Supporting Information

Discovery and Development of 8-Substituted Cycloberberine Derivatives as Novel Antibacterial Agents against MRSA

Tianyun Fan, Xinxin Hu, Sheng Tang, Xiaojia Liu, Yanxiang Wang, Hongbin Deng, Xuefu You, Jiandong Jiang, Yinghong Li, Danqing Song

Beijing Key Laboratory of Antimicrobial Agents, Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100050, China

Experimental section

General

Melting point (mp) was obtained with CXM-300 melting point apparatus and uncorrected. The ^{1}H NMR spectra was performed on a Varian Inova 500 or 600 MHz spectrometer (Varian, San Francisco, CA) and ^{13}C NMR on a Bruker Avance III 500 or 600 spectrometer with Me_4Si as the internal standard. ESI high-resolution mass spectra (HRMS) was recorded on an Autospec UItima-TOF mass spectrometer (Micromass UK Ltd, Manchester, UK). Flash chromatography was performed on CombiflashRf 200 (Teledyne, Nebraska, USA), particle size 0.038 mm.

Chemistry

General synthesis procedures for compounds 5a−l.

To a stirred solution of **1** (7.4 g, 20 mmol) and K_2CO_3 (8.3 g, 60 mmol) in

methanol (250 mL), 5% NaOH (10 mL) solution containing $NaBH_4$ (0.83 g, 22 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 3 h and the precipitated solid was filtered, washed with distilled water (100 mL) and 80% ethanol (100 mL) to give lime-green solid **3** (7.1 g, 81%). Intermediate **3** (7.1 g, 16 mmol) was then reacted with 40% glyoxal (3 mL) in the stirred solvent mixture of CH_3CN (160 mL) and HOAc (40 mL), which was heated to 93 ^oC for 6 h. The solvent was evaporated under vacuum, and methanol/HCl (2:1 by vol., 100 mL) was added into the residue. The reaction mixture was stirred at room temperature for 24 h. And then, the solvent was evaporated and the residue was recrystallized from 95% ethanol to obtain orange solid CBBR (5.6 g, 67%). Mp: 185–187 ^oC.

Then, CBBR (3.6 g, 9.1 mmol) was heated at 195–210 ^oC in a dry oven under vacuum (20–30 mmHg) for 40 min and the crude material was acidified with concentrated HCl/ethanol (5:95 by vol.) to obtain red solid **4** (3.2 g, 92%). KOH (120 mg, 2.08 mmol) was added to a solution of compound **4** (198 mg, 0.52 mmol) in anhydrous DMF (6 mL), and then corresponding bromides (2.08 mmol) were added after 15 min. The reaction mixture was heated at 68−75 ^oC for 4–24 h. The solvent was removed by evaporation, the residue was purified with flash column chromatography on silica gel using CH_2Cl_2 and MeOH as eluent to obtain the desired compounds **5a**−**l**.

*1,2-Methylenedioxy-8-(2-oxobutoxy)-9-methoxycycloberberine bromide (**5a**).* The title compound was prepared from compound **4** (198 mg, 0.52 mmol) and 1-bromo-2-butanone (2.08 mmol, 212 μL) in the same manner as described above to obtain compound **5a** as an orange solid, yield: 27%; Mp: 199 °C (dec.); ^1H NMR (600

MHz, DMSO-d_6) δ 10.22 (s, 1H), 8.90–8.70 (m, 2H), 8.27–8.15 (m, 2H), 7.60 (s, 1H), 6.40 (s, 2H), 5.26 (t, J = 6.6 Hz, 2H), 5.20 (s, 2H), 4.07 (s, 3H), 3.64 (t, J = 6.6 Hz, 2H), 2.63 (q, J = 7.2 Hz, 2H), 1.02 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 206.6, 149.4, 147.1, 146.6, 143.9, 140.9, 129.3, 128.1, 126.5, 126.0, 122.9, 122.0, 121.0, 119.6, 119.1, 117.0, 116.0, 110.4, 102.9, 76.6, 57.1, 56.0, 31.0, 26.1, 7.0; HRMS: calcd for $C_{25}H_{22}NO_5Br$ $[M–Br]^+$: 416.1493, found: 416.1481.

*1,2-Methylenedioxy-8-(2-tert-butyl-2-oxoethoxy)-9-methoxycycloberberine bromide **(5b)**.* The title compound was prepared from compound **4** (198 mg, 0.52 mmol) and 1-bromo-3,3-dimethyl-2-butanone (2.08 mmol, 280 μL) in the same manner as described above to obtain compound **5b** as an orange solid, yield: 28%; Mp: 207 ℃ (dec.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.23 (s, 1H), 8.89 (dd, J = 10.8, 2.4 Hz, 1H), 8.79 (dd, J = 10.8, 1.2 Hz, 1H), 8.26 (d, J = 9.0 Hz, 1H), 8.21 (dd, J = 10.8, 3.6 Hz, 1H), 7.61 (s, 1H), 6.41 (s, 2H), 5.60 (s, 2H), 5.26 (t, J = 7.8 Hz, 2H), 4.07 (s, 3H), 3.64 (t, J = 7.8 Hz, 2H), 1.17 (s, 9H).; ^{13}C NMR (126 MHz, DMSO-d_6) δ 210.1, 149.2, 147.3, 146.7, 144.0, 141.0, 129.4, 128.2, 126.6, 126.0, 123.0, 122.1 (2), 119.7, 118.7, 117.1, 116.1, 110.4, 103.0, 73.5, 57.1, 56.0, 42.3, 26.2, 25.9 (3); HRMS: calcd for $C_{27}H_{26}NO_5Br$ $[M–Br]^+$: 444.1806, found: 444.1792.

*1,2-Methylenedioxy-8-(2-cyclopropyl-2-oxoethoxy)-9-methoxycycloberberine bromide **(5c)**.* The title compound was prepared from compound **4** (198 mg, 0.52 mmol) and 2-bromo-1-cyclopropylethanone (208 mmol, 203 μL) in the same manner as described above to obtain compound **5c** as an orange solid, yield: 31%; Mp: 193 ℃ (dec.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.23 (s, 1H), 8.86 (d, J = 9.0 Hz, 1H), 8.79

(d, J = 9.0 Hz, 1H), 8.27 (d, J = 9.0 Hz, 1H), 8.18 (d, J = 9.0 Hz, 1H), 7.60 (s, 1H), 6.40 (s, 2H), 5.38 (s, 2H), 5.25 (t, J = 6.5 Hz, 2H), 4.08 (s, 3H), 3.63 (t, J = 6.5 Hz, 2H), 2.31–2.22 (m, 1H), 1.08–0.91 (m, 4H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 205.8, 149.4, 147.2, 146.7, 143.9, 141.0, 129.4, 128.1, 126.6, 126.0, 123.0, 122.1, 121.1, 119.6, 119.2, 117.1, 116.0, 110.4, 103.0, 77.1, 57.1, 56.0, 26.1, 16.8, 10.7 (2); HRMS: calcd for $C_{26}H_{22}NO_5Br$ $[M–Br]^+$: 428.1493, found: 428.1481.

*1,2-Methylenedioxy-8-(2-adamantyl-2-oxoethoxy)-9-methoxycycloberberine bromide (**5d**).* The title compound was prepared from compound **4** (198 mg, 0.52 mmol) and 1-adamantyl bromomethyl ketone (2.08 mmol, 535 mg) in the same manner as described above to obtain compound **5d** as an orange solid, yield: 34%; Mp: 223 ℃ (dec.); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.22 (s, 1H), 8.88 (d, J = 9.0 Hz, 1H), 8.77 (d, J = 9.0 Hz, 1H), 8.25 (d, J = 9.6 Hz, 1H), 8.21 (d, J = 9.0 Hz, 1H), 7.60 (s, 1H), 6.41 (s, 2H), 5.56 (s, 2H), 5.26 (t, J = 6.6 Hz, 2H), 4.06 (s, 3H), 3.64 (t, J = 6.6 Hz, 2H), 2.01 (s, 3H), 1.84 (d, J = 2.4 Hz, 6H), 1.74－1.70 (m, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 209.1, 148.9, 147.1, 146.5, 144.0, 140.8, 129.3, 128.1, 126.4, 125.9, 122.8, 121.9, 120.9, 119.5, 118.4, 117.0, 115.9, 110.2, 102.8, 73.4, 57.0, 55.9, 44.4, 37.1 (3), 35.8 (3), 27.1 (3), 26.1; HRMS: calcd for $C_{33}H_{32}NO_5Br$ $[M–Br]^+$: 522.2275, found: 522.2257.

*1,2-Methylenedioxy-8-(2-phenyl-2-oxoethoxy)-9-methoxycycloberberine bromide (**5e**).* The title compound was prepared from compound **4** (198 mg, 0.52 mmol) and α-bromoacetophenone (2.08 mmol, 280 μL) in the same manner as described above to obtain compound **5e** as a brown solid, yield: 31%; Mp: 222 ℃ (dec.); ^{1}H NMR (600

MHz, DMSO-d_6) δ 10.30 (s, 1H), 8.92 (d, J = 9.0 Hz, 1H), 8.84 (d, J = 9.0 Hz, 1H), 8.29 (d, J = 9.0 Hz, 1H), 8.24 (d, J = 9.0 Hz, 1H), 8.02 (d, J = 7.2 Hz, 2H), 7.72 (t, J = 7.2 Hz, 1H), 7.64–7.54 (m, 3H), 6.41 (s, 2H), 5.98 (s, 2H), 5.27 (s, 2H), 4.00 (s, 3H), 3.65 (s, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 194.5, 149.3, 147.3, 146.9, 144.0, 141.0, 134.0, 129.6, 129.4, 129.0 (2), 128.3, 127.8 (2), 126.6, 126.1, 123.0, 122.1, 121.1, 119.7, 119.0, 117.1, 116.1, 110.4, 102.9, 75.0, 57.1, 56.0, 26.2; HRMS: calcd for $C_{29}H_{22}NO_5Br$ $[M–Br]^+$: 464.1493, found: 464.1500.

*1,2-Methylenedioxy-8-(2-p-fluorophenyl-2-oxoethoxy)-9-methoxycycloberberine bromide (**5f**).* The title compound was prepared from compound **4** (198 mg, 0.52 mmol) and 4-fluorophenacyl bromide (2.08 mmol, 288 μL) in the same manner as described above to obtain compound **5f** as a reddish solid, yield: 38%; Mp: 209 ℃ (dec.); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.91 (t, J = 9.6 Hz, 1H), 8.83 (t, J = 9.6 Hz, 1H), 8.28 (dd, J = 9.0, 6.0 Hz, 1H), 8.23 (t, J = 9.6 Hz, 1H), 8.13–8.10 (m, 2H), 7.61 (s, 1H), 7.43 (t, J = 9.0 Hz, 2H), 6.41 (d, J = 2.4 Hz, 2H), 5.96 (s, 2H), 5.27 (t, J = 6.6 Hz, 2H), 4.00 (s, 3H), 3.65 (t, J = 6.6 Hz, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 193.1, 165.3, 149.2, 147.1, 146.6, 143.9, 140.9, 130.8 (2), 130.7, 129.3, 128.1, 126.5, 126.0, 122.9, 122.0, 121.0, 119.6, 118.9, 117.0, 116.0 (2), 115.9, 110.3, 102.8, 74.8, 57.0, 55.9, 26.1; HRMS: calcd for $C_{29}H_{21}FNO_5Br$ $[M–Br]^+$: 482.1398, found: 482.1382.

*1,2-Methylenedioxy-8-(2-p-trifluoromethylphenyl-2-oxoethoxy)-9-methoxycycloberberine bromide (**5g**).* The title compound was prepared from compound **4** (198 mg, 0.52 mmol) and 4-(trifluoromethyl)phenacyl bromide (2.08 mmol, 348 μL) in the same

manner as described above to obtain compound **5g** as an orange solid, yield: 42%; Mp: 211 °C (dec.); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.92–8.89 (m, 1H), 8.86–8.82 (m, 1H), 8.29 (dd, J = 9.0, 6.0 Hz, 1H), 8.25–8.21 (m, 3H), 7.98 (d, J = 8.4 Hz, 2H), 7.61 (s, 1H), 6.41 (s, 2H), 6.00 (s, 2H), 5.27 (t, J = 6.6 Hz, 2H), 4.00 (s, 3H), 3.65 (t, J = 6.6 Hz, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 194.6, 149.7, 147.6, 147.1, 144.3, 141.4, 137.8, 133.5, 129.9, 129.2 (2), 128.7, 127.0, 126.5, 126.4 (2), 124.1, 123.4, 122.6, 121.5, 120.1, 119.1, 117.5, 116.5, 110.8, 103.4, 75.8, 57.6, 56.5, 26.6; HRMS: calcd for $C_{30}H_{21}F_3NO_5Br$ $[M–Br]^+$: 532.1366, found: 532.1349.

*1,2-Methylenedioxy-8-(2-o-trifluoromethoxyphenyl-2-oxoethoxy)-9-methoxycycloberb erine bromide (**5h**).* The title compound was prepared from compound **4** (198 mg, 0.52 mmol) and 2-(trifluoromethoxy)phenacyl bromide (2.08 mmol, 589 mg) in the same manner as described above to obtain compound **5h** as an orange solid, yield: 28%; Mp: 202 °C (dec.); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.24 (s, 1H), 8.88 (d, J = 9.0 Hz, 1H), 8.82 (d, J = 9.0 Hz, 1H), 8.29 (d, J = 9.6 Hz, 1H), 8.20 (d, J = 9.6 Hz, 1H), 8.01 (dd, J = 7.8, 1.8 Hz, 1H), 7.80 (td, J = 8.4, 1.8 Hz, 1H), 7.65–7.59 (m, 2H), 7.57 (d, J = 8.4 Hz, 1H), 6.41 (s, 2H), 5.77 (s, 2H), 5.26 (t, J = 6.6 Hz, 2H), 4.02 (s, 3H), 3.65 (t, J = 6.6 Hz, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 194.1, 149.0, 147.0, 146.6, 145.9, 143.5, 140.8, 134.6, 130.5, 129.3, 128.7, 128.1, 127.9, 126.4, 125.9, 122.9, 122.0, 121.5, 120.9, 119.8, 119.4, 119.0, 117.0, 115.9, 110.3, 102.8, 76.5, 57.0, 56.0, 26.0; HRMS: calcd for $C_{30}H_{21}F_3NO_6Br$ $[M–Br]^+$: 548.1316, found: 548.1297.

*1,2-Methylenedioxy-8-(2-m-trifluoromethoxyphenyl-2-oxoethoxy)-9-methoxycyclober berine bromide (**5i**).* The title compound was prepared from compound **4** (198 mg,

0.52 mmol) and 3-(trifluoromethoxy)phenacyl bromide (2.08 mmol, 589 mg) in the same manner as described above to obtain compound **5i** as a red solid, yield: 23%; Mp: 181 °C (dec.); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.89 (d, J = 9.0 Hz, 1H), 8.83 (d, J = 9.0 Hz, 1H), 8.28 (d, J = 9.0 Hz, 1H), 8.21 (d, J = 9.0 Hz, 1H), 8.11–8.06 (m, 1H), 7.94 (s, 1H), 7.82–7.71 (m, 2H), 7.61 (s, 1H), 6.41 (s, 2H), 5.98 (s, 2H), 5.27 (t, J = 6.6 Hz, 2H), 4.00 (s, 3H), 3.65 (t, J = 6.6 Hz, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 193.5, 149.3, 148.6, 147.2, 146.7, 143.8, 140.9, 136.1, 131.3, 129.4, 128.2, 127.1, 126.5, 126.4, 126.0, 123.0, 122.1, 121.0, 120.0 (2), 119.6, 119.2, 117.1, 116.0, 110.4, 102.9, 75.2, 57.1, 56.0, 26.1; HRMS: calcd for $C_{30}H_{21}F_3NO_6Br$ $[M–Br]^+$: 548.1316, found: 548.1296.

*1,2-Methylenedioxy-8-(2-p-methoxy-m-trifluoromethylphenyl-2-oxoethoxy)-9-metho xycycloberberine bromide (**5j**)*. The title compound was prepared from compound **4** (198 mg, 0.52 mmol) and 2-bromo-1-(4-methoxy-3-(trifluoromethyl)phenyl) ethanone (2.08 mmol, 618 mg) in the same manner as described above to obtain compound **5j** as a red solid, yield: 30%; Mp: 209 °C (dec.); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.90 (d, J = 9.0 Hz, 1H), 8.83 (d, J = 9.6 Hz, 1H), 8.34 (dd, J = 9.0, 1.8 Hz, 1H), 8.28 (d, J = 9.0 Hz, 1H), 8.22 (d, J = 9.6 Hz, 1H), 8.20 (d, J = 1.8 Hz, 1H), 7.61 (s, 1H), 7.46 (d, J = 9.0 Hz, 1H), 6.41 (s, 2H), 5.96 (s, 2H), 5.27 (t, J = 6.6 Hz, 2H), 4.02 (s, 3H), 4.01 (s, 3H), 3.65 (t, J = 6.6 Hz, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.4, 160.9, 149.3, 147.2, 146.6, 143.9, 140.8, 134.5, 129.3, 128.1, 126.6 (2), 126.4, 126.2, 126.0, 123.1, 122.9, 122.0, 121.0, 119.6, 119.0, 117.0, 115.9, 113.1, 110.3, 102.8, 74.8, 57.0, 56.8, 55.9, 26.1; HRMS: calcd for $C_{31}H_{23}F_3NO_6Br$ $[M–Br]^+$:

562.1472, found: 562.1451.

*1,2-Methylenedioxy-8-(2-m-methoxylphenyl-2-oxoethoxy)-9-methoxycycloberberine bromide (**5k**).* The title compound was prepared from compound **4** (198 mg, 0.52 mmol) and 3-methoxylphenacyl bromide (2.08 mmol, 328 μL) in the same manner as described above to obtain compound **5k** as a yellow solid, yield: 33%; Mp: 193 ℃ (dec.); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.30 (s, 1H), 8.94–8.87 (m, 1H), 8.86–8.79 (m, 1H), 8.31–8.25 (m, 1H), 8.25–8.20 (m, 1H), 7.64–7.59 (m, 2H), 7.53–7.46 (m, 2H), 7.29 (dd, J = 8.4, 2.4 Hz, 1H), 6.41 (s, 2H), 5.97 (s, 2H), 5.27 (t, J = 6.6 Hz, 2H), 4.01 (s, 3H), 3.83 (s, 3H), 3.65 (t, J = 6.6 Hz, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 194.2, 159.4, 149.2, 147.2, 146.6, 143.9, 140.8, 135.2, 130.1, 129.3, 128.1, 126.5, 126.0, 122.9, 122.0, 121.0 (2), 119.8, 119.6, 118.9, 117.0, 115.9, 112.2, 110.3, 102.8, 75.0, 57.0, 55.9, 55.3, 26.1; HRMS: calcd for $C_{30}H_{24}NO_6Br$ $[M–Br]^+$: 494.1598, found: 494.1581.

*1,2-Methylenedioxy-8-(2-p-methylphenyl-2-oxoethoxy)-9-methoxycycloberberine bromide (**5l**).* The title compound was prepared from compound **4** (198 mg, 0.52 mmol) and 4-methylphenacyl bromide (2.08 mmol, 446 μL) in the same manner as described above to obtain compound **5l** as a red solid, yield: 37%; Mp: 218 ℃ (dec.); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.30 (s, 1H), 8.88 (d, J = 9.0 Hz, 1H), 8.80 (d, J = 9.0 Hz, 1H), 8.26 (d, J = 9.0 Hz, 1H), 8.21 (d, J = 9.0 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.61 (s, 1H), 7.40 (d, J = 8.4 Hz, 2H), 6.41 (s, 2H), 5.95 (s, 2H), 5.27 (t, J = 6.6 Hz, 2H), 4.00 (s, 3H), 3.65 (t, J = 6.6 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 193.9, 149.2, 147.2, 146.6 144.4, 144.0, 140.8, 131.4, 129.4 (2), 129.3,

128.1, 127.8 (2), 126.5, 126.0, 122.9, 122.0, 121.0, 119.6, 118.8, 117.0, 115.9, 110.3, 102.8, 74.8, 57.0, 55.9, 26.1, 21.2; HRMS: calcd for $C_{30}H_{24}NO_5Br$ $[M–Br]^+$: 478.1649, found: 478.1657.

General synthesis procedures for compounds 6a−c and 7.

The corresponding amines (15.0 mmol) were added to CBBR (395 mg, 1.0 mmol), the mixture was stirred and heated for 4–32 h at 100–116°C. The mixture was cooled, and purified with C18 column using H_2O and MeOH as gradient eluent to obtain the desired compounds **6a**−**c** and **7**.

*1,2-Methylenedioxy-8-benzylamino-9-methoxycycloberberine chloride (**6a**)*. The title compound was prepared from CBBR (395 mg, 1.0 mmol) and phenylmethanamine (1.6 mL, 15.0 mmol) in the same manner as the above procedures to obtain compound **6a** as a purple solid, yield: 37%; Mp: 206 °C (dec.); ^{1}H NMR (600 MHz, CD_3OD, $CDCl_3$) δ 9.63 (s, 1H), 8.53 (d, J = 9.6 Hz, 1H), 8.20 (d, J = 9.0 Hz, 1H), 8.14 (d, J = 9.0 Hz, 1H), 7.88 (d, J = 9.0 Hz, 1H), 7.42 (d, J = 7.8 Hz, 2H), 7.39–7.34 (m, 3H), 7.28 (t, J = 7.2 Hz, 1H), 6.30 (s, 2H), 4.91 (s, 2H), 4.89 (t, J = 6.6 Hz, 2H), 4.04 (s, 3H), 3.63 (t, J = 6.6 Hz, 2H); ^{13}C NMR (151 MHz, CD_3OD, $CDCl_3$) δ 149.5, 148.1, 147.8, 142.8, 140.9, 140.4, 129.7 (3), 129.5, 129.3, 128.6, 128.3 (2), 126.4, 123.9, 122.8, 121.3, 118.8, 117.4, 116.5, 114.0, 111.1, 104.0, 57.2, 57.0, 53.7, 28.0; HRMS: calcd for $C_{28}H_{23}N_2O_3Cl$ $[M–Cl]^+$: 435.1703, found: 435.1698.

*1,2-Methylenedioxy-8-p-methoxybenzylamino-9-methoxycycloberberine chloride (**6b**)*. The title compound was prepared from CBBR (395 mg, 1.0 mmol) and 4-methoxybenzylamine (2.0 mL, 15.0 mmol) in the same manner as the above

procedures to obtain compound **6b** as a purple solid, yield: 30%; Mp: 212 °C (dec.); ^{1}H NMR (600 MHz, CD_3OD, $CDCl_3$) δ 9.64 (s, 1H), 8.54 (d, J = 9.6 Hz, 1H), 8.22 (d, J = 9.0 Hz, 1H), 8.19 (d, J = 9.0 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.35 (s, 1H), 7.32 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 6.33 (s, 2H), 4.91 (t, J = 6.6 Hz, 2H), 4.83 (s, 2H), 4.09 (s, 3H), 3.79 (s, 3H), 3.64 (t, J = 6.6 Hz, 2H); ^{13}C NMR (151 MHz, CD_3OD, $CDCl_3$) δ 160.0, 149.2, 147.8, 147.4, 142.6, 140.6, 131.6, 129.5 (2), 129.1, 128.9, 125.7, 124.0, 123.7, 122.3, 120.9, 118.5, 117.0, 116.2, 114.9 (2), 113.8, 111.0, 103.7, 57.1, 56.7, 55.6, 53.2, 27.9; HRMS: calcd for $C_{29}H_{25}N_2O_4Cl$ $[M–Cl]^+$: 465,1809, found: 465.1803.

*1,2-Methylenedioxy-8-(1-(furan-2-yl)methylamino)-9-methoxycycloberberine chloride **(6c)***. The title compound was prepared from CBBR (395 mg, 1.0 mmol) and 1-(furan-2-yl)methanamine (1.3 mL, 15.0 mmol) in the same manner as the above procedure to obtain compound **6c** as a purple solid, yield: 29%; Mp: 192 °C (dec.); ^{1}H NMR (600 MHz, CD_3OD) δ 9.75 (s, 1H), 8.46 (d, J = 9.0 Hz, 1H), 8.20 (d, J = 9.0 Hz, 1H), 8.03 (d, J = 9.0 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 1.2 Hz, 1H), 7.37 (s, 1H), 6.35–6.25 (m, 5H), 5.05 (t, J = 6.0 Hz, 2H), 4.80 (s, 2H), 4.04 (s, 3H), 3.66 (t, J = 6.0 Hz, 2H); ^{13}C NMR (151 MHz, CD_3OD) δ 154.6, 151.1, 148.5, 148.3, 143.9, 143.1, 140.2, 130.1, 129.9, 127.3, 124.2, 124.1, 123.8, 121.6, 119.1, 118.5, 117.7, 115.9, 111.6, 111.5, 109.1, 104.6, 57.6, 57.5, 47.0, 28.3; HRMS: calcd for $C_{26}H_{21}N_2O_4Cl$ $[M–Cl]^+$: 425.1496, found: 425.1490.

1,2-Methylenedioxy-8-o,p-dimethoxybenzylamino-9-methoxycycloberberine chloride (7). The title compound was prepared from CBBR (395 mg, 1.0 mmol) and

(2,4-dimethoxyphenyl)methanamine (2.3 mL, 15 mmol) in the same manner as the above procedure to obtain compound **7** as a purple solid, yield: 33%; Mp: 170 ℃ (dec.); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.65 (s, 1H), 8.18 (s, 1H), 8.04 (s, 1H), 7.84 (s, 1H), 7.52 (s, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.78 (s, 1H), 6.50 (s, 1H), 6.39 (d, J = 7.8 Hz, 1H), 6.34 (s, 2H), 5.01 (t, J = 6.0 Hz, 2H), 4.72 (d, J = 5.4 Hz, 2H), 3.89 (s, 3H), 3.74 (s, 3H), 3.67 (s, 3H), 3.59 (s, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 160.4, 158.4, 148.3, 148.2, 146.6, 141.2, 140.2, 130.2, 128.7, 128.2, 126.6, 122.9, 122.4 (2), 121.6, 120.0, 117.4, 116.5, 115.7, 112.9, 110.6, 104.7, 103.2, 98.8, 57.2, 55.8, 55.7, 55.6, 47.6, 26.9; HRMS: calcd for $C_{30}H_{27}N_2O_5Cl$ $[M–Cl]^+$: 495.1915, found: 495.1921.

Synthesis procedures for 1,2-methylenedioxy-8-amino-9-methoxycycloberberine chloride (8).

Compound **7** (530 mg, 1.00 mmol) was added to a mixed solution of methanol/HCl (1:1 by vol., 6 mL), and the mixture was reacted for 12 h at room temperature. Then the solution was concentrated to obtain a crude compound, which was further purified through flash column chromatography on silica gel with CH_3OH/CH_2Cl_2 as the eluents to get the desired compound **8** as a purple solid, yield: 81%; Mp: 244 ℃ (dec.); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.69 (d, J = 9.6 Hz, 1H), 8.07 (d, J = 9.6 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 9.6 Hz, 1H), 7.54 (s, 1H), 7.21 (s, 2H), 6.37 (s, 2H), 4.96 (t, J = 6.6 Hz, 2H), 4.03 (s, 3H), 3.59 (t, J = 6.6 Hz, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 147.4, 145.9, 144.0, 140.6, 140.2, 127.9, 126.6, 125.9, 121.7, 121.6, 121.1, 121.0, 116.9, 116.1, 111.1, 110.1,

108.5, 102.6, 56.3, 54.9, 26.3; HRMS: calcd for $C_{21}H_{17}N_2O_3Cl$ $[M–Cl]^+$: 345.1234, found: 345.1237.

General synthesis procedures for compounds 9a−f.

To a stirred solution of compound **8** (100 mg, 0.26 mmol) in anhydrous CH_3CN (6 mL) were added pyridine (2.34–8.19 mmol) and corresponding acyl chloride (1.56–5.46 mmol). The reaction mixture was heated at 40–91 ^oC for 3–72 h. The mixture was cooled, filtered and the resulting residue was purified using flash column chromatography on silica gel with CH_2Cl_2/MeOH as gradient eluent to obtain desired compounds **9a**−**f**.

*1,2-Methylenedioxy-8-(1-adamantanecarbonylamino)-9-methoxycycloberberine chloride (**9a**).* The title compound was prepared from compound **8** (100 mg, 1.0 mmol) and 1-adamantanecarbonyl chloride (872 μL, 5.46 mmol) with pyridine (669 μL, 8.19 mmol) at 48 ^oC for 72 h using the above procedure to obtain compound **9a** as an orange solid, yield: 37%; Mp: 298 °C (dec.); ^1H NMR (600 MHz, DMSO-d_6): δ 9.54 (s, 1H), 9.49 (s, 1H), 9.09 (d, J = 9.6 Hz, 1H), 8.94 (dd, J = 1.8, 9.6 Hz, 1H), 8.32 (d, J = 9.0 Hz, 1H), 8.25 (d, J = 9.0 Hz, 1H), 7.62 (s, 1H), 6.41 (s, 2H), 5.31 (t, J = 6.6 Hz, 2H), 4.07 (s, 3H), 3.64 (t, J = 6.6 Hz, 2H), 2.11 (s, 10H), 1.78 (s, 5H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 177.6, 154.6, 147.0, 146.6, 140.9, 129.3, 128.2, 126.5, 124.7, 124.6, 123.3, 123.1 (2), 122.5, 120.9, 116.9, 116.0, 110.2, 102.8, 57.0, 56.1, 40.8, 38.39, 38.4 (2), 36.1 (3), 27.6 (3), 26.0; HRMS: calcd for $C_{32}H_{31}N_2O_4Cl$ $[M–Cl]^+$: 507.2278, found: 507.2281.

1,2-Methylenedioxy-8-(2-cyclopentylacetamido)-9-methoxycyclocberberine chloride

*(**9b**)*. The title compound was prepared from compound **8** (100 mg, 1.0 mmol) and cyclopentylacetyl chloride (210 μL, 1.56 mmol) with pyridine (189 μL, 2.34 mmol) at 45 ^{o}C for 2 h using the above procedure to obtain compound **9b** as a red solid, yield: 17%; Mp: 219 °C (dec.); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.11 (s, 1H), 9.81 (s, 1H), 9.07 (d, J = 9.6 Hz, 1H), 8.94 (d, J = 9.6 Hz, 1H), 8.32 (d, J = 9.0 Hz, 1H), 8.24 (d, J = 9.6 Hz, 1H), 7.61 (s, 1H), 6.41 (s, 2H), 5.25 (t, J = 6.6 Hz, 2H), 4.09 (s, 3H), 3.65 (t, J = 6.6 Hz, 2H), 2.60 (d, J = 7.2 Hz, 2H), 2.43–2.26 (m, 1H), 1.94–1.15 (m, 8H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.3, 154.1, 147.6, 146.6, 140.9, 129.2, 128.1, 126.4, 124.5, 124.1, 123.1, 123.0, 122.5, 122.4, 120.9, 116.9, 115.9, 110.2, 102.8, 56.9, 55.9, 41.4, 36.2, 31.9 (2), 26.0, 24.6 (2); HRMS: calcd for $C_{28}H_{27}N_2O_4Cl$ $[M–Cl]^+$: 455.1965, found: 455.1950.

*1,2-Methylenedioxy-8-nicotinoylamino-9-methoxycycloberberine chloride (**9c**)*. The title compound was prepared from compound **8** (100 mg, 1.0 mmol) and nicotinoyl chloride (210 μL, 1.56 mmol) with pyridine (189 μL, 2.34 mmol) at 70 ^{o}C for 3 h using the above procedure to obtain compound **9c** as a red solid, yield: 28%; Mp: 227 °C (dec.); ^{1}H NMR (600 MHz, DMSO-d_6): δ 10.90 (s, 1H), 10.12 (s, 1H), 9.35 (s, 1H), 9.14 (d, J = 9.6 Hz, 1H), 8.95 (d, J = 9.0 Hz, 1H), 8.86 (d, J = 3.6 Hz, 1H), 8.52 (d, J = 7.8 Hz, 1H), 8.38 (d, J = 9.6 Hz, 1H), 8.24 (d, J = 9.0 Hz, 1H), 7.67 (dd, J = 7.2, 4.8 Hz, 1H), 7.60 (s, 1H), 6.41 (s, 2H), 5.27 (t, J = 6.6 Hz, 2H), 4.10 (s, 3H), 3.63 (t, J = 6.6 Hz, 2H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 165.0, 154.7, 152.4, 149.3, 147.4, 146.6, 140.9, 135.9, 129.5, 129.1, 128.3, 126.5, 124.5, 123.9, 123.4 (2), 123.1 (2), 122.4, 120.9, 116.9, 115.9, 110.2, 102.8, 56.9, 55.7, 25.9; HRMS: calcd for

$C_{27}H_{20}N_3O_4Cl$ $[M–Cl]^+$: 450.1448, found: 450.1449.

*1,2-Methylenedioxy-8-(1,5-dimethylpyrazole-3-carbonylamino)-9-methoxycycloberbe rine chloride (**9d**).* The title compound was prepared from compound **8** (100 mg, 1.0 mmol) and 1,5-dimethylpyrazole-3-carbonyl chloride (376 μL, 3.12 mmol) with pyridine (567 μL, 7.02 mmol) at 91 ^oC for 48 h using the above procedure to obtain compound **9d** as a red solid, yield: 33%; Mp: 228 °C (dec.); ^1H NMR (600 MHz, DMSO-d_6): δ 10.07 (s, 1H), 9.93 (s, 1H), 9.00–8.97 (m, 1H), 8.84–8.81 (m, 1H), 8.30–8.26 (m, 1H), 8.16–8.14 (m, 1H), 7.58 (s, 1H), 6.66 (s, 1H), 6.39 (s, 2H), 5.26 (t, J = 6.6 Hz, 2H), 4.06 (s, 3H), 3.92 (s, 3H), 3.62 (t, J = 6.6 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 161.1, 154.5, 147.7, 146.5, 143.8, 140.8, 140.7, 129.1, 128.0, 126.4, 124.3, 123.9, 123.2, 122.9, 122.8, 122.2, 120.7, 116.8, 115.8, 110.2, 106.3, 102.8, 56.8, 55.7, 36.5, 26.0, 10.7; HRMS: calcd for $C_{27}H_{23}N_4O_4Cl$ $[M–Cl]^+$: 467.1714, found: 467.1716.

*1,2-Methylenedioxy-8-(1,2,3-thiadiazole-4-carbonylamido)-9-methoxycyclo berberine chloride (**9e**).* The title compound was prepared from compound **8** (100 mg, 1.0 mmol) and 1,2,3-thiadiazole-4-carbonyl chloride (231 mg, 1.56 mmol) with pyridine (189 μL, 2.34 mmol) at 45 ^oC for 2 h using the above procedure to obtain compound **9e** as a red solid, yield: 56%; Mp: 212 °C (dec.); ^1H NMR (600 MHz, DMSO-d_6): δ 11.25 (s, 1H), 10.17 (s, 1H), 10.00 (s, 1H), 9.09 (d, J = 9.6 Hz, 1H), 8.88 (d, J = 9.6 Hz, 1H), 8.35 (d, J = 9.6 Hz, 1H), 8.19 (d, J = 9.0 Hz, 1H), 7.60 (s, 1H), 6.40 (s, 2H), 5.26 (t, J = 6.6 Hz, 2H), 4.11 (s, 3H), 3.63 (t, J = 6.6 Hz, 2H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 158.3, 156.8, 154.8, 147.4, 146.6, 143.3, 140.8, 129.3, 128.2, 126.4, 124.5, 124.0,

123.0 (2), 122.8, 122.3, 120.7, 116.8, 115.8, 110.2, 102.8, 56.9, 55.7, 25.9; HRMS: calcd for $C_{24}H_{17}N_4O_4Cl$ $[M–Cl]^+$: 457.0965, found: 457.0973.

*1,2-Methylenedioxy-8-(3,5-dimethylisoxazole-4-carbonylamido)-9-methoxycycloberbe rine chloride (**9f**).* The title compound was prepared from **8** (100 mg, 1.0 mmol) and 3,5-dimethylisoxazole-4-carbonyl chloride (231 mg, 1.56 mmol) with pyridine (630 μL, 7.80 mmol) at 71 ^oC for 10 h using the above procedure to obtain **9f** as an orange solid, yield: 39%; Mp: 279 °C (dec.); ^1H NMR (600 MHz, DMSO-d_6): δ 10.08 (s, 1H), 10.01 (s, 1H), 9.16 (d, J = 9.0 Hz, 1H), 8.97 (d, J = 9.6 Hz, 1H), 8.38 (d, J = 9.0 Hz, 1H), 8.26 (d, J = 9.6 Hz, 1H), 7.62 (s, 1H), 6.42 (s, 2H), 5.30 (t, J = 6.6 Hz, 2H), 4.13 (s, 3H), 3.65 (t, J = 6.6 Hz, 2H), 2.74 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 171.0, 161.6, 158.8, 154.5, 147.4, 146.7, 140.9, 129.4, 128.3, 126.5, 124.5, 123.8, 123.2, 123.1, 122.8, 122.4, 120.9, 117.0, 115.9, 112.5, 110.3, 102.8, 57.0, 55.8, 26.0, 12.6, 10.8; HRMS: calcd for $C_{27}H_{22}N_3O_5Cl$ $[M–Cl]^+$: 468.1554, found: 468.1552.

Antimicrobial Assays in vitro

Minimum inhibitory concentrations (MICs) of the target compounds were determined by using the agar dilution assay at various concentrations of 64.0, 32.0, 16.0, 8.0, 4.0, 2.0, 1.0, 0.5, 0.25, 0.125, 0.06 and 0.03 mg/mL described by the Clinical Laboratory Standards Institute. Organisms used in this study included strains from the ATCC collection and clinical isolates from Chinese hospitals. The test medium was Mueller-Hinton agar, and the inoculum was 104 colony forming units (cfu)/spot. Culture plates were incubated at 35 °C for 18 h, and MICs were defined as

the lowest concentrations that prevented visible growth of the bacteria.

Blood Stability Assay

The fresh blood were collected from SD rat on the day of experiment and pre-warmed at 37 °C in a water bath. Compounds **2**, **5d** and **9e** (10 mM) or control (enalapril maleate salt stock solutions) were prepared in DMSO, and then diluted with 45% MeOH/H_2O to obtain 100 μM dosing solutions. Each dosing solution (2 μL) was incubated with 98 μL of blank blood at 37 °C in water bath. The testing sample was taken out at 0, 30, 60, 120, 240 and 420 min, respectively. At the end of incubation, for each sample, 100 μL water and 800 μL of stop solution (200 ng/mL tolbutamide plus 20 ng/mL buspirone in ACN) were immediately added to precipitate protein and centrifuge at 4,000 rpm for 20 min. An aliquot of supernatant (100 μL) was then extracted, mixed with 200 μL H_2O and then shook at 800 rpm for about 10 min before submitting to LC-MS/MS analysis. The experiment was repeated two times.

Cytotoxicity Assay

Cell suspensions (100 μL) of A549 cells at concentration of 50% confluence were seeded into the 96-well plates, and then were treated with various concentrations of compounds **2**, **5d** and **9e**. After 24 h of incubation, 20 μL of the MTT (1 mg/mL) solution was added into each plate and incubated for 4 h at 37 °C, 5% CO_2. Subsequently, the culture supernatant was replaced with 150 μL DMSO to dissolve the formazan crystal made from succinic dehydrogenase in the mitochondria and its substrate MTT. The optical density (OD) at 550 and 630 nm were measured using a microplate reader. The net absorbance (OD630–OD550) indicates the enzymatic

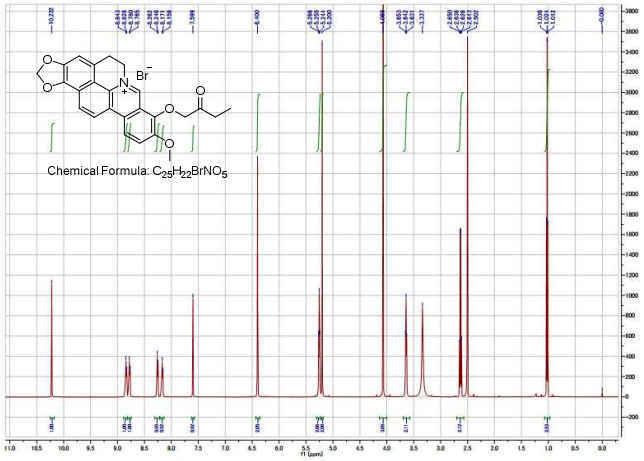
activity of mitochondria and provides information on cell viability.

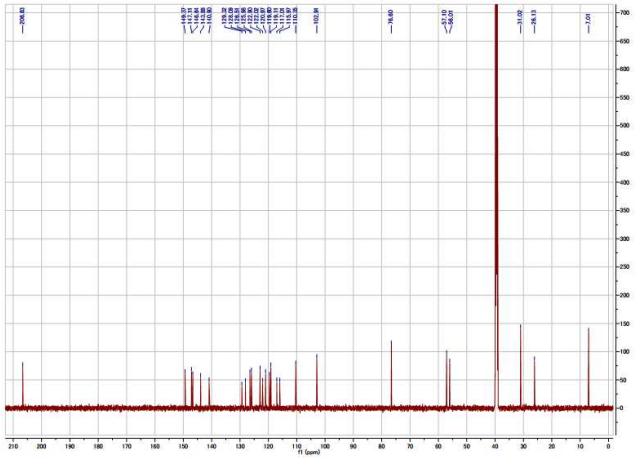
DNA-cleaving Assay

The DNA cleavage experiments were conducted by using the Agarose gel electrophoresis (GEP). *Escherichia coli* (*E. coli*) expression vector (pET-32a vector) was purchased from Novagen. The plasmid pET-32a was transformed into *E. coli* DH5-alpha and *E. coli* cells were grown in Luria-Bertani (LB) broth or on agar at 37 °C supplemented with the following antibiotics as appropriate: Ampicillin at 100 μg/mL. The plasmid was extracted by using plasmid extraction kit (Tiangen, Beijing, China). Typically, a mixture of pET-32a DNA (7 μL) and compound **9e** (6 μL) of varying concentrations (61.5, 123, 246 and 492 μg/mL) in DMSO and incubated at 37 °C for 4 h. The solution was then loaded on 1% agarose gel containing ethidium bromide (EB) (1.0 mg/L). Bands were visualized by UV light and photographed.

^{1}H NMR, ^{13}C NMR, HRMS-ESI spectra of all the target compounds

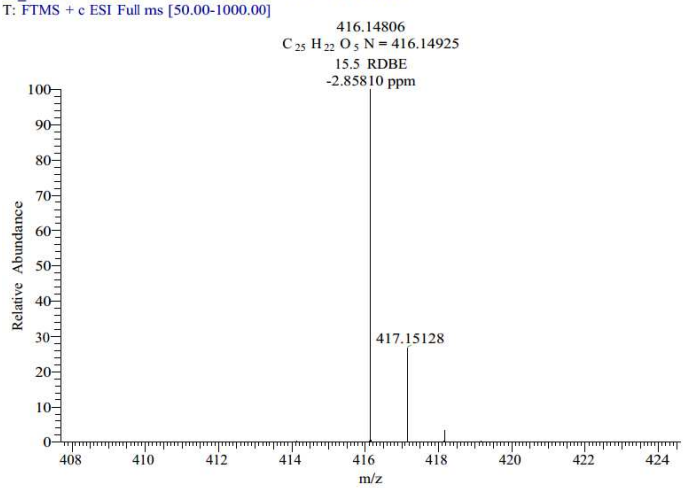
Compound **5a**:



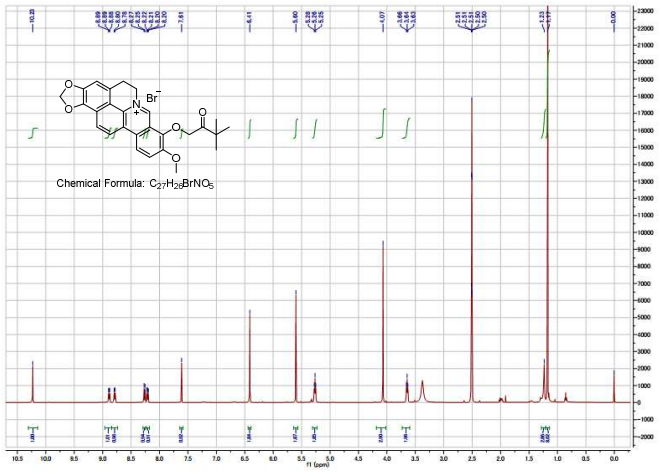


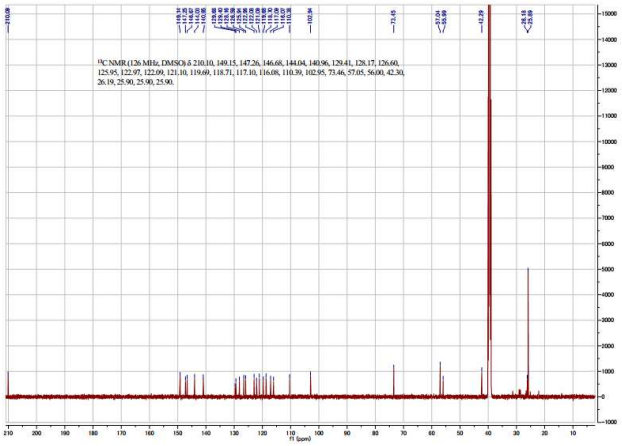
E:\2017\...\5a170711181300 7/11/2017 6:13:00 PM 5a

5a_170711181300 #3-4 RT: 0.08-0.11 AV: 2 NL: 8.10E6
T: FTMS + c ESI Full ms [50.00-1000.00]



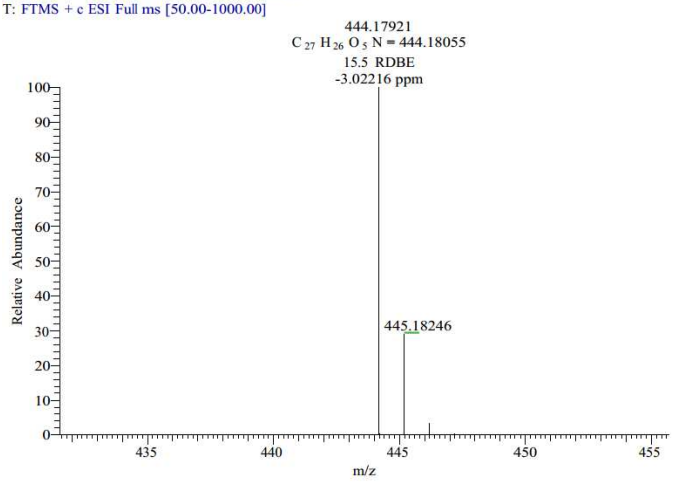
Compound **5b**:



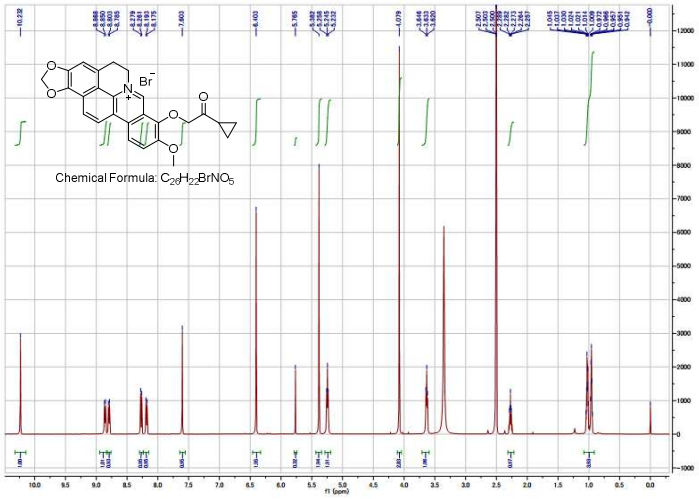


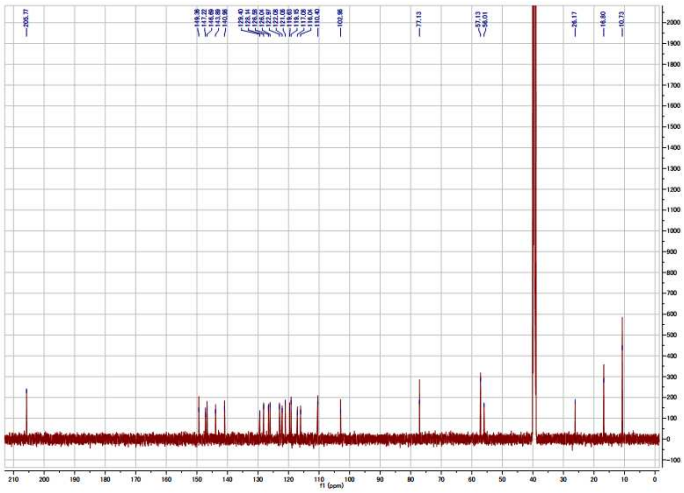
E:\2017\HRMS\20170711\zengqingxuan\5b 7/11/2017 5:58:57 PM 5b

5b #16-23 RT: 0.44-0.64 AV: 8 NL: 4.08E7
T: FTMS + c ESI Full ms [50.00-1000.00]



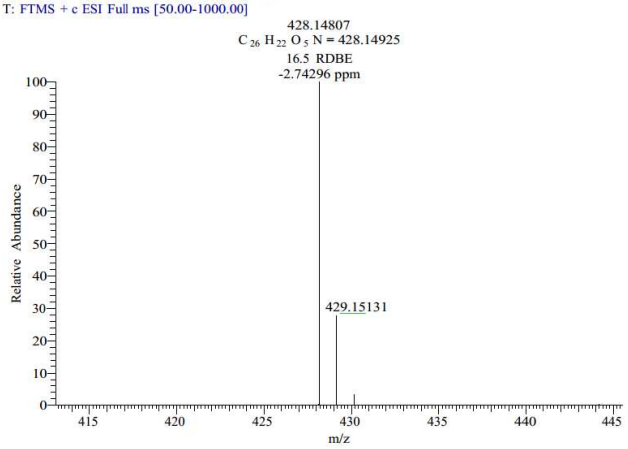
Compound **5c**:



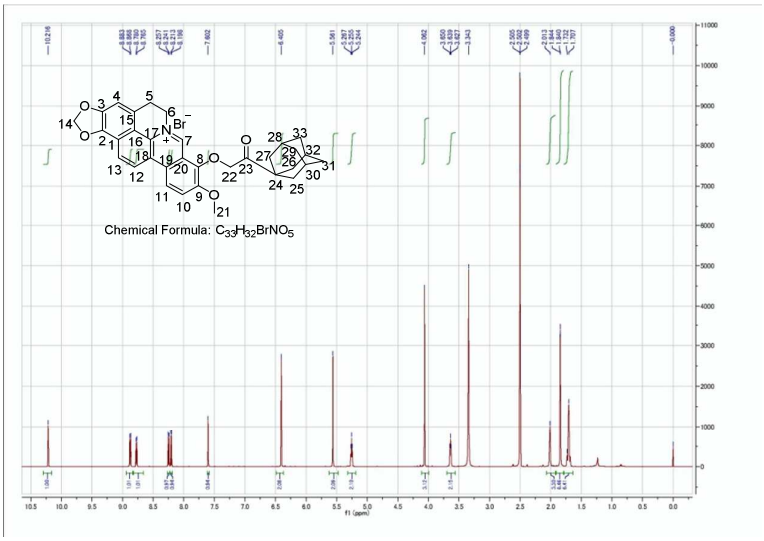


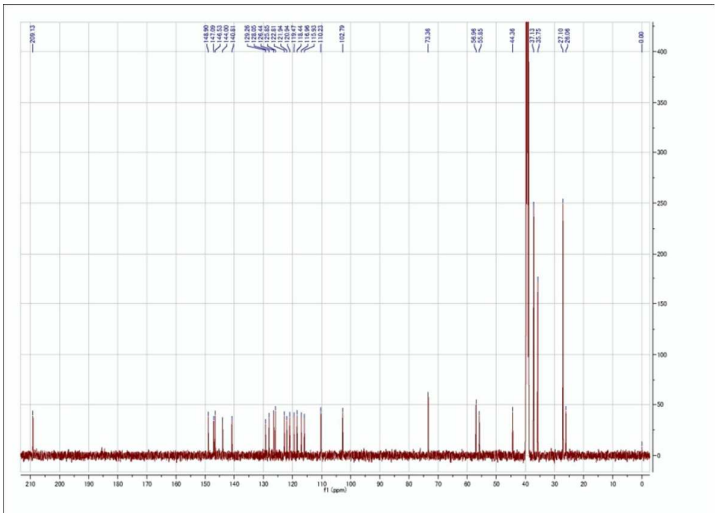
E:\2017\HRMS\20170711\zengqingxuan\5c 7/11/2017 5:57:38 PM 5c

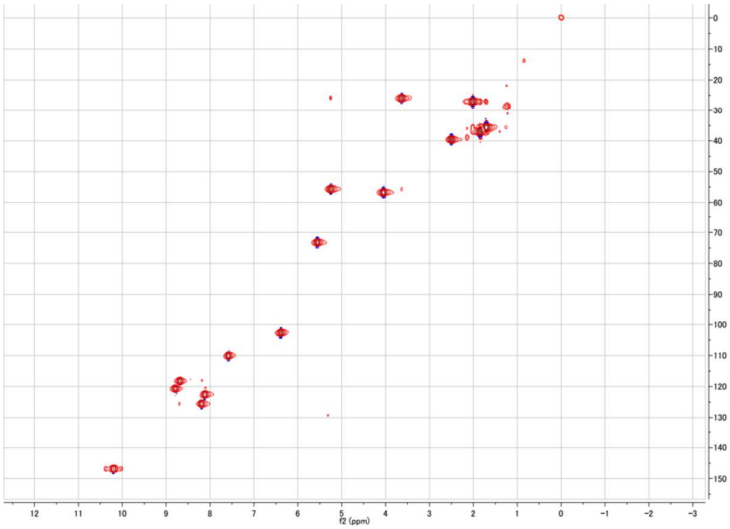
5c #13-21 RT: 0.36-0.58 AV: 9 NL: 3.80E7
T: FTMS + c ESI Full ms [50.00-1000.00]

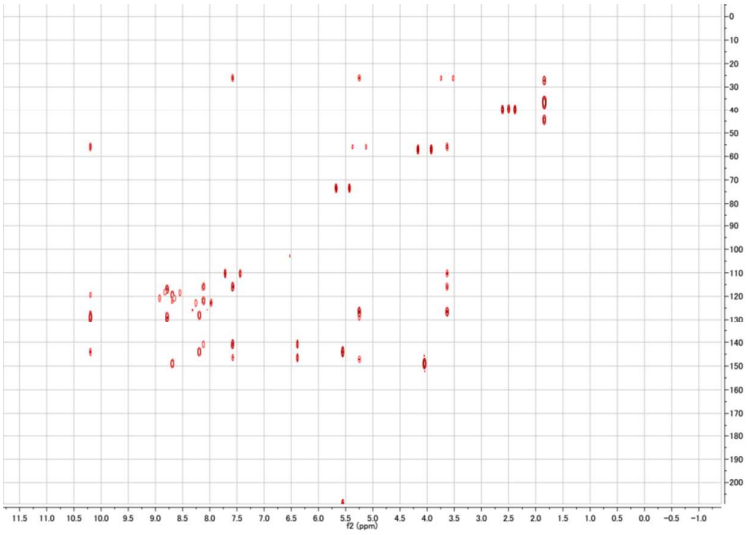


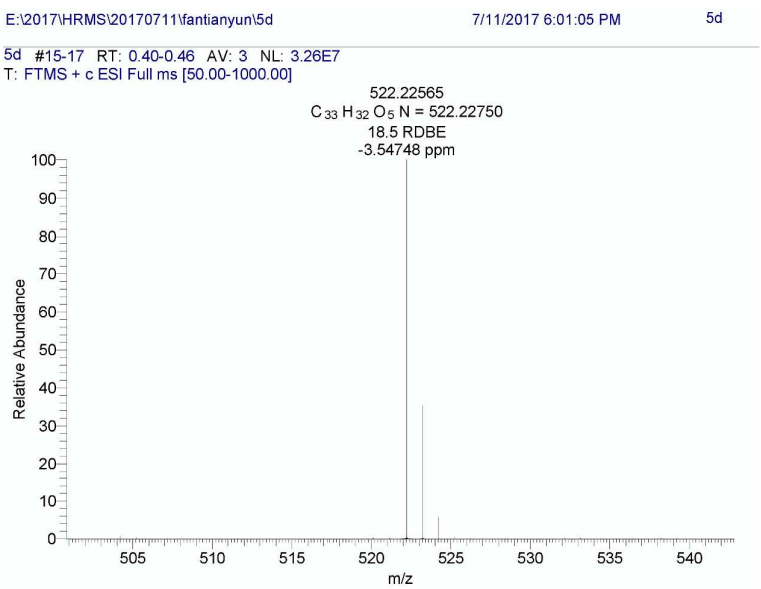
Compound **5d**:







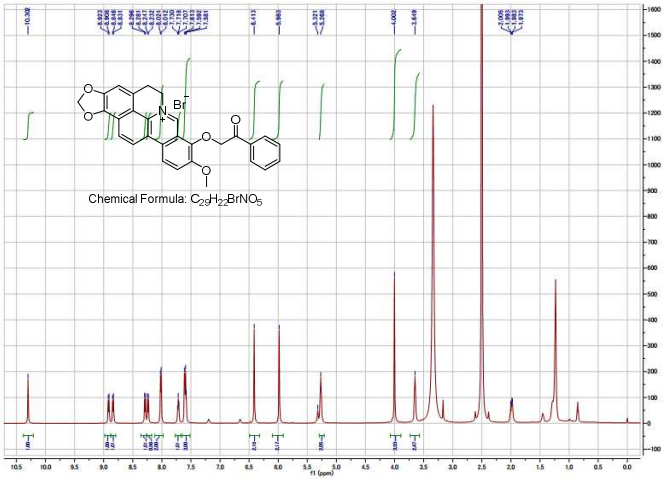


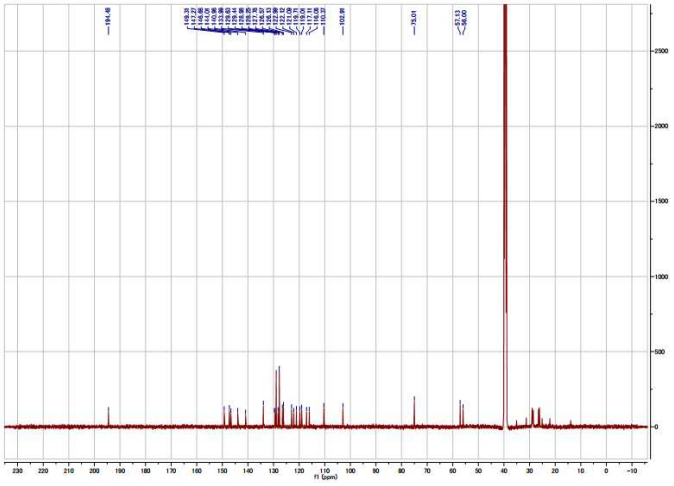


proton	^{13}C NMR chemical chift values	^{1}H NMR chemical chift values
1	121.9	
2	140.8	
3	146.5	
4	110.2	7.60 s
5	26.1	3.64 t
6	55.9	5.26 t
7	147.1	10.22 s
8	144.0	
9	148.9	
10	125.9	8.21 d
11	118.4	8.77 d

12	120.9	8.88 d
13	122.8	8.25 d
14	102.8	6.41 s
15	115.9	
16	126.4	
17	128.1	
18	117.0	
19	129.3	
20	119.4	
21	57.0	4.06 s
22	73.4	5.56 s
23	209.1	
24	44.4	
25	37.1	1.84 d
26	37.1	1.84 d
27	37.1	1.84 d
28	27.1	2.01 s
29	35.8	1.71 m
30	27.1	2.01 s
31	35.8	1.71 m
32	27.1	2.01 s
33	35.8	1.71 m

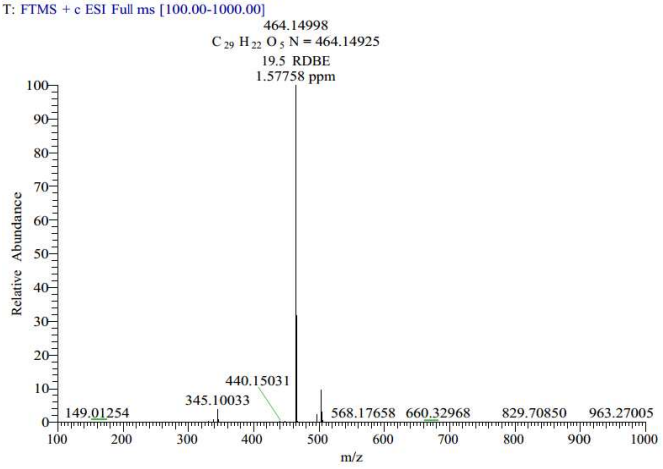
Compound **5e**:



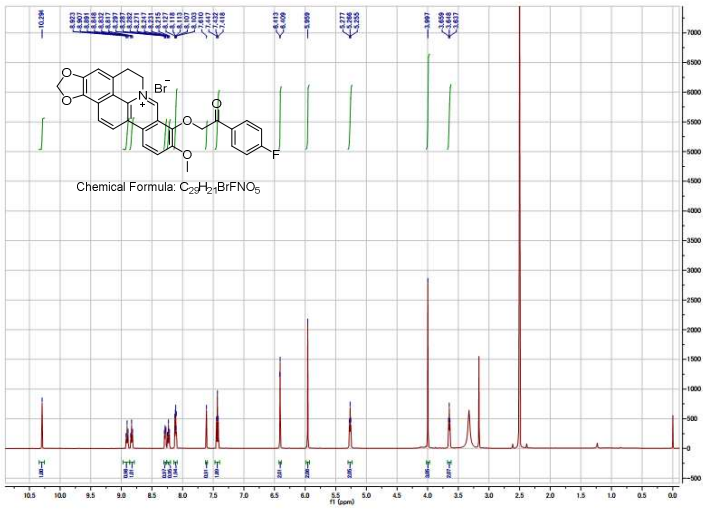


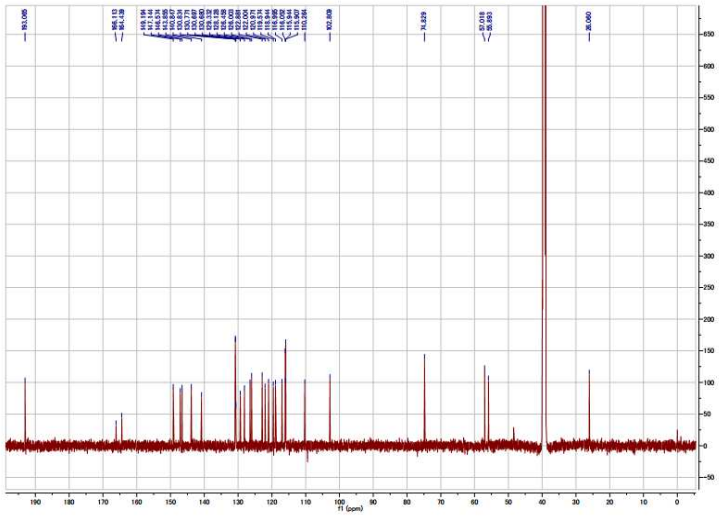
E:\2017\HRMS\0418\F\5e 4/18/2017 10:21:20 AM 5e

5e #9-10 RT: 0.13-0.15 AV: 2 NL: 2.86E8
T: FTMS + c ESI Full ms [100.00-1000.00]



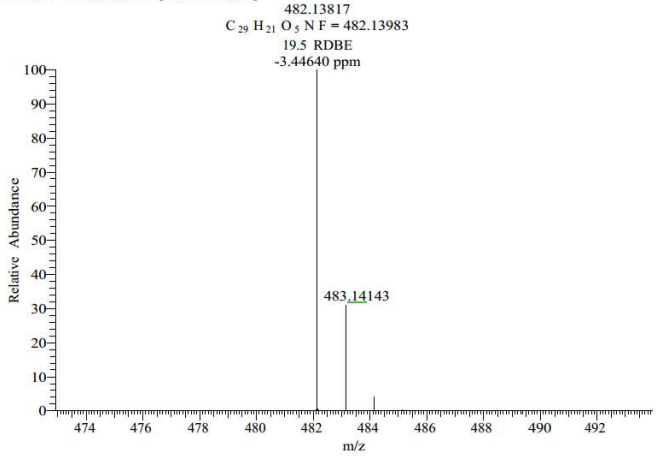
Compound **5f**:



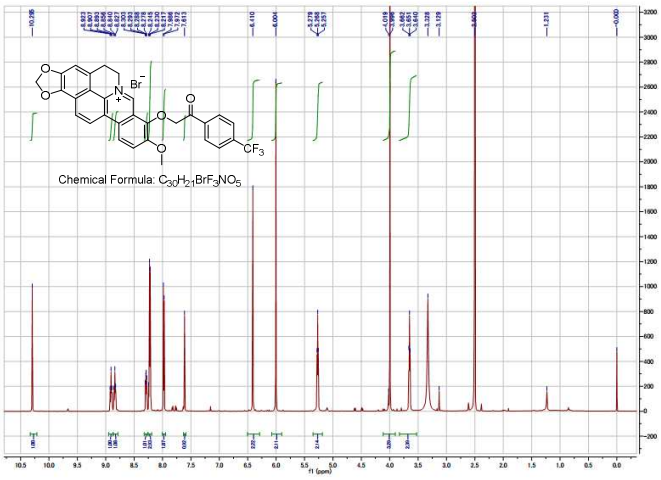


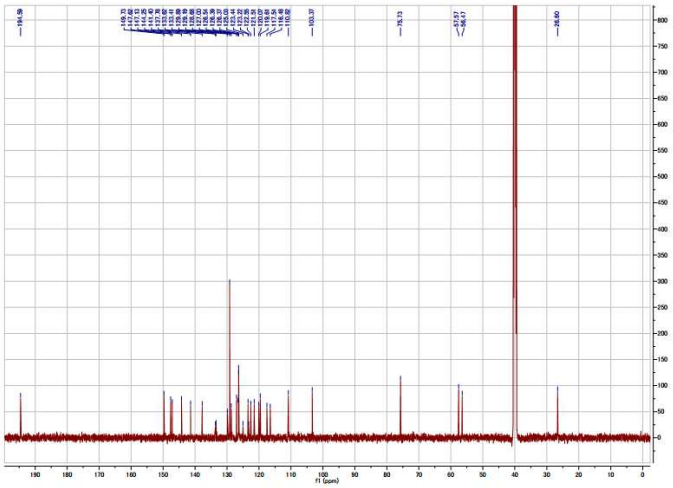
E:\2017\HRMS\20170711\zengqingxuan\5f 7/11/2017 5:55:09 PM 5f

5f #16-25 RT: 0.44-0.70 AV: 10 NL: 1.69E7
T: FTMS + c ESI Full ms [50.00-1000.00]



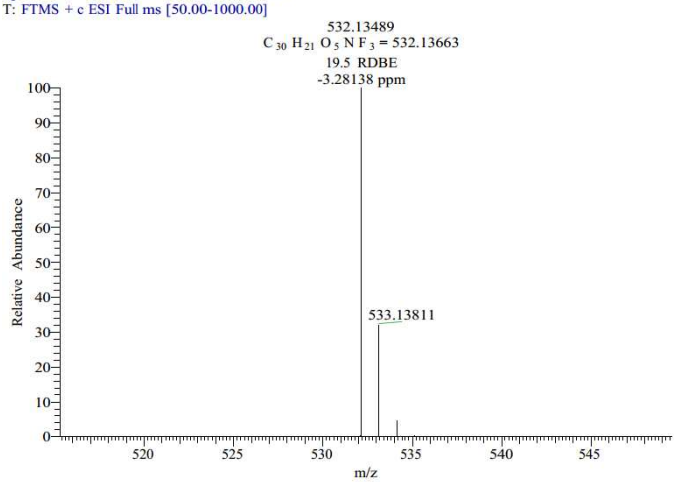
Compound **5g**:



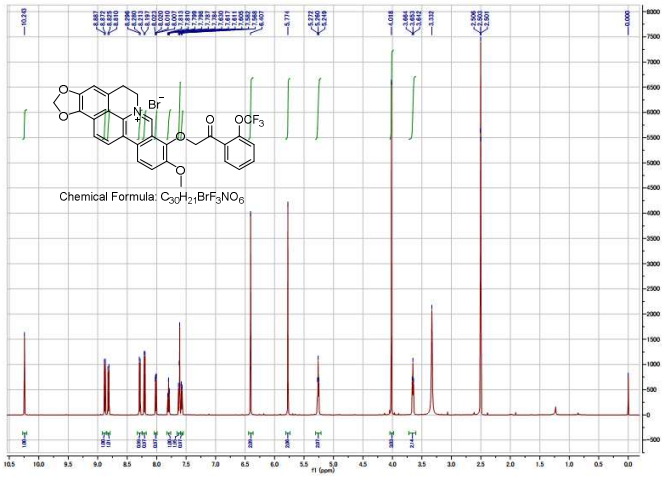


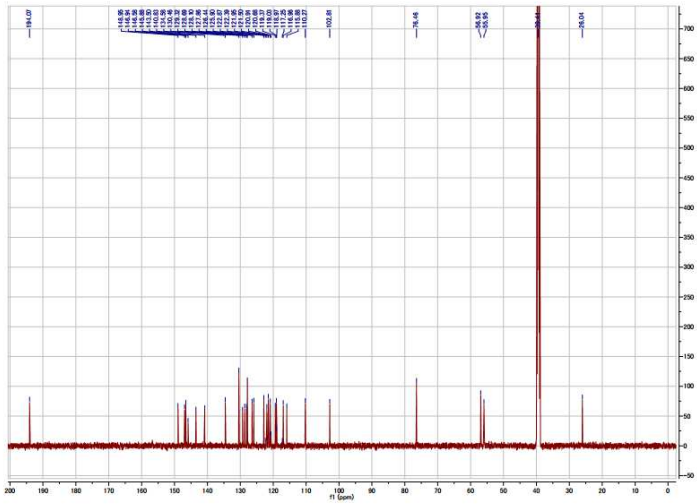
E:\2017\HRMS\20170711\zengqingxuan\5g 7/11/2017 5:52:19 PM 5g

5g #7-9 RT: 0.18-0.23 AV: 3 NL: 8.98E6
T: FTMS + c ESI Full ms [50.00-1000.00]



Compound **5h**:

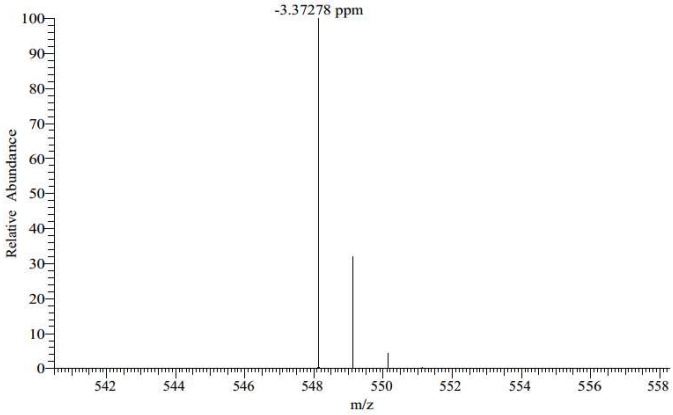




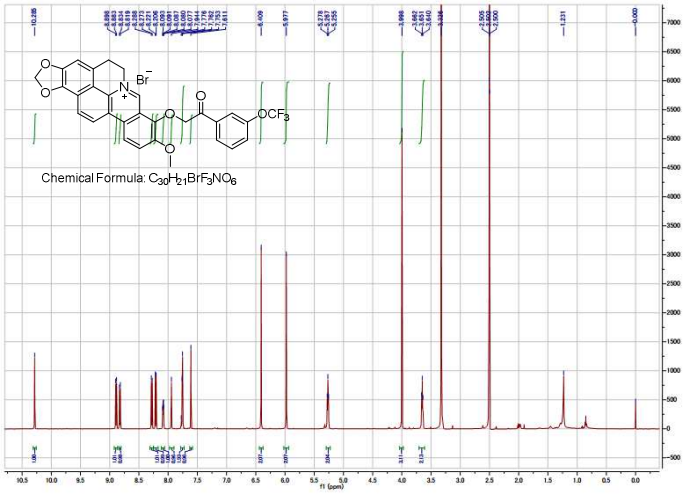
E:\2017\HRMS\20170711\zengqingxuan\5h 7/11/2017 6:02:13 PM 5h

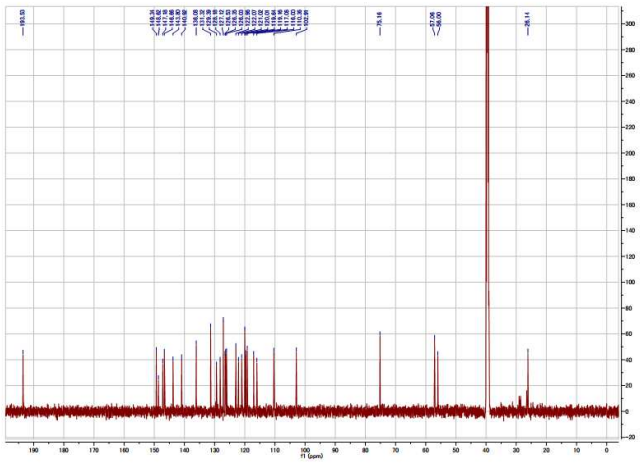
5h #16-19 RT: 0.44-0.52 AV: 4 NL: 1.56E7
T: FTMS + c ESI Full ms [50.00-1000.00]

548.12970
$C_{30}H_{21}O_6NF_3$ = 548.13155
19.5 RDBE
-3.37278 ppm



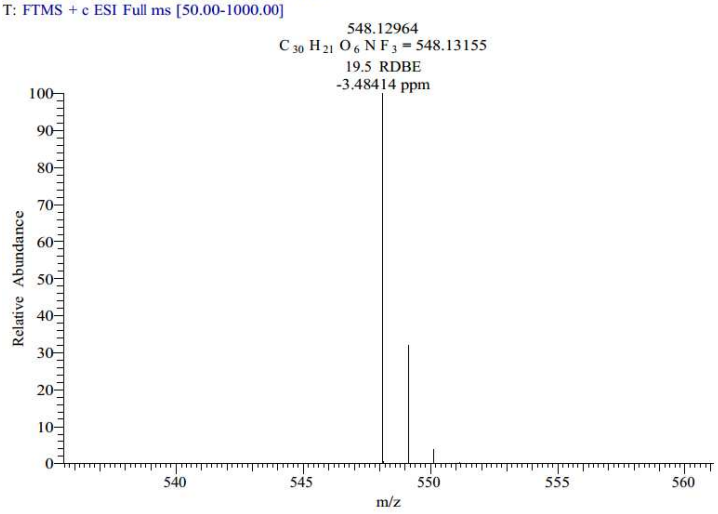
Compound **5i**:



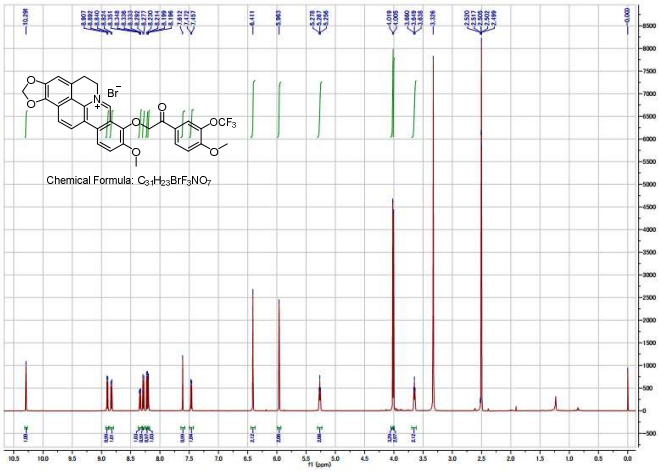


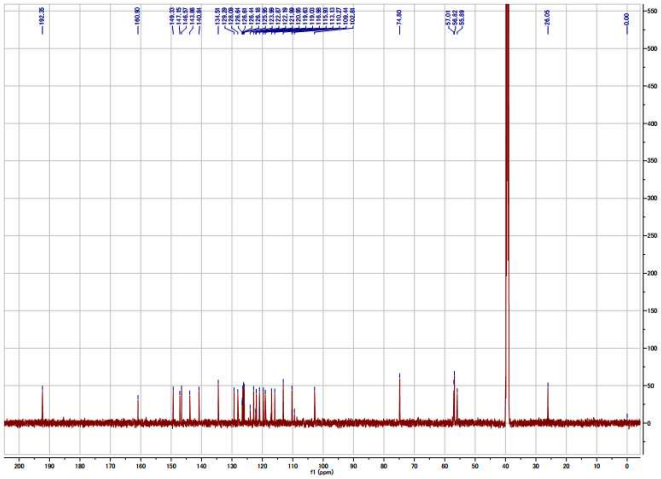
E:\2017\HRMS\20170711\zengqingxuan\5i 7/11/2017 6:03:18 PM 5i

5i #27-30 RT: 0.75-0.83 AV: 4 NL: 8.65E6
T: FTMS + c ESI Full ms [50.00-1000.00]



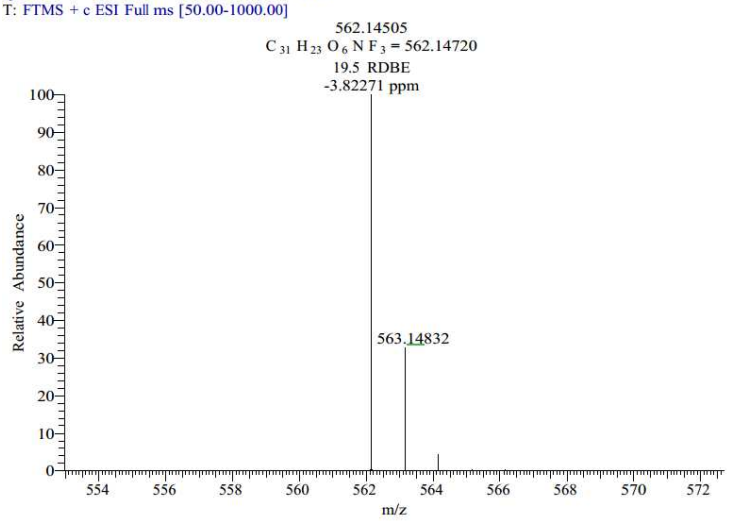
Compound **5j**:



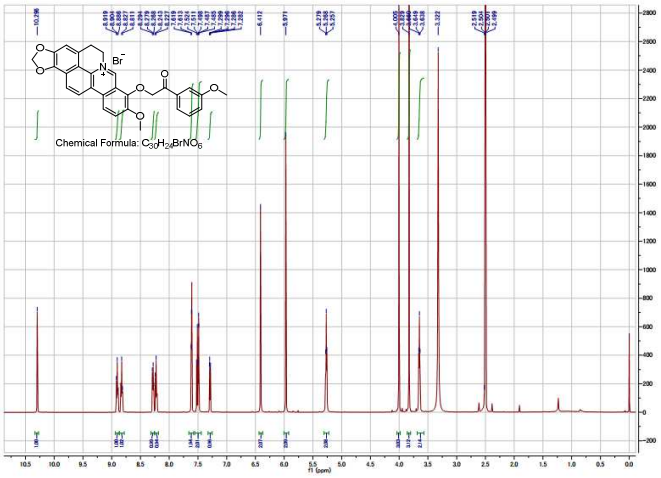


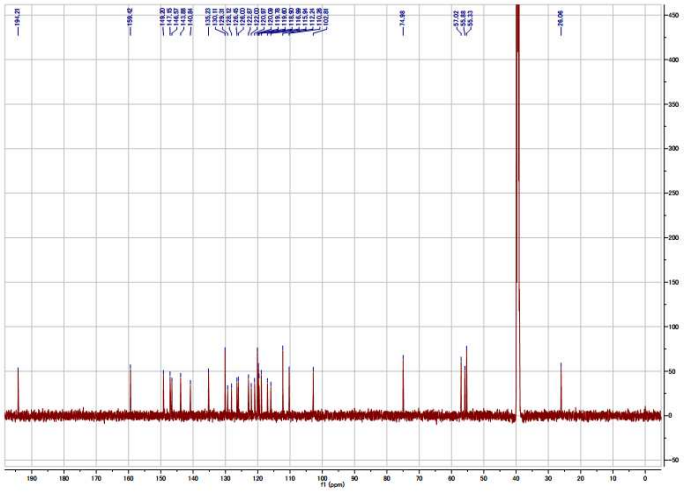
E:\2017\HRMS\20170711\zengqingxuan\5j 7/11/2017 6:04:42 PM 5j

5j #20-27 RT: 0.54-0.74 AV: 8 NL: 7.83E6
T: FTMS + c ESI Full ms [50.00-1000.00]



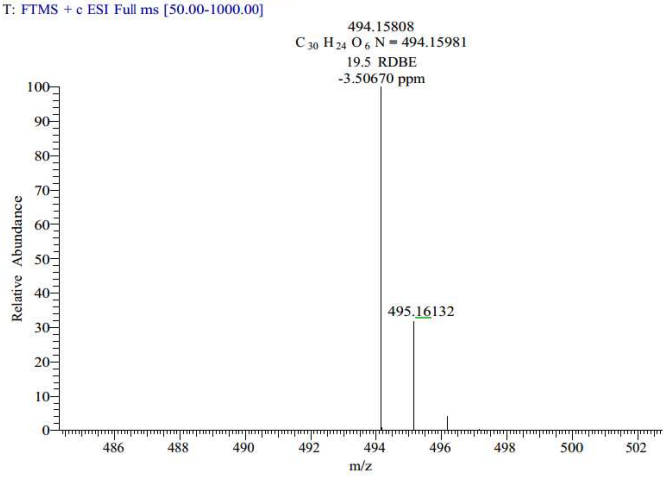
Compound **5k**:



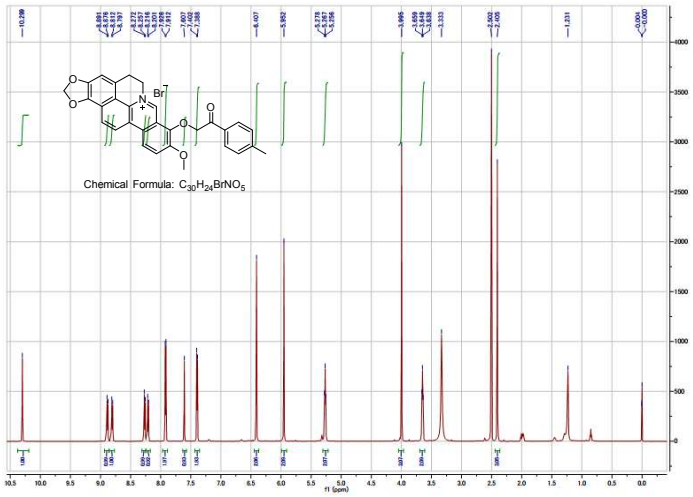


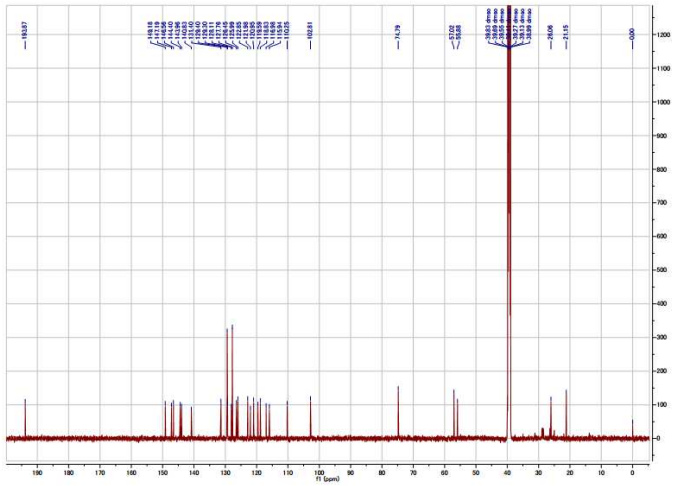
E:\2017\HRMS\20170711\zengqingxuan\5k 7/11/2017 5:56:48 PM 5k

5k #13-21 RT: 0.36-0.59 AV: 9 NL: 1.14E7
T: FTMS + c ESI Full ms [50.00-1000.00]



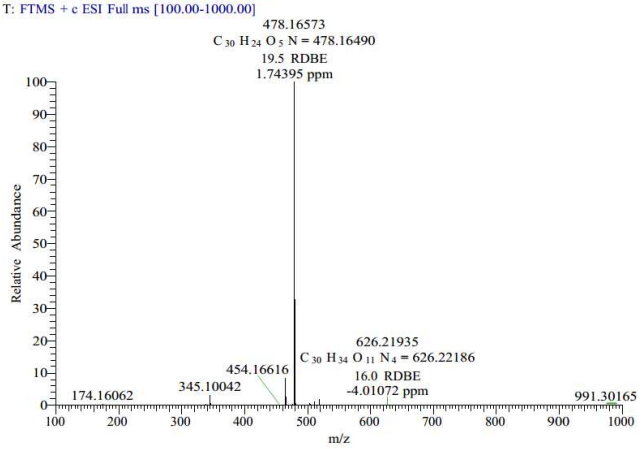
Compound **5l**:



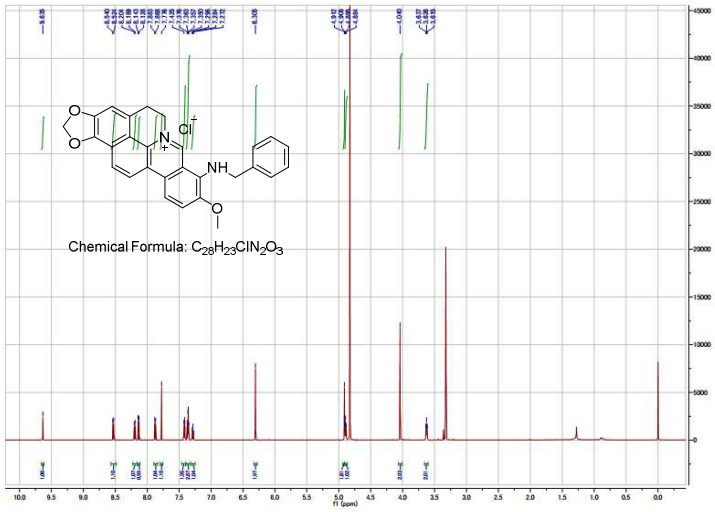


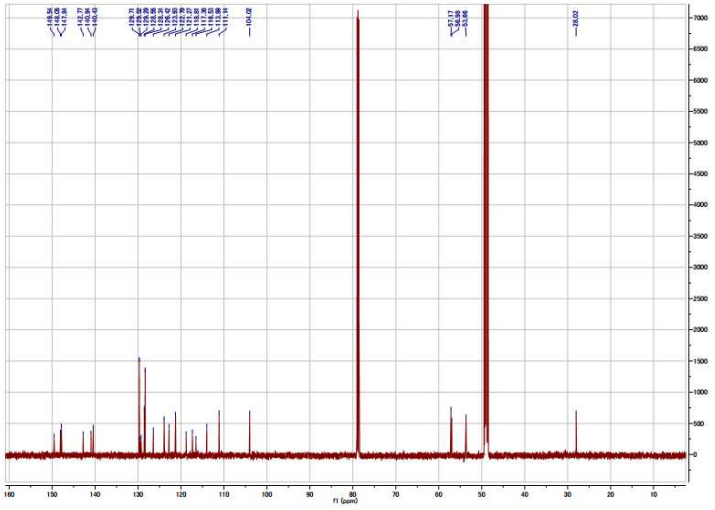
E:\2017\HRMS\0418\F\5l 4/18/2017 10:21:47 AM 5l

5l #7-10 RT: 0.10-0.14 AV: 4 NL: 3.62E8
T: FTMS + c ESI Full ms [100.00-1000.00]



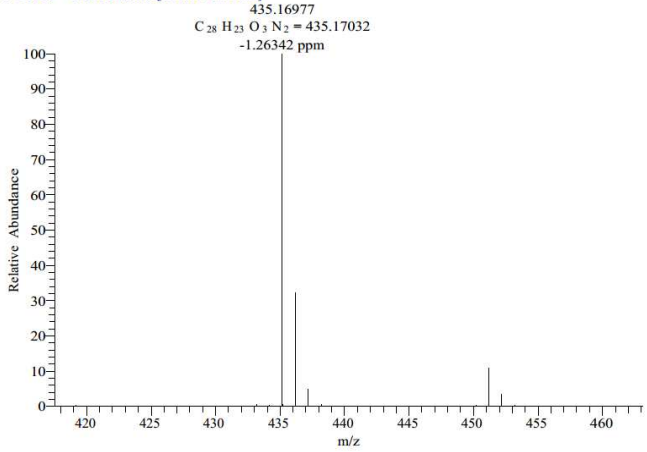
Compound **6a**



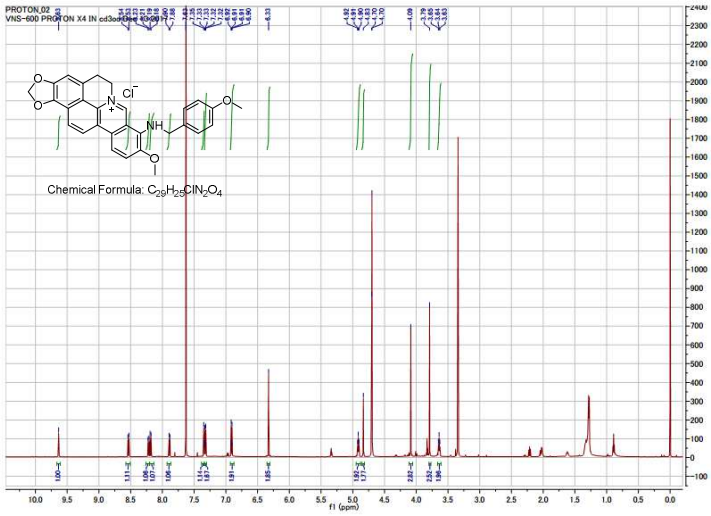


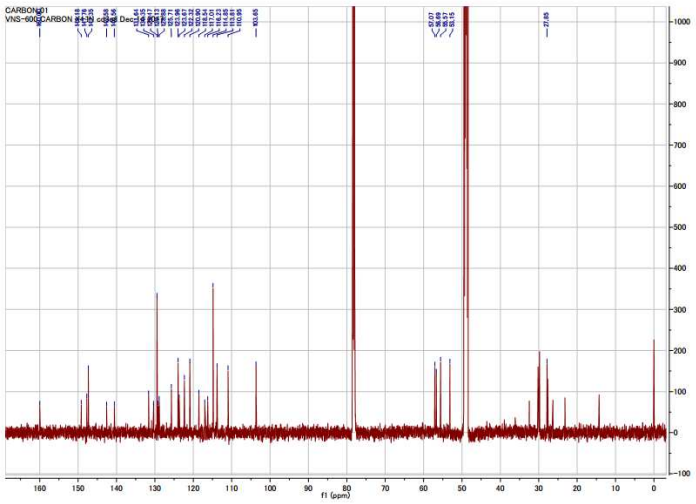
E:\2017\HRMS\20171120\6a 11/20/2017 4:44:25 PM 6a

6a #12 RT: 0.11 AV: 1 NL: 2.71E7
T: FTMS + c ESI Full ms [100.00-1000.00]



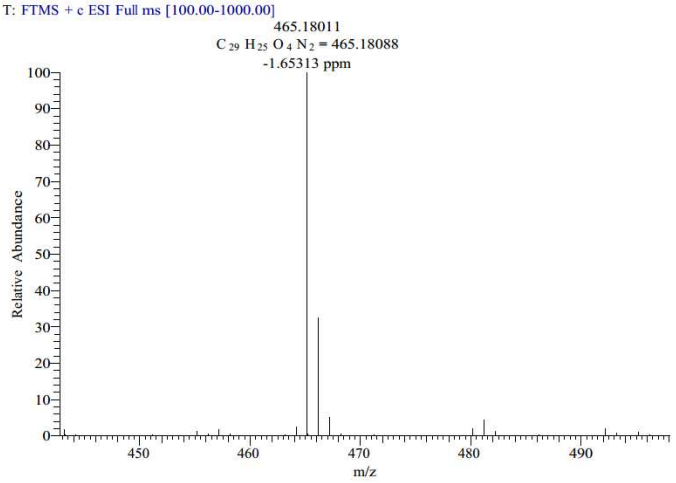
Compound **6b**:



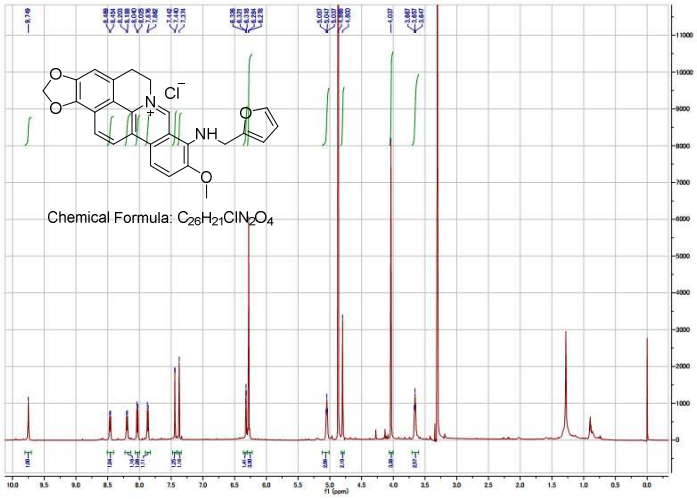


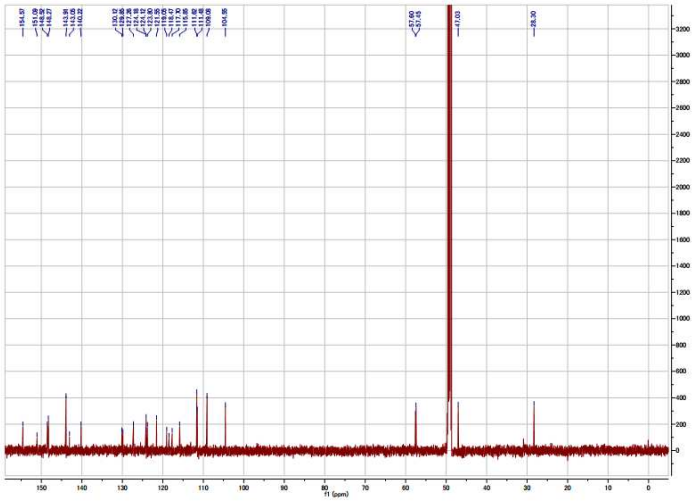
E:\2017\HRMS\20171120\6b 11/20/2017 4:44:49 PM 6b

6b #63 RT: 0.59 AV: 1 NL: 2.22E7
T: FTMS + c ESI Full ms [100.00-1000.00]



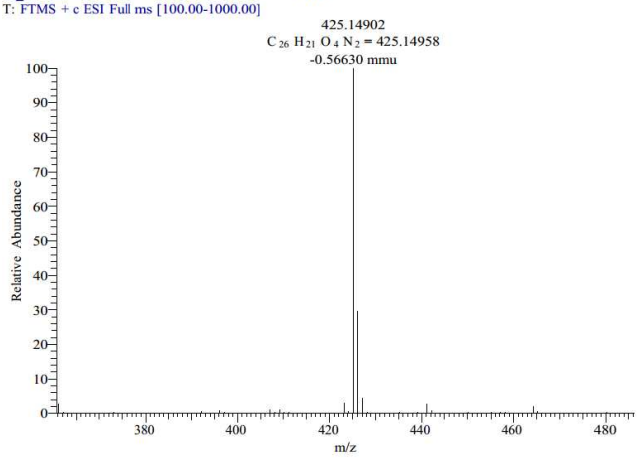
Compound **6c**:



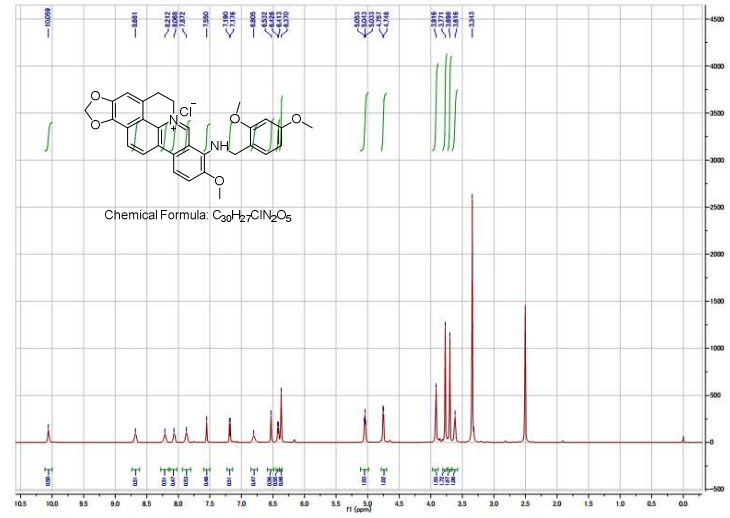


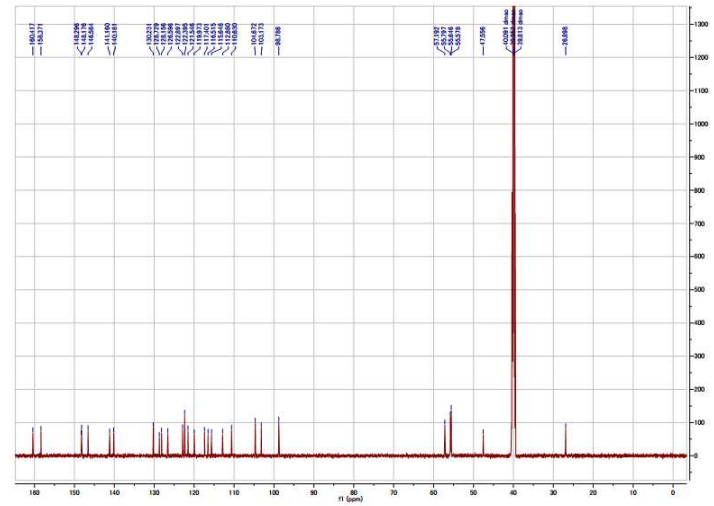
E:\2017\HRMS\20171120\6c_171120165746 11/20/2017 4:57:46 PM 6c

6c_171120165746 #52 RT: 0.48 AV: 1 NL: 1.41E7
T: FTMS + c ESI Full ms [100.00-1000.00]



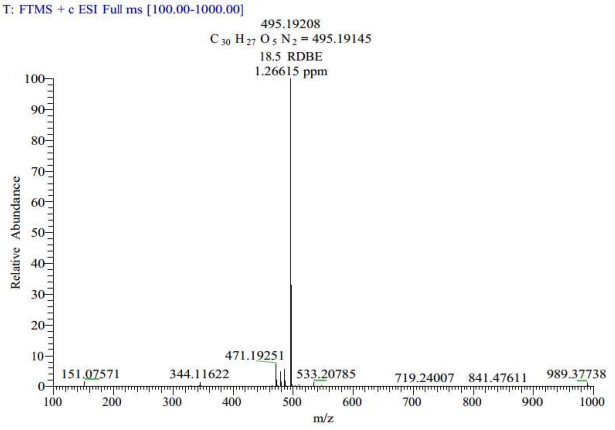
Compound **7**:



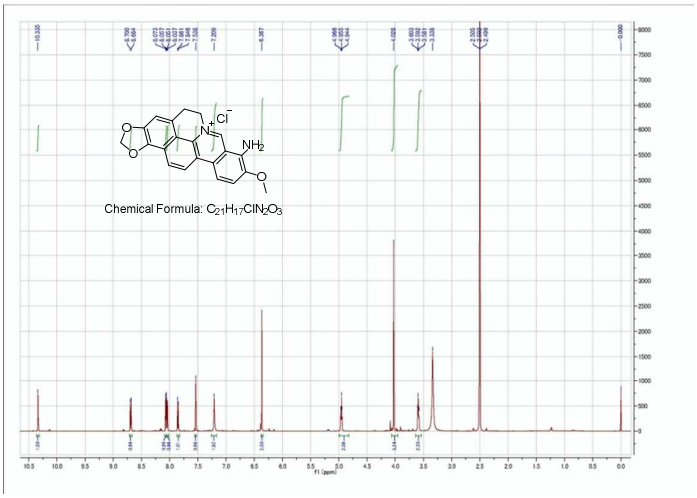


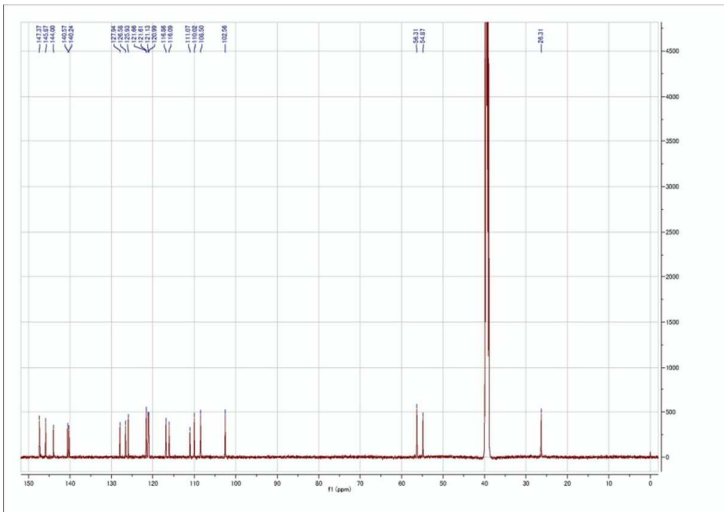
E:\2017\HRMS\0418\F\7 4/18/2017 10:22:20 AM 7

7 #8-10 RT: 0.11-0.14 AV: 3 NL: 2.66E8
T: FTMS + c ESI Full ms [100.00-1000.00]



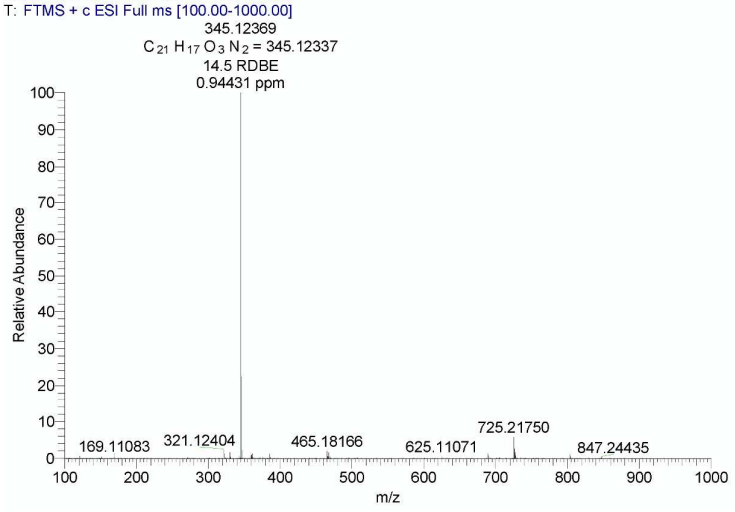
Compound **8**:



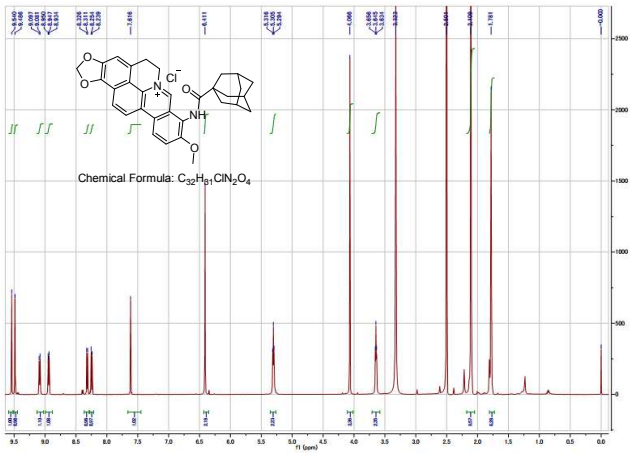


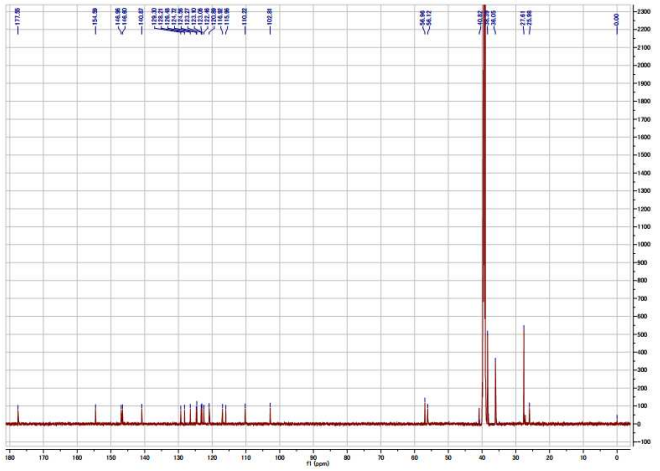
E:\2017\HRMS\fantianyun\F\8 4/18/2017 10:27:41 AM 8

8#7-9 RT: 0.11-0.14 AV: 3 NL: 1.56E8
T: FTMS + c ESI Full ms [100.00-1000.00]



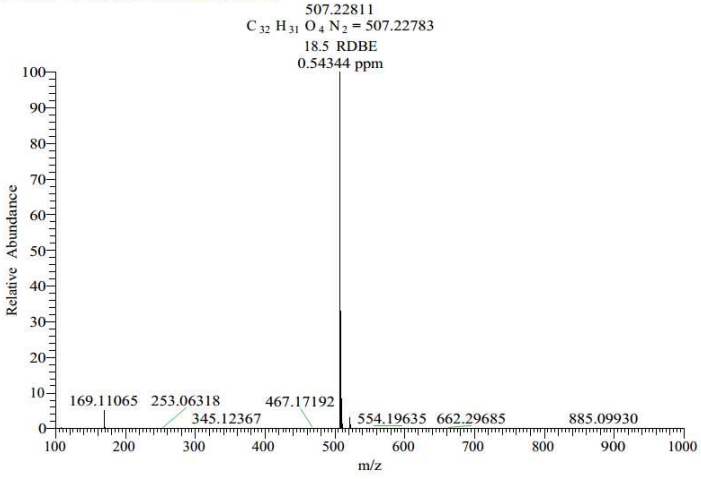
Compound **9a**:



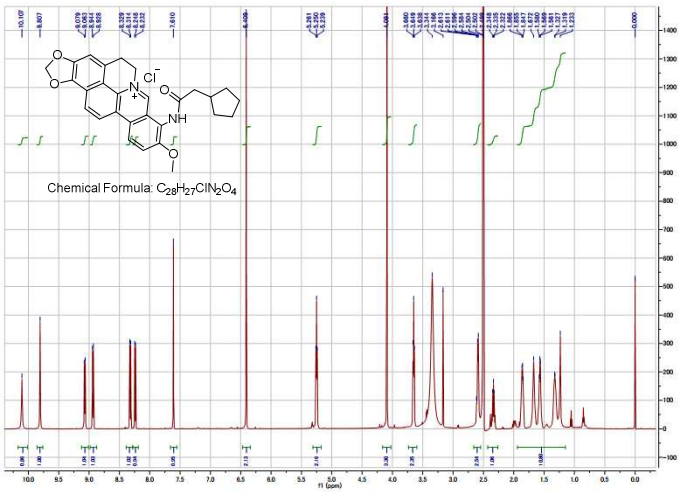


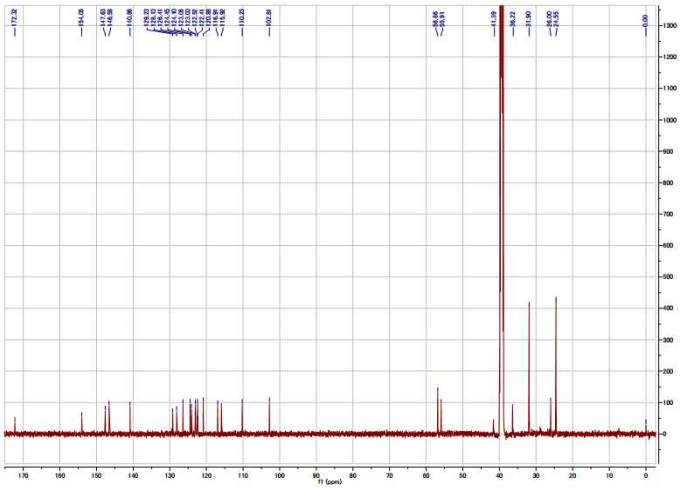
E:\2017\HRMS\0418\F\9a 4/18/2017 10:24:10 AM 9a

9a #9-11 RT: 0.13-0.15 AV: 3 NL: 3.47E8
T: FTMS + c ESI Full ms [100.00-1000.00]



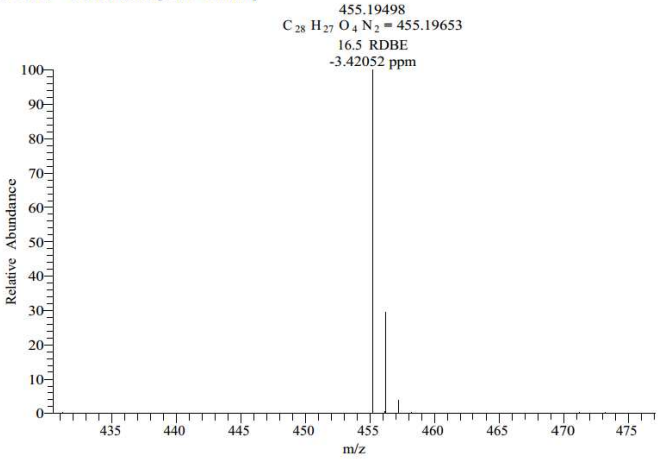
Compound **9b**:



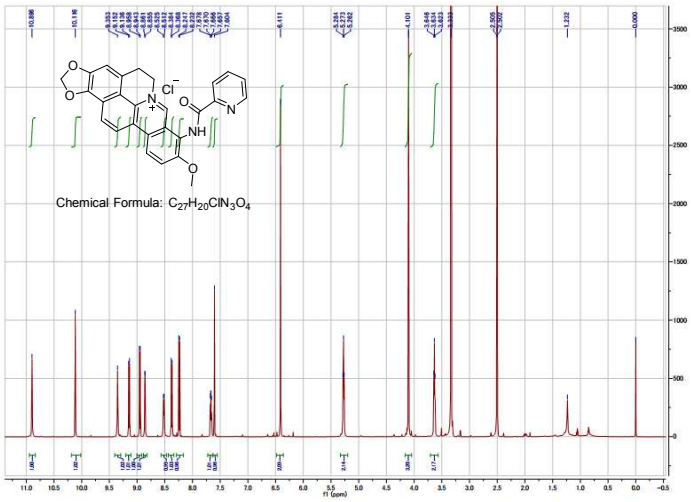


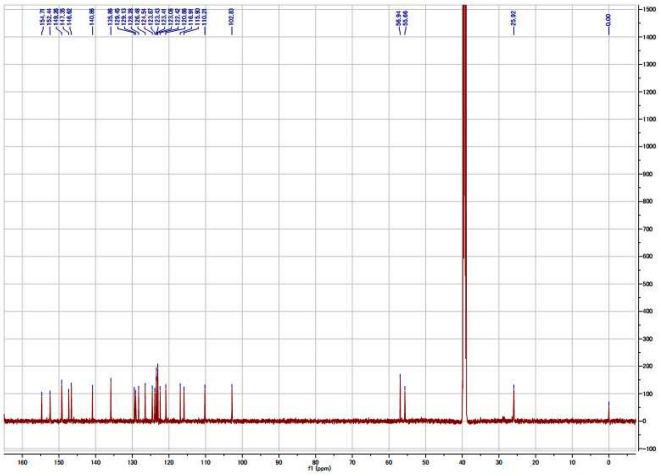
E:\2017\HRMS\20170711\zengqingxuan\9b 7/11/2017 5:35:56 PM 9b

9b #15-18 RT: 0.41-0.49 AV: 4 NL: 1.85E7
T: FTMS + c ESI Full ms [50.00-1000.00]



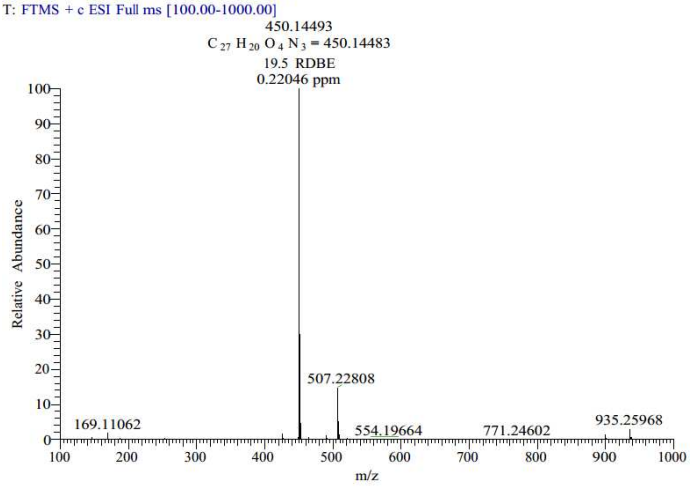
Compound **9c**:



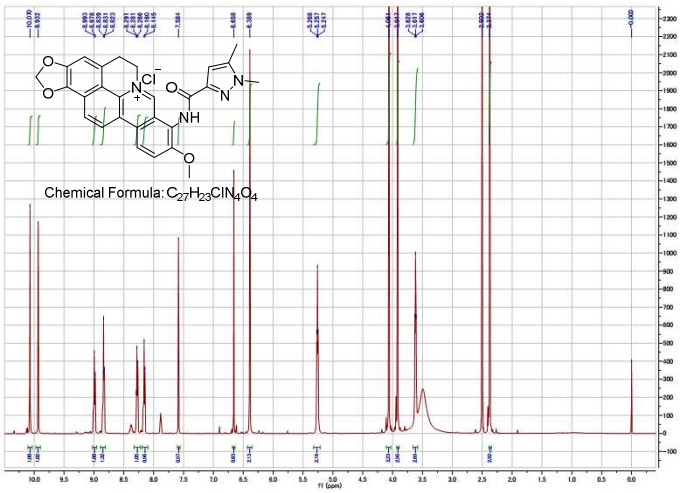


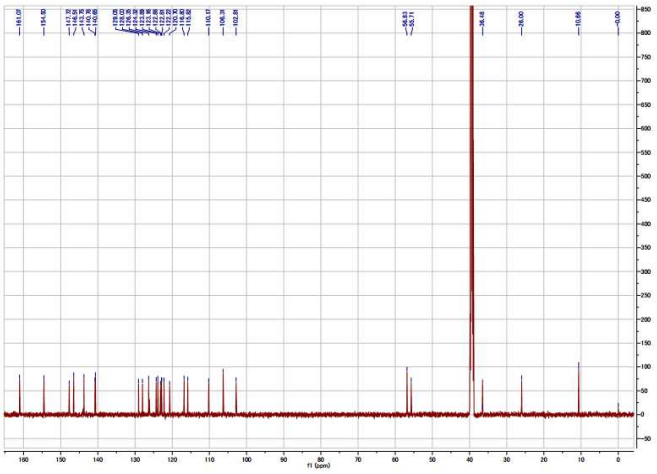
E:\2017\HRMS\0418\F\9c 4/18/2017 10:24:40 AM 9c

9c #7-10 RT: 0.10-0.14 AV: 4 NL: 4.01E8
T: FTMS + c ESI Full ms [100.00-1000.00]



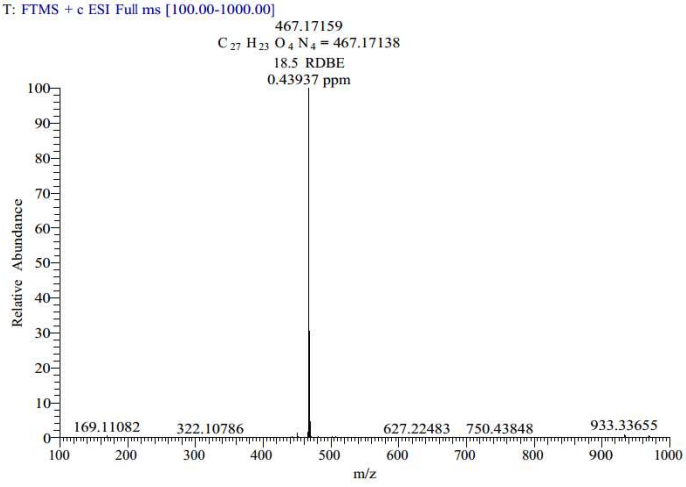
Compound **9d**:



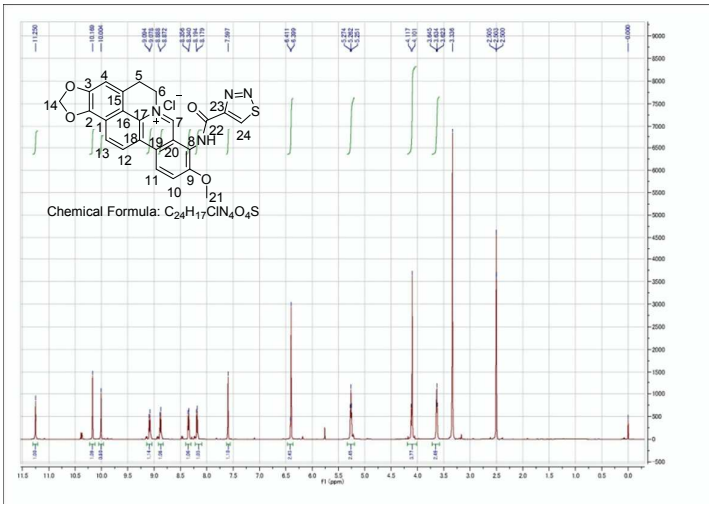


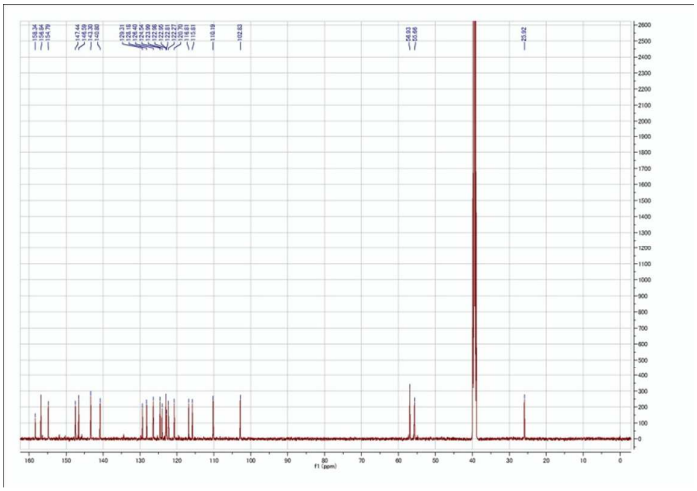
E:\2017\HRMS\0418\F\9d 4/18/2017 10:25:21 AM 9d

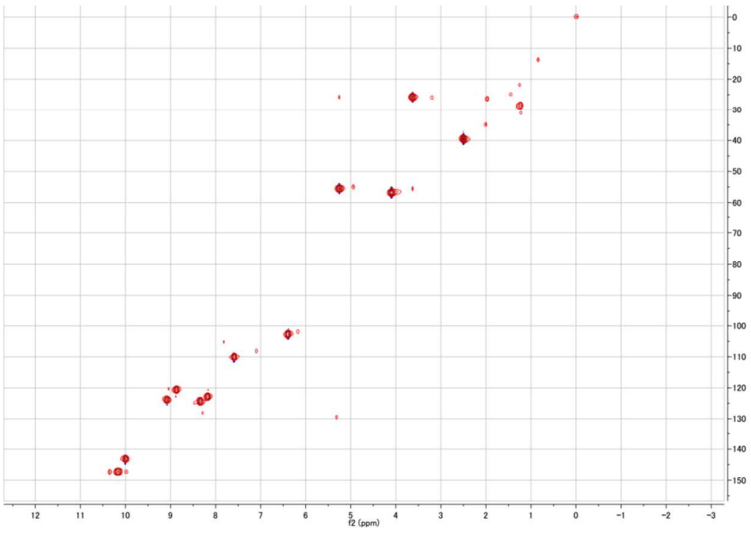
9d #7-9 RT: 0.10-0.13 AV: 3 NL: 5.38E8
T: FTMS + c ESI Full ms [100.00-1000.00]

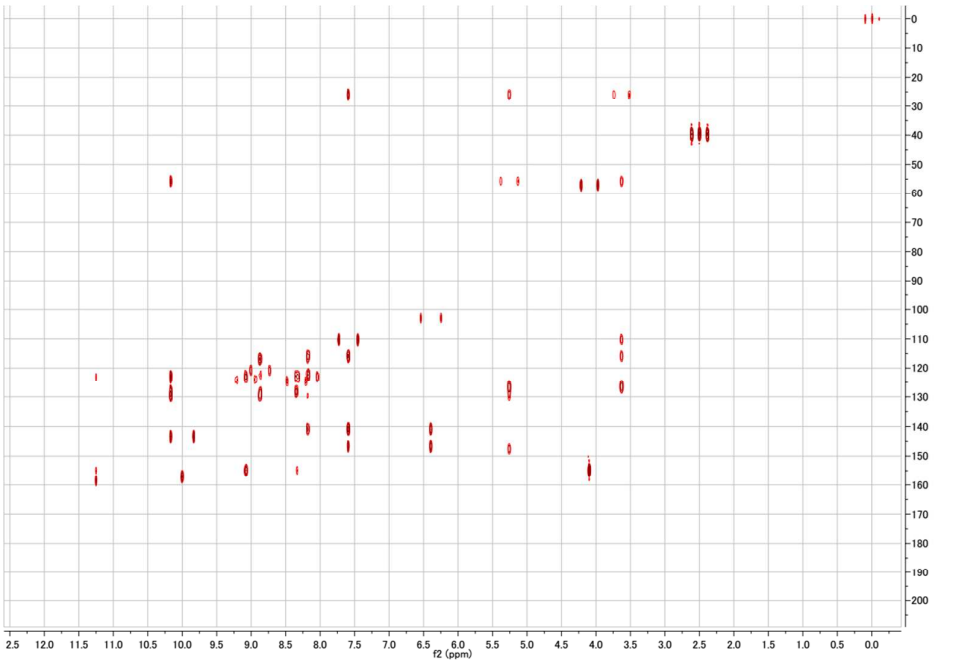


Compound **9e**


Chemical Formula: $C_{24}H_{17}ClN_4O_4S$



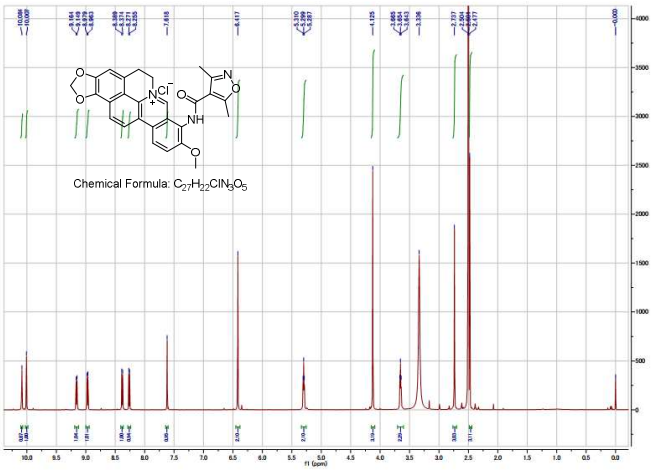


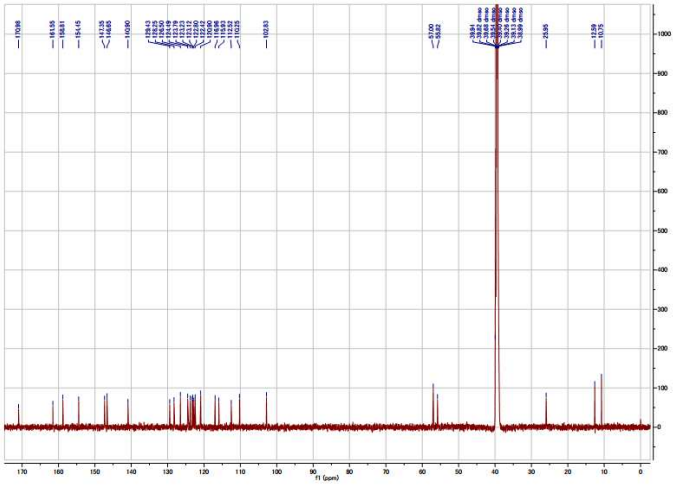


proton	^{13}C NMR chemical shift values	^{1}H NMR chemical shift values

1	122.3	
2	140.8	
3	146.6	
4	110.2	7.60 s
5	25.9	3.63 t
6	55.7	5.26 t
7	147.4	10.17 s
8	123.0	
9	154.8	
10	124.0	9.09 d
11	124.5	8.34 d
12	120.7	8.88 d
13	122.8	8.19 d
14	102.8	6.40 s
15	115.8	
16	126.4	
17	129.3	
18	116.9	
19	128.2	
20	123.0	
21	56.9	4.11 s
22	158.3	
23	156.8	
24	143.3	10.00 s
NH		11.25 s

Compound **9f**:





E:\2017\HRMS\0418\F\9f 4/18/2017 10:27:03 AM 9f

9f #7-8 RT: 0.10-0.12 AV: 2 NL: 4.64E8
T: FTMS + c ESI Full ms [100.00-1000.00]