Supplementary Information

Design, Synthesis and Biological Evaluation of C(6)-indole Celastrol Derivatives as Potential Antitumor Agents

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General Information

Celastrol was extracted from the Traditional Chinese Medicine (*Tripterygiumwilfordii* Hook F.) by ourselves. Silica gel FCP200-300 mesh was used for column chromatography. Indole derivatives were purchased from Sigma Aldrich. Other chemicals were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). ^{1}H-NMR and ^{13}C-NMR spectra were collected in $CDCl_3$ and DMSO-*d*6 at 25 °C on a Varian (300MHz or 500MHz) spectrometer. All chemical shifts are reported in the standard δ notation of parts per million using the peak of residual proton signals of $CDCl_3$ or DMSO-*d*6 as an internal reference. Electrospray ionization (ESI) analyses were performed by using a Thermo LTQ (LC-ESI-MS/MS). Melting point analyses were performed by using a digital micro-melting point apparatus. All compounds were confirmed by ^{1}H-NMR, ^{13}C-NMR, IR, LC-ESI-MS, [α], and the HPLC purity of all compounds was over 95.0%.

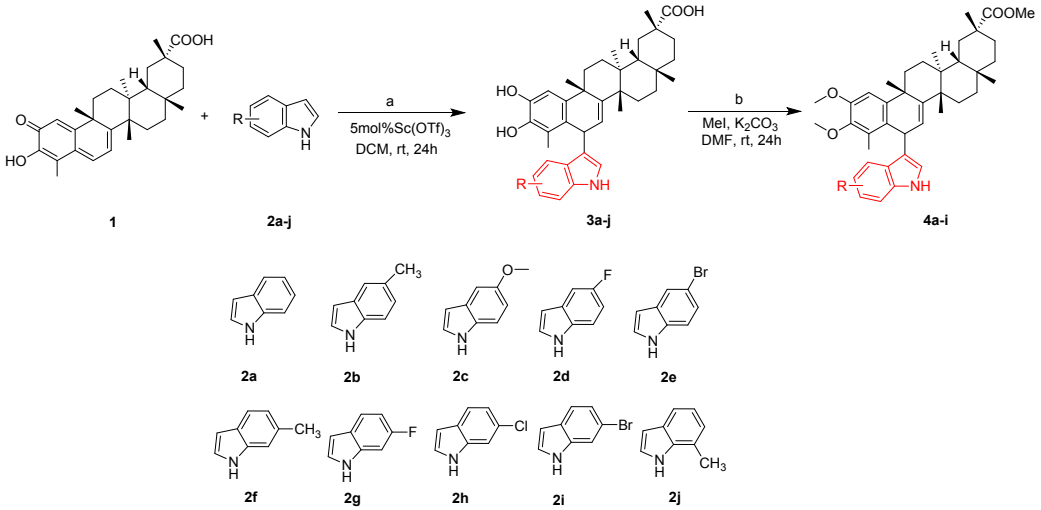
Cytotoxicity Assay

The human hepatocellular carcinoma Bel7402 was purchased from Shanghai Bioleaf Biotech Co.,Ltd (Shanghai, China) and human glioblastoma cell line H4 was purchased from Shanghai BiosunSci&Tech Co.,Ltd (Shanghai, China). All cell lines were propagated with Dulbecco′s Modified Eagle′s Media (DMEM) and supplemented with 10% heat-inactivated fetal bovine serum.

H4 and Bel7402 cells grown to logarithmic growth phase were collected, and centrifuged at 1,000 rpm for 5 min. The cells were seeded at a density of 3.5×10^4/mL in 96-well plate (100 μL/well), and the plate was incubated at 37 °C in 5% CO_2 for 24 h.A range of concentrations of the test compounds were added and the plate was incubated at 37 °C for 72 h before 20 μL MTT (5 mg/mL)/well was added. After 3 h of incubation, the medium was removed and 100 μL DMSO was added to each well. The absorbance was measured using a SpectraMax 340 microplate reader (Molecular Devices, Sunnyvale, CA, USA) at 492 nm and 620 nm. The growth inhibition rate was calculated by GraphPad Prism.

Experimental Procedures

Scheme S1. Synthesis of C(6)-indole analogues of celastrol



Representative procedure for 3a-3j

To a solution of celastrol (1.0 equiv) in anhydrous dichloromethane (2 mL) was added indole derivative (2.0 equiv) followed by scandium(III) triflate (5 mol %). The reaction turned black in several minutes and was stirred at room temperature overnight. Then the solvent was removed under reduced pressure and the resulting mixture was purified by flash chromatography on silica column (petroleum ether/acetone) to give the desired product.

Compound 3a

(2R,4aS,6aS,12bS,14aS,14bR)-10,11-dihydroxy-8-(1H-indol-3-yl)-2,4a,6a,9,12b,14a-hexamethyl-1,2,3,4,4a,5,6,6a,8,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylic acid: Starting from 450.6 mg celastrol, compound **3a** (350 mg, 62%) was obtained as a reddish brown solid according to above - mentioned procedure. mp 114-116°C; [α]20 *D* −89.78° (MeOH, c = 0.2), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.78 (d, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.15-7.20 (m, 2H), 6.83 (s, 1H), 6.32 (s, 1H), 6.23 (d, *J* = 6.3 Hz, 1H), 4.94 (d, *J* = 5.7 Hz, 1H), 2.41 (d, *J* = 15.6 Hz, 1H), 2.03-2.11 (m, 3H), 1.95 (s, 3H), 1.40-1.68 (m, 8H), 1.38 (s, 3H), 1.31-1.23 (m, 2H), 1.16 (s, 3H), 1.02 (s, 3H), 0.94-0.89 (m, 1H), 0.75 (s, 3H).^{13}C-NMR (100 MHz, $CDCl_3$) δ 184.34, 147.47, 142.81, 142.02, 139.89, 136.47, 127.87, 127.11, 121.74, 121.61, 121.45, 121.22, 120.39, 119.33, 119.16, 111.18, 108.86, 44.28, 43.62, 40.34, 37.75, 36.95, 36.73, 35.47, 34.61, 32.81, 31.54, 30.97, 30.68, 30.52, 30.41, 29.60, 28.89, 21.90, 18.80, 11.46. IR (KBr) 3407.8, 2939.5, 1697.6, 1659.5, 1456.0, 1219.5, 741.2 cm^{-1}; HRMS(ESI)*m/z* calcd for $C_{38}H_{46}NO_6$[M+COOH]$^-$ 612.3331, found 612.3325.

Compound 3b

(2R,4aS,6aS,12bS,14aS,14bR)-10,11-dihydroxy-2,4a,6a,9,12b,14a-hexamethyl-8-(5-methyl-1H-indol-3-yl)-1,2,3,4,4a,5,6,6a,8,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylic acid : Starting from 100 mg celastrol, compound **3b** (106 mg, 82%) was obtained as a reddish solid according to above‑mentioned procedure. mp 122-124°C; [α]20 *D* −105.47° (MeOH, c = 0.2),^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.20 – 7.05 (m, 2H), 6.81-6.78 (m, 2H), 6.30 (s, 1H), 6.16 (d, *J* = 4.5 Hz, 2H), 4.85 (d, *J* = 4.5 Hz, 2H), 3.82 (s, 3H), 2.40-2.36 (m, 2H), 2.09-2.04 (m, 2H), 1.92 (s, 3H), 1.74 – 1.39 (m, 8H), 1.33 (s, 3H), 1.26-1.23 (m, 1H), 1.14 (s, 3H), 1.00 (s, 3H), 0.99(s, 3H),0.91-0.86(m,1H),0.71 (s, 3H).^{13}C-NMR (75 MHz, $CDCl_3$) δ 184.38, 153.50, 147.34, 142.74, 142.05, 139.91, 131.75, 127.83, 127.39, 122.47, 121.57, 121.27, 119.98, 111.82, 111.55, 108.84, 101.76, 56.16, 44.28, 43.60, 40.37, 37.76, 36.95, 36.72, 35.52, 35.47, 34.61, 32.86, 31.55, 30.97, 30.66, 30.50, 30.40, 29.61, 28.92, 21.90, 18.81, 11.49.IR (KBr) 3414.3, 2940.5, 2868.6, 1697.8, 1483.2, 1209.8, 1019.6 cm^{-1}; HRMS(ESI)*m/z* calcd for $C_{38}H_{47}NO_4Na[M+Na]^+$ 604.3408, found 604.3397.

Compound 3c

(2R,4aS,6aS,12bS,14aS,14bR)-10,11-dihydroxy-8-(5-methoxy-1H-indol-3-yl)-2,4a,6a,9,12b,14a-hexamethyl-1,2,3,4,4a,5,6,6a,8,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylic acid: Starting from 100 mg celastrol, compound **3c** (98 mg, 74%) was obtained as a reddish solid according to above‑mentioned procedure. mp 90-92°C; [α]20 *D* −90.36° (MeOH, c = 0.2), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.62 (dd, *J* = 8.6, 5.3 Hz, 1H), 7.06 – 6.78 (m, 3H), 6.29 (d, *J* = 1.1 Hz, 1H), 6.17 (d, *J* = 6.3 Hz, 1H), 4.89 (d, *J* = 6.1 Hz, 1H), 2.40 (d, *J* = 15.1 Hz, 2H), 2.10-2.01 (m, 3H), 1.95 (s,3H), 1.78 – 1.39 (m, 9H), 1.35 (s, 3H), 1.32 – 1.24 (m, 1H), 1.15 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H), 0.94 – 0.85 (m, 1H), 0.72 (s, 3H).^{13}C-NMR (125 MHz, $CDCl_3$) δ 179.63, 159.72, 157.86, 146.80, 143.67, 141.05, 140.43, 136.16, 136.06, 125.68, 123.51, 122.18, 120.78, 119.83, 119.08, 108.43, 106.79, 106.60, 97.55, 97.35, 43.93, 43.21, 37.41, 36.52, 36.41, 35.36, 35.15, 34.81, 34.57, 32.52, 31.47, 30.81, 30.25, 30.12, 30.00, 29.71, 29.54, 28.75, 21.98, 18.12, 11.52.IR (KBr) 3412.4, 2940.4, 2868.6, 1698.0, 1483.3,1454.7, 1209.8, 1019.6 cm^{-1}; HRMS(ESI)*m/z* calcd for $C_{38}H_{47}NO_5Na[M+Na]^+$ 620.3344, found 620.3346.

Compound 3d

(2R,4aS,6aS,12bS,14aS,14bR)-8-(5-fluoro-1H-indol-3-yl)-10,11-dihydroxy-2,4a,6a,9,12b,14a-hexamethyl-1,2,3,4,4a,5,6,6a,8,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylic acid: Starting from 300 mg celastrol, compound **3d** (250 mg, 64%) was obtained as a reddish solid according to above‑mentioned procedure. mp 96-98°C; [α]20 *D* −66.31° (MeOH, c = 0.2), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.87 (s, 1H), 7.22 (m, 3H), 6.83 (s, 1H), 6.32 (s, 1H), 6.14 (d, *J* = 6.2 Hz, 1H), 4.86 (d, *J* = 5.8 Hz, 1H), 2.41 (m, 2H), 2.15 – 1.96 (m, 2H), 1.93 (s,

3H), 1.80 – 1.41 (m, 8H), 1.37 (s, 3H), 1.31-1.22(m,2H), 1.17 (s, 3H), 1.04(s,3H), 1.02 (s, 3H), 0.98 – 0.87 (m, 1H), 0.73 (s, 3H).13C-NMR (125 MHz, DMSO-d_6) δ 180.01, 147.09, 144.12, 141.47, 140.75, 135.33, 128.76, 125.93, 123.78, 123.65, 122.51, 121.55, 121.11, 119.17, 113.97, 111.35, 108.82, 44.32, 43.60, 37.82, 36.89, 36.77, 35.79, 35.58, 35.01, 34.94, 32.90, 31.85, 31.19, 30.63, 30.49, 30.38, 29.92, 29.18, 22.31, 18.48, 12.44, 11.93.IR (KBr) 3416.9, 2942.7, 2868.2, 1728.7, 1487.0, 1093.8, 797.7 cm^{-1}; HRMS(ESI)*m/z* calcd for $C_{37}H_{44}FNO_4$ Na[M+Na]$^+$ 608.3147, found 608.3141.

Compound 3e

(2R,4aS,6aS,12bS,14aS,14bR)-8-(5-bromo-1H-indol-3-yl)-10,11-dihydroxy-2,4a,6a,9,12b,14a-hexamethyl-1,2,3,4,4a,5,6,6a,8,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylic acid: Starting from 200 mg celastrol, compound

3e (160 mg, 56%) was obtained as a reddish solid according to above‑mentioned

procedure. mp 110-112°C; [α]20 *D* −88.87° (MeOH, c = 0.2), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.87 (s, 1H), 7.22 (m, 3H), 6.83 (s, 1H), 6.32 (s, 1H), 6.14 (d, *J* = 6.2 Hz, 1H), 4.86 (d, *J* = 5.8 Hz, 1H), 2.41 (m, 2H), 2.15 – 1.96 (m, 2H), 1.93 (s, 3H), 1.80 – 1.41 (m, 8H), 1.37 (s, 3H), 1.31-1.22(m,2H), 1.17 (s, 3H), 1.04(s,3H), 1.02 (s, 3H), 0.98 – 0.87 (m, 1H), 0.73 (s, 3H).^{13}C-NMR (125 MHz, DMSO-d_6) δ 180.01, 147.09, 144.12, 141.47, 140.75, 135.33, 128.76, 125.93, 123.78, 123.65, 122.51, 121.55, 121.11, 119.17, 113.97, 111.35, 108.82, 44.32, 43.60, 37.82, 36.89, 36.77, 35.79, 35.58, 35.01, 34.94, 32.90, 31.85, 31.19, 30.63, 30.49, 30.38, 29.92, 29.18, 22.31, 18.48, 12.44, 11.93.IR (KBr) 3421.4, 2940.2, 2868.3, 1700.7, 1457.7, 794.1 cm^{-1}; HRMS(ESI)*m/z* calcd for $C_{37}H_{44}BrNO_4Na$[M+Na]$^+$ 668.2342, found 668.2346.

Compound 3f

(2R,4aS,6aS,12bS,14aS,14bR)-10,11-dihydroxy-2,4a,6a,9,12b,14a-hexamethyl-8-(6-methyl-1H-indol-3-yl)-1,2,3,4,4a,5,6,6a,8,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylic acid: Starting from 200 mg celastrol, compound

3f (227 mg, 88%) was obtained as a reddish solid according to above‑mentioned

procedure. mp 79-81°C; [α]20 *D* −65.24° (MeOH, c = 0.2), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.78 – 7.52 (m, 3H), 7.13 (s, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.83 (s, 1H), 6.33 – 6.12 (m, 3H), 4.91 (d, *J* = 6.2 Hz, 1H), 2.47 (s, 3H), 2.43-2.38 (m, 2H), 2.10-2.04 (m, 3H), 1.96 (s, 3H), 1.77 – 1.45 (m, 8H), 1.37 (s, 3H), 1.30-1.22 (m, 2H), 1.15 (s, 3H), 1.02(s,3H),1.01 (s, 3H), 0.93-0.89 (m, 2H), 0.73 (s, 3H).^{13}C-NMR (75 MHz, DMSO-d_6) δ 180.01, 146.80, 143.97, 141.39, 140.80, 137.15, 130.15, 126.32, 125.04, 122.73, 121.19, 120.43, 119.03, 111.74, 108.77, 44.32, 43.56, 37.78, 36.91, 36.77, 35.72, 35.53, 35.35, 34.95, 32.91, 31.85, 31.19, 30.63, 30.51, 30.40, 29.93, 29.14, 22.35, 21.85, 18.49, 11.89.IR (KBr) 3412.1, 2940.7, 2868.2, 1701.2, 1455.7, 1221.0, 798.9 cm^{-1}; HRMS(ESI)*m/z* calcd for $C_{38}H_{47}NO_4Na$[M+Na]$^+$ 604.3403, found 604.3397.

Compound 3g

(2R,4aS,6aS,12bS,14aS,14bR)-8-(6-fluoro-1H-indol-3-yl)-10,11-dihydroxy-2,4a,6a,9,12b,14a-hexamethyl-1,2,3,4,4a,5,6,6a,8,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylic acid: Starting from 300 mg celastrol, compound **3g** (250 mg, 64%) was obtained as a reddish solid according to above‑mentioned procedure. mp181-183°C; [α]20 *D* −90.23° (MeOH, c = 0.2), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.64 (dd, *J* = 8.6, 5.3 Hz, 1H), 7.04 – 6.85 (m, 3H), 6.31 (s, 1H), 6.20 (d, *J* = 6.2 Hz, 1H), 4.91 (d, *J* = 6.1 Hz, 1H), 2.45 – 2.40 (m, 2H), 2.15 – 2.03 (m, 2H), 1.98 (s, 3H), 1.87 – 1.43 (m, 8H), 1.38 (s, 3H), 1.28 – 1.24 (m, 1H), 1.17 (s, 3H), 1.05 (s, 3H), 1.03 (s, 3H), 0.95 – 0.90 (m, 1H), 0.74 (s, 3H).^{13}C-NMR (125 MHz, DMSO-d_6) δ 180.01, 160.09, 158.24, 147.18, 144.05, 141.43, 140.81, 136.54, 136.44, 126.06, 123.89, 122.56, 121.16, 120.20, 119.46, 108.81, 107.17, 106.98, 97.92, 97.72, 44.31, 43.59, 37.79, 36.90, 36.78, 35.74, 35.53, 35.18, 34.95, 32.90, 31.85, 31.19, 30.63, 30.50, 30.37, 29.92, 29.13, 22.36, 18.49, 11.90.IR (KBr) 3412.3, 2940.8, 2869.0, 1701.1, 1456.4, 1140.1, 801.3 cm^{-1}; HRMS(ESI)*m/z* calcd for $C_{37}H_{43}FNO_4$[M-H]$^-$ 584.3182, found 584.3197.

Compound 3h

(2R,4aS,6aS,12bS,14aS,14bR)-8-(6-chloro-1H-indol-3-yl)-10,11-dihydroxy-2,4a,6a,9,12b,14a-hexamethyl-1,2,3,4,4a,5,6,6a,8,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylic acid: Starting from 200 mg celastrol, compound **3h** (116 mg, 43%) was obtained as a red purple solid according to above‑mentioned procedure. mp 98-100°C; [α]20 *D* −69.71° (MeOH, c = 0.2), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.32 (s, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.83 (s, 1H), 6.33 (s, 1H), 6.16 (d, *J* = 6.4 Hz, 1H), 4.89 (d, *J* = 6.2 Hz, 3H), 2.40 (d, *J* = 15.3 Hz, 1H), 2.10-2.04(m, 3H), 1.95 (s, 3H),1.68-1.43(m,9H), 1.35 (s, 3H), 1.26-1.22 (m, 3H), 1.16 (s, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.90-0.87 (m, 2H), 0.72 (s, 3H).^{13}C-NMR (75 MHz, DMSO-d_6,)δ 180.01, 147.29, 144.09, 141.46, 140.81, 137.07, 125.97, 125.93, 125.76, 123.18, 122.48, 121.13, 120.71, 119.55, 118.96, 111.54, 108.84, 44.31, 43.60, 37.79, 36.90, 36.79, 35.73, 35.51, 35.11, 34.95, 32.89, 31.85, 31.19, 30.63, 30.50, 30.36, 29.92, 29.77, 29.12, 23.17, 22.36, 18.50, 11.89. IR (KBr) 3421.6, 2955.3, 2868.9, 1697.7, 1455.7, 1216.9, 800.6 cm^{-1}; HRMS(ESI)*m/z* calcd for $C_{37}H_{44}ClNO_4Na$[M+Na]$^+$ 624.2861, found 624.2851

Compound 3i

(2R,4aS,6aS,12bS,14aS,14bR)-8-(6-bromo-1H-indol-3-yl)-10,11-dihydroxy-2,4a,6a,9,12b,14a-hexamethyl-1,2,3,4,4a,5,6,6a,8,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylic acid: Starting from 200 mg celastrol, compound **3i** (162 mg, 57%) was obtained as a reddish solid according to above‑mentioned procedure. mp 82-84°C; [α]20 *D* −71.36° (MeOH, c = 0.2), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.47 (s, 1H), 7.31 – 7.16 (m, 1H),

6.82 (s, 1H), 6.30 (s, 1H), 6.16 (d, *J* = 6.2 Hz, 1H), 4.88 (d, *J* = 5.8 Hz, 1H), 2.40 (d, *J* = 13.7 Hz, 1H), 2.14 – 1.98 (m, 2H), 1.94 (s, 3H), 1.72 – 1.40 (m, 8H), 1.34 (m, 3H), 1.27 (m, 2H), 1.16 (s, 3H), 1.03 (s, 3H), 1.00 (m, 3H), 0.96-0.94 (m, 1H), 0.73 (s, 3H).^{13}C-NMR (125 MHz, DMSO-d_6) δ 179.63, 146.71, 143.75, 141.09, 140.37, 134.95, 128.38, 125.55, 123.40, 123.27, 122.13, 121.17, 120.73, 118.79, 113.59, 110.98, 108.44, 43.94, 43.22, 37.44, 36.51, 36.40, 35.41, 35.20, 34.63, 34.56, 32.52, 31.47, 30.81, 30.25, 30.12, 30.01, 29.54, 28.80, 21.93, 18.10, 11.55.IR (KBr) 3420.3, 2953.2, 2868.6, 1697.9, 1454.9, 1216.9, 799.5 cm^{-1}; HRMS(ESI)*m/z* calcd for $C_{37}H_{44}BrNO_4Na[M+Na]^+$ 668.2346, found 668.2341.

Compound 3j

(2R,4aS,6aS,12bS,14aS,14bR)-10,11-dihydroxy-2,4a,6a,9,12b,14a-hexamethyl-8-(7-methyl-1H-indol-3-yl)-1,2,3,4,4a,5,6,6a,8,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylic acid: Starting from 200 mg celastrol, compound **3j** (202 mg, 78%) was obtained as a reddish solid according to above‑mentioned procedure. mp 92-94°C; [α]20 *D* −78.39° (MeOH, c = 0.2),^{1}H-NMR (300 MHz, $CDCl_3$) 7.72 (s, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 6.99-7.10 (m, 2H)，6.84 (s, 1H), 6.33 (d, *J* = 1.8 Hz, 1H), 6.21 (d, *J* = 6.3 Hz, 1H), 4.93 (d, *J* = 6.3 Hz, 1H), 2.46 (s, 3H), 2.39-2.43 (dd, *J* = 15.0 Hz, 0.6 Hz, 1H), 2.03-2.06 (m, 3H), 1.96 (s, 3H), 1.46-1.73 (m, 9H), 1.38 (s, 3H), 1.16 (s, 3H), 1.02(s, 3H), 1.01 (s, 3H), 0.88-0.93 (m, 1H), 0.73 (s, 3H).^{13}C-NMR (125 MHz, DMSO-d_6) δ 180.01, 146.88, 143.99, 141.41, 140.84, 136.20, 126.72, 126.25, 122.65, 121.77, 121.60, 121.18, 120.92, 119.70, 118.92, 116.94, 108.77, 44.31, 43.56, 37.79, 36.90, 36.77, 35.72, 35.53, 35.39, 34.94, 32.90, 31.85, 31.19, 30.63, 30.50, 30.39, 29.93, 29.14, 22.36, 18.49, 17.24, 11.91.IR (KBr) 3420.2,2940.3, 2868.6, 1701.3, 1616.4, 1453.3, 1215.9, 779.9 cm^{-1}; HRMS(ESI)*m/z* calcd for $C_{38}H_{47}NO_4Na[M+Na]^+$ 604.3396, found 604.3397.

Representative procedure for4a-4i

To a solution of compound **3a-3j** (1.0 equiv) in anhydrous DMF (2 mL) was added K_2CO_3 (4.0 eq) and MeI (3.6 eq). The reaction was stirred at room temperature under argon overnight. The resulting mixture was poured into water and the solid was collected. The crude product was purified by flash chromatography on silica column (PE/acetone) to give the desired product.

Compound 4a

(2R,4aS,6aS,12bS,14aS,14bR)-methyl 8-(1H-indol-3-yl)-10,11-dimethoxy-2,4a,6a,9,12b,14a-hexamethyl-1,2,3,4,4a,5,6,6a,8,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylate: Starting from 140 mg **3a**, compound **4a** (102 mg, 68%) was obtained as a gray solid according to above‑mentioned procedure. mp 100-102°C; [α]20 *D* −90.40° (MeOH, c = 0.2),^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.71 (m, 2H), 7.37 (d, *J* = 7.1 Hz, 1H), 7.26-7.17 (m, 2H), 6.89 (s, 1H), 6.33-6.33 (m, 1H), 6.28-6.26 (d, *J* = 6.3 Hz, 1H), 4.97 (d, *J* = 6.1 Hz, 1H), 3.95 (s, 3H), 3.79 (s, 3H), 3.59 (s, 3H), 2.43-4.29 (m, 1H), 2.18-2.08 (m, 2H), 2.02 (s, 3H), 1.90 – 1.49 (m, 8H),

1.46 (s, 3H), 1.42-1.36 (m, 2H), 1.20 (s, 3H), 1.07 (s, 3H), 1.05(s, 3H),1.00-0.94 (m, 1H), 0.68 (s, 3H).^{13}C-NMR(100 MHz, $CDCl_3$) δ 179.11, 151.27, 147.10, 145.85, 145.24, 136.46, 128.87, 127.94, 127.16, 121.72, 121.28, 120.41, 119.30, 119.15, 111.16, 106.21, 60.31, 55.76, 51.55, 44.44, 43.68, 40.52, 37.74, 37.45, 36.81, 35.44, 35.37, 34.89, 32.94, 31.58, 30.88, 30.55, 30.48, 29.96, 28.89, 21.82, 18.32, 11.58.IR (KBr) 3422.6, 2939.3, 2870.0, 1728.2, 1487.6, 1453.6, 1092.9, 740.2 cm^{-1};HRMS(ESI)*m/z* calcd for $C_{40}H_{52}NO_4[M+H]^+$610.3891, found 610.3901.

Compound 4b

(2R,4aS,6aS,12bS,14aS,14bR)-methyl 10,11-dimethoxy-2,4a,6a,9,12b,14a-hexamethyl-8-(5-methyl-1H-indol-3-yl)-1,2,3,4,4a,5,6,6a,8,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylate: Starting from 200 mg **3b**, compound **4b** (172 mg, 68%) was obtained as a brown yellow solid according to above‑mentioned procedure. mp 98-100°C; [α]20 *D* −93.88° (MeOH, c = 0.2), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.56 (s, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.86 (s, 1H), 6.26 (d, *J* = 1.6 Hz, 1H), 6.20 (d, *J* = 6.3 Hz, 1H), 4.90 (d, *J* = 6.2 Hz, 1H), 3.91 (s, 3H), 3.75 (s, 3H), 3.56 (s, 3H), 2.52 (s, 3H), 2.46-2.41 (m, 1H), 2.18-2.05 (m, 4H), 1.97 (s, 3H), 1.81-1.50 (m, 9H), 1.45 (s, 3H), 1.42 – 1.25 (m, 2H), 1.17 (s, 3H), 1.05 (s, 3H), 1.03 (s, 3H),0.97-.093 (m, 1H), 0.65 (s, 3H).^{13}C-NMR (75 MHz, $CDCl_3$) δ 179.10, 151.26, 146.83, 145.79, 145.27, 134.75, 128.90, 128.34, 128.08, 127.43, 123.38, 121.76, 121.46, 119.98, 118.86, 110.81, 106.19, 60.30, 55.79, 51.55, 44.45, 43.67, 40.53, 37.76, 37.42, 36.84, 35.48, 35.45, 35.41, 34.89, 32.94, 31.59, 30.88, 30.56, 30.50, 29.98, 28.89, 21.78, 21.70, 18.32, 11.60.IR (KBr) 3419.8, 2945.1, 2867.9, 1718.1, 1593.8, 1488.9, 1462.6, 1094.5 cm^{-1}; HRMS(ESI)*m/z* calcd for $C_{41}H_{51}NO_4[M+H]^+$ 624.4047, found 624.4026.

Compound 4c

(2R,4aS,6aS,12bS,14aS,14bR)-methyl 10,11-dimethoxy-8-(5-methoxy-1H-indol-3-yl)-2,4a,6a,9,12b,14a-hexamethyl-1,2,3,4,4a,5,6,6a,8,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylate: Starting from 85 mg **3c**, compound **4c** (69 mg, 76%) was obtained as a yellow solid according to above‑mentioned procedure. mp 108-110°C; [α]20 *D* −93.86° (MeOH, c = 0.2), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.22 (d, *J* = 8.9 Hz, 1H), 7.14 (d, *J* = 1.9 Hz, 1H), 6.87-6.84 (m, 2H), 6.32 (d, *J* = 2.2 Hz, 1H), 6.20 (d, *J* = 6.2 Hz, 1H), 4.88 (d, *J* = 5.9 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.75 (s, 3H), 3.56 (s, 3H), 2.45-2.41 (m, 1H), 2.14 – 2.10 (m, 3H), 1.99 (s, 3H), 1.83 – 1.50 (m, 8H), 1.43 (s, 3H), 1.39-1.26 (m, 2H), 1.17 (s, 3H), 1.05(s, 3H), 1.04(s, 3H), 0.97- 0.92 (m, 1H), 0.65 (s, 3H).^{13}C-NMR (125 MHz, DMSO-d_6) δ 178.49, 153.27, 151.37, 146.08, 145.49, 145.09, 131.81, 128.19, 127.91, 127.13, 122.73, 122.69, 118.31, 112.55, 111.26, 106.82, 101.10, 60.08, 55.89, 55.73, 51.90, 44.28, 43.62, 37.75, 37.46, 36.87, 35.54, 35.24, 35.20, 34.88, 32.84, 31.82, 31.18, 30.68, 30.59, 30.48, 29.93, 29.08, 22.15, 18.19, 11.76.IR (KBr) 3412.6, 2941.6, 2868.6,

1728.6, 1484.9, 1462.5, 1206.0, 1093.6 cm^{-1}; HRMS(ESI)*m/z* calcd for $C_{41}H_{53}NO_5Na[M+Na]^+$ 662.3836, found 662.3816.

Compound 4d

(2R,4aS,6aS,12bS,14aS,14bR)-methyl 8-(5-fluoro-1H-indol-3-yl)-10,11-dimethoxy-2,4a,6a,9,12b,14a-hexamethyl-1,2,3,4,4a,5,6,6a,8,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylate: Starting from 85 mg **3d**, compound **4d** (40 mg, 44%) was obtained as a reddish solid according to above‑mentioned procedure. mp 142-144°C; [α]20 *D* −72.37° (MeOH, c = 0.2), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.80 (s,1H), 7.64-7.60 (m, 1H), 7.00 (d, *J* = 9.9 Hz, 1H), 6.96 – 6.81 (m, 2H), 6.28-6.27 (m, 1H), 6.18 (d, *J* = 5.9 Hz,1H), 4.88 (d, *J* = 6.0 Hz,1H), 3.91 (s,3H), 3.75 (s,3H), 3.55 (s,3H), 2.42 (d, *J* = 16.2 Hz, 1H), 2.16 – 2.01 (m, 3H), 1.98 (s, 3H), 1.81 – 1.42 (m, 8H), 1.41 (s, 3H), 1.38-1.25 (m,1H), 1.16 (s, 3H), 1.04 (s, 3H), 1.02 (s, 3H), 0.98 – 0.80 (m), 0.63 (s, 3H).^{13}C-NMR (75 MHz, DMSO-d_6) δ 178.49, 151.68, 145.59, 145.27, 145.11, 133.88, 132.14, 128.60, 128.27, 126.61, 121.90, 112.00, 111.36, 111.29, 107.23, 103.45, 103.32(17), 60.08, 56.00, 51.90, 44.28, 43.56, 40.57, 37.93, 37.46, 36.87, 35.41, 34.93, 32.83, 31.84, 31.19, 30.68, 30.59, 30.51, 29.94, 29.14, 22.02, 18.12, 12.42, 11.65.IR (KBr) 3385.1, 2942.6, 2869.1, 1730.7, 1488.6, 1093.8, 792.7 cm^{-1}; HRMS(ESI)*m/z* calcd for $C_{40}H_{50}FNO_4Na[M+Na]^+$ 650.8175, found 650.8169.

Compound 4e

(2R,4aS,6aS,12bS,14aS,14bR)-methyl 8-(5-bromo-1H-indol-3-yl)-10,11-dimethoxy-2,4a,6a,9,12b,14a-hexamethyl-1,2,3,4,4a,5,6,6a,8,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylate: Starting from 110 mg **3e**, compound **4e** (15 mg, 14%) was obtained as a brown yellow solid according to above‑mentioned procedure. mp 87-89°C; [α]20 *D* −79.96° (MeOH, c = 0.2), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86-7.85 (m, 2H), 7.21-7.19 (m, 1H), 6.85 (s, 1H), 6.32 (d, *J* = 1.6 Hz, 1H), 6.14 (d, *J* = 6.0 Hz, 1H), 4.85 (d, *J* = 6.4 Hz, 1H), 3.91 (s, 3H), 3.75 (s, 3H), 3.56 (s, 3H), 2.42 (d, *J* = 15.1 Hz, 1H), 2.15-2.03 (m, 3H), 1.96 (s, 3H), 1.88 – 1.44 (m, 8H), 1.42 (s, 3H), 1.39-1.26 (m, 2H), 1.17 (s, 3H), 1.05 (s, 3H), 1.04 (s, 3H),0.98 – 0.92 (m, 1H), 0.64 (s, 3H).^{13}C-NMR (125 MHz, DMSO-d_6) δ 178.50, 151.47, 146.54, 145.51, 145.16, 135.30, 128.68, 128.10, 127.54, 123.78, 123.69, 122.43, 121.44, 118.72, 114.03, 111.48, 106.89, 60.10, 55.92, 51.91, 44.27, 43.64, 37.75, 37.46, 36.82, 35.50, 35.19, 34.93, 34.88, 32.84, 31.83, 31.19, 30.68, 30.59, 30.45, 29.92, 29.13, 22.14, 18.20, 11.76.IR (KBr) 3420.5, 2942.6, 2868.8, 1728.9, 1486.9, 1459.2, 1093.7, 792.7 cm^{-1}; HRMS(ESI)*m/z* calcd for $C_{40}H_{50}BrNO_4Na[M+Na]^+$ 710.2831, found 710.2815.

Compound 4f

(2R,4aS,6aS,12bS,14aS,14bR)-methyl 10,11-dimethoxy-2,4a,6a,9,12b,14a-hexamethyl-8-(6-methyl-1H-indol-3-yl)-1,2,3,4,4a,5,6,6a,8,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylate: Starting from 85 mg **3f**, compound **4f** (62 mg,

68%) was obtained as a light red solid according to above – mentioned procedure. mp 111-113°C; [α]20 *D* −85.77° (MeOH, c = 0.2),^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.14 (s, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.85 (s, 1H), 6.22 (d, *J* = 6.0 Hz, 2H), 4.90 (d, *J* = 6.1 Hz, 1H), 3.91 (s, 3H), 3.75 (s, 3H), 3.56 (s, 3H), 2.47 (s, 3H), 2.45 – 2.40 (m, 1H), 2.19 – 2.02 (m, 4H), 1.99 (s, 3H), 1.77-1.49 (m, 8H), 1.42 (s, 3H), 1.38 – 1.26 (m, 2H), 1.17 (s, 3H), 1.04 (s, 3H), 1.02 (s, 3H), 0.98 – 0.92 (m, 1H), 0.64 (s, 3H).^{13}C-NMR (75 MHz, DMSO-d_6)δ 178.51, 151.32, 146.24, 145.50, 145.05, 137.13, 130.32, 128.13, 127.87, 124.95, 122.63, 121.07, 120.54, 118.90, 118.62, 111.78, 106.75, 60.08, 55.86, 51.92, 44.27, 43.60, 37.71, 37.46, 36.83, 35.44, 35.30, 35.15, 34.89, 32.85, 31.83, 30.69, 30.59, 30.45, 29.92, 29.10, 22.17, 21.85, 18.21, 11.71.IR (KBr) 3414.5, 2943.4, 2868.2, 1728.9, 1462.0, 1093.7, 797.7 cm^{-1}; HRMS(ESI)*m/z* calcd for $C_{41}H_{53}NO_4Na$[M+Na]$^+$ 646.3865, found 646.3867.

Compound 4g

(2R,4aS,6aS,12bS,14aS,14bR)-methyl 8-(6-fluoro-1H-indol-3-yl)-10,11-dimethoxy-2,4a,6a,9,12b,14a-hexamethyl-1,2,3,4,4a,5,6,6a,8,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylate: Starting from 110 mg **3g**, compound **4g** (90 mg, 76%) was obtained as a brown yellow solid according to above – mentioned procedure. mp 84-86°C; [α]20 *D* −76.73° (MeOH, c = 0.2), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.65-7.60 (m, 1H), 7.01 (d, *J* = 9.5 Hz, 1H), 6.90 (dd, *J* = 19.1, 7.8 Hz, 2H), 6.28 (d, *J* = 1.1 Hz, 1H), 6.19 (d, *J* = 6.1 Hz, 1H), 4.89 (d, *J* = 5.9 Hz, 1H), 3.91 (s, 3H), 3.76 (s, 3H), 3.56 (s, 3H), 2.43 (d, *J* = 15.5 Hz, 1H), 2.14-2.04 (m, 3H), 1.99 (s, 3H) 1.69 – 1.49 (m, 8H), 1.41 (s, 3H), 1.37-1.26(m,1H), 1.17 (s, 3H), 1.05 (s, 3H), 1.03 (s, 3H), 0.97-0.93 (m, 1H), 0.64 (s, 3H).^{13}C-NMR (150 MHz, $CDCl_3$) δ 179.11, 160.65, 159.08, 151.33, 147.47, 145.82, 145.25, 136.40, 136.32, 128.80, 127.69, 123.71, 121.52, 120.51, 119.93, 119.87, 107.96, 107.80, 106.25, 97.55, 97.38, 60.31, 55.76, 51.55, 44.44, 43.70, 40.52, 37.75, 37.48, 36.81, 35.46, 35.38, 35.34, 34.89, 32.93, 31.59, 30.96, 30.87, 30.55, 30.46, 29.95, 28.93, 21.86, 18.31, 11.54.IR (KBr) 3354.2, 2945.7, 2868.9, 1715.2, 1488.3, 1488.5, 1094.0, 798.8 cm^{-1}; HRMS(ESI)*m/z* calcd for $C_{40}H_{51}FNO_4$ [M+H]$^+$ 628.3797, found 628.3786.

Compound 4h

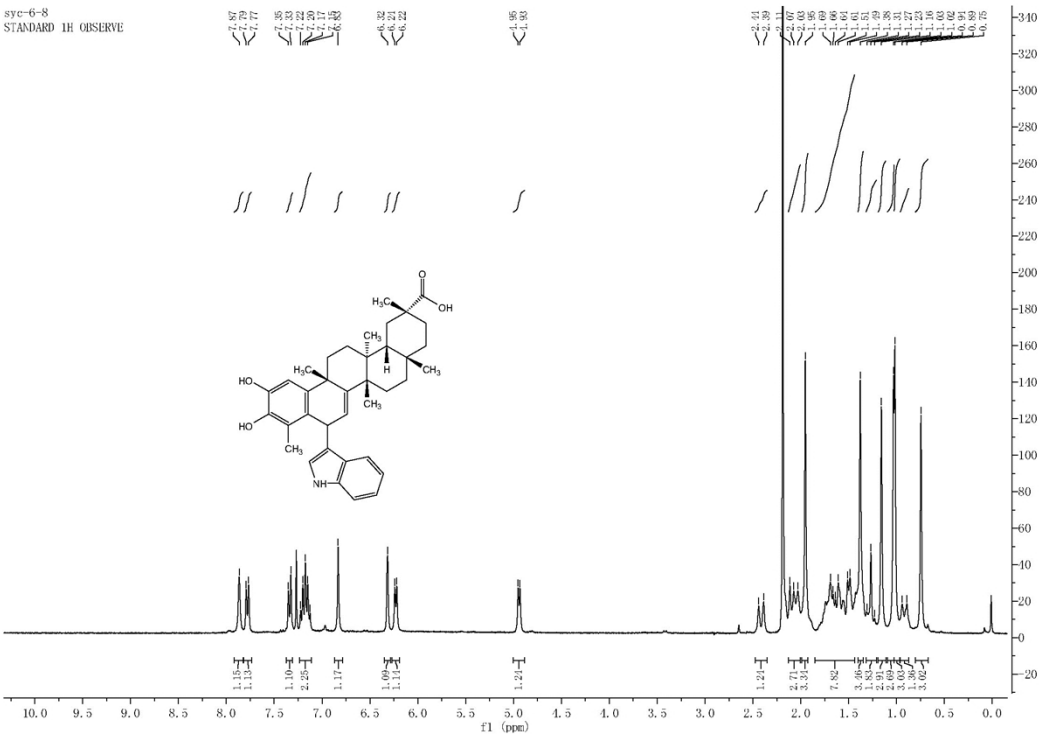
(2R,4aS,6aS,12bS,14aS,14bR)-methyl 8-(6-chloro-1-methyl-1H-indol-3-yl)-10,11-dimethoxy-2,4a,6a,9,12b,14a-hexamethyl-1,2,3,4,4a,5,6,6a,8,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylate: Starting from 85 mg **3h**, compound **4h** (35 mg, 38%) was obtained as a pink solid according to above – mentioned procedure. mp 225-227°C; [α]20 *D* −55.89° (MeOH, c = 0.2), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.4 Hz, 1H), 7.25 (d, *J* = 1.6 Hz, 2H), 7.10-7. 07 (m, 1H), 6.88-6.86 (m, 1H), 6.15-6.14 (m, 2H), 4.87 (d, *J* = 6.0 Hz, 1H), 3.92 (s, 3H), 3.76 (s, 3H), 3.58 (s, 3H), 3.56 (s, 3H), 2.45-2.40 (d, *J* = 15.9 Hz, 1H), 2.18 – 2.09 (m, 4H), 1.97 (s, 3H), 1.77 –

1.46 (m, 8H), 1.42 (s, 3H), 1.39-1.26 (m, 1H), 1.17 (s, 3H), 1.05 (s, 3H), 1.03 (s, 3H), 0.97-0.93 (m, 1H), 0.64 (s, 3H).^{13}C-NMR (125 MHz, DMSO-d_6)δ 178.49, 151.47, 146.71, 145.54, 145.10, 137.49, 128.14, 127.33, 127.25, 126.47, 125.96, 122.34, 120.78, 119.12, 118.57, 110.15, 106.79, 60.08, 55.82, 51.91, 44.26, 43.63, 37.72, 37.60, 37.48, 36.81, 35.57, 35.37, 35.15, 35.02, 34.89, 32.84, 31.81, 30.68, 30.57, 30.43, 29.91, 29.08, 22.14, 18.20, 11.80.IR (KBr) 2954.1, 2869.0, 1731.9, 1489.1, 1459.3, 1095.1, 801.3 cm^{-1}; HRMS(ESI)*m/z* calcd for $C_{41}H_{52}ClNO_4Na[M+Na]^+$ 680.3473, found 680.3477.

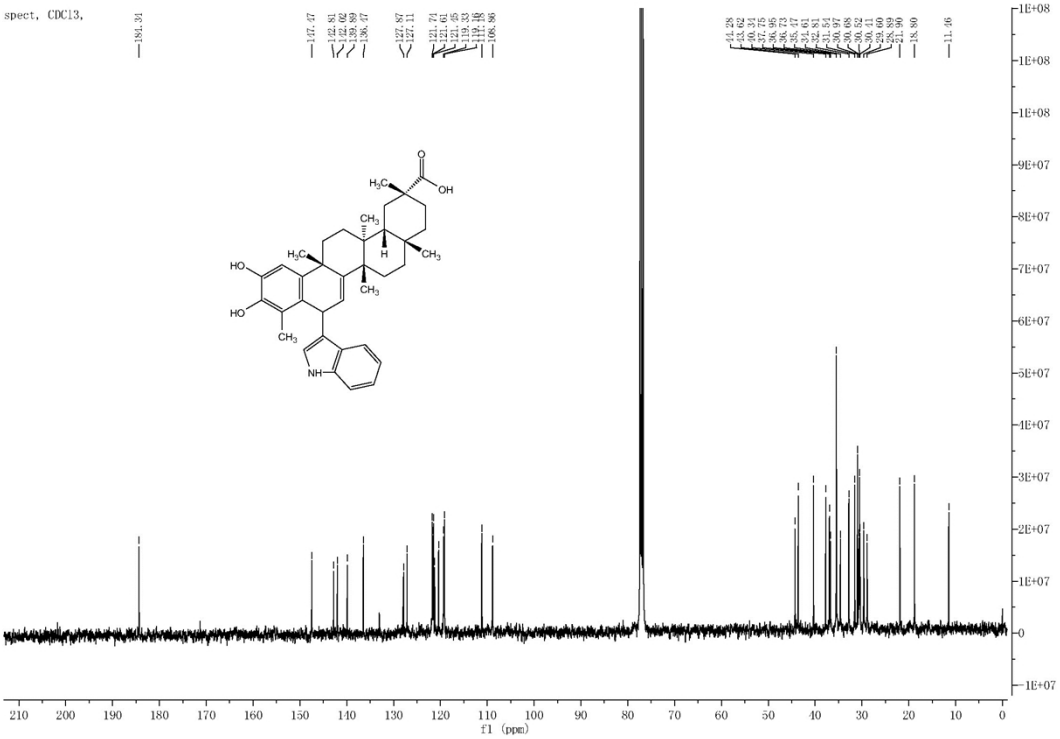
Compound 4i

(2R,4aS,6aS,12bS,14aS,14bR)-methyl 8-(6-bromo-1H-indol-3-yl)-10,11-dimethoxy-2,4a,6a,9,12b,14a-hexamethyl-1,2,3,4,4a,5,6,6a,8,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylate: Starting from 110 mg **3i**, compound **4i** (16 mg, 15%) was obtained as a reddish solid according to above‑mentioned procedure. mp 89-91°C; [α]20 *D* −61.06° (MeOH, c = 0.2), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.80-7.81 (m, 1H), 7.59-7.56 (m, 1H), 7.48 -7.47(m, 1H), 7.23-7.22 (m, 1H), 6.85 (s, 1H), 6.29-6.28 (m, 1H), 6.17 (d, *J* = 6.2 Hz, 1H), 4.88 (d, *J* = 5.8 Hz, 1H), 3.91 (s, 3H), 3.75 (s, 3H), 3.55 (s, 3H), 2.45-2.39 (m, 1H), 2.21-2.03 (m, 4H), 1.97 (s, 3H), 1.68 – 1.44 (m, 8H), 1.39 (s, 3H), 1.32-1.26 (m, 2H), 1.16 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 0.98-0.92 (m, 1H), 0.63 (s, 3H).^{13}C-NMR (125 MHz, DMSO-d_6) δ 178.42, 151.39, 146.45, 145.43, 145.07, 135.21, 128.59, 128.01, 127.46, 123.69, 123.60, 122.35, 121.35, 118.64, 113.94, 111.40, 106.81, 60.01, 55.84, 51.83, 44.19, 43.55, 37.66, 37.38, 36.73, 35.41, 35.11, 34.85, 34.80, 32.76, 31.74, 31.11, 30.59, 30.51, 30.37, 29.83, 29.05, 22.05, 18.12, 11.67.IR (KBr) 3430.9, 2942.7, 2868.6, 1729.0, 1487.4, 1455.4, 1093.8, 799.0 cm^{-1}; HRMS(ESI)*m/z* calcd for $C_{40}H_{50}BrNO_4Na[M+Na]^+$ 710.2824, found 710.2815.

Figure S1 NMR Spectrum of **3a**

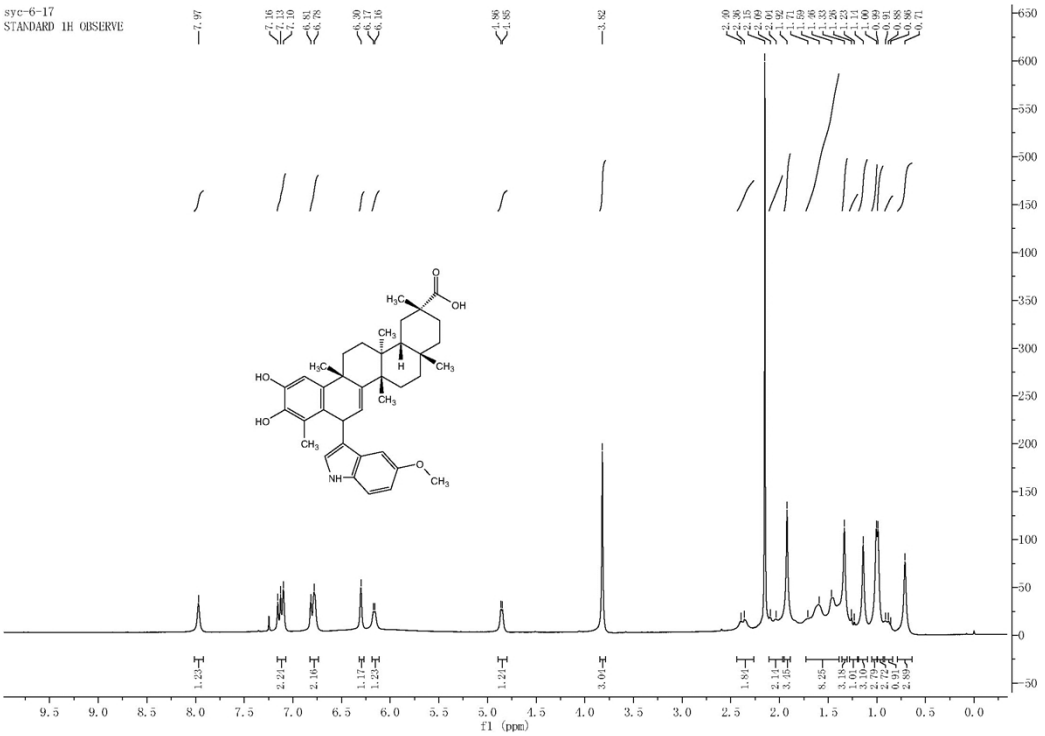


^{1}H-NMR (300 MHz, $CDCl_3$)

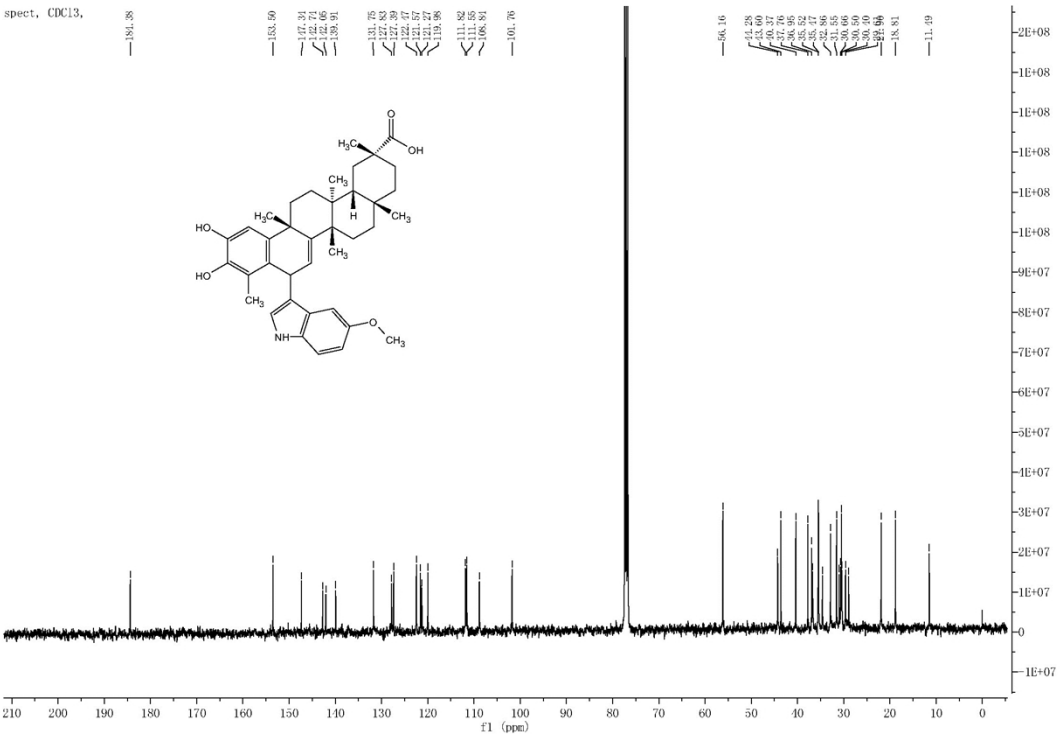


^{13}C-NMR (100 MHz, $CDCl_3$)

Figure S2 NMR Spectrum of **3c**

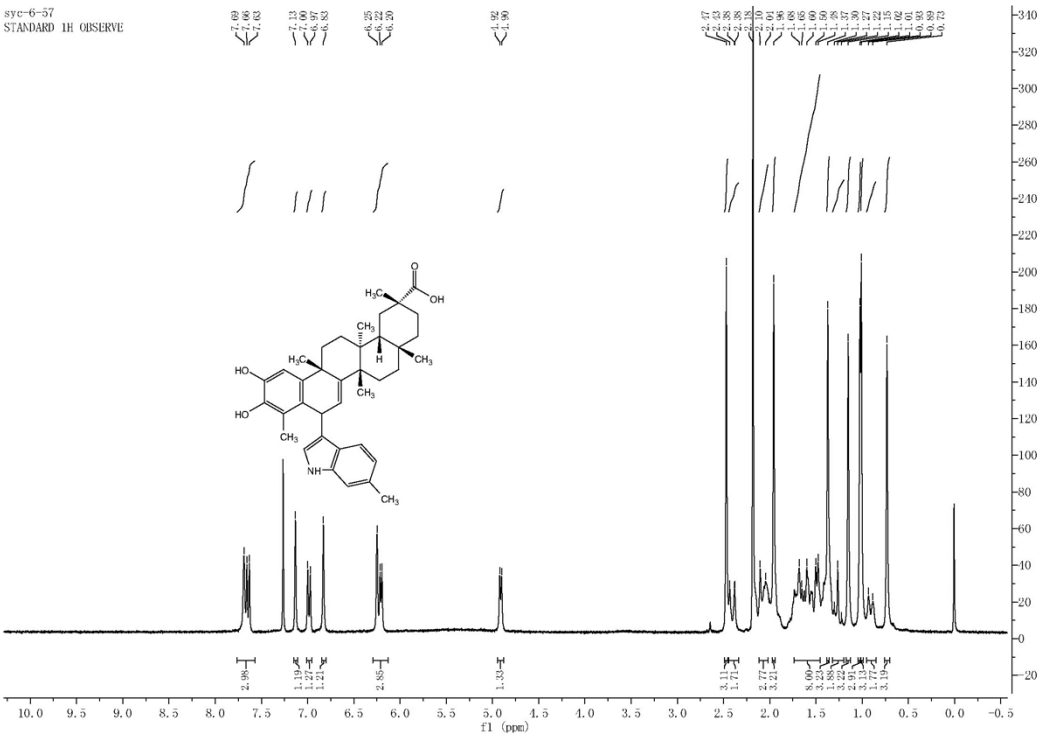


^{1}H-NMR (300 MHz, $CDCl_3$)

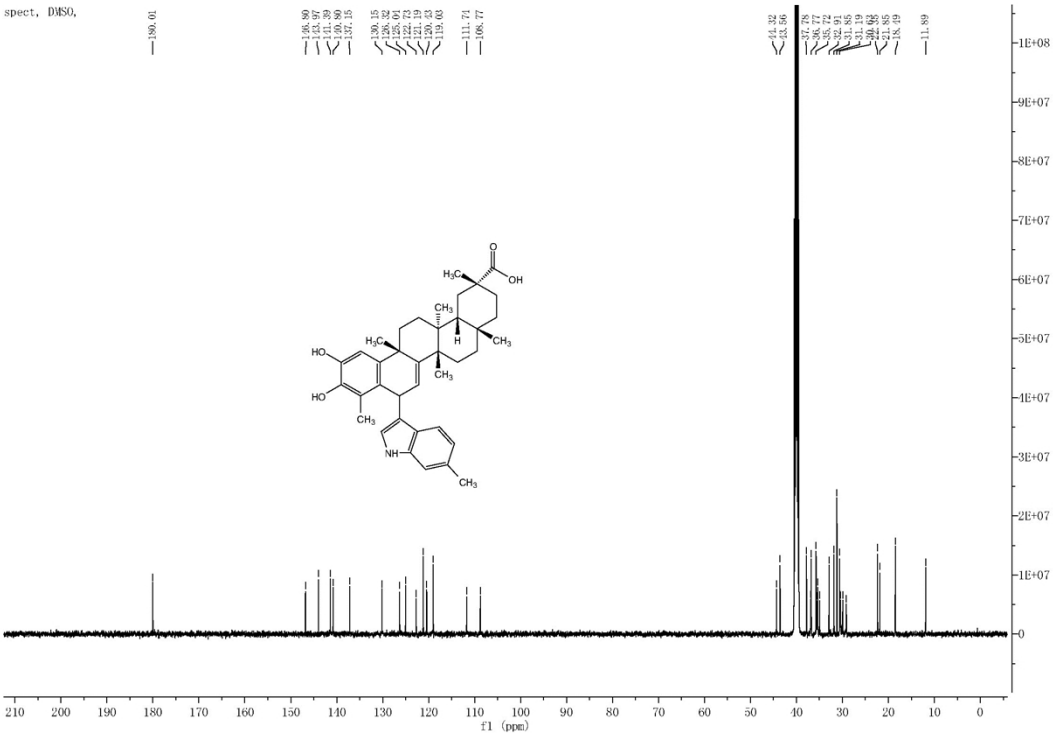


^{13}C-NMR (125 MHz, $CDCl_3$)

Figure S3 NMR Spectrum of **3f**

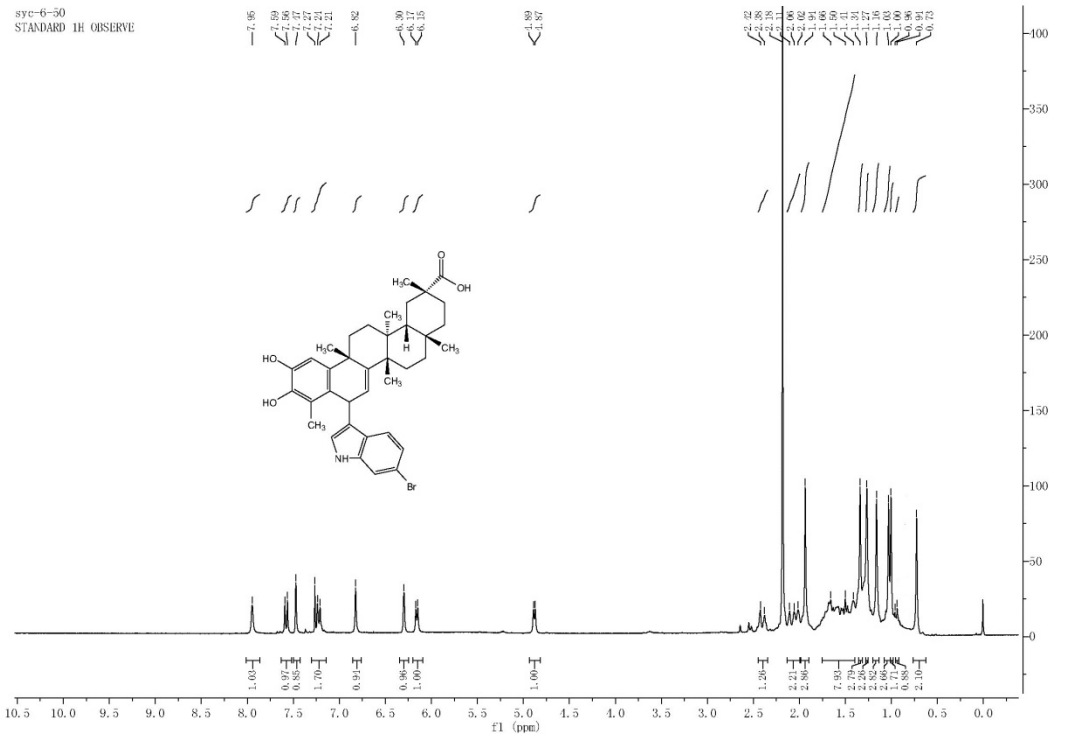


^{1}H-NMR (300 MHz, $CDCl_3$)

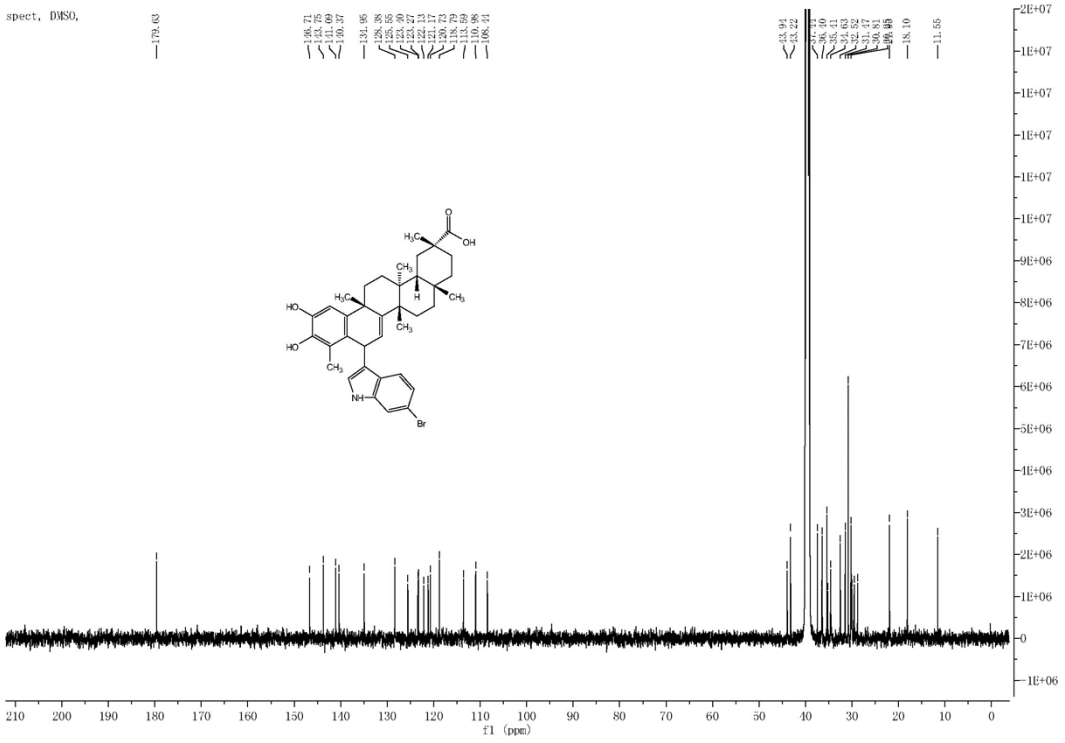


^{13}C-NMR (75 MHz, DMSO-d_6)

Figure S4 NMR Spectrum of **3i**

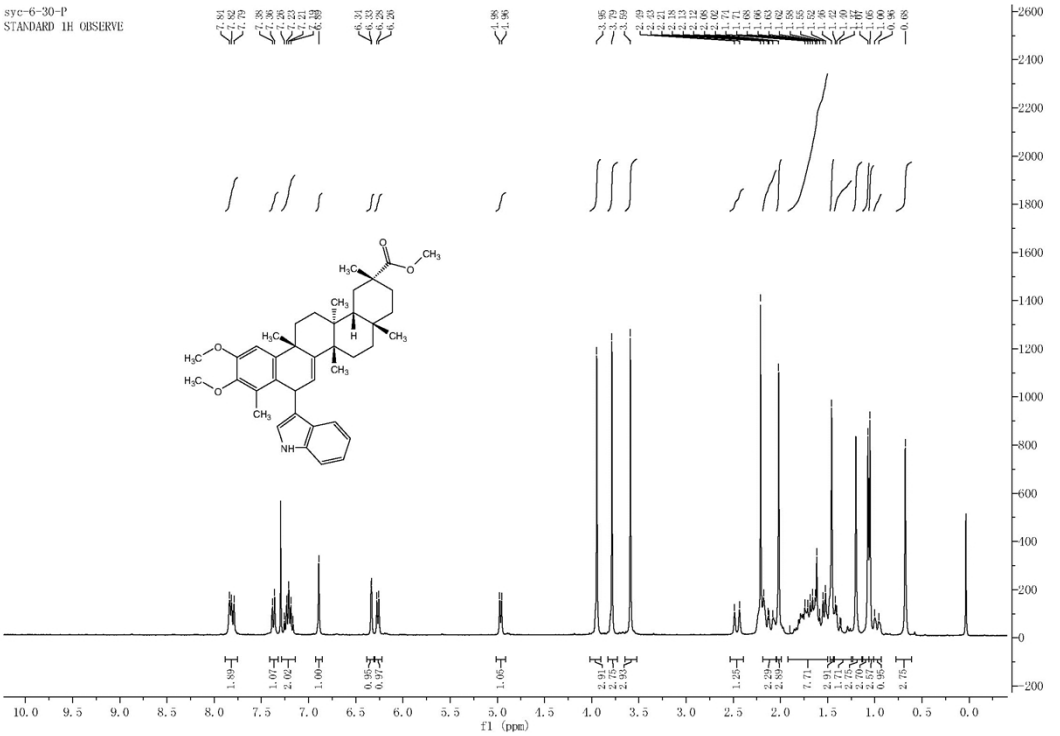


^{1}H-NMR (300 MHz, $CDCl_3$)

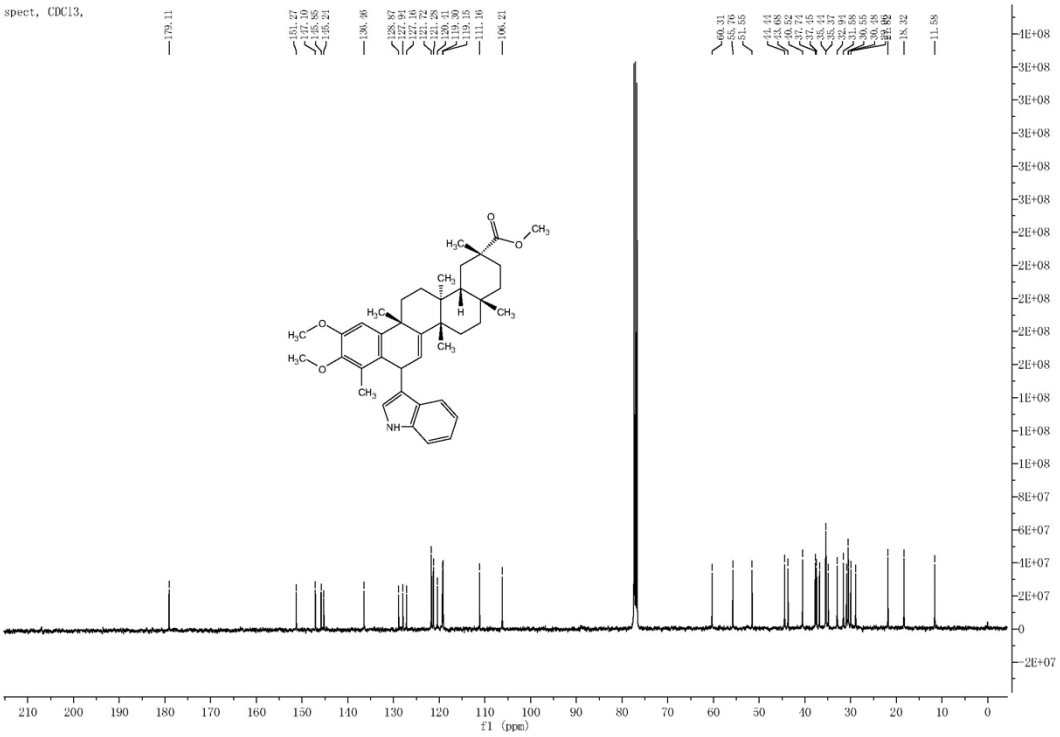


^{13}C-NMR (125 MHz, DMSO-d_6)

Figure S5 NMR Spectrum of **4a**

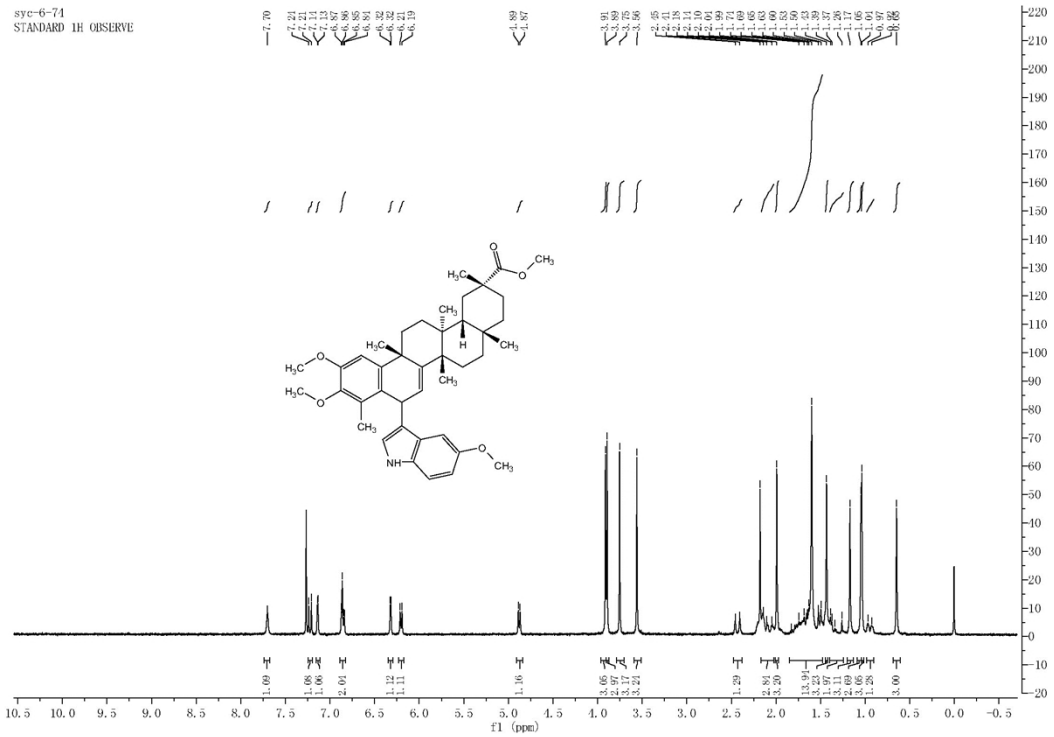


^{1}H-NMR (300 MHz, $CDCl_3$)

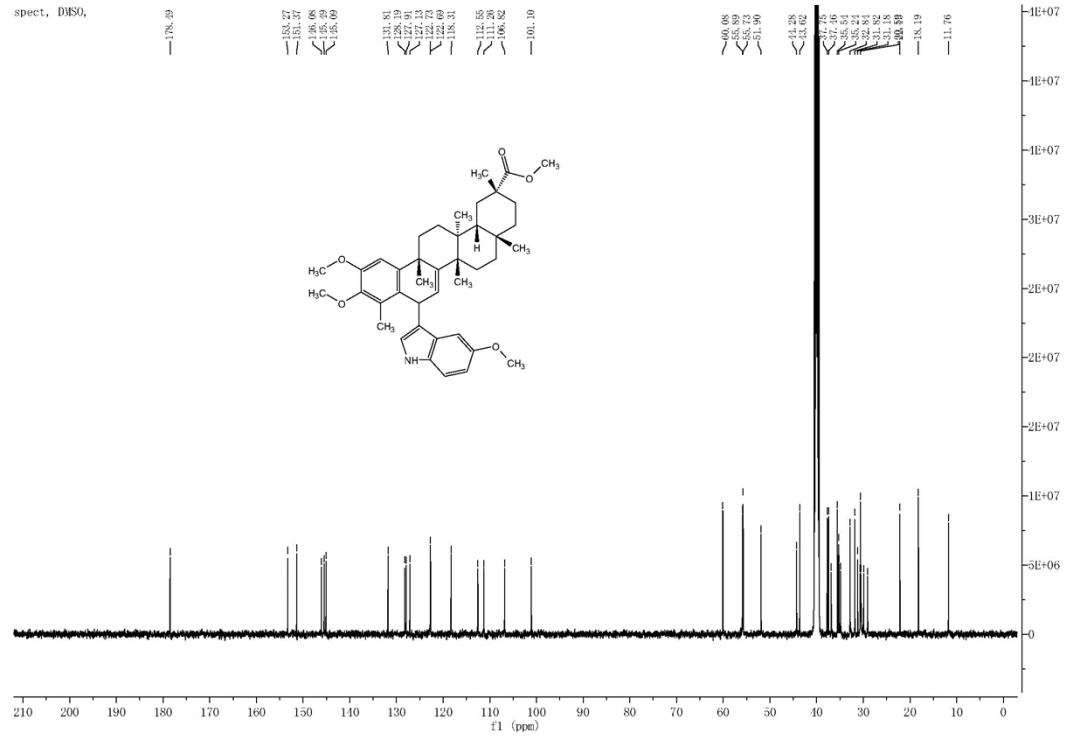


^{13}C-NMR (100 MHz, $CDCl_3$)

Figure S6 NMR Spectrum of **4c**

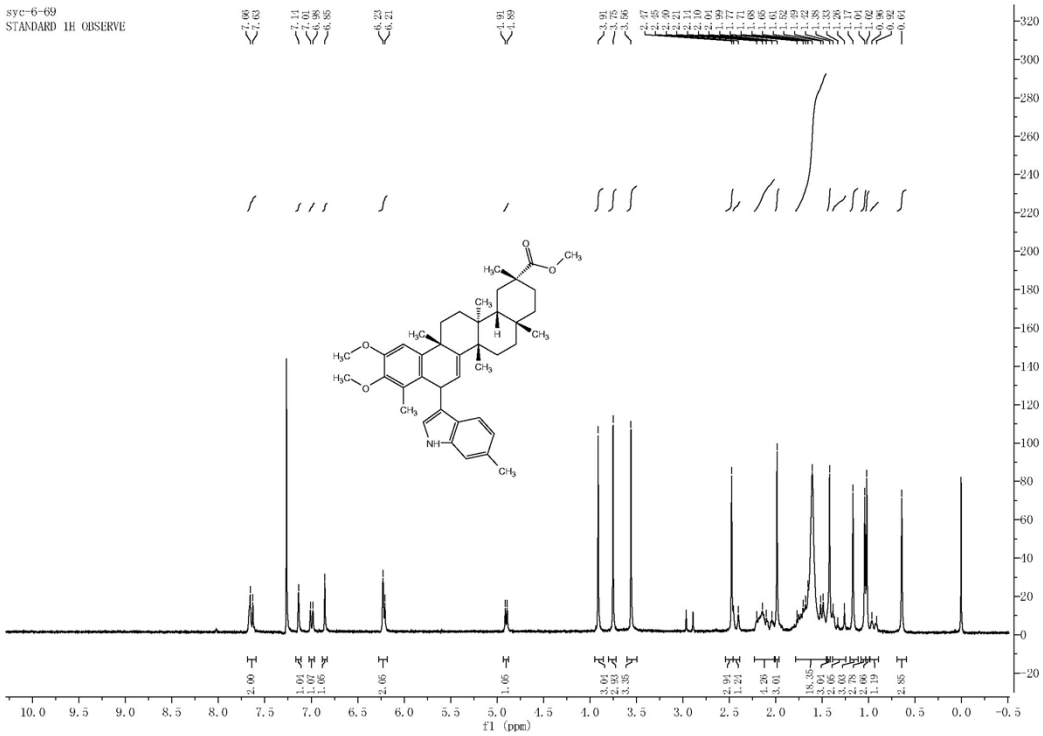


^{1}H-NMR (300 MHz, $CDCl_3$)

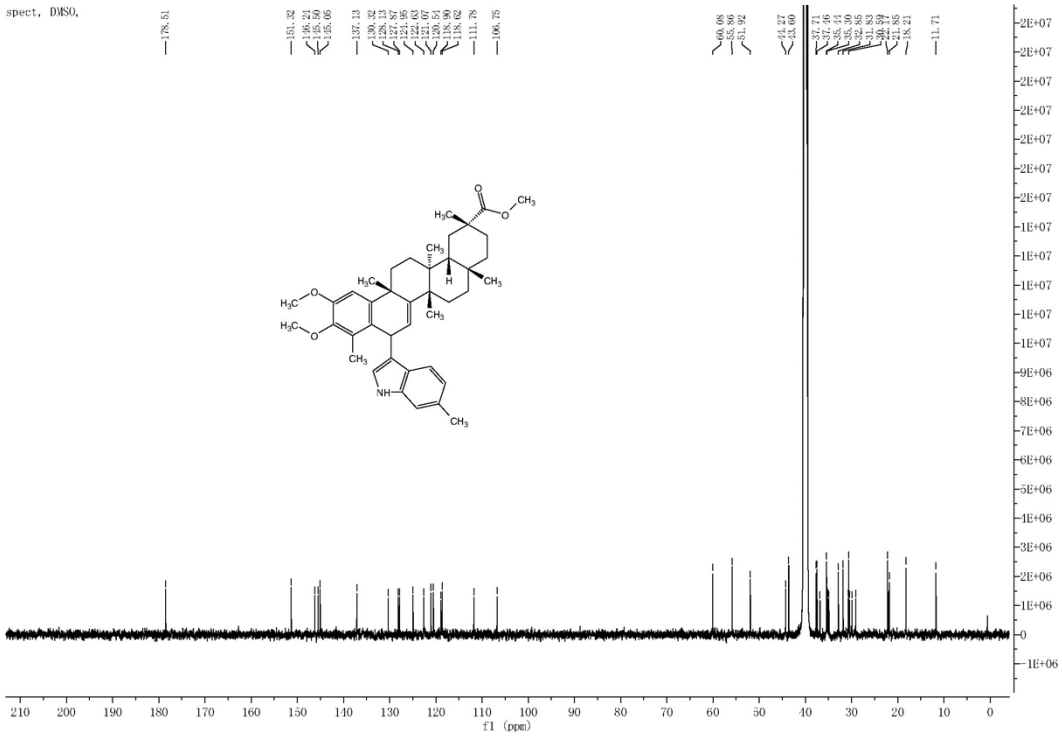


^{13}C-NMR (125 MHz, DMSO-d_6)

Figure S7 NMR Spectrum of **4f**

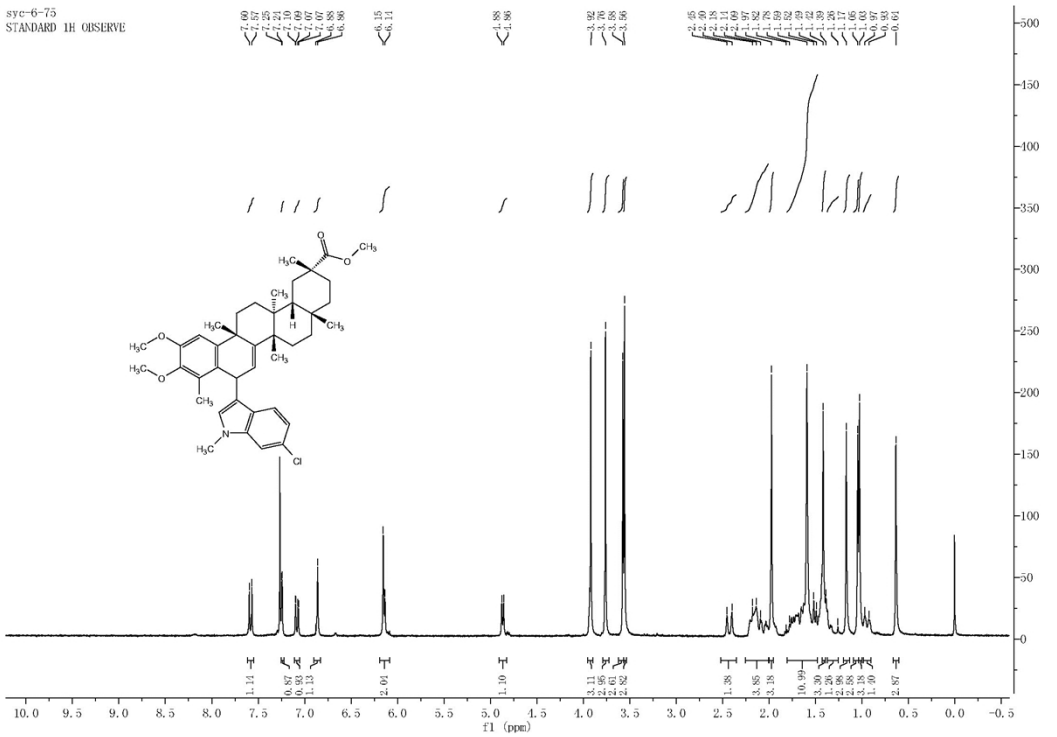


^{1}H-NMR (300 MHz, $CDCl_3$)

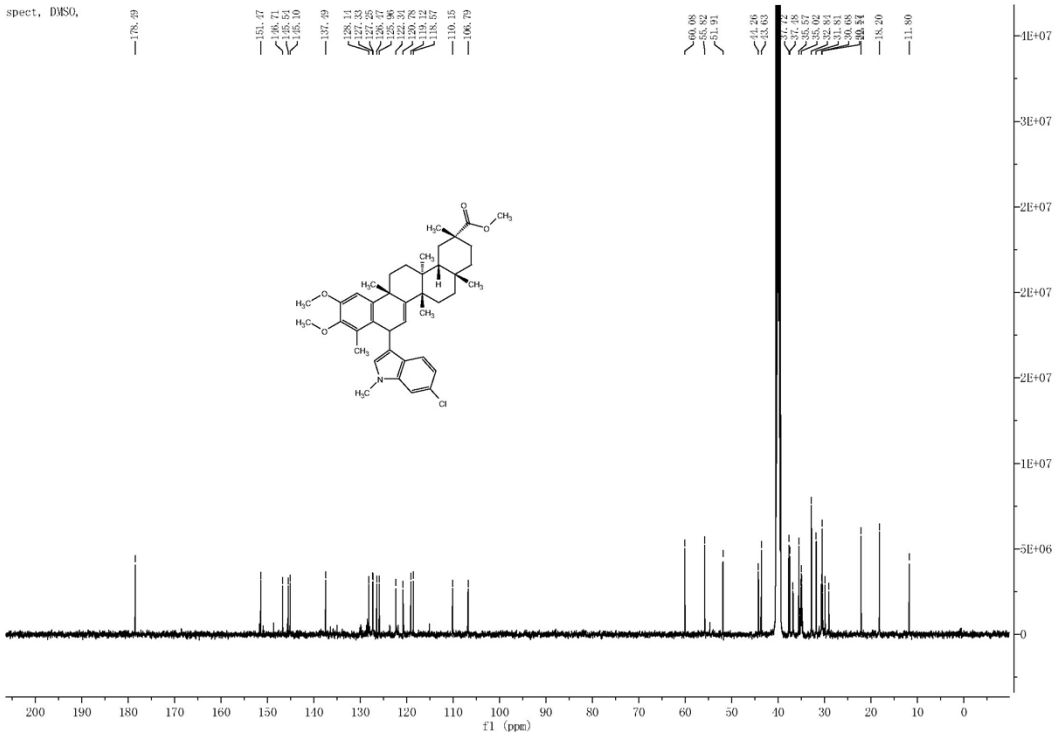


^{13}C-NMR (75 MHz, DMSO-d_6)

Figure S8 NMR Spectrum of **4h**



^{1}H-NMR (300 MHz, $CDCl_3$)



^{13}C-NMR (125 MHz, DMSO-d_6)