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Re-cyclization of 3-(*E*)-methyl 3-(4-oxo-4*H*-chromen-3-yl)acrylate with amines and their potential mechanism

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ABSTRACT

The synthesis of 2-pyridone derivatives from different substituted amines and various 3-(*E*)-methyl 3-(4-oxo-4*H*-chromen-3-yl)acrylate derivatives was proposed and described. The optimized reaction conditions and the generality of the reaction were investigated, respectively. Moreover, less side products could be formed than the traditional method. Finally, based on the fact that (*E*)-methyl 2-(7-methoxy-4-oxo-3-((phenylamino)methylene)chroman-2-yl)acetate was separated and determined via X-ray single crystal diffraction, we could propose an interesting and reasonable reaction mechanism for the first time. The reaction could render this method particularly attractive for the efficient preparation of biologically and medicinally interesting molecules.

1. Introduction

As known to all, the benzopyran-4-one derivatives, also known as chromone, have shown promising a wide range of valuable physiological activities.[1–3] However, the useful application of chromone as starting material affording drug-like aromatic compounds was less known.[4–9] Among them, 3-formylchromone (Fig. 1) derivatives are the most attractive substrates, which were widely used to prepare a variety of heterocyclic compounds.[10–13] The chemical structure of 3-formylchromone has been surveyed previously and the most interesting feature of this molecule is that it contains three potential sites, which could be attacked by nucleophilic species: the C-4 atom, unsaturated keto function; the C-2 atom, a hidden aldehyde function (Fig. 1), which is very reactive electrophilic center; the C-1′ atom, conjugated second carbonyl group at C-3. In addition, the nucleophilic reactivity of C-2 and C-1′ is similar, whereas, the unsaturated keto function is much lower.[5,10–15]

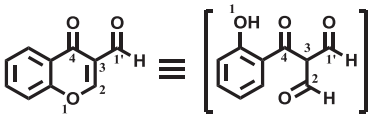

Fig. 1. Chemical structures of 3-formylchromone.

2-Pyridone analogues have been widely found in nature and have a broad range of applications in the medical research.[9,16–23] The synthesis of 2-pyridone derivatives from 3-formylchromone was first proposed by Nohara.[24] However, this method had its own disadvantages, such as low yield, complex products, and incomplete understanding of the reaction mechanism, largely due to the similar reactivity of C-2 and C-1′ mentioned above.[24–29] As shown in Scheme 1, generally, the reaction involved an initial Knoevenagel condensation between aldehyde group and simple nucleophiles (Path **A**, compound **4**). However, 3-formylchromone could be assumed as the synthetic equivalent of the unknown (2-hydroxyphenyl)malonic dialdehyde (Fig. 1). Thus, it is often difficult to tell, which electrophilic center was attacked firstly because of the 'chemical symmetry' of the two centers. Thereby, at the same time, the Michael addition could also occur at position C-2 and subsequent opening of the pyrone moiety (Path **B**, compound **5**).[10,26] For better understanding of the reaction, we had some alteration on the compound **4** to generate compound **6**, which could be easily obtained by Heck reaction.[30] There are two reasons for this change: one is that we kept the basic methyl acrylate side chain at C-3, which is a necessary moiety for 2-pyridone ring cyclization; the other is that C-2 now is the most reactive electrophilic center in this molecule, which is easier and clearer for us to study the next rearrangement step.

2. Results and discussion

In initial investigations, we examined the rearrangement reaction of the model substrate (*E*)-methyl 3-(7-methoxy-4-oxo-4*H*-

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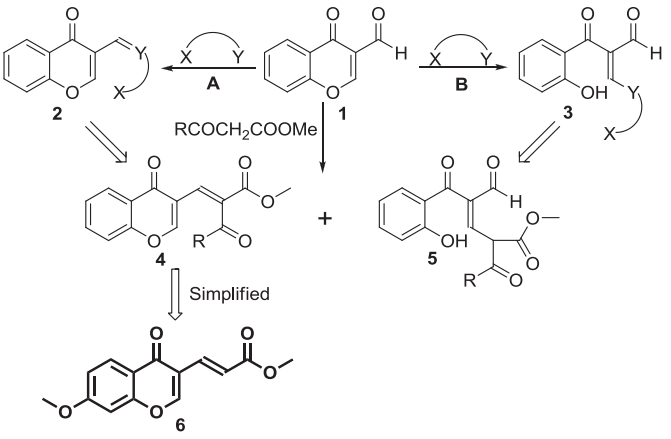


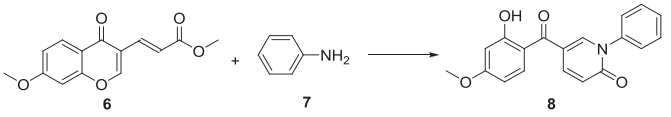
Scheme 1. Design of the compound **6**.

chromen-3-yl)acrylate (**6**) with aniline (**7**), using triethylamine as base, and methanol as solvent at reflux for 10 h (Table 1, entry **1**). A series of different bases, solvents, temperatures, and reaction time were screened. As can be seen from Table 1, of the bases screened, triethylamine, and K_2CO_3 showed the best results and the corresponding products were obtained in 76% and 80% yield, respectively (Table 1, entries **1** and **8**). The results above indicate that either the inorganic base or the organic base could help to have a good yield. There were indications that the choice of solvent had distinct impact. Thereby, solvents, such as methanol, ethanol, acetonitrile, and THF were used, respectively. Considering the nucleophilic reaction, the results reasonably showed that polar protic solvent, such as ethanol and methanol could drastically boost the yields of desired compound because of the solvent effect. Moreover, the higher boiling point made ethanol to be the better selection (Table 1, entries **8** and **11**). Likewise, acetonitrile (strong polar aprotic solvent) have moderate solvent effect and the corresponding product yield was not satisfactory (Table 1, entry **13**). On the contrary, THF is a moderately polar aprotic solvent and was supposed to be negative for this reaction due to its weak solvent effect (Table 1, entry **12**). Finally, reaction time was adjusted to 4, 6, and 8 h, respectively. The results showed that 6 h was exactly the best reaction time for the main product yield (Table 1, entries **14**–**16**).

Thereby, the optimal reaction conditions were using K_2CO_3 (3.0 equiv) as the base and ethanol (25 mL) as the solvent at reflux for 6 h.

Under the optimized reaction conditions, the generality of the reaction was investigated by using substituted (*E*)-methyl 3-(4-oxo-4*H*-chromen-3-yl)acrylate and a variety of substituted amine to produce re-cyclization derivatives. The results are summarized in Tables 2 and 3. The findings showed that these reactions led to production of the corresponding products in moderate to good yields. Notably, although electron-withdrawing group or electron-donating groups with amines were applied and the reaction could be smoothly performed, an electron-donating group was more favorable than an electron-withdrawing group (Table 2, entries **1**–**3**). Furthermore, the presence of hydroxy group on the

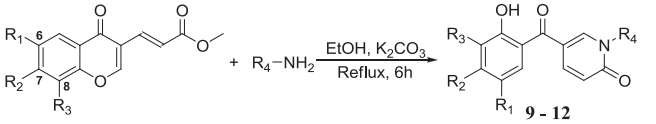
Table 1
Synthesis of compound **8**[a]



Entry	Solvent	Base	Temp (°C)	Time (h)	Yield[b] (%)
1	MeOH	Et_3N	Reflux	10	76
2	MeOH	DMAP	Reflux	10	71
3	MeOH	Pyridine	Reflux	10	0
4	MeOH	NaOH	Reflux	10	69
5	MeOH	KOH	Reflux	10	75
6	MeOH	DBU	Reflux	10	66
7	MeOH	KOAc	Reflux	10	23
8	MeOH	K_2CO_3	Reflux	10	80
9	MeOH	*t*-BuOK	Reflux	10	68
10	EtOH	EtN_3	Reflux	10	82
11	EtOH	K_2CO_3	reflux	10	86
12	THF	K_2CO_3	Reflux	10	Trace
13	MeCN	K_2CO_3	Reflux	10	73
14	EtOH	K_2CO_3	Reflux	8	85
15	EtOH	K_2CO_3	Reflux	6	88
16	EtOH	K_2CO_3	Reflux	4	58

[a] Unless otherwise specified, all reactions were performed with compound **6** (2 mmol), compound **7** (2.4 mmol), and base (6 mmol) in solvent (25 mL) via oil heating.
[b] Isolated yield.

Table 2
Synthesis of compounds **9**–**12**[a]



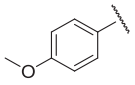
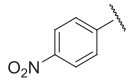
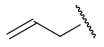
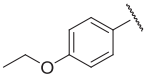
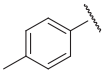
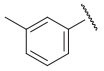
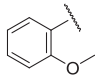
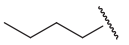
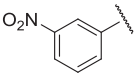
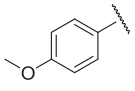
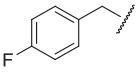
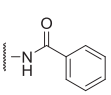
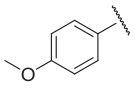
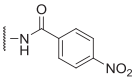
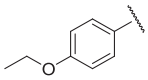
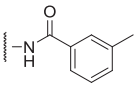
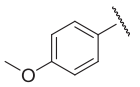
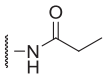
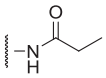
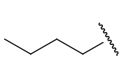
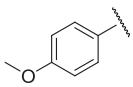
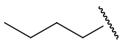
Entry	R_1	R_2	R_3	R_4	Product	Yield[b] (%)
1	H	OCH_3	H		**9a**	91
2	H	OCH_3	H		**9b**	35
3	H	OCH_3	H		**9c**	89
4	H	OH	H		**10a**	66
5	H	OH	H		**10b**	53
6	H	OH	H		**10c**	55
7	H	OH	H		**10d**	68
8	H	OH	H		**10e**	69
9	H	OH	H		**10f**	34
10		OCH_3	H		**11a**	55
11		OCH_3	H		**11b**	33
12	H	OCH_3			**11c**	62

Table 2 (*continued*)

Entry	R_1	R_2	R_3	R_4	Product	Yield[b] (%)
13	H	OCH_3			**11d**	61
14	H	OCH_3			**11e**	71
15	H	OCH_3			**11f**	56
16	H	OCH_3			**11g**	54
17	H	OH	NO_2		**12a**	42
18	H	OH	NO_2		**12b**	50

[a] Unless otherwise specified, all reactions were performed with substituted (*E*)-methyl 3-(4-oxo-4*H*-chromen-3-yl)acrylate (2 mmol), substituted amine (2.4 mmol), and K_2CO_3 (6 mmol) in EtOH (25 mL) via oil heating.
[b] Isolated yield.

position-7 of the (*E*)-methyl 3-(4-oxo-4*H*-chromen-3-yl)acrylate led to decreased yields (Table 2, entries **4**–**9**) as a consequence of weak acidic of the phenol. Moreover, when position-6 of the (*E*)-methyl 3-(4-oxo-4*H*-chromen-3-yl)acrylate was substituted with acetamide, the final yield could also drop to 33–55% (Table 2, entries **10**, **11**). Likewise, different substituted amide at position-8 would also be unfavorable to the re-cyclization and electronic effects of substituents amide affected the reactions and it is clear that an electron-withdrawing group would decrease the reactivity of the reaction (Table 2, entries **12**–**16**). Interestingly, the existence of strong electron-withdrawing group, such as nitro-group on the postion-8 of the benzopyrone did not retard the reaction and the yields were similar to the amide substitutions (Table 2, entries **17**, **18**).

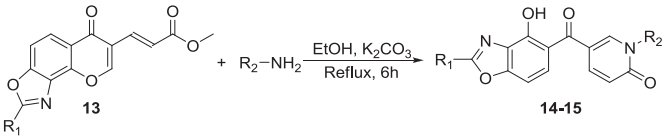
Oxazolyl group at position-7 and position-8 were explored to further probe the scope of the process (Table 3). Clearly, the heterocycle on the benzene ring also strongly contributed to the yield decrease of the re-cyclization. Both steric hindrance effect and electron deficiency of the oxazolyl ring might be the key reasons of the low yields.

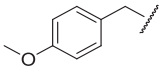
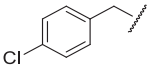
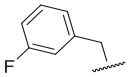
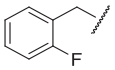
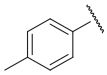
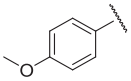
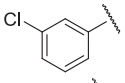
Aliphatic amine (Table 2, entries **3**, **8**, **15**, **16**, and **18**; Table 3, entries **6**–**8**) substations could also be applied for re-cyclization and the yield is similar to the aniline.

In order to further confirm the structure of the 2-pyridone derivative, the crystal structure of compound **9c** was determined. Fig. 2 showed the ORTEP drawing of compound **9c**, indicating that the re-cyclization reaction was successful. Moreover, a key intermediate (**17**) during the re-cyclization was obtained and the crystal structure was also determined. The ORTEP drawing of **17** was shown in Fig. 3.

Based on the fact that intermediates **17** was successfully separated and determined via X-ray single crystal diffraction (Fig. 3), we could propose a tentative reaction mechanism (Scheme 2). There are several proton transfers that have to occur. We have shown a base 'B': carrying out these proton transfers: this might be a molecule of base we used, or it might be a molecule of the solvent. These details do not matter. First of all, amines are good nucleophiles for conjugate addition reactions and the polarization of conjugated C=C bond of compound **6** led to C_2 atom was easily

Table 3
Synthesis of compounds **14**–**15**[a]



Entry	R_1	R_2	Product	Yield[b] (%)
1	H		**14a**	48
2	H		**14b**	47
3	H		**14c**	46
4	H		**14d**	35
5	H		**14e**	45
6	H		**14f**	48
7	H		**14g**	44
8	H		**14h**	39
9	CH_3		**15a**	61
10	CH_3		**15b**	57
11	CH_3		**15c**	56
12	CH_3		**15d**	64

[a] Unless otherwise specified, all reactions were performed with compound **13** (2 mmol), substituted amine (2.4 mmol), and K_2CO_3 (6 mmol) in EtOH (25 mL) via oil heating.
[b] Isolated yield.

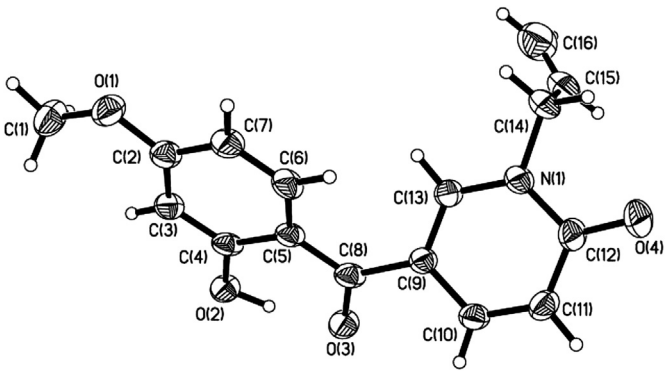


Fig. 2. ORTEP drawing of **9c** (CCDC 705282).

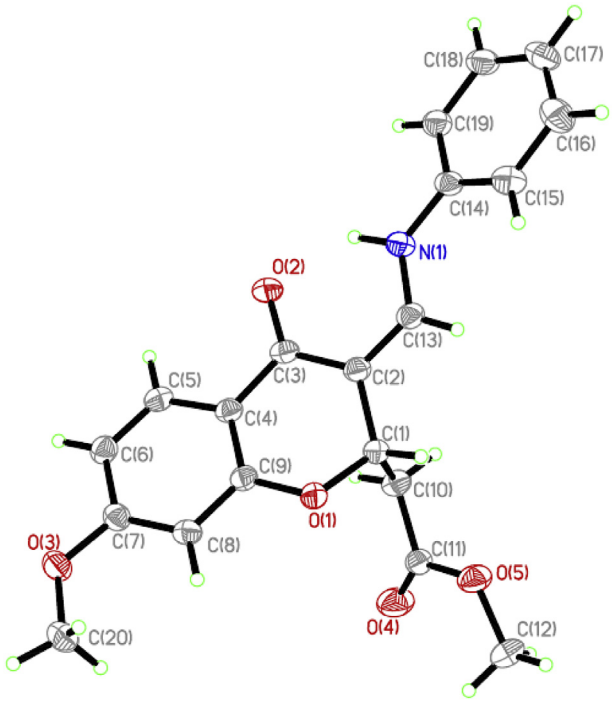


Fig. 3. ORTEP drawing of **17** (CCDC 943099).

attacked by aniline under alkaline condition. Intermediate **B** was then generated by the C–N bond-forming reactions in the next step. Ether linkage cleavage promoted via base resulted in the formation of enamine (intermediate **C**). Transformation among intermediates **C**, **D**, and **E** was evoked by C–C single bond rotation and imine–enamine tautomerism. Moreover, intermediate **E** could undergo another conjugate addition reaction to produce intermediate **17**. However, the ester linkage of **17** was unstable under alkaline condition. As the time went on, the final product **8** could be formed because of the acylation reaction.

cyclization. As expected, compound **18** was also successfully obtained and determined (Scheme 3).

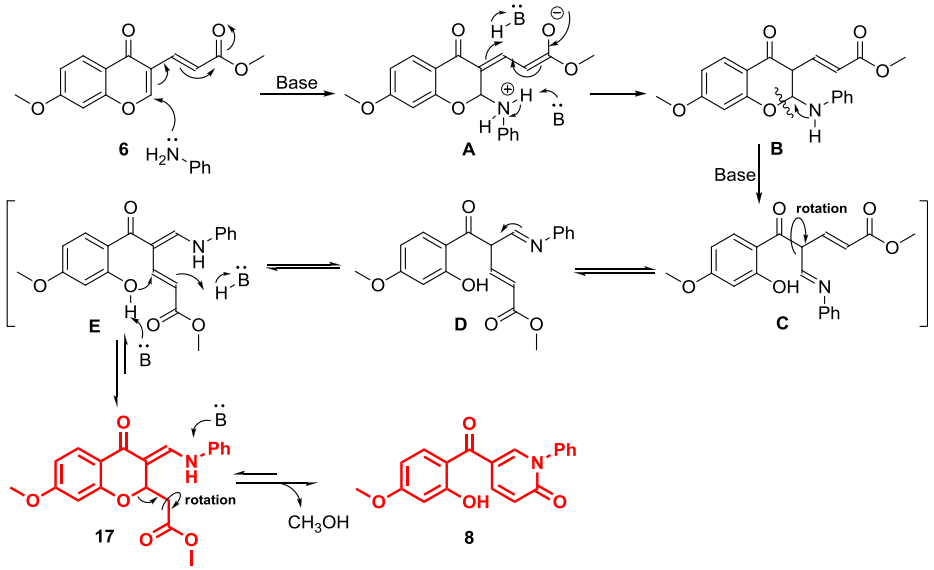
3. Conclusion

In summary, we have developed an efficient and mild procedure for the synthesis of 2-pyridone derivatives with different benzopyran-4-one derivatives and substituted amines. Our reaction condition was as follows: cheap and readily available potassium carbonate and ethanol were used as base and solvent, respectively. The short reaction times and simple reaction conditions render this method particularly attractive for the efficient preparation of biologically and medicinally interesting molecules. Furthermore, the mechanism of this interesting re-cyclization reaction could be obtained according to the key intermediate determination. All these factors contribute to the importance of the described chemistry. This simple method circumvents chemical complexity of the 2-pyridone synthesis reported before and this is also likely to be of value in medicinal chemistry applications.

4. Experimental section

4.1. General

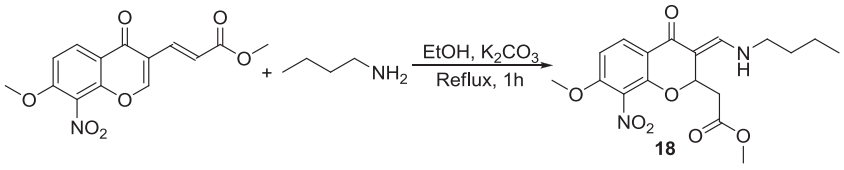
All reactions were carried out in oven-dried glassware. Unless otherwise stated, all chemicals were obtained from commercial sources and used without further purification. Analytical thin layer chromatography (TLC) was performed on precoated silica gel GF-254 plates with visualization by ultraviolet (UV) irradiation at λ=254 nm or staining with I_2. Purifications were performed by silica gel chromatography (230–400 mesh or 200–300 mesh). Melting points reported are of chromatographically purified materials and are uncorrected. NMR experiments were performed on 300 or 600 MHz spectrometer and samples were obtained in $CDCl_3$ (referenced to residual $CHCl_3$ at 7.26 ppm for ^1H and 77.0 ppm for ^{13}C) or DMSO-d_6 (referenced to residual DMSO at 2.50 ppm for ^1H and 39.5 ppm for ^{13}C). Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants



Scheme 2. Putative reaction mechanism.

For further confirming the generality of the reaction mechanism we proposed, (*E*)-methyl 3-(7-methoxy-8-nitro-4-oxo-4*H*-chromen-3-yl)acrylate and aliphatic amine were utilized for this re-

(J) are in hertz (Hz). HRMS analyses were performed using a TOF analyzer, the ionization methods are provided in the compound characterization. Crystal structure was determined on



Scheme 3. Synthesis of intermediate **18**.

a diffractometer equipped with Cu radiation. Yields refer to quantities obtained after chromatography.

4.2. General experimental procedure

4.2.1. Target compounds. A solution of substituted (*E*)-methyl 3-(4-oxo-4*H*-chromen-3-yl)acrylate (2 mmol), substituted amine (2.4 mmol), and K_2CO_3 (6 mmol) in EtOH (25 mL) was stirred under reflux for 6 h. After the mixture was cooled to room temperature and the solvent removed, the crude product was purified by chromatography over silica gel (eluent petroleum ether/acetic ether, 9:1 to 3:1 v/v) to give target compounds.

*4.2.1.1. 5-(2-Hydroxy-4-methoxybenzoyl)-1-phenylpyridin-2(1H)-one (**8**).* Yellow solid (0.56 g, 88%); mp: 179.0–179.7 °C; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 3.86 (s, 3H), 6.45–6.49 (dd, 1H, J_1=9 Hz, J_2=2.7 Hz), 6.51 (d, 1H, J=2.7 Hz), 6.70 (d, 1H, J=9.3 Hz), 7.41–7.52 (m, 2H), 7.53–7.54 (m, 2H), 7.55–7.56 (m, 2H), 7.78–7.82 (dd, 1H, J_1=9.3 Hz, J_2=2.7 Hz), 7.93 (d, 1H, J=2.7 Hz), 12.23 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.7, 102.6, 108.7, 113.8, 114.9, 116.9, 119.4, 127.5, 128.0, 132.6, 139.3, 143.8, 158.5, 161.0, 161.4, 163.5, 192.0 ppm; HRMS (ESI) calculated for $C_{19}H_{15}NO_4$ $[M+H]^+$ 322.1035, found 322.1031.

*4.2.1.2. 5-(2-Hydroxy-4-methoxybenzoyl)-1-(4-methoxyphenyl) pyridin-2(1H)-one (**9a**).* Yellow solid (0.64 g, 91%); mp: 152.2–152.6 °C; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 3.86 (s, 3H), 3.87 (s, 3H), 6.45 (dd, 1H, J_1=9 Hz, J_2=2.7 Hz), 6.52 (d, 1H, J=2.7 Hz), 6.69 (d, 1H, J=9.6 Hz), 7.01–7.04 (m, 2H), 7.32–7.35 (m, 2H), 7.53 (d, 1H, J=9 Hz), 7.77–7.81 (dd, 1H, J_1=9.6 Hz, J_2=2.7 Hz), 7.93 (d, 1H, J=2.7 Hz), 12.24 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.6, 55.7, 76.9, 77.0, 77.4, 101.5, 107.2, 112.6, 114.8, 117.6, 120.7, 127.5, 133.3, 139.4, 143.1, 165.7, 166.3 ppm; HRMS (ESI) calculated for $C_{20}H_{17}NO_5$ $[M+H]^+$ 352.1140, found 352.1135.

*4.2.1.3. 5-(2-Hydroxy-4-methoxybenzoyl)-1-(4-nitrophenyl)pyridin-2(1H)-one (**9b**).* Yellow solid (0.26 g, 35%); mp: 158.6–161.1 °C; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 3.88 (s, 1H), 6.47 (dd, 1H, J_1=9 Hz, J_2=2.4 Hz), 6.62 (d, 1H, J=2.4 Hz), 6.73 (d, 1H, J=9.3 Hz), 7.51 (d, 1H, J=9 Hz), 7.65–7.69 (m, 2H), 7.81–7.85 (dd, 1H, J_1=9.6 Hz, J_2=2.7 Hz), 7.91 (d, 1H, J=2.4 Hz), 8.40–8.41 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.7, 101.5, 107.8, 112.5, 118.0, 120.9, 127.8, 129.8, 133.2, 135.2, 138.5, 139.8, 142.3, 161.5, 165.9, 166.4, 193.6 ppm; HRMS (ESI) calculated for $C_{19}H_{14}N_2O_6$ $[M+H]^+$ 367.0885, found 367.0873.

*4.2.1.4. 1-Allyl-5-(2-hydroxy-4-methoxybenzoyl)pyridin-2(1H)-one (**9c**).* Yellow solid (0.51 g, 89%); mp: 131.7–132.6 °C; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 3.87 (s, 1H), 4.63–4.66 (m, 2H), 5.25–5.38 (m, 2H), 5.92–6.06 (m, 1H), 6.45–6.49 (dd, 1H, J_1=9 Hz, J_2=2.7 Hz), 6.52 (d, 1H, J=2.7 Hz), 6.62 (d, 1H, J=9.6 Hz), 7.46 (d, 1H, J=9 Hz), 7.71–7.75 (dd, 1H, J_1=9.6 Hz, J_2=2.7 Hz), 7.86 (d, 1H, J=2.7 Hz), 12.24 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.9, 51.6, 55.7, 101.5, 107.6, 112.6, 117.7, 119.8, 112.0, 131.7, 133.3, 139.1, 142.0, 161.8, 165.9, 166.2, 193.8 ppm; HRMS (ESI) calculated for $C_{16}H_{15}NO_4$ $[M+H]^+$ 286.1035, found 286.1052.

*4.2.1.5. 5-(2,4-Dihydroxybenzoyl)-1-(4-ethoxyphenyl)pyridin-2(1H)-one (**10a**).* Yellow solid (0.46 g, 66%); mp: 231.0–231.9 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 1.31–1.36 (t, 3H), 4.01–4.10 (t, 2H), 6.31–6.37 (m, 2H), 6.52 (d, 1H, J=9.6 Hz), 6.99–7.03 (m, 2H), 7.36–7.39 (m, 2H), 7.46 (d, 1H, J=8.4 Hz), 7.79–7.83 (dd, 1H, J_1=9.6 Hz, J_2=2.4 Hz), 7.93 (d, 1H, J=2.4 Hz), 10.41 (s, 1H), 11.29 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 14.5, 63.4, 102.7, 107.8, 113.8, 114.6, 116.8, 119.4, 127.8, 132.9, 133.6, 139.3, 144.5, 158.3, 161.1, 161.6, 163.5, 192.0 ppm; HRMS (ESI) calculated for $C_{20}H_{17}NO_5$ $[M+H]^+$ 352.1140, found 352.1119.

*4.2.1.6. 5-(2,4-Dihydroxybenzoyl)-1-p-tolylpyridin-2(1H)-one (**10b**).* Yellow solid (0.34 g, 53%); mp: 264.4–265.2 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 2.35 (s, 3H), 6.31–6.37 (m, 2H), 6.55 (d, 1H, J=9.6 Hz), 7.29–7.36 (m, 4H), 7.46 (d, 1H, J=8.4 Hz), 7.80–7.84 (dd, 1H, J_1=9.6 Hz, J_2=2.4 Hz), 7.93 (d, 1H, J=2.4 Hz), 10.40 (s, 1H), 11.28 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 20.6, 102.7, 107.9, 113.9, 116.9, 119.3, 126.4, 129.5, 133.6, 137.8, 138.2, 139.4, 144.4, 161.0, 161.6, 163.6, 192.0 ppm; HRMS (ESI) calculated for $C_{19}H_{15}NO_4$ $[M+H]^+$ 322.1035, found 322.1032.

*4.2.1.7. 5-(2,4-Dihydroxybenzoyl)-1-m-tolylpyridin-2(1H)-one (**10c**).* Yellow solid (0.35 g, 55%); mp: 155.5–156.8 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 2.53 (s, 3H), 6.31–6.37 (m, 2H), 6.64–6.70 (m, 2H), 6.55 (d, 1H, J=9.6 Hz), 7.29–7.37 (m, 4H), 7.46 (d, 1H, J=8.7 Hz), 7.80–7.84 (dd, 1H, J_1=2.7 Hz, J_2=2.7 Hz), 7.93 (d, 1H, J=2.1 Hz), 10.40 (s, 1H), 11.28 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 20.6, 102.7, 107.9, 113.9, 116.9, 119.5, 126.4, 129.5, 133.6, 137.8, 138.2, 139.4, 144.3, 161.0, 161.6, 163.5, 192.0 ppm; HRMS (ESI) calculated for $C_{19}H_{15}NO_4$ $[M+H]^+$ 322.1035, found 322.1031.

*4.2.1.8. 5-(2,4-Dihydroxybenzoyl)-1-(2-methoxyphenyl)pyridin-2(1H)-one (**10d**).* Yellow solid (0.46 g, 68%); mp: 251.3.2–252.4 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 3.78 (s, 3H), 6.31–6.37 (m, 2H), 6.51 (d, 1H, J=9.6 Hz), 7.04–7.09 (m, 1H), 7.21 (d, 1H, J=7.8 Hz), 7.35–7.49 (m, 3H), 7.79–7.87 (m, 2H), 10.46 (s, 1H), 11.66 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 55.9, 102.8, 107.9, 112.7, 113.8, 116.7, 119.6, 120.6, 128.6, 130.6, 133.6, 139.6, 145.2, 153.8, 160.8, 161.9, 163.7, 192.2 ppm; HRMS (ESI) calculated for $C_{19}H_{15}NO_5$ $[M+H]^+$ 338.0984, found 338.0981.

*4.2.1.9. 1-Butyl-5-(2,4-dihydroxybenzoyl)pyridin-2(1H)-one (**10e**).* Yellow solid (0.4 g, 69%); mp: 172.4–173.3 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 0.89–0.90 (t, 3H), 1.19–1.34 (m, 2H), 1.56–1.66 (m, 2H), 3.92–4.03 (m, 2H), 6.34–6.39 (m, 2H), 6.42 (d, 1H, J=9.3 Hz), 7.39 (d, 1H, J=9.6 Hz), 7.68–7.72 (dd, 1H, J_1=2.4 Hz, J_2=2.4 Hz), 8.19 (d, 1H, J=2.7 Hz), 10.38 (s, 1H), 11.33 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 13.5, 19.1, 102.7, 107.8, 113.8, 116.7, 118.5, 133.4, 139.0, 144.4, 161.2, 161.9, 165.6, 192.3 ppm; HRMS (ESI) calculated for $C_{16}H_{17}NO_4$ $[M+H]^+$ 288.1191, found 288.1188.

*4.2.1.10. 5-(2,4-Dihydroxybenzoyl)-1-(3-nitrophenyl)pyridin-2(1H)-one (**10f**).* Yellow solid (0.24 g, 34%); mp: 269.6–270.9 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 6.32–6.37 (m, 2H), 6.51 (d, 1H, J=2.7 Hz), 6.61 (d, 1H, J=9.6 Hz), 7.54 (d, 1H, J=8.4 Hz), 7.81–7.86 (m, 2H), 7.98–8.01 (m, 1H), 8.13 (d, 1H, J=2.4 Hz), 8.31–8.34 (dd, 1H,

J_1=8.4 Hz, J_2=2.4 Hz), 8.43–8.44 (m, 1H), 10.47 (s, 1H), 11.45 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 102.7, 107.9, 113.9, 116.9, 119.5, 126.4, 129.5, 133.6, 137.8, 138.2, 139.4, 144.3, 161.0, 161.6, 163.5, 192.0 ppm; HRMS (ESI) calculated for $C_{18}H_{12}N_2O_6$ $[M+H]^+$ 353.0771, found 353.0792.

*4.2.1.11. N-(4-Hydroxy-2-methoxy-5-(1-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)phenyl)acetamide (**11a**).* Yellow solid (0.45 g, 55%); mp: 198.6–199.3 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 2.01 (s, 3H), 3.71 (s, 3H), 3.85 (s, 3H), 6.61–6.68 (m, 2H), 6.90 (s, 1H), 7.01 (d, 1H, J=9.6 Hz), 7.44 (d, 2H, J=9.6 Hz), 7.82 (d, 1H, J=9 Hz), 8.10 (s, 1H), 9.17 (s, 1H), 11.16 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 24.2, 55.6, 101.5, 112.6, 115.7, 117.7, 119.8, 120.0, 120.8, 130.3, 133.0, 139.1, 139.5, 142.0, 161.8, 165.6, 166.2, 193.4 ppm; HRMS (ESI) calculated for $C_{22}H_{20}N_2O_6$ $[M+H]^+$ 409.1355, found 409.1376.

*4.2.1.12. N-(5-(1-(4-Fluorobenzyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-4-hydroxy-2-methoxyphenyl)acetamide (**11b**).* Yellow solid (0.27 g, 33%); mp: 197.3–198.9 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 2.04 (s, 3H), 3.86 (s, 3H), 5.14 (s, 2H), 6.46 (d, 1H, J=9.3 Hz), 8.45 (d, 1H, J=2.4 Hz), 9.17 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.2, 56.9, 102.7, 113.7, 116.5, 121.0, 126.0, 130.2, 131.1, 134.4, 137.3, 138.76, 139.6, 143.9, 156.0, 156.6, 161.7, 193.5 ppm; HRMS (ESI) calculated for $C_{22}H_{19}FN_2O_5$ $[M+H]^+$ 411.1352, found 411.1385.

*4.2.1.13. N-(2-Hydroxy-6-methoxy-3-(1-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)phenyl)benzamide (**11c**).* Yellow solid (0.58 g, 62%); mp: 197.5–198.3 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 3.81 (s, 3H), 3.83 (s, 3H), 6.60 (d, 1H, J=9.6 Hz), 6.73 (d, 1H, J=9 Hz), 7.08 (d, 2H, J=8.7 Hz), 7.43 (d, 2H, J=8.7 Hz), 7.51–7.66 (m, 3H), 7.87–7.92 (dd, 1H, J_1=9.6 Hz, J_2=2.7 Hz), 7.90–8.23 (m, 3H), 9.54 (s, 1H), 11.06 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 55.6, 56.1, 103.1, 112.0, 113.5, 114.8, 116.1, 116.7, 119.0, 123.2, 128.0, 128.2, 132.7, 133.3, 134.9, 139.1, 139.5, 156.9, 161.8, 163.5, 165.2, 166.4, 192.2 ppm; HRMS (ESI) calculated for $C_{27}H_{22}N_2O_6$ $[M+H]^+$ 471.1562, found 471.1536.

*4.2.1.14. N-(3-(1-(4-Ethoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-2-hydroxy-6-methoxyphenyl)-4-nitrobenzamide (**11d**).* Yellow solid (0.65 g, 61%); mp: 199.4–199.9 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 1.32–1.37 (t, 3H), 3.83 (s, 3H), 4.07–4.09 (m, 2H), 6.59 (d, 1H, J=9.3 Hz), 6.74 (d, 1H, J=9.0 Hz), 7.02 (d, 2H, J=8.7 Hz), 7.40 (d, 2H, J=8.7 Hz), 7.64 (d, 1H, J=8.7 Hz), 7.86–7.90 (dd, 1H, J_1=9.6 Hz, J_2=2.4 Hz), 8.01 (d, 1H, J=2.4 Hz), 8.20 (d, 2H, J=8.4 Hz), 8.35 (d, 2H, J=8.4 Hz), 9.90 (s, 1H), 11.07 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 14.6, 56.1, 63.4, 103.1, 113.6, 114.6, 116.1, 116.7, 119.7, 123.5, 127.9, 129.3, 131.4, 132.8, 139.2, 139.8, 145.2, 149.1, 156.4, 158.4, 160.0, 161.2, 163.9, 192.2 ppm; HRMS (ESI) calculated for $C_{28}H_{24}N_2O_6$ $[M+H]^+$ 530.1519, found 530.1517.

*4.2.1.15. N-(2-Hydroxy-6-methoxy-3-(1-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)phenyl)-3-methylbenzamide (**11e**).* Yellow solid (0.69 g, 71%); mp: 193.9–194.4 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 2.38 (s, 3H), 3.81–5.11 (m, 5H), 6.59 (d, 1H, J=9.6 Hz), 6.72 (d, 1H, J=9.0 Hz), 7.03–7.21 (m, 2H), 7.38–7.57 (m, 4H), 7.63 (d, 1H, J=9.0 Hz), 7.79–7.82 (m, 2H), 7.86–7.95 (dd, 1H, J_1=9.6 Hz, J_2=2.7 Hz), 8.01 (d, 1H, J=2.7 Hz), 9.47 (s, 1H), 11.07 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 20.9, 55.5, 56.1, 103.1, 114.2, 114.4, 116.0, 116.7, 119.7, 125.0, 128.0, 128.1, 128.4, 131.2, 132.0, 133.0, 134.0, 137.5, 139.2, 145.1, 156.6, 159.1, 160.1, 161.2, 165.6, 192.4 ppm; HRMS (ESI) calculated for $C_{28}H_{24}N_2O_6$ $[M+H]^+$ 485.1668, found 485.1663.

*4.2.1.16. N-(2-Hydroxy-3-(1-isopropyl-6-oxo-1,6-dihydropyridine-3-carbonyl)-6-methoxyphenyl)propionamide (**11f**).* Yellow solid (0.51 g, 56%); mp: 197.4–198.6 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 1.04–1.06 (t, 3H), 1.30 (d, 6H, J=6.6 Hz), 2.32–2.39 (m, 2H), 3.84 (s, 3H), 4.99–5.03 (t, 1H), 6.45 (d, 1H, J=9.6 Hz), 6.71 (d, 1H, J=9.0 Hz), 7.69 (dd, 1H, J_1=9.6 Hz, J_2=2.4 Hz), 8.11 (d, 1H, J=2.4 Hz), 9.17 (s, 1H), 10.72 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 9.8, 21.0, 23.4, 47.4, 56.0, 103.2, 114.5, 116.6, 118.6, 130.2, 138.1, 140.2, 154.0, 158.7, 160.0, 173.1, 192.1 ppm; HRMS (ESI) calculated for $C_{19}H_{22}N_2O_5$ $[M+H]^+$ 459.1562, found 359.1533.

*4.2.1.17. N-(3-(1-Butyl-6-oxo-1,6-dihydropyridine-3-carbonyl)-2-hydroxy-6-methoxyphenyl)propionamide (**11g**).* Yellow solid (0.4 g, 54%); mp: 185.9–186.8 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 0.85–0.91 (t, 3H), 1.02–1.11 (t, 3H), 1.22–1.39 (m, 2H), 1.59–1.64 (m, 2H), 2.34–1.37 (m, 2H), 3.84 (s, 3H), 3.92–3.97 (m, 2H), 6.44 (d, 1H, J=9.6 Hz), 6.70 (d, 1H, J=8.7 Hz), 7.42 (d, 1H, J=8.79 Hz), 7.71–7.75 (dd, 1H, J_1=2.4 Hz, J_2=2.7 Hz), 8.22 (d, 1H, J=2.7 Hz), 9.18 (s, 1H), 10.74 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 9.7, 13.8, 21.7, 28.1, 28.3, 49.2, 56.1, 103.1, 114.6, 116.7, 117.2, 118.6, 130.2, 138.8, 145.1, 154.1, 154.9, 158.6, 161.3, 173.1, 192.1 ppm; HRMS (ESI) calculated for $C_{20}H_{24}N_2O_5$ $[M+H]^+$ 373.1719, found 373.1744.

*4.2.1.18. 5-(2,4-Dihydroxy-3-nitrobenzoyl)-1-(4-methoxyphenyl) pyridin-2(1H)-one (**12a**).* Yellow solid (0.32 g, 42%); mp: 264.1–265.2 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 3.80 (s, 3H), 6.59 (d, 1H, J=9.6 Hz), 6.60 (d, 1H, J=9.0 Hz), 7.04 (d, 2H, J=9.0 Hz), 7.39 (d, 2H, J=9.0 Hz), 7.71 (d, 1H, J=9.0 Hz), 7.78 (dd, 1H, J_1=9.6 Hz, J_2=2.4 Hz), 8.05 (d, 1H, J=3.0 Hz), 12.00 (s, 1H), 12.01 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.2, 56.9, 102.7, 113.7, 116.5, 121.0, 126.0, 130.2, 131.2, 134.34, 137.3, 138.8, 139.6, 143.9, 156.0, 156.6, 161.7, 193.5 ppm; HRMS (ESI) calculated for $C_{19}H_{14}N_2O_7$ $[M+H]^+$ 383.0835, found 383.0833.

*4.2.1.19. 1-Butyl-5-(2,4-dihydroxy-3-nitrobenzoyl)pyridin-2(1H)-one (**12b**).* Yellow solid (0.32 g, 50%); mp: 256.1–257.1 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 0.87–0.88 (t, 3H), 1.27–1.29 (t, 2H), 1.60–1.62 (t, 2H), 3.94–3.97 (t, 2H), 6.48 (d, 1H, J=9.0 Hz), 6.62 (d, 1H, J=9.0 Hz), 7.59 (d, 1H, J=9.0 Hz), 7.74 (dd, 1H, J_1=9.6 Hz, J_2=2.4 Hz), 8.29 (d, 1H, J=3.0 Hz), 11.91 (s, 1H), 12.03 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 13.5, 19.1, 30.6, 49.0, 107.8, 114.2, 115.9, 118.9, 130.7, 134.3, 138.7, 145.5, 152.9, 154.6, 161.2, 191.8 ppm; HRMS (ESI) calculated for $C_{16}H_{16}N_2O_6$ $[M+H]^+$ 333.1042, found 333.1045.

*4.2.1.20. 5-(4-Hydroxybenzo[d]oxazole-5-carbonyl)-1-phenylpyridin-2(1H)-one (**14a**).* Yellow solid (0.29 g, 44%); mp: 198.9–200.1 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 6.59 (d, 1H, J=9.6 Hz), 7.29 (d, 1H, J=8.4 Hz), 7.42–7.53 (m, 6H), 7.90–7.94 (dd, 1H, J_1=9.6 Hz, J_2=2.7 Hz), 7.99 (d, 1H, J=2.7 Hz), 8.74 (s, 1H), 11.43 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 104.6, 119.4, 121.9, 122.7, 129.0, 130.3, 131.95, 131.4, 131.8, 141.3, 142.4, 148.0, 151.5, 155.1, 155.6, 163.3, 193.4 ppm; HRMS (ESI) calculated for $C_{19}H_{12}N_2O_4$ $[M+H]^+$ 333.0831, found 333.0842.

*4.2.1.21. 5-(4-Hydroxybenzo[d]oxazole-5-carbonyl)-1-(4-methoxybenzyl)pyridin-2(1H)-one (**14b**).* Yellow solid (0.35 g, 47%); mp: 135.1–136.0 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 3.71 (s, 3H), 5.07 (s, 2H), 6.45 (d, 1H, J=9.6 Hz), 6.87 (d, 2H, J=8.7 Hz), 7.25–7.31 (m, 3H), 7.37 (d, 1H, J=8.7 Hz), 7.74–7.78 (dd, 1H, J_1=9.6 Hz, J_2=2.7 Hz), 8.37 (d, 1H, J=2.7 Hz), 8.75 (s, 1H), 11.35 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 51.5, 55.1, 102.5, 114.0, 117.4, 118.8, 120.7, 127.9, 128.4, 129.2, 129.7, 138.9, 145.6, 149.3, 152.8, 153.4, 158.9, 161.4, 191.5 ppm; HRMS (ESI) calculated for $C_{21}H_{16}N_2O_5$ $[M+H]^+$ 377.1093, found 377.1092.

*4.2.1.22. 1-(4-Chlorobenzyl)-5-(4-hydroxybenzo[d]oxazole-5-carbonyl)pyridin-2(1H)-one (**14c**).* Yellow solid (0.35 g, 46%); mp:

106.7–107.3 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 5.14 (s, 2H), 6.46 (d, 1H, J=6.3 Hz), 7.12–7.18 (m, 2H), 7.29–7.43 (m, 4H), 7.77–7.81 (dd, 1H, J_1=9.6 Hz, J_2=2.7 Hz), 8.44 (d, 1H, J=2.4 Hz), 8.75 (s, 1H), 11.36 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 51.4, 102.6, 115.3, 115.6, 117.7, 118.9, 120.8, 128.0, 129.2, 130.3, 132.8, 139.1, 145.9, 149.4, 152.9, 153.4, 161.5, 191.5 ppm; HRMS (ESI) calculated for $C_{20}H_{13}ClN_2O_4$ $[M+H]^+$ 382.0534, found 382.0530.

*4.2.1.23. 1-(3-Fluorobenzyl)-5-(4-hydroxybenzo[d]oxazole-5-carbonyl)pyridin-2(1H)-one (**14d**).* Yellow solid (0.25 g, 35%); mp: 156.0–156.8 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 5.17 (s, 2H), 6.48 (d, 1H, J=9.6 Hz), 7.10–7.22 (m, 3H), 7.29–7.51 (m, 3H), 7.79–7.90 (dd, 1H, J_1=9.6 Hz, J_2=2.4 Hz), 8.45 (d, 1H, J=8.7 Hz), 8.75 (s, 1H), 11.35 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 51.6, 102.4, 114.3, 117.6, 118.8, 120.8, 123.7, 127.9, 129.2, 130.6, 130.7, 139.1, 139.5, 146.0, 149.4, 152.8, 153.3, 160.5, 161.3, 191.4 ppm; HRMS (ESI) calculated for $C_{20}H_{13}FN_2O_4$ $[M+H]^+$ 365.0859, found 365.0931.

*4.2.1.24. 1-(2-Fluorobenzyl)-5-(4-hydroxybenzo[d]oxazole-5-carbonyl)pyridin-2(1H)-one (**14e**).* Yellow solid (0.33 g, 45%); mp: 142.9–143.7 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 5.20 (s, 2H), 6.48 (d, 1H, J=9.3 Hz), 7.15–7.66 (m, 6H), 7.81–7.95 (dd, 1H, J_1=9.3 Hz, J_2=2.4 Hz), 8.36 (d, J=2.4 Hz), 8.75 (s, 1H), 11.35 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 47.0, 102.6, 115.4, 115.7, 117.6, 119.0, 120.7, 123.2, 123.3, 124.8, 127.9, 129.3, 130.0, 139.2, 146.3, 149.4, 152.9, 153.4, 161.4, 191.6 ppm; HRMS (ESI) calculated for $C_{20}H_{13}FN_2O_4$ $[M+H]^+$ 365.0859, found 365.0931.

*4.2.1.25. 5-(4-Hydroxybenzo[d]oxazole-5-carbonyl)-1-isopropylpyridin-2(1H)-one (**14f**).* Yellow solid (0.29 g, 48%); mp: 185.6–185.9 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 1.27 (d, 6H, J=6.6 Hz), 4.94–5.04 (m, 1H), 6.44 (d, 1H, J=9.6 Hz), 7.31 (d, 1H, J=8.4 Hz), 7.45 (d, 1H, J=8.4 Hz), 7.71–7.75 (dd, 1H, J_1=9.6 Hz, J_2=2.4 Hz), 8.13 (d, 1H, J=2.4 Hz), 8.77 (s, 1H), 11.44 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 1.0, 47.6, 102.6, 117.2, 118.4, 120.5, 128.1, 129.2, 138.1, 141.4, 149.4, 152.9, 153.4, 161.0, 191.4 ppm; HRMS (ESI) calculated for $C_{16}H_{14}N_2O_4$ $[M+H]^+$ 298.0954, found 298.0967.

*4.2.1.26. 5-(4-Hydroxybenzo[d]oxazole-5-carbonyl)-1-isobutylpyridin-2(1H)-one (**14g**).* Yellow solid (0.27 g, 44%); mp: 163.3–164.0 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 0.79 (d, 6H, J=6.6 Hz), 1.99–2.05 (m, 1H), 3.77 (d, 2H, J=7.2 Hz), 6.46 (d, 1H, J=9.3 Hz), 7.31 (d, 1H, J=8.4 Hz), 7.42 (d, 1H, J=8.4 Hz), 7.78–7.82 (dd, 1H, J_1=9.3 Hz, J_2=2.7 Hz), 8.17 (d, 1H, J=2.4 Hz), 8.77 (s, 1H), 11.34 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 19.4, 27.3, 55.7, 102.4, 116.9, 118.6, 120.8, 127.8, 129.1, 138.5, 146.2, 149.3, 152.7, 253.3, 161.6, 191.5 ppm; HRMS (ESI) calculated for $C_{17}H_{16}N_2O_4$ $[M+H]^+$ 312.1110, found 312.1113.

*4.2.1.27. 5-(4-Hydroxybenzo[d]oxazole-5-carbonyl)-1-propylpyridin-2(1H)-one (**14h**).* Yellow solid (0.23 g, 39%); mp: 163.2–163.9 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 0.81–0.86 (t, 3H), 1.58–1.65 (dd, 2H, J_1=7.5 Hz, J_2=7.5 Hz), 3.86–3.91 (t, 2H), 6.44 (d, 1H, J=9.6 Hz), 7.30 (d, 1H, J=8.4 Hz), 7.42 (d, 1H, J=8.4 Hz), 7.76–7.80 (dd, 1H, J_1=9.6 Hz, J_2=2.7 Hz), 8.23 (d, 1H, J=2.7 Hz), 8.76 (s, 1H), 11.32 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 10.7, 21.9, 50.6, 102.4, 117.0, 118.5, 120.7, 127.9, 129.2, 138.5, 145.9, 149.3, 152.7, 153.3, 161.3, 191.4 ppm; HRMS (ESI) calculated for $C_{16}H_{14}N_2O_4$ $[M+H]^+$ 298.0954, found 298.0936.

*4.2.1.28. 5-(4-Hydroxy-2-methylbenzo[d]oxazole-5-carbonyl)-1-p-tolylpyridin-2(1H)-one (**15a**).* Yellow solid (0.44 g, 61%); mp: 214.7–215.8 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 2.35 (s, 3H), 2.61 (s, 3H), 6.57–6.61 (dd, 1H, J_1=9.0 Hz, J_2=1.2 Hz), 7.19 (d, 1H, J=8.4 Hz), 7.31 (s, 4H), 7.40 (d, 1H, J=8.4 Hz), 7.88–7.93 (m, 2H), 11.28 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 14.0, 20.6, 102.1, 117.1, 119.6, 120.3, 126.4, 127.0, 129.6, 130.2, 137.7, 138.4, 138.9, 145.9, 148.4, 153.8, 161.1, 163.1, 191.5 ppm; HRMS (ESI) calculated for $C_{21}H_{16}N_2O_4$ $[M+H]^+$ 361.1144, found 361.1159.

*4.2.1.29. 5-(4-Hydroxy-2-methylbenzo[d]oxazole-5-carbonyl)-1-(4-methoxyphenyl)pyridin-2(1H)-one (**15b**).* Yellow solid (0.43 g, 57%); mp: 206.8–207.3 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 2.61 (s, 3H), 3.79 (s, 3H), 6.57 (d, 1H, J=9.3 Hz), 7.01–7.04 (m, 2H), 7.19 (d, 1H, J=8.4 Hz), 7.34–7.43 (m, 3H), 7.87–7.93 (m, 2H), 11.28 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 14.0, 55.5, 102.1, 114.3, 117.1, 119.5, 120.3, 127.0, 127.9, 130.2, 133.0, 138.9, 146.0, 148.4, 153.8, 159.2, 161.3, 163.1, 191.3 ppm; HRMS (ESI) calculated for $C_{21}H_{16}N_2O_5$ $[M+H]^+$ 377.1093, found 377.1084.

*4.2.1.30. 1-(3-Chlorophenyl)-5-(4-hydroxy-2-methylbenzo[d]oxazole-5-carbonyl)pyridin-2(1H)-one (**15c**).* Yellow solid (0.42 g, 56%); mp: 222.7–223.6 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 2.62 (s, 3H), 6.60 (d, 1H, J=9.6 Hz), 7.23 (d, 1H, J=8.7 Hz), 7.43–7.47 (m, 2H), 7.54–7.60 (m, 2H), 7.63 (s, 1H), 7.89–7.98 (dd, 1H, J_1=9.6 Hz, J_2=2.4 Hz), 8.03 (d, 1H, J=2.4 Hz), 11.32 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 14.0, 102.1, 117.4, 119.6, 120.1, 125.8, 127.1, 127.2, 138.8, 130.3, 130.8, 133.2, 139.4, 141.2, 145.4, 148.8, 153.9, 160.9, 163.1, 191.4 ppm; HRMS (ESI) calculated for $C_{20}H_{13}ClN_2O_4$ $[M+H]^+$ 380.0564, found 380.0569.

*4.2.1.31. 5-(4-Hydroxy-2-methylbenzo[d]oxazole-5-carbonyl)-1-m-tolylpyridin-2(1H)-one (**15d**).* Yellow solid (0.46 g, 64%); mp: 216.6–217.5 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 2.35 (s, 3H), 2.61 (s, 1H), 6.58 (d, 1H, J=9.3 Hz), 7.19–7.29 (m, 5H), 7.40–7.42 (m, 2H), 7.82–7.94 (m, 2H), 11.29 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 14.0, 21.3, 102.1, 117.3, 119.6, 120.1, 127.1, 128.8, 129.1, 138.8, 130.3, 132.3, 133.2, 138.8, 139.2, 145.5, 148.6, 153.8, 161.0, 163.1, 191.4 ppm; HRMS (ESI) calculated for $C_{21}H_{16}N_2O_4$ $[M+H]^+$ 360.1110, found 360.1121.

*4.2.2. Intermediate **17** and **18**.* The reaction was monitored via TLC every 20 min. The intermediate **17** (**18**) appeared firstly and then the desired compound was formed after 2 h. The reaction was stopped and the solvent was removed, the crude product was purified by chromatography over silica gel (eluent petroleum ether/acetic ether, 9:1 to 3:1 v/v) to give compound **17** (**18**).

*4.2.2.1. (E)-Methyl 2-(7-methoxy-4-oxo-3-((phenylamino)methylene)chroman-2-yl)acetate (**17**).* Yellow solid (0.37 g, 53%); mp: 116.5–116.9 °C; ^{1}H NMR: (600 MHz, DMSO-d_6) δ: 2.81–2.90 (m, 2H), 3.62 (s, 3H), 3.79 (s, 3H), 5.53–5.55 (dd, 1H, J_1=4.8 Hz, J_2=4.8 Hz), 6.43 (d, 1H, J=2.4 Hz), 6.65–6.67 (dd, 1H, J_1=2.4 Hz, J_2=2.4 Hz), 7.04–7.06 (t, 1H), 7.28–7.30 (m, 2H), 7.32–7.36 (m, 2H), 7.72 (d, 1H, J=8.4 Hz), 7.83 (d, 1H, J=12.6 Hz), 11.60 ppm (d, 1H, J=12 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 40.62, 51.54, 55.62, 75.67, 101.51, 102.65, 109.39, 115.89, 116.12, 123.19, 127.62, 129.58, 140.03, 141.63, 158.98, 164.64, 170.05, 180.26 ppm; HRMS (ESI) calculated for $C_{20}H_{19}NO_5$ $[M+H]^+$ 354.1297, found 354.1274.

*4.2.2.2. (E)-Methyl 2-(3-((butylamino)methylene)-7-methoxy-8-nitro-4-oxochroman-2-yl)acetate (**18**).* Yellow solid (0.36 g, 48%); mp: 102.1–102.8 °C; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 0.95–0.97 (t, 3H), 1.35–1.42 (m, 2H), 1.53–1.61 (m, 2H), 2.61–2.68 (m, 1H), 2.91–2.98 (m, 1H), 3.26–3.32 (m, 2H), 3.69 (s, 3H), 3.94 (s, 3H), 5.41–5.46 (t, 3H), 6.69 (d, 1H, J=9 Hz), 6.88 (d, 1H, J=12.9 Hz), 6.94 (d, 1H, J=9 Hz), 10.00–10.04 ppm (t, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.5, 19.6, 32.9, 41.4, 49.1, 51.8, 56.6, 76.6, 98.3, 105.0, 117.5, 128.7, 131.3, 149.5, 151.8, 155.0, 170.2, 178.0 ppm; HRMS

(ESI) calculated for $C_{18}H_{22}N_2O_7$ $[M+H]^+$ 379.1461, found 379.1458.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.08.032.

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