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# Novel total syntheses of oxoaporphine alkaloids enabled by mild Cu-catalyzed tandem oxidation/aromatization of 1-Bn-DHIQs†

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Novel total syntheses of oxoaporphine alkaloids such as lirioidenine, dicentrinone, cassameridine, lysicamine, oxoglaucone and *O*-methylmoschatoline were developed. The key step of these total syntheses is Cu-catalyzed conversion of 1-benzyl-3,4-dihydro-isoquinolines (1-Bn-DHIQs) to 1-benzoyl-isoquinolines (1-Bz-IQs) *via* tandem oxidation/aromatization. This novel Cu-catalyzed conversion has been studied in detail, and was successfully used for constructing the 1-Bz-IQ core.

## Introduction

Oxoaporphines, which have a characteristic carbonyl junction between aromatic B and D rings (see Fig. 1), are a sub-class of aporphinoid alkaloids.<sup>1</sup> Oxoaporphine alkaloids are widespread in the kingdom of plants.<sup>1,2</sup> For example, lirioidenine **1a**,<sup>3</sup> dicentrinone **1b**,<sup>4</sup> cassameridine **1c**,<sup>5</sup> lysicamine **1d**,<sup>6</sup> oxoglaucone **1e**<sup>7</sup> and *O*-methylmoschatoline **1f**<sup>8</sup> (also referred to as liriidine<sup>9</sup> and homomoschatoline<sup>10</sup>) have been isolated from various botanic natural resources.<sup>3–10</sup> Since oxoaporphine alkaloids **1a–f** have shown a broad spectrum of interesting biological activities,<sup>11</sup> so the total syntheses of them have aroused much interest from chemists.<sup>12</sup> However, efficient, benign and practical total syntheses of these alkaloids remained highly desirable. Therefore, we herein report novel total syntheses of oxoaporphine alkaloids **1a–f** *via* a key Cu-catalyzed conversion of 1-benzyl-3,4-dihydro-isoquinolines (1-Bn-DHIQs) to 1-benzoyl-isoquinolines (1-Bz-IQs).

A general retrosynthetic analysis of the above several oxoaporphine alkaloids **1a–f** is depicted in Scheme 1. As can be seen from the Scheme 1, C-ring could be constructed *via* Pischorr cyclization of anilines **A**, which could be obtained from the reduction of nitro groups of compounds **B**. The 1-Bz-IQ core of compounds **B** could be constructed *via* Cu-catalyzed tandem oxidation/aromatization of 1-Bn-DHIQs **C**. B-ring of compounds **C** could be constructed *via* Bischler–Napieralski cyclization of amides **D**, which could be derived from amines **E** and acyl chlorides **F**. Amines **E** could be prepared from aryl aldehydes **G**.

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## Results and discussion

According to the above general retrosynthetic analysis, novel total syntheses of the six targeted oxoaporphine alkaloids **1a–f** are depicted in Scheme 2. As can be seen from the Scheme 2, EDA (ethylenediamine)-catalyzed condensation of aryl aldehydes with nitromethane<sup>13</sup> first produced nitroalkenes **2a–c** in high yields. Next, when compounds **2a–c** were treated with 6.0 equiv. of LiAlH<sub>4</sub> in tetrahydrofuran at reflux, simultaneous reduction of both nitro group and double bond occurred in one-pot to furnish 2-aryl ethanamines **3a–c**, which then immediately exposed to 1.1 equiv. of 2-arylacetyl chlorides and 3.0 equiv. of K<sub>2</sub>CO<sub>3</sub> at 0 °C in a mixed solvent of dichloromethane and water (3 : 1) to afford amides **4a–f**. Subsequently, treatment of compounds **4a–f** with 3.0 equiv. of POCl<sub>3</sub> in anhydrous acetonitrile at reflux gave 1-Bn-DHIQs **5a–f** *via* Bischler–Napieralski cyclization.<sup>14</sup> It was observed that compounds **5a–f** and compounds **5'a–f** were interchangeable

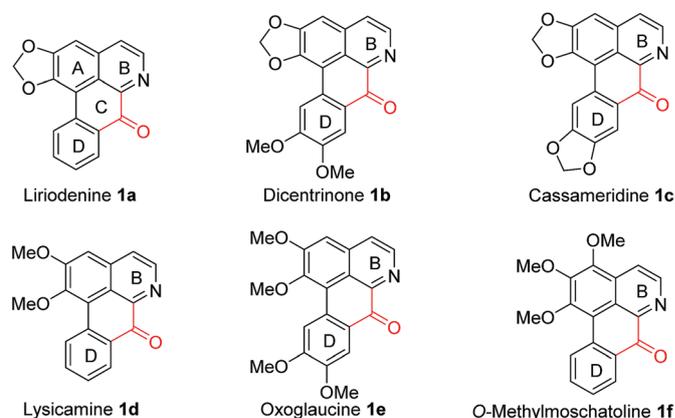


Fig. 1 The targeted oxoaporphine alkaloids **1a–f**.





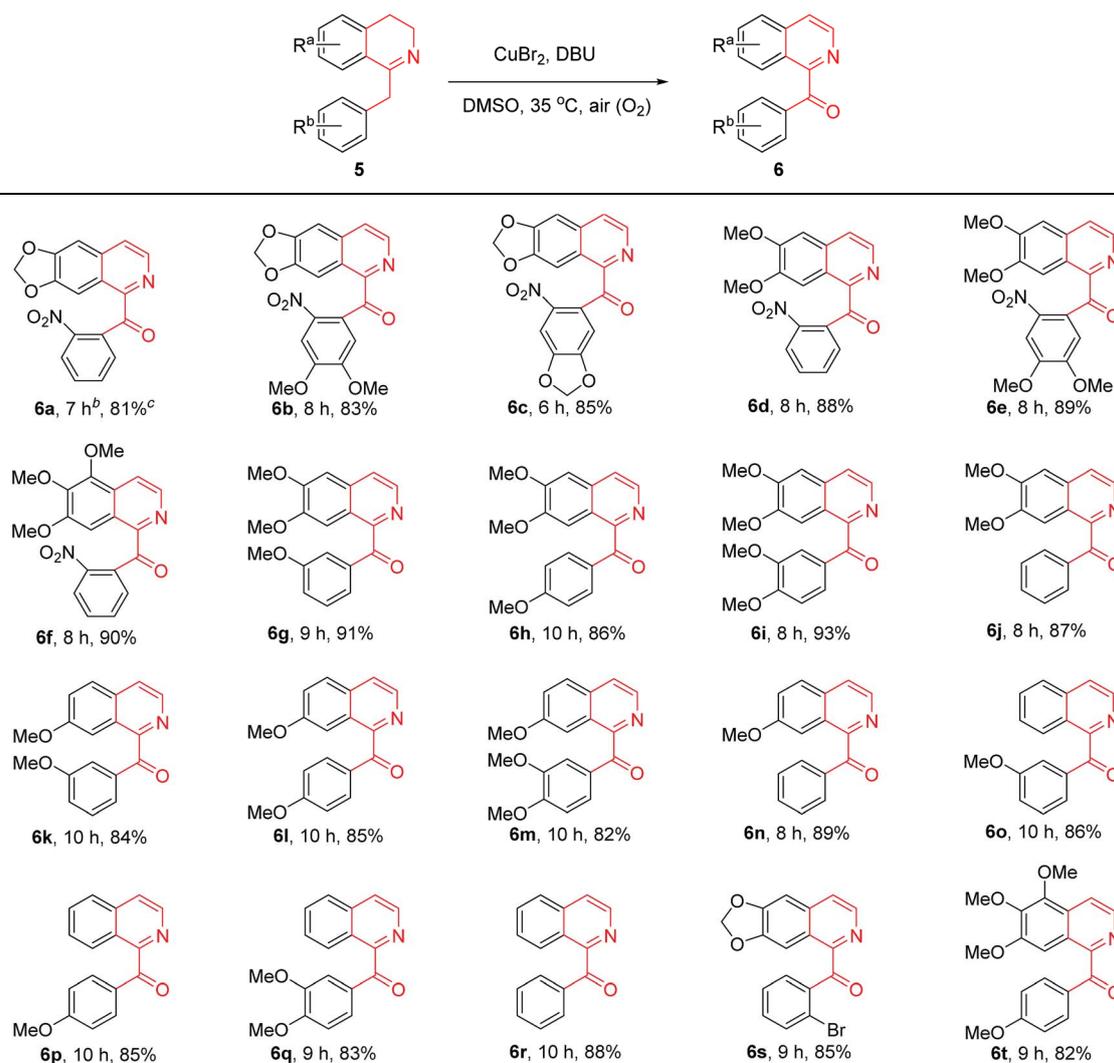
In the above-described total syntheses of oxoaporphine alkaloids **1a–f**, the key step is Cu-catalyzed conversion of 1-Bn-THIQs **5a–f** to 1-Bz-IQs **6a–f**. This key conversion can be achieved by some known methods.<sup>17–21</sup> However, these known methods often suffered from drawbacks such as use of poisonous and hazardous strong oxidants including SeO<sub>2</sub>,<sup>17</sup> Pb(OAc)<sub>4</sub>,<sup>18</sup> and CAN,<sup>19</sup> inconvenient use of the photoactivated singlet O<sub>2</sub>,<sup>20</sup> or need of high reaction temperature<sup>21</sup> (120 °C). Therefore, development of an efficient and benign method for this particular conversion might be very helpful for total syntheses of oxoaporphine alkaloids.

Copper is a cheap transition metal with low toxicity; and air (O<sub>2</sub>) is an eco-friendly clean oxidant. Hence, an increasing amount of copper-catalyzed aerobic oxidations of various compounds have been recently developed.<sup>22</sup> For the above conversion of 1-Bn-THIQs **5a–f** to 1-Bz-IQs **6a–f**, CuBr<sub>2</sub> was used

as the catalyst, and air (O<sub>2</sub>) was used as the clean oxidant. So this Cu-catalyzed method might be much more benign, eco-friendly and practical than the previous known methods.<sup>17–21</sup> Advantages such as mildness (at 35 °C), high efficiency and eco-friendliness prompted us to investigate the details of this potential green chemical method.

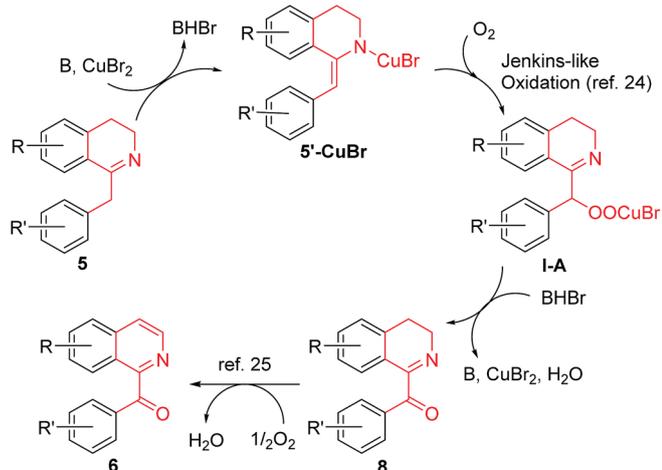
In order to know the scope and limitation of the method, more variously substituted 1-Bn-DHIQs **5** were prepared *via* Bischler–Napieralski cyclization, and a total of twenty substrates **5a–t** have been tested for the CuBr<sub>2</sub>-catalyzed aerobic oxidation under the standard reaction conditions (see footnote of Table 1); the results are summarized in Table 1 (20 examples). As can be seen from the Table 1, the scope of the reaction is wide, it could be applicable to all the tested substrates, and afforded the desired 1-Bz-IQs **6a–t** in good to high yields. We have found that 1-benzyl-3,4-dihydro-β-carbolines could

Table 1 CuBr<sub>2</sub>-catalyzed conversion of variously substituted 1-Bn-DHIQs **5** to 1-Bz-IQs **6**<sup>a</sup>



<sup>a</sup> Standard reaction conditions: 1-Bn-DHIQs **5** (2 mmol), CuBr<sub>2</sub> (0.2 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2 mmol), DMSO (6 mL), 35 °C (inner temperature), air (O<sub>2</sub>). <sup>b</sup> Reaction time. <sup>c</sup> Isolated yields.





Scheme 3 A possible mechanism for the  $\text{CuBr}_2$ -catalyzed conversion of 1-Bn-DHIQs **5** to 1-Bz-IQs **6**.

undergo aerobic oxidation in DMSO to afford 1-benzoyl- $\beta$ -carbolines without a copper catalyst,<sup>23</sup> but herein we found that a copper catalyst is necessary for this one-pot aerobic oxidation, it was sluggish in the absence of copper catalyst. Several copper salts have been tested as the catalyst,  $\text{CuBr}_2$  obviously worked better than  $\text{CuCl}_2$ ,  $\text{Cu}(\text{OAc})_2$ ,  $\text{CuSO}_4$ ,  $\text{Cu}_2(\text{OH})_2\text{CO}_3$ ,  $\text{CuO}$  and  $\text{CuI}$ . Moreover, a base is also necessary for the reaction, DBU worked obviously better than  $\text{Et}_3\text{N}$ , diisopropylethylamine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,5-diazabicyclo [4,3,0]non-5-ene (DBN),  $\text{Na}_2\text{CO}_3$  and  $\text{K}_2\text{CO}_3$ ; DMSO as the solvent is better than DMF,  $\text{CH}_3\text{CN}$ , THF, EtOH,  $\text{Me}_2\text{CO}$ ,  $\text{CH}_2\text{Cl}_2$  and 1,4-dioxane.

A possible mechanism for the  $\text{CuBr}_2$ -catalyzed conversion of 1-Bn-DHIQs **5** to 1-Bz-IQs **6** was proposed in Scheme 3. 1-Bn-DHIQs **5** would first react with  $\text{CuBr}_2$  and a base ( $\text{B} = \text{DBU}$ , etc.) to form enamine-CuBr complexes **5'-CuBr**, which would then undergo Jenkin's-like aerobic oxidation<sup>24</sup> to produce peroxide-CuBr complexes **I-A**. The intermediate Cu-complexes **I-A** would be unstable enough to decompose immediately to furnish 1-Bz-DHIQs **8**. Compounds **8** would finally undergo DBU-promoted oxidation by  $\text{O}_2$  to produce 1-Bz-IQs **6** according to Kumar's reports.<sup>25</sup> The intermediate compounds **8** could be detected by TLC during the reaction, and could also be isolated if the reaction was stopped at a middle point. For example, when  $\text{CuBr}_2$ -catalyzed conversion of compound **5a** to compound **6a** was stopped at 3 h, the intermediate compound **8a** was isolated in 38% yield.

## Conclusions

In conclusion, novel total syntheses of oxoaporphine alkaloids including liriodenine **1a**, dicentrinone **1b**, cassameridine **1c**, lysicamine **1d**, oxoglauanine **1e** and *O*-methyl-moschatoline **1e** were achieved *via* a benign and ecofriendly Cu-catalyzed general approach. They were synthesized from the cheap and commercially available aryl aldehydes *via* seven steps in 39%, 26%, 29%, 38%, 31% and 41% overall yields, respectively.

In addition, a novel practical Cu-catalyzed conversion of 1-Bn-DHIQs **5** to 1-Bz-IQs **6**, which was used as the key step in the above total syntheses, has also been investigated in detail; this Cu-catalyzed method has some advantages such as mildness, eco-friendliness, wide scope, ease of experimental procedure and high yields. It would provide a new general basic approach towards the total syntheses of oxoaporphine alkaloids and their derivatives.

## Experimental

### General

$^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were acquired on a Bruker AM 400 instrument, chemical shifts are given on the  $\delta$  scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded on a Nicolet Magna IR-550 instrument. Mass spectra were performed with a HP1100 LC-MS spectrometer. Melting points were measured on a Meitemp II melting point apparatus. Column chromatography was performed on silica gel (Qingdao Chemical Factory). All reagents and solvents were analytically pure, and were used as such as received from the chemical suppliers.

### Preparation of nitroalkenes **2a-c**

An aryl aldehyde ( $\sim 40$  mmol) was dissolved in nitromethane (30 mL), and then ethylenediamine (0.025 g, 0.416 mmol) was added. The resulting solution was then heated and stirred at reflux for 5 h. After the reaction was complete (checked by TLC, eluent:  $\text{CH}_2\text{Cl}_2/\text{hexane} = 3 : 2$ ), the solution was concentrated under vacuum to give crude product as yellow solid, which was triturated in aqueous methanol ( $\text{MeOH}/\text{H}_2\text{O} = 9 : 1$ ), and was then filtered by suction. Compounds **2a-c** were thus obtained in 89%, 90% and 91% yields, respectively. Characterization data of compounds **2a-c** are as follows:

**(E)-5-(2-Nitrovinyl)benzo[*d*][1,3]dioxole (2a)**. Yellow crystals, mp 158–159 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.93 (d,  $J = 13.5$  Hz, 1H), 7.48 (d,  $J = 13.5$  Hz, 1H), 7.09 (d,  $J = 7.8$  Hz, 1H), 7.00 (s, 1H), 6.88 (d,  $J = 7.8$  Hz, 1H), 6.07 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  151.39, 148.77, 139.13, 135.37, 126.69, 124.18, 109.08, 106.98, 102.10.

**(E)-1,2-Dimethoxy-4-(2-nitrovinyl)benzene (2b)**. Pale yellow crystals, mp 141–142 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.97 (d,  $J = 13.6$  Hz, 1H), 7.56 (d,  $J = 13.6$  Hz, 1H), 7.19 (d,  $J = 8.2$  Hz, 1H), 7.02 (s, 1H), 6.92 (d,  $J = 8.2$  Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  152.78, 149.51, 139.39, 135.13, 124.71, 122.78, 111.30, 110.18, 56.10, 56.02.

**(E)-1,2,3-Trimethoxy-4-(2-nitrovinyl)benzene (2c)**. Pale yellow crystals, mp 192–193 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.09 (d,  $J = 13.6$  Hz, 1H), 7.77 (d,  $J = 13.6$  Hz, 1H), 7.21 (d,  $J = 8.8$  Hz, 1H), 6.73 (d,  $J = 8.8$  Hz, 1H), 4.00 (s, 3H), 3.93 (s, 3H), 3.88 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  157.36, 154.27, 142.39, 136.52, 135.37, 126.65, 117.02, 107.68, 61.19, 60.94, 56.20.

### Preparation of 2-aryl ethanamines **3a-c**

A solution of compound **2** ( $\sim 18$  mmol) in THF (40 mL) was dropwise added into a stirred suspension of  $\text{LiAlH}_4$  (4.102 g,



108.1 mmol) in THF (100 mL) at 0 °C over 20 min. After the addition was finished, the mixture was then heated and stirred at reflux for 7–9 h. The mixture was cooled to 0 °C by an ice-bath. While the mixture was vigorously stirred, water (5 mL) was dropwise added into the reaction mixture over 30 min, and an aqueous solution of NaOH (28 mL, 15% w/w) was then slowly added into the mixture at 0 °C. The ice-bath was removed, and the mixture was further stirred at room temperature for 3 h. The mixture was filtered through a thin layer of celite, and the filter cake was washed twice with THF (2 × 30 mL). The filtrates were combined and dried over anhydrous MgSO<sub>4</sub>. The solution was concentrated under vacuum to give crude product as yellow oil, which was purified by formation of hydrochloride ammonium salt. Pure 2-aryl ethanamines **3a–c** were obtained after neutralization in 87%, 76% and 82% yields, respectively. Characterization data of compounds **3a–c** are as follows:

**2-(Benzo[d][1,3]dioxol-5-yl)ethanamine (3a).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.74 (d, *J* = 7.8 Hz, 1H), 6.69 (s, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 5.92 (s, 2H), 2.91 (t, *J* = 6.9 Hz, 2H), 2.67 (t, *J* = 6.9 Hz, 2H), 1.56 (br. s, 3H, NH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 147.57, 145.80, 133.46, 121.55, 109.02, 108.09, 100.71, 43.49, 39.49.

**2-(3,4-Dimethoxyphenyl)ethanamine (3b).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.79 (d, *J* = 7.9 Hz, 1H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.73 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.93 (t, *J* = 6.9 Hz, 2H), 2.68 (t, *J* = 6.9 Hz, 2H), 1.43 (br. s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 148.81, 147.34, 132.35, 120.65, 111.96, 111.22, 55.83, 55.73, 43.58, 39.51.

**2-(2,3,4-Trimethoxyphenyl)ethanamine (3c).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.84 (d, *J* = 8.5 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 2.91 (t, *J* = 7.0 Hz, 2H), 2.71 (t, *J* = 7.0 Hz, 2H), 2.32 (br. s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 152.31, 152.08, 142.29, 125.46, 124.35, 107.16, 60.92, 60.69, 55.97, 42.81, 33.84.

### Preparation of amides 4a–f

2-Aryl acetic acid (~11 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL), and SOCl<sub>2</sub> (1.790 g, 15.05 mmol) was added. The resulting solution was then heated and stirred at reflux for 4 h. The reaction solution was concentrated under vacuum to dryness, oily residue was then dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL), the solution was immediately used below. 2-Aryl ethanamine **3** (10 mmol) was dissolved in 40 mL CH<sub>2</sub>Cl<sub>2</sub>, and an aqueous solution of K<sub>2</sub>CO<sub>3</sub> (4.150 g, 30.03 mmol) in water (30 mL) was added. The biphasic mixture was cooled by an ice-bath, and was stirred at 0 to 5 °C. The above freshly prepared solution of 2-aryl acetyl chloride was added dropwise into the reaction mixture over 2 min. After the addition was finished, stirring was continued at 0 to 5 °C for 2 h. When the reaction was complete (checked by TLC, eluent: EtOAc/hexane = 1 : 3), the reaction mixture was transferred into a separatory funnel. Two phases were separated, and the aqueous phase was extracted again with CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The organic extracts were combined, dried over anhydrous MgSO<sub>4</sub>, and then concentrated under vacuum to give crude product as pale yellow solid, which was purified by flash chromatography (eluent: EtOAc/hexane = 1 : 4). Amides **4a–f**

were thus obtained in 85%, 62%, 63%, 83%, 71% and 84% yields, respectively. Characterization data of compounds **4a–f** are as follows:

**N-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)-2-(2-nitrophenyl)acetamide (4a).** White crystals, mp 125–126 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.03 (d, *J* = 8.2 Hz, 1H), 7.60 (dd, *J*<sub>1</sub> = 8.0 Hz, *J*<sub>2</sub> = 7.8 Hz, 1H), 7.48–7.42 (m, 2H), 6.69 (d, *J* = 7.9 Hz, 1H), 6.60 (s, 1H), 6.55 (d, *J* = 7.9 Hz, 1H), 5.92 (s, 2H), 5.84 (br. s, 1H, CONH), 3.79 (s, 2H), 3.49–3.42 (m, 2H), 2.69 (t, *J* = 6.8 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 168.93, 148.80, 147.72, 146.11, 133.57, 133.33, 132.44, 130.41, 128.37, 125.12, 121.61, 109.03, 108.30, 100.87, 41.06, 40.89, 35.24; IR (KBr film) 3280, 3070, 2921, 1640, 1552, 1521, 1492, 1350, 1247, 1192, 1034, 923, 809, 790, 715 cm<sup>-1</sup>.

**N-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)-2-(4,5-dimethoxy-2-nitrophenyl)acetamide (4b).** White crystals, mp 206–207 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.97 (t, *J* = 5.8 Hz, 1H, CONH), 7.64 (s, 1H), 7.05 (s, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.79 (s, 1H), 6.65 (d, *J* = 7.9 Hz, 1H), 5.96 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.82 (s, 2H), 3.25–3.17 (m, 2H), 2.61 (t, *J* = 7.2 Hz, 2H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 168.62, 152.57, 147.16, 147.10, 145.42, 140.92, 133.25, 126.01, 121.43, 115.36, 108.98, 108.02, 107.94, 100.58, 56.10, 55.90, 40.78, 40.00, 34.84; IR (KBr film) 3270, 3092, 2933, 1641, 1580, 1525, 1502, 1420, 1330, 1274, 1239, 1186, 1063, 1034, 923, 875, 804, 748 cm<sup>-1</sup>.

**N-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)-2-(6-nitrobenzo[d][1,3]dioxol-5-yl)acetamide (4c).** White crystals, mp 208–209 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.02 (t, *J* = 5.7 Hz, 1H, CONH), 7.63 (s, 1H), 7.01 (s, 1H), 6.82 (d, *J* = 7.9 Hz, 1H), 6.79 (s, 1H), 6.65 (d, *J* = 7.9 Hz, 1H), 6.22 (s, 2H), 5.96 (s, 2H), 3.76 (s, 2H), 3.26–3.18 (m, 2H), 2.61 (t, *J* = 7.2 Hz, 2H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 168.40, 151.26, 147.11, 146.53, 145.43, 142.63, 133.20, 128.10, 121.45, 111.87, 108.99, 108.03, 105.08, 103.20, 100.58, 40.61, 39.95, 34.82; IR (KBr film) 3280, 3064, 2920, 1637, 1548, 1524, 1504, 1480, 1442, 1378, 1328, 1249, 1192, 1032, 924, 877, 816, 722 cm<sup>-1</sup>.

**N-(3,4-Dimethoxyphenethyl)-2-(2-nitrophenyl)acetamide (4d).** White crystals, mp 129–130 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.01 (d, *J* = 8.2 Hz, 1H), 7.58 (dd, *J*<sub>1</sub> = 8.0 Hz, *J*<sub>2</sub> = 8.2 Hz, 1H), 7.46–7.40 (m, 2H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.69 (s, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.78 (s, 2H), 3.52–3.45 (m, 2H), 2.73 (t, *J* = 7.0 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 168.88, 148.98, 148.76, 147.62, 133.58, 133.37, 131.20, 130.38, 128.39, 125.12, 120.60, 111.90, 111.32, 55.92, 55.84, 40.94, 40.85, 35.10; IR (KBr film) 3424, 3065, 2944, 2839, 1651, 1602, 1479, 1280, 1256, 1163, 1125, 1028, 935, 823, 718 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>18</sub>H<sub>21</sub>N<sub>2</sub>O<sub>5</sub> [M + H]<sup>+</sup>: 345.1450, found: 345.1451.

**N-(3,4-Dimethoxyphenethyl)-2-(4,5-dimethoxy-2-nitrophenyl)acetamide (4e).** White crystals, mp 131–132 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.60 (s, 1H), 6.83 (s, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.67 (s, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 5.96 (br. s, 1H, CONH), 3.96 (s, 3H), 3.94 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.77 (s, 2H), 3.53–3.44 (m, 2H), 2.73 (t, *J* = 6.8 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 168.90, 153.35, 148.96, 148.07, 147.59, 140.80, 131.14, 125.48, 120.56, 114.44, 111.88, 111.23, 108.15, 56.57, 56.35, 55.87, 55.82, 41.39, 40.90, 35.09; IR (KBr film) 3467, 3072, 2945, 2832, 1653,



1600, 1475, 1282, 1251, 1168, 1125, 1018, 925, 827, 724  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_7$   $[\text{M} + \text{H}]^+$ : 405.1662, found: 405.1665.

**N-(2,3,4-Trimethoxyphenethyl)-2-(2-nitrophenyl)acetamide (4f)**. White crystals, mp 106–107 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.02 (d,  $J = 7.8$  Hz, 1H), 7.57 (d,  $J = 7.2$  Hz, 1H), 7.48–7.41 (m, 2H), 6.78 (d,  $J = 8.2$  Hz, 1H), 6.58 (d,  $J = 8.2$  Hz, 1H), 6.21 (br. s, 1H, CONH), 3.85 (s, 3H), 3.845 (s, 3H), 3.843 (s, 3H), 3.80 (s, 2H), 3.47–3.41 (m, 2H), 2.73 (t,  $J = 6.8$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  168.94, 152.58, 151.80, 148.89, 142.19, 133.49, 133.42, 130.53, 128.28, 125.06, 124.74, 124.51, 107.43, 60.98, 60.74, 56.00, 40.95, 40.94, 29.63; IR (KBr, film) 3420, 3293, 2958, 2939, 1644, 1548, 1524, 1495, 1467, 1417, 1349, 1240, 1101, 933, 792, 716  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_6$   $[\text{M} + \text{H}]^+$ : 375.1556, found: 375.1537.

### Preparation of 1-benzyl-3,4-dihydroisoquinolines 5

A corresponding amide **4** (~5 mmol) was dissolved in anhydrous acetonitrile (40 mL), and phosphorus oxychloride (2.350 g, 15.33 mmol) was slowly added into the mixture. The resulting solution was then heated and stirred at reflux for 2 h. After the reaction was complete (checked by TLC, eluent:  $\text{CH}_2\text{Cl}_2$ /hexane = 2 : 1), the solution was concentrated under vacuum to dryness, the residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (50 mL). An aqueous solution of  $\text{K}_2\text{CO}_3$  (20 mL, 15% w/w) was added. After the mixture was vigorously stirred for 5 min, two phases were separated, and the aqueous phase was extracted again with  $\text{CH}_2\text{Cl}_2$  (20 mL). The organic extracts were combined, dried over anhydrous  $\text{MgSO}_4$ , and then concentrated under vacuum to give crude solid product as a tautomeric mixture of 1-benzyl-3,4-dihydroisoquinoline **5** and enamine **5'**, which was used as such for the next step.

### General procedure for the $\text{CuBr}_2$ -catalyzed conversion of 1-benzyl-3,4-dihydroisoquinolines **5** to 1-benzoyl-isoquinolines **6**

The above tautomeric mixture of 1-benzyl-3,4-dihydroisoquinoline **5** and enamine **5'** were dissolved in DMSO (10 mL), DBU (0.755 g, 4.959 mmol) and  $\text{CuBr}_2$  (0.113 g, 0.506 mmol) were added. The resulting solution was then stirred at 35 °C for 6–10 h (see Table 1) under an atmosphere of air. After the reaction was complete (checked by TLC, eluent: EtOAc/hexane = 1 : 4), a dilute ammonia aqueous solution (5% w/w, 50 mL) and  $\text{CH}_2\text{Cl}_2$  (40 mL) were added into the mixture. Two phases were separated, and the aqueous phase was twice extracted again with  $\text{CH}_2\text{Cl}_2$  (2  $\times$  30 mL). The organic extracts were combined, and dried over anhydrous  $\text{MgSO}_4$ . Removal of solvent by vacuum distillation gave crude product as pale yellow solid, which was purified by flash chromatography (eluent: EtOAc/ $\text{CH}_2\text{Cl}_2$  = 1 : 10) to afford pure 1-benzoyl-isoquinoline **6** as crystals in a yield (over two steps) as indicated in Table 1. Characterization data of 1-benzoyl-isoquinolines **6a–t** are as follows:

**[(1,3)Dioxolo[4,5-g]isoquinolin-5-yl)(2-nitrophenyl)methanone (6a)**. Pale yellow crystals, mp 244–245 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ -TFA)  $\delta$  8.42 (s, 1H), 8.30 (d,  $J = 8.2$  Hz, 1H), 8.19 (d,  $J = 6.4$  Hz, 1H), 8.09 (d,  $J = 6.4$  Hz, 1H), 7.98 (dd,  $J_1 = 7.5$  Hz,  $J_2 =$

7.8 Hz, 1H), 7.92–7.84 (m, 2H), 7.40 (s, 1H), 6.40 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ -TFA)  $\delta$  186.14, 156.93, 154.17, 146.24, 142.08, 141.68, 135.87, 134.04, 131.80, 131.08, 130.20, 126.47, 125.39, 124.52, 104.36, 103.78, 103.16; IR (KBr, film) 3077, 2917, 1684, 1576, 1518, 1460, 1348, 1275, 1214, 1036, 1017, 946, 867, 788, 706  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{11}\text{N}_2\text{O}_5$   $[\text{M} + \text{H}]^+$ : 323.0668, found: 323.0665.

**(4,5-Dimethoxy-2-nitro-phenyl)[(1,3)dioxolo[4,5-g]isoquinolin-5-yl)methanone (6b)**. Pale yellow crystals, mp 258–259 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ -TFA)  $\delta$  8.37 (s, 1H), 8.16 (d,  $J = 6.3$  Hz, 1H), 8.06 (d,  $J = 6.3$  Hz, 1H), 7.70 (s, 1H), 7.38 (s, 1H), 7.27 (s, 1H), 6.40 (s, 2H), 4.07 (s, 3H), 4.05 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ -TFA)  $\delta$  187.14, 155.78, 154.82, 153.24, 152.19, 144.56, 140.54, 139.96, 131.12, 126.75, 125.71, 124.55, 112.93, 107.34, 103.84, 103.81, 103.35, 56.88, 56.73; IR (KBr, film) 3096, 2916, 1682, 1579, 1520, 1500, 1463, 1397, 1326, 1282, 1261, 1228, 1210, 1077, 1034, 942, 863, 778, 758  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{15}\text{N}_2\text{O}_7$   $[\text{M} + \text{H}]^+$ : 383.0879, found: 383.0881.

**[(1,3)Dioxolo[4,5-g]isoquinolin-5-yl)(6-nitrobenzo[d][1,3]dioxol-5-yl)methanone (6c)**. Pale yellow crystals, mp 229–230 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ -TFA)  $\delta$  8.38 (s, 1H), 8.21 (d,  $J = 6.3$  Hz, 1H), 8.07 (d,  $J = 6.3$  Hz, 1H), 7.64 (s, 1H), 7.38 (s, 1H), 7.16 (s, 1H), 6.39 (s, 2H), 6.30 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ -TFA)  $\delta$  185.29, 156.70, 154.12, 153.93, 151.96, 142.54, 141.76, 141.62, 130.04, 128.24, 126.18, 124.54, 109.97, 105.43, 104.87, 104.22, 103.62, 103.61; IR (KBr, film) 3065, 2917, 1677, 1609, 1577, 1519, 1500, 1464, 1424, 1398, 1326, 1273, 1237, 1203, 1031, 988, 920, 871, 764  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{11}\text{N}_2\text{O}_7$   $[\text{M} + \text{H}]^+$ : 367.0566, found: 367.0565.

**(6,7-Dimethoxyisoquinolin-1-yl)(2-nitrophenyl)methanone (6d)**. Pale yellow crystals, mp 195–196 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.75 (s, 1H), 8.24 (d,  $J = 5.6$  Hz, 1H), 8.15 (d,  $J = 5.6$  Hz, 1H), 7.80 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 7.7$  Hz, 1H), 7.73–7.58 (m, 3H), 7.10 (s, 1H), 4.14 (s, 3H), 4.05 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  195.63, 153.08, 152.47, 148.35, 147.59, 140.15, 137.94, 134.54, 134.02, 130.29, 129.66, 123.67, 123.66, 123.55, 104.74, 104.53, 56.26, 56.07; IR (KBr film) 2945, 2835, 1650, 1600, 1477, 1329, 1282, 1255, 1168, 1125, 1020, 915, 809  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{15}\text{N}_2\text{O}_5$   $[\text{M} + \text{H}]^+$ : 339.0981, found: 339.0985.

**(6,7-Dimethoxyisoquinolin-1-yl)(4,5-dimethoxy-2-nitrophenyl)methanone (6e)**. Pale yellow crystals, mp 212–213 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.65 (s, 1H), 8.24 (d,  $J = 5.4$  Hz, 1H), 7.65 (s, 1H), 7.61 (d,  $J = 5.4$  Hz, 1H), 7.12 (s, 1H), 7.09 (s, 1H), 4.13 (s, 3H), 4.04 (s, 3H), 4.02 (s, 3H), 4.01 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  195.33, 153.69, 153.06, 152.30, 149.68, 149.06, 140.57, 140.01, 134.44, 132.05, 123.54, 111.05, 106.46, 104.72, 104.71, 104.61, 56.64, 56.57, 56.22, 56.07; IR (KBr film) 2981, 2845, 1652, 1603, 1473, 1328, 1282, 1255, 1166, 1123, 1021, 934, 865, 812  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_7$   $[\text{M} + \text{H}]^+$ : 399.1192, found: 399.1190.

**(2-Nitrophenyl)(5,6,7-trimethoxyisoquinolin-1-yl)methanone (6f)**. Pale yellow crystals, mp 113–114 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.56 (s, 1H), 8.26 (d,  $J = 5.2$  Hz, 1H), 8.15 (d,  $J = 8.0$  Hz, 1H), 8.00 (d,  $J = 5.2$  Hz, 1H), 7.80 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 7.7$  Hz, 1H), 7.70 (d,  $J = 7.5$  Hz, 1H), 7.65 (dd,  $J_1 = 7.7$  Hz,  $J_2 = 7.5$  Hz, 1H), 4.12 (s, 3H), 4.05 (s, 3H), 4.04 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  195.45, 156.02, 148.63, 147.48, 146.51, 144.13, 139.55,



137.92, 134.07, 130.33, 129.84, 129.69, 124.45, 123.58, 119.13, 100.86, 61.70, 61.23, 56.26; IR (KBr, film) 2938, 1687, 1612, 1577, 1528, 1476, 1353, 1274, 1243, 1124, 1048, 941, 855, 758, 637  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_6$  [ $\text{M} + \text{H}$ ] $^+$ : 369.1087, found: 369.1085.

**(6,7-Dimethoxyisoquinolin-1-yl)(3-methoxyphenyl)methanone (6g).** White crystals, mp 168–169 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.47 (d,  $J = 5.5$  Hz, 1H), 7.66 (d,  $J = 5.5$  Hz, 1H), 7.60 (s, 1H), 7.56 (s, 1H), 7.44 (d,  $J = 7.6$  Hz, 1H), 7.37 (dd,  $J = 7.9$  Hz,  $J = 7.6$  Hz, 1H), 7.17 (d,  $J = 7.9$  Hz, 1H), 7.14 (s, 1H), 4.05 (s, 3H), 3.96 (s, 3H), 3.85 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  195.18, 159.62, 153.22, 153.02, 151.21, 140.05, 138.40, 134.05, 129.37, 123.99, 122.95, 121.64, 120.13, 114.55, 104.88, 103.95, 56.14, 56.08, 55.47. IR (KBr film) 2937, 2834, 1660, 1591, 1485, 1439, 1310, 1270, 1259, 1148, 1036, 746, 634  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{18}\text{NO}_4$  [ $\text{M} + \text{H}$ ] $^+$ : 324.1236, found: 324.1219.

**(6,7-Dimethoxyisoquinolin-1-yl)(4-methoxyphenyl)methanone (6h).** White crystals, mp 157–158 °C (lit. 21 150–152 °C).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.46 (d,  $J = 5.5$  Hz, 1H), 7.96 (d,  $J = 8.9$  Hz, 2H), 7.65 (d,  $J = 5.5$  Hz), 7.57 (s, 1H), 7.15 (s, 1H), 6.96 (d,  $J = 8.9$  Hz, 2H), 4.06 (s, 3H), 3.96 (s, 3H), 3.88 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  193.92, 163.95, 153.69, 153.15, 151.00, 140.02, 133.98, 133.28 (2C), 129.81, 122.80, 121.29, 113.71 (2C), 104.86, 104.06, 56.12, 56.07, 55.55; IR (KBr film) 2961, 2940, 2836, 1650, 1607, 1511, 1442, 1321, 1264, 1156, 1054, 916, 862, 836, 613  $\text{cm}^{-1}$ .

**(6,7-Dimethoxyisoquinolin-1-yl)(3,4-dimethoxyphenyl)methanone (6i).** White crystals, mp 209–210 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.47 (d,  $J = 5.5$  Hz, 1H), 7.72 (s, 1H), 7.69 (d,  $J = 5.5$  Hz, 1H), 7.55 (s, 1H), 7.42 (d,  $J = 8.4$  Hz, 1H), 7.15 (s, 1H), 6.87 (d,  $J = 8.4$  Hz, 1H), 4.06 (s, 3H), 3.97 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  193.94, 153.79, 153.68, 153.15, 150.98, 149.00, 140.01, 133.93, 129.89, 126.91, 122.80, 121.26, 111.88, 109.94, 104.85, 104.01, 56.11, 56.09, 56.04, 55.99; IR (KBr film) 2970, 2934, 1657, 1505, 1460, 1270, 1227, 1140, 1025, 860, 749  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{20}\text{NO}_5$  [ $\text{M} + \text{H}$ ] $^+$ : 354.1341, found: 354.1343.

**(6,7-Dimethoxyisoquinolin-1-yl)(phenyl)methanone (6j).** White crystals, mp 130–131 °C (lit. 21 131–132 °C).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.47 (d,  $J = 5.5$  Hz, 1H), 7.96 (d,  $J = 8.0$  Hz, 2H), 7.67 (d,  $J = 5.5$  Hz, 1H), 7.65 (s, 1H), 7.63 (t,  $J = 7.8$  Hz, 1H), 7.50 (dd,  $J_1 = 7.8$  Hz,  $J_2 = 8.0$  Hz, 2H), 7.15 (s, 1H), 4.06 (s, 3H), 3.97 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  195.39, 153.20, 152.96, 151.22, 140.07, 137.11, 134.07, 133.42, 130.87 (2C), 128.38 (2C), 123.03, 121.66, 104.88, 103.99, 56.13, 56.08; IR (KBr film) 2971, 2841, 1657, 1510, 1456, 1260, 1232, 1154, 1052, 864, 709, 649  $\text{cm}^{-1}$ .

**(7-Methoxyisoquinolin-1-yl)(3-methoxyphenyl)methanone (6k).** White crystals, mp 106–107 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.50 (d,  $J = 5.5$  Hz, 1H), 7.82 (d,  $J = 8.5$  Hz, 1H), 7.75 (d,  $J = 5.5$  Hz, 1H), 7.58 (s, 1H), 7.57 (s, 1H), 7.45–7.34 (m, 3H), 7.16 (d,  $J = 8.2$  Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  194.98, 159.68, 159.33, 154.03, 139.35, 138.32, 132.64, 129.41, 128.66, 127.93, 124.31, 124.00, 122.73, 120.26, 114.48, 103.22, 55.53, 55.50; IR (KBr film) 3448, 2923, 1660, 1622, 1593, 1452, 1315, 1283, 1263, 1235, 1038, 869, 848, 646  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{16}\text{NO}_3$  [ $\text{M} + \text{H}$ ] $^+$ : 294.1130, found: 294.1136.

**(7-Methoxyisoquinolin-1-yl)(4-methoxyphenyl)methanone (6l).** White crystals, mp 101–103 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.49 (d,  $J = 5.5$  Hz, 1H), 7.96 (d,  $J = 8.9$  Hz, 2H), 7.81 (d,  $J = 9.0$  Hz, 1H), 7.73 (d,  $J = 5.5$  Hz, 1H), 7.54 (s, 1H), 7.38 (d,  $J = 9.0$  Hz, 1H), 6.96 (d,  $J = 8.9$  Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  193.74, 164.02, 159.15, 154.69, 139.33, 133.27 (2C), 132.58, 129.76, 128.60, 127.82, 124.19, 122.35, 113.76 (2C), 103.35, 55.56, 55.51. IR (KBr film) 2926, 2837, 1652, 1622, 1601, 1506, 1427, 1251, 1215, 1185, 1166, 1044, 843, 613  $\text{cm}^{-1}$ . HRMS (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{16}\text{NO}_3$  [ $\text{M} + \text{H}$ ] $^+$ : 294.1130, found: 294.1127.

**(3,4-Dimethoxyphenyl)(7-methoxyisoquinolin-1-yl)methanone (6m).** White crystals, mp 150–152 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.49 (d,  $J = 5.4$  Hz, 1H), 7.82 (d,  $J = 9.0$  Hz, 1H), 7.74 (d,  $J = 5.4$  Hz, 1H), 7.72 (s, 1H), 7.52 (s, 1H), 7.44–7.38 (m, 2H), 6.87 (d,  $J = 8.5$  Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.88 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  193.76, 159.17, 154.68, 153.92, 149.11, 139.27, 132.57, 129.87, 128.60, 127.86, 126.92, 124.23, 122.35, 111.89, 109.99, 103.37, 56.14, 56.04, 55.52; IR (KBr film) 2998, 2931, 1653, 1597, 1585, 1516, 1265, 1232, 1143, 1027, 847, 762, 641  $\text{cm}^{-1}$ . HRMS (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{18}\text{NO}_4$  [ $\text{M} + \text{H}$ ] $^+$ : 324.1236, found: 324.1233.

**(7-Methoxyisoquinolin-1-yl)(phenyl)methanone (6n).** White crystals, mp 120–122 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.50 (d,  $J = 5.4$  Hz, 1H), 7.96 (d,  $J = 8.4$  Hz, 2H), 7.82 (d,  $J = 9.0$  Hz, 1H), 7.75 (d,  $J = 5.4$  Hz, 1H), 7.62 (t,  $J = 8.0$  Hz, 1H), 7.61 (s, 1H), 7.49 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 8.4$  Hz, 2H), 7.40 (d,  $J = 9.0$  Hz, 1H), 3.89 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  195.13, 159.37, 153.95, 139.32, 137.04, 133.50, 132.68, 130.85 (2C), 128.65 (2C), 128.42, 128.00, 124.31, 122.75, 103.29, 55.53; IR (KBr film) 2978, 2923, 1661, 1624, 1502, 1455, 1317, 1247, 1216, 1168, 851, 715, 646  $\text{cm}^{-1}$ . HRMS (ESI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{14}\text{NO}_2$  [ $\text{M} + \text{H}$ ] $^+$ : 264.1025, found: 264.1018.

**(Isoquinolin-1-yl)(3-methoxyphenyl)methanone (6o).** White crystals, mp 62–63 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.60 (d,  $J = 5.6$  Hz, 1H), 8.19 (d,  $J = 8.5$  Hz, 1H), 7.93 (d,  $J = 8.4$  Hz, 1H), 7.82 (d,  $J = 5.6$  Hz, 1H), 7.75 (dd,  $J_1 = 8.2$  Hz,  $J_2 = 8.4$  Hz, 1H), 7.63 (dd,  $J_1 = 8.2$  Hz,  $J_2 = 8.5$  Hz, 1H), 7.58 (s, 1H), 7.41 (d,  $J = 7.6$  Hz, 1H), 7.35 (dd,  $J_1 = 7.6$  Hz,  $J_2 = 8.0$  Hz, 1H), 7.16 (d,  $J = 8.0$  Hz, 1H), 3.86 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  194.61, 159.73, 156.49, 141.16, 137.93, 136.67, 130.78, 129.50, 128.36, 127.14, 126.35, 126.12, 123.99, 122.63, 120.44, 114.33, 55.50; IR (KBr film) 3005, 2937, 1665, 1594, 1463, 1281, 1266, 1147, 1039, 834, 769, 637  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{14}\text{NO}_2$  [ $\text{M} + \text{H}$ ] $^+$ : 264.1025, found: 264.1030.

**(Isoquinolin-1-yl)(4-methoxyphenyl)methanone (6p).** White crystals, mp 67–69 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.60 (d,  $J = 5.7$  Hz, 1H), 8.17 (d,  $J = 8.5$  Hz, 1H), 7.95 (d,  $J = 8.8$  Hz, 2H), 7.94 (d,  $J = 8.0$  Hz, 1H), 7.81 (d,  $J = 5.7$  Hz, 1H), 7.75 (dd,  $J_1 = 8.3$  Hz,  $J_2 = 8.5$  Hz, 1H), 7.61 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 8.3$  Hz, 1H), 6.95 (d,  $J = 8.8$  Hz, 2H), 3.88 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  193.40, 164.16, 157.08, 141.16, 136.67, 133.19 (2C), 130.72, 129.52, 128.19, 127.08, 126.32, 126.30, 122.30, 113.83 (2C), 55.58; IR (KBr film) 3008, 2936, 1651, 1600, 1576, 1412, 1249, 1154, 1022, 828, 745  $\text{cm}^{-1}$ .

**(3,4-Dimethoxyphenyl)(isoquinolin-1-yl)methanone (6q).** White crystals, mp 145–146 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



$\delta$  8.60 (d,  $J$  = 5.7 Hz, 1H), 8.16 (d,  $J$  = 8.5 Hz, 1H), 7.93 (d,  $J$  = 8.1 Hz, 1H), 7.81 (d,  $J$  = 5.7 Hz, 1H), 7.76 (dd,  $J_1$  = 8.3 Hz,  $J_2$  = 8.5 Hz, 1H), 7.74 (s, 1H), 7.62 (dd,  $J_1$  = 8.1 Hz,  $J_2$  = 8.3 Hz, 1H), 7.36 (d,  $J$  = 8.4 Hz, 1H), 6.84 (d,  $J$  = 8.4 Hz, 1H), 3.97 (s, 3H), 3.94 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  193.45, 157.03, 154.04, 149.18, 141.12, 136.66, 130.76, 129.62, 128.20, 127.08, 127.02, 126.36, 126.29, 122.31, 111.52, 109.97, 56.17, 56.08; IR (KBr film) 3002, 2938, 1660, 1582, 1510, 1410, 1266, 1150, 1134, 1019, 825, 752  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{16}\text{NO}_3$   $[\text{M} + \text{H}]^+$ : 294.1130, found: 294.1131.

**(Isoquinolin-1-yl)(phenyl)methanone (6r).** White crystals, mp 74–75 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.61 (d,  $J$  = 5.6 Hz, 1H), 8.22 (d,  $J$  = 8.5 Hz, 1H), 8.00–7.91 (m, 3H), 7.81 (d,  $J$  = 5.6 Hz, 1H), 7.74 (dd,  $J_1$  = 8.2 Hz,  $J_2$  = 8.5 Hz, 1H), 7.64–7.58 (m, 2H), 7.48 (dd,  $J_1$  = 7.8 Hz,  $J_2$  = 8.0 Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  194.81, 156.44, 141.18, 136.71, 136.63, 133.73, 130.78 (2C), 130.74, 128.51, 128.37 (2C), 127.15, 126.42, 126.16, 122.65; IR (KBr film) 2978, 2922, 1663, 1596, 1449, 1402, 1335, 1317, 1279, 1252, 1153, 924, 709, 678, 639  $\text{cm}^{-1}$ .

**(2-Bromophenyl)([1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)methanone (6s).** White crystals, mp 180–181 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.38 (d,  $J$  = 5.4 Hz, 1H), 8.20 (s, 1H), 7.65–7.57 (m, 3H), 7.46 (dd,  $J_1$  = 7.7 Hz,  $J_2$  = 7.9 Hz, 1H), 7.36 (dd,  $J_1$  = 7.9 Hz,  $J_2$  = 8.1 Hz, 1H), 7.15 (s, 1H), 6.15 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  197.22, 151.43, 151.04, 150.38, 141.64, 140.61, 135.97, 133.08, 131.88, 130.72, 127.35, 124.68, 123.63, 120.46, 102.78, 102.53, 102.00; IR (KBr film) 2975, 2908, 1679, 1576, 1497, 1460, 1317, 1261, 1208, 1037, 951, 867, 723, 631  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{11}\text{NO}_3\text{Br}$   $[\text{M} + \text{H}]^+$ : 355.9922, found: 355.9917.

**(4-Methoxyphenyl)(5,6,7-trimethoxyisoquinolin-1-yl)methanone (6t).** White crystals, mp 154–156 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.48 (d,  $J$  = 5.5 Hz, 1H), 8.01 (d,  $J$  = 5.5 Hz, 1H), 7.94 (d,  $J$  = 8.3 Hz, 2H), 7.36 (s, 1H), 6.96 (d,  $J$  = 8.3 Hz, 2H), 4.08 (s, 3H), 4.03 (s, 3H), 3.93 (s, 3H), 3.88 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  193.72, 164.04, 154.58, 154.01, 146.71, 144.30, 139.44, 133.26 (2C), 129.73, 129.21, 123.77, 116.58, 113.75 (2C), 100.36, 61.64, 61.23, 56.10, 55.55; IR (KBr film) 2944, 2839, 1651, 1602, 1479, 1327, 1280, 1256, 1163, 1125, 1028, 935, 823, 702  $\text{cm}^{-1}$ . HRMS (ESI)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{20}\text{NO}_5$   $[\text{M} + \text{H}]^+$ : 354.1341, found: 354.1336.

## Preparation of anilines 7a–f

Nitro compound **6** (~2 mmol) was dissolved in a mixed solvent of EtOH (18 mL) and  $\text{H}_2\text{O}$  (2 mL). Iron powder (1.130 g, 20.23 mmol) and acetic acid (3.610 g, 60.12 mmol) were added into the solution. The mixture was then heated and stirred under  $\text{N}_2$  at 70 °C for 3–5 h. After the reaction was complete (checked by TLC, eluent: EtOAc/hexane = 1 : 2), the mixture was cooled down to room temperature and then filtered. The cake was washed twice with EtOH (2  $\times$  10 mL). The filtrate was concentrated under vacuum to give a residue, which was dissolved in  $\text{CH}_2\text{Cl}_2$  (30 mL). An aqueous solution of  $\text{Na}_3\text{PO}_4$  (20 mL, 10% w/w) was added, the mixture was vigorously stirred for 5 min. Two phases were separated, and the aqueous phase was extracted again with  $\text{CH}_2\text{Cl}_2$  (30 mL). The organic extracts were combined, and dried over anhydrous  $\text{MgSO}_4$ . Solvent was

removed under vacuum to give crude product as pale yellow solid, which was purified by flash chromatography (eluent: EtOAc/hexane = 1 : 2). Anilines **7a–f** were thus obtained in 85%, 85%, 86%, 93%, 90% and 91% yields, respectively. Characterization data of compounds **7a–f** are as follows:

**(2-Aminophenyl)([1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)methanone (7a).** Pale yellow crystals, mp 246–247 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.37 (d,  $J$  = 5.6 Hz, 1H), 7.78 (d,  $J$  = 5.6 Hz, 1H), 7.56 (br. s, 2H,  $\text{NH}_2$ ), 7.47 (s, 1H), 7.29 (dd,  $J_1$  = 8.2 Hz,  $J_2$  = 8.5 Hz, 1H), 7.03 (s, 1H), 6.92–6.87 (m, 2H), 6.37 (dd,  $J_1$  = 8.0 Hz,  $J_2$  = 8.3 Hz, 1H), 6.22 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  196.49, 156.03, 152.65, 150.85, 148.81, 140.43, 135.06, 134.73, 134.12, 122.04, 120.89, 116.90, 115.83, 114.16, 102.77, 102.21, 100.59; IR (KBr film) 3421, 3124, 3078, 2918, 1684, 1576, 1518, 1460, 1348, 1314, 1275, 1260, 1214, 1036, 946, 867, 788, 706, 636  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{13}\text{N}_2\text{O}_3$   $[\text{M} + \text{H}]^+$ : 293.0926, found: 293.0919.

**(2-Amino-4,5-dimethoxyphenyl)([1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)methanone (7b).** Pale yellow crystals, mp 182–183 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.37 (d,  $J$  = 5.6 Hz, 1H), 7.74 (d,  $J$  = 5.6 Hz, 1H), 7.56 (br. s, 2H,  $\text{NH}_2$ ), 7.41 (s, 1H), 7.05 (s, 1H), 6.48 (s, 1H), 6.40 (s, 1H), 6.19 (s, 2H), 3.80 (s, 3H), 3.43 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  193.52, 156.42, 156.34, 150.85, 150.76, 148.67, 140.36, 138.72, 134.74, 122.05, 120.74, 115.72, 108.04, 102.75, 102.17, 100.79, 98.61, 56.07, 55.41; IR (KBr film) 3415, 3310, 2916, 1645, 1585, 1545, 1507, 1465, 1403, 1264, 1221, 1204, 1150, 1110, 1037, 948, 873, 854, 734, 675  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_5$   $[\text{M} + \text{H}]^+$ : 353.1137, found: 353.1142.

**(6-Aminobenzof[*d*][1,3]dioxol-5-yl)([1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)methanone (7c).** Pale yellow crystals, mp 240–241 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.37 (d,  $J$  = 5.6 Hz, 1H), 7.84 (br. s, 2H,  $\text{NH}_2$ ), 7.75 (d,  $J$  = 5.6 Hz, 1H), 7.44 (s, 1H), 7.02 (s, 1H), 6.46 (s, 1H), 6.21 (s, 2H), 6.19 (s, 1H), 5.91 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  193.22, 156.33, 153.63, 152.51, 150.77, 148.66, 140.41, 137.27, 134.70, 121.90, 120.70, 109.29, 108.08, 102.75, 102.17, 101.29, 100.70, 95.69; IR (KBr film) 3393, 3286, 2890, 1684, 1648, 1565, 1500, 1462, 1421, 1392, 1270, 1230, 1207, 1091, 1035, 944, 855, 839, 778, 669  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{13}\text{N}_2\text{O}_5$   $[\text{M} + \text{H}]^+$ : 337.0824, found: 337.0826.

**(2-Aminophenyl)(6,7-dimethoxyisoquinolin-1-yl)methanone (7d).** Pale yellow crystals, mp 170–171 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.42 (d,  $J$  = 5.6 Hz, 1H), 7.57 (d,  $J$  = 5.6 Hz, 1H), 7.25 (s, 1H), 7.25–7.18 (m, 2H), 7.10 (s, 1H), 6.72 (d,  $J$  = 8.2 Hz, 1H), 6.60 (br. s, 2H,  $\text{NH}_2$ ), 6.46 (dd,  $J_1$  = 8.0 Hz,  $J_2$  = 8.2 Hz, 1H), 3.99 (s, 3H), 3.88 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  197.64, 155.57, 153.14, 152.11, 150.72, 140.34, 135.20, 134.79, 133.77, 122.06, 120.45, 117.46, 117.06, 115.57, 104.95, 103.94, 56.10, 56.04; IR (KBr film) 3412, 3302, 2967, 2844, 1672, 1645, 1477, 1282, 1212, 1127, 1090, 938, 854, 735, 674  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_3$   $[\text{M} + \text{H}]^+$ : 309.1239, found: 309.1236.

**(2-Amino-4,5-dimethoxyphenyl)(6,7-dimethoxyisoquinolin-1-yl)methanone (7e).** Pale yellow crystals, mp 156–157 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.44 (d,  $J$  = 5.5 Hz, 1H), 7.59 (d,  $J$  = 5.5 Hz, 1H), 7.33 (s, 1H), 7.13 (s, 1H), 6.68 (s, 1H), 6.56 (br. s, 2H,  $\text{NH}_2$ ), 6.20 (s, 1H), 4.04 (s, 3H), 3.93 (s, 3H), 3.89 (s, 3H), 3.50 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  195.00, 156.42, 155.80,



153.14, 150.65, 149.96, 140.32, 140.01, 133.86, 122.09, 120.34, 115.97, 109.84, 104.88, 104.21, 98.82, 56.38, 56.12, 56.10, 55.93; IR (KBr film) 3421, 3312, 2982, 2834, 1658, 1601, 1470, 1285, 1252, 1203, 1143, 1027, 937, 828, 689  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_5$   $[\text{M} + \text{H}]^+$ : 369.1450, found: 369.1449.

**(2-Aminophenyl)(5,6,7-trimethoxyisoquinolin-1-yl)methanone (7f).** Pale yellow crystals, mp 105–106 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.47 (d,  $J = 5.7$  Hz, 1H), 7.94 (d,  $J = 5.7$  Hz, 1H), 7.27 (dd,  $J_1 = 8.1$  Hz,  $J_2 = 7.8$  Hz, 1H), 7.20 (d,  $J = 8.1$  Hz, 1H), 7.10 (s, 1H), 6.73 (d,  $J = 8.2$  Hz, 1H), 6.55 (br. s, 2H,  $\text{NH}_2$ ), 6.50 (dd,  $J_1 = 8.2$  Hz,  $J_2 = 7.8$  Hz, 1H), 4.07 (s, 3H), 4.02 (s, 3H), 3.89 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  197.48, 155.80, 154.30, 152.05, 146.79, 144.28, 139.82, 135.27, 134.87, 129.00, 123.14, 117.48, 117.04, 115.73, 115.69, 100.23, 61.62, 61.23, 56.10; IR (KBr, film) 3457, 3310, 2958, 2922, 2851, 1668, 1619, 1584, 1547, 1475, 1262, 1203, 1157, 1122, 1049, 940, 749, 657  $\text{cm}^{-1}$ ; HRMS (ESI): calcd for  $\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}_4$   $[\text{M} + \text{H}]^+$ : 339.1345, found: 339.1337.

### Preparation of oxoaporphines 1a–f

Aniline 7 (~1 mmol) was dissolved in an aqueous solution (5 mL, 10% w/w) of sulfuric acid. The solution was cooled to 0–8 °C with an ice bath. A freshly prepared aqueous solution (1 mL, 1 M) of sodium nitrite was dropwise added over 5 min. Stirring was continued at 0–8 °C for 15 min to give a clear pale orange aqueous solution of diazonium salt, which was immediately used below. Copper powder (0.640 g, 10.07 mmol) was added into an aqueous solution (5 mL, 10% w/w) of sulfuric acid. The suspension was warmed and stirred at 60 °C. The above aqueous solution of diazonium salt was dropwise added over 10 min. The mixture was further stirred at 60 °C for 2–4 h. After the reaction was complete (checked by TLC, eluent: EtOAc/hexane = 2 : 1), the mixture was cooled to room temperature.  $\text{CH}_2\text{Cl}_2$  (30 mL) and concentrated ammonia (10 mL, 25% w/w) were added, and the mixture was then vigorously stirred for 5 min. Two phases were separated, and the aqueous phase was extracted again with  $\text{CH}_2\text{Cl}_2$  (30 mL). The organic extracts were combined, and dried over anhydrous  $\text{MgSO}_4$ . The organic solution was concentrated under vacuum to give crude product, which was purified by flash chromatography (eluent: EtOAc/ $\text{CH}_2\text{Cl}_2$  = 1 : 4). Compounds 1a–f were thus obtained in 86%, 77%, 82%, 80%, 79% and 81% yields, respectively. Characterization data of oxoaporphines 1a–f are as follows:

**Liriodenine (1a).** Pale yellow crystals, mp 283–284 °C (lit.<sup>3d</sup> mp 282 °C).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ -TFA)  $\delta$  8.78 (d,  $J = 5.9$  Hz, 1H), 8.66 (d,  $J = 8.1$  Hz, 1H), 8.43 (d,  $J = 8.0$  Hz, 1H), 8.36 (d,  $J = 5.9$  Hz, 1H), 7.93 (dd,  $J_1 = 7.8$  Hz,  $J_2 = 8.1$  Hz, 1H), 7.67 (dd,  $J_1 = 7.8$  Hz,  $J_2 = 8.0$  Hz, 1H), 7.48 (s, 1H), 6.63 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ -TFA)  $\delta$  176.51, 158.50, 152.03, 143.26, 137.16, 134.99, 133.94, 132.15, 130.37, 129.11, 128.27, 128.08, 126.79, 122.36, 108.14, 105.20, 103.66; IR (KBr film) 3034, 2920, 1660, 1597, 1575, 1469, 1486, 1421, 1309, 1260, 1229, 1206, 1125, 1041, 1014, 958, 869, 778, 689, 568  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{10}\text{NO}_3$   $[\text{M} + \text{H}]^+$ : 276.0661, found: 276.0665.

**Dicentrinone (1b).** Pale yellow crystals, mp 292–293 °C (lit.<sup>4b</sup> mp 293–295 °C).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ -TFA)  $\delta$  8.74 (d,  $J =$

5.6 Hz, 1H), 8.33 (d,  $J = 5.6$  Hz, 1H), 8.05 (s, 1H), 7.82 (s, 1H), 7.43 (s, 1H), 6.63 (s, 2H), 4.10 (s, 3H), 4.04 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ -TFA)  $\delta$  174.96, 158.63, 157.13, 152.03, 150.56, 143.27, 135.07, 133.57, 129.04, 126.63, 122.59, 121.78, 109.71, 109.64, 108.06, 105.40, 103.58, 56.46, 56.16; IR (KBr film) 3002, 2918, 2839, 1640, 1593, 1577, 1513, 1476, 1453, 1425, 1368, 1344, 1307, 1276, 1253, 1217, 1136, 1056, 1001, 966, 855, 777, 676, 636, 577  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{14}\text{NO}_5$   $[\text{M} + \text{H}]^+$ : 336.0872, found: 336.0870.

**Cassameridine (1c).** Pale yellow crystals, mp 301–302 °C (lit.<sup>5a</sup> mp 300 °C).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ -TFA)  $\delta$  8.72 (d,  $J = 6.2$  Hz, 1H), 8.35 (d,  $J = 6.2$  Hz, 1H), 8.11 (s, 1H), 7.76 (s, 1H), 7.45 (s, 1H), 6.61 (s, 2H), 6.23 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ -TFA)  $\delta$  174.76, 158.64, 156.46, 152.30, 150.01, 143.18, 134.79, 133.71, 130.79, 126.58, 124.25, 121.60, 108.03, 107.52, 107.12, 105.34, 103.55, 103.54; IR (KBr film) 3029, 2917, 2848, 1648, 1611, 1572, 1503, 1482, 1467, 1444, 1376, 1294, 1268, 1240, 1123, 1101, 1079, 1040, 965, 899, 818, 604; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{10}\text{NO}_5$   $[\text{M} + \text{H}]^+$ : 320.0559, found: 320.0560.

**Lysicamine (1d).** Pale yellow crystals, mp 206–207 °C (lit.<sup>26</sup> mp 207–208 °C).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.17 (d,  $J = 8.2$  Hz, 1H), 8.90 (d,  $J = 5.3$  Hz, 1H), 8.59 (d,  $J = 7.8$  Hz, 1H), 7.80 (d,  $J = 5.3$  Hz, 1H), 7.78 (dd,  $J_1 = 7.8$  Hz,  $J_2 = 8.0$  Hz, 1H), 7.57 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 8.2$  Hz, 1H), 7.22 (s, 1H), 4.10 (s, 3H), 4.02 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.71, 156.85, 152.08, 152.05, 145.39, 145.05, 135.50, 134.34, 132.11, 128.90, 128.80, 128.45, 123.58, 122.11, 119.84, 106.48, 60.67, 56.23; IR (KBr film) 2968, 2920, 2837, 1662, 1610, 1552, 1512, 1465, 1415, 1375, 1260, 1235, 1110, 1079, 1041, 962, 887, 792, 605; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{14}\text{NO}_3$   $[\text{M} + \text{H}]^+$ : 292.0974, found: 292.0970.

**Oxoglucaine (1e).** Pale yellow crystals, mp 225–226 °C (lit.<sup>27</sup> mp 227–229 °C).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.82 (d,  $J = 5.2$  Hz, 1H), 8.72 (s, 1H), 7.95 (s, 1H), 7.69 (d,  $J = 5.2$  Hz, 1H), 7.11 (s, 1H), 4.06 (s, 3H), 4.04 (s, 3H), 4.03 (s, 3H), 3.99 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  181.28, 156.60, 153.65, 150.91, 149.39, 145.38, 144.81, 135.25, 129.05, 126.76, 123.30, 121.53, 119.73, 110.13, 109.67, 105.98, 60.57, 56.18, 56.17, 55.98; IR (KBr film) 2979, 2924, 2841, 1662, 1600, 1554, 1501, 1463, 1403, 1378, 1292, 1266, 1246, 1217, 1100, 1081, 1037, 975, 890, 827, 739, 624; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{18}\text{NO}_5$   $[\text{M} + \text{H}]^+$ : 352.1185, found: 352.1187.

**O-Methylmoschatoline (1f).** Pale yellow crystals, mp 184–185 °C (lit.<sup>10b</sup> mp 186–188 °C).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.00 (d,  $J = 8.2$  Hz, 1H), 8.86 (d,  $J = 5.2$  Hz, 1H), 8.46 (d,  $J = 7.7$  Hz, 1H), 8.11 (d,  $J = 5.2$  Hz, 1H), 7.64 (dd,  $J_1 = 8.2$  Hz,  $J_2 = 7.9$  Hz, 1H), 7.42 (dd,  $J_1 = 7.7$  Hz,  $J_2 = 7.9$  Hz, 1H), 4.11 (s, 3H), 4.03 (s, 3H), 4.00 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.59, 156.48, 148.45, 147.25, 145.43, 144.52, 134.51, 134.34, 131.38, 131.01, 128.85, 128.08, 127.64, 122.77, 119.12, 115.56, 61.81, 61.46, 60.99; IR (KBr, film) 2956, 2923, 2853, 1660, 1579, 1466, 1393, 1311, 1261, 1205, 1092, 970, 800, 723, 612  $\text{cm}^{-1}$ ; HRMS (ESI): calcd for  $\text{C}_{19}\text{H}_{16}\text{NO}_4$   $[\text{M} + \text{H}]^+$ : 322.1079, found: 322.1072.

### Conflicts of interest

There are no conflicts to declare.



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## Notes and references

- (a) M. Shamma and H. Guinaudeau, *Nat. Prod. Rep.*, 1986, **3**, 345; (b) M. Shamma and H. Guinaudeau, *Nat. Prod. Rep.*, 1984, **1**, 201.
- (a) D. L. Custodio and V. F. da Vegia Junior, *RSC Adv.*, 2014, **4**, 21864; (b) N. K. N. A. Zawawi, N. Ahmat, R. Ahmad, F. M. Jaafar and N. A. Ghani, *Biochem. Syst. Ecol.*, 2012, **43**, 7; (c) Z.-Y. Liang, X.-S. Yang, W. Ye and X.-J. Hao, *Chin. J. Chem.*, 2005, **23**, 895; (d) C. Xu, Y. Zhang and R. X. Tan, *Fitoterapia*, 2004, **75**, 239; (e) L. Killer, F. G. Vogt, A. J. Freyer, M. D. Menachery and C. M. Adelman, *J. Nat. Prod.*, 2003, **66**, 115; (f) T.-J. Hsieh, F.-R. Chang, Y.-C. Chia, C.-Y. Chen, H.-C. Liu, H.-F. Chiu and Y.-C. Wu, *J. Nat. Prod.*, 2001, **64**, 1157; (g) W.-L. Lo, F.-R. Chang and Y.-C. Wu, *J. Chin. Chem. Soc.*, 2000, **47**, 1251; (h) N. Xie, Z. H. Cheng and X. G. Yu, *Chin. Chem. Lett.*, 1999, **10**, 675; (i) F.-R. Chang, Y.-C. Chao, C.-M. Teng and Y.-C. Wu, *J. Nat. Prod.*, 1998, **61**, 863; (j) M. D. Menachery, H. M. Mandell, S. A. DeSaw, N. A. DeAntonio, A. J. Freyer and L. B. Killmer, *J. Nat. Prod.*, 1997, **60**, 1328; (k) J.-J. Chen, I.-L. Tsai and I.-S. Chen, *J. Nat. Prod.*, 1996, **59**, 156; (l) G.-G. Harrigan, A. A. L. Gunatilaka, D. G. I. Kingston, G. W. Chan and R. K. Johnson, *J. Nat. Prod.*, 1994, **57**, 68.
- (a) M. Castro-Moreno, C. L. Tinoco-Ojanguren, M. R. Cruz-Ortega and A. R. Gonzalez-Esquinca, *J. Plant Res.*, 2013, **126**, 529; (b) I. de la Cruz Chacon and A. R. Gonzalez-Esquinca, *Nat. Prod. Res.*, 2012, **26**, 42; (c) T. Kametani, H. Terasawa, M. Ihara and J. Iriarte, *Phytochemistry*, 1975, **14**, 1884; (d) M. A. Buchanan and E. E. Dickey, *J. Org. Chem.*, 1960, **25**, 1389.
- (a) W. N. N. Wan Othman, Y. Sivasothy, S. Y. Liew, J. Mohamad, M. A. Nafiah, K. Ahmad, M. Litaudon and K. Awang, *Phytochem. Lett.*, 2017, **21**, 230; (b) K.-S. Chen, Y.-C. Wu, C.-M. Teng, F.-N. Ko and T.-S. Wu, *J. Nat. Prod.*, 1997, **60**, 645; (c) E. M. K. Wijeratne, Y. Hatanaka, T. Kikuchi, Y. Tezuka and A. A. L. Gunatilaka, *Phytochemistry*, 1996, **42**, 1703; (d) C.-C. Chen, C.-F. Lin, Y.-L. Huang, F.-N. Ko and C. M. Teng, *J. Nat. Prod.*, 1995, **58**, 1423.
- (a) M. P. Cava, K. V. Rao, B. Douglas and J. A. Weisbach, *J. Org. Chem.*, 1968, **33**, 2443; (b) Y.-C. Wu, Y.-C. Chao, F.-R. Chang and Y.-Y. Chen, *Phytochemistry*, 1997, **46**, 181; (c) D. Y. Si, S. X. Zhao and J. Z. Deng, *J. Nat. Prod.*, 1992, **55**, 828.
- (a) H. Omar, N. M. Hashim, A. Zajmi, N. Nordin, S. I. Abdelwahab, A. H. S. Azizan, A. H. A. Hadi and H. M. Ali, *Molecules*, 2013, **18**, 8994; (b) E. V. Costa, M. L. B. Pinheiro, A. Barison, F. R. Campos, M. J. Salvador, B. H. L. N. S. Maia, E. C. Cabral and M. N. Eberlin, *J. Nat. Prod.*, 2010, **73**, 1180; (c) M. D. Menachery and D. L. Edgren, *J. Nat. Prod.*, 1988, **51**, 1283.
- (a) F.-R. Chang, J.-L. Wei, C.-M. Teng and Y.-C. Wu, *J. Nat. Prod.*, 1998, **61**, 1457; (b) Y.-Y. Chen, F.-R. Chang and Y.-C. Wu, *J. Nat. Prod.*, 1996, **59**, 904; (c) E. Martinez, A. M. P. de Diaz and P. Joseph-Nathan, *Planta Med.*, 1988, **54**, 361.
- (a) B. Liu, L. Jian, G. Chen, X. Song, C. Han and J. Wang, *Chem. Nat. Compd.*, 2014, **49**, 1172; (b) D. S. Swaffar, C. J. Holley, R. W. Fitch, K. R. Elkin, C. Zhang, J. P. Sturgill and M. D. Menachery, *Planta Med.*, 2012, **78**, 230; (c) J. Sichaem, T. Ruksilp, W. Worawalai, P. Siripong, S. Khumkratok and S. Tip-pyang, *Fitoterapia*, 2011, **82**, 422; (d) S. Fujita, M. Ninomiya, M. Efdi, K. Ohguchi, Y. Nozawa and M. Koketsu, *Nat. Prod. Res.*, 2010, **24**, 1630.
- K. K. Tan, T. J. Khoo, M. Rajagopal and C. Wiart, *Nat. Prod. Res.*, 2015, **29**, 2346.
- (a) R. M. Brash and A. T. Sneden, *J. Nat. Prod.*, 1983, **46**, 437; (b) M. P. Cava, K. T. Buck, I. Noguchi, M. Srinivasan, M. G. Rao and A. I. DaRocha, *Tetrahedron*, 1975, **31**, 1667.
- (a) Z.-H. Li, J. Gao, P.-H. Hu and J.-P. Xiong, *Oncol. Lett.*, 2017, **14**, 1979; (b) N. L. Andrezza, C. C. de Lourenco, A. J. Hernandez-Tasco, M. L. B. Pinheiro, M. E. A. Stefanello, E. V. Costa and M. J. Salvador, *J. Photochem. Photobiol., B*, 2016, **160**, 154; (c) M. Arita, S. Philipov and A. S. Galabov, *Microbiol. Immunol.*, 2015, **59**, 338; (d) Y.-B. Wei, Y.-X. Li, H. Song and X.-J. Feng, *J. Enzyme Inhib. Med. Chem.*, 2014, **29**, 722; (e) C.-C. Wu, C.-L. Wu, S.-L. Huang and H.-T. Chang, *Wood Sci. Technol.*, 2012, **46**, 737; (f) E. V. Costa, M. L. B. Pinheiro, A. D. L. de Souza, A. Barison, F. R. Campos, R. H. Valdez, T. Ueda-Nakamura, B. P. D. Filho and C. V. Nakamura, *Molecules*, 2011, **16**, 9714; (g) E. V. Costa, M. L. B. Pinheiro, C. M. Xavier, J. R. A. Silva, A. C. F. Amaral, A. D. L. Souza, A. Barison, F. R. Campos, A. G. Ferreira, G. M. C. Machado and L. L. P. Leon, *J. Nat. Prod.*, 2006, **69**, 292; (h) R. Saleem, M. Ahmed, S. I. Ahmed, M. Azeem, R. A. Khan, N. Rasool, H. Saleem, F. Noor and S. Faizi, *Phytother. Res.*, 2005, **19**, 881; (i) T.-J. Hsieh, T.-Z. Liu, C.-L. Chern, D.-A. Tsao, F.-J. Lu, Y.-H. Syu, P.-Y. Hsieh, H.-S. Hu, T.-T. Chang and C.-H. Chen, *Food Chem. Toxicol.*, 2005, **43**, 1117; (j) S. H. Woo, M. C. Reynolds, N. J. Sun, J. M. Cassady and R. M. Snapka, *Biochem. Pharmacol.*, 1997, **54**, 467.
- (a) A. F. C. Rossini, A. C. A. Muraca, G. A. Casagrande and C. Raminelli, *J. Org. Chem.*, 2015, **80**, 10033; (b) B. Melzer and F. Bracher, *Org. Biomol. Chem.*, 2015, **13**, 7664; (c) T.-H. Chuang, C.-F. Li, H.-Z. Lee and Y.-C. Wen, *J. Org. Chem.*, 2013, **78**, 4974; (d) O. V. Sigh, V.-J. Huang, C.-H. Chen and S.-S. Lee, *Tetrahedron Lett.*, 2007, **48**, 8166; (e) K. Orito, S. Uchiito, Y. Satoh, T. Tatsuzawa, R. Harade and M. Tokuda, *Org. Lett.*, 2000, **2**, 307; (f) N. Atanes, L. Castedo, E. Guitian, C. Saa, J. M. Saa and R. Suau, *J. Org. Chem.*, 1991, **56**, 2984; (g) L. Castedo, C. Saa, J. M. Saa and R. Suau, *J. Org. Chem.*, 1982, **47**, 513; (h) P. Wiriyachitra and M. P. Cava, *J. Org. Chem.*, 1977, **42**,



- 2274; (i) M. P. Cava, I. Noguchi and K. T. Buck, *J. Org. Chem.*, 1973, **38**, 2394.
- 13 J. Yang, J. Dong, X. Lu, Q. Zhang, W. Ding and X. Shi, *Chin. J. Chem.*, 2012, **30**, 2827.
- 14 (a) A. Bischler and B. Napieralski, *Ber. Dtsch. Chem. Ges.*, 1893, **26**, 1903; (b) W. M. Whaley and T. R. Govindachari, Preparation of 3,4-dihydro-isoquinolines and related compounds by Bischler–Napieralski reaction, in *Organic Reactions*, ed. R. Adams, John Wiley and Sons, New York, 1951, vol. VI, p. 74.
- 15 (a) A. Agrawal and P. G. Tratnyek, *Environ. Sci. Technol.*, 1996, **30**, 153; (b) M. d. F. Pereira and V. Thiery, *Org. Lett.*, 2012, **14**, 4754.
- 16 P. H. Leake, *Chem. Rev.*, 1956, **56**, 27.
- 17 (a) Y.-F. Zhu, K. Wilcoxon, T. Gross, P. Connors, N. Strack, R. Gross, C. Q. Huang, J. R. McCarthy, Q. Xie, N. Ling and C. Chen, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1927; (b) Y. Qian, M. Ahmad, S. Chen, P. Gillespie, N. Le, F. Mennona, S. Mischke, S.-S. So, H. Wang, C. Burghardt, S. Tannu, K. Conde-Knape, J. Kochan and D. Bolin, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 6264.
- 18 G. R. Lenz and C. Costanza, *J. Org. Chem.*, 1988, **53**, 1176.
- 19 R.-Y. Kuo, F.-R. Chang, C.-C. Wu, R. Patnam, W.-Y. Wang, Y.-C. Du and Y.-C. Wu, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2789.
- 20 N. H. Martin and C. W. Jefford, *Helv. Chim. Acta*, 1982, **65**, 762.
- 21 H. Gan, Y. Lu, Y. Huang, L. Ni, J. Xu, H. Yao and X. Wu, *Tetrahedron Lett.*, 2011, **52**, 1320.
- 22 (a) A. E. Wendlandt, A. M. Suess and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2011, **50**, 11062; (b) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas and M. C. Kozlowski, *Chem. Rev.*, 2013, **113**, 6234; (c) S. D. McCann and S. S. Stahl, *Acc. Chem. Res.*, 2015, **48**, 1756; (d) C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev.*, 2012, **41**, 3464.
- 23 T. H. Trieu, J. Dong, Q. Zhang, B. Zheng, T.-Z. Meng, X. Lu and X.-X. Shi, *Eur. J. Org. Chem.*, 2013, 3271.
- 24 M. D. Garcia, A. J. Wilson, D. P. G. Emmerson and P. R. Jenkins, *Chem. Commun.*, 2006, 2586.
- 25 (a) R. Shankar, S. S. More, M. V. Madhubabu, N. Vembu and V. K. S. Kumar, *Synlett*, 2012, **23**, 1013; (b) M. V. Madhubabu, R. Shankar, R. Akula, U. K. S. Kumar and M. V. B. Rao, *Pharma Chem.*, 2014, **6**, 50.
- 26 J. W. Skiles, J. M. Saa and M. P. Cava, *Can. J. Chem.*, 1979, **57**, 1642.
- 27 J. Cohen, W. Von Langenthal and W. I. Taylor, *J. Org. Chem.*, 1961, **26**, 4143.

