JOC The Journal of Organic Chemistry

Note

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b02961 • Publication Date (Web): 05 Feb 2018

ACS Publications

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Synthesis of 4-aryl isoquinolinedione derivatives by palladium-catalyzed coupling reaction of aryl halides with isoquinoline-1,3(2*H*,4*H*)-diones

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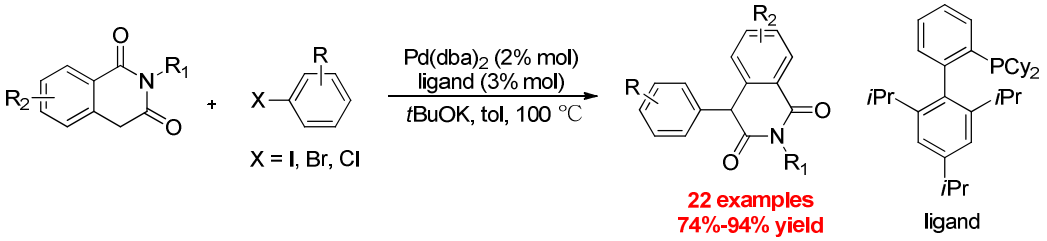
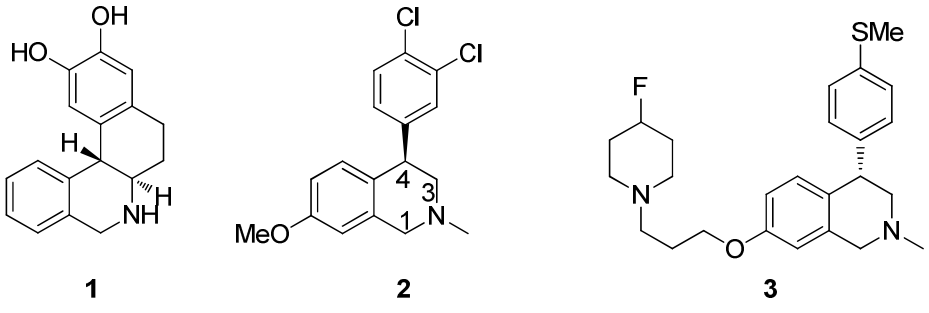


Abstract: Palladium catalyzed cross-coupling reaction of aryl halides with isoquinoline-1,3(2*H*,4*H*)-diones for the synthesis of 4-aryl isoquinoline-1,3(2*H*,4*H*)-diones was developed. The reaction conditions exhibit remarkable compatibility with various aryl halides and isoquinoline-1,3(2*H*,4*H*)-diones and the product could be conveniently transformed to 4-aryl tetrahydroisoquinolines. (±) Dichlorofensine was synthesized using this protocol in two steps with an overall yield of 71%.

Isoquinoline-1,3-dione bears the core structure of tetrahydroisoquinoline, which is an important structural motif present in pharmaceutical compounds and natural products with a broad spectrum of biological

properties.[1] For instance, dihydrexidine **1**[2] is the first high-affinity full dopamine D_1-selective agonist; dichlorofensine **2**[3] can inhibit the uptake of important central neurotransmitters such as norepinephrine or dopamine at postsynaptic receptors and **3**[4] is an important antidepressant compound (Figure 1). The construction of these tetrahydroisoquinoline architectures attracts wide explorations. However, most of the studies focus on the construction of 1-substituted tetrahydroisoquinolines,[5] while 4-substituted tetrahydroisoquinolines were much less explored. This is because C-1 position of tetrahydroisoquinolines could be easily activated by oxygen,[6] electrode,[7] visible light[8] and other mild oxidants,[9] while C-4 position is much harder to be activated. Herein, we would like to report a general method for the synthesis of 4-aryl isoquinoline-1,3(2*H*,4*H*)-diones, which could be conveniently converted to corresponding 4-aryl tetrahydroisoquinolines through simple reductive process.



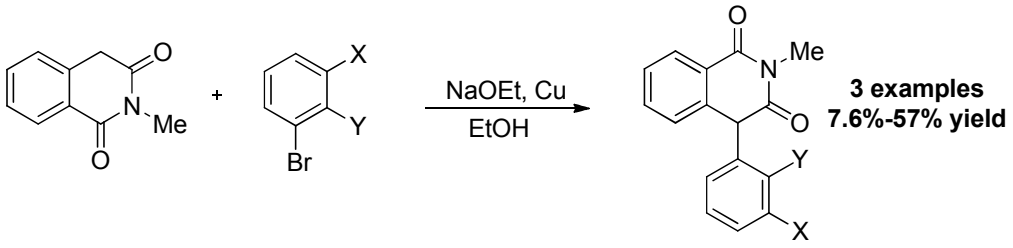
1 **2** **3**

Figure 1. Examples of useful 4-aryl tetrahydroisoquinoline bioactive molecules.

A literature survey revealed that the 4-substituted isoquinoline

architectures can be accessed through radical-promoted, visible-light-induced or other reagent induced intramolecular cyclization reactions[10] or palladium-mediated coupling reactions.[11] Difunctionlization of double bond is the common route for developing isoquinoline-type architectures, which requires preinstall of conjugate double bond for the cyclization. In 1987, Lowe group reported a convenient cross-coupling pathway between isoquinoline-1,3(2*H*,4*H*)-dione and 2-bromobenzoic acid under copper powder catalysis (scheme 1),[12] copper(I) bromide formed insitu was proposed as the active catalyst. Moderate yield could be achieved but the substrate scope is limited to electron withdrawing acid group. Moreover, reaction to isoquinoline-1,3-dione derivatives with groups larger than methyl on nitrogen, such as ethyl, benzyl or m-trifluoromethylphenyl, were unsuccessful. Recently, a range of palladium-catalyzed coupling reactions were developed to prove their versatility and utility in the synthesis of structurally interesting organic compounds.[13] So we envision that palladium-catalyzed coupling reaction of aryl halides and isoquinoline-1,3(2*H*,4*H*)-diones would be a promising procedure to construct this type of carbon framework.

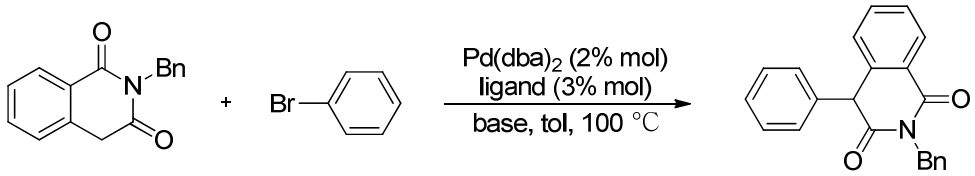
Scheme 1. Copper Catalyzed Coupling of Aryl Bromides and 2-Methyl-isoquinoline-1,3(2*H*,4*H*)-dione.



In our initial studies, the reaction between bromobenzene and 2-benzylisoquinoline-1,3(2*H*,4*H*)-dione was applied as a model reaction and the results were summarized in Table 1. In the presence of 2% mol $Pd(dba)_2$, 3% mol PPh_3 and stoichiometric amount of K_2CO_3, the cross-coupling failed to give any product after 12 hours (Table 1, entry 1). Then, bidentate and electron-rich phosphine ligands were tested, which provided a low conversion of starting material and yield of product (Table 1, entries 2-3). The electron-rich biphenyl-based phosphine ligands **7** and **8** were successfully applied in the α -arylation of oxindoles and C_3-selective mono-arylation of 4-hydroxycoumarins.[14] Therefore, a reaction employing ligand **7** was tested and the expected arylating product was obtained in 43% yield (Table 1, entry 4); moreover, a significant improvement was achieved when more sterically demanding ligand **8** was employed, the expected arylating product was isolated in 75% yield along with the recovered starting material **4a** (Table 1, entry 5). Given the low acidity of cyclic imide, we postulate that stronger base would facilitate this reaction. Indeed, with the increase of basicity, the yield of cross-coupling product increased steadily from 75% to satisfactory 94% when *t*BuOK was applied as base (Table 1, entries 6-8).

$PdCl_2$ and $Pd(OAc)_2$ can also effectively catalyze this coupling reaction (Table 1, entry 9-10). Moreover, THF is an alternative solvent for this coupling reaction with albeit slight lower yield (Table 1, entry 11).

Table 1. Reaction Condition for the Coupling of Bromobenzene and 2-Benzyl-isoquinoline-1,3(2*H*,4*H*)-dione.

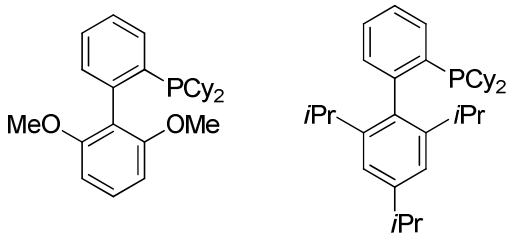


4a **5a** **6aa**

entry[a]	base(1.2 eq)	ligand	time	yield(%)[b]
1	K_2CO_3	PPh_3	12	0
2	K_2CO_3	PCy_3	12	<10
3	K_2CO_3	BINAP	12	<10
4	K_2CO_3	**7**	12	43
5	K_2CO_3	**8**	12	75
6	K_3PO_4	**8**	12	72
7	Cs_2CO_3	**8**	12	91
8	*t*BuOK	**8**	12	94
9[c]	*t*BuOK	**8**	12	82
10[d]	*t*BuOK	**8**	12	91
11[e]	*t*BuOK	**8**	12	92

[a] Conditions: isoquinoline-1,3-dione 4 (0.5 mmol), bromobenzene (0.55 mmol), base (0.55 mmol),

Pd(dba)$_2$ (0.01 mmol), ligand (0.015 mmol), toluene 1ml, 100 ℃. [b] Isolated yields. [c] $PdCl_2$ was used as catalyst. [d] $Pd(OAc)_2$ was used as catalyst. [e] THF was used as solvent, 70 ℃.

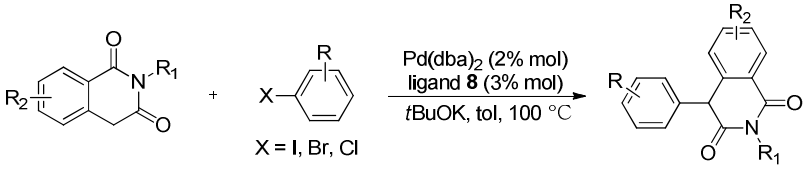


7 **8**

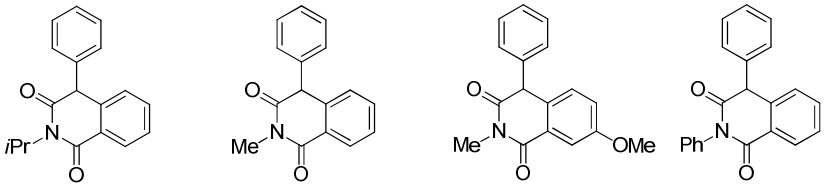
With this established reaction protocol, we next explored variations in both the substitution group on nitrogen and aryl halides coupling partners (Table 2). Bromobenzene was employed first to react with isoquinoline-1,3(2*H*,4*H*)-dione bearing different substitution groups to study the steric effect and electronic effect on the cross-coupling reaction. The results suggest that both steric effect and electronic effect have limited effect on the isolated yield (Table 2, **6ba**-**6fa**). Then the electronic and steric effects on the aryl halides were screened. Other aryl halides like chlorobenzene and iodobenzene proceed smoothly under current reaction condition (Table 2, **6aa**). The reactions also tolerate significant functionalization of the aryl halides; both electron-withdrawing and electron-donating groups can be accommodated, and substituents *ortho*, *meta* or *para* to the halide group can all be included (Table 2, **6ab-6ak**). When both bromo- and chloro-substituents were present in the arene, selective reaction at the bromosubstituent was always observed (Table 2, **6ad**, **6af-6ag**). Besides, heteroarenes are prevalent in bioactive compounds,[15] which could also be accommodated (Table 2, **6am**-**6an**).

However, when β-bromostyrene was applied instead of arylbromide for this cross-coupling reaction, the TLC became messy and no major spot was observed. Oxygen analogue of isoquinoline-dione was also tested. 4H-isochromene-1,3-dione was used to replace isoquinoline-1,3(2*H*,4*H*)-dione for the coupling reaction, the reaction system becomes messy and no coupling product could be separated.

Table 2. Substrate Scope for the Coupling of Aryl Halides and Isoquinoline-1,3(2*H*,4*H*)-diones. [a]



4 **5** **6**

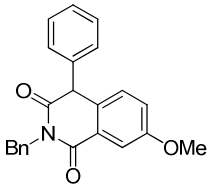


6ba 81% yield

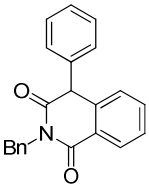
6ca 92% yield

6da 92% yield

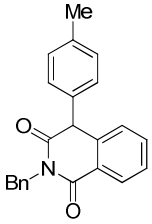
6ea 83% yield



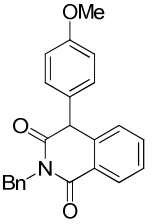
6fa 92% yield



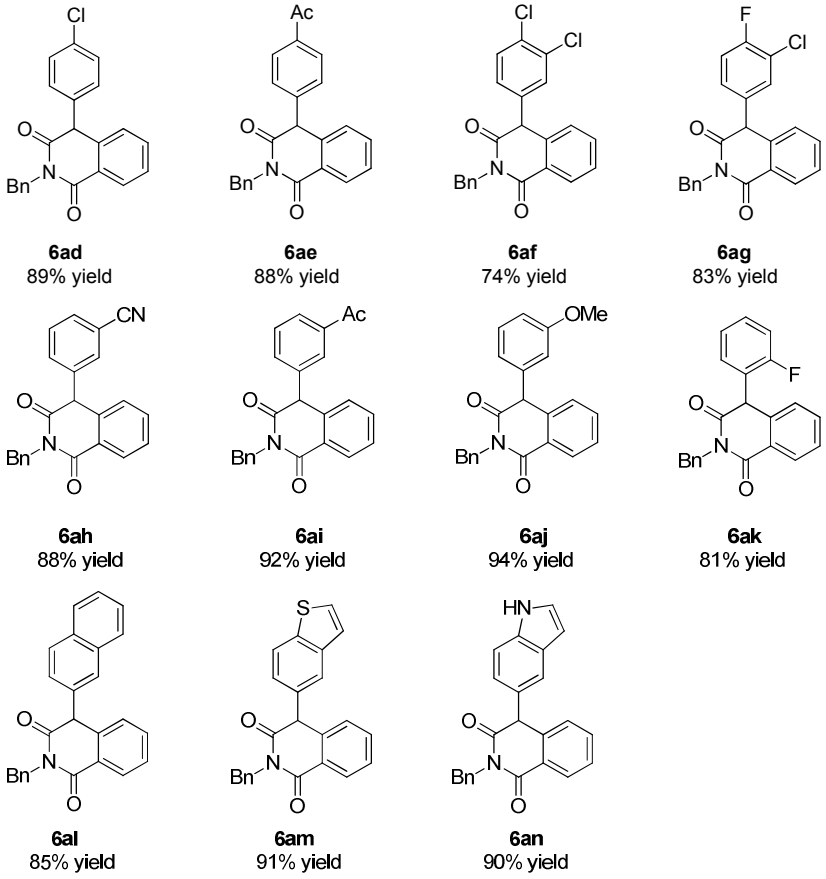
6aa
X = Cl 91% yield, 20h
X = Br 93% yield,12 h
X = I 92% yield, 7 h



6ab 85% yield



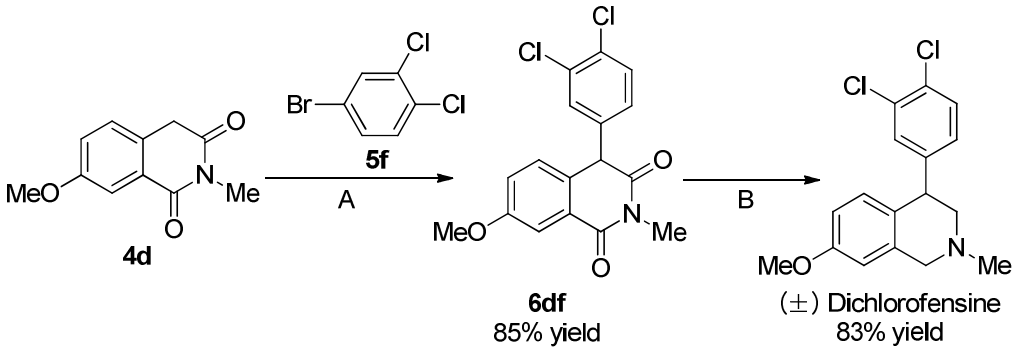
6ac 87% yield



[a] Conditions: isoquinoline-1,3-dione 4 (0.5 mmol), aryl halides (0.55 mmol), base (0.55 mmol), $Pd(dba)_2$ (0.01 mmol), ligand (0.015 mmol), toluene (1ml), 100 ℃.

To further illustrate the versatility of this protocol, the synthesis of (±) dichlorofensine was demonstrated in scheme 2, which could be achieved in two steps from 7-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione and 4-bromo-1,2-dichlorobenzene with an overall yield of 71%.

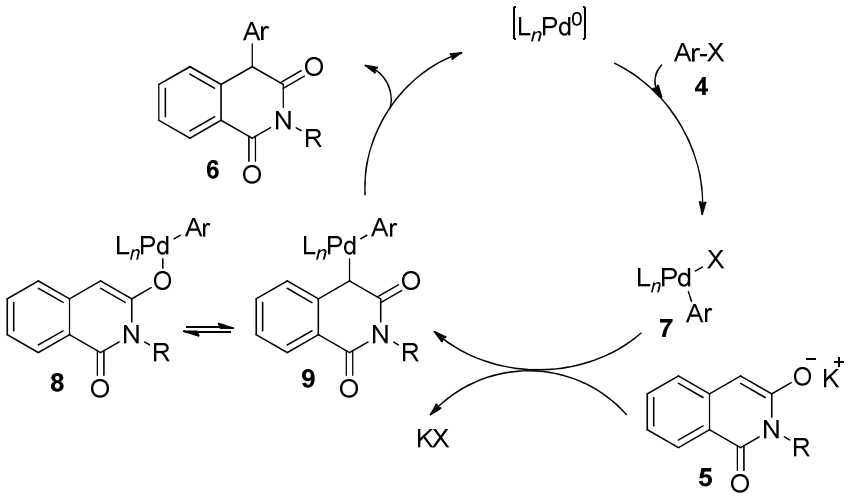
Scheme 2. Synthesis of (±) Dichlorofensine with Established Protocol.



A: Stardant coupling condition; B: BH_3-THF complex, THF, reflux, 6h.

Based on the established mechanism of palladium catalyzed coupling reactions between ketones, esters and amides with aryl halides,[16] the mechanism for this reaction was tentatively proposed in scheme 3. The first step is oxidative addition of palladium complex into C-X bond to form intermediate **7**, then intermediate **7** undergoes transmetalation with enolate **5** to get arylpalladium enolate complexes **8** and **9**, after the oxidative addition, equilibrium between the Pd-O and Pd-C species was the rate-determining step,[16] final reductive elimination of the desired product **6** restores the original palladium catalyst and completes the catalytic cycle.

Scheme 3. Proposed Mechanism for the Coupling Reaction.



In summary, we have demonstrated a palladium catalyzed cross-coupling reaction of aryl halides with isoquinoline-1,3(2*H*,4*H*)-dione to give 4-aryl isoquinoline-1,3(2*H*,4*H*)-diones in high yields. The reaction conditions exhibit remarkable compatibility with various aryl halides and isoquinoline-1,3(2*H*,4*H*)-diones. More importantly, the product could be conveniently reduced to 4-aryl tetrahydroisoquinoline, which is an important complementary protocol for the construction of this core structure.

Experiment Section

General information.

1. All solvents and inorganic reagents were from commercial sources and used without purification unless otherwise noted. Isoquinoline-1,3(2*H*,4*H*)-dione **4a**, **4b**, **4c** and **4e** were known compound,[17] **4d** and **4f** were prepared following the reference. [17a]

2. Instruments: All products were characterized by their ^{1}H NMR, ^{13}C NMR on a INOVA 400 MHz spectrometer (400 MHz and 100 MHz)

spectrometer. Data for ^{1}H NMR are reported as follows chemical shift, integration, multiplicity (s = singlet, d = doublet, dd = doublet doublet, t = triplet, q = quarte, m = multiplet) and coupling constants are reported as values in hertz (Hz). Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$: 0.00 ppm for ^{1}H and 77.00 ppm for ^{13}C). High resolution ESI mass experiments were operated on a Waters G2-XSQTof mass spectrometer for HRMS measurements.

General Procedure. To a schlenk tube was added 2-Benzyl-isoquinoline-1,3(2*H*,4*H*)-dione (0.5 mmol), bromobenzene (0.6 mmol), 2% mol $Pd(dba)_2$ (0.01 mmol), 3% mol **8** (0.015 mmol) and *t*BuOK (0.6 mmol). The mixture was subject to vacuum and back filled with nitrogen five times to remove air, then fresh distilled degassed toluene（0.5 ml）was added. The tube was sealed and heat to 100 ℃ for 12 h and then 1 ml NH_4Cl (sat.) was added to quench the reaction. Extract the mixture with EA (5 ml x 3), and the solvent was removed under rotary vap. The residue was purified by silica gel chromatography (hexane/ethyl acetate = 30:1 to 15:1) to yield the desired product **6a** (153 mg, 94%) as white solid.

Reduction of 6df to (±) Dichlorofensine. To a rbf with 100 mg of **6df** dissolved in 2 ml THF, was added 2 ml of 1M BH_3-THF complex at 0℃. After stirred at 0℃ for 4 h and the mixture was heat to reflux for 10 h,

followed by addition of 2 ml 1M NaOH and heat to reflux for 1 h to quench the reaction. Extract the mixture with EA (5 ml x 3), and the solvent was removed under rotary vap. The residue was purified by silica gel chromatography (DCM/MeOH = 100:1 to 20:1) to yield the desired product Dichlorofensine (75 mg, 81%) as colorless oil.

7-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (4d)

white solid, Mp 159-160 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.4 Hz, 1H), 7.20 – 7.11 (m, 2H), 3.98 (s, 2H), 3.88 (s, 3H), 3.37 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 165.1, 159.0, 128.3, 126.2, 126.1, 122.0, 111.2, 55.6, 35.6, 26.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{12}NO_3$ 206.0817, found 206.0822.

2-benzyl-7-methoxyisoquinoline-1,3(2*H*,4*H*)-dione (4f)

white solid, Mp 126-127 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 1.6 Hz, 1H), 7.45 (d, *J* = 7.1 Hz, 2H), 7.27 (ddd, *J* = 8.9, 7.7, 1.8 Hz, 3H), 7.14 (d, *J* = 2.3 Hz, 2H), 5.18 (s, 2H), 3.99 (s, 2H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 164.8, 159.0, 137.0, 128.9, 128.4, 128.3, 127.5, 126.2, 126.2, 122.1, 111.2, 55.6, 43.3, 35.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{16}NO_3$ 282.1130, found 282.1123.

2-benzyl-4-phenylisoquinoline-1,3(2*H*,4*H*)-dione (6aa)

153 mg, 94% yield, white solid, Mp 83-84 ℃.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.1 Hz, 1H), 7.53 (td, *J* = 7.6, 1.3 Hz, 1H), 7.46 (t,

J = 7.3 Hz, 1H), 7.34 (d, *J* = 6.5 Hz, 2H), 7.31 – 7.17 (m, 6H), 7.15 – 7.05 (m, 3H), 5.23 (d, *J* = 13.9 Hz, 1H), 5.14 – 4.98 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 164.6, 138.9, 138.2, 136.9, 134.0, 129.0, 128.9, 128.7, 128.5, 128.3, 128.3, 128.0, 127.9, 127.4, 125.4, 52.7, 43.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{18}NO_2$ 328.1338, found 328.1335.

2-isopropyl-4-phenylisoquinoline-1,3(2*H*,4*H*)-dione (6ba)

113 mg, 81% yield, white solid, Mp 61-62 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.52 (td, *J* = 7.5, 1.4 Hz, 1H), 7.46 (td, *J* = 7.7, 0.8 Hz, 1H), 7.32 – 7.25 (m, 3H), 7.16 – 7.08 (m, 3H), 5.14 – 5.07 (m, 1H), 5.02 (s, 1H), 1.45 (d, *J* = 6.9 Hz, 3H), 1.35 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 165.0, 138.9, 138.0, 133.6, 129.0, 128.8, 128.1, 127.9, 127.9, 127.9, 126.0, 53.4, 45.5, 20.1, 18.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}NO_2$ 280.1338, found 280.1334.

2-methyl-4-phenylisoquinoline-1,3(2*H*,4*H*)-dione (6ca)

116 mg, 92% yield, white solid, Mp 121-122 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.7 Hz, 1H), 7.54 (td, *J* = 7.5, 1.2 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.33 – 7.25 (m, 3H), 7.13 (dd, *J* = 5.9, 1.8 Hz, 3H), 5.09 (s, 1H), 3.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 164.9, 139.0, 138.2, 133.9, 129.0, 128.7, 128.5, 128.3, 127.9, 127.9, 125.3, 52.4, 27.2.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{14}NO_2$ 252.1025, found 252.1027.

7-methoxy-2-methyl-4-phenylisoquinoline-1,3(2*H*,4*H*)-dione(6da)

130 mg, 92% yield, white solid, Mp 145-146 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 2.7 Hz, 1H), 7.28 (t, *J* = 7.3 Hz, 3H), 7.17 – 7.07 (m, 3H), 7.02 (d, *J* = 8.6 Hz, 1H), 5.03 (s, 1H), 3.89 (s, 3H), 3.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 164.9, 159.1, 139.2, 130.4, 129.6, 129.0, 128.4, 127.8, 126.2, 122.2, 110.7, 55.6, 51.8, 27.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{16}NO_3$ 282.1130, found 282.1125.

2,4-diphenylisoquinoline-1,3(2*H*,4*H*)-dione (6ea)

130 mg, 83% yield, white solid, Mp 182-183 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.61 (td, *J* = 7.5, 1.4 Hz, 1H), 7.51 (td, *J* = 7.7, 0.7 Hz, 1H), 7.47 – 7.38 (m, 3H), 7.36 – 7.29 (m, 3H), 7.23 (td, *J* = 7.5, 2.2 Hz, 3H), 7.10 (d, *J* = 7.2 Hz, 2H), 5.24 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 164.9, 138.7, 138.1, 135.0, 134.2, 129.2, 129.1, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 125.6, 53.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{16}NO_2$ 314.1181, found 314.1189.

2-benzyl-7-methoxy-4-phenylisoquinoline-1,3(2*H*,4*H*)-dione (6fa)

165 mg, 92% yield, white solid, Mp 98-99 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 2.7 Hz, 1H), 7.34 (dd, *J* = 7.7, 1.5 Hz, 2H), 7.29 –

7.21 (m, 6H), 7.14 – 7.06 (m, 3H), 7.01 (d, *J* = 8.6 Hz, 1H), 5.22 (d, *J* = 13.9 Hz, 1H), 5.05 (t, *J* = 6.9 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 164.6, 159.2, 139.1, 136.9, 130.4, 129.6, 129.0, 128.7, 128.4, 128.3, 127.9, 127.4, 126.3, 122.4, 110.8, 55.6, 52.0, 43.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{20}NO_3$ 358.1443, found 358.1445.

2-benzyl-4-(p-tolyl)isoquinoline-1,3(2*H*,4*H*)-dione (6ab)

145 mg, 85% yield, white solid, Mp 101-102 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 7.9 Hz, 1H), 7.57 – 7.40 (m, 2H), 7.35 (d, *J* = 6.5 Hz, 2H), 7.28 – 7.16 (m, 3H), 7.10 (dd, *J* = 12.9, 7.8 Hz, 3H), 6.98 (d, *J* = 8.0 Hz, 2H), 5.22 (d, *J* = 13.9 Hz, 1H), 5.04 (d, *J* = 13.6 Hz, 2H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 164.6, 138.4, 137.7, 136.9, 136.0, 133.9, 129.7, 128.8, 128.7, 128.3, 128.3, 128.3, 127.9, 127.4, 125.3, 52.3, 43.6, 21.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{20}NO_2$ 342.1487, found 342.1486.

2-benzyl-4-(4-methoxyphenyl)isoquinoline-1,3(2*H*,4*H*)-dione (6ac)

156 mg, 87% yield, white solid, Mp 145-146 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.21 (m, 1H), 7.57 – 7.49 (m, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.34 (dd, *J* = 7.7, 1.3 Hz, 2H), 7.26 – 7.19 (m, 3H), 7.13 (d, *J* = 7.7 Hz, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 5.22 (d, *J* = 13.9 Hz, 1H), 5.04 (t, *J* = 6.9 Hz, 2H), 3.76 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 164.6, 159.2, 138.5, 136.9, 133.9, 131.0, 129.5, 128.8,

128.7, 128.3, 128.3, 127.9, 127.4, 125.3, 114.4, 55.3, 51.8, 43.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{20}NO_3$ 358.1443, found 358.1448.

2-benzyl-4-(4-chlorophenyl)isoquinoline-1,3(2*H*,4*H*)-dione (6ad)

161 mg, 89% yield, white solid, Mp 109-110 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 – 8.24 (m, 1H), 7.59 – 7.43 (m, 2H), 7.38 – 7.18 (m, 7H), 7.06 (dd, *J* = 26.8, 8.0 Hz, 3H), 5.22 (d, *J* = 13.8 Hz, 1H), 5.05 (d, *J* = 15.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 164.4, 137.6, 137.3, 136.7, 134.1, 134.0, 129.9, 129.2, 129.1, 128.7, 128.4, 128.2, 127.5, 125.3, 51.9, 43.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{17}ClNO_2$ 362.0940, found 362.0939.

4-(4-acetylphenyl)-2-benzylisoquinoline-1,3(2*H*,4*H*)-dione (6ae)

162 mg, 88% yield, white solid, Mp 147-148 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 – 8.27 (m, 1H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.57 – 7.45 (m, 2H), 7.36 (dd, *J* = 7.6, 1.5 Hz, 2H), 7.27 – 7.17 (m, 5H), 7.08 (d, *J* = 7.6 Hz, 1H), 5.28 – 5.15 (m, 2H), 5.07 (d, *J* = 13.8 Hz, 1H), 2.56 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 170.9, 164.3, 143.8, 137.3, 136.7, 136.5, 134.1, 129.1, 129.0, 128.8, 128.8, 128.4, 128.3, 128.2, 127.5, 125.3, 52.4, 43.7, 26.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{20}NO_3$ 370.1443, found 370.1445.

2-benzyl-4-(3,4-dichlorophenyl)isoquinoline-1,3(2*H*,4*H*)-dione (6af)

146 mg, 74% yield, white solid, Mp 107-108 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 – 8.25 (m, 1H), 7.60 – 7.46 (m, 2H), 7.35 (dd, *J* = 4.7, 3.7 Hz, 3H), 7.23 (ddd, *J* = 15.9, 8.3, 1.9 Hz, 4H), 7.09 (d, *J* = 7.7 Hz, 1H), 6.92 (dd, *J* = 8.3, 2.1 Hz, 1H), 5.21 (d, *J* = 13.8 Hz, 1H), 5.07 (d, *J* = 14.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 164.2, 138.7, 136.9, 136.6, 134.2, 133.1, 132.4, 130.9, 130.5, 129.2, 128.8, 128.5, 128.4, 128.2, 127.9, 127.6, 125.3, 51.5, 43.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{16}Cl_2NO_2$ 396.0545, found 396.0551.

2-benzyl-4-(3-chloro-4-fluorophenyl)isoquinoline-1,3(2*H*,4*H*)-dione (6ag) 157 mg, 83% yield, white solid, Mp 102-103 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.8 Hz, 1H), 7.57 (td, *J* = 7.5, 1.4 Hz, 1H), 7.50 (dd, *J* = 11.3, 3.9 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.31 – 7.18 (m, 3H), 7.16 – 6.91 (m, 4H), 5.21 (d, *J* = 13.8 Hz, 1H), 5.07 (d, *J* = 13.9 Hz, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 171.0, 164.2, 158.7, 156.7, 137.1, 136.6, 135.7, 135.7, 134.2, 130.7, 129.2, 128.7, 128.4, 128.4, 128.4, 128.3, 128.2, 127.6, 125.3, 121.7, 121.5, 117.1, 116.9, 51.4, 43.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{16}ClFNO_2$ 380.0854, found 380.0838.

3-(2-benzyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)benzonitrile (6ah) 155 mg, 88% yield, white solid, Mp 123-124 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.62 – 7.49 (m, 3H), 7.44 – 7.32 (m, 5H), 7.27 – 7.20 (m, 3H), 7.07 (d, *J* = 7.6 Hz, 1H), 5.23 – 5.03

(m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 164.0, 140.2, 136.5, 136.5, 134.3, 133.1, 132.1, 131.6, 129.8, 129.3, 128.7, 128.6, 128.4, 128.1, 127.6, 125.4, 118.1, 113.1, 51.8, 43.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{17}N_2O_2$ 353.1295, found 353.1293.

4-(3-acetylphenyl)-2-benzylisoquinoline-1,3(2*H*,4*H*)-dione (6ai)

170 mg, 92% yield, white solid, Mp 98-99 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.74 (s, 1H), 7.58 – 7.45 (m, 2H), 7.42 – 7.34 (m, 3H), 7.28 – 7.20 (m, 4H), 7.08 (d, *J* = 7.6 Hz, 1H), 5.29 – 5.15 (m, 2H), 5.08 (d, *J* = 13.8 Hz, 1H), 2.52 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 171.2, 164.3, 139.5, 137.7, 137.5, 136.7, 134.1, 133.0, 129.3, 129.1, 128.8, 128.5, 128.4, 128.3, 128.2, 127.9, 127.5, 125.3, 52.3, 43.7, 26.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{20}NO_3$ 370.1443, found 370.1447.

2-benzyl-4-(3-methoxyphenyl)isoquinoline-1,3(2*H*,4*H*)-dione (6aj)

168 mg, 94% yield, white solid, Mp 86-87 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 7.2 Hz, 1H), 7.53 (td, *J* = 7.5, 1.4 Hz, 1H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.36 (d, *J* = 6.5 Hz, 2H), 7.22 (ddd, *J* = 11.3, 8.4, 3.1 Hz, 4H), 7.17 – 7.11 (m, 1H), 6.80 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.64 (dd, *J* = 12.6, 4.8 Hz, 2H), 5.23 (d, *J* = 13.9 Hz, 1H), 5.06 (t, *J* = 6.9 Hz, 2H), 3.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 164.6, 159.9, 140.2, 138.1, 136.9, 134.0, 130.0, 128. 9, 128.8, 128.3, 128.3, 128.0, 127.4, 125.2,

120.7, 114.2, 113.3, 55.2, 52.6, 43.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{20}NO_3$ 358.1443, found 358.1441.

2-benzyl-4-(2-fluorophenyl)isoquinoline-1,3(2*H*,4*H*)-dione (6ak)

140 mg, 81% yield, white solid, Mp 86-87 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.54 – 7.40 (m, 4H), 7.35 – 7.21 (m, 4H), 7.13 – 7.02 (m, 4H), 5.33 – 5.25 (m, 2H), 5.16 (d, *J* = 13.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 164.4, 161.4, 159.4, 137.6, 136.9, 133.9, 130.9 (d, *J* = 3.5 Hz), 130.0 (d, *J* = 8.3 Hz), 129.0 (d, *J* = 14.0 Hz), 128.4, 127.9, 127.5 (d, *J* = 8.8 Hz), 126.4 (d, *J* = 14.6 Hz), 124.9, 124.6 (d, *J* = 3.6 Hz), 116.3, 116.1, 46.8 (d, *J* = 1.9 Hz), 43.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{17}FNO_2$ 346.1243, found 280. 346.1246.

2-benzyl-4-(naphthalen-2-yl)isoquinoline-1,3(2*H*,4*H*)-dione (6al)

161 mg, 85% yield, white solid, Mp 106-107 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.83 – 7.67 (m, 3H), 7.59 – 7.43 (m, 5H), 7.37 (dd, *J* = 7.3, 2.0 Hz, 2H), 7.28 – 7.10 (m, 5H), 5.25 (t, *J* = 6.9 Hz, 2H), 5.07 (d, *J* = 13.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 164.6, 138.1, 136.9, 136.2, 134.0, 133.3, 132.7, 129.0, 129.0, 128.8, 128.4, 128.3, 128.0, 127.9, 127.9, 127.6, 127.4, 126.5, 126.4, 125.7, 125.3, 52.7, 43.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{20}NO_2$ 378.1494, found 378.1510.

4-(benzo[b]thiophen-5-yl)-2-benzylisoquinoline-1,3(2*H*,4*H*)-dione (6am) 174 mg, 91% yield, white solid, Mp 116-117 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.56 – 7.41 (m, 4H), 7.38 – 7.31 (m, 2H), 7.20 (dt, *J* = 4.6, 4.2 Hz, 4H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.07 (dd, *J* = 8.4, 1.7 Hz, 1H), 5.32 – 5.18 (m, 2H), 5.06 (d, *J* = 13.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 164.6, 140.0, 139.3, 138.4, 136.8, 135.2, 134.0, 128.9, 128.8, 128.4, 128.3, 128.0, 127.5, 127.4, 125.3, 124.4, 123.7, 123.6, 123.1, 52.5, 43.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{18}NO_2S$ 384.1058, found 384.1066.

2-benzyl-4-(1H-indol-5-yl)isoquinoline-1,3(2*H*,4*H*)-dione (6an) 165 mg, 90% yield, white solid, Mp 119-120 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 7.9, 1.2 Hz, 2H), 7.49 (td, *J* = 7.5, 1.4 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.37 – 7.31 (m, 3H), 7.24 – 7.11 (m, 6H), 6.88 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.50 – 6.39 (m, 1H), 5.25 (d, *J* = 14.0 Hz, 1H), 5.17 (s, 1H), 5.05 (d, *J* = 14.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 164.9, 139.3, 137.0, 135.2, 133.9, 130.5, 128.7, 128.5, 128.3, 128.1, 127.7, 127.3, 125.2, 125.1, 122.1, 120.8, 111.7, 102.7, 52.8, 43.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{19}N_2O_2$ 367.1438, found 367.1439.

4-(3,4-dichlorophenyl)-7-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dion (6df) 148 mg, 85% yield, white solid, Mp 129-130 ℃. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 2.8 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 1H), 7.21 (d, *J* = 2.1 Hz, 1H), 7.14 (dd, *J* = 8.5, 2.8 Hz, 1H), 7.03 – 6.92 (m, 2H), 4.99 (s, 1H), 3.91 (s, 3H), 3.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 164.5, 159.5, 139.1, 133.0, 132.3, 130.8, 130.6, 129.5, 129.0, 128.0, 126.3, 122.4, 111.1, 55.7, 50.7, 27.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{14}Cl_2NO_3$ 350.0351, found 350.0342.

(±) Dichlorofensine

75 mg, 83% yield, colorless oil, ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.2 Hz, 1H), 7.29 (d, *J* = 2.0 Hz, 1H), 7.03 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 6.70 – 6.65 (m, 1H), 6.62 (d, *J* = 2.5 Hz, 1H), 4.19 – 4.11 (m, 1H), 3.78 (s, 3H), 3.64 (s, 2H), 2.95 (dd, *J* = 11.5, 5.4 Hz, 1H), 2.55 (dd, *J* = 11.5, 7.6 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 145.5, 136.3, 132.1, 130.8, 130.3, 130.2, 128.4, 127.9, 112.9, 110.8, 61.3, 58.3, 55.2, 45.8, 44.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}Cl_2NO$ 322.0761, found 322.0765.

ASSOCIATED CONTENT

Supporting Information

Supporting Information ^{1} H and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

ACKNOWLEDGMENT

Financial support from the National Natural Science Foundation of China (81660348, 81703356, 21502030), GMU(J[2014]015, J[2014]017), Office of Science & Technology of Guiyang ([20151001]06), Office of Science & Technology of Guizhou ([2015]7343, QKHSY[2015]3030), Guizhou Provincial Engineering Laboratory for Chemical Drug R&D, Guizhou High-School Engineering Research Center for Medicinal Chemistry (KY2014-219) were greatly appreciated.

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