Current Chemistry Letters 10 (2021) 43–52

Contents lists available at GrowingScience

Current Chemistry Letters

homepage: www.GrowingScience.com

Ultrasound-assisted synthesis and biological significance of substituted 4H-chromene-3-carbonitrile using greenery approaches

Pravin Chavan[a], Dattatraya Pansare[b*], Rohini Shelke[c], Sumit Shejul[d] and Pratima Bhoir[e]

[a]*Department of Chemistry, Doshi Vakil Arts College, G.C.U.B. Science & Commerce College, Goregaon, Raigad 402103, MS, India*
[b]*Department of Chemistry, Deogiri College, station Road, Aurangabad 431005, MS, India*
[c]*Sadguru Gadage Maharaj College Karad, Satara, 415124, Maharashtra, India*
[d]*Dr. Rafiq Zakariya Womens College, Aurangabad 431001, MS, India*
[e]*M. B. More art's, Commerce and Science women's college, Dhatav, Roha Raigad, MS, India*

C H R O N I C L E

Article history:
Received June 1, 2020
Received in revised form
June 26, 2020
Accepted July 28, 2020
Available online
July 28, 2020

Keywords:
MCRs, 4H-chromene-3-carbonitrile
Orange juice
Reflux
Ultrasonication

A B S T R A C T

A synthesis of 2-amino-4-(*R*)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile derivatives (**4a-l**) in single flasks containing aromatic aldehydes (**1a-l**), malononitrile (**2**), and dimedone **(3)** by using green catalyst, extract of orange without solvent under ultrasound irradiations and reflux condition. Synthesis of 2-amino-4-(*R*)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile derivatives (**4a-l**) show potent *in-vitro* anti-inflammatory activity. All synthesized compounds were characterized by FTIR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic data & elemental analysis.

1. Introduction

Recently, twelve principles of green chemistry have been considered as important factors in the field of organic synthesis due to environment pollution issues. Organic synthetic field is one of the environment pollution contributors. A number of chemical and pharmaceutical industries release hazardous gases and water by using hazardous materials, during their step reactions while manufacturing processes. However, researchers adopt green synthetic routes for synthesis purposes in the view of principles of green chemistry.[1] One pot multi-components (MCRs) condensation is one of the major routes to reduce the environmental pollutions, energy, reaction time and quantity of initial materials at the time of organic synthesis.[2]Also, green solvents and catalysts reduce pollutions and they are easily available and inexpensive. In organic synthesis, excellent yields occur in water due to great polarity of water.[3] What have attracted us in synthesis of 4*H*-chromene-3-carbonitrile derivatives is their medicinal properties that includes antibacterial, anticancer, anticoagulant, diuretic, antianaphylactin, spasmolytic, and anti HIV agent.[4-6] Also, their use to neuro degeration diseases such as Parkinson's, down's syndrome, schizophrenia, alzheimer's and AIDS are associated with dementia

* Corresponding author. Mobile: +91 9850108474
E-mail address: dattatraya.pansare7@gmail.com (D. Pansare)

doi: 10.5267/j.ccl.2020.7.003

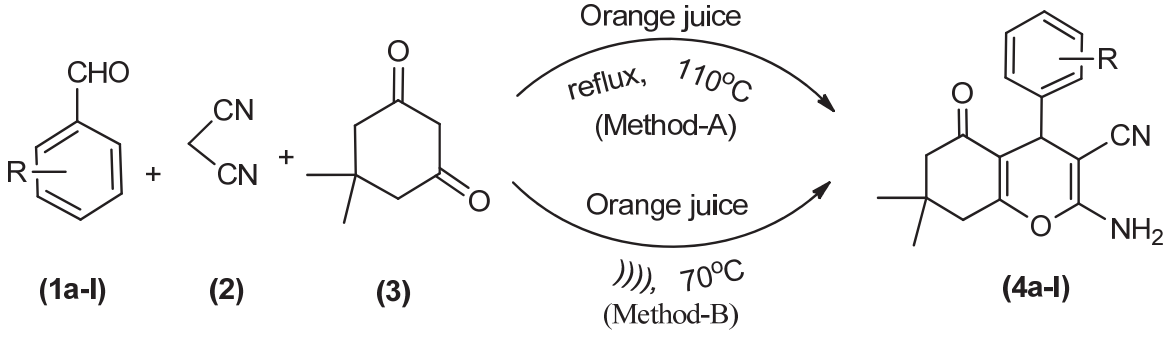
diseases.[7] Furthermore, these derivatives are broadly employed as cosmetic agents, food additives and potential biodegradable agrochemicals.[8] From the details of literature, the derivatives of 4*H*-chromene-3-carbonitrile have been synthesized by using catalysts such as TBABr,[9] I_2 and K_2CO_3, [10] $RE(PFO)_3$, [11] DBU[Ac],[12] HTMAB,[13] TEBA,[14] DBSA,[15] KF/Al_2O_3,[16] K_4PO_4,[17] TBAF,[18] MCM-41-NH_2,[19] MgO,[18 20] triethylamine,[21] piperidine,[22,23] $(NH_4)HPO_4$,[24] *etc*. in different solvents. Also, different methods have been used such as microwave and ultrasonication,[25-27] for its synthesis.

Sonochemistry is one the best applications of ultrasound for chemical reaction and synthesis. Huge number of studies have been done on fundamental of sonochemistry by Luche & co-workers.[28-29]

Recently, ultrasonic method has been widely used in the field of organic synthesis[30-33] as it improves the product of yield and selectivity, shorter reaction time and milder reaction condition.[34-36] Herein, we synthesized substituted 4*H*-chromene-3-carbonitrile in one pot by using extract of orange juice as a catalyst without solvent under ultrasonication and reflux technique.

2. Result and Discussion

Although malononitrile has been extensively used in knoevenagel condensation reaction, but there are limited examples of 4*H*-chromene-3-carbonitrile derivatives synthesized from such reaction. Present work, describes a mild and efficient approach for a synthesis of 4*H*-benzo[*b*]pyren derivatives via knoevenagel condensation using orange extract as a catalyst as well as solvent with moderate to excellent yield. This reaction was firstly examined by stirring a mixture of benzaldehyde (**1e**), Malononitrile (**2**), dimedone (**3**) with orange extract (3ml) at room temperature in ethanol for 2 hrs (**Table 1**). α-cyanocinnamonitrile (**5**) was generated, in situ by the interaction of malononitrile and aromatic aldehydes, but final product was not observed. Then, the same reaction was performed in refluxing C_2H_5OH for 30 minutes at 110 ºC and 65 % product was observed. The same reaction was stirred, but without solvent, for 2 hrs at 80 ºC, yielded 50 % final product. Then, once again the same reaction was refluxed without solvent for 30 minutes at 110 ºC and 79 % final product was observed. The results have shown the significant effect of temperature on the improvement of reaction product; hence, we examined all different aldehydes through entry 4 (**Table 1**) due to suitable condition for method-A. Further, we performed similar experiment under ultrasonic irradiation technique with C_2H_5OH at room temperature for 2 h, and 60 % was final product yield. At, changed temperature (70ºC), this reaction completed in 30 minute and yield was 90 % final product. Similar reaction examined without solvent for 30 minutes, yielded 92 % final product. Thus, we observe the effect of C_2H_5OH, without solvent and mainly ultrasonic irradiations on product of yields (**Table 1**). From the results above, it has been shown that benzaldehyde (**1a)**; Malononitrile (**2**) and dimedone (**3**) with orange extract (3ml) at 70ºC under ultrasonic irradiations presented an efficient procedure in the terms of excellent yield in shorter reaction time (method-B) (**Table 1**).



Scheme 1. Synthesis of 4*H*-chromene-3-carbonitrile derivatives via method-A and method-B

Table 1. Effect of methods, solvents and temperature on model reaction for synthesis of4*H*-chromene-3-carbonitrile derivatives.

Entry	Method	Solvent	Temp. (°C)	Time (min.)	Yield (%)[b]
1	Stirring	C_2H_5OH	r. t.	120	-
2	Refluxing	C_2H_5OH	110	30	65
3	Stirring	-	80	120	50
4	Refluxing	-	110	30	79
5	Ultrasound	C_2H_5OH	r. t.	120	60
6	Ultrasound	C_2H_5OH	70	30	90
7	Ultrasound	-	70	30	92

[a] Reaction condition : Benzaldehyde (1mmol), malononitrile (1mmol), dimedone (1mmol) and orange extract (3 ml).
[b]Isolated yields.

We examined different varieties of aromatic aldehydes (**1a-l**) conventional as well as ultrasonic irradiation techniques (**Table 2**), promoted catalytic Knoevenagel condensation reaction and Michael addition reaction. In every case ultrasonic irradiation improved the yields and the reactions time, but in refluxing case, long time was required for complete reactions. In method –B, products of yields were excellent compared to method-A due to ultrasonic effect and orange juice containing polar water molecules (**Table 2**).

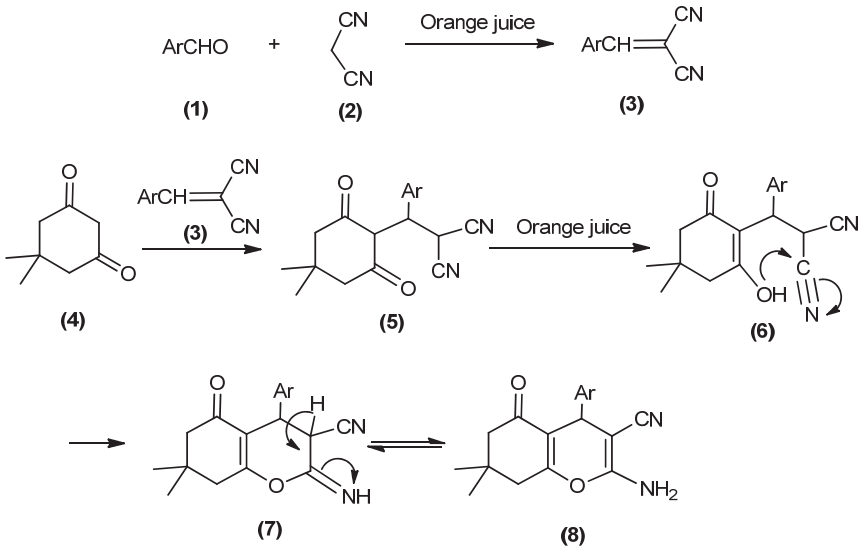
Table 2. Synthesis of 4*H*-chromene-3-carbonitrile derivatives through conventional and ultrasound irradiations techniques.

Entry	Ar	Method-A			Method-B	
		Prod.	Time (min)	Yield (%)[b]	Time (min)	Yield (%)[c]
1	*o*-OCH_3-*m*-OCH_3-C_6H_3	4a	40	80	25	92
2	*m*-OH-*p*-OH-C_6H_3	4b	35	79	23	91
3	*p*-CN-C_6H_4	4c	33	83	18	96
4	*m*-OH-*p*-OCH_3-C_6H_3	4d	46	81	19	93
5	C_6H_5	4e	43	79	20	92
6	*m*-Br-C_6H_4	4f	47	81	22	89
7	*p*-CH_3-C_6H_4	4g	30	78	30	94
8	*p*-Cl-C_6H_4	4h	37	82	25	95
9	*p*-NO_2-C_6H_4	4i	31	85	16	96
10	*p*-F-C_6H_4	4j	52	80	30	93
11	*p*-OCH_3-C_6H_4	4k	43	78	29	94
12	*p*-OH-C_6H_4	4l	39	81	25	91

[a]Reaction condition : Aromatic aldehydes (1mmol), malononitrile (1mmol), dimedone (1mmol), orange extract(3 ml)(Method A- reflux at 110°C and Method B - Ultrasonic irradiation at 70°C). [b & c]Isolated yield.

In continue, the effect of electron withdrawing, electron releasing, and halogen groups in different positions on ring of aromatic aldehydes in the synthesis of 4*H*-chromene-3-carbonitrile derivatives (**4a-l**) were studied and illustrated in **Table 2**. Aldehyde bearing electron withdrawing groups decreased the reaction time with slightly increased the percentage of yields and electron releasing groups increased the reaction times no outstanding effect on the percentage of yields due to ultrasonic effect with aldehyde groups containing electrophilic nature. Consequently, this protocol gives the desired products in good yields and in relatively short reaction times (**Table 2**).

In these works, ultrasonic effect is a major factor observed on each reactions of ultrasonic method, method-B (ultrasonic) gave excellent yields of each products within 30 minutes compared to method-A (refluxing) (**Table 2**).



Scheme 2. Possible mechanisms for synthesis of 4*H*-chromene-3-carbonitrile derivatives via Knoevenagel condensation and Michael addition reaction route.

Initially in this synthesis formation of α-cyanocinnamonitrile (**5**), from condensation of aromatic aldehydes (**1a-l**) with malononitrile (**2**) occured. Then, addition of dimedone (**3**) and α-cyanocinnamonitrile (**5**) to form intermediate (**6**) was set by Michael addition reaction and finally, intermediate (**6**) compound was cyclized by orange juice as a Lewis acid catalyst and to afford 4*H*-chromene-3-carbonitrile compound (**4a-l**) (**Scheme 2**).

Anti-inflammatory activity

All experimented 4*H*-chromene-3-carbonitrile compounds (**4a-l**) were displayed *in-vitro* anti-inflammatory activity and it was tested by 'HRBC membrane stabilization method'. The results are shown in (**Table 3, Fig. 1).**

Table 3. *In-vitro*Anti-inflammatory activity of synthesized 4*H*-benzo[*b*]pyren compounds (**4a-l)**

Entry	Prod.	(%) hemolysis	(%) protection	Entry	Prod.	(%) hemolysis	(%) protection
1.	4a	11.88	88.12	**7.**	4h	18.22	81.78
2.	4b	14.94	85.06	**8.**	4i	16.15	83.85
3.	4c	13.05	86.95	**9.**	4j	22.59	81.72
4.	4d	12.55	87.45	**10.**	4k	11.14	88.86
5.	4e	10.41	89.59	**11.**	4l	15.64	84.36
6.	4f	18.33	81.67	**12.**	Ref.	22.45	77.54
7.	4g	16.26	81.74				

All 4*H*-chromene-3-carbonitrile compounds **(4a-l)** displayed great potential *in–vitro* anti-inflammatory activity. What notifying was, **(5J) =** [22.59 %] of (**4a-l**) derivatives, displayed higher anti-inflammatory activity than the standard Dichlorofenac = [22.45 %] (**Table 3 and Fig. 1**). **Fig. 1.** Shows the *In-vitro* Anti-inflammatory activity of synthesized 4*H*-chromene-3-carbonitrile compounds (**4a-l).**

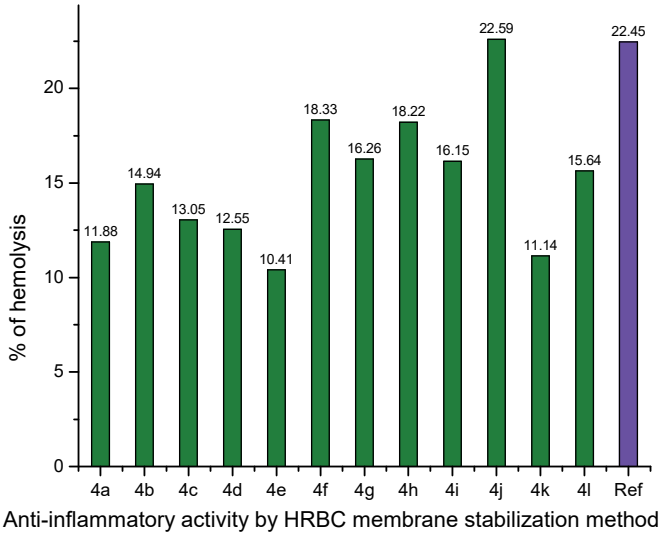


Fig. 1. *In-vitro* Anti-inflammatory activity of synthesized 4*H*-chromene-3-carbonitrile compounds (**4a-l**)

All synthesized compounds were purified by pure ethanol and characterized by FTIR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic data.

3. Conclusion

We conclude that, the discovered method is a simple & eco-friendly for synthesis of synthesis 2-amino-4-(*R*)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile derivatives (**4a-l**). Using this method, we obtain pure, single product and increase the quantity of products yields. Synthesized 2-amino-4-(*R*)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile derivatives (**4a-l**) show potent *in-vitro* anti-inflammatory activity.

4. Material and Methods

4.1 General Methods

All A. R. grade chemicals were purchased from Sigma Aldrich and Avra chemical lab. All reactions were examined in Ultrasonication (frequency of 50 Hz and power of 250 V AC, 5.5 L) at 70ºC temperature. Melting points were recorded on open capillary tube. ^{1}H NMR spectra were recorded on Bruker (400 MHz) and ^{13}C NMR spectra were recorded on Brucker (100 MHz) in DMSO solvent using Me_4Si as an internal standard. Mass spectra were recorded on Micromass -QUATTRO-II of WATER mass spectrometer and IR spectra were recorded on Perkin-Elmer spectrometer.

4.2 General procedure for synthesis of 4H-chromene-3-carbonitrilederivatives

We have taken freshly one orange, crushed, compressed in cotton cloth in centrifuge tube and centrifuged. Collect supernent clear liquid and measured its pH by pH-meter. This was used for catalytic purpose. A mixture of aromatic aldehydes (**1a-l**) (1mmol), Malononitrile (**2**) (1mmol), dimedone (**3**) (1mmol) and orange juice (3 ml) was taken in one pot (Scheme 1). Reaction pot was irradiated at 70 ºC in ultrasonic bath as well as same reaction mixture was refluxed at 110 ºC. Ultrasonic bath temperature was regulated by adding cold water time to time. After changing some physical

properties of mixture, reaction condition was checked by TLC using 7:3 solvent ratio (n-hexane:ethyl acetoacetate). After completion of reaction, mixture was poured in crushed ice containing beaker while stirring, and filtered through a small sintered glass funnel. Product was washed with 10 ml cold water and dry and finally, recrystallized using pure ethanol.

4.3 Biological study: Anti-inflammatory activity

All synthesized 4*H*-chromene-3-carbonitrile compounds (**4a-l**) were tested for *In vitro* anti-inflammatory activity by 'HRBC membrane stabilization method'.[37–40]
Protocol - The fresh blood was collected from a healthy human volunteer who had not taken any NSAIDS for 2 weeks prior to the experiment, mixed with an equal volume of Alsever's solution (2% dextrose, 0.8% sodium citrate, 0.5% citric acid, and 0.42% NaCl), and centrifuged at 3,000 rpm. The packed cells were washed with isosaline, and a 10% suspension was made. Various concentrations of samples were prepared (05, 25, 50, 100 and 250 ppm) using distilled water, and to each concentration 1 mL of phosphate buffer, 2 mL hyposaline, and 0.5 mL of HRBC suspension were added. It was incubated at 37ºC for 30 min and centrifuged at 3,000 rpm for 20 minutes. The hemoglobin content of the supernatant solution was estimated spectrophotometrically at 560 nm. Dichlorofenac sodium was used as standard and distilled water as control in this study. Where the blood control represents 100% hemolysis or zero percent stability, the percentage of HRBC hemolysis calculated by formula:
The percentage of hemolysis of HRBC membrane as calculated as follows,

% of Hemolysis =(O.D. of test sample + O.D. OF control) × 100

The percentage of HRBC membrane stabilization was calculated as follow,

% of Protection = 100 – (O.D. of test sample + O.D. OF control) × 100.

4.4. Mechanistic role under ultrasonic irradiation

The chemistry in liquid medium via pressure waves is sonochemistry. When sonic waves are propagated through a liquid medium, vibrational motions are induced via an alternating compression and rarefaction cycles. When rarefaction cycle surpasses the attractive intermolecular van der Waals forces of attraction between the molecules of the liquid medium, it breaks and leads to cavitation. The micro bubbles stretch, oscillate around their mean position and expand. Since these bubbles are unstable, they implode releasing super high temperature and pressure in short duration which can never be achieved by traditional methods. This in turn sets the platform for the molecular fragmentation and generation of highly reactive species (chemical effects of ultrasound) which are responsible to trigger and enable the reaction in homogeneous solutions. The transmission of ultrasonic energy is higher in the case of water and also the occurrence of cavitation in water is faster in comparison to other solvents.

4.5. Spectral data

2-amino-4-(2,5-dimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4a)
M. P.: 210- 212 ºC. IR (KBr): υ = 3351, 3256, 3196, 2962, 2191, 1662, 1213, 1141 cm^{-1}. ^1H NMR (DMSO-d_6,400 MHz): δ = 6.97 (s, 2H), 6.92 – 6.87 (m, 2H), 6.79 (dd, J = 8.4, 2.2 Hz, 1H), 5.54 (t, J = 1.1 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 2.42 (dd, J = 1.9, 1.0 Hz, 2H), 2.25 (d, J = 16.1 Hz, 1H), 2.09 (d, J = 16.1 Hz, 1H), 1.00 (d, J = 4.0 Hz, 7H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 198.37, 162.62, 159.42, 154.41, 152.53, 129.93, 119.07, 115.59, 115.08, 114.28, 113.04, 57.60, 55.62 (d, J = 1.0 Hz), 50.11, 39.71, 33.70, 31.98, 27.88. Mass (m/z) : Calculated 354.16, Founded 355.10. Anal. Cal. for $C_{20}H_{22}N_2O_4$: C, 67.78, H, 6.26, N, 7.90, O, 18.06 %. Found : C, 67.10, H, 6.32, N, 8.00 %.

2-amino-4-(3,4-dihydoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4b)

M. P.: 216- 218 ºC. IR (KBr): υ = 3390, 3281, 3163, 2189, 1662, 1238, 1178 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ = 8.29 (s, 1H), 6.97 (s, 2H), 6.83 – 6.77 (m, 2H), 6.73 (dd, J = 9.3, 2.0 Hz, 1H), 6.29 (s, 1H), 5.56 – 5.52 (m, 1H), 2.43 (dd, J = 1.8, 1.1 Hz, 2H), 2.25 (d, J = 16.1 Hz, 1H), 2.09 (d, J = 16.1 Hz, 1H), 1.00 (d, J = 4.0 Hz, 7H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 195.85, 163.09, 158.55, 145.67, 145.24, 136.75, 121.22, 119.78, 115.61 (d, J = 17.2 Hz), 114.05, 58.33, 50.09, 39.83, 37.77, 31.98, 27.88. Mass (m/z): Calculated 326.13, Founded 327.00. Anal. Cal. For $C_{18}H_{18}N_2O_4$: C, 66.25, H, 5.56, N, 8.58, O, 19.61 %. Found: C, 66.30, H, 6.42, N, 8.72 %.

2-amino-4-(4-cynophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4c)

M. P.: 228- 230 ºC. IR (KBr): υ = 3440, 3358, 2190, 1689, 1216, 1156 cm^{-1}. ^1H NMR (DMSO-d_6,400 MHz): δ = 7.69 – 7.63 (m, 3H), 7.51 – 7.45 (m, 3H), 6.97 (s, 3H), 5.61 (t, J = 0.9 Hz, 1H), 2.43 (dd, J = 1.8, 1.1 Hz, 2H), 2.25 (d, J = 16.1 Hz, 1H), 2.09 (d, J = 16.1 Hz, 1H), 1.00 (d, J = 4.0 Hz, 8H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 195.72, 162.40, 158.60, 145.50, 139.32, 132.56, 129.14, 119.86, 118.11, 113.07, 58.34, 50.09, 39.83, 37.24, 31.98, 27.88. Mass (m/z) :Calculated 319.13, Founded 320.00. Anal. Cal. For $C_{19}H_{17}N_3O_2$: C, 71.46, H, 5.37, N, 13.16, O, 10.02 %. Found: C, 71.50, H, 5.25, N, 13.21 %.

2-amino-4-(3-hydroxy,4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene -3-carbonitrile (4d)

M. P.: 236- 238 ºC. IR (KBr): υ = 3350, 3256, 3193, 2960, 2228, 2192, 1668, 1214, 1141 cm^{-1}. ^1H NMR (DMSO-d_6,400 MHz): δ = 6.97 (s, 3H), 6.89 – 6.79 (m, 4H), 5.98 (s, 1H), 5.56 – 5.52 (m, 1H), 3.83 (s, 4H), 2.43 (dd, J = 1.8, 1.1 Hz, 2H), 2.25 (d, J = 16.1 Hz, 1H), 2.09 (d, J = 16.1 Hz, 1H), 1.00 (d, J = 4.0 Hz, 8H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 195.85, 163.09, 158.55, 147.90, 146.83, 138.19, 120.85, 119.78, 115.29, 114.05, 113.13, 58.33, 56.21, 50.09, 39.83, 37.68, 31.98, 27.88. Mass (m/z): Calculated 340.14, Found 341.05. Anal. Cal. For $C_{19}H_{20}N_2O_4$: C, 67.05, H, 5.92, N, 8.23, O, 18.80 %. Found: C, 67.30, H, 6.00, N, 8.25 %.

2-amino-4-(phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4e)

M. P.: 225- 227 ºC. IR (KBr): υ = 3389, 3328, 2197, 1677, 1214, 1138 cm^{-1}. ^1H NMR (DMSO-d_6,400 MHz): δ = 7.33 – 7.26 (m, 3H), 7.23 – 7.17 (m, 4H), 6.97 (s, 2H), 4.14 (t, J = 0.8 Hz, 1H), 2.43 (dd, J = 1.8, 1.1 Hz, 2H), 2.25 (d, J = 16.1 Hz, 1H), 2.09 (d, J = 16.1 Hz, 1H), 1.00 (d, J = 4.0 Hz, 8H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 195.72, 162.40, 158.60, 144.83, 128.68, 128.44, 127.29, 119.86, 113.06, 58.27, 50.09, 39.83, 35.63, 31.98, 27.88. Mass (m/z) :Calculated 294.14, Found 294.30. Anal. Cal. For $C_{18}H_{18}N_2O_2$: C, 73.45, H, 6.16, N, 10.78, O, 10.78 %. Found: C, 73.50, H, 6.09, N, 10.80 %.

2-amino-4-(3-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4f)

M. P.: 230- 232 ºC. IR (KBr): υ = 3341, 3399, 2190, 1676, 1215, 1138 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ = 7.55 – 7.51 (m, 1H), 7.41 (dt, J = 7.7, 1.7 Hz, 1H), 7.36 – 7.25 (m, 3H), 6.97 (s, 3H), 5.56 (t, J = 0.9 Hz, 1H), 2.43 (dd, J = 1.8, 1.1 Hz, 2H), 2.25 (d, J = 16.1 Hz, 1H), 2.09 (d, J = 16.1 Hz, 1H), 1.00 (d, J = 4.0 Hz, 8H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 195.85, 163.09, 158.55, 145.19, 132.15, 132.07, 130.32, 127.59, 123.71, 119.79, 112.83, 58.18, 50.09, 39.83, 37.38, 31.98, 27.88. Mass (m/z): Calculated 372.05, Found 372.50. Anal. Cal. For $C_{18}H_{17}BrN_2O_2$: C, 57.92, H, 4.59, Br, 21.41, N, 7.51, O, 8.57 %. Found: C, 57.90, H, 4.68, N, 7.49 %.

2-amino-4-(4-methylphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4g)

M. P.: 212- 214 ºC. IR (KBr): υ = 3384, 3332, 2190, 1676, 1213, 1139 cm^{-1}. ^1H NMR (DMSO-d_6,400 MHz): δ = 7.22 – 7.16 (m, 2H), 7.10 – 7.04 (m, 2H), 6.97 (s, 2H), 5.63 – 5.59 (m, 1H), 2.43 (dd, J = 1.8, 1.1 Hz, 2H), 2.25 (d, J = 16.1 Hz, 1H), 2.09 (d, J = 16.1 Hz, 1H), 1.00 (d, J = 4.0 Hz, 7H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 195.72, 162.40, 158.60, 141.43, 137.11, 129.34, 128.00, 119.86, 113.07, 58.35, 50.09, 39.83, 36.95, 31.98, 27.88, 21.07. Mass (m/z) :Calculated 308.15, Founded 309.00. Anal. Cal. For $C_{19}H_{20}N_2O_2$: C, 74.00, H, 6.54, N, 9.08, O, 10.38 %. Found: C, 74.20, H, 6.58, N, 8.96 %.

2-amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4h)

M. P.: 205- 207 ºC. IR (KBr): υ = 3351, 3256, 3182, 2959, 2228, 2190, 1671, 1214, 1140 cm^{-1}. ^1H NMR (DMSO-d_6,400 MHz): δ = 7.41 – 7.35 (m, 3H), 7.25 – 7.19 (m, 3H), 6.97 (s, 3H), 5.61 (t, J = 0.9 Hz, 1H), 2.43 (dd, J = 1.8, 1.1 Hz, 2H), 2.25 (d, J = 16.1 Hz, 1H), 2.09 (d, J = 16.1 Hz, 1H), 1.00 (d, J = 4.0 Hz, 8H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 195.72, 162.40, 158.60, 141.95, 131.59, 129.43, 128.74, 119.86, 112.88, 58.34, 50.09, 39.83, 36.68, 31.98, 27.88. Mass (m/z) :Calculated 328.10, Founded 328.35. Anal. Cal. for $C_{18}H_{17}ClN_2O_2$: C, 67.75, H, 5.21, Cl, 10.78, N, 8.52, O, 9.73 %. Found: C, 67.69, H, 5.45, N, 8.61 %.

2-amino-4-(4-nitrophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4i)

M. P.: 178- 180 ºC. IR (KBr): υ = 3435, 3356, 2189, 1688, 1217, 1154 cm^{-1}. ^1H NMR (DMSO-d_6,400 MHz): δ = 8.17 – 8.11 (m, 2H), 7.45 – 7.39 (m, 2H), 6.97 (s, 2H), 4.35 (t, J = 0.8 Hz, 1H), 2.43 (dd, J = 1.8, 1.1 Hz, 2H), 2.25 (d, J = 16.1 Hz, 1H), 2.09 (d, J = 16.1 Hz, 1H), 1.00 (d, J = 4.0 Hz, 7H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 195.72, 162.40, 158.60, 152.08, 147.08, 126.90, 124.07, 119.86, 113.51, 58.31, 50.09, 39.83, 35.65, 31.98, 27.88. Mass (m/z) :Calculated 339.12, Found 340.05. Anal. Cal. for $C_{18}H_{17}N_3O_4$: C, 63.71, H, 5.05, N, 12.38, O, 18.86 %. Found: C, 64.00, H, 5.00, N, 12.40 %.

2-amino-4-(4-flurophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4j)

M. P.: 192- 194 ºC. IR (KBr): υ = 3378, 3242, 2195, 1679, 1212, 1145 cm^{-1}. ^1H NMR (DMSO-d_6,400 MHz): δ = 7.39 – 7.32 (m, 3H), 7.15 – 7.07 (m, 3H), 6.97 (s, 3H), 5.61 (t, J = 0.9 Hz, 1H), 2.43 (dd, J = 1.8, 1.1 Hz, 2H), 2.25 (d, J = 16.1 Hz, 1H), 2.09 (d, J = 16.1 Hz, 1H), 1.00 (d, J = 4.0 Hz, 8H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 195.72, 162.98, 162.40, 161.01, 158.60, 140.02 (d, J = 3.8 Hz), 129.88, 129.81, 119.86, 115.82, 115.64, 112.87, 58.32, 50.09, 39.83, 36.83, 31.98, 27.88. Mass (m/z): Calculated 312.13, Founded 313.00. Anal. Cal. for $C_{18}H_{17}FN_2O_2$: C, 69.22, H, 5.49, F, 6.08, N, 8.97, O, 10.24 %. Found: C, 69.35, H, 5.53, N, 9.00 %.

2-amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4k)

M. P.: 201- 202 ºC. IR (KBr): υ = 3380, 3240, 2194, 1681, 1213 cm^{-1}. ^1H NMR (DMSO-d_6,400 MHz): δ = 7.07 – 7.01 (m, 1H), 6.97 (s, 1H), 6.86 – 6.80 (m, 1H), 4.08 (t, J = 0.9 Hz, 0H), 3.80 (s, 1H), 2.43 (dd, J = 1.8, 1.1 Hz, 1H), 1.00 (d, J = 4.0 Hz, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 195.72, 162.40, 158.60, 156.22, 136.87, 128.43, 119.86, 113.57, 113.02, 58.31, 55.35, 50.09, 39.83, 34.79, 31.98, 27.88. Mass (m/z) :Calculated 324.15, Founded 324.70. Anal. Cal. for $C_{19}H_{20}N_2O_3$: C, 70.35, H, 6.21, N, 8.64, O, 14.80 %. Found: C, 71.00, H, 6.80, N, 8.80 %.

2-amino-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4l)

M. P.: 204- 206 ºC. IR (KBr): υ = 3391, 3283, 3161, 2192, 1666, 1240, 1180cm^{-1}. ^1H NMR (DMSO-d_6,400 MHz): δ = 6.97 (s, 2H), 6.95 – 6.89 (m, 2H), 6.69 – 6.63 (m, 2H), 4.08 (t, J = 0.8 Hz, 1H), 2.43 (dd, J = 1.8, 1.1 Hz, 2H), 2.25 (d, J = 16.1 Hz, 1H), 2.09 (d, J = 16.1 Hz, 1H), 1.00 (d, J = 4.0 Hz, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 195.72, 162.40, 158.60, 155.93, 135.12, 128.54, 119.86, 115.37, 113.02, 58.31, 50.09, 39.83, 34.81, 31.98, 27.88. Mass (m/z) :Calculated 310.13, Founded 311.00. Anal. Cal. for $C_{18}H_{18}N_2O_3$: C, 69.66, H, 5.85, N, 9.03, O, 15.47 %. Found: C, 70.00, H, 6.10, N, 8.90 %.

References

1. Sheldon R. A. (**1996**) Selective catalytic synthesis of fine chemicals: opportunities and trends. *J. Mol. Catal*., 107 (1-3) 75-83.
2. Li C. J. (**2005**) Organic Reactions in Aqueous Media with a Focus on Carbon−Carbon Bond Formations: A Decade Update. *Chem. Rev*., 105 (8), 3095-3166.
3. Boy C., and Wolfgang A. H. **(2006)** Aqueous-Phase Organometallic Catalysis: Concepts and Applications, 2nd, *Completely Revised and Enlarged Edition*. 780.

4. Kumar D., Reddy V. B., Sharad S., Dube U., and Kapur S. (**2009**) A facile one-pot green synthesis and antibacterial activity of 2-amino-4H-pyrans and 2-amino-5-oxo-5,6,7,8-tetrahydro-4H-chromenes. *Eur. J. Med. Chem*., 44 (9) 3805-3809.
5. Adreani L. L., and Lapi E. (**1960**) On some new esters of coumarin-3-carboxylic acid with balsamicand bronchodilator action. *Boll. Chim. Farm*., 99 583-586.
6. Bonsignore L., Loy G., SecciD., and Calignano A. (**1993**) Synthesis and pharmacological activity of 2-oxo-(2H) 1-benzopyran-3-carboxamide derivatives. *Eur. J. Med. Chem.,* 28 (6) 517-520.
7. Konkoy C. S., Fick D. B., Cai S. X., and Lan Keana N. C. J. F. W. (**2001**) *PCT Int. Appl. WO 0075123,* (2000); *Chem Abstr*., 134, 29313a.
8. Hafez E. A. A., Elnagdi M. H., Elagamey A. G. A., and El-Taweel F. M. A. A. (**1987**) Nitrilesin heterocyclic synthesis: Novel synthesis of benzo[c]-coumarin and of benzo[c]pyrano[3,2-c]quinoline derivatives. *Heterocycles*, 26 (4) 903-9097.
9. Jin T. S., Xiao J. C., Wang S. J., and Shuang Li. T. (**2004**) Ultrasound-assisted synthesis of 2-amino-2-chromenes with acetyltrimethylammonium bromide in aqueous media, *Ultrasonics Sonochemistry,* 11 (6) 393-397.
10. Ren Y. M., and Cai C. (**2008**) Convenient and efficient method for synthesis of substituted2-amino-2-chromenes using catalytic amount of iodine and K_2CO_3 in aqueous medium. *Catalysis Communications,* 9 (6) 1017-1020.
11. Wang L. M., Shao J. H., Tian H., Wang Y. H., and Liu B. (**2006**) Rare earth perfluorooctanoate [$RE(PFO)_3$] catalyzed one-pot synthesis of benzopyran derivatives, *J. Fluo. Chem*., 127 (1) 97-100.
12. Habibi D., and Shamsian A. (**2013**) An efficient one-pot synthesis of dihydropyrano[c]chromenes and amino-2-chromenes under solvent-free conditions. *J. Chem. Res.*, 37 (4), 253-255.
13. Jin T. S., WangA. Q., Wang X., Zhang J. S., and Tong-Shuang Li. (**2004**) A Clean One-pot Synthesis of Tetrahydrobenzo[*b*]pyran Derivatives Catalyzed by Hexadecyltrimethyl Ammonium Bromide in Aqueous Media. *Synlett.,* 5 871-873.
14. Shi D. Q., Zhang S., Zhuang Q. Y., Tu S. J., and Hu H. W. (**2003**) Clean synthesis of 2-amino-3-cyano-4-aryl-7,7-dimethyl-5-oxo-4H-5,6, 7,8-tetrahydrobenzo[b] pyran in water. *Chin. J. Org. Chem*., 23 877-879.
15. Sofan M. A., El-Taweel F. M. A. A., and Elnagdi, M. H. (**1989**) Studies on cinnamonitriles: The reaction of cinnamonitriles with cyclopentanone. *Liebigs Ann. Chem*., 1989 (9) 935-936.
16. Ballini R., Bigi F., and Conforti M. L. (**2000**) Multicomponent reactions under clay catalysis. *Catal. Today*, 60 (3-4) 305-309.
17. Pore D. M., Undale K. A., Dongare B. B., and Desai U. V. (**2009**) Potassium Phosphate Catalyzed a Rapid Three-Component Synthesis of Tetrahydrobenzo[*b*]pyran at Ambient Temperature. *Catal. Lett.,* 132 104-108.
18. Gao S., Tsai C. H., Tseng C., and Yao C. F. (**2008**) Fluoride ion catalyzed multicomponent reactions for efficient synthesis of 4H-chromene and N-arylquinoline derivatives in aqueous media. *Tetrahedron,* 64 (38) 9143-9149.
19. Mirza-Aghayan M., Nazmde S., Boukherroub R., Rahimifard M., Tarlani A. A., and Abolghasemi-Malakshah M. (**2013**) Convenient and Efficient One-Pot Method for the Synthesis of 2-Aminotetrahydro-4H-chromenes and 2-Amino-4H-benzo[h]-chromenes Using Catalytic Amount of Amino- Functionalized MCM-41 in Aqueous Media. *Syn. Comm.,* 43 (19) 1499-1507.
20. Panel K. H., and Lin A. N. K. (**1996**) Na promotion of Pd/MgO catalysts for low-pressure one-step synthesis of MIBK from acetone + H_2. *Applied Catalysis A: General*., 147 (2) L259-L265.
21. Kumar B. S., Srinivasulu N., and Udupi R. H. (**2002**) *Russ. Chem. Bull. Int. Ed.,* 51 2239.
22. Bloxham J., Dell C. P., and Smith C. W. (**1994**) Preparation of Some New Benzylidenemalononitriles by an SNAr Reaction: Application to Naphtho[1,2-b]pyran Synthesis. *Heterocycles*, 38 (2) 399-408.

23. Zhou J. F., Tu S. J., and Gao Y. (**2001**) One pot synthesis of pyrans and pyrano[2,3-c]pyrazole derivatives under microwave irradiation, Chin. *J. Org. Chem.,* 21 742-745.
24. Abdolmohammadia S., and Balalaie S. (**2007**) Novel and efficient catalysts for the one-pot synthesis of 3,4-dihydropyrano[c]chromene derivatives in aqueous media. *Tet. Lett*., 48 (18) 3299-3303.
25. Kidwai M., Saxena S., and Thukral S. S. (**2005**) Aqua mediated synthesis of substituted 2-amino-4H-chromenes and in vitro study as antibacterial agents. *Bioorg. Med. Chem. Lett*., 15 (19) 4295-4298.
26. Devi I., and Bhuyan P. J. (**2004**) Sodium bromide catalyzed one-pot synthesis of tetrahydrobenzo[b]pyrans via a three-component cyclocondensation under microwave irradiation and solvent free conditions, *Tetrahedron Lett*., 45 (47) 8625-8627.
27. Vinatoru M., Bartha E., Badea F., and Luche J. L. (**1998**) Sonochemical and thermal redox reactions of triphenylmethane and triphenylmethylcarbinol in nitrobenzene. *Ultrason. Sonochem.,* 5 (1) 27-31.
28. Meciarova M., Toma S., and Luche J. L. (**2001**) The sonochemicalarylation of malonic esters mediated by manganese triacetate, *Ultrason. Sonochem.,* 8 (2) 119-122.
29. Cabello N., Cintas P., and Luche J. L. (**2003**) Sonochemical effects in the additions of furan to masked ortho-benzoquinones. *Ultrason. Sonochem*., 10 (1) 25-31.
30. Javed T., Mason T. J., Phull S. S., Baker N. R., and Robertson A. (**1995**) Influence of ultrasound on the Diels-Alder cyclization reaction: synthesis of some hydroquinone derivatives and lonapalene, an anti-psoriatic agent. *Ultrason. Sonochem*., 2 (1) S3-S4.
31. Bravo J. L., Lopez I., Cintas P., Silvero G., and Aravalo M. J. (**2006**) Sonochemical cycloadditions in ionic liquids. Lessons from model cases involving common dienes and carbonyl dienophiles. *Ultrason. Sonochem*., 13 (5) 408-414.
32. Zheng H., Li H., and Shao H. (**2009**) One-pot three-component Mannich-type reactions using Sulfamic acid catalyst under ultrasound irradiation, *Ultrason. Sonochem.,* 16 (6) 758-762.
33. Cella R., and Stefani H. A. (**2009**) Ultrasound in heterocycles chemistry. *Tetrahedron,* 65 (13) 2619-2641.
34. Luche J. L., (**1998**) *Synthetic Organic Sonochemistry*, Plenum Press, New York;
35. Li J. T., Wang S. X., Chen G. F., and Li T. S. (**2005**) Some applications of ultrasound irradiation in organic synthesis. *Curr. Org. Synth.,* 2 (3) 415-436.
36. Kumar H., and Parmar A. (**2008**) Ultrasound promoted $ZrCl_4$ catalyzed rapid synthesis of substituted 1,2,3,4-tetrahydropyrimidine-2-ones in solvent or dry media. *Ultrason. Sonchem.,* 15 (2) 129-132.
37. Kirtikar K. R., and Basu B. D. (**1933**) *Indian Med. Plants*, 2, 1777-1781.
38. Government of India*,* (**2001**) *TheAyurvedic Pharmacopoeia of India: Part I, Vol. II,* Department of Indian Systems of Medicine & Homeopathy, New Delhi, 157.
39. Gandhidasan R., Thamaraichelvan A., and Baburaj S. (**1961**) Anti-inflammatory action of Lanneacoromandelica by HRBC membrane stabilization. *Fitoterapia,* 62, 81-83.
40. Rang H. P., Dale M. M., Ritter J. M., and Moore P. K. (**2005**) *Pharmacology,* 5th ed., Elsevier, India 27.