CHAPTER 5

Solar Energy Mediated Green Synthesis of Tetrahydrobenzo[b]pyran using L-Ascorbic Acid as an Organocatalyst in Aqueous Medium

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5.1 Introduction

In the recent years, organic synthesis is mainly focused on the development of the greener and ecofriendly protocols involving the use of green solvents in place of toxic, volatile and hazardous organic solvents and green biodegradable catalysts in place of hazardous heavy metal catalysts and also alternate energy sources like microwave irradiation, ultrasound irradiation, UV light in place of conventional heating which saves time and energy. In this context, in recent times multicomponent reactions (MCRs) have gained much attention because in these reactions two or more molecules reacts together in one pot. MCRs helps in saving time and effort for isolation and purification of synthetic intermediates, high atom economy and also minimizing energy consumption, which is one of the most important principles of green chemistry and rapidly gaining attention of scientists worldwide. MCRs are highly efficient method for the synthesis of highly functionalized heterocycles by the reactions of small organic molecules. Among the heterocycles, 4*H*-pyrans has received considerable attention because these are the important units of natural products and also shows a variety of biological and pharmacological activities such as emetic, anti-coagulant, anticancer, diuretic, antimalarial, antitumor, antibacterial, antialzheimer, antileukemic, antihyperglycemic and antidyslipidemic

activities (Smith et al. 1995, Tanabe et al. 1988, Gao et al. 2008, Bolognese et al. 2004, Fokialakis et al. 2002, Beagley et al. 2003, Morgan et al. 2002, Bonsignore et al. 1993, Cannon et al. 1975, Biot et al. 1997). **Figure 5.1** shows some medicinally important compounds containing 2-amino-3-cyano-4*H*-pyrans functional group like **A & C** are antimicrobial, **B** is anti-bacterial, **D & E** are anti-tumor and **F** is an anticancer agent.

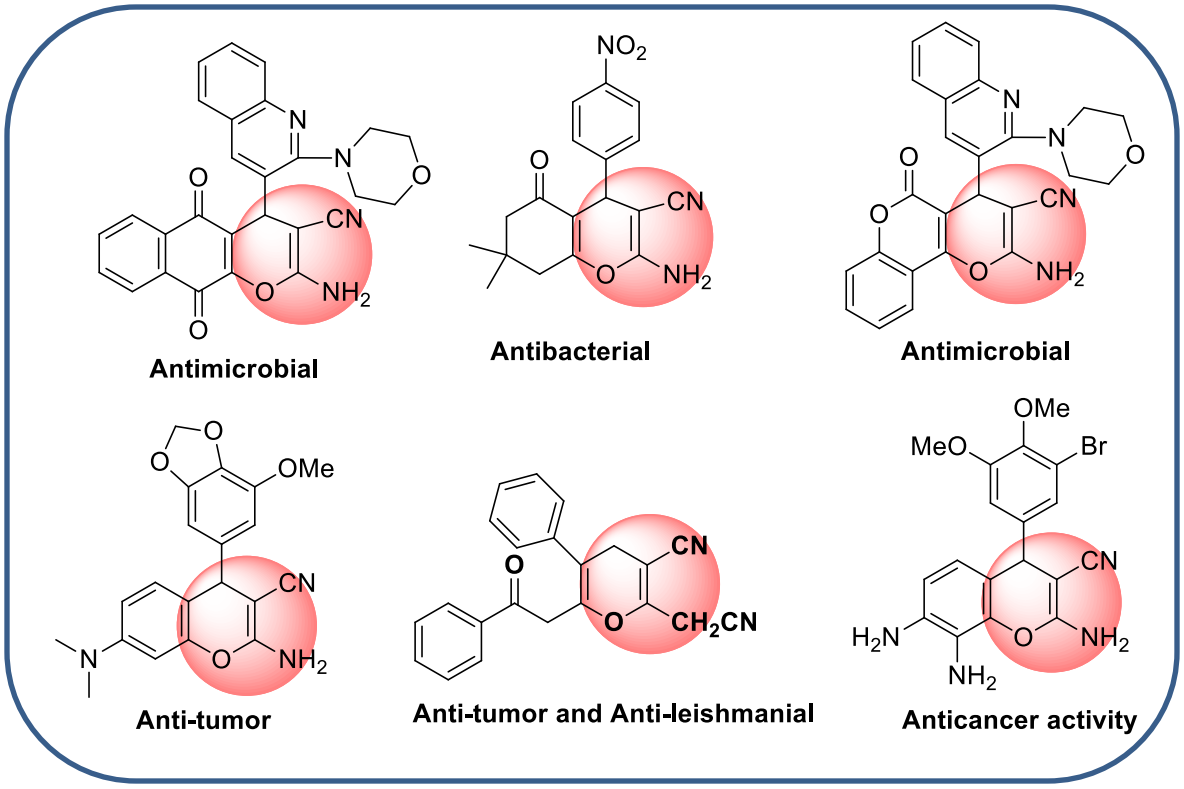


Figure 5.1: Examples of 2-amino-3-cyano-4*H*-pyrans derivatives with pharmacological activities.

The best protocol to synthesize 4*H*-pyrans is the Knoevenagel condensation-Michael cyclization reaction by using aldehyde, carbonitrile and 1,3-dicarbonyl compound by one-

pot multicomponent reaction. A number of conventional reported methods for the synthesis of 4*H*-pyrans performed under various reaction uses different catalysts like piperidine (Ye et al. 2010), DABCO (Tahmassebi et al. 2011), NH_4OAc (Zonouz et al. 2016), K_2CO_3 (Heydari et al. 2017), ethylenediammonium diacetate (EDDA) (Hari et al. 2010), potassium phthalimide (Dekamin et al. 2014), CsF (Wagh et al. 2015), glutamic acid (Hatamjafari et al. 2016), alum (Mohammadi et al. 2017), sulfonic Acid (Ziarani et al. 2011), nano ZnO (Bhattacharyya et al. 2012), nano TiO_2 (Anandgaonker et al. 2014), Fe_3O_4 NPs/MWCNTs (Fallah et al. 2014), MNPs@Cu (Wanzheng et al. 2019), γ-cyclodextrin (Xiong et al. 2019), PEG/Water (Lu et al. 2018).

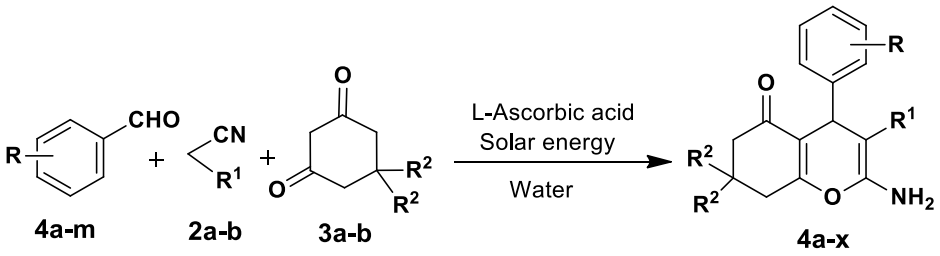
Each of these methods has their own limitations. Therefore, we went ahead and found an alternative green method for synthesis of 4*H*-pyran using biodegradable/biocatalyst natural catalyst. Ascorbic acid has immense possibilities of being used as an organocatalyst in organic transformations. L-Ascorbic acid is biodegradable, natural, inexpensive, non-toxic and easy to handle organocatalyst. Therefore, use of ascorbic acid as a catalyst in MCRs under solar energy is the best selection from green chemistry point of view (Arvind et al. 2016, Das et al. 2018).

To perform an organic reaction, if solvent is necessary, water is the best option in comparison to toxic organic solvents from green and sustainable chemistry point of view. Despite of the economic and environmental friendly nature of water, it also has its own

unique qualities like high surface tension, high polarity, non-toxic, easy handling etc. Since most of the organic compounds are not soluble in water therefore after completion of reaction product can be easily separated by filtration (Gawande et al. 2013, Lindstrom et al. 2008).

Further, to develop a green synthetic approach, naturally available sun light that is solar thermal energy can be utilized as an alternative renewable energy source to induce the chemical transformation. Solar thermochemical method provides more selectivity and mild reaction condition than the conventional energy sources which are also helpful to reduce the side reaction caused by conventional thermal heating process. Sunlight is an exclusive natural source that is cheap, non-polluting, plentiful and endlessly renewable source of clean energy (Yoon et al. 2010, Kumavat et al. 2013).

Considering these aspects we herein report solar energy induced an efficient, ecofriendly, simple and practical way for the synthesis of tetrahydrobenzo[b]pyran derivatives using a biodegradable L-ascorbic acid in aqueous medium (**Scheme 5.1**).

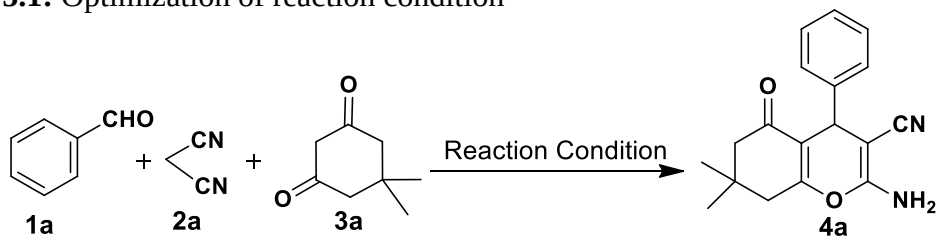


Scheme 5.1: Solar energy mediated synthesis of 4*H*-pyran.

5.2 Results and Discussion

The reaction of benzaldehyde, malononitrile and dimedone was chosen as a model reaction in order to set the optimized reaction condition for the synthesis of 4*H*-pyran. First of all, the model reaction was performed without catalyst in water under sun light (35-40 °C) and in 60 minutes, the maximum 32% yield of product **4a** was obtained. Further, the reaction time increased up to 6 h but only a small increment in product yield was observed (35%). In order to increase the yield of the product, model reaction was performed by using 1 mol% of L-ascorbic acid as a catalyst in water under similar reaction condition and it gave 65% yield in 60 minutes. Further the catalyst amount had been increased from 2-5 mol% and the best result was observed in case of 3 mol% of L-ascorbic acid. It gave the 95% yield of product **4a** in 10 minutes and the results are concise in **Table 5.1** (**entries 1-6**). Further, numerous polar and non-polar solvents were screened over the model reaction performed by using 3 mol% of L-ascorbic acid. In polar solvents like ethanol, methanol, acetonitrile, 1,4-dioxane, dichloromethane and chloroform moderate to good yield (40-80%) was obtained (**Table 5.1, entries 7-12**) while in case of DMF and DMSO poor yield of product was achieved (**Table 5.1, entries 13 and 14**) and in case of nonpolar solvents like hexane, benzene and toluene no reaction was obtained (**Table 5.1, entries 15-17**). Therefore, the optimized reaction condition for model reaction was with 3 mol% of L-ascorbic acid in water under sun light (**Table 5.1, entry 4**). Structure of the model compound (**4a**) was confirmed by ^{1}H & ^{13}C NMR spectral data (**Figure 5.1 & 5.2**).

Table 5.1: Optimization of reaction condition[a]



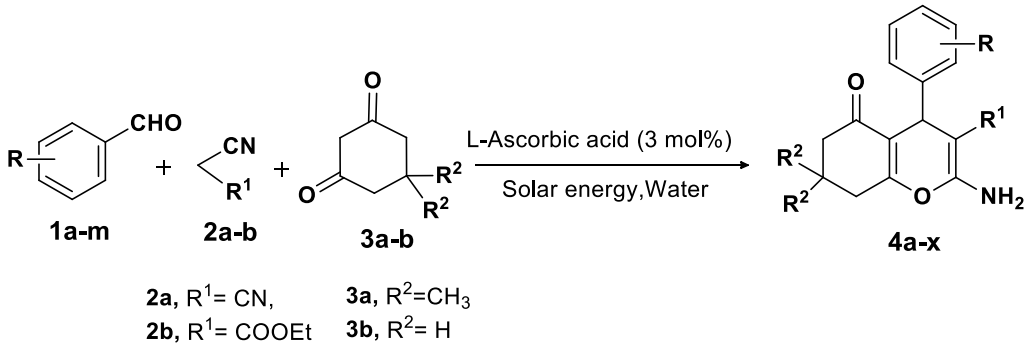
Entry	Solvent	Catalyst (mol%)	Time (min)	Yield[b] (%)
1	Water	Nil	60	32
2	Water	1	60	65
3	Water	2	45	78
4	**Water**	**3**	**10**	**95**
5	Water	4	10	95
6	Water	5	10	95
7	Ethanol	3	40	80
8	Methanol	3	45	73
9	Acetonitrile	3	45	50
10	1,4-Dioxane	3	60	40
11	Dichloromethane	3	60	45
12	Chloroform	3	60	42
13	DMF	3	60	10
14	DMSO	3	60	12
15	Hexane	3	60	NR
16	Benzene	3	60	NR
17	Toluene	3	60	NR

[a] **Reaction condition**: Benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), dimedone (1.0 mmol) and L-ascorbic acid in 5 mL solvent are placed under sunlight. [b] Isolated yield.

After optimizing the reaction conditions, the substrate scope was explored by using different substituted aromatic aldehydes with malononitrile and dimedone. It was observed that aldehyde derivatives with electron withdrawing groups like NO_2, Cl, Br *viz. o*-nitro benzaldehyde (**1e**), *m*-nitro benzaldehyde (**1f**), *p*-nitro benzaldehyde (**1g**), *o*-chloro benzaldehyde (**1h**), *p*-chloro benzaldehyde (**1i**), *p*-bromo benzaldehyde (**1j**), (**Table 5.2, entry 5-10**) and electron donating groups like CH_3, OCH_3 *viz*. *o*-tolualdehyde (**1b**), *p*-tolualdehyde (**1c**) and *p*-methoxy benzaldehyde (**1d**) (**Table 5.2, entries 2-4**) undergo the reaction smoothly to give corresponding 4*H*-pyrans *viz.* 2-amino-7,7-dimethyl-4-(2-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4e**), 2-amino-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4f**), 2-amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3carbonitrile (**4g**), 2-amino-4-(2-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4h**), 2-amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4i**) and 2-Amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitril (**4j**), 2-amino-7,7-dimethyl-5-oxo-4-(o-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4b**), 2-amino-7,7-dimethyl-5-oxo-4-(p-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3 carbonitrile (**4c**), 2-amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4d**) with 91-97% yield in short reaction time. To our surprise, the optimized condition was also found suitable for the heterocyclic aldehyde, furfuraldehyde and gave 2-amino-4-(furan-2-yl)-7,7-dimethyl-5-

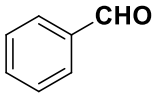
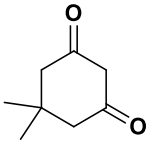
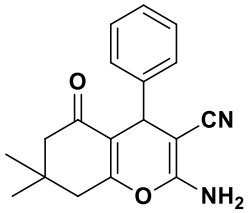
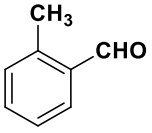
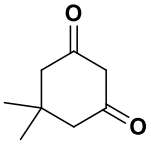
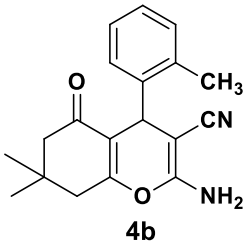
oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4k**) with 94% yield (**Table 5.2, entry 11**). Likewise, 2-naphthylaldehyde was successfully gave the desired product 2-amino-7,7-dimethyl-4-(naphthalen-2-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4l**) in 93% yield (**Table 5.2, entry 12**). In order to explore further substrate scope, the reactions were performed by varying different active methylene compounds like ethylcyano acetate and dimedone/1,3-cyclohexadione to give corresponding 4*H*-pyran derivatives *viz.* 2-amino-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4m**), 2-amino-5-oxo-4-(o-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4n**), 2-amino-4-(4-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4o**), 2-Amino-4-(2-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4p**), 2-amino-4-(4-bromophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4q**), 2-amino-4-(2-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4r**), 2-Amino-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3carbonitrile (**4s**), ethyl 2-amino-5-oxo-4-phenyl- 5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**4t**), ethyl 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**4u**), ethyl 2-amino-4-(4-bromophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**4v**), ethyl 2-amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3 carboxylate (**4w**) and ethyl 2-amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**4x**) in good to excellent yield under this optimized reaction condition (**Table 5.2, entries 13-24**).

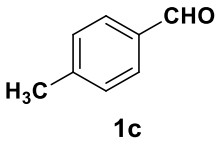
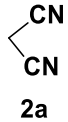
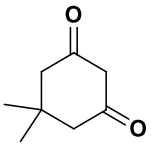
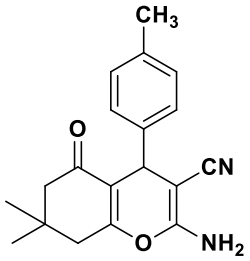
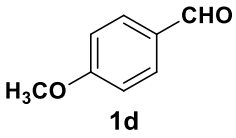
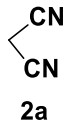
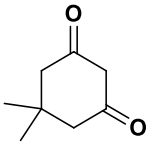
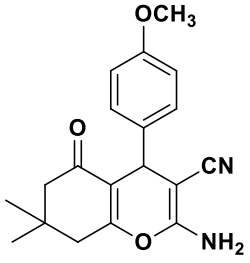
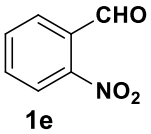
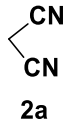
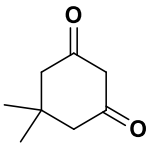
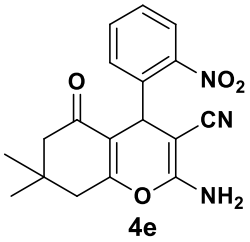
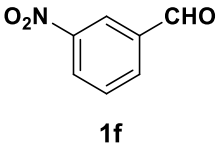
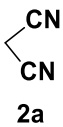
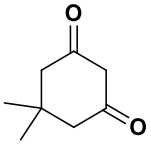
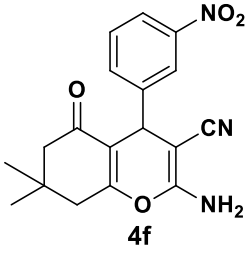
Table 5.2: Synthesis of 4*H*-pyran[a]

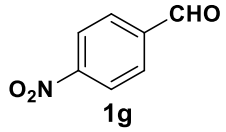
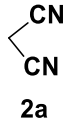
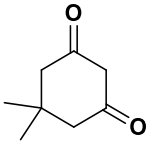
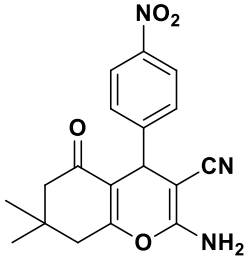
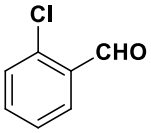
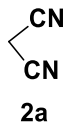
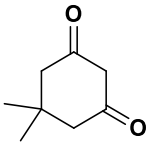
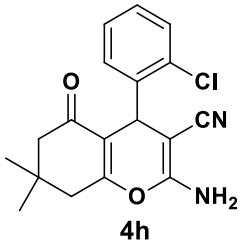
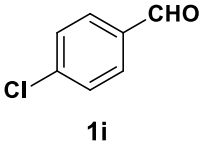
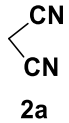
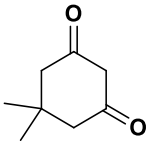
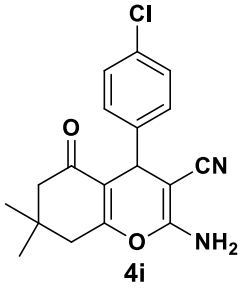
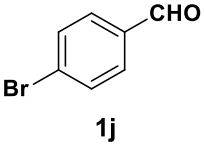
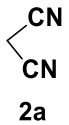
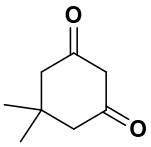
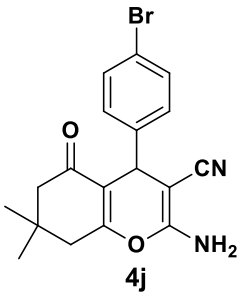


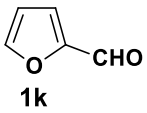
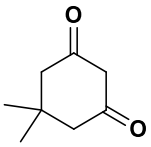
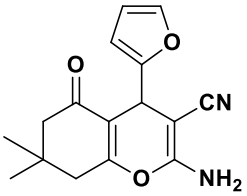
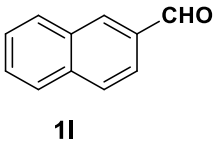
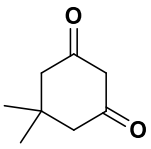
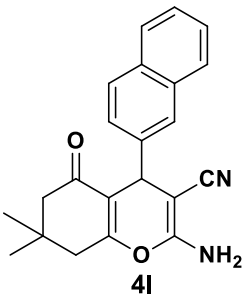
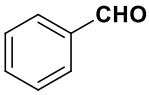
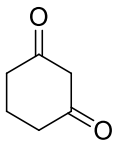
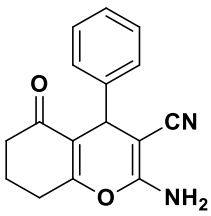
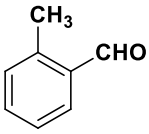
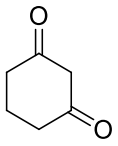
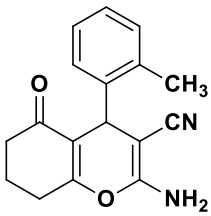
1a-m 2a-b 3a-b 4a-x

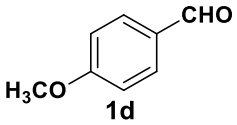
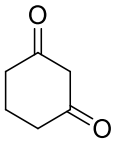
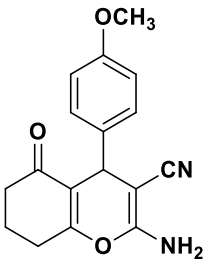
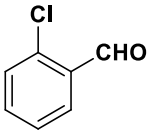
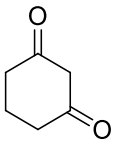
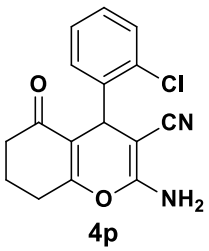
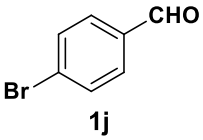
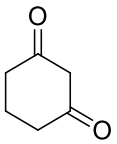
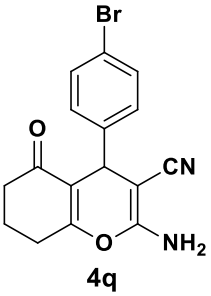
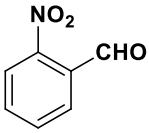
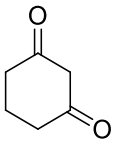
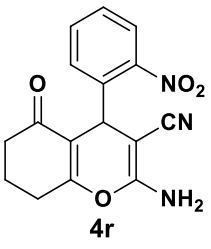
2a, R^1= CN, **3a,** R^2=CH_3
2b, R^1= COOEt **3b,** R^2= H

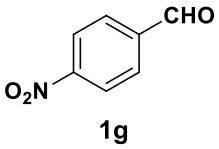
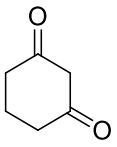
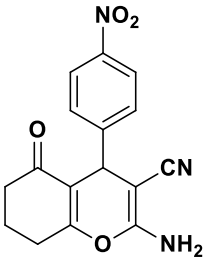
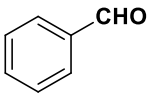
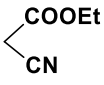
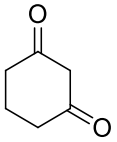
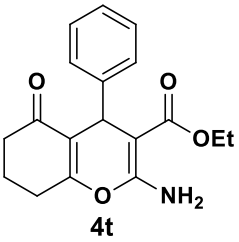
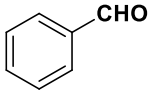
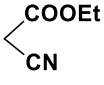
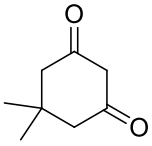
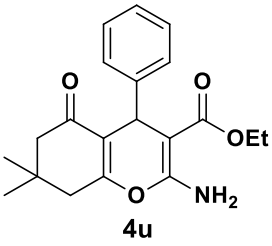
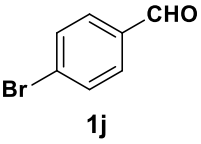
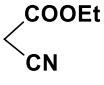
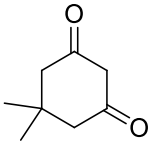
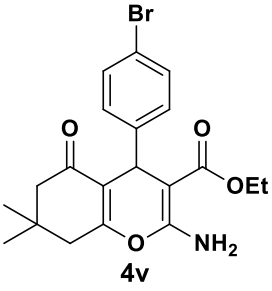
S. No.	Aldehyde	Carbonitrile	1,3-dicarbonyl compound	Product	Time (min)	Yield[b] (%)
1	 1a	 2a	 3a	 4a	10	95
2	 1b	 2a	 3a	 4b	12	93

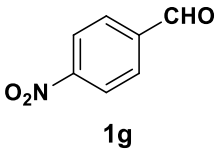
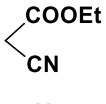
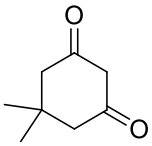
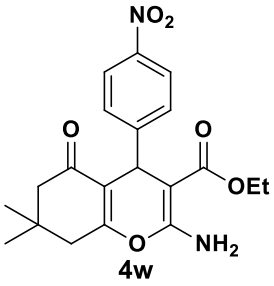
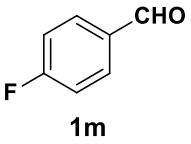
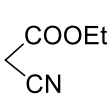
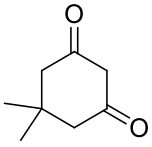
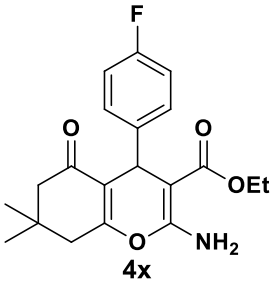
3	 1c	 2a	 3a	 4c	13	92
4	 1d	 2a	 3a	 4d	15	91
5	 1e	 2a	 3a	 4e	10	96
6	 1f	 2a	 3a	 4f	10	96

7	 1g	 2a	 3a	 4g	10	97
8	 1h	 2a	 3a	 4h	12	96
9	 1i	 2a	 3a	 4i	13	96
10	 1j	 2a	 3a	 4j	12	95

11	 1k	 2a	 3a	 4k	10	94
12	 1l	 2a	 3a	 4l	12	93
13	 1a	 2a	 3b	 4m	10	94
14	 1b	 2a	 3b	 4n	12	93

15	 1d	 2a	 3b	 4o	13	92
16	 1h	 2a	 3b	 4p	12	95
17	 1j	 2a	 3b	 4q	13	95
18	 1e	 2a	 3b	 4r	10	96

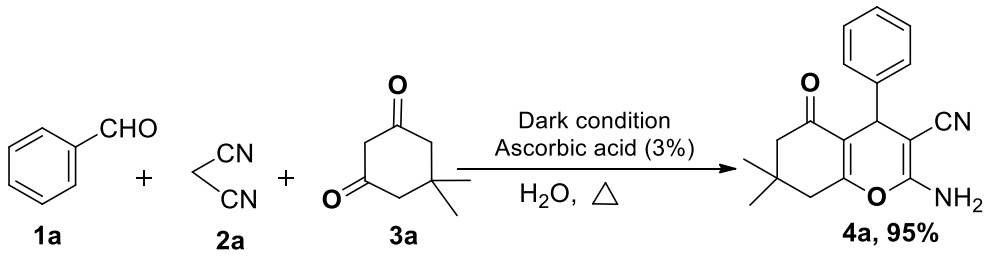
19	 1g	 2a	 3b	 4s	10	96
20	 1a	 2b	 3b	 4t	17	93
21	 1a	 2b	 3a	 4u	15	94
22	 1j	 2b	 3a	 4v	15	95

23	 1g	 2b	 3a	 4w	16	96
24	 1m	 2b	 3a	 4x	15	95

[a]**Reaction conditions**: Benzaldehyde (1.0 mmol), malononitrile/ ethylcyanoacetatae (1.0 mmol), dimedone / 1,3 cyclohexanedione (1.0 mmol) and L-ascorbic acid in 5.0 mL water are placed under sunlight. [b] Isolated yield.

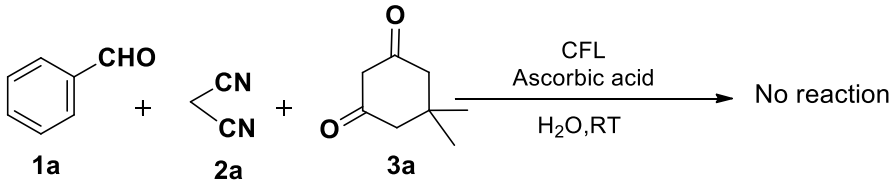
5.3 Mechanistic Study

Deep diving in to the path of reaction, few controlled experiment have been performed in order to confirm whether the reaction proceed via solar thermal or solar photochemical process. The reaction was carried out under dark reaction condition and reaction temperature has been maintained similar as obtained under solar condition (35-40 °C) with 3 mol% of L-ascorbic acid in aqueous medium and it afforded the same product (**4a**) (**Scheme 5.2**).



Scheme 5.2: Control experiment under dark reaction condition.

Further a series of experiments using visible light of different intensities (8 W, 15 W, 20 W) have been performed on the model reaction and no product was obtained. Hence, it rules out the possibility of photochemical reaction (**Scheme 5.3, Table 5.3**).



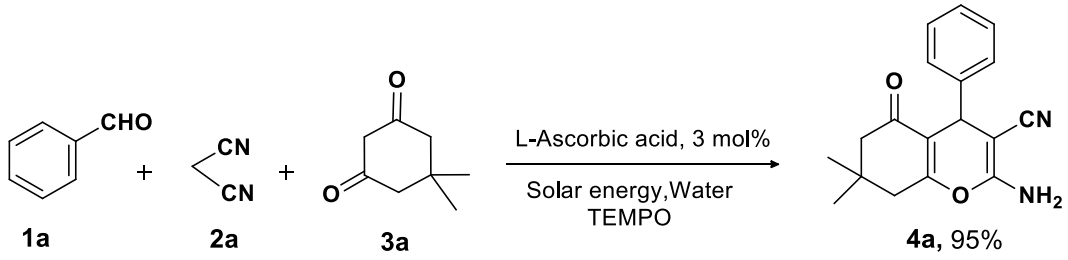
Scheme 5.3: Control experiment under visible light.

Table 5.3: Reaction under solar, thermal and photochemical condition[a]

Entry	Reaction condition	Time (min)	Yield[b]%
1	Solar energy	10	95
2	Dark condition, 35-40 °C	10	95
3	CFL (8W), RT	30	NR
4	CFL (15W), RT	30	NR
5	CFL (20W), RT	30	NR

[a]**Reaction conditions**: Benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), dimedone (1.0 mmol), L-ascorbic acid (3 mol%) in water (5.0 mL). [b] Isolated yield.

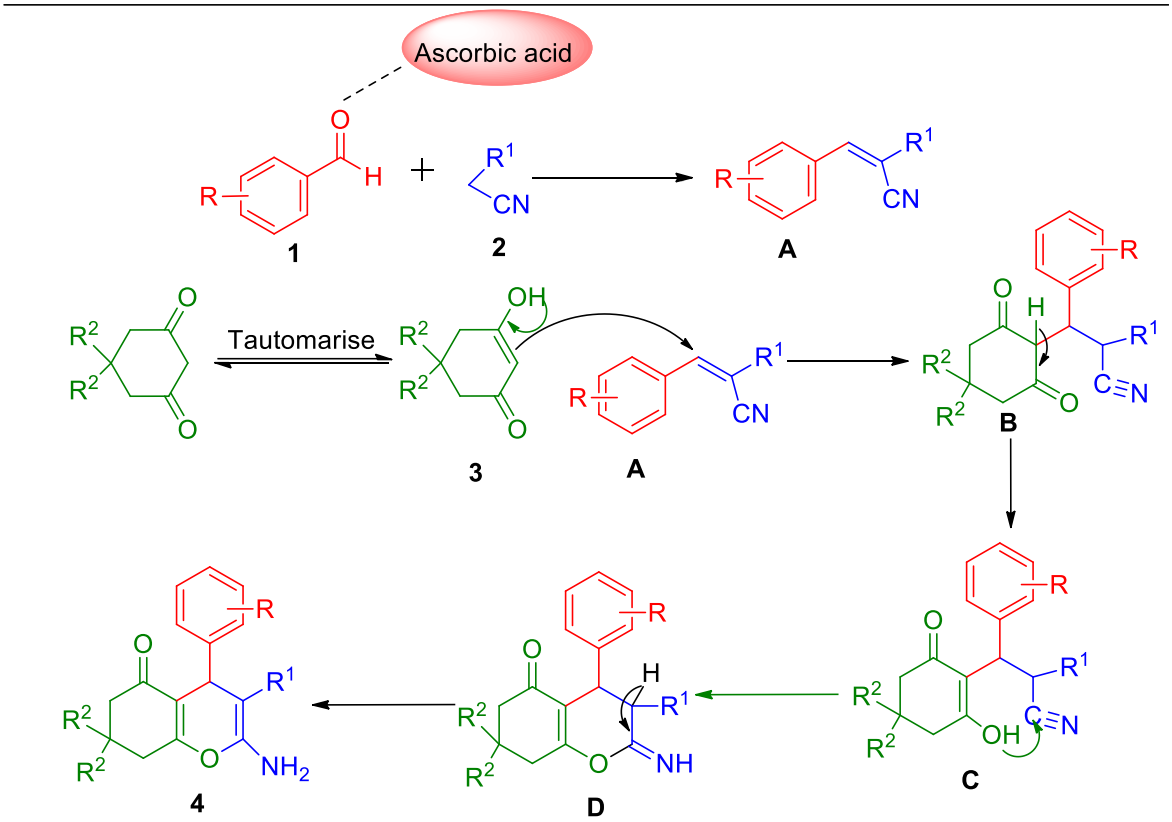
Likewise, when model reaction was performed with radical scavengers like TEMPO and BHT the same product (**4a**) was obtained in good yield and these results show that it is not a radical reaction. This also support that the formation of tetrahydrobenzo[b]pyran catalyzed by ascorbic acid in water is mediated by solar thermal energy and discard the possibility of solar photochemical process (**Scheme 5.4**).



Scheme 5.4: Control experiment with TEMPO.

5.4 Plausible Reaction Mechanism

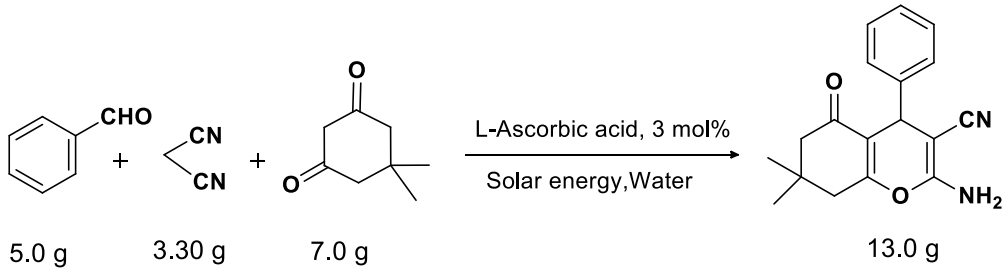
In the proposed mechanism (**Scheme 5.5**), aldehyde (**1**) first condenses with active methylene compound (**2**) and producs α-cyanocinnamonitrile (**A**) via the Knoevenagel condensation. Further, α-cyanocinnamonitrile (**A**) reacts with 1,3-diketone (**3**) give intermediate **B** via Michael addition and finally enolization occurs, followed by amine-enamine tautomarization to produce the expected product 4*H*-pyran (**4**).



Scheme 5.5: Plausible reaction mechanism for the ascorbic acid assisted synthesis of tetrahydrobenzo[b]pyran.

5.5 Gram Scale Synthesis of Tetrahydrobenzo[b]pyran

The reaction was tried on gram scale where 5.30 g of benzaldehyde (**1a**), 3.30 g of malononitrile (**2a**) and 7.0 g of dimedone (**3a**) was successfully converted into desired product (**4a**) in 13.0 g (90%) which evidently validates the practical applicability of the established methodology (**Scheme 5.6**).



Scheme 5.6: Gram scale synthesis of tetrahydrobenzo[b]pyran.

5.6 Experimental Section

5.6.1 General procedure for the synthesis of compounds (4a-4x)

In a stoppered, flat-bottom flask charged with aromatic aldehyde derivatives (1.0 mmol), malononitrile/ethylcyanoacetate (1.0 mmol) dimedone/1,3-cyclohexanedione (1.0 mmol), L-ascorbic acid (3 mol%) and water (5 mL). The reaction mixture was kept in the sunlight for 10 min. The progress of reaction was checked by thin-layer chromatography (TLC). After completion of the reaction, solid product was filtered, dried and recrystallized from hot ethanol to give pure product (**4a-4x**).

5.6.2 Gram-scale procedure

Benzaldehyde (**1a**) (5.30 g, 50.0 mmol), malononitrile (**2a**) (3.30 g 50.0 mmol), dimedone (**3a**) (7.0 g, 50 mmol), L-ascorbic acid (3 mol%) and water were taken in flat-bottom flask. The reaction mixture was kept in the sunlight for 10 min. The progress of the reaction was monitored by TLC. After completion of reaction, solid product was filtered, dried and recrystallized from hot ethanol to give pure product (**4a**).

5.6.3 Procedure for the controlled experiment with TEMPO

In a stoppered, flat-bottom flask charged with benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), dimedone (1.0 mmol), TEMPO (3 mol%), L-ascorbic acid (3 mol%) and water. The reaction mixture was kept in the sunlight and the progress of reaction was checked by thin-layer chromatography (TLC). After completion of the reaction, solid product was filtered, dried and recrystallized from hot ethanol to give pure product in 95% yield (**4a**).

5.7 Analytical Data

5.7.1 2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-*4H*-chromene-3-carbo nitrile (4a): White solid; yield 280 mg (95%); m.p. 228-229 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.26 (d, 2 H), 7.17 (d, 1H), 7.12 (d, 2H), 7.00 (s, 2H, D_2O exchangeable), 4.15 (s, 1H), 2.50 (d, 2H), 2.24 (d, 1H), 2.09 (d, 1H), 1.02 (s, 3H), 0.94 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.7, 162.5, 158.5, 144.7, 128.3, 127.1, 126.6, 119.7, 112.7, 58.3, 50.0, 39.3, 35.6, 31.8, 28.4, 26.8; Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.35; H, 6.14; N, 9.48.

5.7.2 2-Amino-7,7-dimethyl-5-oxo-4-(o-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbo nitrile (4b): White solid; yield 289 mg (93%); m.p. 211-212 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.09 (d, 2H), 7.04 (s, 1H), 6.95 (s, 2H), 6.93 (s, 1H, D_2O

exchangeable), 4.46 (s, 1H), 2.52 (d, 2H), 2.46 (s, 3H), 2.24 (d, 1H), 2.06 (d, 1H), 1.04 (s, 3H), 0.96 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.9, 162.6, 158.3, 143.6, 134.8, 130.0, 127.3, 126.5, 126.3, 119.8, 113.5, 58.3, 50.0, 31.9, 30.9, 28.5, 26.8, 19.1; Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N 9.08. Found: C, 73.89; H, 6.53; N, 9.04.

5.7.3 2-Amino-7,7-dimethyl-5-oxo-4-(p-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4c): Yellow solid; yield 283 mg (92%); m.p. 218-219 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.09 (d, 2H), 7.02 (d, 2H), 6.98 (s, 2H, D_2O exchangeable), 4.13 (s, 1H), 2.51 (d, 2H), 2.25 (s, 4H), 2.09 (d, 1H), 1.04 (s, 3H), 0.95 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.6, 162.3, 158.4, 141.8, 135.6, 128.9, 127.1, 119.7, 112.8, 58.4, 50.0, 35.2, 31.8, 28.4, 26.7, 20.6; Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.19; H, 6.17; N, 8.59.

5.7.4 2-Amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4d): Yellow solid; yield 295 mg (91%); m.p. 200-202 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.05 (d, 2H), 6.94 (s, 2H), 6.84 (d, 2H, D_2O exchangeable), 4.12 (s, 1H), 3.70 (s, 3H), 2.49 (d, 2H), 2.24 (d, 1H), 2.08 (d, 1H), 1.02 (s, 3H), 0.94 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 196.2, 162.6, 158.8, 158.3, 137.3, 128.6, 120.2, 114.1, 113.4, 59.0, 55.4, 50.4, 35.2, 32.2, 28.8, 27.2; Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.19; H, 6.17; N, 8.59.

5.7.5 2-Amino-7,7-dimethyl-4-(2-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4e): Yellow solid; yield 326 mg (96%); m.p. 229-230 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.81 (d, 1H), 7.66 (t, 1H), 7.42 (t, 1H), 7.35 (d, 1H), 7.20 (s, 2H,D_2O exchangeable), 4.93 (s, 1H), 2.45 (d, 2H), 2.20 (d, 1H), 2.01 (d, 1H), 1.01 (s, 3H), 0.88 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.8, 165.1, 158.5, 152.3, 146.2, 128.5, 123.6, 119.3, 112.7, 56.8, 40.0, 36.2, 35.5, 26.5, 19.7; Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.54; H, 5.01; N, 12.34.

5.7.6 2-Amino-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4f): Yellow solid; yield 326 mg (96%); m.p. 213-214 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.11 – 8.05 (m, 1H), 7.98 (s, 1H), 7.67 (d, 1H), 7.62 (d, 1H), 7.18 (s, 2H, D_2O exchangeable), 4.42 (s, 1H), 2.57 (d, 2H), 2.27 (d, 1H), 2.12 (d, 1H), 1.04 (s, 3H), 0.96 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.7, 163.1, 158.6, 147.7, 147.0, 134.2, 130.2, 121.7, 121.6, 119.3, 111.7, 57.2, 49.8, 35.4, 31.8, 28.3, 26.7; Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.56; H, 5.02; N, 12.31.

5.7.7 2-Amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene -3-carbonitrile (4g): Yellow solid; yield 329 mg (97%); m.p. 183-184 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.17 (d, 2H), 7.44 (d, 2H), 7.18 (s, 2H, D_2O exchangeable), 4.36 (s, 1H), 2.54 (s, 2H), 2.26 (d, 1H), 2.11 (d, 1H), 1.04 (s, 3H), 0.96 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.7, 163.1, 158.6, 152.3, 146.2, 128.6, 123.6, 119.3, 111.7,

57.0, 49.8, 35.6, 31.8, 28.2, 26.9; Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.53; H, 5.03; N, 12.32

5.7.8 2-Amino-4-(2-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene -3-carbonitrile (4h): White solid; yield 316 mg (96%); m.p. 212-214 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.33 (d, 1H), 7.24 (t, 1H), 7.15 (dd, 2H), 7.00 (s, 2H, D_2O exchangeable), 4.66 (s, 1H), 2.47 (s, 2H), 2.22 (d, 1H), 2.04 (d, 1H), 1.01 (s, 3H), 0.94 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.8, 163.3, 158.8, 141.6, 132.2, 130.0, 129.5, 128.3, 127.5, 119.4, 111.8, 56.9, 50.0, 40.0, 32.9, 31.8, 28.5, 26.9. Anal. Calcd for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; N, 8.52. Found: C, 65.61; H, 5.18; N, 8.48.

5.7.9 2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene -3-carbonitrile (4i): White solid; yield 316 mg (96%); m.p. 202-204 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.35 (d, 2H), 7.17 (d, 2H), 7.07 (s, 2H, D_2O exchangeable), 4.20 (s, 1H), 2.51 (d, 2H), 2.25 (d 1H), 2.11 (d, 1H), 1.04 (s, 3H), 0.95 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 196.1, 163.0, 158.9, 144.2, 131.5, 129.5, 128.7, 120.0, 112.8, 58.2, 50.4, 32.2, 28.7, 27.3; Anal. Calcd for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; N 8.52. Found: C, 65.59; H, 5.17; N, 8.46.

5.7.10 2-Amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene -3-carbonitril (4j): Yellow solid; yield 355 mg (95%); m.p. 202-203 °C; **^{1}H NMR** (500

MHz, DMSO-d_6) δ (ppm): 7.27 (d, 2H), 7.13 (d, 2H), 7.00 (s, 2H, D_2O exchangeable), 4.16 (s, 1H), 2.50 (s, 2H), 2.23 (s, 1H), 2.11 (s, 1H), 1.03 (s, 3H), 0.94 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 196.1, 162.9, 158.9, 145.2, 128.8, 127.6, 127.0, 120.2, 113.1, 58.7, 50.4, 36.0, 32.2, 28.8, 27.2; Anal. Calcd for $C_{18}H_{17}BrN_2O_2$: C, 57.92; H, 4.59; N, 7.5. Found: C, 57.74; H, 4.54; N, 7.45.

5.7.11 2-Amino-4-(furan-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4k): Brown solid; yield 268 mg (94%); m.p. 223-225 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.47 (d, 1H), 7.06 (s, 2H, D_2O exchangeable), 6.32 (s, 1H), 6.05 (s, 1H), 4.32 (s, 1H), 2.50 – 2.49 (m, 2H), 2.28 (d, 1H), 2.16 (d, 1H), 1.04 (s, 3H), 0.98 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.4, 163.3, 159.3, 155.7, 141.8, 141.6, 119.5, 110.3, 55.4, 49.9, 31.8, 29.0, 28.2, 26.5; Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.4; H, 5.63; N, 9.81.

5.7.12 2-Amino-7,7-dimethyl-4-(naphthalen-2-yl)5-oxo-5,6,7,8-tetrahydro-4*H*-chromene -3-carbonitrile (4l): Cream solid; yield 320 mg (93%); m.p. 258-259 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.89 (d, 1H), 7.85 (d, 2H), 7.67 (s, 1H), 7.48 (t, 2H), 7.28 (d, 1H), 7.07 (s, 2H, D_2O exchangeable), 4.36 (s, 1H), 2.55 (s, 2H), 2.26 (d, 1H), 2.08 (d, 1H), 1.04 (s, 3H), 0.96 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.7, 162.6, 158.5, 142.0, 132.8, 132.0, 128.1, 127.6, 127.4, 126.2, 125.7, 125.6, 125.5, 119.7, 112.5, 58.1, 50.0, 39.1,

31.8, 28.4, 26.7; Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.54; H, 5.81; N, 8.10.

5.7.13 2-Amino-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4m): White solid; yield 251 mg (94%); m.p. 241-243 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.29 (dd, 2H), 7.21 – 7.17 (m, 1H), 7.17 – 7.14 (m, 2H), 7.00 (s, 2H, D_2O exchangeable), 4.19 (s, 1H), 2.62 (s, 2H), 2.27 (dt, 2H), 1.95 (s, 2H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 196.1, 164.7, 158.6, 144.9, 128.52, 127.2, 126.7, 119.9, 113.9, 48.7, 36.4, 35.5, 26.6, 19.9; Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.96; H, 5.27; N, 10.48.

5.7.14 2-Amino-5-oxo-4-(o-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4n): White solid; yield 261 mg (93%); m.p. 198-200 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.13 – 7.08 (m, 2H), 7.05 (dd, 1H), 6.96 (d, 1H), 6.93 (s, 2H), 4.47 (s, 1H), 2.67 – 2.57 (m, 2H), 2.46 (s, 3H), 2.32 – 2.19 (m, 2H), 1.99 – 1.85 (m, 2H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.9, 164.4, 158.2, 143.6, 134.7, 129.8, 127.3, 126.4, 126.1, 114.5, 58.1, 36.3, 31.0, 26.4, 19.8, 19.0; Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.69; H, 5.71; N, 9.94.

5.7.15 2-Amino-4-(4-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4o): White solid; yield 273 mg (92%); m.p. 194-196 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.08 – 7.05 (m, 2H), 6.95 (s, 2H), 6.83 (d, 2H, D_2O exchangeable),

4.14 (s, 1H), 3.71 (s, 3H), 2.59 (dd, 2H), 2.32 – 2.21 (m, 2H), 1.98 – 1.84 (m, 2H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.8, 164.1, 158.4, 157.9, 136.9, 128.1, 119.8, 114.0, 113.6, 58.4, 55.0, 36.3, 34.6, 26.4, 19.8; Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.71; H, 5.40; N, 9.40.

5.7.16 2-Amino-4-(2-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbo nitrile (4p): White solid; yield 286 mg (95%); m.p. 210-212 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.37 – 7.35 (m, 1H), 7.28 – 7.24 (m, 1H), 7.19 (dd, 2H), 7.01 (s, 2H, D_2O exchangeable), 4.71 (s, 1H), 2.62 (dd, 2H), 2.32 – 2.19 (m, 2H), 2.32 – 2.21 (m, 2H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.6, 165.0, 164.0, 158.5, 141.7, 132.0, 129.8, 129.3, 128.1, 127.5, 119.2, 112.8, 56.8, 36.3, 32.6, 26.4, 19.8; Anal. Calcd for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.31. Found: C, 63.71; H, 4.33; N, 9.27.

5.7.17 2-Amino-4-(4-bromophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbo nitrile (4q): White solid; yield 328 mg (95%); m.p. 239-240 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.46 (d, 2H), 7.12 (dd, 2H), 7.02 (s, 2H, D_2O exchangeable), 4.19 (s, 1H), 2.59 (dd, 2H), 2.33 – 2.20 (m, 2H), 2.00 – 1.81 (m, 2H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 196.1, 164.8, 158.6, 144.3, 131.3, 129.6, 119.7, 113.4, 57.8, 36.4, 35.2, 26.6, 19.9; Anal. Calcd for $C_{16}H_{13}BrN_2O_2$: C, 55.67; H, 3.80; N, 8.12. Found: C, 55.49; H, 3.76; N, 8.08.

5.7.18 2-Amino-4-(2-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbo nitrile (4r): Yellow solid; yield 299 mg (96%); m.p. 206-208 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.16 (d, 2H), 7.46 (d, 2H), 7.17 (s, 2H, D_2O exchangeable), 4.36 (s, 1H), 2.63 (t, 2H), 2.28 (d, 2H), 1.99 – 1.87 (m, 2H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.8, 165.1, 158.5, 152.3, 146.2, 128.5, 123.6, 119.3, 112.7, 56.8, 36.2, 35.5, 26.5, 19.7; Anal. Calcd for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.54; H, 4.18; N, 13.46.

5.7.19 2-Amino-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3carbonitrile (4s): Light yellow solid; yield 299 mg (96%); m.p. 237-238 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.16 (d, 2H), 7.46 (d, 2H), 7.17 (s, 2H, D_2O exchangeable), 4.36 (s, 1H), 2.63 (dd, 2H), 2.28 (dd, 2H), 1.99 – 1.88 (m, 2H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.8, 165.1, 158.5, 152.3, 146.2, 128.5, 123.6, 119.3, 112.7, 56.8, 36.2, 35.5, 26.5, 19.7; Anal. Calcd for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.53; H, 4.19; N, 13.47.

5.7.20 Ethyl 2-amino-5-oxo-4-phenyl- 5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (4t): White solid; yield 292 mg (93%); m.p. 183-184 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.21 – 7.18 (m, 2H), 7.13 (t, 2H), 7.04 (s, 1H), 6.11 (s, 2H, D_2O exchangeable), 4.66 (s, 1H), 3.95 (dd, 2H), 2.54 – 2.43 (m, 2H), 2.26 (dt, 2H), 1.97 – 1.83 (m, 2H), 1.07 (t, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 196.6, 169.2, 163.1, 158.4, 146.1, 128.3, 127.9,

126.1, 118.2, 80.9, 59.8, 37.0, 33.9, 27.1, 20.3, 14.3; Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.81; H, 6.07; N, 4.42.

5.7.21 Ethyl 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (4u): White solid; yield 321 mg (94%); m.p. 155-157 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.32 – 7.29 (m, 2H), 7.25 (t, 2H), 7.15 (s, 1H), 6.22 (s, 2H, D_2O exchangeable), 4.75 (s, 1H), 4.08 (dd, 2H), 2.47 (s, 2H), 2.26 (s, 1H), 2.22 (s, 1H), 1.21 (s, 3H), 1.14 (s, 3H), 1.02 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 196.5, 169.2, 161.4, 158.4, 145.9, 128.3, 127.9, 126.1, 116.9, 80.9, 59.8, 50.8, 40.8, 33.9, 32.3, 29.2, 27.5, 14.3; Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.15; H, 6.77; N, 4.06.

5.7.22 Ethyl 2-amino-4-(4-bromophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (4v): White solid; yield 399 mg (95%); m.p. 161-162 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.32 (d, 2H), 7.14 (d, 2H), 6.18 (s, 2H, D_2O exchangeable), 4.65 (s, 1H), 4.02 (dd, 2H), 2.45 – 2.38 (m, 2H), 2.22 (d, 1H), 2.17 (s, 1H), 1.15 (t, 3H), 1.09 (s, 3H), 0.96 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 196.5, 169.0, 161.6, 158.4, 145.0, 130.9, 130.2, 119.9, 116.4, 80.4, 59.9, 50.8, 40.7, 33.6, 32.3, 29.2, 27.5, 14.3; Anal. Calcd for $C_{20}H_{22}BrNO_4$: C, 57.15; H, 5.28; N, 3.33. Found: C, 56.94; H, 5.24; N, 3.30.

5.7.23 Ethyl 2-amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (4w): Yellow solid; yield 371 mg (96%); m.p. 181-182 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.13–8.03 (m, 2H), 7.46–7.41 (m, 2H), 6.26 (s, 2H,

D_2O exchangeable), 4.79 (s, 1H), 4.02 (dd, 2H), 2.49 – 2.39 (m, 2H), 2.24 (d, 1H), 2.15 (d, 1H), 1.13 (t, 3H), 1.11 (s, 3H), 0.96 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 196.3, 168.7, 162.1, 158.5, 153.5, 146.4, 129.3, 123.3, 115.7, 79.5, 60.0, 50.7, 40.8, 34.4, 32.4, 29.2, 27.4, 14.3; Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.96; H, 5.70; N, 7.19.

5.7.24 Ethyl 2-amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (4x): Yellow solid; yield 341 mg (95%); m.p. 160-161 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.23 – 7.19 (m, 2H), 6.88 (t, 2H), 6.17 (s, 2H, D_2O exchangeable), 4.68 (s, 1H), 4.03 (dd, 2H), 2.42 (s, 2H), 2.23 (d, 1H), 2.15 (d,1H), 1.14 (t, 3H), 1.09 (s, 3H), 0.96 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 196.5, 169.1, 162.3, 161.4, 160.4, 158.4, 141.7, 141.7, 129.8, 129.7, 116.8, 114.7, 114.5, 80.8, 59.8, 50.8, 40.8, 33.3, 32.3, 29.2, 27.5, 14.3. Anal. Calcd for $C_{20}H_{22}FNO_4$: C, 66.84; H, 6.17; N, 3.90. Found: C, 66.71; H, 6.13; N, 3.85.

5.8 Spectral Data of 4a

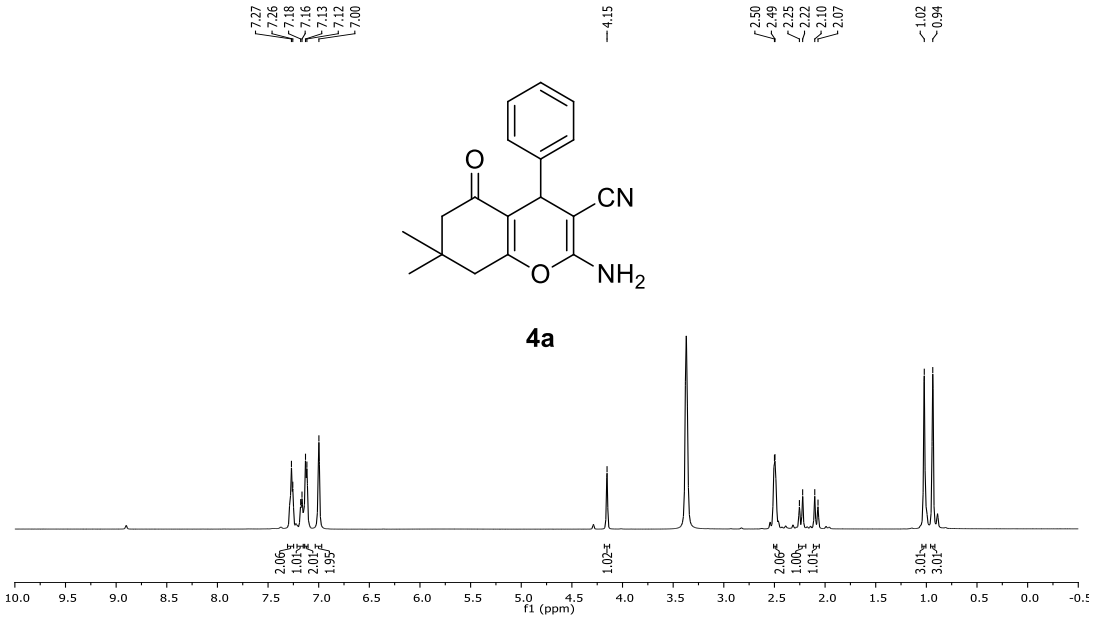


Figure 5.2: ^{1}H NMR spectra of model compound **4a.**

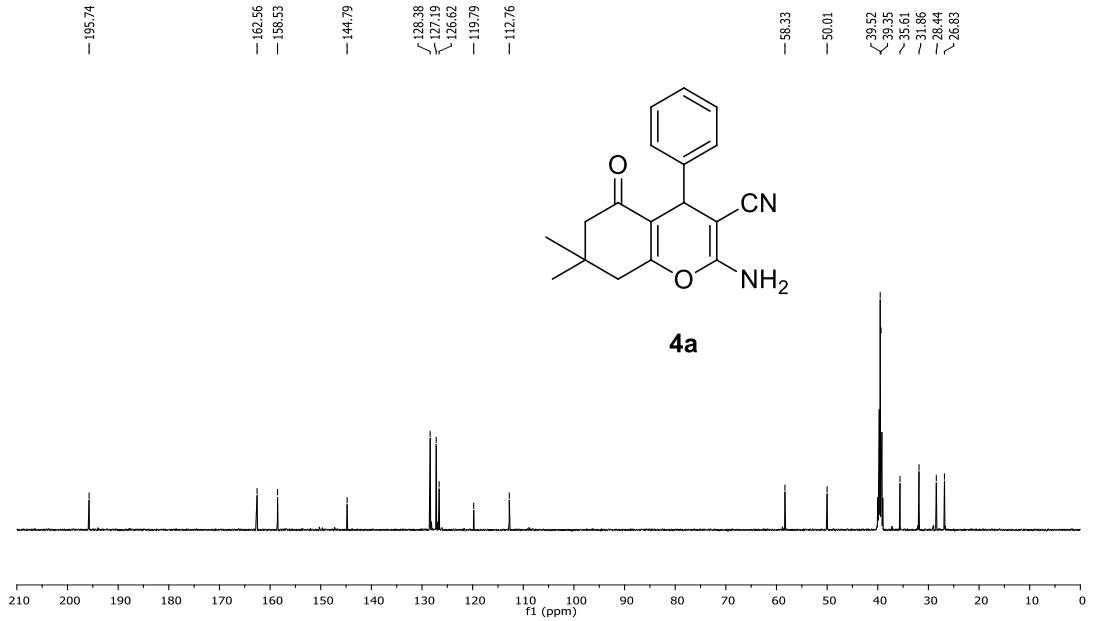


Figure 5.3: ^{13}C NMR spectra of model compound **4a.**

5.9 References

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