Supplementary data for

Novel heterocyclic ring fused oleanolic acid derivatives as osteoclast inhibitors for osteoporosis

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Experimental section

^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX400 spectrometer in $CDCl_3$ solutions using TMS (δ = 0 ppm) as references. ESI-MS and HR-ESI-MS spectra were obtained on a Finnigan TSQ-7000 mass spectrometer. All of the materials and reagents were obtained from commercial suppliers and were used without further purifications. Thin layer chromatography was carried out on precoated Kieselgel F254 plates (0.25 mm). Flash column chromatography was performed with silica gel (200-300 mesh).

The purity of all tested compounds was determined by HPLC method. HPLC analysis was conducted on a reversed-phase column (KR100-5C18, 250 mm × 4.6 mm) at ambient temperature with a flow rate of 1.0 ml/min and 10 μl samples were injected. The retention time was expressed in min at the UV detection of 210 nm. The mobile phase was composed of H_2O/CH_3CN (1:9, v/v). According to HPLC analysis, the purity of most compounds is > 95%.

Synthesis of compounds

Preparation of 3-Oxo olean-12-en-28-oic acid (A)

$Na_2HPO_4 \cdot 12H_2O$ (3.4 g, 9.6 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (1.5 g, 9.6 mmol) were dissolved in water (200 ml). $Na_2WO_4 \cdot 2H_2O$ (8.0 g, 24 mmol) was dissolved in cooled 35% aq. H_2O_2 (60 ml) and mixed with the previously phosphate buffer. OA (**1**) (22 g, 48 mmol) and DMF (70 ml) were added to a RBF with heating to 90 ^{o}C. The cooled mixture of Na_2WO_4-H_2O_2 with phosphete buffer was added dropwise to the DMF solution of OA for over 1 h followed by stirring for 1 h under the same reaction conditions. The aqueous phase was extracted with EtOAc (200 ml × 3). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give product A as white solid (20 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.28 (s, 1H), 2.82 (dd, J = 13.7, 4.0 Hz, 1H), 2.59–2.46 (m, 1H), 2.42–2.30 (m, 1H), 2.02–1.82 (m, 4H), 1.80–1.53 (m, 6H), 1.50–1.26 (m, 7H), 1.24–0.99 (m, 15H), 0.91 (s, 3H), 0.89 (s, 3H), 0.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 217.8, 184.4, 143.6, 122.4, 55.3,

47.4, 46.9, 46.6, 45.8, 41.7, 41.0, 39.3, 39.1, 36.8, 34.1, 33.8, 33.1, 32.4, 32.1, 30.7, 27.7, 26.4, 25.9, 23.6, 23.5, 22.9, 21.4, 19.5, 17.0, 15.0.

Preparation of 2-Hydroxymethylene-3-oxo olean-12-en-28-oic acid (B)

To a solution of A (9 g, 20 mmol) in dry toluene (30 ml) was added MeONa (2.8 mg, 50 mmol) slowly at room temperature. After stirring for 3 hrs, HCOOEt (4.5 g, 61 mmol) was added. The mixture was stirred at room temperature until complete conversion of the starting materials (~16 hrs). Then the mixture was poured into 1 N HCl (100 ml) and extracted with EtOAc (50 ml × 3). The organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated to afford B as white solid, which was used without further purification (yield > 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 14.90 (d, J = 2.6 Hz, 1H), 8.59 (d, J = 2.6 Hz, 1H), 5.33 (t, J = 3.2 Hz, 1H), 2.84 (dd, J = 13.5, 3.6 Hz, 1H), 2.28 (d, J = 14.4 Hz, 1H), 2.07–1.83 (m, 4H), 1.80–1.30 (m, 12H), 1.26–1.05 (m, 13H), 0.93–0.90 (m, 9H), 0.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.6, 188.5, 183.9, 143.6, 122.4, 105.7, 52.1, 46.6, 45.9, 45.7, 41.8, 41.1, 40.1, 39.2, 39.1, 36.4, 33.8, 33.1, 32.4, 31.1, 30.7, 28.5, 27.7, 25.8, 23.6, 22.5, 20.9, 19.5, 16.9, 14.5. ESI-MS *m/z*: 483 $[M + H]^+$.

*Preparation of Pyrazolo[3,4-b]olean-12-en-28-oic acid (**2**)*

To a solution of B (8.0 g, 16.8 mmol) in ethanol (150 ml) was added hydrazine dihydrochloride (1.6 g, 15.4 mmol) at room temperature. The reaction mixture was heated under reflux for 4 hrs. After cooling, the reaction mixture was concentrated. The residue was purified by silica gel chromatography (petroleum ether/AcOEt:5/2 v/v) to give the desired compound **2** (7.0 g, 92%) as yellow solid; mp 236–238 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20 (s, 1H), 5.36 (s, 1H), 2.90 (d, J = 11.6 Hz, 1H), 2.55 (d, J = 14.7 Hz, 1H), 2.03–1.59 (m, 11H), 1.51–1.12 (m, 17H), 0.94 (s, 3H), 0.91 (s, 3H), 0.83 (s, 3H), 0.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 183.0 (*C*=O), 150.3 (*C*-3), 143.9 (*C*-13), 131.8 (*C*-NH), 122.3 (*C*-12), 112.9 (*C*-2), 53.3, 46.6, 46.2, 46.1, 41.9, 41.3, 39.4, 38.4, 36.2, 34.0, 33.4, 33.1, 32.5, 32.1, 31.2, 30.7, 27.8, 25.8, 24.0, 23.6, 23.4, 23.2, 19.2, 16.6, 15.1 (CR_4, CHR_3, CH_2R_2, CH_3R). ESI-MS *m/z*: 479 [M +

H]$^+$, HR-ESI-MS *m/z*: calcd for $C_{31}H_{47}N_2O_2$ [M + H]$^+$ 479.3632; found 479.3631.

*General procedure for preparation of compounds **2a, 2b, 2c** and**2d***

To a RBF was added compound **2** (1.0 g, 2.0 mmol) and $SOCl_2$ (10 ml). The mixture was stirred at room temperature for 2 hrs. The mixture was concentrated to dryness under reduced pressure. Hexane (3 × 50 ml) was added to the residue, then the solution was concentrated to dryness to give acid chloride. To an anhydrous CH_2Cl_2 (50 ml) solution of each corresponding amines (3 mmol) and triethylamine (1 ml) was added the above acid chloride. The reaction mixture was stirred at room temperature for 0.5 hrs, and then concentrated and chromatographed (petroleum ether/ethyl acetate) to yield corresponding compounds **2a**, **2b**, **2c** and **2d**, respectively.

*Compound N-benzyl pyrazolo[3,4-b]olean-12-en-28-amide (**2a**)*, brown solid; yield 69%; mp 213–215 ^{o}C. IR (KBr):2946, 1655, 1517, 1452, 755, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.25 (m, 6H), 6.24 (t, J = 5.2 Hz, 1H), 5.38 (t, J = 3.2 Hz, 1H), 4.63 (dd, J = 14.7, 6.2 Hz, 1H), 4.17 (dd, J = 14.7, 4.3 Hz, 1H), 2.62–2.53 (m, 2H), 2.07–1.91 (m, 4H), 1.84–1.56 (m, 8H), 1.51–1.36 (m, 3H), 1.33–1.10 (m, 14H), 0.92 (s, 6H), 0.84 (s, 3H), 0.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.1 (*C*=O), 144.7 (*C*-13), 138.4, 128.7×2, 127.8×2, 127.4 (Ph), 123.0 (*C*-12), 112.2 (*C*-2), 53.3, 46.7, 46.5, 46.1, 43.6, 42.5, 42.3, 395, 38.4, 36.3, 34.2, 33.3, 33.0, 32.7, 31.9, 31.3, 30.8, 29.7, 27.4, 25.6, 24.0, 23.9, 23.4, 19.2, 16.7, 15.2 (*C*R$_4$, *C*HR$_3$, *C*H$_2$R$_2$, *C*H$_3$R). ESI-MS *m/z*: 568 [M + H]$^+$, HR-ESI-MS *m/z*: calcd for $C_{38}H_{54}N_3O$ [M + H]$^+$ 568.4261; found 568.4261.

*N-(3-morpholinopropyl) pyrazolo[3,4-b]olean-12-en-28-amide (**2b**)*, yellow solid; yield 75%; mp 238–240 ^{o}C. IR (KBr): 2946, 1648, 1508, 1459, 1384, 1364, 1118 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (s, 1H), 6.33 (t, J = 5.1 Hz, 1H), 5.44 (s, 1H), 3.76–3.69 (m, 4H), 3.47–3.42 (m, 1H), 3.12–3.10 (m, 1H), 2.63–2.55 (m, 2H), 2.45–2.37 (m, 6H), 2.06–2.02 (m, 4H), 1.78–1.46 (m, 11H), 1.41–1.29 (m, 6H), 1.23–1.09 (m, 9H), 0.92 (s, 6H), 0.88 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.1 (*C*=O), 144.8 (*C*-13), 122.7 (*C*-12), 112.1 (*C*-2), 66.9 (*C*H$_2$-O), 57.1, 53.8 (*C*H$_2$-N), 53.3, 46.7, 46.2, 46.1, 42.2, 39.4, 38.4, 38.3, 36.3, 34.1, 33.3, 33.0, 32.8,

31.7, 31.3, 30.7, 27.4, 25.7, 25.6, 24.0, 23.8, 23.6, 23.5, 19.2, 16.7, 15.2 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 605 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{38}H_{61}N_4O_2$ $[M + H]^+$ 605.4789; found 605.4792.

*N-(2-(piperidin-1-yl)ethyl) pyrazolo[3,4-b]olean-12-en-28-amide (**2c**)*, yellow solid; yield 68%; mp 177–178 °C. IR (KBr): 2939, 1655, 1637, 1508, 1458 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.24 (s, 1H), 6.70 (s, 1H), 5.45 (t, *J* = 3.4 Hz, 1H), 3.49-3.40 (m, 1H), 3.28–3.16 (m, 1H), 2.58 (d, *J* = 14.7 Hz, 2H), 2.45–2.40 (m, 5H), 2.10–1.92 (m, 4H), 1.77–1.42 (m, 15H), 1.41–1.22 (m, 9H), 1.21 (s, 3H), 1.19 (s, 3H), 1.12–1.08 (m, 1H), 0.93 (s, 3H), 0.92 (s, 3H), 0.87 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 177.9 (*C*=O), 144.4 (*C*-13), 122.8 (*C*-12), 112.4 (*C*-2), 56.9, 54.3 (*C*H_2-N), 53.3, 46.9, 46.4, 46.1, 42.4, 42.2, 39.5, 38.4, 36.3, 35.9, 34.2, 33.4, 33.0, 32.7, 31.9, 31.3, 30.8, 29.7, 27.4, 26,1, 25.7, 24.3, 24.1, 23.7, 23.5, 19.2, 16.6, 15.2 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 589 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{38}H_{61}N_4O$ $[M + H]^+$ 589.4840; found 589.4841.

*N-(1-benzylpiperidin-4-yl) pyrazolo[3,4-b]olean-12-en-28-amide (**2d**)*, brown solid; yield 59%; mp 197–198 °C. IR (KBr): 2946, 1655, 1508, 1455, 1384, 1364, 1177, 739, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.31–7.24 (m, 5H), 5.77 (d, *J* = 7.4 Hz, 1H), 5.39 (s, 1H), 3.85–3.75 (m, 1H), 3.51 (d, *J* = 1.6 Hz, 2H), 2.81 (s, 2H), 2.59–2.53 (m, 2H), 2.15–1.34 (m, 22H), 1.30 (s, 3H), 1.29–1.23 (m, 2H), 1.20 (s, 4H), 1.18 (s, 3H), 1.11 (d, *J* = 13.5 Hz, 1H), 0.91 (s, 6H), 0.87 (s, 3H), 0.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 177.4 (*C*=O), 144.5 (*C*-13), 138.1, 129.2×2, 128.2×2, 127.1 (Ph), 122.7 (*C*-12), 112.3 (*C*-2), 63.2 (N-*C*H_2-Ph), 53.3 (*C*H_2-N), 52.4, 52.3, 46.8, 46.4, 46.1, 42.5, 42.4, 39.5, 38.4, 36.4, 34.2, 33.4, 33.0, 31.3, 30.7, 29.7, 27.4, 25.4, 19.2, 17.3, 15.3 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 651 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{43}H_{63}N_4O$ $[M + H]^+$ 651.4996; found 651.4996.

*Preparation of N-benzyl 1-methylpyrazolo[3,4-b] olean-12-en-28-amide (**3a**)*

To a solution of **2a** (113 mg, 0.2 mmol) and K_2CO_3 (40 mg, 0.3 mmol) in DMF (10 ml) was added CH_3I (0.2 ml) at room temperature. The mixture was stirred at room temperature until complete conversion of the starting material (~2 hrs). The reaction

was quenched by adding aq. NH_4Cl and diluted with DCM. The aqueous phase was extracted with DCM (15 ml × 3). The combined extracts were washed with brine, and then dried (Na_2SO_4) and concentrated in vacuo. Purification by silica gel column chromatography (petroleum ether/AcOEt:2/1 v/v) provided **3a** (90.0 mg, 77%) as white solid; mp 178–181 °C. IR (KBr): 2946, 1655, 1648, 1517, 1453, 755, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.33–7.25 (m, 5H), 6.94 (s, 1H), 6.25–6.17 (m, 1H), 5.37 (s, 1H), 4.63 (dd, J = 14.7, 6.3 Hz, 1H), 4.16 (dd, J = 14.7, 4.3 Hz, 1H), 3.82 (s, 3H), 2.58 (dd, J = 13.0, 3.5 Hz, 1H), 2.52 (d, J = 14.7 Hz, 1H), 2.07–1.89 (m, 4H), 1.83–1.58 (m, 7H), 1.53–1.33 (m, 4H), 1.30 (s, 3H), 1.28–1.26 (m, 2H), 1.21 (s, 3H), 1.19 (s, 3H), 1.14–1.10 (m, 1H), 0.91 (s, 6H), 0.84 (s, 3H), 0.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.1 (*C*=O), 156.5 (*C*-3), 144.8 (*C*-13), 138.5, 128.7×2, 127.8×2, 127.4 (Ph), 127.3 (*C*-N-CH_3), 123.0 (*C*-12), 113.3 (*C*-2), 53.5, 46.7, 46.5, 46.1, 43.6, 42.5, 42.3, 39.4, 38.7, 38.0, 36.4, 34.2, 34.1, 33.0, 32.7, 31.9, 31.7, 30.8, 29.7, 27.4, 25.5, 24.5, 23.9, 23.6, 23.4, 19.4, 16.6, 15.2 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 582 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{39}H_{56}N_3O$ $[M+H]^+$ 582.4418; found 582.4421.

*General procedure for preparation of compounds **3b, 4a-f, 5a-j** and **6a-j***

To a solution of **2a** (113 mg, 0.2 mmol) in dry DCM (15 ml) was added 4-chlorobenzene-1-sulfonyl chloride (60 mg, 0.3 mmol) and triethylamine 0.1 ml) at room temperature. The mixture was stirred at room temperature until complete conversion of the starting materials (~0.5 hrs). The reaction was quenched by adding aq. NH_4Cl and diluted with DCM. The aqueous phase was extracted with DCM (20 ml × 3). The combined extracts were washed with brine, dried with anhydrous Na_2SO_4 and concentrated in vacuo. Purification by silica gel column chromatography (petroleum ether/AcOEt:5/1 v/v) provided **3b** (135.0 mg, 91%) as white solid. Compounds **4a-f, 5a-j** and **6a-j** were prepared following the same protocol.

*N-benzyl 1-(4-chlorophenyl)sulfonylpyrazolo[3,4-b]olean-12-en-28-amide (**3b**)*, white solid; yield 91%; mp 167–169 °C. IR (KBr): 2943, 1655, 1508, 1524, 1459, 1383, 1189, 745, 699, 615, 580 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.87 (d, J = 8.8

Hz, 2H), 7.62 (d, *J* = 0.7 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.35–7.24 (m, 5H), , 6.17 (t, *J* = 5.2 Hz, 1H), 5.35 (t, *J* = 3.4 Hz, 1H), 4.60 (dd, *J* = 14.7, 6.2 Hz, 1H), 4.17 (dd, *J* = 14.6, 4.4 Hz, 1H), 2.62–2.54 (m, 2H), 2.04–1.85 (m, 4H), 1.82–1.61 (m, 6H), 1.55–1.33 (m, 5H), 1.27–1.08 (m, 13H), 0.91 (s, 3H), 0.91 (s, 3H), 0.73 (s, 3H), 0.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 177.9 (*C*=O), 165.1 (*C*-3), 144.8 (*C*-13), 140.6, 138.4, 136.2, 129.4×2, 129.1×2, 128.7×2, 128.5, 127.8×2 (Ph), 127.4 (*C*-NH), 122.6 (*C*-12), 119.1 (*C*-2), 53.0, 46.6, 46.4, 45.8, 43.6, 42.4, 42.2, 39.4, 37.8, 36.0, 34.6, 34.2, 33.0, 32.7, 31.7, 31.3, 30.8, 27.4, 25.5, 24.6, 23.9, 23.6, 23.9, 23.6, 23.4, 19.3, 16.6, 15.1 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 764, 766 $[M + Na]^+$, HR-ESI-MS *m/z*: calcd for $C_{44}H_{56}{}^{35}ClN_3NaO_3S$ $[M + Na]^+$ 764.3623; found 764.3626.

*N-(3-morpholinopropyl) 1-(4-fluorophenyl)sulfonylpyrazolo[3,4-b]olean-12-en-28-amide (**4a**)*, white solid; yield 82%; mp 267–269 °C. IR (KBr): 2950, 2850, 2818, 1655, 1520, 1384, 1191, 827, 759, 667 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.00–7.92 (m, 2H), 7.64 (s, 1H), 7.19–7.11 (m, 2H), 6.32 (s, 1H), 5.41 (t, *J* = 3.3 Hz, 1H), 3.74 (s, 4H), 3.46–3.38 (m, 1H), 3.14–3.07 (m, 1H), 2.67–2.58 (m, 2H), 2.44 (m, 6H), 2.04–1.94 (m, 4H), 1.80–1.67 (m, 4H), 1.65–1.53 (m, 5H), 1.51–1.31 (m, 4H), 1.25 (s, 3H), 1.21 (s, 2H), 1.17 (s, 3H), 1.16 (s, 3H), 1.08 (m, 1H), 0.92 (s, 3H), 0.91 (s, 3H), 0.80 (s, 3H), 0.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 178.0 (*C*=O), 167.0 (*C*-3), 164.9, 164.5 (Ph), 144.9 (C-13), 133.8, 130.6 (Ph), 128.5 (*C*-N-SO_2), 122.3 (*C*-12), 119.0 (*C*-2), 116.5, 116.3 (Ph), 66.8 (*C*H_2-O), 57.1, 53.8 (*C*H_2-N), 53.0, 46.6, 46.2, 45.9, 42.2, 42.1, 39.4, 37.9, 36.0, 34.6, 34.1, 33.0, 32.9, 31.8, 31.3, 30.8, 27.3, 25.6, 24.5, 23.8, 23.6, 23.4, 19.3, 16.6, 15.1 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 763 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{44}H_{64}FN_4O_4S$ $[M + H]^+$ 763.4627; found 763.4628.

*N-(3-morpholinopropyl) 1-(4-chlorophenyl)sulfonylpyrazolo[3,4-b]olean-12-en-28-amide (**4b**)*, white solid; yield 92%; mp 182–183 °C. IR (KBr): 2945, 2860, 1655, 1590, 1384, 1199, 1131, 682, 654, 580 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.87 (d, *J* = 8.7 Hz, 2H), 7.64 (s, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 6.30 (t, *J* = 4.8 Hz, 1H), 5.40 (t, *J* = 3.3 Hz, 1H), 3.73 (t, *J* = 4.6 Hz, 4H), 3.42 (dd, *J* = 13.3, 6.5 Hz, 1H), 3.15–3.06

(m, 1H), 2.64–2.58 (m, 2H), 2.64–2.38 (m, 6H), 2.06–1.92 (m, 4H), 1.79–1.32 (m, 14H), 1.25 (s, 3H), 1.21 (s, 2H), 1.18 (s, 3H), 1.16 (s, 3H), 1.08 (m, 1H), 0.92 (s, 3H), 0.91 (s, 3H), 0.80 (s, 3H), 0.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.9 (*C*=O), 165.0 (*C*-3), 144.9 (*C*-13), 140.6, 136.2, 129.4×2, 129.1×2 (Ph), 128.5 (*C*-N-SO_2), 122.3 (*C*-12), 119.1 (*C*-2), 66.8 (*C*H_2-O), 57.1, 53.8 (*C*H_2-N), 53.0, 46.6, 46.2, 45.9, 42.2, 42.1, 39.3, 38.3, 37.8, 36.0, 34.6, 34.1, 33.0, 32.9, 31.7, 31.3, 30.7, 29.7, 27.3, 25.6, 24.5, 23.8, 23.6, 23.4, 19.3, 16.6, 15.2 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 779, 781 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{44}H_{64}{}^{35}ClN_4O_4S$ $[M + H]^+$ 779.4331; found 779.4335.

*N-(3-morpholinopropyl) 1-(3,5-dimethylisoxazol-4-yl)sulfonylpyrazolo[3,4-b]-olean-12-en-28-amide (**4c**)*, light yellow solid; yield 90%; mp 160–162 °C. IR (KBr): 2943, 2859, 1655, 1587, 1509, 1377, 1265, 1170, 675, 619 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 (s, 1H), 6.32 (s, 1H), 5.42 (t, *J* = 3.3 Hz, 1H), 3.74 (s, 4H), 3.43 (dd, *J* = 13.3, 6.5 Hz, 1H), 3.18–3.05 (m, 1H), 2.72 (s, 3H), 2.64–2.61 (m, 2H), 2.53–2.39 (m, 8H), 2.08–1.92 (m, 4H), 1.82–1.29 (m, 15H), 1.28–1.20 (m, 6H), 1.19 (s, 3H), 1.17 (s, 3H), 1.08–1.11 (m, 1H), 0.92 (s, 3H), 0.91 (s, 3H), 0.82 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.9 (*C*=O), 175.3 (O-*C*-CH_3), 164.6 (*C*-3), 158.0 (N-*C*-CH_3), 144.9 (*C*-13), 127.4 (*C*-N-SO_2), 122.3 (*C*-12), 118.8 (*C*-2), 114.7 (*C*-SO_2), 66.8 (*C*H_2-O), 57.1, 53.8 (*C*H_2-N), 53.0, 46.6, 46.2, 45.9, 42.2, 42.1, 39.4, 38.3, 37.9, 36.0, 34.6, 34.1, 33.0, 32.9, 31.7, 31.3, 30.8, 29.7, 27.3, 25.6, 24.6, 23.8, 23.6, 23.4, 19.3, 16.6, 15.2 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 764 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{43}H_{66}N_5O_5S$ $[M + H]^+$ 764.4779; found 764.4776.

*N-(3-morpholinopropyl) 1-(4-(tert-butyl)phenyl)sulfonylpyrazolo[3,4-b]olean-12-en-28-amide (**4d**)*, white solid; yield 85%; mp 254–255 °C. IR (KBr): 2946, 1654, 1648, 1517, 1453, 1383, 810, 729, 635, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 (d, *J* = 8.3 Hz, 2H), 7.65 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 6.32 (t, *J* = 5.3 Hz, 1H), 5.41 (s, 1H), 3.72 (t, *J* = 4.2 Hz, 4H), 3.45–3.40 (m, 1H), 3.13–3.08 (m, 1H), 2.64–2.58 (m, 2H), 2.45 (s, 4H), 2.39 (t, *J* = 6.8 Hz, 2H), 2.04–1.95 (m, 4H), 1.78–1.36 (m, 12H), 1.30 (s, 9H), 1.26 (s, 6H), 1.22 (s, 2H), 1.19 (s, 3H), 1.16 (s, 3H), 1.08 (d, *J* =

13.8 Hz, 1H), 0.92 (s, 3H), 0.91 (s, 3H), 0.81 (s, 3H), 0.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.9 (*C*=O), 164.3 (*C*-3), 157.8 (Ph), 144.9 (*C*-13), 134.9 (Ph), 128.5 (*C*-N-SO_2), 127.4×2, 126.0×2 (Ph), 122.3 (*C*-12), 118.6 (*C*-2), 66.9 (*C*H_2-O), 57.2, 53.8 (*C*H_2-N), 53.1, 46.6, 46.2, 45.9, 42.2, 39.3, 38.4, 37.9, 36.0, 35.3, 34.6, 34.1, 33.0, 32.9, 31.8, 31.2, 31.0, 30.7, 29.7, 27.3, 25,7, 25.6, 24.5, 23.8, 23.6, 23.4, 22.7, 19.3, 16.6, 15.1, 14.1 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 801 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{48}H_{73}N_4O_4S$ $[M + H]^+$ 801.5347; found 801.5352.

*N-(3-morpholinopropyl) 1-(4-(trifluoromethoxy)phenyl)sulfonylpyrazolo[3,4-b] olean-12-en-28-amide (**4e**)*, white solid; yield 80%; mp 172–174 °C. 2951, 2852, 1658, 1521, 1469, 1377, 1179, 1118, 644, 625, 590 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.66 (s, 1H), 6.32 (t, *J* = 5.2 Hz, 1H), 5.41 (s, 1H), 3.73 (d, *J* = 4.4 Hz, 4H), 3.45–3.40 (m, 1H), 3.17–3.07 (m, 1H), 2.69–2.58 (m, 2H), 2.45 (s, 4H), 2.39 (t, *J* = 6.8 Hz, 2H), 2.04–1.95 (m, 4H), 1.76–1.55 (m, 9H), 1.51–1.31 (m, 4H), 1.25 (s, 4H), 1.22 (s, 2H), 1.18 (s, 3H), 1.16 (s, 3H), 1.08 (d, *J* = 13.7 Hz, 1H), 0.92 (s, 3H), 0.91 (s, 3H), 0.81 (s, 3H), 0.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.9 (*C*=O), 165.5 (*C*-3), 144.9 (*C*-13), 141.2, 135.5, 135.2 (*C*F_3), 128.6 (*C*-N-SO_2), 128.2×2, 126.2, 124.4 (Ph), 122.2 (*C*-12), 121.6 (Ph), 119.5 (*C*-2), 66.9 (*C*H_2-O), 57.2, 53.8 (*C*H_2-N), 53.0, 46.6, 46.2, 45.9, 42.2, 42.1, 39.3, 38.4, 37.8, 35.9, 34.6, 34.1, 33.0, 32.9, 31.7, 31.2, 30.7, 27.3, 25.7, 25.6, 24.5, 23.8, 23.6, 23.4, 19.3, 16.6, 15.1 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 813 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{45}H_{64}F_3N_4O_4S$ $[M + H]^+$ 813.4595; found 813.4597.

*N-(3-morpholinopropyl) 1-(3,4-dimethoxyphenyl)sulfonylpyrazolo[3,4-b]olean-12-en-28-amide (**4f**)*, white solid; yield 90%; mp 236–237 °C. 2948, 2862, 1657, 1518, 1384, 1322, 1182, 1062, 715, 637, 615, 603 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.96 (s, 1H), 7.49 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.28 (d, *J* =3.9 Hz, 1H), 7.26 (m, 1H), 7.15 (d, *J* = 8.8 Hz, 1H), 5.26 (d, *J* = 3.3 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.60–3.52 (m, 4H), 3.12–2.95 (m, 2H), 2.81 (d, *J* = 9.7 Hz, 1H), 2.56 (d, *J* = 15.5 Hz, 1H), 2.41–2.17 (m, 6H), 1.99–1.85 (m, 4H), 1.71–1.21 (m, 14H), 1.18 (s, 3H), 1.08 (m, 8H), 0.96 (m, 1H), 0.88 (s, 3H), 0.87 (s, 3H), 0.71 (s, 3H), 0.68 (s, 3H). ^{13}C NMR

(100 MHz, DMSO-d_6) δ: 176.1 (*C*=O), 163.6 (*C*-3), 153.5, 148.7 (Ph), 144.0 (*C*-13), 129.3 (Ph), 128.1(*C*-N-SO_2), 121.4 (*C*-12), 121.2 (Ph), 118.5 (*C*-2), 111.3, 109.3 (Ph), 66.1 (*C*H_2-O), 56.2 (*C*H_2-N), 56.0, 55.9 (O-*C*H_3), 53.4 (*C*H_2-N), 52.2, 45.2, 41.4, 40.5, 37.4, 35.2, 34.0, 33.6), 32.9, 31.1, 30.4, 27.0, 25.9, 25.4, 24.5, 23.5, 22.3 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 805 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{46}H_{69}N_4O_6S$ $[M + H]^+$ 805.4932; found 805.4934.

N-(2-(piperidin-1-yl)ethyl) 1-(4-fluorophenyl)sulfonylpyrazolo[3,4-b]olean-12-en-28-amide（***5a)***, white solid; yield 80%; mp 160–162 °C. IR (KBr): 2936, 1654, 1648, 1383, 745, 638, 622 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01–7.92 (m, 2H), 7.64 (s, 1H), 7.20–7.11 (m, 2H), 6.69 (s, 1H), 5.42 (t, *J* = 3.3 Hz, 1H), 3.43–3.38 (m, 1H), 3.27–3.15 (m, 1H), 2.63–2.57 (m, 2H), 2.47–2.42 (m, 6H), 2.03–1.91 (m, 4H), 1.81–1.66 (m, 4H), 1.65–1.53 (m, 7H), 1.50–1.33 (m, 6H), 1.27–1.20 (m, 6H), 1.17 (s, 3H), 1.16 (s, 3H), 1.08 (d, *J* = 13.7 Hz, 1H), 0.92 (s, 3H), 0.91 (s, 3H), 0.81 (s, 3H), 0.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.9 (*C*=O), 165.0 (*C*-3), 167.0, 164.5 (Ph), 144.6 (*C*-13), 133.8, 130.6 (Ph), 128.5 (*C*-N-SO_2), 122.4 (*C*-12), 119.1 (*C*-2), 116.5, 116.3 (Ph), 56.9, 54.3 (*C*H_2-N), 53.1, 46.8, 46.4, 45.9, 42.3, 42.2, 39.4, 37.9, 36.0, 35.8, 34.6, 34.2, 33.0, 32.7, 31.7, 31.3, 30.7, 29.7, 27.4, 25.9, 25.5, 24.5, 24.2, 23.6, 23.5, 23.4, 19.3, 16.5, 15.1 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 747 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{44}H_{64}FN_4O_3S$ $[M + H]^+$ 747.4678; found 747.4689.

*N-(2-(piperidin-1-yl)ethyl) 1-(4-chlorophenyl)sulfonylpyrazolo[3,4-b]olean-12-en-28-amide (**5b**)*, white solid; yield 85%; mp 129–131 °C. IR (KBr): 2930, 1654, 1648, 1383, 1188, 759, 638, 622 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88 (dd, *J* = 10.3, 5.4 Hz, 2H), 7.63 (s, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 6.70 (s, 1H), 5.42 (s, 1H), 3.43–3.38 (m, 1H), 3.24–3.20 (m, 1H), 2.63–2.58 (m, 2H), 2.50–2.37 (m, 5H), 1.98–1.94 (m, 4H), 1.81–1.52 (m, 11H), 1.50–1.34 (m, 5H), 1.26 (s, 3H), 1.25 (s, 3H), 1.21 (s, 2H), 1.18 (s, 3H), 1.16 (s, 3H), 1.10–1.04 (m, 1H), 0.92 (s, 3H), 0.91 (s, 3H), 0.82 (d, *J* = 8.4 Hz, 3H), 0.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.9 (*C*=O), 144.5 (*C*-13), 129.4×2, 129.1×2 (Ph), 128.5 (*C*-N-SO_2), 122.4 (*C*-12), 119.2 (*C*-2), 56.9, 54.3 (*C*H_2-N), 53.0, 46.8, 46.4, 45.9, 42.2, 42.1, 39.4, 37.9, 36.0, 35.8, 34.6, 34.2,

33.0, 32.7, 31.7, 31.3, 30.7, 29.7, 27.4, 25.8, 25.5, 24.5, 24.2, 23.6, 23.5, 23.4, 19.3, 16.5, 15.1. ESI-MS *m/z*: 763, 765 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{44}H_{64}{}^{35}ClN_4O_3S$ $[M + H]^+$ 763.4382; found 763.4379.

*N-(2-(piperidin-1-yl)ethyl) 1-(4-bromophenyl)sulfonylpyrazolo[3,4-b]olean-12-en-28-amide (**5c**)*, light yellow solid; yield 84%; mp 161–163 °C. IR (KBr): 2939, 1654, 1595, 1498, 1378, 1263, 1167, 677, 588 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.80 (d, J = 8.6 Hz, 2H), 7.68–7.58 (m, 3H), 6.71 (s, 1H), 5.42 (s, 1H), 3.43–3.48 (m, 1H), 3.23 (m, 1H), 2.63–2.59 (m, 2H), 2.51–2.35 (m, 6H), 2.01–1.94 (m, 4H), 1.80–1.32 (m, 17H), 1.25 (s, 4H), 1.21 (s, 2H), 1.18 (s, 3H), 1.16 (s, 3H), 1.09 (d, J = 13.9 Hz, 1H), 0.92 (s, 3H), 0.91 (s, 3H), 0.81 (s, 3H), 0.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.9 (*C*=O), 165.1 (*C*-3), 144.5 (*C*-13), 136.8, 132.4, 129.2×2, 129.1×2 (Ph), 128.5 (*C*-N-SO_2), 122.4 (*C*-12), 119.2 (*C*-2), 56.9, 54.3 (*C*H_2-N), 53.0, 46.8, 46.4, 45.9, 42.2, 42.2, 39.4, 37.9, 36.0, 35.8, 34.6, 34.2, 33.0, 32.7, 31.7, 31.3, 30.7, 27.4, 25.9, 25.5, 24.6, 24.2, 23.6, 23.5, 23.4, 19.3, 16.5, 15.2 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 807, 809 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{44}H_{64}{}^{79}BrN_4O_3S$ $[M + H]^+$ 807.3877; found 807.3879.

*N-(2-(piperidin-1-yl)ethyl) 1-(4-(tert-butyl)phenyl)sulfonylpyrazolo[3,4-b]olean-12-en-28-amide (**5d**)*, white solid; yield 88%; mp 130–132 °C. IR (KBr): 2934, 1655, 1508, 1459, 1380, 1179, 644, 590 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.84 (d, J = 8.6 Hz, 2H), 7.64 (s, 1H), 7.47 (d, J = 8.6 Hz, 2H), 6.71 (s, 1H), 5.42 (s, 1H), 3.43–3.39 (m, 1H), 3.24 (s, 1H), 2.62–2.58 (m, 2H), 2.45 (s, 5H), 2.01–1.94 (m, 4H), 1.80–1.67 (m, 4H), 1.64–1.57 (m, 5H), 1.54–1.34 (m, 7H), 1.30 (s, 9H), 1.26 (s, 6H), 1.21 (s, 2H), 1.18 (s, 3H), 1.15 (s, 3H), 1.08 (d, J = 13.6 Hz, 1H), 0.92 (s, 3H), 0.91 (s, 3H), 0.81 (s, 3H), 0.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.9 (*C*=O), 144.5 (*C*-13), 134.9 (Ph), 128.5 (*C*-N-SO_2), 127.4×2, 126.0×2 (Ph), 122.5 (*C*-12), 118.7 (*C*-2), 56.9, 54.3 (*C*H_2-N), 53.1, 46.8, 46.4, 45.9, 42.2, 42.1, 39.4, 37.9, 36.0, 35.7, 35.3, 34.6, 34.2, 33.0, 32.7, 31.8, 31.3, 31.0, 30.7, 29.7, 27.4, 25.8, 25.5, 24.5, 24.1, 23.6, 23.5, 23.4, 19.3, 16.5, 15.1 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 785 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{48}H_{73}N_4O_3S$ $[M + H]^+$ 785.5398; found 785.5398.

*N-(2-(piperidin-1-yl)ethyl) 1-(4-(trifluoromethyl)phenyl)sulfonylpyrazolo[3,4-b] olean-12-en-28-amide (**5e**)*, light yellow solid; yield 86%; mp 123–125 °C. IR (KBr): 2929, 1655, 1633, 1508, 1458, 1386, 1199, 1130 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.65 (s, 1H), 6.77 (s, 1H), 5.42 (t, J = 3.3 Hz, 1H), 3.46–3.41 (m, 1H), 3.31–3.21 (m, 1H), 2.61 (d, J = 15.4 Hz, 2H), 2.50 (s, 6H), 2.07–1.90 (m, 4H), 1.79–1.29 (m, 17H), 1.25 (s, 4H), 1.21 (s, 2H), 1.18 (s, 3H), 1.15 (s, 3H), 1.09 (d, J = 13.8 Hz, 1H), 0.92 (s, 3H), 0.91 (s, 3H), 0.82 (s, 3H), 0.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.0 (*C*=O), 165.6 (*C*-3), 144.5 (*C*-13), 141.2, 135.2 (CF_3), 128.6 (*C*-N-SO_2), 128.2, 126.2, 124.4 (Ph), 122.4 (*C*-12), 121.7 (Ph), 119.6 (*C*-2), 56.9, 54.3 (*C*H_2-N), 53.0, 46.8, 46.4, 45.9, 42.1, 39.4, 37.9, 36.0, 35.7, 34.7, 34.2, 33.0, 32.8, 31.7, 31.3, 30.7, 27.4, 25.5, 24.6, 24.0, 23.6, 23.5, 23.4, 19.3, 16.5, 15.2 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 797 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{45}H_{64}F_3N_4O_3S$ $[M + H]^+$ 797.4646; found 797.4650.

*N-(2-(piperidin-1-yl)ethyl) 1-m-tolylsulfonylpyrazolo[3,4-b]olean-12-en-28-amide (**5f**)*, white solid; yield 87%; mp 155–157 °C. IR (KBr): 2929, 2852, 1654, 1526, 1459, 1381, 1176, 1121, 1067, 695, 639 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74 (s, 1H), 7.70 (d, J = 7.1 Hz, 1H), 7.64 (s, 1H), 7.42–7.31 (m, 2H), 6.72 (s, 1H), 5.42 (t, J = 3.2 Hz, 1H), 3.47–3.34 (m, 1H), 3.24 (m, 1H), 2.66–2.56 (m, 2H), 2.53–2.37 (m, 9H), 2.03–1.91 (m, 4H), 1.80–1.66 (m, 4H), 1.64–1.52 (m, 7H), 1.50–1.33 (m, 5H), 1.32–1.23 (m, 5H), 1.21 (s, 2H), 1.18 (s, 3H), 1.16 (s, 3H), 1.08 (d, J = 13.5 Hz, 1H), 0.92 (s, 3H), 0.91 (s, 3H), 0.81 (s, 3H), 0.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.0 (*C*=O), 164.6 (*C*-3), 144.5 (*C*-13), 139.3, 137.7, 134.6, 128.7 (Ph), 128.6 (*C*-N-SO_2), 127.8, 124.6 (Ph), 122.4 (*C*-12), 118.8 (*C*-2), 56.9, 54.3 (*C*H_2-N), 53.1, 46.8, 46.4, 45.9, 42.2, 42.2, 39.4, 37.9, 36.0, 35.8, 34.6, 34.2, 33.0, 32.7, 31.8, 31.3, 30.7, 27.4, 25.8, 25.5, 24.5, 24.2, 23.6, 23.5, 23.4, 21.3, 19.3, 16.5, 15.1 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 743 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{45}H_{67}N_4O_3S$ $[M + H]^+$ 743.4928; found 743.4927.

*N-(2-(piperidin-1-yl)ethyl) 1-(4-methoxyphenyl)sulfonylpyrazolo[3,4-b]olean-12-en-28-amide (**5g**)*, white solid; yield 91%; mp 157–159 °C. IR (KBr): 2937, 1655,

1509, 1473, 1187, 1175, 746, 617, 590 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.87 (d, J = 9.0 Hz, 2H), 7.63 (s, 1H), 6.93 (d, J = 9.0 Hz, 2H), 6.69 (s, 1H), 5.42 (s, 1H), 3.85 (s, 3H), 3.43–3.38 (m, 1H), 3.29–3.14 (m, 1H), 2.67–2.54 (m, 2H), 2.51–2.34 (m, 6H), 2.05–1.93 (m, 4H), 1.80–1.32 (m, 17H), 1.25 (s, 4H), 1.21 (s, 2H), 1.17 (s, 3H), 1.16 (s, 3H), 1.10–1.07 (m, 1H), 0.92 (s, 3H), 0.91 (s, 3H), 0.81 (s, 3H), 0.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.9 (*C*=O), 164.3 (*C*-3), 163.8 (Ph), 144.5 (*C*-13), 130.0, 129.3×2 (Ph), 128.2 (*C*-N-SO_2), 122.5 (*C*-12), 118.5 (*C*-2), 114.2×2 (Ph), 56.9 (*C*H_2-N), 55.7 (O-*C*H_3), 54.3 (*C*H_2-N), 53.1, 46.8, 46.4, 45.9, 42.3, 42.2, 39.4, 37.9, 36.0, 35.8, 34.6, 34.2, 33.0, 32.7, 31.8, 31.3, 30.7, 27.4, 25.9, 25.5, 24.5, 24.2, 23.6, 23.5, 23.4, 19.3, 16.5, 15.1 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 759 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{45}H_{67}N_4O_4S$ $[M + H]^+$ 759.4878; found 759.4876.

*N-(2-(piperidin-1-yl)ethyl) 1-(3,4-dimethoxyphenyl)sulfonylpyrazolo[3,4-b] olean-12-en-28-amide (**5h**)*, white solid; yield 87%; mp 153–155 °C. IR (KBr): 2939, 1655, 1508, 1459, 1388, 1322, 1182, 1062, 715, 637, 617 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.62 (s, 1H), 7.55 (dd, J = 8.5, 1.9 Hz, 1H), 7.41 (d, J = 1.8 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H), 6.69 (s, 1H), 5.42 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.43–3.38 (m, 1H), 3.24–3.20 (m, 1H), 2.63–2.58 (m, 2H), 2.49–2.37 (m, 5H), 1.98–1.94 (m, 4H), 1.80–1.66 (m, 4H), 1.59–1.54 (m, 6H), 1.47 (s, 3H), 1.39–1.33 (m, 2H), 1.26 (m, 8H), 1.20 (s, 3H), 1.16 (s, 3H), 1.11–1.00 (m, 2H), 0.92 (s, 3H), 0.91 (s, 3H), 0.81 (s, 3H), 0.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.9 (*C*=O), 164.3 (*C*-3), 153.5, 149.0 (Ph), 144.7 (*C*-13), 129.4 (Ph), 128.2 (*C*-N-SO_2), 122.4 (*C*-12), 121.7 (Ph), 118.6 (*C*-2), 110.3, 110.0 (Ph), 56.9 (*C*H_2-N), 56.3 (O-*C*H_3), 56.2 (O-*C*H_3), 54.3 (*C*H_2-N), 53.1, 46.8, 46.4, 45.9, 42.3, 42.2, 39.4, 37.9, 36.0, 35.8, 34.6 34.2, 33.0, 32.7, 31.7, 31.23, 30.7, 27.4, 26.0, 25.5, 24.6, 23.6, 23.5, 19.3, 16.5, 15.2 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 789 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{46}H_{69}N_4O_5S$ $[M + H]^+$ 789.4983; found 789.4982.

*N-(2-(piperidin-1-yl)ethyl) 1-(3,5-dimethylisoxazol-4-yl)sulfonylpyrazolo[3,4-b] olean-12-en-28-amide (**5i**)*, white solid; yield 75%; mp 167–169 °C. IR (KBr): 2932, 1637, 1493, 1458, 1384, 1239, 1189, 675, 589 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ:

7.62 (s, 1H), 6.68 (s, 1H), 5.43 (s, 1H), 3.43–3.48 (m, 1H), 3.23 (m, 1H), 2.72 (s, 3H), 2.65–2.58 (m, 2H), 2.44 (m, 8H), 2.07–1.93 (m, 4H), 1.81–1.68 (m, 4H), 1.61–1.31 (m, 12H), 1.29–1.22 (m, 10H), 1.18 (s, 3H), 1.18 (s, 3H), 1.10 (d, J = 13.7 Hz, 1H), 0.93 (s, 3H), 0.91 (s, 3H), 0.83 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.9 (*C*=O), 175.3 (O-*C*-CH_3), 164.6 (*C*-3), 158.0 (N-*C*-CH_3), 144.6 (*C*-13), 127.4 (*C*-N-SO_2), 122.4 (*C*-12), 118.8 (*C*-2), 114.7 (*C*-SO_2), 56.9, 54.3 (*C*H_2-N), 53.0, 46.8, 46.4, 45.9, 42.2, 42.2, 39.4, 37.9, 36.0, 35.8, 34.7, 34.2, 33.0, 32.8, 31.7, 31.3, 30.8, 29.7, 27.4, 25.9, 25.5, 24.6, 24.2, 23.6, 23.5, 23.5, 19.3, 16.5, 15.2, 13.0, 10.9 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 748 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{43}H_{66}N_5O_4S$ $[M + H]^+$ 748.4830; found 748.4833.

*N-(2-(piperidin-1-yl)ethyl) 1-(1-methyl-1H-imidazol-4-yl)sulfonylpyrazolo[3,4-b] olean-12-en-28-amide (**5j**)*, white solid; yield 76%; mp 168–170 °C. IR (KBr): 2936, 1641, 1509, 1456, 1377, 1178, 701, 609, 596 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (s, 1H), 7.73 (d, J = 1.2 Hz, 1H), 7.43 (d, J = 1.1 Hz, 1H), 6.70 (s, 1H), 5.43 (t, J = 3.2 Hz, 1H), 3.75 (s, 3H), 3.44–3.35 (m, 1H), 3.23 (m, 1H), 2.64 (d, J = 15.2 Hz, 1H), 2.58 (d, J = 10.0 Hz, 1H), 2.46–2.42 (m, 5H), 2.06–1.91 (m, 4H), 1.81–1.67 (m, 4H), 1.64–1.54 (m, 7H), 1.49–1.35 (m, 5H), 1.25–1.23 (m, 9H), 1.17 (s, 6H), 1.09 (d, J = 13.8 Hz, 1H), 0.93 (s, 3H), 0.91 (s, 3H), 0.82 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.9 (*C*=O), 164.2 (*C*-3), 144.4 (*C*-13), 139.3 (CH_3-N-*C*-N), 137.8 (CH_3-N-*C*-C), 129.2 (*C*-N-SO_2), 126.2 (*C*-SO_2), 122.6 (*C*-12), 118.0 (*C*-2), 56.9, 54.3 (*C*H_2-N), 53.2, 46.8, 46.4, 45.9, 42.3, 42.2, 39.4, 37.9, 36.1, 35.8, 34.6, 34.2, 33.0, 32.7, 31.8, 30.7, 29.7, 27.4, 26.0, 25.5, 24.5, 24.2, 23.6, 23.5, 23.5, 19.3, 16.5, 15.2 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 733 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{42}H_{65}N_6O_3S$ $[M + H]^+$ 733.4833; found 733.4830.

*N-(1-benzylpiperidin-4-yl) 1-(4-fluorophenyl)sulfonylpyrazolo[3,4-b]olean-12-en-28-amide (**6a**)*, white solid; yield 82%; mp 172–174 °C. IR (KBr): 2950, 1634, 1590, 1524, 1493, 1383, 1189, 1090, 1066, 675, 589, 539 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (dd, J = 8.5, 4.9 Hz, 2H), 7.64 (s, 1H), 7.30 (s, 5H), 7.15 (t, J = 8.4 Hz, 2H), 5.68 (d, J = 7.3 Hz, 1H), 5.36 (s, 1H), 3.78 (s, 1H), 3.51 (s, 2H), 2.82 (s, 2H),

2.60 (d, *J* = 15.5 Hz, 1H), 2.54 (d, *J* = 12.0 Hz, 1H), 2.12 (d, *J* = 9.2 Hz, 2H), 1.98–1.70 (m, 8H), 1.66–1.31 (m, 13H), 1.24 (s, 3H), 1.20 (s, 2H), 1.16 (s, 3H), 1.15 (s, 3H), 1.09 (d, *J* = 12.9 Hz, 1H), 0.90 (s, 6H), 0.82 (s, 3H), 0.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 177.2 (*C*=O), 164.9 (*C*-3), 164.5 (Ph), 144.7 (*C*-13), 133.8, 130.6, 130.5, 129.3 (Ph), 128.5 (*C*-N-SO_2), 128.3, 127.2(Ph) , 122.3 (*C*-12), 119.0 (*C*-2), 116.5, 116.3 (Ph), 63.1 (*C*H_2-Ph), 53.1, 52.4 (*C*H_2-N), 52.3, 46.7, 46.4, 45.8, 42.4, 39.4, 37.9, 36.1, 34.6, 34.2, 33.0, 33.0, 31.9, 31.3, 30.7, 27.4, 25.4, 24.5, 23.7, 23.5, 23.5, 19.3, 17.2, 15.2 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 809 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{49}H_{66}FN_4O_3S$ $[M + H]^+$ 809.4834; found 809.4832.

*N-(1-benzylpiperidin-4-yl) 1-(4-chlorophenyl)sulfonylpyrazolo[3,4-b]olean-12-en-28-amide (**6b**)*, white solid; yield 84%; mp 198–200 °C. IR (KBr): 2946, 1654, 1508, 1524, 1476, 1383, 1189, 1087, 1061, 759, 640, 580 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.87 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.64 (s, 1H), 7.45 (dd, *J* = 9.0, 2.2 Hz, 2H), 7.34–7.20 (m, 5H), 5.69 (d, *J* = 7.6 Hz, 1H), 5.36 (s, 1H), 3.85–3.72 (m, 1H), 3.49 (s, 2H), 2.80 (s, 2H), 2.60 (d, *J* = 15.3 Hz, 1H), 2.54 (d, *J* = 9.6 Hz, 1H), 2.11 (dd, *J* = 20.0, 9.2 Hz, 2H), 2.01–1.82 (m, 7H), 1.79–1.53 (m, 7H), 1.49–1.28 (m, 6H), 1.24 (s, 3H), 1.20 (s, 2H), 1.17 (s, 3H), 1.15 (s, 3H), 1.09 (d, *J* = 13.5 Hz, 1H), 0.90 (s, 6H), 0.83 (s, 3H), 0.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 177.2 (*C*=O), 165.1(*C*-3), 144.7 (*C*-13), 140.6, 138.0, 136.2, 129.4×2, 129.2×2, 129.1×2 (Ph), 128.5 (*C*-N-SO_2), 128.2×2, 127.1 (Ph), 122.3 (*C*-12), 119.2 (*C*-2), 63.1 (*C*H_2-Ph), 53.0, 52.4 (*C*H_2-N), 52.3, 46.7, 46.4, 45.8, 42.4, 39.4, 37.8, 36.0, 34.63, 34.2, 33.0, 32.3, 31.9, 31.8, 31.3, 30.7, 27.3, 25.4, 24.5, 23.7, 23.5, 23.5, 19.3, 17.2, 15.3 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 825, 827 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{49}H_{66}{}^{35}ClN_4O_3S$ $[M + H]^+$ 825.4539; found 825.4537.

*N-(1-benzylpiperidin-4-yl) 1-(4-bromophenyl)sulfonylpyrazolo[3,4-b]olean-12-en-28-amide(**6c**)*, white solid; yield 80%; mp 175–177 °C. IR (KBr): 2943, 1658, 1505, 1471, 1391, 1187, 1091, 1067, 746, 637, 587 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.83–7.75 (m, 2H), 7.61 (m, 3H), 7.34–7.23 (m, 5H), 5.68 (d, *J* = 7.6 Hz, 1H), 5.36 (t, *J* = 3.3 Hz, 1H), 3.79 (dd, *J* = 7.3, 3.7 Hz, 1H), 3.50 (s, 2H), 2.81 (s, 2H), 2.60 (d, *J*

= 15.4 Hz, 1H), 2.54 (d, *J* = 9.1 Hz, 1H), 2.12 (dd, *J* = 19.4, 8.7 Hz, 2H), 1.98–1.78 (m, 6H), 1.76–1.52 (m, 8H), 1.50–1.30 (m, 7H), 1.24 (s, 3H), 1.22–1.18 (m, 3H), 1.17 (s, 3H), 1.15 (s, 3H), 1.09 (d, *J* = 13.0 Hz, 1H), 0.90 (s, 6H), 0.83 (s, 3H), 0.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 177.2 (*C*=O), 165.1 (*C*-3), 144.7 (*C*-13), 136.8, 132.3×2, 129.3×2, 129.2×2, 129.1 (Ph), 128.5 (*C*-N-SO_2), 128.3×2, 127.2 (Ph), 122.3 (*C*-12), 119.2 (*C*-2), 63.1 (*C*H_2-Ph), 53.0, 52.4 (*C*H_2-N), 52.3, 46.7, 46.4, 45.8, 42.4, 39.4, 37.8, 36.0, 34.6, 34.2, 33.0, 32.3, 31.9, 31.3, 30.7, 27.4, 25.4, 24.5, 23.7, 23.5, 23.5, 19.3, 17.2, 15.3 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 869, 871 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{49}H_{66}{}^{79}BrN_4O_3S$ $[M + H]^+$ 869.4034; found 869.4031.

*N-(1-benzylpiperidin-4-yl) 1-(4-(tert-butyl)phenyl)sulfonylpyrazolo[3,4-b]olean-12-en-28-amide (**6d**)*, white solid; yield 80%; mp 181–183 °C. IR (KBr): 2950, 1656, 1506, 1455, 1381, 1179, 1088, 1067, 746, 645, 590 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.89–7.79 (m, 2H), 7.65 (s, 1H), 7.52–7.44 (m, 2H), 7.34–7.21 (m, 5H), 5.70 (d, *J* = 7.6 Hz, 1H), 5.37 (d, *J* = 3.3 Hz, 1H), 3.84–3.73 (m, 1H), 3.49 (s, 2H), 2.81 (s, 2H), 2.60 (d, *J* = 15.3 Hz, 1H), 2.54 (d, *J* = 9.3 Hz, 1H), 2.19–2.06 (m, 3H), 2.01–1.33 (m, 20H), 1.30 (s, 9H), 1.26 (s, 3H), 1.24–1.17 (m, 6H), 1.15 (s, 3H), 1.09 (d, *J* = 13.3 Hz, 1H), 0.90 (s, 6H), 0.83 (s, 3H), 0.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 177.2 (*C*=O), 164.4 (*C*-3), 144.6 (*C*-13), 134.9, 129.2×2 (Ph), 128.5 (*C*-N-SO_2), 128.3×2, 127.4×2, 127.2, 126.0×2 (Ph), 122.4 (*C*-12), 118.6 (*C*-2), 63.1 (*C*H_2-Ph), 53.1, 52.4 (*C*H_2-N), 52.3, 46.7, 46.4, 45.9, 42.4, 39.4, 37.9, 36.1, 35.3, 34.6, 34.2, 33.0, 32.3, 31.9, 31.8, 31.3, 31.0, 30.7, 27.3, 25.4, 24.5, 23.7, 23.5, 19.3, 17.2, 15.2 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 847 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{53}H_{75}N_4O_3S$ $[M + H]^+$ 847.5554; found 847.5551.

*N-(1-benzylpiperidin-4-yl) 1-(4-(trifluoromethyl)phenyl)sulfonylpyrazolo[3,4-b]olean-12-en-28-amide (**6e**)*, white solid; yield 81%; mp 163–165 °C. IR (KBr): 2948, 1647, 1521, 1453, 1389, 1322, 1182, 1061, 715, 636, 604 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.07 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.66 (s, 1H), 7.34–7.25 (m, 1H), 5.67 (d, *J* = 7.5 Hz, 1H), 5.36 (s, 1H), 3.84–3.72 (m, 1H), 3.49 (s, 2H), 2.81 (s, 2H), 2.61 (d, *J* = 15.4 Hz, 1H), 2.54 (d, *J* = 9.6 Hz, 1H), 2.11 (dd, *J* = 19.8, 8.9 Hz,

2H), 2.01–1.71 (m, 8H), 1.70–1.53 (m, 6H), 1.50–1.29 (m, 7H), 1.24 (s, 3H), 1.20 (s, 1H), 1.17 (s, 3H), 1.14 (s, 3H), 1.09 (d, *J* = 13.7 Hz, 1H), 0.90 (s, 6H), 0.82 (s, 3H), 0.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 177.2 (*C*=O), 165.5 (*C*-3), 144.7 (*C*-13), 141.2 (Ph), 135.6, 135.2 (CF_3), 129.3 (Ph), 128.6 (*C*-N-SO_2), 128.3, 128.2, 127.2, 126.2 (Ph), 122.3 (*C*-12), 119.5 (*C*-2), 63.1 (*C*H_2-Ph), 53.0, 52.4 (*C*H_2-N), 52.3, 46.7, 46.4, 46.3, 45.8, 42.4, 39.4, 37.9, 36.0, 34.7, 34.2, 33.0, 32.3, 31.9, 31.7, 31.3, 30.7, 27.4, 25.4, 24.5, 23.7, 23.5, 19.3, 17.2, 15.3 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 859 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{50}H_{66}F_3N_4O_3S$ $[M +H]^+$ 859.4802; found 859.4879.

*N-(1-benzylpiperidin-4-yl) 1-(4-(trifluoromethoxy)phenyl)sulfonylpyrazolo[3,4-b] olean-12-en-28-amide (**6f**)*, white solid; yield 79%; mp 166–168 °C. IR (KBr): 2945, 1655, 1508, 1496, 1384, 1259, 1214, 1187, 742, 699, 588 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.04–7.95 (m, 2H), 7.65 (s, 1H), 7.29–7.247 (m, 7H), 5.69 (d, *J* = 7.6 Hz, 1H), 5.36 (t, *J* = 3.2 Hz, 1H), 3.79 (d, *J* = 7.2 Hz, 1H), 3.51 (d, *J* = 1.4 Hz, 2H), 2.82 (s, 2H), 2.60 (d, *J* = 15.3 Hz, 1H), 2.55 (d, *J* = 9.5 Hz, 1H), 2.13 (dd, *J* = 19.7, 8.8 Hz, 2H), 1.99–1.82 (m, 6H), 1.78–1.53 (m, 8H), 1.50–1.30 (m, 7H), 1.24 (s, 3H), 1.20 (s, 1H), 1.16 (s, 3H), 1.15 (s, 3H), 1.09 (d, *J* = 13.5 Hz, 1H), 0.90 (s, 6H), 0.83 (s, 3H), 0.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 177.2 (*C*=O), 165.2 (*C*-3), 153.0 (Ph), 144.7 (*C*-13), 135.9 (CF_3), 129.9, 129.3 (Ph), 128.6 (*C*-N-SO_2), 128.3, 127.3 (Ph), 122.3 (*C*-12), 120.7, 119.3 (*C*-2), 63.1 (*C*H_2-Ph), 53.0 (*C*H_2-N), 52.3, 46.7, 46.4, 45.8, 42.4, 39.4, 37.9, 36.0, 34.6, 34.2, 33.0, 32.3, 31.9, 31.7, 31.3, 30.7, 27.4, 25.4, 24.5, 23.7, 23.5, 23.5, 19.3, 17.2, 15.2 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 875 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{50}H_{66}F_3N_4O_4S$ $[M + H]^+$ 875.4751; found 875.4754.

*N-(1-benzylpiperidin-4-yl) 1-(4-methoxyphenyl)sulfonylpyrazolo[3,4-b]olean-12-en-28-amide (**6g**)*, white solid; yield 89%; mp 200–202 °C. IR (KBr): 3108, 2952, 2848, 1625, 1594, 1577, 1498, 1458, 1371, 837, 804, 715, 676 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.95–7.82 (m, 2H), 7.63 (s, 1H), 7.31–7.25 (m, 1H), 6.93 (d, *J* = 9.0 Hz, 2H), 5.69 (d, *J* = 7.6 Hz, 1H), 5.37 (d, *J* = 3.3 Hz, 1H), 3.84 (s, 3H), 3.80–3.77 (m, 1H), 3.50 (s, 2H), 2.81 (s, 2H), 2.59 (d, *J* = 15.3 Hz, 1H), 2.54 (d, *J* = 9.6 Hz, 1H),

2.16–2.08 (m, 2H), 1.98–1.29 (m, 20H), 1.25 (s, 3H), 1.22–1.19 (m, 2H), 1.16 (s, 3H), 1.15 (s, 3H), 1.09 (d, *J* = 13.1 Hz, 1H), 0.90 (s, 6H), 0.82 (s, 3H), 0.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 177.2 (*C*=O), 164.2 (*C*-3), 163.8 (Ph), 144.6 (*C*-13), 130.0×2, 129.3×2 (Ph), 128.3 (*C*-N-SO_2), 127.2×2 (Ph), 122.4 (*C*-12), 118.5 (*C*-2), 114.2×2 (Ph), 63.1 (*C*H_2-Ph), 55.7 (O-CH_3), 53.1, 52.4 (*C*H_2-N), 52.3, 46.7, 46.4, 45.9, 42.4, 39.4, 37.9, 36.1, 34.6, 34.2, 33.0, 32.3, 31.9, 31.7, 31.3, 30.7, 27.4, 25.4, 24.5, 23.7, 23.5, 23.5, 19.3, 17.2, 15.2 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 821 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{50}H_{69}N_4O_4S$ $[M + H]^+$ 821.5034; found 821.5032.

*N-(1-benzylpiperidin-4-yl) 1-(3,4-dimethoxyphenyl)sulfonylpyrazolo[3,4-b]olean-12-en-28-amide (**6h**)*, white solid; yield 86%; mp 175–177 °C. IR (KBr): 3092, 2936, 2850, 1638, 1572, 1509, 1470, 1383, 821, 746, 635, 616 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.62 (s, 1H), 7.56 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.41 (d, *J* = 2.2 Hz, 1H), 7.34–7.25 (m, 1H), 6.88 (d, *J* = 8.6 Hz, 1H), 5.69 (d, *J* = 7.6 Hz, 1H), 5.36 (t, *J* = 3.2 Hz, 1H), 3.91 (d, *J* = 6.1 Hz, 6H), 3.84–3.74 (m, 1H), 3.50 (s, 2H), 2.81 (s, 2H), 2.59 (d, *J* = 15.3 Hz, 1H), 2.54 (d, *J* = 9.6 Hz, 1H), 2.12 (dd, *J* = 19.6, 9.0 Hz, 2H), 1.99–1.35 (m, 20H), 1.33–1.20 (m, 8H), 1.19 (s, 3H), 1.15 (s, 3H), 1.09 (d, *J* = 13.2 Hz, 1H), 0.90 (s, 6H), 0.83 (s, 3H), 0.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 177.2 (*C*=O), 164.2 (*C*-3), 153.5, 149.0 (Ph), 144.7 (*C*-13), 129.4×2, 129.3×2 (Ph), 128.3 (*C*-N-SO_2), 127.2 (Ph), 122.4 (*C*-12), 121.7 (Ph), 118.6 (*C*-2), 110.3, 110.0 (Ph), 63.1 (*C*H_2-Ph), 56.3, 56.2 (O-*C*H_3), 52.4 (*C*H_2-N), 52.3, 46.7, 46.4, 45.9, 42.4, 39.4, 37.9, 36.1, 34.6, 34.2, 33.0, 32.3, 31.9, 31.7, 31.3, 30.7, 27.4, 25.4, 24.5, 23.7, 23.5, 23.5, 19.3, 17.2, 15.3 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 851 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{51}H_{71}N_4O_5S$ $[M + H]^+$ 851.5140; found 851.5137.

*N-(1-benzylpiperidin-4-yl) 1-(3,5-dimethylisoxazol-4-yl)sulfonylpyrazolo[3,4-b]olean-12-en-28-amide (**6i**)*, white solid; yield 78%; mp 140–142 °C. IR (KBr): 2943, 1655, 1509, 1493, 1384, 1199, 1131, 1068, 742, 653, 580 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.63 (s, 1H), 7.34–7.24 (m, 5H), 5.69 (d, *J* = 7.6 Hz, 1H), 5.37 (d, *J* = 3.2 Hz, 1H), 3.86–3.72 (m, 1H), 3.49 (d, *J* = 1.5 Hz, 2H), 2.80 (s, 2H), 2.72 (s, 3H), 2.62

(d, *J* = 15.4 Hz, 1H), 2.55 (d, *J* = 9.7 Hz, 1H), 2.44 (s, 3H), 2.11 (dd, *J* = 19.2, 8.7 Hz, 2H), 2.02–1.77 (m, 8H), 1.71–1.48 (m, 7H), 1.46–1.29 (m, 5H), 1.26 (s, 4H), 1.23–1.21 (m, 2H), 1.17 (s, 3H), 1.17 (s, 3H), 1.10 (d, *J* = 13.9 Hz, 1H), 0.90 (s, 6H), 0.84 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.2 (*C*=O), 175.3 (O-*C*-CH_3), 164.6 (*C*-3), 158.0 (N-*C*-CH_3), 144.7 (*C*-13), 138.1, 129.2×2, 128.2×2 (Ph), 127.4 (*C*-N-SO_2), 127.1 (Ph), 122.3 (*C*-12), 118.8 (*C*-2), 114.7 (*C*-SO_2), 63.2 (*C*H_2-Ph), 53.0, 52.4 (*C*H_2-N), 52.3, 46.7, 46.4, 45.9, 42.4, 39.4, 37.9, 36.0, 34.6, 34.2, 33.0, 33.0, 32.4, 31.9, 31.8, 31.3, 30.7, 27.4, 25.4, 24.6, 23.7, 23.5, 23.5, 19.3, 17.2, 15.3, 13.0, 10.9 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 810 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{48}H_{68}N_5O_4S$ $[M + H]^+$ 810.4987; found 810.4985.

*N-(1-benzylpiperidin-4-yl) 1-(1-methyl-1H-imidazol-4-yl)sulfonylpyrazolo[3,4-b] olean-12-en-28-amide (**6j**)*, white solid; yield 72%; mp 187–189°C. IR (KBr): 2943, 2853, 1655, 1526, 1459, 1381, 1177, 1067, 745, 645 588 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (s, 1H), 7.73 (d, *J* = 1.3 Hz, 1H), 7.44 (d, *J* = 1.1 Hz, 1H), 7.30 (d, *J* = 4.1 Hz, 4H), 7.25 (d, *J* = 4.3 Hz, 1H), 5.73 (d, *J* = 7.5 Hz, 1H), 5.38 (s, 1H), 3.85–3.76 (m, 1H), 3.75 (s, 3H), 3.50 (s, 2H), 2.80 (s, 2H), 2.64 (d, *J* = 15.2 Hz, 1H), 2.54 (d, *J* = 9.9 Hz, 1H), 2.12 (dd, *J* = 19.5, 9.0 Hz, 2H), 2.01–1.84 (m, 6H), 1.81–1.63 (m, 4H), 1.57–1.29 (m, 11H), 1.24 (s, 3H), 1.21 (s, 2H), 1.16 (s, 6H), 1.09 (d, *J* = 13.3 Hz, 1H), 0.90 (s, 6H), 0.84 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.3 (*C*=O), 164.1 (*C*-3), 144.6 (*C*-13), 139.4 (CH_3-N-*C*-N), 137.8 (CH_3-N-*C*-C), 129.3×2, 129.1, 128.3×2 (Ph), 127.2 (*C*-N-SO_2), 126.2(*C*-SO_2), 122.5 (*C*-12), 118.0 (*C*-2), 63.1 (*C*H_2-Ph), 53.2, 52.3 (*C*H_2-N), 52.2, 46.7, 46.4, 46.3, 45.8, 42.4, 42.4, 39.4, 37.9, 36.1, 34.6, 34.2, 34.2, 33.0, 32.3, 31.9, 31.7, 31.3, 30.7, 27.4, 25.4, 24.5, 23.7, 23.5, 23.5, 19.3, 17.2, 15.3 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 795 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{47}H_{66}N_6NaO_3S$ $[M + Na]^+$ 817.4809; found 817.4811.

*Preparation of Isoxazolo[4,5-b]olean-12-en-28-oic acid (**7**)*

To a solution of B (1.0 g, 2.1 mmol) in ethanol (40 ml) was added hydroxylamine hydrochloride (0.2 g, 2.9 mmol) at room temperature. The reaction mixture was heated under reflux for 3 hrs. After cooling, the reaction mixture was concentrated.

The residue was purified by silica gel chromatography (petroleum ether/AcOEt: 5/1 v/v) to give the desired compound **7** (0.9 g, 89%) as light yellow solid. mp 194–196 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (s, 1H), 5.34 (s, 1H), 2.86 (dd, J = 13.5, 3.5 Hz, 1H), 2.43 (d, J = 15.1 Hz, 1H), 2.10–1.90 (m, 4H), 1.83–1.71 (m, 3H), 1.69–1.55 (m, 4H), 1.54–1.28 (m, 8H), 1.25–1.10 (m, 9H), 0.94 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H), 0.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 184.5 (*C*=O), 173.0 (*C*-O), 150.2 (*C*-3), 143.6 (*C*-13), 122.3 (*C*-12), 108.8 (*C*-2), 53.5, 46.6, 46.2, 45.9, 41.8, 41.0, 39.4, 38.7, 35.3, 34.7, 33.8, 33.1, 32.4, 31.9, 30.7, 28.8, 27.7, 25.8, 23.6, 23.3, 22.9, 21.4, 18.8, 16.8, 15.3 (*C*R$_4$, *C*HR$_3$, *C*H$_2$R$_2$, *C*H$_3$R). ESI-MS *m/z*: 480 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{31}H_{46}NO_3$ $[M + H]^+$ 480.3472; found 480.3481.

*General procedure for preparation of compounds **7a**, **7b**, **7c** and **7d***

To a RBF was added compound **7** (95.6 mg, 0.2 mmol) and $SOCl_2$ (2 ml). The mixture was stirred at room temperature for 2 hrs. The mixture was concentrated to dryness under reduced pressure. Hexane (3 × 50 ml) was added to the residue, then the solution was concentrated to dryness to give acid chloride. To an anhydrous CH_2Cl_2 (10 ml) solution of each corresponding amines (0.3 mmol) and triethylamine (0.1 mL) was added the above acid chloride. The reaction mixture was stirred at room temperature for 0.5 h, and then concentrated and chromatographed (petroleum ether/ethyl acetate) to yield compounds **7a**, **7b**, **7c** and **7d**.

*N-benzyl isoxazolo[3,4-b]olean-12-en-28-amide (**7a**)*, yellow solid; yield 76%; mp 237–239 ^{o}C. IR (KBr): 2930, 2856, 1658, 1512, 1458, 1176, 755, 699, 617 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (s, 1H), 7.37–7.25 (m, 5H), 6.20 (s, 1H), 5.37 (s, 1H), 4.61 (dd, J = 14.7, 6.2 Hz, 1H), 4.18 (dd, J = 14.7, 4.4 Hz, 1H), 2.61 (d, J = 9.7 Hz, 1H), 2.40 (d, J = 15.1 Hz, 1H), 2.06–1.89 (m, 4H), 1.83–1.57 (m, 7H), 1.34–1.09 (m, 17H), 0.92 (s, 6H), 0.85 (s, 3H), 0.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.9 (*C*=O), 173.0 (*C*-O), 150.1 (*C*-3), 144.8 (*C*-13), 138.4, 128.7×2, 127.8×2, 127.4 (Ph), 122.6 (*C*-12), 108.7 (*C*-2), 53.4, 46.6, 46.4, 46.1, 43.6, 42.4, 42.2, 39.4, 38.6, 35.4, 34.7, 34.1, 33.0, 32.7, 31.9, 31.7, 30.8, 29.7, 29.4, 28.8, 27.4, 25.5, 23.8, 23.6, 23.4, 22.7, 21.4, 18.8, 16.6, 15.3, 14.1 (*C*R$_4$, *C*HR$_3$, *C*H$_2$R$_2$, *C*H$_3$R). ESI-MS *m/z*: 569

[M + H]$^+$, HR-ESI-MS *m/z*: calcd for $C_{38}H_{52}N_2NaO_2$ [M + Na]$^+$ 591.3921; found 591.3925.

*N-(3-morpholinopropyl) isoxazolo[3,4-b]olean-12-en-28-amide (**7b**)*, yellow solid: yield 70%; mp 190–192 ^{o}C. 2945, 2861, 1648, 1522, 1459, 1384, 1364, 1118 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, J = 2.4 Hz, 1H), 6.30 (t, J = 5.2 Hz, 1H), 5.42 (s, 1H), 3.72 (m, 4H), 3.44–3.41 (m, 1H), 3.17–3.04 (m, 1H), 2.63 (d, J = 10.1 Hz, 1H), 2.45–2.37 (m, 7H), 2.09–1.95 (m, 4H), 1.82–1.47 (m, 11H), 1.42–1.27 (m, 6H), 1.23–1.04 (m, 8H), 0.92 (s, 6H), 0.89 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.9 (*C*=O), 173.0 (*C*-O), 150.2 (C-3), 144.9 (*C*-13), 122.3 (*C*-12), 108.7 (*C*-2), 66.9 (*C*H_2-O), 57.2, 53.8 (*C*H_2-N), 53.4, 46.7, 46.2, 46.1, 42.2, 39.4, 38.7, 38.4, 35.4, 34.7, 34.1, 33.0, 32.9, 31.7, 30.8, 28.9, 27.4, 25.7, 25.6, 23.8, 23.6, 23.4, 21.4, 18.9, 16.7, 15.3 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 606 [M + H]$^+$, HR-ESI-MS *m/z*: calcd for $C_{38}H_{60}N_3O_3$ [M + H]$^+$ 606.4629; found 606.4628.

*N-(2-(piperidin-1-yl)ethyl) isoxazolo[3,4-b]olean-12-en-28-amide (**7c**)*, light yellow solid; yield 73%; mp 163–165 ^{o}C. IR (KBr): 2939, 1655, 1508, 1459, 1383 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (s, 1H), 6.70 (s, 1H), 5.42 (t, J = 3.4 Hz, 1H), 3.39 (dd, J = 13.7, 6.5 Hz, 1H), 3.21 (dd, J = 13.4, 5.1 Hz, 1H), 2.58 (d, J = 9.3 Hz, 1H), 2.50–2.36 (m, 6H), 2.09–1.91 (m, 4H), 1.81–1.33 (m, 18H), 1.30 (s, 3H), 1.23 (s, 2H), 1.19 (s, 3H), 1.16 (s, 3H), 1.10–1.04 (m, 1H), 0.91 (s, 3H), 0.89 (s, 3H), 0.86 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.9 (*C*=O), 173.1 (*C*-O), 150.2 (*C*-3), 144.5 (*C*-13), 122.3 (*C*-12), 108.7 (*C*-2), 56.9, 54.3 (*C*H_2-N), 53.4, 46.8, 46.4, 46.1, 42.2, 42.1, 39.4, 38.7, 35.8, 35.4, 34.7, 34.2, 33.0, 32.7, 31.7, 30.7, 29.7, 28.9, 27.4, 25.9, 25.6, 24.2, 23.6, 23.5, 21.4, 18.9, 16.6, 15.3 (*C*R_4, *C*HR_3, *C*H_2R_2, *C*H_3R). ESI-MS *m/z*: 590 [M + H]$^+$, HR-ESI-MS *m/z*: calcd for $C_{38}H_{60}N_3O_2$ [M + H]$^+$ 590.4680; found 590.4683.

*N-(1-benzylpiperidin-4-yl) isoxazolo[3,4-b]olean-12-en-28-amide (**7d**)*, light yellow solid; yield 75%; mp 148–150 ^{o}C. IR (KBr): 2943, 1655, 1508, 1455, 1384, 1364, 1176, 738, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (s, 1H), 7.31–7.21 (m, 5H), 5.70 (d, J = 7.5 Hz, 1H), 5.38 (t, J = 3.3 Hz, 1H), 3.85–3.73 (m, 1H), 3.49 (d, J =

1.9 Hz, 2H), 2.80 (s, 2H), 2.55 (dd, *J* = 12.6, 3.2 Hz, 1H), 2.43 (d, *J* = 15.1 Hz, 1H), 2.15–1.34 (m, 21H), 1.31 (s, 3H), 1.26 (s, 1H), 1.21 (s, 4H), 1.18 (s, 3H), 1.15–1.06 (m, 2H), 0.91 (s, 6H), 0.89 (s, 3H), 0.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.2 (*C*=O), 173.0 (*C*-O), 150.2 (*C*-3), 144.7 (*C*-13), 138.1, 129.2×2, 128.2×2, 127.1 (Ph), 122.3 (*C*-12), 108.7 (*C*-2), 63.1 (CH_2-Ph), 53.4 (CH_2-N), 52.4, 46.7, 46.3, 46.1, 42.4, 42.3, 39.5, 38.7, 35.4, 34.7, 34.2, 33.0, 33.0, 32.4, 31.9, 31.8, 30.7, 28.9, 27.4, 25.4, 23.6, 23.5, 23.5, 21.4, 18.8, 17.3, 15.4 (CR_4, CHR_3, CH_2R_2, CH_3R). ESI-MS *m/z*: 652 $[M + H]^+$, HR-ESI-MS *m/z*: calcd for $C_{43}H_{62}N_3O_2$ $[M + H]^+$ 652.4837; found 652.4840.

Formation of OCLs

RAW264.7 cells were cultured in α modification of Eagle's medium (α-MEM) with 10% fetal bovine serum (FBS), 100 U/ml penicillin and 10 mg/ml streptomycin. For proliferation, the cells were cultured at 37 ^oC in atmosphere of 5% CO_2. After reaching confluence of about 80%, the cells were trypsinated and seeded at a final density of 1 × 10^3 cells/well in 96-well plates. Cells were incubated in complete medium in the presence of RANKL (40 ng/ml) or RANKL plus each compound at designed concentrations. Cultures were fed every 36 hours by replacing with fresh medium. After 5 days, the cells were stained with the osteoclast marker (TRAP kit), following the manufacturer's protocols. $TRAP^+$ cells with three or more nuclei were counted as osteoclasts. Data are expressed as mean ± S.D. (n = 3).

MTT assay

RAW264.7 cells were seeded into 96-well plates at a density of 1 × 10^4 cells/well. Cells were incubated with each compound at designed concentrations for 24 h at 37 ^oC. After incubation with MTT at 37 ^oC for 4 h, 150 μl DMSO was added to each well, followed by gently shaking for 5 min to achieve complete dissolution. The absorbance was determined at 570 nm. Data are expressed as mean ± S.D. (n = 3).

In vivo experiments

The animal study was approved by the Jiangsu Animal Care and Use Committee

and all of the protocols complied with the national and institutional rules regarding animal experiments.

Eight-week-old female rats (Jiangning Animal Farm, Nanjing, China) were subjected to either bilateral OVX or sham operation and treated from the following day with vehicle (5% ethanol and 95% distilled water, OVX-vehicle and Sham group), alendronate sodium (AS, 1mg/kg/day, orally) or increasing amounts of **6g** (0.1, 1 or 10 mg/kg/day, orally) for 4 weeks, alternatively. After killing, lumbar spine (L3-L5) were dissected and cleaned, fixed overnight in 3.7% paraformaldehyde and processed for dual-energy X-ray absorptiometry (PIXImus2, GE Lunar Co., Madison, WI). Uteri were dissected, weighed and embedded in paraffin for histological analysis after haematoxylin/eosin staining to control OVX efficiency (Olympus DP72, original magnification: × 100 for uterine).

Western blotting

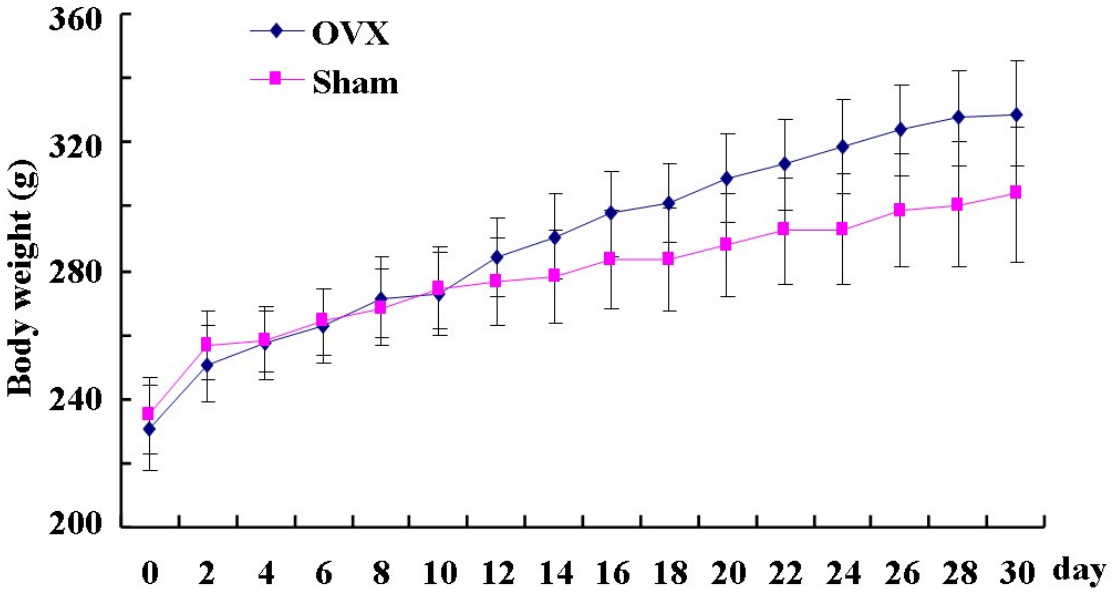
Protein expressions were examined using antibodies specific to c-Fos, and NFATc1, all from Cell Signaling Technology (Danvers, USA). Cells were lysed in radioimmunoprecipitation assay (RIPA) buffer. A quantity of 20-30 μg of lysates were subjected to 10% gradient SDS-polyacrylamide gel electrophoresis (SDS-PAGE), and then transferred to a nitrocellulose membrane. Blots were probed with the primary antibody for the indicated proteins, overnight at 4 ^{o}C, washed and incubated with the appropriate horseradish peroxidase (HRP)-conjugated secondary antibody for 1 hour at room temperature, subsequently detected with an enhanced chemoluminescence kit according to the manufacturer's instructions.

Quantitative real-time PCR

Total RNA was extracted using an RNeasy plus kit (QIAGEN) and cDNA was generated with an oligo (dT) primer and the Superscript II system (Invitrogen) followed by analysis using iCycler PCR with SYBR Green PCR master Mix (Applied Biosystems). The following primer sets were used: CathK, CTR, TRAP, c-Fos and NFATc1. CathK: forward 5'-GGGAGAAAAACCTGAAGC-3', reverse 5'- ATTCT

GGGGACTCAGAGC-3'; CTR: 5'-TGGTTGAGGTTGTGCCCA-3', reverse 5'-CTC GTGGGTTTGCCTCATC-3'; TRAP: 5'-TCCCCAATGCCCCATTC-3', reverse 5'-CGGTTCTGGCGATCTCTTTG-3'; c-Fos: forward 5'-ATGATGTTCTCGGG TTTCAACG-3', reverse 5'-CAGTCTGCTGCATAGAAGGAACCG-3'; NFATc1: forward 5'-GGGTCAGTGTGACCGAAGAT-3', reverse 5'-GGAAGTCAGAAGTG GGTGGA-3'.

Body weight of OVX group and sham group



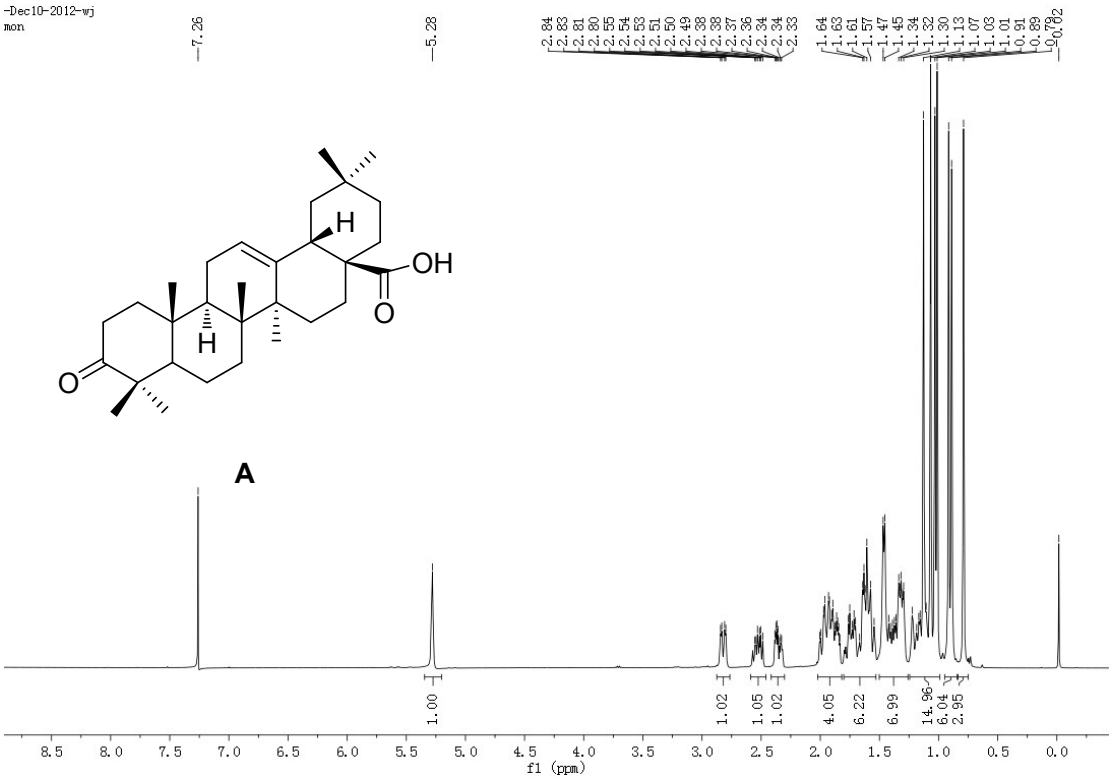
Supplementary Fig. S1 Body weight of OVX group and sham group after the surgical procedure (mean ± s.d., $n = 10$).

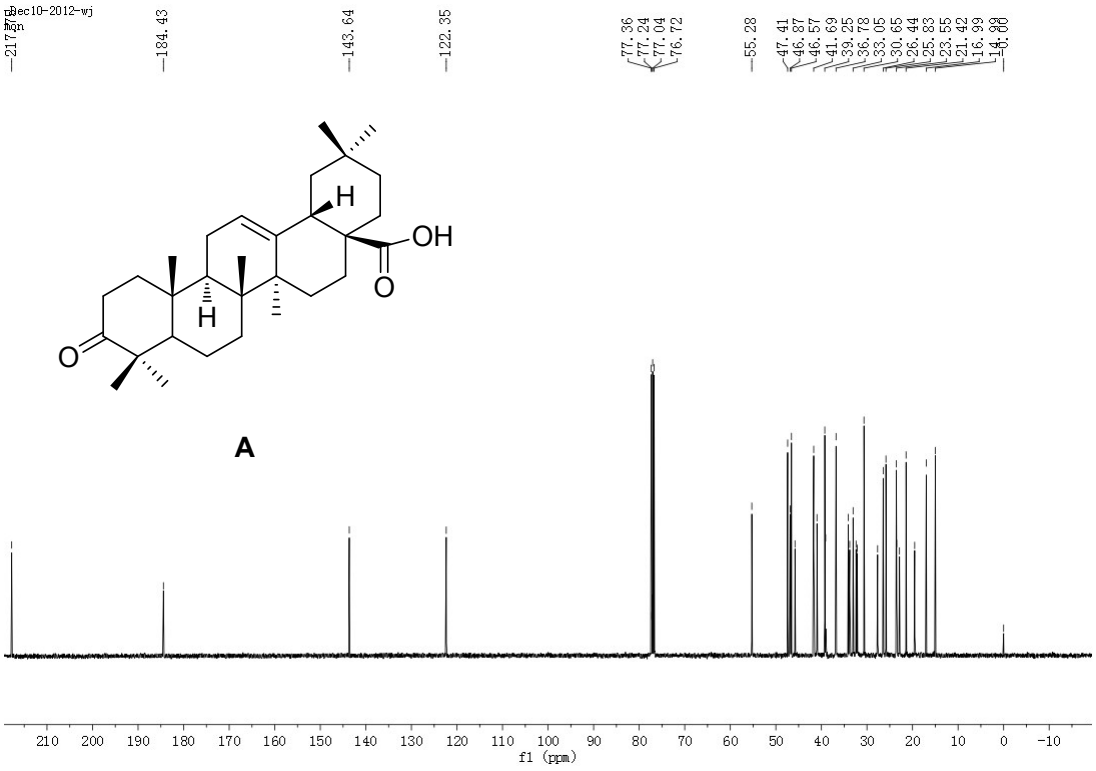
Purity of the tested compounds by HPLC analysis

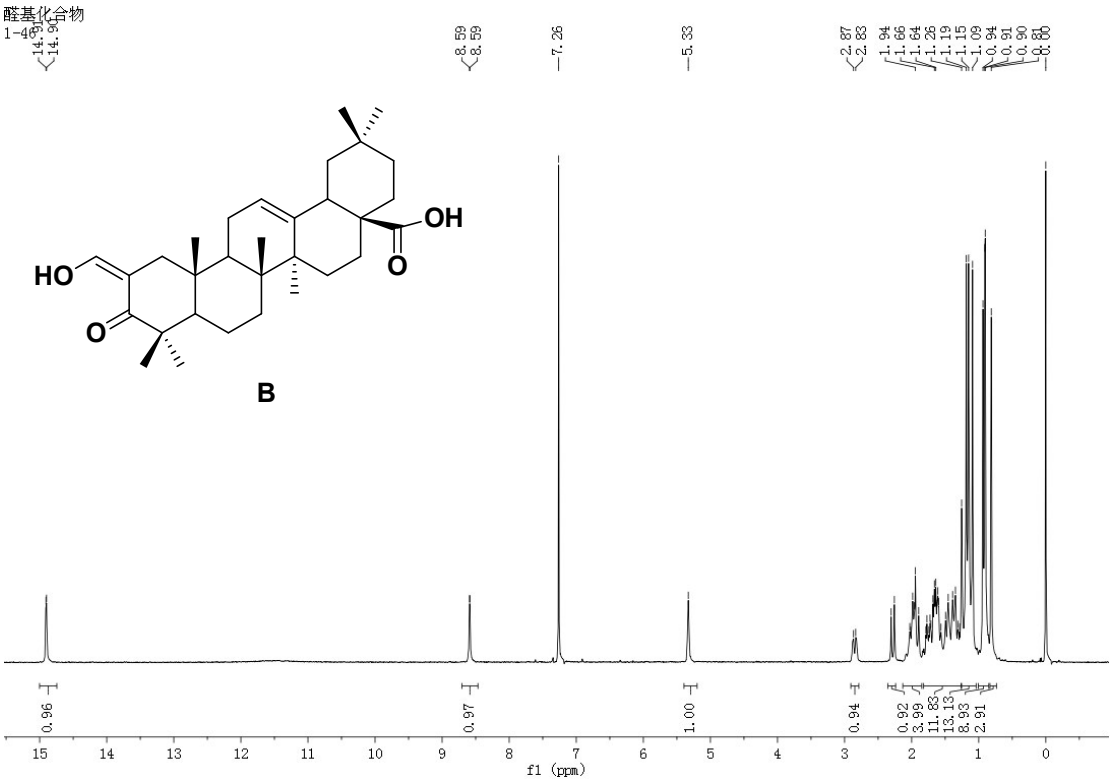
The purity of final compounds was determined by HPLC (Shimadzu, SPD-M20A) with C18 reverse-phase column (KR100-5C18, 250 mm × 4.6 mm) at UV detection of 210 nm. Compounds were dissolved in MeOH. H_2O/CH_3CN (1:9, v/v) was used as the mobile phase; flow rate: 1.0 ml/min. The retention time (t_R) is expressed in min at 210 nm.

Comp	t_R (min)	Purity (Area %)	Comp	t_R (min)	Purity (Area %)
2a	6.634	98.201	**5g**	2.494	95.128
2b	2.498	98.239	**5h**	2.493	93.480
2c	2.499	96.448	**5i**	2.482	96.288
2d	2.502	96.796	**5j**	2.481	92.134
3a	7.116	95.672	**6a**	2.500	97.448
3b	8.329	97.233	**6b**	2.498	94.174
4a	2.483	97.900	**6c**	2.492	98.254
4b	2.484	97.479	**6d**	2.495	97.671
4c	2.484	97.479	**6e**	2.505	95.441
4d	2.493	96.228	**6f**	2.497	99.716
4e	2.495	97.345	**6g**	2.502	99.107
4f	2.484	98.158	**6h**	2.497	96.455
5a	2.505	98.235	**6i**	2.503	95.676
5b	2.475	94.494	**6j**	2.495	96.909
5c	2.487	95.974	**7a**	7.116	96.673
5d	2.495	93.796	**7b**	2.477	99.574
5e	2.487	96.772	**7c**	2.493	94.935
5f	2.495	98.696	**7d**	2.504	97.129

^{1}H NMR and ^{13}C NMR spectra of tested compounds



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1.19
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1.09
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0.91
0.90
0.80
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O
OH
O
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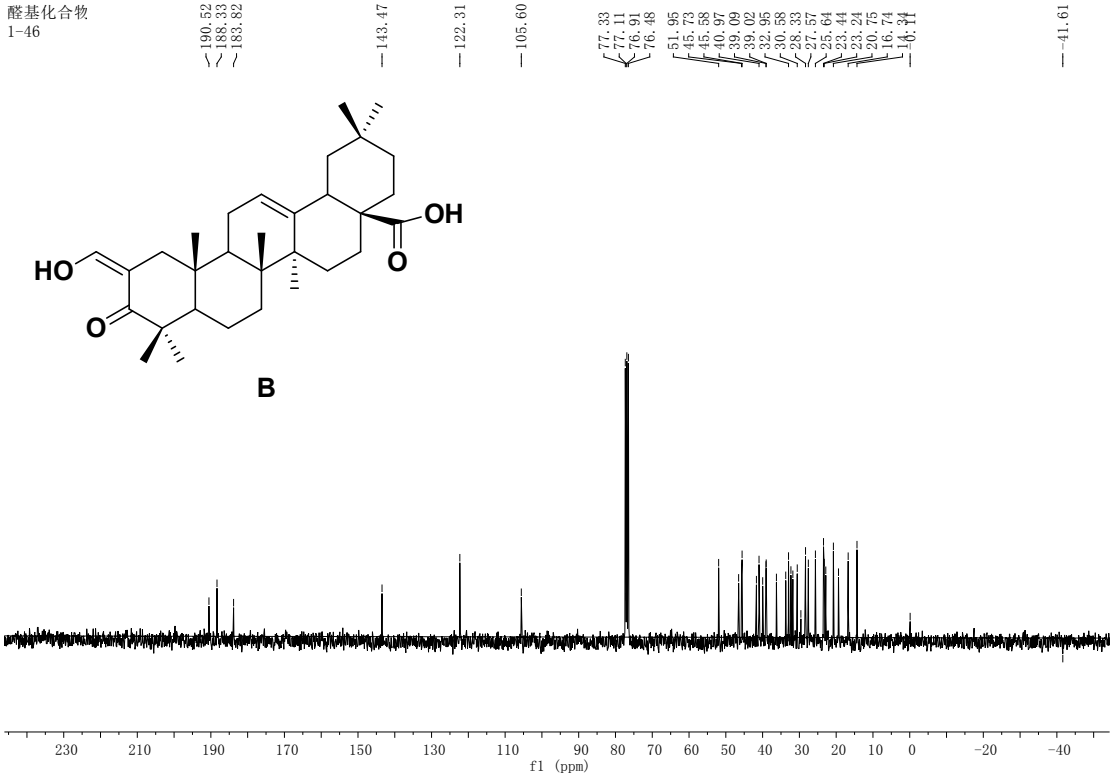
f1 (ppm)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51.95
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45.58
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39.09
39.02
32.95
30.58
28.33
27.57
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OH
O
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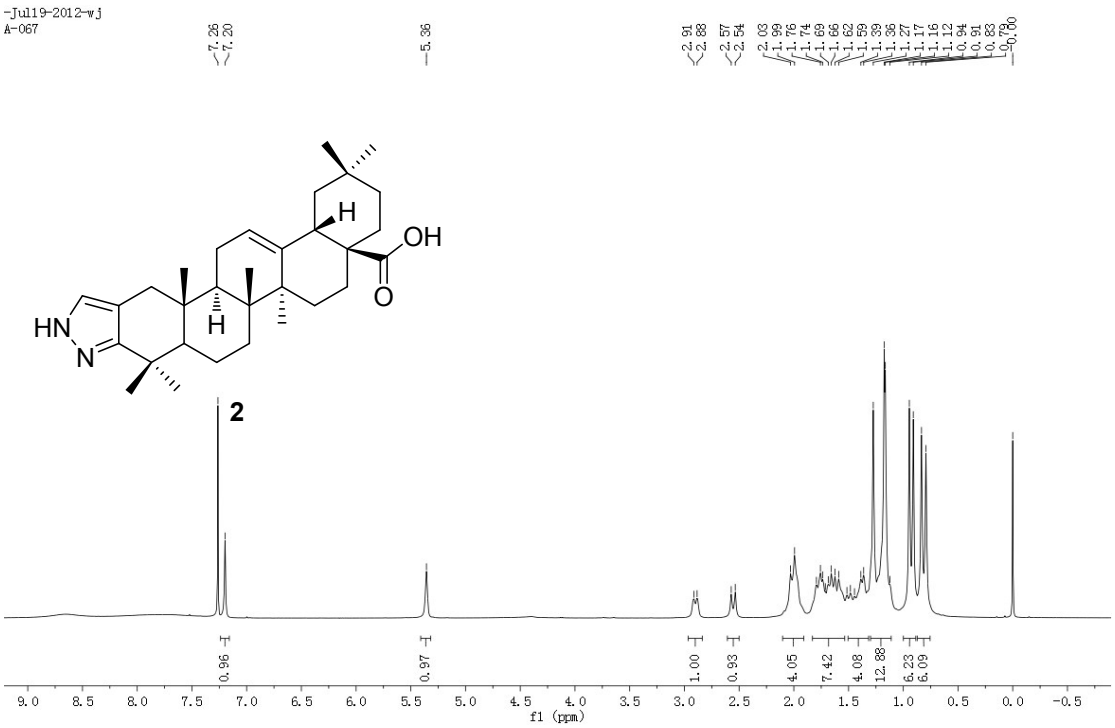
f1 (ppm)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1.27
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1.16
1.12
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OH
O
HN
N
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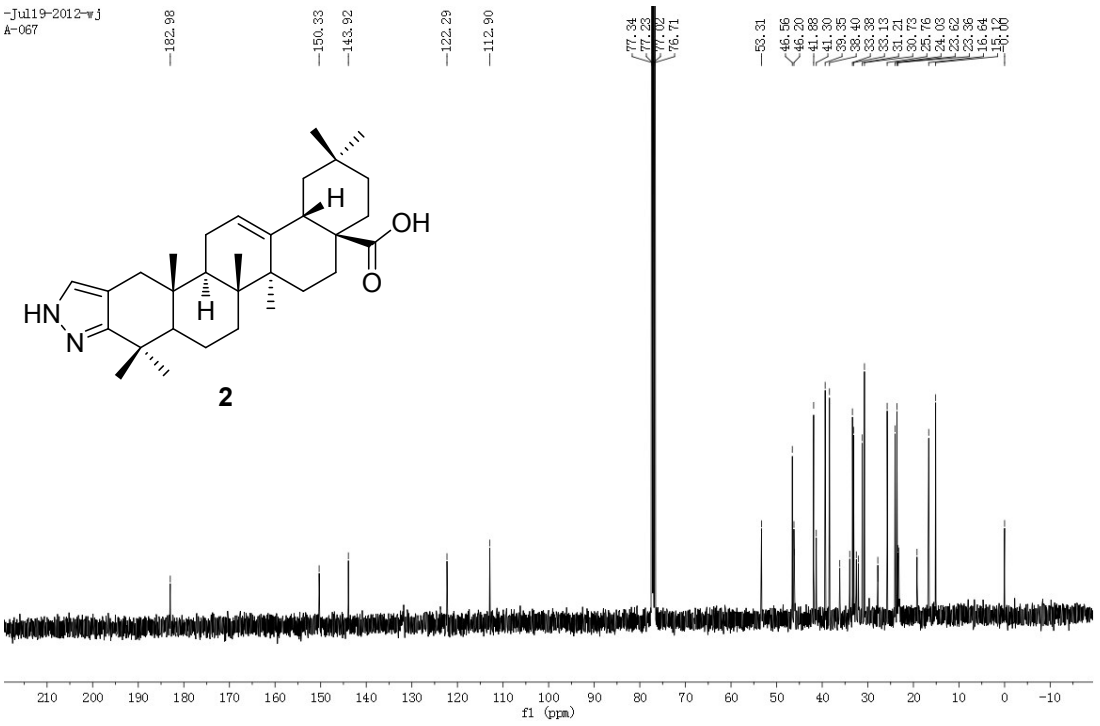
6.09
f1 (ppm)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41.30
39.35
38.49
38.38
33.13
31.21
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N
H
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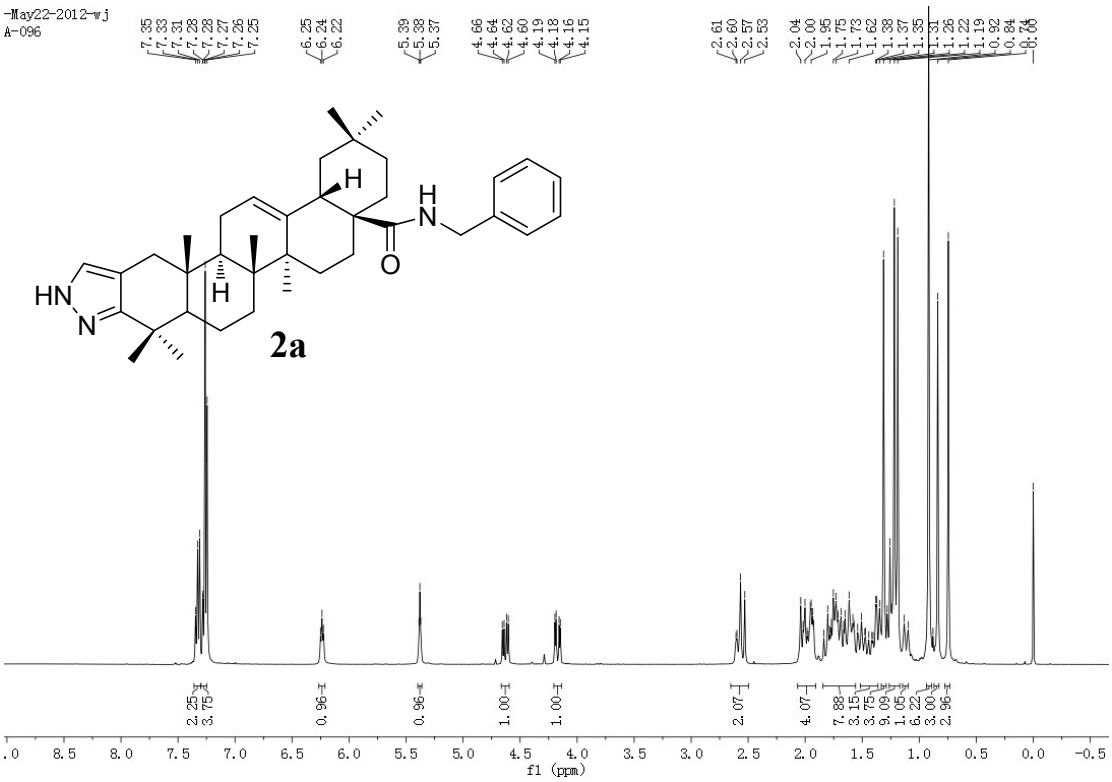
f1 (ppm)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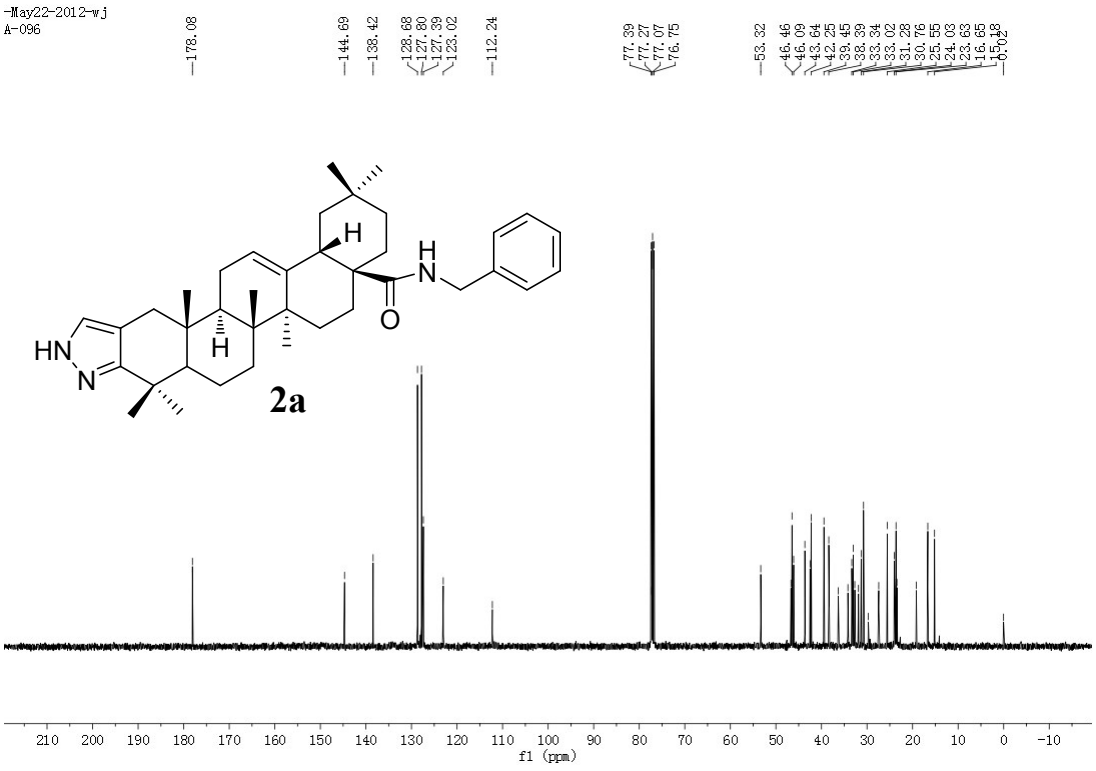
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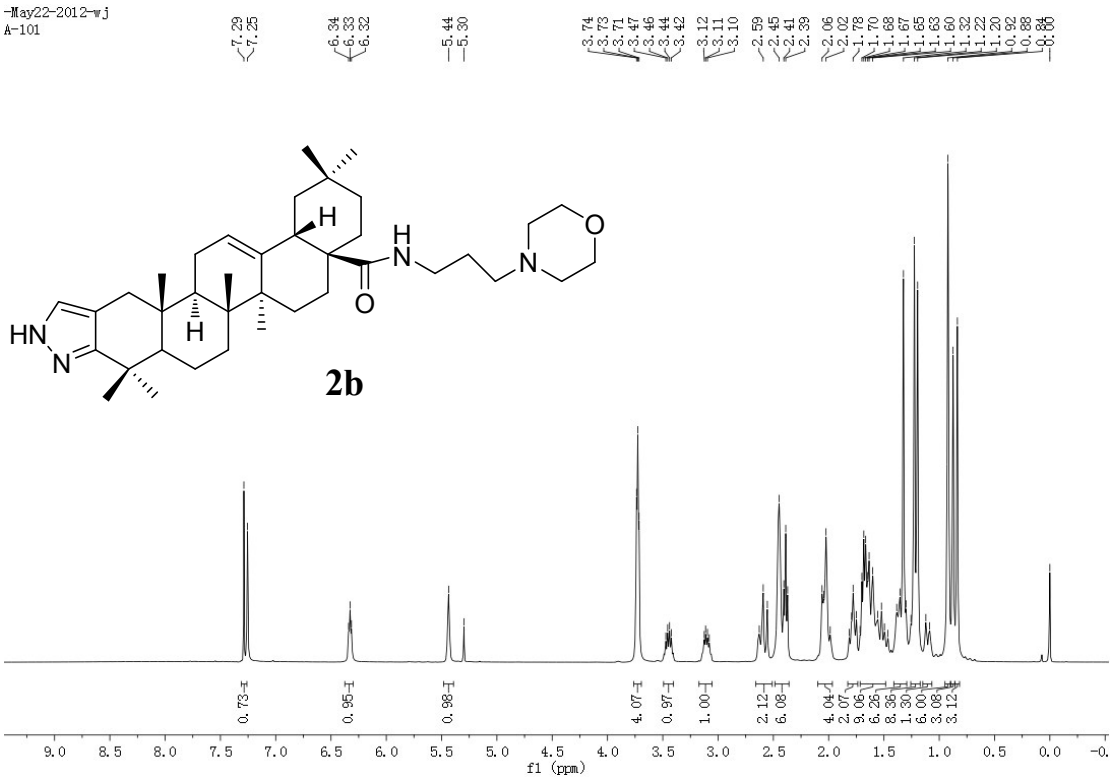
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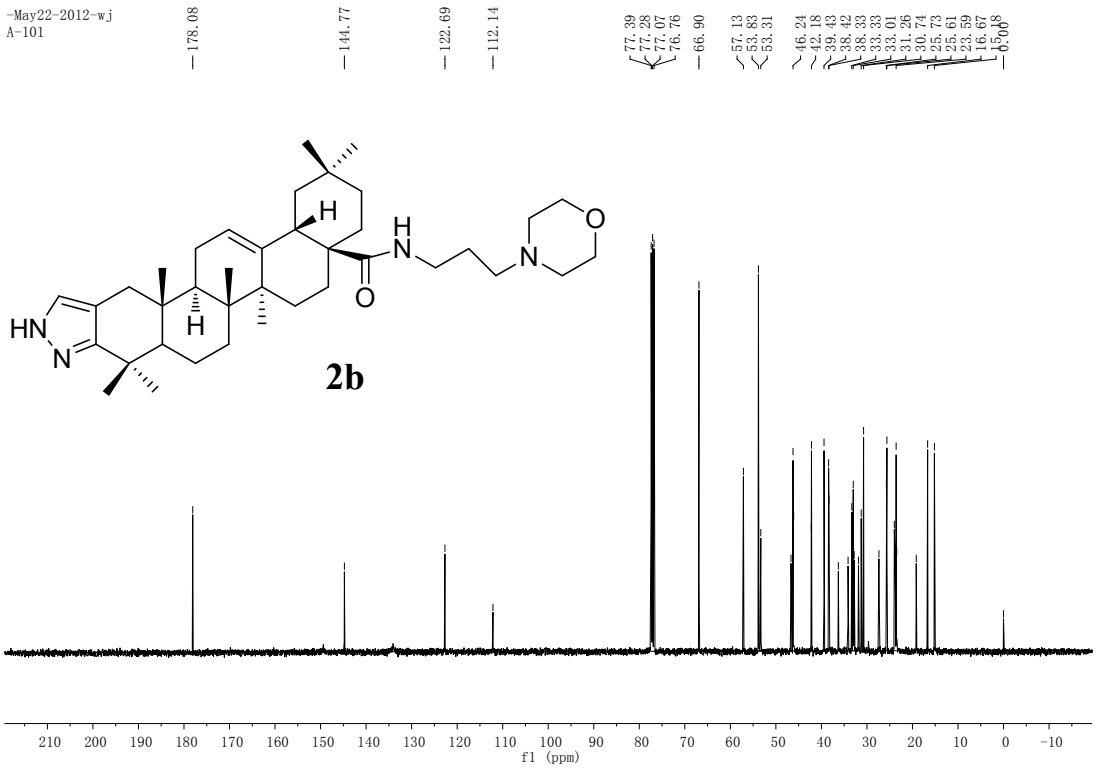
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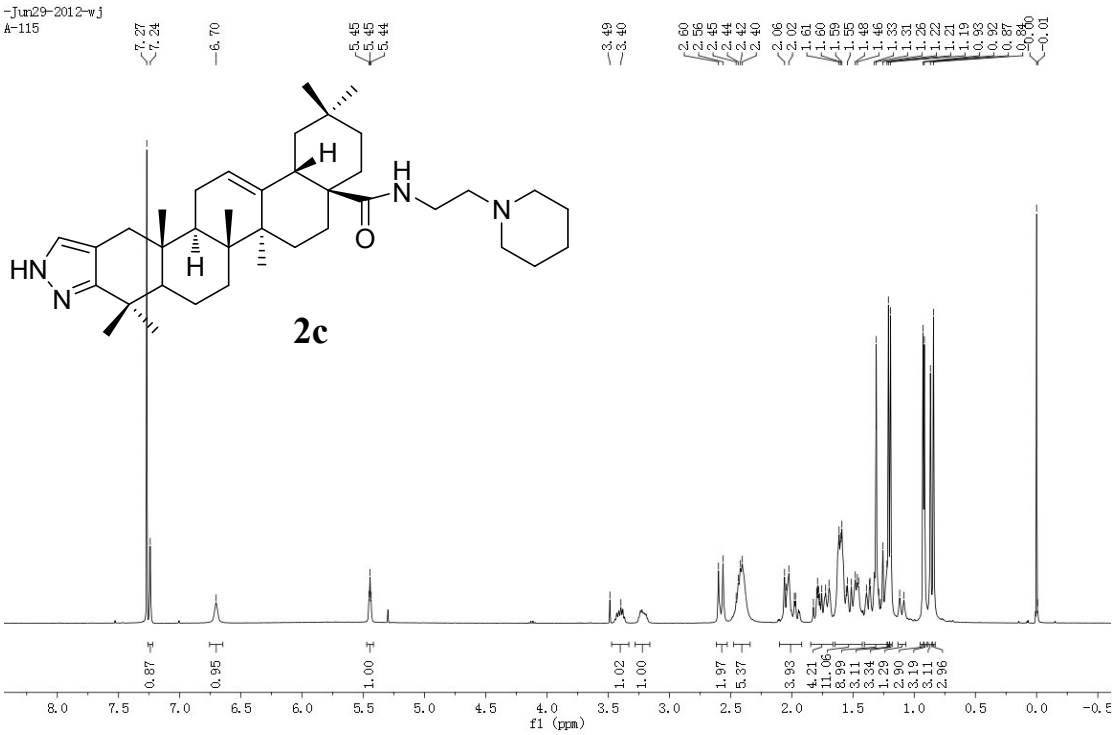
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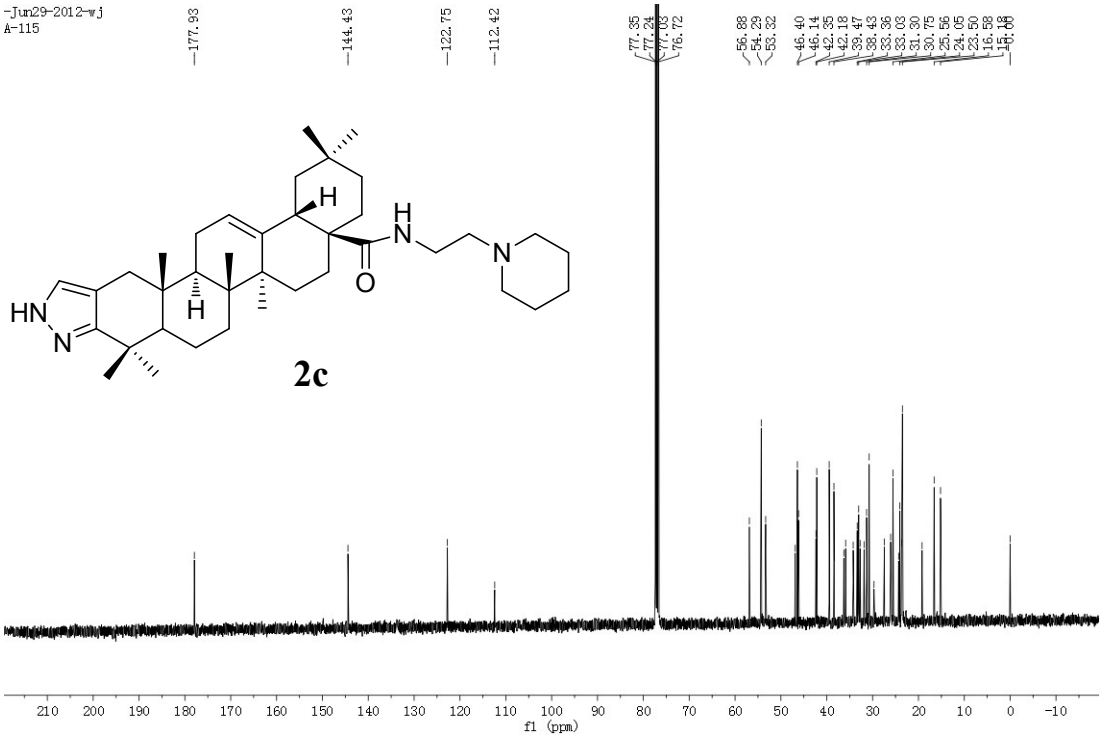
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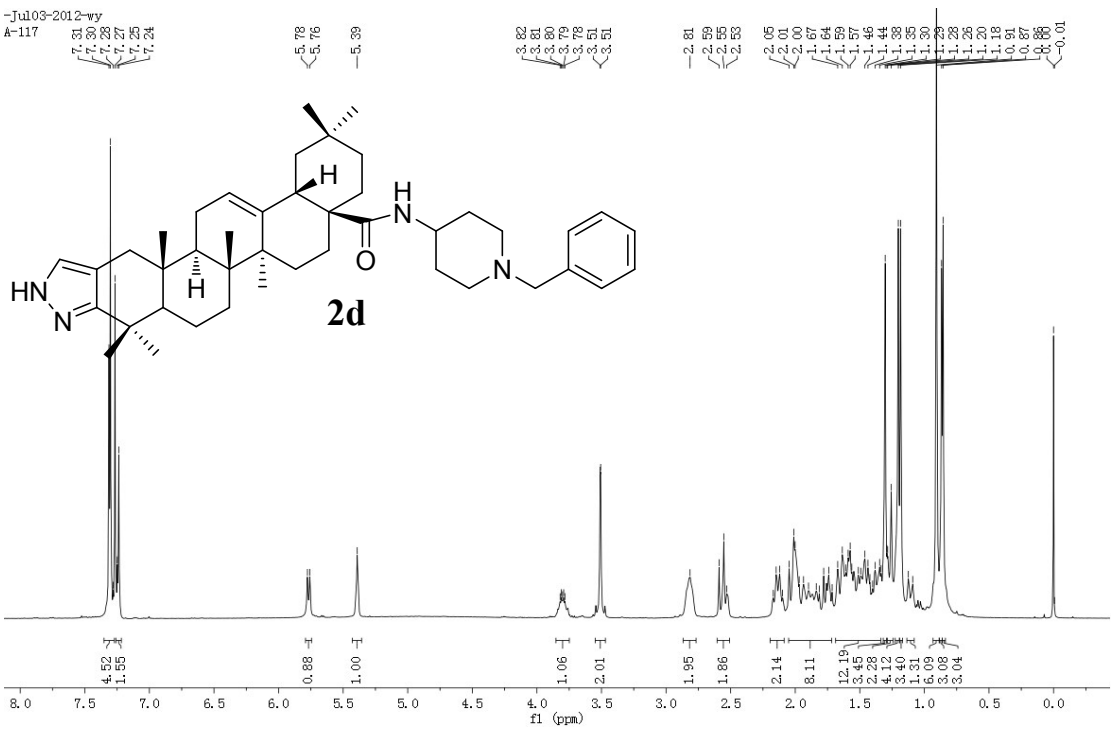
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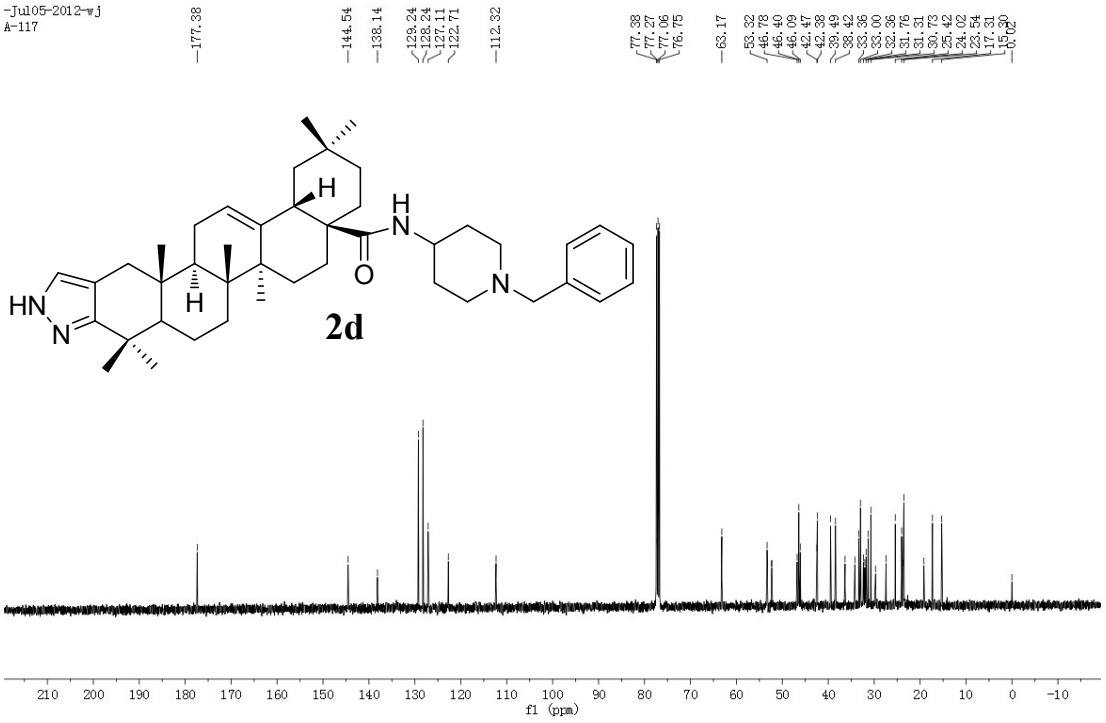
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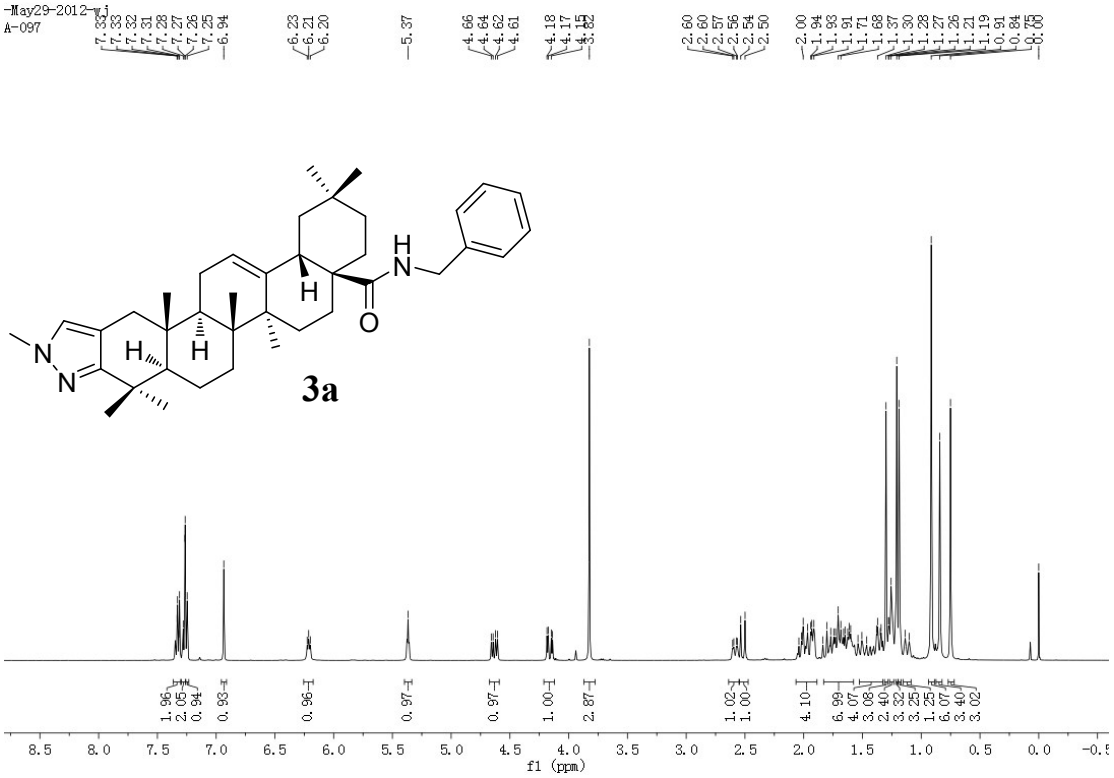
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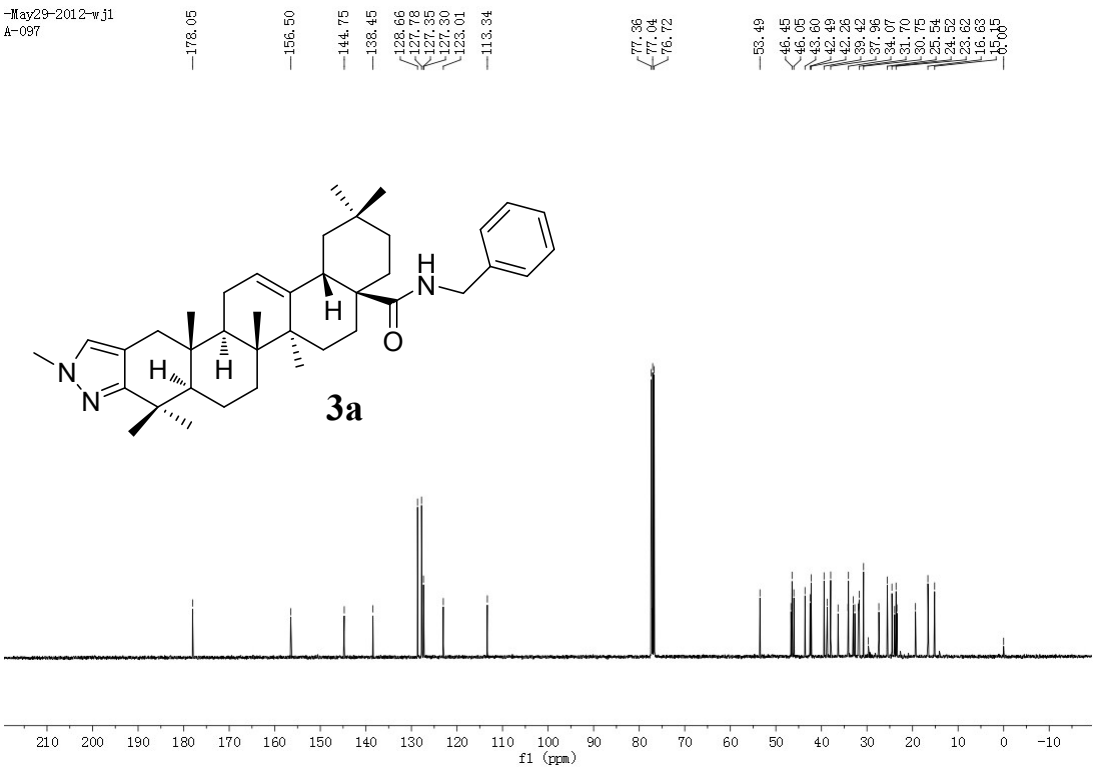
f1 (ppm)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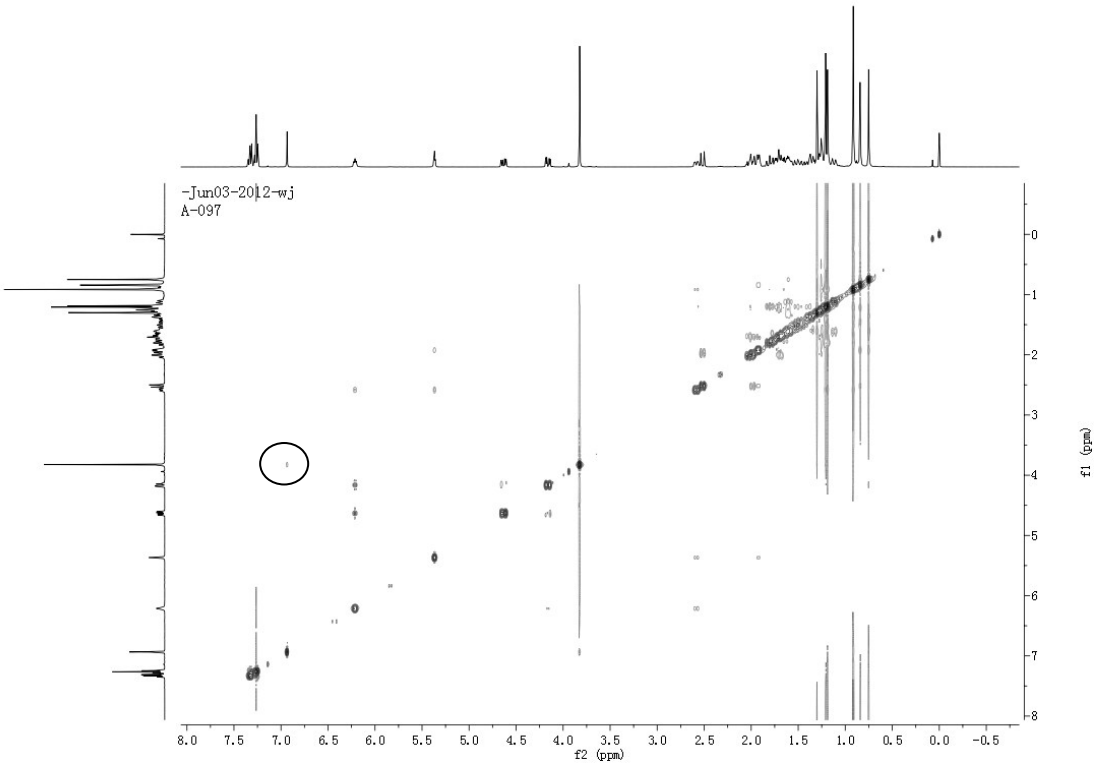
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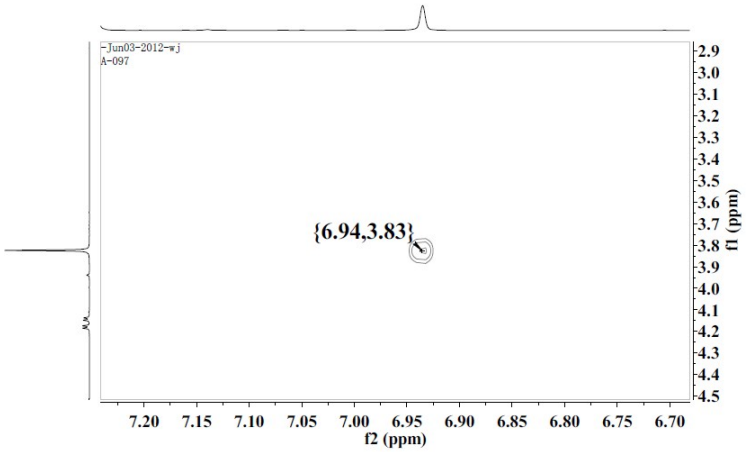
f2 (ppm)
f1 (ppm)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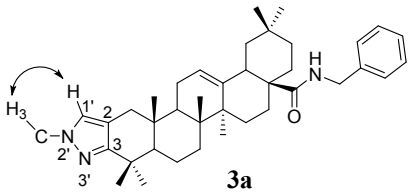
f1 (ppm)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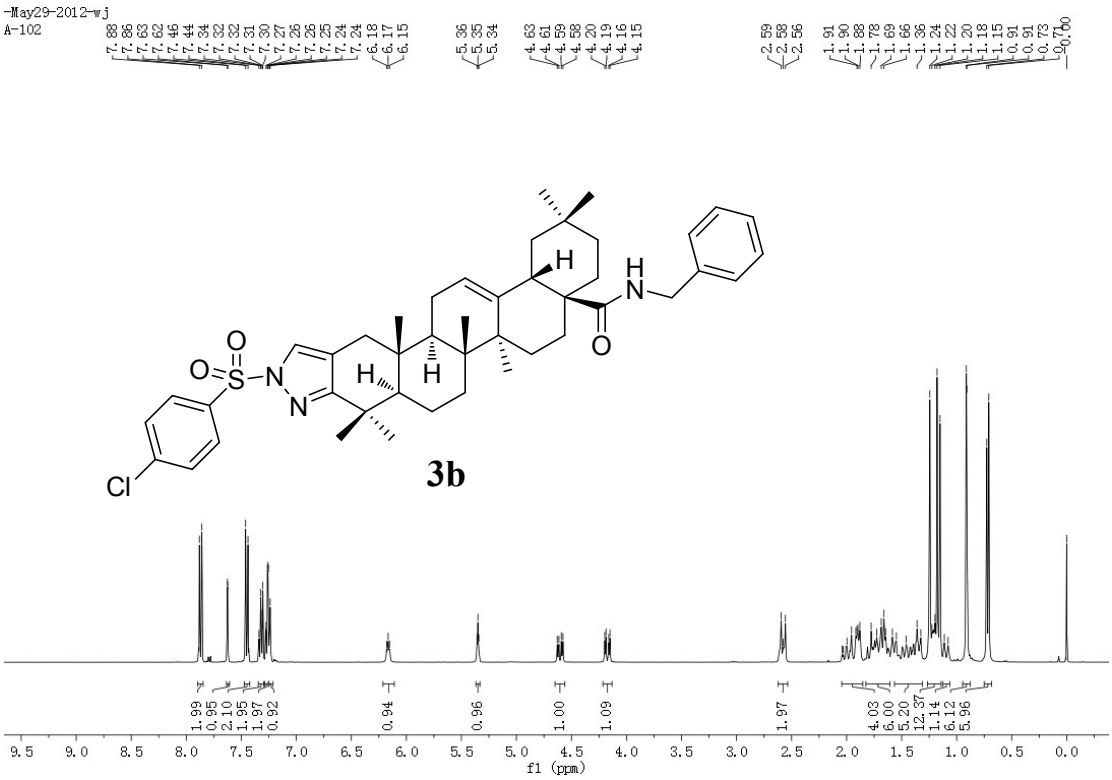
2
2'
3
3'
N
H
O

3a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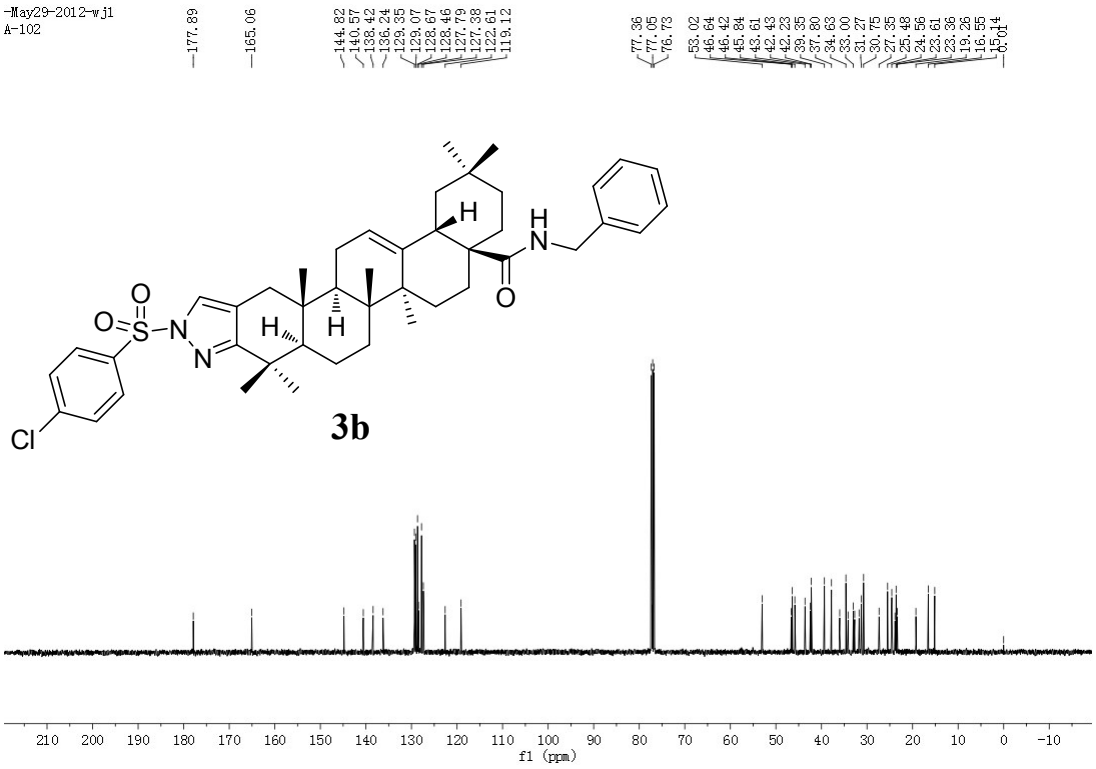
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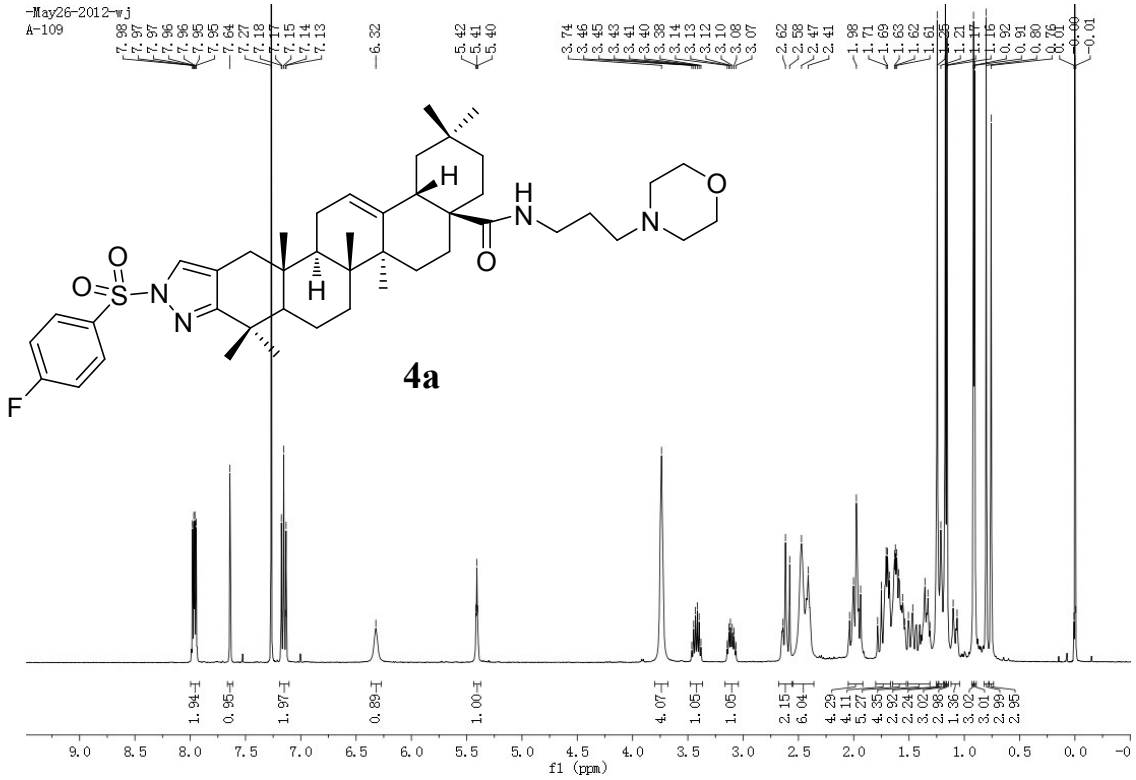
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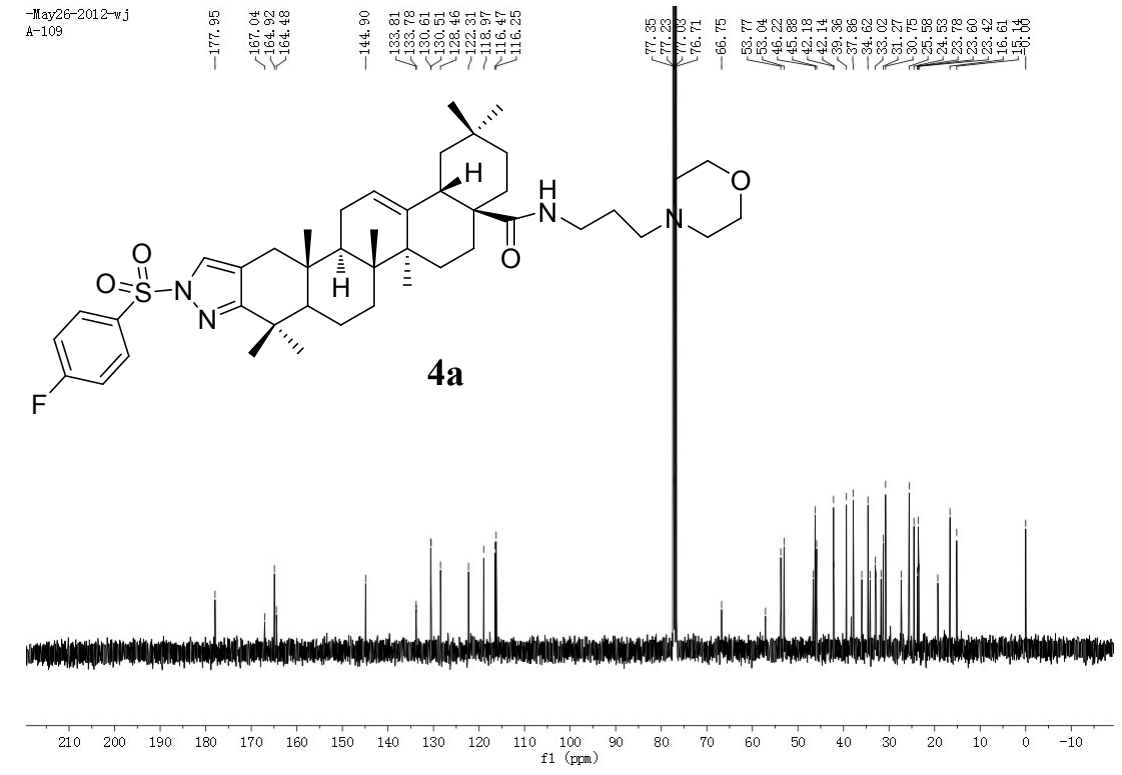
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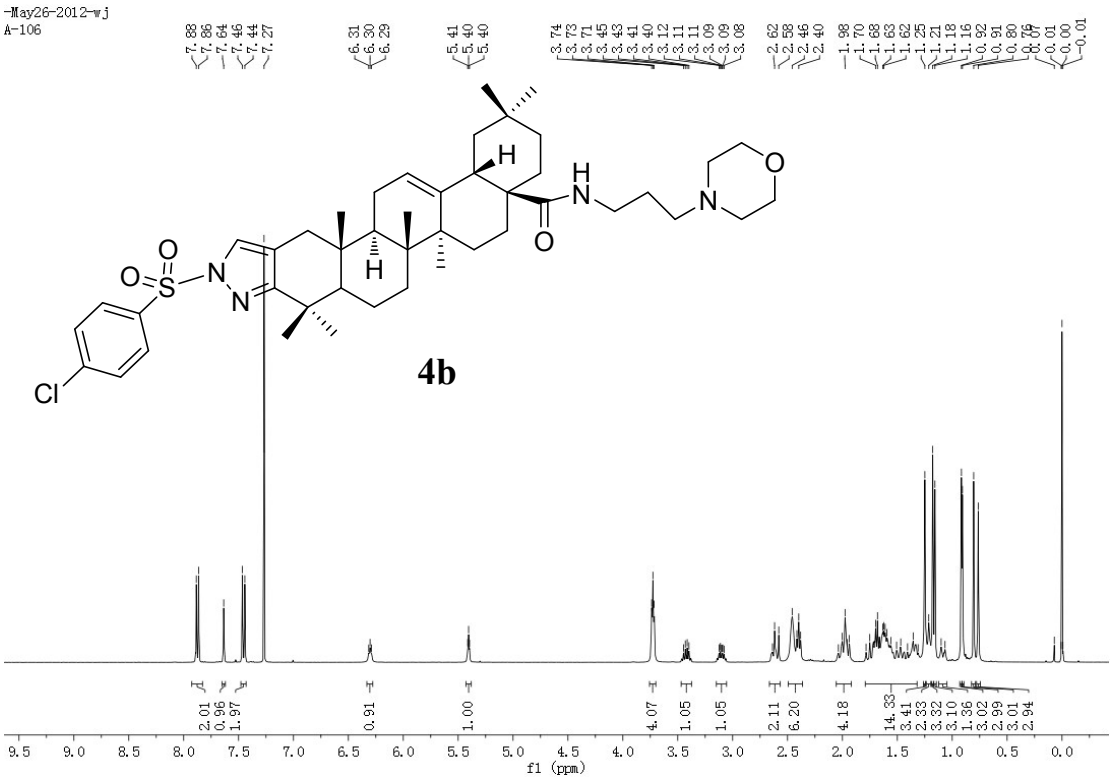
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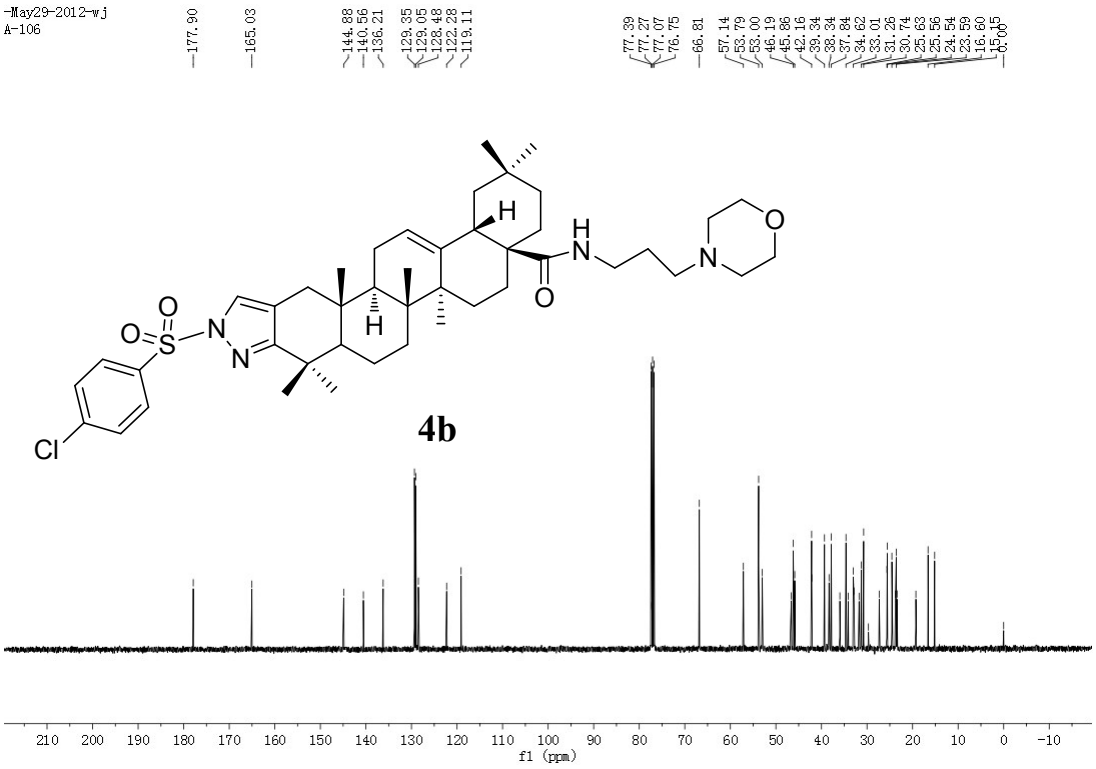
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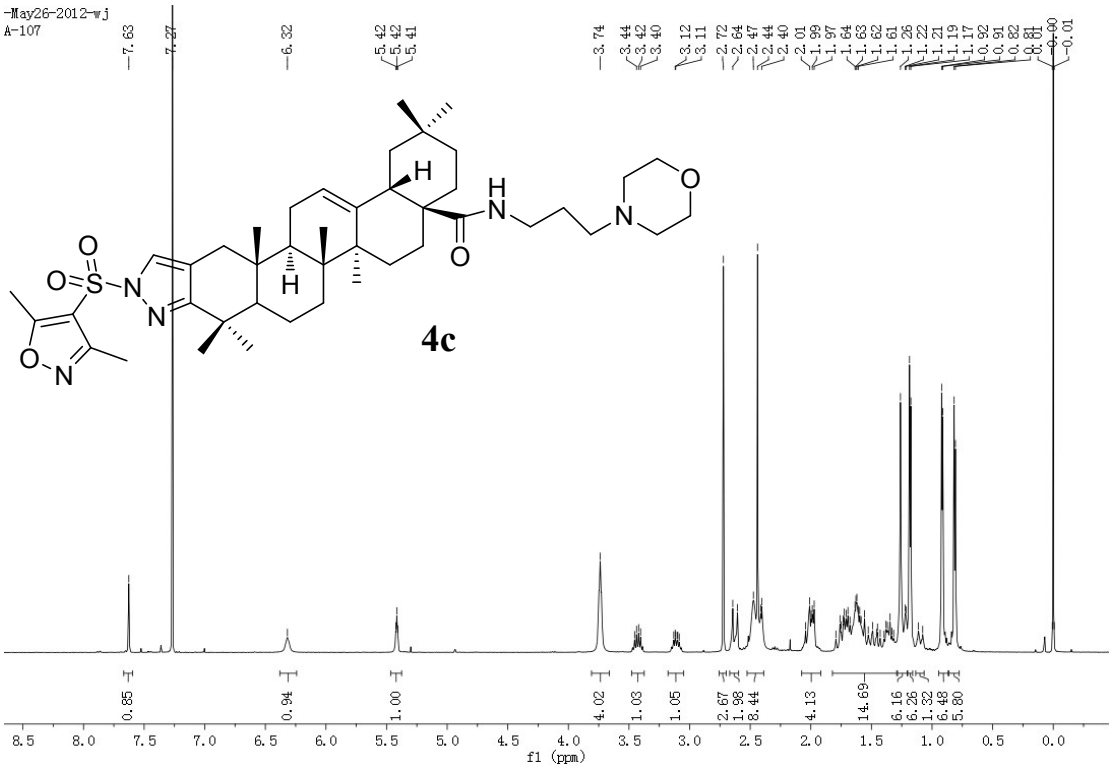
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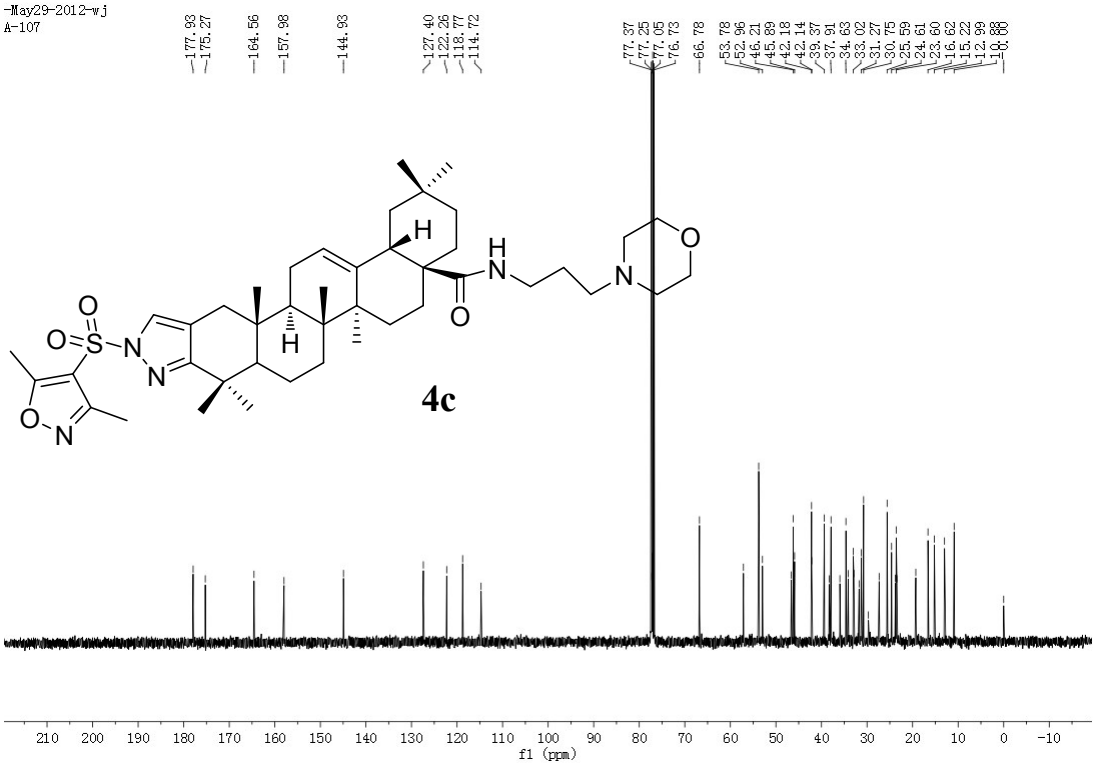
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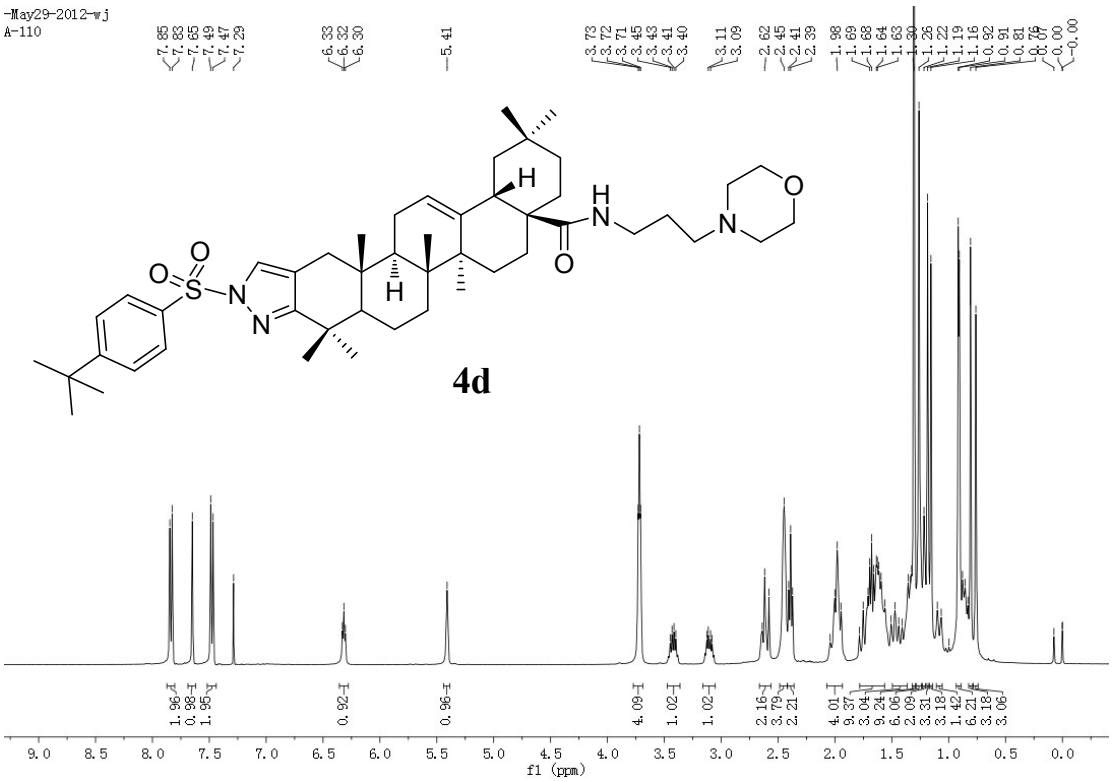
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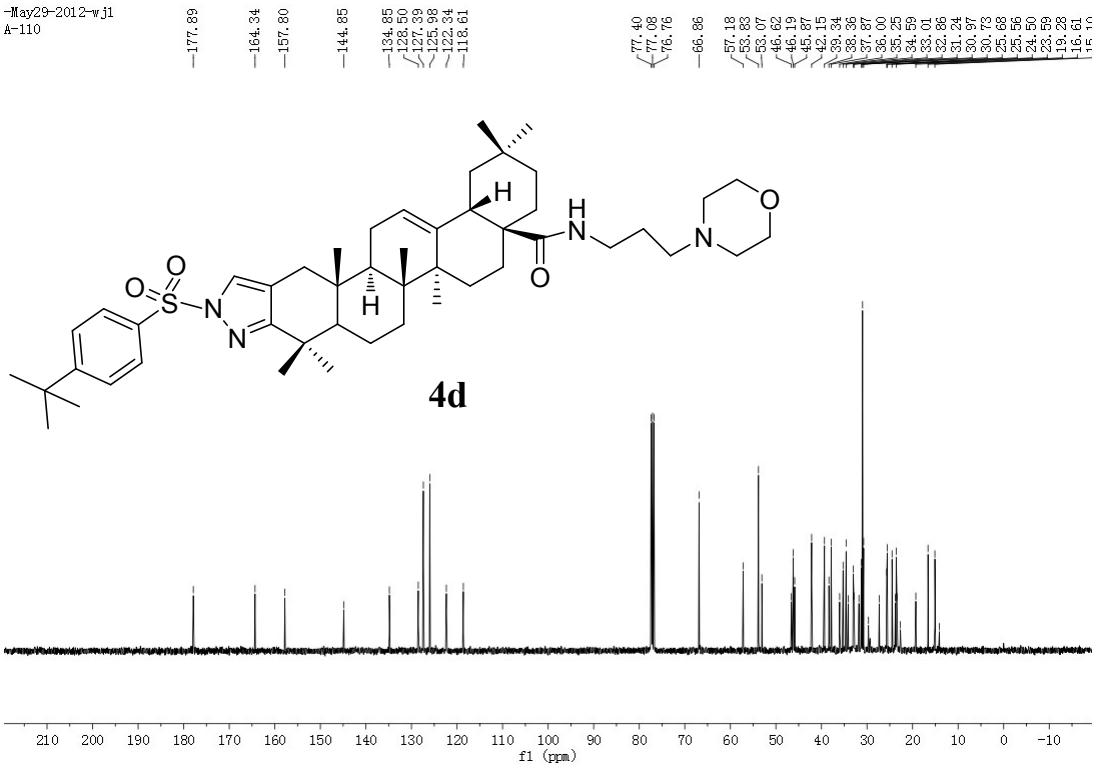
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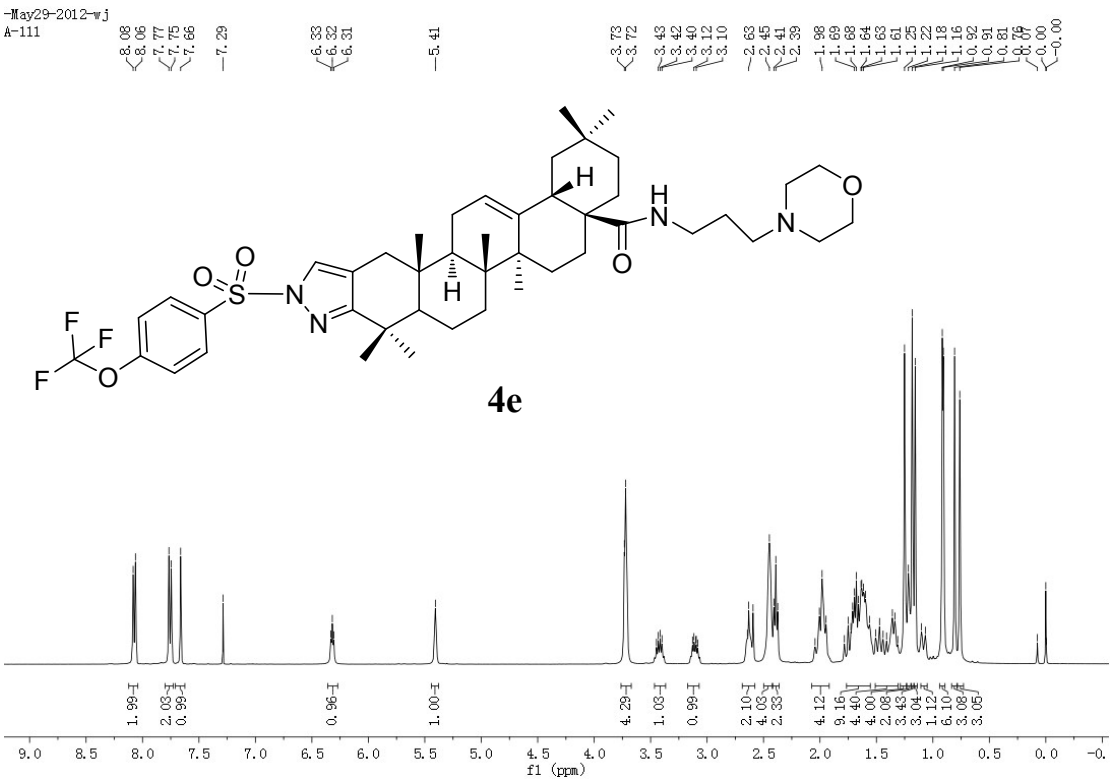
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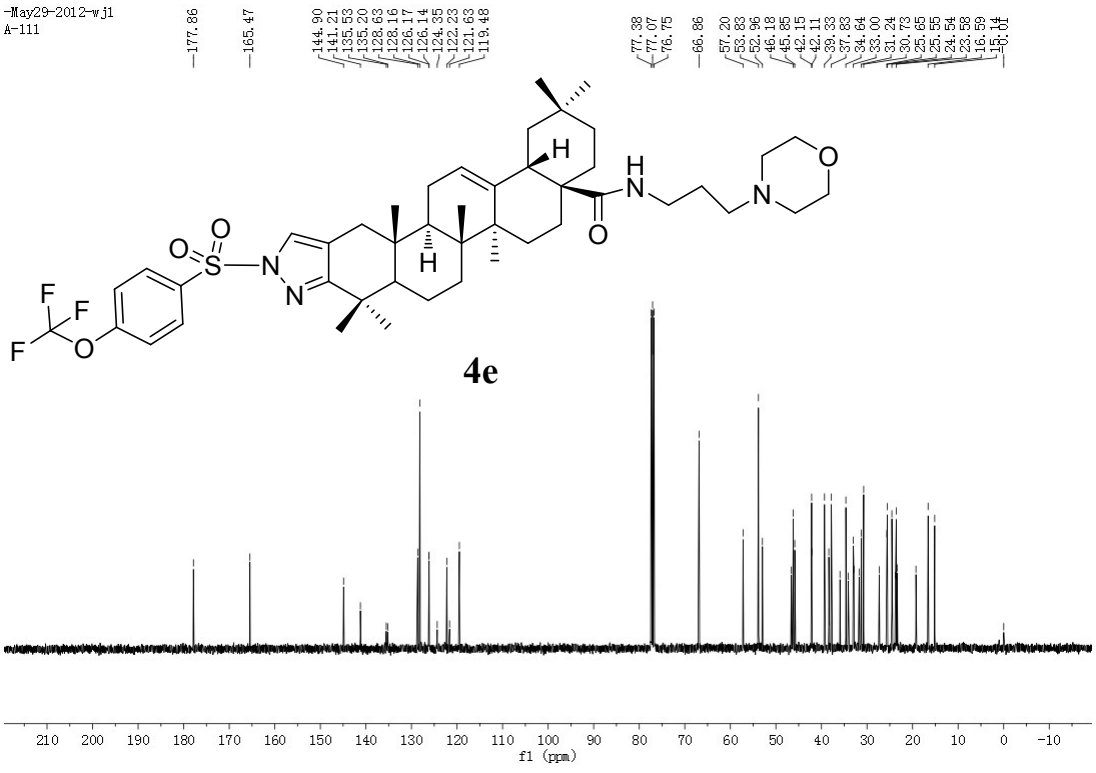
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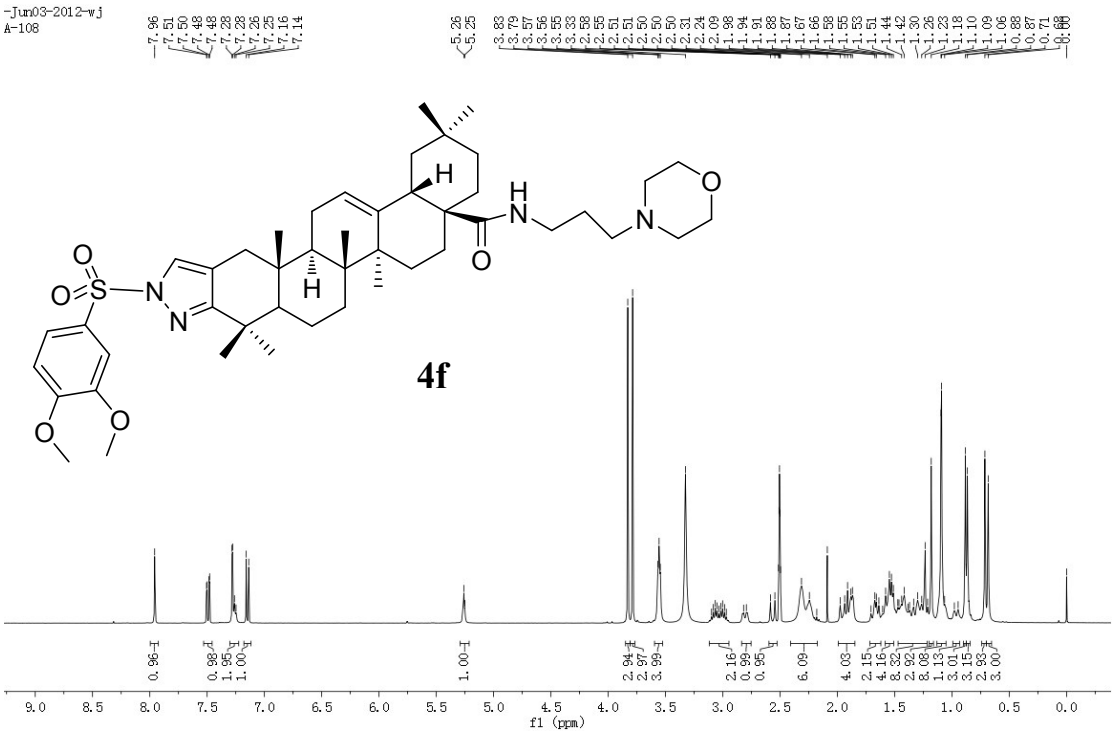
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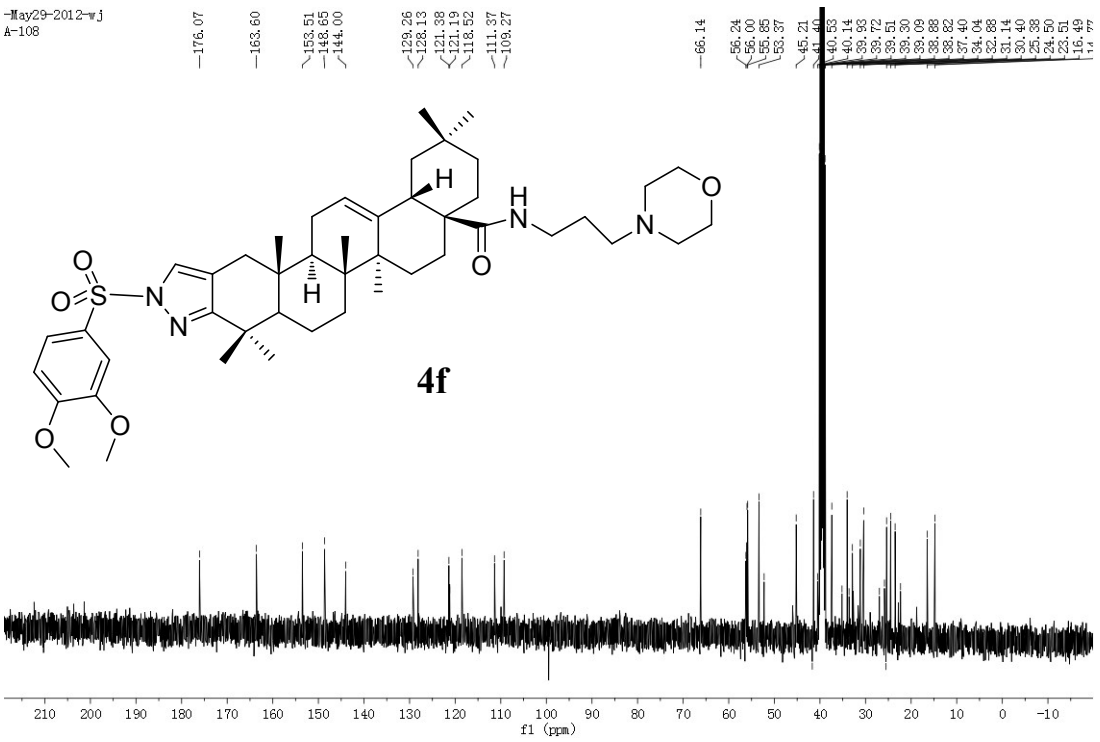
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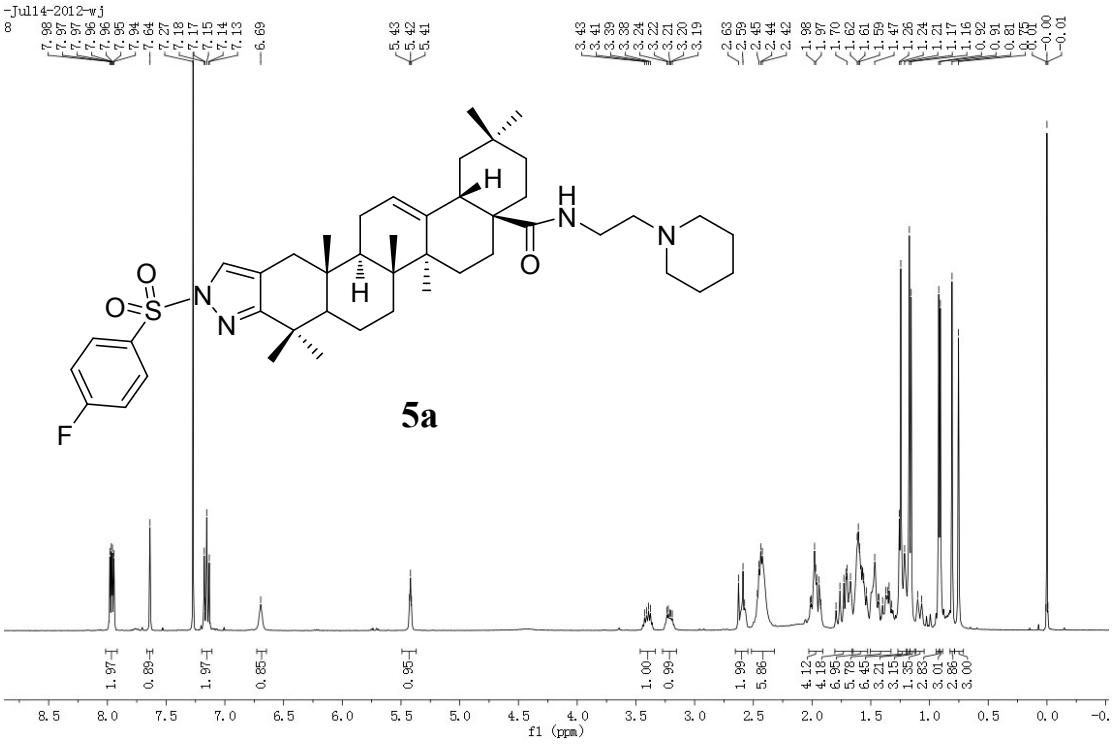
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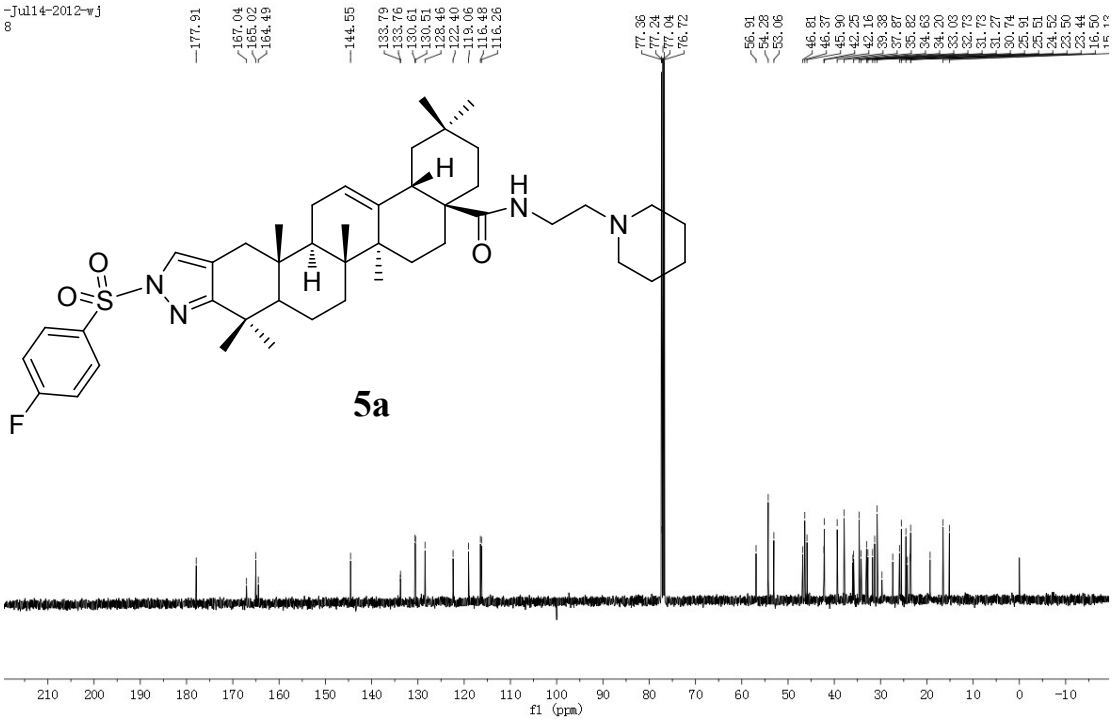
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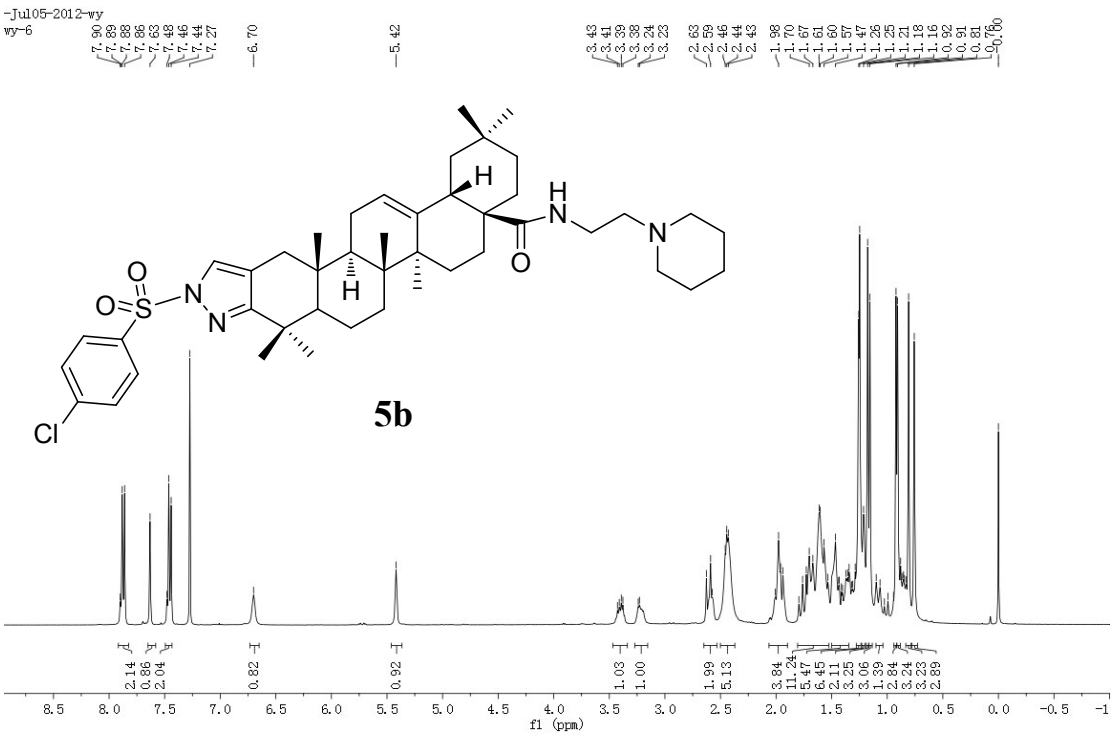
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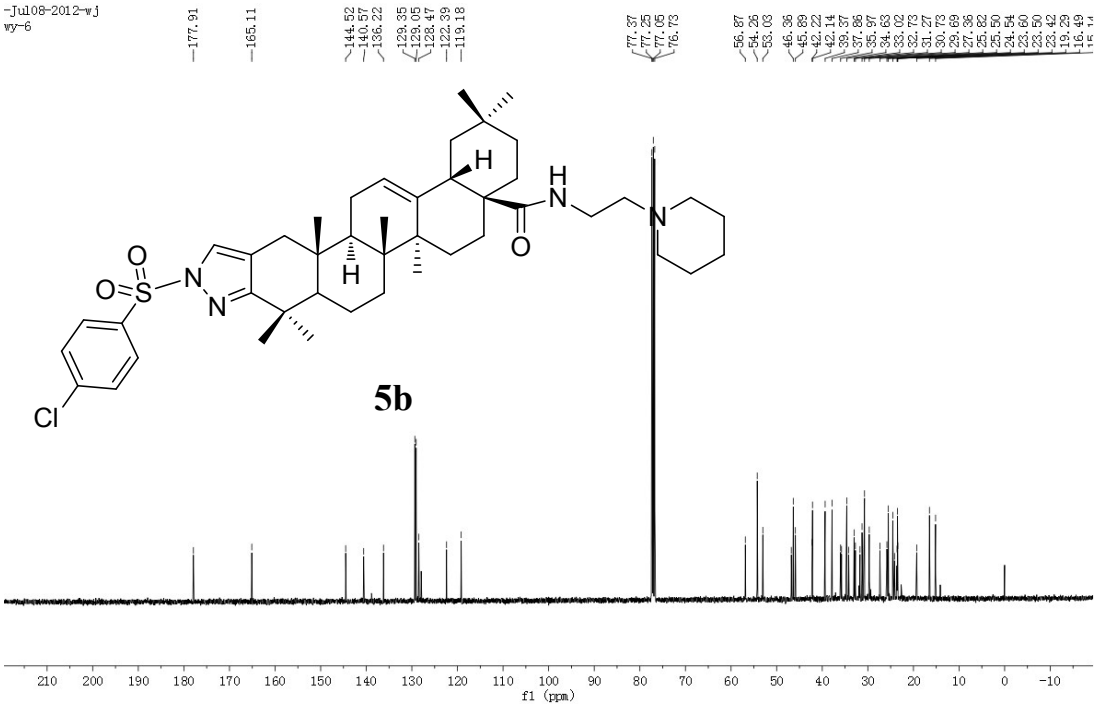
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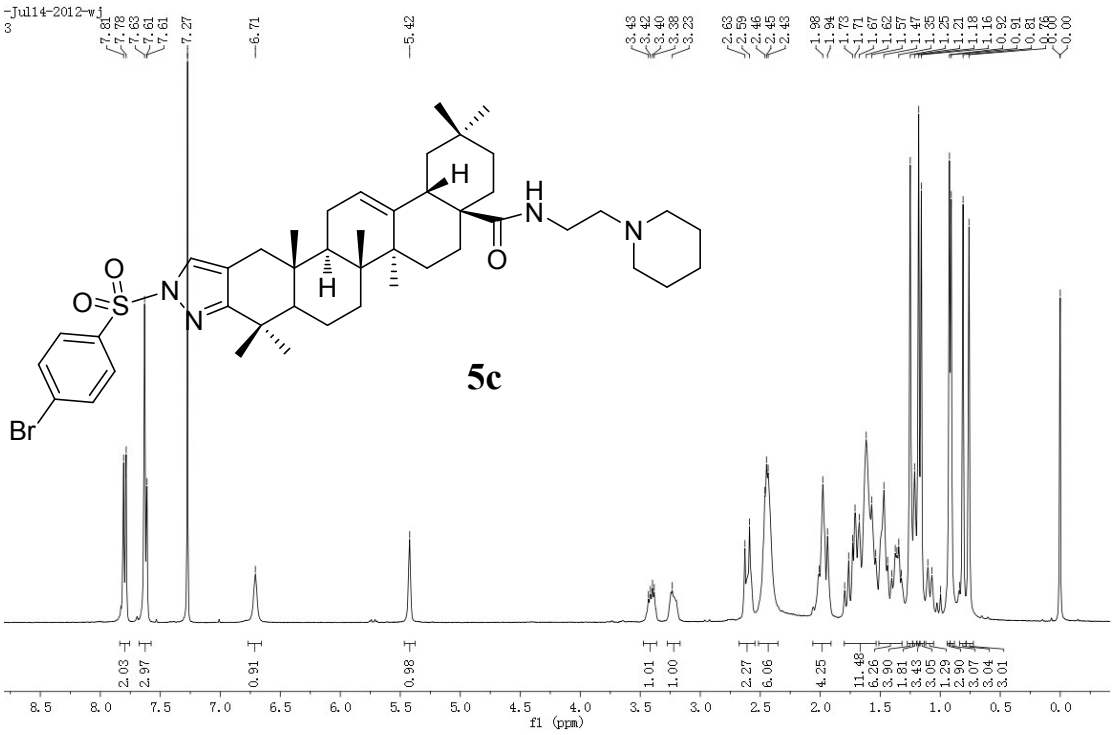
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2.63
2.59
2.46
2.45
2.43
1.98
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1.73
1.71
1.67
1.62
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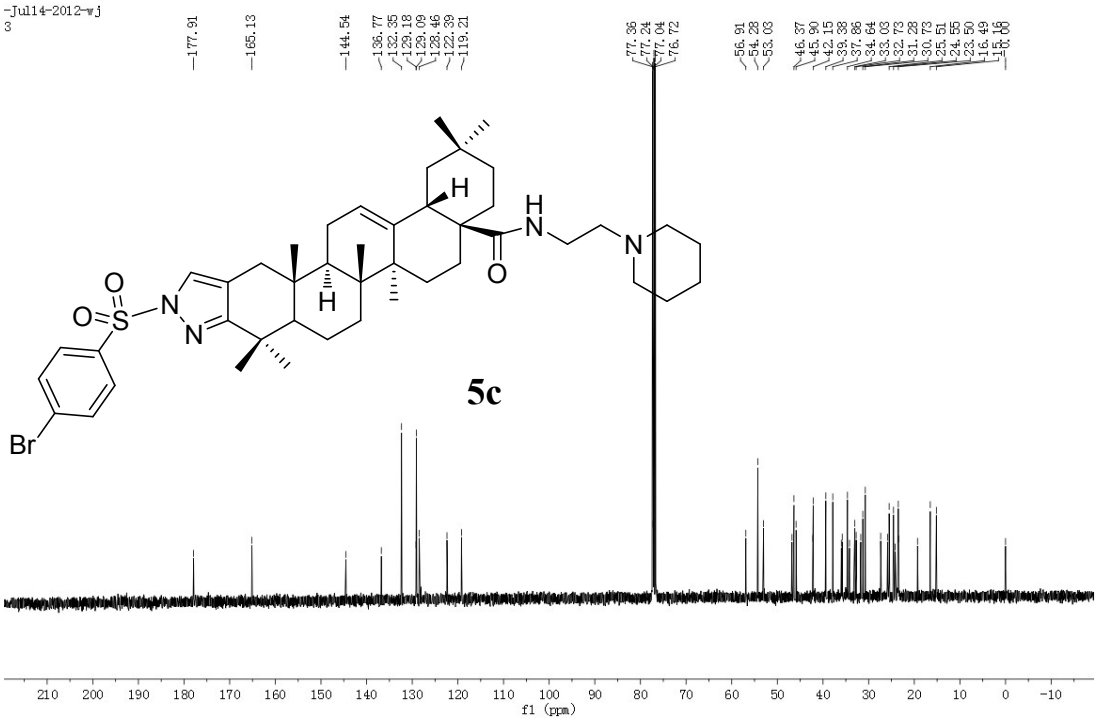
1.35
1.25
1.21
1.18
1.16
0.92
0.91
0.81
0.08
0.00
2.03
2.97
0.91
0.98
1.01
1.00
2.27
6.06
4.25
11.48
6.26
3.90
1.81
3.43
3.05
1.29
2.90
3.07
3.04
3.01
f1 (ppm)
5c
Br


-Jul14-2012-wj
3
177.91
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132.35
129.18
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122.39
119.21
77.36
77.24
77.04
76.72
56.91
54.28
53.03
46.37
45.90
42.15
39.38
37.86
34.64
33.03
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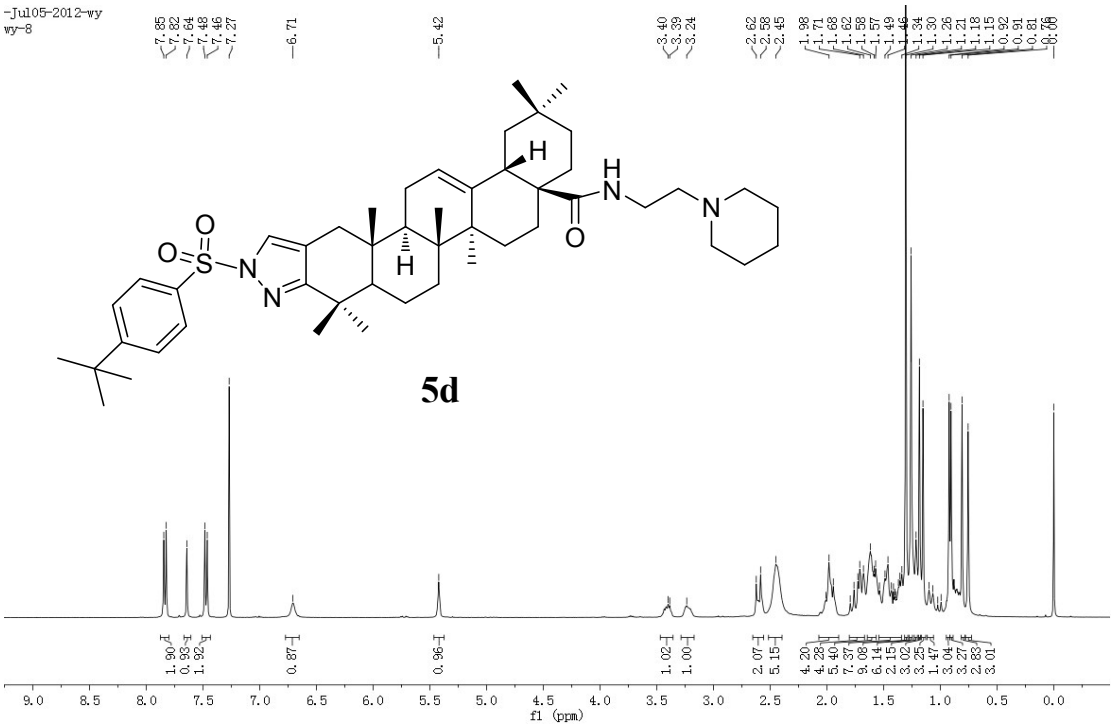
25.51
24.55
23.50
16.49
15.08
15.06
f1 (ppm)
5c
Br


-Jul05-2012-wy
wy-8
7.85
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7.46
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3.40
3.39
3.24
2.62
2.58
2.45
1.98
1.71
1.68
1.62
1.58
1.57
1.49
1.46
1.34
1.30
1.26
1.21
1.18
1.15
0.92
0.91
0.81
0.76
0.00
1.90
0.93
1.92
0.87
0.96
1.02
1.00
2.07
5.15
4.20
4.28
5.40
7.37
9.08
6.14
2.15
3.02
3.25
1.47
3.04
3.27
2.83
3.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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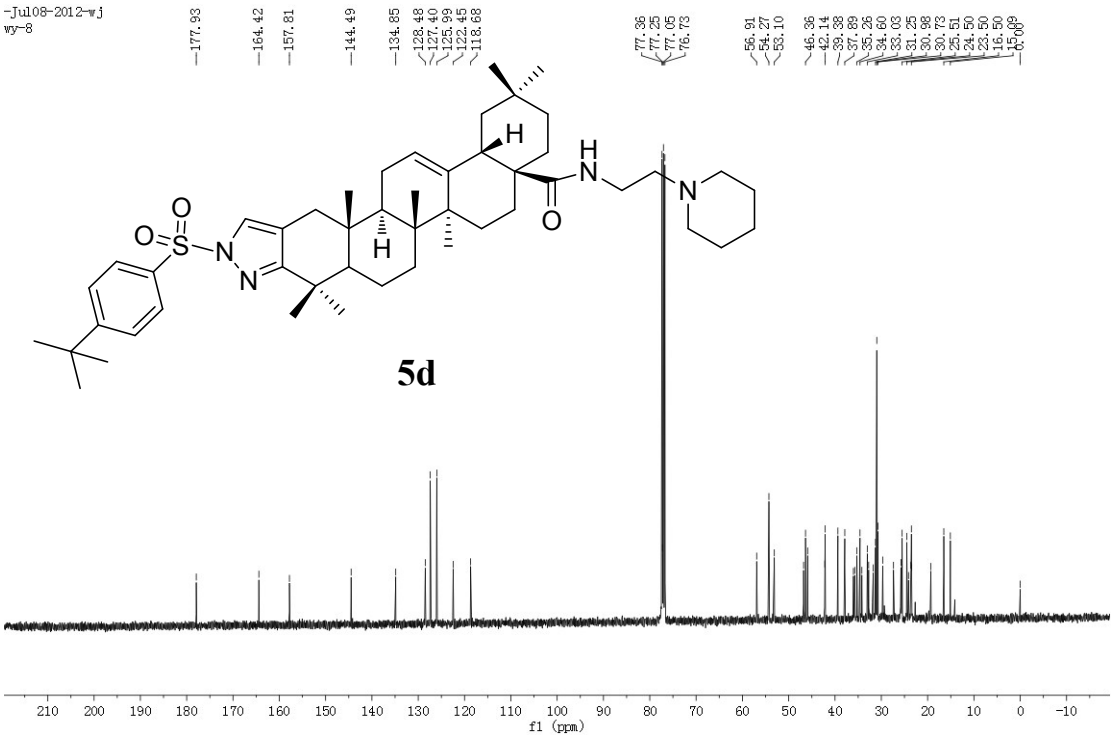
0.0
f1 (ppm)
5d


-Jul08-2012-wj
wy-8
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125.99
122.45
118.68
77.36
77.25
77.05
76.73
56.91
54.27
53.10
46.36
42.14
39.38
37.89
35.26
34.60
33.03
31.23
30.68
30.73
25.51
24.50
23.50
16.50
15.09
0.00
210
200
190
180
170
160
150
140
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120
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100
90
80
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60
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40
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20
10
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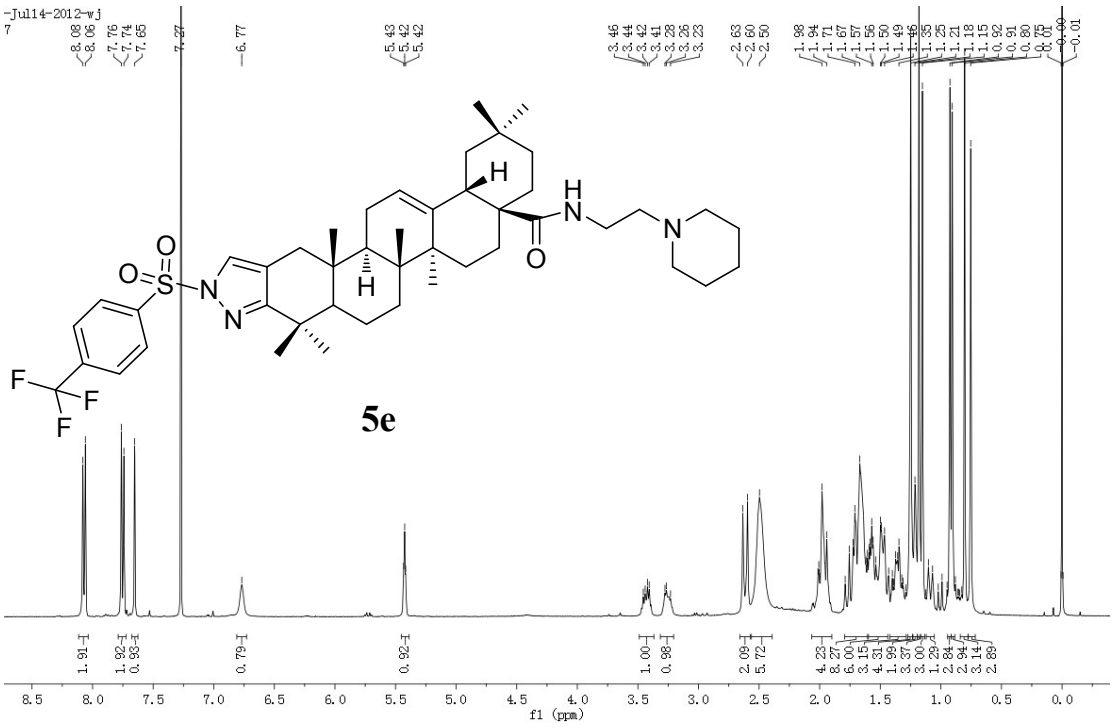
-10
f1 (ppm)
5d


-Jul14-2012-wj
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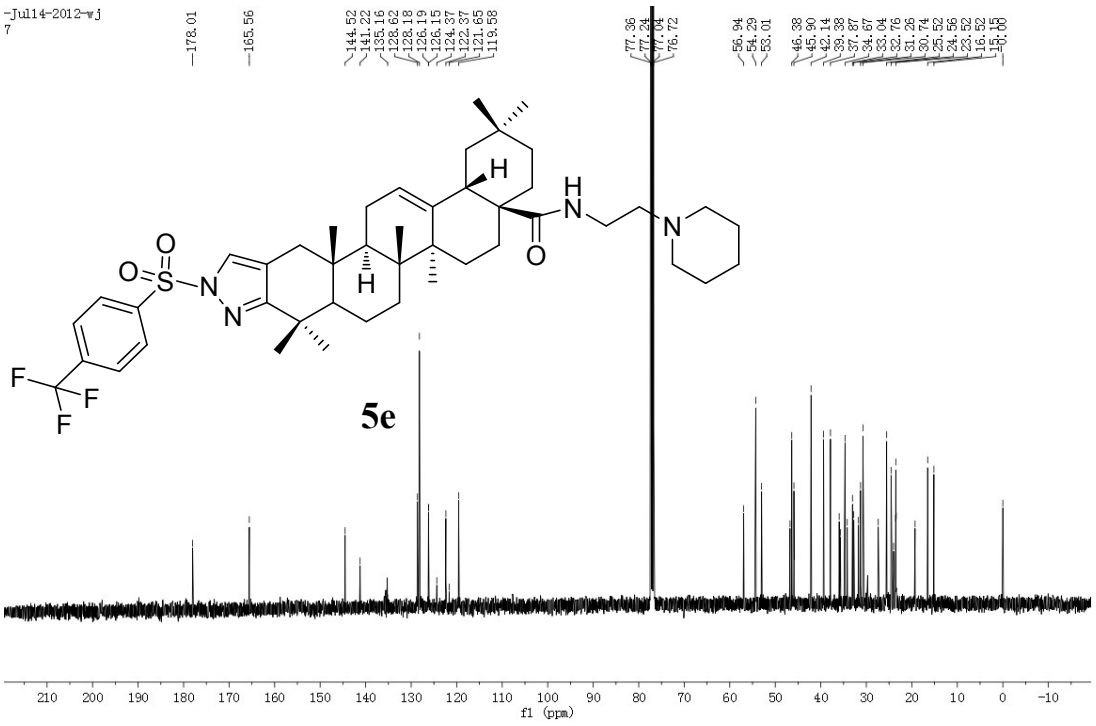
7.65
7.27
6.77
5.43
5.42
5.42
3.46
3.44
3.42
3.41
3.28
3.26
3.23
2.63
2.60
2.50
1.98
1.94
1.71
1.67
1.57
1.55
1.50
1.49
1.46
1.35
1.25
1.21
1.18
1.15
0.92
0.91
0.80
0.55
0.07
0.00
-0.01
1.91
1.92
0.93
0.79
0.92
1.00
0.98
2.09
5.72
4.23
8.27
6.00
3.15
4.31
1.99
3.37
3.00
1.29
2.84
2.94
3.14
2.89
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
5e


-Jul14-2012-wj
7
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135.15
128.62
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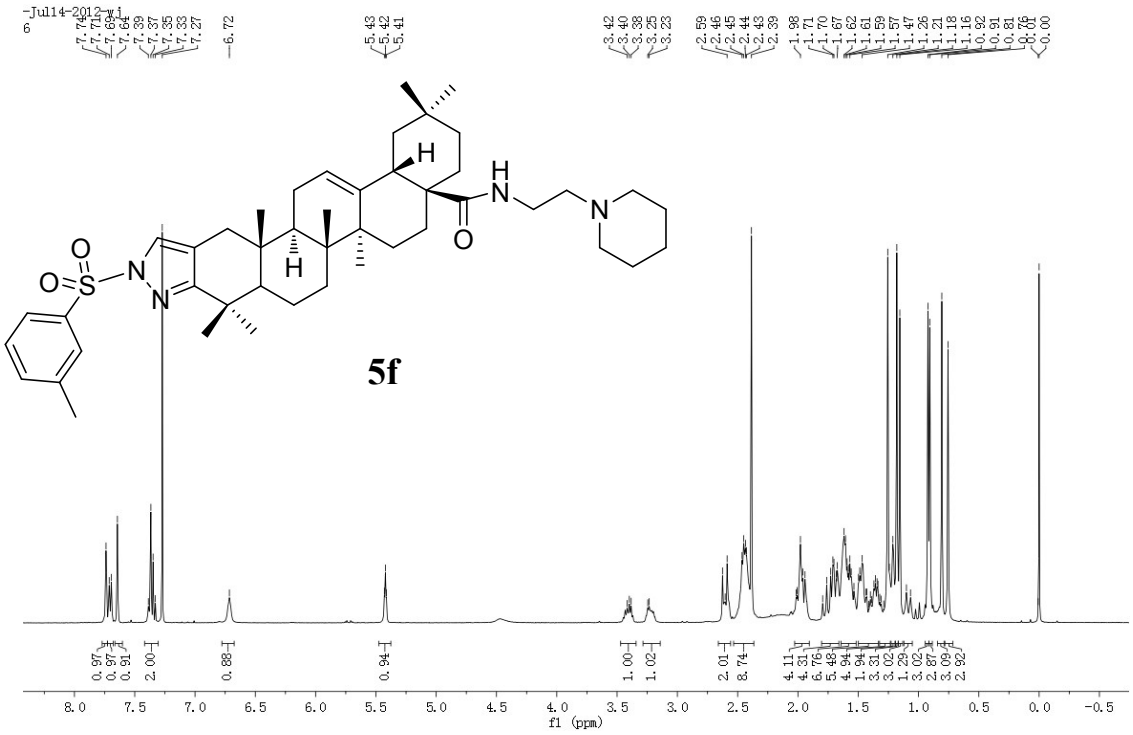
126.15
124.37
122.37
121.65
119.58
77.36
77.24
77.04
76.72
56.94
54.29
53.01
46.38
45.90
42.14
39.38
37.87
34.67
33.04
32.76
31.26
30.74
25.52
25.56
23.52
16.52
15.00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
5e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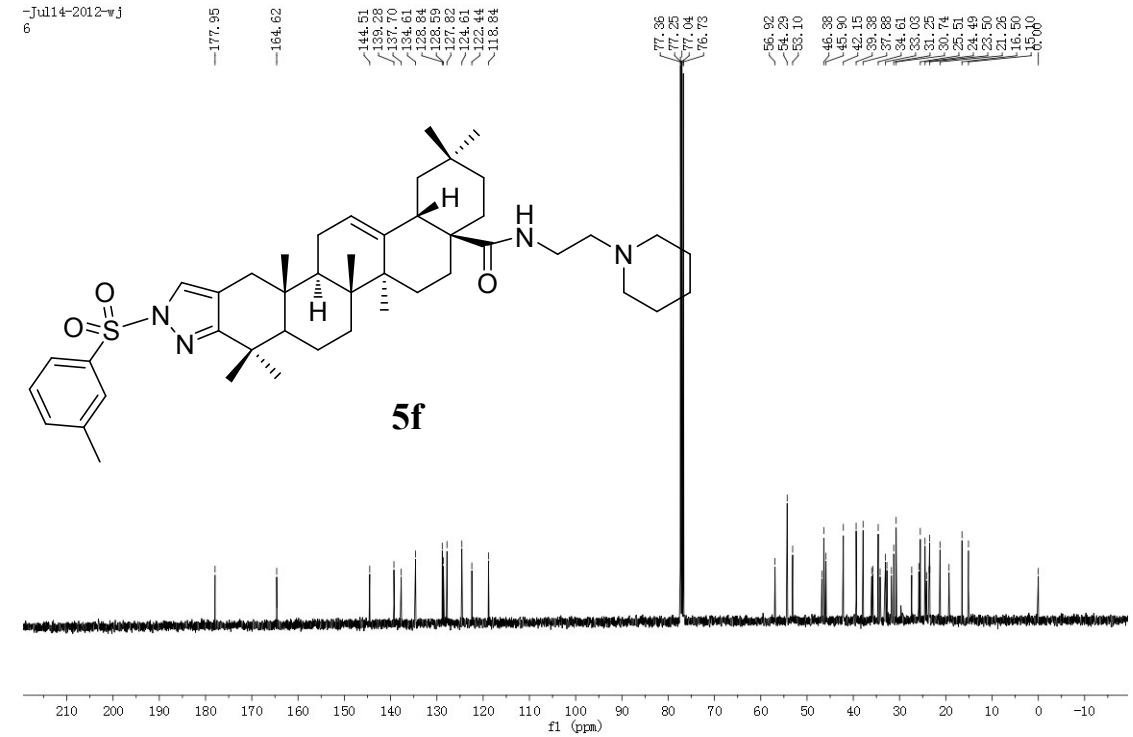
7.74
7.68
7.64
7.39
7.37
7.35
7.33
7.27
6.72
5.43
5.42
5.41
3.42
3.40
3.38
3.25
3.23
2.59
2.46
2.45
2.44
2.43
2.39
1.98
1.71
1.70
1.67
1.62
1.61
1.59
1.57
1.47
1.26
1.21
1.18
1.16
0.92
0.91
0.81
0.76
0.01
0.00
0.97
0.97
0.91
2.00
0.88
0.94
1.00
1.02
2.01
8.74
4.11
4.31
6.76
5.48
4.94
4.94
1.31
3.02
1.29
3.02
2.87
3.09
2.92
f1 (ppm)

5f


-Jul14-2012-wj
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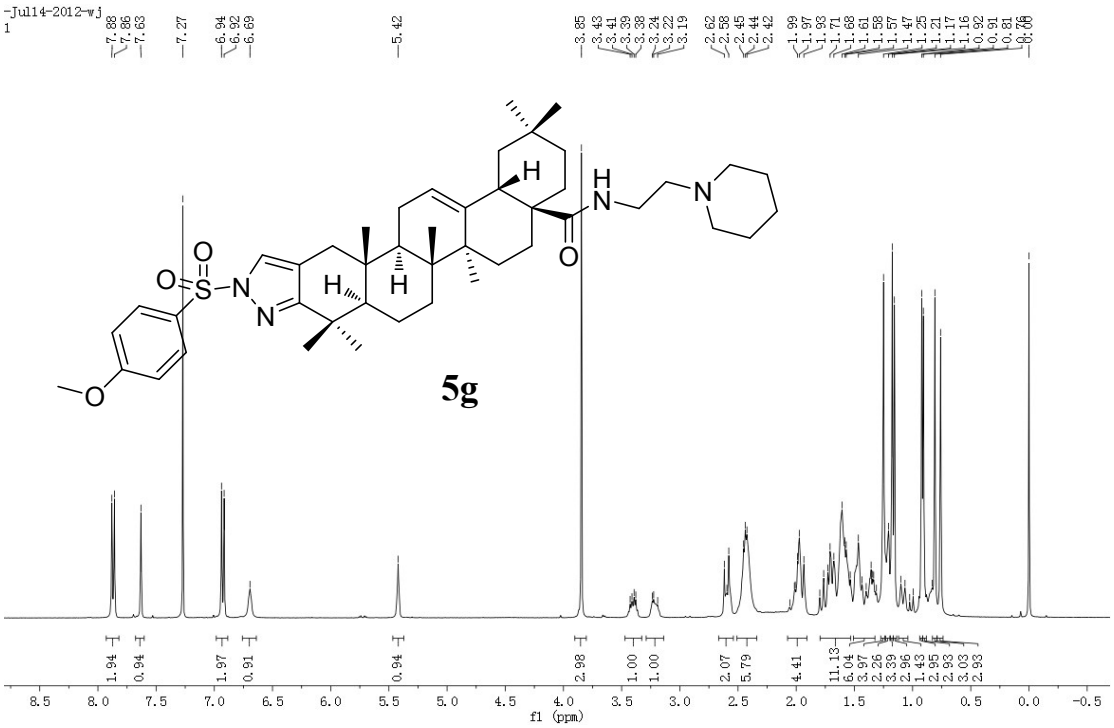
128.59
127.82
124.61
122.44
118.84
77.36
77.25
77.04
76.73
56.92
54.29
53.10
46.38
45.90
42.15
39.38
37.88
34.61
33.03
31.25
30.74
25.51
24.49
23.50
21.26
16.50
15.00
f1 (ppm)

5f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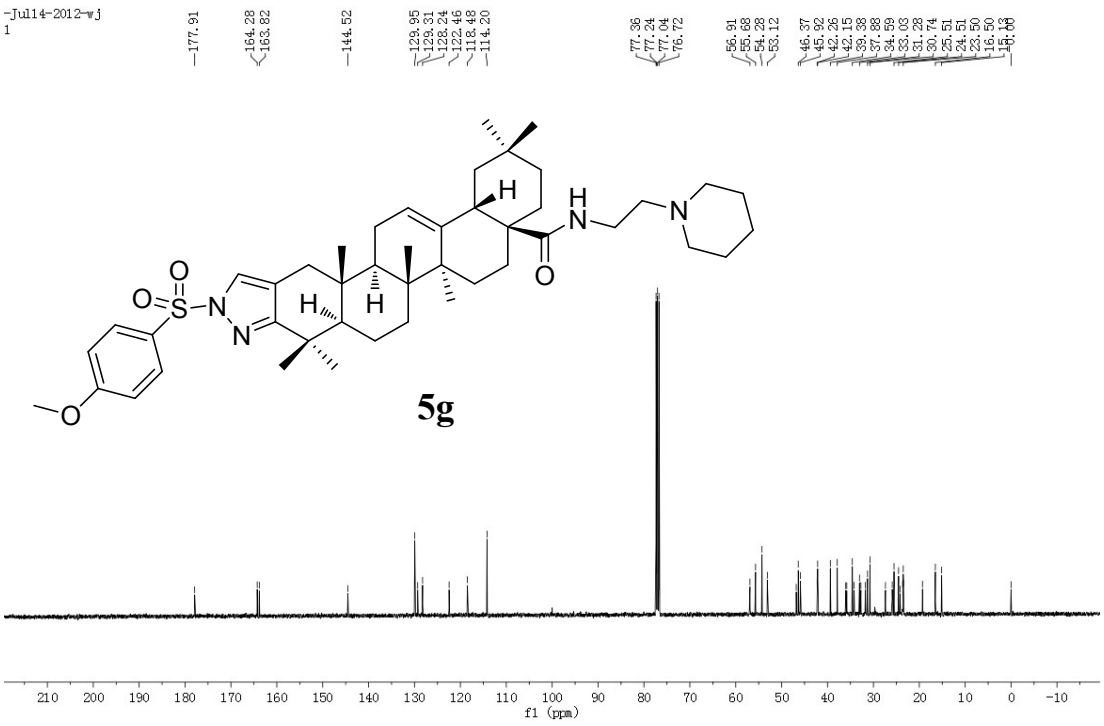
6.92
6.69
5.42
3.85
3.43
3.41
3.39
3.38
3.24
3.22
3.19
2.62
2.58
2.45
2.44
2.42
1.99
1.97
1.93
1.71
1.68
1.61
1.58
1.57
1.47
1.25
1.21
1.17
1.16
0.92
0.91
0.81
0.76
0.00
1.94
0.94
1.97
0.91
0.94
2.98
1.00
1.00
2.07
5.79
4.41
11.13
6.04
3.97
2.26
3.39
2.96
1.43
2.95
2.93
3.03
2.93
f1 (ppm)

5g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163.82
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129.31
128.24
122.46
118.48
114.20
77.36
77.24
77.04
76.72
56.91
55.88
54.28
53.12
46.37
45.92
42.26
42.15
39.38
37.88
34.59
33.03
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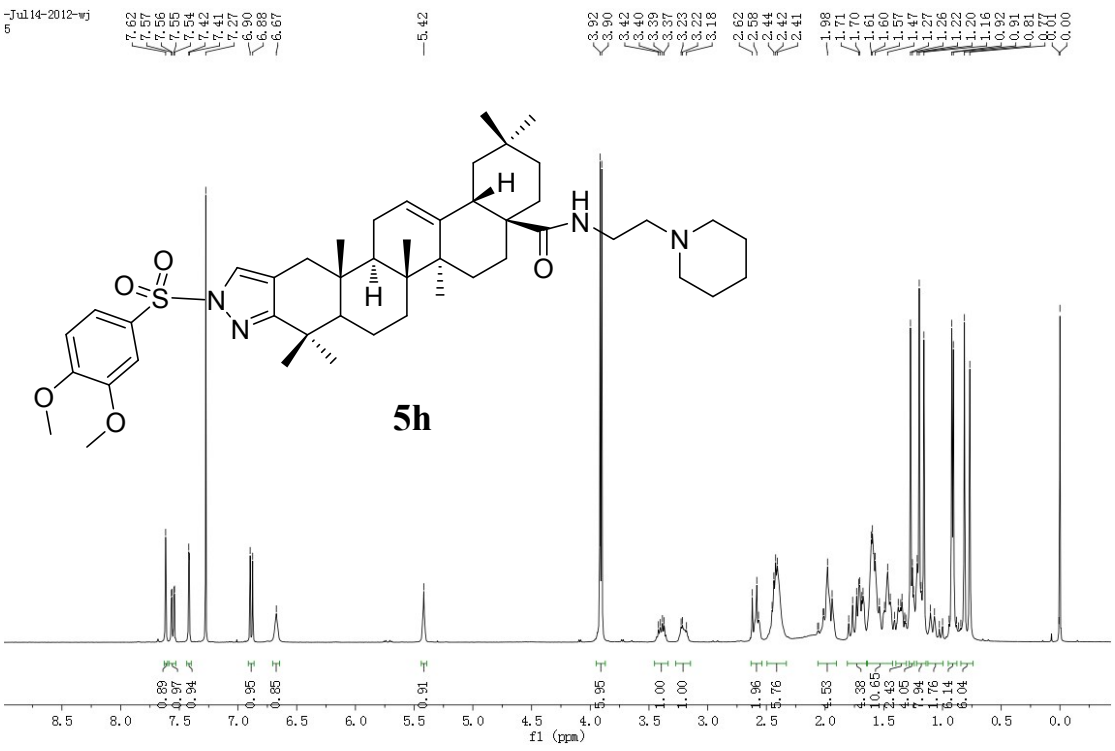
30.74
25.51
24.51
23.50
16.50
15.43
15.00
f1 (ppm)

5g


-Jul14-2012-wj
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7.54
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7.41
7.27
6.90
6.88
6.67
5.42
3.92
3.90
3.42
3.40
3.39
3.37
3.23
3.22
3.18
2.62
2.58
2.44
2.42
2.41
1.98
1.71
1.70
1.61
1.60
1.57
1.47
1.27
1.26
1.22
1.20
1.16
0.92
0.91
0.81
0.77
0.01
0.00
5h
0.89
0.97
0.94
0.95
0.85
0.91
5.95
1.00
1.00
1.96
5.76
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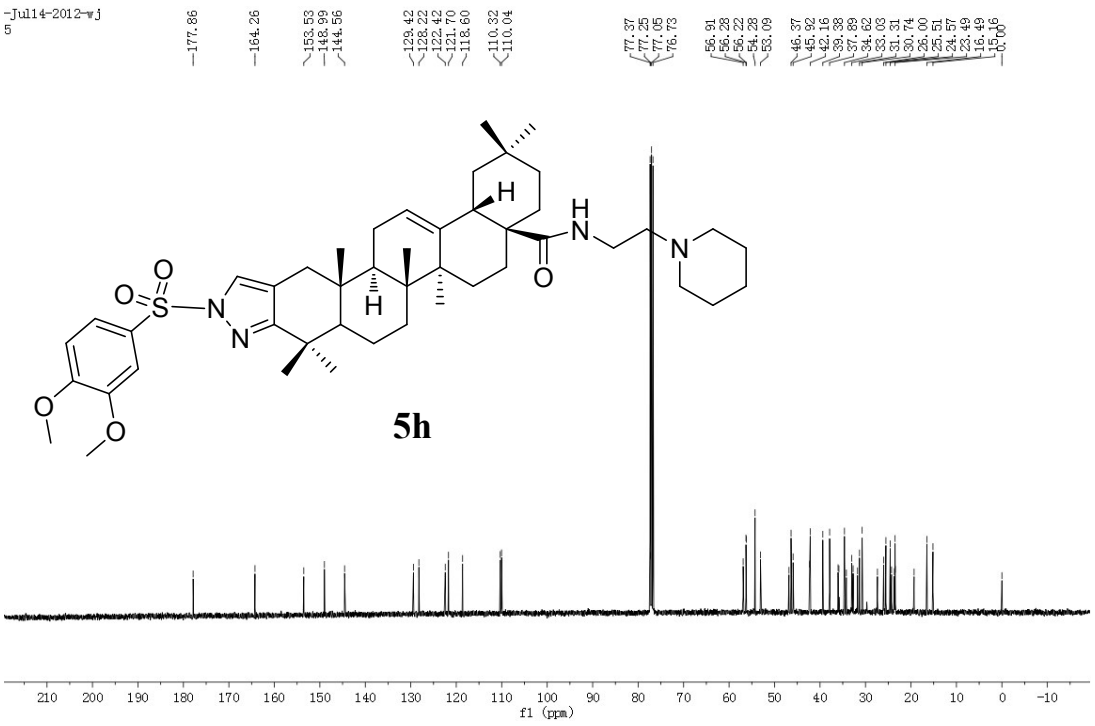
4.38
10.65
2.43
4.05
7.94
1.76
6.14
6.04
f1 (ppm)


-Jul14-2012-wj
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144.56
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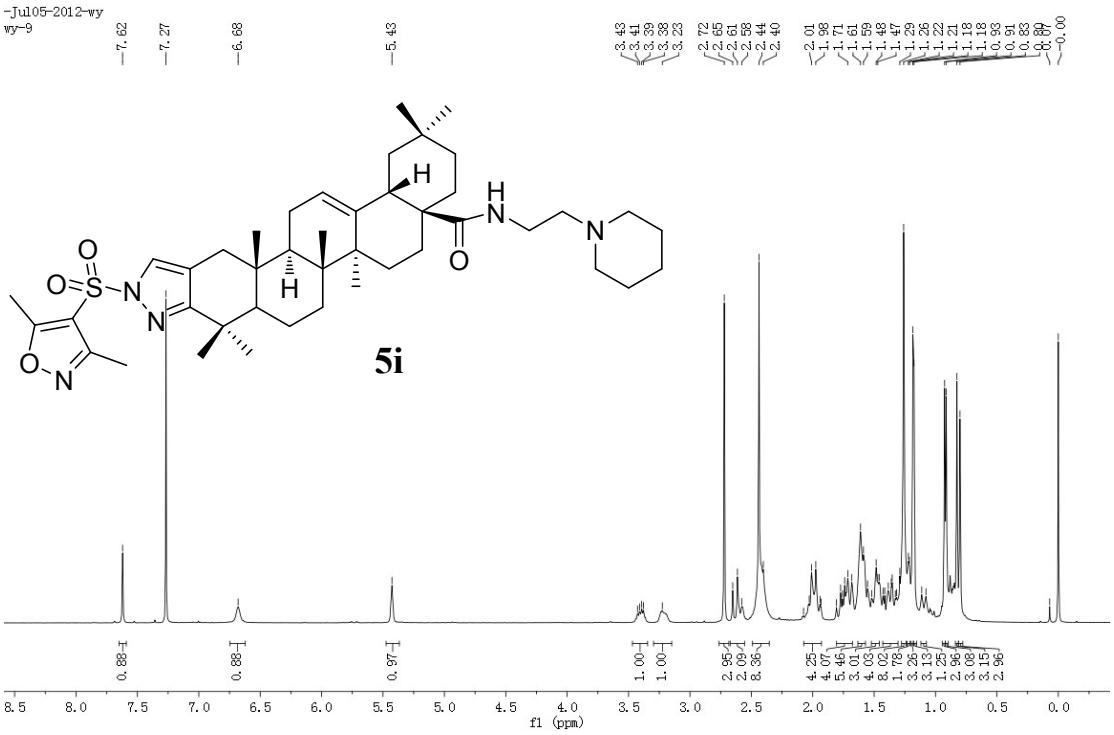
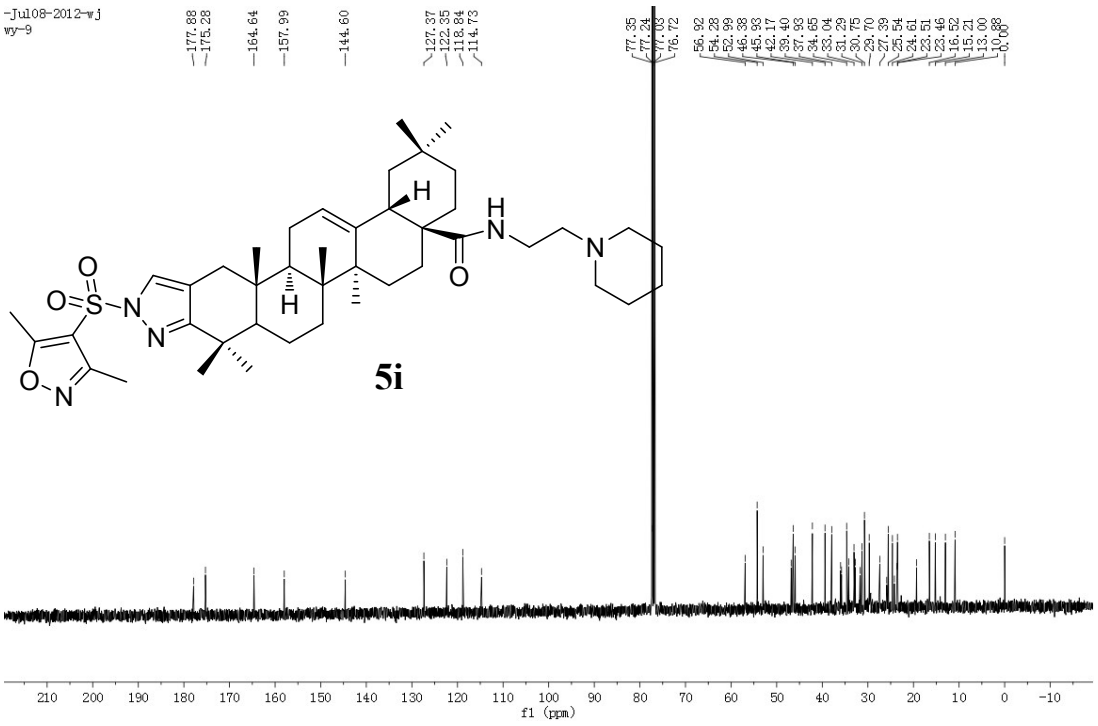
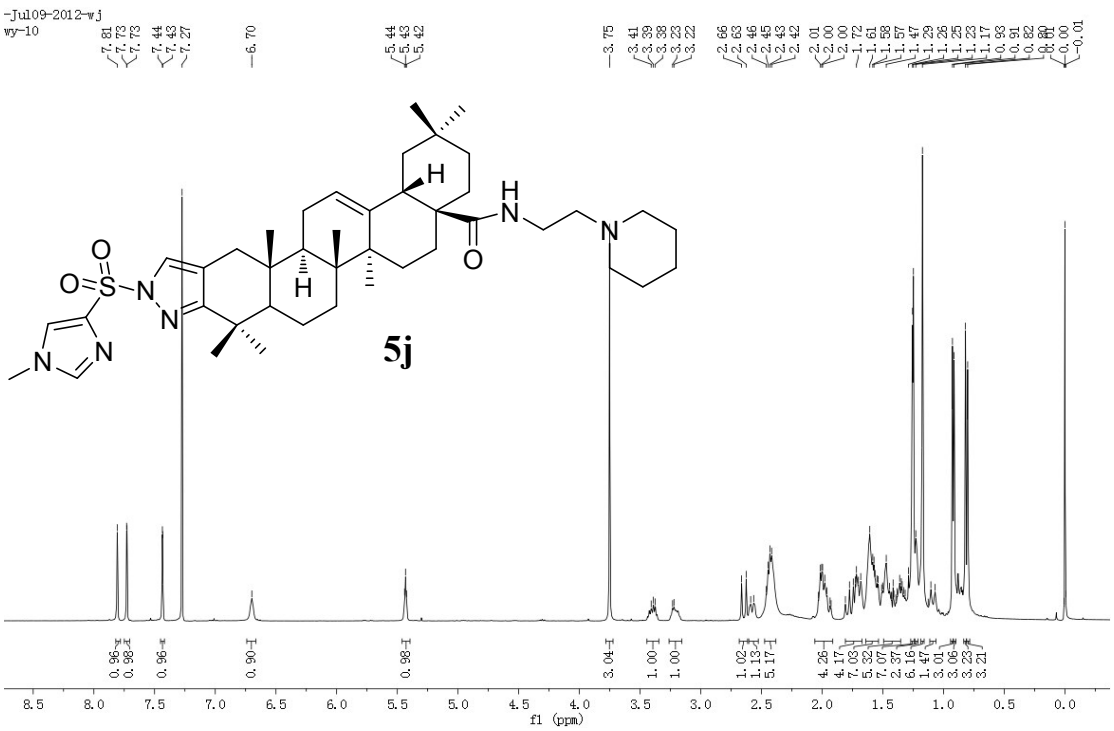
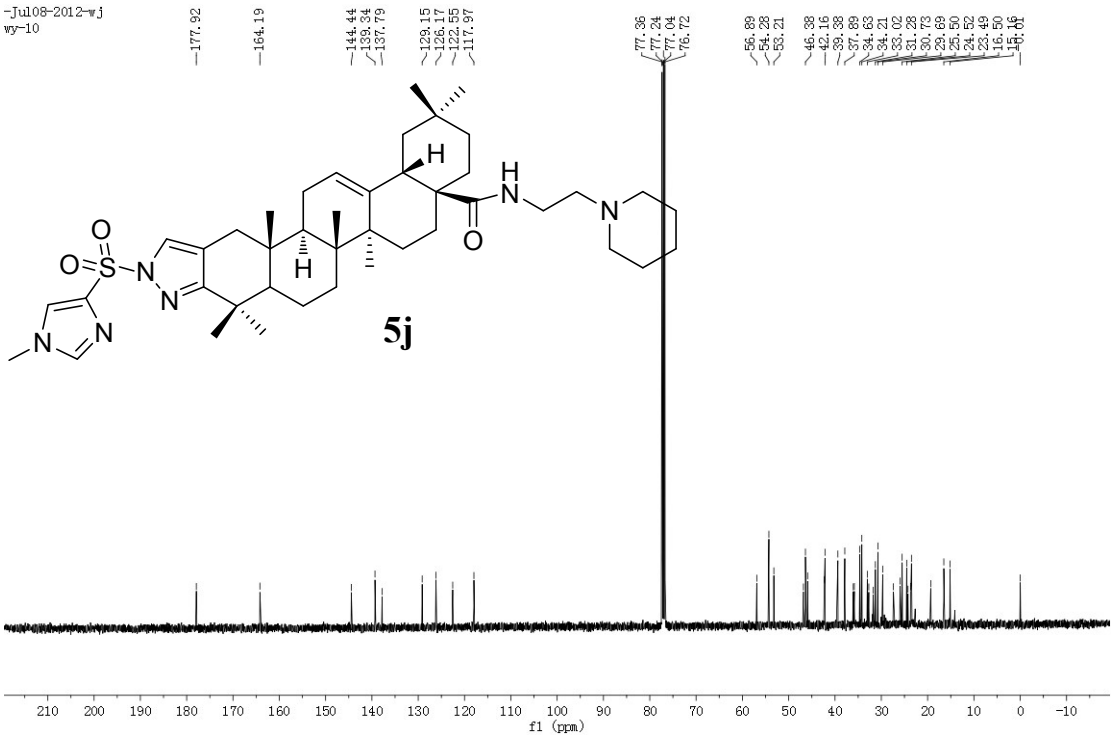
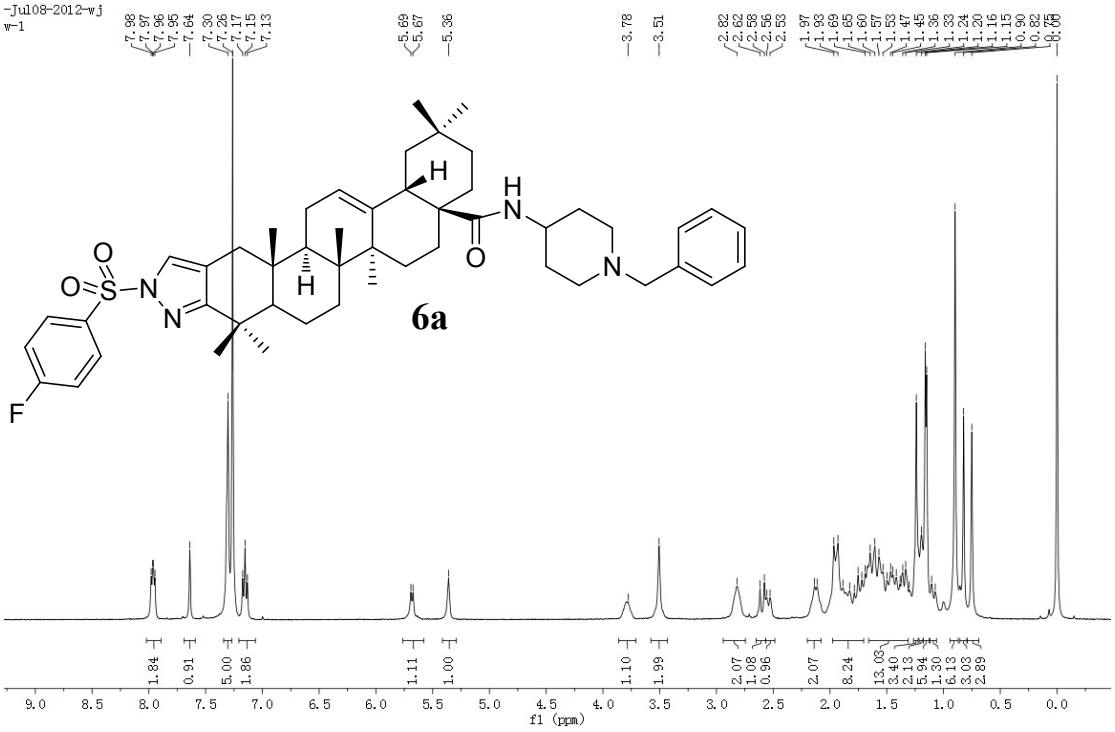
128.22
122.42
121.70
118.60
110.32
110.04
77.37
77.25
77.05
76.73
56.91
56.28
56.22
54.28
53.09
46.37
45.92
42.16
39.38
37.89
34.62
33.03
31.31
30.74
26.00
25.51
24.57
23.49
16.49
15.16
0.00
5h
f1 (ppm)

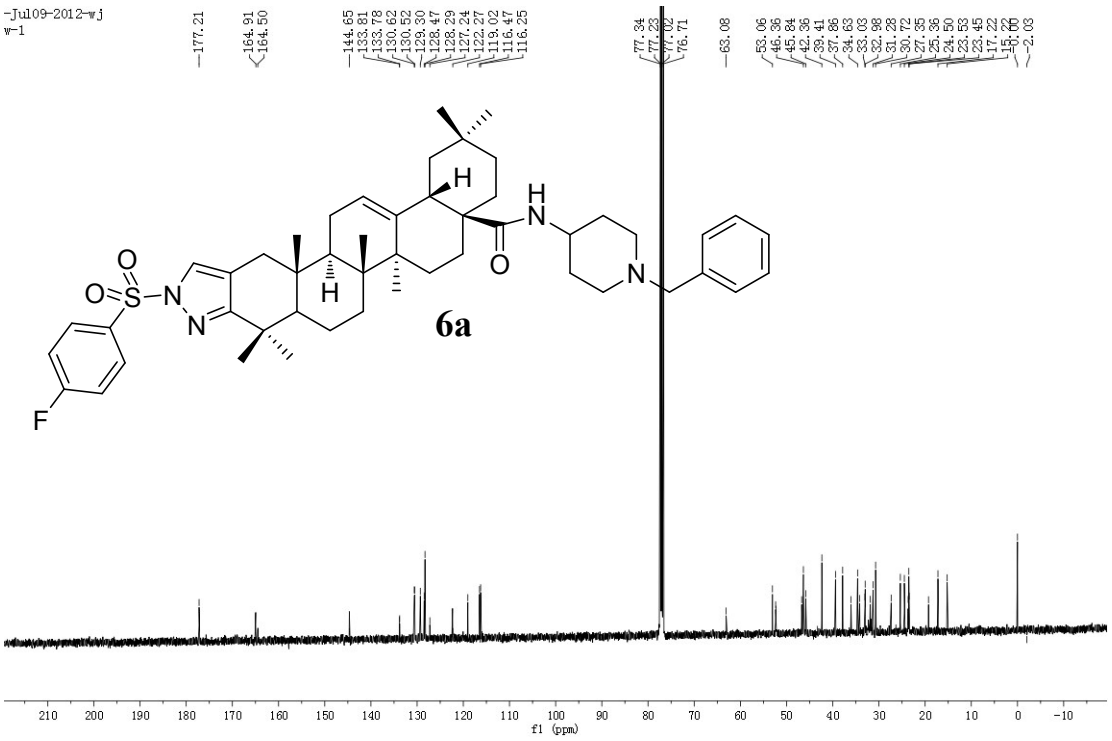

-Jul05-2012-wy
wy-9
5i
f1 (ppm)

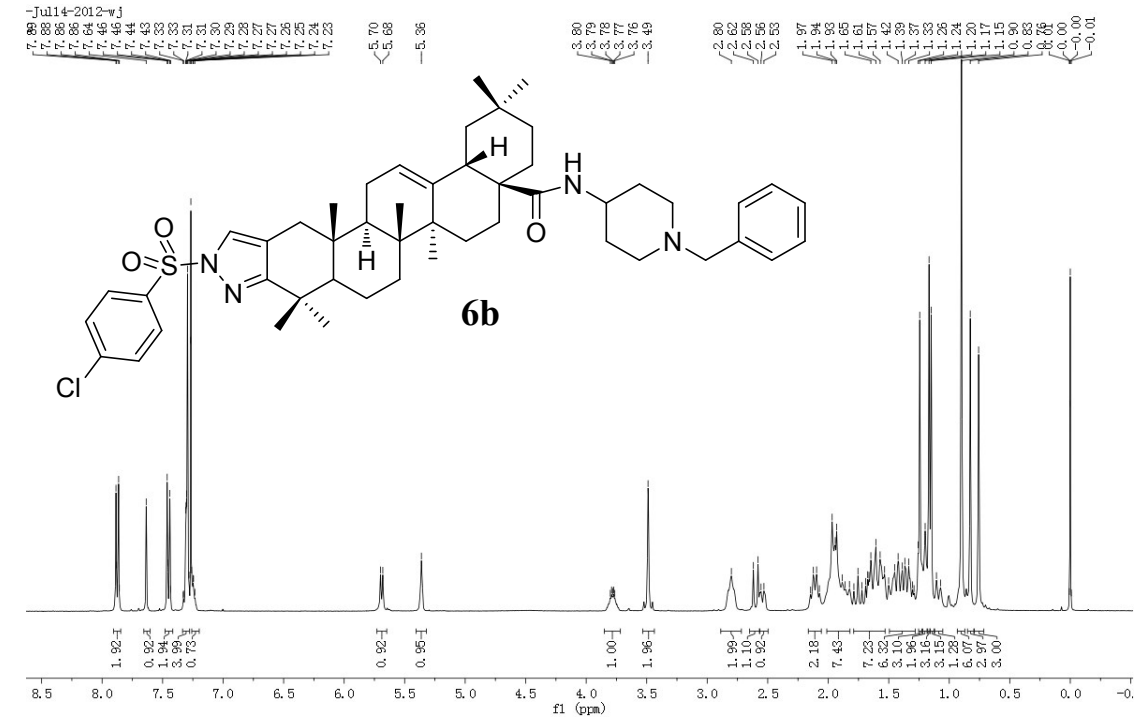

-Jul08-2012-wj
wy-9
5i
f1 (ppm)

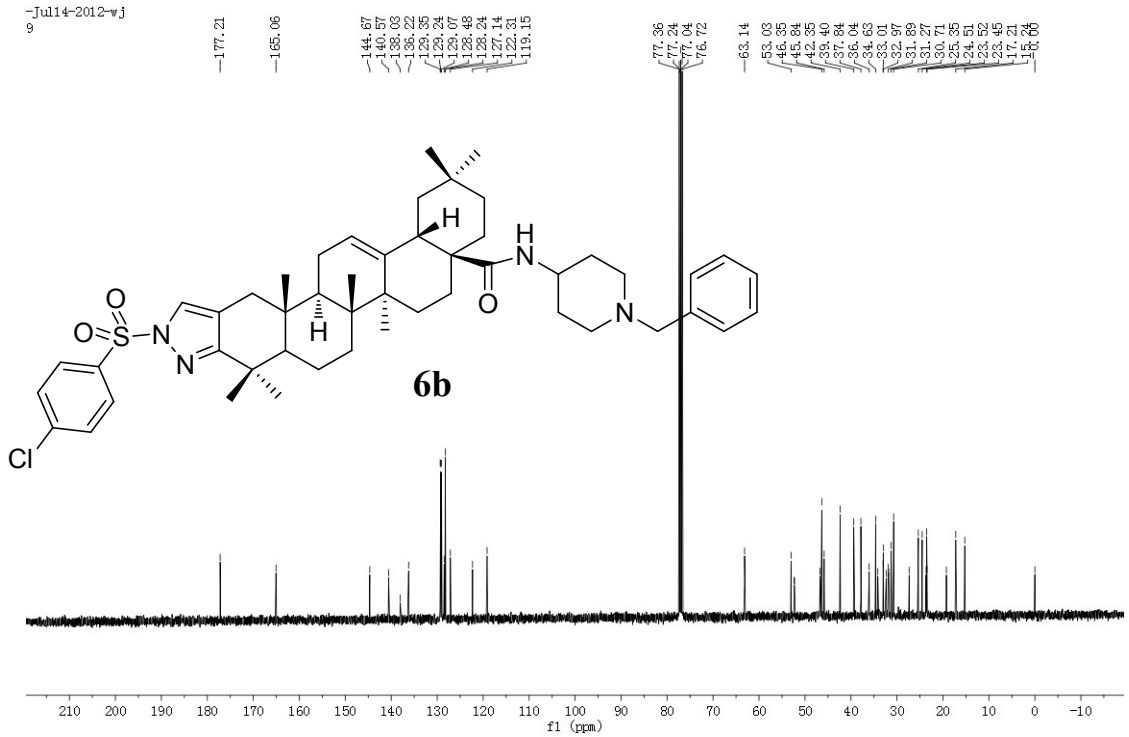

-Jul09-2012-wj
wy-10
5j
f1 (ppm)

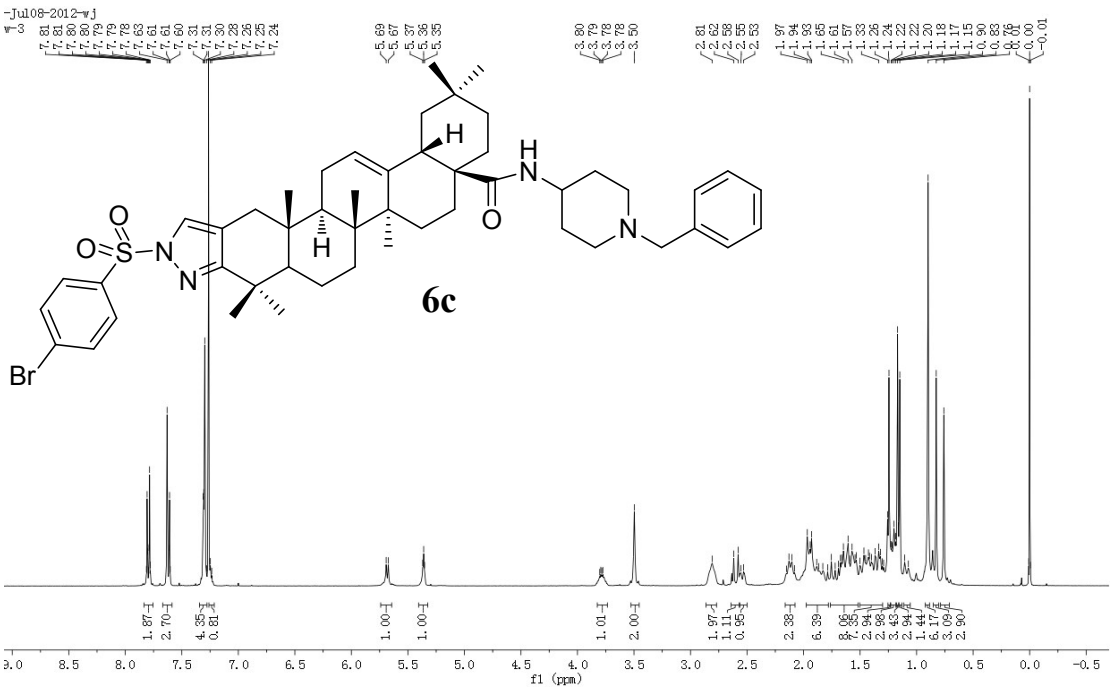

-Jul08-2012-wj
wy-10
5j
f1 (ppm)

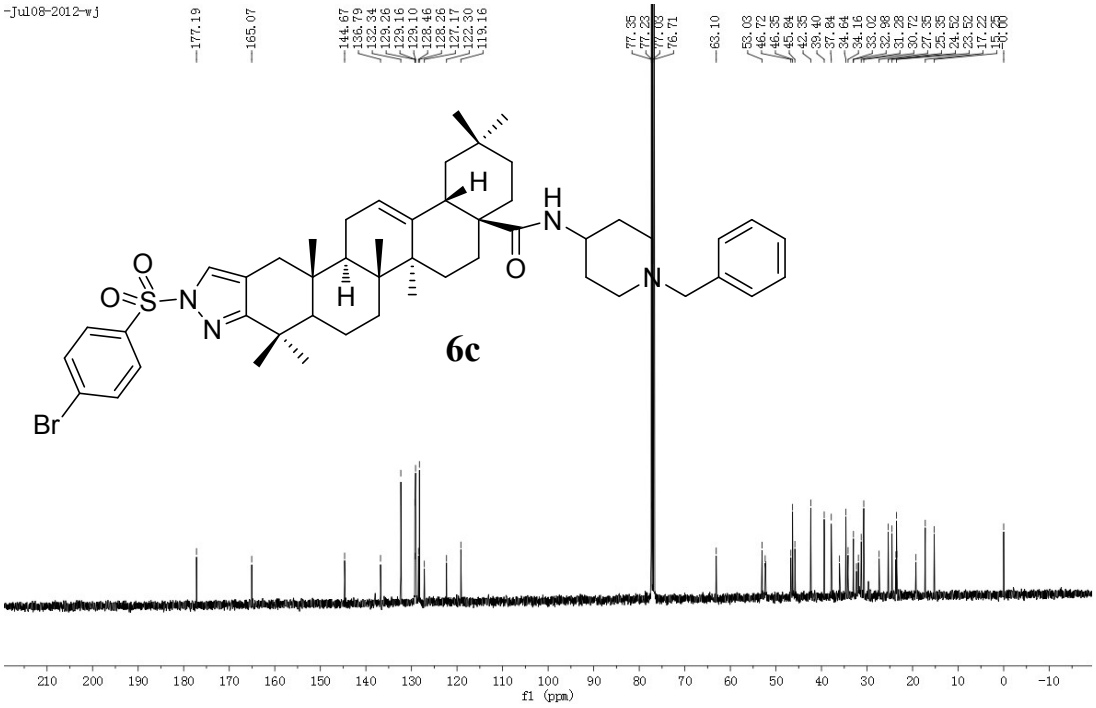

-Jul08-2012-wj
w-1
6a

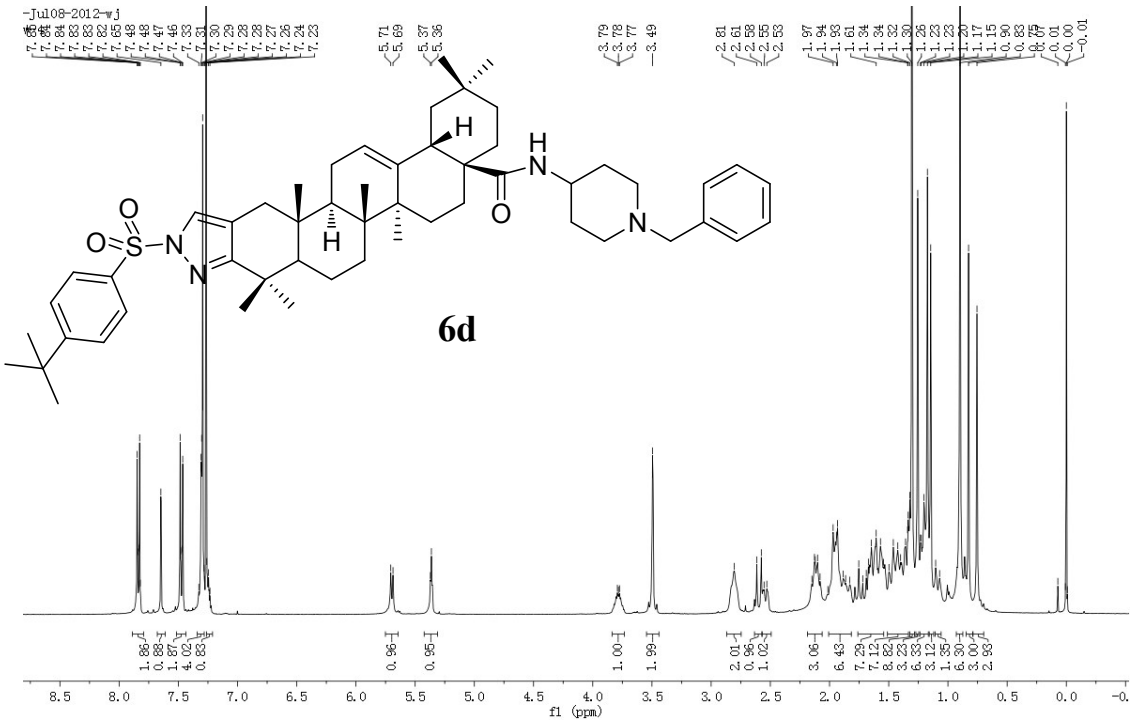

-Jul09-2012-wj
w-1
6a

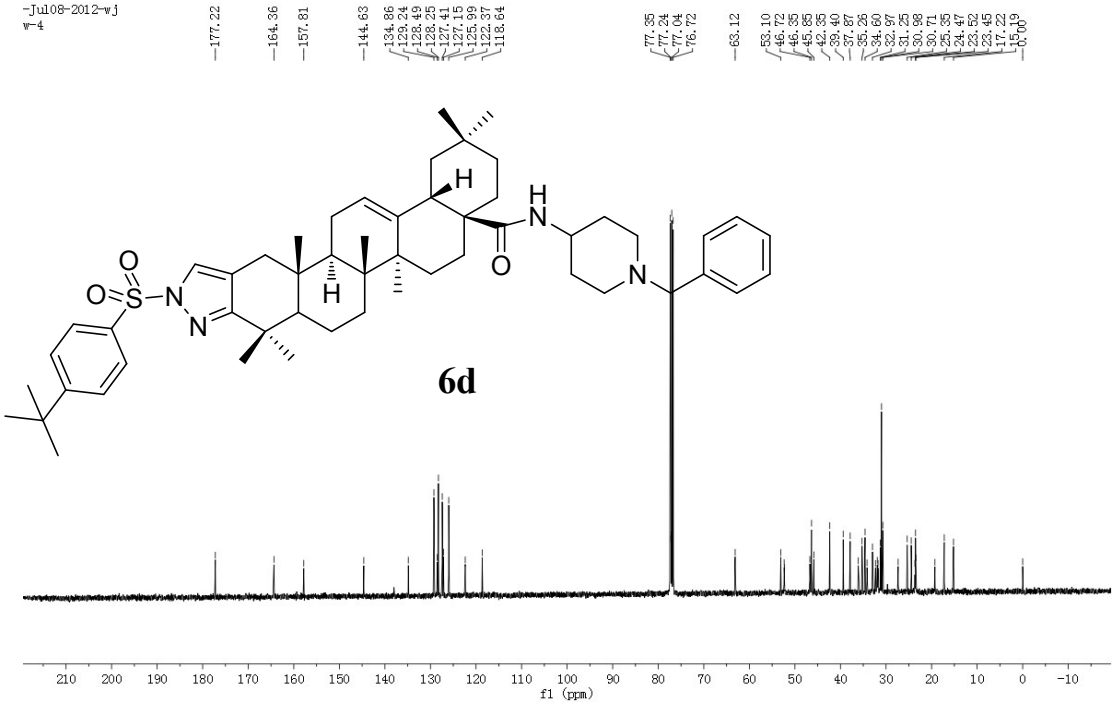

-Jul14-2012-wj
6b
f1 (ppm)

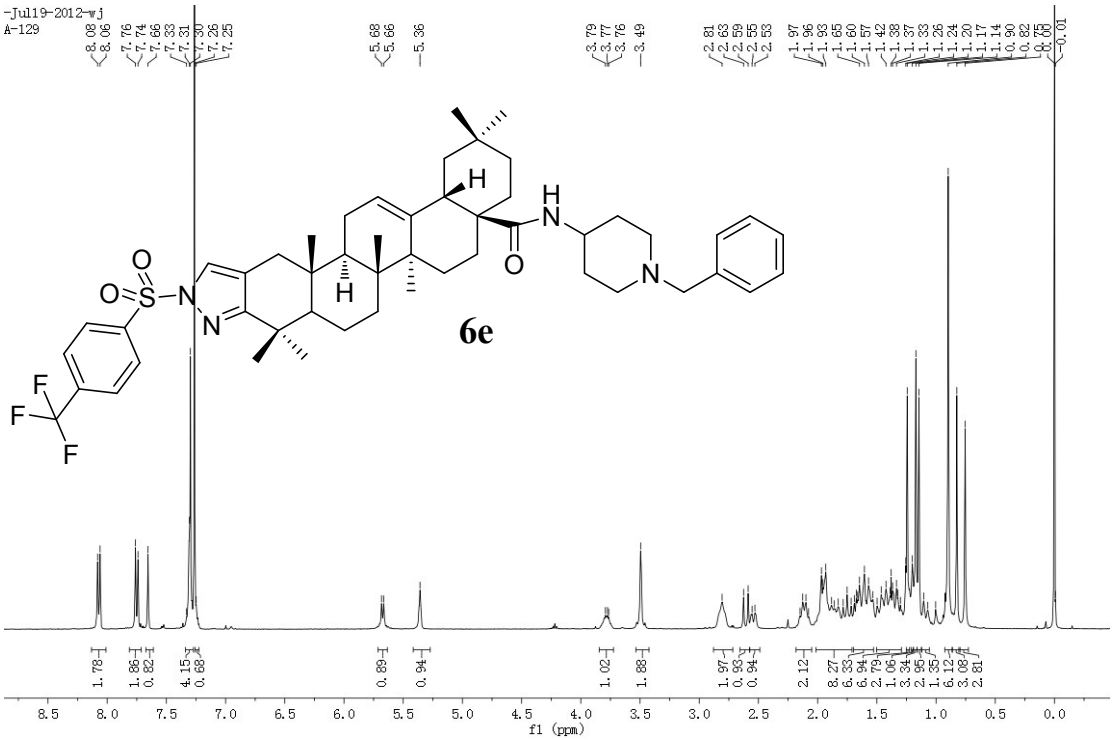

-Jul14-2012-wj
9
6b
f1 (ppm)


-Jul08-2012-wj
w-3
6c
f1 (ppm)


-Jul08-2012-wj
6c
f1 (ppm)


-Jul08-2012-wj
6d
f1 (ppm)


-Jul08-2012-wj
w-4
6d
f1 (ppm)


-Jul19-2012-wj
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7.26
7.25
5.68
5.66
5.36
3.79
3.77
3.76
3.49
2.81
2.63
2.59
2.55
2.53
1.97
1.96
1.93
1.65
1.60
1.57
1.42
1.38
1.37
1.33
1.26
1.24
1.20
1.17
1.14
0.90
0.82
0.08
0.01
1.78
1.86
0.82
4.15
0.68
0.89
0.94
1.02
1.88
1.97
0.93
0.94
2.12
8.27
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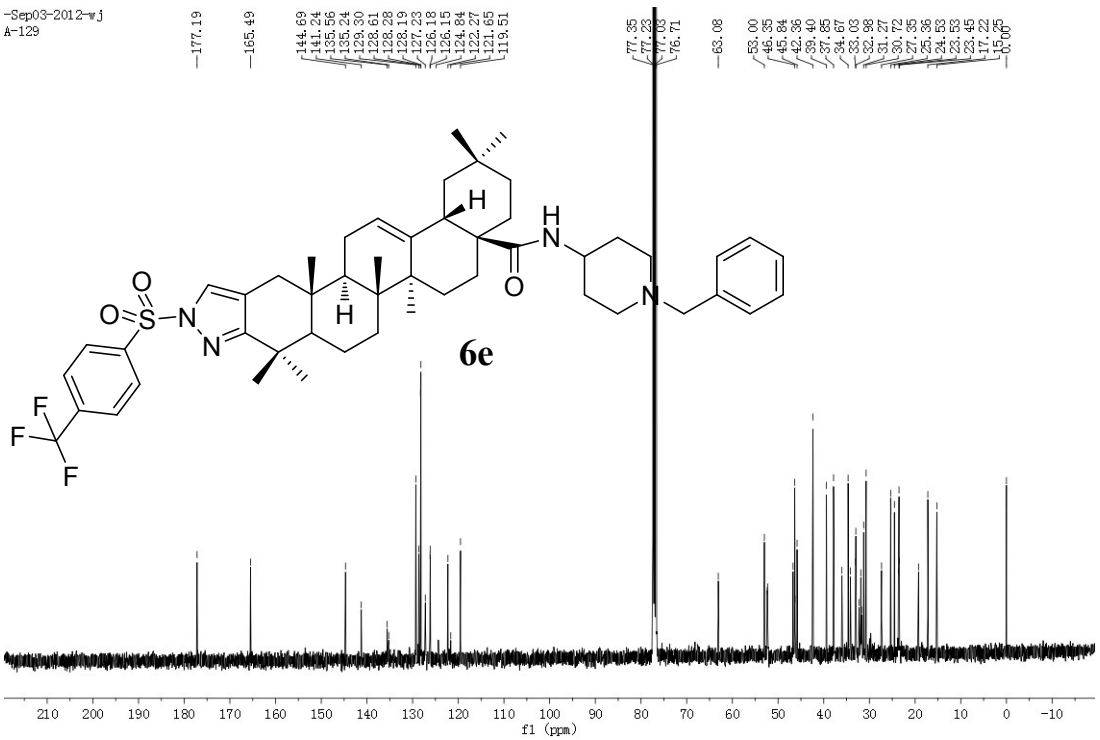
6.94
2.79
1.06
3.34
2.95
1.35
6.12
3.08
2.81
f1 (ppm)
6e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128.28
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127.23
126.18
126.15
124.84
122.27
121.65
119.51
77.35
77.23
77.03
76.71
63.08
53.00
46.35
45.84
42.36
39.40
37.85
34.67
33.03
32.98
31.27
30.72
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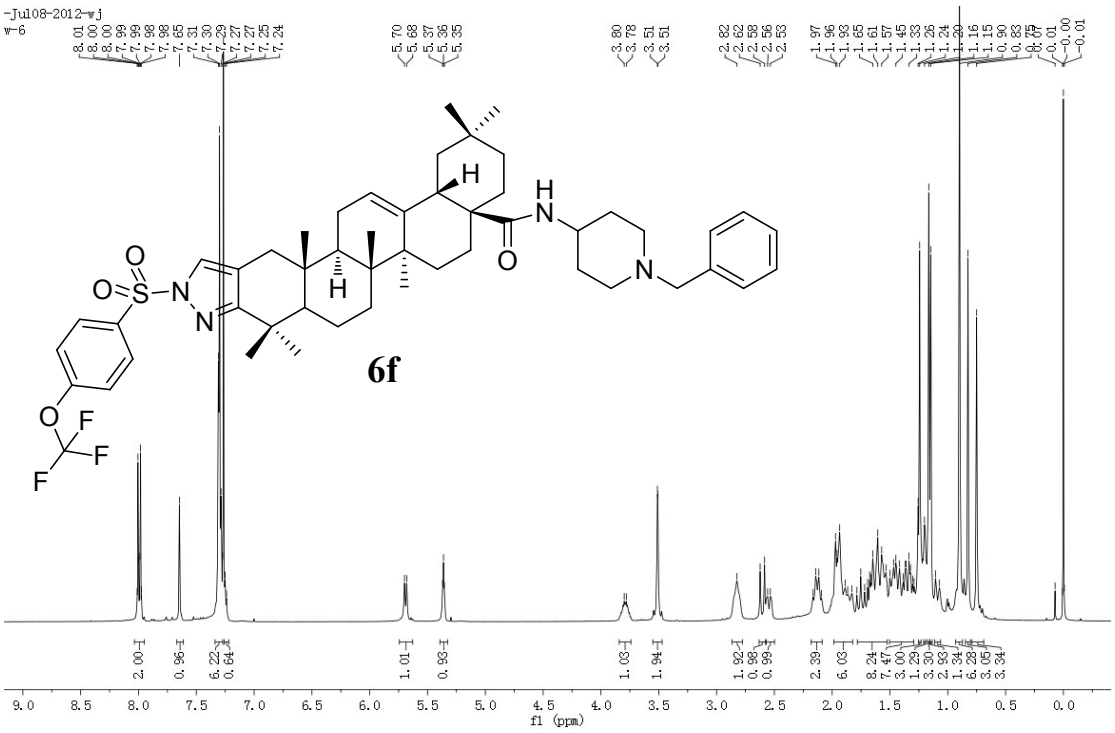
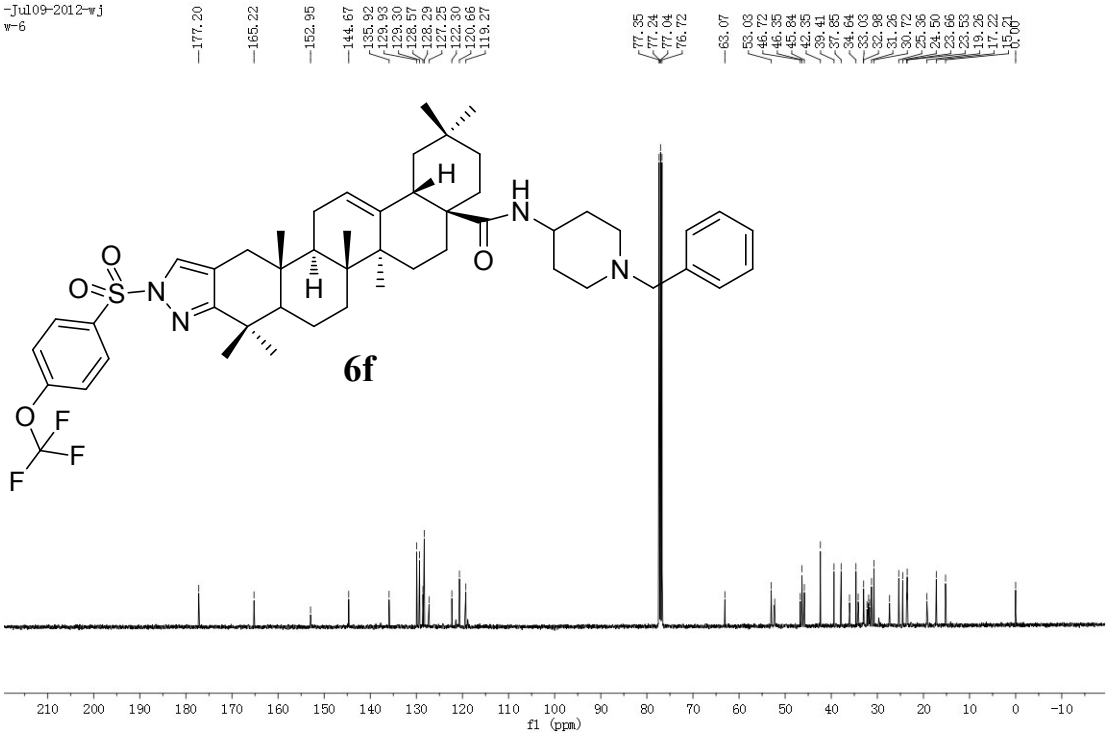
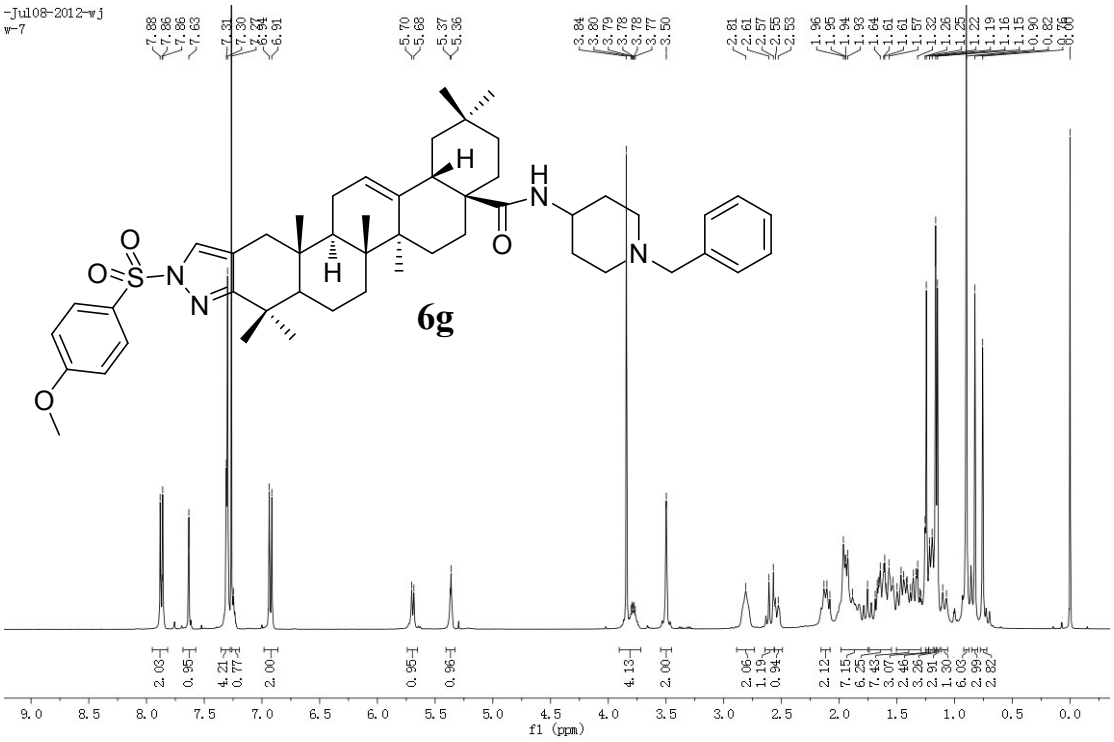
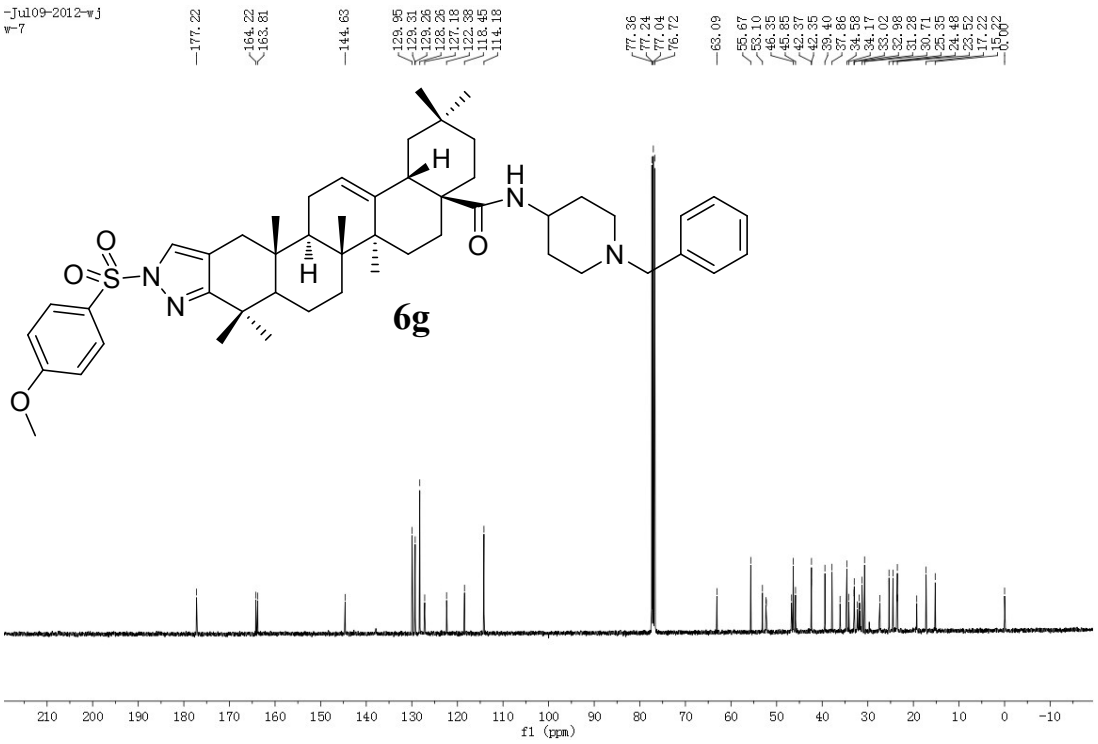
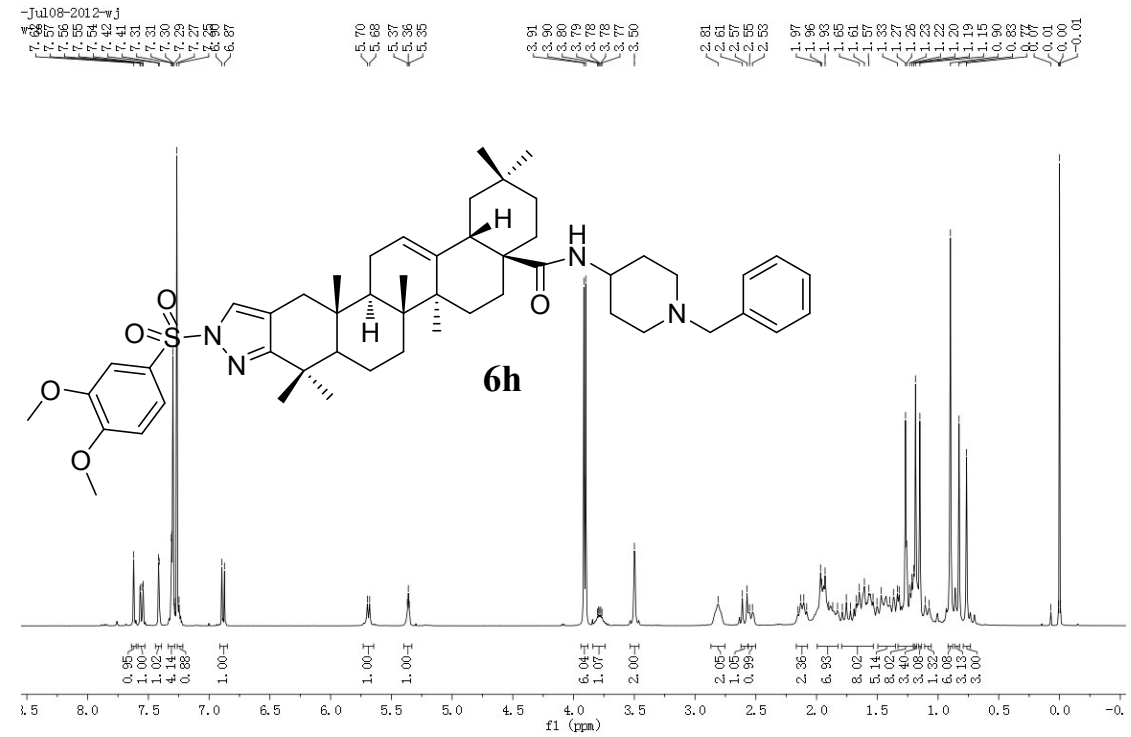
27.36
25.36
24.53
23.45
17.22
15.65
0.00
f1 (ppm)
6e

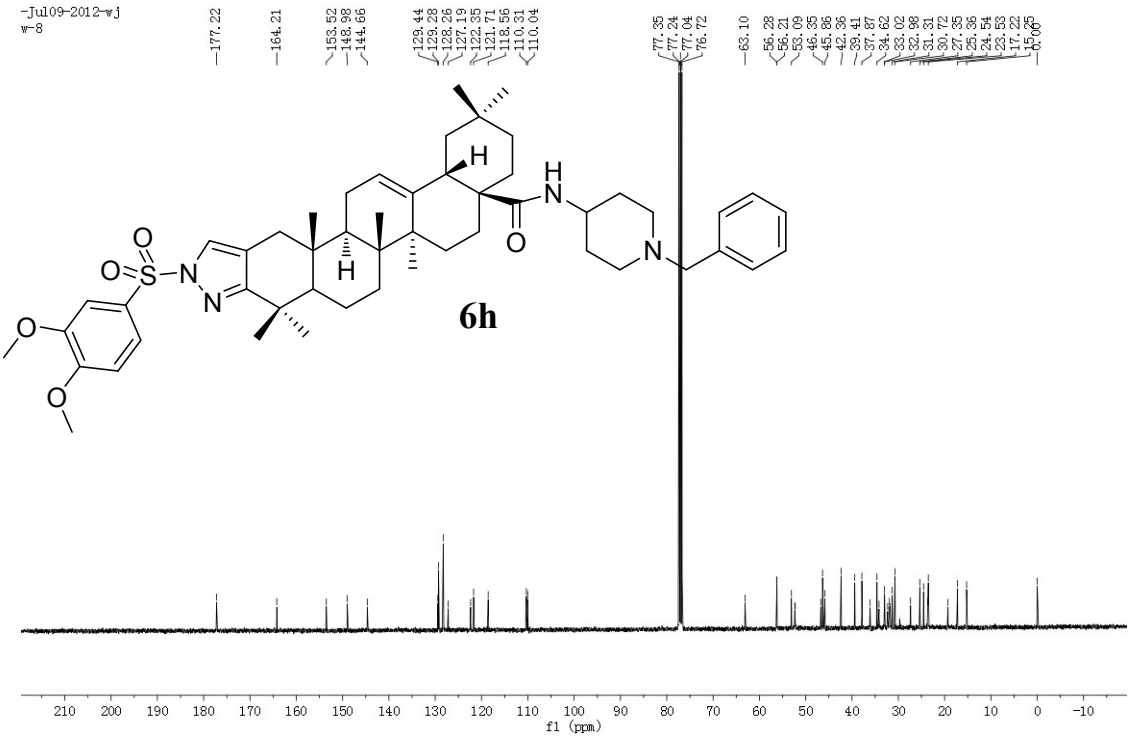

-Jul08-2012-wj
w-6
6f
f1 (ppm)

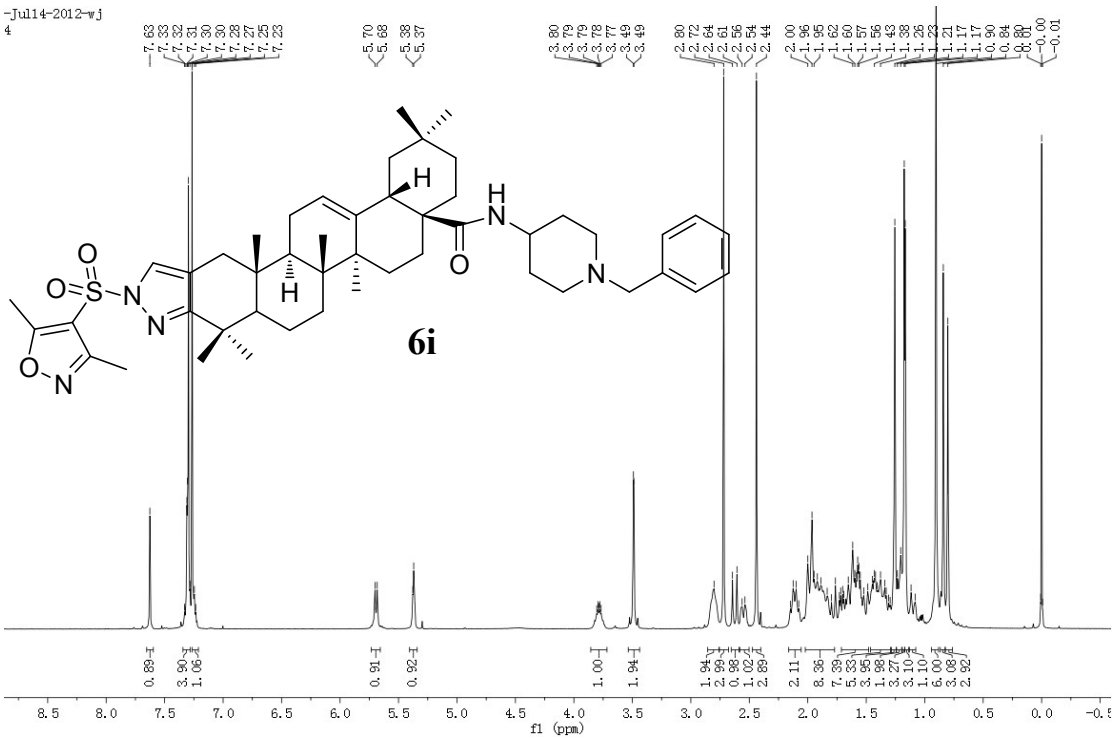

-Jul09-2012-wj
w-6
6f
f1 (ppm)

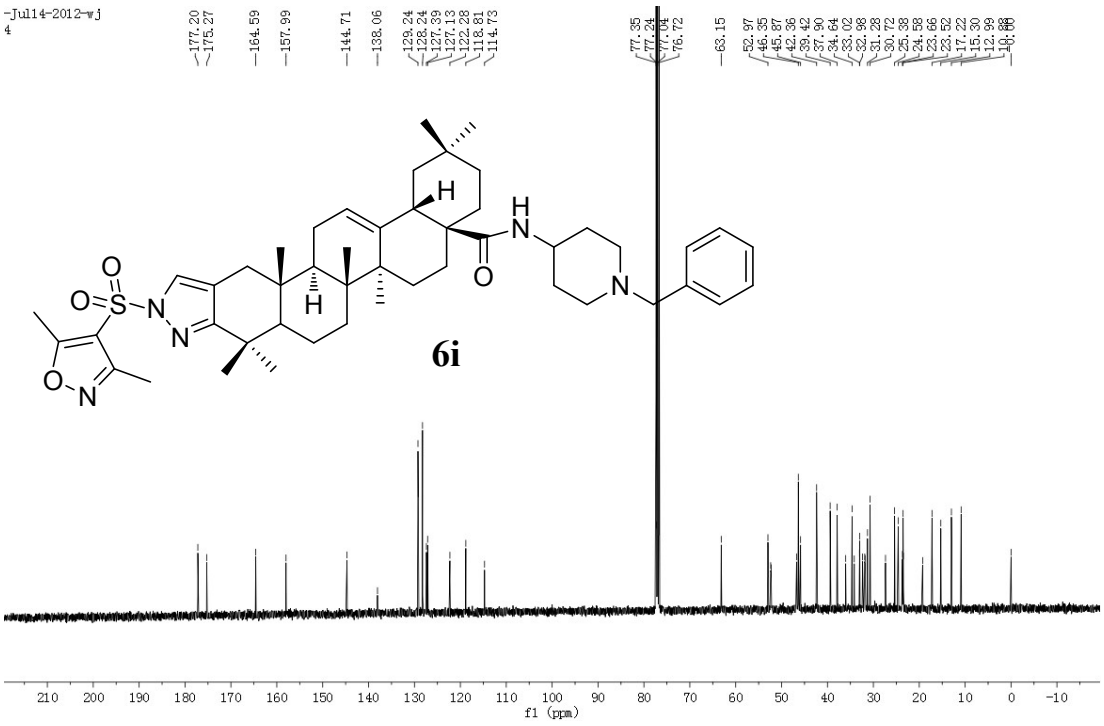

-Jul08-2012-wj
w-7
6g
f1 (ppm)

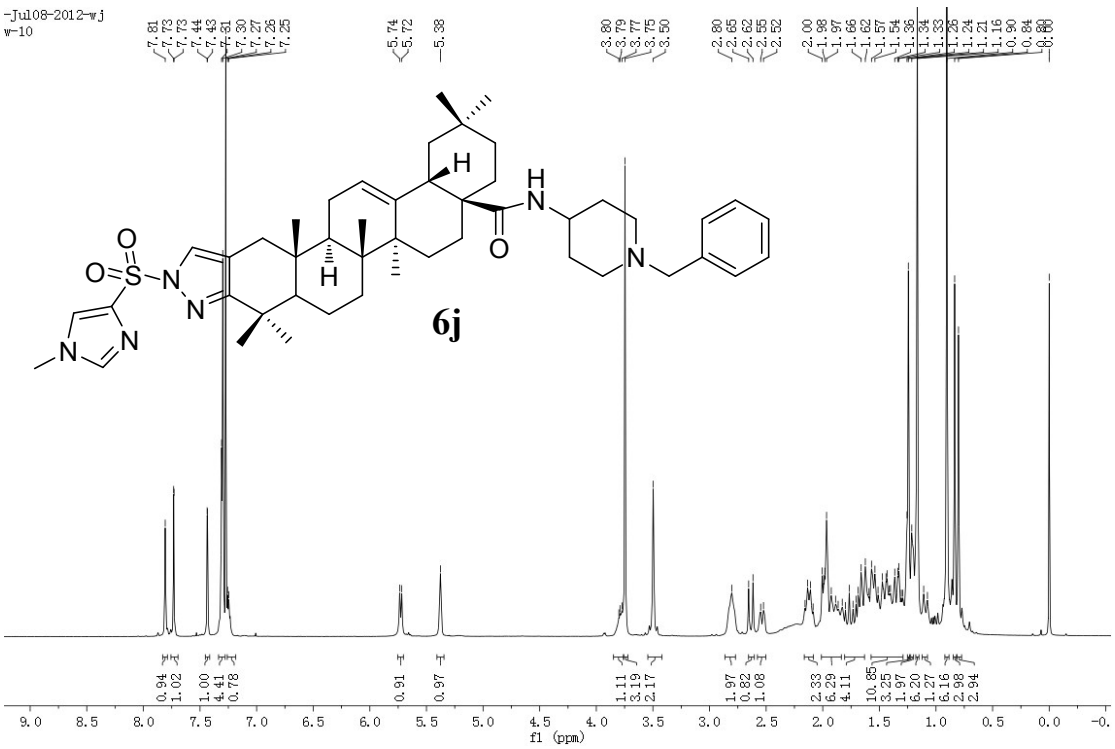

-Jul09-2012-wj
w-7
6g
f1 (ppm)

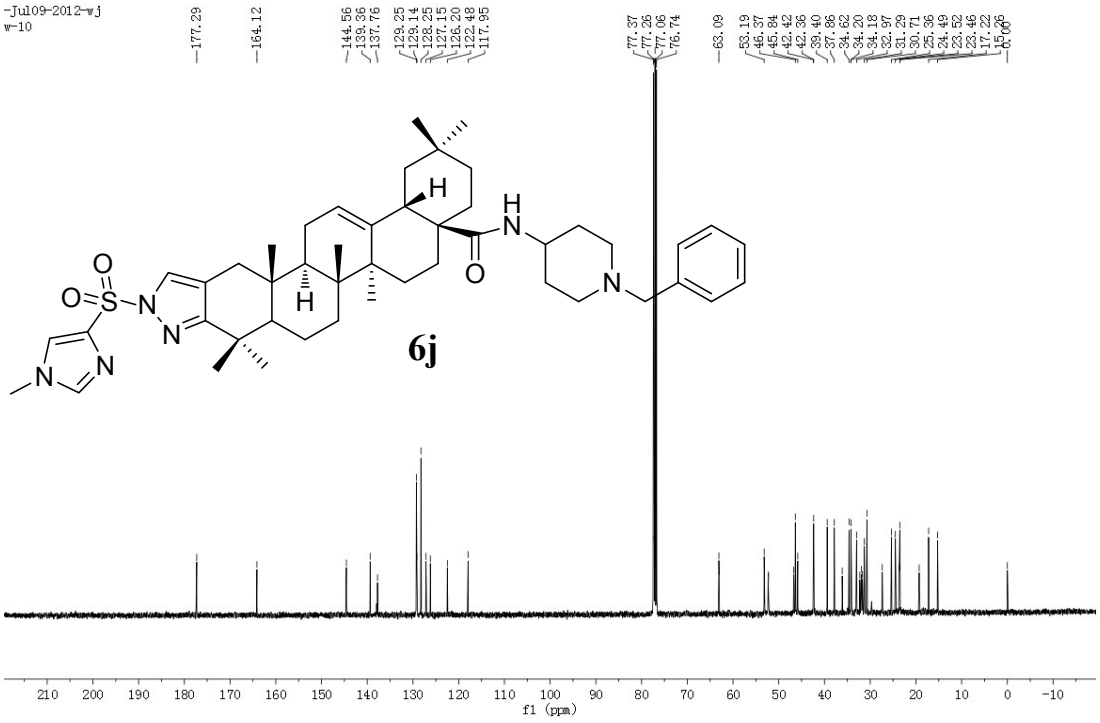

-Jul08-2012-wj
6h
f1 (ppm)

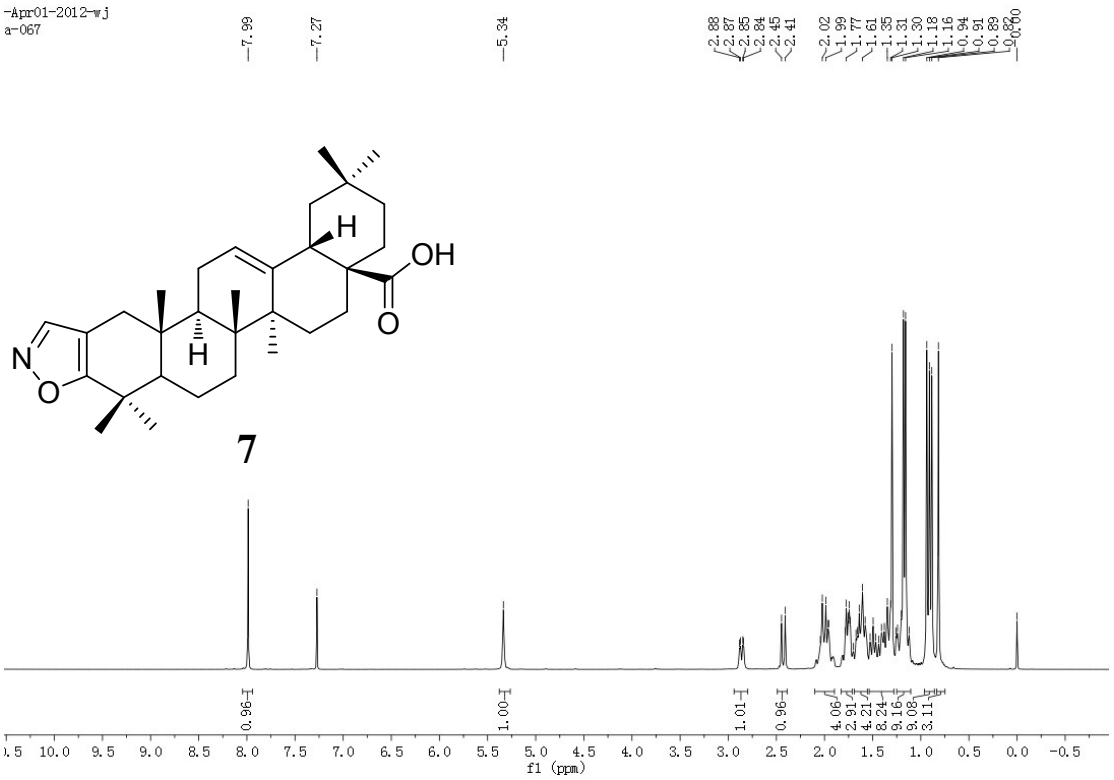

-Jul09-2012-wj
w-8
6h
f1 (ppm)

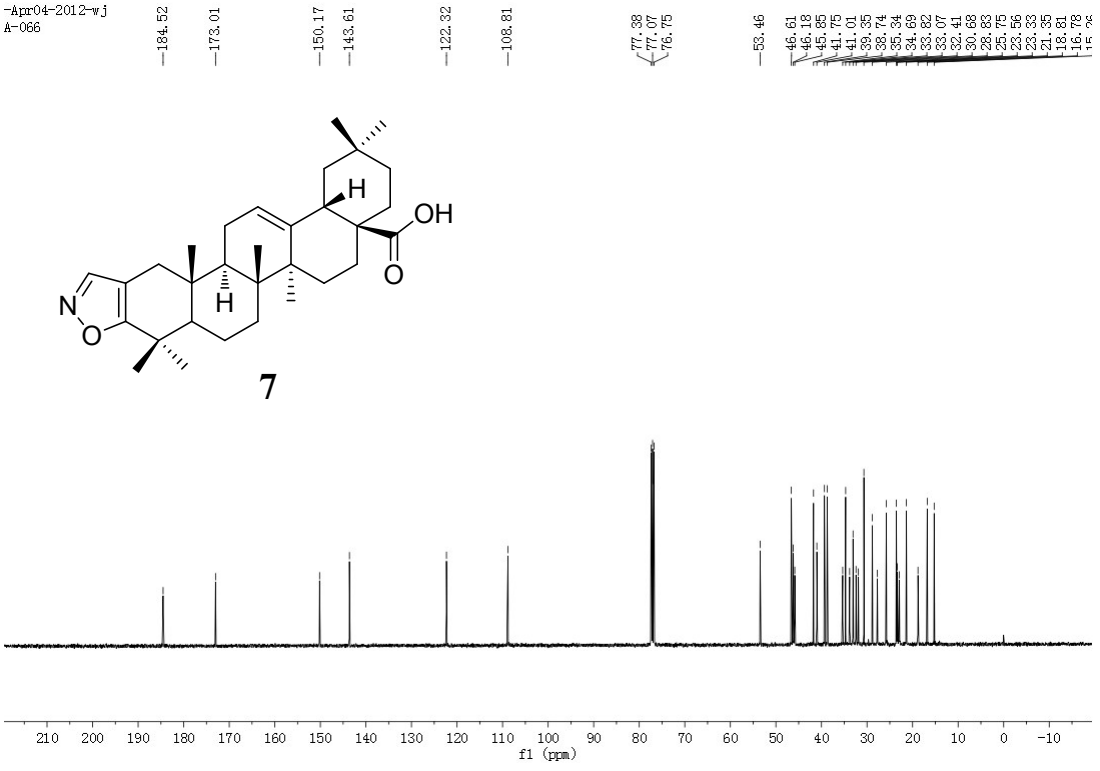

-Jul14-2012-wj
4
6i
f1 (ppm)

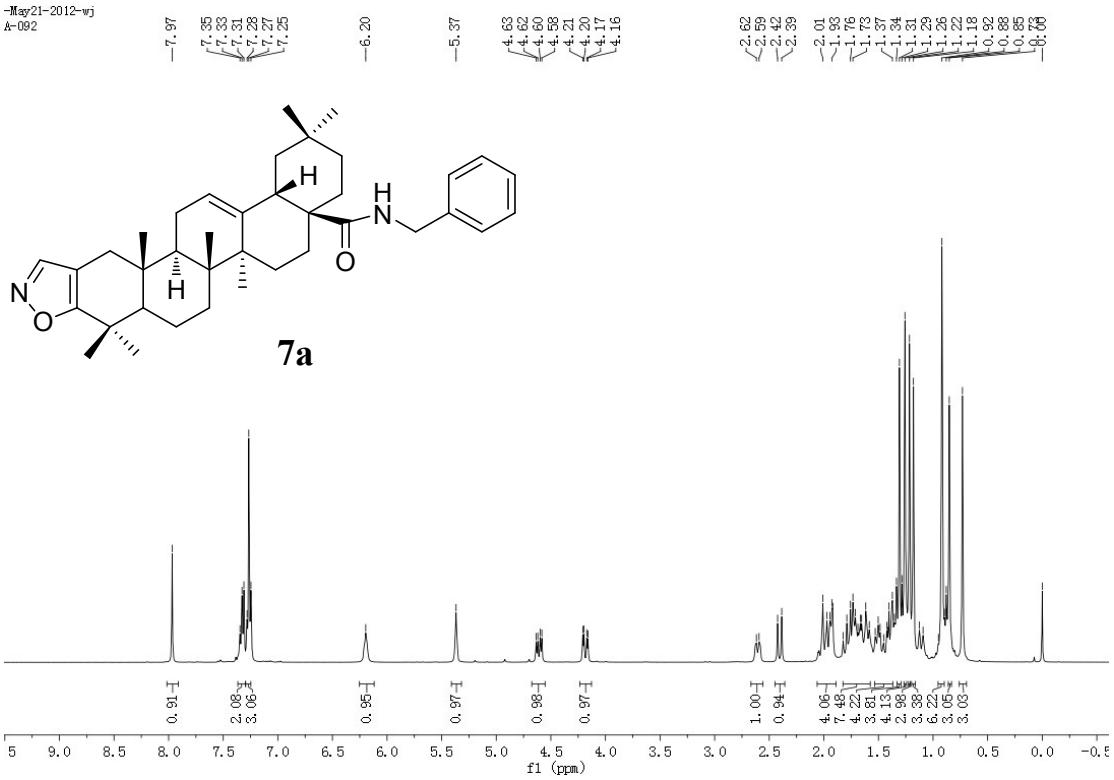

-Jul14-2012-wj
4
6i
f1 (ppm)

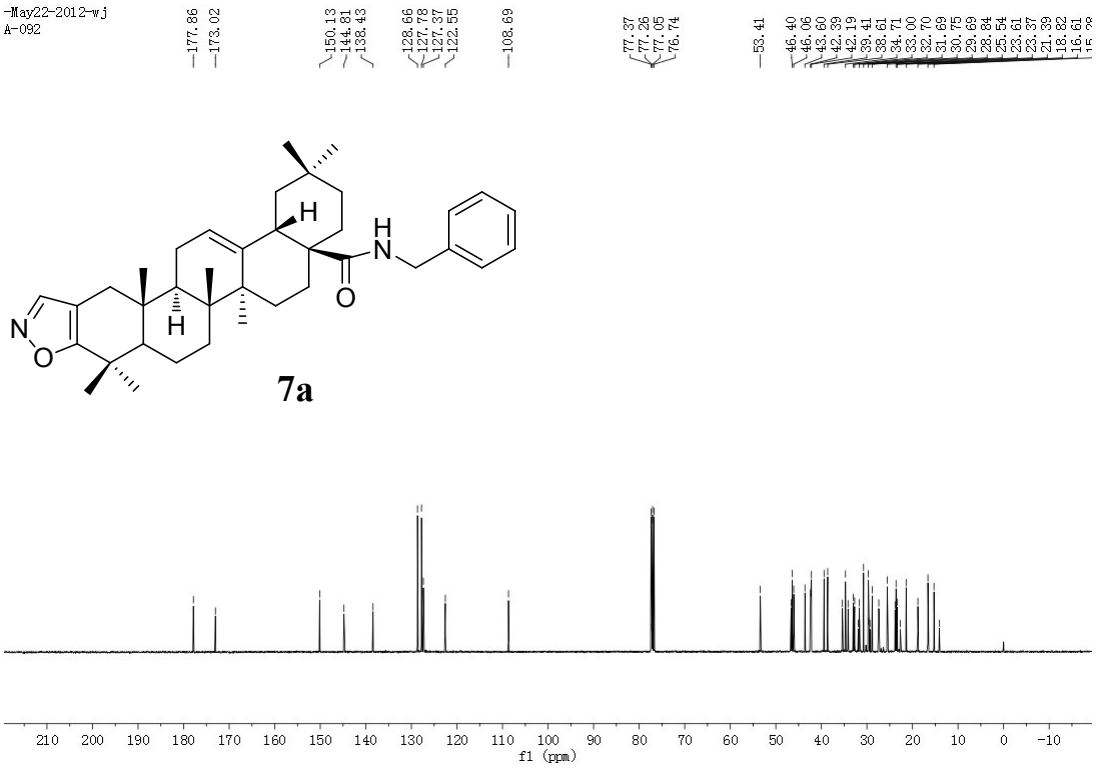

-Jul08-2012-wj
w-10
6j
f1 (ppm)

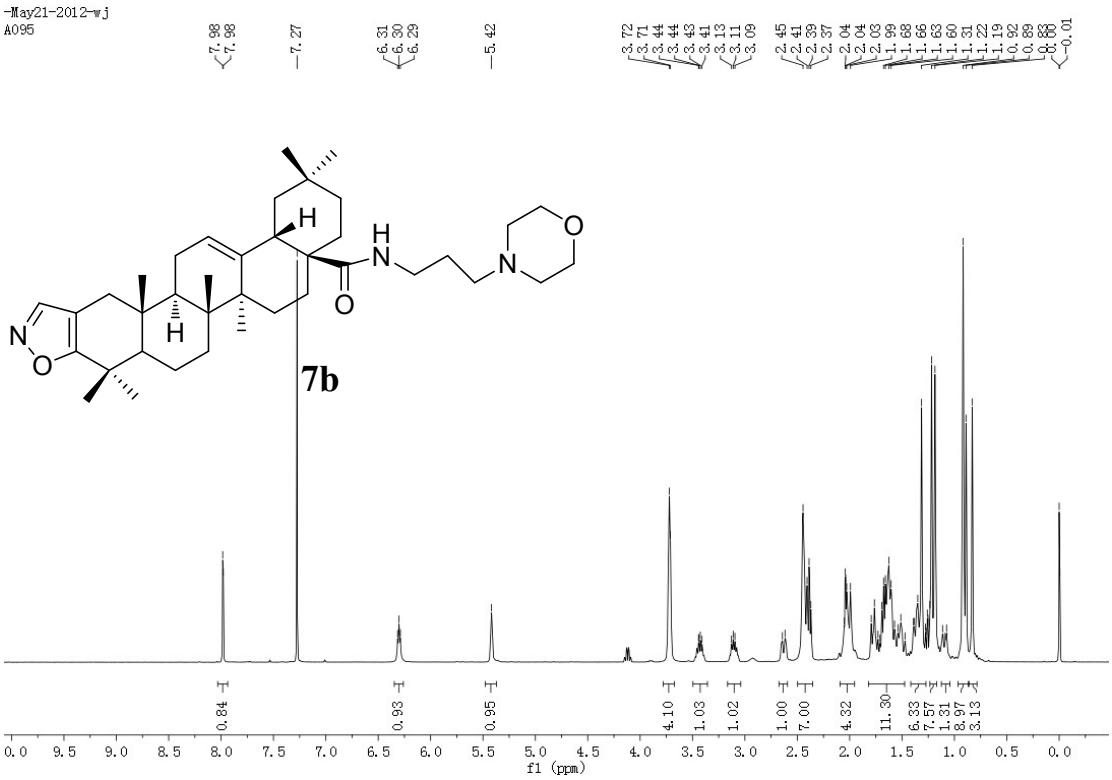

-Jul09-2012-wj
w-10
6j
f1 (ppm)

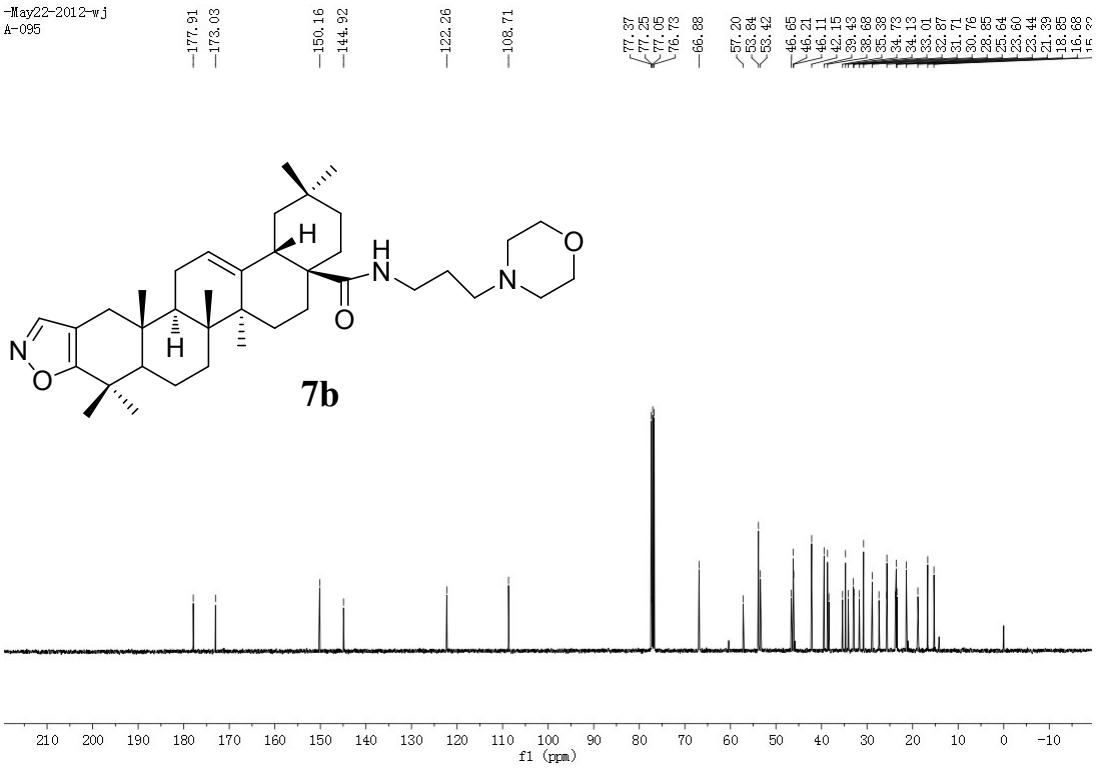

-Apr01-2012-wj
a-067
7.99
7.27
5.34
2.88
2.87
2.85
2.84
2.45
2.41
2.02
1.99
1.77
1.61
1.35
1.31
1.30
1.18
1.16
0.94
0.91
0.89
0.860
H
OH
O
N
O
H
7
0.96
1.00
1.01
0.96
4.06
2.91
4.21
8.24
9.16
9.08
3.11
f1 (ppm)

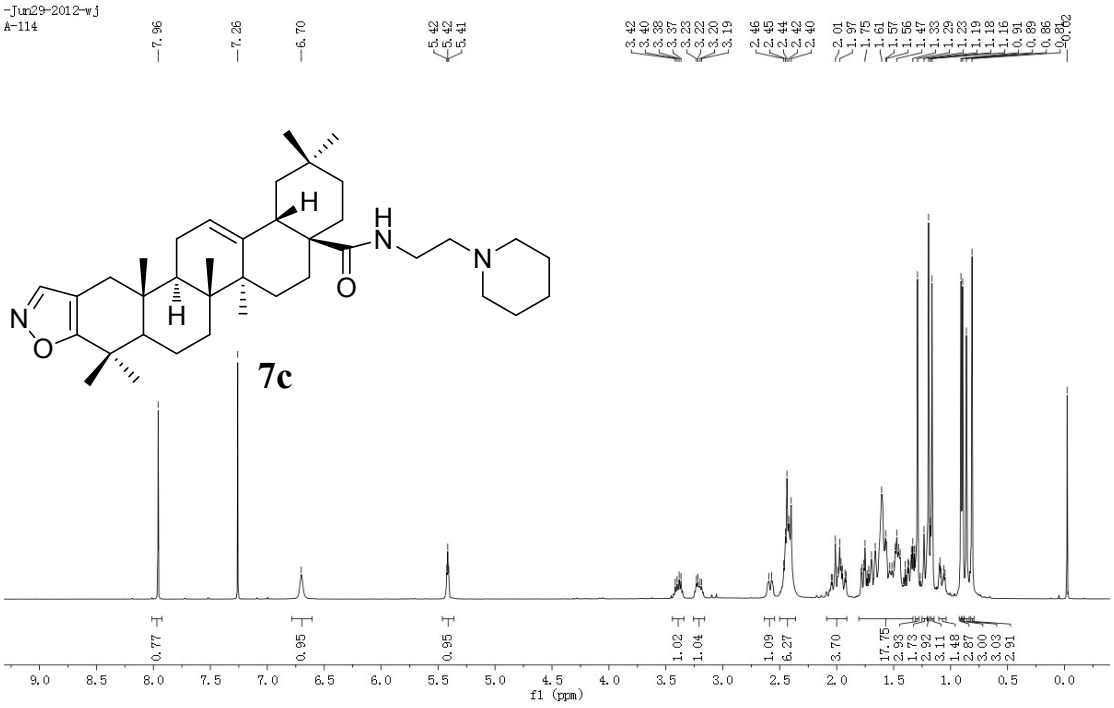

-Apr04-2012-wj
A-066
184.52
173.01
150.17
143.61
122.32
108.81
77.38
77.07
76.75
53.46
46.61
46.18
45.85
41.75
41.01
39.35
38.74
35.34
34.69
33.82
33.07
32.41
30.68
28.83
25.75
23.56
23.33
21.35
18.81
16.78
H
OH
O
N
O
H
7
f1 (ppm)

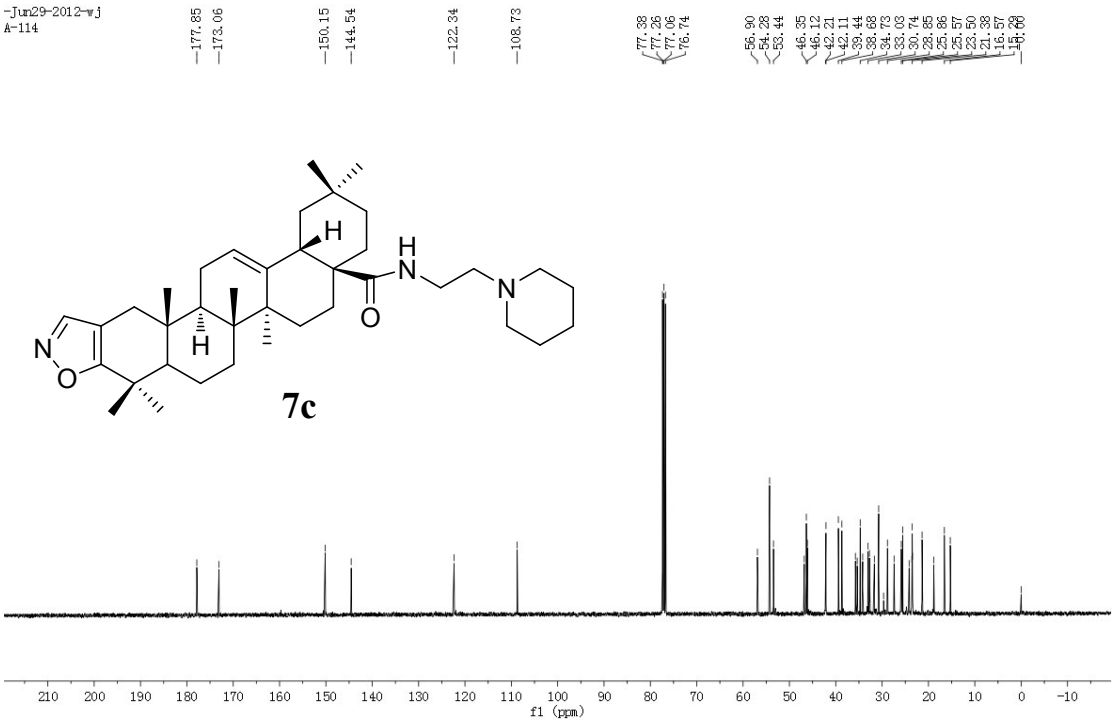

-May21-2012-wj
A-092
7a
f1 (ppm)

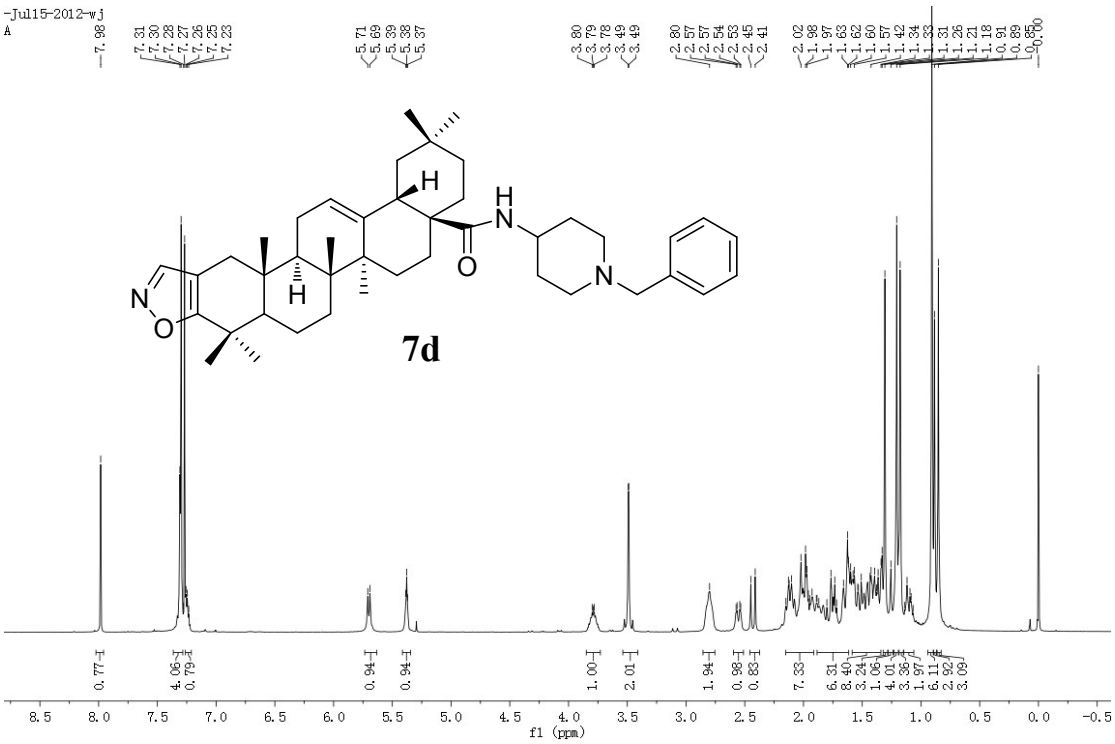

-May22-2012-wj
A-092
7a
f1 (ppm)

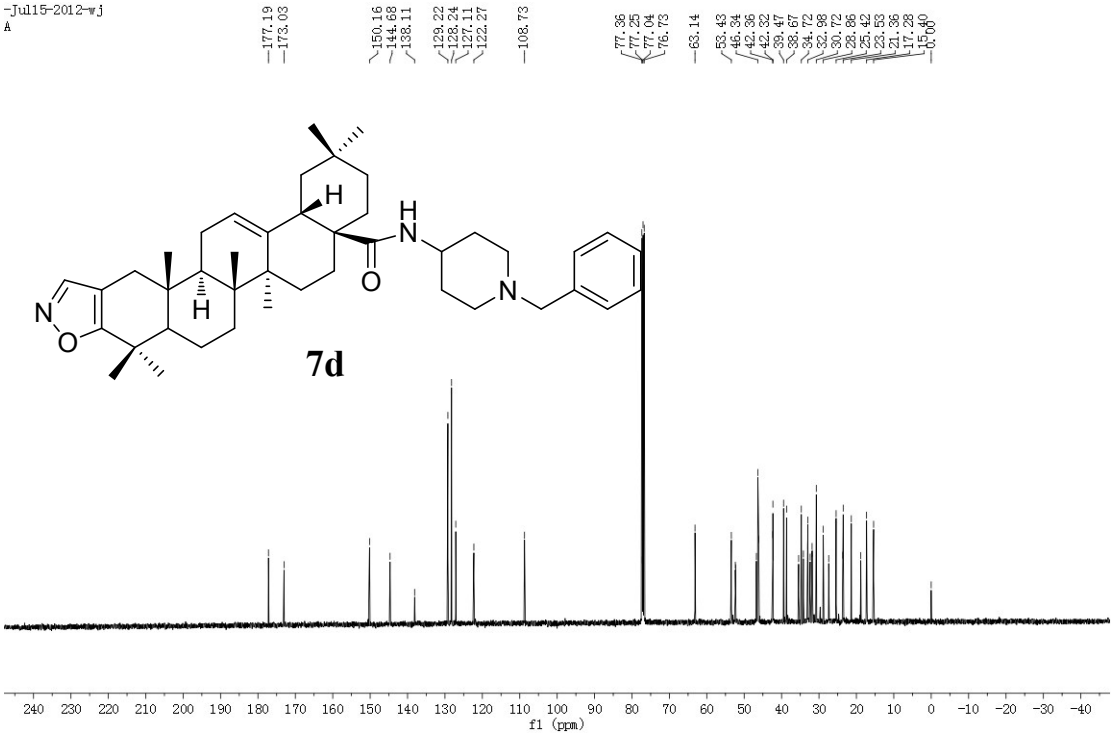

-May21-2012-wj
A095
7b
f1 (ppm)


-May22-2012-wj
A-095
7b
f1 (ppm)


-Jun29-2012-wj
A-114
7.96
7.26
6.70
5.42
5.41
3.42
3.40
3.38
3.37
3.23
3.22
3.20
3.19
2.46
2.45
2.44
2.42
2.40
2.01
1.97
1.75
1.61
1.57
1.56
1.47
1.33
1.29
1.23
1.19
1.18
1.16
0.91
0.89
0.86
0.81
0.02
7c
0.77
0.95
0.95
1.02
1.04
1.09
6.27
3.70
17.75
2.93
1.13
2.92
3.11
1.48
2.87
3.00
3.03
2.91
f1 (ppm)


-Jun29-2012-wj
A-114
177.85
173.06
150.15
144.54
122.34
108.73
77.38
77.26
77.06
76.74
56.90
54.28
53.44
46.35
46.12
42.21
42.11
39.44
38.88
34.73
33.03
30.74
28.85
25.86
25.57
23.50
21.38
16.57
15.60
7c
f1 (ppm)


-Jul15-2012-wj
A
7d


-Jul15-2012-wj
A
7d