Advanced Synthesis & Catalysis

Accepted Article

Title: Oxidative Radical Relay Functionalization for the Synthesis of Benzimidazo[2,1-a]iso-quinolin-6(5H)-ones

Authors: Kai Sun, Guofeng Li, Yuyang Li, Jie Yu, Qing Zhao, Zhiguo Zhang, and Guisheng Zhang

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.202000040

Link to VoR: http://dx.doi.org/10.1002/adsc.202000040

COMMUNICATION

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Oxidative Radical Relay Functionalization for the Synthesis of Benzimidazo[2,1-*a*]iso-quinolin-6(5*H*)-ones

Kai Sun,[a,b,*] Guofeng Li,[b] Yuyang Li,[a] Jie Yu,[a] Qing Zhao,[a] Zhiguo Zhang,[b,*] and Guisheng Zhang[b,*]

[a] College of Chemistry and Chemical Engineering, Anyang Normal University, Anyang 455000, P. R. China
E-mail: sunk468@nenu.edu.cn
[b] School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, 453007, P. R. China
E-mail: zhangzg@htu.edu.cn; zgs@htu.cn

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. Here, a mild and general oxidative radical relay carbocyclization reaction with 2-arylbenzoimidazoles and cyclic ethers is reported. This method provides an efficient access to a wide range of structurally diverse benzimidazo[2,1-*a*]isoquinoline-6(5*H*)-ones under metal-free conditions. The wide substrate scope, good functional group tolerance, and scale-up operation of this method are expected to promote its potential applications in biotechnology and pharmacy.

Keywords: Radical relay; Carbocyclization; Metal-free; Scale-up operation; Heterocycles

Nitrogen-containing heterocycles are important compounds owing to their prevalence in natural products, functional materials, and pharmaceutical agents.[1] Among which, structurally diverse polycyclic benzimidazo-isoquinolines, containing fused five-membered and six-membered ring frameworks, are ubiquitous structural motifs found in antidiabetic,[2] anti-inflammatory[3] and antitumor[4] compounds, with powerful biological properties (Figure 1). Therefore, much effort has been directed towards exploring efficient methods for their synthesis. Compared with the established multi-step condensation reactions with pre-functionalized starting materials and limited functional group tolerability,[5] the search for atom- and step-economic methods, in particular metal-free strategies, towards benzimidazo-isoquinolines is highly desirable. In 2018, Song *et al.* reported the Cp*Rh(III)-catalyzed [4+2] annulative reaction for the synthesis of benzimidazole[2,1-*a*]isoquinolines with 2-arylimidazoles and *a*-diazoketoesters (Scheme 1a).[6] Recently, Chen and Yu *et al.* developed a silver-catalyzed decarboxylative radical addition cyclization

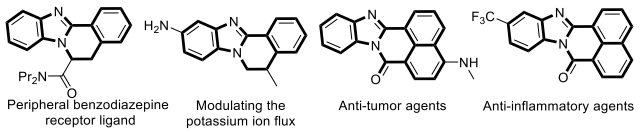
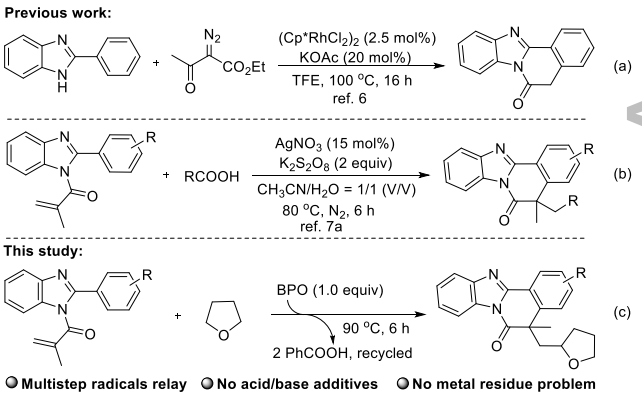


Figure 1. Examples of benzimidazole[2,1-*a*]isoquinolines.

to access benzimidazole[2,1-*a*]isoquinolines (Scheme 1b).[7a] Later that year, an elegant metal-free visible-light promoted radical cyclization to access perfluoroalkyl-substituted benzimidazole[2,1-*a*]isoquinolines with a stoichiometric base additivewas reported by the same group.[7b] However despite these advances, the use of potentially explosive diazo compounds, expensive metal catalyst, stoichiometric acid/base additives, environmentally unfriendly halohydrocarbons and the inevitable metal residue, could severely limit the synthetic application of these protocols, especially in biotechnology and pharmacy.

Radical relay reactions are synthetically attractive as they enable facile accesses to highly complex and often polycyclic molecular skeletons in an atom- and step-economical manner.[8] In particular, the mild reaction conditions are compatible with a lot of functional groups, thus time-consuming protection strategies can be minimized. Because tetrahydrofuran



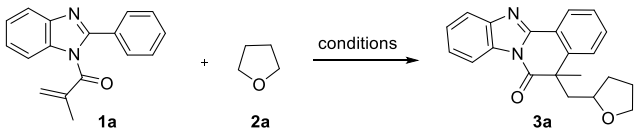
Scheme 1. Synthesis of benzimidazo-isoquinoline fused frameworks.

(THF) and 1,4-dioxane are important chemical feed stocks for the synthesis of many important organic compounds, efforts employing such simple ether derivatives in C−C bond forming reactions to construct higher-functionalized ethers are highly desirable.[9] Over recent years, many reports for the construction of higher-functionalized ethers involving an oxidative radical coupling strategy have been reported.[10] With our continued interest in the derivatization of nitrogen-containing heterocycles[11] and radical chemistry,[12] we reasoned that, with a suitable oxidative coupling system, the radical relay functionalization initiated by intermolecular addition of carbon-centered radicals generated *in situ* to π systems, may be a mild and concise manner for the synthesis of benzimidazole[2,1-*a*]isoquinolines (Scheme 1c).

To test the feasibility of the idea, we began by optimizing the reaction of *N*-methacryloyl-2-phenylbenzoimidazole (**1a**) with THF (Table 1). Initially, a series of oxidants, including *tert*-butyl peroxybenzoate (TBPB), benzoyl peroxide (BPO), *tert*-butyl hydrogenperoxide (TBHP, 70% in water), di-*tert*-butyl peroxide (DTBP), and dicumylperoxide (DCP) were investigated (entries 1–5). Results show that TBPB and BPO performed well, delivering **3a** in high yields (75% and 76%). The reaction proceeded with the other three peroxides but the yields were inferior to those with TBPB and BPO (entries 3–5). It also was observed that O_2 was an ineffective oxidant for this carbocyclization reaction (entry 6). Considering that readily available, inexpensive and non-toxic carboxylic acids are among the most commonly used starting materials, and that the carboxy group can be viewed as a chemoselective leaving group *via* extruding traceless CO_2, BPO was selected as the optimal oxidant.[13,14] Screening of the amount of oxidant revealed that a higher amount of BPO had no positive effect on the reaction efficiency; pleasingly, 75% of **3a** could be obtained with just 1 equiv. of BPO (entries 7–9). Further screenings found that a higher reaction temperature of 120 °C did not improve the yield compared with the result at 90 °C, but lower temperatures (60–80 °C) dramatically reduced the yields (entries 10–13). Notably, the reaction was transferable to a 1 gram scale of **1a**, affording the desired product **3a** in good yield (entry 14).

After the optimized reaction conditions had been established, we then investigated the generality of this metal-free oxidative radical relay carbocyclization reaction (Table 2). It was clearly observed that substrates **1** bearing electron-donating groups (-Me, -OMe, -Ph) and electron-withdrawing groups (-Cl, -Br, -I, -CN, -CF_3, -COOMe, -SO_2Me) at the *ortho*-, *meta*- and *para*-positions of the phenyl rings, underwent the reaction smoothly to generate the corresponding products **3b**−**3q** in 59−84% yields. The structure of **3g** was unambiguously determined by X-ray crystallography analysis.[15] In this reaction, reactive functional groups (-I, and -COOMe), which

Table 1. Screening of reaction conditions[a]



Entry	Oxidant (equiv)	Temp (°C)	Time (h)	Yield (%)[b]
1	TBPB (2.0)	100	4	75
2	BPO (2.0)	100	4	76
3	TBHP (2.0)	100	4	58
4	DTBP (2.0)	100	4	33
5	DCP (2.0)	100	4	41
6	O_2 (1 atm)	100	24	0
7	BPO (3.0)	100	4	75
8	BPO (1.3)	100	4	74
9	BPO (1.0)	100	4	75
10	BPO (1.0)	120	2	72
11	BPO (1.0)	90	6	74
12	BPO (1.0)	80	24	66
13	BPO (1.0)	60	24	43
14	BPO (1.0)	90	24	68[c]

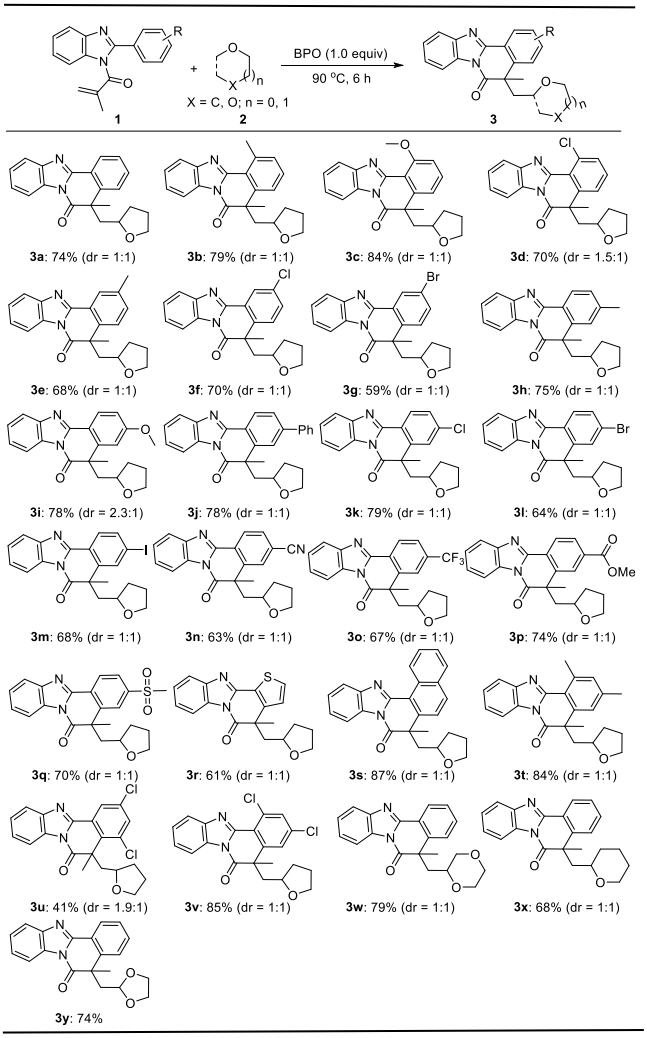
[a] Reactions were carried out with 2-methyl-1-(2-phenyl-1*H*-benzo[*d*]imidazol-1-yl)prop-2-en-1-one (**1a**) (0.3 mmol), THF (**2a**) (2.0 mL), and BPO (1.0-2.0 equiv) from 60-120 °C. [b] The reactions were conducted in sealed tubes, yield of the isolated product. [c] The reaction was performed with 1 gram scale of **1a**.

are usually sensitive in reactions containing metal and base, were well tolerated. Notably, halo and cyano-substituents on the phenyl ring, provide a handle for further transformations. In addition, 2-thiophen- and 2-naphthalen- substituted 1*H*-benzo[*d*]imidazoles **1r** and **1s** were also smoothly converted in this reaction, and the corresponding products **3r** and **3s** were obtained in 61% and 87% yields, respectively. Substrates with multiple substituents, such as **1t**, **1u** and **1v**, were also converted to the corresponding products **3t**, **3u** and **3v** in moderate to high yields (41−85%). We reasoned that the low yield of **3u** may be due to steric hindrance. Furthermore, cyclic ethers 1,4-dioxane, tetrahydro-2*H*-pyran and 1,3-dioxolane were found to be good coupling partners, giving the desired **3w** and **3y** in good yields (68−79%). Unfortunately, no reaction occurred using acyclic ethers as the coupling partners.

Control experiments showed that the reaction of **1a** with **2a** and BPO was severely suppressed when radical inhibitors, including 2,6-di-*tert*-butyl-4-methylphenol (BHT, 2.0 equiv) and 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO, 2.0 equiv) were added (eq 1 and eq 2). In addition, the adduct **4** was formed from **2a** and BHT (eq 2, see ESI). These results suggested that this oxidative radical relay carbocyclization is initiated by the formation of alkyl radicals from ethers **2**. Furthermore, the BPO was undoubtedly converted to benzoic acid, which can be

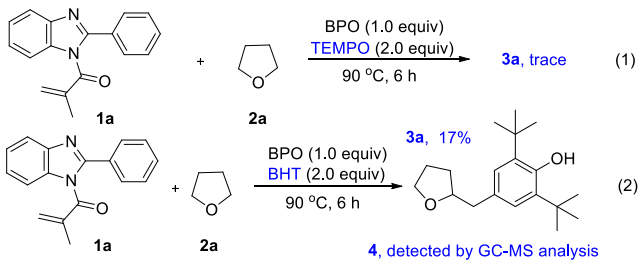
10.1002/adsc.202000040

Table 2. Substrates scope[a,b]

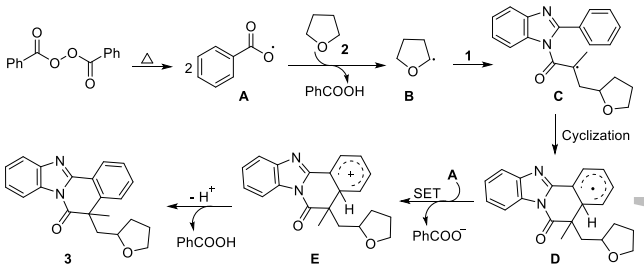


[a] Reactions were carried out with **1** (0.3 mmol), ether **2** (2.0 mL), and BPO (1.0 equiv) at 90 °C for 4-6 h. [b] The reactions were conducted in sealed tubes, yield of the isolated product.

detected by GC-MS analysis at the beginning of the reaction, and can be isolated after the reaction. No decarboxylative benzene product was detected by GC-MS analysis.



Based on the present results and previous literature reports,[16] the mechanism for this oxidative radical relay carbocyclization reaction is proposed in Scheme 2. Initially, thermal decomposition of BPO occurs to form two O-centered radical species **A**. The C(sp^3)−H bond adjacent to the oxygen atom in cyclic ethers **2** is then cleaved by radical specie **A**, and then alkyl radical intermediate **B** is generated. Next, the addition of intermediate **B** to the carbon-carbon double bond of **1** leads to the formation of radical intermediate **C**, which undergoes an intramolecular cyclization to deliver radical intermediate **D**. Subsequent reaction of intermediate **D** with the second O-centered radical specie **A** leads to cationic intermediate **E**. Finally, loss of a proton from **E** affords the desired product **3**.



Scheme 2. Proposed mechanism.

In summary, we have developed the first metal-free oxidative radical relay carbocyclization reaction of 2-arylbenzoimidazoles with cyclic ethers for the synthesis of a series of structurally diverse and privileged benzimidazo[2,1-*a*]isoquinoline-6(5*H*)-ones. During the overall process, non-toxic, readily available bulk chemical raw material benzoic acid is the only by-product. More importantly, due to its metal-free nature, this reaction satisfies purity requirements to enable use in biological and medicinal chemistry. This simple oxidative radical relay strategy features easy-handling, wide substrate scope, mild reaction conditions and is easily scaled up. These encouraging results will pave the way for investigating potential applications for this novel reaction, and related studies are currently underway in our laboratory.

Experimental Section

General Remarks: Unless otherwise stated, all commercial reagents and solvents were used without additional purification. All the reactions were carried out under air atmosphere. ^{1}H NMR spectra of compounds **3** were recorded at 25°C on a Bruker Ascend™ 400 spectrometer. Chemical shifts (in ppm) were referenced TMS in $CDCl_3$ (0 ppm). ^{13}C-NMR spectra were obtained by using the same NMR spectrometers and were calibrated with $CDCl_3$ (δ = 77.00 ppm). Melting points were obtained with a micro melting point XT4A Beijing Keyi electrooptic apparatus and are uncorrected. HRMS data were obtained on a Waters LCT Premierxe™ (USA). All reactions were monitored by TLC with Taizhou GF254 silica gel coated plates. Flash column chromatography was carried out using 200-300 mesh silica gel at increased pressure.

The general procedure for the synthesis of 1 (1b as an example):

Step 1: In a round-bottomed flask (50 mL) equipped with a magnetic stirrer, a mixture of *o*-methylbenzaldehyde (5.0 mmol, 578 μL) and $NaHSO_3$ (11.0 eq, 5.73 g) in H_2O (20.0 mL) was prepared. When the mixture reached refluxing temperature, *o*-phenylenediamine (5.0 mmol, 541 mg) were added. The resulting mixture was stirred for

appropriate time. After completion of the reaction, the reaction mixture was vacuum filtered after cooling to room temperature by a glass funnel. The residues were washed by water (20 mL × 2), dried in air dry oven to give the corresponding product.

Step 2: To the solution of 2-(*o*-tolyl)-1*H*-benzo[*d*]imidazole (3 mmol, 625 mg) and DMAP (0.6 mmol. 73 mg) in DCM (0.5 M) was added Et_3N (6 mmol, 834 μL) and methacryloyl chloride (6 mmol, 581 μL) at 0 °C. The solution was warmed up to room temperature and stirred for 12 h. The reaction was complete according to TLC analysis, and water (20 mL) was added to the mixture, which was extracted with CH_2Cl_2 (15 mL × 3). Then the organic solvent was concentrated in vacuo. The residue was purified by flash column chromatography with Ethyl acetate and Petroleum ether as eluent to give **1b**.

The general procedure for the synthesis of 3 (3a as an example):

To a screw-cap test tube (15 mL), **1a** (79 mg, 0.3 mmol) and BPO (73 mg, 1.0 equiv) were added, and then the mixture was stirred for 6 h in 2 mL THF at 90 °C. After completion of the reaction, the mixture was quenched with $NaHCO_3$ (sat. aq. 15 mL), extracted with CH_2Cl_2 (3 × 5 mL). Then the organic phase was concentrated in vacuo. The residue was purified by flash column chromatography with Ethyl acetate and Petroleum ether as eluent to give **3a**.

5-methyl-5-((tetrahydrofuran-2-yl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3a). Flash column chromatography (petroleum ether/ethyl acetate = 10:1) gave 74 mg of product as a white solid in 74% yield; mp: 79-80 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.55-8.44 (m, 1H), 8.42-8.31 (m, 1H), 7.87-7.77 (m, 1H), 7.61-7.35 (m, 5H), 3.55-3.40 (m, 2H), 3.35 (dd, J = 14.0, 7.6 Hz, 0.5H), 3.18 (dd, J = 14.8, 7.6 Hz, 0.5H), 2.72 (dd, J = 13.6, 11.6 Hz, 0.5H), 2.59 (dd, J = 14.0, 7.6 Hz, 0.5H), 2.46 (dd, J = 13.6, 5.2 Hz, 0.5H), 2.16 (dd, J = 14.0, 2.8 Hz, 0.5H), 1.87-1.73 (m, 2H), 1.73-1.48 (m, 4H), 1.35-1.20 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.4, 173.3, 150.1, 150.0, 144.2, 144.2, 141.8, 141.5, 131.9, 131.8, 131.5, 127.8, 127.7, 126.7, 126.3, 126.2, 126.0, 126.0, 125.7, 125.5, 125.3, 123.5, 122.7, 119.9, 119.7, 115.8, 115.7, 76.0, 75.2, 67.3, 67.3, 48.3, 47.8, 47.8, 47.5, 31.3, 30.2, 29.8, 25.8, 25.4. HRMS (ESI), *m/z* calcd. for $C_{21}H_{21}N_2O_2$ ($[M+H]^+$) 333.1598, found: 333.1596.

1,5-dimethyl-5-((tetrahydrofuran-2-yl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3b). Flash column chromatography (petroleum ether/ethyl acetate = 10:1) gave 82 mg of product as a white solid in 79% yield; mp: 90-91 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.48-8.36 (m, 1H), 7.89-7.78 (m, 1H), 7.47-7.38 (m, 3.5H), 7.35-7.28 (m, 1.5H), 3.58-3.33 (m, 2.5H), 3.20 (dd, J = 14.8, 7.2 Hz, 0.5H), 3.08 (s, 1.5H), 3.06 (s, 1.5H), 2.73 (dd, J = 14.0, 11.2 Hz, 0.5H), 2.55 (dd, J = 14.0, 7.2 Hz, 0.5H), 2.45 (dd, J = 14.0, 5.2 Hz, 0.5H), 2.14 (dd, J = 14.0, 3.2 Hz, 0.5H), 1.90-1.75 (m, 2H), 1.74-1.59 (m, 3 H), 1.59-1.39 (m, 1H), 1.34-1.22 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.5, 173.4, 150.3, 150.1, 144.3, 144.2, 142.6, 142.5, 139.9, 139.8, 131.1, 131.0, 130.6, 130.5, 130.2, 125.7, 125.3, 125.2, 124.5, 124.1, 122.0, 121.3, 120.2, 120.0, 115.8, 76.0, 75.2, 67.2, 67.2, 48.4, 48.3, 47.6, 47.3, 31.3, 31.2, 30.8, 30.0, 25.8, 25.3, 25.0, 24.8. HRMS (ESI), *m/z* calcd. for $C_{22}H_{23}N_2O_2$ ($[M+H]^+$) 347.1754, found: 347.1749.

1-methoxy-5-methyl-5-((tetrahydrofuran-2-yl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3c). Flash column chromatography (petroleum ether/ethyl acetate = 2:1) gave 91 mg of product as a white solid in 84% yield; mp: 85-86 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44-8.32 (m, 1H), 7.94-7.83 (m, 1H), 7.56-7.46 (m, 1H), 7.45-7.33 (m, 2H), 7.20-6.95 (m, 2H), 4.13 (s, 1.5H), 4.12 (s, 1.5H), 3.55-3.33 (m, 2.5H), 3.14 (dd, J = 14.8, 7.2 Hz, 0.5H), 2.71 (dd, J = 14.0, 10.8 Hz, 0.5H), 2.54 (dd, J = 13.6, 7.6 Hz, 0.5H), 2.43 (dd, J = 13.6, 4.8 Hz, 0.5H), 2.15 (dd, J = 14.0, 3.6 Hz, 0.5H), 1.85-1.47 (m, 5H), 1.45-1.35 (m, 1H), 1.30-1.21 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.3, 173.1, 158.8, 158.8, 148.2, 148.1, 144.5, 144.4, 144.2, 144.2, 132.3, 131.9, 130.8, 130.4, 125.8, 125.7, 125.4, 125.1, 120.6, 120.4, 119.0, 118.6, 115.6, 112.9, 112.1, 110.4, 110.2, 75.9, 75.2, 67.3, 56.7, 56.7, 48.6, 48.5, 47.5, 47.3, 31.4, 31.1, 30.5, 30.0, 25.9, 25.4. HRMS (ESI), *m/z* calcd. for $C_{22}H_{23}N_2O_3$ ($[M+H]^+$) 363.1703, found: 363.1707.

1-chloro-5-methyl-5-((tetrahydrofuran-2-yl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3d). Flash column chromatography (petroleum ether/ethyl acetate = 10:1) gave 77 mg of product as a white solid in 70% yield; mp: 130-131 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.46-8.34 (m, 1H), 7.98-7.88 (m, 1H), 7.60-7.53 (m, 1H), 7.52-7.37 (m, 4H), 3.56-3.28 (m, 2.4H), 3.16 (dd, J = 15.2, 7.2 Hz, 0.6H), 2.74 (dd, J = 14.0, 11.2 Hz, 0.6H), 2.54 (dd, J = 14.0, 6.8 Hz, 0.4H), 2.39 (dd, J = 14.0, 6.0 Hz, 0.4H), 2.16 (dd, J = 14.0, 3.6 Hz, 0.6H), 1.87-1.72 (m, 2H), 1.71-1.63 (m, 2H), 1.61-1.39 (m, 2H), 1.34-1.21 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.6, 172.5, 147.5, 147.4, 144.6, 144.4, 144.0, 144.0, 133.6, 133.5, 131.3, 131.3, 131.1, 131.1, 130.7, 130.6, 126.4, 126.1, 126.0, 125.5, 125.5, 125.5, 121.6, 120.9, 120.9, 120.7, 115.8, 115.7, 75.8, 75.0, 67.4, 67.4, 48.5, 48.1, 47.7, 31.5, 31.4, 30.7, 29.5, 25.7, 25.4. HRMS (ESI), *m/z* calcd. for $C_{21}H_{20}ClN_2O_2$ ($[M+H]^+$) 367.1208, found: 367.1213.

2,5-dimethyl-5-((tetrahydrofuran-2-yl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3e). Flash column chromatography (petroleum ether/ethyl acetate = 10:1) gave 71 mg of product as a colorless oil in 68% yield; mp: 35-36 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.42-8.25 (m, 2H), 7.85-7.76 (m, 1H), 7.48-7.29 (m, 4H), 3.53-3.30 (m, 2.5H), 3.17 (dd, J = 14.8, 7.2 Hz, 0.5H), 2.69 (dd, J = 14.0, 11.6 Hz, 0.5H), 2.56 (dd, J = 14.0, 7.2 Hz, 0.5H), 2.50-2.37 (m, 3.5H), 2.13 (dd, J = 13.6, 3.2 Hz, 0.5H), 1.85-1.69 (m, 2.5H), 1.68-1.43 (m, 4H), 1.33-1.25 (m, 0.5H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.5, 173.4, 150.2, 150.2, 144.2, 144.1, 138.8, 138.5, 137.7, 137.5, 132.9, 132.6, 131.9, 131.5, 126.5, 126.3, 126.2, 126.1, 125.9, 125.5, 125.4, 125.2, 123.1, 122.3, 119.8, 119.6, 115.8, 115.7, 76.0, 75.2, 67.3, 67.2, 48.2, 47.7, 47.5, 47.2, 31.3, 31.2, 30.1, 29.8, 25.8, 25.3, 21.0. HRMS (ESI), *m/z* calcd. for $C_{22}H_{23}N_2O_2$ ($[M+H]^+$) 347.1754, found: 347.1747.

2-chloro-5-methyl-5-((tetrahydrofuran-2-yl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3f). Flash column chromatography (petroleum ether/ethyl acetate = 20:1) gave 77 mg of product as a white solid in 70% yield; mp: 102-103 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.55-8.21 (m, 2H), 7.86-7.74 (m, 1H), 7.53-7.31 (m, 4H), 3.51-3.28 (m, 2.5H), 3.16 (dd, J = 14.4, 7.2 Hz, 0.5H), 2.70 (dd, J = 14.0, 11.2 Hz, 0.5H), 2.57 (dd, J = 14.0, 6.4 Hz, 0.5H), 2.37 (dd, J = 14.0, 6.0 Hz, 0.5H), 2.12 (dd, J = 14.0, 3.2 Hz, 0.5H), 1.88-1.68 (m, 2.5H), 1.68-1.39 (m, 4H), 1.35-1.21 (m, 0.5H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.8, 172.7, 148.7, 144.0, 143.9, 140.2, 139.6, 133.8, 131.8, 131.7, 131.5, 131.4, 128.2, 127.8, 126.1, 126.0, 125.8, 125.7, 125.6, 125.5, 125.0, 124.2, 120.1, 119.9, 115.8, 115.7, 75.9, 75.0, 67.4, 67.3, 48.1, 47.7, 47.3, 47.2, 31.5, 31.3, 30.0, 29.7, 25.6, 25.3. HRMS (ESI), *m/z* calcd. for $C_{21}H_{20}ClN_2O_2$ ($[M+H]^+$) 367.1208, found: 367.1200.

2-bromo-5-methyl-5-((tetrahydrofuran-2-yl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3g). Flash column chromatography (petroleum ether/ethyl acetate = 20:1) gave 73 mg of product as a white solid in 59% yield; mp: 127-128 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.69-8.55 (m, 1H), 8.39-8.27 (m, 1H), 7.86-7.75 (m, 1H), 7.65 (s, 0.5H), 7.63 (s, 0.5H), 7.48-7.27 (m, 3H), 3.53-3.27 (m, 2.5H), 3.15 (dd, J = 15.2, 7.2 Hz, 0.5H), 2.69 (dd, J = 14.0, 11.2 Hz, 0.5H), 2.56 (dd, J = 14.0, 6.4 Hz, 0.5H), 2.36 (dd, J = 13.9, 6.0 Hz, 0.5H), 2.12 (dd, J = 14.0, 3.2 Hz, 0.5H), 1.79-1.46 (m, 6.5H), 1.36-1.25 (m, 0.5H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.7, 172.6, 148.6, 143.99, 143.9, 140.7, 140.1, 134.5, 134.3,

131.8, 131.4, 128.8, 128.5, 128.4, 128.0, 126.1, 126.0, 125.7, 125.6, 125.3, 124.5, 121.7, 121.7, 120.1, 119.9, 115.8, 115.7, 75.9, 75.0, 67.4, 67.3, 48.0, 47.8, 47.6, 47.3, 31.5, 31.3, 30.0, 29.6, 25.6, 25.3. HRMS (ESI), *m/z* calcd. for $C_{21}H_{20}BrN_2O_2$ ($[M+H]^+$) 411.0703, found: 411.0699.

3,5-dimethyl-5-((tetrahydrofuran-2-yl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3h). Flash column chromatography (petroleum ether/ethyl acetate = 10:1) gave 78 mg of product as a white solid in 75% yield; mp: 130-131 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.47-8.28 (m, 2H), 7.86-7.73 (m, 1H), 7.49-7.37 (m, 2H), 7.35-7.22 (m, 2H), 3.56-3.34 (m, 2.5H), 3.20 (dd, J = 14.8, 7.2 Hz, 0.5H), 2.71 (dd, J = 14.0, 11.2 Hz, 0.5H), 2.59 (dd, J = 13.6, 8.0 Hz, 0.5H), 2.53-2.40 (m, 3.5H), 2.16 (dd, J = 14.0, 3.6 Hz, 0.5H), 1.88-1.73 (m, 3H), 1.72-1.60 (m, 2H), 1.59-1.38 (m, 1H), 1.36-1.10 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.5, 173.4, 150.3, 150.2, 144.2, 144.2, 142.5, 142.0, 141.6, 141.4, 131.9, 131.4, 128.9, 128.8, 127.0, 126.6, 126.1, 126.0, 125.4, 125.4, 125.1, 120.8, 120.0, 119.7, 119.5, 115.7, 115.6, 76.0, 75.2, 67.3, 67.2, 48.2, 47.8, 47.5, 47.4, 31.3, 31.1, 30.2, 29.9, 25.9, 25.3, 22.1, 22.1. HRMS (ESI), *m/z* calcd. for $C_{22}H_{23}N_2O_2$ ($[M+H]^+$) 347.1754, found: 347.1748.

3-methoxy-5-methyl-5-((tetrahydrofuran-2-yl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3i). Flash column chromatography (petroleum ether/ethyl acetate = 8:1) gave 85 mg of product as a white solid in 78% yield; mp: 90-91 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.48-8.27 (m, 2H), 7.83-7.72 (m, 1H), 7.46-7.30 (m, 2H), 7.07-6.88 (m, 2H), 3.91 (s, 3H), 3.57-3.33 (m, 2.3H), 3.19 (dd, J = 15.2, 7.2 Hz, 0.7H), 2.70 (dd, J = 14.0, 11.2 Hz, 0.7H), 2.56 (dd, J = 14.0, 7.2 Hz, 0.3H), 2.42 (dd, J = 14.0, 5.2 Hz, 0.3H), 2.11 (dd, J = 14.0, 3.6 Hz, 0.7H), 1.89-1.71 (m, 2H), 1.71-1.54 (m, 3H), 1.51-1.38 (m, 1H), 1.34-1.22 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.3, 173.3, 162.6, 162.4, 150.2, 150.2, 144.3, 144.2, 143.8, 143.5, 131.8, 131.4, 128.1, 127.9, 125.9, 125.3, 125.2, 124.8, 119.5, 119.3, 116.4, 115.6, 115.6, 115.5, 113.7, 113.1, 112.2, 112.2, 75.9, 75.2, 67.3, 67.2, 55.7, 48.3, 48.0, 47.8, 47.6, 31.3, 31.2, 30.3, 29.8, 25.9, 25.3. HRMS (ESI), *m/z* calcd. for $C_{22}H_{23}N_2O_3$ ($[M+H]^+$) 363.1703, found: 363.1709.

5-methyl-3-phenyl-5-((tetrahydrofuran-2-yl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3j). Flash column chromatography (petroleum ether/ethyl acetate = 10:1) gave 95 mg of product as a light green solid in 78% yield; mp: 165-166 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.67-8.48 (m, 1H), 8.46-8.28 (m, 1H), 7.91-7.79 (m, 1H), 7.77-7.59 (m, 4H), 7.56-7.35 (m, 5H), 3.61-3.33 (m, 2.5H), 3.21 (dd, J = 15.2, 7.2 Hz, 0.5H), 2.77 (dd, J = 13.6, 11.2 Hz, 0.5H), 2.64 (dd, J = 13.6, 7.2 Hz, 0.5H), 2.53 (dd, J = 13.6, 5.6 Hz, 0.5H), 2.24 (dd, J = 14.0, 3.2 Hz, 0.5H), 1.92-1.78 (m, 2H), 1.78-1.47 (m, 4.5H), 1.38-1.27 (m, 0.5H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.3, 173.3, 149.9, 149.9, 144.6, 144.4, 144.3, 144.2, 142.2, 141.9, 140.2, 140.1, 131.9, 131.5, 129.1, 128.4, 128.3, 127.3, 126.7, 126.5, 126.0, 125.6, 125.5, 125.3, 124.8, 122.3, 121.5, 119.9, 119.7, 115.8, 115.7, 76.0, 75.2, 67.3, 67.3, 48.2, 47.9, 47.8, 47.6, 31.4, 30.3, 29.9, 25.8, 25.4. HRMS (ESI), *m/z* calcd. for $C_{27}H_{25}N_2O_2$ ($[M+H]^+$) 409.1911, found: 409.1917.

3-chloro-5-methyl-5-((tetrahydrofuran-2-yl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3k). Flash column chromatography (petroleum ether/ethyl acetate = 15:1) gave 87 mg of product as a white solid in 79% yield; mp: 139-140 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.50-8.27 (m, 2H), 7.87-7.70 (m, 1H), 7.54-7.32 (m, 4H), 3.55-3.28 (m, 2.5H), 3.17 (dd, J = 14.8, 7.2 Hz, 0.5H), 2.71 (dd, J = 14.0, 11.6 Hz, 0.5H), 2.57 (dd, J = 14.0, 6.4 Hz, 0.5H), 2.36 (dd, J = 14.0, 6.4 Hz, 0.5H), 2.12 (dd, J = 14.0, 3.2 Hz, 0.5H), 1.91-1.71 (m, 2.5H), 1.69-1.39 (m, 4H), 1.36-1.22 (m, 0.5H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.6, 172.5, 149.2, 149.1, 144.1, 144.0, 143.7, 143.1, 137.9, 137.6, 131.8, 131.4, 128.3, 128.2, 127.6, 127.3, 126.9, 126.4, 126.1, 125.8 , 125.6, 125.5, 122.1, 121.3, 119.9, 119.8, 115.7, 115.6, 75.8, 75.0, 67.4, 67.3, 48.1, 47.9, 47.5, 31.5, 31.3, 30.0, 29.6, 25.7, 25.3. HRMS (ESI), *m/z* calcd. for $C_{21}H_{20}ClN_2O_2$ ($[M+H]^+$) 367.1208, found: 367.1201.

3-bromo-5-methyl-5-((tetrahydrofuran-2-yl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3l). Flash column chromatography (petroleum ether/ethyl acetate = 10:1) gave 79 mg of product as a yellow solid in 64% yield; mp: 121-122 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41-8.28 (m, 2H), 7.85-7.76 (m, 1H), 7.68-7.56 (m, 2H), 7.49-7.36 (m, 2H), 3.57-3.45 (m, 1H), 3.45-3.29 (m, 1.5H), 3.18 (dd, J = 15.2, 7.2 Hz, 0.5H), 2.72 (dd, J = 14.0, 11.6 Hz, 0.5H), 2.57 (dd, J = 14.4, 6.4 Hz, 0.5H), 2.37 (dd, J = 14.0, 6.4 Hz, 0.5H), 2.12 (dd, J = 14.4, 3.6 Hz, 0.5H), 1.88-1.71 (m, 3H), 1.71-1.43 (m, 3H), 1.36-1.26 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.6, 172.5, 149.3, 149.2, 144.1, 144.0, 143.9, 143.3, 131.9, 131.4, 131.2, 131.1, 129.9, 129.4, 127.7, 127.4, 126.3, 126.2, 126.1, 125.9, 125.6, 125.6, 122.6, 121.7, 120.0, 119.8, 115.8, 115.7, 75.8, 75.0, 67.4, 67.4, 48.1, 47.9, 47.9, 47.5, 31.5, 31.4, 30.1, 29.6, 25.7, 25.4. HRMS (ESI), *m/z* calcd. for $C_{21}H_{20}BrN_2O_2$ ($[M+H]^+$) 411.0703, found: 411.0699.

3-iodo-5-methyl-5-((tetrahydrofuran-2-yl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3m). Flash column chromatography (petroleum ether/ethyl acetate = 10:1) gave 93 mg of product as a white solid in 68% yield; mp: 124-125 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.43-8.29 (m, 1H), 8.27-8.11 (m, 1H), 7.92-7.70 (m, 3H), 7.52-7.35 (m, 2H), 3.57-3.45 (m, 1H), 3.45-3.29 (m, 1.5H), 3.17 (dd, J = 14.4, 6.8 Hz, 0.5H), 2.70 (dd, J = 13.6, 11.6 Hz, 0.5H), 2.56 (dd, J = 14.0, 6.8 Hz, 0.5H), 2.36 (dd, J = 14.0, 6.0 Hz, 0.5H), 2.12 (dd, J = 14.0, 3.2 Hz, 0.5H), 1.90-1.71 (m, 3H), 1.69-1.39 (m, 3H), 1.37-1.21 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.5, 172.4, 149.4, 149.3, 144.1, 144.0, 143.7, 143.2, 136.9, 135.8, 135.4, 131.9, 131.4, 127.5, 127.2, 126.2, 126.0, 125.6, 125.6, 123.0, 122.2, 120.0, 119.8, 115.8, 115.7, 98.5, 98.2, 75.8, 75.0, 67.4, 67.4, 48.1, 47.8, 47.6, 47.3, 31.4, 31.3, 30.1, 29.6, 25.7, 25.4. HRMS (ESI), *m/z* calcd. for $C_{21}H_{20}IN_2O_2$ ($[M+H]^+$) 459.0564, found: 459.0569.

5-methyl-6-oxo-5-((tetrahydrofuran-2-yl)methyl)-5,6-dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinoline-3-carbonitrile (3n). Flash column chromatography (petroleum ether/ethyl acetate = 20:3) gave 67 mg of product as a white solid in 63% yield; mp: 101-102 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.65-8.50 (m, 1H), 8.42-8.32 (m, 1H), 7.88-7.69 (m, 3H), 7.54-7.38 (m, 2H), 3.58-3.49 (m, 0.5H), 3.48-3.34 (m, 1H), 3.34-3.23 (m, 1H), 3.16 (dd, J = 14.8, 6.8 Hz, 0.5H), 2.76 (dd, J = 14.0, 11.6 Hz, 0.5H), 2.60 (dd, J = 14.4, 5.2 Hz, 0.5H), 2.31 (dd, J = 14.0, 7.6 Hz, 0.5H), 2.17 (dd, J = 14.0, 3.2 Hz, 0.5H), 1.91-1.73 (m, 3H), 1.72-1.44 (m, 3.5H), 1.38-1.26 (m, 0.5H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.0, 148.3, 148.0, 144.1, 144.0, 143.3, 142.3, 131.9, 131.5, 130.9, 130.8, 130.6, 130.5, 127.5, 126.9, 126.6, 126.6, 126.5, 126.4, 126.3, 125.9, 120.4, 120.3, 118.4, 118.3, 115.9, 115.8, 114.7, 114.6, 75.8, 74.9, 67.6, 67.5, 48.1, 48.0, 47.5, 31.9, 31.3, 30.0, 29.5, 25.4, 25.4. HRMS (ESI), *m/z* calcd. for $C_{22}H_{20}N_3O_2$ ($[M+H]^+$) 358.1550, found: 358.1547.

5-methyl-5-((tetrahydrofuran-2-yl)methyl)-3-(trifluoromethyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3o). Flash column chromatography (petroleum ether/ethyl acetate = 15:1) gave 80 mg of product as a white solid in 67% yield; mp: 105-106 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.69-8.53 (m, 1H), 8.47-8.31 (m, 1H), 7.91-7.65 (m, 3H), 7.53-7.37 (m, 2H), 3.62-3.50 (m, 0.5H), 3.49-3.36 (m, 1H), 3.34-3.24 (m, 1H), 3.17 (dd, J = 14.8, 7.2 Hz, 0.5H), 2.76 (dd, J = 14.0, 11.6 Hz, 0.5H), 2.60 (dd, J = 14.0, 5.6 Hz, 0.5H), 2.38 (dd, J = 14.0, 7.2 Hz, 0.5H), 2.20 (dd, J = 14.0, 3.2 Hz, 0.5H), 1.9-1.74 (m, 3H), 1.74-1.54 (m, 3H), 1.38-1.27 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.5, 148.7, 148.6, 144.1, 144.0, 143.0, 142.1, 133.0 (q, J = 28.7 Hz), 131.9, 131.5, 126.9, 126.8, 126.5, 126.3, 126.0, 125.9, 125.9, 125.8, 124.6, 124.5 (q, J = 3.6

Hz), 124.3 (q, *J* = 3.6 Hz), 123.9 (q, *J* = 272.2 Hz), 123.8 (q, *J* = 3.9 Hz), 123.3 (q, *J* = 3.8 Hz), 120.3, 120.1, 115.9, 115.8, 75.8, 75.0, 67.4, 48.2, 48.2, 48.0, 47.7, 31.7, 31.4, 30.1, 29.6, 25.5, 25.4. ^{19} F NMR (376 MHz, $CDCl_3$): -62.73, -62.82. HRMS (ESI), *m/z* calcd. for $C_{22}H_{20}F_3N_2O_2$ ($[M+H]^+$) 401.1471, found: 401.1465.

Methyl 5-methyl-6-oxo-5-((tetrahydrofuran-2-yl)methyl)-5,6-dihydrobenzo[4,5]imidazo [2,1-*a*]isoquinoline-3-carboxylate (3p). Flash column chromatography (petroleum ether/ethyl acetate = 5:1) gave 86 mg of product as a white solid in 74% yield; mp: 144-145 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.65-8.47 (m, 1H), 8.44-8.30 (m, 1H), 8.24-8.03 (m, 2H), 7.89-7.76 (m, 1H), 7.52-7.32 (m, 2H), 3.98 (s, 1.5H), 3.97 (s, 1.5H), 3.56-3.21 (m, 2.5H), 3.20-3.09 (m, 0.5H), 2.80-2.67 (m, 0.5H), 2.65-2.55 (m, 0.5H), 2.51-2.40 (m, 0.5H), 2.30-2.19 (m, 0.5H), 1.89-1.75 (m, 2H), 1.74-1.48 (m, 4H), 1.35-1.20 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.9, 172.8, 166.5, 166.3, 149.1, 149.0, 144.2, 144.1, 142.3, 141.6, 132.6, 132.5, 132.0, 131.5, 128.5, 128.5, 128.1, 127.8, 127.4, 126.5, 126.3, 126.2, 126.0, 125.9, 125.7, 120.2, 120.1, 115.9, 115.8, 75.9, 75.1, 67.4, 52.6, 48.1, 48.0, 47.6, 31.5, 31.3, 30.0, 29.6, 25.6, 25.4. HRMS (ESI), *m/z* calcd. for $C_{23}H_{23}N_2O_4$ ($[M+H]^+$) 391.1652, found: 391.1659.

5-methyl-3-(methylsulfonyl)-5-((tetrahydrofuran-2-yl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3q). Flash column chromatography (petroleum ether/ethyl acetate = 3:1) gave 86 mg of product as a colorless oil in 70% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 8.2 Hz, 0.5H), 8.65 (d, *J* = 8.2 Hz, 0.5H), 8.44-8.33 (m, 1H), 8.13-7.94 (m, 2H), 7.89-7.80 (m, 1H), 7.52-7.40 (m, 2H), 3.61-3.51 (m, 0.5H), 3.48-3.33 (m, 1H), 3.25 (t, *J* = 6.8 Hz, 1H), 3.19-3.07 (m, 3.5H), 2.76 (dd, *J* = 14.0, 11.6 Hz, 0.5H), 2.64 (dd, *J* = 14.0, 4.4 Hz, 0.5H), 2.38 (dd, *J* = 14.0, 8.0 Hz, 0.5H), 2.25 (dd, *J* = 14.0, 3.6 Hz, 0.5H), 1.88-1.74 (m, 3H), 1.72-1.45 (m, 3.5H), 1.39-1.29 (m, 0.5H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.2, 172.2, 148.3, 148.0, 144.1, 144.0, 143.7, 142.7, 142.4, 131.9, 131.5, 128.3, 127.4, 127.4, 127.0, 126.6, 126.4, 126.4, 126.3, 126.1, 126.0, 125.5, 120.4, 120.3, 115.9, 115.8, 76.0, 75.0, 67.5, 67.5, 48.6, 47.9, 47.9, 47.6, 44.6, 32.0, 31.3, 30.0, 29.8, 25.4, 25.3. HRMS (ESI), *m/z* calcd. for $C_{22}H_{23}N_2O_4S$ ($[M+H]^+$) 411.1373, found: 411.1377.

4-methyl-4-((tetrahydrofuran-2-yl)methyl)benzo[4,5]imidazo[1,2-*a*]thieno[2,3-c]pyridin-5(4*H*)-one (3r). Flash column chromatography (petroleum ether/ethyl acetate = 5:1) gave 62 mg of product as a white solid in 61% yield; mp: 99-100 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.38-8.26(m, 1H), 7.82-7.71 (m, 1H), 7.59 (d, *J* = 5.2 Hz, 1H), 7.45-7.32 (m, 2H), 7.14 (d, *J* = 5.2 Hz, 0.5H), 7.06 (d, *J* = 5.2 Hz, 0.5H), 3.60-3.35 (m, 2.5H), 3.23 (dd, *J* = 14.4, 7.2 Hz, 0.5H), 2.64 (dd, *J* = 13.6, 11.2 Hz, 0.5H), 2.55 (dd, *J* = 13.6, 7.2 Hz, 0.5H), 2.36 (dd, *J* = 13.6, 5.2 Hz, 0.5H), 2.06 (dd, *J* = 13.6, 3.2 Hz, 0.5H), 1.84-1.55 (m, 6H), 1.49-1.39 (m, 0.5H), 1.36-1.27 (m, 0.5H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 173.8, 147.9, 147.2, 147.0, 146.9, 144.1, 144.0, 131.3, 130.9, 130.8, 130.6, 126.2, 125.9, 125.6, 125.5, 125.4, 125.3, 124.4, 123.3, 119.8, 119.6, 115.3, 115.2, 76.0, 75.4, 67.5, 67.2, 48.1, 47.9, 47.6, 47.2, 31.5, 31.3, 29.1, 29.0, 25.8, 25.3. HRMS (ESI), *m/z* calcd. for $C_{19}H_{19}N_2O_2S$ ($[M+H]^+$) 339.1162, found: 339.1167.

7-methyl-7-((tetrahydrofuran-2-yl)methyl)benzo[*h*]benzo[4,5]imidazo[2,1-*a*]isoquinolin-8(7*H*)-one (3s). Flash column chromatography (petroleum ether/ethyl acetate = 30:1) gave 100 mg of product as a colorless oil in 87% yield; **^{1}H NMR** (400 MHz, CDCl3) δ 10.64-10.47 (m, 1H), 8.53-8.41 (m, 1H), 8.07-7.99 (m, 1H), 7.99-7.88 (m, 2H), 7.87-7.77 (m, 1H), 7.68-7.44 (m, 4H), 3.58-3.26 (m, 2.5H), 3.16 (dd, *J* = 14.8, 7.2 Hz, 0.5H), 2.80 (dd, *J* = 14.2, 11.2 Hz, 0.5H), 2.70 (dd, *J* = 14.0, 8.0 Hz, 0.5H), 2.62 (dd, *J* = 13.6, 4.8 Hz, 0.5H), 2.29 (dd, *J* = 14.0, 3.6 Hz, 0.5H), 1.87-1.59 (m, 5H), 1.53-1.37 (m, 1.5H), 1.34-1.28 (m, 0.5H).**^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 173.5, 173.3, 150.3, 150.1, 144.3, 144.2, 142.3, 141.9, 132.8, 132.8, 132.7, 132.4, 131.0, 130.6, 130.5, 130.4, 128.8, 128.7, 128.5, 128.5, 128.4, 128.2, 126.9, 126.8, 126.0, 125.9, 125.6, 125.4, 123.7, 123.3, 120.3, 120.1, 118.7, 117.8, 115.9, 115.8, 76.1, 75.3, 67.3, 67.2, 48.0, 47.8, 47.3, 31.4, 31.1, 30.1, 30.1, 25.8, 25.4. HRMS (ESI), *m/z* calcd. for $C_{25}H_{23}N_2O_2$ ($[M+H]^+$) 383.1754, found: 383.1759.

1,3,5-trimethyl-5-((tetrahydrofuran-2-yl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3t). Flash column chromatography (petroleum ether/ethyl acetate = 20:1) gave 91 mg of product as a white solid in 84% yield; mp: 104-105 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.44-8.35 (m, 1H), 7.85-7.77 (m, 1H), 7.45-7.34 (m, 2H), 7.23-7.07 (m, 2H), 3.53 (dd, *J* = 14.8, 7.3 Hz, 1H), 3.47-3.34 (m, 1.5H), 3.20 (dd, *J* = 15.0, 7.3 Hz, 0.5H), 3.03 (s, 1.5H), 3.01 (s, 1.5H), 2.71 (dd, *J* = 13.8, 11.1 Hz, 0.5H), 2.59-2.34 (m, 4.5H), 2.13 (dd, *J* = 13.9, 3.3 Hz, 0.5H), 1.81-1.65 (m, 4.5H), 1.49-1.30 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 173.7, 173.5, 150.5, 150.3, 144.4, 144.4, 142.6, 140.9, 140.4, 139.8, 139.7, 132.2, 132.1, 131.1, 130.7, 125.7, 125.5, 125.1, 125.1, 124.7, 120.0, 119.9, 119.5, 118.8, 115.8, 115.7, 76.0, 75.3, 67.2, 67.2, 48.5, 48.4, 47.5, 47.3, 31.4, 31.0, 30.8, 30.0, 26.0, 25.4, 24.7, 24.6, 21.8, 21.8. HRMS (ESI), *m/z* calcd. for $C_{23}H_{25}N_2O_2$ ($[M+H]^+$) 361.1911, found: 361.1919.

2,4-dichloro-5-methyl-5-((tetrahydrofuran-2-yl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3u). Flash column chromatography (petroleum ether/ethyl acetate = 50:1) gave 50 mg of product as a white solid in 41% yield; mp: 97-98 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.59 (d, *J* = 2.2 Hz, 0.65H), 8.54 (d, *J* = 2.2 Hz, 0.35H), 8.41-8.30 (m, 1H), 7.86-7.78 (m, 1H), 7.55 (d, *J* = 2.2 Hz, 1H), 7.48-7.41 (m, 2H), 3.61-3.47 (m, 1H), 3.37-3.25 (m, 1.65H), 3.18-3.09 (m, 1.35H), 2.67 (dd, *J* = 14.2, 11.8 Hz, 0.65H), 2.55 (dd, *J* = 14.3, 5.5 Hz, 0.35H), 1.95 (s, 1H), 1.89-1.76 (m, 3.5H), 1.68-1.47 (m, 2.5H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 173.1, 172.9, 148.2, 148.1, 144.1, 144.0, 136.6, 135.6, 134.5, 134.3, 134.2, 134.0, 131.8, 131.4, 127.5, 126.5, 126.4, 126.2, 125.9, 125.6, 125.2, 120.2, 120.0, 116.0, 115.8, 76.4, 75.7, 67.7, 67.3, 49.2, 43.7, 42.7, 31.5, 31.2, 25.8, 25.5, 25.5, 25.0. HRMS (ESI), *m/z* calcd. for $C_{21}H_{19}Cl_2N_2O_2$ ($[M+H]^+$) 401.0818, found: 401.0811.

1,3-dichloro-5-methyl-5-((tetrahydrofuran-2-yl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3v). Flash column chromatography (petroleum ether/ethyl acetate = 10:1) gave 102 mg of product as a white solid in 85% yield; mp: 185-186 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.47-8.28 (m, 1H), 7.98-7.81 (m, 1H), 7.62-7.51 (m, 1H), 7.50-7.33 (m, 3H), 3.59-3.27 (m, 2.5H), 3.15 (dd, *J* = 14.8, 7.2 Hz, 0.5H), 2.74 (dd, *J* = 13.6, 11.6 Hz, 0.5H), 2.52 (dd, *J* = 14.0, 6.0 Hz, 0.5H), 2.30 (dd, *J* = 14.0, 6.8 Hz, 0.5H), 2.12 (dd, *J* = 14.0, 3.2 Hz, 0.5H), 1.85-1.48 (m, 6.5H), 1.35-1.28 (m, 0.5H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 171.8, 171.7, 146.7, 146.1, 145.6, 144.0, 143.9, 136.6, 136.4, 134.5, 134.3, 131.1, 131.0, 130.5, 126.5, 126.2, 126.1, 125.9, 125.6, 125.4, 120.8, 120.7, 120.3, 119.6, 115.7, 75.7, 74.8, 67.5, 67.4, 48.6, 48.4, 48.3, 47.8, 31.6, 31.4, 30.5, 29.3, 25.6, 25.4. HRMS (ESI), *m/z* calcd. for $C_{21}H_{19}Cl_2N_2O_2$ ($[M+H]^+$) 401.0818, found: 401.0823.

5-((1,4-dioxan-2-yl)methyl)-5-methylbenzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3w). Flash column chromatography (petroleum ether/ethyl acetate = 5:1) gave 82 mg of product as a white solid in 79% yield; mp: 99-100 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.55-8.42 (m, 1H), 8.41-8.27 (m, 1H), 7.86-7.74 (m, 1H), 7.63-7.52 (m, 1H), 7.52-7.35 (m, 4H), 3.50-3.10 (m, 5H), 3.12-2.79 (m, 2H), 2.63 (dd, *J* = 14.0, 11.2 Hz, 0.5H), 2.43 (dd, *J* = 14.0, 4.8 Hz, 0.5H), 2.19 (dd, *J* = 14.4, 6.4 Hz, 0.5H), 1.95 (dd, *J* = 14.0, 2.4 Hz, 0.5H), 1.74 (s, 1.5H), 1.72 (s, 1.5H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 173.2 173.0, 150.0, 150.0, 144.2, 144.0, 141.7, 140.8, 131.8, 131.7, 131.5, 128.0, 127.9, 126.6, 126.2, 126.1, 126.0, 125.7, 125.7, 125.5, 123.5, 122.8, 119.9, 119.7, 115.8, 115.7, 73.1, 72.7, 70.7, 70.5, 66.5, 66.5, 66.2, 66.0, 47.5, 46.5, 44.2,

43.8, 29.6, 29.3. HRMS (ESI), *m/z* calcd. for $C_{21}H_{21}N_2O_3$ ($[M+H]^+$) 349.1547, found: 349.1553.

5-methyl-5-((tetrahydro-2H-pyran-2-yl)methyl)benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3x). Flash column chromatography (petroleum ether/ethyl acetate = 15:1) gave 70 mg of product as a white solid in 68% yield; mp: 180-181 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.63-8.26 (m, 2H), 7.90-7.68 (m, 1H), 7.63-7.34 (m, 5H), 3.46 (d, *J* = 9.2 Hz, 0.5H), 3.01 (dd, *J* = 10.8, 3.6 Hz, 1H), 2.88 (td, *J* = 11.2, 2.4 Hz, 0.5H), 2.68 (dd, *J* = 13.6, 11.2 Hz, 0.5H), 2.54 (t, *J* = 10.4 Hz, 0.5H), 2.48-2.37 (m, 1H), 2.26 (dd, *J* = 14.2, 7.6 Hz, 0.5H), 2.02 (dd, *J* = 14.0, 2.0 Hz, 0.5H), 1.82-1.68 (m, 3H), 1.41-0.98 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.6, 173.4, 150.3, 150.1, 144.2, 144.0, 142.5, 141.5, 131.9, 131.6, 127.7, 127.5, 126.7, 126.4, 125.9, 125.8, 125.5, 125.5, 125.4, 123.6, 122.6, 119.8, 119.5, 115.9, 115.7, 75.3, 74.9, 68.2, 68.1, 50.2, 49.1, 47.8, 46.9, 31.9, 31.4, 29.0, 28.8, 25.5, 25.1, 23.3, 23.1. HRMS (ESI), *m/z* calcd. for $C_{22}H_{23}N_2O_2$ ($[M+H]^+$) 347.1754, found: 347.1759.

5-((1,3-dioxolan-2-yl)methyl)-5-methylbenzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (3y). Flash column chromatography (petroleum ether/ethyl acetate = 8:1) gave 74 mg of product as a white solid in 74% yield; mp: 135-136 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 7.6 Hz, 1H), 8.43-8.35(m, 1H), 7.86-7.78(m, 1H), 7.60-7.53 (m, 1H), 7.53-7.40 (m, 4H), 4.56 (dd, *J* = 7.6, 2.4 Hz, 1H), 3.61 (dd, *J* = 14.0, 6.8 Hz, 1H), 3.53 (dd, *J* = 14.0, 7.2 Hz, 1H), 3.43-3.32 (m, 2H), 2.87 (dd, *J* = 14.0, 7.2 Hz, 1H), 2.51 (dd, *J* = 14.0, 2.4 Hz, 1H), 1.71 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.0 149.9, 144.1, 141.0, 131.7, 131.6, 127.8, 126.7, 126.0, 125.7, 125.5, 122.8, 119.7, 115.8, 101.53, 65.0, 64.5, 46.2, 45.1, 30.4. HRMS (ESI), *m/z* calcd. for $C_{20}H_{19}N_2O_3$ ($[M+H]^+$) 335.1390, found: 335.1397.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (21801007), the Program for Innovative Research Team of Science and Technology in the University of Henan Province (18IRTSTHN004), the Science and Technology Plan Projects of Henan Province (19A150015, 20B150002) and the Jilin Province Key Laboratory of Organic Functional Molecular Design & Synthesis (130028911).

References

[1] a) T. Henkel, R. M. Brunne, H. Müller, F. Reichel, *Angew. Chem.* **1999**, *111*, 688−691; *Angew. Chem. Int. Ed.* **1999**, *38*, 643−647; b) R. Hili, A. K. Yudin, *Nat. Chem. Biol.* **2006**, *2*, 284−287.

[2] a) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395−3442; b) A. V. Lygin, A. D. Meijere, *Angew. Chem.* **2010**, *122*, 9028−9331; *Angew. Chem. Int. Ed.* **2010**, *49*, 9094−9124; c) X.-X. Guo, D.-W. Gu, Z.-X. Wu, W.-B. Zhang, *Chem. Rev.* **2015**, *115*, 1622−1651.

[3] a) K. Alam, S. W. Hong, K. H. Oh, J. K. Park, *Angew. Chem.* **2017**, *129*, 13572−13576; *Angew. Chem. Int. Ed.* **2017**, *56*, 13387−13391; b) K. Sun, Y.-F. Si, X.-L. Chen, Q.-Y. Lv, Y.-Y. Peng, L.-B. Qu, B. Yu, *Asian J. Org. Chem.* **2019**, *8*, 2042−2045.

[4] a) L.W. Deady, T. Rodemann, *Aust. J. Chem.* **2001**, *54*, 529−534; b) B. Wu, N. Yoshikai, *Org. Biomol. Chem.* **2016**, *14*, 5402−5416; c) F. Pan, C. Shu, L.-W. Ye, *Org. Biomol. Chem.* **2016**, *14*, 9456−9465; d) W.-L. Xie, Y.-Q. Wu, J.-A. Zhang, Q.-H. Mei, Y.-H. Zhang, N. Zhu, R.-Z. Liu, H.-L. Zhang, *Eur. J. Med. Chem.* **2018**, *145*, 35−40.

[5] a) G. Meng, H.-Y. Niu, G.-R. Qu, J. S. Fossey, J.-P. Li, H.-M. Guo, *Chem. Commun.* **2012**, *48*, 9601−9603; b) V. O. Iaroshenko, D. Ostrovskyi, M. Miliutina, A. Maalik, A. Villinger, A. Tolmachev, D. M. Volochnyuk, P. Langer, *Adv. Synth. Catal.* **2012**, *354*, 2495−2503; c) X. Sun, X. Hu, S.-Z. Nie, Y.-Y. Yan, X.-J. Zhang, M. Yan, *Adv. Synth. Catal.* **2013**, *355*, 2179−2184; d) X. Sun, X.-H. Lv, L.-M. Ye, Y. Hu, Y.-Y. Chen, X.-J. Zhang, M. Yan, *Org. Biomol. Chem.* **2015**, *13*, 7381−7383; e) Y. G. Liu, G.-Q. Chen, C.-W. Tse, X. G. Guan, Z.-J. Xu, J.-S. Huang, C.-M. Che, *Chem.−Asian J.* **2015**, *10*, 100−105; f) T. B. Nguyen, L. Ermolenkoa, A. Al-Mourabit, *Chem. Commun.* **2016**, *52*, 4914−4917 and references therein.

[6] a) S.-Y. Mai, Y.-X. Luo, X.-Y. Huang, Z.-H. Shu, B.-N. Li, Y. Lan, Q.-L. Song, *Chem. Commun.* **2018**, *54*, 10240−10243.

[7] a) K. Sun, S.-J. Li, X.-L. Chen, Y. Liu, X.-Q. Huang, D.-H. Wei, L.-B. Qu, Y.-F. Zhao, B. Yu, *Chem. Commun.* **2019**, *55*, 2861−2864; b) F.-L. Zeng, K. Sun, X.-L. Chen, X.-Y. Yaun, S.-Q. He, Y. Liu, Y.-Y. Peng, L.-B. Qu, Q.-Y. Lv, B. Yu, *Adv. Synth. Catal.* **2019**, *361*, 5176−5181.

[8] a) P. J. Parsons, C. S. Penkett, A. J. Shell, *Chem. Rev.* **1996**, *96*, 195−206; b) U. Wille, *Chem. Rev.* **2013**, *113*, 813−853.

[9] a) S. M. Miles, S. P. Marsden, R. J. Leatherbarrow, W. J. Coates, *J. Org. Chem*. **2004**, *69*, 6874−6882; b) C. E. Rye, D. Barker, *Synlett* **2009**, *20*, 3315−3319; c) V. Mammoli, A. Bonifazi, F. D. Bello, E. Diamanti, M. Giannella, A. L. Hudson, L. Mattioli, M. Perfumi, A. Piergentili, W. Quaglia, F. Titomanlio, M. Pigini, *Bioorg. Med. Chem.* **2012**, *20*, 2259−2265.

[10] a) S.-R. Guo, P. S. Kumar, M.-H. Yang, *Adv. Synth. Catal.* **2017**, *359*, 2−25; b) D. Xia, Y. Li, T. Miao, P.-H. Li, L. Wang, *Green Chem.* **2017**, *19*, 1732−1739; c) W. Ou, G.-Q. Zhang, J. Wu, C.-L. Su, *ACS Catal.* **2019**, *9*, 5178−5183 and references therein.

[11] a) K. Sun, X. Wang, L.-L. Liu, J.-J. Sun, X. Liu, Z.-D. Li, Z.-G. Zhang, G.-S. Zhang, *ACS Catal.* **2015**, *5*, 7194−7198; b) K. Sun, Y. Li, Q. Zhang, *Sci. China Chem.* **2015**, *58*, 1354−1358.

[12] a) K. Sun, X. Wang, G. Li, Z.-H. Zhu, Y.-Q. Jiang, B.-B. Xiao, *Chem. Commun.* **2014**, *50*, 12880−12883; b) K. Sun, Z.-D. Shi, Z.-H. Liu, B.-X. Luan, J.-L. Zhu, Y.-R. Xue, *Org. Lett.* **2018**, *20*, 6687−6690; c) K. Sun. S.-N. Wang, R.-R. Feng, Y.-X. Zhang, X. Wang, Z.-G. Zhang, B. Zhang, *Org. Lett.* **2019**, *21*, 2052−2055; d) X. Wang, C.-H. Li, Y.-X. Zhang, B. Zhang, K. Sun, *Org. Biomol. Chem.* **2019**, *17*, 8364−8368.

[13] a) E. Scott, F. Peter, J. Sanders, *Appl. Microbiol. Biotechnol.* **2007**, *75*, 751−762; b) J. Schwarz, B. König, *Green Chem.* **2018**, *20*, 323−361.

[14] The catch: Usually, BPO are not stable and have the potential to explode under heat conditions. In this reaction, the oxidative radical relay carbocyclization could proceed smoothly.

[15] CCDC 1969589 (**3g**) contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] a) M. Hu, J.-H. Fan, Y. Liu, X.-H. Ouyang, R.-J. Song, J.-H. Li, *Angew. Chem. Int. Ed.* **2015**, *54*, 9577−9580; b) M. Hu, R.-J. Song, J.-H Li, *Angew. Chem.* **2015**, *127*, 618−622; *Angew. Chem. Int. Ed.* **2015**, *54*, 608−612; c) C. Wang, R.-J. Song, J.-H. Li, *Org. Lett.* **2019**, *21*, 2800−2803; d) Y.-H. Guo, Y.-F. Xiang, L. Wei, J.-P. Wan, *Org. Lett.* **2018**, *20*, 3971−3974; e) L.-L. Wang, Y.-L. Zhang, M. Zhang, P.-L. Bao, X.-X. Lv, H.-G. Liu, X.-H. Zhao, J.-S. Li, Z. D. Luo, W. Wei, *Tetrahedron Lett.* **2019**, *60*, 1845−1848; f) G.-Q. Li, Z.-Y. Gan, K.-X. Kong, X.-M. Dou, D.-S. Yang, *Adv. Synth. Catal.* **2019**, *361*, 1808−1814; g) T.-S. Zhang, H.-P. Zhang, R. Fu, J.-Y. Wang, W.-J. Hao, S.-J. Tu, B. Jiang, *Chem. Commun.* **2019**, *55*, 13231–13234; h) L. Ji, Q.-F. Deng, P. Liu, P.-P. Sun, *Org. Biomol. Chem.* 2019, *17*, 7715–7722; i) J.-P. Wan, Z, Tu, Y.-Y. Wang, *Chem. Eur. J.* **2019**, *25*, 6907−6910; j) L.-H. Tian, Y.-H. Guo, L. Wei, J.-P. Wan, S.-R. Sheng, *Asian J. Org. Chem.* **2019**, *8*, 1484−1489; k) Y.-Y. Liu, J. Xiong, L. Wei J.- P. Wan, *Adv. Synth. Catal.* **2020**, DOI: 10.1002/adsc.201901234.

10.1002/adsc.202000040

COMMUNICATION

Oxidative Radical Relay Functionalization for the Synthesis of Benzimidazo[2,1-*a*]iso-quinolin-6(5H)-ones

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Kai Sun* Guofeng Li, Yuyang Li, Jie Yu, Qing Zhao, Zhiguo Zhang* and Guisheng Zhang*