Article

Multicomponent cascade reaction by metal-free aerobic oxidation for synthesis of highly functionalized 2-amino-4-cumarinyl-5-arylpyrroles

Quan-Xing Zi, Chang-Long Yang, Kun Li, Qin Luo, Jun Lin, and Sheng-Jiao Yan

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b02063 • Publication Date (Web): 04 Dec 2019

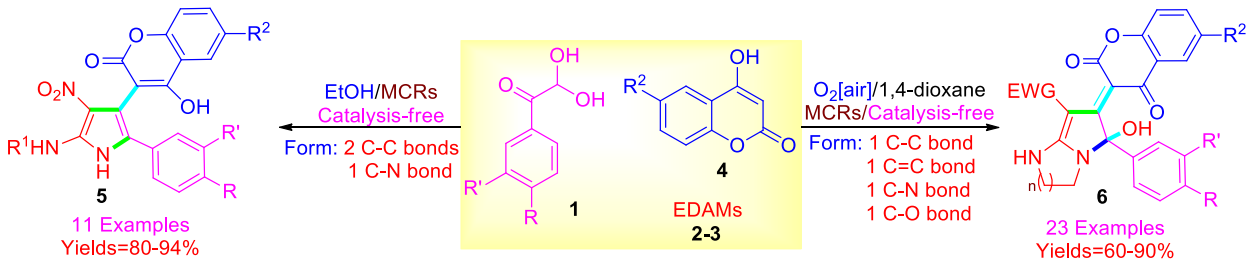
Multicomponent cascade reaction by metal-free aerobic oxidation for synthesis of highly functionalized 2-amino-4-cumarinyl-5-arylpyrroles

Quan-Xing Zi, Chang-Long Yang, Kun Li, Qin Luo, Jun Lin* and Sheng-Jiao Yan*

Key Laboratory of Medicinal Chemistry for Natural Resource (Yunnan University), Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming, 650091, P. R. China.

KEYWORDS: *2-Aminopyrroles, cascade reaction, aerobic oxidation, 1,1-enediamines.*

ABSTRACT: A novel approach has been constructed for the synthesis of two types of 2-amino-4-cumarinyl-5-arylpyrroles (ACAPs, **5**–**6**) through a cascade reaction and a metal-free catalyzed aerobic oxidation reaction of arylglyoxal monohydrates **1**, 1,1-enediamines (EDAMs) **2**–**3**, and 4-hydroxy-2*H*-chromen-2-ones **4** *via* multicomponent reactions to produce the target compounds with good to excellent yields. Specifically, hydroxyl-substituted 2-amino-4-cumarinyl-5-arylpyrroles, that is, 2-amino-4-cumarinyl-5-aryl-6-hydroxylpyrroles (ACAHPs) **6**, were obtained by metal-free aerobic oxidation in 1,4-dioxane at simple reflux for approximately 10 hours. As a result, ACAHPs **6** have been produced without metal catalysts or traditional oxidizing agents. This method represents a route to obtain the novel ACAPs in an environmentally friendly, concise, rapid, and practical manner with potential biological activity of the product.



■ INTRODUCTION

2-Aminopyrroles, as a representative heterocyclic skeleton structure, widely exist in numerous pharmaceuticals and natural products. These types of compounds have a diverse range of bioactivities including metallo-β-lactamase (MBL) inhibitor,[1] MAPK/ERK kinase (MEK) inhibitor[2] (Fig. 1), tumor necrosis factor (TNF)-α production inhibitor, phosphodiesterase (PDE) inhibitor,[3] and protein kinase casein kinase 2 (CK2) inhibitor, as well as antimalarial, antibacterial, and cytotoxic activities.[4] Furthermore, 2-aminopyrroles have been used as precursors for the synthesis of purine analogues, including pyrrolopyrimidines, pyrrolotriazines, and pyrrolopyridines.

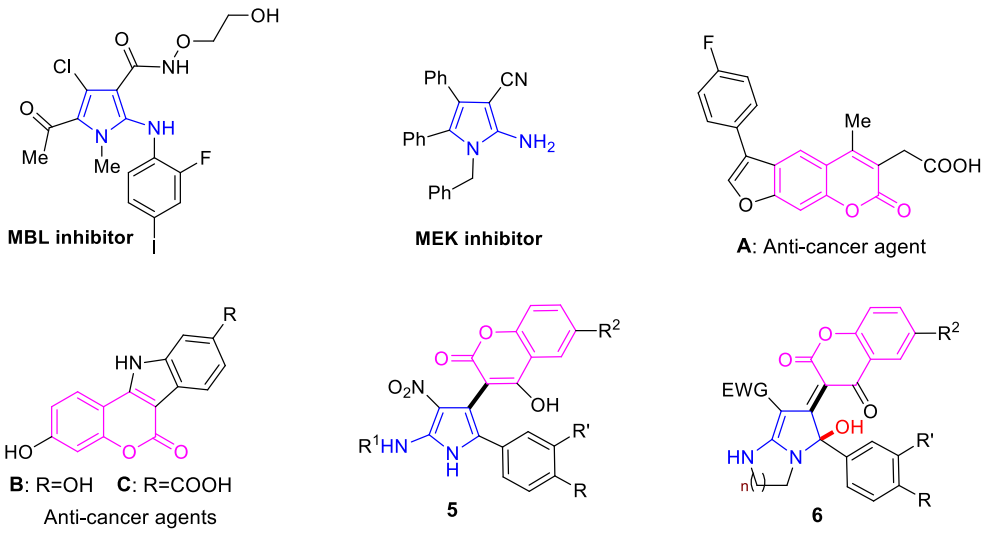


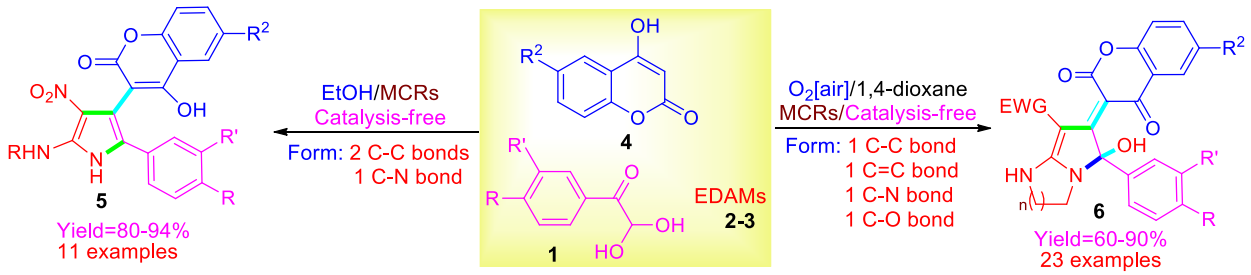
Figure 1. Bioactive 2-aminopyrroles, coumarins and target compounds **5**–**6**.

The methodology for synthesis of pyrrole derivatives has been previously reported, and various substituted pyrroles have been obtained.[5-9] However, only a few protocols have been used to construct a library of 2-aminopyrroles through classic methods.[10-13] The classic synthesis methods for 2-aminopyrroles include multicomponent reactions based on nitriles or isocyanides,[10-11] and cycloisomerization of alkyne and allene-containing substrates catalyzed by

transition metal complexes.[12-13] Although these methods have laid a solid foundation for the synthesis of 2-aminopyrroles, they usually have some shortcomings, such as reliance on expensive transition metals or requiring harsh reaction conditions or tedious workup procedures.[14]

Currently, there is a lack of efficient and practical methods for synthesis of highly functionalized 2-aminopyrroles, for example, cumarin-substituted 2-aminopyrroles. However, the functionalized groups usually have important and widespread biological activities. Among them, the cumarin, as a "privileged" structural motif, is distributed in naturally occurring compounds with a broad spectrum of significant biological activities including anti-HIV,[15] anti-tumor (Fig. 1, Compounds **A**−**C**)[16] anti-inflammatory, anti-microbial, and anti-hyperglycemic activities.[17-19] Consequently, there has been great interest in hybrid molecules of functionalized group with *N*-containing heterocycles. Here, our goal is to incorporate the chromene skeleton into 2-aminopyrroles and design and synthesize 2-amino-4-cumarinyl-5-aryl pyrroles (ACAPs). Additionally, it is extremely desirable to develop an efficient and metal-free approach toward ACAPs, aiming at achieving diversity in molecular structures from available building blocks and under mild reaction conditions.

Scheme 1. Methods for the construction of 2-amino-4-cumarinyl-5-arylpyrroles



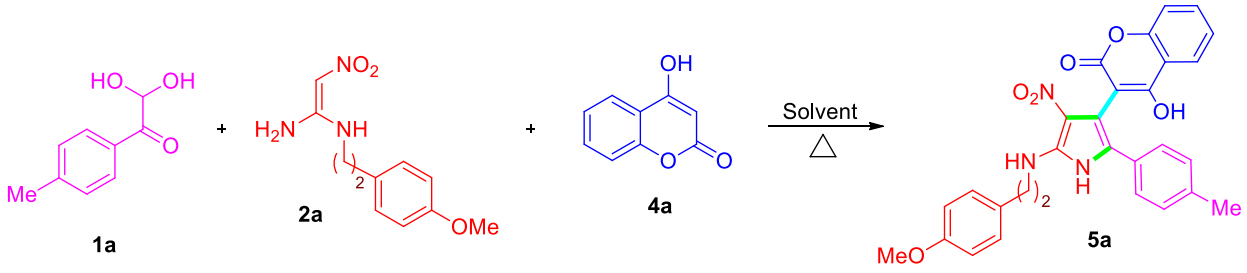
1,1-Enediamines (EDAMs) are versatile building blocks that are widely used to construct various fused heterocycles.[20-27] Some of these compounds have broad-spectrum biological activities such as anti-tumor,[22-23] herbicide, pesticide,[24] anti-anxiety,[25] anti-leishmanial,[26] and anti-bacterial.[27] To further synthesize functionalized heterocyclic compounds with pharmacological activity and from EDAMs, we designed and constructed chromene-substituted 2-aminopyrroles, that is, ACAPs (Scheme 1). Unexpectedly, as cyclic EDAMs are used in this reaction, we can obtain a 2-amino-4-cumarinyl-5-aryl-6-hydroxylpyrroles library (ACAHPs) **6** by metal-free aerobic oxidation in 1,4-dioxane at simple reflux for approximately 10 hours. Using this property, various ACAHPs can be regioselectively constructed based on the cyclic EDAM building blocks. This provides the key information to design new substrates to capture the free radical intermediate (for examples, see Scheme 2, intermediate **16**). However, based on the mechanism of this cascade reaction, different functionalized groups such as pyridine- and quinoline-functionalized 2-aminopyrroles will be constructed in the future. Optimal conditions will result in the production of the dimer of intermediate **16**.

RESULTS AND DISCUSSION

To obtain the optimal reaction conditions for the synthesis of the target compounds, the reaction of 2,2-dihydroxy-1-(*p*-tolyl)ethanone **(1a)**, *N*-(3-methoxyphenethyl)-2-nitroethene-1,1-diamine (**2a**), and 4-hydroxy-2*H*-chromen-2-one (**4a**) was chosen as the model reaction. First, the three-component reaction was refluxed in different solvents, which included 1,4-dioxane, H_2O, and acetone (Table 1, entries 1−3). The results showed that the reaction could not proceed in the prospective solvents (Table 1, entries 1−3). Then, the green solvent EtOH was used under the same conditions, and the reaction produced the target compound with an excellent yield

(91%) (Table 1, entry 4). Then, Et_3N as a basic additive was added to the mixture in 1,4-dioxane, H_2O, and acetone at the reflux temperature (Table 1, entries 5−7). The results revealed that Et_3N could not promote the reaction and also could not produce the target compound (Table 1, entries 5−7). Next, Et_3N as an additive was incorporated in this reaction, which was refluxed in ethanol, and it was found that the reaction was more complex. The result showed that Et_3N is not suitable for this cascade reaction. Finally, the reaction times were also screened, and it was found that the optimal reaction time was approximately 6 h (Table 1, entry 9 vs. 4 and 10). Based on the above results, we determined that the optimal reaction conditions were the use of EtOH as the solvent and refluxing for approximately 6 hours without any additives. These conditions produced the target compound with an excellent yield (93%) (Table 1, entry 9).

Table 1. Optimization of the reaction conditions for the model reaction[a]



entry	solvent	Additive[b]	*t* (°C)	time/min	Yield[c] (%)
1	1,4-dioxane	–	reflux	12	complex
2	H_2O	–	reflux	12	complex
3	acetone	–	reflux	12	complex
4	EtOH	–	reflux	12	91
5	1,4-dioxane	Et_3N	reflux	12	complex
6	H_2O	Et_3N	reflux	12	complex
7	acetone	Et_3N	reflux	12	complex
8	EtOH	Et_3N	reflux	12	complex

9	EtOH	−	reflux	6	93
10	EtOH	−	reflux	4	89

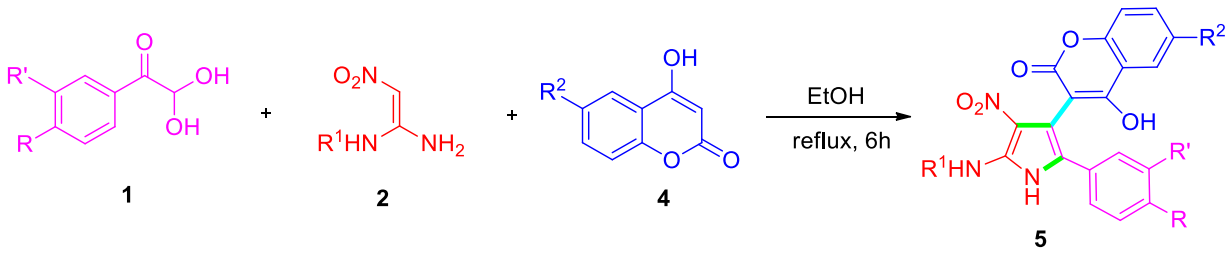
[a] Reagents and conditions: Arylglyoxal monohydrate **1a** (166.1 mg, 1.0 mmol), EDAM **2a** (237.1 mg, 1.0 mmol), 4-hydroxy-2*H*-chromen-2-one **4a** (162.0 mg, 1.0 mmol) and solvent (10 mL). [b] Additive (1.0 mmol). [c] Isolated yield based on **2a**.

After determining the most optimal reaction conditions, we explored the scope and limitations of the three-component cascade reaction with various arylglyoxal monohydrates **1**, EDAMs **2**, and 4-hydroxy-2*H*-chromen-2-ones **4**. The results revealed that in all cases, the reaction proceeded smoothly in EtOH at reflux conditions for approximately 6 hours (Table 2, entries 1−11). The different substituent groups (R) of arylglyoxal monohydrates **1** and 4-hydroxy-2*H*-chromen-2-ones **4** usually had a slight effect on the yields, but the difference was very small, and we could not ascertain the effect of any specific substituent. However, the substituent group of EDAMS **2** had an obvious effect on the yield of compounds **5**. In general, EDAMs **2a**−**2e** with a longer chain usually produce the target compounds with higher yields as compared to reactions using EDAMs (**2f**−**2g**) with a shorter chain (Table 2, entry 4 *vs.* 7). Overall, reactions with different substituted substrates **1**−**3** can proceed smoothly and produce compounds **5** with excellent yields (80%−94%).

The feasibility of the present method was also examined by gram-scale experimentation that was conducted with a mixture of 2,2-dihydroxy-1-phenylethanone **1b** (0.456 g, 3.0 mmol), (*Z*)-2-nitro-*N*-phenethylethene-1,1-diamine **2c** (0.622 g, 3.0 mmol), and 4-hydroxy-2*H*-chromen-2-one **4a** (0.486 g, 3.0 mmol), with ethanol (20 mL) as the solvent. The reaction mixture was then refluxed for 6 hours. The reaction was found to proceed smoothly, producing the desired product of target compounds **5e** with a yield of 87% (1.220 g), which was similar in all respects with the

1 mmol scale entry (Table 2, entry 5 *vs.* 12). This result demonstrates that this cascade reaction is efficient for gram-scale production as well (Table 2, entry 12).

Table 2. The synthesis of 2-amino-4-cumarinyl-5-arylpyrroles (ACAPs) 5a–5k[a]



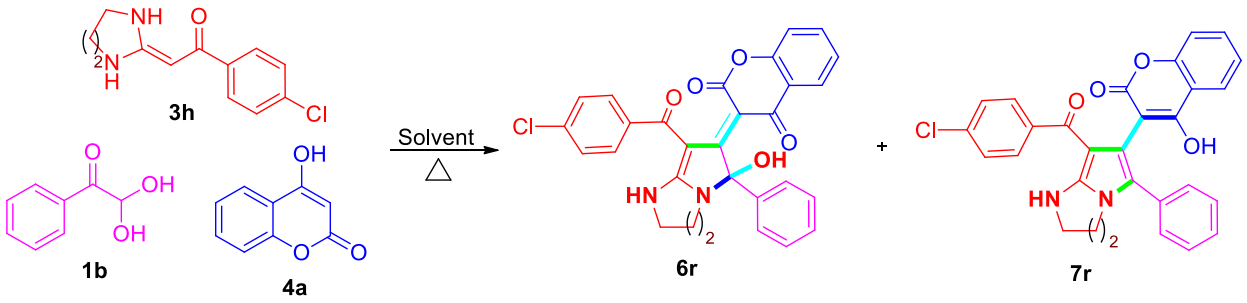
Entry	**1**/R/R'	**2**/R^1	**4**/R^2	**5**	Yield (%)
1	**1a**/CH_3	**2a**/*p*-$MeOC_6H_4(CH_2)_2$	**4a**/H	**5a**	93
2	**1a**/CH_3	**2d**/*p*-$ClC_6H_4(CH_2)_2$	**4b**/Br	**5b**	92
3	**1b**/H	**2a**/*p*-$MeOC_6H_4(CH_2)_2$	**4a**/H	**5c**	94
4	**1b**/H	**2b** /*p*-$MeC_6H_4(CH_2)_2$	**4a**/H	**5d**	93
5	**1b**/H	**2c**/$C_6H_5(CH_2)_2$	**4a**/H	**5e**	90
6	**1b**/H	**2e**/*p*-$FC_6H_4(CH_2)_2$	**4a**/H	**5f**	91
7	**1b**/H	**2f**/*p*-$MeC_6H_4CH_2$	**4a**/H	**5g**	85
8	**1b**/H	**2g**/*p*-MeC_6H_5	**4b**/Br	**5h**	80
9	**1c**/F	**2a**/*p*-$MeOC_6H_4(CH_2)_2$	**4a**/H	**5i**	90
10	**1c**/F	**2b** /*p*-$MeC_6H_4(CH_2)_2$	**4a**/H	**5j**	92
11	**1c**/F	**2c**/$C_6H_5(CH_2)_2$	**4b**/Br	**5k**	94
12	**1b**/H	**2c**/$C_6H_5(CH_2)_2$	**4a**/H	**5e**	87[b]

[a] Unless otherwise mentioned, the reaction conditions are arylglyoxal monohydrates **1** (1.0 mmol), EDAMs **2** (1.0 equiv), 4-hydroxy-2*H*-chromen-2-ones **4** (1.0 equiv), Ethanol (10 mL). [b] Arylglyoxal monohydrates **1** (3.0 mmol), EDAMs **2** (1.0 equiv), 4-hydroxy-2*H*-chromen-2-ones **4** (1.0 equiv), Ethanol (20 mL).

To further explore the scope and limitations of the cascade reaction, we used various 2,2-dihydroxy-1-phenylethanone **1b** and 4-hydroxy-2*H*-chromen-2-one **4a** compounds as substrates to react with 1-(4-chlorophenyl)-2-(tetrahydropyrimidin-2(1*H*)-ylidene)ethanone **3h** and screen for the optimal conditions. First, the three-component reaction was refluxed in different solvents including Triton X-100, propylene carbonate (PC), 3-methyl-1-octylimidazolium hexafluorophosphate ([MOMIM]PF_6), EtOH, H_2O, H_2O_2 and 2-methyl-2-butanol (MBTL) at reflux conditions (Table 3, entries 1−7). The results showed that the reaction could not proceed in Triton X-100 or PC or [MOMIM]PF_6 (Table 3, entries 1−3). However, when EtOH was used as the solvent under the same conditions, the reaction produced the target compound with 70% yield (Table 3, entry 4). When water or H_2O_2 was used as the solvent under the same conditions, the reaction produced the target compound with moderate yield (52% vs. 60%) (Table 3, entry 5 vs. 6). Then, MBTL or 1,4-dioxane was screened using the same conditions, and we found that 1,4-dioxane was the optimal solvent and produced compounds **6r** with good yield (80%) (Table 3, entry 8 vs. 1−7). Then, basic additives such as Et_3N or piperidine were added to the mixture in 1,4-dioxane at the reflux temperature. The results showed that the basic additives could not advance the reaction at all (Table 3, entry 8 *vs.* 9−10). Finally, the reaction times were also screened, and it was determined that the optimal time was approximately 10 hours (Table 3, entry 8 *vs.* 11−12). Based on the results, we consequently found that the optimal conditions were 1,4-dioxane as the solvent at reflux for approximately 10 hours without any additives. Unexpectedly, we found that the target compounds were 2-amino-4-cumarinyl-5-aryl-6-hydroxylpyrroles (ACAHPs) **6** rather than 2-amino-4-cumarinyl-5-aryl-pyrroles (ACAPs) **7**. It is must be pointed out that the reaction produced two target compounds, ACAHP (**6r**) and ACAP (**7r**), when EtOH was used as the solvent (Table 3, entry 4), although it is easy to oxidize (ACAP)

7r to ACAHP (**6r**) during column chromate-graphic separation or reduced pressure concentration. After our best efforts, we obtained a little of **7r**. This is important data that will contribute to the hypothesis mechanism (Scheme 2).

Table 3. Optimization of the reaction conditions for the model reaction[a]

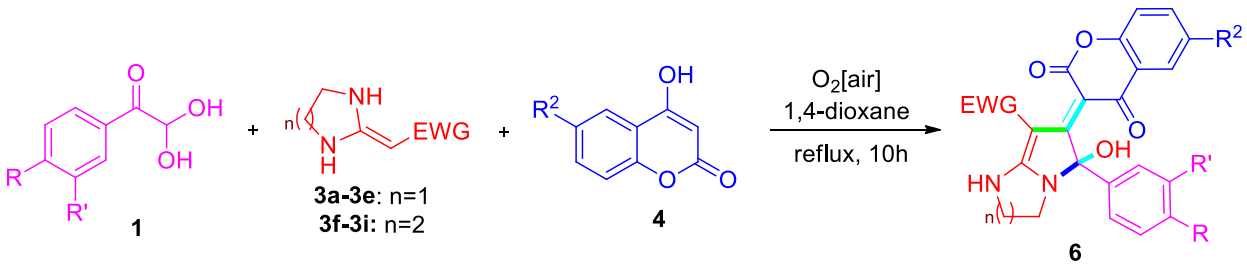


Entry	Solvent	Additive[b]	*T*(°C)	*t* (h)	**6r**/Yield[b](%)	**7r**/Yield[c] (%)
1	Tritonx-100	–	reflux	10	–	–
2	PC	–	reflux	10	–	–
3	[MOMIM]PF_6	–	reflux	10	–	–
4	EtOH	–	reflux	10	70	15
5	H_2O	–	reflux	10	52	trace
6	H_2O_2	–	reflux	10	60	trace
7	MBTL	–	reflux	10	50	trace
8	1,4-dioxane	–	reflux	10	80	–
9	1,4-dioxane	Et_3N	reflux	10	30	36
10	1,4-dioxane	Piperidine	reflux	10	–	–
11	1,4-dioxane	–	reflux	8	76	–
12	1,4-dioxane	–	reflux	12	79	–

[a] Reagents and conditions: Arylglyoxal monohydrate **1b** (166.1 mg, 1.0 mmol), HKA **3h** (236.1 mg, 1.0 mmol), 4-hydroxy-2*H*-chromen-2-one **4a** (162.0 mg, 1.0 mmol), solvent (10 mL). [b] Additive (1.0 mmol). [c] Isolated yield based on **3h**.

To further explore the scope and limitations of the cascade reaction, various arylglyoxal monohydrates **1**, EDAMs **3,** and 4-hydroxy-2*H*-chromen-2-ones **4** were tested with the optimal conditions (Table 4, entries 1−24). The results demonstrated that in all cases except nitro-substituted EDMA **3k**, the reaction proceeded smoothly in 1,4-dioxane at reflux conditions for approximately 10 hours (Table 4, entries 1−23). The different substituent groups of arylglyoxal monohydrates and 4-hydroxy-2*H*-chromen-2-ones usually had a slight effect on the yields, but the difference was very small, and we could not ascertain the effect of any specific substituent. However, the ring size of EDAMs affected the yield of the cascade reaction. In general, the six-numbered EDAMs are usually more favorable to the yield of the target compounds than that of five-numbered EDAMs. However, after using nitro-substituted EDMA **3k** as the substrate to react with arylglyoxal monohydrates **1b** and 4-hydroxy-2*H*-chromen-2-one **4a**, complicated compounds were produced, and we could not obtain the pure products. Overall, the different substituted substrates **3** other than **3k** reacted with **1** and **4** and produced compound **6** with good yields (60%−90%).

Table 4. The synthesis of 2-amino-4-cumarinyl-5-aryl-6-hydroxylpyrroles (ACAHPs) 6[a]



Entry	**1**/R/R '	**3**/n/EWG	**4**/R^2	**6**	Yield[b] (%)
1	**1a**/CH_3/H	**3b**/1/PhCO	**4a**/H	**6a**	76
2	**1a**/CH_3/H	**3d**/1/*p*-ClPhCO	**4a**/H	**6b**	82
3	**1b**/H/H	**3b**/1/PhCO	**4c**/Cl	**6c**	78

4	**1b**/H/H	**3e**/1/*p*-FPhCO	**4a**/H	**6d**	83
5	**1b**/H/H	**3e**/1/*p*-FPhCO	**4c**/Cl	**6e**	80
6	**1b**/H/H	**3d**/1/*p*-ClPhCO	**4a**/H	**6f**	80
7	**1b**/H/H	**3c**/1/*p*-BrPhCO	**4c**/Cl	**6g**	85
8	**1d**/F/F	**3a**/1/*p*-MePhCO	**4a**/H	**6h**	73
9	**1d**/F/F	**3d**/1/*p*-ClPhCO	**4a**/H	**6i**	77
10	**1a**/CH_3/H	**3g**/2/PhCO	**4d**/CH_3	**6j**	88
11	**1a**/CH_3/H	**3g**/2/PhCO	**4c**/Cl	**6k**	89
12	**1a**/CH_3/H	**3i**/2/*p*-FPhCO	**4a**/H	**6l**	90
13	**1a**/CH_3/H	**3h**/2/*p*-ClPhCO	**4d**/CH_3	**6m**	87
14	**1b**/H/H	**3f**/2/*p*-MePhCO	**4a**/H	**6n**	85
15	**1b**/H/H	**3f**/2/*p*-MePhCO	**4b**/Br	**6o**	87
16	**1b**/H/H	**3g**/2/PhCO	**4a**/H	**6p**	87
17	**1b**/H/H	**3i**/2/*p*-FPhCO	**4a**/H	**6q**	87
18	**1b**/H/H	**3h**/2/*p*-ClPhCO	**4a**/H	**6r**	86
19	**1b**/H/H	**3h**/2/*p*-ClPhCO	**4c**/Cl	**6s**	89
20	**1c**/F/H	**3g**/2/PhCO	**4c**/Cl	**6t**	86
21	**1c**/F/H	**3i**/2/*p*-FPhCO	**4a**/H	**6u**	88
22	**1d**/F/F	**3h**/2/*p*-ClPhCO	**4a**/H	**6v**	87
23	**1b**/H/H	**3j**/1/MeCO	**4a**/H	**6w**	60
24	**1b**/H/H	**3k**/1/NO_2	**4a**/H	**6x**	complex

[a] Reagents and conditions: Arylglyoxal monohydrates **1** (1.0 mmol), HKAs **3** (1.0 equiv), 4-hydroxy-2*H*-chromen-2-ones **4** (1.0 equiv), 1,4-dioxane (10 mL). [b] Isolated yield based on **2**.

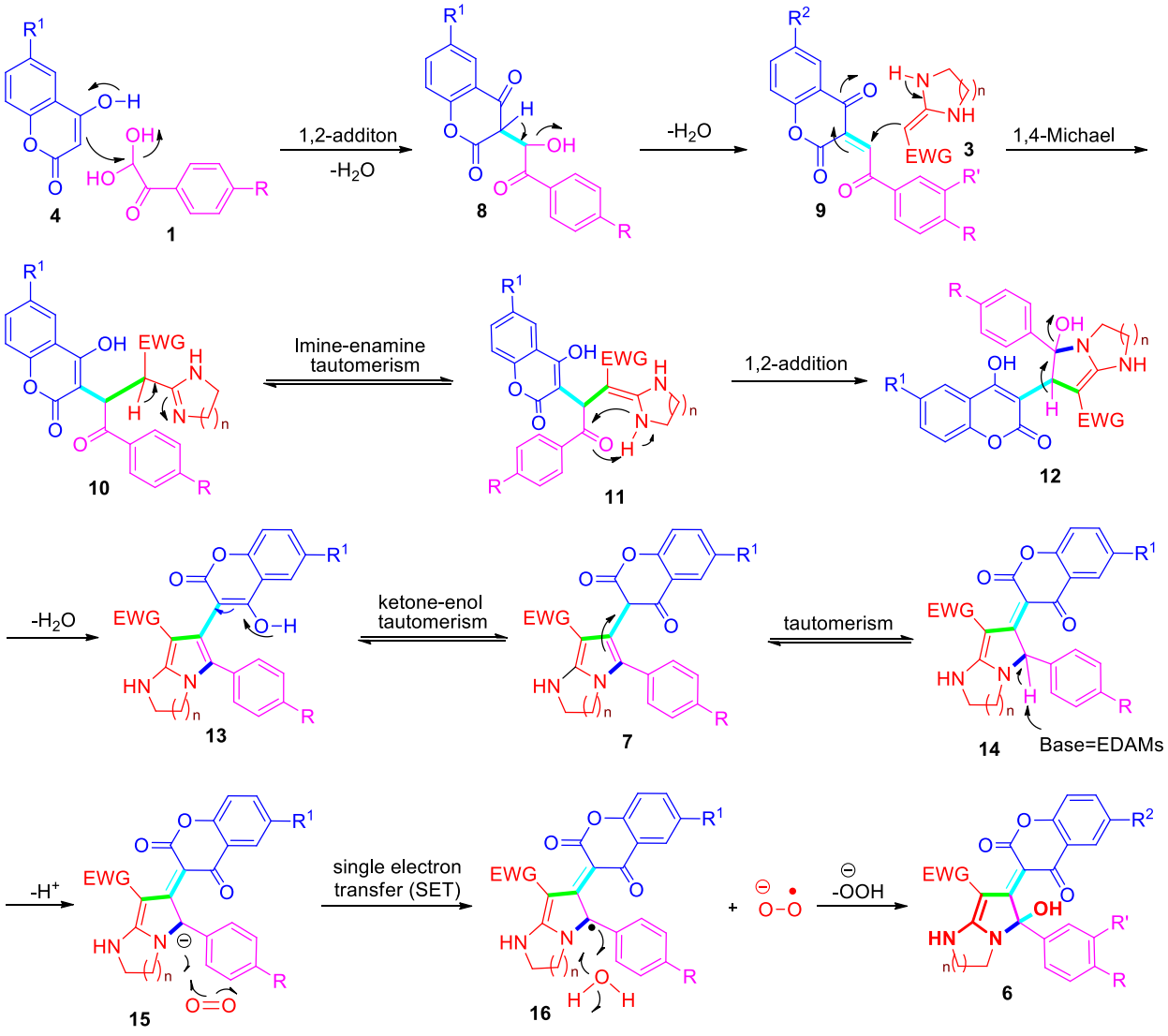
The chemical structure of all target derivatives **(5**–**6)** was fully characterized by infrared (IR) spectroscopy, proton (^{1}H) nuclear magnetic resonance (NMR), carbon-13 (^{13}C) NMR, and high-resolution mass spectrometry (HRMS). To further clarify the structure of the target products,

compounds **6c** and **6v** were selected as representative compounds to cultivate single crystals, and were unequivocally confirmed by X-ray diffraction (XRD) analysis (Supporting Information, Figure S1 and Figure S2, CCDC1916446 and CCDC1916449).

Based on the above experimental results, we propose a mechanism, which is shown as Scheme 2. First, the *α*-C of 4-hydroxy-2*H*-chromen-2-ones **4** attack the hemiacetal group of arylglyoxal monohydrates **1** and one molecule of water is lost, which subsequently results in the formation of intermediates **8**. Intermediates **8** lose another molecule of water to produce intermediates **9**. Then, the *α*-C of EDAMs **3** attack the *α,β*-unsaturated double bond via Michael reaction to give intermediates **10**. Next, compounds **10,** via imine-enamine tautomerism followed by a 1,2-addition reaction, give intermediates **12**. Compounds **7** are formed by successively losing one molecule of H_2O and ketone-enol tautomerism. Next, compounds **7** undergo tautomerism and lose protons to form intermediates **15**. Intermediates **15** react with the oxygen in the air to produce intermediates **16** through single electron transfer (SET). Eventually, intermediates **16** are attacked by water in the mixture to obtain the target compound **6**.

To confirm the mechanism used for this cascade reaction, 1-(4-chlorophenyl)-2-(imidazolidin-2-ylidene)ethanone (**3d)**, 4-hydroxy-2*H*-chromen-2-one (**4a**), and 1,4-dioxane were charged in a round-bottom flask. Then, 2,2-dihydroxy-1-(*p*-tolyl)ethanone (**1a)** was added to the mixture, and the reaction mixture was refluxed for only 3 hours. The reaction mixture was then injected into the high-performance liquid chromatography-high-resolution mass spectrometry (HPLC-HRMS) system. The molecular ion peaks that appeared in the high-resolution mass spectrum were: HRMS (TOF ES^+): *m/z* calcd. for $C_{29}H_{24}ClN_2O_5$ $[M+H]^+$, 515.1368; found, 515.1364; HRMS (TOF ES^+): *m/z* calcd. for $C_{29}H_{24}ClN_2O_5$ $[M+H]^+$, 515.1368; found, 515.1359; HRMS (TOF ES^+): *m/z* calcd. for $C_{29}H_{24}ClN_2O_5$ $[M+H]^+$, 515.1368; found, 515.1356. There are the HRMS

Scheme 2. The proposed mechanism for the formation of ACAHPs 6



spectra of intermediates **10b/11b/12b** (supporting information, Figure S97−Figure S99); HRMS (TOF ES$^+$): *m/z* calcd. for $C_{29}H_{22}ClN_2O_4$ [M+H]$^+$, 497.1263; found, 497.1259, HRMS (TOF ES$^+$): *m/z* calcd. for $C_{29}H_{22}ClN_2O_4$ [M+H]$^+$, 497.1263; found, 497.1264, HRMS (TOF ES$^+$): *m/z* calcd. for $C_{29}H_{22}ClN_2O_4$ [M+H]$^+$, 497.1263; found, 497.1257. There are the HRMS spectra of intermediates **13b/7b/14b** (SI, Figure S100−Figure S102); HRMS (TOF ES$^+$): *m/z* calcd. for $C_{29}H_{22}ClN_2O_5$ [M+H]$^+$, 513.1212; found, 513.1204, which are the HRMS spectra of the target

compounds **6b** (SI, Figure S103). More importantly, intermediate **7b** could easily have been oxidized by oxygen to afford compound **6b**.

To prove that a single electron transfer (SET) occurred within the key intermediate **16f**, we used 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to trap the free radical intermediate **16f**. 2,2-Dihydroxy-1-phenylethanone (**1b**), **3d**, **4a** and 1,4-dioxane were charged in a round-bottom flask. Then, TEMPO was added to the mixture, and the reaction mixture was refluxed for only 3 hours. Then, the reaction mixture was injected into the HPLC-HRMS system. The molecular ion peaks that appeared in the high-resolution mass spectrum were: HRMS (TOF ES^+): *m/z* calcd. for $C_{37}H_{37}ClN_3O_5$ $[M+H]^+$, 638.2416; found, 5638.2430. The HRMS spectra of intermediates **16f-TEMPO** is shown in the Supporting Information, Figure S104.

Based on the above results, the proposed mechanism of the cascade reaction is described in Scheme 2.

CONCLUSIONS

We have developed a green and practical strategy for the preparation of highly functionalized ACAPs through a cascade reaction and a metal-free catalyzed aerobic oxidation reaction of arylglyoxal monohydrates **1**, EDAMs **2**−**3**, and 4-hydroxy-2*H*-chromen-2-ones **4** *via* multicomponent reactions. Interestingly, ACAHPs **6** were unexpectedly obtained by metal-free aerobic oxidation in 1,4-dioxane at simple reflux for approximately 10 hours. Based on this protocol, ACAHP **6** was constructed without metal catalysts or traditional oxidizing agents. This method represents a route to obtain ACAHPs using an environmentally friendly oxidation reaction, in a concise, rapid, and practical manner and with potential biological activity of the product. Moreover, testing of this series of highly functionalized ACAHPs is underway to

determine if any possess potential anti-inflammatory activity and then to test further to determine which candidates possess good anti-inflammatory activity. Their biological activity, including anti-inflammatory activity, will be reported in the future.

■ EXPERIMENTAL SECTION

General Methods. All compounds were fully characterised by spectroscopic data. The NMR spectra were recorded on a Bruker DRX500 & DRX600. Chemical shifts (δ) are expressed in ppm, *J* values are given in Hz, and deuterated DMSO-d_6 & $CDCl_3$ were used as solvent. IR spectra were recorded on a FT-IR Thermo Nicolet Avatar 360 using a KBr pellet. The reactions were monitored by thin layer chromatography (TLC) using silica gel GF_{254}. The melting points were determined on a XT-4A melting point apparatus and are uncorrected. HRMs were performed on an Agilent LC/Msd TOF instrument. Column chromatography was performed on silica gel (200–300 mesh).

EDAMs **2–3** were synthesized by known literature procedures.[28-29] All the other chemicals used in the experiment were purchased from commercial sources and were used without further purification.

General procedure for the synthesis of ACAPs 5. Arylglyoxal monohydrates **1** (1.0 mmol), 4-hydroxy-2*H*-chromen-2-ones **4** (1.0 mmol), and ethanol (10 mL) were placed into a 25-mL round-bottom flask. Then, 1,1-enediamines (EDAMs) **2** (1.0 mmol) was added to this mixture, and the mixture was refluxed until the completion of the reaction (approximately 6 hours), which was monitored by thin-layer chromatography (TLC). The reaction mixture was cooled to room temperature. Finally, the crystals were collected using a Buchner funnel and were washed with a few milliliters of ethanol to obtain the target compounds **5** with good to excellent yield of 80%−94%.

*4-Hydroxy-3-(5-((4-methoxyphenethyl)amino)-4-nitro-2-(p-tolyl)-1H-pyrrol-3-yl)-2H-chromen-2-one (**5a**).* Yellow solid (475.4 mg, 93%); Mp: 275.6–276.0 °C; IR (KBr): 3300.1, 1618.6, 1642.5, 1433.7, 963.2, 825.9 cm^{-1}; ^1H NMR (600MHz, DMSO-d_6): δ = 2.25 (s, 3H, CH_3), 2.93–3.77 (m, 2H, CH_2), 3.73–3.77 (m, 2H, $NHCH_2$), 3.75 (s, 3H, OCH_3), 6.92–6.93 (m, 2H, ArH), 7.13–7.15 (m, 2H, ArH), 7.26–7.41 (m, 6H, ArH), 7.62–7.65 (m, 1H, ArH), 7.82–7.84 (m, 1H, ArH), 8.14–8.16 (m, 1H, CH_2NH), 11.11 (br, 1H, NH), 11.13 (s, 1H, OH); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6): δ = 21.2, 34.7, 44.6, 55.5, 99.7, 103.0, 114.3, 116.5, 116.6, 118.2, 124.0, 124.4, 127.0, 127.3, 128.6, 129.4, 130.3, 132.6, 137.4, 147.4, 152.9, 158.4, 161.4, 162.3; HRMS (TOF ES^+): *m/z* calcd for $C_{29}H_{25}N_3NaO_6$ $[M+Na]^+$, 534.1636; found, 534.1634.

*6-Bromo-3-(5-((4-chlorophenethyl)amino)-4-nitro-2-(p-tolyl)-1H-pyrrol-3-yl)-4-hydroxy-2H-chromen-2-one (**5b**).* Red solid (545.6 mg, 92%); Mp: 280.1–280.5 °C; IR (KBr): 3455.7, 1694.9, 1644.9, 1428.4, 111.8, 820.4 cm^{-1}; ^1H NMR (600MHz, DMSO-d_6): δ = 2.25 (s, 3H, CH_3), 2.98–3.01 (m, 2H, CH_2), 3.73–3.77 (m, 2H, $NHCH_2$), 7.14–7.15 (m, 2H, ArH), 7.24–7.26 (m, 2H, ArH), 7.38–7.42 (m, 5H, ArH), 7.79–7.80 (m, 1H,ArH), 7.92–7.93 (m, 1H, ArH), 8.20–8.22 (m, 1H, CH_2NH), 11.18 (br, 1H, NH), 11.48 (s, 1H, OH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 21.2, 34.9, 44.2, 100.6, 102.7, 116.3, 118.2, 118.5, 119.1, 126.2, 127.0, 127.3, 128.5, 128.8, 129.4, 131.2, 131.5, 135.1, 137.5, 138.3, 147.3, 151.9, 160.2, 161.8; HRMS (TOF ES^+): *m/z* calcd for $C_{28}H_{21}BrClN_3O_5$ $[M+H]^+$, 594.0668; found, 594.0666.

*4-Hydroxy-3-(5-((4-methoxyphenethyl)amino)-4-nitro-2-phen-yl-1H-pyrrol-3-yl)-2H-chromen-2-one (**5c**).* Yellow solid (467.3 mg, 94%); Mp: 269.9–270.3 °C; IR (KBr): 3244.6, 1681.7, 1643.9, 1434.2, 827.4, 768.5 cm^{-1}; ^1H NMR (600MHz, DMSO-d_6): δ = 2.94–2.96 (m, 2H, CH_2), 3.73–3.78 (m, 2H, NCH_2), 3.75 (s, 3H, OCH_3), 6.92–6.93 (m, 2H, ArH), 7.24–7.41 (m, 9H, ArH), 7.63–7.65 (m, 1H,ArH), 7.83–7.84 (m, 1H, ArH), 8.16–8.18 (m, 1H, CH_2NH), 11.19 (br, 1H,

NH), 11.19 (s, 1H, OH); $^{13}C\{^{1}H\}$ NMR (150 MHz, DMSO-d_6): δ = 34.7, 44.6, 55.5, 99.6, 103.6, 114.3, 116.5, 116.7, 118.3, 124.1, 124.4, 126.8, 127.4, 128.0, 128.8, 130.3, 131.0, 131.5, 158.4, 161.6, 162.3; HRMS (TOF ES$^+$): *m/z* calcd for $C_{28}H_{23}N_3O_6$ $[M+H]^+$, 498.1660; found, 498.1660.

*4-Hydroxy-3-(5-((4-methylphenethyl)amino)-4-nitro-2-phenyl-1H-pyrrol-3-yl)-2H-chromen-2-one (**5d**).* Yellow solid (447.5 mg, 93%); Mp: 268.0–268.4 °C; IR (KBr): 3301.9, 1684.3, 1641.5, 1434.0, 808.8, 696.7 cm^{-1}; ^{1}H NMR (600MHz, DMSO-d_6): δ = 2.29 (s, 3H, CH_3), 2.95–2.97 (m, 2H, CH_2), 3.73–3.74 (m, 2H, $NHCH_2$), 7.15–7.25 (m, 6H, ArH), 7.33–7.41 (m, 6H, ArH), 7.62–7.65 (m, 1H,ArH), 7.82–7.83 (m, 1H, ArH), 8.15–8.18 (m, 1H, CH_2NH), 11.20 (br, 1H, NH), 11.20 (s, 1H, OH); $^{13}C\{^{1}H\}$ NMR (150 MHz, DMSO-d_6): δ = 21.2, 35.2, 44.5, 99.6, 103.6, 116.5, 116.7, 118.3, 124.0, 124.4, 126.8, 127.4, 128.0, 128.8, 129.2, 129.5, 131.5, 132.6, 135.8, 136.1, 147.4, 152.9, 161.5, 162.3; HRMS (TOF ES$^+$): *m/z* calcd for $C_{28}H_{23}NaN_3O_5$ $[M+Na]^+$, 504.1530; found,504.1532.

*4-Hydroxy-3-(4-nitro-5-(phenethylamino)-2-phenyl-1H-pyrrol -3-yl)-2H-chromen-2-one (**5e**).* Yellow solid (1.220 g, 87%); Mp: 271.7–272.1 °C; IR (KBr): 3067.9, 1643.1, 1560.7, 1430.3, 762.1, 696.7 cm^{-1}; ^{1}H NMR (600MHz, DMSO-d_6): δ = 3.00–3.02 (m, 2H, NCH_2), 3.77–3.78 (m, 2H, NCH_2), 7.23–7.26 (m, 2H, ArH), 7.32–7.41 (m, 10H, ArH), 7.62–7.65 (m, 1H,ArH), 7.82–7.83 (m, 1H, ArH), 8.19–8.21 (m, 1H, CH_2NH), 11.20 (br, 1H, NH), 11.21 (s, 1H, OH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 35.6, 44.4, 99.6, 103.6, 116.5, 116.7, 118.3, 124.0, 124.4, 126.8, 127.4, 128.0, 128.8, 128.9, 129.3, 131.5, 132.6, 139.3, 147.1, 152.9, 161.5, 162.3; HRMS (TOF ES$^+$): *m/z* calcd for $C_{27}H_{21}N_3NaO_5$ $[M+Na]^+$, 490.1373; found, 490.1374.

*3-(5-((4-Fluorophenethyl)amino)-4-nitro-2-phenyl-1H-pyrrol-3-yl)-4-hydroxy-2H-chromen-2-one (**5f**).* Yellow solid (441.5 mg, 91%); Mp: 267.8–268.2 °C; IR (KBr): 3296.9, 1679.5, 1643.0, 1433.3, 767.2, 697.3 cm^{-1}; ^{1}H NMR (600MHz, DMSO-d_6): δ =3.03–3.07 (m, 2H, CH_2), 3.78–

3.82 (m, 2H, NCH_2), 7.10–7.40 (m, 11H, ArH), 7.83–7.85 (m, 1H, ArH), 7.89–7.93 (m, 1H,ArH), 8.22– 8.26 (m, 1H, CH_2NH), 11.21 (br, 1H, NH), 11.21 (s, 1H, OH); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6): δ =35.5, 44.0, 99.6, 103.6, 113.6, 113.7, 116.0 (d, J = 21.0 Hz), 116.7, 118.3, 124.1, 124.4, 125.5, 126.8, 127.4, 128.0, 128.9, 130.8 (d, J = 7.5 Hz), 131.5, 132.6, 142.3, 147.3, 152.9, 161.6, 162.3, 162.8 (d, J = 234 Hz); HRMS (TOF ES^+): *m/z* calcd for $C_{27}H_{20}FN_3NaO_5$ $[M+Na]^+$, 508.1279; found, 508.1280.

*4-Hydroxy-3-(5-((4-methylbenzyl)amino)-4-nitro-2-phenyl-1H -pyrrol-3-yl)-2H-chromen-2-one (**5g**).* Yellow solid (397.1 mg, 85%); Mp: 244.5–244.9 °C; IR (KBr): 3175.6, 1685.8, 1636.9, 1434.7, 761.1, 695.9 cm^{-1}; ^1H NMR (600MHz, DMSO-d_6): δ = 2.30 (s, 3H, CH_3), 4.73–4.74 (m, 2H, CH_2), 7.21–7.24 (m, 3H, ArH), 7.32–7.41 (m, 8H, ArH), 7.62–7.65 (m, 1H,ArH), 7.82–7.83 (m, 1H, ArH), 8.59–8.61 (m, 1H, CH_2NH), 11.19 (br, 1H, NH), 11.25 (s, 1H, OH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 21.2, 45.9, 99.6, 103.7, 116.6, 118.4, 124.1, 124.4, 126.6, 127.3, 127.9, 128.1, 128.8, 129.6, 129.8, 131.4, 132.6, 137.0, 147.4, 152.9, 161.6, 162.3; HRMS (TOF ES^+): *m/z* calcd for $C_{27}H_{21}N_3NaO_5$ $[M+Na]^+$,490.1372; found, 490.1371.

*6-Bromo-4-hydroxy-3-(4-nitro-2-phenyl-5-(p-tolylamino)-1H-pyrrol-3-yl)-2H-chromen-2-one (**5h**).* Yellow solid (424.8 mg, 80%); Mp: 293.8–294.2 °C; IR (KBr): 3379.9, 1696.0, 1637.8, 1436.4, 1113.5, 974.1 cm^{-1}; ^1H NMR (600MHz, DMSO-d_6): δ = 2.13 (s, 3H, CH_3), 7.21– 7.42 (m, 10H, ArH), 7.80–7.81 (m, 1H, ArH), 7.92–7.96 (m, 1H,ArH), 9.52–9.56 (m, 1H, CH_2NH), 11.57 (br, 1H, NH), 11.66 (s, 1H, OH); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6): δ = 21.0, 100.3, 103.6, 116.4, 118.4, 119.2, 120.3, 121.8, 126.2, 127.1, 127.5, 128.0, 128.7, 130.4, 131.2, 133.9, 135.2, 136.7, 142.6, 151.9, 160.5, 161.9; HRMS (TOF ES^+): *m/z* calcd for $C_{26}H_{18}BrN_3NaO_5$ $[M+Na]^+$, 554.0322; found, 554. 0322.

3-(2-(4-Fluorophenyl)-5-((4-methoxyphenethyl)amino)-4-nitro-1H-pyrrol-3-yl)-4-hydroxy-2H-

*chromen-2-one (**5i**).* Yellow solid (463.6 mg, 90%);; Mp: 279.7–280.1 °C; IR (KBr): 3236.9, 1681.1, 1616.2, 1432.0, 1247.7, 825.7 cm^{-1}; ^1H NMR (600MHz, DMSO-d_6): δ = 2.93–2.95 (m, 2H, CH_2), 3.71–3.74 (m, 2H, NCH_2), 3.73 (s, 3H, OCH_3), 6.91–6.93 (m, 2H, ArH), 7.21–7.22 (m, 2H, ArH), 7.27–7.29 (m, 2H,ArH), 7.33–7.41 (m, 4H, ArH), 7.63–7.65 (m, 1H, ArH), 7.82–7.85 (m, 1H, ArH), 8.16–8.17 (m, 1H, CH_2NH), 11.20 (br, 1H, NH), 11.20 (s, 1H, OH); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6): δ = 34.7, 44.6, 55.5, 99.4, 103.6, 114.3, 115.9 (d, J = 22.5 Hz), 116.5, 116.7, 118.1, 124.1, 124.4, 125.9, 128.0, 129.5, 130.3, 131.1, 132.7, 147.4, 152.9, 158.4, 161.1, 161.66, 162.3, 162.9 (d, J = 244.5 Hz); HRMS (TOF ES^+): *m/z* calcd for $C_{28}H_{22}FN_3NaO_6$ $[M+Na]^+$, 538.1385; 538.1384.

*3-(2-(4-Fluorophenyl)-5-((4-methylphenethyl)amino)-4-nitro-1H-pyrrol-3-yl)-4-hydroxy-2H-chromen-2-one (**5j**).* Yellow solid (459.2 mg, 92%);; Mp: 263.8–264.2 °C; IR (KBr): 3304.7, 1683.6, 1642.3, 1435.5, 1111.5, 695.4 cm^{-1}; ^1H NMR (600MHz, DMSO-d_6): δ =2.29 (s, 3H, CH_3), 2.95–2.97 (m, 2H, CH_2), 3.73–3.74 (m, 2H, NCH_2), 7.15–7.25 (m, 6H, ArH), 7.33–7.41 (m, 4H, ArH), 7.62–7.65 (m, 1H,ArH), 7.82–7.83 (m, 1H, ArH), 8.15–8.17 (m, 1H, CH_2NH), 11.20 (br, 1H, NH), 11.20 (s, 1H, OH); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6): δ = 21.1, 35.1, 44.5, 99.4, 103.6, 115.9 (d, J = 21.0 Hz), 116.5, 116.7, 118.1, 124.1, 124.4, 125.9, 127.9, 129.2, 129.5, 129.5, 132.7, 135.8, 136.1, 147.4, 152.9, 161.1, 161.6, 162.3, 161.9 (d, J = 244.5 Hz); HRMS (TOF ES^+): *m/z* calcd for $C_{28}H_{22}FN_3NaO_5$ $[M+Na]^+$, 522.1436; found, 522.1436.

*6-Bromo-3-(2-(4-fluorophenyl)-4-nitro-5-(phenethylamino)-1H-pyrrol-3-yl)-4-hydroxy-2H-chromen-2-one (**5k**).* Yellow solid (529.3 mg, 94%);; Mp: 294.6–295.0 °C; IR (KBr): 3311.3, 1694.4, 1647.0, 1423.6, 1116.8, 840.4 cm^{-1}; ^1H NMR (600MHz, DMSO-d_6): δ = 2.99–3.03 (m, 2H, CH_2), 3.73–3.78 (m, 2H, NCH_2), 7.10–7.14 (m, 11H, ArH), 7.21–7.37 (m, 2H, ArH), 8.18–8.22 (m, 1H, CH_2NH), 11.24 (br, 1H, NH), 11.55 (s, 1H, OH); $^{13}C\{^1H\}$ NMR (150 MHz,

DMSO-d_6): δ = 35.6, 44.4, 100.3, 103.3, 115.9 (d, J = 21.0 Hz), 116.3, 118.1, 118.4, 119.1, 126.0, 126.2, 126.9, 127.8, 128.9, 129.3, 129.6, 135.2, 139.2, 147.3, 151.9, 160.4, 161.1 (d, J = 213.0 Hz), 161.1; HRMS (TOF ES$^+$): *m/z* calcd for $C_{27}H_{19}BrFN_3NaO_5$ $[M+Na]^+$, 586.0384; found, 586.0384.

General procedure for the synthesis of ACAHPs 6. Arylglyoxal monohydrates **1** (1.0 mmol), 4-hydroxy-2*H*-chromen-2-ones **4** (1.0 mmol), and 1,4-dioxane (10 mL) were placed into a 25-mL round-bottom flask. Then, 1,1-enediamines (EDAMs) **3** (1.0 mmol) was added to this mixture, and the mixture was refluxed until the completion of the reaction (approximately 10 hours), which was monitored by TLC. Then, the mixture was cooled to room temperature and added to 50 mL of water, followed by extraction with an appropriate amount of ethyl acetate. The organic phases were combined and dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and then purified by fast column chromatography (with the appropriate proportion of petroleum ether and ethyl acetate). Eventually, the target compounds **6** were obtained with yields of 73−90%.

*(E)-3-(7-Benzoyl-5-hydroxy-5-(p-tolyl)-2,3-dihydro-1H-pyrro-lo[1,2-a]imidazol-6(5H)-ylid-ene)chromane-2,4-dione (**6a**).* Yellow solid (363.4 mg, 76%);; Mp: 233.8–234.2 °C; IR (KBr): 3411.5, 1667.8, 1606.9, 1405.2, 1286.5, 1119.2, 765.7 cm^{-1}; ^{1}H NMR (600MHz, DMSO-d_6): δ = 2.13 (s, 3H, CH_3), 3.21–3.24 (m, 1H, NCH_2), 3.70–3.75 (m, 1H, NCH_2), 4.10–4.14 (m, 2H, $NHCH_2$), 6.88–6.94 (m, 1H, ArH), 7.03–7.06 (m, 3H, ArH), 7.15–7.17 (m, 2H,ArH), 7.26–7.28 (m, 2H, ArH), 7.33–7.36 (m, 2H, ArH), 7.63–7.66 (m, 3H, ArH), 10.11 (br, 1H, NH), 10.94 (s, 1H, OH); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ = 21.14, 41.4, 50.6, 93.1, 98.1, 113.9, 116.3, 120.6, 123.7, 125.7, 126.0, 128.2, 128.6, 129.4, 133.1, 133.5, 136.0, 137.6, 138.5, 153.3, 162.5, 169.3, 172.8, 175.6, 188.2; HRMS (TOF ES$^+$): *m/z* calcd for $C_{29}H_{23}N_2O_5$ $[M+H]^+$, 479.1601;

found, 479.1603.

*(E)-3-(7-(4-Chlorobenzoyl)-5-hydroxy-5-(p-tolyl)-2,3-dihydro-1H-pyrrolo[1,2-a]imidazol-6-(5H)-ylidene)chromane-2,4-dione (**6b**).* Yellow solid (419.9 mg, 82%); Mp: 225.6–226.0 °C; IR (KBr): 3450.3, 1637.5, 1464.8, 1290.4, 1120.1, 766.2 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.21 (s, 3H, CH_3), 3.29–3.30 (d, 1H, NCH_2, J = 27.0 Hz), 3.76–3.82 (m, 1H, NCH_2), 4.17–4.22 (m, 2H, $NHCH_2$), 7.00–7.02 (m, 1H, ArH), 7.12–7.14 (m, 3H, ArH), 7.22–7.24 (m, 2H, ArH), 7.44–7.46 (m, 3H, ArH), 7.71–7.75 (m, 3H, ArH), 10.18 (br, 1H, NH), 10.88 (s, 1H, OH); $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6): δ = 21.1, 41.4, 50.1, 93.0, 98.1,113.3, 116.4, 120.5, 123.9, 125.7, 126.1, 128.8, 129.4, 130.0, 133.6, 135.9, 136.4, 137.8, 138.5, 153.3, 162.6, 169.1, 172.7, 175.7, 187.0; HRMS (TOF ES^+): *m/z* calcd for $C_{29}H_{22}ClN_2O_5$ $[M+H]^+$, 513.1212; found, 513.1209.

*(E)-3-(7-Benzoyl-5-hydroxy-5-phenyl-2,3-dihydro-1H-pyrrolo-[1,2-a]imidazol-6(5H)-ylidene) -6-chlorochromane-2,4-dione (**6c**).* Yellow solid (388.5 mg, 78%); Mp: 202.2–202.6 °C; IR (KBr): 3432.3, 1655.0, 1438.5, 1289.2, 1125.4, 820.4, 755.6 cm^{-1}; ^{1}H NMR (500MHz, DMSO-d_6): δ = 3.33–3.34 (m, 1H, NCH_2), 3.38–3.84 (m, 1H, NCH_2), 4.22–4.23 (m, 2H, $NHCH_2$), 7.03–7.05 (m, 1H, ArH), 7.29–7.30 (m, 1H, ArH), 7.30–7.38 (m, 6H, ArH), 7.44–7.48 (m, 2H, ArH), 7.63–7.64 (m, 1H, ArH), 7.73–7.74 (m, 2H, ArH),10.31 (br, 1H, NH), 10.80 (s, 1H, OH); $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6): δ = 41.4, 50.2, 93.1, 97.9, 114.8, 118.6, 121.9, 124.9, 125.7, 128.1, 128.3, 128.6, 128.9, 129.2, 133.1, 133.2, 137.3, 138.7, 151.8, 162.0, 169.3, 172.1, 174.0, 188.1; HRMS (TOF ES^+): *m/z* calcd for $C_{28}H_{20}ClN_2O_5$ $[M+H]^+$, 499.1055; found, 499.1055.

*(E)-3-(7-(4-Fluorobenzoyl)-5-hydroxy-5-phenyl-2,3-dihydro-1H-pyrrolo[1,2-a]imidazol-6-(5H) -ylidene)chromane-2,4-dione (**6d**).* Yellow solid (398.5 mg, 83%); Mp: 216.1–216.5 °C; IR (KBr): 3449.3, 1633.2, 1413.5, 1289.4, 1118.9, 755.9, 606.9 cm^{-1}; ^{19}F NMR (470 MHz, DMSO-

d_6): δ = -106.6; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.30 (t, 1H, NCH_2), 3.79–3.84 (m, 1H, NCH_2), 4.16–4.25 (m, 1H, $NHCH_2$), 6.99–7.00 (m, 1H, ArH), 7.12–7.15(m, 1H, ArH), 7.19–7.23 (m, 2H, ArH), 7.26–7.28 (m, 1H, ArH), 7.32–7.37 (m, 4H, ArH), 7.43–7.46 (m, 1H, ArH), 7.71–7.73 (m, 1H, ArH), 7.80–7.83 (m, 1H, ArH), 10.22 (br, 1H, NH), 10.97 (s, 1H, OH); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ = 41.4, 50.1, 93.0, 98.0, 113.8, 115.7 (d, J = 22.5 Hz), 116.3, 120.5, 123.8, 125.7, 126.0, 128.8, 129.2, 131.0, 131.1, 133.6, 134.3, 138.9, 153.3, 163.2 (d, J = 225.0 Hz), 166.0, 169.3, 175.7, 186.8; HRMS (TOF ES$^+$): *m/z* calcd for $C_{28}H_{19}FN_2NaO_5$ $[M+Na]^+$, 505.1170; found, 505.1166.

(E)-6-Chloro-3-(7-(4-fluorobenzoyl)-5-hydroxy-5-phenyl-2,3-dihydro-1H-pyrrolo[1,2-a]imid-azol-6(5H)-ylidene)chromane-2,4-dione ***(6e)***. Yellow solid (412.9 mg, 80%); Mp: 199.6–200.0 °C; IR (KBr): 3414.6, 1638.5, 1437.2, 1229.7, 1124.6, 791.8, 607.5 cm$^{-1;}$ ^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.32–3.34 (m, 1H, NCH_2), 3.81–3.83 (m, 1H, NCH_2), 4.20–4.24 (m, 2H, $NHCH_2$), 7.06–7.07 (m, 1H, ArH), 7.20–7.23 (m, 2H, ArH), 7.28–7.29 (m, 1H, ArH), 7.33–7.36 (m, 4H, ArH), 7.47–7.49 (m, 1H, ArH), 7.64–7.64 (m, 1H, ArH),7.79–7.82 (M, 2H, ArH), 10.29 (br, 1H, NH), 10.74 (s, 1H, OH); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ = 41.4, 50.2, 93.1, 97.8, 114.6, 115.7 (d, J = 21.0 Hz), 118.7, 121.9, 125.0, 125.7, 128.1, 129.0, 129.2, 131.1 (d, J = 9.0 Hz), 133.2, 134.1, 138.6, 151.9, 162.1, 165.1 (d, J = 250.5 Hz), 169.2, 172.0, 174.1, 186.7; HRMS (TOF ES$^+$): *m/z* calcd for $C_{28}H_{19}ClFN_2O_5$ $[M+H]^+$, 517.0961; found, 517.0961.

(E)-3-(7-(4-Chlorobenzoyl)-5-hydroxy-5-phenyl-2,3-dihydro-1H-pyrrolo[1,2-a]imidazol-6 (5H) -ylidene)chromane-2,4-dione ***(6f)***. Yellow solid (398.5 mg, 80%); Mp: 222.2–222.6 °C; IR (KBr): 3438.3, 1652.0, 1338.5, 1269.2, 1117.4, 830.4, 765.6 cm^{-1}; ^{1}H NMR (600MHz, DMSO-d_6): δ = 3.293–3.31 (m, 1H, NCH_2), 3.79–3.81(m, 1H, NCH_2), 4.19–4.20 (m, 2H, $NHCH_2$), 7.00–7.01 (m, 1H, ArH), 7.14–7.15 (m, 1H, ArH), 7.27–7.28 (m, 1H, ArH), 7.32–7.36 (m, 4H,

ArH), 7.44–7.47 (m, 3H, ArH), 7.70–7.75 (m, 3H, ArH), 10.21 (br, 1H, NH),10.86 (s, 1H, OH); $^{13}C\{^{1}H\}$ NMR (150MHz, DMSO-d_6): δ = 41.4, 50.1, 93.0, 98.1, 113.4, 116.4, 120.5, 123.9, 125.7, 126.0, 126.3, 128.8, 128.8, 129.2, 130.0,133.7, 136.4, 137.8, 138.8, 153.3, 169.2, 176.9, 186.9; HRMS (TOF ES$^+$): *m/z* calcd for $C_{28}H_{20}ClN_2O_5$ $[M+H]^+$, 499.1055; found, 499.1055.

*(E)-3-(7-(4-Bromobenzoyl)-5-hydroxy-5-phenyl-2,3-dihydro-1H-pyrrolo[1,2-a]imidazol-6-(5H) -ylidene)-6-chlorochromane-2,4-dione (**6g**).* Yellow solid (489.6 mg, 85%); Mp: 225.5–225.9 °C; IR (KBr): 3442.6, 1655.7, 1431.1, 1296.2, 1208.9, 788.8, 744.5 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.30–3.32 (m, 1H, NCH_2), 3.80–3.82 (m, 1H, NCH_2), 4.21–4.22 (m, 2H, $NHCH_2$), 7.07–7.09 (m, 1H, ArH), 7.28–7.29 (m, 5H, ArH), 7.48–7.50 (m, 1H, ArH), 7.59–7.67 (m, 5H, ArH), 10.28 (br, 1H, NH), 10.66 (s, 1H, OH); $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6): δ = 41.4, 50.2, 93.1, 97.9, 114.2, 118.7, 121.9, 125.0, 125.7, 127.1, 128.2, 128.9, 129.2, 130.2, 131.8, 133.3, 136.6, 138.6, 151.8, 162.2, 169.1, 172.0, 174.2, 187.1; HRMS (TOF ES$^+$): *m/z* calcd for $C_{28}H_{19}BrClN_2O_5$ $[M+H]^{+,}$ 577.0160; found, 577.0160.

*(E)-3-(5-(3,4-Difluorophenyl)-5-hydroxy-7-(4-methylbenzoyl)-2,3-dihydro-1H-pyrrolo[1,2-a]- imidazol-6(5H)-ylidene)chromane -2,4-dione (**6h**).* Yellow solid (375.3 mg, 73%); Mp: 197.6–198.0 °C; IR (KBr): 3440.3, 1650.9, 1438.4, 1280.1, 1125.3, 820.4, 755.6 cm$^{-1;}$ ^{19}F NMR (470 MHz, DMSO-d_6): δ = 137.7 (t, 1F, ArF), 138.3 (d, 1F, ArF); ^{1}H NMR (600MHz, DMSO-d_6): δ = 2.23 (s, 3H, CH_3), 3.37–3.42 (m, 1H, NCH_2), 3.80–3.82 (d, J = 10.0 Hz, 1H, NCH_2), 4.19–4.24 (m, 2H, $NHCH_2$), 7.00–7.01 (m, 1H, ArH), 7.12–7.18 (m, 4H, ArH), 7.38–7.46 (m, 3H, ArH), 7.66–7.68 (m, 2H, ArH), 7.75–7.76 (m, 1H, ArH), 10.35 (br, 1H, NH), 11.24 (br, 1H, OH); $^{13}C\{^{1}H\}$ NMR (150 MHz, DMSO-d_6): δ = 21.5, 41.4, 50.3, 92.3, 97.8, 114.4, 115.4, 116.4, 118.2, 120.5, 122.9, 123.8, 126.0, 128.4, 129.3, 133.6, 134.9, 137.0, 143.6, 143.6, 149.5 (d, J = 244.5 Hz), 149.9 (d, J = 246.0 Hz),153.4,162.3, 169.6, 171.3, 175.7, 187.5; HRMS (TOF ES$^+$): *m/z*

calcd for $C_{29}H_{20}F_2N_2NaO_5$ $[M+Na]^+$, 537.1232; found, 537.1227.

*(E)-3-(7-(4-Chlorobenzoyl)-5-(3,4-difluorophenyl)-5-hydroxy-2,3-dihydro-1H-pyrrolo[1,2-a]-imidazol-6(5H)-ylidene)chromane -2,4-dione (**6i**).* Yellow solid (411.2, 77%); Mp: 217.5–217.9 °C; IR (KBr): 3299.0, 1610.9, 1409.1, 1281.2, 1117.5, 997.4, 765.0 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 3.34–3.42 (m, 1H, NCH_2), 3.78–3.83 (m, 1H, $NHCH_2$), 4.17–4.26 (m, 1H, $NHCH_2$),7.02–7.04 (m, 1H, ArH), 7.14–7.17 (m, 2H, ArH),7.39–7.49 (m, 5H, ArH), 7.34–7.78 (m, 3H, ArH), 10.32 (br, 1H, NH), 10.99 (s, 1H, OH); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6): δ = 41.3, 50.3, 92.2, 97.9, 113.6, 115.4, 116.4, 118.1, 120.4, 122.9, 124.0, 126.0, 128.8, 130.0, 133.8, 136.6, 136.9, 137.9, 149.7 (d, J = 244.5 Hz), 149.9 (d, J = 244.5 Hz), 153.4, 162.5, 169.3, 171.6, 175.8, 186.8; HRMS (TOF ES^+): *m/z* calcd for $C_{28}H_{17}ClF_2N_2NaO_5$ $[M+H]^+$, 557.0686; found, 557.0684.

*(E)-3-(8-Benzoyl-6-hydroxy-6-(p-tolyl)-1,2,3,4-tetrahydropyr-rolo[1,2-a]pyrimidin-7(6H)-ylid-ene)-6-methylchromane-2,4-di-one (**6j**).* Yellow solid (445.4 mg, 88%); Mp: 225.6–226.0 °C; IR (KBr): 3415.8, 1671.7, 1396.8, 1182.4, 1001.2, 912.3, 767.4 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 1.86–1.88 (m, 1H, CH_2), 1.96–1.98 (m, 1H, CH_2), 2.21 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.90–2.94 (m, 1H, NCH_2), 3.43–3.52 (m, 3H, $NHCH_2$, NCH_2), 6.81–6.83 (m, 1H, ArH), 7.11–7.12 (m, 2H, ArH), 7.20–7.22 (m, 3H, ArH), 7.31–7.34 (m, 2H, ArH), 7.40–7.43 (m, 1H, ArH), 7.52–7.53 (m, 1H, ArH), 7.72–7.74 (m, 2H, ArH), 9.27 (br, 1H, NH), 11.56 (s, 1H, OH); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6): δ = 19.1, 20.7, 21.1, 37.1, 39.1, 96.5, 96.8, 116.0, 116.6, 120.3, 125.5, 125.8, 128.4, 128.5, 129.4, 132.7, 133.1, 133.9, 135.9, 137.6, 138.5, 151.4, 158.5, 160.0, 162.7, 175.2, 189.2; HRMS (TOF ES^+): *m/z* calcd for $C_{31}H_{26}N_2NaO_5[M+Na]^+$, 529.1734; found, 529.1736.

(E)-3-(8-Benzoyl-6-hydroxy-6-(p-tolyl)-1,2,3,4-tetrahydropyr-rolo[1,2-a]pyrimidin-7(6H)-ylid

*-ene)-6-chlorochromane-2,4-di-one (**6k**).* Yellow solid (468.3 mg, 89%); Mp: 210.4–210.8 °C; IR (KBr): 3414.9, 1678.9, 1471.5, 1199.3, 1125.3, 992.9, 766.8 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 1.78–1.81(m, 2H, CH_2), 1.89 (t, 3H, CH_3), 2.85–2.88 (m, 1H, NCH_2), 3.34–3.45 (m, 3H, NCH_2, $NHCH_2$), 6.91–6.92 (m, 1H, ArH), 7.03–7.05 (m, 2H, ArH), 7.13–7.14 (m, 2H, ArH), 7.24–7.26 (m, 2H, ArH), 7.32–7.36 (m, 2H, ArH), 7.54–7.57 (m, 1H, ArH),7 .64–7.65 (m, 2H, ArH), 9.27 (br, 1H, NH), 11.15 (s, 1H, OH); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6): δ = 19.0, 21.1, 37.2, 39.2, 96.3, 96.8, 117.7, 118.5, 122.0, 124.8, 125.8, 127.9, 128.4, 128.6, 129.5, 132.8, 132.2, 135.6, 135.6, 137.4, 138.6, 151.8, 158.4, 162.2, 164.1, 173.6, 189.2; HRMS (TOF ES^+): *m/z* calcd for $C_{30}H_{24}ClN_2O_5$ $[M+H]^+$,527.1368; found, 527.1368.

*(E)-3-(8-(4-Fluorobenzoyl)-6-hydroxy-6-(p-tolyl)-1,2,3,4-tetra-hydropyrrolo[1,2-a]pyrimidin-7(6H)-ylidene)chromane-2,4-di-one (**6l**).* Yellow solid (459.1 mg, 90%); Mp: 242.6–243.0 °C; IR (KBr): 3417.5, 1673.4, 1401.6, 1198.0, 1124.6, 782.2, 621.9 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 1.78–1.79 (m, 2H, CH_2), 2.13 (s, 3H, CH_3), 2.84 (t, 1H, $NHCH_2$), 3.35–3.44 (m, 3H, $NHCH_2$,NCH_2), 6.88–6.90 (m, 1H, ArH), 7.03–7.15 (m, 7H, ArH), 7.32–7.35 (m, 1H, ArH), 7.65–7.73 (m, 3H, ArH), 9.20 (br, 1H, NH), 11.32 (s, 1H, OH); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6): δ = 19.0, 21.1, 37.2, 39.1, 96.3, 96.8, 115.5 (d, J = 21.3 Hz), 116.2, 116.7, 120.6, 123.6, 125.8, 125.9, 131.3, 133.2, 134.3, 135.8, 138.6, 153.3, 158.3, 164.0, 163.6 (d, J = 242.5 Hz), 166.0, 175.2, 187.8; HRMS (TOF ES^+): *m/z* calcd for $C_{30}H_{24}FN_2O_5$ $[M+H]^+$, 511.1664; found, 511.1664.

*(E)-3-(8-(4-Chlorobenzoyl)-6-hydroxy-6-(p-tolyl)-1,2,3,4-tetra-hydropyrrolo[1,2-a]pyrimidin-7(6H)-ylidene)-6-methylchromane -2,4-dione (**6m**).* Yellow solid (469.9 mg, 87%); Mp: 219.8–220.2 °C; IR (KBr): 3415.1, 1637.6, 1617.5, 1522.3, 1181.8, 997.8, 815.6 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 1.80–1.97 (m, 2H, CH_2,), 2.21 (s, 3H, CH_3), 2.26 (s, 2H,CH_3), 2.92–2.93

(m, 1H, NCH_2), 3.47–3.51(m, 3H, NCH_2, $NHCH_2$, $NHCH_2$), 6.86–6.87 (m, 1H, ArH), 7.11–7.12 (m, 2H, ArH), 7.20–7.24 (m, 3H, ArH), 7.42–7.44 (m, 2H, ArH), 7.52 (m, 1H, ArH), 7.71–7,73 (m, 2H, ArH), 9.26 (br, 1H, NH), 11.41 (s, 1H, OH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 19.1, 20.7, 21.1, 37.1, 39.6, 96.5, 96.8, 116.0, 116.2, 120.2, 125.6, 125.7, 128.6, 129.4, 130.2, 132.8, 134.1, 135.8, 136.5, 137.7, 138.5, 151.4, 158.3, 162.8, 165.0, 175.4, 188.0; HRMS (TOF ES^+): *m/z* calcd for $C_{31}H_{25}ClN_2NaO_5$ $[M+Na]^+$,563.1344; found, 563.1343.

*(E)-3-(6-Hydroxy-8-(4-methylbenzoyl)-6-phenyl-1,2,3,4-tetra-hydropyrrolo[1,2-a]pyrimidin-7(6H)-ylidene)chromane-2,4-di-one (**6n**).* Yellow solid (418.3 mg, 85%); Mp: 214.5–214.9 °C; IR (KBr): 3367.9, 1676.1, 1604.4, 1448.3, 1412.2, 1200.3, 775.0, 760.5 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 1.87–1.96 (m, 2H, CH_2,), 2.22 (s, 3H, CH_3), 2.90–2.93 (m, 1H, NCH_2), 3.40–3.41(m, 1H, NCH_2), 3.50–3.53 (m, 2H, $NHCH_2$), 6.94–6.95 (m, 1H, ArH), 7.10–7.15(m, 3H, ArH), 7.26–7.35 (m, 5H, ArH), 7.40–7.42 (m, 1H, ArH), 7.65–7.67 (m, 2H, ArH), 7.73–7.74 (m, 1H, ArH), 9.28 (br, 1H, NH), 11.59 (s, 1H, OH); $^{13}C\{^1H\}$NMR (125 MHz, DMSO-d_6): δ = 19.1, 21.5, 37.2, 39.1, 96.3, 96.8, 116.2, 117.3, 120.6, 123.6, 125.8, 125.9, 128.6, 128.8, 129.1, 129.2, 133.1, 135.1, 138.8, 143.5, 153.3, 158.6, 162.5, 164.0, 175.2, 188.7; HRMS (TOF ES^+): *m/z* calcd for $C_{30}H_{25}N_2O_5$ $[M+H]^+$, 493.1758, found, 493.1762.

*(E)-6-Bromo-3-(6-hydroxy-8-(4-methylbenzoyl)-6-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]-pyr-imidin-7(6H)-ylidene)chromane -2,4-dione (**6o**).* Yellow solid (495.9 mg, 87%); Mp: 234.0–234.4 °C; IR (KBr): 3414.7, 1678.4, 1440.7, 1198.4, 1177.2, 832.8, 786.0 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 1.90–1.97 (m, *2*H, CH_2),2.22 (s, *3*H, CH_3), 2.93 (t, 1H, NCH_2), 3.44–3.54 (m, *3*H, NCH_2, $NHCH_2$), 6.94–6.96 (m, 1H, ArH), 7.14–7.16 (m, 2H, ArH), 7.27–7.27 (m, *5*H, ArH), 7.54–7.55 (m, 1H, ArH), 7.65–7.67 (m, 2H, ArH), 7.80–7.80 (m, 1H, ArH), 9.36 (br, 1H, NH), 11.32 (s, 1H, OH); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6): δ =19.0, 21.5, 37.2, 39.1,

96.1,96.8, 115.6, 118.0, 118.8, 122.5, 125.8, 127.9, 128.7,128.9, 129.1, 129.2, 134.9, 135.5, 138.6, 143.7, 151.8, 158.5, 162.1, 163.5, 173.7, 188.6; HRMS (TOF ES$^+$): *m/z* calcd for $C_{30}H_{24}BrN_2O_3$ $[M+H]^+$, 571.0863; found, 571.0864.

*(E)-3-(8-Benzoyl-6-hydroxy-6-phenyl-1,2,3,4-tetrahydropyrr-olo[1,2-a]pyrimidin-7(6H)-ylid-ene)chromane-2,4-dione (**6p**).* Yellow solid (415.9 mg, 87%); Mp: 252.9–253.3 °C; IR (KBr): 3354.3, 1670.9, 1408.6, 1199.9, 1123.3, 906.6, 763.8 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.88–1.99 (m, 2H, CH_2), 2.91–2.94 (m, 1H, NCH_2), 3.44–3.55 (m, 3H, NCH_2,$NHCH_2$), 6.92–6.93 (m, 1H, ArH), 7.10–7.12 (m, 1H, ArH), 7.25–7.43 (m, 9H, ArH), 7.72–7.75 (m, 3H, ArH), 9.31 (br, 1H, NH), 11.54 (s, 1H, OH); ^{13}C{^{1}H} NMR (125MHz, DMSO-d_6): δ = 19.1, 37.2, 39.1, 96.4, 96.8, 116.1, 117.0, 120.6, 123.6, 125.8, 125.8, 128.4, 128.5, 128.8, 129.2, 133.1, 133.1, 137.6, 138.8, 153.3, 158.5, 162.6, 164.5, 175.2, 189.2; HRMS (TOF ES$^+$): *m/z* calcd for $C_{29}H_{23}N_2O_5$ $[M+H]^+$, 479.1601; found, 479.1600.

*(E)-3-(8-(4-Fluorobenzoyl)-6-hydroxy-6-phenyl-1,2,3,4-tetrahy -dropyrrolo[1,2-a]pyrimidin-7(6H)-ylidene)chromane-2,4-dione (**6q**).* Yellow solid (431.6 mg, 87%); Mp: 267.8–268.2 °C; IR (KBr): 3414.0, 1682.5, 1540.8, 1404.7, 1198.2, 1122.5, 608.8 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.88–1.99 (m, 2H, CH_2), 2.91–2.93 (m, 1H, $NHCH_2$), 3.51–3.54 (m, 1H, $NHCH_2$), 3.51–3.54 (m, 2H, NCH_2), 6.95–6.97 (m, 1H, ArH), 7.10–7.20 (m,3H, ArH), 7.25–7.43 (m, 6H,ArH), 7.73–7.82 (m, 3H, ArH), 9.30 (br, 1H, NH), 11.47 (s, 1H, OH); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ = 19.1, 37.2, 39.1, 96.3, 96.8, 115.6 (d, J = 22.5 Hz), 116.2, 116.8, 120.6, 123.7, 125.8, 125.8 (d, J = 5.0 Hz), 128.8, 129.2, 131.3 (d, J = 10.0 Hz), 133.2, 134.3, 138.8, 153.3, 158.4, 163.5 (d, J = 227.5 HZ), 164.0, 166.0, 175.3, 187.8; HRMS (TOF ES$^+$): *m/z* calcd for $C_{29}H_{22}FN_2O_5$ $[M+H]^+$ 497.1507; found, 497.1507.

(E)-3-(8-(4-chlorobenzoyl)-6-hydroxy-6-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-7-

*(6H)-ylidene)chromane-2,4-dione (**6r**).*Yellow solid; Mp: 170–172 °C; IR (KBr): 3361.5, 1680.0, 1413.0, 1205.9, 1123.4, 906.9, 769.4 cm^{-1}; 1H NMR (600 MHz, DMSO-d_6): δ = 1.77–1.90 (m, 2H, CH_2), 2.81–2.85 (m, 1H, NCH_2), 3.33–3.46 (m, 3H, NCH_2, $NHCH_2$), 6.88–6.90 (m, 1H, ArH), 7.03–7.06 (m, 1H, ArH), 7.13–7.15 (m, 1H, ArH), 7.17–7.39 (m, 4H, ArH), 7.55–7.67 (m, 3H, ArH), 7 .91–7.92 (m, 3H, ArH), 9.23 (br, 1H, NH); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6): δ = 19.1, 37.2, 39.1, 96.3, 96.7, 116.2, 116.5, 120.5, 123.7, 125.2, 125.8, 125.9, 128.7, 128.8, 129.3, 130.2, 133.3, 136.5, 137.8, 138.7, 153.2, 158.4, 162.7, 175.3, 188.0; HRMS (TOF ES^+): *m/z* calcd for $C_{29}H_{21}ClN_2NaO_5$ $[M+Na]^+$, 535.1031; found, 535.1034.

*(E)-6-Chloro-3-(8-(4-chlorobenzoyl)-6-hydroxy-6-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]-pyrimidin-7(6H)-ylidene)chromane-2,4-dione (**6s**).* Yellow solid (486.0 mg, 89%); Mp: 247.0–247.4 °C; IR (KBr): 3415.2, 1679.0, 1438.6, 1223.2, 1013.2, 841.0, 786.0 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ =1.89–1.98 (m, 2H, CH_2), 2.91–2.94 (m, 1H, NCH_2), 3.43–3.53(m,3 H, NCH_2, $NHCH_2$), 7.03–7.04 (m, 1H, ArH),7.27–7.9 (m, 1H, ArH), 7.31–7.33 (m, 4H, ArH), 7.43–7.46 (m, 3H, ArH), 7.65–7.65 (m, 2H, ArH), 7.74 (m, 1H, ArH), 9.37 (br, 1H, NH), 11.16 (s, 1H, OH); $^{13}C\{^1H\}$ NMR (150MHz, DMSO-d_6): δ = 19.0, 37.2, 39.2, 96.2, 96.8, 117.3, 118.6, 121.9, 124.9, 128.0, 125.8, 128.7, 128.9, 129.3, 130.3, 132.9, 136.3, 138.0, 138.4, 151.8, 158.4, 162.3, 164.0, 173.8, 188.0; HRMS (TOF ES^+): *m/z* calcd for $C_{29}H_{20}Cl_2N_2NaO_5$ $[M+Na]^+$, 569.0641; found, 569.0643.

*(E)-3-(8-Benzoyl-6-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetra-hydropyrrolo[1,2-a]pyrimidin-7-(6H)-ylidene)-6-chlorochrom-ane-2,4-dione (**6t**).* Yellow solid (455.9 mg, 86%); Mp: 270.4–270.8 °C; IR (KBr): 3346.2, 1675.9, 1440.3, 1243.3, 1047.9, 907.6, 823.8 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 1.90–1.99 (m, 2H, CH_2),2.94–2.98 (m, 1H, NCH_2), 3.44–3.55 (m, 3H, NCH_2, $NHCH_2$), 7.00–7.01 (m, 1H, ArH), 7.15–7.18 (m, 2H, ArH), 7.32–7.39 (m, 4H, ArH),

7.41–7.45 (m,. 2H, ArH), 7.65–7.66 (m, 1H, ArH), 7.73–7.74 (m, 2H, ArH), 9.42 (br, 1H, NH), 11.34(s, 1H, OH); $^{13}C\{^{1}H\}$ NMR (150 MHz, DMSO-d_6): δ = 19.0, 37.2, 39.2, 96.1, 96.4, 115.8 (d, J = 21.0 Hz), 117.8, 118.5, 121.9, 124.8, 128.0, 128.2, 128.5, 128.6, 132.8, 133.3, 134.8, 137.3, 151.8, 158.4, 161.8, 162.9 (d, J = 220.5 Hz), 163.4, 173.7, 189.1; HRMS (TOF ES$^+$): *m/z* calcd for $C_{29}H_{21}ClFN_2O_5$ $[M+H]^+$, 531.1118; found, 531.1116.

*(E)-3-(8-(4-Fluorobenzoyl)-6-(4-fluorophenyl)-6-hydroxy-1,2, 3,4-tetrahydropyrrolo[1,2-a]-pyrimidin-7(6H)-ylidene)chrom-ane-2,4-dione (**6u**).* Yellow solid (452.4 mg, 88%); Mp: 247.4–247.6 °C; IR (KBr): 3414.6, 1637.9, 1507.7, 1414.7, 1230.0, 1154.4, 784.3, 849.6 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.89–1.98 (m, 2H, CH_2), 2.92–2.97 (m, 1H, $NHCH_2$), 3.50–3.55 (m, 1H, $NHCH_2$), 3.50–3.55 (m, 2H, NCH_2), 6.97–6.98 (m, 1H, ArH), 7.12–7.20 (m, 5H, ArH), 7.36–7.45 (m, 1H, ArH), 7.73–7.82 (m, 3H, ArH), 9.34 (br, 1H, NH), 11.52 (s, 1H, OH); $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6): δ =20.1, 38.2, 40.2, 97.2, 94.4, 116.7, 117.3, 117.9, 121.5, 124.7, 126.9, 129.2 (d, J = 8.8 Hz), 129.2 (d, J = 8.8 Hz), 132.3 (d, J = 8.8 Hz), 134.3, 135.3, 136.0, 154.3, 159.4, 164.3 (d, J = 208.5 Hz), 164.4 (d, J = 225.0 Hz), 165.1, 167.0, 176.4, 188.8; HRMS (TOF ES$^+$): *m/z* calcd for $C_{29}H_{21}F_2N_2O_5$ $[M+H]^+$,515.1413; found, 515.1413.

*(E)-3-(8-(4-Chlorobenzoyl)-6-(3,4-difluorophenyl)-6-hydroxy-1,2,3,4-tetrahydropyrrolo[1,2-a]-pyrimidin-7(6H)-ylidene)chrom -ane-2,4-dione (**6v**).* Yellow solid (468.8 mg, 87%); Mp: 218.9–219.3 °C; IR (KBr): 3448.7, 1676.8, 1516.2, 1410.7, 1281.1, 912.7, 766.2 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ =1.95–1.96 (m, 2H, CH_2), 2.96–3.00(m, 1H, NCH_2), 3.41–3.55 (m, *3*H, NCH_2, $NHCH_2$), 6.98–7.00 (m, 1H, ArH), 7.13–7.16 (m, 2H, ArH), 7.37–7.46 (m, 5H, ArH), 7.73–7.76 (m, 3H, ArH), 9.39 (br, 1H, NH), 11.57 (s, 1H, OH); $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6): δ = 19.9, 36.5, 39.7, 95.8, 96.0, 115.5 (d, J = 18.8 Hz), 116.3, 116.8, 118.2 (d, J = 7.5 Hz), 120.4, 123.0, 123.8, 125.9, 128.7, 130.2, 133.4, 136.3, 136.7, 137.9, 149.5 (d, J = 243.8

Hz), 149.7 (d, *J* = 250.0 Hz), 153.3, 158.5, 162.7, 163.4, 175.4, 187.9; HRMS (TOF ES$^+$): *m/z* calcd for $C_{29}H_{19}F_2ClN_2NaO_5$ $[M+Na]^+$, 571.0843; found, 571.0843.

*(E)-3-(7-acetyl-5-hydroxy-5-phenyl-2,3-dihydro-1H-pyrrolo[1,2-a]imidazol-6(5H)-ylidene)-chromane-2,4-dione (**6w**).* Yellow solid (241.0 mg, 60%); Mp: 217.0–217.4 °C; IR (KBr): 3309.0, 1659.4, 1405.7, 1285.0, 1223.1, 765.3, 617.0cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ =2.20 (s, 3H, CH_3), 3.22–3.27 (m, 1H, NCH_2), 3.69–3.74 (m, 1H, $NCH_{2,}$), 4.11–4.20 (m, 2H, $NCH_{2,}$), 7.17–7.33 (m, 7H, ArH),7.53–7.55 (m, 1H, ArH), 7.82–7.83(m, 1H, ArH), 10.14 (br, 1H, NH), 10.64 (br, 1H, OH); ^{13}C{^{1}H} NMR (150MHz, DMSO-d_6): δ = 28.1, 41.1, 50.0, 93.0, 97.7, 116.6, 116.8, 118.1, 120.7, 124.0, 125.7, 126.1, 128.8, 129.1, 133.7, 138.9, 153.6, 163.0, 168.6, 172.5, 176.0, 194.5; HRMS (TOF ES$^+$): *m/z* calcd for $C_{23}H_{18}N_2NaO_5$ $[M+Na]^+$, 425.1108; found, 425.1105.

*3-(8-(4-Chlorobenzoyl)-6-phenyl-1,2,3,4-tetrahydropyrrolo-[1,2-a]pyrimidin-7-yl)-4-hydroxy-2H-chromen-2-one (**7r**).* Yellow solid; Mp: 224.3 °C; IR (KBr): 3415.3, 1617.6, 1528.3, 1215.2, 1086.2, 833.1, 754.2 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.02 (s, 2H, CH_2), 3.45–3.54 (m, 2H, NCH_2), 3.75–7.77 (m, 2H, $NHCH_2$), 6.88–6.89 (m, 2H, ArH), 7.06–7.08 (m, 2H, ArH), 7.13–7.15 (m, 2H, ArH), 7.19–7.30 (m, 6H, ArH), 7.47–7.55 (s, 1H, ArH), 7.55–7.56 (m, 1H, ArH), 7.99 (br, 1H, NH), 10.76 (S, 1H, OH); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ = 21.3, 38.3, 42.0, 100.7, 102.2, 107.5, 115.9, 116.0, 123.5, 124.0, 127.01, 127.7, 127.9, 128.0, 129.5, 131.2, 132.2, 133.4, 141.2, 148.7, 152.6, 161.5, 162.1, 187.4; HRMS (TOF ES$^+$): *m/z* calcd for $C_{29}H_{22}ClN_2O_4$ $[M+H]^+$, 497.1263; found, 497.1268.

■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic and analytical data as well as the original copy of ^{1}H and ^{13}C NMR spectra of all

new compounds and X-ray crystallographicdata (CIF file) of compound **6c** and **6v** (CCDC1916446 and CCDC1916449). This material is available free of charge *via* the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: linjun@ynu.edu.cn (J. L)

*E-mail: yansj@ynu.edu.cn (S.-J. Y). Tel/Fax: +86 87165031633.

ORCID

Jun Lin: 0000-0002-2087-6013.

Sheng-Jiao Yan: 0000-0002-7430-4096

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Program for Changjiang Scholars and Innovative Research Team in University (IRT17R94), the National Natural Science Foundation of China (Nos. 21662042, 81760621, 21362042), the Natural Science Foundation of Yunnan Province (2017FA003), Joint Fund of Yunnan Science and Technology Department-Yunnan University (2019FY003003), and Scientific and Technological Innovation Team of Green Synthesis and Activity Research of Natural-like Heterocyclic Compound Libraries in Universities of Yunnan Province. We also thank Dr. Rong Huang of Advanced Analysis and Measurement Center of Yunnan University for helpful testing the NMR.

■ REFERENCES

(1) McGeary, R. P.; Tan, D. T. C.; Selleck, C.; Pedroso, M. M.; Sidjabat, H. E.; Schenk, G.

Structure-activity Relationship Study and Optimisation of 2-Aminopyrrole-1-benzyl-4,5-diphenyl-1*H*-pyrrole-3-carbonitrile as a Broad Spectrum Metallo-*β*-lactamase Inhibitor. *Eur. J. Med. Chem*. **2017**, *137*, 351–364.

(2) Wallace, M. B.; Adams, M. E.; Kanouni, T.; Mol, D. C.; Dougan, D. R.; Feher , V. A.; O'Connell, S. M.; Shi, L.; Halkowycz, P.; Dong, Q. Structure-based Design and Synthesis of Pyrrole Derivatives as MEK Inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4156–4158.

(3) Wang, D.; Kosh, J. W.; Sowell, J. S.; Wang, T. Treatment or Prevention of Cardiovascular and Respiratory Disorders with Novel Substituted Cyclic AMP-specific Phosphodiesterase Inhibitors. PCT Int. Appl. WO 2005046676 A1, **2005**.

(4) Nakazato, A.; Okubo, T.; Nozawa, D.; Tamita T.; Kennis, L. E. J. Pyrrolopyrimidine and Pyrrolotriazine Derivatives. US 8106194 B2. **2012**.

(5) Reviews see: (a) Douchez, A.; Geranurimi, A.; Lubell, W. D. Applications of γ,δ-Unsaturated Ketones Synthesized by Copper-Catalyzed Cascade Addition of Vinyl Grignard Reagents to Esters *Acc. Chem. Res.* **2018**, *51*, 2574–2588. (b) Li, Y.; Yang, H.; Zhai, H. The Expanding Utility of RhodiumThe Expanding Utility of Rhodium-Iminocarbenes: Recent Advances in the Synthesis of Natural Products and Related Scaffolds. *Chem. Eur. J.* **2018**, *24*, 12757–12766.

(6) (a) Qiu, G.; Wang, Q.; Zhu, J. Palladium-Catalyzed Three-Component Reaction of Propargyl Carbonates, Isocyanides, and Alcohols or Water: Switchable Synthesis of Pyrroles and Its Bicyclic Analogues *Org. Lett.* **2017**, *19*, 270−273. (b) Tukhtaev, H. B.; Ivanov, K. L.; Bezzubov, S. I.; Cheshkov, D. A.; Melnikov, M. Y.; Budynina, E. M. aza-Wittig Reaction with Nitriles: How Carbonyl Function Switches from Reacting to Activating *Org. Lett.* **2019**, *21*, 1087−1092. (c) Reekie, T. A.; Donckele, E. J.; Manenti, G.; Püntener, S.; Trapp, N.; Diederich, F. A. Three-

Step Synthesis of Tetrasubstituted NH-Pyrroles. *Org. Lett.* **2016**, *18*, 2252−2255. (d) Wang, J.-Y.; Zhou, P.; Li, G.-G.; Hao, W.-J.; Tu, S.-J.; Jiang, B. Synthesis of Functionalized Benzo[*g*]indoles and 1-Naphthols via Carbon–Carbon Triple Bond Breaking/Rearranging. *Org. Lett.* **2017**, *19*, 6682−6685. (e) Jiang, B.; Li, Q.-Y.; Zhang, H.; Tu, S.-J. ; Pindi, S.; Li, G.-G. Selective Synthesis of Seven- and Eight-Membered Ring Sultams via Two Tandem Reaction Protocols from One Starting Material. *Org. Lett.* **2012**, *14*, 3700−3703.

(7) (a) Bertuzzi, G.; Thogersen, M. K; Giardinetti, M.; Vidal-Albalat, A.; Simon, A.; Houk, K. N.; Jorensen, K. A. Catalytic Enantioselective Hetero-[6+4] and -[6+2] Cycloadditions for the Construction of Condensed Polycyclic Pyrroles, Imidazoles, and Pyrazoles. *J. Am. Chem. Soc.* **2019**, *141*, 3288−3297. (b) Kawakita, K.; Beaumier, V. P.; Kakiuchi, Y.; Tsurugi, H.; Tonks, I. A.; Mashima, K. Bis(imido)vanadium(V)-Catalyzed [2+2+1] Coupling of Alkynes and Azobenzenes Giving Multisubstituted Pyrroles. *J. Am. Chem. Soc.* **2019**, *141*, 4194−4198. (c) He, X.-L.; Zhao, H.-R.; Song, X.; Jiang, B.; Du, W.; Chen, Y.-C. Asymmetric Barton–Zard Reaction To Access 3-Pyrrole-Containing Axially Chiral Skeletons. *ACS Catal.* **2019**, *9*, 4374−4381. (d) Chiu, H.-C.; See, X.-Y.; Tonks, I. A. Dative Directing Group Effects in Ti-Catalyzed [2+2+1] Pyrrole Synthesis: Chemo- and Regioselective Alkyne Heterocoupling. *ACS Catal.* **2019**, *9*, 216−223. (e) Lang, X.-D.; You, F.; He, X.; Yu, Y.-C.; He, L.-N. Rhodium(I)-catalyzed Pauson-Khand-type Reaction Using Formic Acid as a CO Surrogate: An Alternative Approach for Indirect CO_2 Utilization. *Green Chem.* **2019**, *21*, 509−514.

(8) (a) Dutta, S.; Mallick, R. K.; Prasad, R.; Gandon, V.; Sahoo, A. K. Alkyne Versus Ynamide Reactivity: Regioselective Radical Cyclization of Yne-Ynamides. *Angew. Chem. Int. Ed.* **2019**, *58*, 2289−2294. (b) Kardile, R. D.; Kale, B. S.; Sharma, P.; Liu, R.-S. Gold-Catalyzed [4+1]-Annulation Reactions between 1, 4-Diyn-3-ols and Isoxazoles To Construct a Pyrrole Core. *Org.*

Lett. **2018**, *20*, 3806−3809. (c) Liang, S.; Zeng, C.-C.; Luo, X.-G.; Ren, F.-Z.; Tian, H.-Y.; Sun, B.-G.; Littled, R. D. Electrochemically Catalyzed Amino-oxygenation of Atyrenes: n-Bu_4NI Induced *C–N* Followed by a *C–O* Bond Formation Cascade for the Synthesis of Indolines. *Green Chem.* **2016**, *18*, 2222−2230. (d) Man, N.-N.; Wang, J.-Q.; L.-M. Zhang, L.-R. Wen; Li, M. Chemo-, Regio-, and Stereoselective Construction of Core Skeleton of Furo [2,3-*b*] pyrrole via Multicomponent Bicyclization Reaction. *J. Org. Chem.* **2017**, *82*, 5566−5573. (e) Yang, L.; Lu, W.; Zhou, W.; Zhang, F. Metal-free Cascade Oxidative Decarbonylative Alkylarylation of Acrylamides with Aliphatic Aldehydes: A Convenient Approach to Oxindoles via Dual C (sp2)–H Bond Functionalization. *Green Chem.* **2016**, *18*, 2941−2945.

(9) (a) Zhou, B.; Liu, Z.-C.; Qu, W.-W.; Yang, R.; Lin, X.-R.; Yan, S.-J.; Lin, J. An Environmentally Benign, Mild, and Catalyst-free Reaction of Quinones with Heterocyclic Ketene Aminals in Ethanol: Site-selective Synthesis of Rarely Fused [1,2-*a*]Indolone Derivatives via an Unexpected Anti-Nenitzescu Strategy. *Green. Chem*. **2014**, 16, 4359−4370; (b) Chen, X.-B.; Liu, Z.-C.; Lin, X.-R.; Huang, R.; Yan, S.-J.; Lin, J. Highly Diastereoselective Convergent Synthesis of Polycyclic Pyrroles with Consecutive Quaternary Stereocenters: Cascade Construction of Multiple C−C and C−Hetero Bonds. *ACS Sustainable Chem. Eng.*, **2014**, 2, 2391−2398.

(10) (a) Estevez, V.; Villacampa, M.; Menendze, J. C. Recent Advances in the Synthesis of Pyrroles by Multicomponent Reactions *Chem. Soc. Rev.* **2014**, *43*, 4633–4657. (b) Wang, X.; Xu, X.-P.; Wang, S.-Y.; Zhou, W.; Ji, S.-J. Highly Efficient Chemoselective Synthesis of Polysubstituted Pyrroles via Isocyanide-based Multicomponent Domino Reaction. *Org. Lett.* **2013**, *15*, 4246−4249. (c) Estevez, V.; Villacampa, M.; Menendez, J. C. Multicomponent Reactions for the Synthesis of Pyrroles. *Chem. Soc. Rev.* **2010**, *39*, 4402–4421. (d) Nair, V.;

Viond, A. U.; Rajesh, C. A novel Synthesis of 2-Aminopyrroles Using a Three-component Reaction *J. Org. Chem.* **2001**, *66*, 4427–4429.

(11) Fontaine, P.; Masson, G.; Zhu, J. Synthesis of Pyrroles by Consecutive Multicomponent Reaction/[4+1] Cycloaddition of α-Iminonitriles with Isocyanides. *Org. Lett.* **2009**, *11*, 1555−1558.

(12) (a) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. Transition Metal-mediated Synthesis of Monocyclic Aromatic Heterocycles. *Chem. Rev.* **2013**, *113*, 3084–3213. (b) Ackermann, L. Carboxylate-Assisted Ruthenium-Catalyzed Alkyne Annulations by C–H/Het–H Bond Functionalizations. *Acc. Chem. Res.* **2014**, *47*, 281–295. (c) Wu, Y.; Zhu, L.; Yu, Y.; Lou, X.; Huang, X. Polysubstituted 2-Aminopyrrole Synthesis via Gold-Catalyzed Intermolecular Nitrene Transfer from Vinyl Azide to Ynamide: Reaction Scope and Mechanistic Insights. *J. Org. Chem.* **2015**, *80*, 11407–11416. (d) Li, L.; Tan, T.-D.; Zhang, Y.-Q.; Liu, X.; Ye, L.-W. Recent Advances in Transition-metal-catalyzed Reactions of Alkynes with Isoxazoles. *Org. Biomol. Chem*. **2017**, *15*, 8483–8492.

(13) Shu, C.; Wang, Y.-H.; Shen, C.-H.; Ruan, P.-P.; Lu, X.; Ye, L.-W. Gold-Catalyzed Intermolecular Ynamide Amination-Initiated Aza-Nazarov Cyclization: Access to Functionalized 2-Aminopyrroles. *Org. Lett.* **2016**, *18*, 3254−3257.

(14) Liu, J.; Li, Q.; Cao, Z.-M.; Jin, Y.; Lin, J.; Yan, S.-J. Cascade Reaction of Morita–Baylis–Hillman Acetates with 1,1-Enediamines or Heterocyclic Ketene Aminals: Synthesis of Highly Functionalized 2-Aminopyrroles. *J. Org. Chem.* **2019**, *84*, 1797−1807.

(15) Thaisrivongs, S.; Watenpaugh, K. D.; Howe, W. J.; Tomich, P. K.; Dolak, L. A.; Chong, K. T.; Tomich, C. S. C.; Tomasselli, A. G.; Turner, S. R.; Strohbach, J. W.; Strohbach, J. W.; Mulichak, A. M.; Janakiraman, M. N.; Moon, J. B.; Lynn, J. C.; Horng, M. M.; Hinshaw, R. R.;

Curry, K. A.; Rothrock, D. J. Structure-Based Design of Novel HIV Protease Inhibitors: Carboxamide-Containing 4-Hydroxycoumarins and 4-Hydroxy-2-pyrones as Potent Nonpeptidic Inhibitors. *J. Med. Chem*. **1995**, *38*, 3624−3637.

(16) (a) Melis, C.; Distinto, S.; Bianco, G.; Meleddu, R.; Cottiglia, F.; Fois, B.; Taverna D.; Angius, R.; Alcaro, S., Ortuso, F.; Gaspari, M.; Angeli, A.; Prete, S. D.; Capasso, C.; Supuran, C. T.; Maccioni, E. Targeting Tumor Associated Carbonic Anhydrases IX and XII: Highly Isozyme Selective Coumarin and Psoralen Inhibitors. *ACS Med. Lett.* **2018**, *9*, 725−729. (b) Dey, A.; Ali, M. A.; Jana, S.; Samanta, S.; Hajra, A. Palladium-catalyzed synthesis of indole fused coumarins via cross-dehydrogenative coupling. *Tetrahedron Lett.* **2017**, *58*, 313−316. (c) Wang, W.; Shenqing, F. Z. CN, 102321090, **2012**. (d) Bonardi, A.; Falsini, M.; Catarzi, D.; Varano, F.; Mannelli, L. D. C.; Tenci, B.; Ghelardini, C., Angeli, A.; Supruan, C. T.; Colotta, V. Structural Investigations on Coumarins Leading to Chromeno[4,3-*c*] pyrazol-4-ones and Pyrano[4,3-*c*] pyrazol-4-ones: New Scaffolds for the Design of the Tumor-associated Carbonic Anhydrase Isoforms IX and XII. *Eur. J. Med. Chem.* **2018**, *146*, 47−59. (e) Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Crogan- Grundy, C.; Labreque, D.; Bubenick, M.; Attardo, G.; Denis, R.; Lamothe, S.; Gourdeau, H.; Tseng, B.; Kasibhatla, S.; Cai, S. X. Discovery of 4-Aryl-4*H*-chromenes as a New Series of Apoptosis Inducers Using a Cell- and Caspase-Based High Throughput Screening Assay. 4. Structure–Activity Relationships of *N*-Alkyl Substituted Pyrrole Fused at the 7,8-Positions. *J. Med. Chem.* **2008**, *51*, 417–423. (f) Das, S. G.; Doshi, J.; Tian, M.; D.; Addo S. N.; Srinivasan, B.; Hermanson, D. L.; Xing, C. Structure−Activity Relationship and Molecular Mechanisms of Ethyl 2-Amino-4-(2-ethoxy-2-oxoethyl)-6-phenyl-4*H*-chromene-3-carboxylate (sHA 14-1) and Its Analogues. *J. Med. Chem.* **2009**, 52, 5937–5949.

(17) (a) Lv, H.-N.; Wang, S.; Zeng, K.-W.; Li, J.; Guo, X.-Y.; Ferreira, D.; Zjawiony, J. K., Tu, P.-F.; Jiang, Y. Anti-inflammatory Coumarin and Benzocoumarin Derivatives from Murraya alata. *J. Nat. Prod.* **2015**, *78*, 279−285. (b) Medina, F. G.; Marrero, J. G.; Macías-Alonso, M.; González, M. C.; órdova-Guerrero, I. A.; García, G. T.; Osegueda-Robles, S. Coumarin Heterocyclic Derivatives: Chemical Synthesis and Biological Activity. *Nat. Prod. Rep.* **2015**, *32*, 1472–1507. (c) Gaudino, E. C.; Tagliapietra, S.; Martina, K.; Palmisano, G.; Cravotto, G. Recent Advances and Perspectives in the Synthesis of Bioactive Coumarins. *RSC Adv.* **2016**, *6*, 46394–46405. (d) Kumar, D.; Sharma, P.; Singh, H.; Nepali, K.; Gupta, G. K.; Jain, S. K.; Ntie-Kang, F. The Value of Pyrans as Anticancer Scaffolds in Medicinal Chemistry. *RSC Adv.* **2017**, *7*, 36977–36999.

(18) (a) Anand, P.; Singh.; B.; Singh, N. A review on Coumarins as Acetylcholinesterase Inhibitors for Alzheimer's Diseas. *Bioorg. Med. Chem*. **2012**, *20*, 1175−1180. (b) Musa, M. A.; Cooperwood, S.; Khan, M.; Omar, F. A. Review of Coumarin Derivatives in Pharmacotherapy of Breast Cancer. *Curr. Med. Chem*. **2008**, *15*, 2664−2679. (c) Zheng, J.; He, M.; Xie, B.; Yang, L.; Hu, Z.; Zhou, H.; Dong, C. Enantioselective Synthesis of Novel Pyrano[3,2-*c*]chromene Derivatives as AChE Inhibitors via an Organocatalytic Domino Reaction. *Org. Biomol. Chem.* **2018**, *16*, 472–479.

(19) (a) Mangasuli, S. N.; K. Hosamani, M.; Devarajegowda, H. C.; Kurjogi, M. M.; Joshi, S. D. Synthesis of Coumarin-theophylline Hybrids as a New Class of Anti-tubercular and Anti-microbial Agents. *Eur. J. Med. Chem.* **2018**, *146*, 747–756. (b) Bonardi. A., Falsini, M.; Catarzi, D.; Varano, F.; Mannelli, L. D. C.; Tenci, B.; Ghelardini, C.; Angeli, A.; Supruan, C. T.; Colotta, V. Structural Investigations on Coumarins Leading to Chromeno[4,3-*c*]pyrazol-4-ones and Pyrano[4,3-*c*]pyrazol-4-ones: New Scaffolds for the Design of the Tumor-associated Carbonic

Anhydrase Isoforms IX and XII. *Eur. J. Med. Chem.* **2018**, *146*, 47−59. (c) Das, S. G.; Doshi, J. M.; Tian, D.; S. Addo, N.; Srinivasan, B.; Hermanson, D. L.; Xing, C. Structure−Activity Relationship and Molecular Mechanisms of Ethyl 2-Amino-4-(2-ethoxy-2-oxoethyl)-6-phenyl-4H-chromene-3-carboxylate (sHA 14-1) and Its Analogues. *J. Med. Chem.* **2009**, *52*, 5937–5949.

(20) (a) Wang, K.-M.; Yan, S.-J.; Lin, J. Heterocyclic Ketene Aminals: Scaffolds for Heterocycle Molecular Diversity. *Eur. J. Org. Chem.* **2014**, *6*, 1129−1145. (b) M, Y.-L.; Wang, K.-M.; Huang, R.; Lin, J.; Yan, S.-J. An Environmentally Benign Double Michael Addition Reaction of Heterocyclic Ketene Aminals with Quinone Monoketals for Diastereoselective Synthesis of Highly Functionalized Morphan Derivatives in Water. *Green Chem.* **2017**, *19*, 3574−3584. (c) Yu, F.; Huang, R.; Ni, H.; Fan, J.; Yan, S.; Lin, J. Three-component Stereoselective Synthesis of Spirooxindole Derivatives. *Green Chem*. **2013**, *15*, 453–462.

(21) (a) Li, M.; Shao, P.; Wang, S.; Kong, W.; Wen, L.-R. Four-Component Cascade Heteroannulation of Heterocyclic Ketene Aminals: Synthesis of Functionalized Tetrahydroimidazo [1,2-*a*] pyridine Derivatives. *J. Org. Chem.* **2012**, *77*, 8956–8967. *(*b) Wang, B.-Q.; Zhang, C-H.; Tian, X.-X.; Lin, J.; Yan, S.-J. Cascade Reaction of Isatins with 1,1-Enediamines: Synthesis of Multisubstituted Quinoline-4-carboxamides. *Org. Lett*. **2018**, *20*, 660–663. (c) Zhang, C.-H.; Huang, R.; Hu, X.-M.; Lin, J.; Yan, S.-J. Three-Component Site-Selective Synthesis of Highly Substituted 5*H*-Chromeno-[4,3-*b*] pyridines. *J. Org. Chem.* **2018**, *83*, 4981–4989. (d) Chen, L.; Huang, R.; Du, X.-X.; Yan, S.-J.; Lin, J. One-Pot Synthesis of Highly Functionalized Bicyclic Imidazopyridinium Derivatives in Ethanol. *ACS Sustainable Chem. Eng.* **2017**, *5*, 1899−1905. (e) Zeng, C.-C.; Liu, F.-J.; Ping, D.-W.; Hu, L.-M.; Cai, Y.-L.; Zhong, R.-G. One-Pot Electrochemical Synthesis of Fused Indole Derivatives

Containing Active Hydroxyl Groups in Aqueous Medium. *J. Org. Chem*. **2009**, *74*, 6386−6389.

(22) (a) Huang, C.; Yan, S.-J.; Zeng, X.-H.; Dai, X.-Y.; Zhang, Y.; Qing, C.; Lin, J. Biological Evaluation of Polyhalo 1,3-Diazaheterocycle Fused Isoquinolin-1(2*H*)-imine Derivatives. *Eur. J. Med. Chem.* **2011**, *46*, 1172–1180. (b) Yan, S. J.; Liu, Y.-J.; Chen, Y.-L.; Liu, L.; Lin, J. An Efficient One-pot Synthesis of Heterocycle-fused 1,2,3-Triazole Derivatives as Anti-cancer Agents. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5225−5228.

(23) (a) Yu, F.-C.; Lin, X.-R.; Zhang, J.-H.; Liu, F.-F.; Wu, W.; Ma, Y.-L.; Qu, W.-W.; Yan, S.-J.; Lin, J. Beyond the Antagonism: Self-Labeled Xanthone Inhibitors as Modeled "Two-in-One" Drugs in Cancer Therapy. *ACS Omega*. **2017**, *2*, 873−889. (b) Du, X.-X.; Huang, R.; Yang, C.-L.; Lin, J.; Yan, S.-J. Synthesis and Evaluation of the Antitumor Activity of Highly Functionalised Pyridin-2-ones and Pyrimidin-4-ones. *RSC Adv.* **2017**, *7*, 40067–40073. (c) Liu, J.; Wang, Y.-L.; Zhang, J.-H.; Yang, J.-S.; Mou, H.-C.; Lin, J.; Yan, S.-J. Phosphatase CDC25B Inhibitors Produced by Basic Alumina-Supported One-Pot Gram-Scale Synthesis of Fluorinated 2-Alkylthio-4-aminoquinazolines Using Microwave Irradiation. *ACS Omega*. **2018**, *3*, 4534–4544.

(24) Bao, H.; Shao, X.; Zhang, Y.; Deng, Y.; Xu, X.; Liu, Z.; Li, Z. Specific Synergist for Neonicotinoid Insecticides: IPPA08, a *cis*-Neonicotinoid Compound with a Unique Oxabridged Substructure. *J. Agric. Food Chem.* **2016**, *64*, 5148−5155.

(25) Kondo, H.; Taguchi, M.; Inoue, Y.; F.; Tsukamoto, G. Synthesis and Antibacterial Activity of Thiazolo-, Oxazolo-, and Imidazolo[3,2-*a*][1,8] naphthyridinecarboxylic Acids. *J. Med. Chem.* **1990**, *33*, 2012−2015.

(26) Suryawanshi, S. N.; Pandey, S.; Rashmirathi; B. Bhatt, A.; Gupta, S. Chemotherapy of Leishmaniasis Part VI: Synthesis and Bioevaluation of Some Novel Terpenyl *S*,*N*- and *N*,*N*-

Acetals. *Eur. J. Med. Chem.* **2007**, *42*, 511−516.

(27) Abdelhalim, M. M.; El-Saidi, M. M. T.; Rabie, S. T.; Elmegeed, G. A. Synthesis of Novel Steroidal Heterocyclic Derivatives as Antibacterial Agents. *Steroids* **2007**, *72*, 459−465.

(28) (a) Mertens, H.; Troschütz, R. Synthese primärer Nitroketenaminale. *Arch. Pharm.* **1986**, *319*, 161−167. (b) Li, K.; Chen, L.; Fan, Y.-X.; Wei, Y.; Yan, S.-J. Multicomponent Tether Catalysis Synthesis of Highly Functionalized 4-(Pyridin-2-ylmethyl)-2-aminopyrroles via Cascade Reaction Is Accompanied by Decarboxylation. *J. Org. Chem.* **2019**, *84*, 11971−11982.

(29) (a) Huang, Z.-T.; Wang, M.-X. A New Route to 3*H*-1,5-Benzodiazepines and Heterocylic Ketene Aminals from Benzoyl Substituted Ketene Dithioacetals and Diamines. *Synthesis* **1992**, *12*, 1273−1276. (b) Huang, Z.-T.; Liu, Z.-R. Synthesis of 2-(Benzoylmethylene)imidazoldines and Hexahdropyrimidines by Condensation of Ethyl Benzoylacetimidates With 1,2-Ethamediamine or 1,3-Propandiamine, and Some Addition Reactions. *Synthesis* **1987**, *4*, 357−362. (c) Huang, Z.-T.; Liu, Z.-R. Synthesis of Benzoyl Substituted Heterocyclic Ketene Aminals by Condensation of Benzoyl Ketene Mercaptals with Diamines. *Synth. Commun.* **1989**, *19*, 943−958. (d) Li, Z.-J.; Smith, C. D. THE Synthesis of Fluoroheterocyclic Ketene Aminals. *Synth. Commun.* **2001**, *31*, 527−533.