135[16]
3h	4-$CH_3OC_6H_4$	0.5	90	113–114	114.5–115[17]
3i	2-OHC_6H_4	1.5	90	159–160	160[18]
3j	4-OHC_6H_4	1	93	187–188	188–189.5[17]
3k	2-Cl-5-$NO_2C_6H_3$	1	95	118–119	119–120[14]
3l	4-OH-3-$CH_3OC_6H_3$	0.5	95	134–135	134–135[13]
3m	C_4H_3O	2	92	71–72	72[18]

malononitrile, and dimedone are mixed together in water in a tightly closed tube and subjected to microwave radiation, the corresponding pure 2-amino-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**5a**) has been obtained in a 92% yield.

Similarly, several aldehydes also reacted smoothly with malononitrile and dimedone in water under the influence of microwave, for 3–4 min (Scheme 3). The corresponding chromene derivatives **5** were produced efficiently without the use of any catalyst in good yields (90–96%). The results are outlined in Table 3.

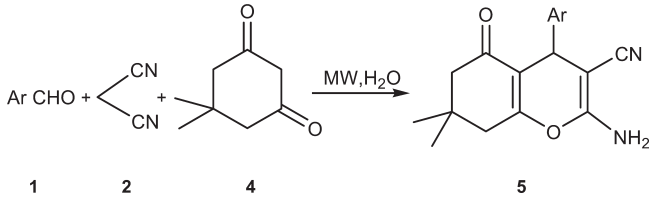
All new products were characterized by IR, ^{1}H NMR, and mass spectra.



Scheme 2.

Table 2. Michael addition reaction of **3** to **4** in water using microwave irradiation under pressure

Entry	Ar	Reaction time (min)	Isolated yield (%)	Mp (°C)	Mp (°C) [Ref.]
5a	C_6H_5	2	95	231–231	233–234[19]
5b	4-BrC_6H_4	4	92	196–198	197–198[19]
5c	4-ClC_6H_4	4	95	238–240	238–240[20]
5d	4-FC_6H_4	2	97	191–193	193[20]
5e	2,4-$(Cl)_2C_6H_3$	5	90	178–180	Not reported
5f	2,6-$(Cl)_2C_6H_3$	4	90	236–238	Not reported
5g	2-Cl-5-$NO_2C_6H_3$	3	95	172–174	Not reported
5h	4-$CH_3OC_6H_4$	4	96	194–195	194–195[20]
5i	2,4-$(CH_3O)_2C_6H_3$	5	90	180–182	181–183[20]
5j	2,4,6-$(CH_3O)_3C_6H_2$	5	97	249–251	Not reported
5k	4-OHC_6H_4	5	95	205–207	207[19]
5l	4-OH-3-$CH_3OC_6H_3$	4	99	229–231	230–231[19]
5m	$C_{10}H_7$	4	90	248–250	Not reported
5n	$C_7H_5O_2$	5	90	210–212	Not reported
5o	C_4H_3O	4	92	198–200	Not reported
5p	C_4H_3S	3	91	209–211	Not reported



Scheme 3.

Table 3. One-pot synthesis of 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile derivatives using microwave irradiation in water

Entry	Ar	Reaction time (min)	Isolated yield (%)
5a	C_6H_5	4	92
5b	4-BrC_6H_4	3	90
5d	4-FC_6H_4	3	95
5l	4-OH-3-$CH_3OC_6H_3$	4	95
5m	$C_{10}H_7$	4	96
5o	C_4H_3O	3	93

In conclusion, we have demonstrated a simple and an efficient synthetic route for arylidenemalononitrile and 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-1-chromene-3-carbonitrile derivatives in water under microwave irradiation to give the desired products in excellent yields. Compared to the classical synthetic method, this approach has the advantage of being inexpensive, simple, and environmentally benign.

EXPERIMENTAL

Apparatus and Analysis

All melting points were measured on a Gallenkamp melting-point apparatus and are uncorrected. The infrared spectra were recorded in potassium bromide disks on Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz, and ^{13}C spectra were run at 75.46 MHz in deuterated chloroform ($CDCl_3$) or dimethyl sulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses was carried out at the Microanalytical Center of Cairo University, Giza, Egypt. Microwave irradiation was carried out by a domestic microwave oven (2450 MHz, 800 W) under atmospheric pressure.

General Procedure for the Knoevenagel Condensation in Water using Microwave Irradiation

A mixture of aromatic aldehyde (**1**, 0.5 mmol) and malononitrile (**2**, 0.5 mmol) were mixed together in water (2 ml) in a tightly closed tube and subjected to microwave irradiation for the appropriate time until completion of the reaction (monitored by thin-layer chromatography TLC). The precipitate formed was filtered and washed with water to give the pure product **3** with sharp melting-point (see Table 1).

General Procedure for Synthesis of 2-Amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile Derivatives 5

Method 1 Michael Additions

An equimolar amount of arylidene (**3**, 0.5 mmol) and dimedone (**4**, 0.5 mmol) were allowed to react as described before under microwave irradiation, after filtration and washing with water, to give pure product **5** (see Table 2).

Method 2

One-Pot Synthesis of **5** using Microwave Irradiation in Water Equimolar amounts of aldehyde (**1**, 0.5 mmol), malononitrile (**2**, 0.5 mmol), and dimedone (**4**, 0.5 mmol) were mixed together in water (2 ml) in a tightly closed tube and subjected to microwave irradiation as previously described. The precipitate left after filtration and washing afforded the pure product **5** (see Table 3).

Data

2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-phenyl-4H-chromene-3-carbonitrile (5a): Mp 231–232°C. IR (KBr) ν_{max}/cm^{-1}: 3313, 3205 (NH_2), 2211 (C≡N), 1688 (C=O); ^1H NMR (300 MHz, $CDCL_3$): $\delta = 1.05$ (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 2.12 (d, 1H, $J_{AB} = 16$ Hz, H-8a), 2.29 (d, 1H, $J_{AB} = 16$ Hz, H-8b), 2.46 (s, 2H, C^6-H), 4.42 (s, 1H, C^4-H), 4.58 (s, 2H, NH_2, D_2O exchangeable), 7.25–7.38 (m, 5H, Ar-H).

2-Amino-4-(4-bromophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (5b): Mp 196–198°C. IR (KBr) ν_{max}/cm^{-1}: 3390, 3285 (NH_2), 2198 (C≡N), 1690 (C=O); ^1H NMR (300 MHz, $CDCL_3$): $\delta = 0.96$ (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.14 (d, 1H, $J_{AB} = 16$ Hz, H-8a), 2.27 (d, 1H, $J_{AB} = 16$ Hz, H-8b), 2.42 (s, 2H, C^6-H), 4.41 (s, 1H, C^4-H), 6.01 (s, 2H, NH_2, D_2O exchangeable), 7.35–7.48 (m, 4H, Ar-H).

2-Amino-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (5c): Mp 238–240°C. IR (KBr) ν_{max}/cm^{-1}: 3365, 3200 (NH_2), 2199 (C≡N), 1672 (C=O); ^1H NMR (300 MHz, $CDCL_3$): $\delta = 1.09$ (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.11 (d, 1H, $J_{AB} = 16$ Hz, H-8a), 2.23 (d, 1H, $J_{AB} = 16$ Hz, H-8b), 2.53 (s, 2H, C^6-H), 4.52 (s, 1H, C^4-H), 6.10 (s, 2H, NH_2, D_2O exchangeable), 7.15–7.38 (m, 4H, Ar-H).

2-Amino-4-(4-fluorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (5d): Mp 191–193°C. IR (KBr) ν_{max}/cm^{-1}: 3360, 3200 (NH_2), 2201 (C≡N), 1678 (C=O); ^1H NMR (300 MHz, $CDCL_3$): $\delta = 1.00$ (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 2.19 (d, 1H, $J_{AB} = 16$ Hz, H-8a), 2.28 (d, 1H, $J_{AB} = 16$ Hz, H-8b), 2.57 (s, 2H, C^6-H), 4.22 (s, 1H, C^4-H), 5.55 (s, 2H, NH_2, D_2O exchangeable), 7.17–7.28 (m, 4H, Ar-H).

2-Amino-4-(2,4-dichlorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (5e): Mp 178–180°C. IR (KBr) ν_{max}/cm^{-1}: 3388, 3267 (NH_2), 2140 (C≡N), 1710 (C=O); ^1H NMR (300 MHz, $CDCL_3$): $\delta = 1.10$ (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.15 (d, 1H, $J_{AB} = 16$ Hz, H-8a), 2.25 (d, 1H, $J_{AB} = 16$ Hz, H-8b), 2.57 (s, 2H, C^6-H), 4.21 (s, 1H, C^4-H), 5.95 (s, 2H,

NH_2, D_2O exchangeable), 7.15–7.29 (m, 3H, Ar-H). MS (m/z): 362 (M^+). Calcd. for $C_{18}H_{16}Cl_2N_2O_2$ (362.24): C, 59.52; H, 4.44; N, 7.71%. Found: C, 59.65; H, 4.00; N, 7.62%.

2-Amino-4-(2,6-dichlorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4 H-chromene-3-carbonitrile (5f): Mp 236–238°C. IR (KBr) ν_{max}/cm^{-1}: 3388, 3267 (NH_2), 2149 (C≡N), 1700 (C=O); ^1H NMR (300 MHz, $CDCL_3$): $\delta = 1.10$ (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.22 (d, 1H, $J_{AB} = 16$ Hz, H-8a), 2.29 (d, 1H, $J_{AB} = 16$ Hz, H-8b), 2.44 (s, 2H, C^6-H), 4.16 (s, 1H, C^4-H), 5.89 (s, 2H, NH_2, D_2O exchangeable), 7.17–7.31 (m, 3H, Ar-H). MS (m/z): 362 (M^+). Calcd. for $C_{18}H_{16}Cl_2N_2O_2$ (362.24): C, 59.52; H, 4.44; N, 7.71%. Found: C, 59.40; H, 4.50; N, 7.77%.

2-Amino-4-(2-chloro-5-nitrophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (5g): Mp 172–174°C. IR (KBr) ν_{max}/cm^{-1}: 3370, 3250 (NH_2), 2120 (C≡N), 1688 (C=O); ^1H NMR (300 MHz, $CDCL_3$): $\delta = 1.09$ (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 2.17–2.29 (m, 2H, C^8-H), 2.48–2.55 (m, 2H, C^6-H), 4.01 (s, 1H, C^4-H), 5.55 (s, 2H, NH_2, D_2O exchangeable), 7.23–7.39 (m, 3H, Ar-H). MS (m/z): 373 (M^+). Calcd. for $C_{18}H_{16}ClN_3O_4$ (373.79): C, 57.84; H, 4.31; N, 11.24%. Found: C, 57.96; H, 4.40; N, 11.03%.

2-Amino-4-(4-methoxyphenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (5h): Mp 194–196°C. IR (KBr) ν_{max}/cm^{-1}: 3377, 3189 (NH_2), 2156 (C≡N), 1676 (C=O); ^1H NMR (300 MHz, $CDCL_3$): $\delta = 1.03$ (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 2.23 (d, 1H, $J_{AB} = 16$ Hz, H-8a), 2.31 (d, 1H, $J_{AB} = 16$ Hz, H-8b), 2.45 (s, 2H, C^6-H), 3.79 (s, 3H, OCH_3), 4.02 (s, 1H, C^4-H), 4.95 (s, 2H, NH_2, D_2O exchangeable), 7.11–7.29 (m, 4H, Ar-H).

2-Amino-4-(2,4-dimethoxyphenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (5i): Mp 180–182°C. IR (KBr) ν_{max}/cm^{-1}: 3372, 3160 (NH_2), 2230 (C≡N), 1653 (C=O); ^1H NMR (300 MHz, $CDCL_3$): $\delta = 0.95$ (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.11 (d, 1H, $J_{AB} = 16$ Hz, H-8a), 2.29 (d, 1H, $J_{AB} = 16$ Hz, H-8b), 2.53 (s, 2H, C^6-H), 3.71 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.23 (s, 1H, C^4-H), 5.45 (s, 2H, NH_2, D_2O exchangeable), 7.01–7.37 (m, 3H, Ar-H).

2-Amino-4-(2,4,6-trimethoxyphenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (5j): Mp 249–251°C. IR (KBr) ν_{max}/cm^{-1}: 3382, 3150 (NH_2), 2235 (C≡N), 1670 (C=O); ^1H NMR (300 MHz, $CDCL_3$): $\delta = 1.01$ (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 2.11 (d, 1H, $J_{AB} = 16$ Hz, H-8a), 2.23 (d, 1H, $J_{AB} = 16$ Hz, H-8b), 2.44 (s, 2H, C^6-H), 3.75 (s, 3H, OCH_3), 3.81 (s, 6H, $2OCH_3$), 4.33 (s, 1H, C^4-H), 5.32 (s, 2H, NH_2, D_2O exchangeable), 7.21–7.35 (m, 2H, Ar-H).

2-Amino-4-(4-hydroxyphenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (5 k): Mp 205–207°C. IR (KBr) ν_{max}/cm^{-1}: 3650 (OH), 3325,3100 (NH_2), 2195 (C≡N), 1679 (C=O); ^1H NMR (300 MHz, $CDCL_3$): $\delta = 1.05$ (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.12 (d, 1H, $J_{AB} = 16$ Hz, H-8a), 2.23 (d, 1H, $J_{AB} = 16$ Hz, H-8b), 2.44 (s, 2H, C^6-H), 4.33 (s, 1H, C^4-H), 5.59 (s, 2H, NH_2, D_2O exchangeable), 7.01–7.33 (m, 4H, Ar-H), 8.1 (br s, 1H, OH, D_2O exchangeable).

2-Amino-4-(3-hydroxy-4-methoxphenyl)-5,6,7,8-tetrahydro-7,7-dimethyl -5-oxo-4H-chromene-3-carbonitrile (5l): Mp 229–231°C. IR (KBr) ν_{max}/cm^{-1}: 3440 (OH), 3310, 3172 (NH_2), 2240 (C≡N), 1680 (C=O); ^1H NMR (300 MHz, $CDCL_3$): $\delta = 1.05$ (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 2.22 (d, 1H, $J_{AB} = 16$ Hz, H-8a), 2.32 (d, 1H, $J_{AB} = 16$ Hz, H-8b), 2.50 (s, 2H, C^6-H), 3.75 (s, 3H, OCH_3), 4.52 (s, 1H, C^4-H), 5.15 (s, 2H, NH_2, D_2O exchangeable), 7.21–7.42 (m, 4H, Ar-H), 7.61 (br s, 1H, OH, D_2O exchangeable).

2-Amino-4-(naphthalen-2-yl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (5 m): Mp 248–250°C. IR (KBr) ν_{max}/cm^{-1}: 3379, 3170 (NH_2), 2236 (C≡N), 1678 (C=O); ^1H NMR (300 MHz, DMSO- d_6): $\delta = 0.96$ (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.15 (d, 1H, $J_{AB} = 16$ Hz, H-8a), 2.29 (d, 1H, $J_{AB} = 16$ Hz, H-8b), 2.55 (s, 2H, C^6-H), 4.34 (s, 1H, C^4-H), 5.51 (s, 2H, NH_2, D_2O exchangeable), 6.99–7.39 (m, 7H, Ar-H). MS (m/z): 344 (M^+). Calcd. for $C_{22}H_{20}N_2O_2$ (344.41): C, 76.72; H, 5.85; N, 8.13%. Found: C, 76.90; H, 5.80; N, 8.00%.

2-Amino-4-(benzo[d][1,3]dioxol-5-yl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (5n): Mp 210–212°C. IR (KBr) ν_{max}/cm^{-1}: 3388, 3179 (NH_2), 2240 (C≡N), 1675 (C=O); ^1H NMR (300 MHz, DMSO-d_6): $\delta = 1.06$ (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.12 (d, 1H, $J_{AB} = 16$ Hz, H-8a), 2.27 (d, 1H, $J_{AB} = 16$ Hz, H-8b), 2.49 (s, 2H, C^6-H), 4.33 (s, 1H, C^4-H), 4.59 (s, 2H, NH_2, D_2O exchangeable), 5.91 (s, 2H, CH_2) 6.69–6.74 (m, 3H, Ar-H); ^{13}C NMR (DMSO-d_6), $\delta = 195.65$ (CO), 162.32 (C-8a), 158.47 (C-2), 147.23, 145.89, 138.89, 120.34 (4C), 119.70 (CN), 112.84 (C-4a), 108.01, 107.58 (2C), 100.91 (1C)., 58.61 (C-3), 50.11 (C-6), 39.9 (C-8), 35.30 (C-4), 31.8 (C-7), 28.35, 27.00. MS (m/z): 338 (M^+). Calcd. for $C_{19}H_{18}N_2O_4$ (338.36): C, 67.44; H, 5.36; N, 8.28%. Found: C, 67.30; H, 5.40; N, 8.38%.

2-Amino-4-(fur-2-yl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (5o): Mp 198–200°C. IR (KBr) ν_{max}/cm^{-1}: 3374, 3146 (NH_2), 2235 (C≡N), 1679 (C=O); ^1H NMR (300 MHz, $CDCL_3$): $\delta = 1.06$ (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 2.17 (d, 1H, $J_{AB} = 16$ Hz, H-8a), 2.29 (d, 1H, $J_{AB} = 16$ Hz, H-8b), 2.46 (s, 2H, C^6-H), 4.58 (s, 1H, C^4-H), 4.79 (s, 2H, NH_2, D_2O exchangeable), 6.18–7.27 (m, 3H, furyl-H); ^{13}C

NMR (DMSO-d_6), $\delta = 195.22$ (CO), 159.12 (C-8a), 158.98 (C-2), 150.01, 140.87, (2C), 119.80 (CN), 112.89 (C-4a), 111.00, 108.25 (2C), 60.10 (C-3), 49.23 (C-6), 39.88 (C-8), 37.24 (C-4), 32.69 (C-7), 28.18, 27.45. MS (m/z): 284 (M^+). Calcd. for $C_{16}H_{16}N_2O_3$ (284.31): C, 67.59; H, 5.67; N, 9.85%. Found: C, 67.39; H, 5.72; N, 10.00%.

2-Amino-4-(thien-2-yl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (5p): Mp 209–211°C. IR (KBr) ν_{max}/cm^{-1}: 3369, 3146 (NH_2), 2235 (C≡N), 1685 (C=O); ^{1}H NMR (300 MHz, DMSO- d_6): $\delta = 1.06$ (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.15 (d, 1H, $J_{AB} = 16$ Hz, H-8a), 2.24 (d, 1H, $J_{AB} = 16$ Hz, H-8b), 2.48 (s, 2H, C^6-H), 4.51 (s, 1H, C^4-H), 4.80 (s, 2H, NH_2, D_2O exchangeable), 6.67–7.02 (m, 3H, thienyl-H); ^{13}C NMR (DMSO-d_6), $\delta = 193.15$ (CO), 160.02 (C-8a), 159.05 (C-2), 140.81, 127.25, 126.99, 122.00 (4C), 119.71 (CN), 111.23 (C-4a), 59.00 (C-3), 50.56 (C-6), 39.42 (C-8), 36.31 (C-4), 31.8 (C-7), 28.15, 27.06. MS (m/z): 300 (M^+). Calcd. for $C_{16}H_{16}N_2O_2S$ (300.38): C, 63.98; H, 5.37; N, 9.33; S, 10.68%. Found: C, 64.19; H, 5.30; N, 9.30; S, 10.56%.

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