Visible-light-promoted biomimetic reductive functionalization of quaternary benzophenanthridine alkaloids

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1. Blue-light mediated reduction of sanguinarine by NADH

A solution of sanguinarine (0.2 mmol) and NADH (0.2 mmol) in DMSO (2mL) was stirred under the irradiation of 455 nm blue light. After 12 hours, the reaction solution was analyzed by Agilent 6530 HPLC-Q-TOF/MS system. Results was shown in Figure S1 and S2.

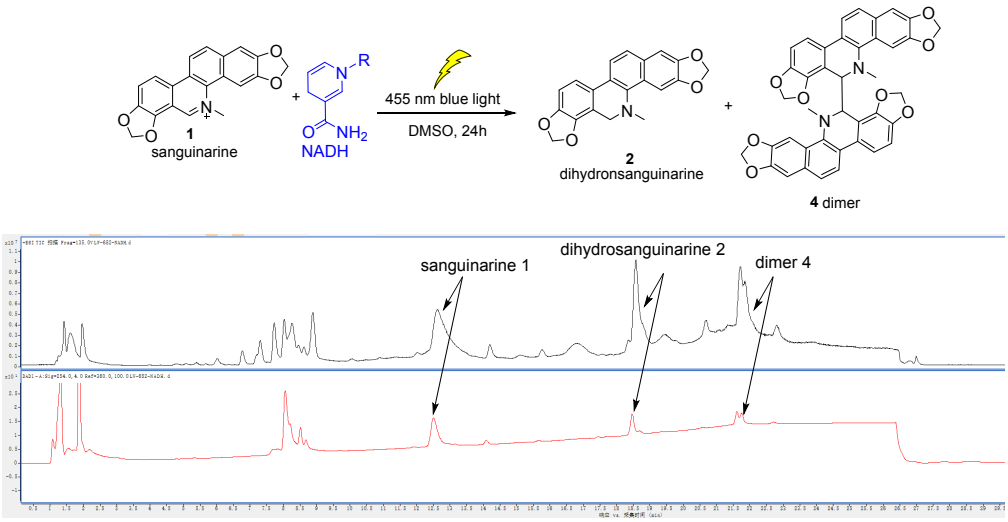


Figure S1. HPLC-HRMS results of light-mediated reduction of sanguinarine 1 by NADH

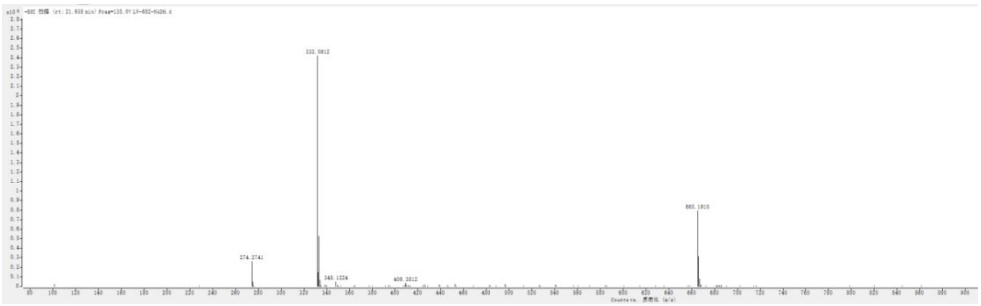


Figure S2. HRMS of dimer **4**, calculated 665.1918 for $C_{40}H_{29}N_2O_8^+$ $[M+H]^+$, found 665.1910

2. Photoreactor and general procedure for photoreaction

A Schlenk tube equipped with a magnetic stir bar (Figure S3) was charged with 0.2 mmol quaternary benzophenanthridine **1** or **8**, 2.0 equivalent of a 6-substituted DHP **6** and 2 mL DMSO under N_2 atmosphere. The flask was sealed by a plastic screw-cap with a Teflon sealed inlet for a glass rod. A high power LED (λ = 455 nm) was attached to the top of the glass rod, which then could act as an optical fiber. After irradiation at room temperature for 24 h, the LED was removed, the solvent was poured in 20 mL H_2O and extracted with 20 mL EtOAc for three times. The combined

organic layer was then washed with 20 mL H_2O for three times and evaporated, to give a crude product, which was purified by silica gel chromatography and eluted with PE/EA to give target compounds **7**.

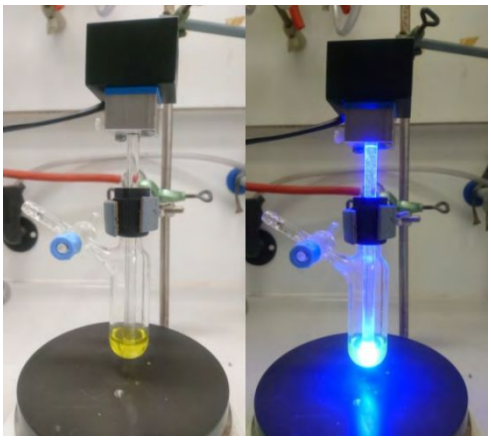
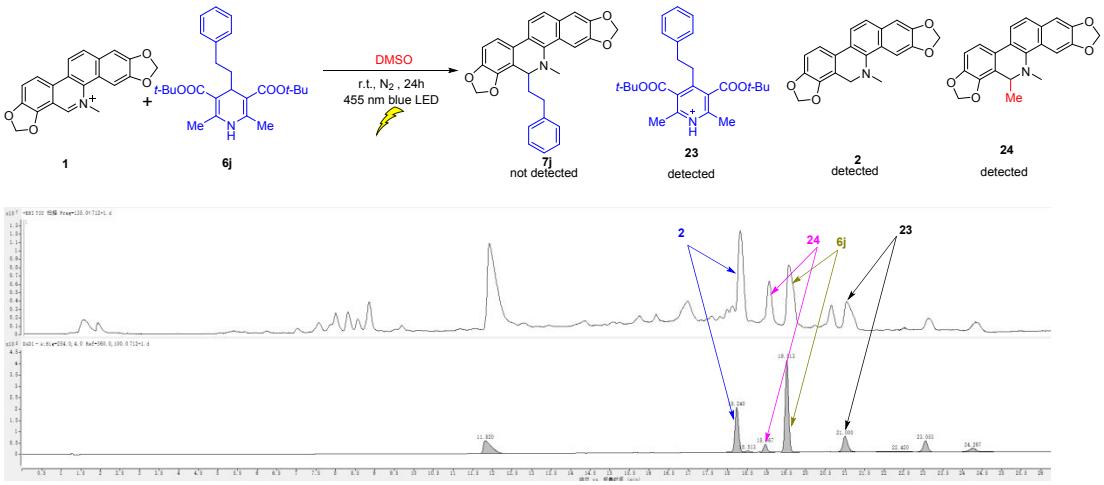


Figure S3. Photoreactor

3. Using primary 4-alkyl DHP **6j** as reductant and alkylation reagent

We also evaluated the reaction efficacy with primary C-radicals as coupling partners. While the desired compounds were not detected, unexpectedly methylation to **19** apparently utilizing DMSO as the methyl source, had taken place instead. This hypothesis was confirmed with the generation of 6-CD_3 substituted dihydrosanguinarine under "standard" reaction conditions when deuterated DMSO (DMSO-d6) was used as solvent (Figure S4).



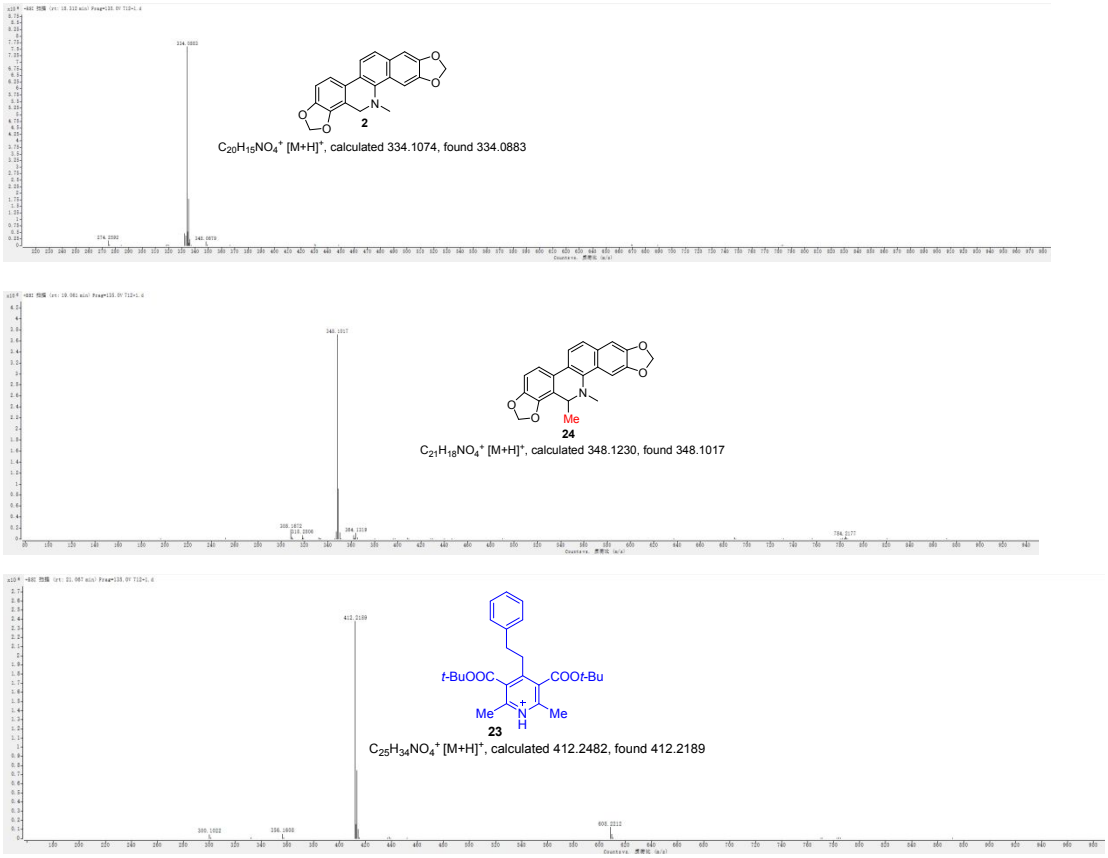
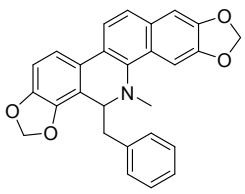
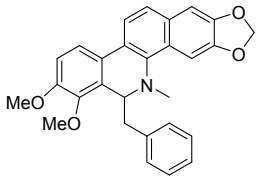


Figure S4. HPLL-MS results for 4-alkyl DHP **6j** as reductant and alkylation reagent

4. NMR spectra data of target compounds

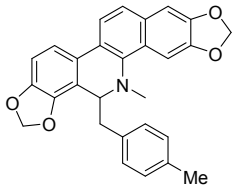


Compound **7a**, obtained as pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80(d, J = 8.4 Hz, 1H), 7.59 (s, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.28-7.24 (m, 3H), 7.18 (s, 1H), 7.08 (d, J = 6.4 Hz, 2H), 6.90 (d, J =8.4 Hz, 1H), 6.10 (dd, J = 15.2, 1.2 Hz, 2H), 5.98 (d, J = 1.6 Hz, 1H), 5.81 (d, J = 1.2 Hz, 1H), 4.46 (dd, J = 8.8, 6.0 Hz, 1H), 2.79-2.67 (m, 2H), 2.61(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0, 147.5, 146.9, 144.7, 140.0, 139.3, 131.1, 129.8(×2), 127.8(2), 127.6, 125.9, 125.7, 123.7, 123.7, 120.1, 117.3, 116.3, 107.3, 104.3, 101.3(×2), 101.0, 60.1, 43.1, 40.2. HRMS (ESI$^+$): calcd 424.1543 for $C_{27}H_{22}NO_4^+$ [M+H]$^+$; found, 424.1543.

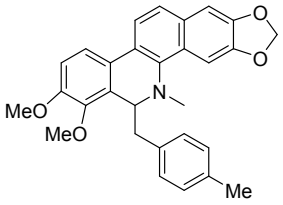


Compound **7aa**, obtained as pale yellow solid, ^{1}H NMR (400MHz, $CDCl_3$): δ 7.81(d, J = 8.4 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.56-7.53 (m, 2H), 7.33-7.27 (m, 3H), 7.18 (s, 1H),

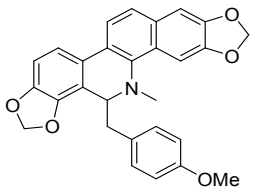
7.15-7.13 (m, 2H), 7.01 (d, J = 8.4 Hz, 1H), 6.12 (d, J =1.2 Hz, 1H), 6.07 (d, J = 1.2 Hz, 1H), 4.68 (dd, J = 10.8, 6.8 Hz, 1H), 3.97 (d, J =4.8 Hz, 6H), 2.74-2.59 (m, 2H), 2.56(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 147.9, 147.5, 145.9, 140.2, 140.1, 131.2, 129.8(×2), 129.8, 127.8(×2), 127.4, 125.8, 125.0, 123.6, 123.5, 119.8, 118.7, 111.5, 104.3, 101.4, 100.9, 60.8, 60.3, 55.9, 42.9, 40.3. HRMS (ESI$^+$): calcd 440.1856 for $C_{28}H_{26}NO_4^+$ $[M+H]^+$; found, 440.1857.



Compound **7b**, obtained as white solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79(d, J = 8.4 Hz, 1H), 7.61(s, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.17 (s, 1H), 7.10(d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.0 Hz, 2H), 6.89(d, J = 8.0 Hz, 1H), 6.12(d, J = 1.2 Hz, 1H), 6.08(d, J = 0.8 Hz, 1H), 5.99(d, J = 1.2 Hz, 1H), 5.84 (d, J = 1.2 Hz, 1H), 4.42 (dd, J = 9.2, 6.0 Hz, 1H), 2.73-2.65 (m, 2H), 2.60 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0, 147.5, 146.9, 144.7, 140.1, 136.5, 135.2, 131.1(×2), 129.7 (×2), 128.5 (×2), 127.6, 125.7, 123.7, 120.1, 117.4, 116.3, 107.2, 104.3, 101.3 (×2), 101.0, 60.2, 43.2, 39.8, 21.0. HRMS (ESI$^+$): calcd 438.1700 for $C_{28}H_{24}NO_4^+$ $[M+H]^+$; found, 438.1695.

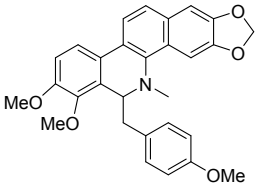


Compound **7bb**, obtained as white powder, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.60 (s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.20 (s, 1H), 7.15(d, J = 7.6 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 7.01 (d, J = 8.8 Hz, 1H), 6.14 (d, J = 0.8 Hz, 1H), 6.09 (d, J = 0.8 Hz, 1H), 4.67 (dd, J = 10.8, 8 Hz, 1H), 3.99 (s, 6H), 2.71-2.66 (m, 2H), 2.58(s, 3H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 147.9, 147.5, 145.7, 140.1, 137.2, 135.2, 131.1, 130.0, 129.7 (×2), 128.6 (×2), 127.4, 124.8, 123.7, 123.6, 119.9, 118.8, 111.2, 104.3, 101.4, 101.0, 60.9, 60.4, 55.8, 43.0, 39.8, 21.2. HRMS (ESI$^+$): calcd 454.2013 for $C_{29}H_{28}NO_4^+$ $[M+H]^+$; found, 454.2014.

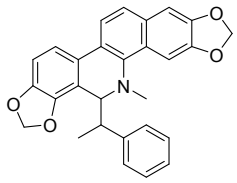


Compound **7c**, obtained as white solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 9.2 Hz, 1H), 7.61 (s, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.28 (s, 1H), 7.17 (s, 1H),

7.00 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.4 Hz, 2H), 6.12 (d, J = 1.2 Hz, 1H), 6.08 (d, J = 0.8 Hz, 1H), 5.99 (d, J = 1.2 Hz, 1H), 5.85 (d, J = 1.2 Hz, 1H), 4.40 (dd, J = 8.8, 6.0 Hz, 1H), 3.84(s, 3H), 2.72-2.63 (m, 2H), 2.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 148.0, 147.5, 146.8, 144.7, 140.0, 131.5, 131.1, 130.8(×2), 127.5, 125.6, 123.7(×2), 120.1, 117.4, 116.3, 113.2(×2), 107.3, 104.3, 101.4, 101.3, 101.0, 60.3, 55.3, 43.2, 39.3. HRMS (ESI$^+$): calcd 454.1649 for $C_{28}H_{24}NO_5^+$ $[M+H]^+$; found, 454.1649.

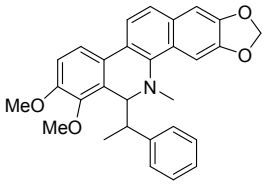


Compound **7cc**, obtained as white solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.56 (s, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.18 (s, 1H), 7.06 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.4 Hz, 1H),6.86 (d, J = 8.8 Hz, 2H), 6.12 (d, J = 1.2 Hz, 1H), 6.07 (d, J = 1.2 Hz, 1H), 4.62 (dd, J = 10.4, 4 Hz, 1H), 3.97(s, 6H), 3.85(s, 3H), 2.68-2.53 (m, 2H), 2.57 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 152.1, 147.9, 147.5, 145.7, 140.1, 132.4, 131.1, 130.7(×2), 130.0, 127.3, 124.8, 123.6, 123.5, 119.9, 118.8, 113.3 (×2), 111.2, 104.3, 101.4, 101.0, 60.9, 60.4, 55.8, 55.3, 43.0, 39.3. HRMS (ESI$^+$): calcd 470.1962 for $C_{29}H_{28}NO_5^+$ $[M+H]^+$; found, 470.1963.

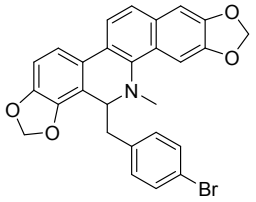


Compound **7d** ， obtained as white solid, diastereomeric ratio is 4:3, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.55(d, J = 8.4 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.41(d, J = 8.4 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.27-7.25 (m, 3H), 7.19-7.13 (m, 4H), 7.03-6.94 (m, 6H), 6.78(d, J = 8.0 Hz, 1H), 6.14-6.09 (m, 4H), 6.01 (d, J = 1.2 Hz, 1H), 5.74 (d, J = 1.2 Hz, 1H), 5.07 (d, J = 1.2 Hz, 1H), 4.36 (d, J = 10.4 Hz, 1H), 4.14 (d, J = 10 Hz, 1H), 2.74 (s, 3H), 2.6-2.60 (m, 2H), 2.48 (s, 3H), 1.47 (d, J = 6.8 Hz, 3H), 1.22 (d, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 147.6, 147.5, 147.4, 146.7, 146.3, 145.9, 1145.8, 144.1, 140.2, 139.8, 131.0(×2), 128.6, 127.8(×2), 127.4(×2), 127.2, 126.0(×2), 125.9(×2), 125.9, 125.5, 124.2, 123.9, 123.7, 123.4, 120.1, 119.9, 116.8, 116.3, 116.2, 107.5, 107.0, 104.5, 104.0, 101.7, 101.2, 101.1, 101.0, 100.9, 64.7, 64.1, 43.2, 43.0, 42.9,

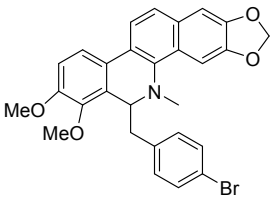
42.8, 18.6, 18.0. HRMS (ESI$^+$): calcd 438.1700 for $C_{28}H_{24}NO_4^+$ [M+H]$^+$; found, 438.1704.



Compound **7dd**，obtained as pale yellow solid, obtained as white solid, diastereomeric ratio is 5:4, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83-7.76 (m, 2H), 7.60-7.48 (m, 2H), 7.22-7.13 (m, 4H), 7.06-6.91 (m, 3H), 6.10-6.01 (m, 2H), 4.58-4.48 (m, 1H), 4.04-3.42 (6H) including 4.04 (s), 4.00 (s), 3.83(s) and 3.41(s), 2.78-2.48 (m. 1H), 2.74-2.48 (3H) including 2.74(s) and 2.48(s), 1.28-1.15 (3H) including 1.27 (d, J = 7.8 Hz) and 1.16 (d, J = 7.6 Hz) . ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 151.8, 148.0, 147.5, 147.4(×2), 147.0, 146.5, 146.3, 144.9, 140.6, 140.3, 131.0(×2), 128.5(×2), 127.8, 127.7(×6), 127.1, 127.0, 125.9, 125.7, 125.2, 125.1, 124.4, 123.9, 123.3, 123.2, 119.8, 119.7, 119.1, 118.3, 111.6, 111.2, 104.5, 140.1, 101.6, 101.0(×2), 100.9, 63.8(×2), 60.9, 60.1, 55.9, 55.8, 43.8, 42.9, 42.6, 42.4, 18.7, 17.6. HRMS (ESI$^+$): calcd 454.2013 for $C_{29}H_{28}NO_4^+$ [M+H]$^+$; found, 454.2016.

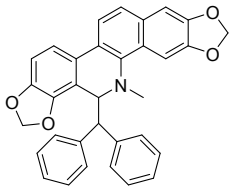


Compound **7e**, obtained as yellow white solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.8 Hz, 1H), 7.55-7.52 (m, 2H), 7.40-7.37 (m, 3H), 7.16 (s, 1H), 6.94-6.88 (m, 3H), 6.12 (d, J = 0.8 Hz, 1H), 6.08 (d, J = 1.2 Hz, 1H), 5.99 (d, J = 1.2 Hz, 1H), 5.85 (d, J = 1.2 Hz, 1H), 4.39 (dd, J = 9.2, 6.0 Hz, 1H), 2.71-2.63 (m, 2H), 2.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 147.6, 146.9, 144.7, 139.7, 138.3, 131.6 (×2), 131.1, 130.8 (×2), 127.4, 125.6, 123.9, 123.6, 120.1, 119.8, 116.8, 116.4, 107.4, 104.4, 101.4, 101.1 (×2), 59.9, 43.2, 39.5. HRMS (ESI$^+$): calcd 502.0648 for $C_{27}H_{21}BrNO_4^+$ [M+H]$^+$; found, 502.0643.

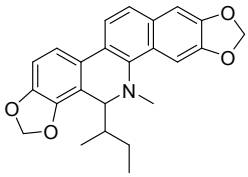


Compound **7ee**, obtained as white solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.50 (s, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.17 (s, 1H), 7.00 (dd, J = 8.0, 2.4 Hz, 3H), 6.13 (s, 1H), 6.08 (s, 1H), 4.61 (dd, J = 10.4, 3.6 Hz, 1H), 3.97 (s, 3H), 3.97 (s, 3H), 2.67-2.51 (m, 2H),

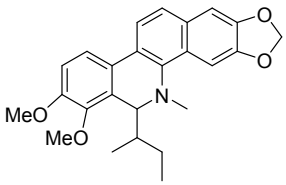
2.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1, 148.0, 147.5, 145.8, 139.8, 139.1, 131.5 (×2), 131.2, 130.8 (×2), 129.4, 127.3, 124.9, 123.6 (×2), 119.8, 119.7, 118.7, 111.6, 104.4, 101.1, 101.0, 60.8, 60.1, 55.9, 42.9, 39.6. HRMS (ESI$^+$): calcd 518.0961 for $C_{28}H_{25}BrNO_4^+$ [M+H]$^+$; found, 518.0964.



Compound **7f**, obtained as pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.29 (s, 3H), 7.25-7.23 (m, 3H), 7.11-7.08 (m, 3H), 7.01-6.99 (m, 2H), 6.79 (d, J = 6.0 Hz, 1H), 5.98 (dd, J = 14.0, 1.2 Hz, 2H), 5.78 (d, J = 1.6 Hz, 1H), 5.10 (d, J = 1.6 Hz, 1H), 4.93 (d, J = 11.2 Hz, 1H), 3.81 (d, J = 11.2 Hz, 1H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 147.4, 146.4, 145.5, 142.4, 141.8, 139.5, 131.0, 129.4 (×2), 128.7 (×2), 127.9 (×2), 127.6, 127.4 (×2), 125.9 (×2), 125.8, 123.9, 123.5, 119.8, 116.3, 115.5, 107.2, 103.9, 101.2, 100.9, 100.7, 61.4, 54.8, 42.4. HRMS (ESI$^+$): calcd 500.1856 for $C_{33}H_{26}NO_4^+$ [M+H]$^+$; found, 500.1858.

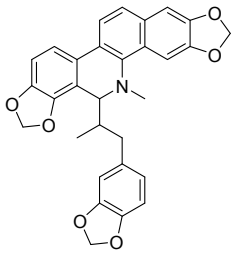


Compound **7e**, obtained as white solid, diastereomeric ratio is 1:1, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.71(m, 2H), 7.48(d, J = 8.4 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.13 (s, 1H), 6.88 (dd, J = 8.4, 1.2 Hz, 1H), 6.09-6.01 (m, 4H), 3.93-3.87 (2H), including 3.92 (d, J = 9.6Hz) and 3.98 (d , J = 9.2 Hz), 2.67-2.77 (3H) including 2.67 (s) and 2.66 (s), 1.45-1.15 (m, 3H), 0.97-0.77 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0 (×2), 147.4, 146.7, 145.6, 145.5, 140.9, 140.6, 131.0, 127.3(×2), 126.2, 126.1, 124.4, 124.3, 123.4, 120.1, 120.0, 117.2, 116.6, 107.0, 104.4, 101.0 (×2), 100.9 (×2), 63.1, 62.4, 43.1, 42.9, 38.4, 37.0, 25.8, 25.6, 16.0, 15.5, 11.5, 10.2. HRMS (ESI$^+$): calcd 390.1700 for $C_{24}H_{24}NO_4^+$ [M+H]$^+$; found, 390.1704.

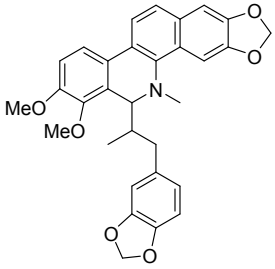


Compound **7ee**, obtained as white solid, diastereomeric ratio is 1:1, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.73(m, 2H), 7.54(dd, J = 8.4, 2.0 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.14 (s, 1H), 6.97 (dd, J = 8.4, 1.2 Hz, 1H), 6.08(s, 2H), 4.16-4.10

(1H) including 4.14 (d, J = 9.2 Hz) and 4.11 (d, J = 8.4 Hz),3.96 (s, 3H), 3.94 (s, 3H), 2.68-2.67 (3H) including 2.68 (s) and 2.67 (s), 1.38-1.20 (m, 3H), 0.93-0.74 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 147.9(×2), 147.3(×2), 146.8(×2), 140.8, 140.7, 130.9, 128.9, 128.8, 127.2, 127.1, 125.1, 125.0, 124.2, 124.3, 123.2, 119.8(×2), 119.0(×2), 110.8, 104.5, 104.4, 101.0, 100.9(×2), 62.7, 62.0, 60.8, 55.7, 42.8, 42.5, 38.5, 36.9, 25.9, 25.7, 16.2, 15.7, 11.9, 10.5. HRMS (ESI^+): calcd 406.2013 for $C_{25}H_{28}NO_4^+$ $[M+H]^+$; found, 406.2017.

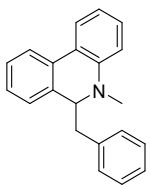


Compound **7f**, obtained as pale yellow solid, diastereomeric ratio is 1:1, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80-7.72(m, 2H), 7.50 (m, 1H), 7.36 (m, 1H), 7.17-7.13 (1H) including 7.17 (s) and 7.13 (s), 6.90-6.87 (m, 1H), 6.66-6.34 (m, 1H), 6.49-6.40 (m, 2H), 6.09-6.00 (m, 4H), 5.88-5.86 (m, 2H), 3.98-3.89 (1H) including 3.97 (d, J = 8.8 Hz) and 3.91 (d, J = 10.4 Hz), 2.84-2.61 (m, 1H), 2.69 (3H) including 2.69 (s) and 2.68 (s), 2.46-2.30 (m, 1H), 1.74-1.56 (m, 1H), 0.82-0.72 (3H) including 0.81 (d, J = 6.4 Hz) and 0.73 (d, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 148.1, 147.5, 147.4, 147.3, 147.2, 146.7(×2), 145.6, 145.4, 145.3, 140.8, 140.2, 135.2, 135.0, 131.1, 127.3, 127.2, 126.2, 126.0, 124.5, 124.3, 123.7, 123.5, 122.3, 121.8, 120.1(×2), 116.8, 116.7(×2), 109.8, 109.4, 107.8(×2), 107.3, 107.2, 104.5, 104.4, 101.1, 101.0(×2), 100.9, 100.8, 100.6(×2), 100.5, 62.8, 62.6, 43.4, 42.6, 39.6, 39.5, 39.3, 38.1, 16.2, 15.8. HRMS (ESI^+): calcd 496.1755 for $C_{30}H_{26}NO_6^+$ $[M+H]^+$; found, 496.1757.

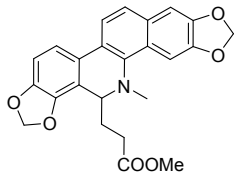


Compound **7ff**, obtained as white powder, diastereomeric ratio is 5:4, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81-7.75(m, 2H), 7.59-7.47(m, 2H), 7.18-7.16 (1H) including 7.18 (s) and 7.14 (s), 6.9-6.96 (m, 1H), 6.69-6.55 (m, 2H), 6.40-6.31 (m, 1H), 6.09-6.08 (m, 2H), 5.89-5.84 (m, 2H), 4.19-4.15 (m, 1H), 3.98-3.89 (m, 6H), 2.77-2.57(m, 4H), 2.43-2.30 (m, 1H), 1.80-1.50 (m, 1H), 0.71-0.68 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0, 151.9, 148.0(×2), 147.4(×2), 147.2, 147.1, 146.8, 145.2(×2), 141.2, 140.3, 135.7, 135.6, 131.0, 128.6, 128.3, 127.2, 126.9,

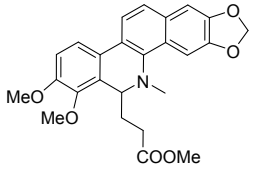
125.4, 125.0, 124.4, 124.2, 123.6, 123.3, 122.2, 121.9, 119.9, 119.8, 119.1, 118.8, 111.0(×2), 109.7, 109.5, 107.7(×2), 104.5(×2), 101.0(×2), 100.8, 100.6(×2), 100.5, 62.4, 61.7, 60.8, 60.7, 55.7, 43.4, 42.3, 39.9, 39.7, 39.6, 38.3, 16.1, 15.9. HRMS (ESI$^+$): calcd 512.2068 for $C_{31}H_{30}NO_6^+$ [M+H]$^+$; found, 512.2070.



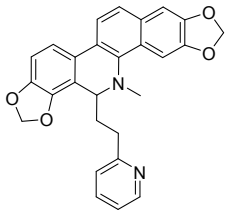
Compound **12**, obtained as white powder, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (m, 2H), 7.34-7.29 (m, 2H), 7.25-7.20 (m, 3H), 7.08 (t, J = 7.6 Hz, 1H), 7.00-6.90 (m, 3H), 6.73 (d, J = 8.0 Hz, 1H), 6.60 (d, J = 7.2 Hz, 1H), 4.43 (dd, J = 8.0, 2.0 Hz, 1H), 3.02-2.97 (m, 1H), 2.99 (s, 3H), 2.70-2.64 (m, 1H). calcd 286.1590 for $C_{21}H_{20}N^+$ [M+H]$^+$; found, 286.1583.



Compound 16**a**: obtained as white solid, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71(d, J = 8.5 Hz, 1H), 7.71 (s, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.14 (s, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.08 (s, 3H), 6.05 (d, J = 1.5 Hz, 1H), 4.32 (dd, J = 5.5, 10.0 Hz, 1H), 3.65 (s, 3H), 2.67 (s, 3H), 2.59-2.46 (m, 2H), 1.83-1.68 (m, 2H). ^{13}CNMR (125 MHz, $CDCl_3$): δ 174.1, 148.2, 147.5, 147.0, 144.7, 139.6, 131.0, 127.5, 125.6, 123.9, 123.6, 120.1, 117.3, 116.5, 107.4, 104.4, 101.4, 101.0, 100.7, 56.8, 51.5, 43.1, 30.4, 28.6. HRMS (ESI$^+$): calcd 420.1442 for $C_{24}H_{22}NO_6^+$ [M+H]$^+$; found, 420.1438.

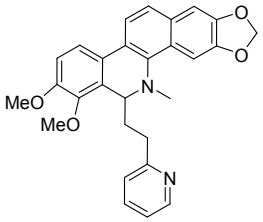


Compound 16**aa**: obtained as white solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.71 (s,1H), 7.55 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.13 (s, 1H), 6.96 (d, J = 8.8 Hz, 1H), 6.07 (s, 2H), 4.50 (dd, J = 10.4, 4.8 Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.64 (s, 3H), 2.66 (s, 3H), 2.62-2.47 (m, 2H), 1.80-1.61 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 152.2, 148.1, 147.5, 146.0, 139.6, 131.0, 129.7, 127.4, 124.8, 123.7, 123.6, 119.9, 118.8, 111.4, 104.4, 101.0, 100.7, 61.0, 56.9, 55.8, 51.3, 42.7, 30.8, 29.1. HRMS (ESI$^+$): calcd 436.1755 for $C_{25}H_{26}NO_6^+$ [M+H]$^+$; found, 436.1764, 436.1759.

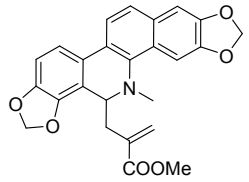


Compound 16**b**: obtained as white solid, ^{1}H NMR (400 MHz,

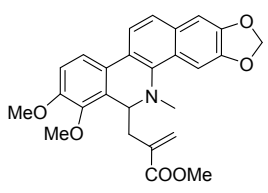
$CDCl_3$): δ 8.48 (d, J = 4.4 Hz, 1H), 7.78 (s, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.53-7.47 (m, 2H), 7.35 (d, J = 8.0 Hz, 1H), 7.13 (s, 1H), 7.09-7.03 (m, 2H), 6.86 (d, J = 8.0 Hz, 1H), 6.06-6.01 (m, 4H), 4.30-4.27 (m, 1H), 3.10-2.92 (m, 2H), 2.68 (s, 3H), 1.94-1.85 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 149.1, 148.1, 147.5, 147.0, 144.6, 139.9, 136.1, 131.0, 127.6, 125.8, 123.8, 123.7, 122.8, 120.8, 120.2, 117.8, 116.4, 107.2, 104.4, 101.3, 101.0, 100.8, 57.4, 43.0, 34.9, 33.6. HRMS (ESI$^+$): calcd 439.1652 for $C_{27}H_{23}N_2O_4^+$ $[M+H]^+$; found, 439.1654.



Compound 16bb: obtained as white solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (d, J = 4.4 Hz, 1H), 7.79 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.56-7.48 (m, 3H), 7.13-7.12 (d, m, 2H), 7.06 (dd, J = 6.8, 5.2 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 6.07 (s, 2H), 4.44 (dd, J = 10.0, 4.8 Hz, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 3.04 (t, J = 7.6 Hz, 2H), 2.66 (s, 3H), 1.88-1.79 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 152.2, 149.0, 148.0, 147.4, 145.9, 140.0, 136.0, 131.0, 130.3, 127.5, 124.9, 123.8, 123.5, 122.9, 120.7, 119.9, 118.8, 111.2, 104.4, 101.0, 100.8, 60.8, 57.1, 55.8, 42.7, 34.9, 33.7. HRMS (ESI$^+$): calcd 455.1965 for $C_{28}H_{27}N_2O_4^+$ $[M+H]^+$; found, 455.1961.

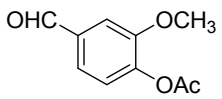


Compound **16c**: Obtained as white solid, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J = 8.5 Hz, 1), 7.6 (s, 1H), 7.47(d, J = 8.5 Hz, 1H), 7.34 (d, J = 8.5 Hz, 1), 7.10 (s, 1H), 6.85 (d, J = 8.5 Hz, 1H), 6.14 (d, J = 1.0 Hz, 1H), 6.06-6.01 (m, 4H), 5.15 (s, 1H), 4.57 (dd, J = 6.5, 9.0 Hz, 1H), 3.76 (s, 3H), 2.62 (s, 3H), 2.44-2.34 (m, 2H). ^{13}C NMR (125MHz, $CDCl_3$): δ 167.6, 147.9, 147.4, 146.8, 144.8, 139.6, 136.7, 130.9, 128.0, 127.4, 125.4, 123.7, 123.4, 120.0, 116.9, 116.2, 107.2, 104.2, 101.2, 101.0, 56.6, 51.8, 43.0, 36.5. HRMS (ESI$^+$): calcd 432.1442 for $C_{25}H_{22}NO_6^+$ $[M+H]^+$; found, 432.1448.

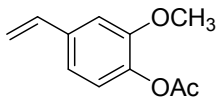


Compound **16cc**: Obtained as white solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.4 Hz, 1H), 7.60 (s, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.13 (s, 1H), 6.96 (d, J = 8.8 Hz, 1H), 6.17 (d, J = 1.6 Hz, 1H), 6.06 (dd, J = 9.2, 1.2 Hz,

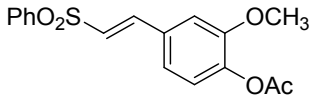
2H), 5.15 (d, *J* = 1.2 Hz, 1H), 4.77 (dd, *J* = 10, 4.8 Hz, 1H), 3.99 (s, 3H), 3.94(s, 3H), 3.77 (s, 3H), 2.62 (s, 3H), 2.48-2.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 152.2, 147.8, 147.4, 146.1, 139.8, 137.3, 131.0, 129.4, 127.5, 127.3, 124.8, 123.5, 123.5, 119.8, 118.7, 111.4, 104.3, 101.1, 101.0, 60.9, 56.9, 55.8, 51.6, 42.7, 36.6. HRMS (ESI$^+$): calcd 448.1755 for $C_{26}H_{26}NO_6^+$ $[M+H]^+$; found, 448.1755.



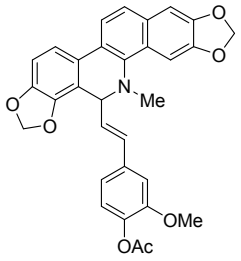
Compound **18:** Obtained as white solid, ^{1}H NMR (500MHz, CDCl3): δ 9.87 (s, 1H), 7.45 (s, 1H), 7.42 (d, J = 7.5 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 3.85 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (125MHz, CDCl3): δ 190.9, 168.2, 151.8, 144.8, 135.0, 124.4, 123.2, 110.7, 55.9, 20.4.



Compound **19:** Obtained as white solid, ^{1}H NMR (500MHz, $CDCl_3$): δ 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}C NMR (125MHz, $CDCl_3$): δ 168.7, 150.9, 139.2, 136.4, 136.0, 122.5, 118.6, 113.8, 109.7, 55.5, 20.3.



Compound **20:** Obtained as white solid, ^{1}H NMR (500MHz, $CDCl_3$): δ 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}C NMR (125MHz, $CDCl_3$): δ 168.5, 151.5, 142.1, 141.8, 140.6, 133.4, 131.2, 129.3 ×2, 127.6×2, 127.4, 123.4, 121.7, 111.7, 55.9, 20.5.



Compound **21**. Obtained as white amorphous powder, ^{1}H NMR (500MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.12 (s, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.76 (s, 1H), 6.73 (d, J = 7.5 Hz, 1H), 6.32 (d, J = 15.5 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}C NMR (125MHz, $CDCl_3$): δ 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 $C_{31}H_{26}NO_7^+$ $[M+H]^+$; found, 524.1708.

5. NMR spectra of target compounds

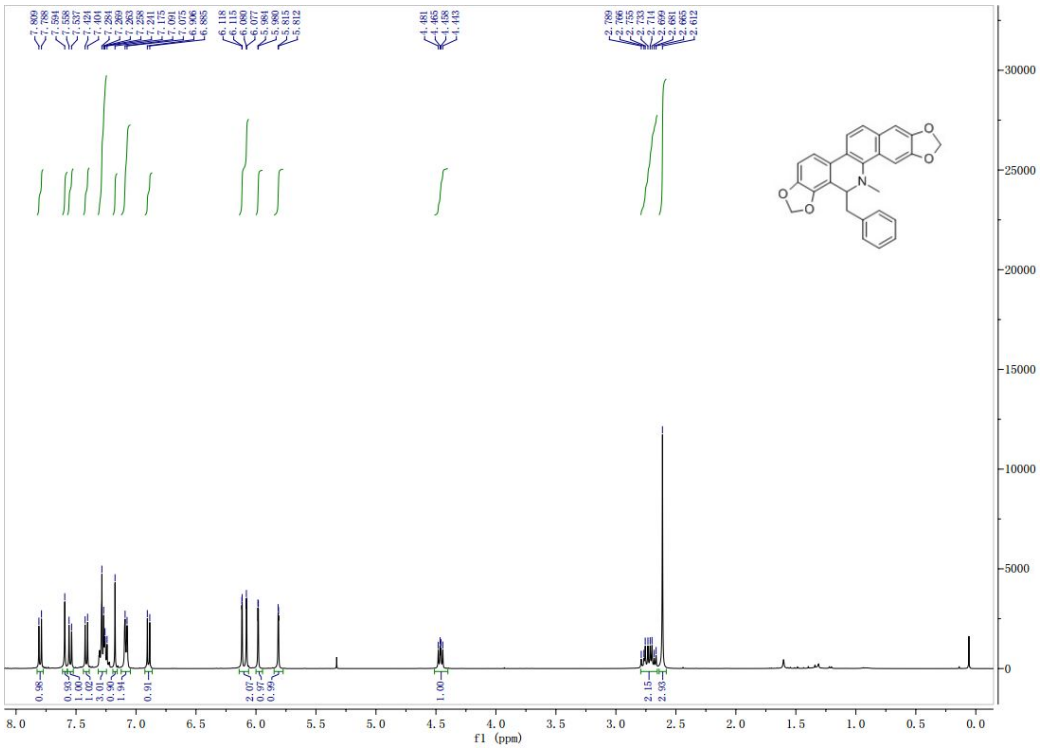


Figure S5. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7a**

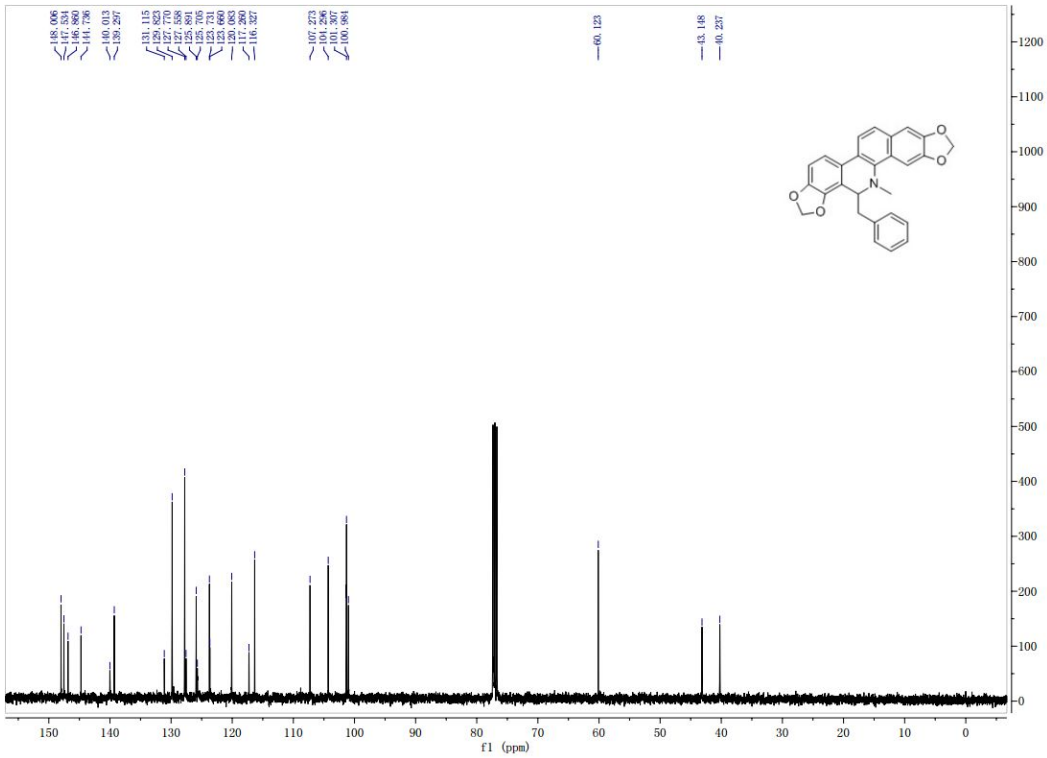


Figure S6. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **7a**

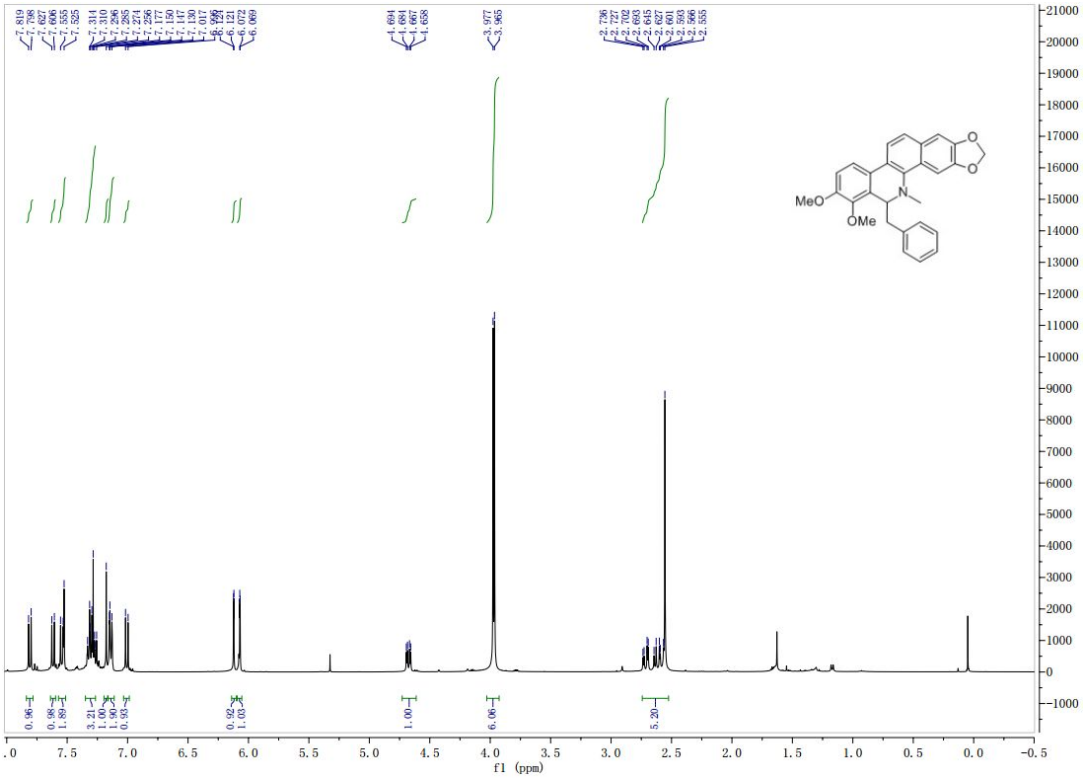


Figure S7. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7aa**

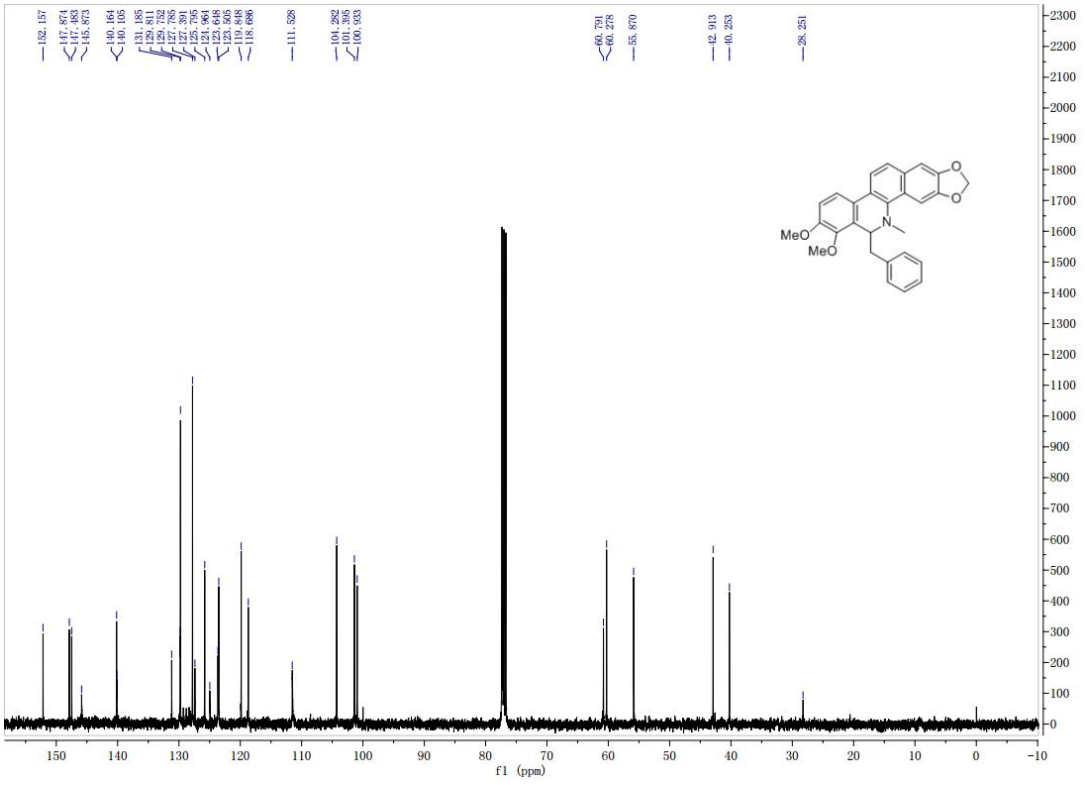


Figure S8. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **7aa**

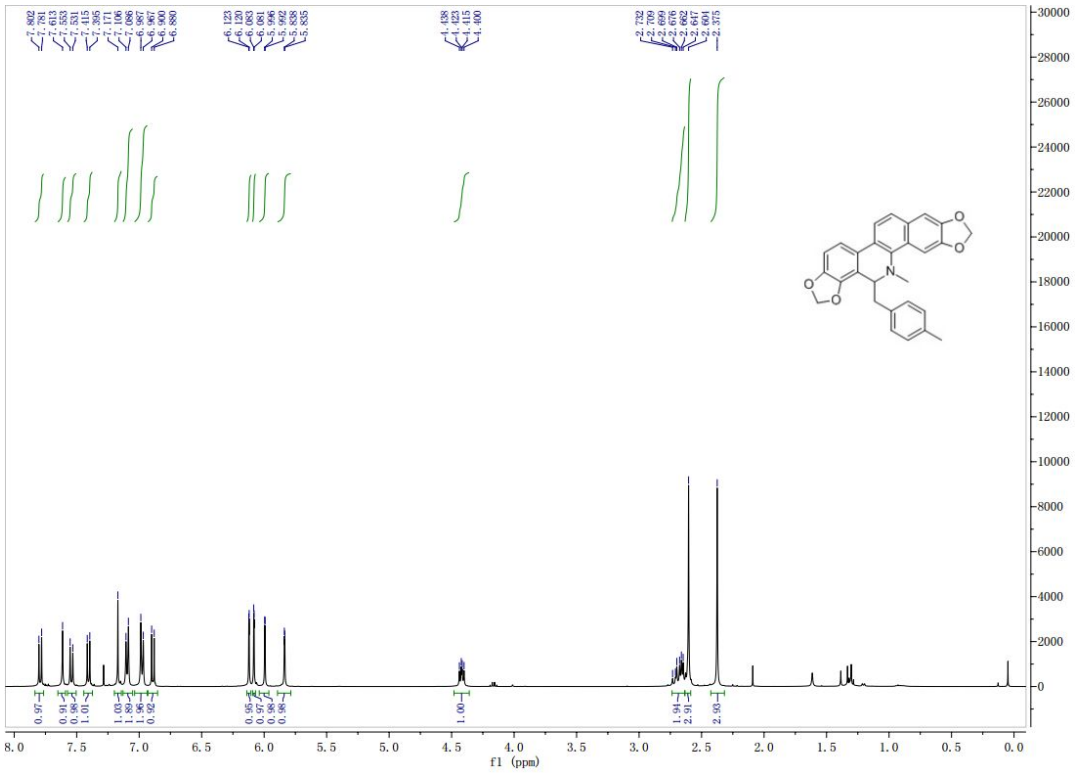


Figure S9. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7b**

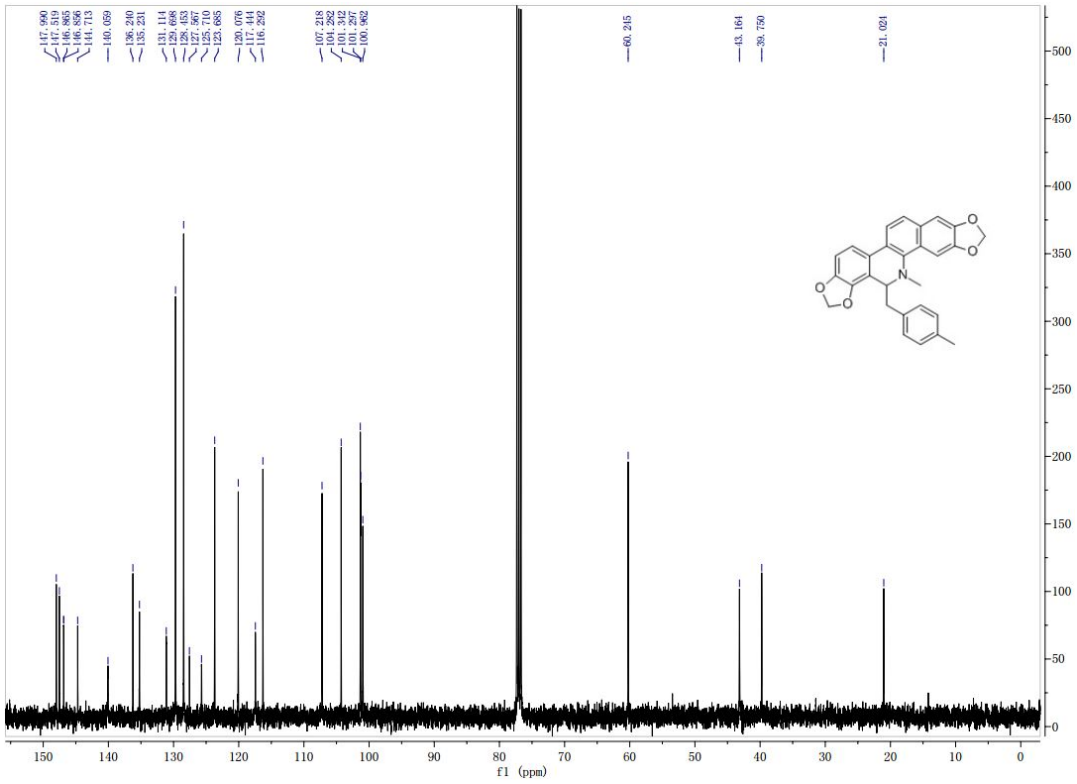


Figure S10. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **7b**

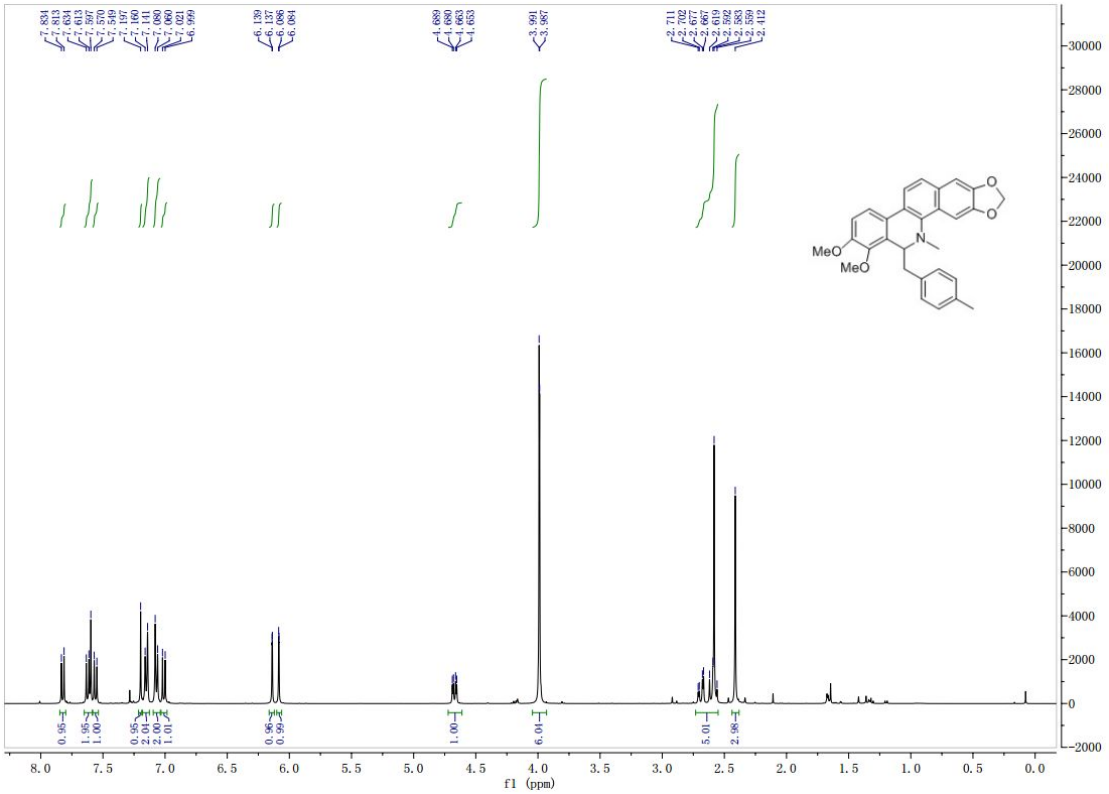


Figure S11. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7bb**

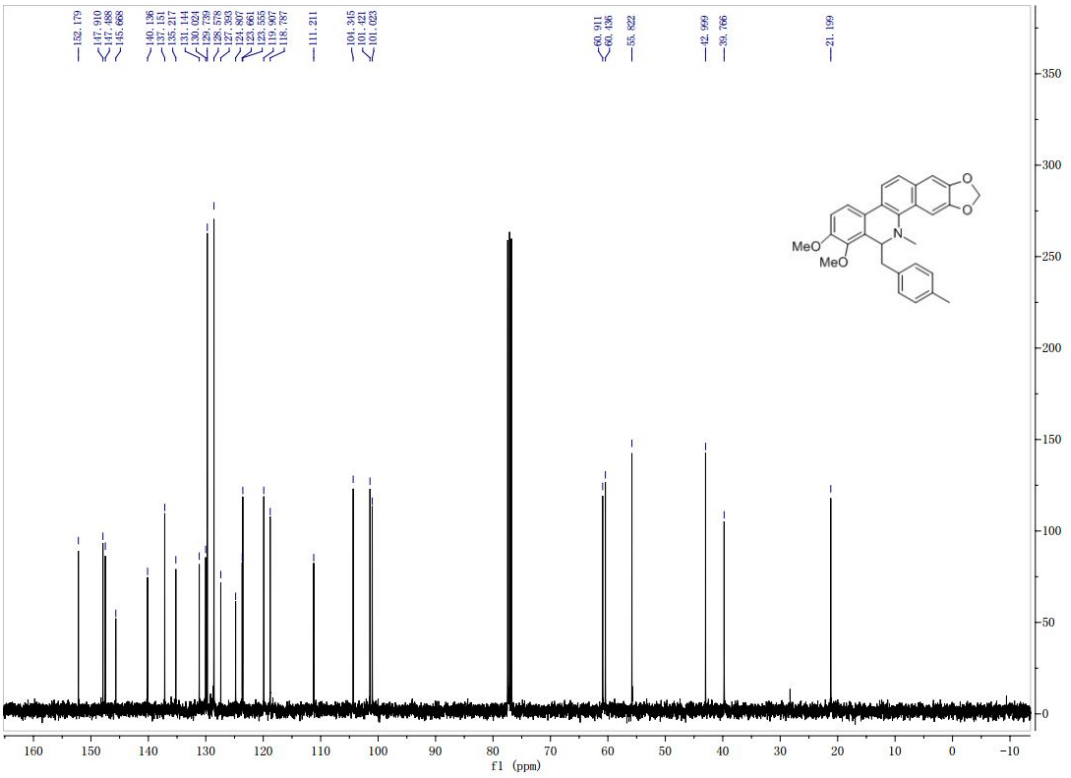


Figure S12. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **7bb**

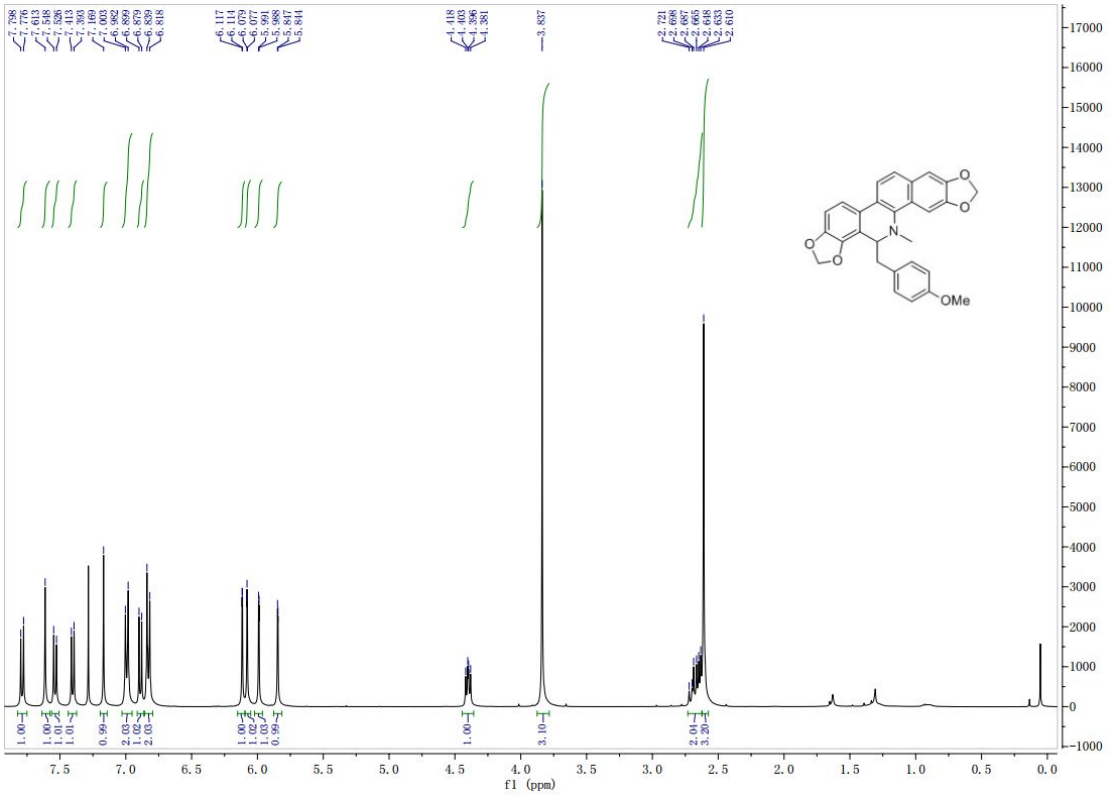


Figure S13. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7c**

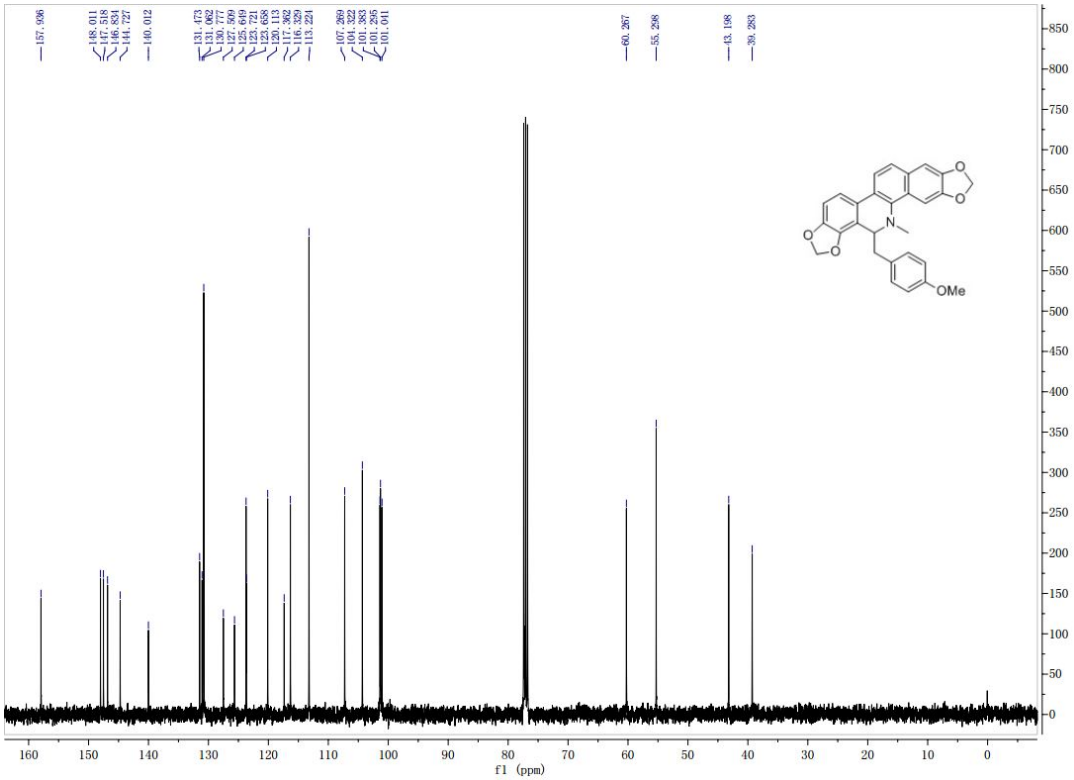


Figure S14. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **7c**

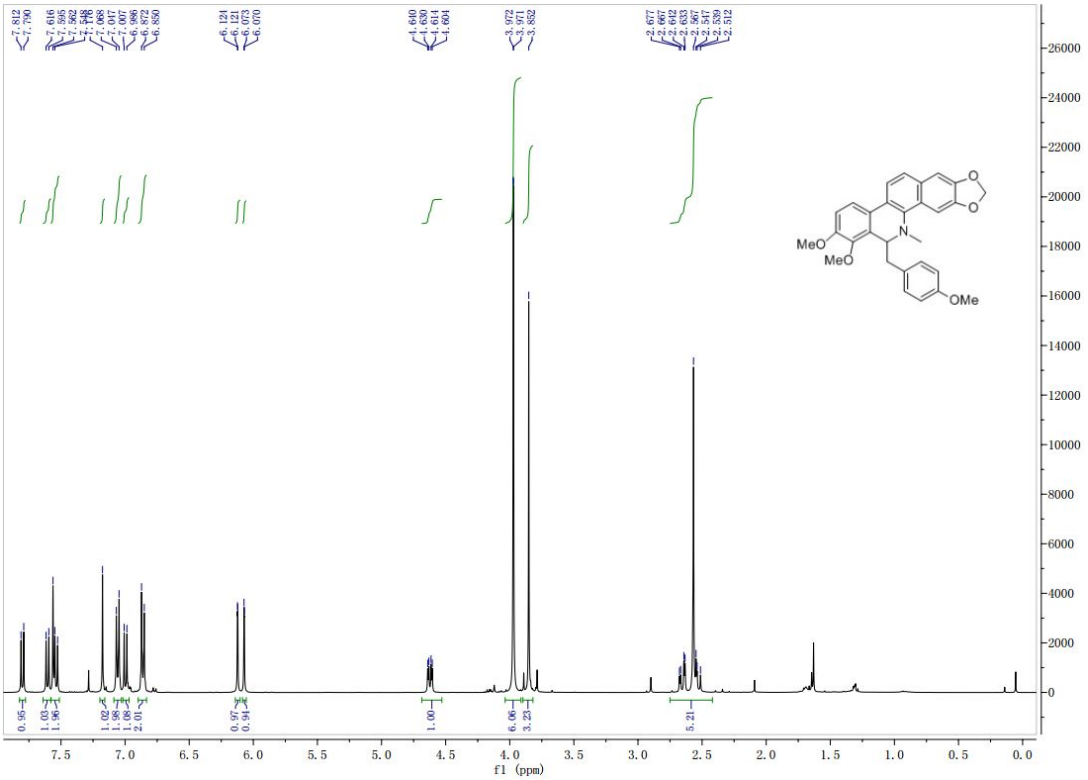


Figure S15. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7cc**

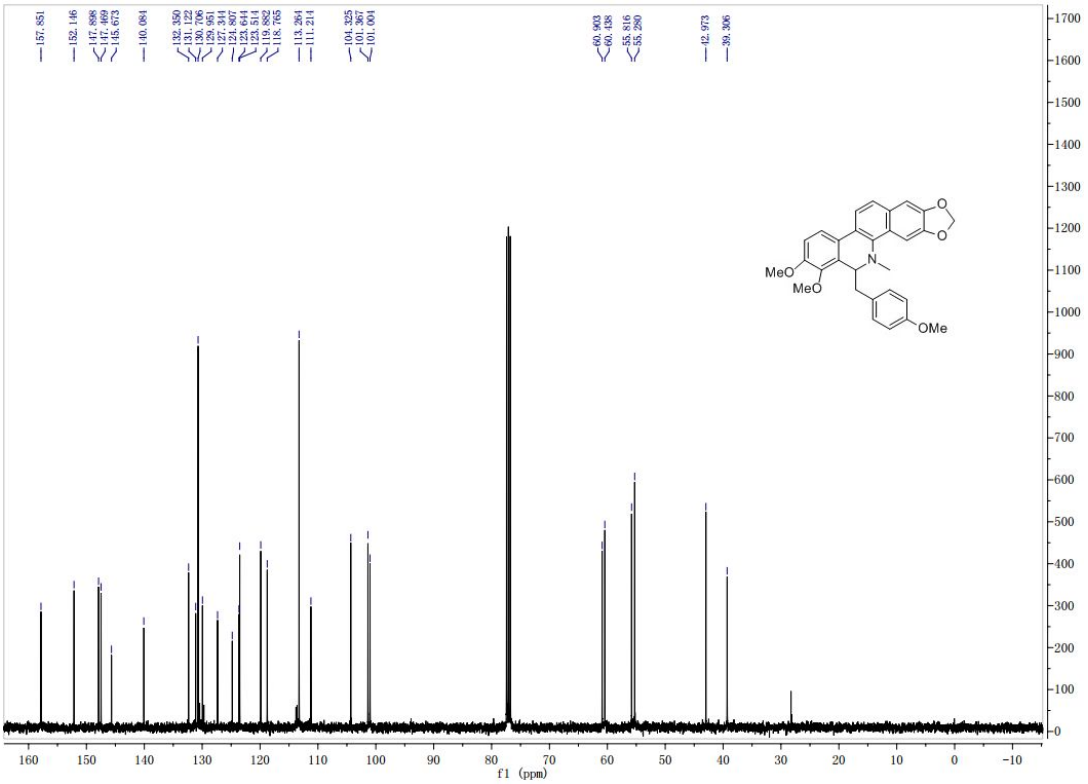


Figure S16. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **7cc**

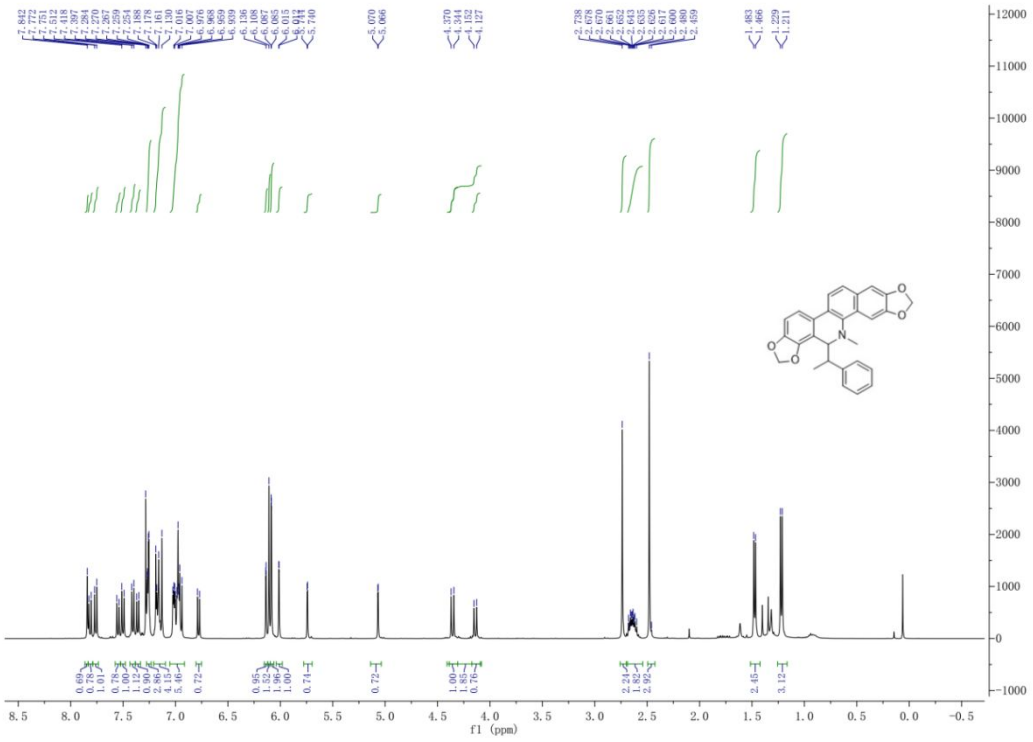


Figure S17. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7d**

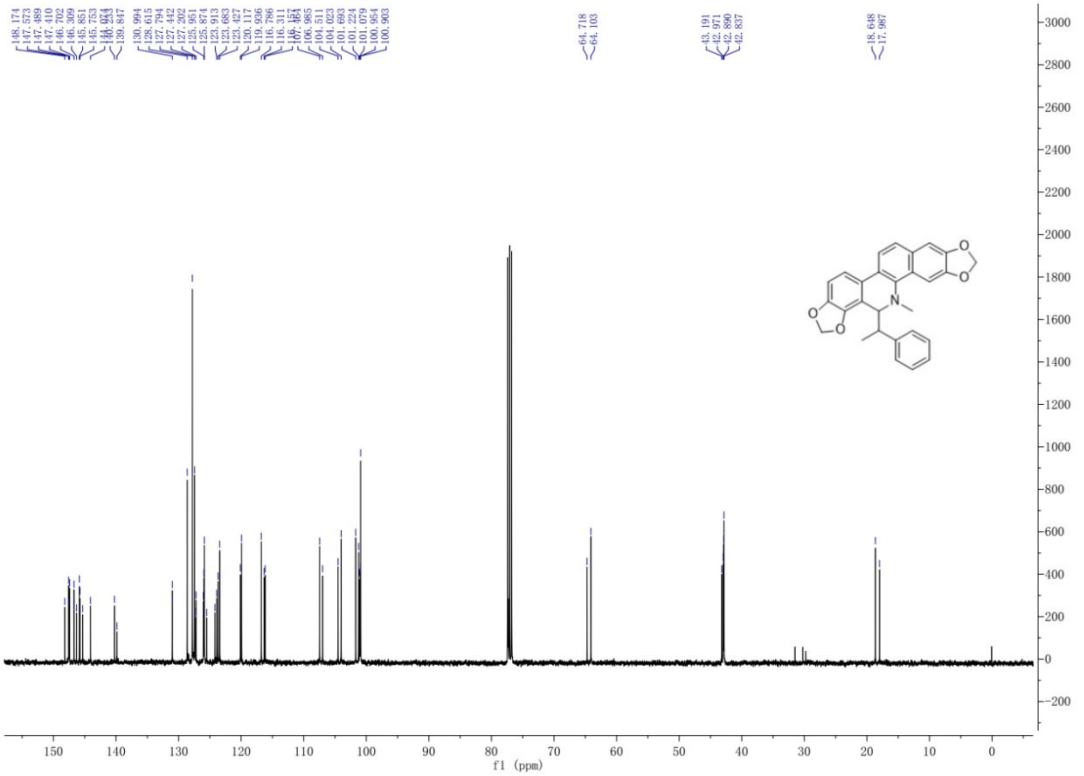


Figure S18. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **7d**

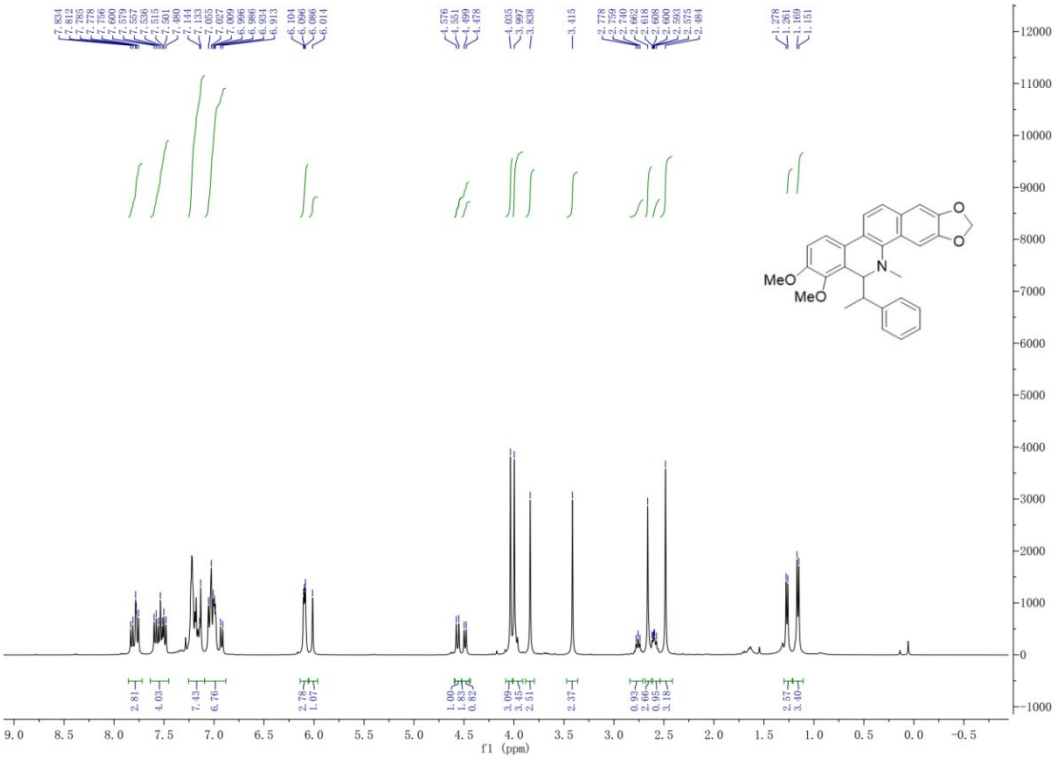


Figure S19. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7dd**

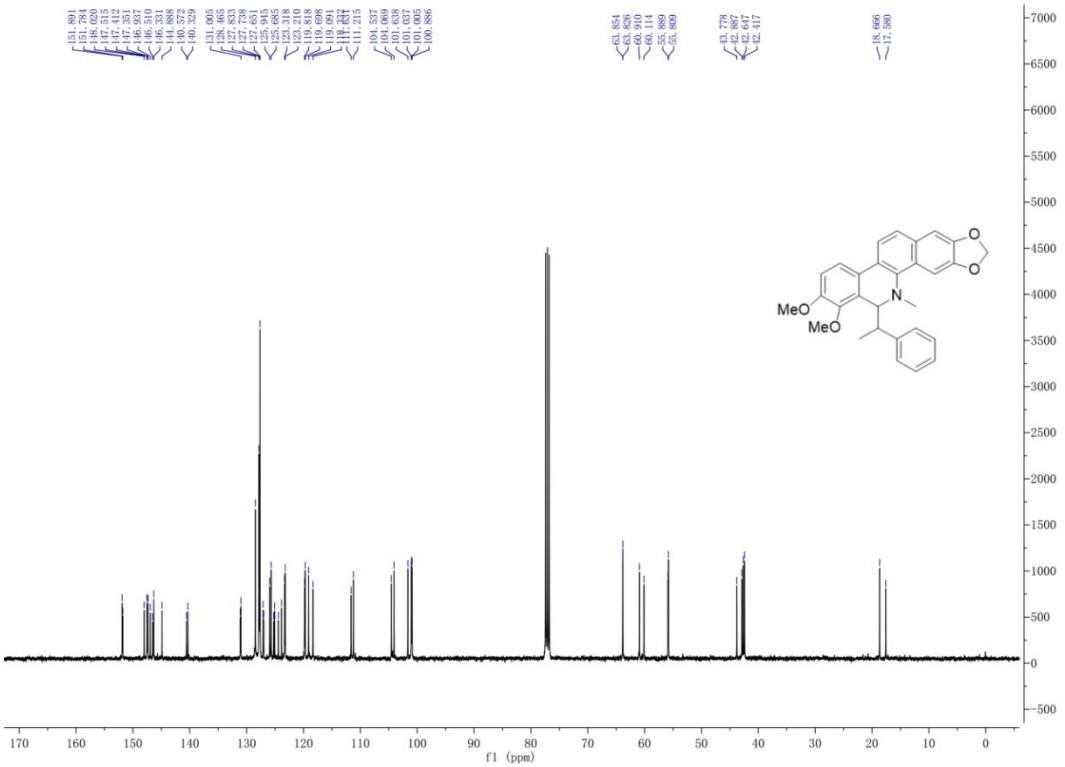


Figure S20. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **7dd**

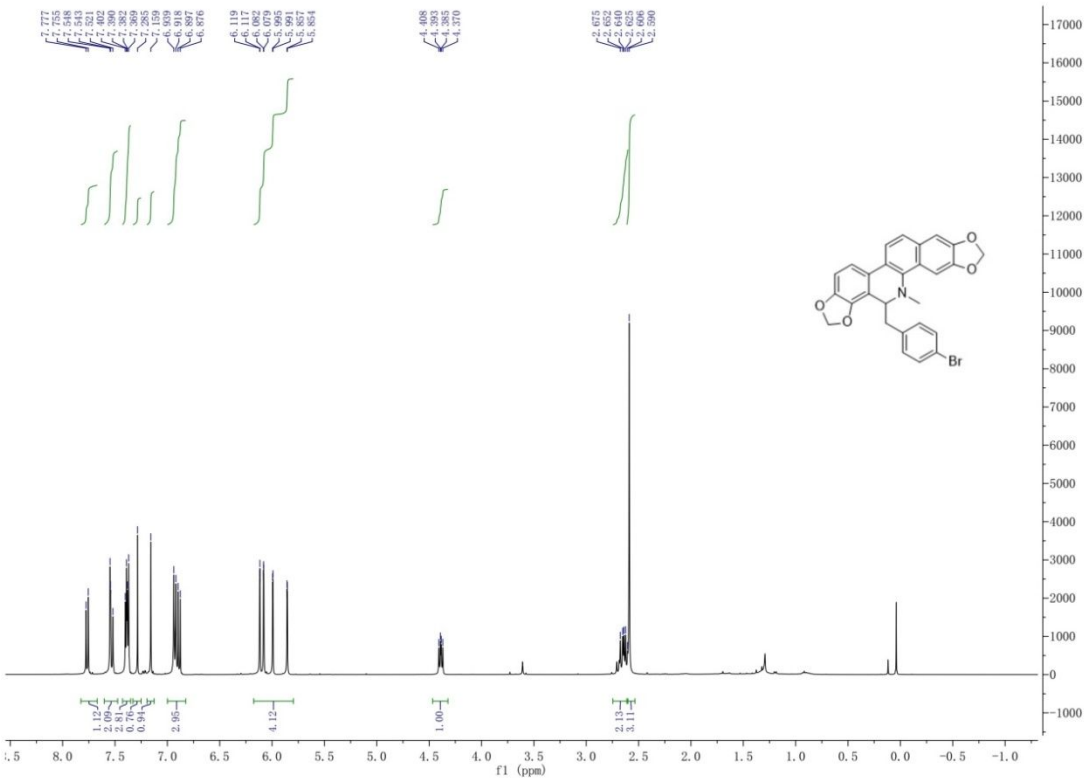


Figure S21. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7e**

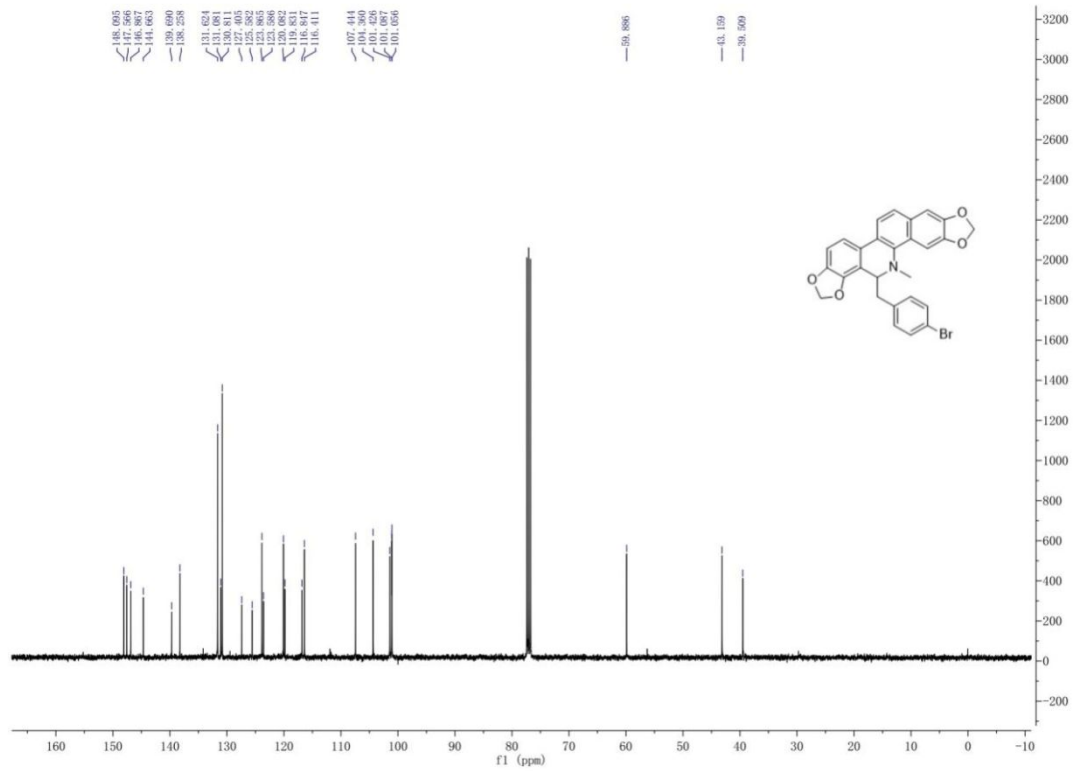


Figure S22. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **7e**

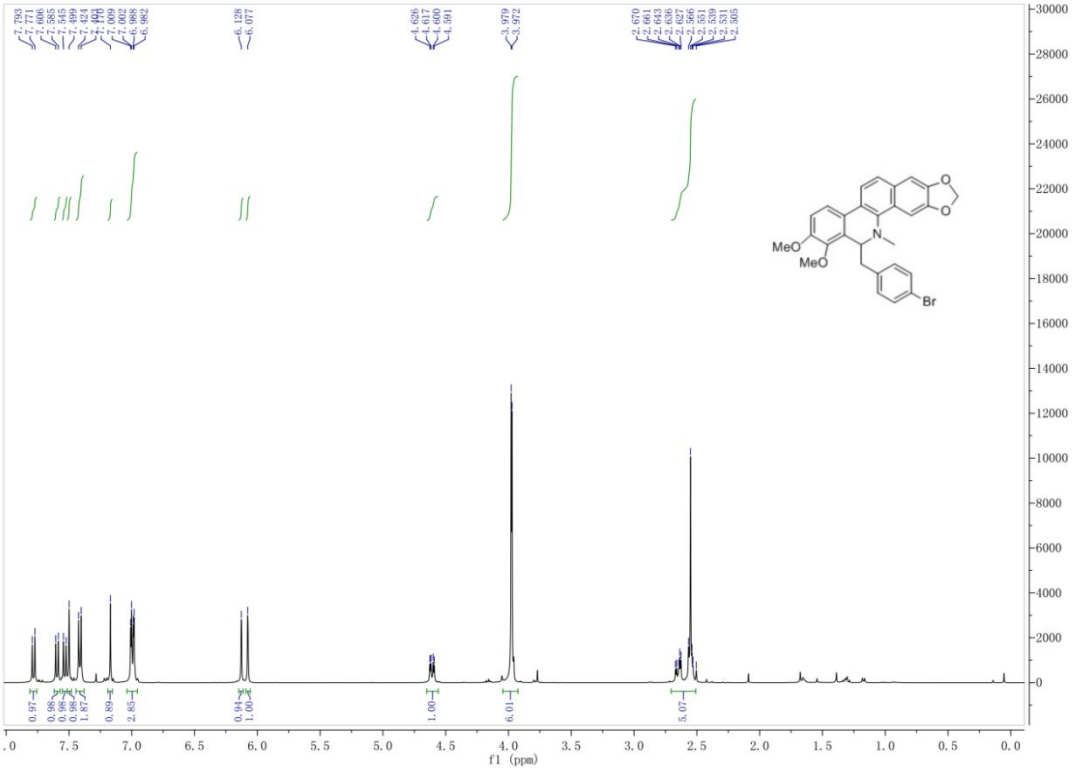


Figure S23. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7ee**

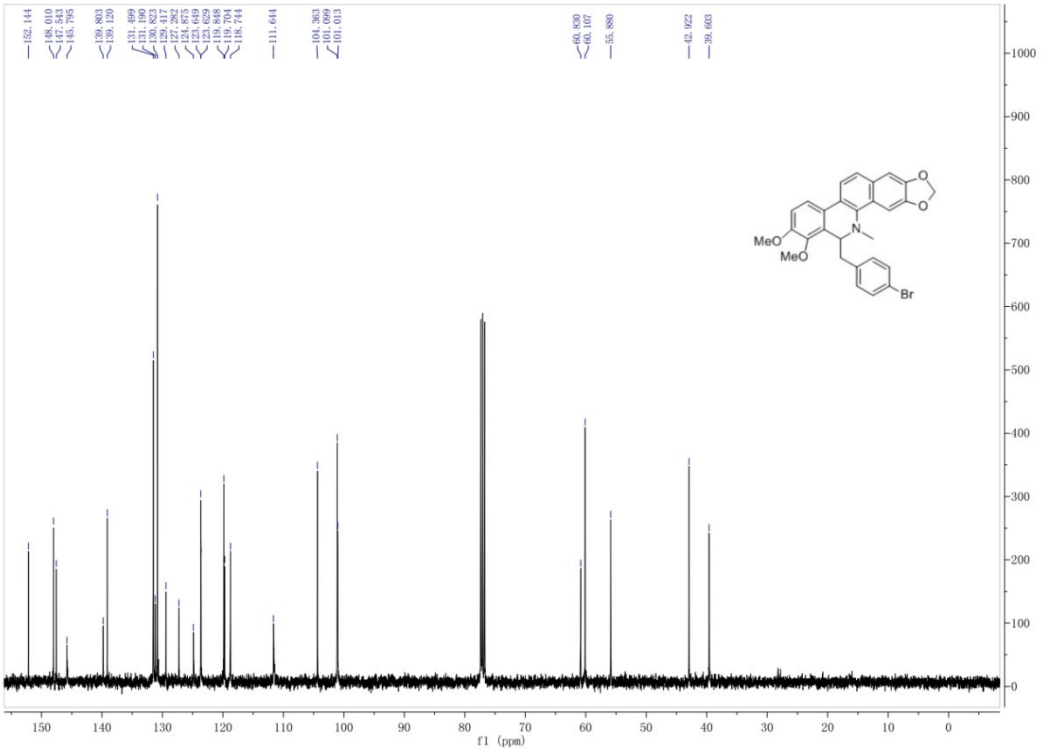


Figure S24. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **7ee**

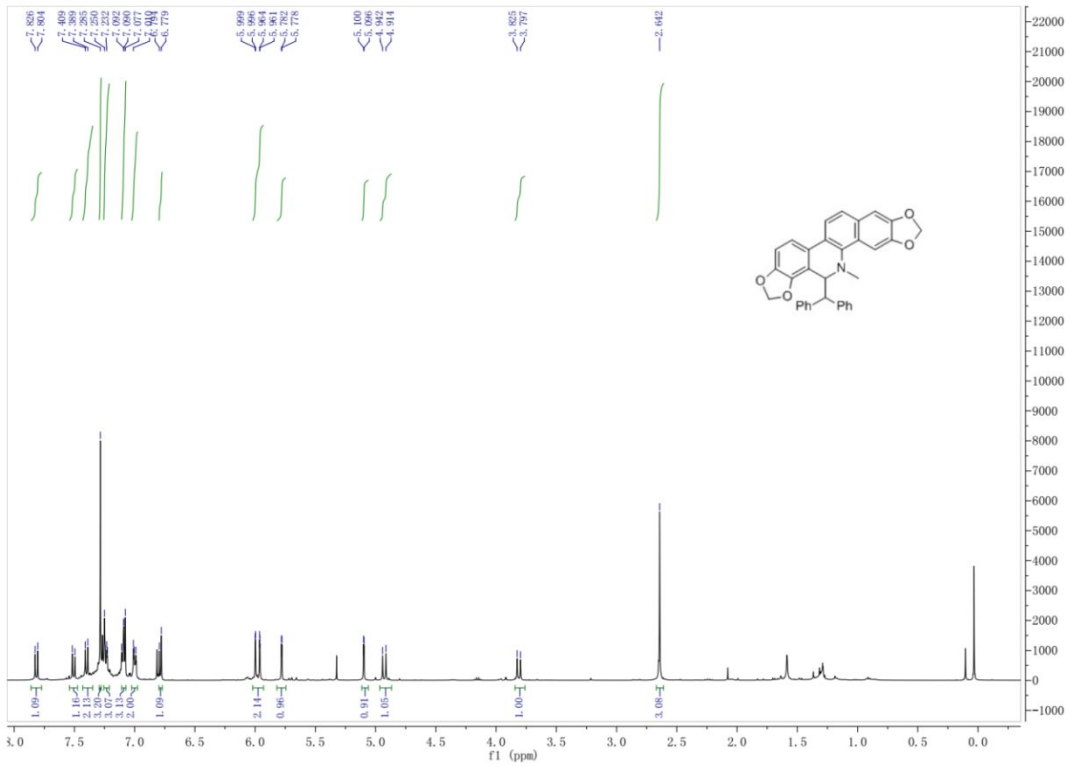


Figure S25. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7f**

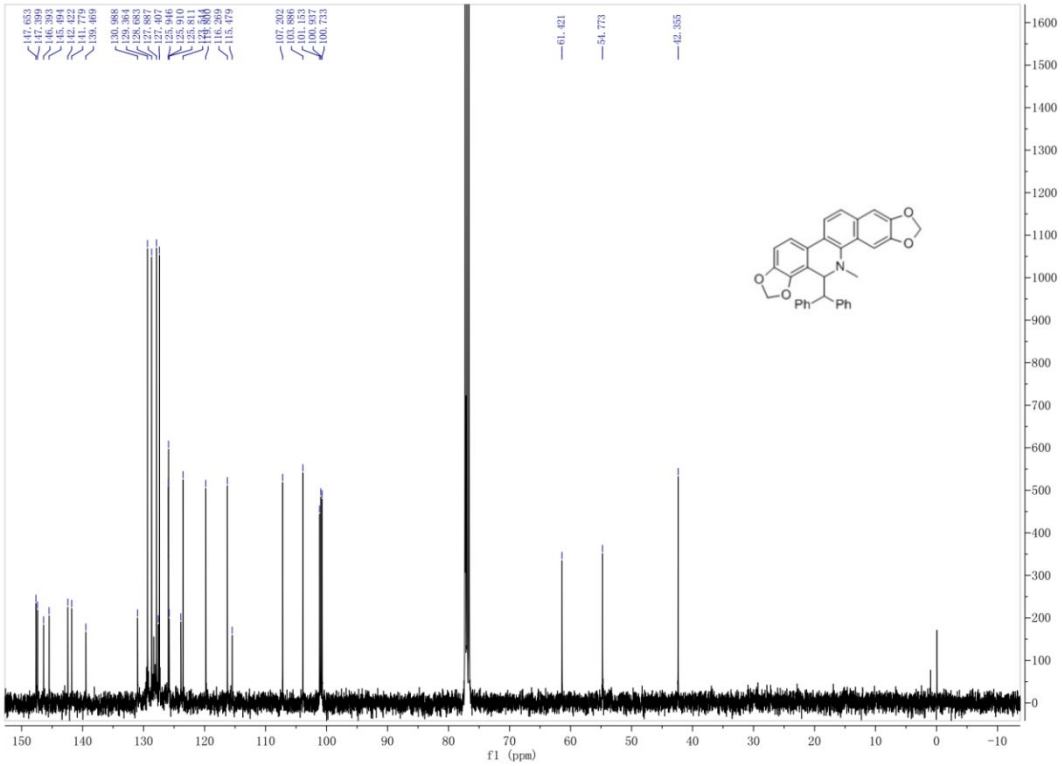


Figure S26. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **7f**

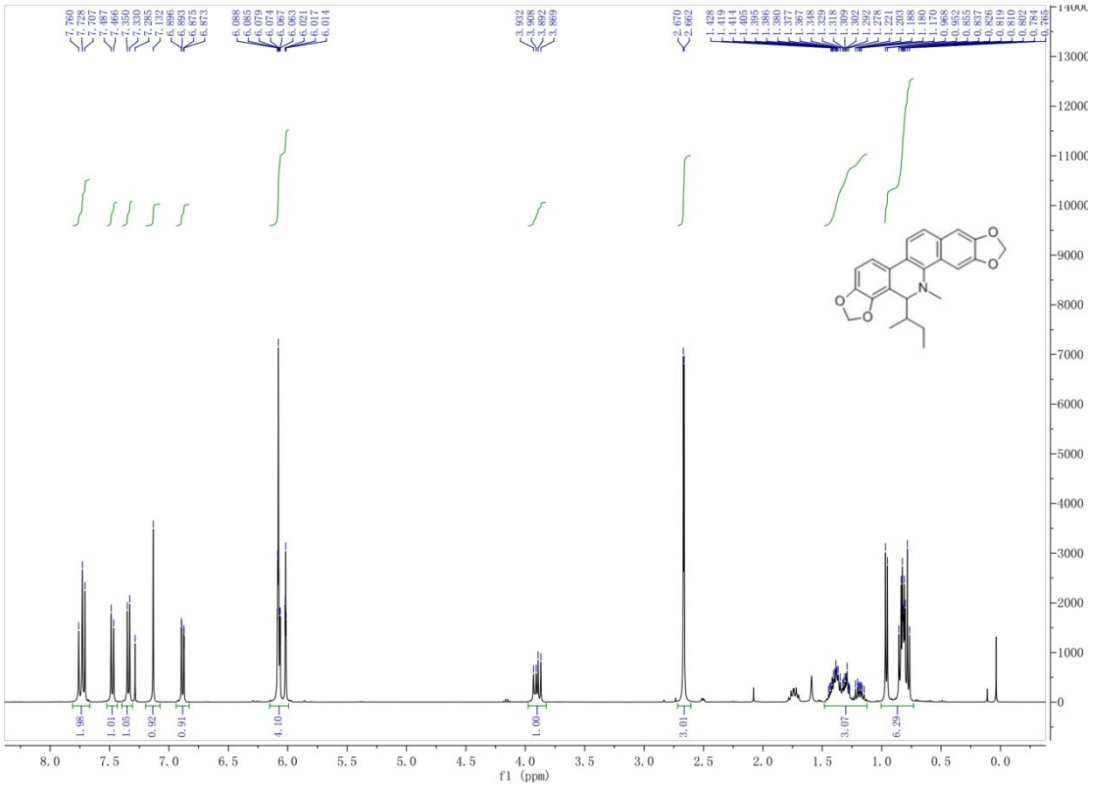


Figure S27. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7g**

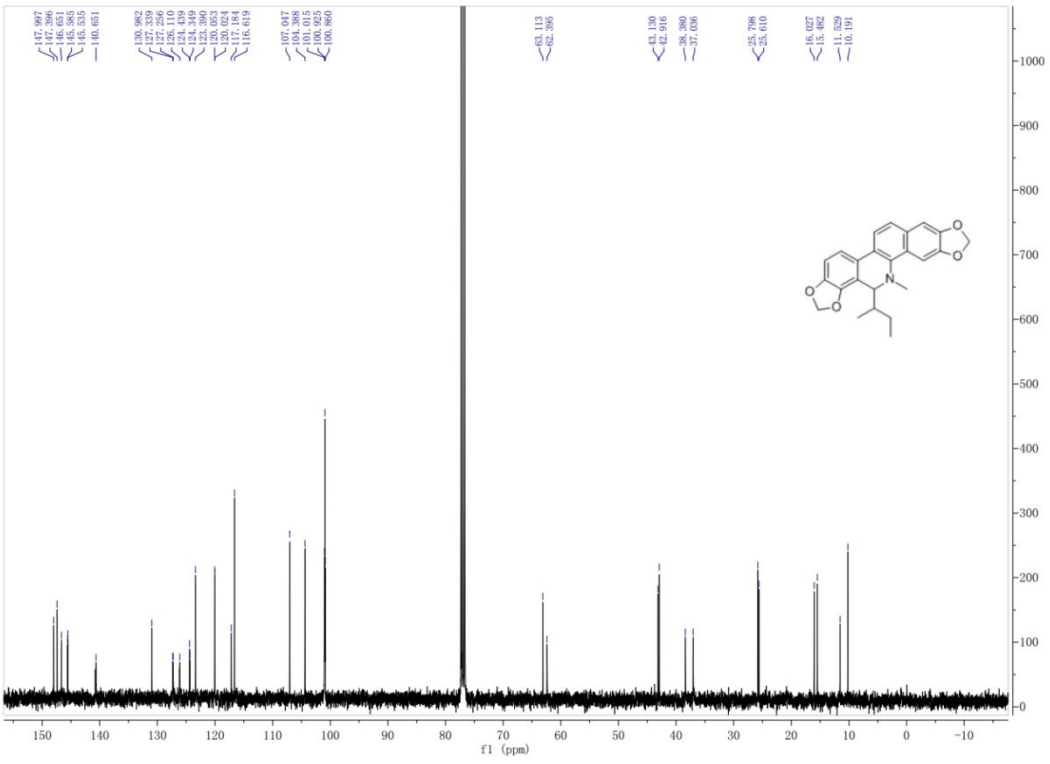


Figure S28. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **7g**

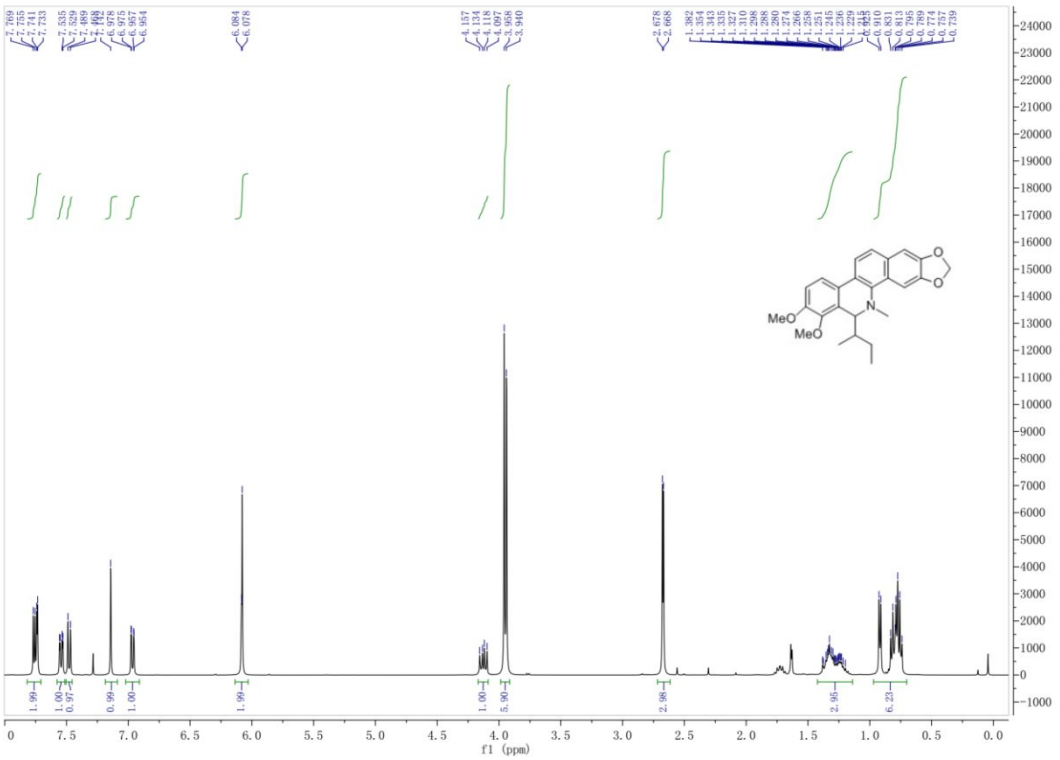


Figure S29. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7gg**

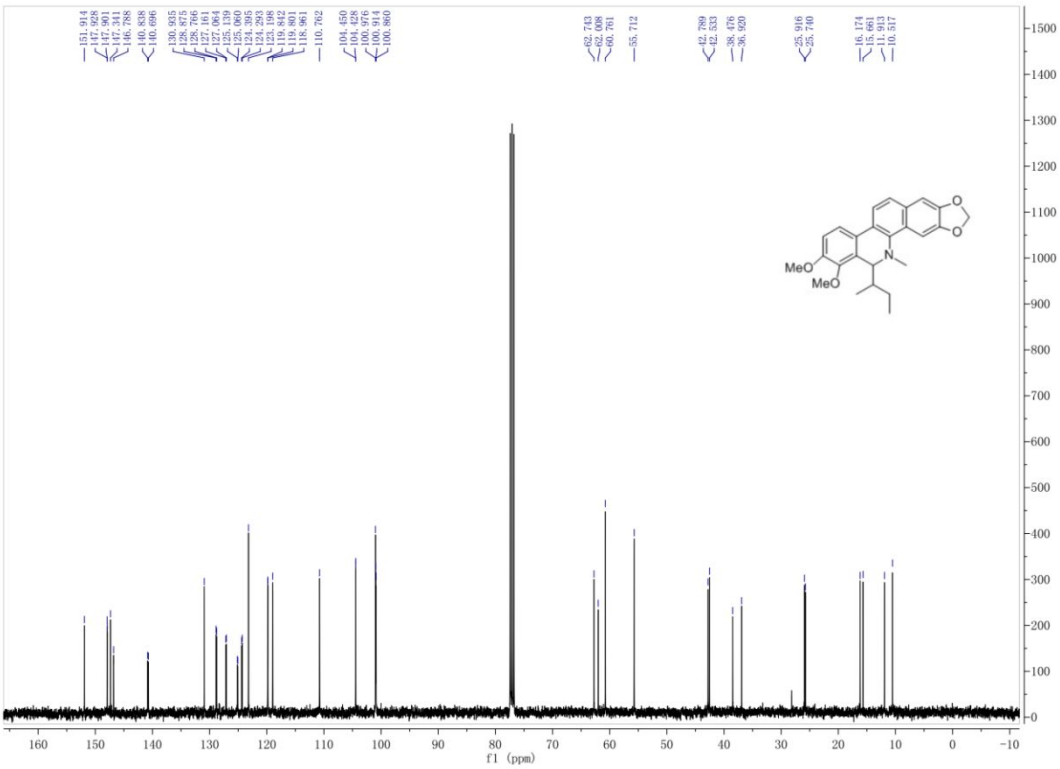


Figure S30. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **7gg**

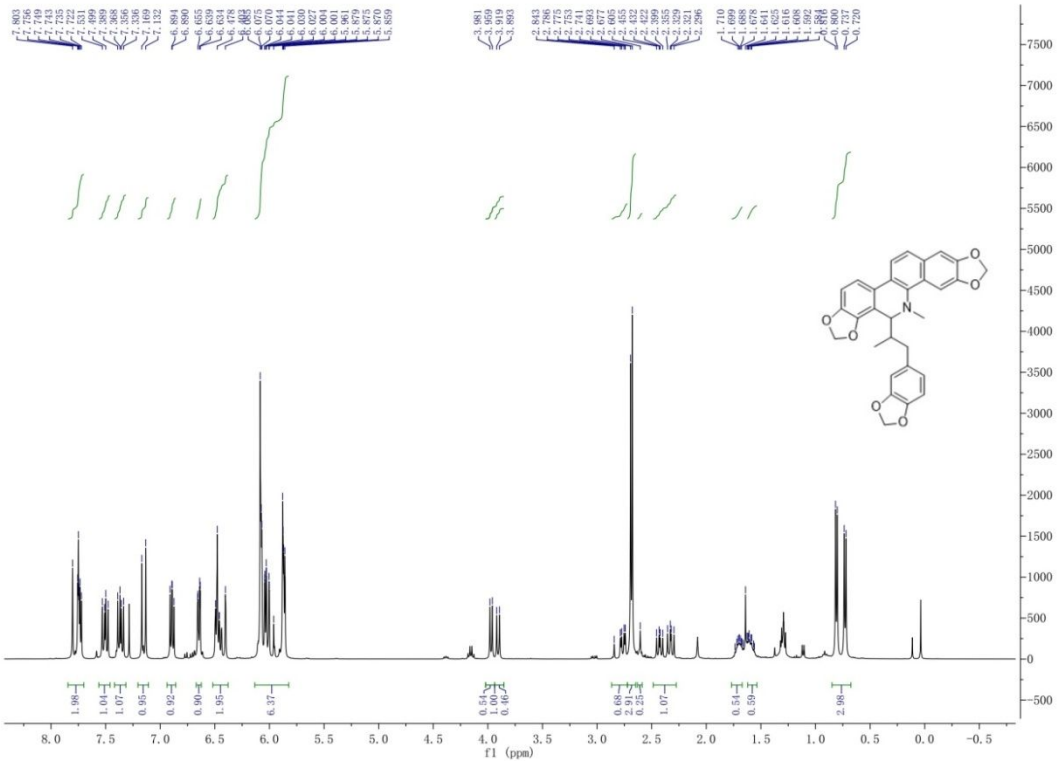


Figure S31. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7h**

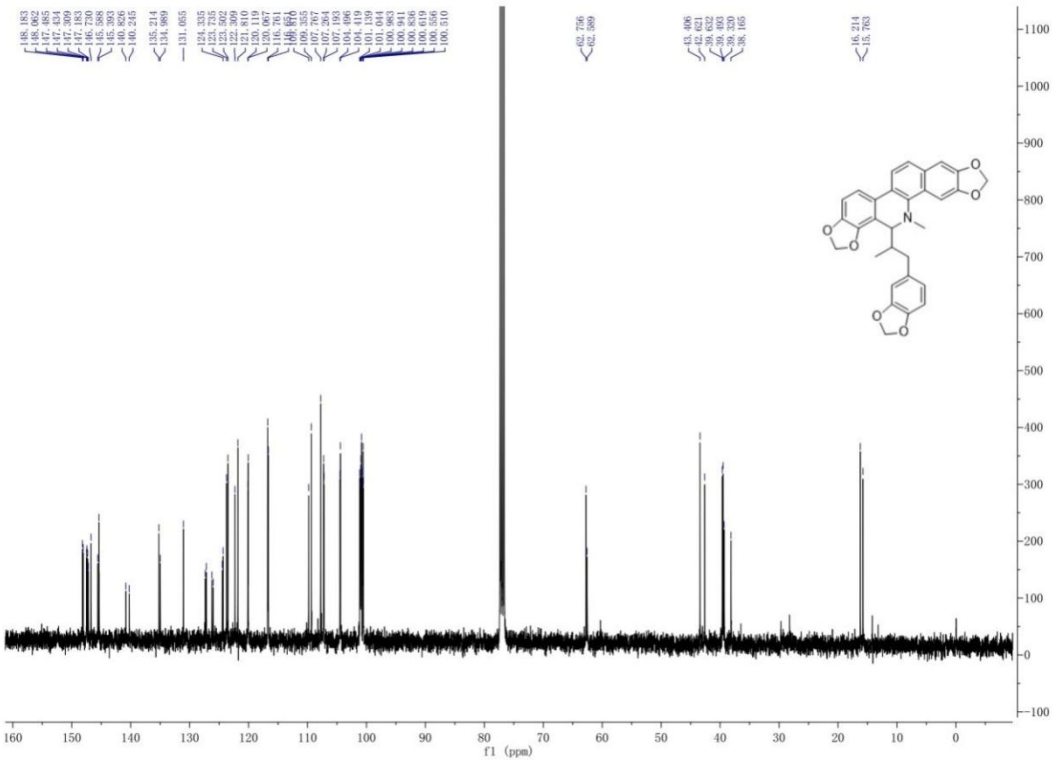


Figure S32. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **7h**

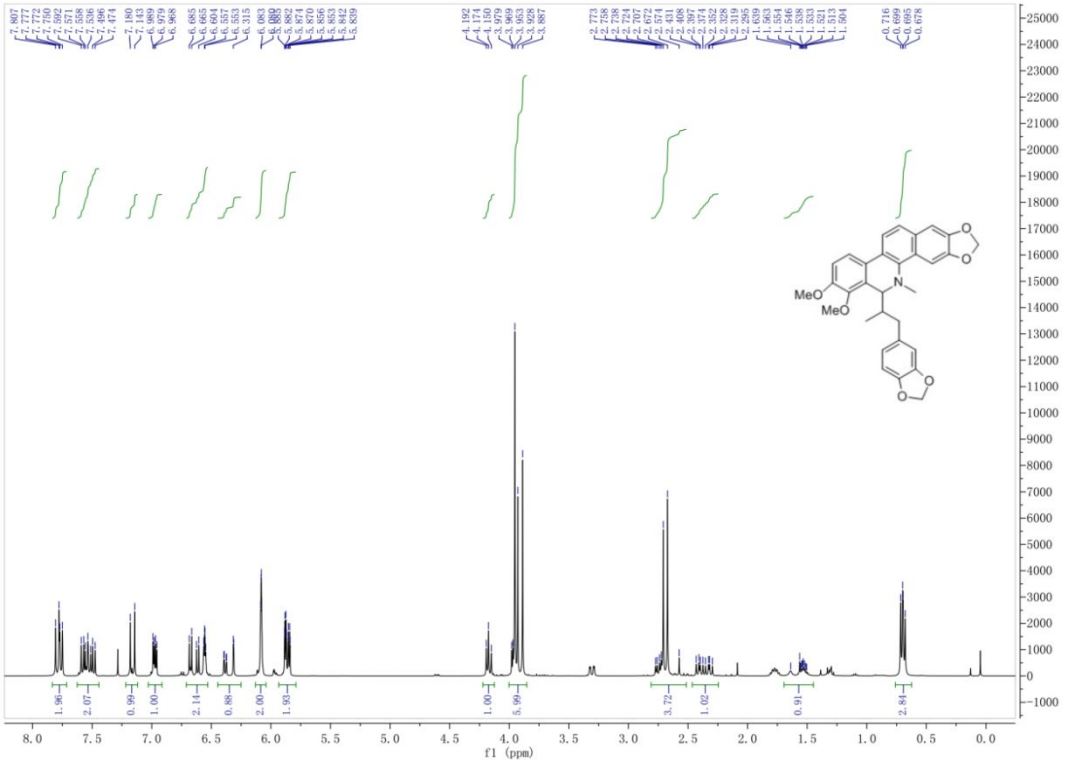


Figure S33. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7hh**

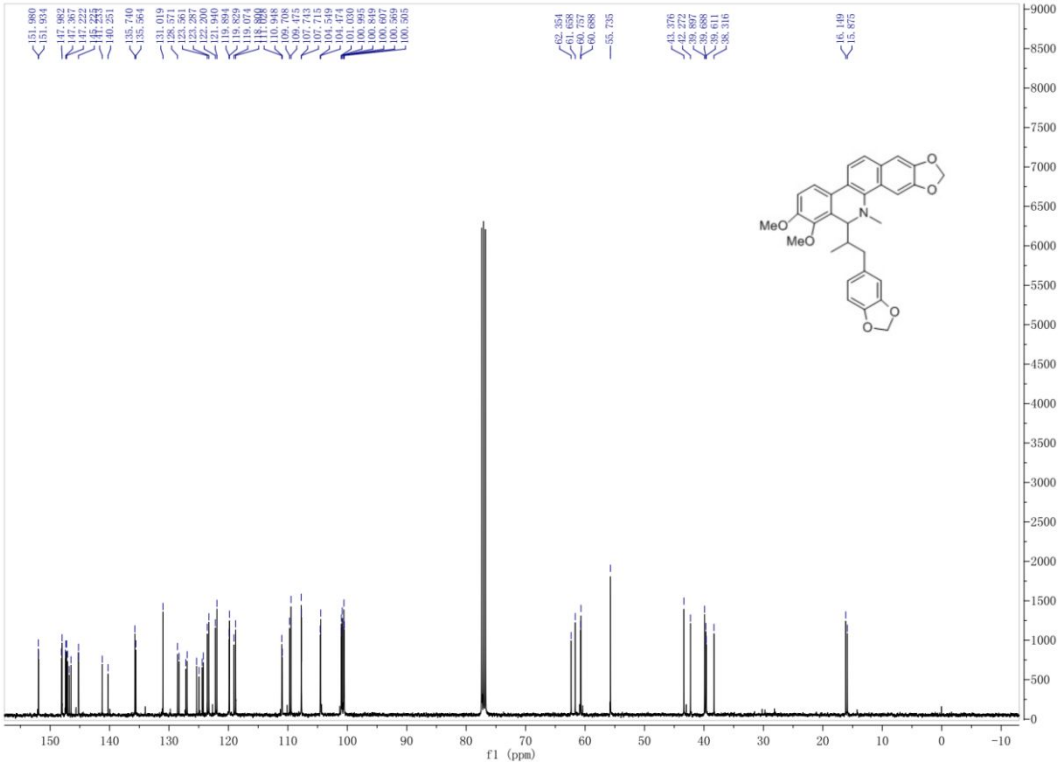


Figure S34. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **7hh**

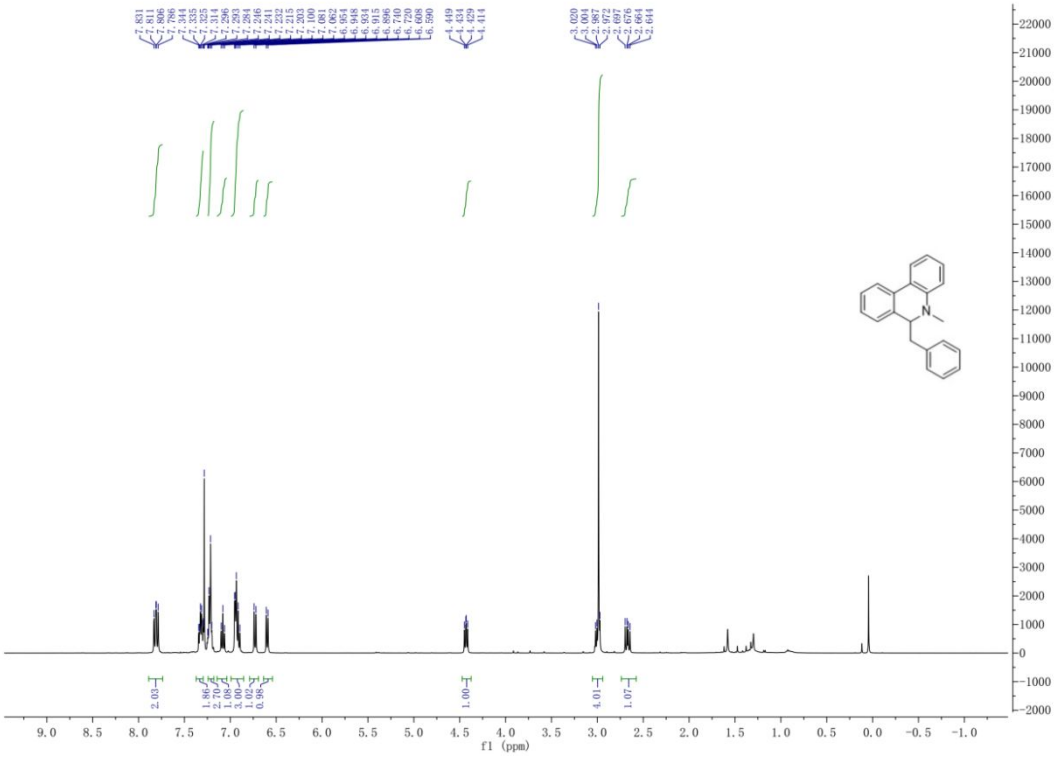


Figure S35. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **12**

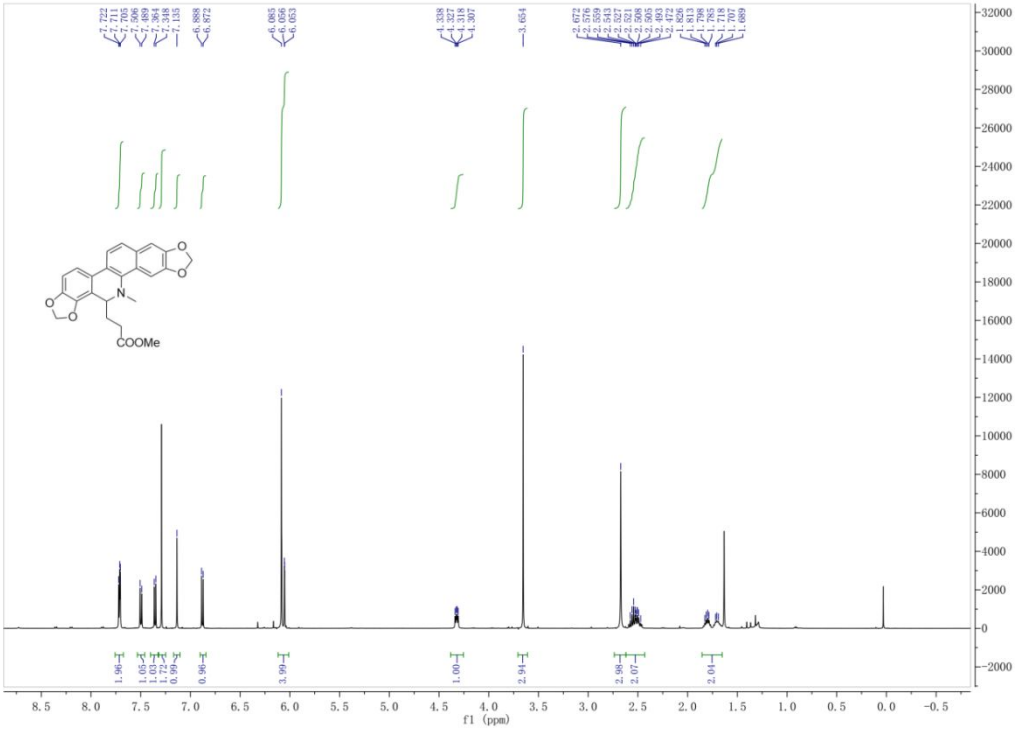


Figure S36. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **16a**

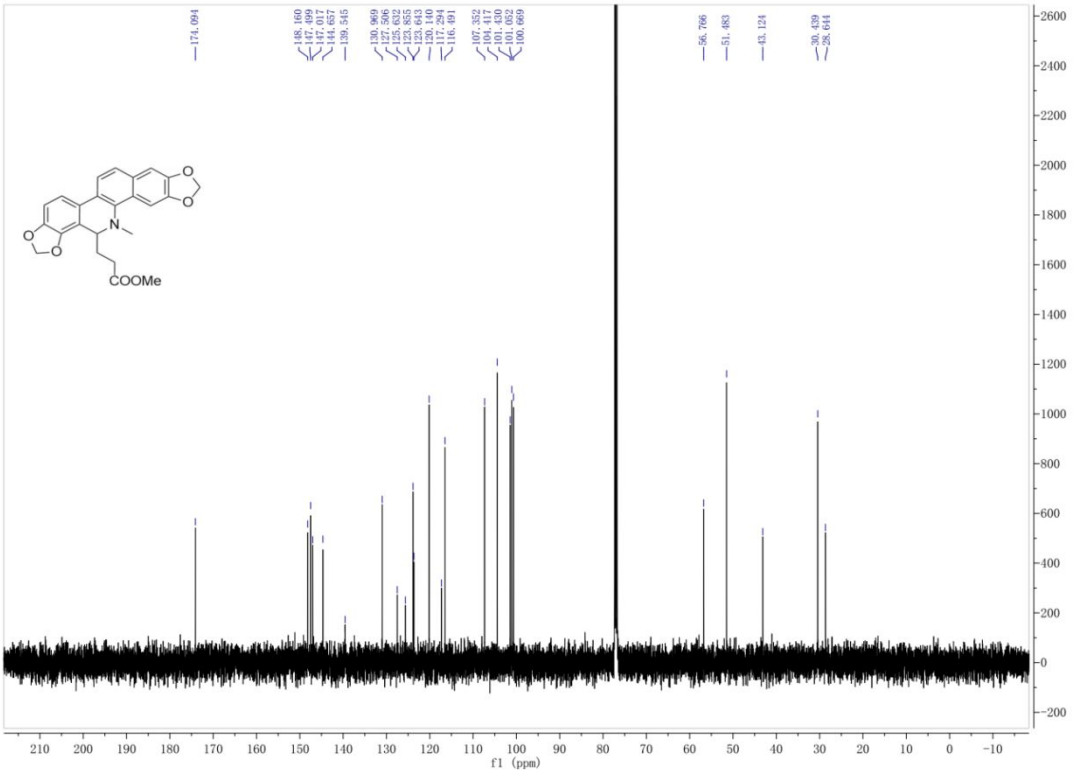


Figure S37. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **16a**

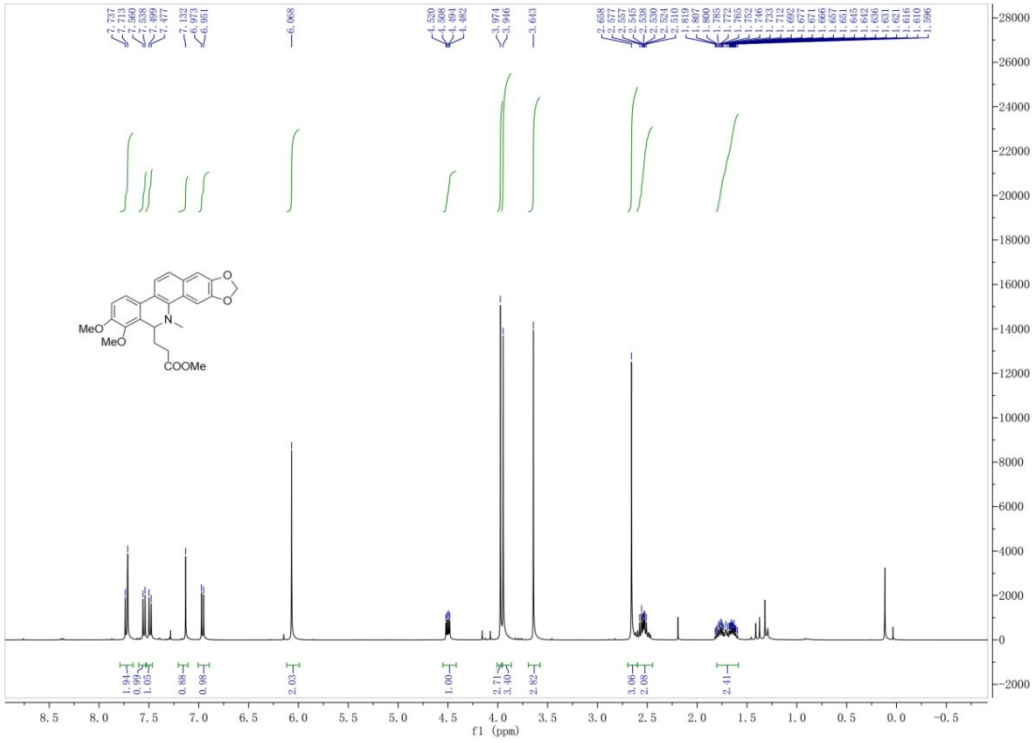


Figure S38. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **16aa**

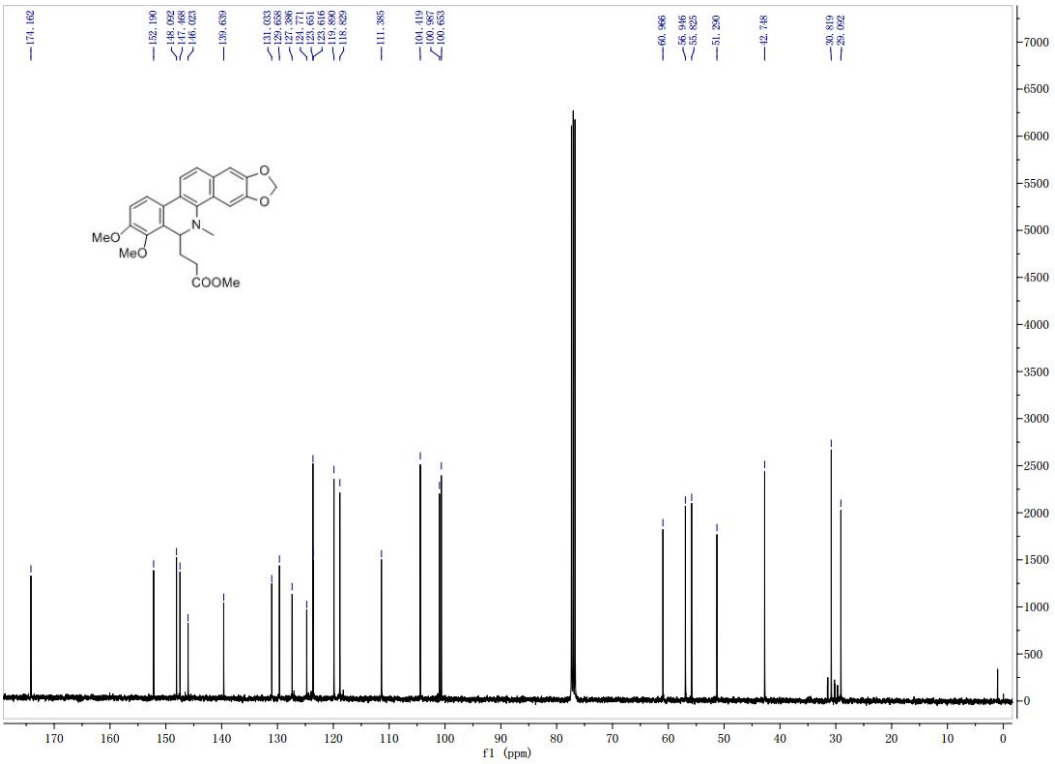


Figure S39. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **16aa**

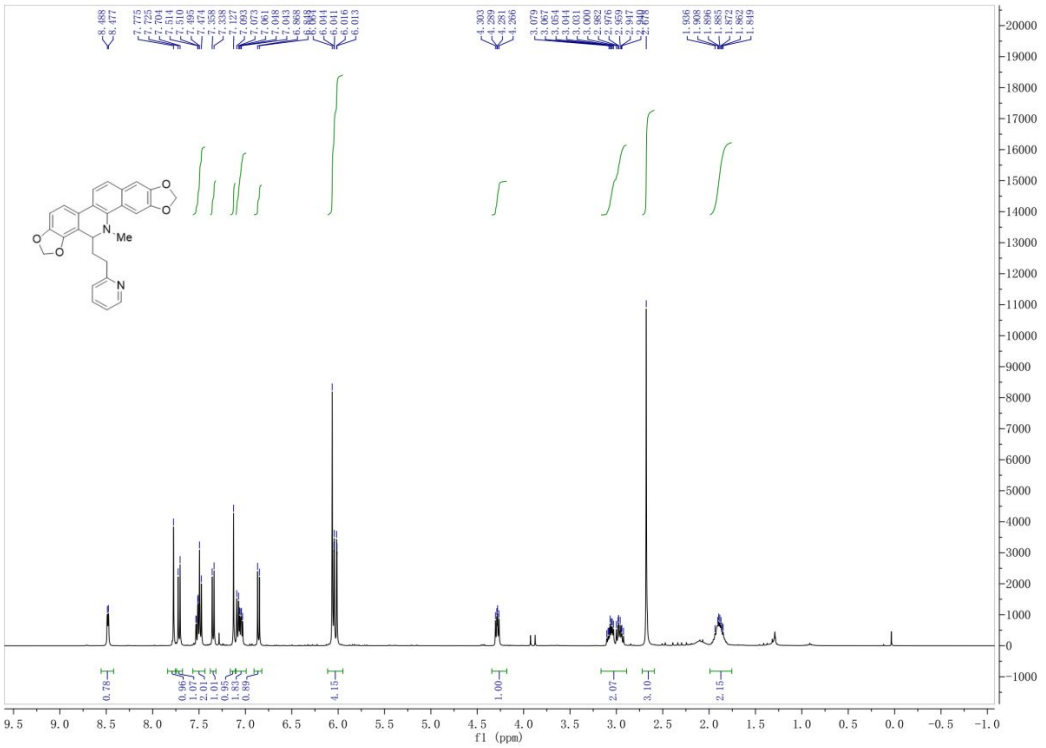


Figure S40. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **16b**

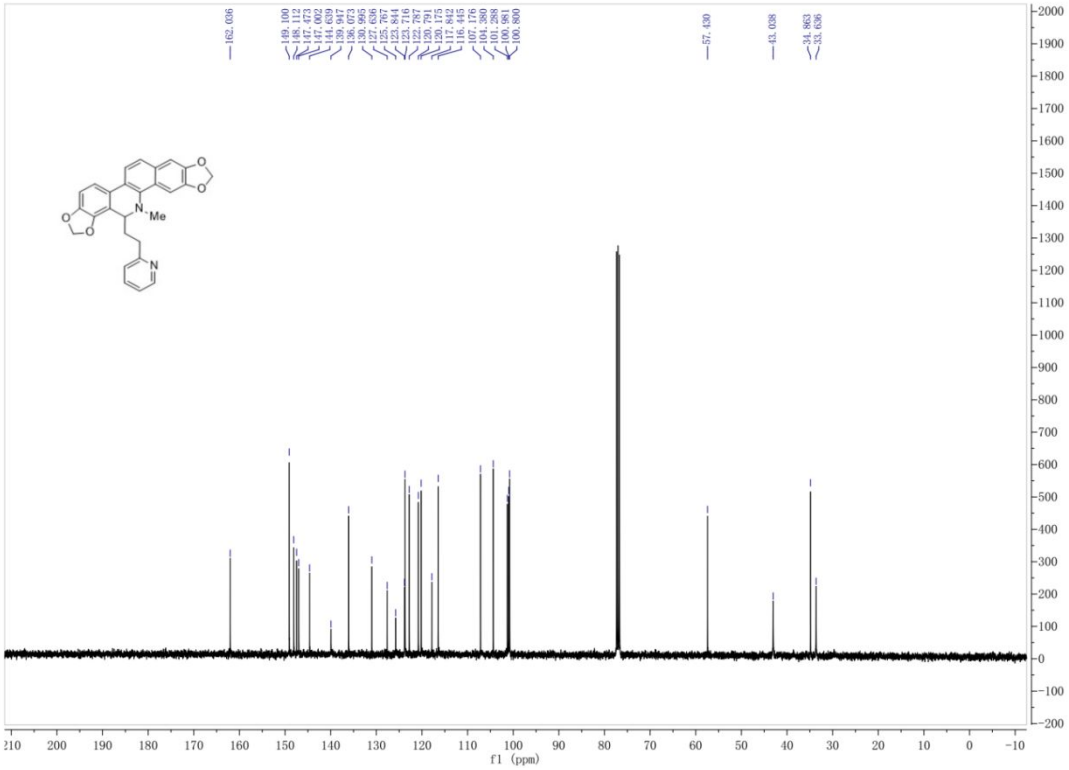


Figure S41. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **16b**

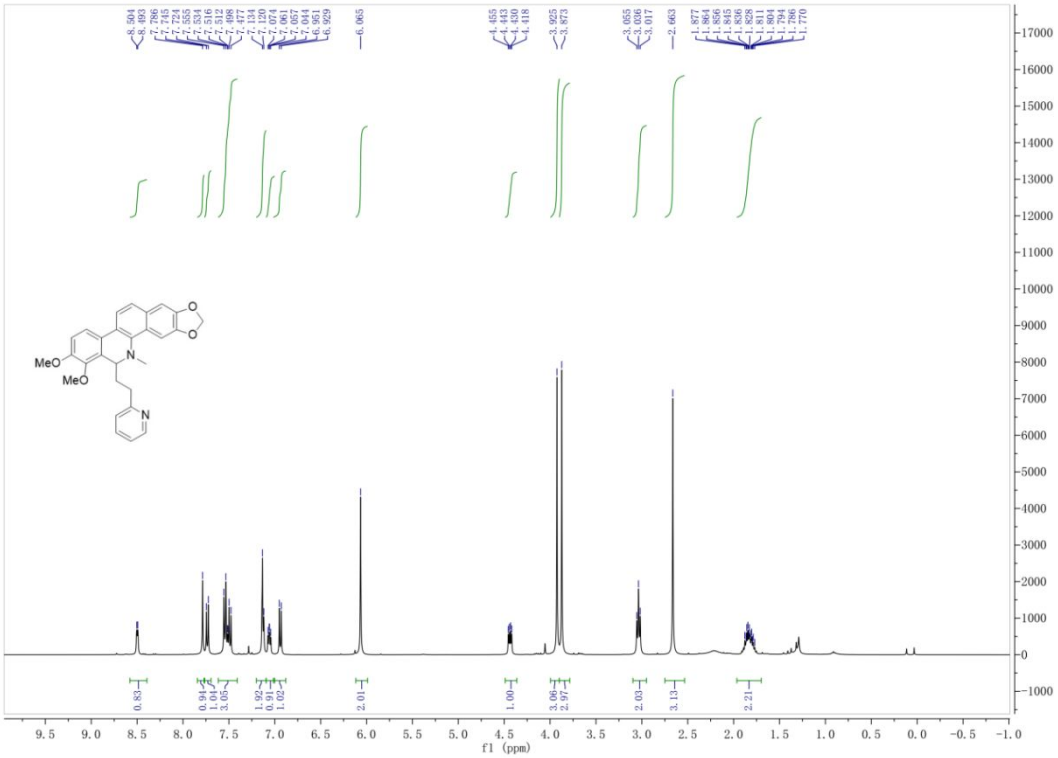


Figure S42. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **16bb**

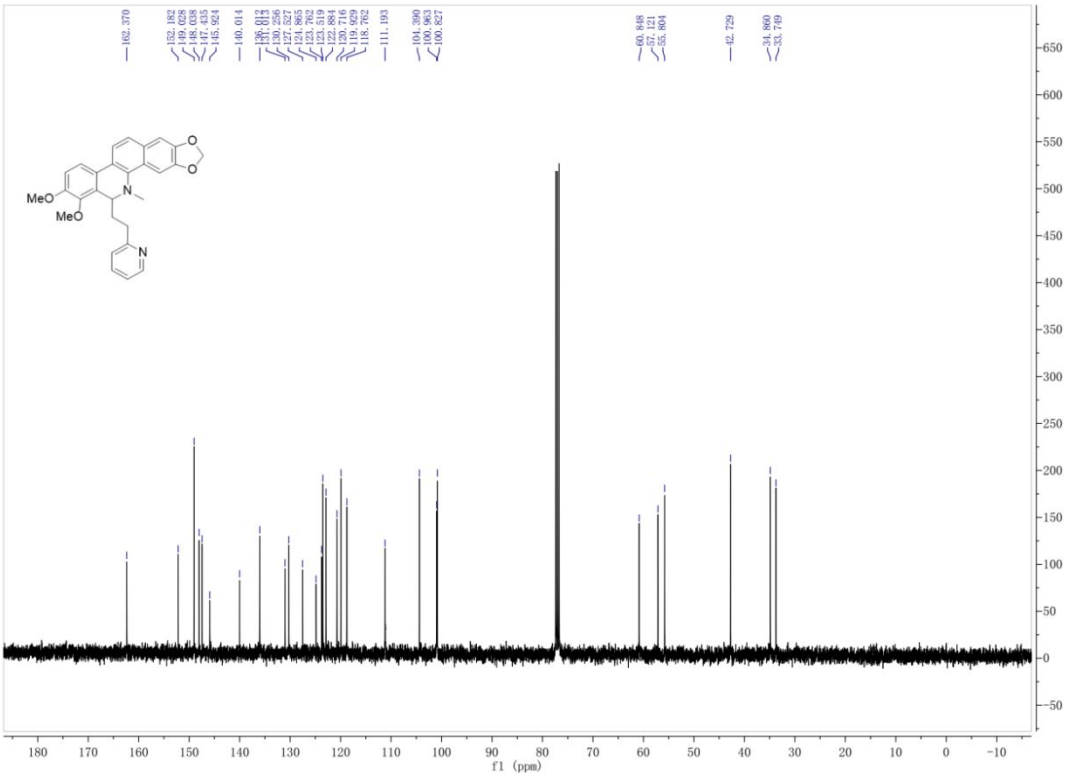


Figure S43. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **16bb**

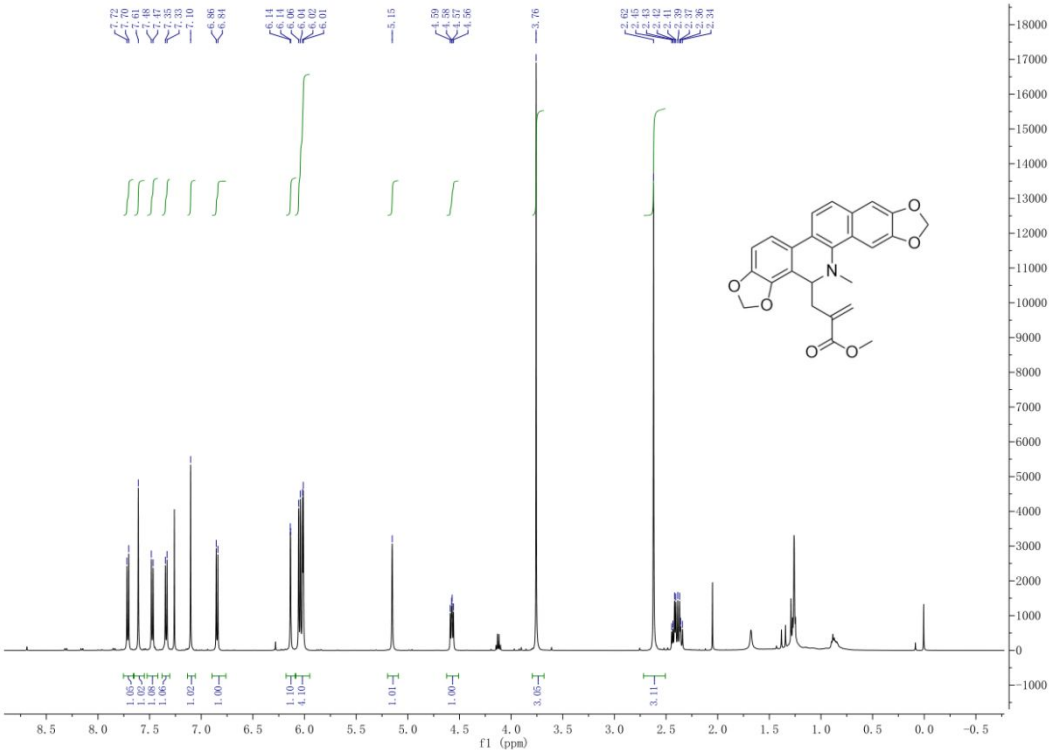


Figure S44. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **16c**

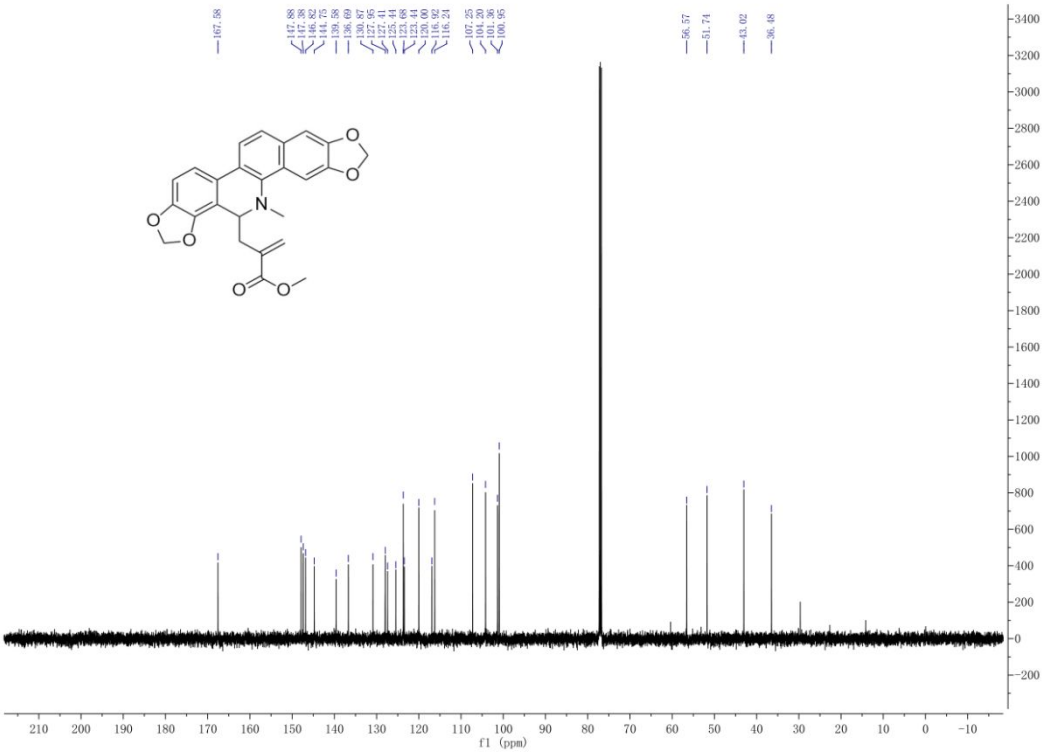


Figure S45. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **16c**

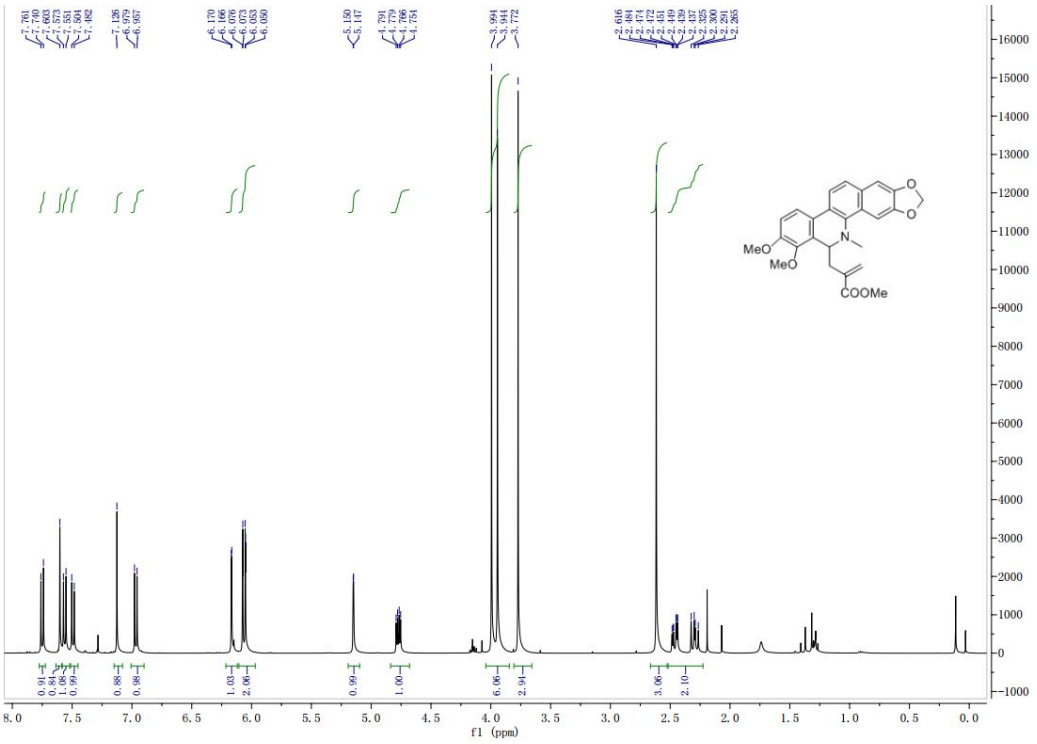


Figure S46. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **16cc**

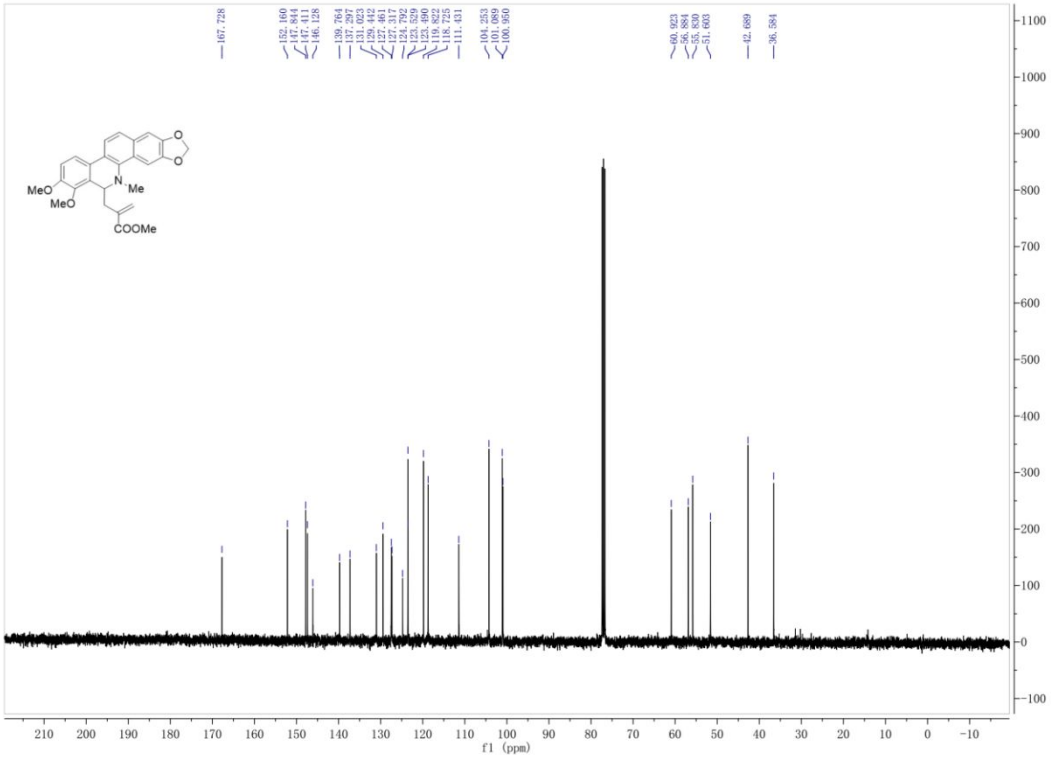


Figure S47. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **16cc**

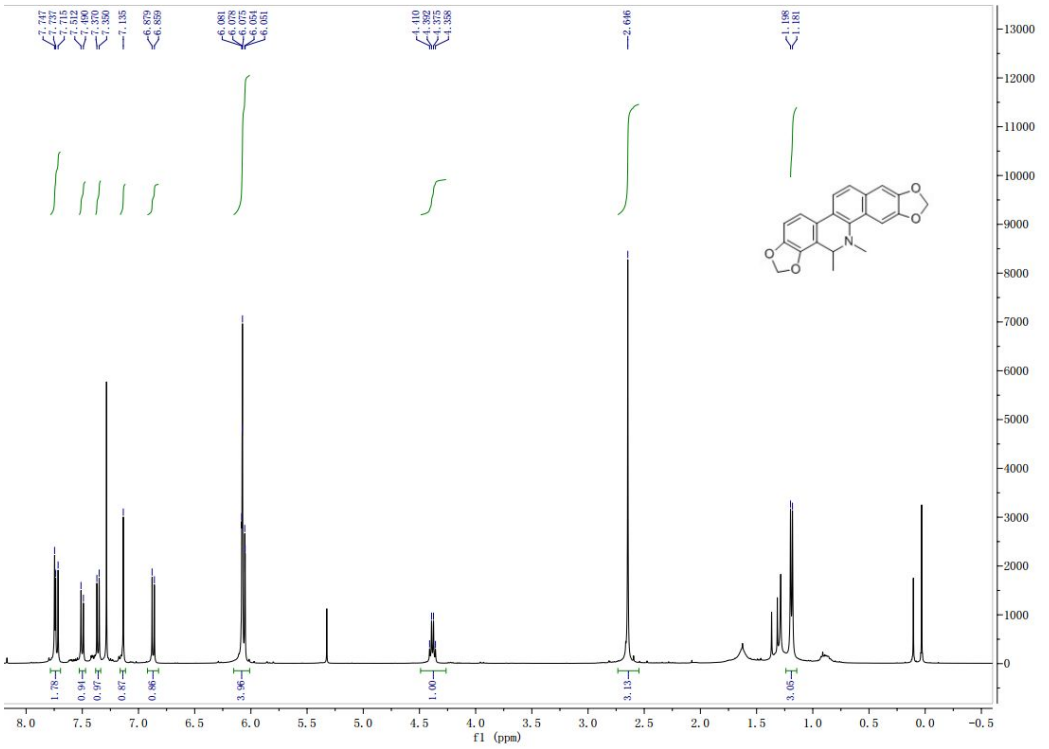


Figure S48. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 6-Me dihydrosauguinarine

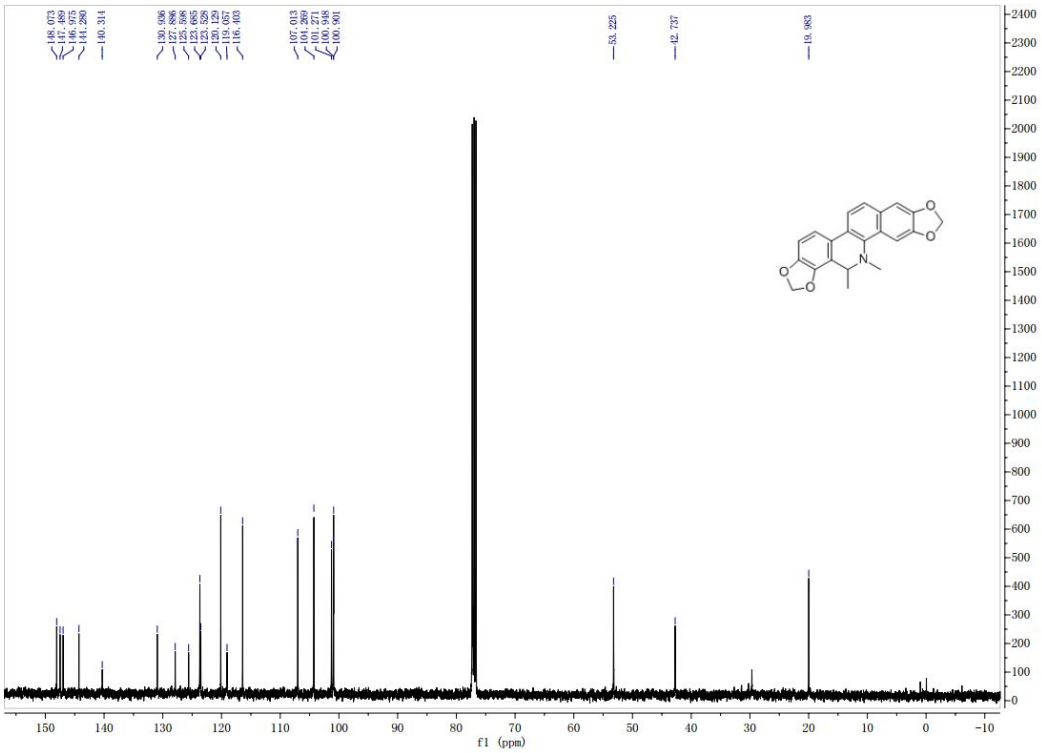


Figure S49. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of 6-Me dihydrosauguinarine

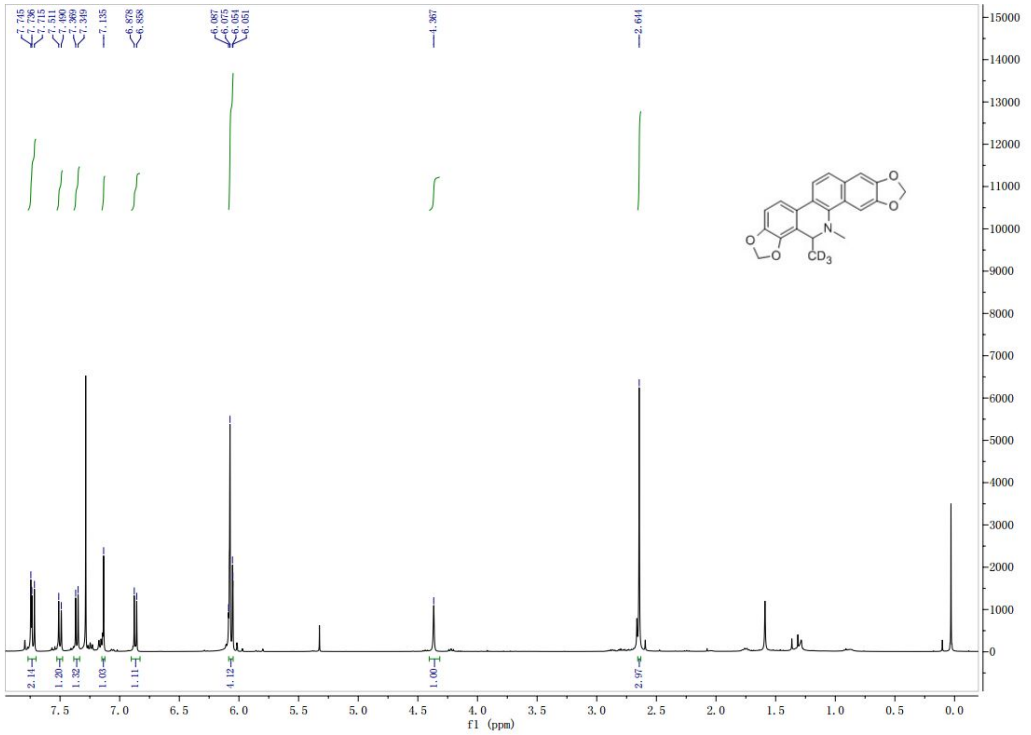


Figure S50. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 6-CD_3 dihydrosauguinarine

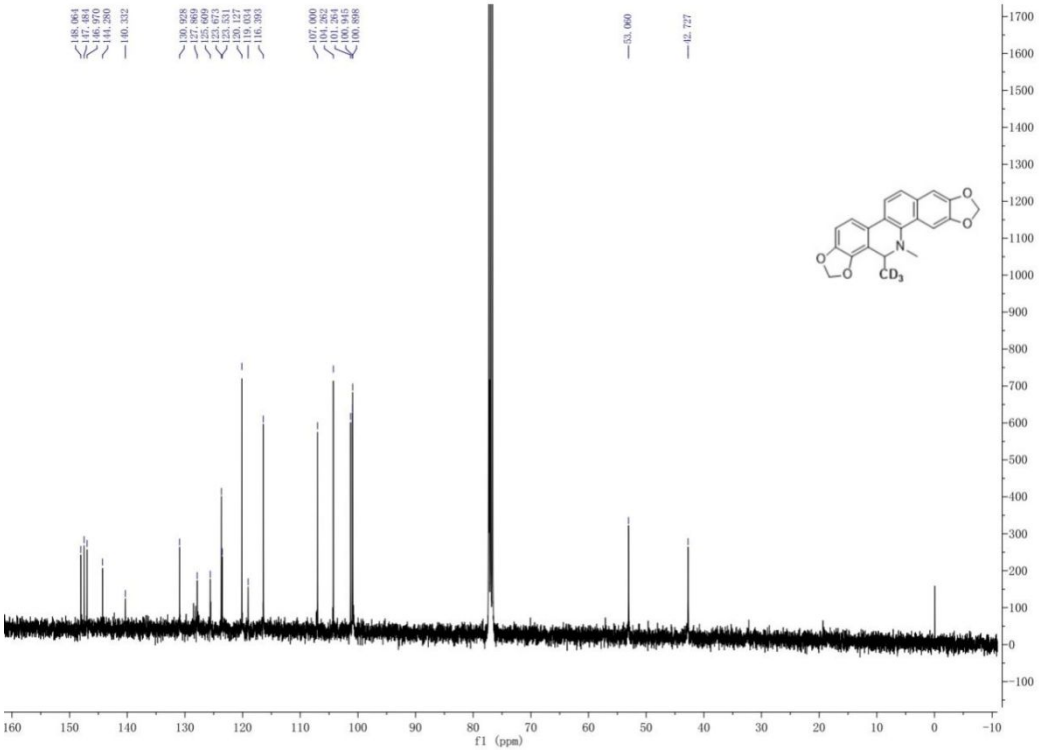


Figure S51. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of 6-CD_3 dihydrosauguinarine

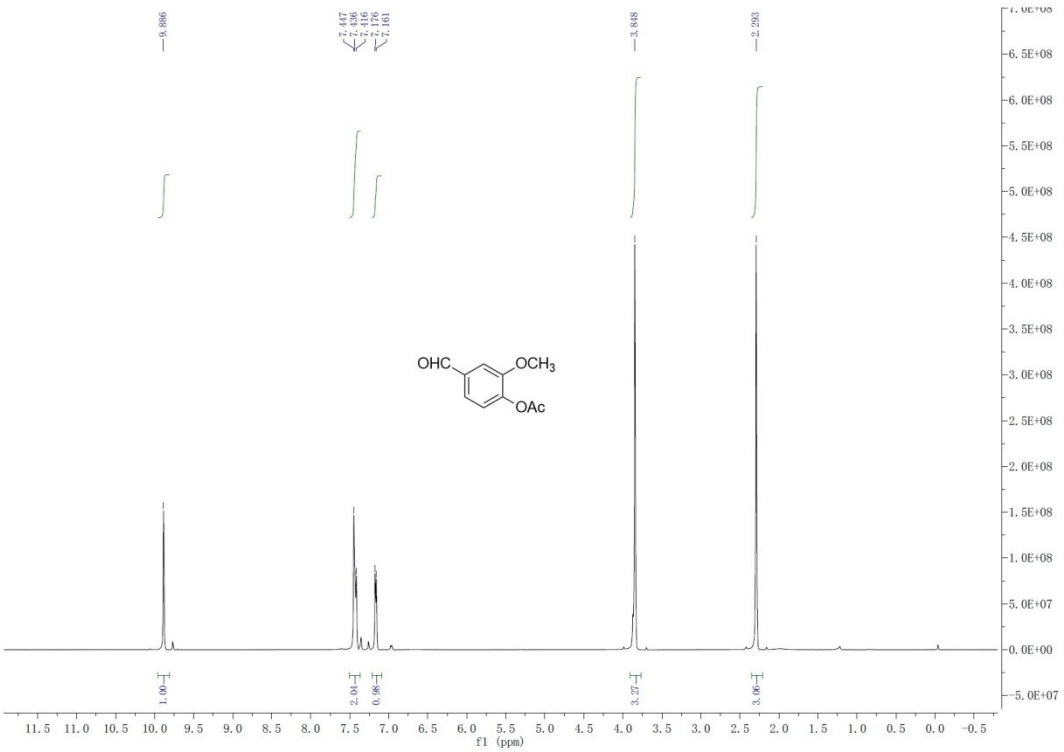


Figure S52. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **18**

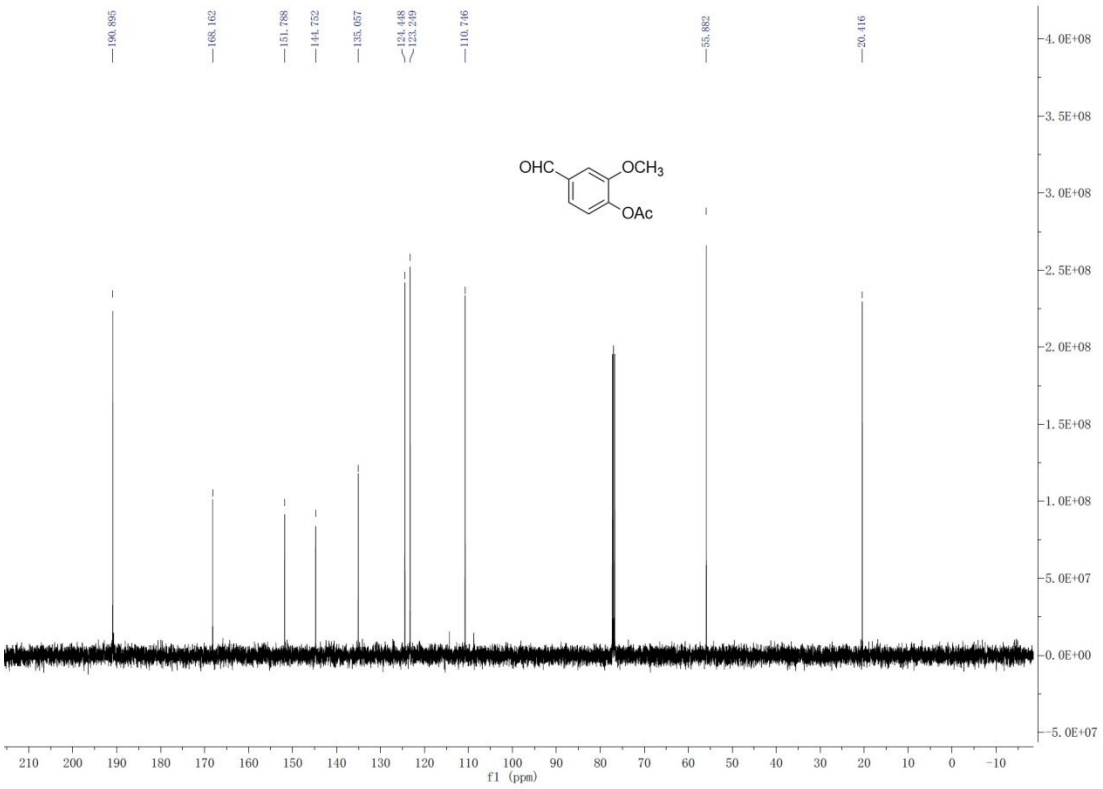


Figure S53. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **18**

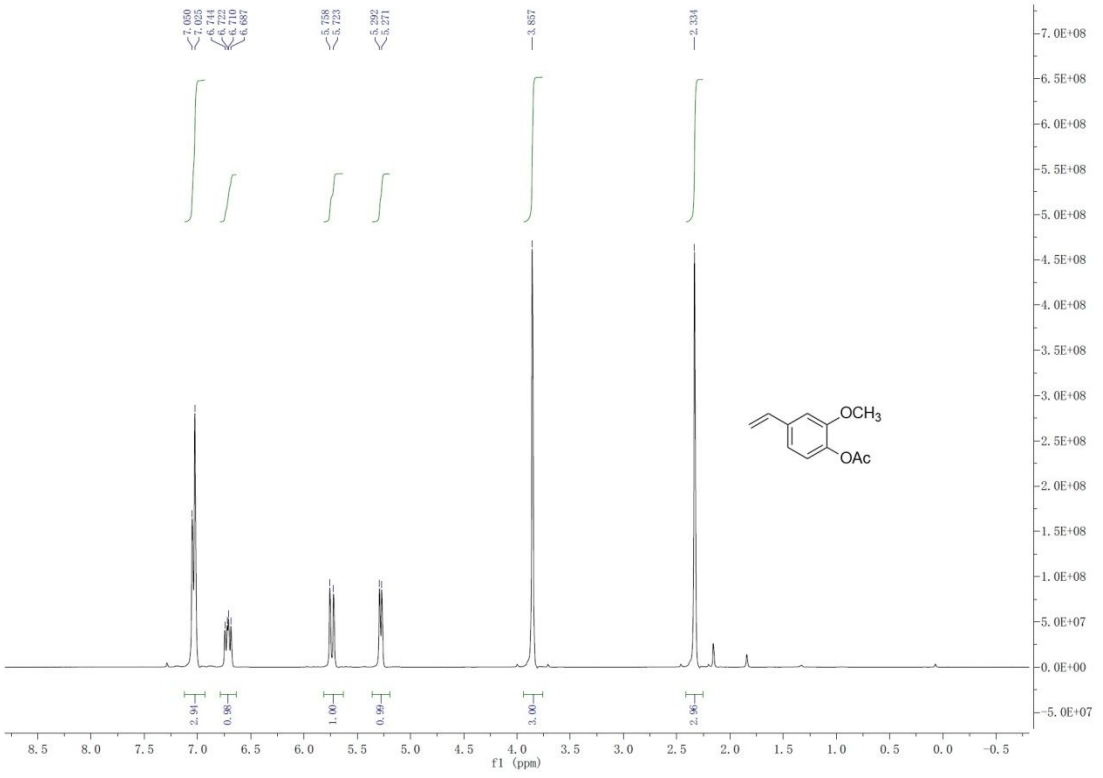


Figure S54. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **19**

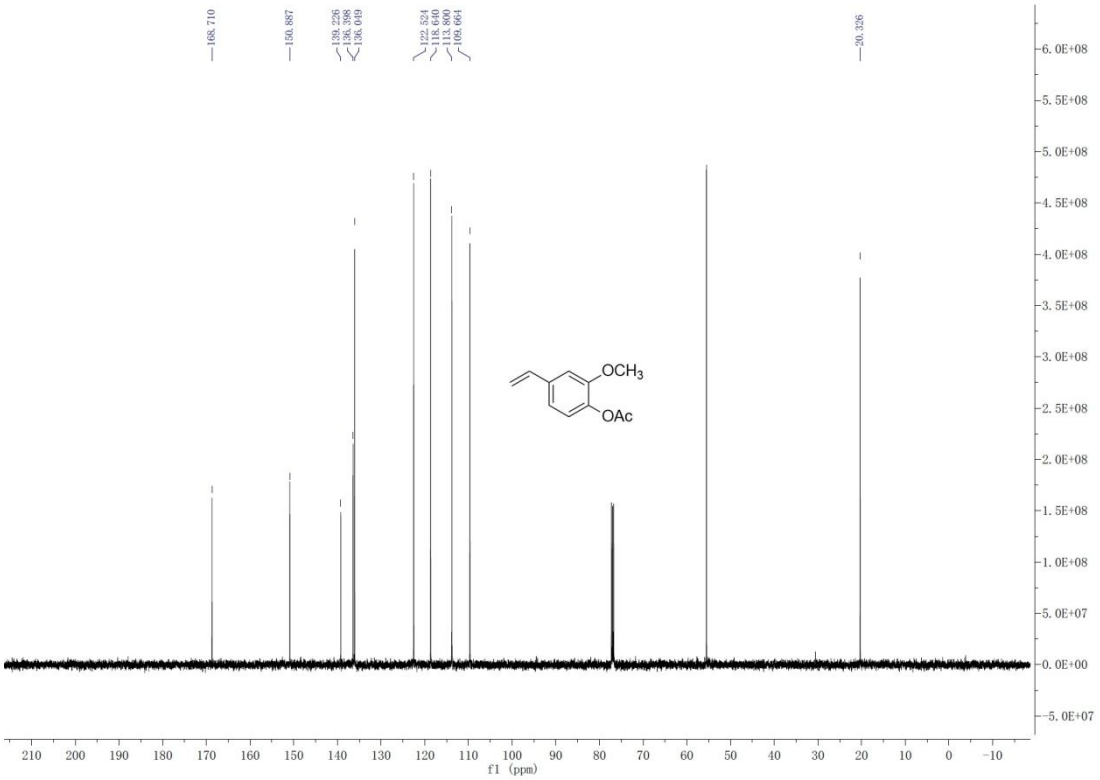


Figure S55. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **19**

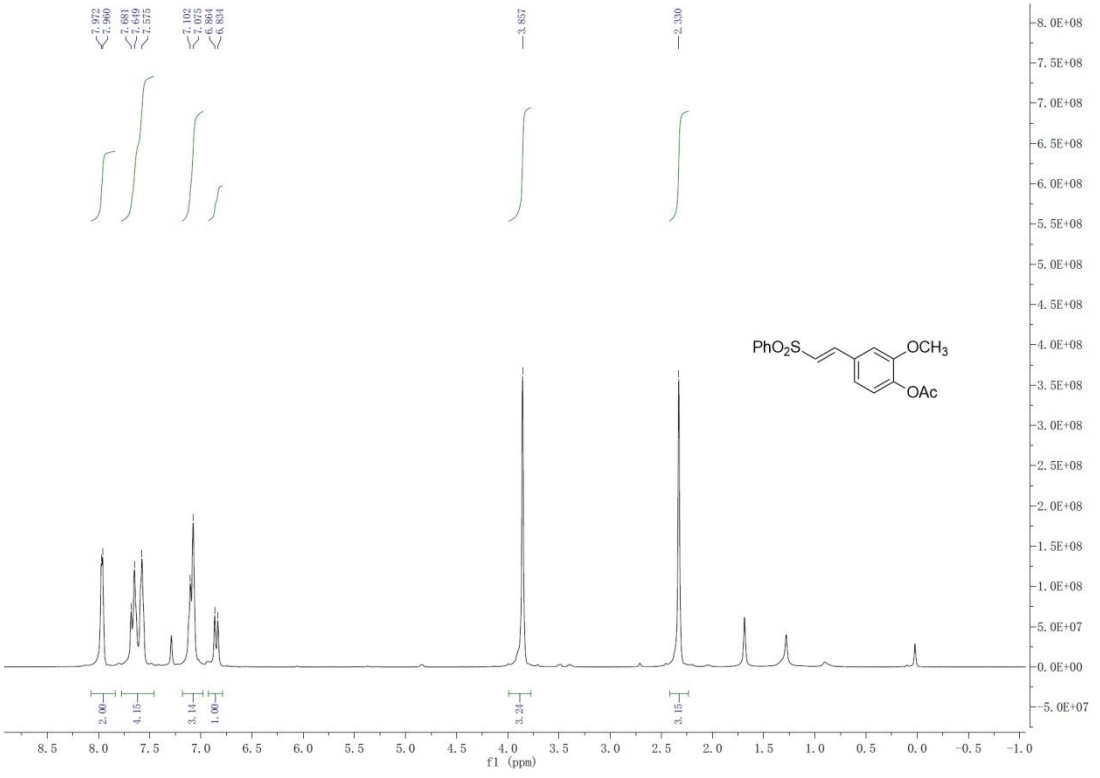


Figure S56. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **20**

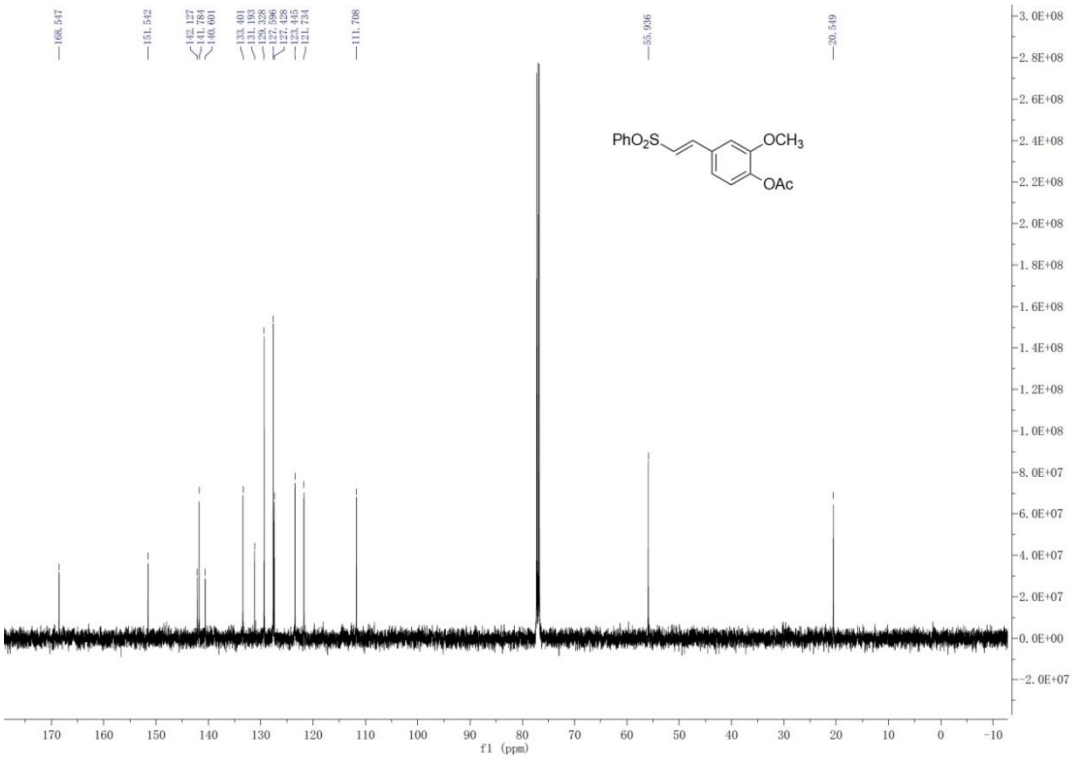


Figure S57. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **20**

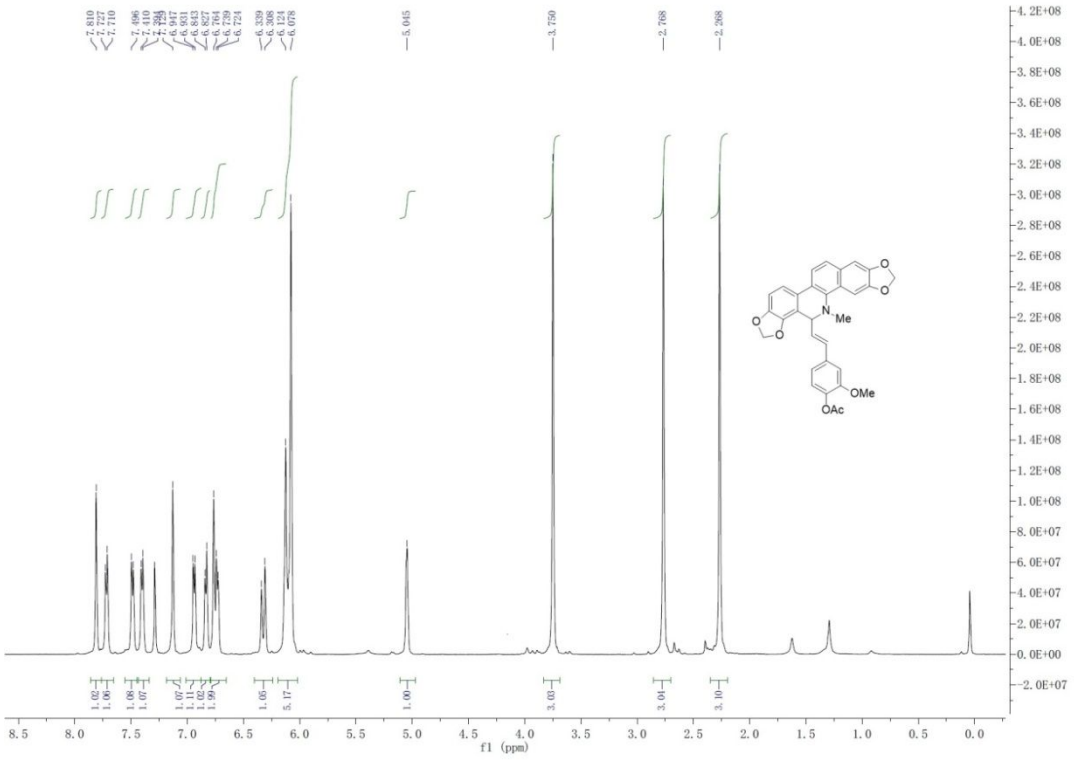


Figure S58. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **21**

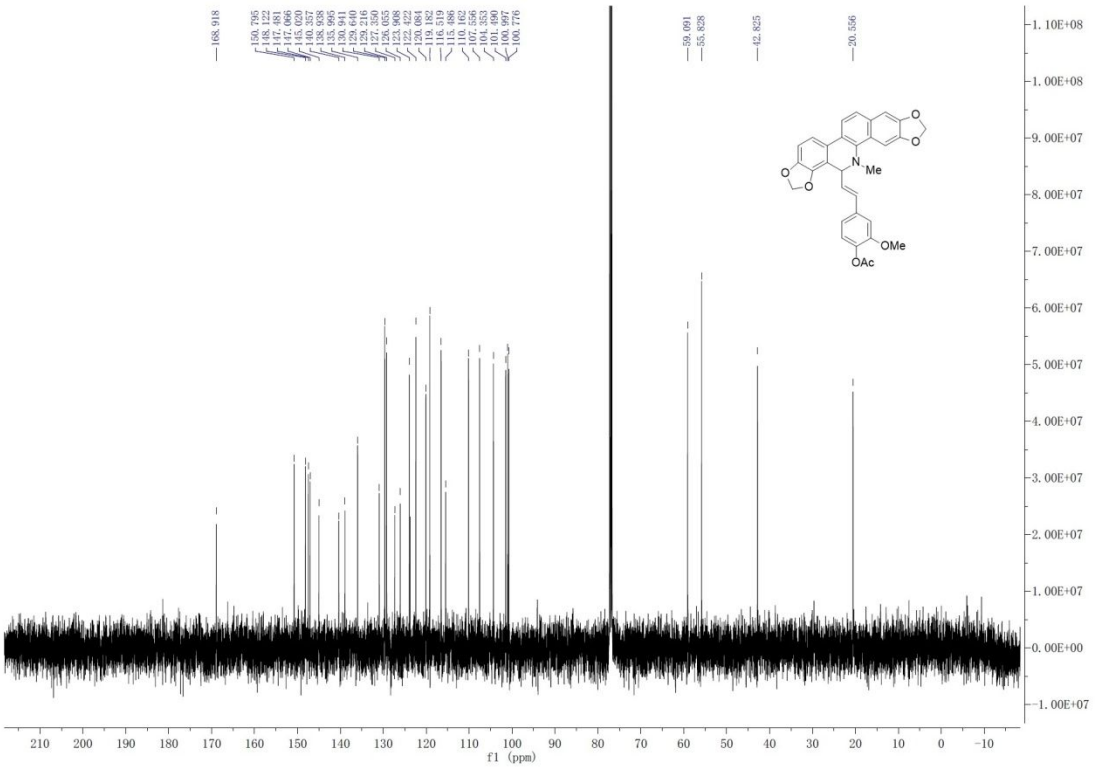


Figure S59. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **21**