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Research Article – Chemistry

Grindstone Chemistry: An Efficient and Green Synthesis of 2-Amino-4*H*-benzo[*b*]pyrans

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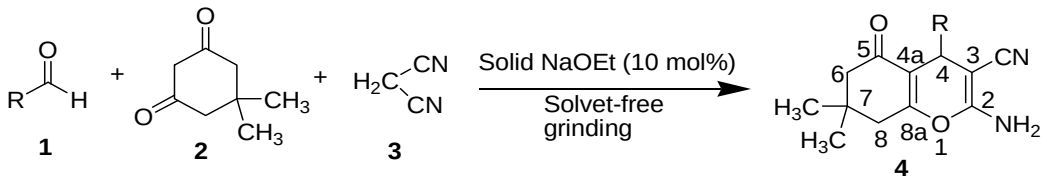
Abstract

A single step, mild, environmentally friendly green method has been developed for the synthesis of physiologically active 2-amino-4*H*-benzo[*b*]pyrans employing solid sodium ethoxide as catalyst under solvent free conditions at room temperature *via* grinding. The procedure is efficient, time saving and gives high yield. The structures and purity of these compounds were confirmed by elemental and spectral analysis (IR, ^{1}H-NMR and ^{13}C-NMR).



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Key words: Multicomponent reaction**,** Solvent-free synthesis**,** Grinding**,** Tetrahydrobenzo[*b*]pyrans

Introduction

Development of less hazardous synthetic methodologies for organic reactions is one of the most sought after problems in contemporary research. For synthesis of complex molecules employing environment friendly green methods, reactions conducted in aqueous media have received much attention [1]. But there have been associated drawbacks as well; primarily owing to very poor ability of water in solubilizing organic reactants making the reaction mixture heterogeneous [2]. This difficulty can be overcome using phase transfer catalysts but this will cause the process to be more expensive [2]. Reactions in dry media or under solvent free condition are especially appealing, as they provide an opportunity to work in an open vessel, thus avoiding the risk of high internal pressure development and with the possibility of up-scaling the reaction to the larger scale [3]. Recently, grindstone chemistry has been shown to be a highly viable green and rapid method for the synthesis of organic compounds without the complicacies associated with the use of different solvents, including water [4]. The proposed technique does not require external heating, leading to energy efficient synthesis and may be regarded as more economical and ecologically favorable procedure in chemistry [5]. Toda and co-workers showed that many of the exothermic organic reactions can be performed in good yield using mortar and pestle only [4]. Grindstone chemistry has been shown to be a very useful method for desktop as well as kilogram scale synthesis [4].

Multicomponent reactions, on the other hand, have become very popular in the discovery of biologically active novel compounds due to its

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simple experimentation, atom economy and high yield of the products [6].

4*H*-pyran and its derivatives occur frequently in numerous natural compounds [7], exhibiting important biological activities and find wide applications in pharmaceutical use such as antiallergic, antitumor and antibacterial agents [8-10]. Furthermore, these compounds exhibit unique pharmacological activities including treatment of human inflammatory TNF-mediated diseases, Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease and Parkinson's disease [11, 12]. Moreover, functionally substituted 4*H*-pyrans have played increasing role in synthetic approaches to promising compounds in the field of medicinal chemistry [13, 14]. For example, 2-amino-4*H*-pyran derivatives bearing nitrile functionality exhibit potential applications in the treatment of psoriatic arthritis and rheumatoid, and also in cancer therapy [15-18]. The 4*H*-pyran ring can be transformed to pyridine systems, which relate to pharmacologically important calcium antagonists of the dihydropyridine (DHP) type [19, 20]. 2-Amino-3-cyano-4*H*-pyrans possess photochemical activity [21]. Because of their important use in organic synthesis, the synthetic methodologies for 4*H*-pyran have been studied for many years. The known procedure for the synthesis of 4*H*-pyran derivatives uses a three component reaction of cyclic 1,3-diketones, arylaldehydes and malononitrile and is performed under various reaction conditions. The conventional reported synthesis of 4*H*-pyran derivatives uses piperidine and triethylamine in organic solvents. A variety of other reagents such as HMTAB [22], TEBA, $Re(PFO)_3$ [23], NaBr [24], *S*-proline [25], *L*-proline [26] the use of microwave irradiation [27], infrared radiation [28], KF-basic alumina in dimethylformamide (DMF) [29], ultrasound irradiation [30], aminofunctionalized ionic liquids [31], SBA-15 mesoporous silica [32], silica nanoparticals [33] and ammonium acetate under microwave irradiation [34] were found to catalyze this reaction. Most of the mentioned methods have at least one of the limitations such as low yield, long reaction times, effluent pollution, harsh reaction conditions, formation of by-products, the use of toxic organic solvents, the use of additional instruments such as ultra sound and tedious workup procedures. Moreover sodium ethoxide solid based catalysts are much cheaper than ionic liquids. Herein, we report an efficient, one-pot, three-component method for the preparation of 2-amino-4*H*-benzo[*b*]pyran derivatives (**4**) by condensation of aromatic aldehydes (**1**), dimedone (**2**) and malononitrile (**3**) under solvent-free conditions at room temperature *via* grinding **(Scheme 1)**.

Results and discussion

Preliminary studies were mainly focused on the optimization of reaction conditions. The yields of 2-amino-4*H*-benzo[*b*]pyrans derivatives obtained by reacting dimedone, malononitrile and 3-bromobenzaldehyde are given in **Table 1**. This three-component cyclocondensation reaction proceeds smoothly in presence of solid sodium ethoxide to give the desired product 2-amino-3-cyano-4-(3-bromophenyl)-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran **(4f)** in high to excellent yields under mechanochemical approach (i.e., using pestle and mortar). The mechanochemical approach facilitates higher reaction rates and yields in a very short period (5 min). The catalyst plays a crucial role in ensuring very efficient reaction rate and excellent yields. The catalytic activity of solid sodium ethoxide is established by the fact that no product formation is observed in the absence of solid sodium ethoxide even after longer reaction times **(Table 1, entry1)**. When carried out in conventional bases such as piperidine and *L*-proline **(Table 1, entries 2-3)**, decreased yield and longer reaction time are noticed in solvent less conditions and an additional handicap is that the product separation from the reaction mixture is difficult. With ethylenediamine **(Table 1, entry 4)**, no product was formed. When solid sodium ethoxide is used as the catalyst, the reaction proceeds with higher yield with the various solvents used, the reaction works well when polar solvents such as DMSO, DMF and ethanol are used (**Table 1, entries 5-7)**. On the other hand, to our surprise, when the catalyst is mixed with the reactants under mechanochemical approach (i.e., using pestle and mortar), 95% yield is obtained **(entry 8)** in five minutes. However, lowering the mole percentage of solid sodium ethoxide decreases the overall yield significantly **(entries 9 and 10)**.

Table 1 Optimization of reaction conditions in the synthesis of 2-amino-4*H*-benzo[*b*]pyrans from 3-bromobenzaldehyde and dimedone[a]

Entry	Catalyst	Medium	Time	Yield (%)[b]
1	Nil	EtOH	24 h	Nil
2	Piperidine	-	30 min	65[c]
3	*L*-Proline	-	30 min	70[c]
4	Ethylenediamine	-	24 h	Nil[d]
5	Sodium ethoxide	DMSO	1h	76[e]
6	Sodium ethoxide	DMF	1 h	81[e]
7	Sodium ethoxide	EtOH	1 h	86[e]
8	Sodium ethoxide	-	5 min	95[e,f]
9	Sodium ethoxide	-	1 min	29[f,g]
10	Sodium ethoxide	-	1 min	53[f,h]

[a]Reactions are performed on a 1 mmol scale of all reactants. [b]isolated yield; [c]30 mol% catalyst; [d]4 equiv. catalyst used and bisimine of aldehyde obtained; [e]10 mol% catalyst; [f]grinding; [g]3mol % catalyst ; [h]6mol % catalyst.

Scheme 1. Synthesis of 2-amino-4*H*-benzo[*b*]pyrans from various substituted aldehydes, dimedone and malononitrile using solid sodium ethoxide at room temperature *via* grinding.

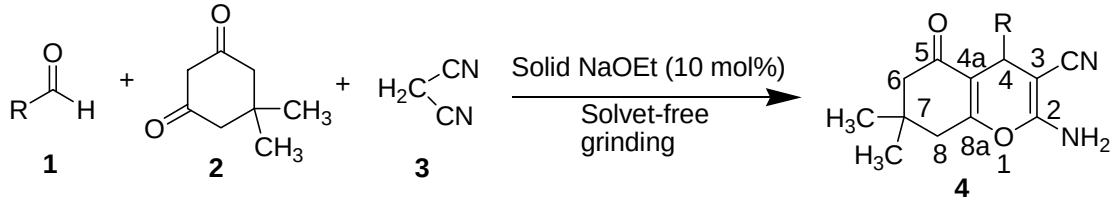


Table 2 Synthesis of 2-amino-4*H*-benzo[*b*]pyrans with various substituted aldehydes and dimedone

S. No.	R	Product	Time (min)	Yield (%)
1	C_6H_5-	**4a**	4	95
2	2-Cl-C_6H_4-	**4b**	6	90
3	3-Cl-C_6H_4-	**4c**	4	92
4	4-CH_3-C_6H_4-	**4d**	5	89
5	4-OCH_3-C_6H_4-	**4e**	7	87
6	3-Br-C_6H_4-	**4f**	5	95
7	4-F-C_6H_4-	**4g**	6	97

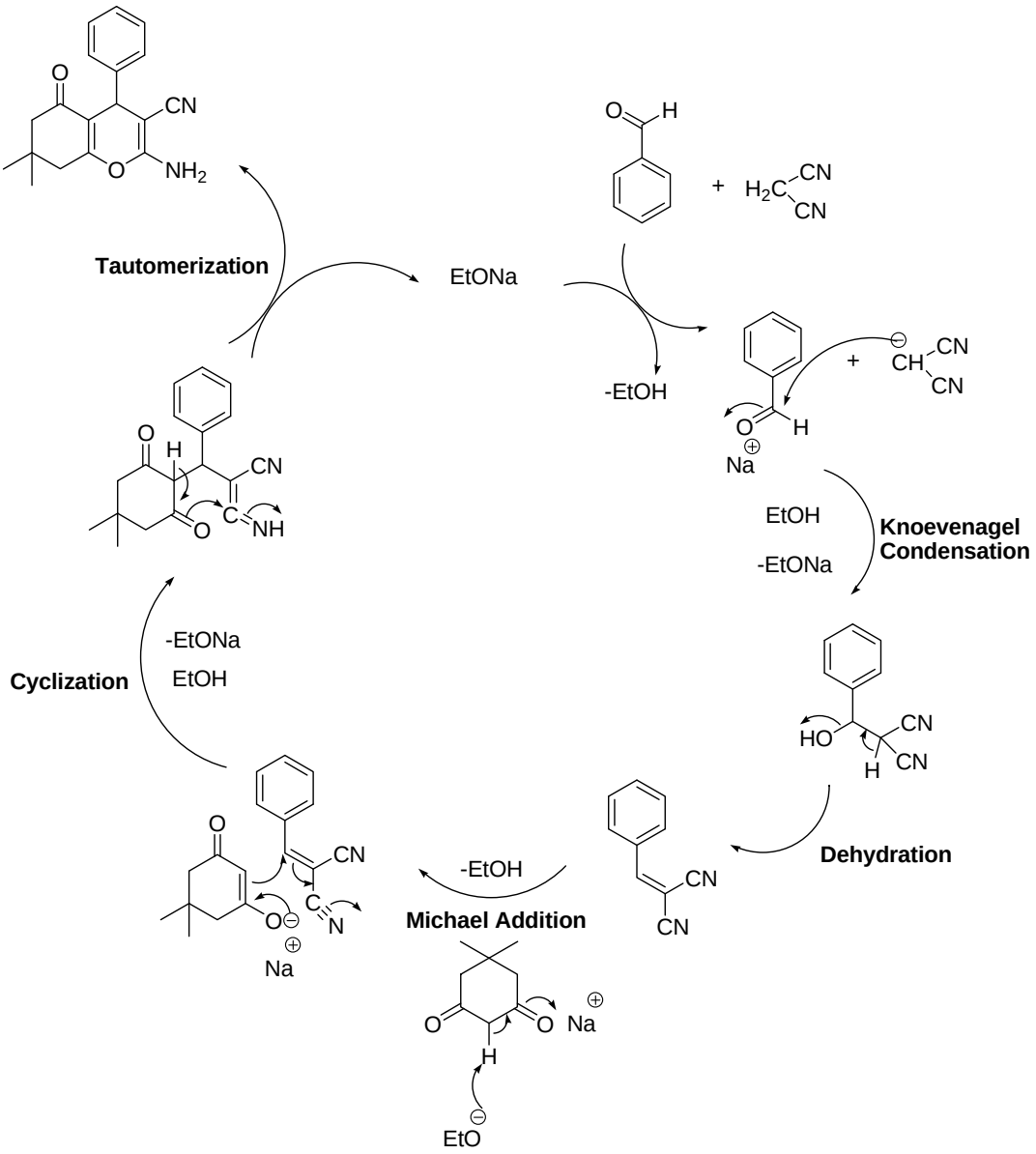
Reaction Conditions: Reactants 1 mmol; Catalyst 10 mol%; grinding.

The generality and functional group tolerance of this procedure in the direct synthesis of 2-amino-4*H*-benzo[*b*]pyran derivatives **4** were examined using a number of substituted aromatic aldehydes in the presence of sodium ethoxide as solid base catalyst under the optimized conditions **(Table 2)**. In all the cases, the reactions gave the corresponding products in good to excellent yields **(Table 2)** in very short reaction times. This method offers significant improvements with regard to the scope of the transformation, simplicity and green aspects by avoiding expensive or corrosive catalysts.

As shown in **Table 2**, aromatic aldehydes bearing electron-donating or electron-withdrawing substituents gave the desired 2-amino-4*H*-benzo[*b*]pyran derivatives **4** in high yields. The method tolerates key functional groups such as halides, alkyl, and methoxy and besides the *para* and *meta* positions on the aromatic ring of aldehyde, different functional groups were also introduced to *ortho* position, indicating that the method is not sensitive to steric or electronic *ortho* variation of substituents.

To explore the mechanism of the reaction, the initial Knoevenagel condensation of aromatic aldehyde with malononitrile in the presence of NaOEt leads to the formation of arylidenemalononitrile with the loss of a water molecule. The nucleophilic (Michael) addition of the enolizable dimedone to arylidenemalononitrile followed by intramolecular cyclization and tautomerization gives the 2-amino-4*H*-benzo[*b*]pyrans **4 (Scheme 2)**.

Scheme 2. Proposed mechanism for solid NaOEt-catalyzed synthesis of 2-amino-4*H*-benzo[*b*]pyrans **4**.



The formation of the products **4** was confirmed by spectral (IR, ^{1}H-NMR and ^{13}C-NMR and elemental analysis. Thus, the IR spectrum of 2-amino-3-cyano-4(3-bromophenyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran **4f**, exhibited bands at 3343, 3167, 2191, 1687, and 1603 cm^{-1} indicating the presence of NH_2, CN, C=O and C=C functionalities, respectively. In the ^{1}H NMR spectrum of **4f**, the NH_2 protons appeared as a broad singlet at 7.09 ppm. The phenyl ring attached to the chromene moiety (C-4H) exhibited a singlet at 4.20 ppm. For compound **4f**, the two protons on C-6 appear as an AB system, with a coupling constant of ~16 Hz, indicating that these protons are not equivalent. The protons on C-8 appear as a broad singlet at 2.53 ppm. The two methyl groups of the cyclohexenone ring appear as singlets at 1.04 and 0.96 ppm. The aromatic protons appear as multiplets in the region of 7.15-7.40 ppm. The ^{13}C NMR spectrum of **4f** exhibited signals at 196.20, 119.96, 28.78, and 27.24 ppm indicating the presence of C=O, CN and two CH_3

functionalities, respectively. For both heterocyclic systems, the spectrum showed five quaternary carbon signals (C-2, C-3, C-4a, C-7 and C-8a), one tertiary carbon signal (C-4) and two secondary carbon signals (C-6 and C-8). These observed chemical shift values are in accordance with the structure of the compound **4f**.

To assign unequivocally all of these signals, we used one dimensional (1D) and two dimensional (2D) techniques: distortionless enhancement by polarization (DEPT)- 135, heteronuclear multiple quantum correlation (HMQC) and heteronuclear multiple bond correlation (HMBC).

It is worth mentioning that the ^{13}C NMR spectrum of compound **4f** showed two signals one each for C-2 and C-8a at higher δ values than expected for typical olefinic carbons. In contrast, carbons C-3 and C-4a appeared at unusually lower δ values. These findings could be accounted for the strong push–pull effect of the groups linked to the olefinic double bond. Thus, C-2 and C-8a are electron-deficient whereas C-3 and C-4a exhibited high electron density. The atom economy observed in the reaction is excellent, with only water as the eliminated product. This study thus demonstrates the efficiency of sodium ethoxide as an excellent solid base catalyst.

Conclusion

An environmentally benign protocol for the synthesis of 2-amino-4*H*-benzo[*b*]pyrans is developed in excellent yields and purity with very short reaction times from readily available starting materials by using minimum amount of sodium ethoxide as a solid base catalyst, in solventless conditions. This novel environmentally friendly methodology has excellent green chemistry credentials such as use of minimum amount of solid base catalyst and shorter reaction time without any byproduct in solvent-free conditions. This attractive atom economical protocol can also be efficient on a multigram scale and thus has promising industrial applications.

Experimental

Apparatus and analysis

Thin-layer chromatography (TLC) was used to monitor the progress of the reaction and the purity of the products. The melting points were recorded in open capillaries and are uncorrected. IR spectra were recorded in AVATAR-330 FT-IR spectrophotometer (Thermo Nicolet) and only strong absorption bands (reciprocal centimeters) are listed. ^{1}H NMR spectra were recorded at 500 MHz on a BRUKER DRX 500 MHz spectrophotometer using DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal standard. ^{13}C NMR spectra were recorded at 125 MHz on a BRUKER DRX 500 MHz spectrometer in DMSO-d_6. Microanalysis was performed by Heraeus Carlo Erba 1108 CHN analyzer. Unless otherwise stated, all the reagents and solvents used were of high grade and purchased from Fluka and Merck. All solvents were distilled prior to use. The following abbreviations are used to indicate the peak multiplicities were: s-singlet, br s-broad singlet, d-doublet, t-triplet, br t-broad triplet, q-quartet and m-multiplet.

*General procedure for the synthesis of 2-amino-4H-benzo[b]pyrans **(4)***

Aldehyde **1**(1.0 mmol), dimedone **2** (1.0 mmol) and malononitrile **3** (1.0 mmol) were added successively to solid sodium ethoxide (10 mol%). The reaction mixture was ground well using a pestle for 4-7 minutes at room temperature. Distilled water has then been to the reaction mixture and the solid thus obtained after stirring has been filtered, washed well with water and dried in vacuum. The crude products were purified by recrystallization from 95% EtOH to give the product. The products were characterized by IR, ^{1}H- NMR and ^{13}C-NMR spectral techniques and elemental analysis.

2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-phenyl-4*H*-chromene-3-carbonitrile **(4a).** Reaction time 4 min, mp 226-228ºC, yield 95 %. IR: ν_{max} (KBr, cm^{-1}) 3396 (NH_2), 3211 (NH_2), 2198 (CN), 1682 (C=O), 1601 (C=C). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 0.93 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 2.08 (H-6a) (d, 1H, J_{AB} = 16 Hz), 2.22 (H-6b) (d, 1H, J_{AB} = 16 Hz), 2.49 (H-8) (br s, 2H), 4.14 (H-4) (s, 1H), 6.99 (br s, 2H, NH_2), 7.07-7.28 (H-2', H-3', H-4', H-5' & H-6') (m, 5H, -Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6) δ_C: 26.76 (CH_3), 28.35 (CH_3), 31.73 (C-7), 35.55 (C-4), 39.89 (C-8), 49.95 (C-6), 58.35 (C-3), 112.74 (C-4a), 119.64 (CN), 126.50 (C-4'), 127.10

(C-3' & C-5'), 128.27 (C-2' & C-6'), 144.69 (C-1'), 158.47 (C-2), 162.41 (C-8a), 195.56 (C=O). Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52 %. Found: C, 73.49; H, 6.10; N, 9.60 %.

2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-(2-chlorophenyl)-4*H*-chromene-3-carbonitrile **(4b).** Reaction time 6 min, mp 218-219ºC, yield 90 %. IR: ν_{max} (KBr, cm^{-1}) 3469 (NH_2), 3328 (NH_2), 2196 (CN), 1683 (C=O), 1600 (C=C). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 0.99 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.08 (H-6a) (d, 1H, J_{AB} = 16 Hz), 2.25 (H-6b) (d, 1H, J_{AB} = 16 Hz), 2.54 (H-8) (br s, 2H), 4.71 (H-4) (s, 1H), 7.04 (br s, 2H, NH_2), 7.17-7.29 (H-4', H-5' & H-6') (m, 3H, -Ar-H), 7.37 (H-3') (dd, 1H, J = 1.5, 7.5 Hz, -Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6) δ_C: 27.34 (CH_3), 28.88 (CH_3), 32.23 (C-7), 33.33 (C-4), 40.56 (C-8), 50.40 (C-6), 57.31 (C-3), 112.55 (C-4a), 119.71 (CN), 127.90 (C-5'), 128.67 (C-4'), 129.91 (C-3'), 130.42 (C-6'), 132.56 (C-2'), 142.03 (C-1'), 159.14 (C-2), 163.62 (C-8a), 196.02 (C=O). Anal. Calcd. for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; N, 8.52 %. Found: C, 65.81; H, 5.15; N, 8.48 %.

2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-(3-chlorophenyl)-4*H*-chromene-3-carbonitrile **(4c).** Reaction time 4 min, mp 234-236ºC, yield 92 %. IR: ν_{max} (KBr, cm^{-1}) 3419 (NH_2), 3319 (NH_2), 2191 (CN), 1660 (C=O), 1600 (C=C). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 0.96 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.13 (H-6a) (d, 1H, J_{AB} = 16 Hz), 2.26 (H-6b) (d, 1H, J_{AB} = 16 Hz), 2.53 (H-8) (br s, 2H), 4.21 (H-4) (s, 1H), 7.09 (br s, 2H, NH_2), 7.11-7.13 (H-6') (m, 1H, -Ar-H), 7.17 (H-5') (br t, 1H, J = 2 Hz, -Ar-H), 7.26-7.27 (H-2') (m, 1H, -Ar-H), 7.34 (H-4') (t, 1H, J = 7.8 Hz, -Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6) δ_C: 27.29 (CH_3), 28.74 (CH_3), 32.30 (C-7), 35.81 (C-4), 40.56 (C-8), 50.39 (C-6), 58.09 (C-3), 112.55 (C-4a), 119.66 (CN), 126.43 (C-4'), 127.10 (C-6'), 127.51 (C-2'), 130.78 (C-5'), 133.35 (C-3'), 147.69 (C-1'), 159.01 (C-2), 163.33 (C-8a), 196.20 (C=O). Anal. Calcd. for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; N, 8.52 %. Found: C, 65.81; H, 5.27; N, 8.55 %.

2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-(4-methylphenyl)-4*H*-chromene-3-carbonitrile **(4d).** Reaction time 5 min, mp 215-217ºC, yield 89 %. IR: ν_{max} (KBr, cm^{-1}) 3426 (NH_2), 3329 (NH_2), 2191 (CN), 1682 (C=O), 1601 (C=C). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 0.95 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.09 (H-6a) (d, 1H, J_{AB} = 16 Hz), 2.24 (s, 3H, CH_3), 2.25 (H-6b) (d, 1H, J_{AB} = 16 Hz), 2.51 (H-8) (br s, 2H), 4.13 (H-4) (s, 1H), 6.97 (br s, 2H, NH_2), 7.03 (H-3'& H-5') (d, 2H, J = 8 Hz, -Ar-H), 7.09 (H-2'& H-6') (d, 2H, J = 8 Hz, -Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6) δ_C: 21.05 (CH_3), 27.23 (CH_3), 28.89 (CH_3), 32.25 (C-7), 35.65 (C-4), 40.54 (C-8), 50.46 (C-6), 58.95 (C-3), 113.35 (C-4a), 120.22 (CN), 127.54 (C-3' & C-5'), 129.35 (C-2' & C-6'), 136.10 (C-4'), 142.28 (C-1'), 158.91 (C-2), 162.77 (C-8a), 196.12 (C=O). Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.40; H, 6.54; N, 9.08 %. Found: C, 74.50; H, 6.58; N, 9.12 %.

2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-(4-methoxyphenyl)-4*H*-chromene-3-carbonitrile **(4e).** Reaction time 7 min, mp 200-201ºC, yield 87 %. IR: ν_{max} (KBr, cm^{-1}) 3375 (NH_2), 3185 (NH_2), 2193 (CN), 1683 (C=O), 1605 (C=C). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 0.94 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.08 (H-6a) (d, 1H, J_{AB} = 16 Hz), 2.24 (H-6b) (d, 1H, J_{AB} = 16 Hz), 2.49 (H-8) (br s, 2H), 3.71 (s, 3H, OCH_3), 4.11 (H-4) (s, 1H), 6.84 (H-3'& H-5') (d, 2H, J = 8.6 Hz, -Ar-H), 6.97 (br s, 2H, NH_2), 7.05 (H-2'& H-6') (d, 2H, J = 8.5 Hz, -Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6) δ_C: 26.76 (CH_3), 28.38 (CH_3), 31.74 (C-7), 34.77 (C-4), 39.93 (C-8), 50.00 (C-6), 54.97 (OCH_3), 58.60 (C-3), 113.00 (C-3' & C-5'), 113.66 (C-4a), 119.74 (CN), 128.19 (C-2' & C-6'), 136.83 (C-1'), 157.90 (C-4'), 158.81 (C-2), 162.09 (C-8a), 196.60 (C=O). Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64 %. Found: C, 70.30; H, 6.25; N, 8.60 %.

2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-(3-bromophenyl)-4*H*-chromene-3-carbonitrile **(4f).** Reaction time 5 min, mp 225-226ºC, yield 95 %. IR: ν_{max} (KBr, cm^{-1}) 3343 (NH_2), 3167 (NH_2), 2191 (CN), 1687 (C=O), 1603 (C=C). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 0.96 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.13 (H-6a) (d, 1H, J_{AB} = 16 Hz), 2.26 (H-6b) (d, 1H, J_{AB} = 16 Hz), 2.53 (H-8) (br s, 2H), 4.20 (H-4) (s, 1H), 7.09 (br s, 2H, NH_2), 7.15-7.17 (H-6') (m, 1H,-Ar-H), 7.27 (H-5') (t, 1H, J = 7.7 Hz, -Ar-H), 7.30 (H-3') (br t, 1H, J = 1.7 Hz, -Ar-H), 7.38-7.40 (H-4') (m, 1H, -Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6) δ_C: 27.24 (CH_3), 28.78 (CH_3), 32.33

(C-7), 35.79 (C-4), 40.55 (C-8), 50.39 (C-6), 58.13 (C-3), 112.56 (C-4a), 119.96 (CN), 122.01 (C-3'), 126.82 (C-6'), 129.99 (C-4'), 130.39 (C-5'), 131.10 (C-2'), 147.93 (C-1'), 159.00 (C-2), 163.34 (C-8a), 196.20 (C=O). Anal. Calcd. for $C_{18}H_{17}BrN_2O_2$: C, 57.92; H, 4.59; N, 7.51 %. Found: C, 60.00; H, 4.62; N, 7.46 %.

2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-(4-fluorophenyl)-4*H*-chromene-3-carbonitrile **(4g).** Reaction time 6 min, mp 177-179ºC, yield 97 %. IR: ν_{max} (KBr, cm^{-1}) 3356 (NH_2), 3178 (NH_2), 2190 (CN), 1682 (C=O), 1600 (C=C). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 0.95 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.11 (H-6a) (d, 1H, J_{AB} = 16 Hz), 2.25 (H-6b) (d, 1H, J_{AB} = 16 Hz), 2.51 (H-8) (br s, 2H), 4.21 (H-4) (s, 1H), 7.03 (br s, 2H, NH_2), 7.11 **(**H-3'& H-5') (t, 2H, J = 8.7 Hz, -Ar-H), 7.17-7.20 **(**H-2'& H-6') (m, 2H, -Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6) δ_C: 27.30 (CH_3), 28.78 (CH_3), 32.25 (C-7), 35.38 (C-4), 40.44 (C-8), 50.43 (C-6), 58.59 (C-3), 113.07 (C-4a), 115.48 (C-3' & C-5') (d, J_{CF} = 21.25 Hz), 120.10 (CN), 129.50 (C-2' & C-6') (d, J_{CF} = 8.7 Hz), 141.39 (C-1') (d, J_{CF} = 2.5 Hz), 158.95 (C-2), 161.36 (C-4') (d, J_{CF} = 214.2 Hz), 162.96 (C-8a), 196.18 (C=O). Anal. Calcd. for $C_{18}H_{17}FN_2O_2$: C, 69.22; H, 5.49; N, 8.97 %. Found: C, 69.30; H, 4.45; N, 9.02 %.

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