Supporting Information

Synthesis and biological evaluation of novel sinomenine derivatives as anti-inflammatory and analgesic agents

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Materials and Methods

Chemistry

Reagents were obtained from commercial suppliers and used without further purification. All melting points were determined on a micro melting point apparatus and were uncorrected. Purification by flash chromatography was performed on Reveleris X2 flash chromatography system (BUCHI Corporation, New Castle, DE). Bruker 400 spectrometer (^{1}H at 400 MHz and ^{13}C at 100 MHz) equipped with a z-axis gradient probe was used to record NMR experiments. The internal standard was tetramethyl silane (TMS).

Preparation of SIN-1-Br

SIN (1.0 equiv.) and N-Bromo succinimide (1.2 equiv.) was dissolved in 20 mL dichloromethane (DCM). The mixture was stirred for 10 h at room temperature. After completion of the reaction (as monitored by TLC), the mixture was added 10 mL of water and extracted with DCM (3 × 20 mL). Then, the organic solvent was removed under reduced pressure. The crude product was purified using silica (200-300 mesh) gel column chromatography and eluted with DCM: methanol (20: 1) to afford the compound SIN-1-Br.

Preparation of SIN-1-CH_2OH

SIN (1.0 equiv.) and polyformaldehyde (2.0 equiv.) was dissolved in 10 mL of 2 M HCl solution. Then the mixture was stirred at 60℃ for 2 h. After completion of the reaction (as monitored by TLC), the pH of the solvent was adjusted to 9 ~ 10 with 0.1

M NaOH. The mixture was filtered and the solvent were evaporated to afford SIN-1-CH_2OH as a white solid.

General procedure for esterification at -*OH* of SIN

SIN (1.0 equiv.) was dissolved in dry 20 mL of DCM, then DMAP (0.2 equiv.), EDCI (1.5 equiv.) and N-Boc-L-amino acid or nitrogen-based heterocycles (1.2 equiv.) were added. The mixture was stirred for 12 h at room temperature. After completion of the reaction (as monitored by TLC), the collected organic portions were washed with brine, dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure. Then the corresponding intermediates was dissolved in 20 mL of DCM, and 2 mL of TFA were added and the mixture was stirred at room temperature for 30 min. Finally, the crude product was purified using silica (200-300 mesh) gel column chromatography with dichloromethane- methanol.

4-(N-Boc-alanine) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **1**). Compound 1 was obtained as white powder; yield: 85.1%, m. p.: 123.7℃, [α]25 D = -93.33 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.89, 6.74 (d, each, 1H, Ph-H, J = 8.8 Hz), 5.45 (brs, 1H), 4.58 (m, 1H), 3.81(d, 1H), 3.69 (s, 3H), 3.47 (s, 3H), 3.18 - 2.52 (m, 6H), 2.42 (s, 3H), 2.10 - 1.85 (m, 3H), 1.62 (m, 1H), 1.57 (d, 3H), 1.55 (m, 1H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.6, 171.0, 155.3, 152.6, 149.6, 139.5, 130.2, 130.0, 125.7, 114.9, 111.0, 80.0, 77.5, 77.2, 76.8, 56.5, 56.0, 55.0, 50.1, 46.8, 46.1, 42.8, 40.7, 37.1, 28.5, 24.3, 18.9. HRMS (ESI) *m/z* $[M + H]^+$ 501.2616, calcd. for $C_{27}H_{37}N_2O_7$ 501.2601.

4-(N-Boc-glycine) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **2**). Compound 2 was obtained as white powder; yield: 79.4%, m.p.: 129.9℃, [α]25 D = -96.67 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.90, 6.76 (d, each, 1H, Ph-H, J = 8.4 Hz), 5.46 (brs, 1H), 4.27 (m, 1H), 4.17 (m, 1H), 3.75 (m, 1H), 3.71 (s, 3H), 3.47 (s, 3H), 3.20 - 2.50 (m, 6H), 2.44 (s, 3H), 2.25 - 1.91 (m, 3H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.5, 168.7, 155.8, 152.7, 149.8, 139.2, 130.1, 129.9, 125.8, 114.8, 111.1, 80.1, 77.5, 77.2, 76.8, 56.6, 56.1, 55.0, 50.3, 46.8, 45.9, 43.0, 42.8, 40.8, 37.2, 28.4, 24.4. HRMS (ESI) *m/z* $[M + H]^+$ 487.2432,

calcd. for $C_{26}H_{35}N_2O_7$ 487.2444.

4-(N-Boc-phenylalanine) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (Compound **3**). Compound 3 was obtained as white powder; yield: 83.6%, m. p.: 132.3℃, [α]25 D = -83.33 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.32 (m, 4H), 7.24 (m, 1H), 6.90, 6.74(d, each, 1H, Ph-H, J = 8.4 Hz), 5.45 (brs, 1H), 4.82 (s, 1H), 3.69 (s, 3H), 3.47 (d, 3H), 3.35 - 2.53 (m, 7H), 2.43 (s, 3H), 2.10 - 1.59 (m, 3H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.6, 171.0, 155.3, 152.7, 149.6, 139.4, 136.7, 129.8, 129.8, 129.6, 128.7, 128.6, 127.1, 126.9, 125.7, 114.8, 110.9, 80.0, 77.5, 77.2, 76.8, 56.5, 55.8, 55.4, 55.0, 50.0, 46.7, 46.0, 42.7, 40.7, 38.6, 37.1, 28.5, 24.3. HRMS (ESI) *m/z* $[M + H]^+$ 577.2915, calcd. for $C_{33}H_{41}N_2O_7$ 577.2914.

4-(N-Boc-proline) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **4**). Compound 4 was obtained as white powder; yield: 86.7%, m. p.: 138.4℃, [α]25 D = -160.00 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.89, 6.71 (d, each, 1H, Ph-H, J = 8.4 Hz), 5.41 (brs, 1H), 4.48 (m, 1H), 3.89 (m, 1H), 3.70 (s, 3H), 3.46 (s, 3H), 3.35 - 2.64 (m, 5H), 2.49 (s, 3H), 2.42 - 1.71 (m, 8H), 1.48 (s, 9H), 1.42 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.4, 170.8, 154.7, 152.7, 150.0, 139.6, 130.1, 128.9, 125.6, 113.9, 110.9, 80.1, 77.5, 77.1, 76.8, 60.3, 56.6, 55.8, 55.0, 49.9, 49.7, 47.0, 45.2, 42.3, 40.4, 36.3, 28.7, 24.5, 24.3, 23.6. HRMS (ESI) *m/z* $[M + H]^+$ 527.2726, calcd. for $C_{29}H_{39}N_2O_7$ 527.2757.

4-(N-Boc-isoleucine) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound 5). Compound 5 was obtained as white powder; yield: 77.9%, m. p.: 105.8℃, [α]25 D = -116.67 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.89, 6.74 (d, each, 1H, Ph-H, J = 8.4 Hz), 5.44 (brs, 1H), 4.53 (m, 1H), 3.68 (s, 3H), 3.46 (s, 3H), 3.18 - 2.50 (m, 5H), 2.43 (s, 3H), 2.25 - 1.85 (m, 4H), 1.46 (s, 9H), 1.42 (m, 2H), 1.25 (m, 2H), 1.08 (m, 3H), 0.97 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.6, 155.8, 152.7, 149.7, 139.5, 130.3, 129.9, 125.8, 114.8, 110.9, 79.9, 77.5, 77.2, 76.8, 56.5, 55.6, 55.0, 50.0, 46.8, 46.1, 42.8, 40.7, 37.8, 37.1, 28.5, 24.7, 24.4, 15.6, 11.7. HRMS (ESI) *m/z* $[M + H]^+$ 543.3051, calcd. for $C_{30}H_{43}N_2O_7$ 543.3070.

4-(N-Boc-leucine) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **6**). Compound 6 was obtained as white powder; yield: 81.0%, m. p.:

173.2℃, [α]25 D = -126.67 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.88, 6.73 (d, each, 1H, Ph-H, J = 8.4 Hz), 5.44 (brs, 1H), 4.53 (m, 1H), 3.68 (s, 3H), 3.46 (s, 3H), 3.21 - 2.52 (m, 5H), 2.43 (s, 3H), 2.12 - 1.67 (m, 6H), 1.46 (s, 9H), 1.00 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.7, 171.2, 155.5, 152.7, 149.7, 139.5, 130.3, 129.8, 125.7, 114.7, 110.9, 79.9, 77.5, 77.2, 76.8, 56.5, 55.8, 55.0, 53.2, 50.0, 46.8, 45.9, 42.7, 41.9, 40.7, 37.0, 28.6, 24.7, 24.4, 22.9, 22.1. HRMS (ESI) *m/z* $[M + H]^+$ 543.3051, calcd. for $C_{30}H_{43}N_2O_7$ 543.3070.

4-(N-Boc-sarcosine) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **7**). Compound 7 was obtained as white powder; yield: 72.0%, m. p.: 136.2℃, [α]25 D = -126.67 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.90, 6.74 (d, each, 1H, Ph-H, J = 8.4 Hz), 5.46 (brs, 1H), 4.25 (m, 2H), 3.81 (m, 1H), 3.72 (s, 3H), 3.47 (s, 3H), 3.19 (m, 1H), 3.06 (s, 2H), 3.00 (s, 3H), 2.75 (m, 1H), 2.43 (s, 3H), 2.10 - 1.62 (m, 3H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.4, 168.3, 156.2, 152.6, 149.7, 139.4, 130.3, 130.0, 125.8, 114.7, 111.0, 80.4, 77.5, 77.2, 76.9, 56.5, 56.1, 55.0, 51.1, 50.1, 46.7, 46.0, 42.8, 40.7, 37.4, 35.4, 28.5, 24.3. HRMS (ESI) *m/z* $[M + H]^+$ 501.2593, calcd. for $C_{27}H_{37}N_2O_7$ 501.2601.

4-(L-alanine) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **8**). Compound 8 was obtained as white powder; yield :69.9%, m. p.: 179.6℃, [α]25 D = -40.00 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.76 (s, 2H), 7.14, 7.07 (d, each, 1H, Ph-H, J = 8.4 Hz), 5.79 (brs, 1H), 4.53 (m, 1H), 4.00 (d, 1H), 3.71 (s, 3H), 3.40 (s, 3H), 3.25 - 3.17 (m, 4H), 2.90 (s, 3H), 2.77 (m, 1H), 2.11 (m, 1H,) 1.68 (m, 3H),1.24 (m, 1H), 0.86 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 190.7, 158.6, 158.3, 152.1, 149.1, 138.1, 127.3, 118.7, 115.7, 112.8, 112.0, 56.9, 56.1, 54.7, 48.6, 39.5, 31.0, 28.5, 26.4, 22.5, 22.1, 18.7, 14.0, 11.3. HRMS (ESI) *m/z* $[M + H]^+$ 401.2070, calcd. for $C_{22}H_{29}N_2O_5$ 401.2076.

4-(L-glycine) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **9**). Compound 9 was obtained as white powder; yield: 61.6%, m. p.: 145.7℃, [α]25 D = -36.67 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.61 (s, 2H), 7.11, 7.08 (d, each, 1H, Ph-H, J = 8.4 Hz), 5.77 (brs, 1H), 4.23 (s, 1H), 3.71 (s, 3H), 3.59 - 3.55 (m, 2H), 3.39 (s, 3H), 3.25 (m, 2H), 3.17 (s, 3H), 2.89 -

2.76 (m, 4H), 2.06 (m, 1H), 1.63 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 190.8, 158.7, 158.4, 152.0, 149.3, 137.8, 128.3, 118.7, 115.7, 112.0, 56.9, 56.1, 54.7, 52.5, 48.6, 48.1, 42.2, 39.5, 27.4, 23.2. HRMS (ESI) *m/z* $[M + H]^+$ 387.1919, calcd. for $C_{21}H_{27}N_2O_5$ 387.1920.

4-(L-phenylalanine) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **10**). Compound 10 was obtained as white powder; yield: 64.6%, m. p.: 131.5℃, [α]25 D = -40.00 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.20 (s, 2H), 7.32 - 7.21 (m, 4H), 7.04 (m, 1H), 6.74, 6.55 (d, each, 1H, Ph-H, *J* = 8.4 Hz), 5.71 (brs, 1H), 4.18 (m, 1H), 3.71 (s, 3H), 3.64 (m, 1H), 3.47 (m, 1H), 3.37 (s, 3H), 3.10 - 2.72 (m, 3H), 2.53 (s, 3H), 2.43 - 2.13 (m, 2H), 1.88 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 192.3, 151.6, 145.7, 145.0, 129.9, 129.5, 128.8, 128.4, 128.2, 122.5, 118.1, 114.7, 110.1, 56.4, 55.8, 55.7, 54.4, 48.6, 47.9, 46.8, 43.1, 41.8, 41.4, 33.7, 24.2. HRMS (ESI) *m/z* $[M + H]^+$ 477.2373, calcd. for $C_{28}H_{33}N_2O_5$ 477.2389.

4-(L-proline) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **11**). Compound 11 was obtained as white powder; yield: 59.8%, m. p.: 156.7℃, [α]25 D = -33.33 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.02, 6.88 (d, each, 1H, Ph-H, *J* = 8.8 Hz), 5.49 (brs, 1H), 4.04 (s, 1H), 3.73 (s, 3H), 3.44 (s, 3H), 3.20 (m, 4H), 2.85 (s, 3H), 2.63 (m, 3H), 2.44 (m, 3H), 2.16 (m, 4H), 1.25 (m,1H), 0.85 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 190.6, 170.6, 152.1, 149.1, 146.1, 137.9, 127.4, 127.0, 118.6, 115.6, 58.8, 56.9, 56.1, 54.7, 48.6, 48.3, 47.3, 45.3, 40.2, 28.0, 23.2, 23.0. HRMS (ESI) *m/z* $[M + H]^+$ 427.2227, calcd. for $C_{24}H_{31}N_2O_5$ 427.2233.

4-(L-isoleucine) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **12**). Compound 12 was obtained as white powder; yield: 63.8%, m. p.: 105.8℃, [α]25 D = -26.67 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.62 (s, 2H), 7.13, 7.11 (d, each, 1H, Ph-H, *J* = 8.4 Hz), 5.75 (brs, 1H), 4.48 (s, 1H), 4.00 (s, 1H), 3.70 (s, 3H), 3.41 (s, 3H), 3.39 - 3.01 (m, 6H), 2.88 (s, 3H), 2.40 - 1.37 (m, 4H), 1.14 (m, 3H), 0.96 (m,3H), 0.86 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 190.8, 173.8, 158.6, 158.3, 129.4, 127.0, 118.7, 115.7, 115.3, 112.7, 62.8, 61.0, 56.8, 54.7, 54.3, 48.6, 42.2, 39.5, 36.4, 34.2, 23.5, 23.2, 14.9, 12.6, 11.8, 11.6.

HRMS (ESI) *m/z* $[M + H]^+$ 443.2539, calcd. for $C_{25}H_{35}N_2O_5$ 443.2546.

4-(L-leucine) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **13**). Compound 13 was obtained as white powder; yield: 66.5%, m. p.: 111.5℃, [α]25 D = -46.67 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.29 (s, 2H), 6.70, 6.52 (d, each, 1H, Ph-H, J = 8.0 Hz), 5.71 (brs, 1H), 4.13 (m, 1H), 3.70 (s, 3H), 3.36 (s, 3H), 2.97 - 2.77 (m, 4H), 2.44 (m, 1H), 2.37(s, 3H), 1.97 - 1.23 (m, 7H), 0.86 (m, 6H).^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 192.7, 151.5, 145.5, 145.0, 122.9, 117.8, 115.8, 109.8, 55.9, 55.7, 54.3, 48.6, 48.3, 46.7, 44.2, 42.0, 39.5, 34.6, 24.0, 23.7, 23.1, 22.9, 22.4, 22.0. HRMS (ESI) *m/z* $[M + H]^+$ 443.2547, calcd. for $C_{25}H_{35}N_2O_5$ 443.2546.

4-(L-sarcosine) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **14**). Compound 14 was obtained as white powder; yield: 73.6%, m. p.: 165.6℃, [α]25 D = -50.00 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.14, 7.07 (d, each, 1H, Ph-H, J = 8.4 Hz), 5.78 (brs, 1H), 4.42 (s, 2H), 4.01 (s, 1H), 3.71 (s, 3H), 3.53 (m, 2H), 3.39 (s, 3H), 3.25 - 3.17 (m, 4H), 2.90 (s, 3H), 2.69 (s, 3H), 2.60 - 1.61 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 190.7, 158.2, 152.1, 149.2, 137.6, 128.2, 127.3, 127.0, 115.7, 112.1, 94.8, 56.9, 56.0, 54.9, 54.7, 48.6, 48.15, 48.0, 32.4, 23.2, 22.4. HRMS (ESI) *m/z* $[M + H]^+$ 401.2045, calcd. for $C_{22}H_{29}N_2O_5$ 401.2076.

4-(ligustrazine) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **15**). Compound 15 was obtained as white powder; yield: 59.1%, m. p.: 166.3℃, [α]25 D = -110.00 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.95, 6.82 (d, each, 1H, Ph-H, J = 8.4 Hz), 5.45 (brs, 1H), 3.73 (s, 3H), 3.47 (s, 3H), 3.46 - 3.07 (m, 5H), 2.84 (s, 3H), 2.62 (s, 3H), 2.59 (s, 3H), 2.51 (m, 2H), 2.48 (s, 3H), 2.24 - 1.89 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.6, 155.0, 152.7, 152.1, 149.9, 149.7, 139.4, 139.1, 130.2, 129.6, 125.9, 114.3, 111.1, 77.5, 77.2, 76.8, 56.7, 56.0, 55.0, 53.6, 46.9, 45.6, 42.6, 40.7, 30.4, 22.4, 21.7, 21.5, 20.7. HRMS (ESI) *m/z* $[M + H]^+$ 478.2347, calcd. for $C_{27}H_{32}N_3O_5$ 478.2342.

4-(5-Methylpyrazine-2-carboxylic acid) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **16**). Compound 16 was obtained as white powder; yield:

65.3%, m. p.: 105.6℃, [α]25 D = -73.33 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.59 (s, 1H), 8.68 (s, 1H), 6.98, 6.83 (d, each, 1H, Ph-H, J = 8.4 Hz), 5.47 (brs, 1H), 3.69 (s, 3H), 3.48 (s, 3H), 3.40 - 2.89 (m, 5H), 2.71 (s, 3H), 2.60 (m, 2H) 2.52 (s, 3H), 2.28 - 1.96 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.5, 162.0, 152.8, 152.7, 150.3, 149.3, 138.7, 130.2, 130.1, 127.0, 126.6, 126.3, 114.9, 111.0, 77.5, 77.2, 76.8, 56.4, 56.1, 55.1, 53.6, 51.1, 46.4, 46.3, 42.8, 41.17, 37.4, 24.2. HRMS (ESI) *m/z* $[M + H]^+$ 450.2039, calcd. for $C_{25}H_{28}N_3O_5$ 450.2029.

4-(2-Pyrazinecarboxylic acid) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **17**). Compound 17 was obtained as white powder; yield: 74.4%, m. p.: 164.0℃, [α]25 D = -53.33 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.61 (s, 1H), 8.87 (d, 1H), 8.84 (d, 1H), 7.05, 6.91 (d, each, 1H, Ph-H, J = 8.4 Hz), 5.51 (brs, 1H), 3.82 (m, 1H), 3.72 (s, 3H), 3.64 (m, 1H), 3.50 (s, 3H), 3.27 - 3.13 (m, 3H), 2.88 (s, 3H), 2.68 - 2.35 (m, 4H), 1.75 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 191.0, 167.3, 153.2, 148.5, 147.4, 145.2, 139.3, 128.7, 126.6, 125.9, 112.1, 111.3, 57.8, 56.3, 55.3, 48.9, 47.6, 42.7, 41.3, 39.5, 34.8, 29.8. HRMS (ESI) *m/z* $[M + H]^+$ 436.1887, calcd. for $C_{24}H_{26}N_3O_5$ 436.1872.

4-(4-Picolinic acid) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **18**). Compound 18 was obtained as white powder; yield: 52.2%, m. p.: 192.6℃, [α]25 D = -66.67 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.31 (s, 1H), 8.85, 8.03 (d, each, 1H, J = 5.2 Hz), 6.68, 6.59 (d, each, 1H, Ph-H, J = 8.4 Hz), 5.40 (brs, 1H), 3.80 (s, 3H), 3.48 (s, 3H), 3.46 - 3.08 (m, 5H), 2.79 (s, 3H), 2.54 - 1.26 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.6, 170.1, 160.7, 158.9, 158.2, 152.9, 147.0, 145.1, 126.4, 120.9, 120.7, 118.8, 111.7, 110.0, 77.5, 77.2, 76.8, 57.5, 56.2, 55.1, 53.5, 47.8, 42.5, 40.9, 39.2, 33.7, 24.9. HRMS (ESI) *m/z* $[M + H]^+$ 436.1872, calcd. for $C_{24}H_{26}N_3O_5$ 436.1872.

4-(4-Pyridazinecarboxylicacid) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **19**). Compound 19 was obtained as white powder; yield: 61.3%, m. p.: 223.2℃, [α]25 D = -63.33 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.88 (s, 1H), 9.57, 8.42 (d, each, 1H, J = 6.4 Hz), 6.99, 6.81 (d, each, 1H, Ph-H, J = 8.4 Hz), 5.50 (brs, 1H), 3.68 (s, 3H), 3.50 (s, 3H), 3.22 - 2.79 (m, 5H),

2.55 (m, 2H), 2.46 (s, 3H), 2.21 - 1.41 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.6, 162.0, 152.9, 152.7, 150.3, 149.3, 138.7, 130.2, 127.0, 126.6, 126.4, 114.9, 111.0, 56.4, 56.1, 55.1, 51.1, 51.0, 46.5, 46.3, 42.9, 41.2, 37.4, 24.2. HRMS (ESI) *m/z* $[M + H]^+$ 436.1868, calcd. for $C_{24}H_{26}N_3O_5$ 436.1872.

1-Br, 4-(ligustrazine) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **20**). Compound 20 was obtained as light-yellow powder; yield: 46.6%, m. p.: 165.9℃, [α]25 D = -46.67 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.11 (s, 1H), 5.44 (brs, 1H), 3.74 (s, 3H), 3.49 (s, 3H), 3.47 - 3.02 (m, 4H), 2.83 (s, 3H), 2.62 (s, 3H), 2.60 (s, 3H), 2.56 (m, 2H), 2.45 (s, 3H), 2.12 - 1.25 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.4, 163.7, 155.3, 154.7, 152.8, 150.3, 149.8, 138.8, 135.4, 132.5, 129.1, 121.5, 115.4, 114.2, 77.5, 77.2, 76.8, 56.4, 56.2, 55.0, 53.6, 46.7, 45.8, 42.8, 41.4, 29.8, 26.2, 22.8, 22.4, 21.7. HRMS (ESI) *m/z* $[M + H]^+$ (79/81Br) 556.1432 and 558.1417, calcd. for $C_{27}H_{31}BrN_3O_5$ 556.1447.

1-Br, 4-(5-Methylpyrazine-2-carboxylic acid) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **21**). Compound 21 was obtained as light-yellow powder; yield: 57.2%, m. p.: 212.4℃, [α]25 D = -43.33 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.50 (s, 1H), 8.69 (s, 1H), 7.10 (s, 1H), 5.45 (brs, 1H), 3.70 (s, 3H), 3.49 (s, 3H), 3.47 (m, 2H), 3.28 - 3.03 (m, 2H), 2.71 (s, 3H), 2.53 (m, 2H), 2.45 (s, 3H), 2.16 - 1.24 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.1, 162.0, 158.7, 152.8, 150.1, 146.5, 145.1, 138.6, 132.4, 129.1, 121.8, 115.4, 114.3, 113.2, 77.5, 77.2, 76.8, 56.3, 55.1, 53.6, 50.3, 46.5, 45.9, 42.8, 41.5, 29.8, 26.3, 22.2. HRMS (ESI) *m/z* $[M + H]^+$ (79/81Br) 528.1132 and 530.1116, calcd. for $C_{25}H_{27}BrN_3O_5$ 528.1134.

1-Br, 4-(2-Pyrazinecarboxylic acid) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **22**). Compound 22 was obtained as light-yellow powder; yield: 66.6%, m. p.: 169.6℃, [α]25 D = -30.00 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.61 (s, 1H), 8.86 (d, 1H), 8.84 (d, 1H), 7.13 (s, 1H), 5.44 (brs, 1H), 3.71 (s, 3H), 3.50 (s, 3H), 3.47 (m, 2H), 3.42 - 3.13 (m, 3H), 2.64 (m, 2H), 2.50 (s, 3H), 2.21 - 1.63 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 191.8, 161.72, 152.3, 150.2, 148.4, 147.4, 143.1, 138.6, 132.1, 128.4, 122.0, 115.7, 113.7, 113.3, 77.5,

77.2, 76.8, 56.4, 55.1, 53.6, 50.0, 46.4, 45.0, 42.3, 41.2, 29.8, 26.3, 22.8. HRMS (ESI) *m/z* $[M + H]^+$ (79/81 Br) 514.0960 and 516.0942, calcd. for $C_{24}H_{25}BrN_3O_5$ 514.0978.

1-Br, 4-(4-Picolinic acid) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **23**). Compound 23 was obtained as light-yellow powder; yield: 65.4%, m. p.: 102.7℃, [α]25 D = -30.00 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* (ppm) 9.56 (s, 1H), 9.49 (d, 1H), 9.27 (d, 1H), 7.16 (s, 1H), 5.43 (brs, 1H), 3.72 (s, 3H), 3.51 (s, 3H), 3.47 (m, 2H), 3.18 - 2.84 (m, 3H), 2.69 (s, 3H), 2.61 - 1.24 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* (ppm) 191.1, 166.7, 162.4, 159.1, 158.2, 153.2, 150.5, 138.5, 131.4, 126.7, 123.1, 122.2, 116.1, 112.1, 77.5, 77.2, 76.8, 56.7, 55.3, 50.9, 49.9, 46.5, 43.8, 41.6, 40.7, 35.5, 26.5. HRMS (ESI) *m/z* $[M + H]^+$ (79/81 Br) 514.0967 and 516.0951, calcd. for $C_{24}H_{25}BrN_3O_5$ 514.0978.

1-Br, 4-(4-Pyridazinecarboxylicacid) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **24**). Compound 24 was obtained as light-yellow powder; yield: 61.3%, m. p.: 223.2℃, [α]25 D = -63.33 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* (ppm) 9.87 (s, 1H), 9.58 (d, 1H), 8.40 (d, 1H), 6.91 (s, 1H), 5.43 (brs, 1H), 3.80 (s, 3H), 3.69 (m, 1H), 3.49 (s, 3H), 3.25 - 2.54 (m, 6H), 2.43 (s, 3H) 2.12 - 1.25 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* (ppm) 192.2, 161.8, 152.7, 152.2, 150.2, 144.3, 138.2, 132.3, 129.2, 126.5, 122.1, 115.5, 114.5, 113.6, 77.5, 77.2, 76.8, 56.3, 55.2, 53.6, 50.9, 42.8, 41.7, 37.1, 29.8, 26.3, 22.8. HRMS (ESI) *m/z* $[M + H]^+$ (79/81 Br) 514.0960 and 516.0944, calcd. for $C_{24}H_{25}BrN_3O_5$ 514.0978.

1-hydroxymethyl-ligustrazine, 4-(ligustrazine) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **25**). Compound 25 was obtained as light-yellow powder; yield: 59.8%, m.p.: 202.6℃, [α]25 D = -30.00 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* (ppm) 7.10 (s, 1H), 5.42 (brs, 1H), 5.39 (s, 2H), 3.77 (s, 3H), 3.46 (s, 3H), 3.44 (s, 3H), 3.37 - 2.83 (m, 5H), 2.75 (s, 3H), 2.67 (s, 3H), 2.62 (s, 3H), 2.60 (s. 3H), 2.56 (s, 3H), 2.51 (s, 3H), 2.35 - 1.75 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* (ppm) 189.5, 165.6, 155.3, 155.1, 153.0, 151.9, 150.1, 148.2, 139.7, 138.9, 138.5, 131.0, 130.3, 127.4, 120.9, 120.0, 113.4, 112.7, 77.5, 77.2, 76.8, 65.1, 56.6, 56.1, 55.0, 53.6, 50.9, 49.2, 47.0, 44.0, 41.8, 40.3, 22.8, 22.4, 21.7, 21.4. HRMS (ESI) *m/z* $[M + H]^+$ 656.3084, calcd. for $C_{36}H_{42}N_5O_7$ 656.3084.

1-hydroxymethyl-5-Methylpyrazine-2-carboxylic acid, 4-(5-Methylpyrazine-2-carboxylic acid) -7, 8-didehydro-3, 7-dimethoxy-17-methyl-morphinan-6-one (compound **26**). Compound 26 was obtained as light-yellow powder; yield: 44.5%, m.p.: 102.1℃, [α]25 D = -46.67 (c 0.3 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.51 (s, 1H), 9.17 (s, 1H), 8.68 (s, 1H), 8.56 (s, 1H), 7.04 (s, 1H), 5.46 (m, 3H), 3.71 (s, 3H), 3.46 (s, 3H), 3.45 - 3.03 (m, 5H), 2.71 (s, 3H), 2.66 (s, 3H), 2.54 (m, 2H), 2.44 (s, 3H), 2.18 - 1.60 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.3, 164.8, 164.1, 158.3, 158.0, 152.8, 149.6, 146.5, 145.5, 144.5, 144.4, 140.5, 139.6, 138.4, 136.2, 129.2, 114.4, 113.0, 110.6, 77.5, 77.2, 76.8, 65.6, 63.1, 56.1, 55.0, 53.6, 53.1, 50.9, 50.5, 42.8, 41.1, 29.8, 22.2, 22.1. HRMS (ESI) *m/z* $[M + H]^+$ 600.2453, calcd. for $C_{32}H_{34}N_5O_7$ 600.2458.

Bio-evaluation mathods

Cell culture

RAW264.7 cells were obtained from the Chinese Academy of Medical Sciences & Peking Union Medical College. Cultures were maintained as monolayer in DMEM supplemented with 1% (v/v) penicillin/streptomycin and 10% (v/v) fetal bovine serum (FBS; Thermo Technologies, New York, NY, USA) under a humidified atmosphere containing 5% CO_2 at 37℃.

Cytotoxicity assay

The cytotoxicity of these compounds was tested on RAW264.7 cells *in vitro* by the MTT assay. In short, the cells were plated onto 96-well plates, 100 μL of cells with a density of 5×10^4 cells/mL were added to per well, and incubated for 24 h at 37℃ with 5% CO_2. Then the cells were exposed to various concentrations of the tested compounds and incubated for 24 h. The MTT solution (20 μL, 5 mg/mL) was added to each well. After 4 h of incubation, the solution was throwed away and 150 μL of DMSO was added to dissolve the formazan crystals. The absorbance was measured at a wavelength of 490 nm. Wells without drugs were used as the blanks. The IC_{50} values were defined as the concentration of compounds that produced a 50% proliferation inhibition of surviving cells and calculated with the GraphPad Prism 8. The inhibitory rate was calculated in the following equation (1):

% Inhibition = 100% × [1 - ($OD_{Sample\ group}$ - $OD_{Blank\ group}$)/($OD_{Control\ group}$ - $OD_{Blank\ group}$) (1)

Detection of NO levels

NO production was determined by measuring the accumulation of nitrite in the culture supernatant using the Griess reagent according to manufacturer's instructions [1]. Briefly, the cells were plated onto 96-well plates, 100 μL per well at a density of 1 × 10^6 cells/mL, and incubated for 24 h at 37℃ with 5% CO_2. Then, the cells were pre-treated with drugs for 1 h and lipopolysaccharide (LPS) for an additional 24 h, the culture supernatant from each well was collected at the end of scheduled experiments and used to measure NO production. 100 μL of culture supernatant was transferred into a new 96-well plate and mixed with 100 μL of Griess reagent. After 5 min, the absorbance was measured at a wavelength of 540 nm. The inhibitory rate of NO release was calculated in the following equation (2):

% Inhibition = 100% × [LPS (OD_{540}) - Compounds (OD_{540})]/[LPS (OD_{540}) - Control (OD_{540})] (2)

Examination of iNOS, TNF-α, IL-6 mRNA by qPCR assay

RAW264.7 cells were seeded in 6-well plates for 24 h at 37°C. Total RNA of cells was extracted and cDNA was synthesized. qPCR was performed to identify genes including iNOS, TNF-α, IL-6. The sequence of primers was design as Table 1:

Table 1 Primers sequences used for qPCR analysis

Gene name		Primer (5' - 3')
iNOS	Forward	ACTCAGCCAAGCCCTCACCTAC
	Reverse	TCCAATCTCTGCCTATCCGTCTCG
TNF-α	Forward	GCGACGTGGAACTGGCAGAAG
	Reverse	GCCACAAGCAGGAATGAGAAGAGG
IL-6	Forward	CTCCCAACAGACCTGTCTATAC
	Reverse	CCATTGCACAACTCTTTTCTCA
GAPDH	Forward	GTGCAAAAGACCCTGAACAATG
	Reverse	GAAGCTATTCTAGTCTGATAACCTCC

The PCR program was set as follows: 95℃ 5 min; (95℃ 10 s, 60℃ 30 s，95℃ 15 s) × 40; 60℃ 60 s, 95℃ 15 s. The results were analyzed by a relative quantitative $2^{-\Delta\Delta Ct}$ method, and then the expression of mRNA in each group was calculated and compared.

λ-Carrageenan-induced paw inflammation suppression test

Evaluation of the degree of paw edema in mice over time

The ICR mice (body weight about 20 g) were procured from Model Animal Research Center of Charles River (Beijing, China). All the mice were free to access food and water.

Mice were marked with a permanent marker on the ankles of their right hind paws to define the area of the paws to be monitored. Animals were randomly divided into 4 groups (8 mice per group): Control group (treated with λ-carrageenan), Indo group (positive control, λ-carrageenan + indomethacin i. g. at a dose of 10 mg/kg, 2 h before λ-carrageenan challenge) and Compound 17 groups (λ-carrageenan + compound 17 i. g. at 25 mg/kg or 50 mg/kg, 2 h before λ-carrageenan challenge). λ-Carrageenan (1% w/v in saline, 50 μL) was injected into the plantar surface of the right hind paw to induce acute inflammation. The volume of the paw was measured pre injection (as normal data) and at 2, 4, and 6 h after the λ-carrageenan treatment, using drainage method. Percentage of increase in paw volume was calculated by the following equation (3):

$$\%\ \text{Increase in paw thickness} = 100 \times (\text{volume}_{(\text{tested compound})} - \text{volume}_{(\text{normal})}) / \text{volume}_{(\text{normal})} \quad (3)$$

H&E Staining

The right edematous paws of the mice were removed from 10% buffered formalin, dehydrated in a graded series of ethanol, and embedded in paraffin wax. 5 μm sections were deparaffinized in xylene and ethanol, and then stained with H&E (Beyotime Institute of Biotechnology, Shanghai, China). Morphological changes were observed by using a light microscope (Olympus IX71, Tokyo, Japan).

Immunostaining with TNF-α antibodies

Paraffin-embedded paws tissue sections (5 μm thick) were mounted on poly sine-coated glass slides. The slides were then incubated with primary antibodies at 4°C

overnight. Following washes, sections were incubated with secondary antibody for 30 min at 37℃. Use DAB for color rendering and DAPI (Biomol, 1 μg/mL) for nuclear counter staining. After further washing in a graded series of ethanol, sections were mounted and visualized by microscopy. Tissue sections were scored for fluorescence with a light microscope (Olympus IX71, Tokyo, Japan).

Acetic acid-induced writhing analgesic test

The Kunming mice (body weight about 20 g) were procured from Model Animal Research Center of Charles River (Beijing, China). All the mice are free to access food and water.

Animals were randomly divided into 6 groups (6 mice per group): voltaren group (positive control, voltaren i.g. at a dose of 19.5 mg/kg), Compound 17 groups (17 i.g. at 50 mg/kg, 100 mg/kg and 200 mg/kg) and Control group (treated with physiological saline). Continuous intragastric administration for 3 days. After 60 min of the last administration of the drug, 0.8% acetic acid solution (0.1 mL per 10 g of body weight) was intraperitoneally injected, and the number of writhing times in the mouse within 15 minutes was recorded. Percentage of pain inhibition was calculated by the following equation (4):

$$\% \text{ Inhibition rate} = 100 \times (\text{Writhes}_{(\text{Control})} - \text{Writhes}_{(\text{treatment})}) / \text{Writhes}_{(\text{Control})} \quad (4)$$

Molecular docking

In the molecular docking study, the crystal structures of NF-κB P65 in complex with roflumilast (PDB: 1VKX) and iNOS (PDB: 4NOS) was obtained from the Protein Data Bank. Briefly, the protein-ligand complexes were prepared by the protein preparation wizard module in the Discovery Studio 2019. And Water molecules were removed. Based on the native ligand, active binding sites were defined uSing the Receptor Grid Generation model. Then the obtained protein-ligand complexes were optimized and minimized. Based on the refined protein-ligand complexes, the active binding sites were defined, and a grid file was produced for ligand docking by receptor grid generation panel. The docking procedure of active compounds was performed by a ligand docking program.

HRMS, ^{1}H NMR and ^{13}C NMR spectra of compounds 1-26

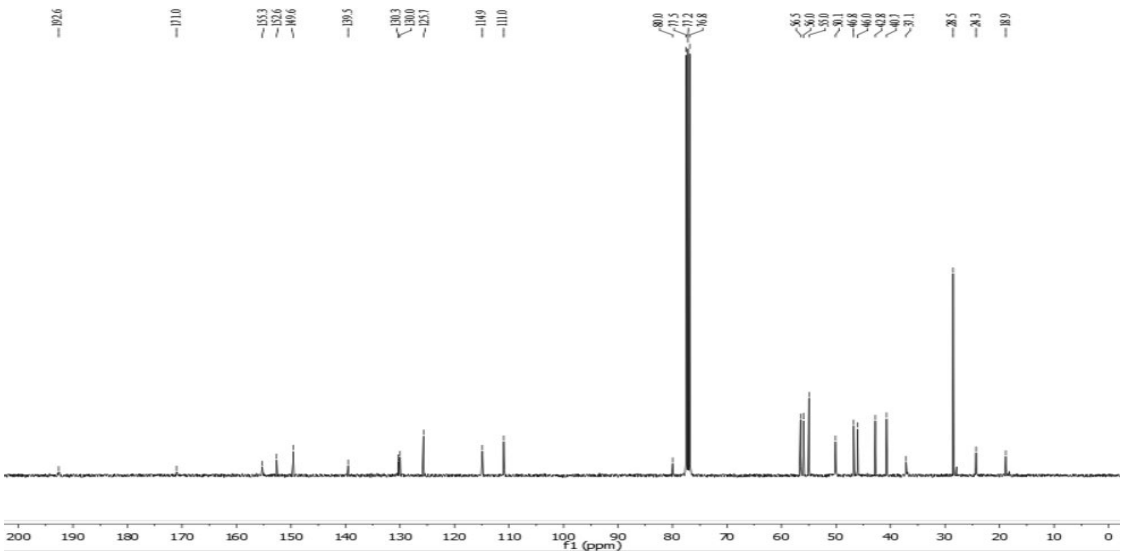

Figure S1. ^{13}C NMR spectrum of compound 1.

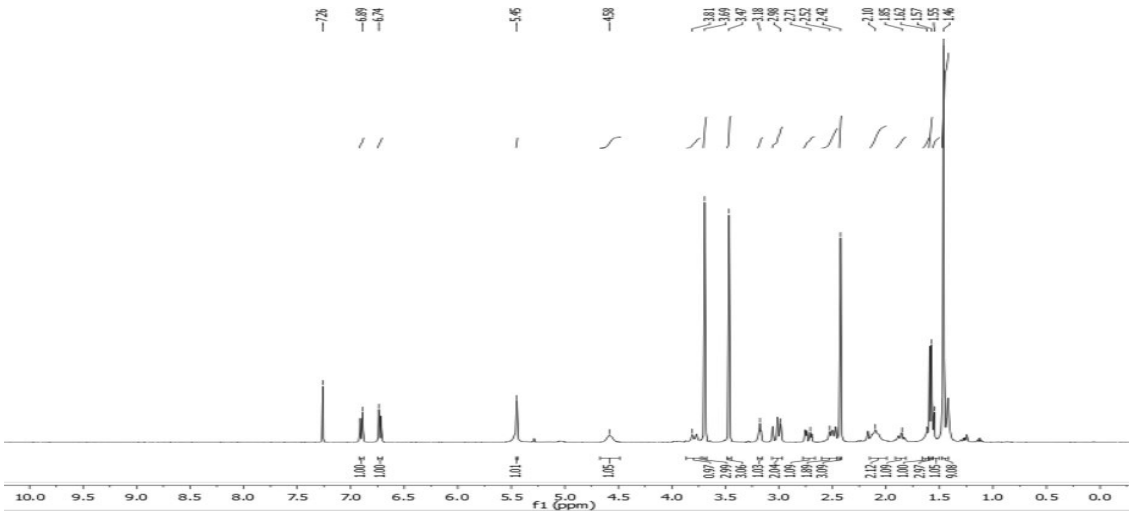

Figure S2. ^{1}H NMR spectrum of compound 1.

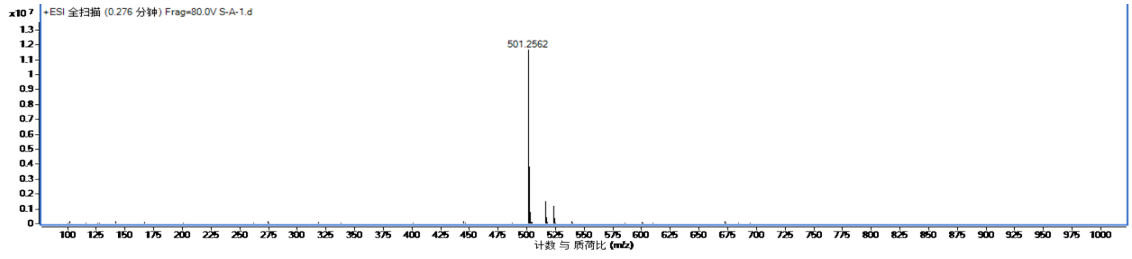

Figure S3. HRMS of compound 1.

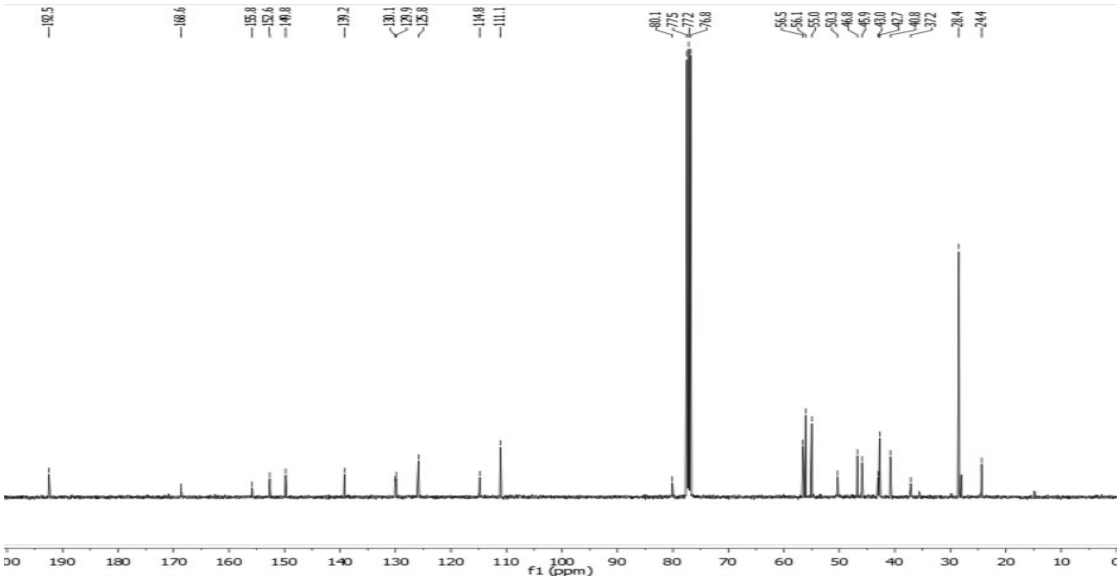

Figure S4. ^{13}C NMR spectrum of compound 2.

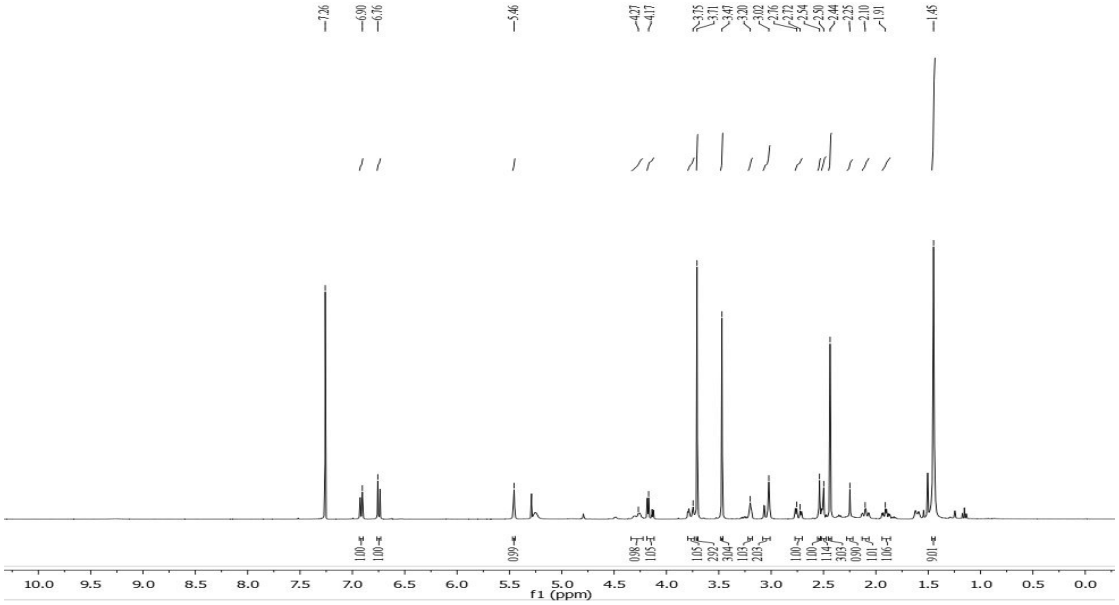

Figure S5. ^{1}H NMR spectrum of compound 2.

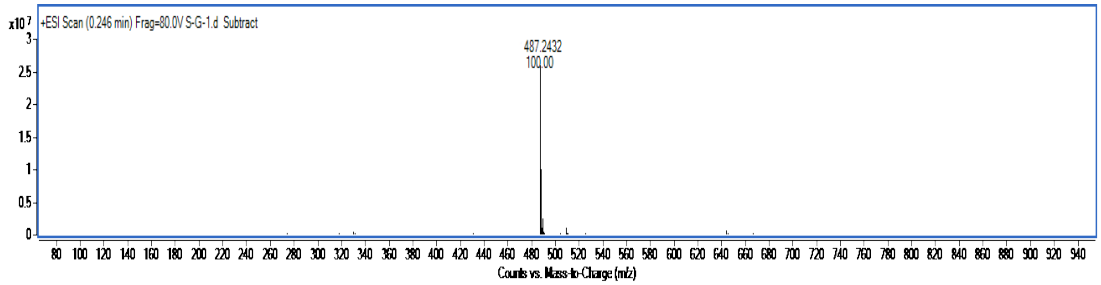

Figure S6. HRMS of compound 2.

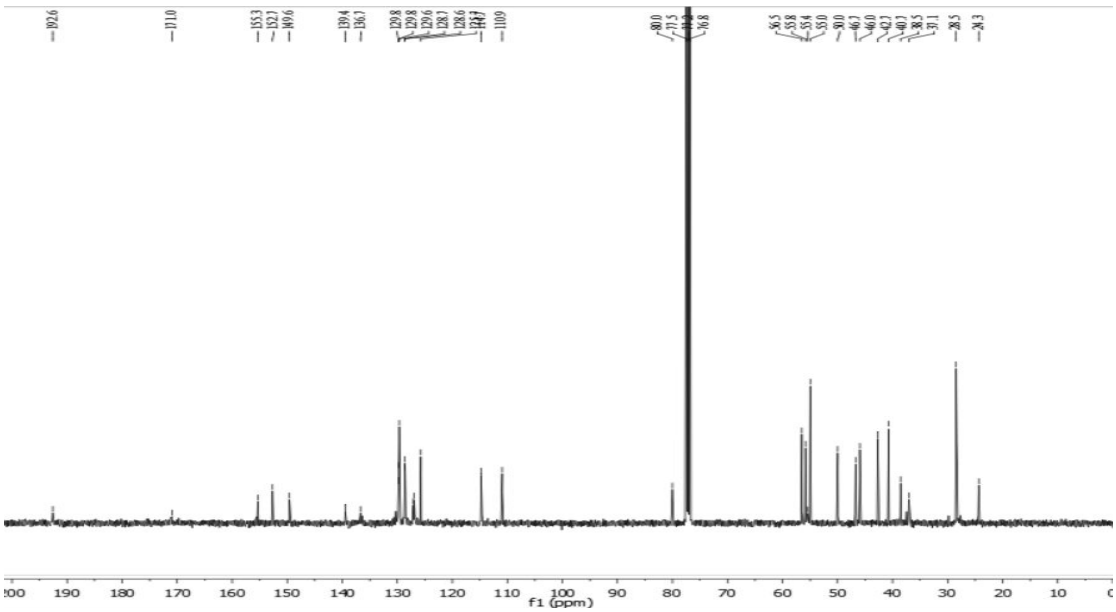

Figure S7. ^{13}C NMR spectrum of compound 3.

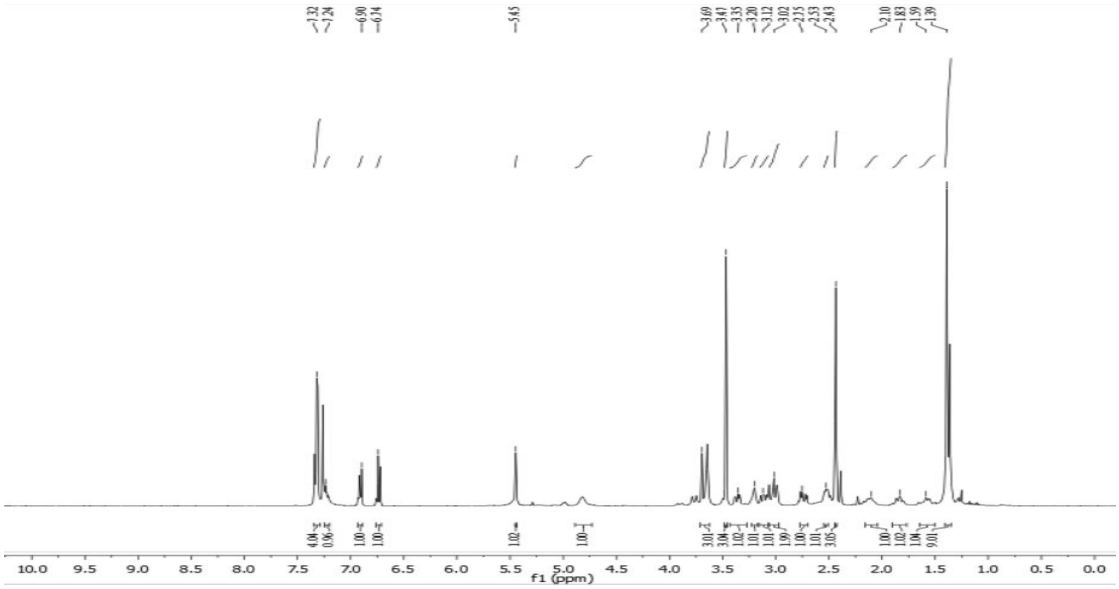

Figure S8. ^{1}H NMR spectrum of compound 3.

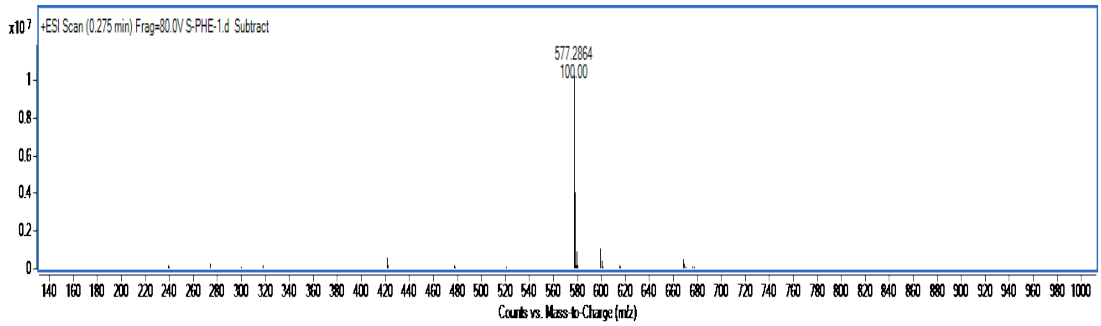

Figure S9. HRMS of compound 3.

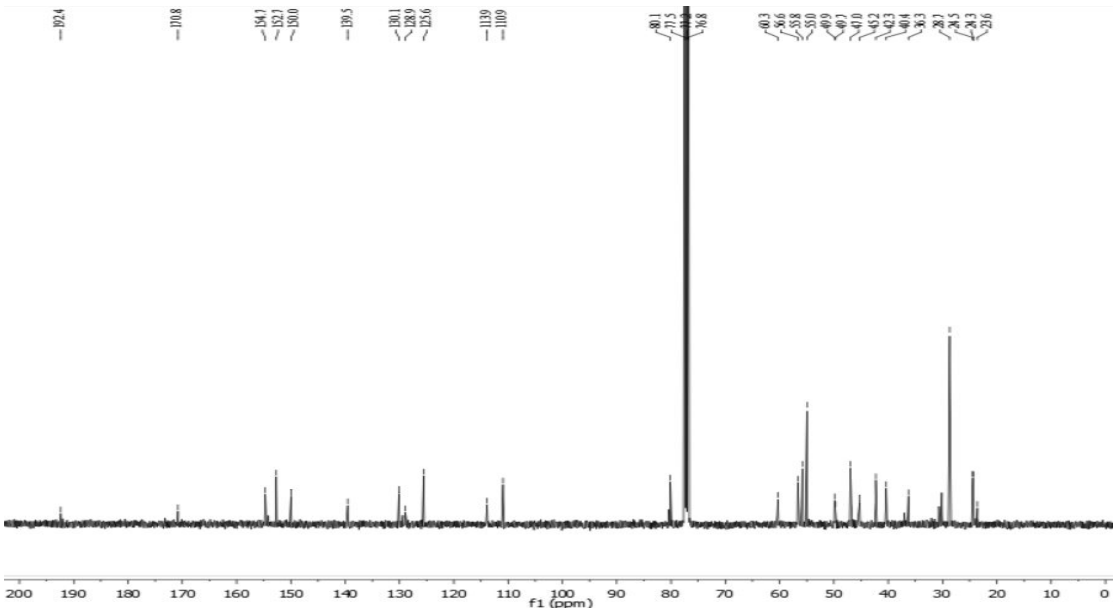

Figure S10. ^{13}C NMR spectrum of compound 4.

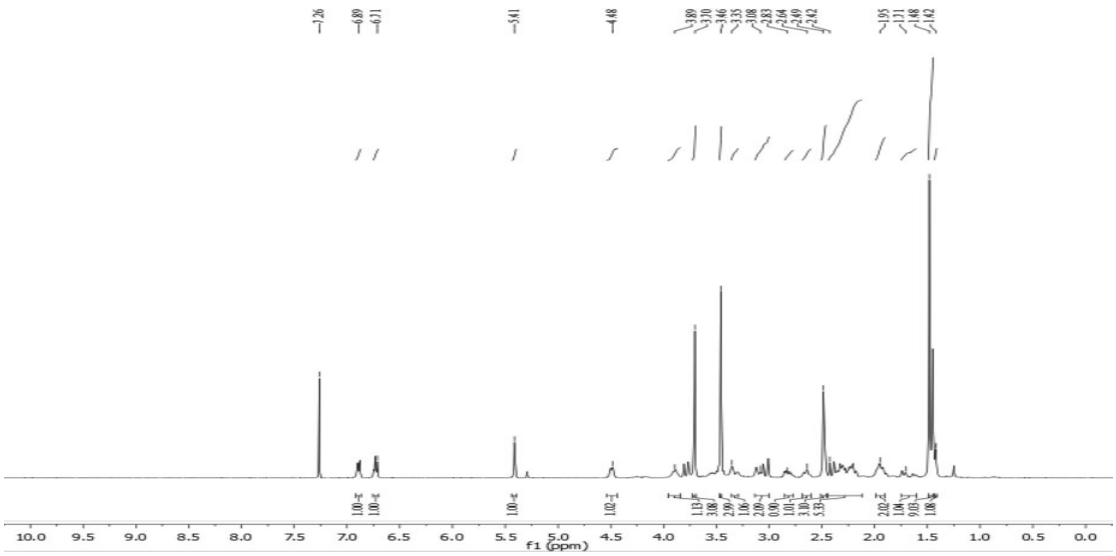

Figure S11. ^{1}H NMR spectrum of compound 4.

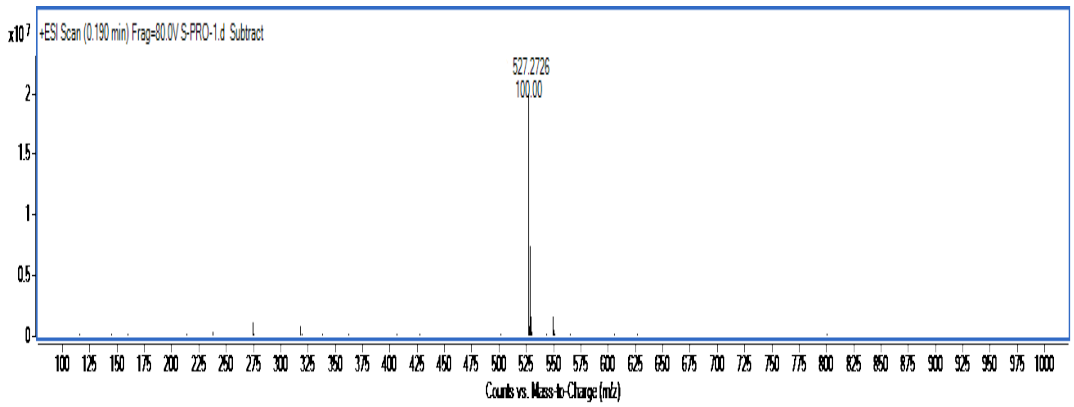

Figure S12. HRMS of compound 4.

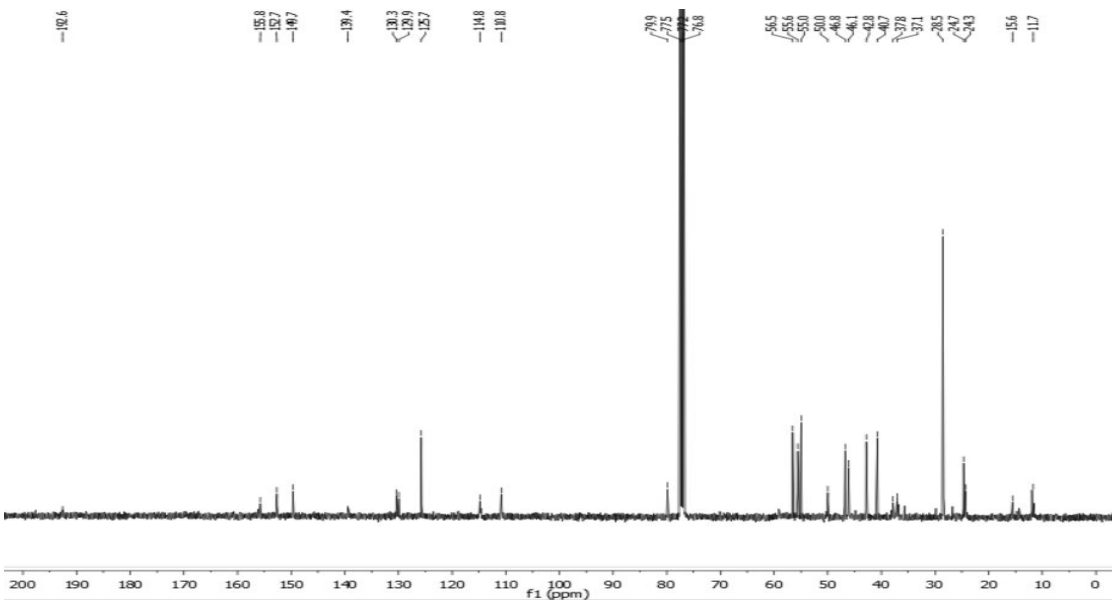

Figure S13. ^{13}C NMR spectrum of compound 5.

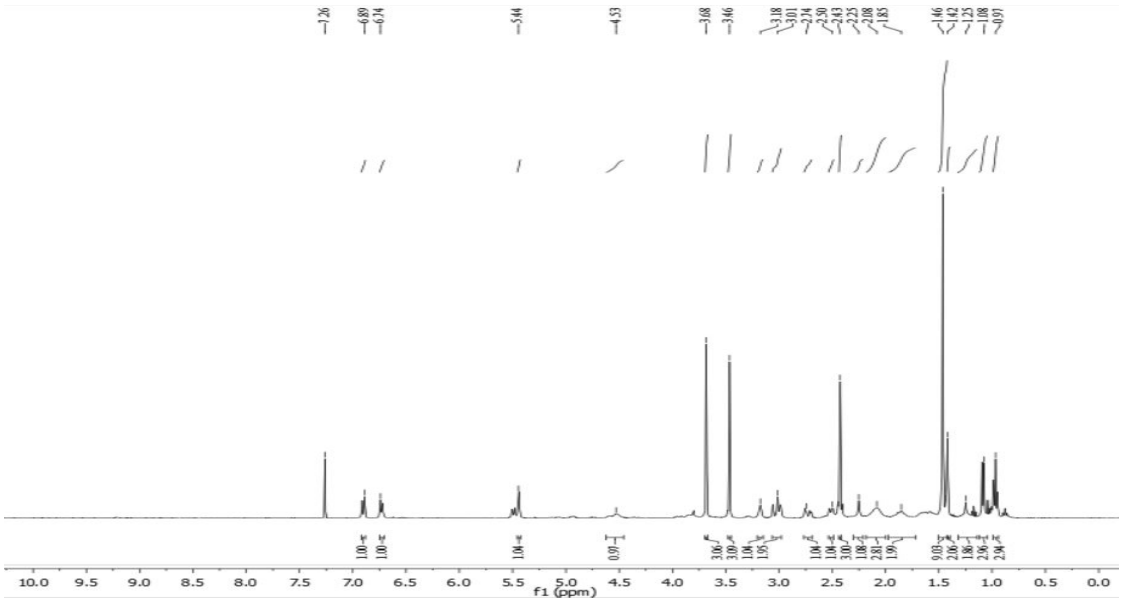

Figure S14. ^{1}H NMR spectrum of compound 5.

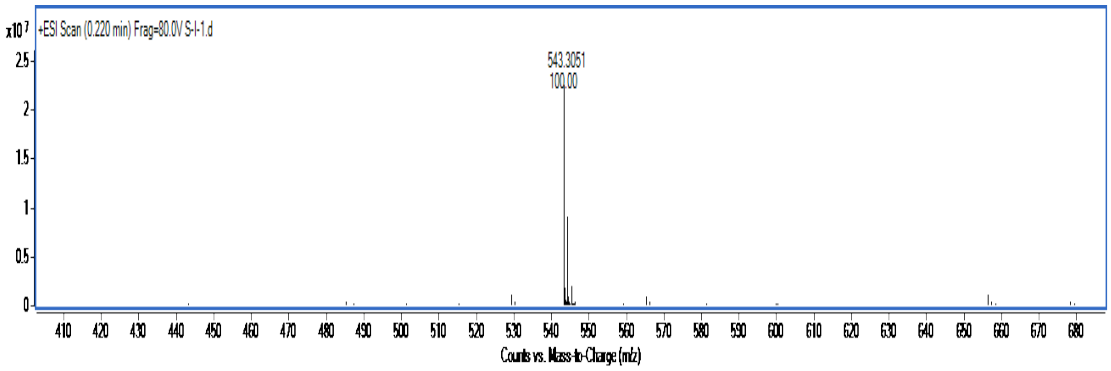

Figure S15. HRMS of compound 5.

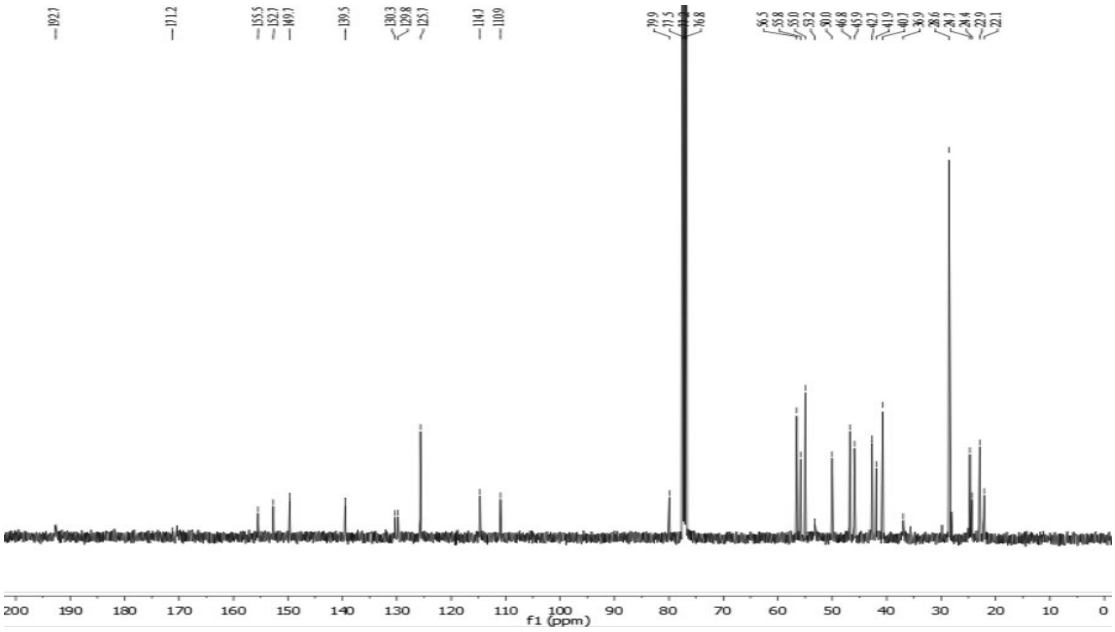

Figure S16. ^{13}C NMR spectrum of compound 6.

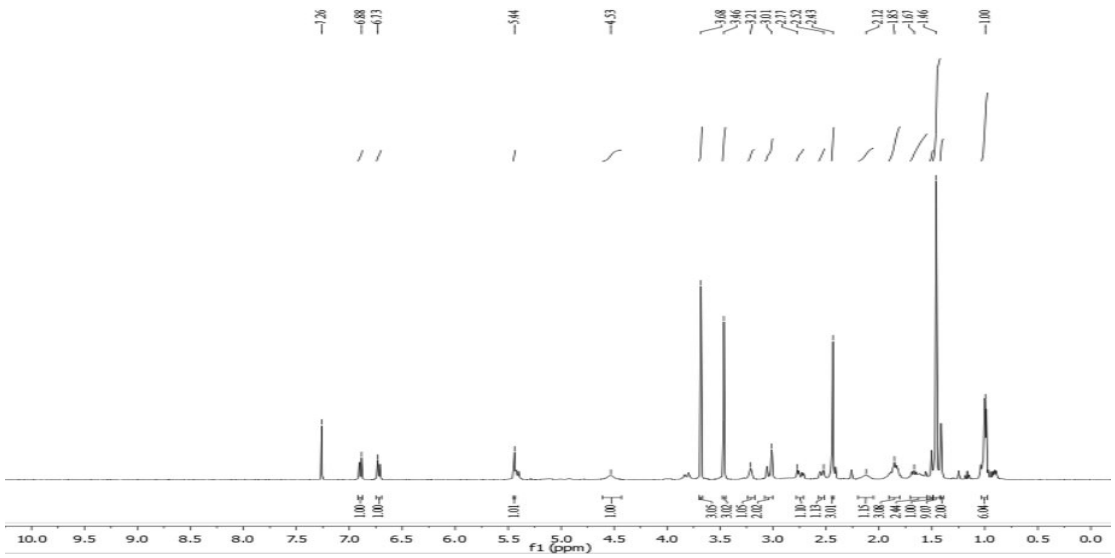

Figure S17. ^{1}H NMR spectrum of compound 6.

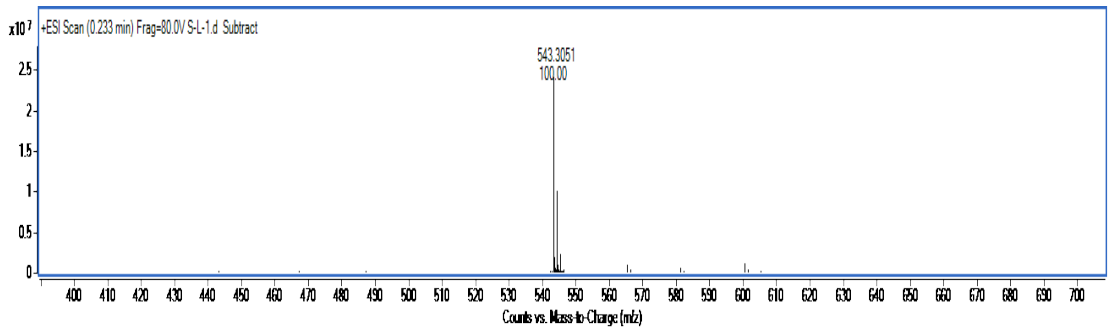

Figure S18. HRMS of compound 6.

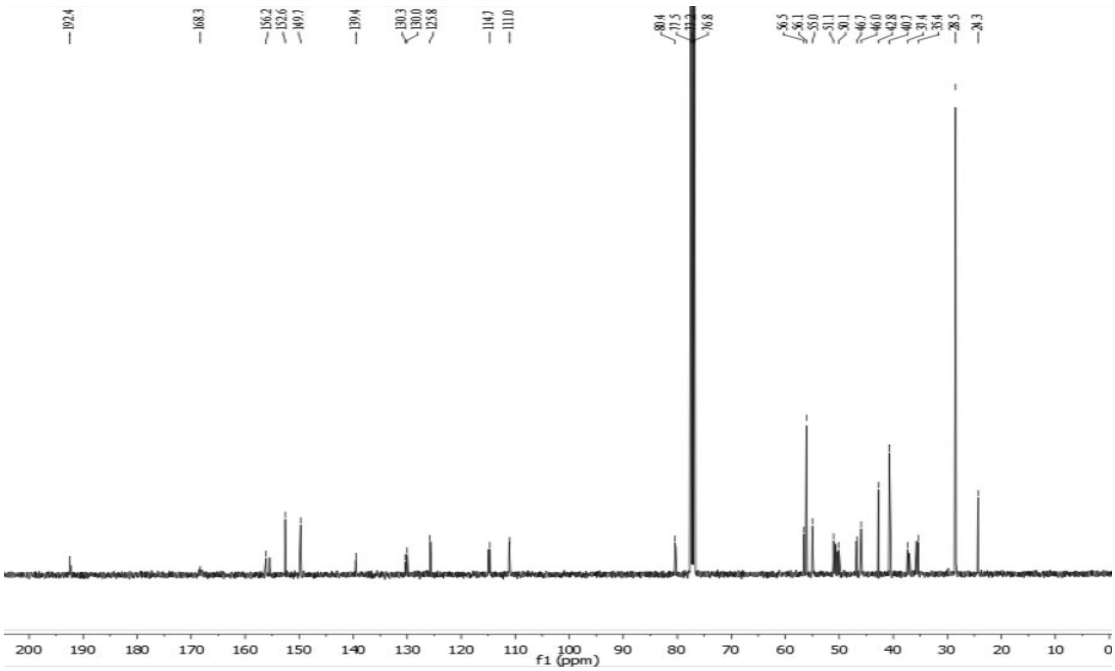

Figure S19. ^{13}C NMR spectrum of compound 7.

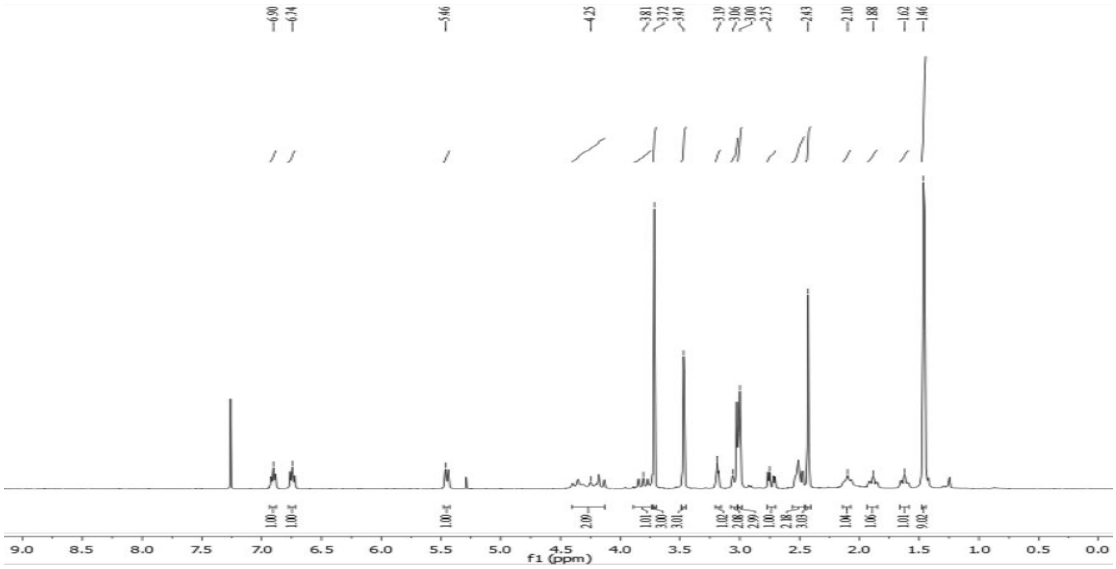

Figure S20. ^{1}H NMR spectrum of compound 7.

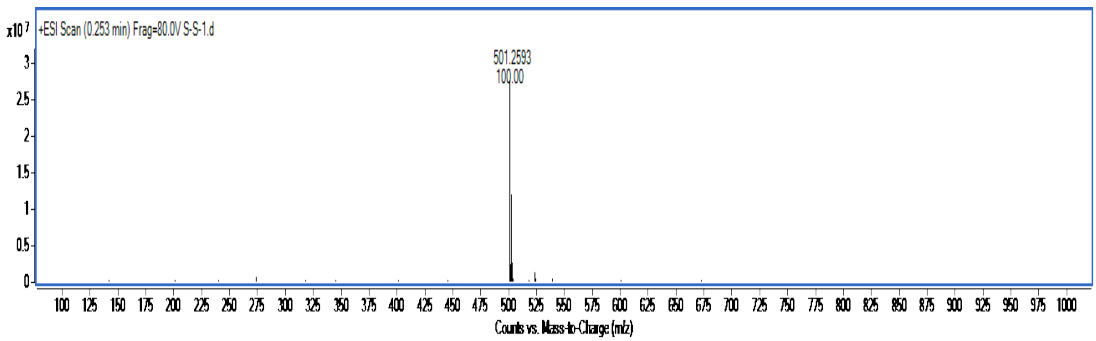

Figure S21. HRMS of compound 7.

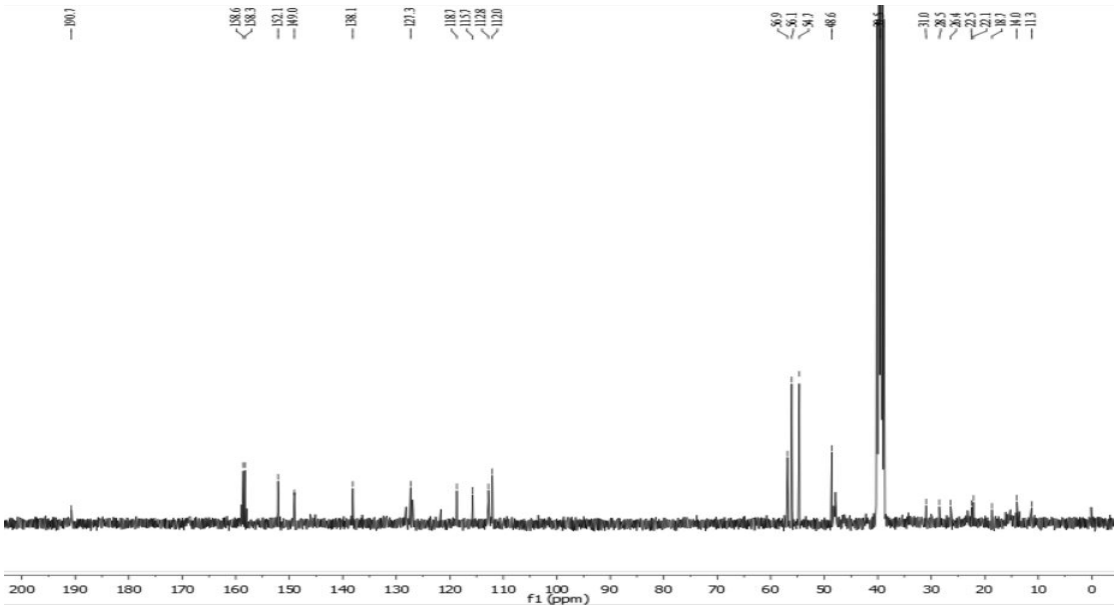

Figure S22. ^{13}C NMR spectrum of compound 8.

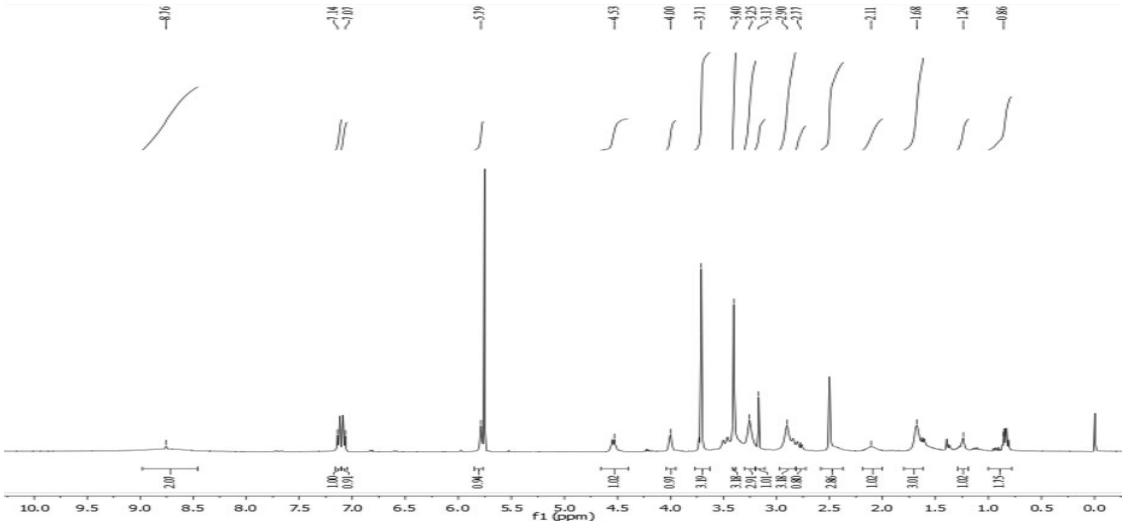

Figure S23. ^{1}H NMR spectrum of compound 8.

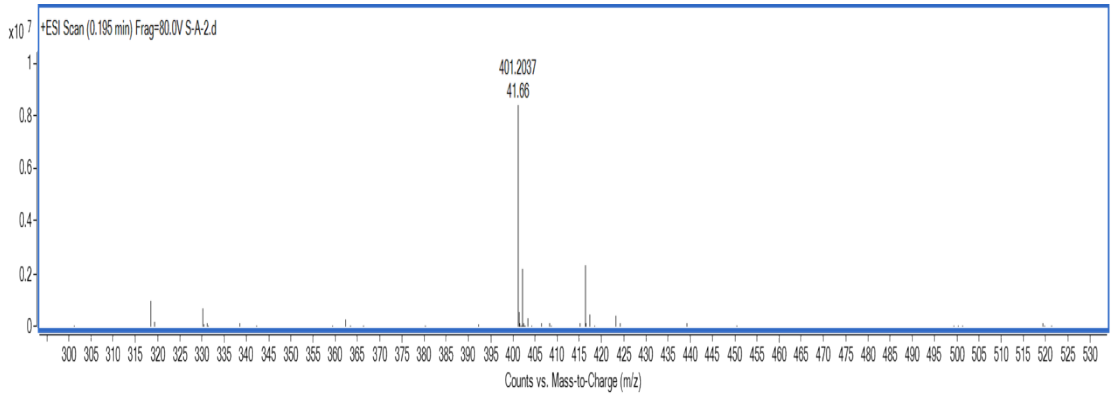

Figure S24. HRMS of compound 8.

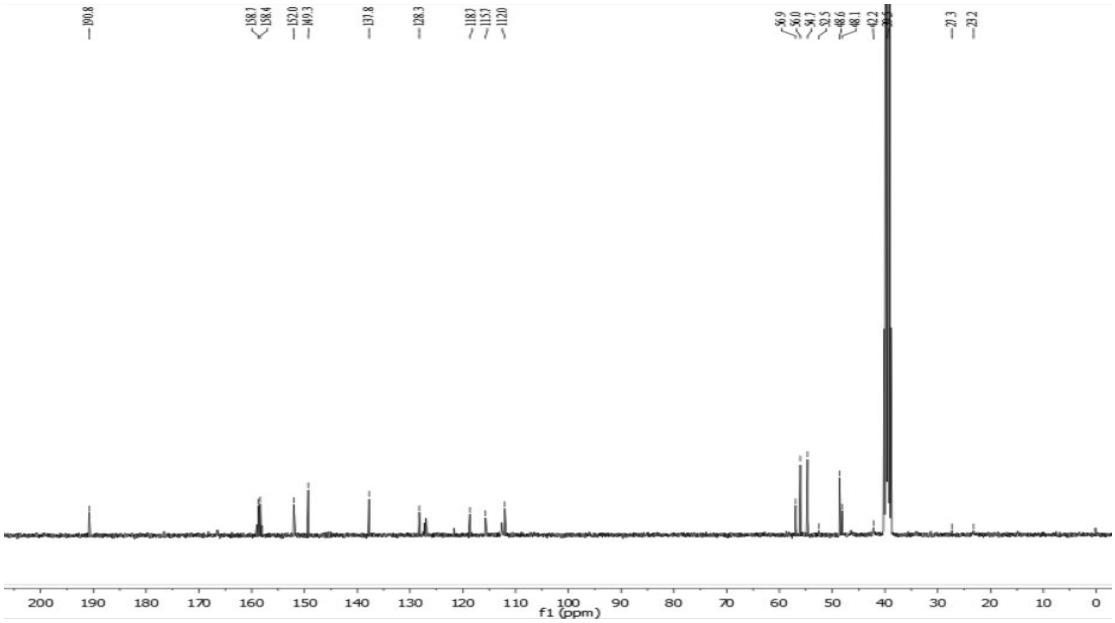

Figure S25. ^{13}C NMR spectrum of compound 9.

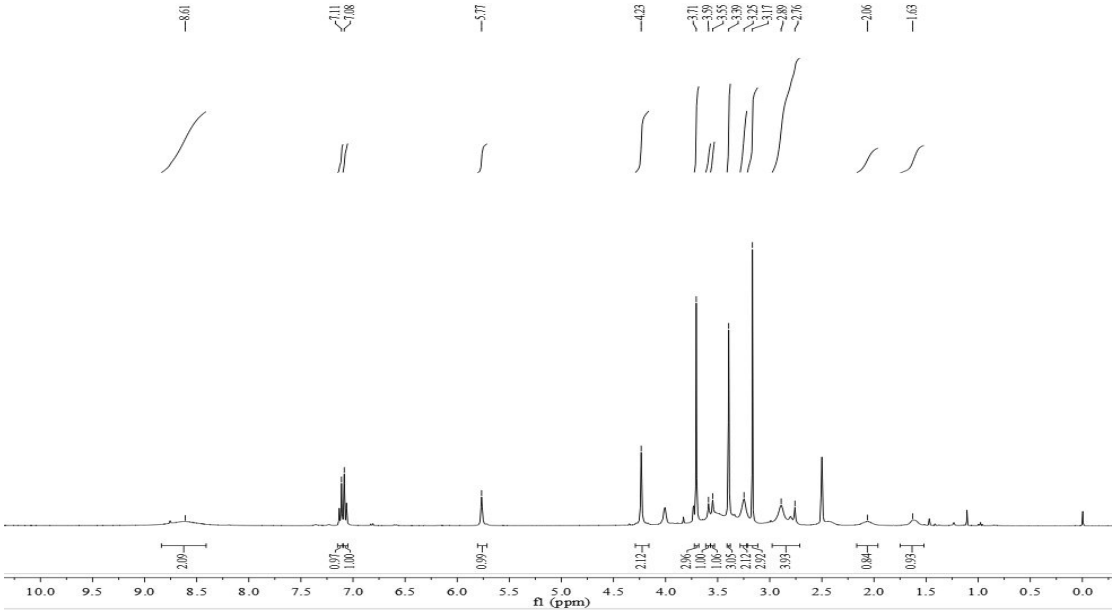

Figure S26. ^{1}H NMR spectrum of compound 9.

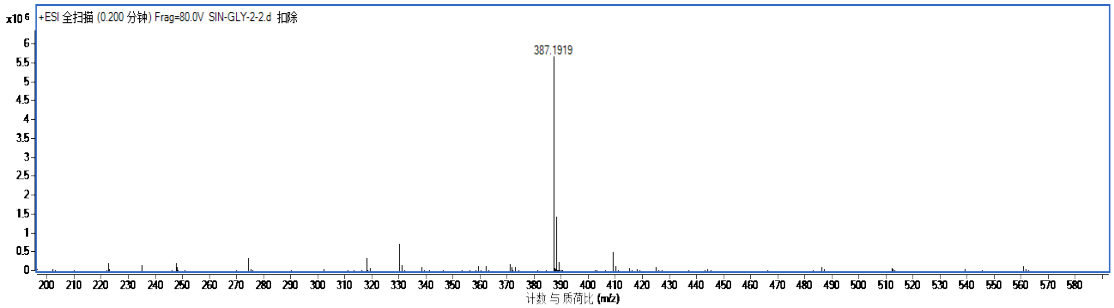

Figure S27. HRMS of compound 9.

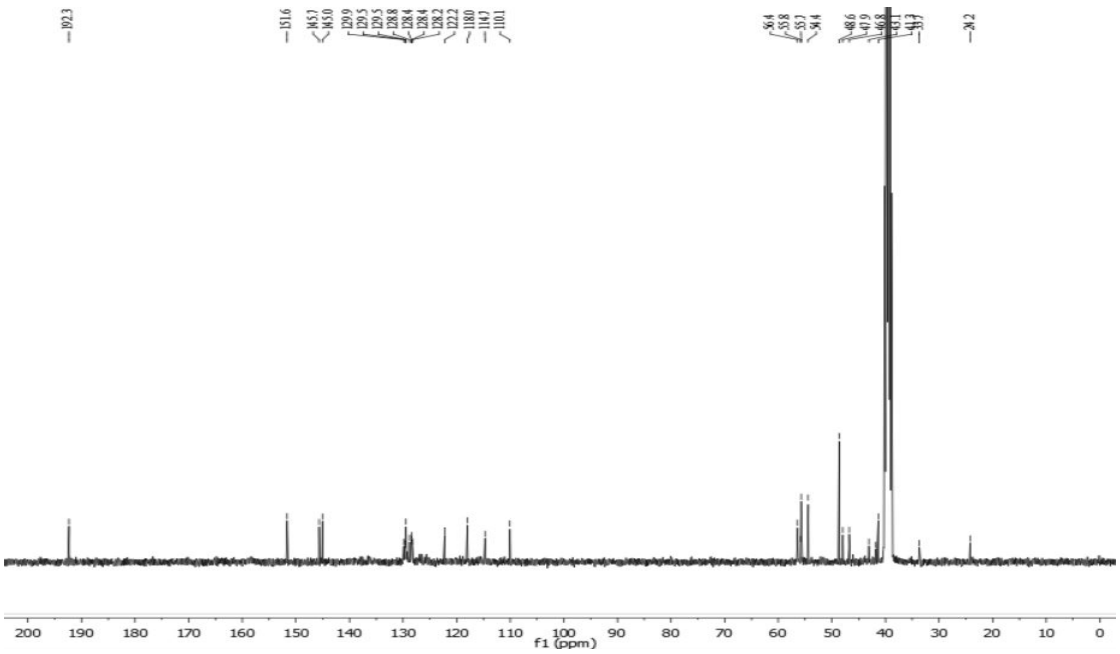

Figure S28. ^{13}C NMR spectrum of compound 10.

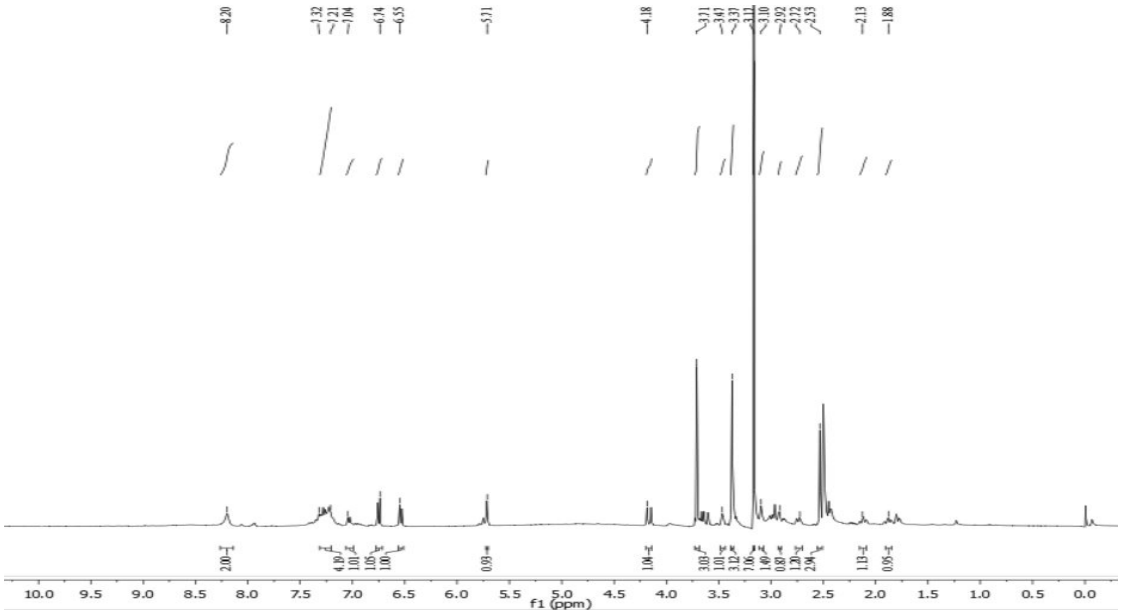

Figure S29. ^{1}H NMR spectrum of compound 10.

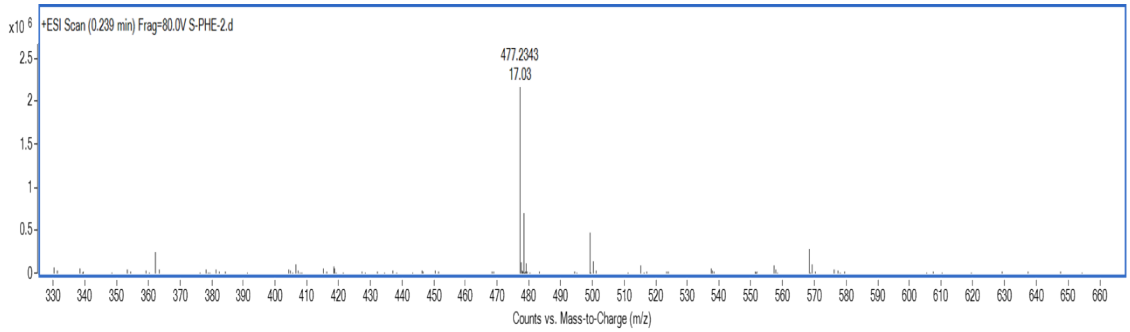

Figure S30. HRMS of compound 10.

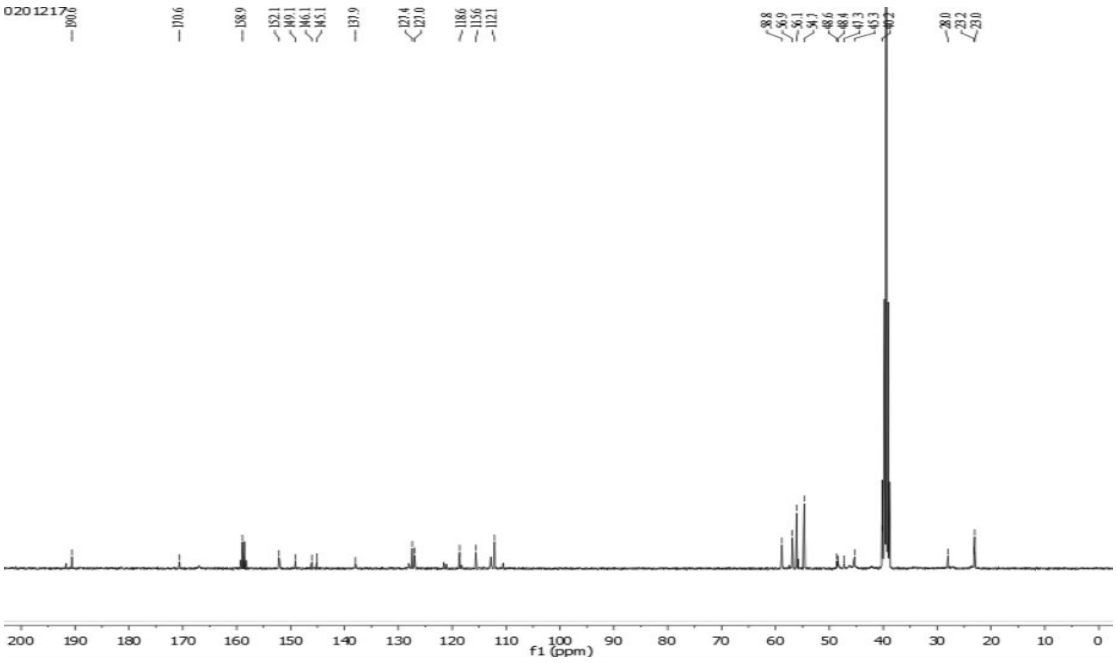

Figure S31. ^{13}C NMR spectrum of compound 11.

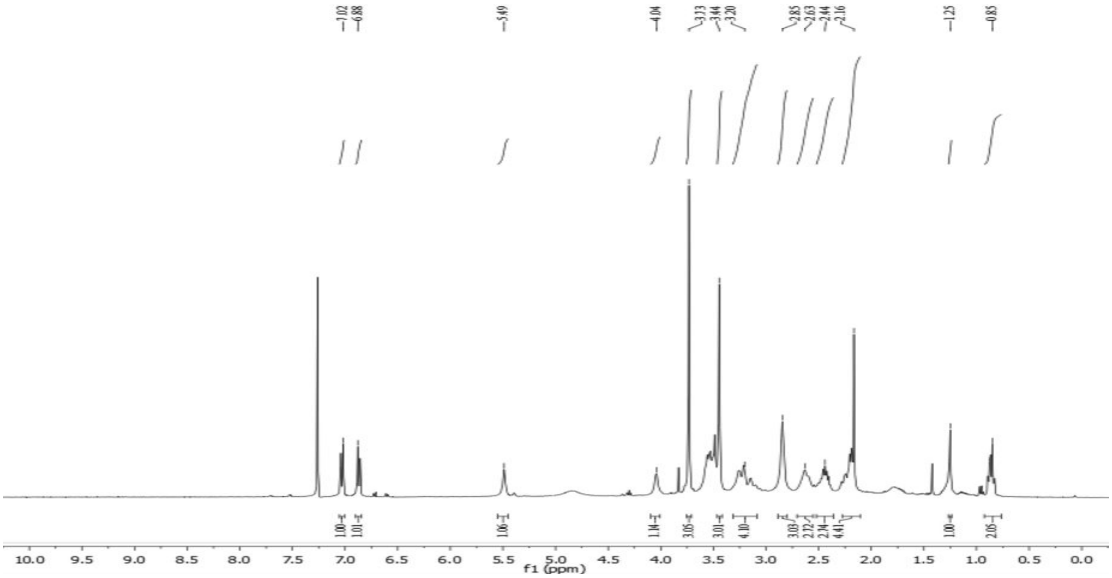

Figure S32. ^{1}H NMR spectrum of compound 11.

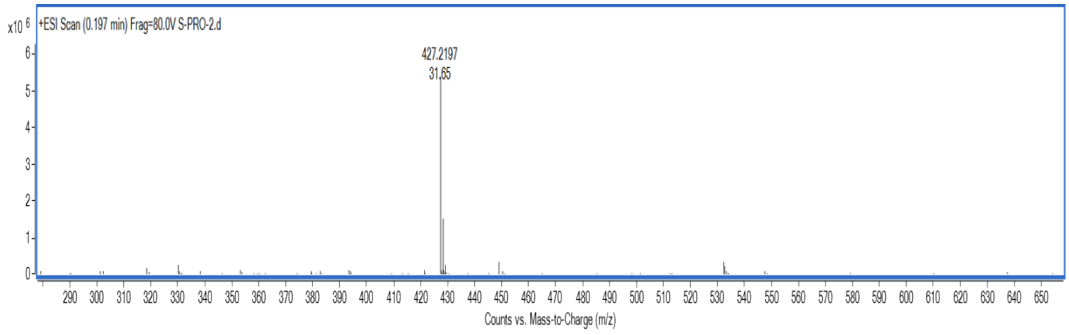

Figure S33. HRMS of compound 11.

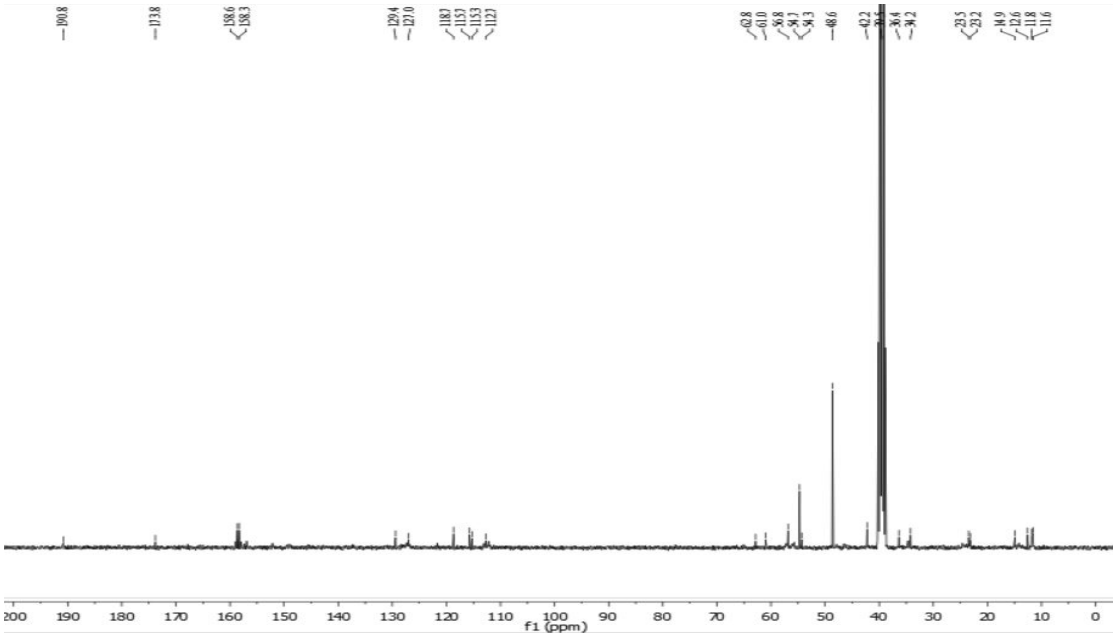

Figure S34. ^{13}C NMR spectrum of compound 12.

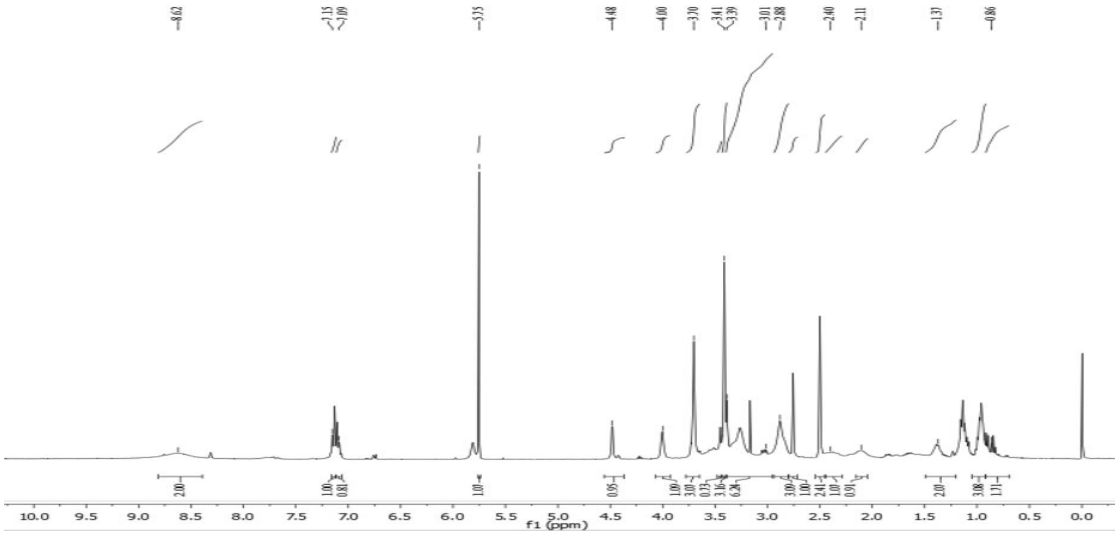

Figure S35. ^{1}H NMR spectrum of compound 12.

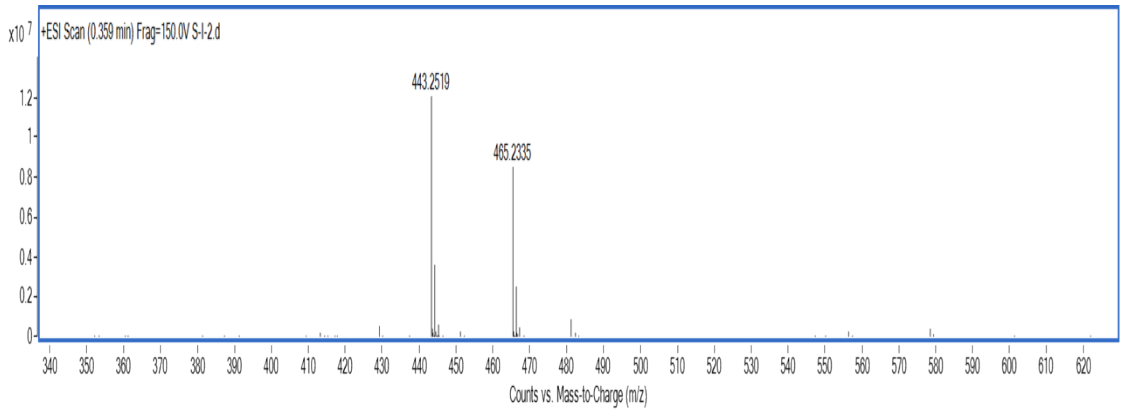

Figure S36. HRMS of compound 12.

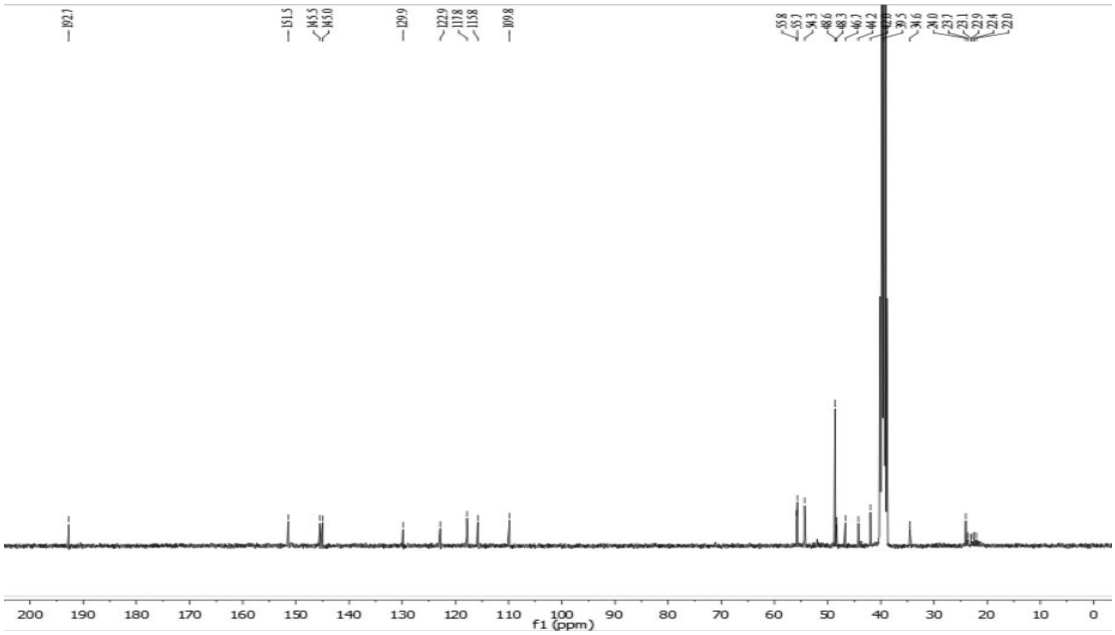

Figure S37. ^{13}C NMR spectrum of compound 13.

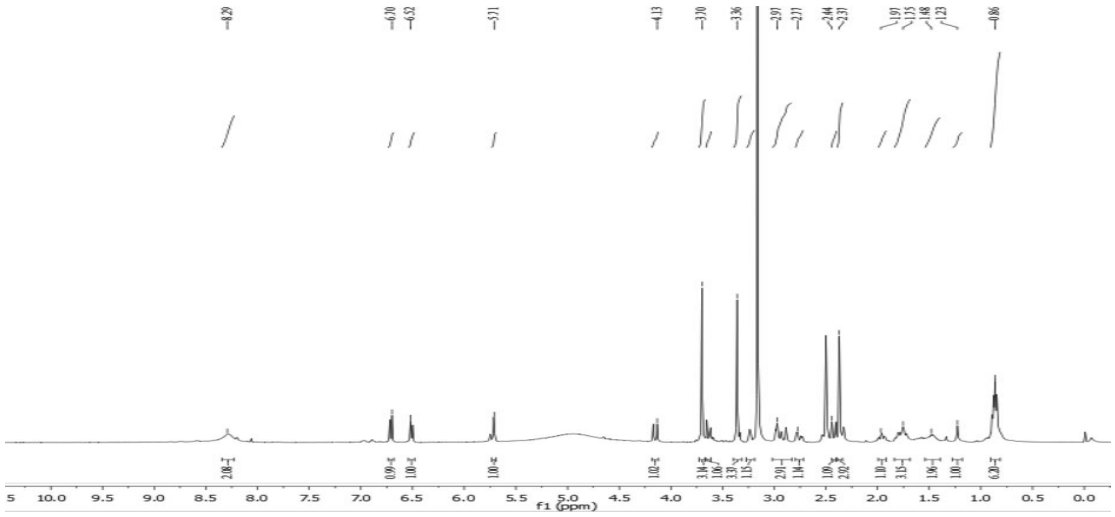

Figure S38. ^{1}H NMR spectrum of compound 13.

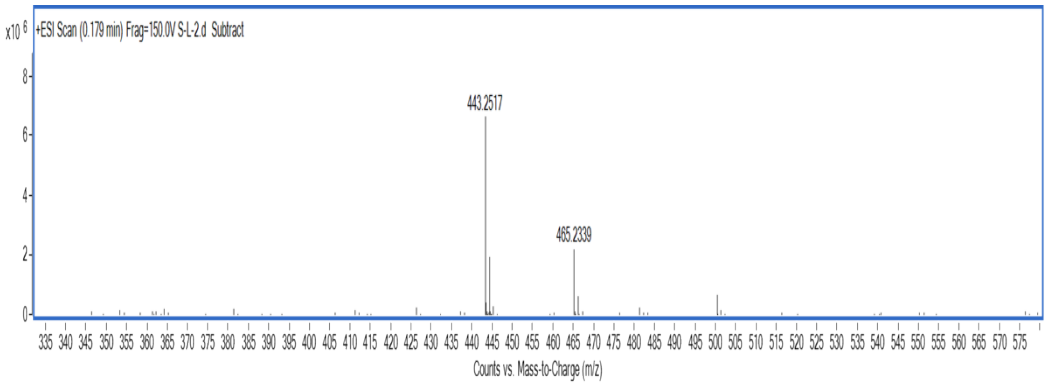

Figure S39. HRMS of compound 13.

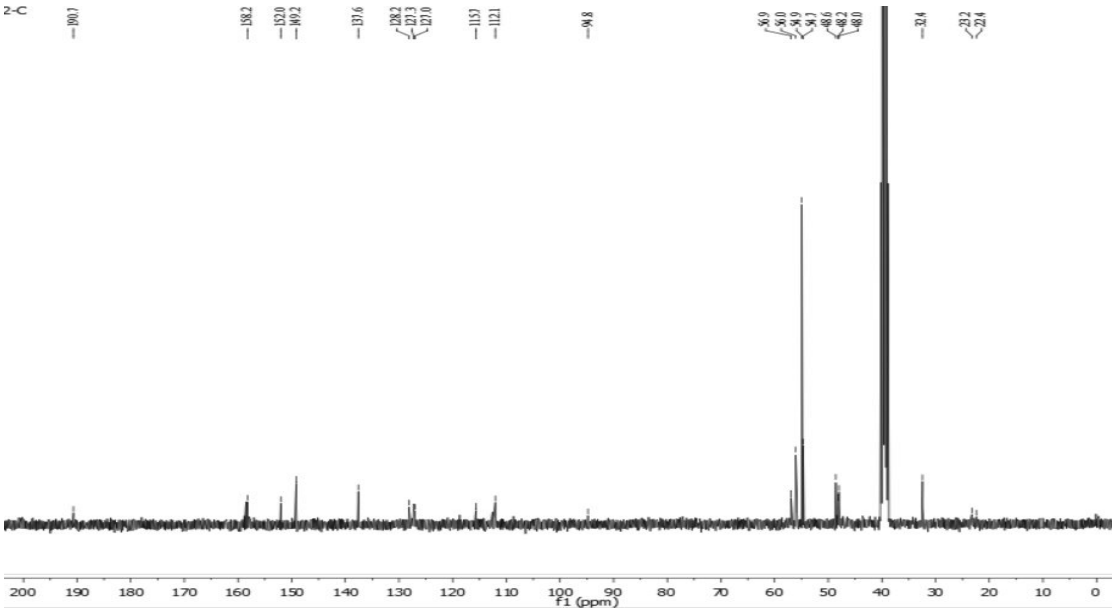

Figure S40. ^{13}C NMR spectrum of compound 14.

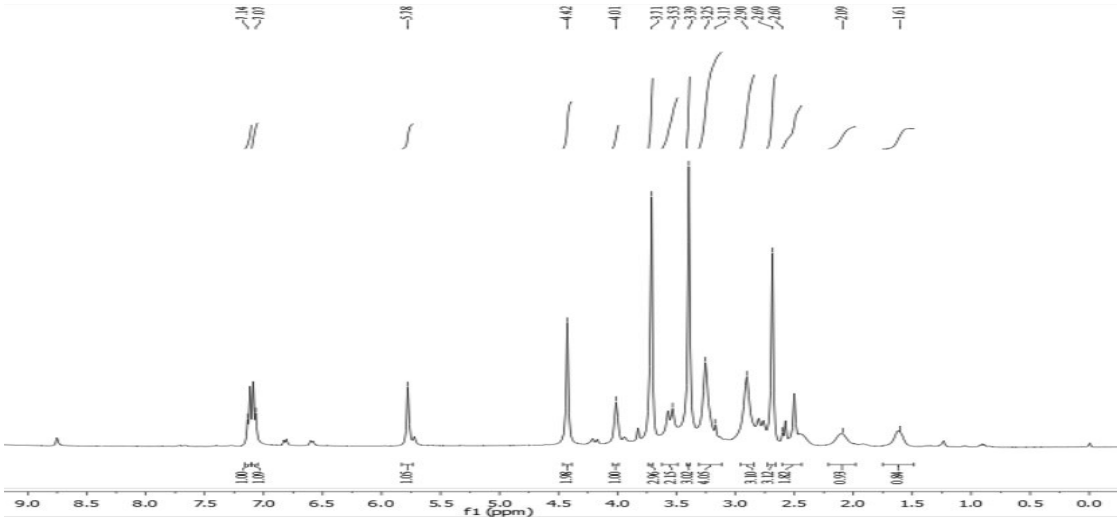

Figure S41. ^{1}H NMR spectrum of compound 14.

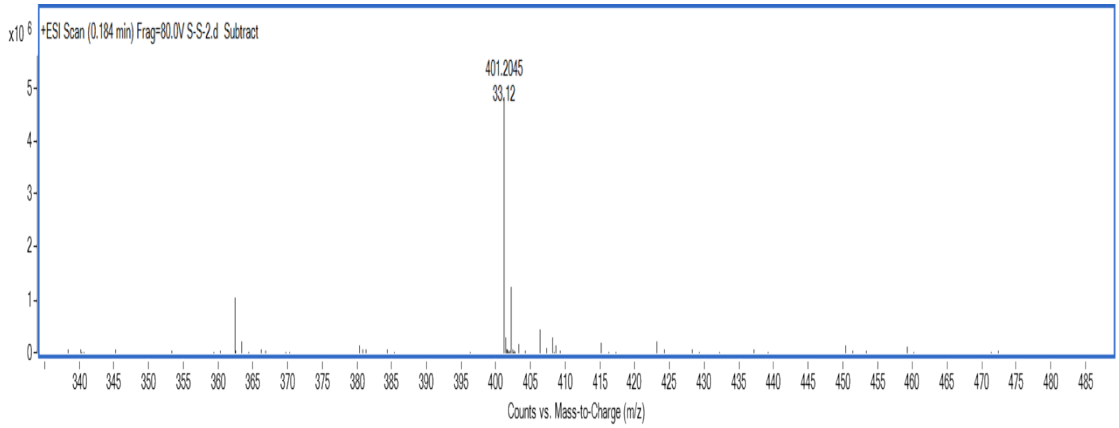

Figure S42. HRMS of compound 14.

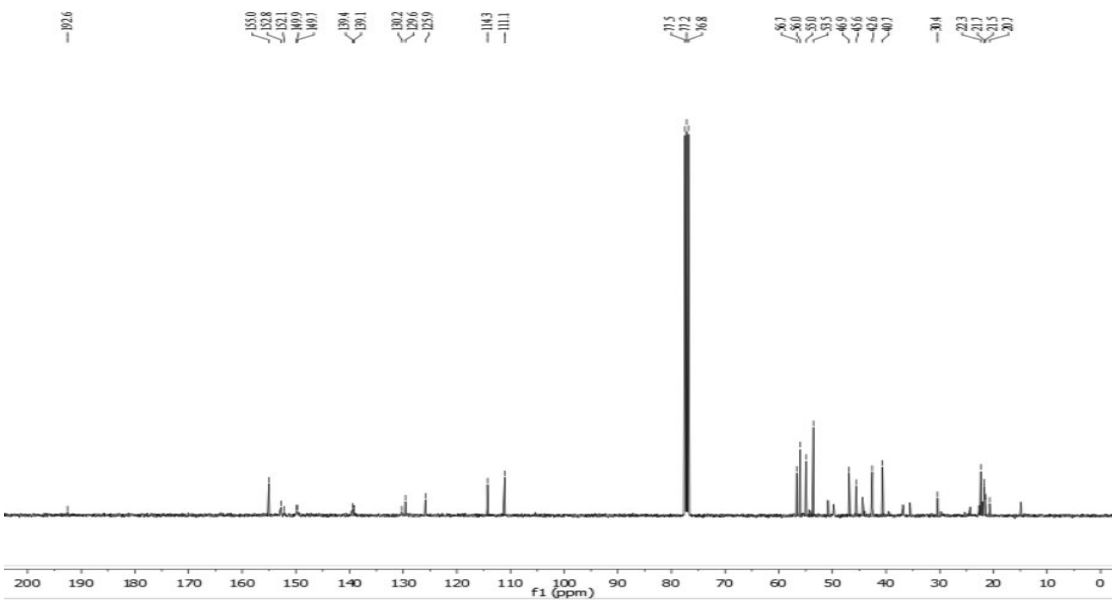

Figure S43. ^{13}C NMR spectrum of compound 15.

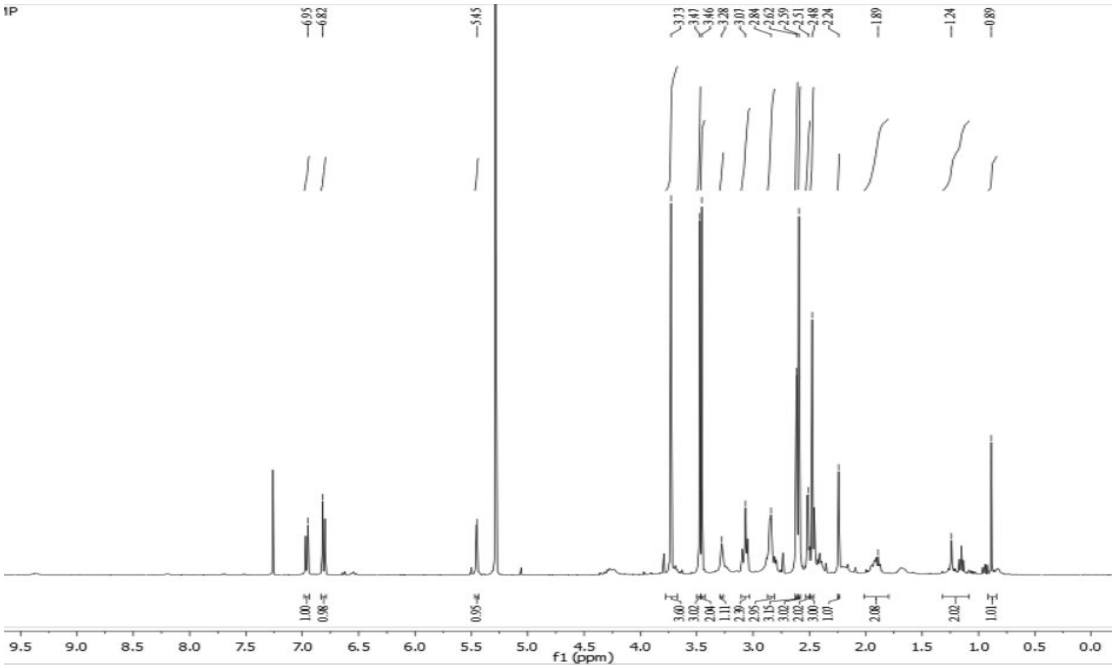

Figure S44. ^{1}H NMR spectrum of compound 15.

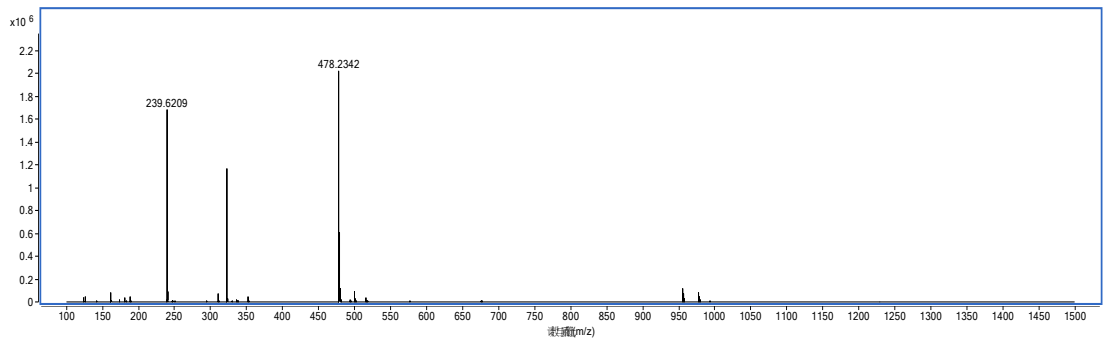

Figure S45. HRMS of compound 15.

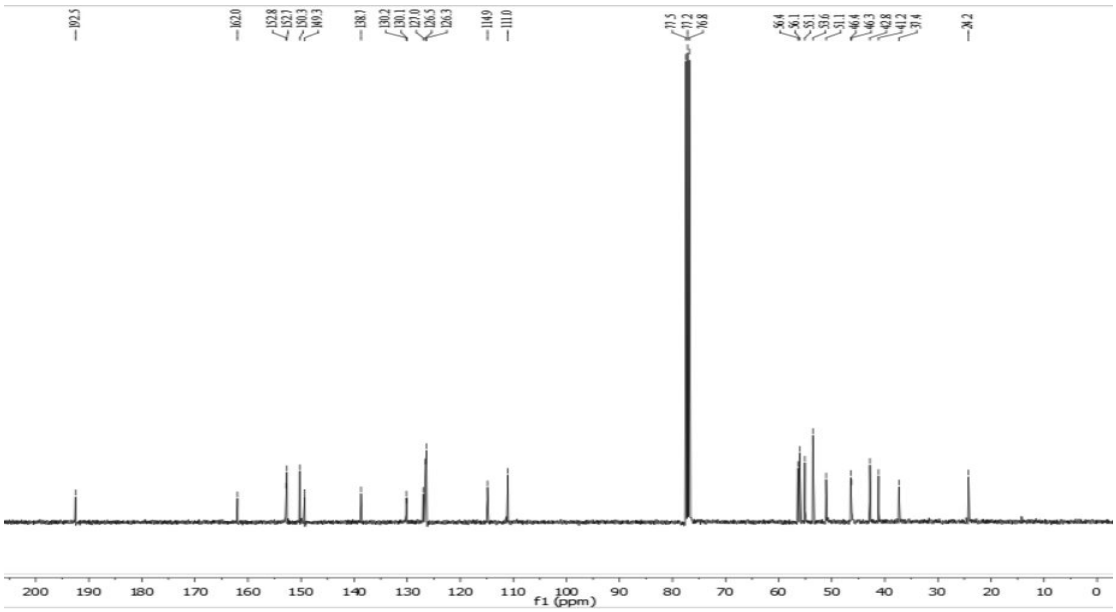

Figure S46. ^{13}C NMR spectrum of compound 16.

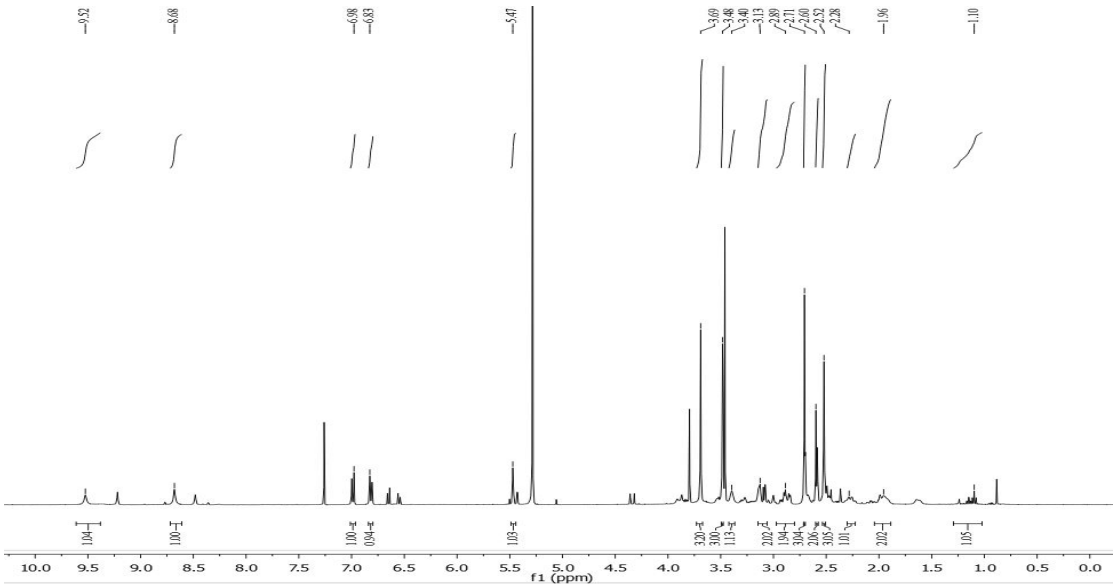

Figure S47. ^{1}H NMR spectrum of compound 16.

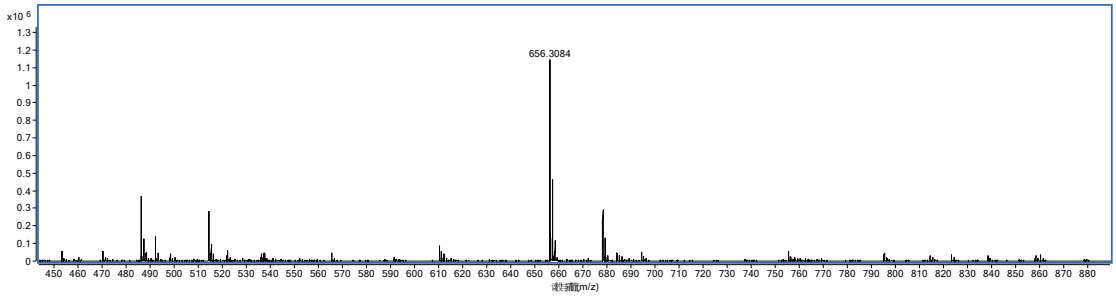

Figure S48. HRMS of compound 16.

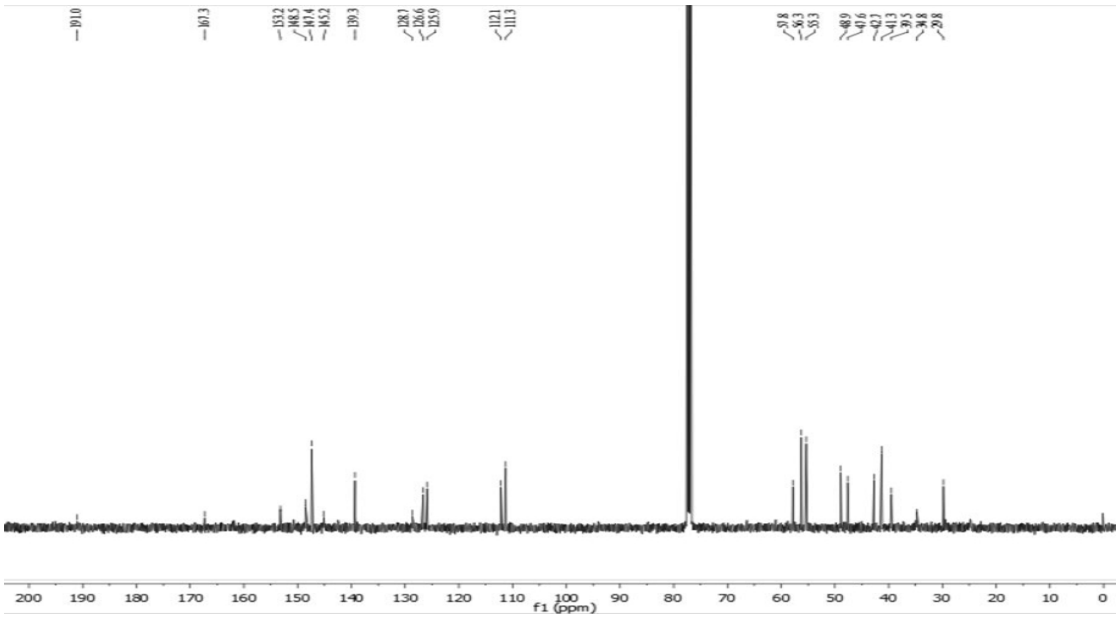

Figure S49. ^{13}C NMR spectrum of compound 17.

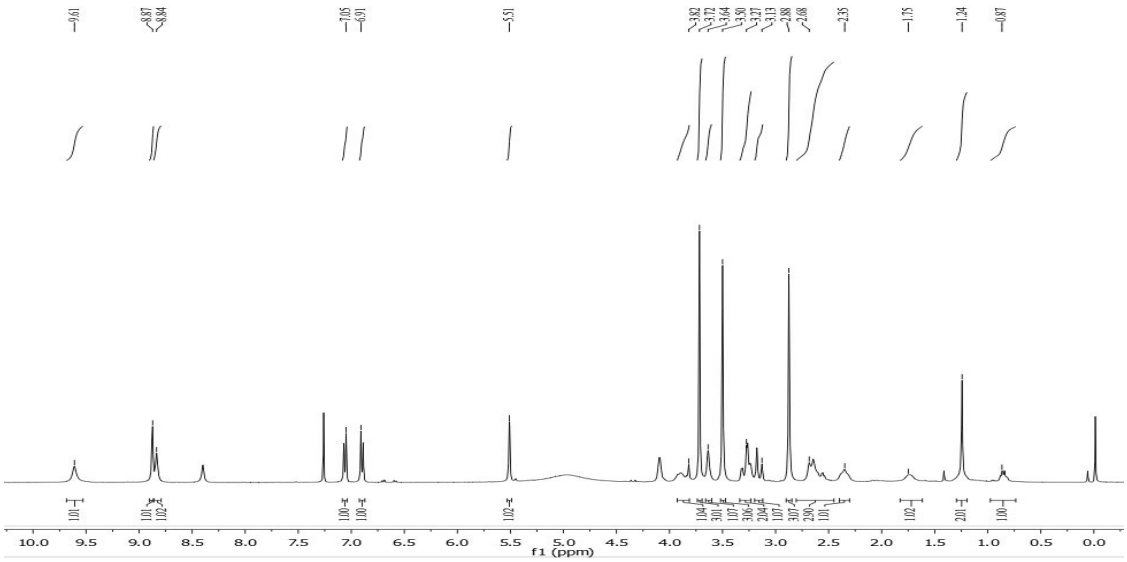

Figure S50. ^{1}H NMR spectrum of compound 17.

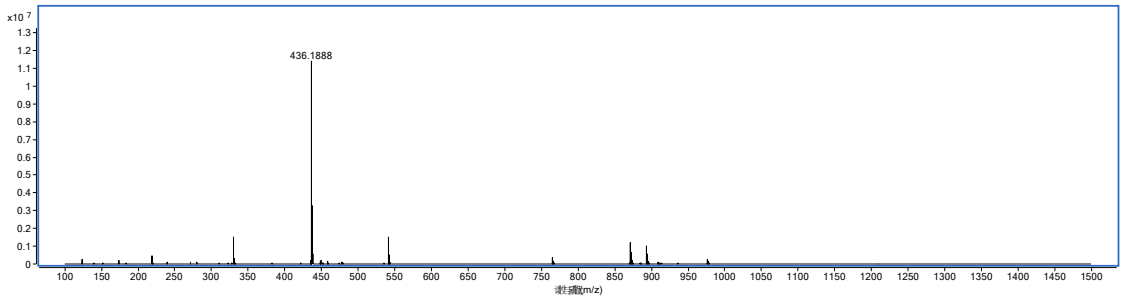

Figure S51. HRMS of compound 17.

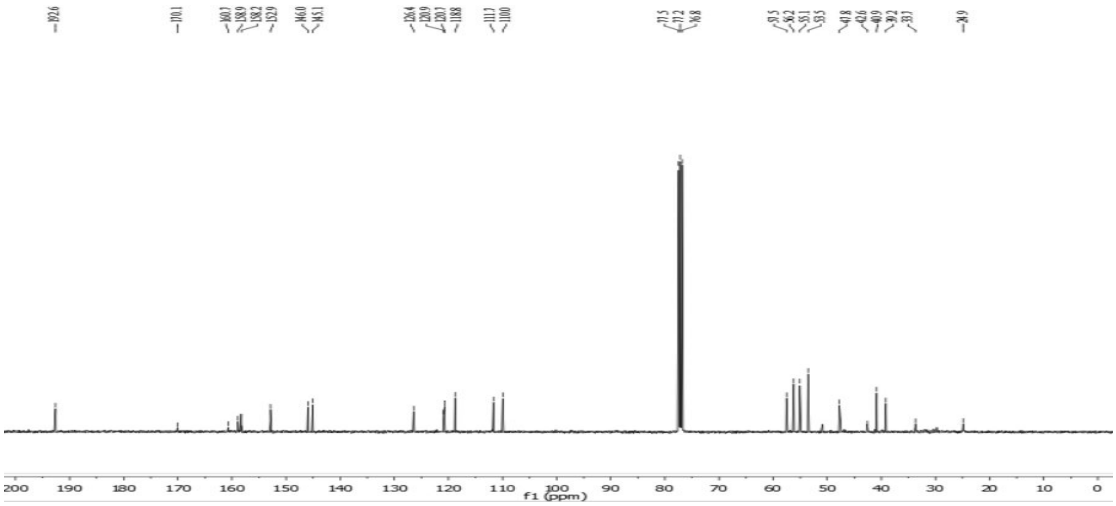

Figure S52. ^{13}C NMR spectrum of compound 18.

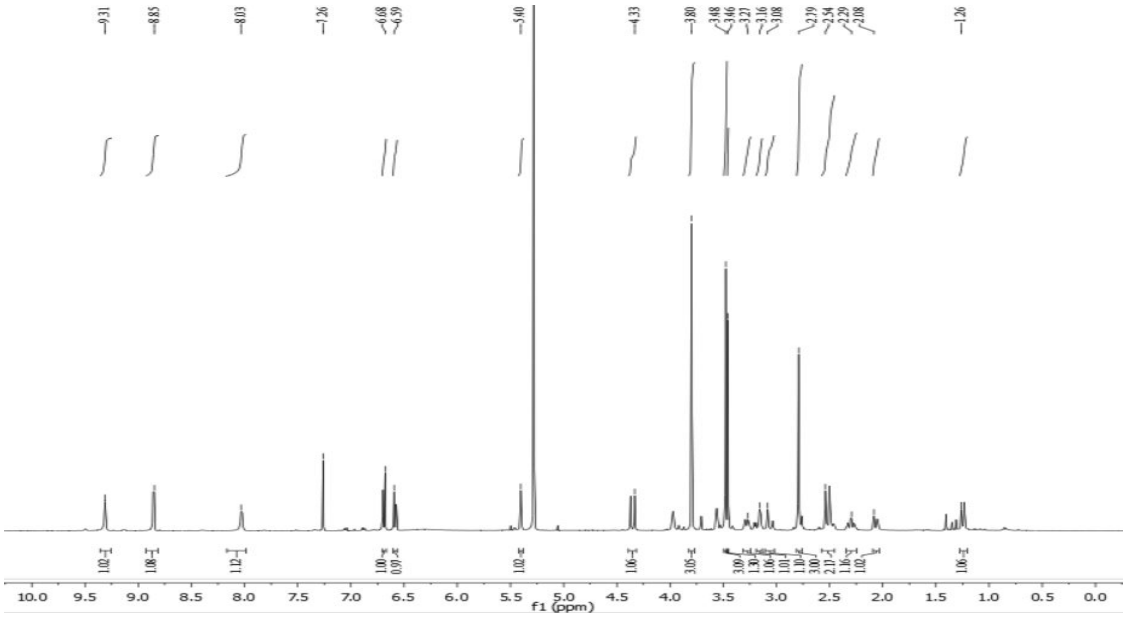

Figure S53. ^{1}H NMR spectrum of compound 18.

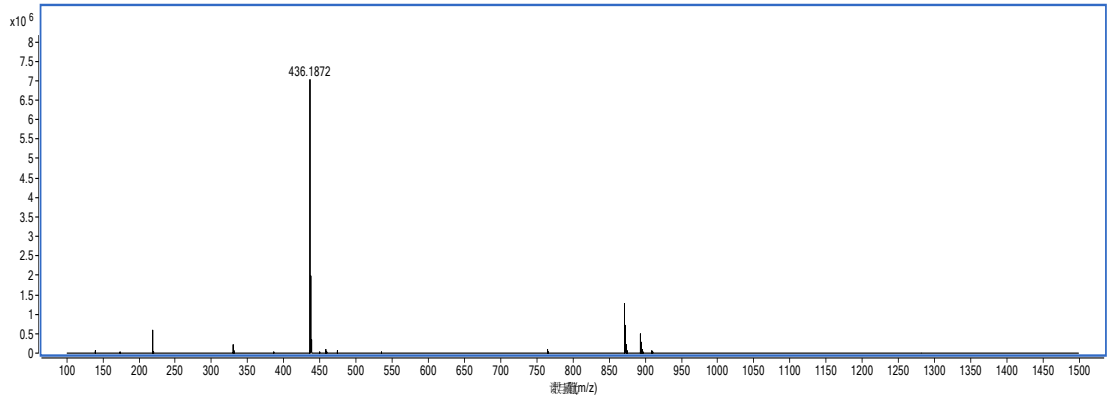

Figure S54. HRMS of compound 18.

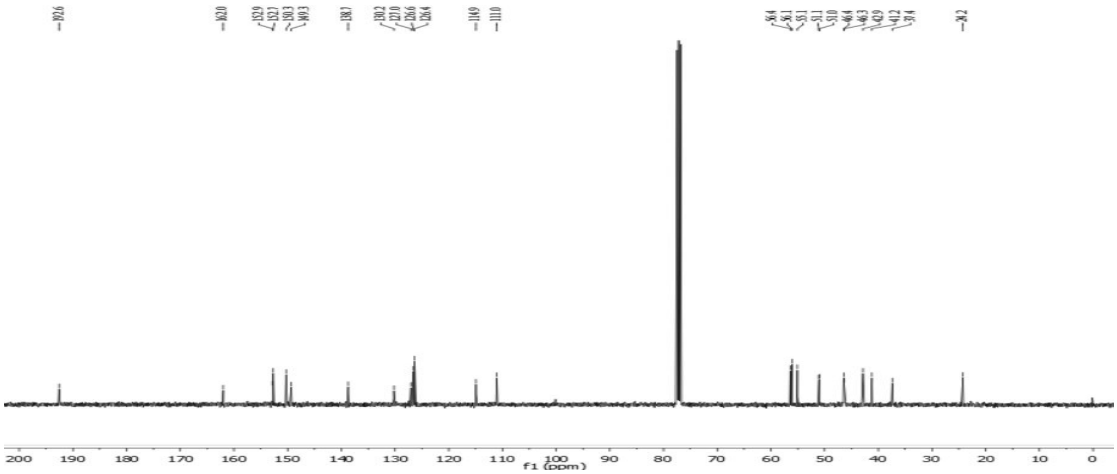

Figure S55. ^{13}C NMR spectrum of compound 19.

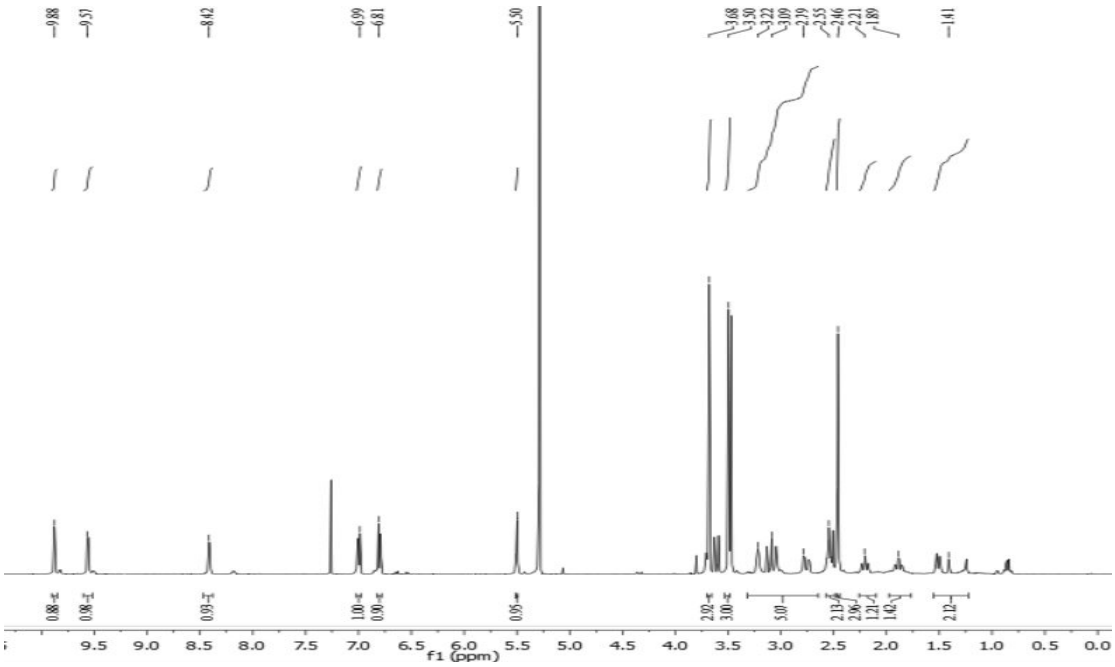

Figure S56. ^{1}H NMR spectrum of compound 19.

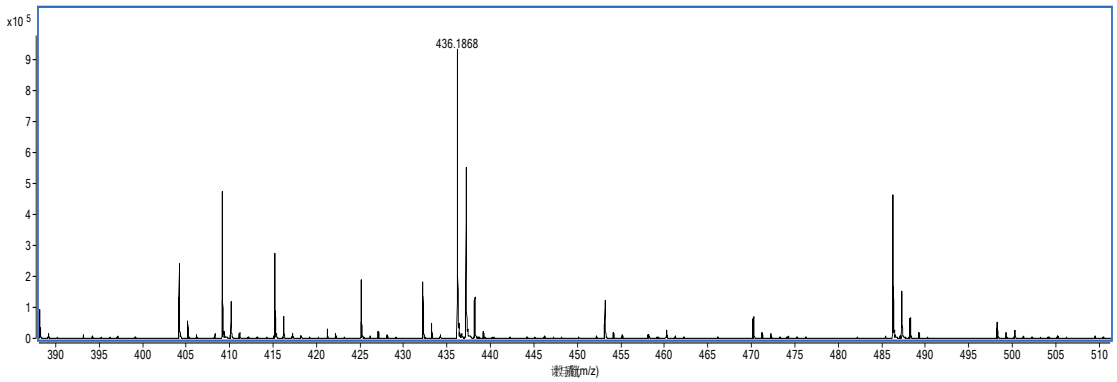

Figure S57. HRMS of compound 19.

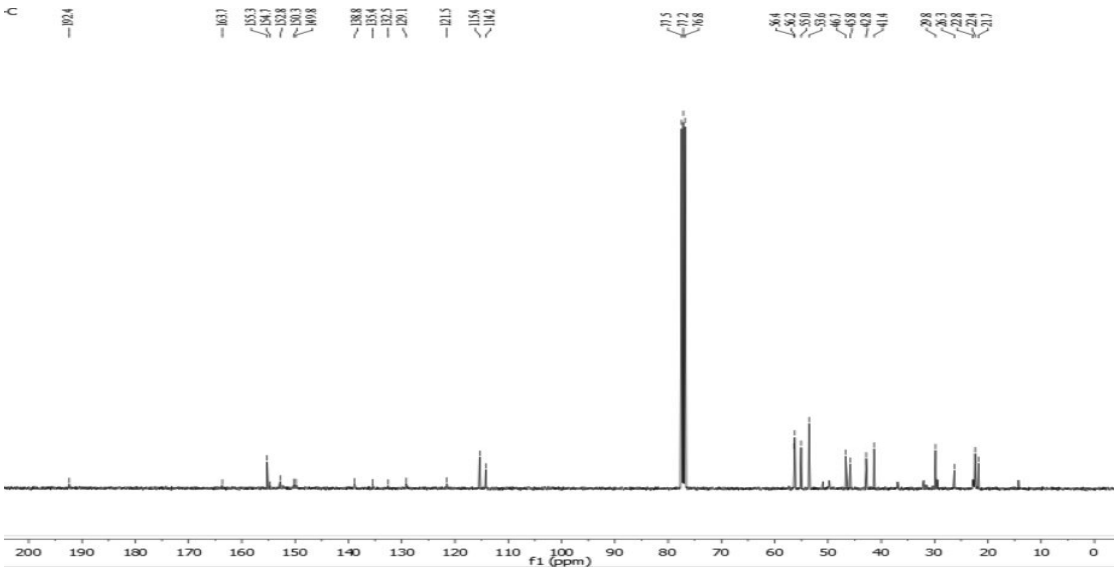

Figure S58. ^{13}C NMR spectrum of compound 20.

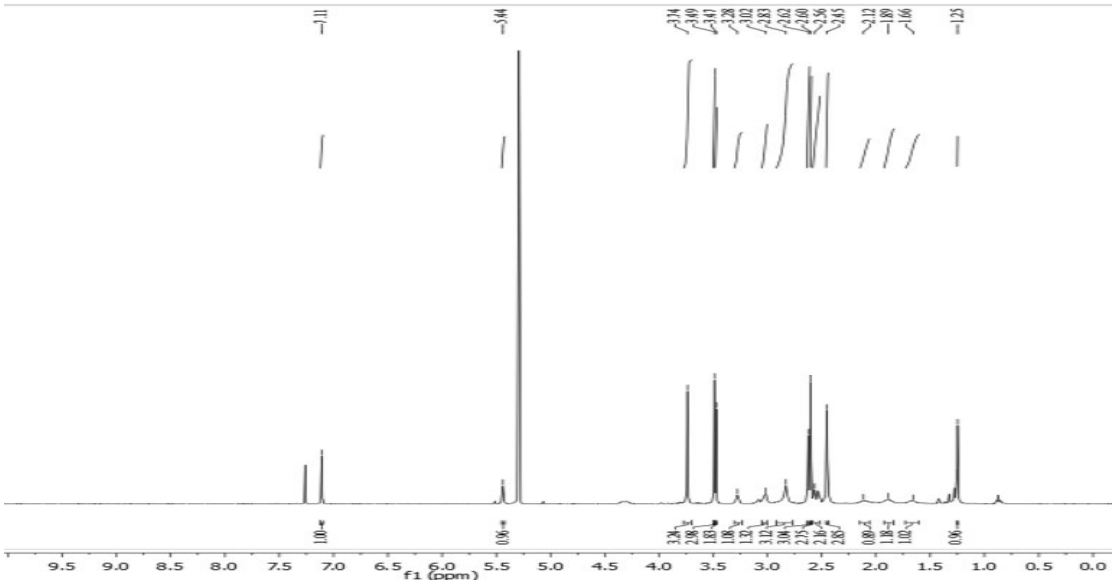

Figure S59. ^{1}H NMR spectrum of compound 20.

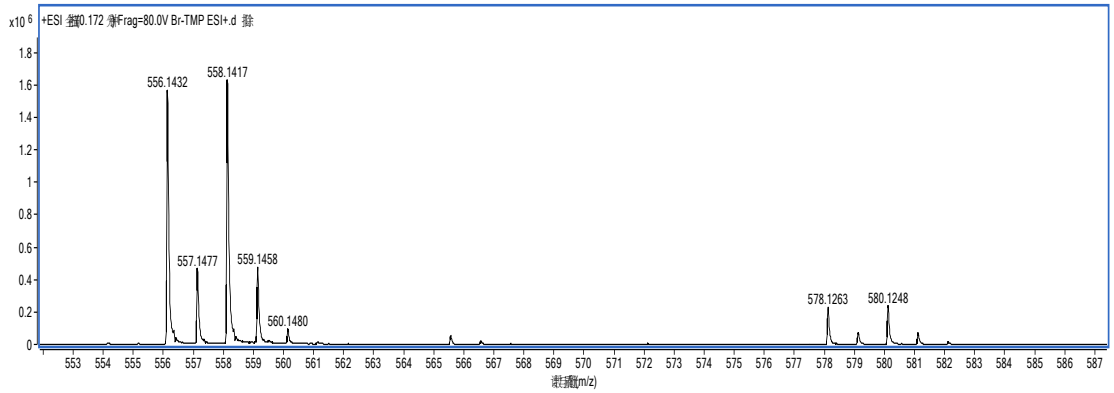

Figure S60. HRMS of compound 20.

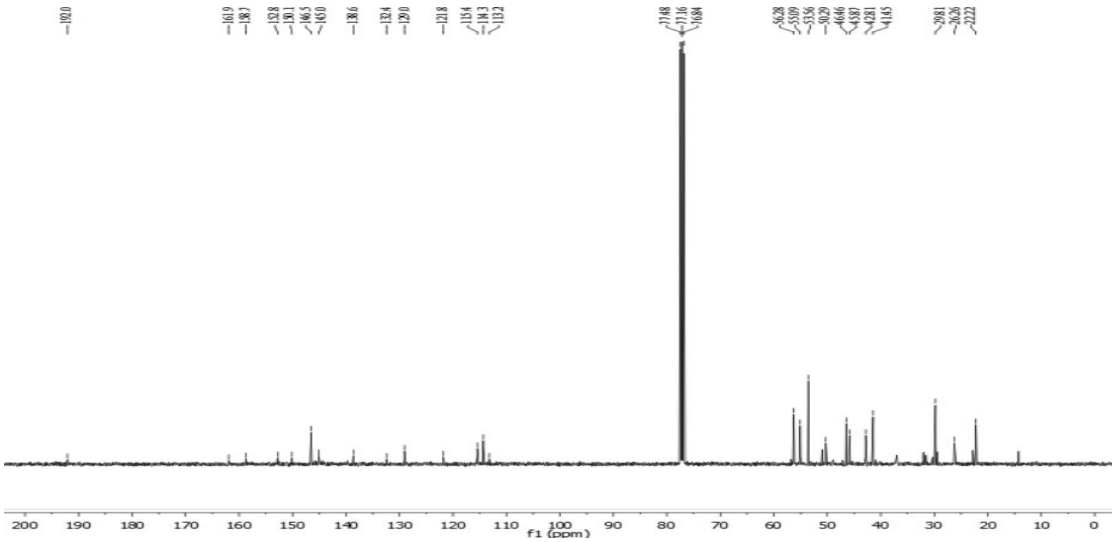

Figure S61. ^{13}C NMR spectrum of compound 21.

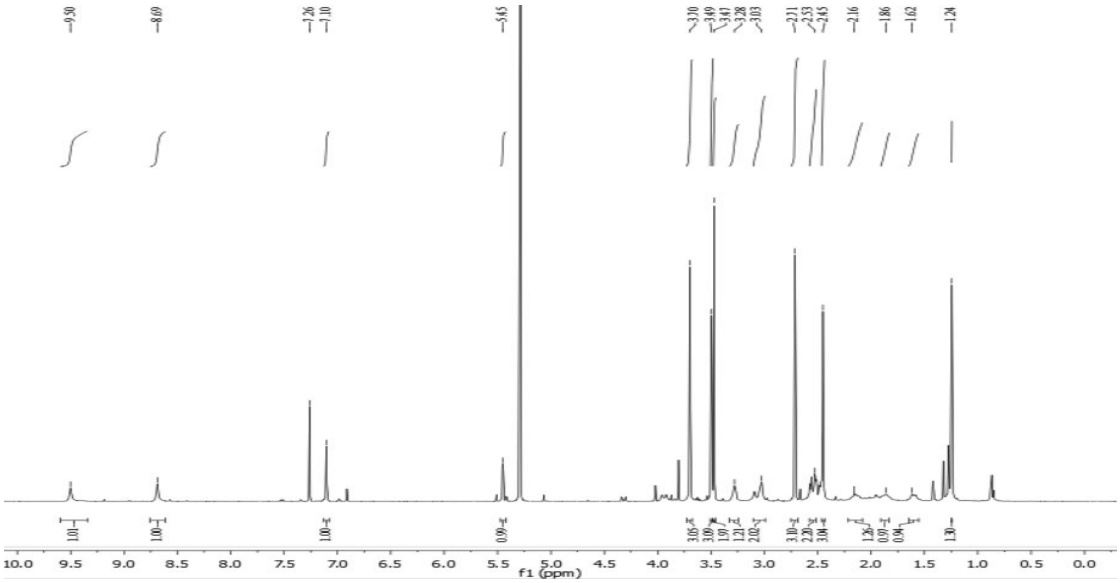

Figure S62. ^{1}H NMR spectrum of compound 21.

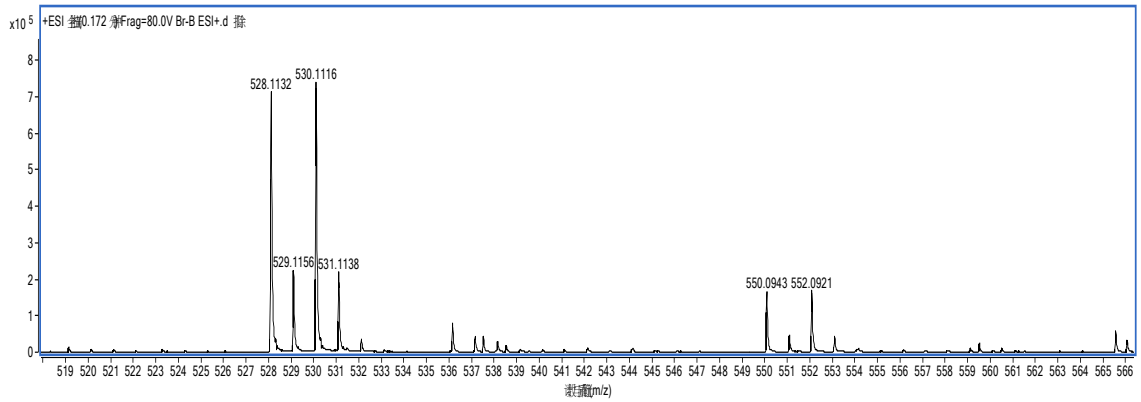

Figure S63. HRMS of compound 21.

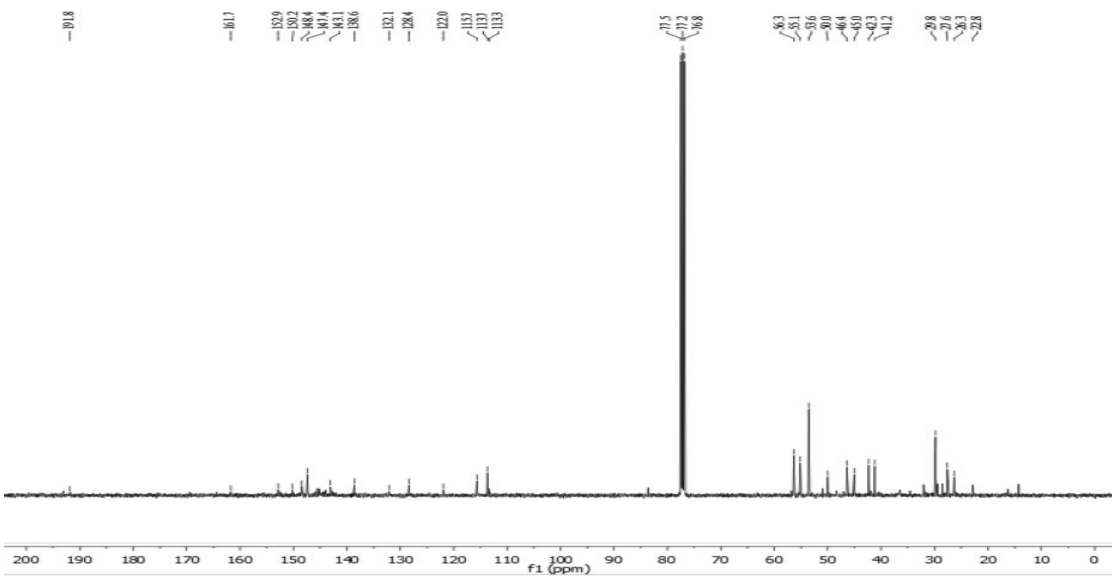

Figure S64. ^{13}C NMR spectrum of compound 22.

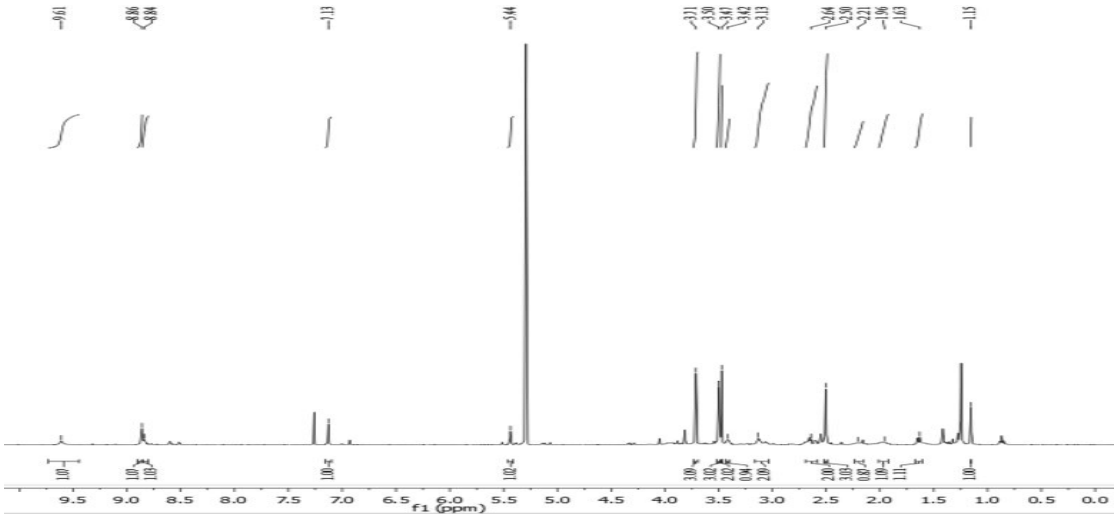

Figure S65. ^{1}H NMR spectrum of compound 22.

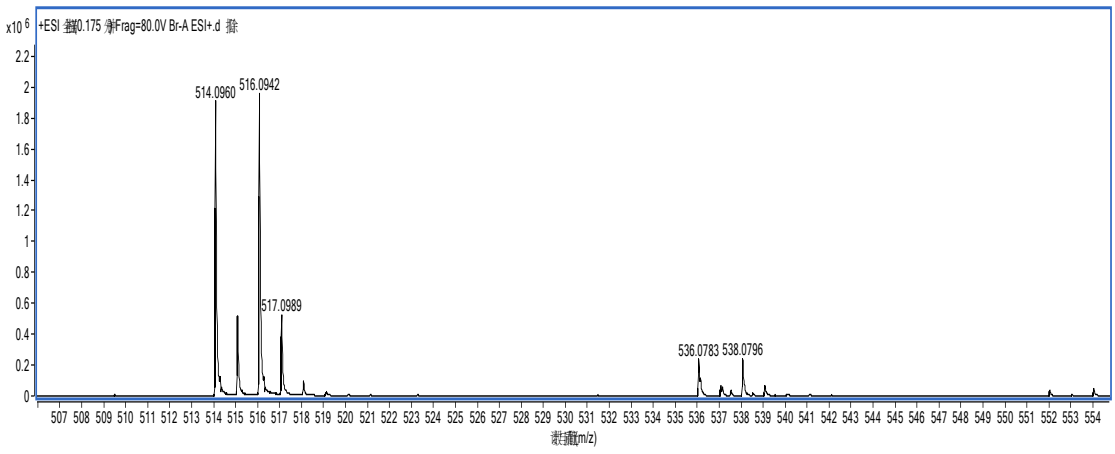

Figure S66. HRMS of compound 22.

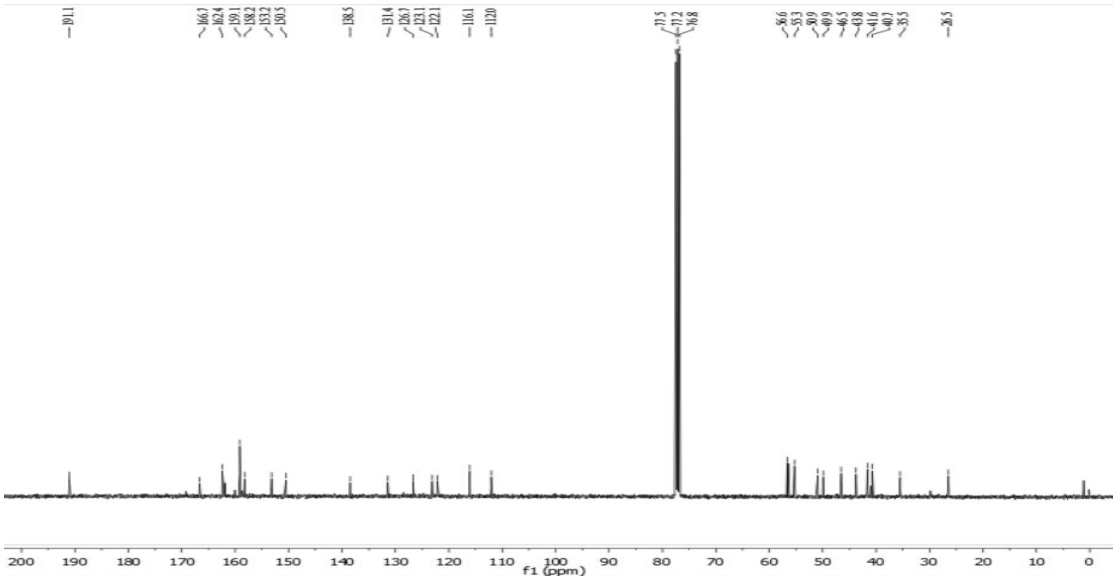

Figure S67. ^{13}C NMR spectrum of compound 23.

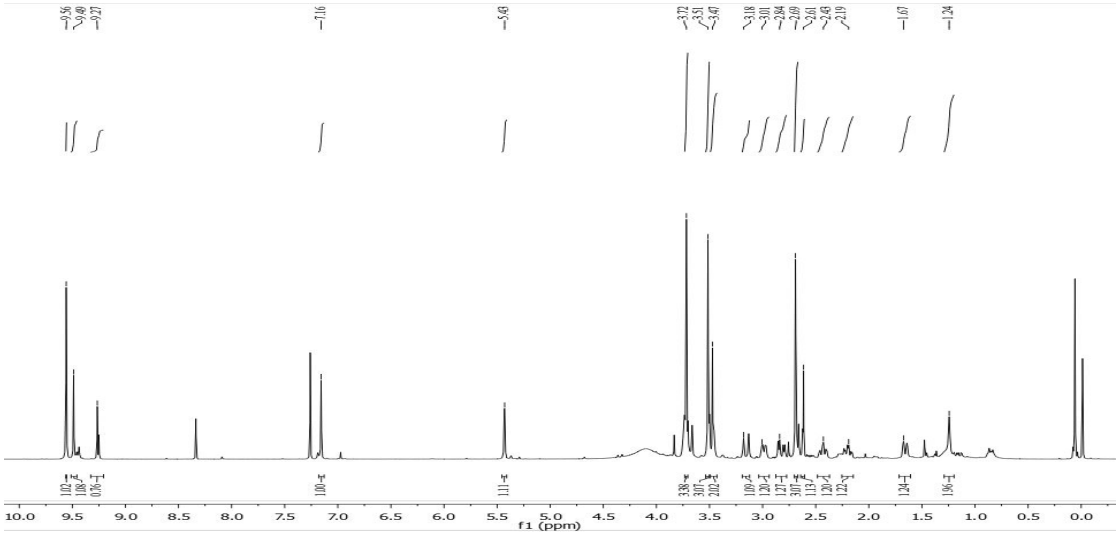

Figure S68. ^{1}H NMR spectrum of compound 23.

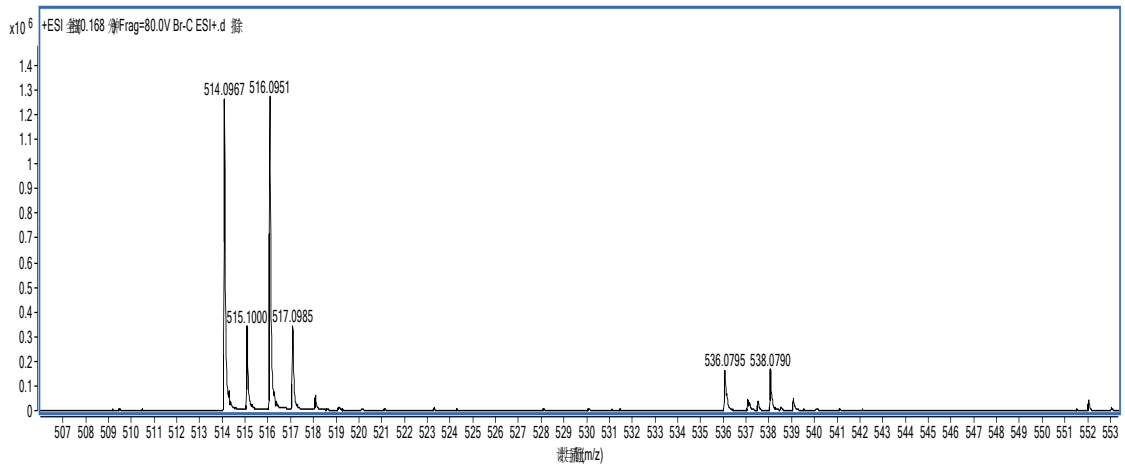

Figure S69. HRMS of compound 23.

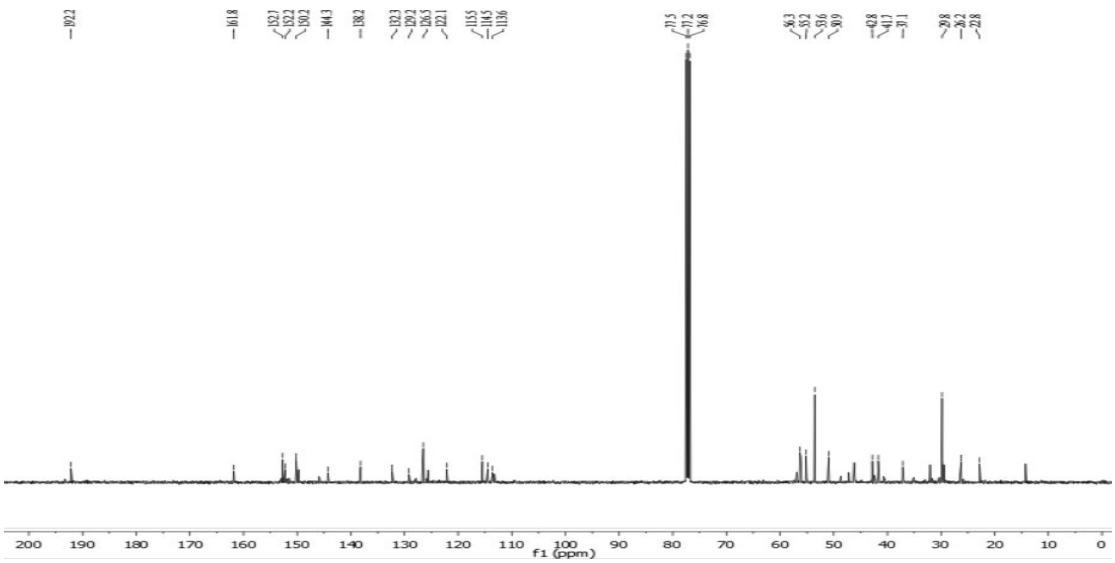

Figure S70. ^{13}C NMR spectrum of compound 24.

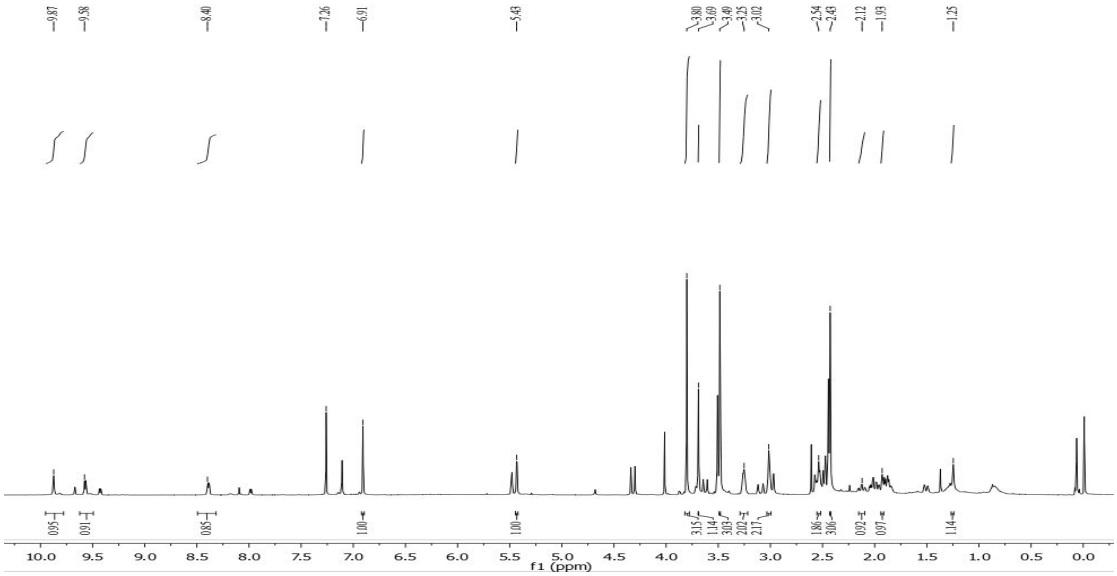

Figure S71. ^{1}H NMR spectrum of compound 24.

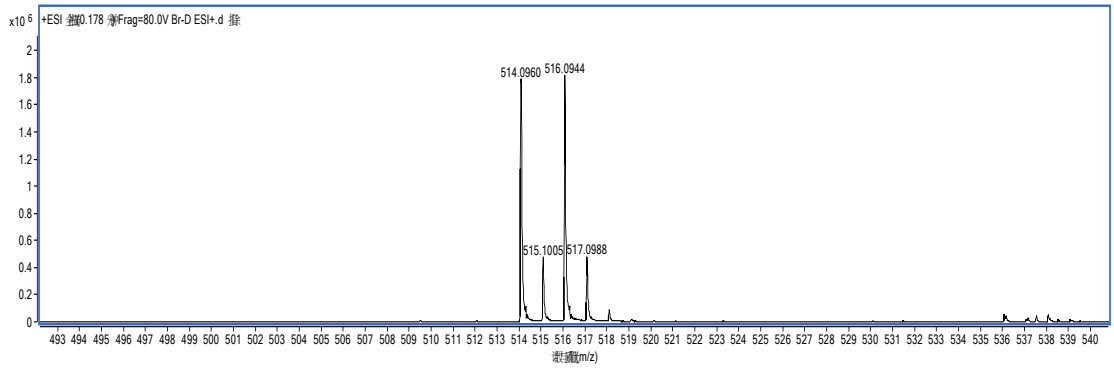

Figure S72. HRMS of compound 24.

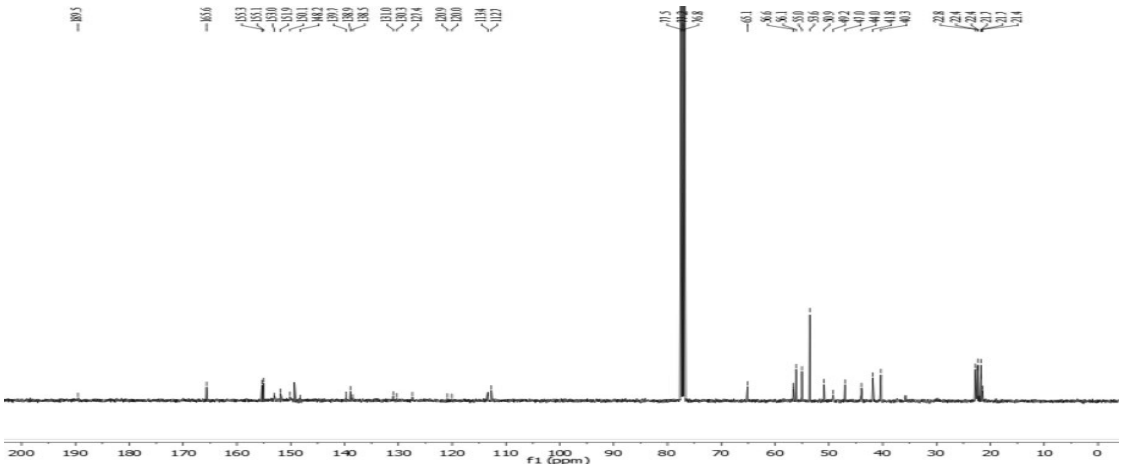

Figure S73. ^{13}C NMR spectrum of compound 25.

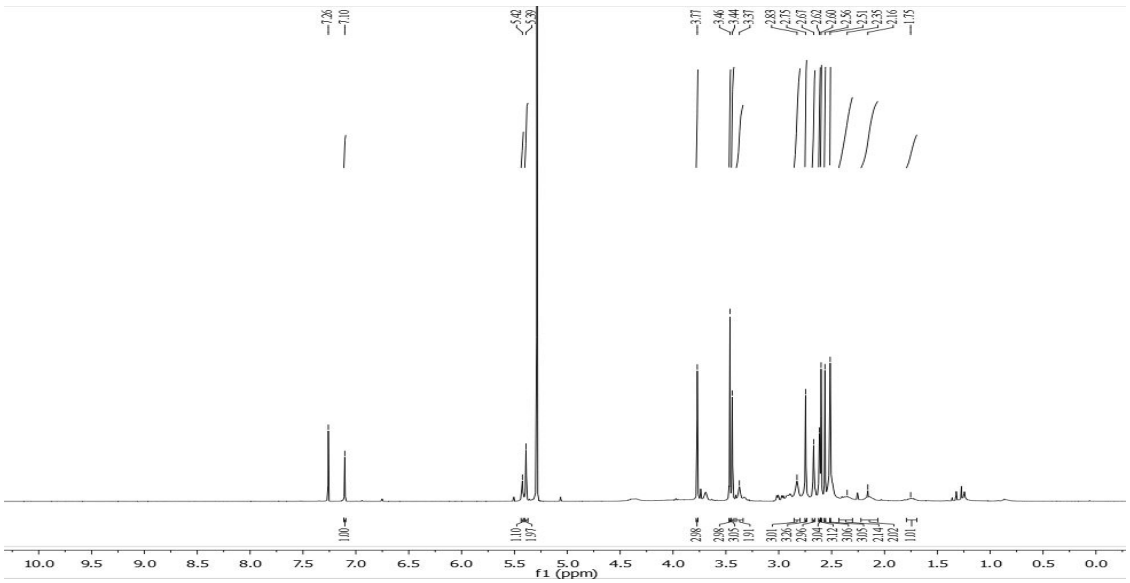

Figure S74. ^{1}H NMR spectrum of compound 25.

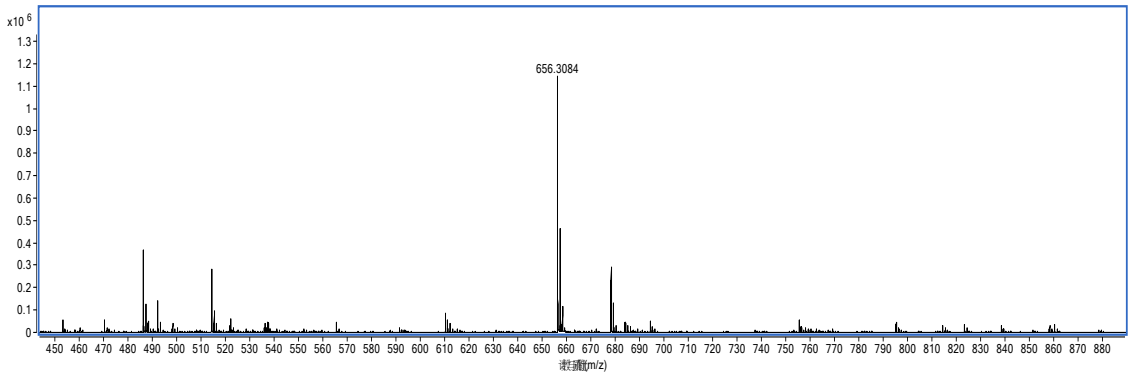

Figure S75. HRMS of compound 25.

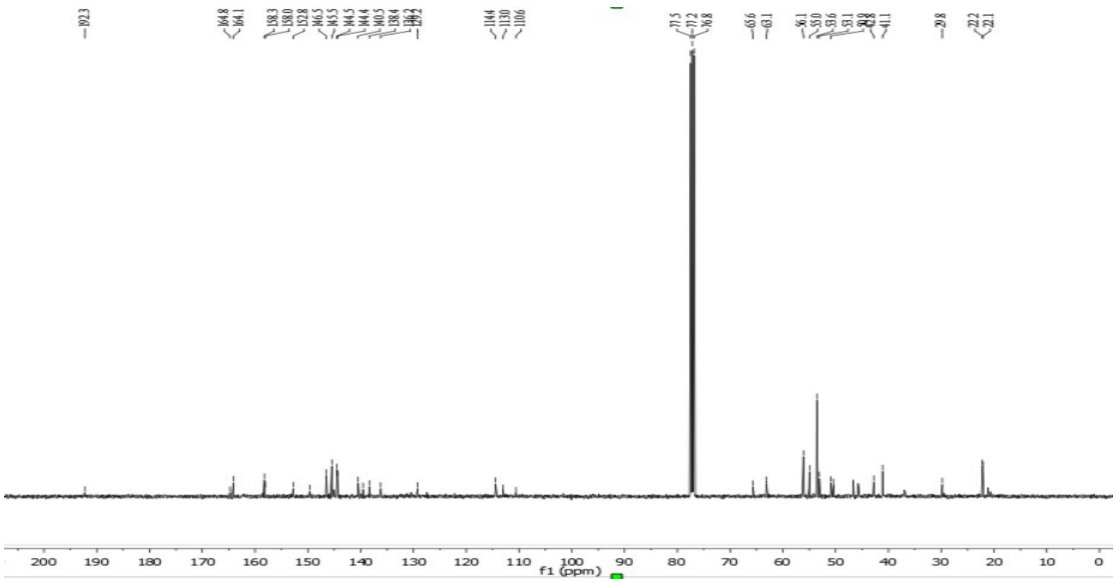

Figure S76. ^{13}C NMR spectrum of compound 26.

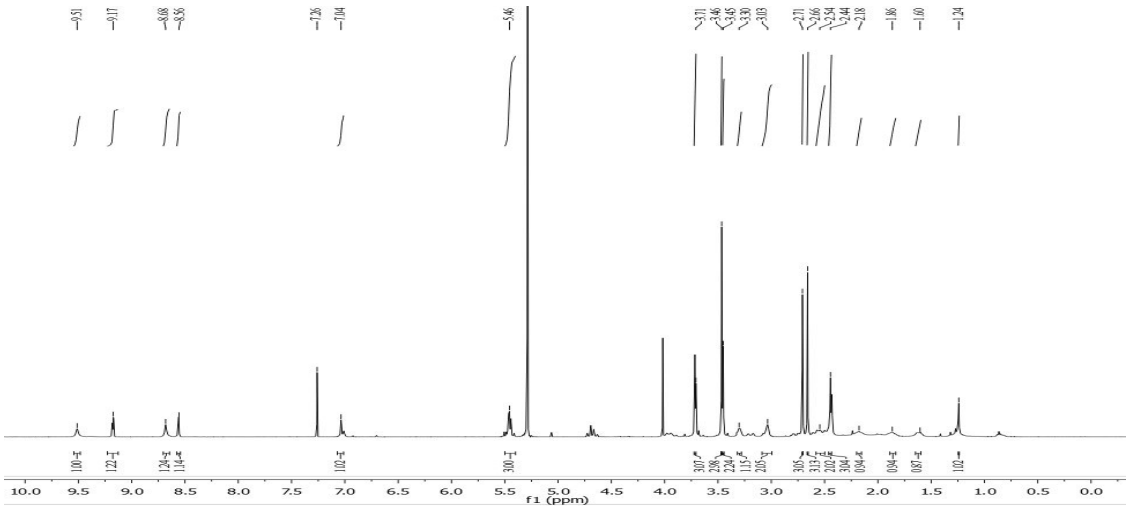

Figure S77. ^{1}H NMR spectrum of compound 26.

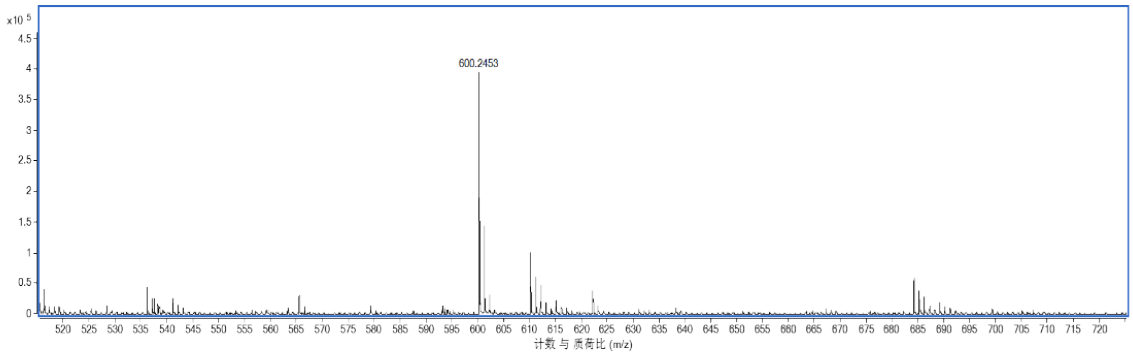

Figure S78. HRMS of compound 26.

1 Cao Y, Chen J, Ren G, et al. Punicalagin prevents inflammation in LPS-induced RAW264. 7 macrophages by inhibiting FoxO3a/autophagy signaling pathway,

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