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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, oxoglaucline 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.¹ Oxoaporphine alkaloids are widespread in the kingdom of plants.^{1,2} For example, lirioidenine **1a**,³ dicentrinone **1b**,⁴ cassameridine **1c**,⁵ lysicamine **1d**,⁶ oxoglaucline **1e**⁷ and *O*-methylmoschatoline **1f**⁸ (also referred to as liriidine⁹ and homomoschatoline¹⁰) have been isolated from various botanic natural resources.^{3–10} Since oxoaporphine alkaloids **1a–f** have shown a broad spectrum of interesting biological activities,¹¹ so the total syntheses of them have aroused much interest from chemists.¹² 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 nitromethane¹³ first produced nitroalkenes **2a–c** in high yields. Next, when compounds **2a–c** were treated with 6.0 equiv. of LiAlH₄ 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 K₂CO₃ 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 POCl₃ in anhydrous acetonitrile at reflux gave 1-Bn-DHIQs **5a–f** *via* Bischler–Napieralski cyclization.¹⁴ It was observed that compounds **5a–f** and compounds **5'a–f** were interchangeable

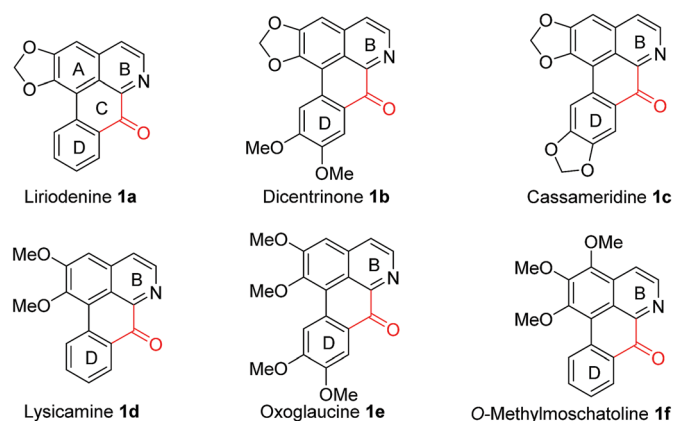


Fig. 1 The targeted oxoaporphine alkaloids **1a–f**.



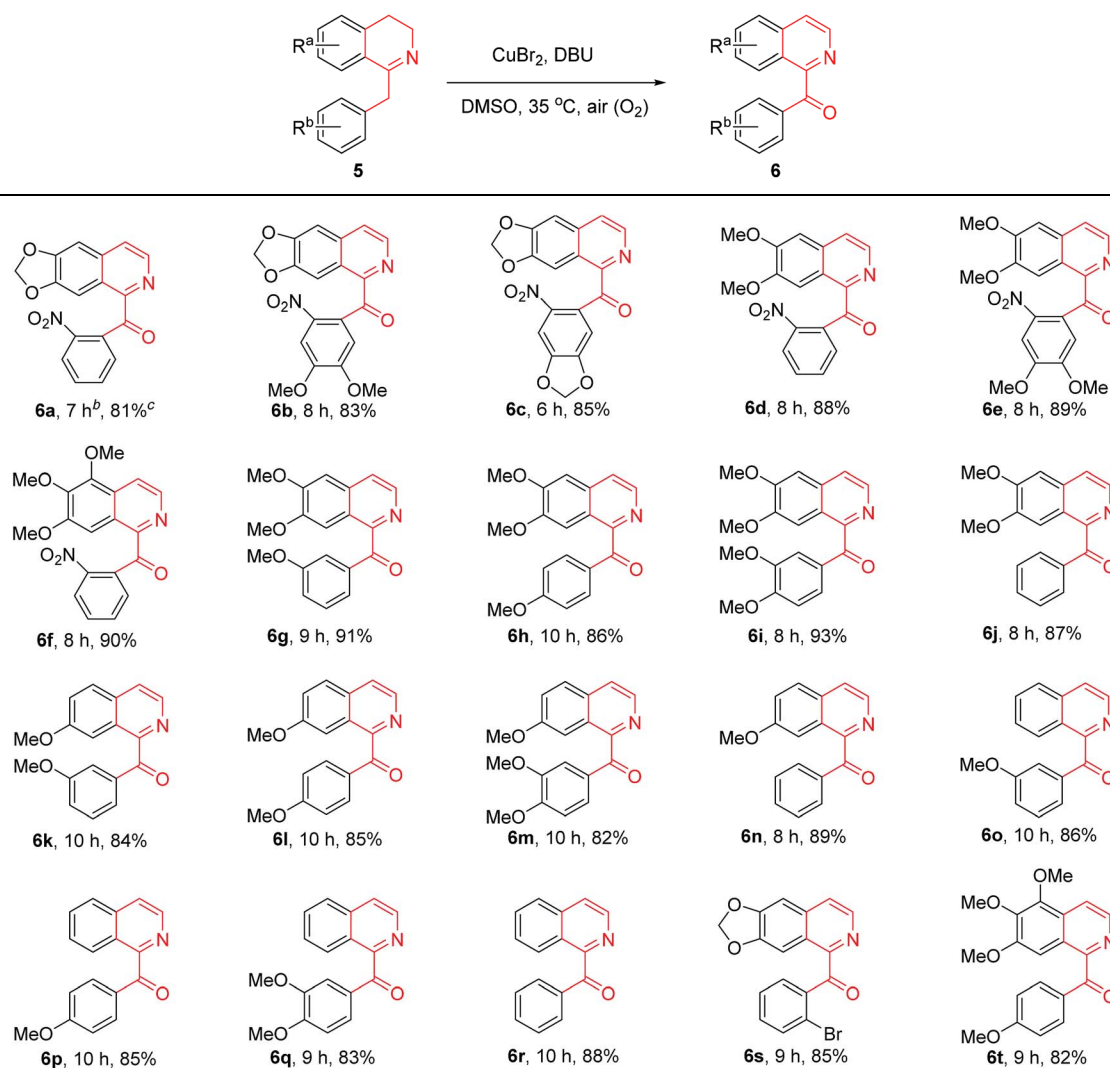
In the above-described total syntheses of oxoaporphine alkaloids **1a–f**, the key step is Cu-catalyzed conversion of 1-Bn-THIQs **5a–f** to 1-Bz-IQs **6a–f**. This key conversion can be achieved by some known methods.^{17–21} However, these known methods often suffered from drawbacks such as use of poisonous and hazardous strong oxidants including SeO₂,¹⁷ Pb(OAc)₄,¹⁸ and CAN,¹⁹ inconvenient use of the photoactivated singlet O₂,²⁰ or need of high reaction temperature²¹ (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 (O₂) is an eco-friendly clean oxidant. Hence, an increasing amount of copper-catalyzed aerobic oxidations of various compounds have been recently developed.²² For the above conversion of 1-Bn-THIQs **5a–f** to 1-Bz-IQs **6a–f**, CuBr₂ was used

as the catalyst, and air (O₂) 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.^{17–21} Advantages such as mildness (at 35 °C), high efficiency and eco-friendliness prompted us to investigate the details of this potential green chemical method.

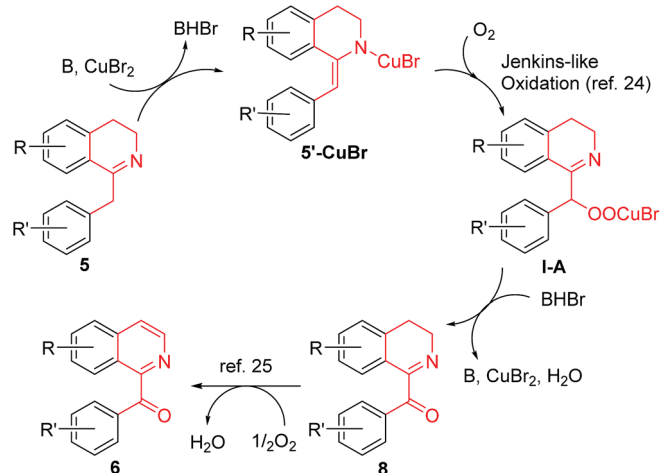
In order to know the scope and limitation of the method, more variously substituted 1-Bn-DHIQs **5** were prepared *via* Bischler–Napieralski cyclization, and a total of twenty substrates **5a–t** have been tested for the CuBr₂-catalyzed aerobic oxidation under the standard reaction conditions (see footnote 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 CuBr₂-catalyzed conversion of variously substituted 1-Bn-DHIQs **5** to 1-Bz-IQs **6**^a



^a Standard reaction conditions: 1-Bn-DHIQs **5** (2 mmol), CuBr₂ (0.2 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2 mmol), DMSO (6 mL), 35 °C (inner temperature), air (O₂). ^b Reaction time. ^c Isolated yields.





Scheme 3 A possible mechanism for the CuBr_2 -catalyzed conversion of 1-Bn-DHIQs **5** to 1-Bz-IQs **6**.

undergo aerobic oxidation in DMSO to afford 1-benzoyl- β -carbolines without a copper catalyst,²³ 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, CuBr_2 obviously worked better than CuCl_2 , $\text{Cu}(\text{OAc})_2$, CuSO_4 , $\text{Cu}_2(\text{OH})_2\text{CO}_3$, CuO and CuI . Moreover, a base is also necessary for the reaction, DBU worked obviously better than Et_3N , diisopropylethylamine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,5-diazabicyclo [4,3,0]non-5-ene (DBN), Na_2CO_3 and K_2CO_3 ; DMSO as the solvent is better than DMF, CH_3CN , THF, EtOH, Me_2CO , CH_2Cl_2 and 1,4-dioxane.

A possible mechanism for the 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 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 oxidation²⁴ 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 O_2 to produce 1-Bz-IQs **6** according to Kumar's reports.²⁵ 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 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

^1H NMR and ^{13}C NMR spectra were acquired on a Bruker AM 400 instrument, chemical shifts are given on the δ 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 Me-TEMP 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 (~ 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. ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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. ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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. ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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** (~ 18 mmol) in THF (40 mL) was dropwise added into a stirred suspension of 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 MgSO₄. 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). ¹H NMR (400 MHz, CDCl₃) 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, NH₂); ¹³C NMR (100 MHz, CDCl₃) 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). ¹H NMR (400 MHz, CDCl₃) 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, NH₂); ¹³C NMR (100 MHz, CDCl₃) 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). ¹H NMR (400 MHz, CDCl₃) 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, NH₂); ¹³C NMR (100 MHz, CDCl₃) 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 CH₂Cl₂ (20 mL), and SOCl₂ (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 CH₂Cl₂ (10 mL), the solution was immediately used below. 2-Aryl ethanamine **3** (10 mmol) was dissolved in 40 mL CH₂Cl₂, and an aqueous solution of K₂CO₃ (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 CH₂Cl₂ (20 mL). The organic extracts were combined, dried over anhydrous MgSO₄, 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. ¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, *J* = 8.2 Hz, 1H), 7.60 (dd, *J*₁ = 8.0 Hz, *J*₂ = 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); ¹³C NMR (100 MHz, CDCl₃) 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⁻¹.

***N*-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)-2-(4,5-dimethoxy-2-nitrophenyl)acetamide (4b).** White crystals, mp 206–207 °C. ¹H NMR (400 MHz, DMSO-*d*₆) 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); ¹³C NMR (100 MHz, DMSO-*d*₆) 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⁻¹.

***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. ¹H NMR (400 MHz, DMSO-*d*₆) 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); ¹³C NMR (100 MHz, DMSO-*d*₆) 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⁻¹.

***N*-(3,4-Dimethoxyphenethyl)-2-(2-nitrophenyl)acetamide (4d).** White crystals, mp 129–130 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.01 (d, *J* = 8.2 Hz, 1H), 7.58 (dd, *J*₁ = 8.0 Hz, *J*₂ = 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); ¹³C NMR (100 MHz, CDCl₃) 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⁻¹; HRMS (ESI) *m/z* calcd for C₁₈H₂₁N₂O₅ [M + H]⁺: 345.1450, found: 345.1451.

***N*-(3,4-Dimethoxyphenethyl)-2-(4,5-dimethoxy-2-nitrophenyl)acetamide (4e).** White crystals, mp 131–132 °C. ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 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. ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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 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: CH_2Cl_2 /hexane = 2 : 1), the solution was concentrated under vacuum to dryness, the residue was dissolved in CH_2Cl_2 (50 mL). An aqueous solution of K_2CO_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 CH_2Cl_2 (20 mL). The organic extracts were combined, dried over anhydrous 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 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 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 CH_2Cl_2 (40 mL) were added into the mixture. Two phases were separated, and the aqueous phase was twice extracted again with CH_2Cl_2 (2 \times 30 mL). The organic extracts were combined, and dried over anhydrous MgSO_4 . Removal of solvent by vacuum distillation gave crude product as pale yellow solid, which was purified by flash chromatography (eluent: EtOAc/ CH_2Cl_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. ^1H NMR (400 MHz, CDCl_3 -TFA) δ 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}C NMR (100 MHz, CDCl_3 -TFA) δ 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 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. ^1H NMR (400 MHz, CDCl_3 -TFA) δ 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}C NMR (100 MHz, CDCl_3 -TFA) δ 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 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. ^1H NMR (400 MHz, CDCl_3 -TFA) δ 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}C NMR (100 MHz, CDCl_3 -TFA) δ 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 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. ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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 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. ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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 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. ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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 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. ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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 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). ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (101 MHz, CDCl_3) δ 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 cm^{-1} .

(6,7-Dimethoxyisoquinolin-1-yl)(3,4-dimethoxyphenyl)methanone (6i). White crystals, mp 209–210 °C. ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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 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). ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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 cm^{-1} .

(7-Methoxyisoquinolin-1-yl)(3-methoxyphenyl)methanone (6k). White crystals, mp 106–107 °C. ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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 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. ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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 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. ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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 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. ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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 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. ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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 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. ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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 cm^{-1} .

(3,4-Dimethoxyphenyl)(isoquinolin-1-yl)methanone (6q). White crystals, mp 145–146 °C. ^1H NMR (400 MHz, CDCl_3)



δ 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}C NMR (100 MHz, CDCl_3) δ 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 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. ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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 cm^{-1} .

(2-Bromophenyl)([1,3]dioxolo[4,5-g]isoquinolin-5-yl)methanone (6s). White crystals, mp 180–181 °C. ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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 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. ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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 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 H_2O (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 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 CH_2Cl_2 (30 mL). An aqueous solution of Na_3PO_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 CH_2Cl_2 (30 mL). The organic extracts were combined, and dried over anhydrous 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. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.37 (d, $J = 5.6$ Hz, 1H), 7.78 (d, $J = 5.6$ Hz, 1H), 7.56 (br. s, 2H, 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}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 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 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-dimethoxy-phenyl)([1,3]dioxolo[4,5-g]isoquinolin-5-yl)methanone (7b). Pale yellow crystals, mp 182–183 °C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.37 (d, $J = 5.6$ Hz, 1H), 7.74 (d, $J = 5.6$ Hz, 1H), 7.56 (br. s, 2H, 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}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 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 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-Aminobenzod[*d*][1,3]dioxol-5-yl)([1,3]dioxolo[4,5-g]isoquinolin-5-yl)methanone (7c). Pale yellow crystals, mp 240–241 °C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.37 (d, $J = 5.6$ Hz, 1H), 7.84 (br. s, 2H, 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}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 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 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. ^1H NMR (400 MHz, CDCl_3) δ 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, 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}C NMR (100 MHz, CDCl_3) δ 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 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. ^1H NMR (400 MHz, CDCl_3) δ 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, NH_2), 6.20 (s, 1H), 4.04 (s, 3H), 3.93 (s, 3H), 3.89 (s, 3H), 3.50 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 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 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. ^1H NMR (400 MHz, CDCl_3) δ 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, 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}C NMR (100 MHz, CDCl_3) δ 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 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. CH_2Cl_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 CH_2Cl_2 (30 mL). The organic extracts were combined, and dried over anhydrous MgSO_4 . The organic solution was concentrated under vacuum to give crude product, which was purified by flash chromatography (eluent: EtOAc/ CH_2Cl_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.^{3d} mp 282 °C). ^1H NMR (400 MHz, CDCl_3 -TFA) δ 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}C NMR (100 MHz, CDCl_3 -TFA) δ 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 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.^{4b} mp 293–295 °C). ^1H NMR (400 MHz, CDCl_3 -TFA) δ 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}C NMR (100 MHz, CDCl_3 -TFA) δ 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 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.^{5a} mp 300 °C). ^1H NMR (400 MHz, CDCl_3 -TFA) δ 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}C NMR (100 MHz, CDCl_3 -TFA) δ 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.²⁶ mp 207–208 °C). ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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.²⁷ mp 227–229 °C). ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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.^{10b} mp 186–188 °C). ^1H NMR (400 MHz, CDCl_3) δ 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}C NMR (100 MHz, CDCl_3) δ 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 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

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