A Platinum Open Access Journal for Organic Chemistry

Paper

Free to Authors and Readers

DOAJ Seal

Arkivoc **2022**, part vi, 0-0

to be inserted by editorial office

Greener route for the synthesis of chromone using Amberlyst®15 via enaminones

Kalidasu Sheelam, [a,b] Pradeepkumar Thota,[a] Shrinivas Kottawar,[a] Srilalitha Vinnakota,[b,c] Sridhar Chidara,[a] Satyanarayana Yennam,[a] and Manoranjan Behera*[a]

[a]*Chemistry Services, Aragen Life Sciences, Survey NO : 125 (part) & 126, IDA Mallapur, Hyderabad-500076, Telangana, India*

[b]*Department of Chemistry, JNTU, Hyderabad-500082, Telangana, India*

[c]*Department of Chemistry, Faculty of Science of Technology, ICFI Foundation for Higher Education, Dontanpally, Hyderabad-501203, Telangana, India*

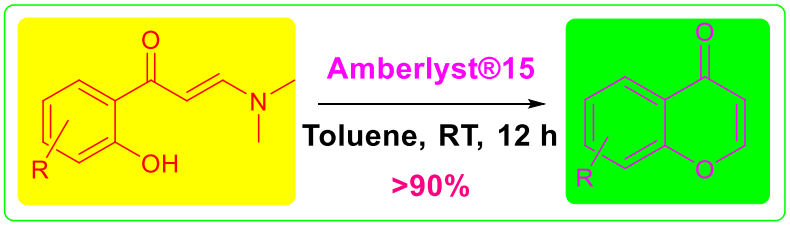
E-mail: Manoranjan.behera@aragen.com

Dedicated to Prof. Sambasivarao Kotha on the occasion of his 65th birthday

Received 06-28-2022 **Accepted Manuscript** 10-23-2022 **Published on line** 11-01-2022

Abstract

An efficient and novel methodology is reported for the synthesis of various 4H-chromene-4-ones via enamino ketone followed by cyclization with Amberlyst®15 was described. The Amberlyst®15 worked well as deaminating agent as well as enhances the efficiency of cyclization reaction for the synthesis of chromones. This method offers several advantages including mild reaction conditions, high yielding, catalyst reusability, lower the reaction toxicity, operational easiness and broad substrate scope.



16 examples with excellent yields

R= Aryl, Hetero aryl, Alkyl, Halo etc.

Keywords: Medicinal chemistry, cyclization, chromone, enamine, Amberlyst-15

Introduction

Chromone derivatives have a wide range of biological activities.[1] Chromone derivatives were shown to be tyrosine and protein kinase inhibitors,[2-3] anti-inflammatory,[4] antiviral,[5] antioxidant[6-7] and antihypertensive agents.[5] Compounds containing chromone moiety are also active at benzodiazepine receptors,[8] on lipooxygenase and cyclooxygenase.[9] In addition to this, they have shown to be anticancer agents[10] and in the treatment of cystic, as they activate the cystic fibrosis trans-membrane conductance regulator.[11] The vast range of biological effects associated with this chromone moiety has resulted in the chromone ring system being considered as a privilege structure.[12-13] A variety of biologically active compounds synthesized from chromones have been found widespread use in medicinal chemistry (Figure 1). [14]

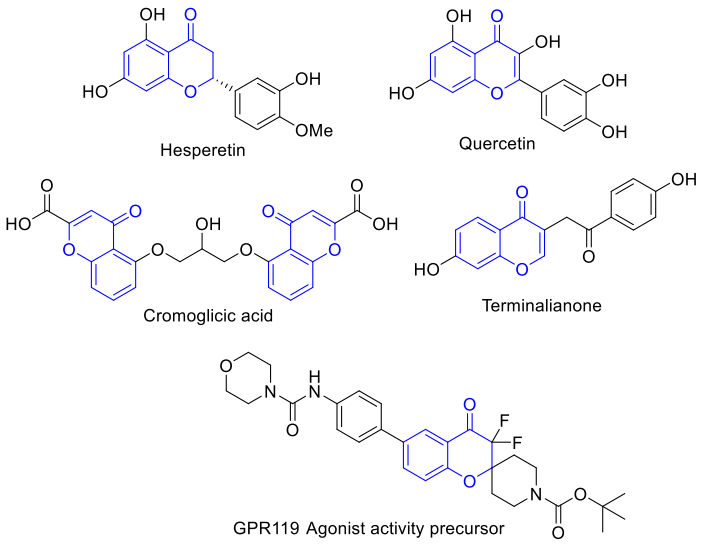
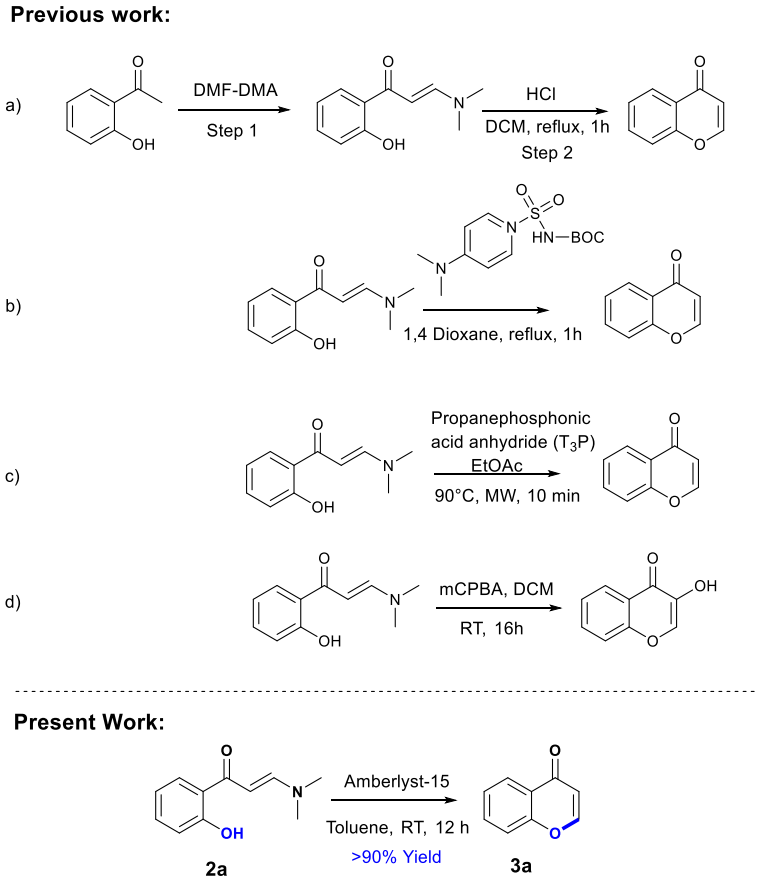


Figure 1. Biologically Active Compounds Derived from Chroman-4-ones.

The chemistry of Amberlyst®15 is well known in the past decade.[15] It is a heterogeneous macro reticular polystyrene-based ion exchange resin and contains strongly acidic sulfonic group functionality. Amberlyst®15 has many avantages viz. safe to use, easy to measure and easily separable at the end of reaction. Amberlyst-15 is now commonly used as a heterogeneous reusable acid catalyst in organic synthesis for a variety of selective transformations of simple and complex molecules.[16-17]

In general, synthesis of chromones has required acidic or basic conditions. One of the first methods for the synthesis of chromone was introduced by Heywang and Kostanecki which involved decarboxylation of chromone-2-carboxylic acid.[18] The traditional 2,3-disubtituted benzopyranone were synthesized under acidic condition with 3-aryl-1-(2-hydroxyphenyl) propane-1,3-dione derivatives undergoing intramolecular condensation. Mostly, Claisen ester condensation and Bayer-Venkataraman rearrangement are commonly used for synthesis of 1,3-dione derivatives. Most of the synthesis was reported under acidic reaction conditions whereas by using basic reaction condition for ring closure required several hours. *Gammill. R. B. et.al* was reported synthesis of chromone scaffolds and their 3-halogenated derivatives.[19-20] Recently, *Joussot and co-workers* reported an efficient synthesis of 3-substituted chromones via enamino ketones.[21] Synthesis of 3-benzylated chromones are also reported in the presence of NaI from enamino ketones and benzyl bromide.[22] There are limited studies on the synthesis of 2, 3-unsubstitued chromones from enaminones, compared to 3-substituted chromones.[23] For example, chromone **3a** was synthesized by cyclization via

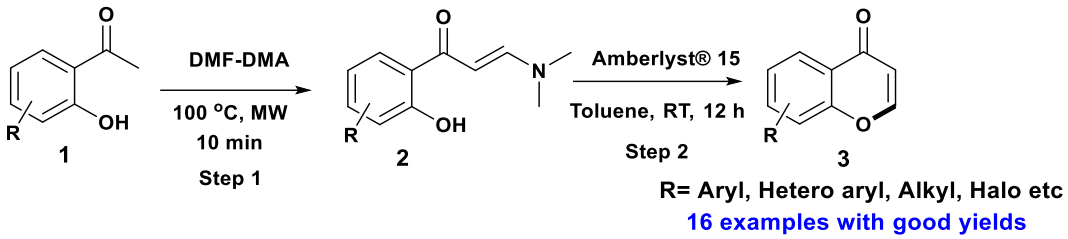
deamination of enamino ketone **2a** by using TMSCl/DMF. By using hydrochloric acid, Chromone synthesis was reported by Pleier A.K. et al, (Scheme 1, entry a).[25] Chromone-3- one was synthesized from enamino ketones (2a) using several sulfamoylating reagents was reported by *Thiel Engelhart* and *Aldrich* (Scheme 1, entry b).[26] T3P was used for chromone synthesis under micro-wave reaction condition, reported by *C. Balakrishna et al,* (Scheme 1, entry c).[27] Using *m*CPBA as an oxidative reagent was used for 3-Hydroxy Chromone synthesis reported by *R. Gudipati et al.* (Scheme 1, entry d).[28] The reported method involves use of stringent reaction conditions like micro-wave, elevated temperature and not used environnemental compatibility solvents. To overcome all these limitations, the development of new methodologies for the synthesis of chromon-4-one is still required.



Scheme 1. Synthetic approach of chromone using Ameberlyst®15.

Results and Discussion

In our continued ongoing efforts to produce innovative synthetic methodologies[29-34] for the synthesis of Chromone-4-one analogues. We envisioned that Amberlyst-15 can be used for the cyclization of enamino ketone to prepare the chromone-4-one by taking advantage of suitable position of the hydroxyl group in the aromatic ring. Herein, we have described the synthesis of chromone-4-one derivatives by using Amberlyst®15. We have introduced first time, Amberlyst-15 as deamination reagent for the synthesis of chromone derivatives.



Scheme 2. Preparation of Chromone Using Ameberlyst®15.

Initially, 1-(2-hydroxyphenyl) ethanone **1a** was treated with N, N-Dimethylformamide dimethyl acetal under microwave irradiation to synthesized enaminone **2a**,[32] was analyzed by LCMS and ^{1}H-NMR data. The peak at 8.2 ppm in ^{1}H-NMR Spectrum shows the olefinic proton which was close to the nitrogen. The conversion of enaminoketone **(2a)** to chromone **(3a)** was executed by using Amberlyst®15 at room temperature. Thus the model reaction was conducted by treating enaminone (**2a**, 1 mmol) in Toluene solvent with Amberlyst 15 (40% w/w) at ambient temperature. We are pleased to find that this reaction condition worked well for synthesis of chromone with the good yield. (Table 1, Entry 4).

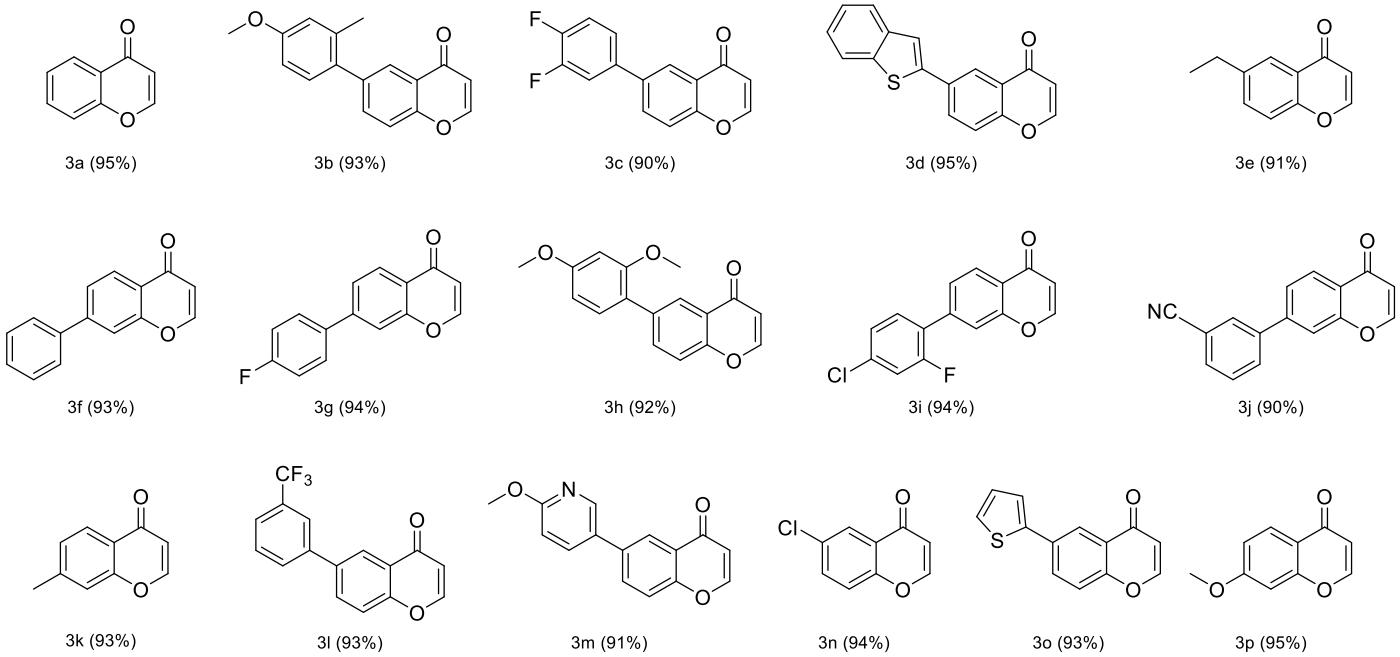
Table 1. Screening optimal reaction conditions

Entry	Reaction conditions[a]	Yield (%)
1	Toluene, RT, 12 h	00
2	Amberlyst, Toluene, RT, 2 h	46
3	Amberlyst, Toluene, RT, 6 h	61
4	Amberlyst, Toluene, RT, 12 h	95
5	Amberlyst, Toluene, 100°C, MW, 2 h	55
6	Amberlyst, DCM, RT, 16 h	89
7	Amberlyst, Acetone, RT, 18 h	40
8	Amberlyst, Dimethyl carbonate, RT, 24 h	46
9	Amberlyst, Acetonitrile, RT, 12 h	59
10[b]	Amberlyst (25 %, w/w), Toluene, RT, 12 h	43

[a]Reaction conditions: Compound **2** (1 mmol), Amberlyst (40% w/w according to **2a**)
[b]25 % w/w according to **2a**

To optimize the reaction conditions, we have screened several réaction conditions (Table 1). Initially, we have performed the reaction without Ameberlyst-15 at room temperature and observed no product formation (entry 1) then we have introduced the Amberlyst-15 and monitored the reaction and showed 46% conversion of desired chromone product, further we have continued the reaction at room temperature for 12 h and observed 95% conversion of desired chromone product (entry 2 to 4). In order to reduce the reaction time, we have performed the reaction under micro-wave irradiation at 100 °C however, not observed much promising conversion of chromone (entry 5).

Table 2. Synthesis of Substituted Chromones with Amberlyst®15



% isolated yield

Standard condition : Enaminone (1 mmol), Amberlyst (40%, w/w), Toluene, RT, 12 h.

To validate further we have changed the solvents like acetone, dimethyl carbonate, acetonitrile and DCM. However, these solvents not shown the good conversion compared to toluene and in DCM conversion was observed 89% (entry 6 to 9). In addition, we have performed controlled experiment by a decrease in the amount to 25% w/w of Amberlyst-15, resulted 43% conversion of chromone (entry 10**).** These experiments showed that the optimized reaction conditions were 40 wt% Amberlyst-15 in toluene at room temperature for 12 h to obtain an 95% yield of 3a (entry 4, Table 1). The work-up procedure also simplified by filtering the Amberlyst-15 and evaporated the reaction mixture under reduced pressure to get pure chromone product. We did not used any toxic solvents or reagents.

We have examined the recyclability of Amberlyst-15 ion-exchange resin up to five cycles. In the first and second cycle, we have observed the 95% yield of chromone **(3a)** consistantly. From third to five cycles yields are 88%, 84% and 75% respectively. We have activated the recycled catalyst Amberlyst-15 using aqueous HCl follwed by water and methanol. When we have used recovered catalyst as such without activation, the reaction was unsuccessful.

Thus, a series of enaminones **2a-p** were taken for the reaction to prove this method applicability. Excellent yield of the intended chromone derivatives **3a-p** (Table 2) was obtained in each case under the optimum reaction conditions. This methodology was tolerant of various halides (Cl, Br, and F) and aryl halides. Both electon rich and deficient aromatic rings showed reactivity similar under this optimal conditions. In Table 2, synthesized Chromones **3a**[27]**, 3e**[35]**, 3k**[36]**, 3n**[27]**, 3o**[37] **and 3p**[38] are reported in the literature, **3b, 3c, 3d, 3f, 3g, 3h, 3i, 3j, 3i and 3m** are unknown compounds. A one-pot chromone synthesis was also tried, *o*-hydroxy acetophenone (**1a**) and DMF-DMA in toluene with amberlyst®15 at RT for 12 hours, chromone **3a** was not formed, instead we have observed the formation of compound **2a** which was confirmed by LCMS data.

Conclusions

In summary, we have developed an efficient and novel methodology, simply reproducible of substituted chromone derivatives by using an excellent Heterogeneous catalyst as amberlyst®15. This method offers an effective alternative to the mild acidic conditions that are required generally for this conversion. The reaction conditions are easy and sufficiently mild to tolerate various functionalities which will function the potential for further functionalization of the chromone products. We anticipate that this method is going to be find widespread application in preparation of chromone derivatives. This methodology can also be used to synthesize chromones on a gram scale.

Experimental Section

General. Dry solvents were purchased from chemical suppliers. Analytical thin-layer chromatography (TLC) was performed on commercially available Merck TLC Silica gel 60 F_{254}. Silica gel column chromatography was performed on silica gel 60 (spherical 100-200 μm). IR spectrawere recorded on Perkin-Elmer FT/IR-4000 using ATR.^{1}H NMR spectra were recorded onVarian-400 (400 MHz) spectrometer. Chemical shifts of ^{1}H NMR spectra were reported relative to tetramethylsilane (^{13}C NMR spectra were recordedon Varian-400 (100 MHz) spectrometer. Chemical shifts of ^{13}C NMR spectra were reported to relative to $CDCl_3$ (77.16) and DMSO-d_6 (39.5). Splitting patterns were reported as s, singlet ; d, doublet ; t, triplet ; q, quartet ; m, multiplet ; br, broad.

General procedure for the synthesis of chromen-4-one derivatives. To a stirred solution of compound Enaminone **2** (1 mmol) was dissolved in toluene (4 ml), was added amberlyst-15 (40% w/w) and the reaction mixture was stirred at RT for 12 h. The progress of the reaction was monitored by TLC (30% Ethyl acetate & Pet ether). After completion of the reaction, the reaction mixture was filtered through celite pad and washed with toluene. The filtrate was evaporated under reduced pressure to obtained crude compound 3, which was further triturated with n-pentane to get pure compond **3** as off white solid.

4*H*-Chromen-4-one (3a). The title compund was prepared following general procedure compound *3a* was off white solid in 95% yield. Mp 51-54 °C. FTIR (KBr): 3479, 3078, 2926, 1647, 1465, 1406, 1348, 1246, 1192, 1128, 1045, 1008 cm−1. 1H NMR (400 MHz, CDCl3): δ 8.23 (dd, *J* 8 Hz, 1.6Hz, 1 H), 7.85 (d, *J* 6 Hz, 1 H), 7.70-7.65 (m, 1 H), 7.47–7.39 (m, 2 H), 6.34 (d, *J* 6 Hz, 1 H) ppm. 13C NMR (125 MHz, CDCl3): δ = 177.6, 156.5, 155.3, 133.8, 125.8, 125.2, 124.9, 118.2, 113.0. MS (EI): *m/z* 147(M+1,100). HRMS : (ESI) : Calcd for $C_9H_7O_2$ [M+H]+ : 147.1450; Found: 147.1368.

7-(4-Methoxy-2-methylphenyl)-4*H*-chromen-4-one (3b). The titled compund was prepared following general procedure compound *3b* was isolated as off white solid in 93% yield. Mp 118-121 °C. FTIR (KBr) : 3406, 3055, 2833, 2223, 1622, 1504, 1421, 1330, 1251, 1141, 1037 cm−1. 1H NMR (400 MHz, CDCl3) : δ 8.14 (d, *J* 1.6 Hz, 1 H), 7.88 (d, *J* 6 Hz, 1 H), 7.63(dt, *J* 8.4 Hz, 1.2 Hz, 1 H),7.49 (d, *J* 8.4 Hz, 1 H), 7.18(d, *J* 8.4 Hz, 1 H), 6.83-6.80 (m, 1H), 6.37 (d, *J* 6 Hz, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 177.7, 159.1, 155.3, 155.2, 139.0, 136.7, 135.2, 132.6, 131.0, 125.9, 124.5, 117.8, 115.9, 113.0, 111.3, 55.3, 20.7. MS (EI) : *m/z* 267(M+1,100). HRMS : (ESI) : Calcd for $C_{17}H_{14}O_3$ [M+H]+ : 267.2960; Found: 267.3283.

6-(3,4-Difluorophenyl)-4*H*-chromen-4-one (3c). The titled compund was prepared following general procedure compound *3c* was isolated as off-white solid in 90% yield. Mp 161-163 °C. FTIR (KBr): 3278, 3095, 3024, 2943, 2860, 1649, 1562, 1485, 1404, 1286, 1205, 1130, 1035 cm−1. 1H NMR (400 MHz, CDCl3): δ 8.36 (d, *J* 2 Hz, 1 H), 7.89 (d, *J* 6 Hz, 1 H), 7.84 (dd, *J* 8.8 Hz, 2.4 Hz, 1 H), 7.56 (d, *J* 8.8 Hz, 1 H), 7.54-7.43 (m, 1 H),

7.39-7.38 (m, 1 H), 7.38-7.27 (m, 1 H),6.38 (d, *J* 6 Hz, 1 H) ppm. 13C NMR (125 MHz, CDCl3): δ = 177.4, 156.1, 155.4, 136.3, 132.3, 125.1, 123.7, 123.2, 119.0, 117.9, 117.8, 116.2, 116.1, 113.1. MS (EI): *m/z* 259(M+1,100). HRMS: (ESI): Calcd for $C_{15}H_8F_2O_2$ [M+H]+: 259.2238; Found: 259.2113.

6-(Benzo[b]thiophen-2-yl)-4*H*-chromen-4-one (3d). The titled compund was prepared following general procedure compound 3a was isolated as off white solid in 95% yield. Mp 121-125 °C. FTIR (KBr): 3074, 1647, 1527, 1510, 1433, 1309, 1236, 1134, 1028, 839, 748 cm−1.1H NMR (400 MHz, CDCl3): δ = 8.43 (d, *J* 2 Hz, 1 H), 7.93-7.89 (m, 4 H), 7.60 (d, *J* 8.8 Hz, 1 H), 7.50 (s, 1 H), 7.43-7.41 (m, 2 H), 6.40 (d, *J* 6 Hz, 1 H). 13C NMR (125 MHz, CDCl3): δ = 177.5, 155.9, 155.3, 140.7, 137.4, 136.1, 134.1, 133.4, 125.3, 125.1, 124.7, 124.6, 123.0, 122.5, 118.7, 113.1. MS (EI): *m/z* 279(M+1,100). HRMS: (ESI): Calcd for $C17H_{10}O_2S$ [M+H]+: 279.3250; Found: 279.2479.

6-Ethyl-4*H*-chromen-4-one (3e). The titled compund was prepared following general procedure compound *3e* was isolated as pale yellow solid in 91% yield. Mp 85-88 °C. FTIR (KBr): 2980, 2916, 2858, 1653, 1541, 1490, 1425, 1319, 1257, 1199, 1128, 1029 cm−1. 1H NMR (500 MHz, CDCl3): δ 8.02 (d, *J* 1.5 Hz, 1 H), 7.84 (d, *J* 6 Hz, 1 H), 7.52 (dd, *J* 8.5 Hz, 2 Hz, 1 H), 7.39 (d, *J* 8.5 Hz, 1 H), 6.33 (d, *J* 6 Hz, 1 H), 2.76 (m, 2 H), 1.28 (t, *J* 15 Hz, 3 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 176.8, 154.1, 140.5, 132.9, 123.6, 122.9, 117.0, 111.7, 28.7, 27.3, 14.4. MS (EI): *m/z* 175(M+1,100). HRMS: (ESI): Calcd for $C_{11}H_{10}O_2$ [M+H]+: 175.1990; Found: 175.1980.

7-Phenyl-4*H*-chromen-4-one (3f). The titled compund was prepared following general procedure compound *3f* was isolated as pale yellow solid in 93% yield. Mp 147-150 °C. FTIR (KBr): 3332, 3151, 3078, 2920, 2848, 1641, 1544, 1494, 1460, 1421, 1352, 1313, 1242, 1145, 1010 cm−1. 1H NMR (400 MHz, CDCl3) : δ 8.27 (d, *J* 8.8 Hz, 1 H), 7.88 (d, *J* 6 Hz, 1 H), 7.67-7.04 (m, 4 H), 7.52-7.42 (m. 3H), 6.37 (d, *J* 7.2 Hz, 1 H) ppm. 13C NMR (125 MHz, CDCl3) : δ =177.5, 156.9, 155.4, 147.0, 139.1, 129.1, 128.7, 127.4, 126.3, 124.4, 123.6, 116.2, 113.1. MS (EI): *m/z* 223(M+1,100). HRMS : (ESI): Calcd for $C_{15}H_{10}O_2$ [M+H]+: 223.2430; Found: 223.2121

7-(4-Fluorophenyl)-4*H*-chromen-4-one (3g). The titled compund was prepared following general procedure compound *3g* was isolated as off white solid in 94% yield. Mp 111-114 °C. FTIR (KBr): 3421, 3055, 2964, 2918, 2850, 1649, 1606, 1462, 1386, 1346, 1261, 1178, 1097, 1020 cm−1. 1H NMR (400 MHz, CDCl3) : δ 8.41 (d, *J* 2 Hz, 1 H), 7.90-7.87 (m, 2 H), 7.56 (d, *J* 8.8 Hz, 1 H), 7.44-7.40 (m, 2 H), 7.34 (dt, *J* 10 Hz, 1.6 Hz, 1 H), 7.11-7.06 (m, 1H), 6.39 (d, *J* 6 Hz, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 176.4, 163.4, 161.0, 155.1, 154.3, 140.4, 136.1, 131.4, 129.4, 124.0, 122.8, 121.8, 117.9, 113.6, 112.9, 112.0. MS (EI) : *m/z* 241(M+1,100). HRMS : (ESI): Calcd for $C_{15}H_9FO_2$ [M+H]+: 241.2334; Found: 241.2789.

6-(2,4-Dimethoxyphenyl)-4*H*-chromen-4-one (3h). The titled compund was prepared following general procedure compound *3h* was isolated as brown solid in 92% yield. Mp 119-122 °C. 1H NMR (400 MHz, CDCl3): δ 8.29 (d, *J* 2 Hz, 1 H), 7.87-7.85 (m, 1 H), 7.47 (d, *J* 8.8 Hz, 1 H), 7.30 (d, *J* 8.4 Hz, 1 H), 6.59 (d, *J* 2.4 Hz, 1 H), 6.57 (s, 1 H), 6.35 (d, *J* 6 Hz, 1 H), 3.86 (s, 3 H), 3.81 (s, 3 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 176.7, 159.8, 156.4, 154.3, 154.1, 134.8, 134.4, 130.4, 124.7, 123.6, 120.6, 116.5, 111.9, 103.8, 97.9, 54.5, 54.4. MS (EI): *m/z* 283(M+1,100). HRMS: (ESI): Calcd for $C_{17}H_{14}O_4$ [M+H]+: 283.2950; Found: 283.3358.

7-(4-Chloro-2-fluorophenyl)-4*H*-chromen-4-one (3i). The titled compund was prepared following general procedure compound *3i* was isolated as off white solid in 94% yield. Mp 131-134 °C. 1H NMR (400 MHz, CDCl3): δ = 8.23 (d, *J* 8.4 Hz, 1 H), 7.892 (d, *J* 6 Hz, 1 H), 7.63 (s, 1 H), 7.56(d, *J* 8 Hz, 1 H), 7.44 (t, *J* =16.8 Hz, 1 H), 7.24 (d, *J* 1.6 Hz, 1 H), 7.28 (s, 1 H), 6.38 (d, *J* 6 Hz, 1 H) ppm. MS (EI): *m/z* 275(M+1,100).

3-(4-Oxo-4*H*-chromen-7-yl)benzonitrile (3j). The titled compund was prepared following general procedure compound *3j* was isolated as off white solid in 90% yield. Mp 118-120 °C. 1H NMR (400 MHz, CDCl3): δ 8.41 (d, *J* 2.4 Hz, 1 H), 7.93-7.87 (m, 1 H), 7.69 (d, *J* 7.6 Hz, 1 H), 7.61-7.57 (m, 2 H), 6.41 (d, *J* 6 Hz, 1 H) ppm. 13C NMR (125 MHz, CDCl3): δ = 177.3, 156.4, 155.5, 140.5, 136.0, 132.3, 131.5, 131.3, 130.7, 129.9, 125.2, 124.1, 119.3,

118.5, 113.3, 113.2. MS (EI): *m/z* 248(M+1,100). HRMS: (ESI): Calcd for $C_{16}H_9NO_2$ [M+H]+: 248.2530; Found: 248.2057.

7-Methyl-4*H*-chromen-4-one (3k). The titled compund was prepared following general procedure compound 3k was isolated as off white solid in 93% yield. Mp 87-90 °C. FTIR (KBr): 3431, 3070, 2922, 2862, 1639, 1446, 1396, 1348, 1303, 1259, 1215, 1145, 1095, 1029 cm−1. 1H NMR (400 MHz, CDCl3): δ 8.10 (d, *J* 8.4 Hz, 1 H), 7.81 (d, *J* 6 Hz, 1 H), 7.26-7.21 (m, 2 H), 6.31 (d, *J* 6 Hz, 1 H), 2.48 (s, 3 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 176.5, 155.6, 154.0, 144.1, 125.7, 124.5, 121.6, 116.8, 111.9, 20.8. MS (EI): *m/z* 161(M+1,100). HRMS: (ESI): Calcd for $C10H_8O_2$ [M+H]+: 161.1720; Found: 161.1520.

6-(3-(Trifluoromethyl) phenyl)-4H-chromen-4-one (3l). The titled compund was prepared following general procedure compound *3l* was isolated as off white solid in 93% yield. Mp 92-95 °C. FTIR (KBr): 3496, 3064, 2927, 1761, 1643, 1481, 1375, 1294, 1103, 1012 cm−1. 1H NMR (400 MHz, CDCl3): δ 8.44 (d, *J* 2 Hz, 1 H), 7.94–7.83 (m, 4 H), 7.64–7.57 (m, 3 H), 6.41 (d, *J* 5.2 Hz, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 176.4, 155.2, 154.4, 139.0, 135.9, 131.5, 129.4, 128.5, 124.1, 123.5, 123.5, 123.0, 122.9, 122.9, 118.0, 112.1. MS (EI): *m/z* 291(M+1,100). HRMS: (ESI): Calcd for $C_{16}H_9F_3O_2$ [M+H]+: 291.2412; Found: 291.2344.

6-(6-Methoxypyridin-3-yl)-4*H*-chromen-4-one (3m). The titled compund was prepared following general procedure compound *3m* was isolated as pale yellow solid in 91% yield. Mp 135-138 °C. FTIR (KBr): 3317, 3138, 3068, 2922, 1722, 1635, 1543, 1475, 1327, 1255, 1199, 1136, 1095, 1058, 1014 cm−1. 1H NMR (400 MHz, CDCl3): δ 8.44 (d, *J* 2.4 Hz, 1 H), 8.35 (d, *J* 2.4 Hz, 1 H), 7.89–7.83 (m, 3 H), 7.56 (d, *J* 8.4 Hz, 1 H), 6.86 (d, *J* 8.4 Hz, 1 H), 6.39 (d, *J* 6 Hz, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 176.5, 162.9, 154.8, 154.3, 144.1, 136.4, 134.2, 131.0, 127.3, 124.1, 122.2, 118.0, 112.0, 110.0, 52.6. MS (EI): *m/z* 254(M+1,100). HRMS: (ESI): Calcd for $C_{15}H_{11}NO_3$ [M+H]+: 254.2570; Found: 254.2617.

6-Chloro-4*H*-chromen-4-one (3n). The titled compund was prepared following general procedure compound *3n* was isolated as off white solid in 94% yield. Mp 133-136 °C. FTIR (KBr): 3479, 3078, 2926, 1647, 1465, 1406, 1348, 1246, 1192, 1128, 1045, 1008 cm−1. 1H NMR (400 MHz, CDCl3): δ 8.18 (d, *J* 2.4 Hz, 1 H), 7.86 (d, *J* 6 Hz, 1 H), 7.63-7.60 (dd, *J* 8.8 Hz, *J* 2 Hz, 1 H), 7.43 (d, *J* 8.8 Hz, 1 H), 6.36 (d, *J* 6 Hz, 1 H) ppm. 13C NMR (125 MHz, CDCl3): δ = 176.3, 155.4, 154.8, 134.0, 131.3, 125.8, 125.3, 119.9, 112.9.
MS (EI): *m/z* 181(M+1,100).

6-(Thiophen-3-yl)-4*H*-chromen-4-one (3o). The titled compund was prepared following general procedure compound *3o* was isolated as off white solid in 93% yield. Mp 101-104 °C. FTIR (KBr): 3093, 2966, 2920, 2852, 1647, 1602, 1525, 1477, 1438, 1390, 1352, 1305, 1261, 1222, 1184, 1136, 1093, 1016 cm−1. 1H NMR (400 MHz, CDCl3): δ 8.41 (d, *J* 1.6 Hz, 1 H), 7.93–7.90 (dd, *J* 8.8 Hz, J=2 Hz, 1 H), 7.87 (d, *J* 6 Hz, 1 H), 7.56 (s, 1 H), 7.51-7.42 (m, 3 H), 6.37 (d, *J* 6 Hz, 1 H) ppm. 13C NMR (125 MHz, CDCl3): δ = 177.6, 155.6, 155.3, 140.4, 133.2, 132.0, 126.8, 126.2, 125.0, 122.7, 121.3, 118.7, 112.9. MS (EI): *m/z* 229(M+1,100). HRMS: (ESI): Calcd for $C_{13}H_8O_2S$ [M+H]+: 229.2650; Found: 229.1784.

7-Methoxy-4*H*-chromen-4-one (3p). The titled compund was prepared following general procedure compound *3p* was isolated as off white solid in 95% yield. Mp 56-57 °C. 1H NMR (400 MHz, CDCl3): δ 8.13 (d, *J* 8.8 Hz, 1 H), 7.78 (d, *J* 6 Hz, 1 H), 6.99–6.96 (dd, *J* 8.8 Hz, *J* =2 Hz, 1 H), 6.84 (d, *J* 2 Hz, 1 H), 6.29 (d, *J* 6 Hz, 1 H), 3.90 (s, 3 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 177.0, 164.1, 158.2, 154.8, 127.2, 118.8, 114.5, 112.9, 100.4, 55.8. MS (EI): *m/z* 177(M+1,100). HRMS: (ESI): Calcd for $C_{10}H_8O_3$ [M+H]+: 177.1710; Found: 177.2031.

Acknowledgements

Authors are grateful to aragen Life Sciences for the encouragement and financial support. Assistance from analytical department is appreciated. We thank Dr. Somesh Sharma for his invaluable continue support.

Supplementary Material

Supplementary data associated with this paper can be found in the online version

References

1. Reis, J.; Gaspar, A.; Milhazes, N.; Borges, M. *J. Med. Chem.* **2017**, *60*, 7941. https://doi.org/10.1021/acs.jmedchem.6b01720
2. Leahy, J. J. J.; Golding, B. T.; Griffin, R. J.; Hardcastle, I. R.; Richardson, C.; Rigoreau, L.; Smith, G. C. M. *Biorg. Med. Chem. Lett.* **2004**, *14*, 6083. https://doi.org/10.1016/j.bmcl.2004.09.060
3. Griffin, R. J.; Fontana, G.; Golding, B. T.; Guird, S.; Hardcastle, I.R.; Leahy, J.J.J. ; Martin, N.; Richardson, L.; Rigoreau, M.; Stockley, G. C. M.; Smith, *C. J.Med. Chem*. **2005**, 48, 569. https://doi.org/10.1021/jm049526a
4. Kim, H. P.; Son, K. H.; Chang, H. W.; Kang, S. S. *J. Pharmacol. Sci.* **2004**, *14*, 6083.
5. Bhat, A. S.; Whetstone, J. L.; Brueggemeier, R. *Tetrahedron Lett*. **1999**, *40*, 2469. https://doi.org/10.1016/S0040-4039(99)00279-8
6. Benett, C. J.; Caldwell, S. T.; McPhail, D. B.; Morrice, P. C.; Duthie, G. G.; Hartley, R. C. *Bioorg. Med. Chem.* **2004**, *12*, 2079. https://doi.org/10.1016/j.bmc.2004.02.031
7. Krishnamachari, V.; Levin, L. H.; Zhou, C.; Pare, P. W. *Chem. Res. Toxicol.* **2004**, *17*, 795. https://doi.org/10.1021/tx034242z
8. Marder, M.; Viola, H.; Bacigaluppo, J. A.; Colombo, m. I.; Wasowski, C.; Wolfman, C.; Medina, V.; Ruveda, V.; Paladini, A. C. *Biochem. Biophys. Res. Commn.* **1998**, *249*, 481. https://doi.org/10.1006/bbrc.1998.9146
9. Hoult, J. R. S.; Moroney, M. A.; Paya, M. *Methods. Enzymol*. **1994**, *234*, 443. https://doi.org/10.1016/0076-6879(94)34115-X
10. Parmar, V. S.; Bracke, M. E.; Philippe, J.; Wengel, J.; Jain, S. C.; Olsen, C. E.; Bish, K. S.; Sharma, N. K.; Courtens, A.; Sharma, S. K.; Venneken, K.; Van Marck, V.; Singh, S. K.; Kumar, N.; Kumar, A.; Malhothra, S.; Kumar, R.; Rajwansh, V. K.; Jain, R.; Maree, M. M. *Bioorg. Med. Chem.* **1997,** *5*, 1609. https://doi.org/10.1016/S0968-0896(97)00091-6
11. Galietta, L. J.; Springsteel, M. F.; Eda, M.; Neidzinsk, E. J.; By, K.; Haddadin, M. J.; Nantz, M. H.; Verkman, A. S. *J. Boil. Chem* **.2001**, *276*, 19723. https://doi.org/10.1074/jbc.M101892200
12. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev*. **2003**, *103,* 893. https://doi.org/10.1021/cr020033s
13. Gaspar, A.; Matos, J. M.; Garrideo, J.; Uriarte, E.; Borges, F. *Chem Rev.* **2014**, *114*, 4960.

https://doi.org/10.1021/cr400265z
14. Lewinsohn, E.; Britsch, L.; Mazur, Y.; Gressel, J. Plant Physiol. **1989**, *91*, 1323. https://doi.org/10.1104/pp.91.4.1323
15. Pal, R.; Sarkar, T.; Khasnobis, S. *Arkivoc* **2012**, (i), 570. http://dx.doi.org/10.3998/ark.5550190.0013.114
16. Thirupathi, P.; Venkatagiri, N.; Krishna Reddy, C. *Chemistry Select* **2018**, 3, 9911. https://doi.org/10.1002/slct.201801664
17. Jadhav, H.; Annapure, U. *J. Chem. Sci.* 2012, 133, 1.
18. Li, N G.; Shi, Z. H.; Tang, Y P.; Ma, H Y.; Yang, J. P.; Li, B. Q.; Wang, Z J.; Song, S. L.; Duan J. A. *J. Het. Chem.* **2010**, *47*, 785. https://doi.org/10.1002/jhet.393
19. Gammill, R. B. *Synthesis* **1979**, 901. https://doi.org/10.1055/s-1979-28869
20. Ravikumar, P.; Balakrishna, C.; Murali, B.; Gudipati, R.; Hota, P. K.; Chaudhary, A. B.; Jaya Shree, A.; Yennam, S.; Behera, M. *J. Chem. Sci*. **2016**, *129*, 441. https://doi.org/10.1007/s12039-016-1042-z
21. Joussot, J.; Schoenfelder, A.; Larquetoux, L.; Nicolas, M.; Suffet, J.; Blond, G. *Synthesis* **2016**, *48*, 3364. https://doi.org/10.1055/s-0035-1562513
22. Lin, Y. F.; Fong, C.; Peng, W. L.; Tang, K. C.; Liang, Y. E.; Li, W. T. *J. Org. Chem.* **2017**, *82*, 1085 https://doi.org/10.1055/s-0035-1562513
23. Khoobi, M.; Alipour, M.; Zarei, S.; Jafarpour, F.; Shafiee, A. *Chem. Commun.,* **2012**, *48*, 2985. https://doi.org/10.1039/c2cc18150a
24. Iaroshenko, V. O.; Mkrtchyan, S.; Gevorgyan, A.; Miliutina, M.; Villinger, A.; Volochnyuk, D.; Sosnovskikh, V. Y.; Langer, P. *Org. Biomol. Chem*. **2012**, *10*, 890. https://doi.org/10.1039/C1OB06494K
25. M. Spadafora, V. Y. Postupalenko, V. V. Shvadchak, A. S. Klymchenko, *Tetrahedron* **2009**, 65, 7809 https://doi.org/10.1016/j.tet.2009.07.021
26. Engelhart, C. A.; Aldrich, C. C. *J. Org. Chem*. **2013**, *78*, 7470. https://doi.org/10.1021/jo400976f
27. C. Balakrishna, V. Kandula, R. Gudipati, S. Yennam, P. U. Devi, M. Behera, *Synlett*, **2018**, *29*, 1087. https://doi.org/10.1055/s-0036-1591898
28. Gudipati, Ramakrishna; Kandula, Venu; Raghavulu, K.; Basavaiah, K.; Yennam, Satyanarayana; Behera, Manoranjan, *Chemistry Select*, **2020**, 5, 7093. https://doi.org/10.1002/slct.202001749
29. Ravi Kumar, P.; Behera, M.; Raghavulu, K.; Jaya Shree, A.; Satyanarayana, Y. *Tetrahedron Lett*. **2012**, *53*, 4108. https://doi.org/10.1016/j.tetlet.2012.05.123
30. Ravi Kumar, P.; Behera, M.; Sambaiah, M.; Venu, K.; Nagaraju, P.; Jaya Shree, A.; Satyanarayana, Y. *Journal of Amino Acids*. **2014** Article ID *721291* https://doi.org/10.1155/2014/721291
31. Balakrishna, C.; Nagaraju, P.; Satyanarayana, Y. Uma Devi, P.; Behera, M. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4753. https://doi.org/10.1016/j.bmcl.2015.07.099
32. Sambaiah, M.; Raghavulu, K.; Shiva Kumar, K.; Satyanarayana, Y.; Behera, M. *New J. Chem* **2017**, *41*, 10020.

https://doi.org/10.1039/C7NJ01839H
33. Venu, K.; Ramakrishna, G.; Muralidharan, K.; Anindita, C.; Satyanarayana, Y.; Behera, M. *J. Chem. Sci*. **2017**, *129*, 1233.
https://doi.org/10.1007/s12039-017-1328-9
34. Kandula, V.; Thota. P. K.; Mallesham, P.; Raghavulu, K.; Chatterjee, A., Yennam, S., Behera, M., *Synlett* **2019**, 30, 2295.
https://doi.org/10.1055/s-0039-1691489
35. Qi, Xueyu; Xiang, Haoyue; Yang, Yuhong; Yang, Chunhao. *RSC Advances* **2015**, 5, 98549
https://doi.org/10.1039/C5RA21915A
36. Trost, B.M.; Gnanamani, E.; Kalnmals, C. A.; Hung, C. J.; Tracy, J. S. *Journal of the American Chemical Society* **2019**, 141, 1489
https://doi.org/10.1021/jacs.8b13367
37. Yang, Y.; Oldenhius, N. J.; Buchwald, S. L. *Angewandte Chemie* **2013**, 52, 615
https://doi.org/10.1002/anie.201207750
38. Jin, C.; Zhang, X.; Sun, B.; Yan, Z.; Xu, T. *Synlett* **2019**, 30, 1585
https://doi.org/10.1055/s-0037-1611864