

# **Visible light photoredox catalyzed semisynthesis of the analogues of maclekarpine E: a series of 6- vinyl substituted dihydrobenzophenanthridine alkaloids**

Zhixing Qing<sup>1,3</sup>, Hualiang Cao<sup>1</sup>, Pi Cheng<sup>1,2\*</sup>, Wei Wang<sup>1</sup>, Jianguo Zeng<sup>1,2,3</sup>, Hongqi Xie<sup>2\*</sup>

<sup>1</sup> National and Local Union Engineering Research Center of Veterinary Herbal Medicine Resource and Initiative, Hunan Agricultural University, Changsha, Hunan 410128, China

<sup>2</sup> Hunan Co-Innovation Center for Utilization of Botanical Functional Ingredients, Hunan Agricultural University, Changsha, Hunan 410128, China.

<sup>3</sup> School of Pharmacy, Hunan University of Chinese Medicine, Changsha 410208, China

\* Corresponding authors:

E-mail: picheng55@126.com; Fax: +86 731 84686560 (P.C.); xiehongqi2006@126.com (H. X.)

**General:**

Column chromatography silica gel (200-300 mesh) and TLC plate were purchased from Qingdao Meijin Chemical Inc(Qingdao; China); HRMS data were obtained in the ESI mode on an Agilent 6530 Q-TOF/MS system.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on Bruker 400 MHz spectrometer and chemical shifts were given in  $\delta$  with TMS as an internal reference. Dihydrosanguinarine and dihydrochelerythrine were isolated from *Macleaya Cordata* in our lab.

***Isolation of dihydrosanguinarine and dihydrochelerythrine from M. cordata***

Dry fruits of *M. cordata* (100 kg, harvested at Hunan Agricultural University, China) were extracted with 95% EtOH at 70°C under reflux (2×2 h), and the ratio of solids and liquid was 1:6. The extract was suspended in 150 L (3×50) of a hydrochloric acid solution (pH=3) for 24 h. Then KOH was added to adjust the pH of media to 10. After 24 hour standing, the undissolved residue was isolated by filtering through a 500 mesh nylon and then subjected to a silica gel column eluted with  $\text{CH}_2\text{Cl}_2$ -MeOH (10:1-5:1) to provide four fractions, which were detected using TLC [solvent system:  $\text{CH}_2\text{Cl}_2$ -MeOH (8:1)]. Fraction 2 (17.8 g) was separated through repeated column chromatography on silica gel (200-300 mesh) eluted with PE-acetone (10:1) to obtain dihydrosanguinarine (550 mg) and dihydrochelerythrine (277 mg).

***General procedures for the synthesis of vinyl sulfones:***

Vinyl sulfones were prepared as reported by Noble et al (*J. Am. Chem. Soc.* **2014**, 136, 11602.): To a suspension of benzenesulfinic acid sodium salt (15.0 mmol, 3.00 equiv.) and NaOAc (7.5 mmol, 1.50 equiv.) in MeCN (20 mL) was added styrene (5.0 mmol, 1.00 equiv.) followed by iodine (7.5mmol, 1.50 equiv.). The mixture was heated to reflux for 1 h before being allowed to cool and the excess iodine quenched with 10% aq. sodium thiosulfate. Sat. aq.  $\text{NaHCO}_3$  was added and the product extracted into EtOAc (3×20 mL). The combined organic phases were washed with

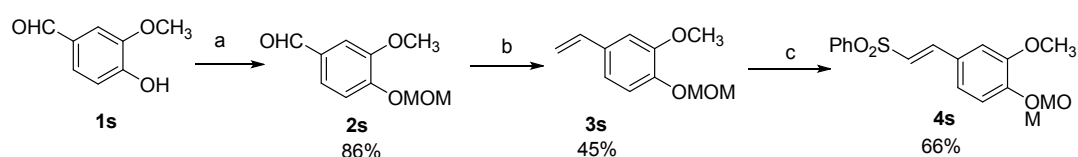
H<sub>2</sub>O (20 mL), brine (20 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography.

***Representative experimental procedure for visible light promoted synthesis of 6-substituted 5,6-dihydrobenzophenanthridine.***

A solution of dihydrosanguinarine **5** (0.2 mmol), 3.0 eq of Na<sub>2</sub>HPO<sub>4</sub>, Ir(ppy)<sub>2</sub>(dtbbpy)PF<sub>6</sub> (2 mol%) and 3.0 equiv of vinyl sulphones in DMSO (2 mL) was firstly bubbled with nitrogen for 10 minutes and then irradiated with 25 W household compact fluorescent lamp under nitrogen atmosphere. After 24 h reaction, the resulting mixture was poured into water (50 mL) and then extracted with EtOAc (20 mL × 3). The combined organic solution was then washed with water (20 mL × 3). The organic layers were washed with brine and dried over MgSO<sub>4</sub>. The solvent were removed via vacuo and the residue was purified by flash column chromatography (SiO<sub>2</sub>) with petroleum ether/AcOEt (8:1) to give target compound **8**.

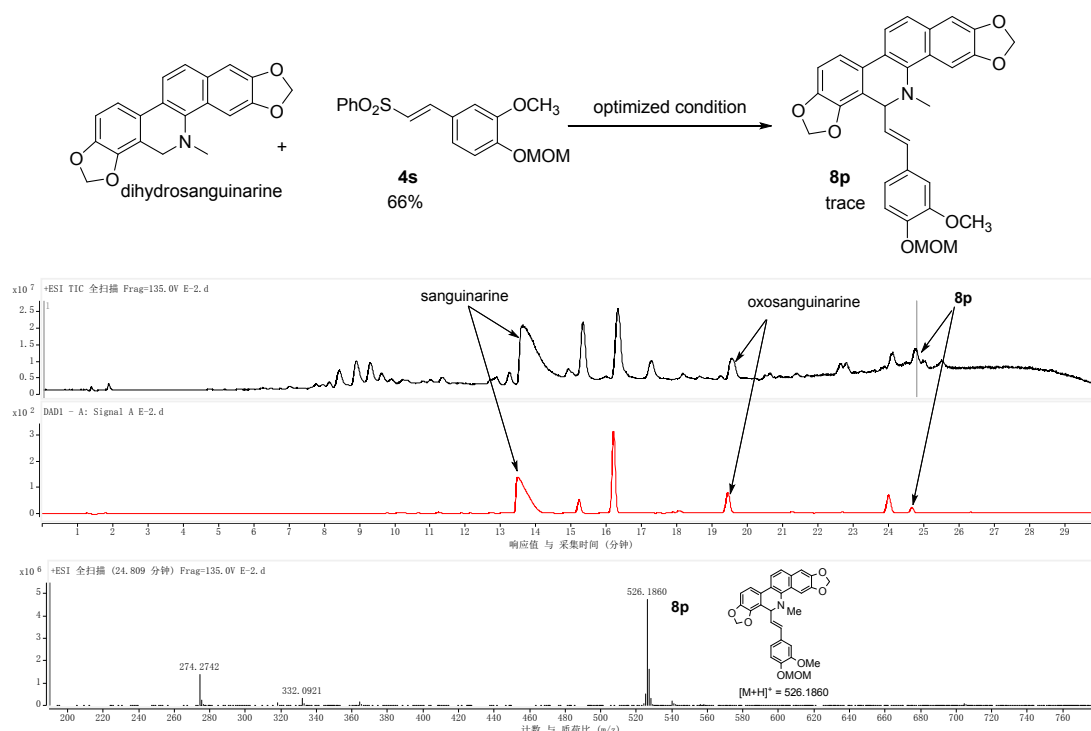
***Tentative synthesis of O-MOM protected Maclekarpine E***

The *O*-methoxymethyl (O-MOM protected) sulfone material **4s** with vanilline **1s** as starting material in three steps (Scheme 1s). The synthesis of intermediate **3s** was slightly modified based on previous literature (*Chem. Comm.* **2015**, 51, 7393.)



**Scheme 1s.** Reaction conditions: (a) 3.0 eq MOMBr, 6.0 eq. NaH, 0°C-rt, 8 h; (b) 3.0 eq. CH<sub>3</sub>PPh<sub>3</sub>Br, 4.0 eq. *t*-BuOK, THF, reflux 4h; (c) 3.0 eq. PhSO<sub>2</sub>Na, 1.5 eq. NaOAc, 1.5 eq. I<sub>2</sub>, MeCN reflux 1h.

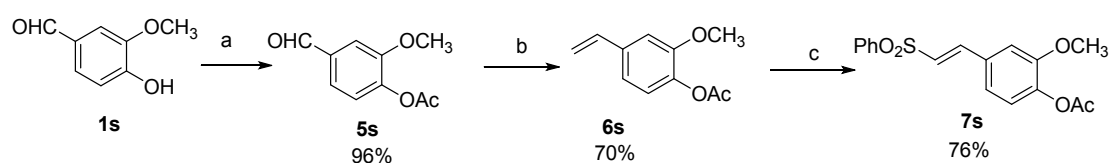
As shown in scheme 2s, the *O*-MOM protected maclekarpine E (**8p**) was only detected in trace yield under the optimized photocatalytic condition according to HPLC-Q-TOF-MS analysis. However, the reaction product is different from the reaction with *O*-Bn protected sulfone, because corresponding target compound can't be detected under the optimized condition when *O*-Bn protected sulfone is used as coupling partner.



**Scheme 2s.** HPLC-Q-TOF analysis of crude product with **10** as substrate

### ***Tentative synthesis of O-Ac protected maclekarpine E***

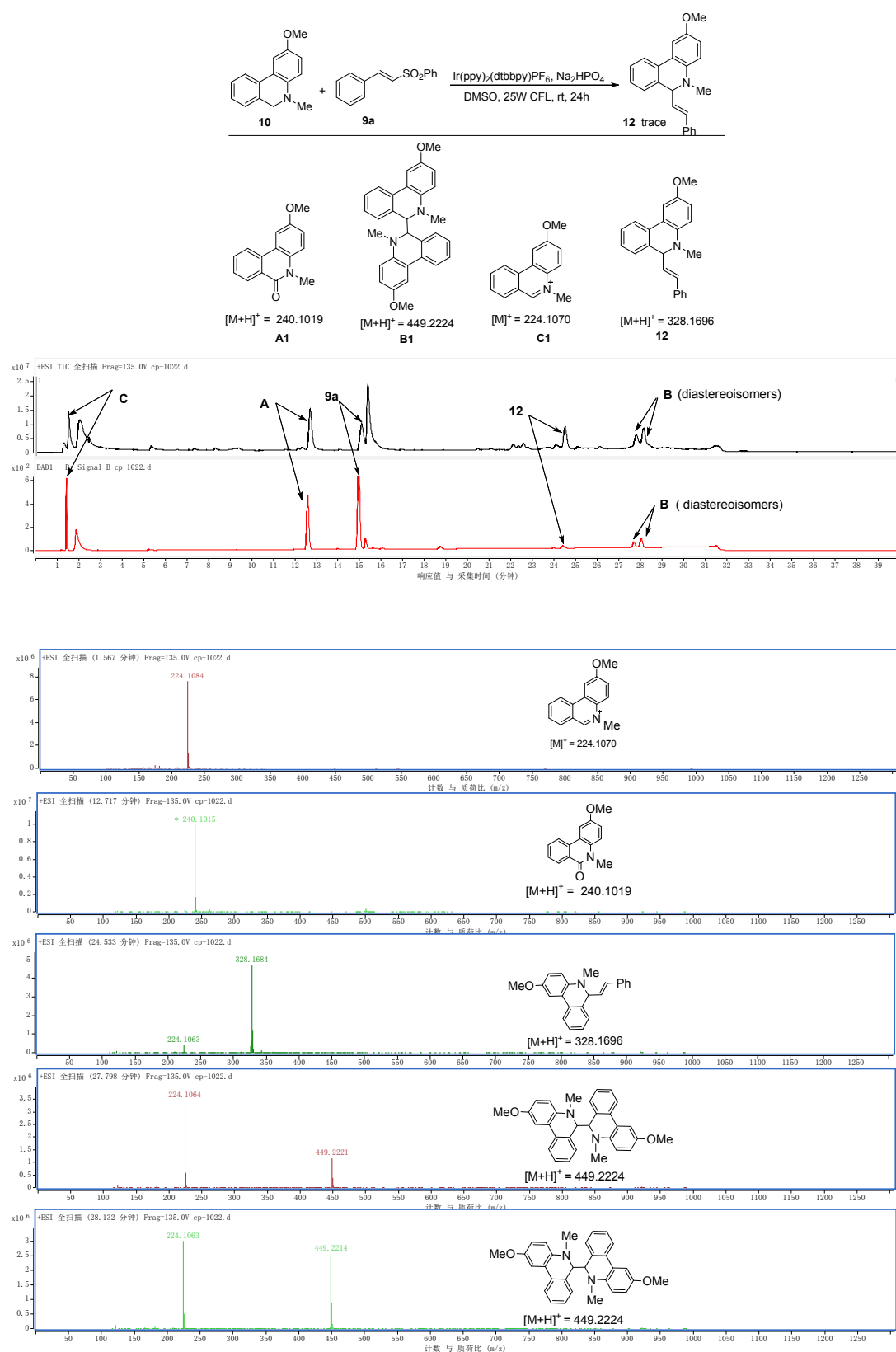
The *O*-Ac protected sulfone material **7s** with vanilline **1s** as starting material in three steps (Scheme 3s). The synthesis of intermediate **6s** was slightly modified based on previous literature (*Org. Biomol. Chem.* **2013**, 11, 3674.)



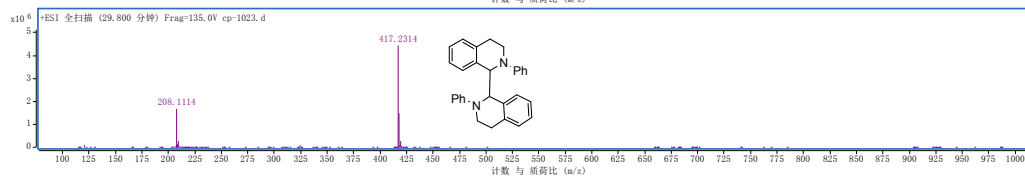
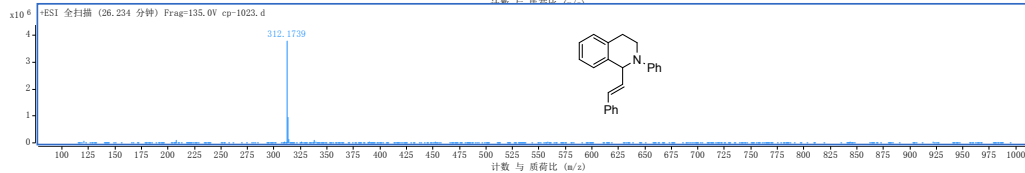
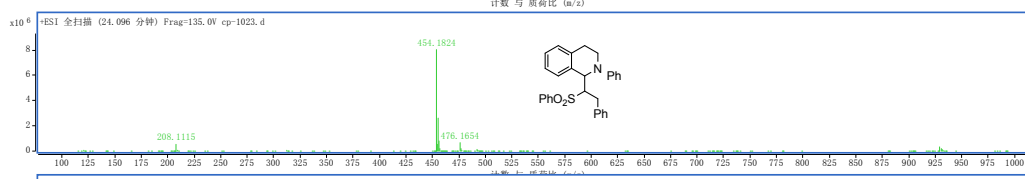
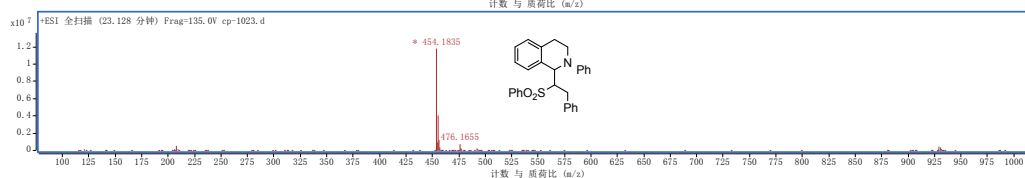
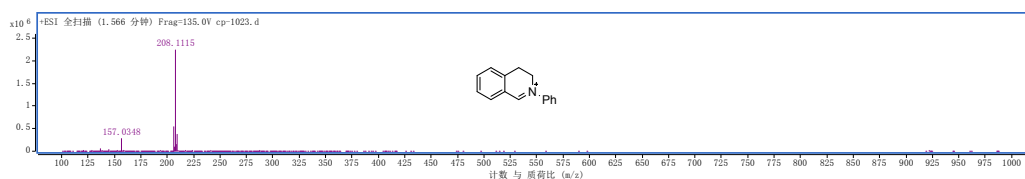
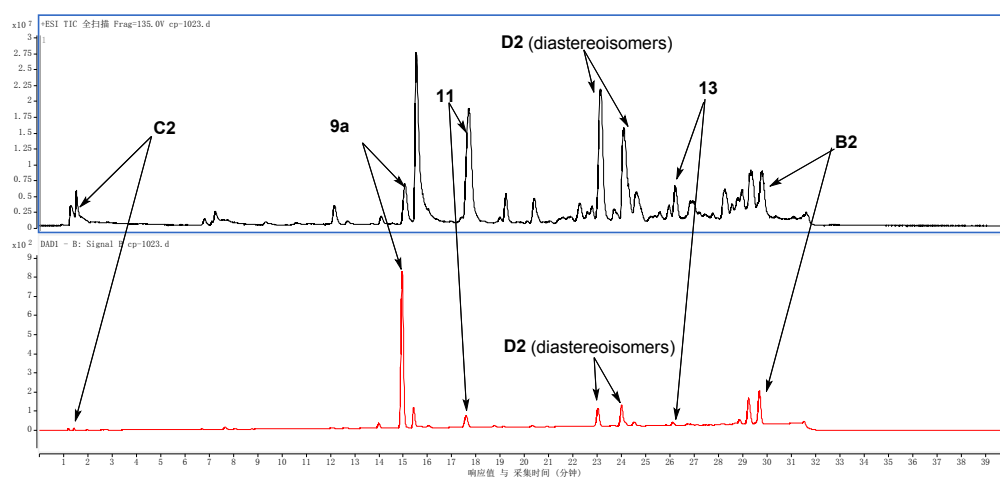
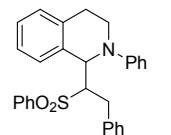
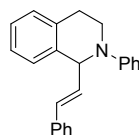
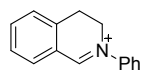
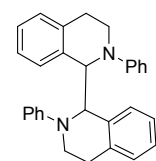
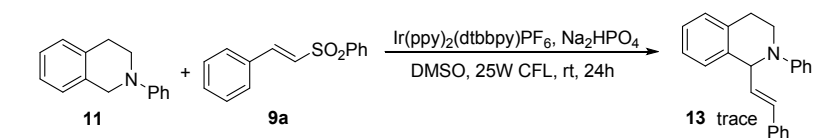
**Scheme 3s.** Reaction conditions: (a) 6.0 eq.  $\text{Ac}_2\text{O}$ , pyridine, rt, 12 h; (b) 1.5 eq.  $\text{CH}_3\text{PPh}_3\text{Br}$ , 2.0 eq.  $\text{K}_2\text{CO}_3$ , THF, reflux 4h; (c) 3.0 eq.  $\text{PhSO}_2\text{Na}$ , 1.5 eq.  $\text{NaOAc}$ , 1.5 eq.  $\text{I}_2$ , MeCN reflux 1h.

### **Scheme 2s**

**HPLC-Q-TOF analysis for the crude product with dihydrophenanthridine and *N*-phenyl-1,2,3,4-tetrahydroisoquinone as amine substrates (scheme 3 in the manuscript).**



**Scheme 4s.** HPLC-Q-TOF analysis of crude product with **10** as substrate

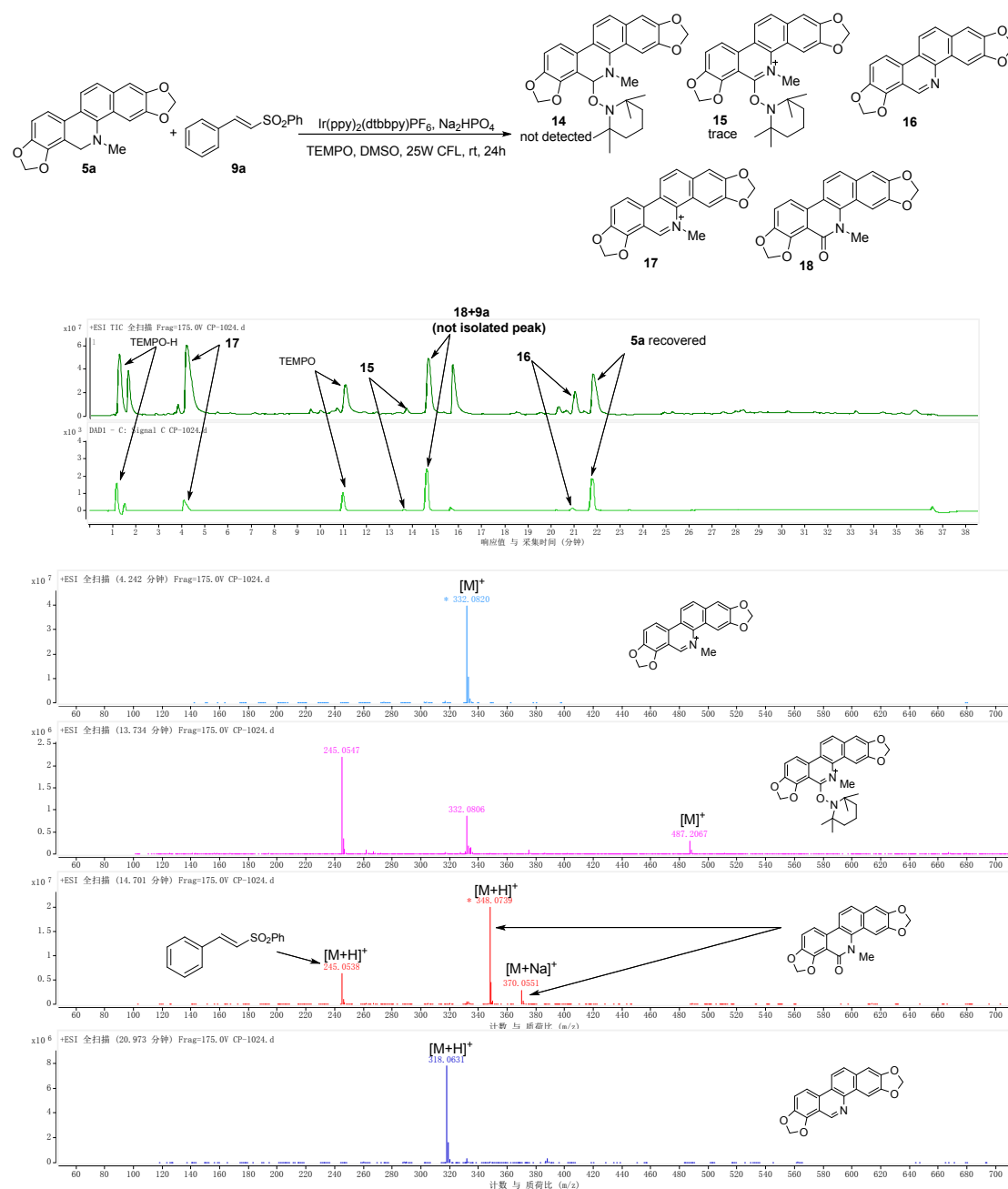


**Scheme 5s.** HPLC-Q-TOF analysis of crude product with **11** as substrate

As shown in scheme s1-s2, only trace of desired compounds **12-13** could be detected through HPLC-Q-TOF analysis in both reactions. However, the byproducts in these two cases were different. In scheme s1, oxophenanthridine (**A1**) was detected as major byproducts, which indicated that trace molecular oxygen in the reaction system could be trapped by corresponding  $\alpha$ -amino C-radical. In scheme s2, the radical addition products (**D2**) were detected as major byproducts, which indicated that the hydrogen atom abstraction process was favored under the optimized reaction condition. In both cases, the radical-radical coupling products (**B1** and **B2**) between two  $\alpha$ -amino C-radicals were observed. The above result helps us have a better understanding of the reaction mechanism.

### ***Radical trapping experiment***

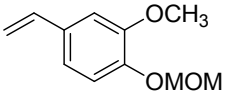
Under standard reaction conditions, 3.0 equiv of 2,2,6,6-tetramethylpiperidinoxy free radical (TEMPO) was added to the reaction system (scheme 6s). After 24 h reaction, HPLC-HRMS analysis of the crude product showed that coupling reaction was totally shutdown. From the HPLC analysis, we could observe that demethylsanguinarine (**16**), sanguinarine (**17**) and oxosanguinarine (**18**) were detected after 24 hours reaction. However, oxosanguinarine (**18**) and starting material were not isolated under present HPLC condition. Moreover, dihydrosanguinarine (**5a**) was found recovered. The trapping product (**14**) was not detected, but its oxidized quaternary salt (**15**) could be observed through HPLC-HRMS analysis.

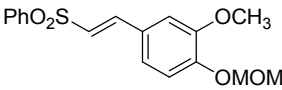


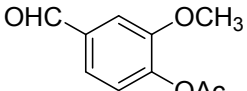
**Scheme 6s.** HPLC-Q-TOF analysis of trapping experiment

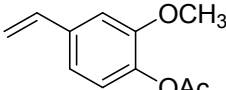
### Characterization data of intermediates **2s**, **3s**, **4s**, **5s**, **6s** and **7s**

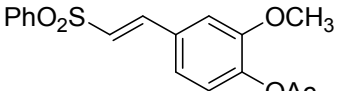
**Compound 2s:** Obtained as colorless oil,  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ ):  $\delta$  9.83 (s, 1H), 7.40 (s, 1H), 7.39 (dd,  $J = 1.0, 8.0$  Hz, 1H), 7.23 (d,  $J = 8.0$  Hz, 1H), 5.29 (s, 2H), 3.91 (s, 3H), 3.48 (s, 3H),  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ ):  $\delta$  190.8, 151.9, 150.0, 131.0, 126.2, 114.6, 109.5, 94.9, 56.4, 55.9.


**Compound 3s:** Obtained as colorless oil,  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ ):  $\delta$  7.09 (d,  $J = 8.5$  Hz, 1H), 6.97 (d,  $J = 2.0$  Hz, 1H), 6.92 (dd,  $J = 2.0, 8.0$  Hz, 1H), 6.45 (dd,  $J = 11.0, 17.5$  Hz, 1H), 5.63 (d,  $J = 17.5$  Hz, 1H), 5.22 (s, 2H), 5.15 (d,  $J = 11.0$  Hz, 1H), 3.90 (s, 3H), 3.51 (s, 3H).  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ ):  $\delta$  149.7, 146.3, 136.4, 132.3, 119.3, 116.2, 112.3, 109.1, 95.4, 56.1, 55.8.

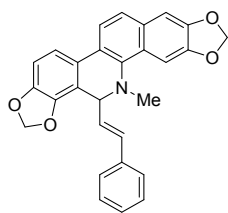

**Compound 4s:** Obtained as colorless oil,  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ ):  $\delta$  7.91 (d,  $J = 7.5$  Hz, 2H), 7.60 (d,  $J = 15.5$  Hz, 1H), 7.56 (d,  $J = 7.5$  Hz, 1H), 7.50 (t,  $J = 7.5$  Hz, 2H), 7.10 (d,  $J = 8.5$  Hz, 1H), 7.20 (dd,  $J = 2.0, 8.5$  Hz, 1H), 6.99 (d,  $J = 2.0$  Hz, 1H), 6.77 (d,  $J = 15.5$  Hz, 1H). 5.21 (s, 2H), 3.84 (s, 3H), 3.45 (s, 3H).  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ ):  $\delta$  149.8, 149.1, 142.3, 140.9, 133.1, 129.1 ( $\times 2$ ), 127.4 ( $\times 2$ ), 126.4, 125.2, 122.9, 115.6, 110.7, 95.0, 56.2, 55.8.


**Compound 5s:** Obtained as white solid,  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ ):  $\delta$  9.87 (s, 1H), 7.45 (s, 1H), 7.42 (d,  $J = 7.5$  Hz, 1H), 7.16 (d,  $J = 7.5$  Hz, 1H), 3.85 (s, 3H), 2.29 (s, 3H).  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ ):  $\delta$  190.9, 168.2, 151.8, 144.8, 135.0, 124.4, 123.2, 110.7, 55.9, 20.4.

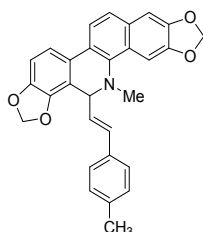

**Compound 6s:** Obtained as white solid,  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ ):  $\delta$  7.05 (s, 1H), 7.02 (s, 2H), 6.70 (dd,  $J = 17.0, 11.0$  Hz, 1H), 5.74 (d,  $J = 17.5$  Hz, 1H), 5.28 (d,  $J = 10.5$  Hz, 1H), 3.86 (s, 3H), 2.33 (s, 3H).  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ ):  $\delta$  168.7, 150.9, 139.2, 136.4, 136.0, 122.5, 118.6, 113.8, 109.7, 55.5, 20.3.


**Compound 7s:** Obtained as white solid,  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ ):  $\delta$  7.96 (d,  $J = 6.0$  Hz, 2H), 7.67-7.58 (m, 4H), 7.10 (s, 1H), 7.07 (s, 2H), 6.85 (d,  $J = 15.0$  Hz, 1H). 3.86 (s, 3H), 2.33 (s, 3H).  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ ):  $\delta$  168.5, 151.5, 142.1, 141.8, 140.6, 133.4, 131.2, 129.3 $\times 2$ , 127.6 $\times 2$ , 127.4, 123.4, 121.7, 111.7, 55.9, 20.5.

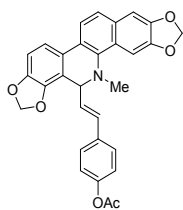
### Characterization data of compounds 8



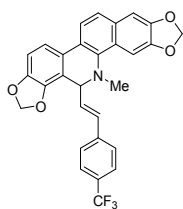
**Compound 8a.** Obtained as pale yellow amorphous powder,  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  7.82 (s, 1H), 7.71 (d,  $J=8.4$  Hz, 1H), 7.48 (d,  $J=8.4$  Hz, 1H), 7.39 (d,  $J=8.4$  Hz, 1H), 7.10-7.17 (m, 6H), 6.92 (d,  $J=8.4$  Hz, 1H), 6.38 (d,  $J=16.0$  Hz, 1H), 6.17 (dd,  $J=16.0, 5.2$  Hz, 1H), 6.12 (s, 1H), 6.08 (s, 3H), 5.05 (d,  $J=5.2$  Hz, 1H), 2.77 (s, 3H).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta$  148.1, 147.5, 147.1, 145.0, 140.5, 137.0, 131.0, 130.1, 128.9, 128.2 ( $\times 2$ ), 127.4, 127.2, 126.5 ( $\times 2$ ), 126.0, 123.9, 120.2, 116.5, 115.7, 107.5, 104.4, 101.5, 101.0, 100.8, 59.2, 42.8. HRMS ( $\text{ESI}^+$ ): calcd 436.1543 for  $\text{C}_{28}\text{H}_{22}\text{NO}_4^+ [\text{M}+\text{H}]^+$ ; found, 436.1537.



**Compound 8b.** Obtained as pale yellow amorphous powder,  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  7.81 (s, 1H), 7.70 (d,  $J=8.4$  Hz, 1H), 7.47 (d,  $J=8.8$  Hz, 1H), 7.38 (d,  $J=8.4$  Hz, 1H), 7.12 (s, 1H), 7.05 (d,  $J=8.0$  Hz, 2H), 6.97 (d,  $J=8.0$  Hz, 2H), 6.91 (d,  $J=8.0$  Hz, 1H), 6.34 (d,  $J=16.0$  Hz, 1H), 6.13-6.06 (m, 5H), 5.04 (d,  $J=4.2$  Hz, 1H), 2.76 (s, 3H), 2.25 (s, 3H).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta$  148.1, 147.5, 147.1, 145.0, 136.9, 134.2, 130.9, 130.0, 128.9 ( $\times 2$ ), 127.8, 127.4, 126.3 ( $\times 2$ ), 126.0, 123.9, 123.8, 120.2, 116.5, 115.7, 107.5, 104.3, 101.5, 101.0, 100.9, 59.2, 42.8, 21.1. HRMS ( $\text{ESI}^+$ ): calcd 450.1700 for  $\text{C}_{29}\text{H}_{24}\text{NO}_4^+ [\text{M}+\text{H}]^+$ ; found, 450.1687.

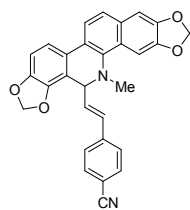


**Compound 8c.** Obtained as pale yellow amorphous powder,  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  7.80 (s, 1H), 7.70 (d,  $J=8.4$  Hz, 1H), 7.47 (d,  $J=8.8$  Hz, 1H), 7.38 (d,  $J=8.4$  Hz, 1H), 7.14 (d,  $J=8.4$  Hz, 2H), 7.12 (s, 1H), 6.91 (d,  $J=8.0$  Hz, 1H), 6.88 (d,  $J=8.4$  Hz, 2H), 6.34 (d,  $J=16.0$  Hz, 1H), 6.13-6.08 (m, 5H), 5.03 (d,  $J=4.8$  Hz, 1H), 2.75 (s, 3H), 2.24 (s, 3H).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta$  169.3, 149.7, 148.2, 147.5, 147.1, 145.0, 140.4, 134.8, 131.0, 129.1, 129.1, 127.4 ( $\times 3$ ), 126.0, 123.9, 123.8, 121.3 ( $\times 2$ ), 120.1, 116.5, 115.6, 107.5, 104.5, 101.5, 101.0, 100.7, 59.0, 42.8, 21.0. HRMS ( $\text{ESI}^+$ ): calcd 494.1598 for  $\text{C}_{30}\text{H}_{24}\text{NO}_6^+ [\text{M}+\text{H}]^+$ ; found, 494.1588.

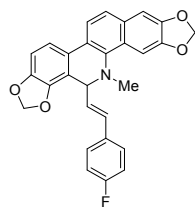


**Compound 8d.** Obtained as pale yellow amorphous powder,  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  7.82 (s, 1H), 7.72 (d,  $J=8.8$  Hz, 1H), 7.49 (d,  $J=8.4$  Hz, 1H), 7.41-7.38 (m, 3H), 7.22 (d,  $J=8.0$  Hz, 2H), 7.13 (s, 1H), 6.94 (dd,  $J=8.4$

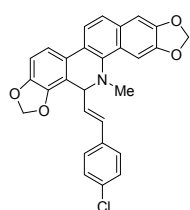
Hz, 1H), 6.40 (d,  $J = 8.0$  Hz, 1H), 6.27 (dd,  $J = 4.8, 8.0$  Hz, 1H), 6.11 (s, 1H), 6.08 (s, 3H), 5.08 (d,  $J = 8.4$  Hz, 1H), 2.78 (s, 3H).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta$  148.2, 147.6, 147.2, 145.0, 140.4, 140.2, 131.7, 131.0, 128.9 (q,  $J = 32.4$  Hz), 128.8, 127.3, 126.6 ( $\times 2$ ), 126.0, 125.1 ( $\times 2$ ) (q,  $J = 3.7$  Hz), 124.0, 123.8, 124.2 (q,  $J = 272.0$  Hz), 120.1, 116.6, 115.2, 107.8, 104.4, 101.6, 101.1, 100.7, 59.1, 42.8. HRMS ( $\text{ESI}^+$ ): calcd 504.1417 for  $\text{C}_{29}\text{H}_{21}\text{F}_3\text{NO}_4^+ [\text{M}+\text{H}]^+$ ; found, 504.1344.



**Compound 8e.** Obtained as pale yellow amorphous powder,  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  7.79 (s, 1H), 7.70 (d,  $J=8.4$  Hz, 1H), 7.48 (d,  $J=8.4$  Hz, 1H), 7.43 (d,  $J=8.4$  Hz, 2H), 7.39 (d,  $J=8.4$  Hz, 1H), 7.20 (d,  $J=8.4$  Hz, 2H), 7.13 (s, 1H), 6.93 (d,  $J=8.0$  Hz, 1H), 6.37 (d,  $J=16.0$  Hz, 1H), 6.28 (dd,  $J=16.0, 4.8$  Hz, 1H), 6.10 (s, 1H), 6.09 (s, 3H), 5.06 (d,  $J=4.0$  Hz, 1H), 2.77 (s, 3H).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta$  148.3, 147.6, 147.2, 145.0, 141.5, 140.1, 133.1, 132.0 ( $\times 2$ ), 131.0, 128.6, 127.3, 127.0 ( $\times 2$ ), 125.9, 124.1, 123.7, 120.1, 119.0, 116.7, 114.9, 110.3, 107.8, 104.4, 101.6, 101.1, 100.6, 59.0, 42.9. HRMS ( $\text{ESI}^+$ ): calcd 461.1496 for  $\text{C}_{29}\text{H}_{21}\text{N}_2\text{O}_4^+ [\text{M}+\text{H}]^+$ ; found, 461.1487.

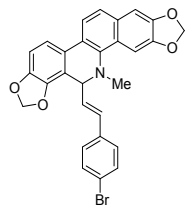


**Compound 8f.** Obtained as pale yellow amorphous powder,  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  7.81 (s, 1H), 7.71 (d,  $J=8.4$  Hz, 1H), 7.48 (d,  $J=8.4$  Hz, 1H), 7.39 (d,  $J=8.0$  Hz, 1H), 7.12-7.10 (m, 3H), 6.92 (d,  $J=8.0$  Hz, 1H), 6.84 (t,  $J=8.4\text{Hz}$ , 2H), 6.33 (d,  $J=16.0$  Hz, 1H), 6.11-6.08 (m, 5H), 5.03(d,  $J=4.4$  Hz, 1H), 2.76 (s, 3H).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta$  162.1 (d,  $J=244.8$  Hz), 148.2, 147.5, 147.1, 145.0, 140.4, 133.1 (d,  $J=3.2$  Hz), 131.0, 129.0, 128.7 (d,  $J=2.0$  Hz), 127.9 ( $\times 2$ ) (d,  $J=7.9$  Hz), 127.4, 126.0, 123.9, 123.8, 120.1, 116.6, 115.6, 115.0 ( $\times 2$ ) (d,  $J=21.4$  Hz), 107.6, 104.4, 101.5, 101.0, 100.8, 59.1, 42.8. HRMS ( $\text{ESI}^+$ ): calcd 454.1449 for  $\text{C}_{28}\text{H}_{21}\text{FNO}_4^+ [\text{M}+\text{H}]^+$ ; found, 454.1385.



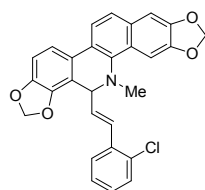
**Compound 8g.** Obtained as pale yellow amorphous powder,  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  7.79 (s, 1H), 7.71 (d,  $J=8.4$  Hz, 1H), 7.48 (d,  $J=8.0$  Hz, 1H), 7.38 (d,  $J=8.0$  Hz, 1H), 7.13-7.06(m, 5H), 6.92 (d,  $J=8.0$  Hz, 1H), 6.31 (d,  $J=16.0$  Hz, 1H), 6.15-6.08 (m, 5H), 5.03 (d,  $J=4.8$  Hz, 1H), 2.76(s, 3H).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta$  148.2, 147.5, 147.1, 145.0, 140.3, 135.5, 132.7, 131.0, 129.6, 128.9,

128.3 (×2), 127.7 (×2), 127.4, 126.0, 123.9, 120.1, 116.6, 115.4, 107.6, 104.4, 101.5, 101.0, 100.8, 59.1, 42.8. HRMS (ESI<sup>+</sup>): calcd 470.1154 for C<sub>28</sub>H<sub>21</sub>ClNO<sub>4</sub><sup>+</sup> [M+H]<sup>+</sup>; found, 470.1150.



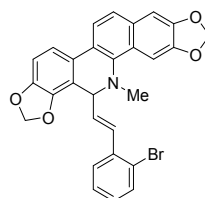
**Compound 8h.** Obtained as pale yellow amorphous powder, <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 7.81 (s, 1H), 7.71 (d, *J*=8.4 Hz, 1H), 7.48 (d, *J*=8.4 Hz, 1H), 7.39 (d, *J*=8.0 Hz, 1H), 7.27 (d, *J*=8.0 Hz, 2H), 7.13 (s, 1H), 7.01 (d, *J*=8.0 Hz, 2H), 6.93 (d, *J*=8.0 Hz, 1H), 6.33 (d, *J*=16.0 Hz, 1H), 6.16 (dd, *J*=16.0, 8.4

Hz 1H), 6.12-6.06 (m, 4H), 5.04 (d, *J*=3.2 Hz, 1H), 2.77 (s, 3H). <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>): δ 148.2, 147.6, 147.1, 145.0, 140.3, 135.9, 131.3 (×2), 131.0, 129.8, 129.0, 128.0 (×2), 127.4, 126.0, 124.0, 123.8, 120.9, 120.1, 116.6, 115.4, 107.7, 104.4, 101.5, 101.1, 100.8, 59.1, 42.7. HRMS (ESI<sup>+</sup>): calcd 514.0648 for C<sub>28</sub>H<sub>21</sub>BrNO<sub>4</sub><sup>+</sup> [M+H]<sup>+</sup>; found, 514.0646.



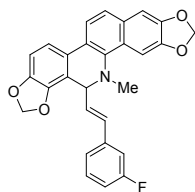
**Compound 8i.** Obtained as pale yellow amorphous powder, <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 7.85 (s, 1H), 7.71 (d, *J*=8.4 Hz, 1H), 7.49 (d, *J*=8.8 Hz, 1H), 7.39 (d, *J*=8.0 Hz, 1H), 7.28-7.27 (m, 1H), 7.20-7.18 (m, 1H), 7.13 (s, 1H), 7.03-7.01 (m, 2H), 6.92 (d, *J*=8.0 Hz, 1H), 6.86 (d, *J*=16.0 Hz, 1H),

6.14-6.07 (m, 5H), 5.10 (d, *J*=4.0 Hz, 1H), 2.79 (s, 3H). <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>): δ 148.2, 147.5, 147.2, 145.0, 140.4, 135.1, 133.0, 131.2, 131.0, 129.4, 128.1, 127.5, 126.8, 126.6, 126.4, 126.0, 124.0, 123.8, 120.2, 116.5, 107.6, 104.4, 101.6, 101.0, 101.0, 59.2, 42.8. HRMS (ESI<sup>+</sup>): calcd 470.1154 for C<sub>29</sub>H<sub>21</sub>ClNO<sub>4</sub><sup>+</sup> [M+H]<sup>+</sup>; found, 470.1159.

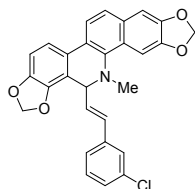


**Compound 8j.** Obtained as pale yellow amorphous powder, <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 7.87 (s, 1H), 7.72 (d, *J*=8.8 Hz, 1H), 7.49 (d, *J*=8.8 Hz, 1H), 7.39 (t, *J*=8.4, 2H), 7.27 (d, *J*=8.0 Hz, 1H), 7.13 (s, 1H), 7.07 (t, *J*=8.0Hz,1H), 6.94 (d, *J*=8.0 Hz, 2H), 6.90 (d, *J*=16.0 Hz, 1H), 6.12- 6.06 (m,

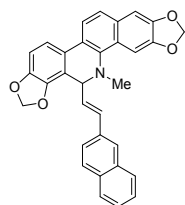
5H), 5.11 (d, *J*=4.0 Hz, 1H), 2.80 (s, 3H). <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>): δ 148.2, 147.5, 147.2, 144.9, 140.4, 136.9, 132.6, 131.4, 131.0, 129.3, 128.4, 127.4, 127.1, 127.0, 126.0, 124.0, 123.8, 123.6, 120.2, 116.5, 115.6, 107.7, 104.4, 101.6, 101.0, 101.1, 59.0, 42.8. HRMS (ESI<sup>+</sup>): calcd 514.0648 for C<sub>28</sub>H<sub>21</sub>BrNO<sub>4</sub><sup>+</sup> [M+H]<sup>+</sup>; found, 514.0655.



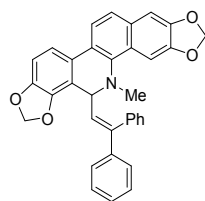
**Compound 8k.** Obtained as pale yellow amorphous powder,  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ ):  $\delta$  7.80 (s, 1H), 7.70 (d,  $J = 8.5$  Hz, 1H), 7.47 (d,  $J = 8.5$  Hz, 1H), 7.38 (d,  $J = 8.5$  Hz, 1H), 7.11 (s, 1H), 7.10-7.07 (m, 1H), 6.91 (d,  $J = 8.0$  Hz, 1H), 6.90 (d,  $J = 8.5$  Hz, 1H), 6.85 (d,  $J = 8.5$  Hz, 1H), 6.78 (dt,  $J = 2.0$ , 8.0 Hz, 1H), 6.34 (d,  $J = 16.0$  Hz, 1H), 6.17 (dd,  $J = 5.5$ , 16.0 Hz, 1H), 6.10 (d,  $J = 1.5$  Hz, 1H), 6.06 (s, 3H), 6.04 (dd,  $J = 1.5$ , 5.0 Hz, 1H), 2.76 (s, 3H).  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ ):  $\delta$  162.8 (d,  $J = 243.1$  Hz), 148.2, 147.5, 147.1, 145.0, 140.2, 139.3 (d,  $J = 7.5$  Hz), 130.9, 130.3, 129.5 (d,  $J = 8.4$  Hz), 129.0, 127.3, 125.9, 123.9, 123.8, 122.3, 120.1, 116.5, 115.3, 113.8 (d,  $J = 21.1$  Hz), 112.8 (d,  $J = 21.5$  Hz), 107.6, 104.4, 101.5, 101.0, 100.7, 59.0, 42.8. HRMS ( $\text{ESI}^+$ ): calcd 454.1449 for  $\text{C}_{28}\text{H}_{21}\text{FNO}_4$   $[\text{M}+\text{H}]^+$ ; found, 454.1451.



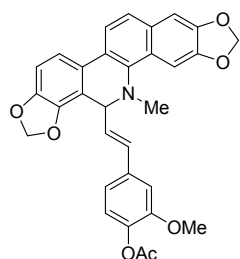
**Compound 8l.** Obtained as pale yellow amorphous powder,  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ ):  $\delta$  7.79 (s, 1H), 7.69 (d,  $J = 8.5$  Hz, 1H), 7.46 (d,  $J = 8.5$  Hz, 1H), 7.37 (d,  $J = 8.0$  Hz, 1H), 7.12 (s, 1H), 7.11 (s, 1H), 7.06-7.05 (m, 2H), 7.00-6.99 (m, 1H), 6.91 (d,  $J = 8.0$  Hz, 1H), 6.30 (dd,  $J = 1.5$ , 16 Hz, 1H), 6.16 (dd,  $J = 5.0$ , 16 Hz, 1H), 6.10 (d,  $J = 1.5$  Hz, 1H), 6.06 (s, 3H), 5.03 (dd,  $J = 1.5$ , 5.0 Hz, 1H), 2.75 (s, 3H).  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ ):  $\delta$  148.2, 147.5, 147.1, 145.0, 140.2, 138.8, 134.1, 130.9, 130.5, 129.4, 128.8, 127.3, 127.0, 126.3, 125.9, 124.6, 123.9, 123.7, 120.1, 116.6, 115.3, 107.6, 104.4, 101.5, 101.0, 100.7, 59.0, 42.8. HRMS ( $\text{ESI}^+$ ): calcd 470.1154 for  $\text{C}_{28}\text{H}_{21}\text{ClNO}_4$   $[\text{M}+\text{H}]^+$ ; found, 470.1154.



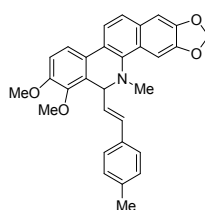
**Compound 8m.** Obtained as pale yellow amorphous powder,  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  7.91 (s, 1H), 7.73 (t,  $J = 8.0$  Hz, 2H), 7.63 (d,  $J = 8.0$  Hz, 1H), 7.52 (d,  $J = 8.0$  Hz, 1H), 7.41 (d,  $J = 8.0$  Hz, 1H), 7.38-7.32 (m, 2H), 7.230-7.20 (m, 4H), 7.17 (s, 1H), 7.12 (d,  $J = 16.0$  Hz, 1H), 6.93 (d,  $J = 8.0$  Hz, 1H), 6.14-6.06 (m, 4H), 5.18 (d,  $J = 2.8$  Hz, 1H), 2.84 (s, 3H).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta$  148.3, 147.5, 147.2, 144.9, 140.5, 135.0, 133.4, 131.2, 131.1, 131.0, 128.2, 127.7, 127.5, 127.4, 126.1, 125.5, 125.4, 125.3, 124.0, 123.9, 123.8, 123.4, 120.2, 116.6, 116.0, 107.6, 104.4, 101.6, 101.1, 100.8, 59.2, 42.6. HRMS ( $\text{ESI}^+$ ): calcd 486.1700 for  $\text{C}_{32}\text{H}_{24}\text{NO}_4$   $[\text{M}+\text{H}]^+$ ; found, 486.1704.



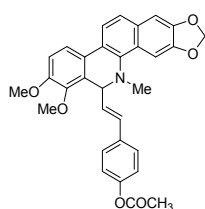
**Compound 8n.** Obtained as pale yellow amorphous powder,  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  7.78 (d,  $J=8.0\text{Hz}$ , 1H), 7.77 (s, 1H), 7.59-7.46 (m, 6H), 7.39 (d,  $J=8.0\text{Hz}$ , 1H), 7.13 (brs, 4H), 7.09 (brs, 2H), 6.89 (d,  $J=8.0\text{ Hz}$ , 1H), 6.08-6.06 (m, 2H), 5.99 (s, 1H), 5.92 (s, 1H), 5.88 (d,  $J=9.6\text{ Hz}$ , 1H), 4.85 (d,  $J=9.6\text{ Hz}$ , 1H), 2.58 (s, 3H).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta$  148.0, 147.5, 147.2, 146.0, 143.6, 142.0, 140.9, 139.9, 130.9, 130.4 ( $\times 2$ ), 128.0 ( $\times 2$ ), 127.8 ( $\times 2$ ), 127.6 ( $\times 2$ ), 127.6, 127.4, 127.3, 127.2, 126.8, 124.0, 123.8, 120.2, 116.5, 116.3, 107.3, 104.3, 101.3, 101.1, 101.0, 66.1, 41.5. HRMS (ESI $^+$ ): calcd 512.1856 for  $\text{C}_{34}\text{H}_{26}\text{NO}_4^+$  [M+H] $^+$ ; found, 512.1850.



**Compound 8q.** Obtained as white amorphous powder,  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ ):  $\delta$  7.80 (s, 1H), 7.72 (d,  $J = 8.5\text{ Hz}$ , 1H), 7.49 (d,  $J = 8.5\text{ Hz}$ , 1H), 7.40 (d,  $J = 8.0\text{ Hz}$ , 1H), 7.12 (s, 1H), 6.94 (d,  $J = 8.0\text{ Hz}$ , 1H), 6.83 (d,  $J = 8.0\text{ Hz}$ , 1H), 6.76 (s, 1H), 6.73 (d,  $J = 7.5\text{ Hz}$ , 1H), 6.32 (d,  $J = 15.5\text{ Hz}$ , 1H), 6.12-6.08 (m, 5H), 5.04 (br.s, 1H), 3.75 (s, 3H), 2.77 (s, 3H), 2.27 (s, 3H).  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ ):  $\delta$  168.9, 150.8, 148.1, 147.5, 147.1, 145.0, 140.4, 138.9, 136.0, 130.9, 129.6, 129.2, 127.3, 126.0, 123.9, 123.8, 122.4, 120.1, 119.2, 116.5, 115.5, 110.2, 107.6, 104.4, 101.5, 101.0, 100.8, 59.1, 55.8, 42.8, 20.6. HRMS (ESI $^+$ ): calcd 524.1704 for  $\text{C}_{31}\text{H}_{26}\text{NO}_7^+$  [M+H] $^+$ ; found, 524.1708.

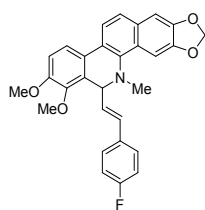


**Compound 8r.** Obtained as pale yellow amorphous powder,  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  7.81 (s, 1H), 7.72 (d,  $J=8.8\text{ Hz}$ , 1H), 7.59 (d,  $J=8.4\text{ Hz}$ , 1H), 7.46 (d,  $J=8.8\text{ Hz}$ , 1H), 7.12 (s, 1H), 7.03-7.00 (m, 3H), 6.94 (d,  $J=8.4\text{ Hz}$ , 2H), 6.29 (d,  $J=16.0\text{ Hz}$ , 1H), 6.18 (dd,  $J=16.0, 5.2\text{ Hz}$ , 1H), 6.07 (s, 2H), 5.28 (d,  $J=4.8\text{ Hz}$ , 1H), 3.98 (s, 3H), 3.97 (s, 3H), 2.73 (s, 3H), 2.23 (s, 3H).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta$  152.2, 148.0, 147.4, 146.3, 140.7, 136.7, 134.4, 130.9, 129.9, 129.0, 128.8 ( $\times 2$ ), 128.1, 127.3, 126.3 ( $\times 2$ ), 125.2, 123.8, 123.6, 119.9, 119.0, 111.4, 104.4, 101.0, 100.9, 61.0, 59.2, 55.8, 42.5, 21.0. HRMS (ESI $^+$ ): calcd 466.2013 for  $\text{C}_{30}\text{H}_{28}\text{NO}_4^+$  [M+H] $^+$ ; found, 466.2017.

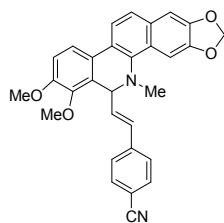


**Compound 8s.** Obtained as pale yellow amorphous powder,  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  7.81 (s, 1H), 7.72 (d,  $J=8.4\text{ Hz}$ , 1H), 7.59 (d,  $J=8.4\text{ Hz}$ ,

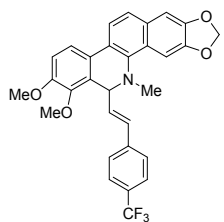
1H), 7.47 (d,  $J=8.4$  Hz, 1H), 7.13 (s, 1H), 7.11 (d,  $J=8.4$  Hz, 2H), 7.02 (d,  $J=8.8$  Hz, 1H), 6.86 (d,  $J=8.4$  Hz, 2H), 6.30 (d,  $J=16.0$  Hz, 1H), 6.13 (dd,  $J=16.0, 4.8$  Hz, 1H), 6.07 (s, 2H), 5.28 (d,  $J=4.8$  Hz, 1H), 3.98 (s, 3H), 3.97 (s, 3H), 2.74 (s, 3H), 2.23 (s, 3H).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta$  169.4, 152.2, 149.6, 148.1, 147.5, 146.3, 140.6, 135.0, 131.0, 130.4, 129.1, 127.8, 127.3 ( $\times 2$ ), 125.2, 125.1, 123.8, 121.2 ( $\times 2$ ), 119.9, 119.0, 111.5, 104.4, 101.0, 100.8, 61.0, 59.1, 55.8, 42.4, 21.0. HRMS (ESI $^+$ ): calcd 510.1911 for  $\text{C}_{31}\text{H}_{28}\text{NO}_6$  $^+$  [M+H] $^+$ ; found, 510.1902.



**Compound 8t.** Obtained as pale yellow amorphous powder,  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  7.81 (s, 1H), 7.72 (d,  $J=8.8$  Hz, 1H), 7.59 (d,  $J=8.4$  Hz, 1H), 7.48 (d,  $J=8.4$  Hz, 1H), 7.13 (s, 1H), 7.09-7.06 (m, 2H), 7.02 (d,  $J=8.4$  Hz, 1H), 6.82 (t,  $J=8.4$  Hz, 2H), 6.28 (d,  $J=16.0$  Hz, 1H), 6.08 (dd,  $J=16.0, 3.6$  Hz, 1H), 6.08 (s, 2H), 5.26 (d,  $J=3.6$  Hz, 1H), 3.98 (s, 6H), 2.74 (s, 3H).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta$  162.0 (d,  $J=244.0$  Hz), 152.2, 148.1, 147.5, 146.2, 140.6, 133.3, 133.3, 131.0, 129.8 (d,  $J=2.0$  Hz), 128.8, 127.8, 127.8 ( $\times 2$ ) (d,  $J=7.9$  Hz), 127.2, 125.1, 123.7, 119.9, 119.0, 115.0 ( $\times 2$ ) (d,  $J=21.4$  Hz), 111.5, 104.4, 101.0, 100.8, 60.9, 59.1, 56.8, 42.5. HRMS (ESI $^+$ ): calcd 470.1762 for  $\text{C}_{29}\text{H}_{25}\text{FNO}_4$  $^+$  [M+H] $^+$ ; found, 470.1770.

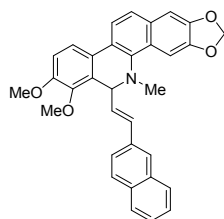


**Compound 8u.** Obtained as pale yellow amorphous powder,  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  7.80 (s, 1H), 7.72 (d,  $J=8.8$  Hz, 1H), 7.60 (d,  $J=8.4$  Hz, 1H), 7.48 (d,  $J=8.4$  Hz, 1H), 7.41 (d,  $J=8.4$  Hz, 2H), 7.17 (d,  $J=8.4$  Hz, 2H), 7.13 (s, 1H), 7.03 (d,  $J=8.4$  Hz, 1H), 6.31-6.30 (m, 2H), 6.09 (d,  $J=2.0$  Hz, 2H), 5.29 (d,  $J=3.0$  Hz, 2H), 3.99 (s, 6H), 2.75 (s, 3H).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta$  152.2, 148.2, 147.6, 146.2, 141.7, 140.3, 134.3, 132.0 ( $\times 2$ ), 131.0, 128.4, 127.1, 127.1, 126.8 ( $\times 2$ ), 125.0, 123.9, 123.6, 119.9, 119.1, 119.0, 111.7, 110.1, 104.5, 101.1, 100.6, 61.0, 59.1, 55.8, 42.5. HRMS (ESI $^+$ ): calcd 477.1809 for  $\text{C}_{30}\text{H}_{25}\text{N}_2\text{O}_4$  $^+$  [M+H] $^+$ ; found, 477.1798.



**Compound 8v.** Obtained as pale yellow amorphous powder,  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  7.82 (s, 1H), 7.72 (d,  $J=8.8$  Hz, 1H), 7.60 (d,  $J=8.4$  Hz, 1H), 7.48 (d,  $J=8.8$  Hz, 1H), 7.36 (d,  $J=8.0$  Hz, 2H), 7.19 (d,  $J=8.0$  Hz, 2H), 7.13 (s, 1H), 7.03 (d,  $J=8.4$  Hz, 2H), 6.35 (d,  $J=16.0$  Hz, 1H), 6.27 (dd,

$J=16.0$ , 4.4 Hz, 1H), 6.06 (s, 2H), 5.30 (d,  $J=4.0$  Hz, 1H), 3.99 (s, 6H), 2.76 (s, 3H).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta$  152.2, 148.2, 147.5, 146.2, 140.7, 140.4, 132.9, 131.0, 128.8(q,  $J = 32.4$  Hz), 128.7, 127.4, 127.2, 126.5 ( $\times 2$ ), 125.1( $\times 2$ ) (q,  $J = 1.4$  Hz), 125.0, 124.1(q,  $J = 272.0$  Hz), 123.8, 123.7, 119.9, 119.0, 111.6, 104.4, 101.0, 100.7, 61.0, 59.1, 55.8, 42.5. HRMS ( $\text{ESI}^+$ ): calcd 520.1730 for  $\text{C}_{30}\text{H}_{25}\text{F}_3\text{NO}_4^+ [\text{M}+\text{H}]^+$ ; found, 520.1731.



**Compound 8w.** Obtained as pale yellow amorphous powder,  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  7.93 (s, 1H), 7.75 (d,  $J=8.0$  Hz, 1H), 7.71 (d,  $J=8.4$  Hz, 1H), 7.64-7.62 (m, 2H), 7.54 (d,  $J=8.4$  Hz, 1H), 7.36-7.33 (m, 2H), 7.29-7.27 (m, 2H), 7.20 (d,  $J=8.4$  Hz, 1H), 7.19 (s, 1H), 7.08 (d,  $J=16.0$  Hz, 1H), 7.03 (d,  $J=8.8$  Hz, 1H), 6.14 (dd,  $J=16$ , 4.4 Hz, 1H), 6.09 (s, 1H), 6.06 (s, 1H), 5.43 (d,  $J=2.8$  Hz, 1H), 4.06 (s, 3H), 3.99 (s, 3H), 2.84 (s, 3H).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta$  152.3, 148.2, 147.5, 146.3, 140.8, 135.2, 133.4, 132.4, 131.2, 131.0, 128.2, 128.1, 127.6, 127.4, 127.3, 125.5, 125.4( $\times 2$ ), 125.3, 124.0, 123.9, 123.8, 123.4, 120.1, 119.1, 111.6, 104.5, 101.0 100.8, 61.1, 59.2, 55.9, 42.3. HRMS ( $\text{ESI}^+$ ): calcd 502.2013 for  $\text{C}_{33}\text{H}_{28}\text{NO}_4^+ [\text{M}+\text{H}]^+$ ; found, 502.2025.

