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Short communication

A facile one-pot green synthesis and antibacterial activity of 2-amino-4*H*-pyrans and 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes

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ABSTRACT

A facile one-pot expeditious synthesis of 2-amino-4*H*-pyrans and 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes has been described under solvent-free conditions using magnesium oxide as a catalyst in very good yields. The reaction catalyst, magnesium oxide was reused and recycled without any loss of activity and product yield. All the synthesized compounds were screened for in vitro antibacterial activity, and compounds **3a**, **3b**, **3f**, **4b**, **4c**, **4d**, **4e** and **4g** showed complete inhibition of bacterial growth at 128 μg/mL or less and the rest of the compounds exhibited incomplete inhibition.

1. Introduction

The development of environmentally benign, efficient and economical methods for the synthesis of biologically interesting compounds remains a significant challenge in synthetic chemistry. The chemical industry is one of the major contributors to environment pollution, owing to the use of hazardous chemicals and in particular, large amounts of flammable, volatile and often toxic organic solvents. Green chemistry emphasizes the need for environmentally clean synthesis, which involves improvement in selectivity, high atom efficiency, elimination of hazardous reagents, and easy separation with recovery and reuse of reagents. As a result, volatile organic solvents are being replaced by non-toxic, non-volatile media such as ionic liquids, polyethylene glycol, and water. Alternatively, the reactions are carried out under solvent-free conditions. The phenomenal response, as evident from the growing number of publications, in order to achieve this goal is overwhelming. It is more advantageous to carry out reactions under solvent-free conditions [1]. Particularly, in recent years, reactions under solvent-free conditions have continuously attracted the attention of researchers both from academia and industry. This is due to the fact that without solvent, reactions usually need shorter reaction time, simpler reactors, and require simple and efficient workup procedures.

Multicomponent reactions, on the other hand, have become very popular in the discovery of biologically active novel compounds due to its simple experimentation, atom economy and high yields of the products [2].

Heterogeneous catalysts are advantageous over conventional homogeneous catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be reused after activation, thereby making the process economically viable. Among the heterogeneous basic catalysts, magnesium oxide is a versatile material used as catalyst for several base-catalyzed organic transformations [3], toxic waste remediation [4], and as additive in refractory, paint, and superconductor products [5,6].

2-Amino-4*H*-pyran derivatives represent an important class of compounds. They are often used in cosmetics and pigments, and utilized as potentially biodegradable agrochemicals [7–9]. Polyfunctionalized 4*H*-pyrans also constitute a structural unit of many natural products [10,11] and biologically interesting compounds which possess various pharmacological activities [12], such as antiallergic [8], antitumor [13] antibacterial [14–18]. 4*H*-Pyran derivatives are also potential calcium channel antagonists [19]

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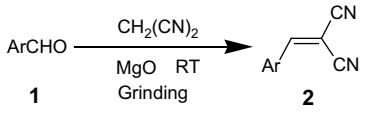


Scheme 1.

which are structurally similar to biologically active 1,4-dihydropyridines.

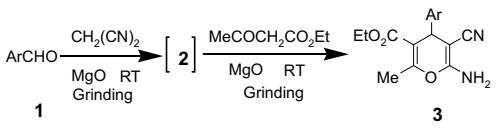
Earlier 2-amino-4*H*-pyrans were synthesized by the cyclization of arylidenemalononitriles with β-dicarbonyl compounds in the presence of base such as piperidine [20], morpholine, pyridine [21] triethylamine [22,23], sodium methoxide, or 1,1,3,3-tetramethylguanidine. Most of these methods also involve use of volatile solvents, require longer reaction time (~12 h) and difficult to recover catalysts. In view of our recent success with magnesium oxide [24] and interesting antibacterial activity [14–18] of 2-amino-pyrans, we report herein one-pot synthesis of these compounds using sequential reactions of aromatic aldehyde, malononitrile and β-dicarbonyl compounds in the presence of magnesium oxide as a catalyst under solvent-free condition at room temperature. The synthesized compounds were screened for in vitro antibacterial activity against gram negative and gram positive standard strains of bacteria using Broth Microdilution MIC (Minimum Inhibitory Concentration) method and zone of inhibition assay [25].

2. Results and discussion

2.1. Chemistry

In our attempts to develop a facile one-pot solvent-free protocol, initially we focused on the efficient condensation of benzaldehyde (1.0 mmol) and malononitrile (1.0 mmol) at room temperature with mechanochemical mixing. This provided only traces of **2** even with extended grinding. However, continuously grinding the mixture of benzaldehyde (1 mmol) and malononitrile (1 mmol) at room temperature in the presence of MgO (4 mg, 0.1 mmol) turned out to be successful with almost quantitative formation of **2** within 5 min (Scheme 1).

Subsequent addition of ethylacetoacetate (1 mmol) to the reaction mixture with vigorous grinding afforded the 2-amino-4*H*-pyrans **3a** in poor yield. However, addition of another 16 mg (0.4 mmol) of MgO led to the formation of **3a** in good yield along with traces of unreacted benzylidenemalononitrile and ethylacetoacetate. Further, addition of a few drops of water and grinding the reaction mixture at room temperature led to rapid (15 min) formation of pure 2-amino-4*H*-pyran **3a** (Scheme 2). After the completion of reaction, the residue was taken into methanol and filtered. The crude product is obtained by evaporating the filtrate. Recrystallization of the crude product led to the isolation of crystalline solid **3a** in 77% yield. The IR spectrum of **3a** exhibited bands at 3412, 3334, 2199, 1693 cm^{-1} indicating the presence of NH_2, C≡N and C═O functionalities, respectively. The ^1H NMR spectrum evidenced a characteristic singlet at δ 4.43 due to C-4H. The spectral data and physical properties of **3a** were found to be in agreement with the literature [26].

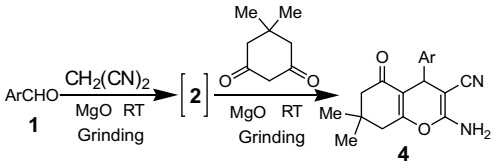


Scheme 2.

Table 1
Synthesis of 2-amino-4*H*-pyrans **3a–h** and tetrahydro-4*H*-chromenes **4a–g**.

Compd.[a]	Ar	Yield[b] [%]	M.p. [°C]
3a	C_6H_5	77	195–196
3b	3-ClC_6H_4	94	153–156
3c	4-ClC_6H_4	79	172–174
3d	4-$CH_3C_6H_4$	87	177–179
3e	3-OHC_6H_4	88	164–165
3f	4-$OCH_3C_6H_4$	89	142–144
3g	4-$NO_2C_6H_4$	86	180–183
3h	3-$NO_2C_6H_4$	92	182–183
4a	C_6H_5	75	226–228
4b	4-$OCH_3C_6H_4$	86	197–199
4c	3-$NO_2C_6H_4$	83	201–205
4d	4-$NO_2C_6H_4$	78	175–176
4e	4-ClC_6H_4	86	202–203
4f	4-$CH_3C_6H_4$	73	209–211
4g	3-OHC_6H_4	75	224–226

[a] Compounds were characterized by their spectral data (IR and ^1H NMR).
[b] Yields refer to pure isolated products.

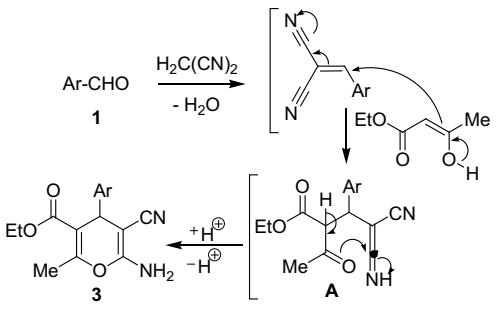


Scheme 3.

Encouraged by this successful three-component reaction, synthesis of diverse 2-amino-4*H*-pyrans **3b–h** was undertaken. The aromatic aldehydes bearing electron-withdrawing and electron-donating groups were found to be equally effective to produce 2-amino-4*H*-pyrans **3b–h** in very good yields (Table 1). The scope of this one-pot reaction was further extended by replacing ethylacetoacetate with 5,5-dimethyl-cyclohexane-1,3-dione (Scheme 3) and various 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes **4a–g** were prepared (Table 1).

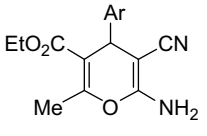
The catalyst can be recycled by a simple protocol. After the completion of reaction, MgO was removed by filtration, washed with methanol and dried at the pump. The recovered catalyst was reused for second and third consecutive cycles without any significant loss in catalytic activity (77%, 77% and 76%, respectively, for the three consecutive cycles in the synthesis of **3a**).

Mechanistically, the initial condensation of aromatic aldehyde with malononitrile in the presence of MgO leads to the formation of arylidenemalononitrile **2** with the loss of a water molecule [27]. The nucleophilic addition of the enolizable ethylacetoacetate to arylidenemalononitrile **2** followed by intramolecular cyclization of the resulting species A produce the 2-amino-4*H*-pyrans **3** (Scheme 4).

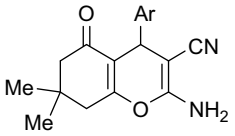


Scheme 4.

Table 2
MIC (μg/mL) and the zone of inhibition (in mm) values of various 2-amino-4*H*-pyrans (**3a**–**h**) and tetrahydro-4*H*-chromenes (**4a**–**g**) in gram positive and gram negative bacteria.



3a-h



4a-g

Compd.	Ar	*E. coli*			*S. aureus*			*P. putida*		
		MIC (μg/mL)	Zone of inhibition (mm)		MIC (μg/mL)	Zone of inhibition (mm)		MIC (μg/mL)	Zone of inhibition (mm)	
			128 μg/mL	64 μg/mL		128 μg/mL	64 μg/mL		128 μg/mL	64 μg/mL
3a	C_6H_5	64	>3	>3	128	>3	<1	128	>3	<1
3b	3-ClC_6H_4	128	>3	<1	128	>3	<1	128	>3	<1
3c	4-ClC_6H_4	>128	<1	<1	>128	<1	<1	>128	<1	<1
3d	4-$CH_3C_6H_4$	>128	<1	<1	>128	<1	<1	>128	<1	<1
3e	3-OHC_6H_4	>128	<1	<1	>128	<1	<1	128	>3	<1
3f	4-$OCH_3C_6H_4$	128	>3	<1	128	>3	<1	128	>3	<1
3g	4-$NO_2C_6H_4$	>128	<1	<1	>128	<1	<1	>128	<1	<1
3h	3-$NO_2C_6H_4$	>128	<1	<1	>128	<1	<1	>128	<1	<1
4a	C_6H_5	>128	>2	<1	>128	<1	<1	>128	>2	>2
4b	4-$OCH_3C_6H_4$	64	>3	>3	>128	>2	>2	128	>3	>2
4c	3-$NO_2C_6H_4$	128	>3	<1	128	>3	>2	128	>3	<1
4d	4-$NO_2C_6H_4$	64	>3	>3	64	>3	>3	128	>3	<1
4e	4-ClC_6H_4	128	>3	>2	128	>3	>2	128	>3	>2
4f	4-$CH_3C_6H_4$	>128	>2	>2	>128	>2	>2	128	>3	>2
4g	3-OHC_6H_4	128	>3	>2	>128	>2	>2	64	>3	>3
Standard	Ampicillin	16	>5	>5	16	>5	>5	>256	0	0

Similar reaction mechanism applies for the synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes **4a**–**g**.

2.2. Antibacterial activity

The synthesized compounds were screened for their antibacterial activity against three bacterial strains, namely *Escherichia coli* (MTCC 41), *Staphylococcus aureus* (MTCC 1144) and *Pseudomonas putida* (MTCC 1072). The non-pathogenic strain *P. putida* is ampicillin resistant and is closely related to the pathogenic strain *Pseudomonas aeruginosa.* The antimicrobial activity assay (MIC and the zone of inhibition) was performed for the compounds at 0.5, 1.0, 2.0, 4.0, 8.0, 16.0, 32.0, 64.0 and 128.0 μg/mL concentrations. The MIC assay is to test the sensitivity of microorganisms to an antimicrobial agent. A set of tubes with multiple concentrations of compounds was prepared in growth medium (LB broth). The tubes were then inoculated with the microorganisms, incubated for 12–16 h, and examined for growth of bacteria. Broth tubes that appear turbid are indicative of bacterial growth while tubes that remain clear indicate no growth. Growth seems to diminish as the concentration of some compounds increase, and eventually appeared to reduce at higher concentrations.

The zone of inhibition assay is to find the extent of sensitivity of microorganisms to the organic compound being tested. This antimicrobial activity assay was performed for the compounds at different concentrations. The bacterial isolate was inoculated uniformly on to the surface of an agar plate. A filter disk impregnated with a known amount of compound was applied to the surface of the plate and the compound was allowed to diffuse into the adjacent medium. A bacterial lawn appeared on the plate after incubation for 16 h. The antimicrobial activity of the compound was recorded as the size of zone inhibition. The size of the zone obtained at a particular concentration is directly proportional to the sensitivity of the organism to the compound and thus the zone of inhibition in the disk diffusion test is inversely related to the MIC.

The results of antibacterial studies are given in Table 2. Among the synthesized **3a**–**h** and **4a**–**g**, the compounds **3a**, **3b**, **3f**, **4b**, **4c**, **4d**, **4e** and **4g** were showing complete inhibition at 128 μg/mL or less. The rest of the compounds showed incomplete inhibition.

Among the 2-amino-4*H*-pyrans (**3a**–**h**), the compound **3a** completely inhibited *E. coli* at 64 μg/mL but it could inhibit *S. aureus* and *P. putida* at 128 μg/mL. Introducing a methoxy group at *para* position of the C-4 aryl ring (**3f**) made it relatively ineffective towards *E. coli* but found to be active against other two strains. The compound **3b** with a chloro group at the *meta* position of C-4 aryl ring exhibited activity similar to the compound **3f**. Any other substitution at the positions 3 and 4 of the C-4 aryl ring retarded the efficiency of the resulting compounds. The compound **4a** resulted in decreased activity when compared to **3a** but placing a nitro group at *para* position of the C-4 aryl ring on 2-amino-4*H*-chromene resulted in a potent compound **4d**, when compared to all other compounds, especially with its counterpart **3g**. Placing a hydroxy group at *meta* position of the C-4 aryl ring in 2-amino-4*H*-pyran resulted in **3e**, which was active towards *P. putida* and the activity is enhanced when positions 5 and 6 of the 2-amino-4*H*-pyran were fused to give **4g**. Further, the MIC of **4g** towards *P. putida* is 64 μg/mL whereas ampicillin was inactive upto 256 μg/mL. Though a possible explanation for this cause is unclear, fusing the positions 5 and 6 of the 4*H*-pyran ring resulted in compounds **4b**–**g** with the activity increased substantially.

3. Conclusion

We have developed a facile, convenient and environmentally benign one-pot synthesis of 2-amino-4*H*-pyrans and 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes under solvent-free conditions using magnesium oxide as a recyclable catalyst in good yields. The antibacterial assay of the compounds **3a**, **3b**, **3f**, **4b**, **4c**, **4d**, **4e** and **4g** showed complete inhibition of bacterial growth at 128 μg/mL or less and the rest of the compounds exhibited incomplete inhibition. The noteworthy compound **4d** proved to be active in terms of overall potency and the compound **4g** showed selective inhibition towards *P. putida*. Further modifications can be easily imparted by altering any of the three components, *viz.* aromatic aldehydes, α-cyano active methylene compounds and enolisable β-diketones.

4. Experimental

All the laboratory grade reagents were obtained commercially. Melting points were recorded on Buchi530 melting point apparatus and are uncorrected. Infrared spectra were recorded on Shimadzu IRPrestige-21 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance II 400 NMR spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in parts per million (δ) and coupling constants (J) in Hz. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} precoated aluminium sheets.

*4.1. General procedure for the synthesis of 2-amino-4H-pyran derivatives (**3a–h**) and 2-amino-4H-chromenes (**4a–g**)*

A mixture of aromatic aldehyde (1.0 mmol), malononitrile (1.0 mmol) and MgO (0.5 mmol) was grinded at room temperature till it formed a solid (10 min). Ethylacetoacetate (1.0 mmol) or 5,5-dimethyl-cyclohexane-1,3-dione (1.0 mmol) and 2–3 drops of water were added to the mixture and continued grinding till it formed a solid (15 min). On completion of the reaction, as indicated by TLC, the solid was dissolved in methanol and filtered. The solvent was distilled off under vacuum and residue so obtained was recrystallized from methanol.

*4.1.1. Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate (**3a**)*

M.p. 195–196 °C (lit. 194–196 °C) [26]. IR (KBr, ν cm^{-1}): 3412 (NH_2), 3334 (NH_2), 2199 (C≡N), 1693 (C=O); ^{1}H NMR ($CDCl_3$): δ 7.31–7.19 (m, 5H), 4.44 (s, 2H), 4.43 (s, 1H), 4.06–4.00 (m, 2H), 2.38 (s, 3H), 1.09 (t, J = 7.12 Hz, 3H).

*4.1.2. Ethyl 6-amino-4-(3-chlorophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate (**3b**)*

M.p. 153–156 °C. IR (KBr, ν cm^{-1}): 3400 (NH_2), 3329 (NH_2), 2191 (C≡N), 1693 (C=O), 779 (C–Cl); ^{1}H NMR ($CDCl_3$): δ 7.28–7.12 (m, 4H), 4.55 (s, 2H), 4.40 (s, 1H), 4.08–4.00 (m, 2H), 2.35 (s, 3H), 1.09 (t, J = 7.12 Hz, 3H).

*4.1.3. Ethyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate (**3c**)*

M.p. 172–174 °C (lit. 175–177 °C) [28]. IR (KBr, ν cm^{-1}): 3410 (NH_2), 3333 (NH_2), 2193 (C≡N), 1693 (C=O), 760 (C–Cl). ^{1}H NMR (DMSO-d_6): δ 7.25 (d, J = 8 Hz, 2H), 7.15 (d, J = 8 Hz, 2H), 5.93 (s, 2H), 4.38 (s, 1H), 4.06–4.00 (m, 2H), 2.36 (s, 3H), 1.12 (t, J = 7.16 Hz, 3H).

*4.1.4. Ethyl 6-amino-5-cyano-2-methyl-4-(4-methylphenyl)-4H-pyran-3-carboxylate (**3d**)*

M.p. 177–179 °C. IR (KBr, ν cm^{-1}): 3414 (NH_2), 3336 (NH_2), 2202 (C≡N), 1693 (C=O). ^{1}H NMR (DMSO-d_6): δ 7.07 (s, 4H), 5.80 (s, 2H), 4.35 (s, 1H), 4.03–4.01 (m, 2H), 2.35 (s, 3H), 2.30 (s, 3H), 1.12 (t, J = 7.12 Hz, 3H).

*4.1.5. Ethyl 6-amino-5-cyano-4-(3-hydroxyphenyl)-2-methyl-4H-pyran-3-carboxylate (**3e**)*

M.p. 164–165 °C. IR (KBr, ν cm^{-1}): 3414 (NH_2), 3336 (NH_2), 2202 (C≡N), 1693 (C=O); ^{1}H NMR (DMSO-d_6): δ 8.85 (s, 1H), 7.07 (t, J = 8 HZ, 1H), 6.67–6.64 (m, 3H), 5.74 (s, 2H), 4.31 (s, 1H), 4.05–4.02 (m, 2H), 2.35 (s, 3H), 1.13 (t, J = 7.12 Hz, 3H).

*4.1.6. Ethyl 6-amino-5-cyano-4-(4-methoxyphenyl)-2-methyl-4H-pyran-3-carboxylate (**3f**)*

M.p. 142–144 °C (lit. 137–139 °C) [28]. IR (KBr, ν cm^{-1}): 3405 (NH_2), 3323 (NH_2), 2210 (C≡N), 1693 (C=O); ^{1}H NMR (DMSO-d_6): δ 6.96 (d, J = 14.6 Hz, 2H), 6.66 (d, J = 14.6 Hz, 2H), 5.53 (s, 2H), 4.21 (s, 1H), 3.92–3.84 (m, 2H), 3.61 (s, 3H), 2.19 (s, 3H), 1.12 (t, J = 7.16 Hz, 3H).

*4.1.7. Ethyl 6-amino-5-cyano-2-methyl-4-(4-nitrophenyl)-4H-pyran-3-carboxylate (**3g**)*

M.p. 180–183 °C. IR (KBr, ν cm^{-1}): 3408 (NH_2), 3331 (NH_2), 2198 (C≡N), 1693 (C=O), 1520 (N=O); ^{1}H NMR (DMSO-d_6): δ 8.15 (d, J = 4.8 Hz, 2H), 7.39 (d, J = 4.8 Hz, 2H), 6.20 (s, 2H), 4.52 (s, 1H), 4.04–4.02 (m, 2H), 2.41 (s, 3H), 1.11 (t, J = 7.08 Hz, 3H).

*4.1.8. Ethyl 6-amino-5-cyano-2-methyl-4-(3-nitrophenyl)-4H-pyran-3-carboxylate (**3h**)*

M.p. 182–183 °C (lit. 184 °C) [29]. IR (KBr, ν cm^{-1}): 3402 (NH_2), 3327 (NH_2), 2191 (C≡N), 1693 (C=O), 1531 (N=O). ^{1}H NMR (DMSO-d_6): δ 8.10–8.03 (m, 2H), 7.61–7.49 (m, 2H), 5.98 (s, 2H), 4.55 (s, 1H), 4.08–4.01 (m, 2H), 2.41 (s, 3H), 1.12 (t, J = 7.12 Hz, 3H).

*4.1.9. 2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-phenyl-4H-chromene-3-carbonitrile (**4a**)*

M.p. 226–228 °C (lit. 233–234 °C) [30]. IR (KBr, ν cm^{-1}): 3394 (NH_2), 3325 (NH_2), 2199 (C≡N), 1676 (C=O), 1215 (C–O). ^{1}H NMR (DMSO-d_6): δ 7.27–7.18 (m, 5H), 4.50 (s, 2H), 4.40 (s, 1H), 2.45 (s, 2H), 2.25 (H-6a, J_{AB} = 16 Hz), 2.19 (H-6b, J_{AB} = 16 Hz), 1.11 (s, 3H), 1.04 (s, 3H).

*4.1.10. 2-Amino-5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (**4b**)*

M.p. 197–199 °C. IR (KBr, ν cm^{-1}): 3379 (NH_2), 3325 (NH_2), 2195 (C≡N), 1682 (C=O), 1211 (C–O); ^{1}H NMR (DMSO-d_6): δ 7.14 (d, J = 8.68 Hz, 2H), 6.80 (d, J = 8.68 Hz, 2H), 5.60 (s, 2H), 4.30 (s, 1H), 3.76 (s, 3H), 2.45 (s, 2H), 2.23 (H-6a, J_{AB} = 16 Hz), 2.16 (H-6b, J_{AB} = 16 Hz), 1.10 (s, 3H), 1.02 (s, 3H).

*4.1.11. 2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-4H-chromene-3-carbonitrile (**4c**)*

M.p. 201–205 °C. IR (KBr, ν cm^{-1}): 3437 (NH_2), 3333 (NH_2), 2187 (C≡N), 1674 (C=O), 1211 (C–O); ^{1}H NMR (DMSO-d_6): δ 8.06–8.04 (m, 2H), 7.65–7.62 (m, 1H), 7.52–7.48 (m, 1H), 6.30 (s, 2H), 4.47 (s, 1H), 2.52 (s, 2H), 2.26 (H-6a, J_{AB} = 16 Hz), 2.17 (H-6b, J_{AB} = 16 Hz), 1.12 (s, 3H), 1.03 (s, 3H).

*4.1.12. 2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-4H-chromene-3-carbonitrile (**4d**)*

M.p. 175–176 °C (lit. 174–176 °C) [30]. IR (KBr, ν cm^{-1}): 3518 (NH_2), 3375 (NH_2), 2187 (C≡N), 1682 (C=O), 1215 (C–O); ^{1}H NMR (DMSO-d_6): δ 8.14 (d, J = 8.72 Hz, 2H), 7.43 (d, J = 8.72 Hz, 2H), 6.07 (s, 2H), 4.47 (s, 1H), 2.50 (s, 2H), 2.26 (H-6a, J_{AB} = 16 Hz), 2.17 (H-6b, J_{AB} = 16 Hz), 1.12 (s, 3H), 1.02 (s, 3H).

*4.1.13. 2-Amino-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile(**4e**)*

M.p. 202–203 °C (lit. 218 °C) [30]. IR (KBr, ν cm^{-1}): 3379 (NH_2), 3325 (NH_2), 2187 (C≡N), 1674 (C=O), 1215 (C–O); ^{1}H NMR (DMSO-d_6): δ 7.24 (d, J = 8.52 Hz, 2H), 7.18 (d, J = 8.52 Hz, 2H), 5.79 (s, 2H), 4.33 (s, 1H), 2.46 (s, 2H), 2.24 (H-6a, J_{AB} = 16 Hz), 2.16 (H-6b, J_{AB} = 16 Hz), 1.11 (s, 3H), 1.02 (s, 3H).

*4.1.14. 2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-(4-methylphenyl)-4H-chromene-3-carbonitrile (**4f**)*

M.p. 209–211 °C. IR (KBr, ν cm^{-1}): 3398 (NH_2), 3329 (NH_2), 2195 (C≡N), 1672 (C=O), 1211 (C–O); ^{1}H NMR (DMSO-d_6): δ 7.11–7.05 (m, 4H), 5.60 (s, 2H), 4.30 (s, 1H), 2.46 (s, 2H), 2.28 (s, 3H), 2.19 (H-6a, J_{AB} = 16 Hz), 2.16 (H-6b, J_{AB} = 16 Hz), 1.10 (s, 3H), 1.03 (s, 3H).

*4.1.15. 2-Amino-5,6,7,8-tetrahydro-4-(3-hydroxyphenyl)-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile(**4g**)*

M.p. 224–226 °C. IR (KBr, ν cm^{-1}): 3452 (NH_2), 3414 (NH_2), 2199 (C≡N), 1651 (C═O), 1215 (C–O); ^{1}H NMR (DMSO-d_6): δ 8.91 (s, 1H), 7.05 (t, $J = 7.76$ Hz, 1H), 6.63 (m, 3H), 6.11 (s, 2H), 4.20 (s, 1H), 2.47 (s, 2H), 2.23 (H-6a, $J_{AB} = 16$ Hz), 2.16 (H-6b, $J_{AB} = 16$ Hz), 1.11 (s, 3H), 1.05 (s, 3H).

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