


 Cite this: *RSC Adv.*, 2021, **11**, 29702

Copper(II)-catalyzed and acid-promoted highly regioselective oxidation of tautomerizable C(sp³)-H bonds adjacent to 3,4-dihydroisoquinolines using air (O₂) as a clean oxidant†

 Yun-Gang He, Yong-Kang Huang, Qi-Qi Fan, Bo Zheng, Yong-Qiang Luo, Xing-Liang Zhu and Xiao-Xin Shi *

A mild, efficient and eco-friendly method for the oxidation of 1-Bn-DHIQs to 1-Bz-DHIQs without concomitant excessive oxidation of 1-Bz-DHIQs to 1-Bz-IQs is very important for the syntheses of 1-Bz-DHIQ alkaloids and analogues. In this article, we developed a novel Cu(II)-catalyzed and acid-promoted highly regioselective oxidation of tautomerizable C(sp³)-H bonds adjacent to the C-1 positions of various 1-Bn-DHIQs. It was observed that when 0.2 equiv. of Cu(OAc)₂·2H₂O was used as the catalyst, 3.0 equiv. of AcOH was used as the additive and air (O₂) was used as a clean oxidant, various 1-Bn-DHIQs could be efficiently oxidized to corresponding 1-Bz-DHIQs at 25 °C in DMSO. Especially, almost no concomitant excessive oxidation of 1-Bz-DHIQs to 1-Bz-IQs was observed during the above reaction. In addition, this method was successfully applied in the first total synthesis of the alkaloid canellinixine.

 Received 24th July 2021
 Accepted 30th August 2021

DOI: 10.1039/d1ra05671a

rsc.li/rsc-advances

Introduction

Oxidation of organic compounds is a kind of fundamental transformation in organic and medicinal chemistry. Development of novel efficient and highly selective oxidation of activated or non-activated C(sp³)-H bonds under mild reaction conditions is a challenging task for chemists due to its great importance, and it has become an exciting and promising research area in modern organic synthesis.¹ Recently, significant efforts of chemists have been devoted to solving the issues of oxidation of C(sp³)-H bonds in a variety of substrates.² Although many oxidants can be used in the above oxidation of C(sp³)-H bonds, air (O₂) is certainly the best choice in the light of its abundance, easy availability, cheapness and eco-friendliness. On the other hand, copper is a low toxic and inexpensive transition metal. Therefore, an increasing amount of copper-catalyzed aerobic oxidations of various organic compounds have been recently developed.³

1-Benzoyl-3,4-dihydroisoquinolines (1-Bz-DHIQs) represent an important kind of isoquinoline alkaloids, which could be isolated from numerous plants.⁴ Since 1-Bz-DHIQ alkaloids and their synthetic analogues have exhibited various interesting biological activities,⁵ a mild, efficient and eco-friendly method for synthesis of 1-Bz-DHIQ alkaloids might be highly desirable

for organic and medicinal chemists. 1-Bz-DHIQs usually can be synthesized *via* oxidation of 1-benzyl-3,4-dihydroisoquinolines (1-Bn-DHIQs), which could be readily prepared *via* the Bischler-Napieralski cyclization⁶ of corresponding amides. Some known methods for the oxidation of 1-Bn-DHIQs to 1-Bz-DHIQs have been reported.⁷⁻¹⁴ However, these known methods usually suffered from some serious drawbacks: (a) use of poisonous and hazardous strong oxidants such as CrO₃,⁷ SeO₂,⁸ MnO₂,⁹ CAN [Ce(NH₄)₂(NO₃)₆],¹⁰ Pb(OAc)₄,¹¹ and singlet oxygen (¹O₂);^{8,12} (b) concomitant excessive oxidation of 1-Bz-DHIQs could not be avoided, significant amount of undesired 1-benzoyl-isoquinolines (1-Bz-IQs) were formed as by-products during the reaction;⁷⁻¹³ (c) yields of 1-Bz-DHIQs as the desired products are only moderate in most instances; (d) use of precious palladium catalyst (Pd/C) in Andreu's method.¹⁴ In order to overcome the above-mentioned drawbacks, development of a mild, efficient and eco-friendly method for the oxidation of 1-Bn-DHIQs to 1-Bz-DHIQs without concomitant excessive oxidation of 1-Bz-DHIQs to 1-Bz-IQs remains a challenge to organic chemists. Herein, we want to disclose a very mild and efficient copper(II)-catalyzed and acid-promoted highly regioselective oxidation of tautomerizable C(sp³)-H bonds adjacent to the C-1 positions of various 1-Bn-DHIQs using air (O₂) as a clean oxidant.

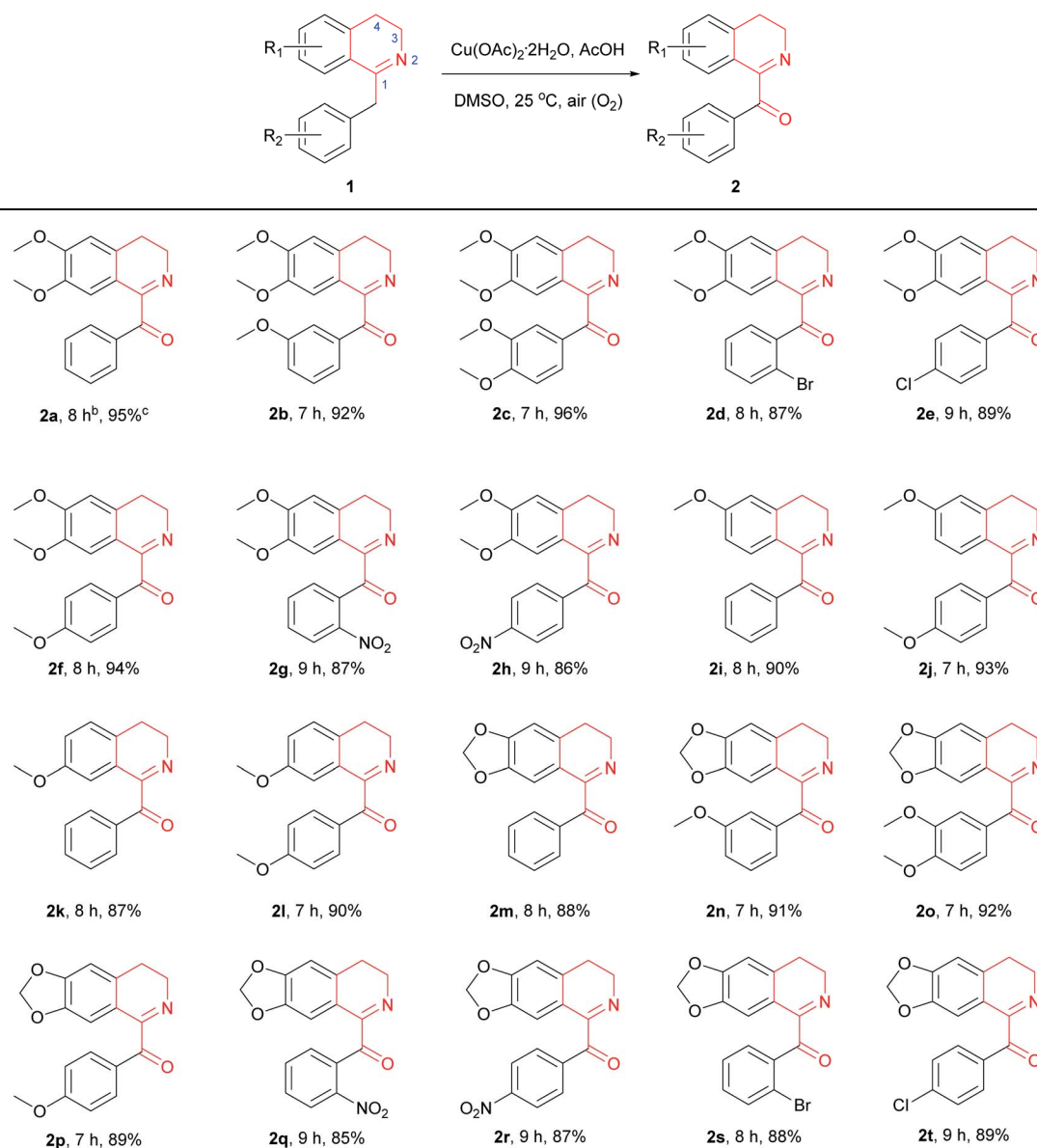
Results and discussion

At first, we chose the oxidation of 1-Bn-DHIQ **1a** in dimethyl sulfoxide (DMSO) as the model reaction, and tried this model reaction under various conditions, the results are summarized

Engineering Research Center of Pharmaceutical Process Chemistry of the Ministry of Education, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, People's Republic of China. E-mail: xxshi@ecust.edu.cn

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ra05671a



Table 2 Cu(OAc)₂-Catalyzed and acid-promoted oxidation of variously substituted 1-Bn-THIQs 1 to afford 1-Bz-DHIQs 2.^a

^a Reaction conditions: 1-Bn-DHIQ **1** (2 mmol), Cu(OAc)₂·2H₂O (0.4 mmol), AcOH (6 mmol), DMSO (4 mL), 25 °C, air (O₂). ^b Reaction time. ^c Isolated yields.

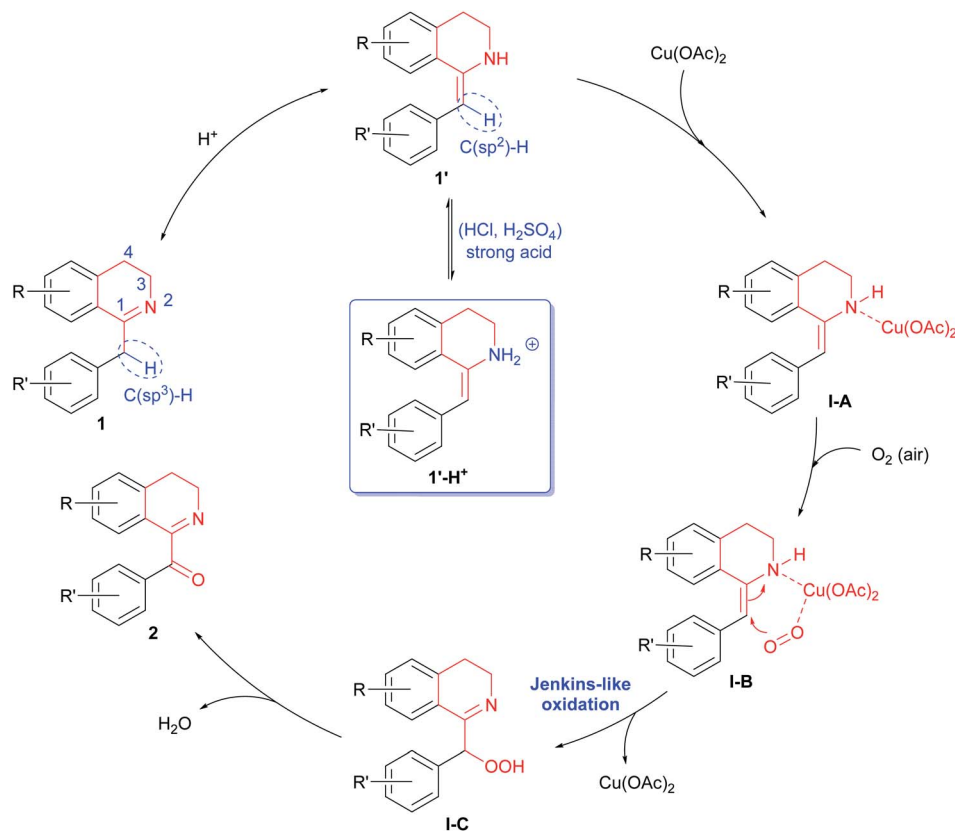
also a benzylic position, almost none of oxidation of C(sp³)-H bond at the C-4 position happened.

A possible mechanism for the above Cu(OAc)₂-catalyzed and acid promoted aerobic oxidation of 1-Bn-DHIQs **1** was proposed in Scheme 1. 1-Bn-DHIQs **1** would first undergo acid-promoted tautomerization¹⁶ to form enamines **1'**. Enamines **1'** would then coordinate with Cu(OAc)₂ to produce Cu-complex **I-A**, which would further coordinate with molecule O₂ (in air) to give more reactive Cu-complex **I-B**.¹⁷ Next, complex **I-B** would undergo intramolecular Jenkins-like oxidation¹⁸ to furnish an unstable perhydroxide compound **I-C**. Finally, decomposition¹⁹ of **I-C** would afford 1-Bz-DHIQs **2**. Although acids can speed up tautomerization of imines **1** to enamines **1'**, strong acids (HCl,

H₂SO₄, etc.) would also react with imines **1** to form ammonium **1'-H⁺** reversibly, which could not coordinate with Cu(OAc)₂ to form **I-A**, and that would retard the oxidation (Table 1, entries 9–12).

To demonstrate the utility of above-described methodology, we have applied the protocol to an efficient total synthesis of 1-Bz-DHIQ canelillinoxine **4**. The alkaloid canelillinoxine **4** was isolated from the stem bark of *Aniba canelilla* H.B.K. (Lauraceae) in 1993.²⁰ Herein we would like to report the first total synthesis of canelillinoxine **4** starting from vanillin by using the above mild Cu(OAc)₂-catalyzed and acid-promoted oxidation of as the key step. As depicted in the Scheme 2, EDA-catalyzed condensation of vanillin with nitromethane produced nitroalkene **5** in

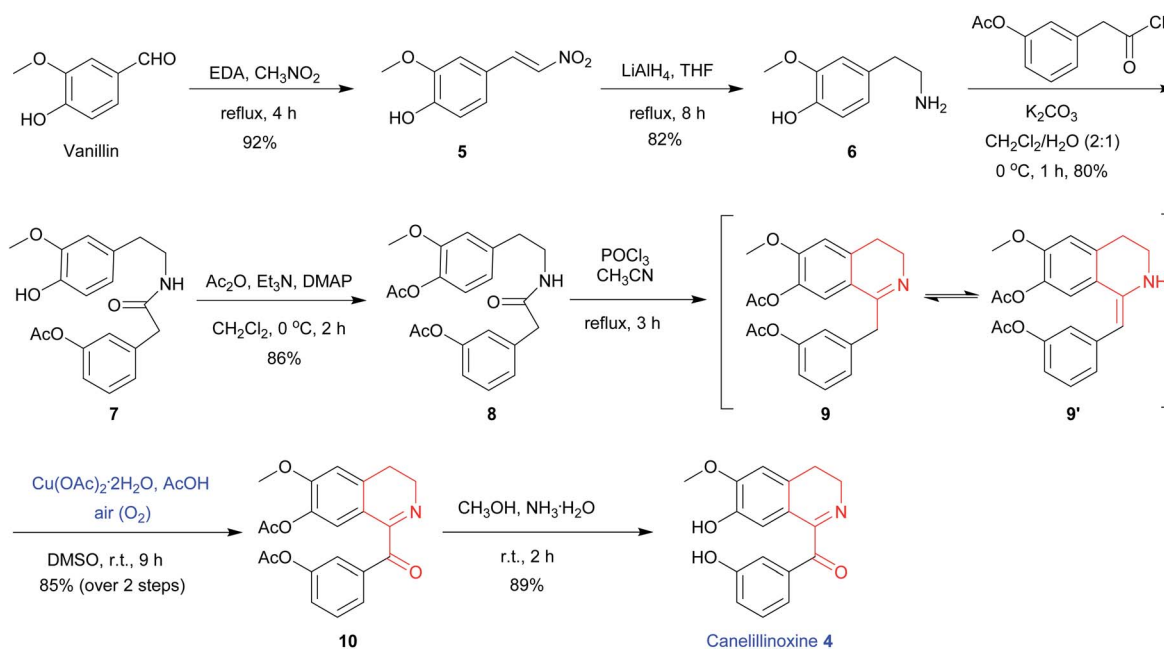




Scheme 1 Possible mechanism for the $\text{Cu}(\text{OAc})_2$ -catalyzed and acid-promoted aerobic oxidation of $\text{C}(\text{sp}^3)\text{-H}$ bonds adjacent to the C-1 positions of 1-Bn-DHIQs 1.

92% yield.²¹ Compound 5 was then treated with 5.0 equiv. of LiAlH_4 , simultaneous reduction of the double bond and nitro group took place to give amine 6 in 82% yield. When compound 6 was exposed to 1.1 equiv. of freshly prepared 2-(3-acetoxy-

phenyl) acetyl chloride and 3.0 equiv. of K_2CO_3 , amide 7 was obtained in 80% yield. Treatment of compound 7 with 3.0 equiv. of Ac_2O , 3.0 equiv. of Et_3N and 0.1 equiv. of *N,N*-dimethylamino-pyridine (DMAP) gave compound 8 in 86% yield. Next, exposure



Scheme 2 The first total synthesis of canelillinoxine 4 from vanillin.



of amide **8** to 3.0 equiv. of POCl₃, Bischler–Napieralski cyclization⁶ took place smoothly to produce the tautomeric mixture of imine **9** and enamine **9'**, which were then treated with 0.2 equiv. of Cu(OAc)₂·2H₂O and 3.0 equiv. of AcOH in DMSO under an air atmosphere at 25 °C to furnish compound **10** in 85% yield (over 2 steps from **8**). Finally, when compound **10** was treated with excessive NH₃·H₂O, protecting groups (two Ac groups) were removed to afford 1-Bz-DHIQ canelillinoxine **4** in 89% yield.

Conclusions

In conclusion, we have studied the Cu(OAc)₂-catalyzed and acid-promoted highly regioselective oxidation of tautomerizable C(sp³)-H bonds adjacent to C-1 positions of 1-Bn-DHIQs, and found that Cu(OAc)₂·2H₂O is the most effective catalyst, DMSO is the best solvent, weak acid AcOH is the best additive, and air (O₂) is the suitable oxidant. The reaction is highly controlled by acid/base additives, acid additives led to formation of 1-Bz-DHIQ as the major product, while base additives led to formation of 1-Bz-IQ as the major product. The reaction is applicable for a variety of substituted 1-Bn-DHIQs to afford 1-Bz-DHIQs in high yields. The present method is superior to the known methods^{7–14} due to some advantages such as mildness, high regioselectivity, high yields, good practicability and eco-friendliness. In addition, the methodology was successfully applied to the first total synthesis of 1-Bz-DHIQ alkaloid canelillinoxine, it was synthesized from vanillin *via* 7 steps in 39% overall yield.

Experimental

General methods

¹H and ¹³C NMR spectra were acquired on a Bruker AM-400 magnetic resonance instrument. Chemical shifts were 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 spectrometer. MS spectra were recorded on a Mariner mass spectrum equipment. Melting points were determined on a Mei-TEMP II apparatus. Column chromatography was performed on silica gel (Qingdao Chemical Factory). All chemicals are analytically pure, and were used as such as received from the chemical suppliers.

Preparation of 1-Bn-DHIQs 1 (ref. 15). A corresponding amide (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: CH₂Cl₂/hexane = 3 : 1), the solution was concentrated under vacuum to dryness, the residue was dissolved in CH₂Cl₂ (50 mL). An aqueous solution of K₂CO₃ (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 twice with CH₂Cl₂ (2 × 25 mL). Organic extracts were combined, dried over anhydrous MgSO₄, and then concentrated under vacuum to give crude product 1-Bn-DHIQ **1** in an almost quantitative yield, which was used as such for the next step.

General procedure for the Cu(OAc)₂-catalyzed and acid-promoted oxidation of 1-Bn-DHIQs 1 into 1-Bz-DHIQs 2. 1-Bn-DHIQ **1** (2.000 mmol) was dissolved in DMSO (4 mL). Cu(OAc)₂·2H₂O (87.10 mg, 0.4002 mmol) and CH₃COOH (360.5 mg, 6.003 mmol) were added. The resulting solution was stirred at room temperature under an atmosphere of air. After the reaction was complete (checked by TLC, EtOAc/hexane = 1 : 1), a dilute ammonia aqueous solution (5% w/w, 20 mL) and EtOAc (20 mL) were added into the mixture. After the mixture was vigorously stirred for 5 min, two phases were separated. The aqueous phase was twice extracted with EtOAc (20 mL × 2). The organic extracts were combined, and dried over anhydrous MgSO₄. Removal of solvent by vacuum distillation gave crude product, which was purified by flash chromatography (eluent: CH₂Cl₂/EtOAc = 20 : 1 to 5 : 1) to afford 1-Bz-DHIQ **2** in 85–96% yields. Characterization data of compounds **2a–t** are as follows:

(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone **2a**: pale yellow crystals, m.p. 78–79 °C (lit.²² m.p. 78.8–79.4 °C). ¹H NMR (400 MHz, CDCl₃) δ 8.04 (d, *J* = 7.3 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (dd, *J*₁ = 7.3 Hz, *J*₂ = 7.4 Hz, 2H), 6.95 (s, 1H), 6.76 (s, 1H), 3.99–3.87 (m, 2H), 3.92 (s, 3H), 3.78 (s, 3H), 2.88–2.77 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 193.97, 164.39, 151.72, 147.62, 135.57, 133.85, 131.17, 130.43, 128.54, 119.30, 110.57, 109.59, 56.07, 56.02, 47.31, 25.37. IR (KBr film) ν 3080, 2936, 2907, 2844, 1656, 1586, 1516, 1485, 1265, 1239, 1146, 1024, 929, 865, 752 cm⁻¹.

(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)(3-methoxyphenyl)methanone **2b**: pale yellow crystals, m.p. 98–100 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (s, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.37 (dd, *J*₁ = 7.8 Hz, *J*₂ = 7.9 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 6.93 (s, 1H), 6.76 (s, 1H), 3.98–3.89 (m, 2H), 3.94 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H), 2.88–2.77 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 193.82, 164.54, 159.73, 151.77, 147.66, 136.85, 131.15, 129.58, 123.63, 120.63, 119.30, 113.96, 110.54, 109.58, 56.11, 56.05, 55.48, 47.21, 25.40. IR (KBr film) ν 3070, 2921, 2852, 1666, 1596, 1592, 1569, 1515, 1461, 1425, 1135, 1072, 1033, 935, 807, 754, 709 cm⁻¹. HRMS (ESI) *m/z* calcd for C₁₉H₁₉NO₄Na [M + Na]⁺: 348.1212, found: 348.1211.

(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)(3,4-dimethoxyphenyl)methanone **2c**: pale yellow crystals, m.p. 188–189 °C (lit.²³ m.p. 188–190 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.68 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 6.91 (s, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.76 (s, 1H), 3.96 (s, 3H), 3.95–3.88 (m, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 3.79 (s, 3H), 2.89–2.76 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 192.76, 164.63, 154.16, 151.67, 149.16, 147.64, 131.08, 128.59, 126.61, 119.49, 111.21, 110.50, 110.02, 109.61, 56.16, 56.11, 56.04, 56.02, 47.25, 25.43. IR (KBr film) ν 3013, 2935, 2833, 2604, 1659, 1583, 1514, 1461, 1278, 1133, 1023, 866, 791, 755 cm⁻¹.

(2-Bromophenyl)(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)methanone **2d**: pale yellow crystals, m.p. 159–161 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.44 (dd, *J*₁ = 7.8 Hz, *J*₂ = 7.7 Hz, 1H), 7.36 (dd, *J*₁ = 7.7 Hz, *J*₂ = 7.7 Hz, 1H), 7.32 (s, 1H), 6.74 (s, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.88–3.80 (m, 2H), 2.83–2.62 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 195.75, 163.67, 151.61, 147.54, 140.23, 133.14, 132.51, 131.68, 131.11, 127.51, 120.75, 119.16, 110.32, 110.28, 56.15,



56.02, 48.19, 25.12. IR (KBr film) ν 3054, 2942, 2899, 2844, 1681, 1587, 1499, 1478, 1460, 1381, 1315, 1266, 1032, 924, 868 cm^{-1} . HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{16}\text{NO}_3\text{Na}$ $[\text{M} + \text{Na}]^+$: 396.0211, found: 396.0215.

(4-Chlorophenyl)(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)methanone 2e: white crystals, m.p. 132–133 °C (lit.²⁴ m.p. 130–131 °C). ^1H NMR (400 MHz, CDCl_3) δ 7.99 (d, $J = 8.6$ Hz, 2H), 7.45 (d, $J = 8.6$ Hz, 2H), 6.96 (s, 1H), 6.75 (s, 1H), 3.97–3.89 (m, 2H), 3.94 (s, 3H), 3.80 (s, 3H), 2.86–2.76 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 192.56, 163.93, 151.83, 147.69, 140.35, 134.01, 131.87, 131.22, 128.85, 119.17, 110.55, 109.61, 56.12, 56.06, 47.38, 25.38.

(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)(4-methoxyphenyl)methanone 2f: pale yellow crystals, m.p. 92–93 °C (lit.²⁵ m.p. 91–92 °C). ^1H NMR (400 MHz, CDCl_3) δ 8.03 (d, $J = 8.9$ Hz, 2H), 6.96 (d, $J = 8.9$ Hz, 2H), 6.92 (s, 1H), 6.75 (s, 1H), 3.96–3.89 (m, 2H), 3.94 (s, 3H), 3.88 (s, 3H), 3.78 (s, 3H), 2.87–2.77 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 192.73, 164.67, 164.26, 151.61, 147.62, 132.91, 131.10, 128.50, 119.48, 113.87, 110.47, 109.61, 56.12, 55.56, 47.27, 29.72, 25.45.

(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)(2-nitrophenyl)methanone 2g: pale yellow crystals, m.p. 98–100 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.09 (d, $J = 7.8$ Hz, 1H), 7.78 (dd, $J_1 = 7.8$ Hz, $J_2 = 7.9$ Hz, 1H), 7.71–7.61 (m, 3H), 6.70 (s, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.74–3.62 (m, 2H), 2.70–2.56 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 192.66, 163.10, 151.69, 147.81, 147.56, 136.08, 134.17, 131.81, 131.04, 130.19, 123.57, 119.03, 110.97, 109.92, 56.17, 56.00, 47.84, 25.20. IR (KBr film) ν 3072, 2964, 2919, 2851, 1697, 1600, 1562, 1529, 1512, 1468, 1405, 1346, 1280, 1197, 1147, 1047, 906, 877, 800, 750, 707 cm^{-1} . HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_5$ $[\text{M} + \text{H}]^+$: 341.1137, found: 341.1135.

(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)(4-nitrophenyl)methanone 2h: white crystals, m.p. 160–161 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.31 (d, $J = 8.8$ Hz, 2H), 8.20 (d, $J = 8.8$ Hz, 2H), 7.07 (s, 1H), 6.77 (s, 1H), 4.00–3.92 (m, 2H), 3.95 (s, 3H), 3.84 (s, 3H), 2.89–2.76 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 191.71, 163.27, 152.06, 150.42, 147.75, 140.75, 131.53, 131.43, 123.49, 118.87, 110.58, 109.68, 56.16, 56.12, 47.57, 25.32. IR (KBr film) ν 3003, 2924, 2853, 1674, 1637, 1606, 1564, 1519, 1458, 1347, 1200, 1043, 906, 859, 800, 781 cm^{-1} . HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_5$ $[\text{M} + \text{H}]^+$: 341.1137, found: 341.1143.

(6-Methoxy-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone 2i: pale yellow crystals, m.p. 89–90 °C (lit.²⁶ m.p. 88–90 °C). ^1H NMR (400 MHz, CDCl_3) δ 8.03 (d, $J = 7.4$ Hz, 2H), 7.58 (t, $J = 7.5$ Hz, 1H), 7.45 (dd, $J_1 = 7.4$ Hz, $J_2 = 7.5$ Hz, 2H), 7.31 (d, $J = 8.5$ Hz, 1H), 6.76 (s, 1H), 6.73 (d, $J = 8.5$ Hz, 1H), 3.99–3.88 (m, 2H), 3.81 (s, 3H), 2.91–2.79 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 194.09, 164.86, 162.02, 139.57, 135.56, 133.86, 130.37, 128.56, 128.50, 120.16, 113.47, 112.13, 55.42, 47.13, 26.19.

(6-Methoxy-3,4-dihydroisoquinolin-1-yl)(4-methoxyphenyl)methanone 2j: white crystals, m.p. 156–157 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.02 (d, $J = 9.0$ Hz, 2H), 7.29 (d, $J = 8.5$ Hz, 1H), 6.94 (d, $J = 9.0$ Hz, 2H), 6.76 (s, 1H), 6.72 (d, $J = 8.5$ Hz, 1H), 3.97–3.87 (m, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 2.90–2.80 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 192.81, 165.11, 164.24, 161.93, 139.53, 132.77, 128.53, 128.50, 120.28, 113.87, 113.40, 112.09, 55.56, 55.38, 47.05, 26.20. HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{18}\text{NO}_3$ $[\text{M} + \text{H}]^+$: 296.1287, found: 296.1292.

(7-Methoxy-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone 2k: pale yellow crystals, m.p. 130–131 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.03 (d, $J = 7.7$ Hz, 2H), 7.60 (t, $J = 7.8$ Hz, 1H), 7.48 (dd, $J_1 = 7.7$ Hz, $J_2 = 7.8$ Hz, 2H), 7.17 (d, $J = 8.2$ Hz, 1H), 6.97 (d, $J = 8.2$ Hz, 1H), 6.92 (s, 1H), 4.03–3.89 (m, 2H), 3.73 (s, 3H), 2.87–2.76 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 193.80, 165.11, 158.55, 135.49, 133.94, 130.41, 129.19, 128.74, 128.60, 127.16, 117.68, 111.67, 55.49, 47.77, 24.78. IR (KBr film) ν 3058, 2973, 2946, 2836, 1664, 1598, 1575, 1498, 1475, 1448, 1353, 1311, 1259, 1222, 1199, 1112, 1031, 921, 879, 858, 740, 698 cm^{-1} . HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_2\text{Na}$ $[\text{M} + \text{Na}]^+$: 288.1000, found: 288.1005.

(7-Methoxy-3,4-dihydroisoquinolin-1-yl)(4-methoxyphenyl)methanone 2l: white crystals, m.p. 58–60 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.02 (d, $J = 9.0$ Hz, 2H), 7.16 (d, $J = 8.2$ Hz, 1H), 6.95 (d, $J = 8.2$ Hz, 1H), 6.94 (d, $J = 9.0$ Hz, 2H), 6.90 (s, 1H), 3.98–3.91 (m, 2H), 3.87 (s, 3H), 3.73 (s, 3H), 2.86–2.76 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 192.53, 165.38, 164.32, 158.54, 132.82, 129.17, 128.69, 128.42, 117.60, 113.91, 113.76, 111.69, 55.57, 55.48, 47.67, 24.80. IR (KBr film) ν 3037, 2947, 2924, 2833, 1652, 1603, 1572, 1499, 1468, 1422, 1357, 1317, 1259, 1222, 1209, 1169, 1126, 1040, 1019, 948, 926, 881, 819, 767 cm^{-1} . HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_3\text{Na}$ $[\text{M} + \text{Na}]^+$: 318.1106, found: 318.1102.

(7,8-Dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)(phenyl)methanone 2m: pale yellow crystals, m.p. 76–77 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.93 (d, $J = 8.0$ Hz, 2H), 7.50 (t, $J = 8.1$ Hz, 1H), 7.37 (dd, $J_1 = 8.0$ Hz, $J_2 = 8.1$ Hz, 2H), 6.76 (s, 1H), 6.62 (s, 1H), 5.85 (s, 2H), 3.88–3.74 (m, 2H), 2.74–2.63 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 193.80, 164.41, 149.91, 146.51, 135.42, 133.88, 132.99, 130.34, 128.55, 120.37, 108.29, 106.88, 101.48, 47.19, 25.85. IR (KBr film) ν 3054, 2921, 2846, 1664, 1621, 1581, 1502, 1483, 1461, 1058, 1037, 991, 931, 869, 730, 688 cm^{-1} . HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{13}\text{NO}_3\text{Na}$ $[\text{M} + \text{Na}]^+$: 302.0793, found: 302.0800.

(7,8-Dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)(3-methoxyphenyl)methanone 2n: pale yellow crystals, m.p. 70–72 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.58 (s, 1H), 7.55 (d, $J = 7.9$ Hz, 1H), 7.36 (dd, $J_1 = 7.9$ Hz, $J_2 = 8.0$ Hz, 1H), 7.14 (d, $J = 8.0$ Hz, 1H), 6.83 (s, 1H), 6.72 (s, 1H), 5.96 (s, 2H), 3.93–3.85 (m, 2H), 3.86 (s, 3H), 2.83–2.74 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 193.77, 164.53, 159.76, 149.94, 146.54, 136.71, 132.99, 129.59, 123.59, 120.71, 120.45, 113.82, 108.31, 106.98, 101.49, 55.51, 47.23, 25.92. IR (KBr film) ν 3077, 2941, 2903, 2837, 1677, 1592, 1568, 1481, 1459, 1429, 1375, 1318, 1264, 1191, 1104, 1038, 992, 935, 872, 751, 679 cm^{-1} . HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_4\text{Na}$ $[\text{M} + \text{Na}]^+$: 332.0899, found: 332.0907.

(7,8-Dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)(3,4-dimethoxyphenyl)methanone 2o: pale yellow crystals, m.p. 154–155 °C (lit.^{5d} m.p. 153–154 °C). ^1H NMR (400 MHz, CDCl_3) δ 7.56 (s, 1H), 7.50 (d, $J = 8.4$ Hz, 1H), 6.80 (d, $J = 8.4$ Hz, 1H), 6.74 (s, 1H), 6.64 (s, 1H), 5.88 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.85–3.76 (m, 2H), 2.76–2.65 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 192.72, 164.68, 154.19, 149.87, 149.20, 146.52, 132.93, 128.47, 126.55, 120.64, 111.07, 110.01, 108.27, 107.04, 101.46, 56.18, 56.06, 47.18, 25.93.

(7,8-Dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)(4-methoxyphenyl)methanone 2p: pale yellow crystals, m.p. 131–132 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.01 (d, $J = 8.9$ Hz, 2H), 6.94 (d, $J = 8.9$ Hz, 2H), 6.83 (s, 1H), 6.71 (s, 1H), 5.95 (s, 2H), 3.94–3.82 (m, 2H), 3.86 (s, 3H), 2.84–2.73 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3)



δ 192.60, 164.70, 164.27, 149.83, 146.49, 132.95, 132.80, 128.33, 120.57, 113.88, 108.26, 107.04, 101.45, 55.59, 47.17, 25.93. IR (KBr film) ν 3069, 2920, 2841, 1650, 1599, 1505, 1486, 1257, 1171, 1038, 932, 849, 768 cm^{-1} . HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{16}\text{NO}_4$ $[\text{M} + \text{H}]^+$: 310.1079, found: 310.1073.

(7,8-Dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)(2-nitrophenyl)methanone **2q**: pale yellow crystals, m.p. 180–181 °C (lit.⁷ m.p. 180–183 °C). ^1H NMR (400 MHz, CDCl_3) δ 8.01 (d, $J = 7.8$ Hz, 1H), 7.70 (dd, $J_1 = 7.8$ Hz, $J_2 = 7.9$ Hz, 1H), 7.63–7.54 (m, 2H), 7.48 (s, 1H), 6.60 (s, 1H), 5.94 (s, 2H), 3.62–3.50 (m, 2H), 2.56–2.44 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 192.38, 163.19, 149.90, 147.77, 146.52, 136.00, 134.21, 133.78, 131.08, 130.26, 123.61, 120.01, 108.49, 107.70, 101.47, 47.78, 25.79.

(7,8-Dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)(4-nitrophenyl)methanone **2r**: white crystals, m.p. 160–161 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.31 (d, $J = 8.9$ Hz, 2H), 8.18 (d, $J = 8.9$ Hz, 2H), 6.96 (s, 1H), 6.75 (s, 1H), 6.00 (s, 2H), 4.01–3.81 (m, 2H), 2.88–2.60 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 191.55, 163.31, 150.44, 150.25, 146.66, 140.56, 133.33, 131.46, 123.51, 119.95, 108.37, 106.99, 101.62, 47.47, 25.81. HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{13}\text{N}_2\text{O}_5$ $[\text{M} + \text{H}]^+$: 325.0824, found: 325.0821.

(2-Bromophenyl)(7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)methanone **2s**: pale yellow crystals, m.p. 147–148 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.62 (d, $J = 7.7$ Hz, 1H), 7.56 (d, $J = 7.9$ Hz, 1H), 7.43 (dd, $J_1 = 7.7$ Hz, $J_2 = 7.8$ Hz, 1H), 7.35 (dd, $J_1 = 7.8$ Hz, $J_2 = 7.9$ Hz, 1H), 7.25 (s, 1H), 6.71 (s, 1H), 6.00 (s, 2H), 3.91–3.73 (m, 2H), 2.77–2.63 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 195.61, 163.63, 149.79, 146.43, 140.24, 133.04, 132.46, 131.05, 127.53, 120.66, 120.22, 108.02, 107.81, 101.46, 48.20, 25.70. HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{12}\text{BrNO}_3\text{Na}$ $[\text{M} + \text{Na}]^+$: 379.9898, found: 379.9895.

(4-Chlorophenyl)(7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)methanone **2t**: pale yellow crystals, m.p. 133–134 °C (lit.^{5d} m.p. 132–133 °C). ^1H NMR (400 MHz, CDCl_3) δ 7.97 (d, $J = 8.2$ Hz, 2H), 7.45 (d, $J = 8.2$ Hz, 2H), 6.86 (s, 1H), 6.73 (s, 1H), 5.97 (s, 2H), 3.99–3.83 (m, 2H), 2.87–2.72 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 192.36, 164.05, 150.10, 146.60, 140.45, 133.82, 133.14, 131.79, 128.90, 120.24, 108.33, 107.01, 101.53, 47.20, 25.88. IR (KBr film) ν 3004, 2923, 2852, 1668, 1622, 1587, 1502, 1484, 1462, 1208, 1089, 1041, 936, 899, 821, 769 cm^{-1} .

Preparation of (E)-2-methoxy-4-(2-nitrovinyl)phenol (5). Vanillin (9.902 g, 65.08 mmol) was dissolved in nitromethane (100 mL). Ethylenediamine (78.10 mg, 1.300 mmol) was added. The resulting solution was then heated to reflux, and stirring was continued at reflux for around 4 h. After the reaction was complete (TLC: EtOAc/hexane = 1 : 2), the nitromethane was removed by vacuum distillation to give a crude yellowish solid product, which was then triturated in aqueous methanol ($\text{CH}_3\text{OH}/\text{H}_2\text{O} = 2 : 1$, 20 mL). Pale yellow crystals were collected on a Buchner funnel by suction, and rinsed twice with aqueous methanol ($\text{CH}_3\text{OH}/\text{H}_2\text{O} = 1 : 1$, 2×10 mL). After being dried overnight under a warm air, compound **5** (11.68 g, 59.84 mmol) was obtained as yellow crystals in 92% yield, m.p. 164–165 °C (lit.²⁷ m.p. 162–164 °C). ^1H NMR (400 MHz, acetone- d_6) δ 8.58 (brs, 1H, OH), 8.02 (d, $J = 13.5$ Hz, 1H), 7.91 (d, $J = 13.5$ Hz, 1H), 7.49 (s, 1H), 7.32 (d, $J = 8.2$ Hz, 1H), 6.94 (d, $J = 8.2$ Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, acetone- d_6) δ 151.85, 149.02, 140.44, 136.03, 126.41, 123.18, 116.47, 112.21, 56.42.

Preparation of 4-(2-aminoethyl)-2-methoxyphenol (6). A solution of compound **5** (5.856 g, 30.00 mmol) in THF (60 mL) was dropwise added into a stirred suspension of LiAlH_4 (5.693 g, 150.0 mmol) in THF (60 mL) at 0 °C over 20 min. After the addition was finished, the mixture was then heated and stirred at reflux for 8 h. The mixture was cooled to 0 °C by an ice-bath. While the mixture was vigorously stirred, water (20 mL) was dropwise added into the reaction mixture over 30 min, and NaHCO_3 (12.60 g, 150.0 mmol) was then slowly added into the mixture at 0 °C. The ice-bath was removed, and the mixture was further stirred at reflux for 3 h. After cooled to room temperature, the mixture was filtered through a thin layer of celite, and the filter cake was washed twice with EtOH (2×30 mL). The filtrates were combined and dried over anhydrous MgSO_4 . The solution was concentrated under vacuum to give crude product as a viscous oil, which was purified by flash chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH} = 1 : 1$) to afford pure compound **6** (4.115 g, 24.61 mmol) as white crystals in 82% yield, m.p. 158–160 °C (lit.²⁸ m.p. 158.5–160.5 °C). ^1H NMR (400 MHz, DMSO- d_6) δ 6.83 (s, 1H), 6.76 (d, $J = 8.0$ Hz, 1H), 6.63 (d, $J = 8.0$ Hz, 1H), 3.76 (s, 3H), 3.02–2.91 (m, 2H), 2.81 (t, $J = 7.9$ Hz, 2H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 147.51, 145.24, 128.02, 120.71, 115.47, 112.74, 55.52, 55.47, 32.61.

Preparation of 3-(2-((4-hydroxy-3-methoxyphenethyl)amino)-2-oxoethyl)phenyl acetate (7). 2-(3-Acetoxyphenyl)acetic acid (3.841 g, 19.78 mmol) was dissolved in CH_2Cl_2 (25 mL), and SOCl_2 (4.706 g, 39.56 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_2Cl_2 (10 mL), the solution was immediately used below. Compound **6** (3.006 g, 17.98 mmol) was dissolved in CH_2Cl_2 (50 mL), and an aqueous solution of K_2CO_3 (7.456 g, 53.95 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-(3-acetoxyphenyl)acetyl chloride was added slowly into the reaction mixture over 2 min. After the addition was finished, stirring was continued at 0–5 °C for 1 h. When the reaction was completed, the reaction mixture was transferred into a separatory funnel. 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 product, which was purified by flash chromatography (eluent: EtOAc/hexane = 1 : 2) to afford pure compound **7** (4.945 g, 14.40 mmol) as white crystals in 80% yield, m.p. 108–110 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.30 (dd, $J_1 = 7.9$ Hz, $J_2 = 7.8$ Hz, 1H), 7.02 (d, $J = 7.8$ Hz, 1H), 7.00 (d, $J = 7.9$ Hz, 1H), 6.94 (s, 1H), 6.77 (d, $J = 8.0$ Hz, 1H), 6.60 (s, 1H), 6.51 (d, $J = 8.0$ Hz, 1H), 5.70 (brs, 1H, NH), 3.79 (s, 3H), 3.49 (s, 2H), 3.47–3.36 (m, 2H), 2.66 (t, $J = 6.9$ Hz, 2H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 170.55, 169.52, 150.95, 146.76, 144.30, 136.41, 130.37, 129.88, 126.83, 122.60, 121.28, 120.51, 114.50, 111.23, 55.84, 43.37, 40.97, 35.02, 21.10. IR (KBr film) ν 3378, 3301, 3079, 2935, 2848, 1762, 1736, 1653, 1607, 1512, 1449, 1371, 1278, 1206, 1147, 1124, 1032, 963, 933, 861, 791, 693 cm^{-1} . HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{Na}$ $[\text{M} + \text{Na}]^+$: 366.1317, found: 366.1313.



Preparation of 3-(2-((4-acetoxy-3-methoxyphenethyl)amino)-2-oxoethyl)phenyl acetate (8). Compound **7** (4.005 g, 11.66 mmol) was dissolved in CH₂Cl₂ (100 mL). After the solution was cooled to triethylamine (3.540 g, 34.98 mmol), DMAP (142.5 mg, 1.166 mmol) and acetic anhydride (3.571 g, 34.98 mmol) and were added in turn. The mixture was further stirred at 0 °C for 2 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1 : 1), an aqueous solution of hydrochloric acid (1 N, 50 mL) was added. After the mixture was vigorously stirred for 5 min, two phases were separated, and organic layer was washed with an aqueous solution of potassium carbonate (15% w/w, 30 mL). The aqueous phase was extracted again with CH₂Cl₂ (30 mL). The organic extracts were combined, dried over anhydrous MgSO₄, and then concentrated under vacuum to give crude product, which was purified by flash chromatography (eluent: EtOAc/hexane = 1 : 3) to afford pure compound **8** (3.866 g, 10.03 mmol) as white crystals in 86% yield, m.p. 95–97 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.32 (dd, *J*₁ = 7.8 Hz, *J*₂ = 7.9 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.96 (s, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.71 (s, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 5.71 (brs, 1H, NH), 3.76 (s, 3H), 3.50 (s, 2H), 3.48–3.40 (m, 2H), 2.72 (t, *J* = 6.9 Hz, 2H), 2.30 (s, 3H), 2.29 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 170.46, 169.46, 169.23, 151.01, 150.95, 138.25, 137.73, 136.44, 129.94, 126.82, 122.69, 122.60, 120.79, 120.51, 112.78, 55.85, 43.39, 40.69, 35.36, 21.13, 20.67. IR (KBr film) ν 3300, 3037, 2938, 2854, 1769, 1649, 1601, 1540, 1448, 1424, 1373, 1267, 1206, 1151, 1120, 1028, 967, 905, 807, 790, 690 cm⁻¹. HRMS (ESI) *m/z* calcd for C₂₁H₂₃NO₆Na [M + Na]⁺: 408.1423, found: 408.1425.

Preparation of 3-(7-acetoxy-6-methoxy-3,4-dihydroisoquinoline-1-carbonyl)phenyl acetate (10). Amide **8** (3.002 g, 7.789 mmol) was dissolved in anhydrous acetonitrile (30 mL), and phosphorus oxychloride (3.583 g, 23.37 mmol) was slowly added into the mixture. The resulting solution was then heated and stirred at reflux for 3 h. After the reaction was complete, the solution was concentrated under vacuum to dryness, the residue was dissolved in EtOAc (60 mL). An aqueous solution of K₂CO₃ (35 mL, 20% w/w) was added. After the mixture was vigorously stirred for 5 min, two phases were separated, and the aqueous phase was extracted twice with EtOAc (20 mL × 2). The organic extracts were combined, dried over anhydrous MgSO₄, and then concentrated under vacuum to give crude solid as a tautomeric mixture of 3,4-dihydroisoquinoline **9** and enamine **9'**, which was used as such for the next step.

The above tautomeric mixture of 3,4-dihydroisoquinoline **9** and enamine **9'** were dissolved in DMSO (15 mL). Cu(OAc)₂·2H₂O (339.0 mg, 1.557 mmol) and CH₃COOH (1.400 g, 23.31 mmol) were added. The resulting solution was then stirred at room temperature for 9 h under an atmosphere of air. After the reaction was completed (checked by TLC, EtOAc/hexane = 1 : 1), a dilute ammonia aqueous solution (5% w/w, 60 mL) and EtOAc (60 mL) were added. After the mixture was vigorously stirred for 5 min, two phases were separated, and the aqueous phase was extracted again with EtOAc (50 mL). The organic extracts were combined, and dried over anhydrous MgSO₄. Removal of

solvent by vacuum distillation gave crude product, which was purified by flash chromatography (eluent: EtOAc/hexane = 1 : 3) to afford pure compound **10** (2.525 g, 6.621 mmol) as pale yellow crystals in 85% yield, m.p. 80–82 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.78 (s, 1H), 7.47 (dd, *J*₁ = 8.0 Hz, *J*₂ = 7.9 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.16 (s, 1H), 6.83 (s, 1H), 4.01–3.94 (m, 2H), 3.88 (s, 3H), 2.92–2.79 (m, 2H), 2.31 (s, 3H), 2.27 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 192.12, 169.11, 168.90, 163.37, 153.78, 150.74, 138.18, 137.11, 136.82, 129.54, 128.14, 127.25, 123.21, 121.52, 119.38, 111.55, 56.10, 47.10, 25.71, 21.13, 20.54. IR (KBr film) ν 3072, 2923, 2849, 1763, 1673, 1608, 1585, 1563, 1512, 1438, 1367, 1282, 1200, 1127, 1068, 1045, 1008, 912, 886, 808, 756, 701 cm⁻¹. HRMS (ESI) *m/z* calcd for C₂₁H₂₀NO₆ [M + H]⁺: 382.1291, found: 382.1291.

Preparation of (7-hydroxy-6-methoxy-3,4-dihydroisoquinolin-1-yl)(3-hydroxyphenyl)methanone (canelillinoxine 4). Compound **10** (1.003 g, 2.630 mmol) was dissolved in methanol (15 mL), and concentrated aqueous ammonia (25%, w/w, 2 mL) was slowly added. After the addition was finished, the mixture was further stirred at room temperature for about 2 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1 : 1), solvents were removed by vacuum distillation to give crude product, which was then purified by flash chromatography (eluent: CH₂Cl₂/CH₃OH = 10 : 1) to afford pure compound **4** (696.0 mg, 2.341 mmol) as pale yellow crystals in 89% yield, m.p. 120–122 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.42 (d, *J* = 7.9 Hz, 1H), 7.20 (s, 1H), 7.17 (dd, *J*₁ = 7.9 Hz, *J*₂ = 8.0 Hz, 1H), 6.89 (s, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.70 (s, 1H), 3.93 (s, 3H), 3.87–3.80 (m, 2H), 2.81–2.73 (m, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 194.03, 164.32, 157.60, 150.45, 144.86, 136.16, 129.99, 128.87, 121.44, 120.80, 118.63, 115.64, 112.52, 111.46, 55.63, 46.65, 24.46. IR (KBr film) ν 3391, 3072, 2928, 2847, 1672, 1600, 1585, 1513, 1452, 1374, 1286, 1133, 1048, 1024, 1000, 880, 826, 762 cm⁻¹. HRMS (ESI) *m/z* calcd for C₁₇H₁₆NO₄ [M + H]⁺: 298.1079, found: 298.1075.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the National Natural Science Foundation of China (No. 20972048) for the financial support of this work.

Notes and references

- Recent reviews, see: (a) T. G. Saint-Denis, R.-Y. Zhu, G. Chen, Q.-F. Wu and J.-Q. Yu, *Science*, 2018, **359**, eaao4798; (b) P. Wang and L. Deng, *Chin. J. Chem.*, 2018, **36**, 1222; (c) Q. Zhang and B.-F. Shi, *Chin. J. Chem.*, 2019, **37**, 647; (d) G. Qiu and J. Wu, *Org. Chem. Front.*, 2015, **2**, 169; (e) H. Sterckx, B. Morel and B. U. W. Maes, *Angew. Chem., Int. Ed.*, 2019, **58**, 7946; (f) R. Wang, Y. Luan and M. Ye, *Chin. J. Chem.*, 2019, **37**, 720; (g) M. C. White and J. Zhao, *J. Am. Chem. Soc.*, 2018, **140**, 13988; (h) X. Lu, B. Xiao, R. Shang and L. Liu, *Chin. Chem. Lett.*, 2016, **27**, 305; (j) T. Aneesa,



- M. Neetha, C. M. A. Afsina and G. Anilkumar, *RSC Adv.*, 2020, **10**, 34429.
- 2 Recent examples for the oxidation of C(sp³)-H bonds: (a) G. Laudadio, S. Govaerts, Y. Wang, D. Ravelli, H. F. Koolman, M. Fagnoni, S. W. Djuric and T. Noel, *Angew. Chem., Int. Ed.*, 2018, **57**, 4078; (b) Q.-L. Yang, Y.-Q. Li, C. Ma, P. Fang, X.-J. Zhang and T.-S. Mei, *J. Am. Chem. Soc.*, 2017, **139**, 3293; (c) J. Romero-Ibanez, S. Cruz-Gregorio, J. Sandoval-Lira, J. M. Hernandez-Perez, L. Quintero and F. Sartillo-Piscil, *Angew. Chem., Int. Ed.*, 2019, **58**, 8867; (d) Y. Kawamata, M. Yan, Z. Liu, D.-H. Bao, J. Chen, J. T. Starr and P. S. Baran, *J. Am. Chem. Soc.*, 2017, **139**, 7448; (e) J. B. C. Mack, J. D. Gipson, J. D. Bois and M. S. Sigman, *J. Am. Chem. Soc.*, 2017, **139**, 9503; (f) T. Nanjo, E. C. de Lucca Jr and M. C. White, *J. Am. Chem. Soc.*, 2017, **139**, 14586; (g) M. Lee and M. S. Sanford, *J. Am. Chem. Soc.*, 2015, **137**, 12796; (h) M. N. Wenzel, P. K. Owens, J. T. W. Bray, J. M. Lynam, P. M. Aguiar, C. Reed, J. D. Lee, J. F. Hamilton, A. C. Whitwood and I. J. S. Fairlamb, *J. Am. Chem. Soc.*, 2017, **139**, 1177; (i) T. K. Beng, V. Shearer, R. Davey and I. Redman, *RSC Adv.*, 2020, **10**, 20264; (j) R. Chen, B. Liu, W. Li, K.-K. Wang, C. Miao, Z. Li, Y. Lv and L. Liu, *RSC Adv.*, 2021, **11**, 8051.
- 3 (a) S. D. McCann and S. S. Stahl, *Acc. Chem. Res.*, 2015, **48**, 1756; (b) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas and M. C. Kozlowski, *Chem. Rev.*, 2013, **113**, 6234; (c) A. E. Wendlandt, A. M. Suess and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2011, **50**, 11062; (d) T.-Z. Meng, J. Zheng, T. H. Trieu, B. Zheng, J.-J. Wu, Y. Zhang and X.-X. Shi, *ACS Omega*, 2018, **3**, 544; (e) B. Zheng, T. H. Trieu, F.-L. Li, X.-L. Zhu, Y.-G. He, Q.-Q. Fan and X.-X. Shi, *ACS Omega*, 2018, **3**, 8243; (f) B. Zheng, T. H. Trieu, T.-Z. Meng, X. Lu, J. Dong, Q. Zhang and X.-X. Shi, *RSC Adv.*, 2018, **8**, 6834.
- 4 (a) A. F. Marinho, E. d. J. Oliveira, J. F. Tavares, R. B. Filho and J. M. Barbosa-Filho, *Magn. Reson. Chem.*, 2013, **51**, 312; (b) S. N. Sulaiman, M. R. Mukhtar, A. H. A. Hadi, K. Awang, H. Hazni, A. Zahari, M. Litaudon, K. Zaima and H. Morita, *Molecules*, 2011, **16**, 3119; (c) Y. Dang, H. F. Gong, J. X. Liu and S. J. Yu, *Chin. Chem. Lett.*, 2009, **20**, 1218; (d) X. H. Duan and J. Q. Jiang, *Chin. Chem. Lett.*, 2008, **19**, 308; (e) L. Gan, X. Zhao, W. Yao, L. Wu, L. Li and C. J. Zhou, *J. Chem. Res.*, 2008, **2008**, 285; (f) Y. Nishiyama, M. Moriyasu, M. Ichimaru, K. Iwasa, A. Kato, S. G. Mathenge, P. B. C. Mutiso and F. D. Juma, *Phytochemistry*, 2006, **67**, 2671; (g) H. Zhang and J.-M. Yue, *Nat. Prod. Res.*, 2006, **20**, 553; (h) B. Chen, C. Feng, B.-G. Li and G.-L. Zhang, *Nat. Prod. Res.*, 2003, **17**, 397; (i) G. A. d. Lira, L. M. d. Andrade, K. C. Florencio, M. S. d. Silva, J. M. Barbosa-Filho and E. V. L. da-Cunha, *Fitoterapia*, 2002, **73**, 356; (j) M. Lebeuf, A. Ranaivo, A. Cave and H. Moskowitz, *J. Nat. Prod.*, 1989, **52**, 516.
- 5 (a) A. A. Salim, N. Bidin, A. S. Lafi and F. Z. Huyop, *Mater. Des.*, 2017, **132**, 486; (b) K. N. Yogendra, D. Dhokane, A. C. Kushalappa, F. Sarmiento, E. Rodriguez and T. Mosquera, *Plant Sci.*, 2017, **256**, 208; (c) A. Bermejo, I. Andreu, F. Suvire, S. Leonce, D. H. Caignard, P. Renard, A. Pierre, R. D. Enriz, D. Cortes and N. Cabedo, *J. Med. Chem.*, 2002, **45**, 5058; (d) J. A. Weisbach, J. L. Kirkpatrick, E. Macko and B. Douglas, *J. Med. Chem.*, 1968, **11**, 752.
- 6 (a) A. Bischler and B. Napieralski, *Ber. Dtsch. Chem. Ges.*, 1893, **26**, 1903; (b) Z. M. A. Judeh, C. B. Ching, J. Bu and A. McCluskey, *Tetrahedron Lett.*, 2002, **43**, 5089; (c) M. A. Epishina, A. S. Kulikov, M. I. Struchkova, N. V. Ignat'ev, M. Schulte and N. N. Makhova, *Mendeleev Commun.*, 2012, **22**, 267; and the references cited therein.
- 7 W. I. Taylor, *Tetrahedron*, 1961, **14**, 42.
- 8 N. H. Martin, S. L. Champion and P. B. Belt, *Tetrahedron Lett.*, 1980, **21**, 2613.
- 9 S. V. Kessar, T. Mohammad and Y. P. Gupta, *Indian J. Chem., Sect. B*, 1983, **22**, 321.
- 10 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.
- 11 G. R. Lenz and C. Costanza, *J. Org. Chem.*, 1988, **53**, 1176.
- 12 N. H. Martin and C. W. Jefford, *Helv. Chim. Acta*, 1982, **65**, 762.
- 13 P. B. Wakchaure and N. P. Argade, *Synthesis*, 2008, **15**, 2321.
- 14 I. Andreu, N. Cabedo, G. Atassi, A. Pierre, D. H. Caignard, P. Renard, D. Cortes and A. Bermejo, *Tetrahedron Lett.*, 2002, **43**, 757.
- 15 B. Zheng, H.-Y. Qu, T.-Z. Meng, X. Lu, J. Zheng, Y.-G. He, Q.-Q. Fan and X.-X. Shi, *RSC Adv.*, 2018, **8**, 28997.
- 16 (a) R. A. Clark and D. C. Parker, *J. Am. Chem. Soc.*, 1971, **93**, 7257; (b) S.-P. Lu and A. H. Lewin, *Tetrahedron*, 1998, **54**, 15097; (c) L. O. Davis, M. A. Putri, C. L. Meyer and C. P. Durant, *Tetrahedron Lett.*, 2014, **55**, 3100.
- 17 P. Gamez, P. G. Aubel, W. L. Driessen and J. Reedijk, *Chem. Soc. Rev.*, 2001, **30**, 376; and the references cited therein.
- 18 M. D. Garcia, A. J. Wilson, D. P. G. Emmerson and P. R. Jenkins, *Chem. Commun.*, 2006, 2586–2588.
- 19 (a) K. Maeda, M. Nakamura and M. J. Sakai, *Chem. Soc. Perkin Trans.*, 1983, **1**, 837; (b) Y. Mori and K. Maeda, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 1204.
- 20 J.-M. Oger, A. Fardeau, P. Richomme, H. Guinaudeau and A. Fournet, *Can. J. Chem.*, 1993, **71**, 1128.
- 21 J.-X. Yang, J. Dong, X. Lu, Q. Zhang, W. Ding and X. Shi, *Chin. J. Chem.*, 2012, **30**, 2827.
- 22 M. D. Rozwadowska, M. Chrzanowska, A. Brossi, C. R. Creveling, M. E. Bembenek and C. W. Abell, *Helv. Chim. Acta*, 1988, **71**, 1598.
- 23 R. Zhu, Z. Xu, W. Ding, S. Liu, X. Shi and X. Lu, *Chin. J. Chem.*, 2014, **32**, 1039.
- 24 S.-D. Cho, D.-H. Kweon, Y.-J. Kang, S.-G. Lee, W. S. Lee and Y.-J. Yoon, *J. Heterocycl. Chem.*, 1999, **36**, 1151.
- 25 C. C. Silveira, C. R. Bernardi, A. L. Braga and T. S. Kaufman, *Tetrahedron Lett.*, 2001, **42**, 8947.
- 26 B.-X. Zhao, Y. Yu and S. Eguchi, *Org. Prep. Proced. Int.*, 1997, **29**, 185.
- 27 A. Fierroa, M. C. Rezendea, S. Sepúlveda-Bozab, M. Reyes-Paradab and B. K. Cassels, *J. Chem. Res.*, 2001, 294.
- 28 K. Rice and A. Brossi, *J. Org. Chem.*, 1980, **45**(4), 592.

