Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Supporting Information

Discovery and Structural Modification of Novel Inhibitors of PTP1B Inspired by the ACT Fragment of Scleritodermin A

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Table of Contents:

General Methods

(A) Chemistry

Starting materials, reagents and solvents were purchased from commercial suppliers and used without further purification, unless otherwise stated. Anhydrous THF and CH_2Cl_2 were obtained from a distillation over sodium wire or CaH_2. All non-aqueous reactions were run under an inert atmosphere (nitrogen or argon) with rigid exclusion of moisture from reagents and all reaction vessels were oven-dried. The progress of reactions was monitored by silica gel thin layer chromatography (TLC) plates, visualized under UV or charred using phosphomolybdic acid solution followed by heating. Products were purified by flash column chromatography (FCC) on 200-300 mesh silica gel. Petroleum ether refers to the fraction with boiling range 60-90℃or 30-60℃. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a spectrometer operating at 300 MHz or 600 MHz. Data is reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, br = broad, m = multiplet). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a spectrometer operating at 75 MHz or 125 MHz. High-resolution mass data were obtained on a Micromass Q-Tof UltimaTM spectrometer. Purity was evaluated by analytical HPLC chromatograms using Agilent 1200 series LC system equipped with Zorbax SB C18 column , 4.6 ×150 mm, 5μm partical size, at room temperature. Mobile phase: MeOH: 0.1% TFA in H_2O (75:25). Flow rate: 1.0 mL/min. UV detection: 285nm.

(B) Biology

(a) Enzyme-based assay of PTP1B. A colorimetric high throughput assay to measure inhibition against PTP1B was performed in 96-well plates. Briefly, the tested compounds were solubilized in DMSO and serially diluted into concentrations for the inhibitory test. The assays were carried out in a final volume of 100 μL containing 50 mmol/L MOPS, pH 6.5, 2 mmol/L pNPP, 30 nmol/L GST-PTP1B, and 2% DMSO, and the catalysis of pNPP was continuously monitored on a SpectraMax 340 microplate reader at 405 nm for 2 min at 30 °C. The IC_{50} value was calculated from

the nonlinear curve fitting of the percent inhibition [inhibition (%)] vs the inhibitor concentration [I] using the following equation: %inhibition=100/{1+(IC_{50}/[I])k}, where k is the Hill coefficient.

(b) ***Enzyme-based assay of PTPs.*** PTPase family members, such as Src homology domain 2(SH2)-containing tyrosine phosphatase-1(SHP1), Src homology domain 2 (SH2)-containing tyrosine phosphatase-2(SHP2), leukocyte antigen-related phosphatase (LAR), CDC25B were prepared for the selectivity assay of compounds as previously mentioned[S1]. Assays for these PTPases were performed at the optimal pH for each individual enzyme activity. These enzymes and inhibitors were preincubated for 3 min at 4 °C, and the assays were initiated by adding substrates. Assays performed for CDC25B, SHP1 and SHP2, LAR were done using OMFP as a substrate.

	TCPTP	PTP1B	SHP1	SHP2	LAR	CDC25B
Positive control	Oleanolic acid(μM)[S2]		Na_3VO_4(μM)			
	3.02±0.31	2.01±0.26	31.65±0.78	20.65±0.59	25.32±1.25	3.04±0.16

Experimental and Spectroscopic Data for Compounds:

(2Z,4E)-ethyl 5-(2-((S)-1-amino-2-(4-(benzyloxy)phenyl)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (2)

To a solution of **1** (130mg) in CH_2Cl_2 (1.3mL), trifluoroacetic acid (0.55mL) was added and stirred for 2h at room temperature. The reaction mixture was diluted with ethyl acetate and washed successively with saturated sodium bicarbonate, water and brine. The organic layer was dried over sodium sulfate and evaporated in vacuo to afford amine **2** (105mg, 98%). The crude amine **2** was used without further purification. ^{1}HNMR (300MHz, CDCl3): δ 1.24 (t, 3H, J=7Hz), 1.99 (s, 3H), 2.19 (s,

3H), 3.23 (m, 1H), 3.42 (m, 1H), 4.17 (q, 2H, J=7Hz), 4.84 (m, 1H), 4.98 (s, 2H), 6.21 (s, 1H), 6.38 (s, 1H), 6.83 (d, 2H, J=9Hz), 6.97 (d, 2H, J=9Hz), 6.99 (s, 1H), 7.30-7.41 (5H).

(2Z,4E)-ethyl 5-(2-((S)-2-(4-(benzyloxy)phenyl)-1-(cyclopropanecarboxamido)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (3a)

A solution of amine **2** (287mg) and DIPEA (0.1mL, 2.2eq) in dry CH_2Cl_2 (5mL) was cooled in an ice bath and cyclopropanecarbonyl chloride (77μL, 1.5eq) was added. The reaction mixture was stirred at room temperature overnight. After the solvent was concentrated in vacuo, the residue was purified by chromatography (petroleum ether / acetone = 3/1) to afford **3a** (237mg, 72%). ^{1}H NMR (300MHz, $CDCl_3$): δ 0.74 (m, 2H), 0.90 (m, 2H), 1.25 (t, 3H, *J*=7Hz), 1.38 (m, 1H), 2.03 (s, 3H), 2.14 (s, 3H), 3.24 (dq, 2H, *J*=6, 14Hz), 4.21 (q, 2H, *J*=7Hz), 5.01 (s, 2H), 5.53 (q, 1H, *J*=7Hz), 6.27 (d, 1H), 6.50 (br, 2H), 6.86 (d, 2H, *J*=9Hz), 6.98 (d, 2H, *J*=9Hz), 7.00 (s, 1H), 7.30-7.43 (m, 5H); HRMS (ESI) m/z calc for $C_{31}H_{34}N_2NaO_4S$ $[M+Na]^+$ is 553.2137, found 553.2153; HPLC purity: 95.3 %.

(2Z,4E)-ethyl 5-(2-((S)-2-(4-(benzyloxy)phenyl)-1-(cyclopentanecarboxamido)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (3b)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.25 (t, 3H, *J*=7Hz), 1.50-1.90 (m, 8H), 2.03 (s, 3H), 2.14 (s, 3H), 2.53 (m, 1H), 3.23 (d, 2H, *J*=7Hz) , 4.21 (q, 2H, *J*=7Hz), 5.01 (s, 2H), 5.53 (q, 1H, *J*=8Hz), 6.27 (br, 2H), 6.48 (s, 1H), 6.84 (d, 2H, *J*=9Hz), 6.97 (d, 2H, *J*=9Hz), 6.99 (s, 1H), 7.31-7.43 (m, 5H); HRMS (ESI) m/z calc for $C_{33}H_{39}N_2O_4S$ $[M+H]^+$ is 558.2631, found 559.2603; HPLC purity: 96.7 %.

(2Z,4E)-ethyl 5-(2-((S)-2-(4-(benzyloxy)phenyl)-1-(4-fluorobenzamido)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (3c)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.24 (t, 3H, *J*=7Hz), 1.99 (s, 3H), 2.14 (s, 3H), 3.34 (dq, 2H, *J*=6, 14Hz), 4.17 (q, 2H, *J*=7Hz), 5.01 (s, 2H), 5.69 (q, 1H, *J*=7Hz), 6.27 (s, 1H), 6.49 (s, 1H), 6.84 (d, 2H, *J*=8Hz), 7.00 (s, 1H), 7.02 (d, 2H, *J*=8Hz), 7.09 (m, 2H), 7.31-7.42 (m, 5H), 7.76 (m, 2H); HRMS (ESI) m/z calc for $C_{34}H_{33}FN_2NaO_4S$ $[M+Na]^+$ is 607.2043, found 607.2039; HPLC purity: 95.0 %.

(2Z,4E)-ethyl 5-(2-((S)-2-(4-(benzyloxy)phenyl)-1-isobutyramidoethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (3d)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.11 (dd, 6H, *J*=5, 7Hz), 1.21 (d, 2H, *J*=7Hz), 1.26 (t, 3H, *J*=7Hz), 2.03 (s, 3H), 2.14 (s, 3H), 2.38 (m, 1H), 3.22 (dd, 2H, *J*=2, 6Hz) , 4.21 (q, 2H, *J*=7Hz), 5.02 (s, 2H), 5.53 (q, 1H, *J*=8Hz), 6.27 (s, 1H), 6.37 (d, 1H, *J*=8Hz), 6.48 (s, 1H), 6.84 (d, 2H, *J*=8Hz), 6.98 (d, 2H, *J*=8Hz), 7.00 (s, 1H), 7.28-7.42 (m, 5H); HRMS (ESI) m/z calc for $C_{31}H_{37}N_2O_4S$ $[M+H]^+$ is 533.2474, found 533.2484; HPLC purity: 95.6 %.

(2Z,4E)-ethyl 5-(2-((S)-2-(4-(benzyloxy)phenyl)-1-pentanamidoethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (3e)

^{1}H NMR (300MHz, $CDCl_3$): δ 0.88 (t, 3H, *J*=7Hz), 1.24-1.31 (m, 6H), 1.55(m, 2H), 2.03 (s, 3H), 2.14 (s, 3H), 2.18 (m, 2H), 3.22 (d, 2H, *J*=6Hz), 4.21 (q, 2H, *J*=7Hz), 5.00 (s, 2H), 5.53 (q, 1H, *J*=7Hz), 6.27 (s, 1H), 6.33 (d, 1H, *J*=8Hz), 6.48 (s, 1H), 6.84 (d, 2H, *J*=7Hz), 6.98 (d, 2H, *J*=7Hz), 6.99 (s, 1H), 7.31-7.40 (m, 5H) ; HRMS (ESI) m/z calc for $C_{32}H_{39}N_2O_4S$ $[M+H]^+$ is 547.2631, found 547.2638; HPLC purity: 96.5 %.

(2Z,4E)-ethyl 5-(2-((S)-2-(4-(benzyloxy)phenyl)-1-(cyclohexanecarboxamido)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (3f)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.26 (t, 3H, *J*=7Hz), 1.30-1.44 (m, 4H), 1.66-1.80 (m,

6H), 2.03 (s, 3H), 2.07 (m, 1H), 2.14 (s, 3H), 3.22 (dd, 2H, *J*=2, 7Hz) , 4.20 (q, 2H, *J*=7Hz), 5.02 (s, 2H), 5.53 (q, 1H, *J*=8Hz), 6.27 (s, 1H), 6.32 (d, 1H, *J*=8Hz), 6.48 (s, 1H), 6.84 (d, 2H, *J*=9Hz), 6.98 (d, 2H, *J*=9Hz), 6.99 (s, 1H), 7.30-7.43 (m, 5H); ^{13}C NMR (300MHz, $CDCl_3$): δ 14.3, 17.6, 21.9, 25.8, 25.8, 25.9, 29.9, 40.8, 45.5, 52.1, 60.9, 70.2, 115.0, 117.1, 124.5, 127.6, 128.1, 128.7, 128.9, 129.3, 130.7, 136.3, 137.1, 137.8, 153.2, 157.9, 169.7, 175.6, 177.6, 177.7, 177.9, 177.9, 178.0; HRMS (ESI) m/z calc for $C_{34}H_{40}N_2NaO_4S$ $[M+Na]^+$ is 595.2606, found 595.2619; HPLC purity: 95.4 %.

(2Z,4E)-ethyl 5-(2-((S)-1-benzamido-2-(4-(benzyloxy)phenyl)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (3g)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.26 (t, 3H, *J*=7Hz), 2.03 (s, 3H), 2.16 (s, 3H), 3.34 (dq, 2H, *J*=6, 15Hz), 4.21 (q, 2H, *J*=7Hz), 5.01 (s, 2H), 5.72 (q, 1H, *J*= 8Hz), 6.28 (s, 1H), 6.50 (s, 1H), 6.85 (d, 2H, *J*=9Hz), 7.05 (s, 1H), 7.08 (d, 2H, *J*= 9Hz), 7.12 (d, 1H, *J*=8Hz), 7.31-7.74 (m, 8H), 7.75 (d, 2H, *J*=6Hz); HRMS (ESI) m/z calc for $C_{34}H_{35}N_2O_4S$ $[M+H]^+$ is 567.2318, found 567.2344; HPLC purity: 95.5 %.

(2Z,4E)-ethyl 5-(2-((S)-2-(4-(benzyloxy)phenyl)-1-(furan-2-carboxamido)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (3h)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.26 (t, 3H, *J*=7Hz), 2.03 (s, 3H), 2.17 (s, 3H), 3.33 (dq, 2H, *J*=6, 14Hz), 4.21 (q, 2H, *J*=7Hz), 5.01 (s, 2H), 5.68 (q, 1H, *J*=7Hz), 6.28 (s, 1H), 6.49 (br, 2H), 6.85 (d, 2H, *J*=9Hz), 7.00 (s, 1H), 7.04 (d, 2H, *J*=9Hz), 7.12 (d, 1H, *J*=3Hz), 7.17 (d, 1H, *J*=11Hz), 7.31-7.43 (m, 5H); HRMS (ESI) m/z calc for $C_{32}H_{33}N_2O_5S$ $[M+H]^+$ is 557.2110, found 557.2103; HPLC purity: 95.6 %.

(2Z,4E)-ethyl 5-(2-((S)-1-(benzo[b]thiophene-2-carboxamido)-2-(4-(benzyloxy)phenyl)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (3i)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.27 (t, 3H, *J*=7Hz), 2.04 (s, 3H), 2.17 (s, 3H), 3.37 (dq, 2H, *J*=6, 15Hz), 4.21 (q, 2H, *J*=7Hz), 5.00 (s, 2H), 5.72 (q, 1H, *J*=7Hz), 6.29 (s, 1H), 6.51 (s, 1H), 6.86 (d, 2H, *J*=8Hz), 7.02 (s, 1H), 7.04 (d, 2H, *J*=8Hz), 7.24 (d, 2H, *J*=8Hz), 7.28-7.45 (m, 8H), 7.78 (s, 1H), 7.82 (t, 2H, *J*=8Hz); HRMS (ESI) m/z calc for $C_{36}H_{35}N_2O_4S_2$ $[M+H]^+$ is 623.2038, found 623.2042; HPLC purity: 95.4 %.

(2E,4E)-ethyl 5-(2-((S)-2-(4-(benzyloxy)phenyl)-1-(cyclohexanecarboxamido)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (6a)

The cis-trans isomers are synthesized as previously reported.[S3] ^{1}H NMR (300MHz, $CDCl_3$): δ 1.20-1.44 (m, 7H), 1.66-1.80 (m, 6H), 2.10 (s, 3H), 2.15 (br, 1H), 2.30 (s, 3H), 3.24 (d, 2H, *J*=6Hz) , 4.24 (q, 2H, *J*=7Hz), 5.02 (s, 2H), 5.57 (q, 1H, *J*=7Hz), 6.33 (d, 1H, *J*=8Hz), 6.60 (s, 1H), 6.85 (d, 2H, *J*=8Hz), 7.00 (d, 2H, *J*=8Hz), 7.07 (s, 1H), 7.28-7.42 (m, 5H); HRMS (ESI) m/z calc for $C_{34}H_{40}N_2NaO_4S$ $[M+Na]^+$ is 595.2606, found 595.2576; HPLC purity: 96.3 %.

(2E,4Z)-ethyl 5-(2-((S)-2-(4-(benzyloxy)phenyl)-1-(cyclohexanecarboxamido)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (6b)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.30 (t, 3H, *J*=7Hz), 1.32-1.41 (m, 4H), 1.66-1.80 (m, 6H), 1.90 (s, 3H), 2.11 (s, 3H), 2.13 (m, 1H), 3.20 (m, 2H) , 4.22 (q, 2H, *J*=7Hz), 5.02 (s, 2H), 5.51 (q, 1H, *J*=8Hz), 6.36 (d, 1H, *J*=8Hz), 6.55 (s, 1H), 6.90 (d, 2H, *J*=9Hz), 6.95 (d, 2H, *J*=9Hz), 6.97 (s, 1H), 7.31-7.43 (m, 5H), 7.79 (s, 1H); HRMS (ESI) m/z calc for $C_{34}H_{41}N_2O_4S$ $[M+H]^+$ is 573.2787, found 573.2813; HPLC purity: 95.0 %.

(2Z,4Z)-ethyl 5-(2-((S)-2-(4-(benzyloxy)phenyl)-1-(cyclohexanecarboxamido)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (6c)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.26 (t, 3H, *J*=7Hz), 1.32-1.41 (m, 4H), 1.66-1.80 (m, 6H), 2.03 (br, 6H), 2.10 (m, 1H), 3.21 (d, 2H, *J*=7Hz) , 4.16 (q, 2H, *J*=7Hz), 5.01 (s,

2H), 5.49 (q, 1H, *J*=8Hz), 6.36 (d, 1H, *J*=8Hz), 6.40 (s, 1H), 6.75 (s, 1H), 6.84 (d, 2H, *J*=8Hz), 6.91 (s, 1H), 6.97 (d, 2H, *J*=8Hz), 7.32-7.43 (m, 5H); HRMS (ESI) m/z calc for $C_{34}H_{40}N_2NaO_4S$ $[M+Na]^+$ is 595.2606, found 595.2603; HPLC purity: 95.1 %.

ethyl

5-(2-((S)-2-(4-(benzyloxy)phenyl)-1-(cyclohexanecarboxamido)ethyl)thiazol-4-yl)-2,4-dimethylpentanoate (6d)

^{1}H NMR (300MHz, $CDCl_3$): δ 0.89 (d, 3H, *J*=7Hz), 1.10-1.28 (m, 8H), 1.29-1.43 (m, 4H), 1.66-1.80 (m, 6H), 1.96 (m, 1H), 2.09 (m, 1H), 2.57 (m, 2H), 2.70 (m, 1H), 3.20 (m, 2H) , 4.11 (dq, 2H, *J*=3, 7Hz), 5.01 (s, 2H), 5.51 (q, 1H, *J*=8Hz), 6.40 (m, 1H), 6.73 (m, 1H), 6.83 (d, 2H, *J*=8Hz), 6.96 (m, 2H), 7.30-7.42 (m, 5H); HRMS (ESI) m/z calc for $C_{34}H_{45}N_2O_4S$ $[M+H]^+$ is 577.3100, found 577.3138, mixture of diastereoisomers.

(S,E)-ethyl

3-(2-(2-(4-(benzyloxy)phenyl)-1-(cyclohexanecarboxamido)ethyl)thiazol-4-yl)-2-methylacrylate (6e)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.16-1.40 (m, 7H), 1.66-1.80 (m, 6H), 2.11 (m, 1H), 2.33 (s, 3H), 3.25 (d, 2H, *J*= 6Hz) , 4.27 (q, 2H, *J*=7Hz), 5.02 (s, 2H), 5.57 (q, 1H, *J*=7Hz), 6.28 (d, 1H, *J*=7Hz), 6.86 (d, 2H, *J*=8Hz), 6.99 (d, 2H, *J*=8Hz), 7.29 (s, 1H), 7.29-7.42 (m, 5H), 7.62 (s, 1H); HRMS (ESI) m/z calc for $C_{31}H_{36}N_2NaO_4S$ $[M+Na]^+$ is 555.2293, found 555.2281; HPLC purity: 98.0 %.

(S,Z)-ethyl

3-(2-(2-(4-(benzyloxy)phenyl)-1-(cyclohexanecarboxamido)ethyl)thiazol-4-yl)-2-methylacrylate (6f)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.27 (t, 3H, *J*=7Hz), 1.32-1.41 (m, 4H), 1.66-1.80 (m, 6H), 2.09 (m, 1H), 2.11 (d, 3H, *J*=2Hz), 3.20 (dq, 2H, *J*=6, 9Hz) , 4.23 (m, 2H), 5.01 (s, 2H), 5.48 (q, 1H, *J*= 8Hz), 6.25 (d, 1H, *J*=8Hz), 6.55 (d, 1H, *J*=1Hz), 6.85 (d, 2H,

J=9Hz), 6.98 (d, 2H, *J*=9Hz), 7.28-7.42 (m, 5H); HRMS (ESI) m/z calc for $C_{31}H_{36}N_2NaO_4S$ $[M+Na]^+$ is 555.2293, found 555.2287; HPLC purity: 95.4 %.

(S)-ethyl 2-(2-(4-(benzyloxy)phenyl)-1-(cyclohexanecarboxamido)ethyl)thiazole-4-carboxylate (6g)

^{1}HNMR (300MHz, $CDCl_3$): δ 1.18-1.42 (m, 7H), 1.65-1.80 (m, 6H), 2.07 (m, 1H), 3.25 (dd, 2H, *J*=3, 7Hz) , 4.42 (q, 2H, *J*=7Hz), 5.01 (s, 2H), 5.54 (q, 1H, *J*=8Hz), 6.28 (d, 1H, *J*=8Hz), 6.85 (d, 2H, *J*=9Hz), 6.97 (d, 2H, *J*=9Hz), 7.31-7.42 (m, 5H), 8.01 (s, 1H). HRMS (ESI) m/z calc for $C_{28}H_{33}N_2O_4S$ $[M+H]^+$ is 493.2161, found 493.2177; HPLC purity: 97.6 %.

ethyl 2-((2Z,4E)-5-(2-((R)-2-(4-(benzyloxy)phenyl)-1-(tert-butoxycarbonylamino)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienamido)acetate (10a)

Acid **9** was synthesized as previously reported.[S3] To a solution of acid **9** (20mg), glycine ethyl ester hydrochloride (10mg, 1.5eq) and triethylamine (10μL, 3eq) in DMF (1mL), DCC (9mg, 1.2eq), HOBt (7mg, 1.2eq) were added and stirred at room temperature overnight. The reaction mixture wad diluted with ethyl acetate and washed successively with 1M HCL, water and brine. The organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was purified by chromatography (petroleum ether / ethyl acetate = 3/1) to afford **10a** (22mg, 59%) as a white solid. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.26 (t, 3H, J=7.1Hz), 1.41 (s, 9H), 2.05 (s, 3H), 2.21 (s, 3H), 3.22 (d, 2H, J=2.0Hz), 4.09 (d, 2H, J=5.4Hz), 4.19 (q, 2H, J=7.2Hz), 5.02 (s, 2H), 5.18 (m, 1H), 6.192 (s, 1H), 6.530 (s, 1H), 6.86 (d, 2H, J=8.7Hz), 6.99-7.01 (d, 3H), 7.31-7.43 (m, 5H); HRMS (ESI) m/z calc for $C_{34}H_{42}N_3O_6S$ $[M+H]^+$ is 620.2794, found 620.2823; HPLC purity: 95.5 %.

methyl 3-((2Z,4E)-5-(2-((R)-2-(4-(benzyloxy)phenyl)-1-(tert-butoxycarbonylamino)ethyl)

thiazol-4-yl)-2,4-dimethylpenta-2,4-dienamido)propanoate (10b)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.02 (s, 3H), 2.15 (s, 3H), 2.55 (t, 2H), 3.29 (m, 2H), 3.61 (s, 3H), 3.61 (t, 2H), 5.02 (s, 2H), 6.11 (s, 1H), 6.54 (s, 1H), 6.87 (d, 2H), 7.02 (d, 3H), 7.31-7.42 (m, 5H); HRMS (ESI) m/z calc for $C_{34}H_{42}N_3O_6S$ $[M+H]^+$ is 620.2794, found 620.2786; HPLC purity: 95.0 %.

ethyl

4-((2Z,4E)-5-(2-((R)-2-(4-(benzyloxy)phenyl)-1-(tert-butoxycarbonylamino)ethyl)

thiazol-4-yl)-2,4-dimethylpenta-2,4-dienamido)butanoate (10c)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.23 (t, 3H, J=7.2Hz), 1.41 (s, 9H), 1.82 (t, 3H, J=7.1Hz), 2.02 (s, 3H), 2.20 (s, 3H), 2.32 (t, 2H, J=7.1Hz), 3.22 (d, 2H), 3.33 (q, 2H, J=6.6Hz), 4.10 (q, 2H, J=7.1Hz), 5.02 (s, 2H), 5.21(m, 1H), 6.11 (s, 1H), 6.51 (m, 1H), 6.86 (d, 2H, J=8.1Hz), 7.31-7.43 (m, 5H); HRMS (ESI) m/z calc for $C_{36}H_{45}N_3NaO_6S$ $[M+Na]^+$ is 670.2927, found 670.2900; HPLC purity: 95.5 %.

methyl

5-((2Z,4E)-5-(2-((R)-2-(4-(benzyloxy)phenyl)-1-(tert-butoxycarbonylamino)ethyl)

thiazol-4-yl)-2,4-dimethylpenta-2,4-dienamido)pentanoate (10d)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.40 (s, 9H), 1.54-1.59 (m, 4H), 2.02 (s, 3H), 2.19 (s, 3H), 2.27 (t, 2H, J=7.1Hz), 3.22 (d, 2H), 3.29 (q, 2H, J=6.5), 3.64 (s, 3H), 5.02 (s, 2H), 5.19 (m, 1H), 6.10 (s, 1H), 6.49 (s, 1H), 6.86 (d, 2H, J=8.7Hz), 7.01 (d, 2H, J=9.0Hz), 7.33-7.40 (m, 5H); HRMS (ESI) m/z calc for $C_{36}H_{46}N_3O_6S$ $[M+H]^+$ is 648.3107, found 648.3115; HPLC purity: 99.1 %.

(2Z,4E)-2-ethoxy-2-oxoethyl

5-(2-((R)-2-(4-(benzyloxy)phenyl)-1-(tert-butoxycarbonylamino)ethyl)thiazol-4-yl

)-2,4-dimethylpenta-2,4-dienoate (10e)

To a solution of acid **9** (20mg) in DMF (1mL) was added cesium carbonate (8mg, 0.6eq). The mixture was stirred at room temperature for 1h. Ethyl 2-bromoacetate (5μL, 1.2eq) was added and the reaction mixture was stirred at room temperature

overnight. The mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was purified by chromatography (petroleum ether / ethyl acetate = 8/1) to afford **10e** (16mg, 69%) as a white solid. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.28 (t, 3H, J=7.1Hz), 1.41 (s, 9H), 2.04 (s, 3H), 2.18 (s, 3H), 3.22 (d, 2H), 4.22 (q, 2H, J=7.1Hz), 4.68 (s, 2H), 5.02 (s, 2H), 5.20 (m, 1H), 6.40 (s, 1H), 6.55 (s, 1H), 6.86 (d, 2H, J=8.4Hz), 7.00 (d, 2H, J=8.7Hz), 7.04 (s, 1H), 7.31-7.44 (m, 5H); HRMS (ESI) m/z calc for $C_{34}H_{41}N_2O_7S$ $[M+H]^+$ is 621.2634, found 621.2618; HPLC purity: 95.1 %.

(2Z,4E)-4-ethoxy-4-oxobutyl 5-(2-((R)-2-(4-(benzyloxy)phenyl)-1-(tert-butoxycarbonylamino)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (10f)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.23 (t, 3H, J=7.2Hz), 1.41 (s, 9H), 1.96-2.00 (m, 2H), 2.03 (s, 3H), 2.15 (s, 3H), 2.37 (t, 2H, J=7.5Hz), 3.228 (d, 2H), 4.12 (q, 2H, J=7.2Hz), 4.18 (t, 2H, J=6.5Hz), 5.02 (s, 2H), 5.21 (m, 1H), 6.29 (s, 1H), 6.48 (s, 1H), 6.86 (d, 2H, J=8.7Hz), 7.01 (d, 2H, J=8.7Hz), 7.01 (s, 1H), 7.31-7.43 (m, 5H); HRMS (ESI) m/z calc for $C_{36}H_{45}N_2O_7S$ $[M+H]^+$ is 649.2947, found 649.2964; HPLC purity: 95.0 %.

(2Z,4E)-5-ethoxy-5-oxopentyl 5-(2-((R)-2-(4-(benzyloxy)phenyl)-1-(tert-butoxycarbonylamino)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (10g)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.24 (t, 3H, J=7.2Hz), 1.40 (s, 9H), 1.68 (m, 4H), 2.03(s, 3H), 2.15 (s, 3H), 2.29 (t, 2H), 3.23 (m, 1H), 4.11 (q, 2H, J=6.9Hz), 4.15 (t, 2H), 5.02 (s, 2H), 5.21(m, 1H), 6.28 (s, 1H), 6.48 (s, 1H), 6.86 (d, 2H, J=8.1Hz), 7.01 (d, 2H, J=8.4Hz), 7.00 (s, 1H), 7.31-7.43 (m, 5H); HRMS (ESI) m/z calc for $C_{37}H_{46}N_2NaO_7S$ $[M+Na]^+$ is 685.2923, found 685.2950; HPLC purity: 95.0 %.

(2Z,4E)-2-ethoxy-2-oxoethyl 5-(2-((S)-2-(4-(benzyloxy)phenyl)-1-((S)-2-(tert-butoxycarbonylamino)-3-(1H-ind

ol-3-yl)propanamido)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (12a)

To a solution of **10e** (1.22g) in CH_2Cl_2 (12mL), trifluoroacetic acid (3mL) was added and stirred for 2h at room temperature. The reaction mixture was diluted with ethyl acetate and washed successively with saturated sodium bicarbonate, water and brine. The organic layer was dried over sodium sulfate and evaporated in vacuo to afford amine **11** (1.01mg, 99%). The crude amine **11** was used without further purification.

To a solution of amine **11** (10mg) in CH_2Cl_2 (1mL) was added Boc-Trp-OH (7mg, 1.2eq), EDC hydrochloride (5mg, 1.2eq) and DMAP (1mg, 04eq). The reaction mixture was stirred at room temperature overnight. After the solvent was concentrated in vacuo, the residue was purified by chromatography (petroleum ether / ethyl acetate = 2/1) to afford **12a** (10mg, 72%). ^{1}H NMR (300MHz, $CDCl_3$): δ 1.28 (t, 3H, J=7.7Hz), 1.42 (s, 9H), 2.10 (s, 3H), 2.12 (s, 3H), 2.94-3.08 (m, 3H), 3.32 (d, 2H, J=14.4Hz), 4.21 (q, 2H, J=7.1Hz), 4.71 (q, 1H, J=9Hz), 4.98 (s, 2H), 6.22 (d, 1H, J=6.9Hz), 6.45 (d, 2H, J=3.9Hz), 6.70-6.77 (m, 5H), 6.91 (s, 1H), 7.04 (m, 2H), 7.18 (m, 1H), 7.28-7.41 (m, 5H), 7.61-7.64 (m, 1H); HRMS (ESI) m/z calc for $C_{45}H_{51}N_4O_8S$ $[M+H]^+$ is 807.3428, found 807.3387; HPLC purity: 95.3 %.

2-((2Z,4E)-5-(2-((S)-2-(4-(benzyloxy)phenyl)-1-((S)-2-(tert-butoxycarbonylamino)-3-(1H-indol-3-yl)propanamido)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoyloxy)acetic acid (12b)

To a solution of **12a** (10mg) in dioxane/H_2O (0.5mL/0.5mL) was added LiOH · H_2O (5mg, 10eq) and stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and the water layer was acidified with 1M HCl. The organic layer was then washed with water and brine, dried over sodium sulfate and concentrated in vacuo. The residue was purified by chromatography (CH_2Cl_2 / MeOH = 7/1) to afford **12b** (9mg, 93%).

^{1}H NMR (300MHz, CD_3OD): δ 1.36 (s, 9H), 2.08 (s, 3H), 2.14 (s, 3H), 3.01-3.13 (m, 4H), 4.35 (t, 1H), 4.63 (s, 2H), 4.96 (s, 2H), 5.35 (q, 1H), 6.42 (s, 1H), 6.52 (s, 1H), 6.84 (d, 3H), 6.97-7.11 (m, 5H), 7.24-7.39 (m, 5H), 7.57 (d, 1H) ; HRMS (ESI) m/z calc for $C_{43}H_{46}N_4NaO_8S$ $[M+Na]^+$ is 801.2934, Found 801.2870; HPLC purity:98.2 %

(two peaks, inferred as rotamer).

(2Z,4E)-2-ethoxy-2-oxoethyl 5-(2-((S)-1-((S)-2-amino-3-(1H-indol-3-yl)propanamido)-2-(4-(benzyloxy)phenyl)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (12c)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.26 (t, 3H, J=7.1Hz), 2.09 (s, 3H), 2.17 (s, 3H), 2.93 (br, 1H), 3.16-3.75 (m, 3H), 4.21 (q, 2H, J=6.9Hz), 4.64 (s, 2H), 5.00 (s, 2H), 5.50 (q, 1H), 6.40 (s, 1H), 6.53 (s, 1H), 6.79-6.84 (m, 3H), 6.92 (d, 2H, J=8.1Hz), 7.02 (s, 1H), 7.09-7.20 (m, 3H), 7.30-7.42 (m, 7H), 7.63 (d, 1H, J=7.5Hz), 7.79 (dbr, 1H), 8.18 (s, 1H); HRMS (ESI) m/z calc for $C_{40}H_{43}N_4O_6S$ $[M+H]^+$ is 707.2903, found 707.2932; HPLC purity: 98.2 %.

(2Z,4E)-2-ethoxy-2-oxoethyl 5-(2-((S)-1-((S)-2-acetamido-3-(1H-indol-3-yl)propanamido)-2-(4-(benzyloxy)phenyl)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (12d)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.22 (t, 3H), 2.03 (s, 3H), 2.09 (s, 3H), 2.13 (s, 3H), 2.86-2.99 (m, 3H), 3.33 (dd, 1H, J=15Hz, J=5.1Hz), 4.21 (q, 2H, J=6.9Hz), 4.73 (q, 2H, J=13.8Hz), 4.98 (s, 2H), 5.18 (q, 1H, J=6.9), 6.13(d, 1H, J=7.5Hz), 6.38-6.46 (m, 2H), 6.65 (s, 1H), 6.74 (d, 2H, J=9Hz), 6.80 (d, 2H, J=8.4), 6.91 (s, 1H), 6.96-7.05 (m, 2H), 7.15 (m, 2H), 7.34-7.39 (m, 5H), 7.69 (d, 1H), 8.62 (s, 1H); ^{13}C NMR (300MHz, $CDCl_3$): δ 14.3, 18.4, 21.5, 23.6, 29.5, 41.0, 52.6, 54.4, 61.2, 61.8, 70.1, 110.3, 111.4, 114.9, 118.1, 118.7, 119.6, 122.1, 123.3, 123.4, 127.7, 128.2, 128.8, 130.6, 134.5, 136.4, 138.9, 142.5, 153.1, 157.8, 167.2, 167.9, 169.9, 170.6; HRMS (ESI) m/z calc for $C_{42}H_{44}N_4NaO_7S$ $[M+Na]^+$ is 771.2828, Found 771.2770; HPLC purity: 98.8 %.

2-((2Z,4E)-5-(2-((S)-1-((S)-2-acetamido-3-(1H-indol-3-yl)propanamido)-2-(4-(benzyloxy)phenyl)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoyloxy)acetic acid (12e)

^{1}H NMR (300MHz, CD_3OD): δ 1.89 (s, 3H), 2.07 (s, 3H), 2.13 (s, 3H), 2.97-3.24 (m, 4H), 4.67 (t, 1H), 5.00 (s, 2H), 5.33 (t, 1H), 6.39 (s, 1H), 6.49 (s, 1H), 6.84 (d, 2H,

J=8.4Hz), 6.96-7.07 (m, 6H), 7.20 (s, 1H), 7.23-7.40 (m, 6H), 7.56 (d, 1H, J=7.8Hz); ^{13}C NMR (300MHz, CD_3OD): δ 16.8, 20.6, 21.4, 27.8, 39.7, 53.2, 54.5, 60.9, 69.8, 72.1, 109.6, 111.1, 114.6, 117.8, 118.1, 118.6, 121.2, 123.3, 124.5, 127.3, 127.6, 127.6, 128.3, 128.4, 129.5, 130.3, 136.1, 136.9, 137.6, 139.0, 153.2, 157.9, 169.8, 170.9, 171.8, 172.5; HRMS (ESI) m/z calc for $C_{40}H_{40}N_4NaO_7S$ $[M+Na]^+$ is 743.2515, Found 743.2557; HPLC purity: 95.3 %.

(2Z,4E)-2-ethoxy-2-oxoethyl 5-(2-((S)-1-(2-(1H-indol-3-yl)acetamido)-2-(4-(benzyloxy)phenyl)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (12f)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.29 (t, 3H, J=7.2Hz), 2.03 (s, 3H), 2.09 (s, 3H), 2.94-3.12 (m, 2H), 3.75 (s, 2H), 4.25 (q, 2H, J=7.2Hz), 4.70 (s, 2H), 5.00 (s, 2H), 5.50 (q, 1H, J=8.1Hz), 6.35 (s, 1H), 6.40 (s, 1H), 6.52-6.59 (m, 4H), 6.98 (d, 2H, J=13.5Hz), 7.14 (t, 1H, J=7.4Hz), 7.24 (t, 1H, J=7.2Hz), 7.36-7.43 (m, 5H), 7.53 (d, 1H, J=7.5Hz), 8.47 (s, 1H); ^{13}C NMR (300MHz, $CDCl_3$): δ 14.3, 17.5, 19.4, 22.1, 29.9, 33.4, 40.8, 52.3, 61.2, 61.8, 70.0, 108.6, 111.6, 114.7, 117.9, 118.9, 120.2, 122.7, 124.1, 125.4, 127.2, 127.2, 127.7, 128.2, 128.2, 128.8, 129.0, 130.6, 131.1, 136.0, 136.6, 137.4, 140.6, 153.2, 157.6, 168.3, 169.1, 169.4, 171.1; HRMS (ESI) m/z calc for $C_{39}H_{39}N_3NaO_6S$ $[M+Na]^+$ is 700.2457, Found 700.2439; HPLC purity: 96.0 %.

2-((2Z,4E)-5-(2-((S)-1-(2-(1H-indol-3-yl)acetamido)-2-(4-(benzyloxy)phenyl)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoyloxy)acetic acid (12g)

^{1}H NMR (300MHz, CD_3OD): δ 2.07 (s, 3H), 2.11 (s, 3H), 3.04 (dd, 1H, J=13.8Hz, J=9.2Hz), 3.23 (dd, 1H, J=14.1Hz, J=5.3Hz), 3.63 (s, 2H), 4.61 (s, 2H), 4.98 (s, 2H), 5.41 (m, 1H), 6.40 (s, 1H), 6.50 (s, 1H), 6.71 (d, 2H, J=8.4Hz), 6.87 (d, 2H, J=8.4Hz), 6.98 (t, 1H, J=7.7Hz), 7.08 (s, 1H), 7.11 (t, 1H, J=7.1Hz), 7.27-7.44 (m, 8H), 8.17 (d, 1H, J=8.1Hz); ^{13}C NMR (300MHz, CD_3OD): δ 18.0, 21.9, 30.9, 34.0, 41.0, 54.4, 71.1, 109.0, 122.5, 155.9, 199.0, 120.2, 122.8, 125.3, 127.3, 128.6, 128.7, 129.0, 130.4, 131.4, 131.7, 135.3, 137.5, 138.3, 139.0, 140.5, 154.6, 159.2, 169.1, 170.8, 172.8, 174.7; HRMS (ESI) m/z calc for $C_{37}H_{35}N_3NaO_6S$ $[M+Na]^+$ is 672.2144, Found

672.2131; HPLC purity: 95.2 %.

(2Z,4E)-2-ethoxy-2-oxoethyl 5-(2-((S)-1-(3-(1H-indol-3-yl)propanamido)-2-(4-(benzyloxy)phenyl)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (12h)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.26 (t, 3H, J=7.2Hz), 2.10 (s, 3H), 2.14 (s, 3H), 2.59 (t, 2H, J=7.1Hz), 2.99-3.16 (m, 4H), 4.20 (q, 2H, J=7.2Hz), 4.68 (s, 2H), 4.99 (s, 2H), 5.48 (q, 1H, J=7.8Hz), 6.07 (d, 1H, J=8.4Hz), 6.41 (s, 1H), 6.51 (s, 1H), 6.74 (d, 2H, J=8.7Hz), 6.80 (d, 2H, J=8.4Hz), 7.00 (s, 1H), 7.08 (t, 1H, J=6.9Hz), 7.17 (t, 1H, J=7.2Hz), 7.31-7.42 (m, 6H), 7.57 (d, 1H, J=7.5Hz), 8.13 (s, 1H); ^{13}C NMR (300MHz, $CDCl_3$): δ 14.2, 17.8, 21.3, 21.7, 37.2, 40.5, 52.2, 61.0, 61.6, 70.0, 111.4, 114.4, 114.8, 117.7, 118.7, 119.3, 122.0, 122.0, 125.1, 127.2, 127.4, 127.6, 128.1, 128.7, 128.8, 130.5, 135.8, 136.5, 137.1, 140.7, 153.1, 157.7, 167.8, 168.9, 169.3, 172.4; HRMS (ESI) m/z calc for $C_{40}H_{41}N_3NaO_6S$ $[M+Na]^+$ is 714.2614, Found 714.2637; HPLC purity: 99.2 %.

2-((2Z,4E)-5-(2-((S)-1-(3-(1H-indol-3-yl)propanamido)-2-(4-(benzyloxy)phenyl)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoyloxy)acetic acid (12i)

^{1}H NMR (300MHz, CD_3OD): δ 2.00 (s, 3H), 2.14 (s, 3H), 2.54 (t, 2H, J=6.6Hz), 2.90-2.98 (m, 3H), 3.24-3.32 (m, 1H), 4.63 (s, 2H), 4.98 (s, 2H), 5.40 (q, 1H), 6.40 (s, 1H), 6.51 (s, 1H), 6.82 (d, 2H, J=8.4Hz), 6.92 (s, 1H), 6.95-7.09 (m, 5H), 7.23-7.39 (m, 6H), 7.51 (d, 1H, J=7.8Hz); ^{13}C NMR (300MHz, CD_3OD): δ 18.0, 21.9, 22.7, 30.9, 38.1, 41.0, 54.5, 71.1, 112.4, 115.0, 116.0, 119.0, 119.5, 119.7, 122.4, 123.2, 126.0, 128.7, 129.0, 129.5, 129.6, 131.0, 131.5, 137.5, 138.3, 138.9, 140.3, 154.5, 159.2, 171.0, 173.1, 175.8; HRMS (ESI) m/z calc for $C_{38}H_{37}N_3NaO_6S$ $[M+Na]^+$ is 686.2301, Found 686.2321; HPLC purity: 96.9 %.

(2Z,4E)-2-ethoxy-2-oxoethyl 5-(2-((S)-1-(4-(1H-indol-3-yl)butanamido)-2-(4-(benzyloxy)phenyl)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoate (12j)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.26 (t, 3H, J=7.1Hz), 2.08 (s, 3H), 2.15 (s, 3H), 2.01-2.29 (m, 4H), 2.66-2.81 (m, 2H), 3.14-3.24 (m, 2H), 4.21 (q, 2H, J=7.2Hz), 4.68 (s, 2H), 4.97 (s, 2H), 5.55 (q, 1H, J=7.8Hz), 6.23 (d, 1H, J=8.4Hz), 6.41 (s, 1H), 6.54 (s, 1H), 6.81-6.84 (m, 3H), 6.98 (d, 2H, J=8.7Hz), 7.01 (s, 1H), 7.09 (t, 1H, J=7.4Hz), 7.17 (t, 1H, J=7.1Hz), 7.30-7.39 (m, 5H), 7.57 (d, 1H, J=7.8Hz), 8.16 (s, 1H); ^{13}C NMR (300MHz, $CDCl_3$): δ 14.3, 17.9, 19.4, 21.9, 24.5, 25.8, 36.0, 41.0, 52.4, 61.2, 61.7, 70.1, 111.4, 115.0, 115.4, 117.9, 119.1, 119.3, 120.5, 122.1, 125.3, 127.6, 127.7, 128.2, 128.8, 128.9, 130.7, 136.2, 136.6, 137.2, 140.7, 153.2, 157.9, 168.0, 168.6, 169.3, 172.6; HRMS (ESI) m/z calc for $C_{41}H_{43}N_3NaO_6S$ $[M+Na]^+$ is 728.2770, Found 728.2758; HPLC purity: 95.4 %.

2-((2Z,4E)-5-(2-((S)-1-(4-(1H-indol-3-yl)butanamido)-2-(4-(benzyloxy)phenyl)ethyl)thiazol-4-yl)-2,4-dimethylpenta-2,4-dienoyloxy)acetic acid (12k)

^{1}H NMR (300MHz, CD_3OD): δ 2.07 (s, 3H), 2.14 (s, 3H), 2.54 (t, 2H, J=7.2Hz), 2.91-2.98 (m, 3H), 3.244-3.30 (m, 1H), 4.62 (s, 2H), 5.00 (s, 2H), 5.40 (q, 1H), 6.40 (s, 1H), 6.51 (s, 1H), 6.90 (s, 1H), 6.92-7.09 (m, 5H), 7.25-7.40 (m, 6H), 7.52 (d, 1H, J=7.5Hz); ^{13}C NMR (300MHz, CD_3OD): δ 16.7, 20.6, 21.4, 29.6, 36.8, 39.7, 53.1, 69.8, 111.0, 113.6, 114.7, 117.7, 118.1, 118.4, 121.1, 121.9, 124.7, 127.4, 127.6, 128.3, 129.7, 130.1, 136.2, 137.0, 137.6, 139.0, 153.2, 157.9, 169.6, 171.7, 174.5; HRMS (ESI) m/z calc for $C_{39}H_{39}N_3NaO_6S$ $[M+Na]^+$ is 700.2457, Found 700.2513; HPLC purity: 95.6 %.

^{1}H, ^{13}C NMR and HRMS Spectra

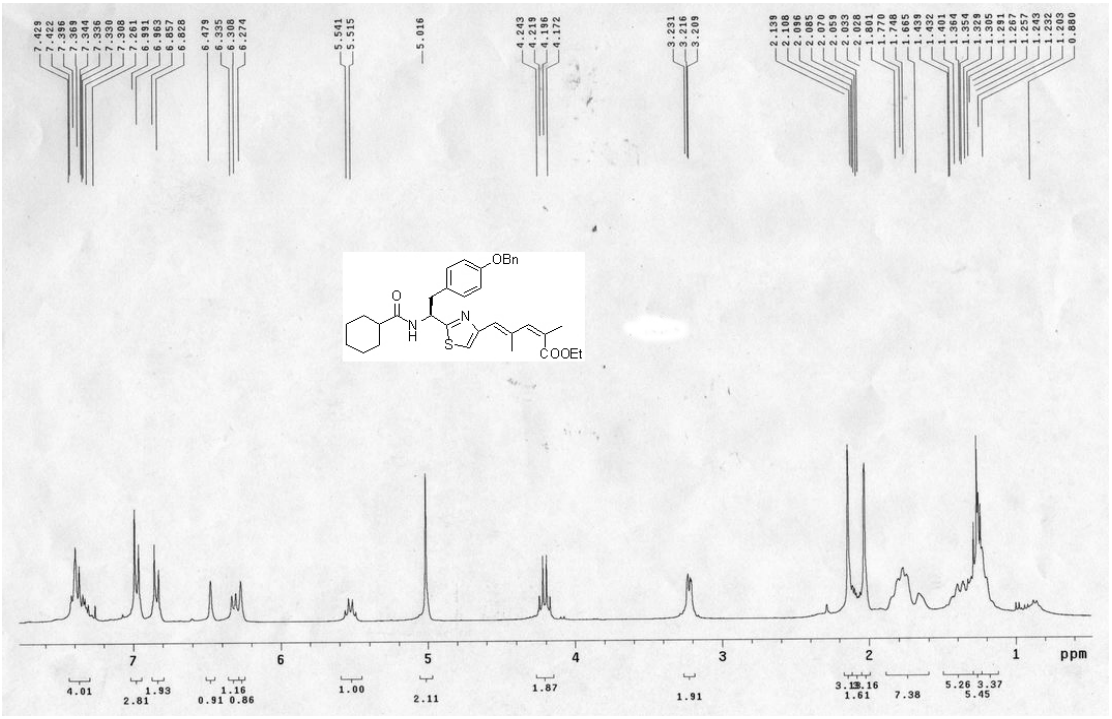


Figure S1 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **3f**.

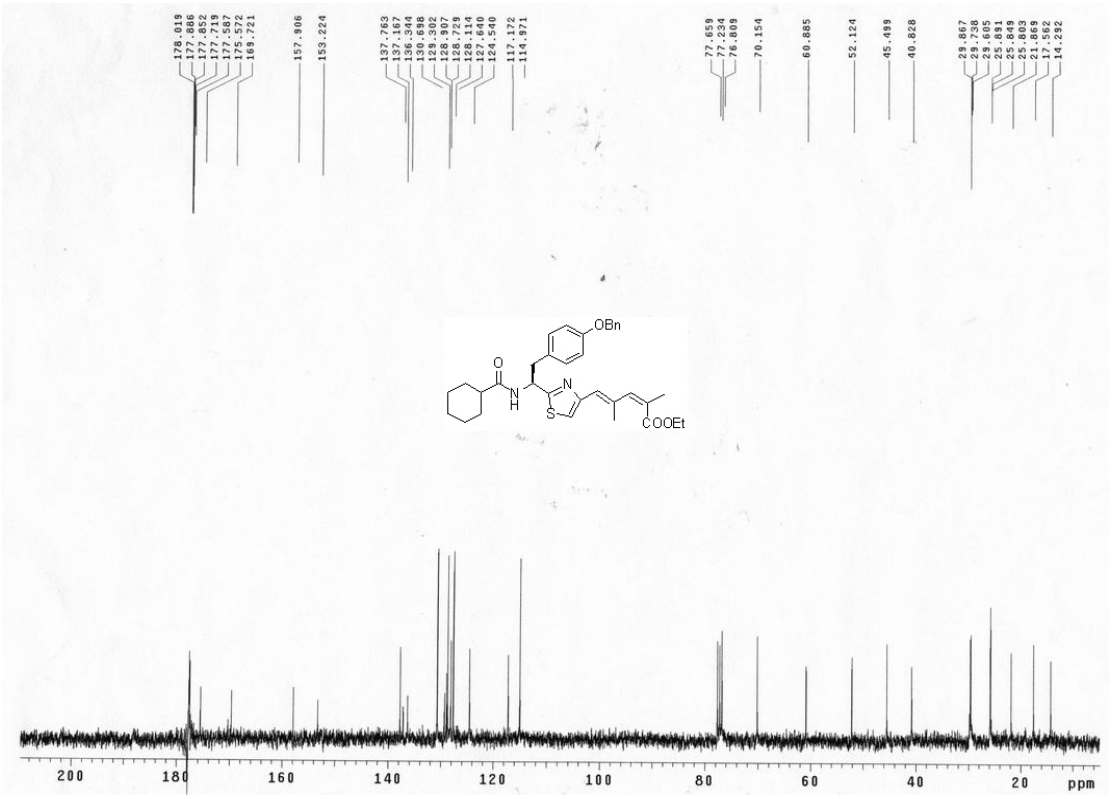


Figure S2 ^{13}C NMR (300 MHz, $CDCl_3$) spectrum of compound **3f**.

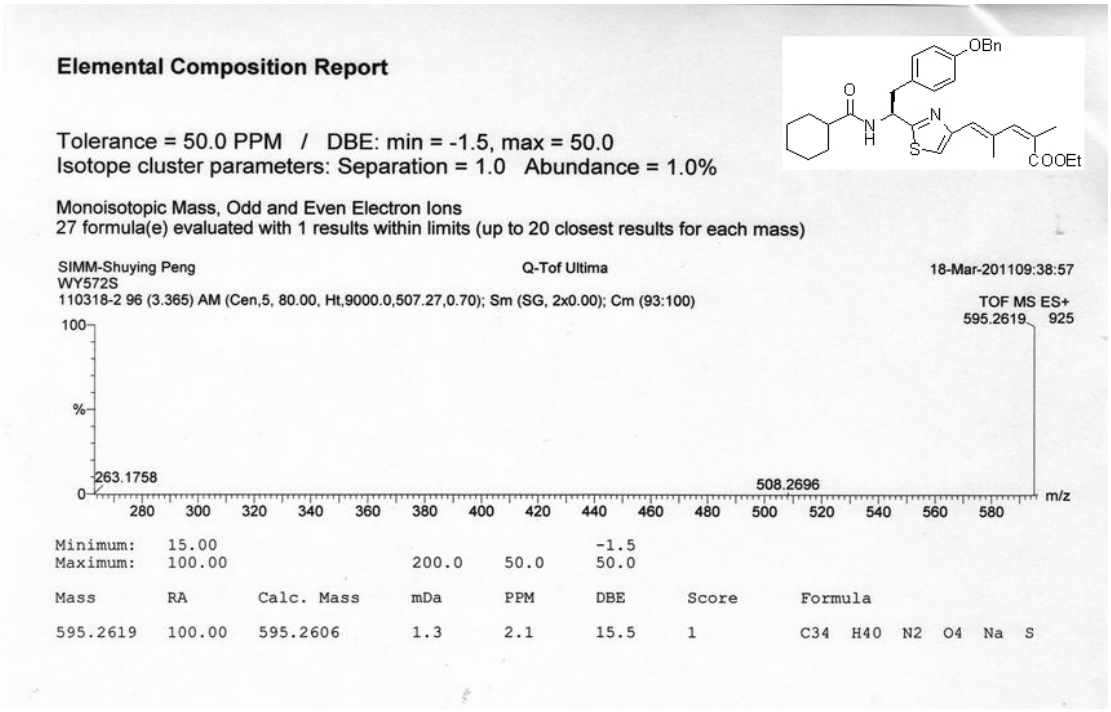


Figure S3 High resolution mass spectrum of compound **3f**.

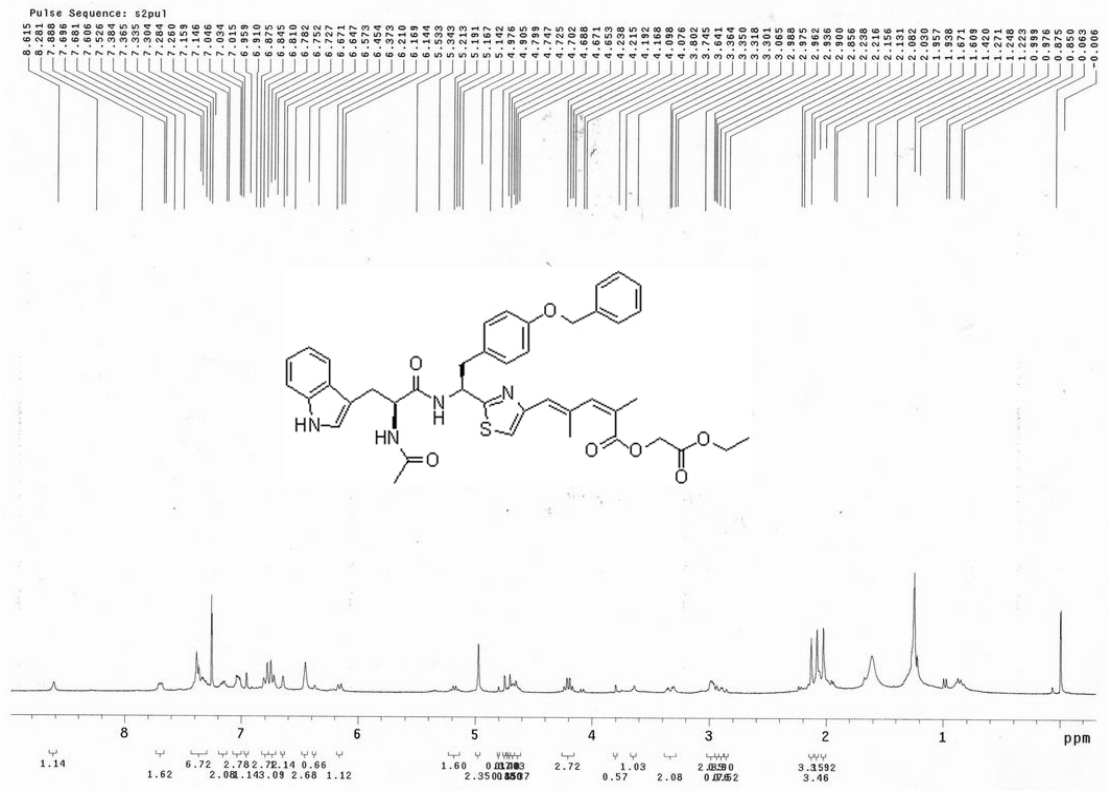


Figure S4 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **12d**.

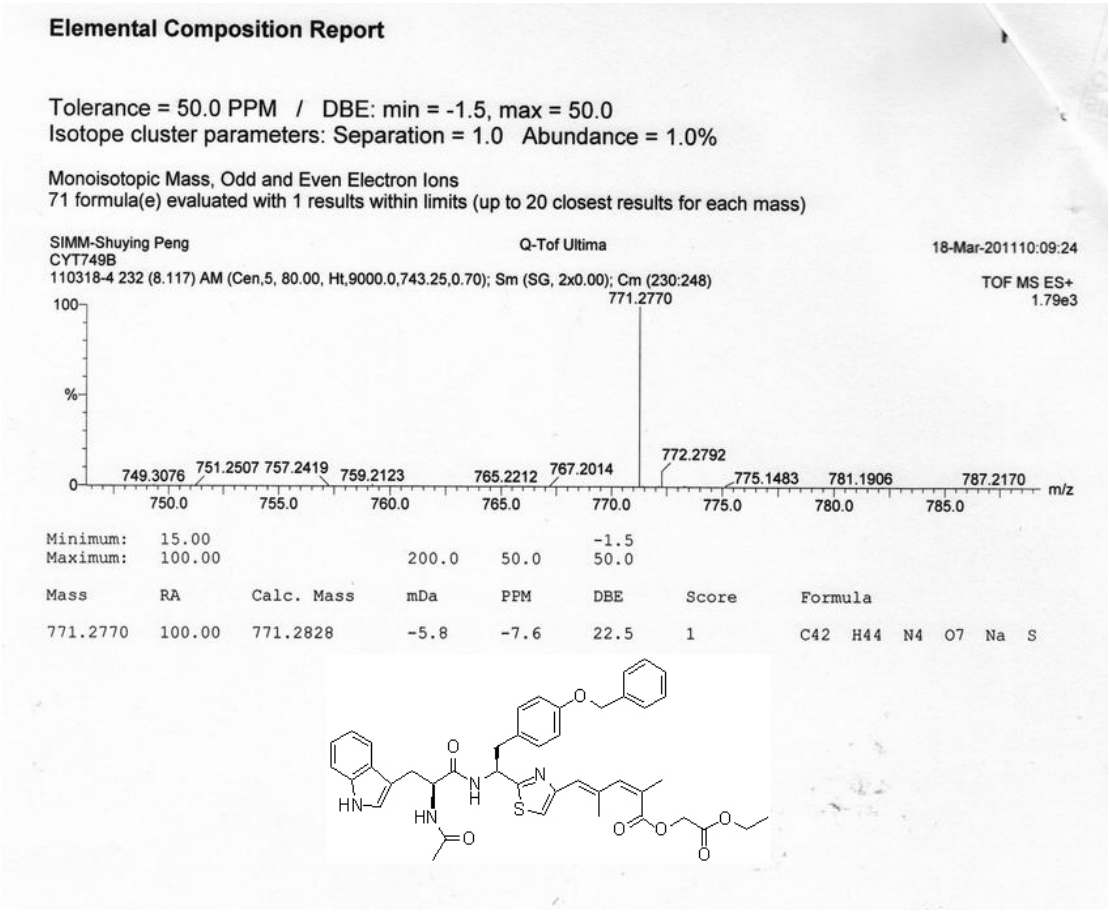


Figure S5 High resolution mass spectrum of compound **12d**.

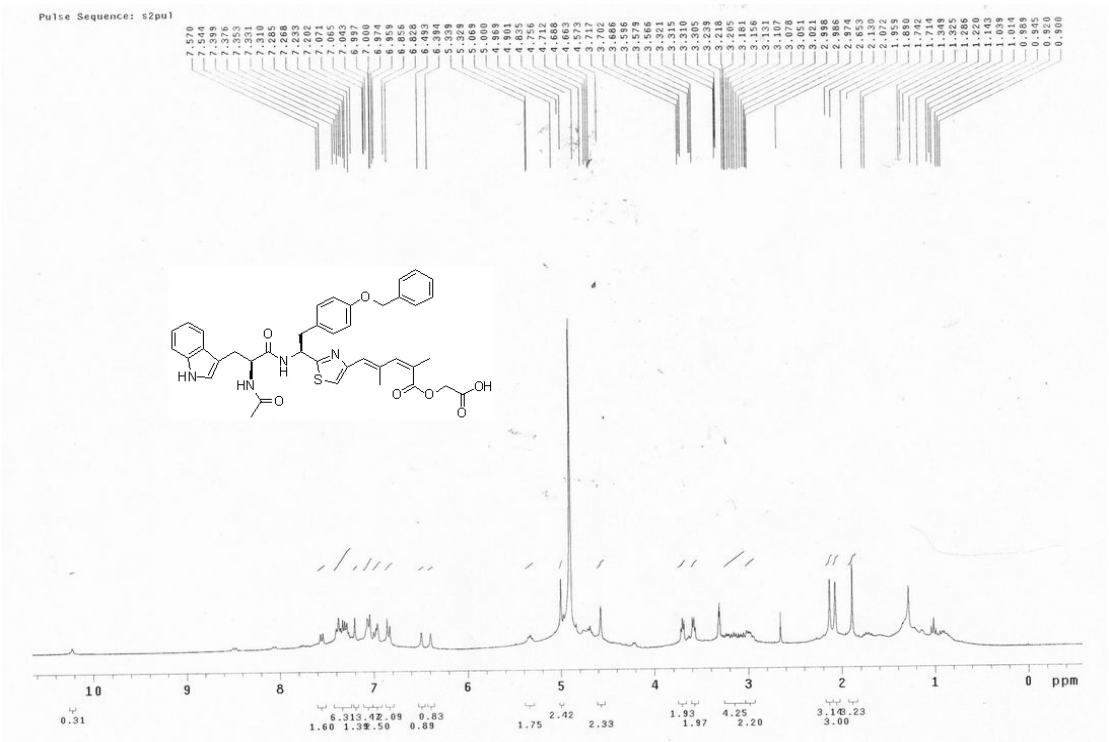


Figure S6 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **12e**.

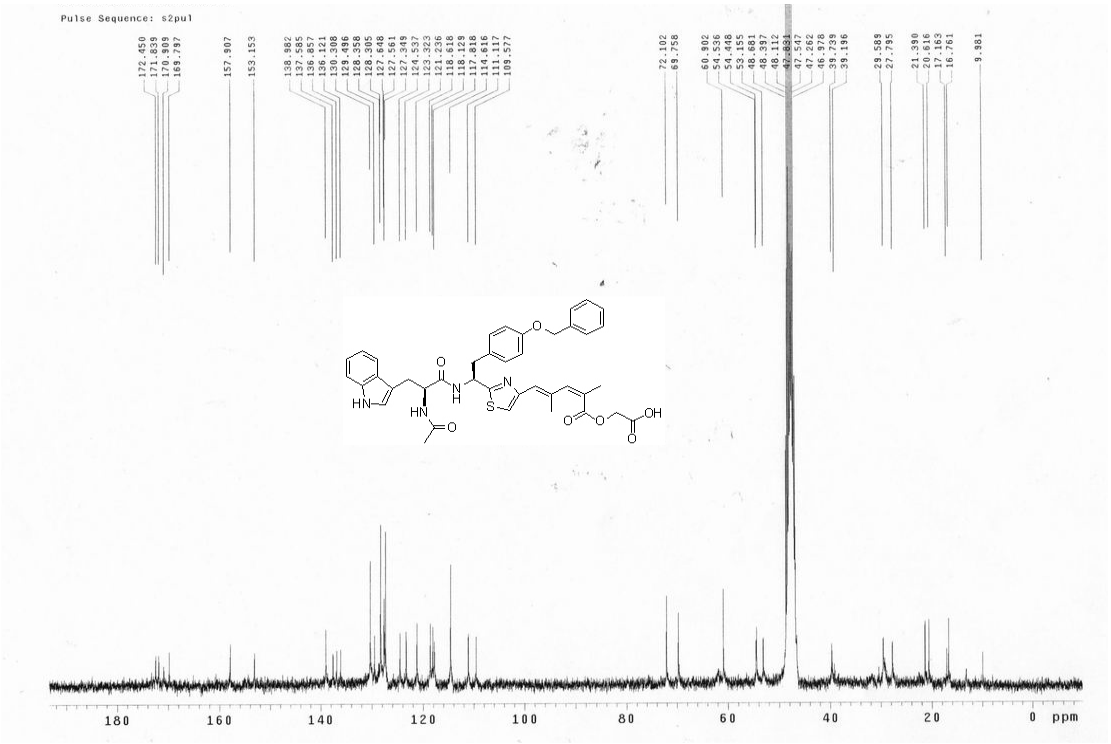


Figure S7 ^{13}C NMR (300 MHz, $CDCl_3$) spectrum of compound **12e**.

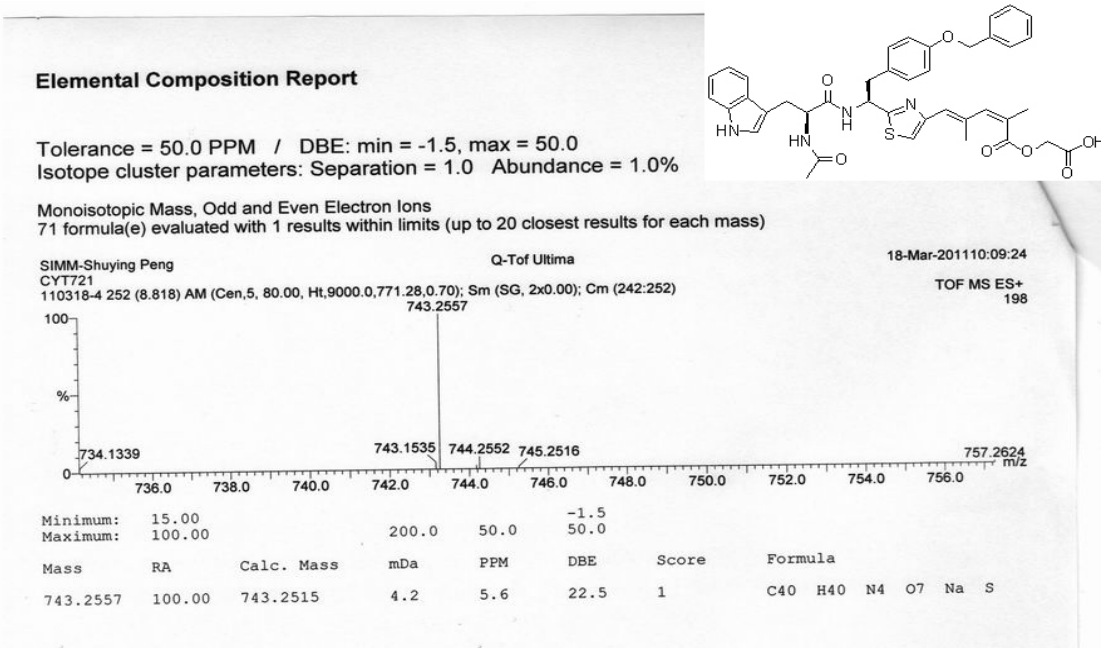


Figure S8 High resolution mass spectrum of compound **12e**.

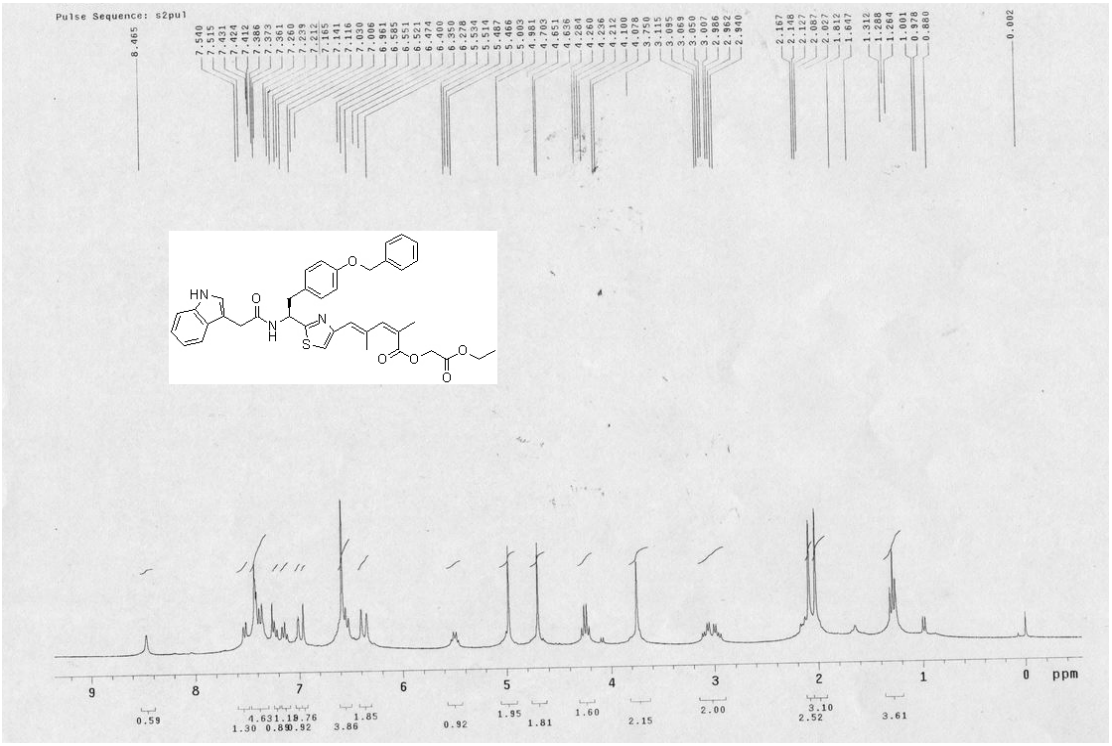


Figure S9 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **12f**.

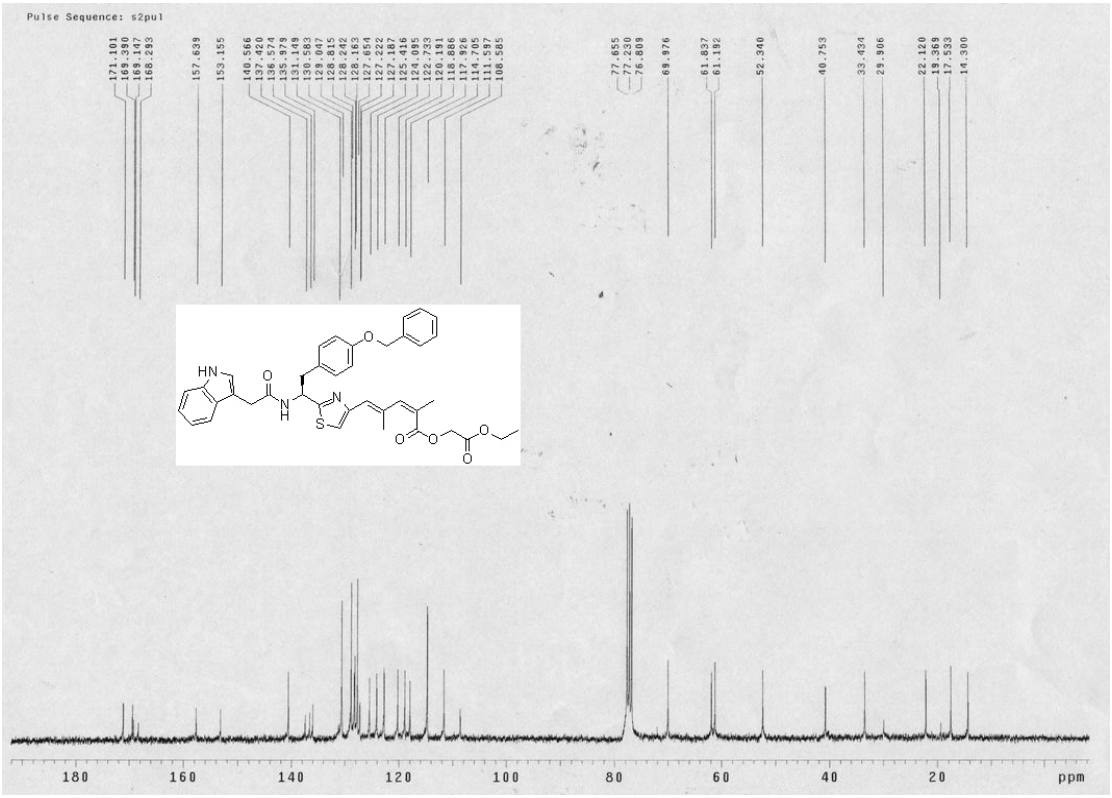


Figure S10 ^{13}C NMR (300 MHz, $CDCl_3$) spectrum of compound **12f**

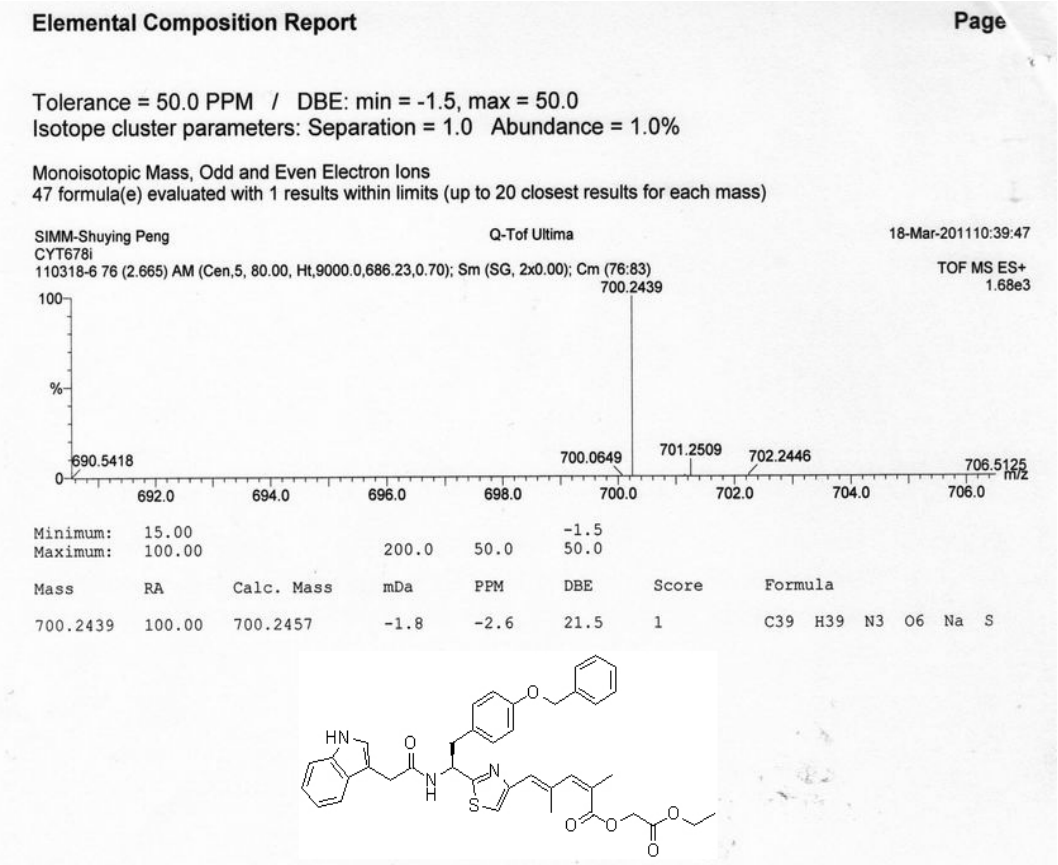


Figure S11 High resolution mass spectrum of compound **12f**.

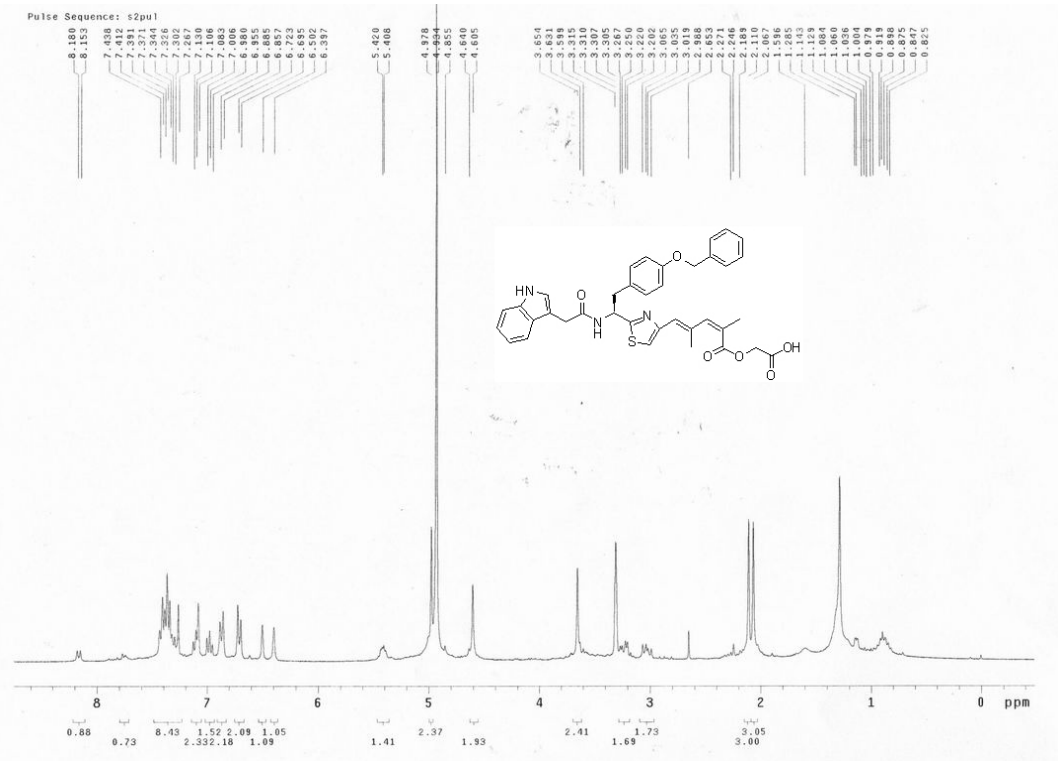


Figure S12 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **12g**.

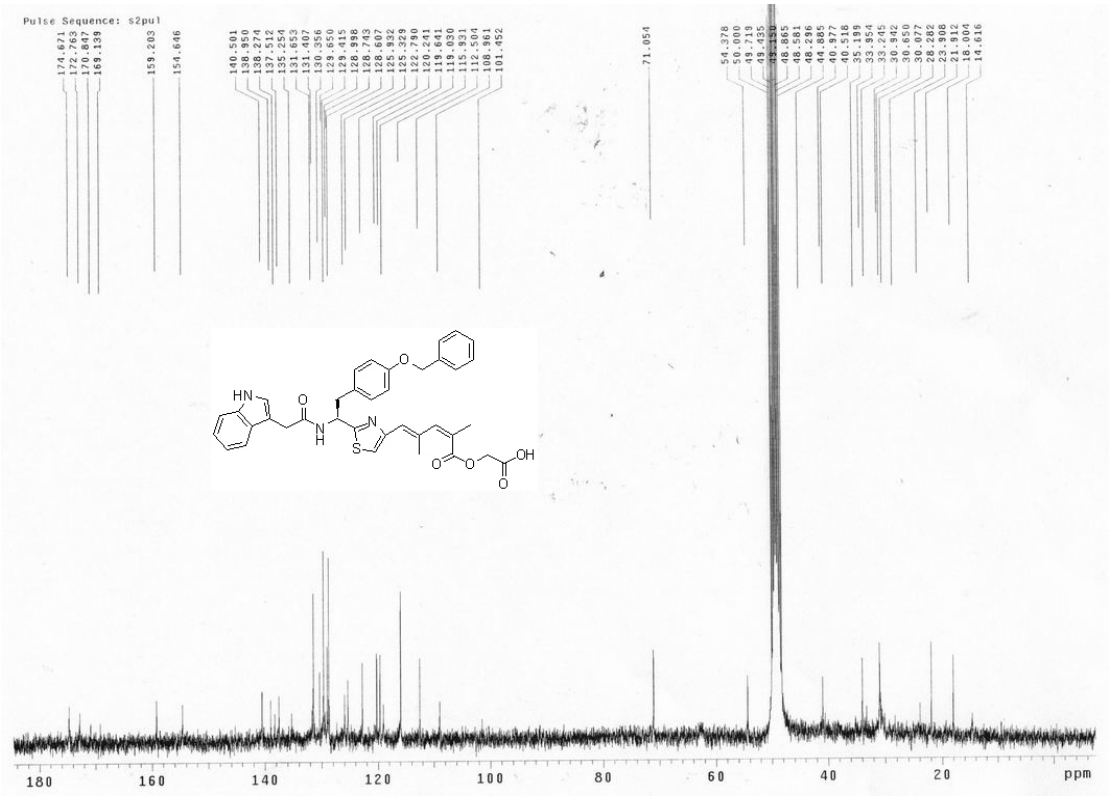


Figure S13 ^{13}C NMR (300 MHz, $CDCl_3$) spectrum of compound **12g**.

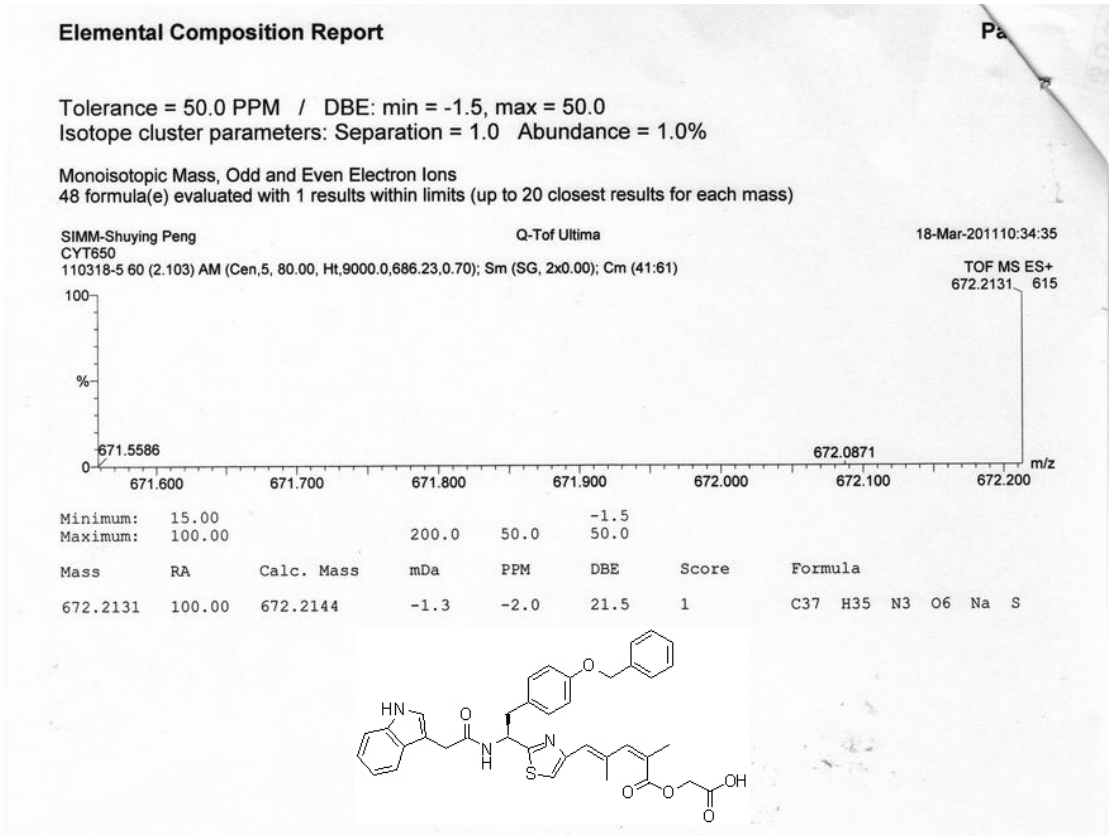


Figure S14 High resolution mass spectrum of compound **12g**.

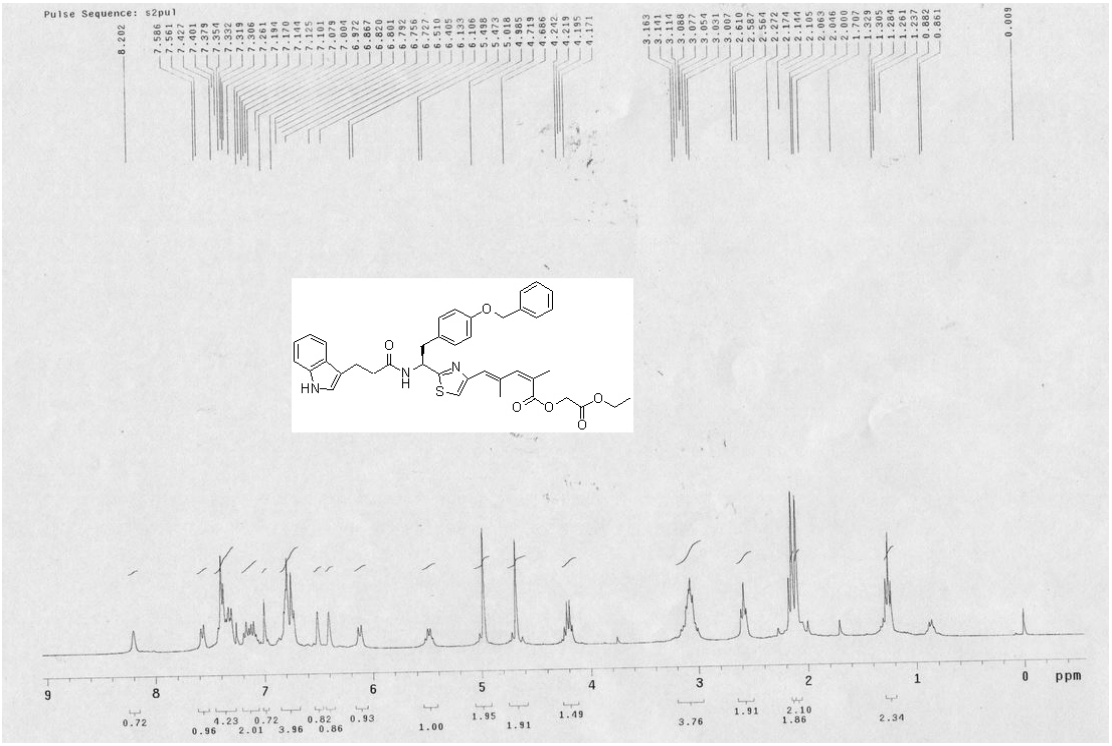


Figure S15 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **12h**.

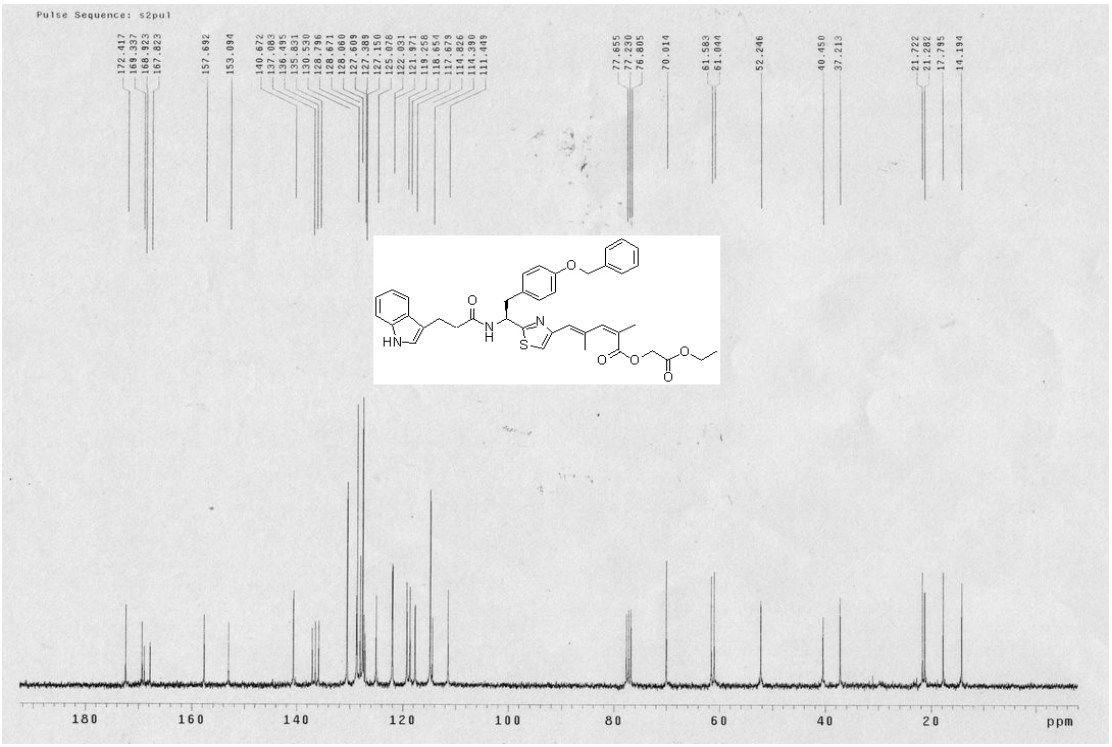


Figure S16 ^{13}C NMR (300 MHz, $CDCl_3$) spectrum of compound **12h**.

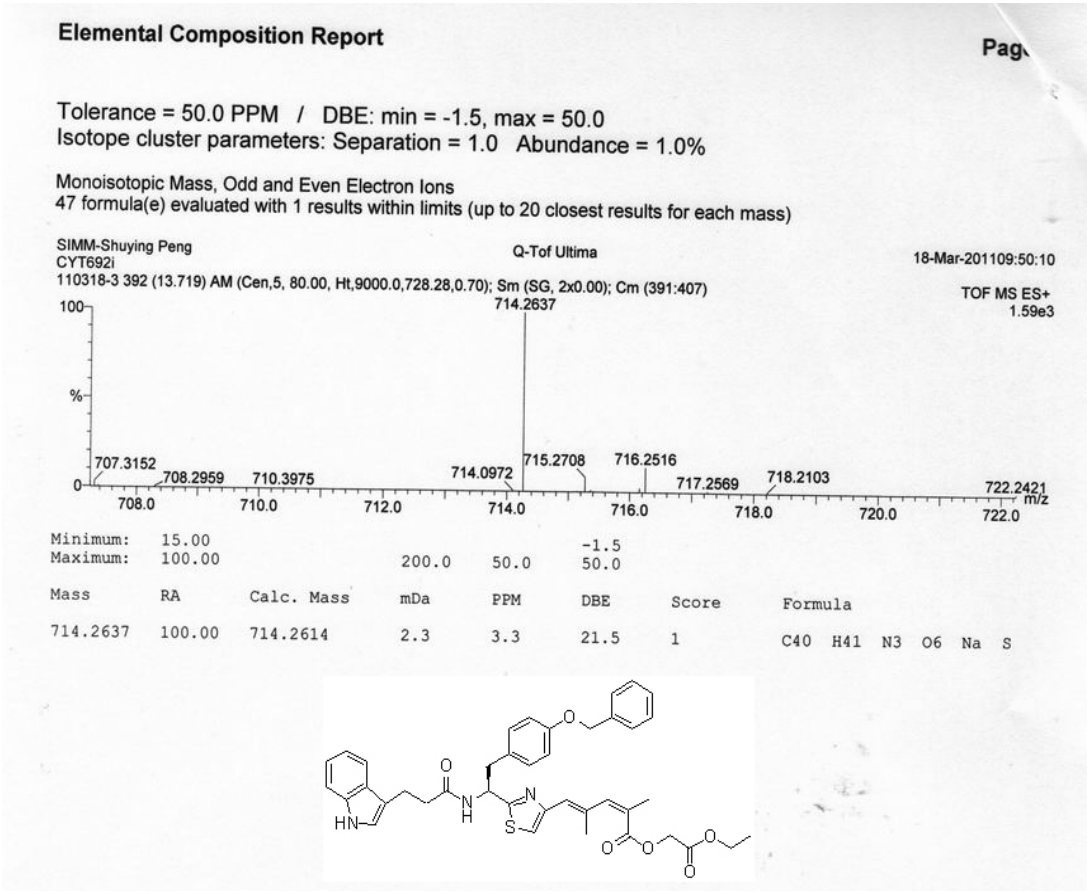


Figure S17 High resolution mass spectrum of compound 12**h**.

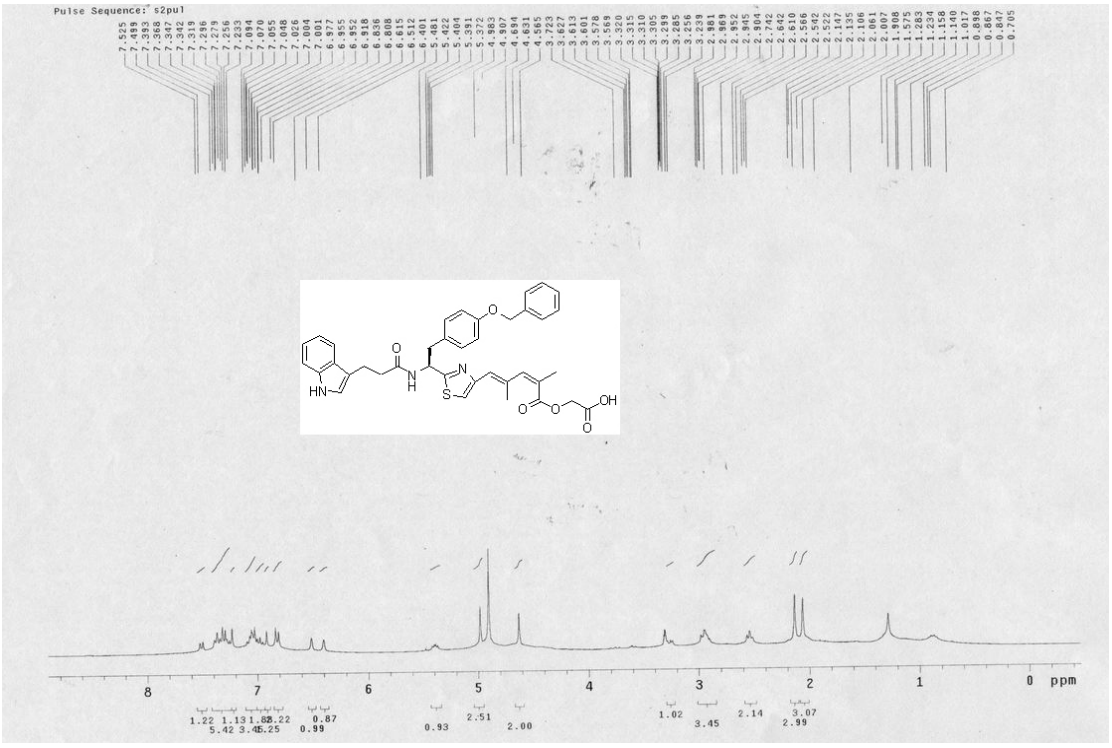


Figure S18 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **12i**.

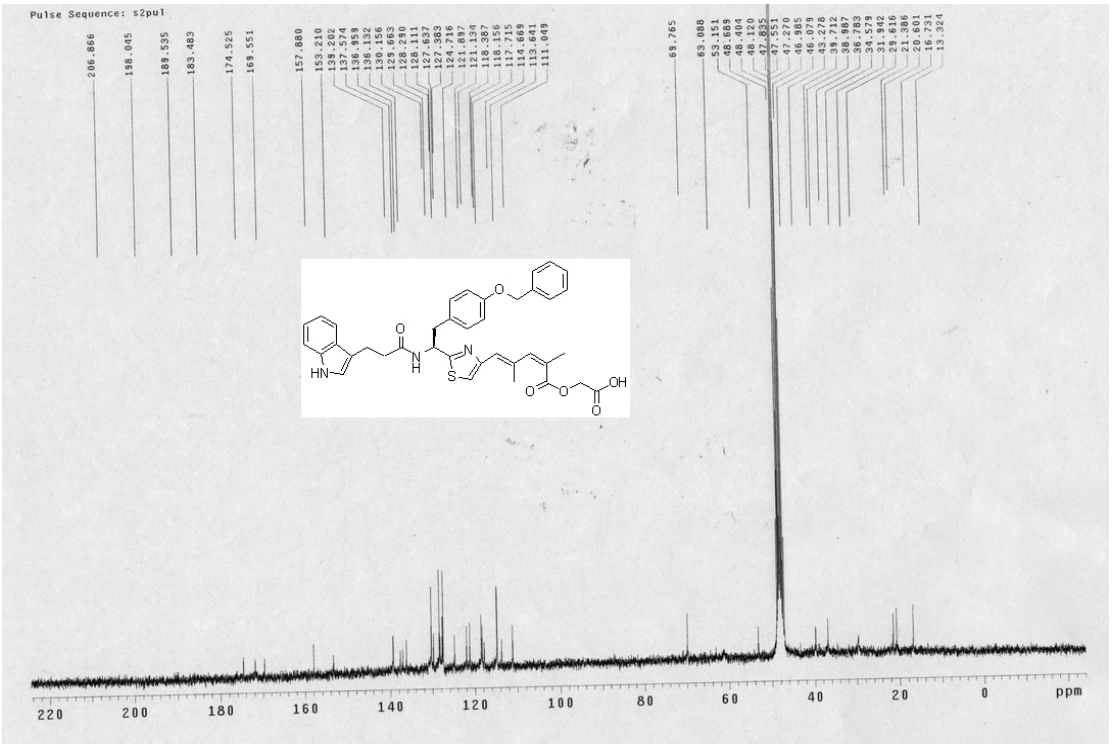


Figure S19 ^{13}C NMR (300 MHz, $CDCl_3$) spectrum of compound **12i**.

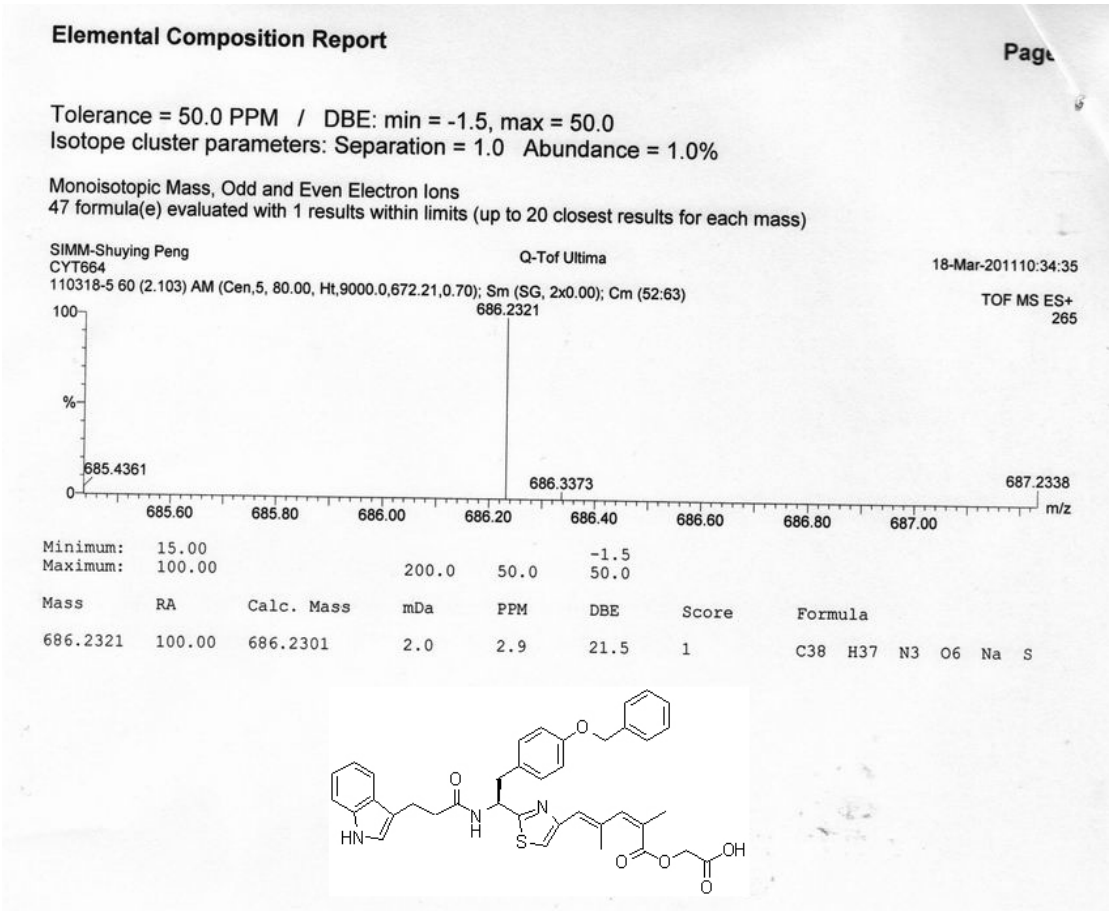


Figure S20 High resolution mass spectrum of compound **12i**.

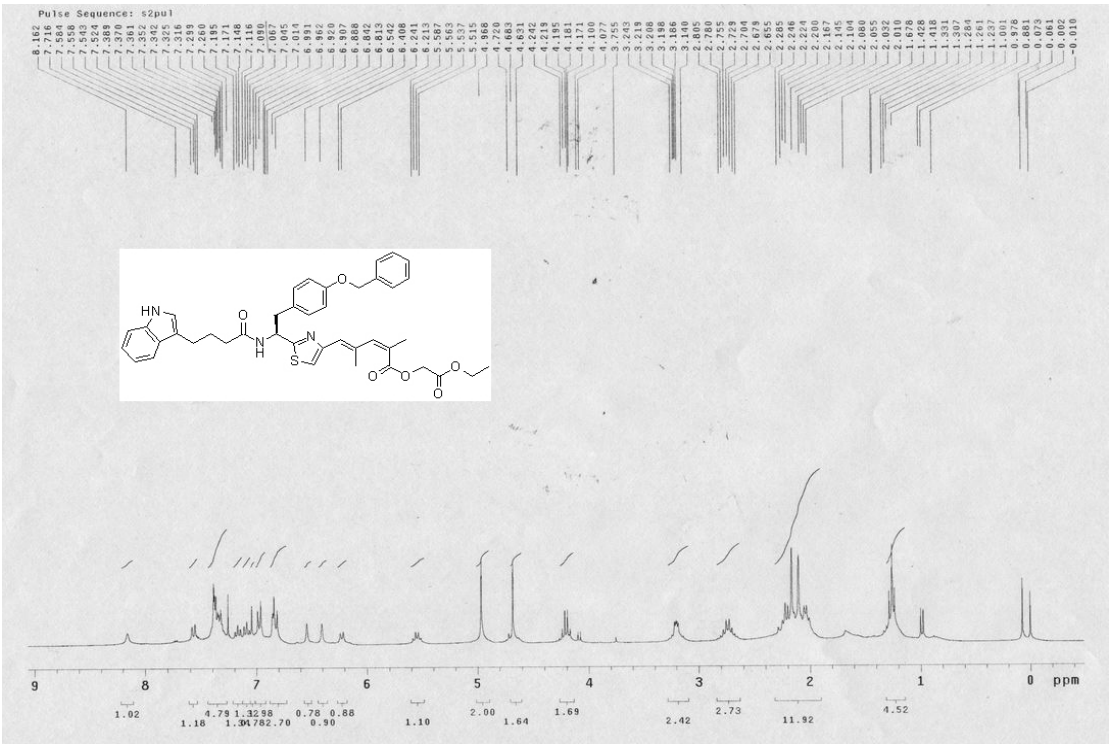


Figure S21 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **12j**.

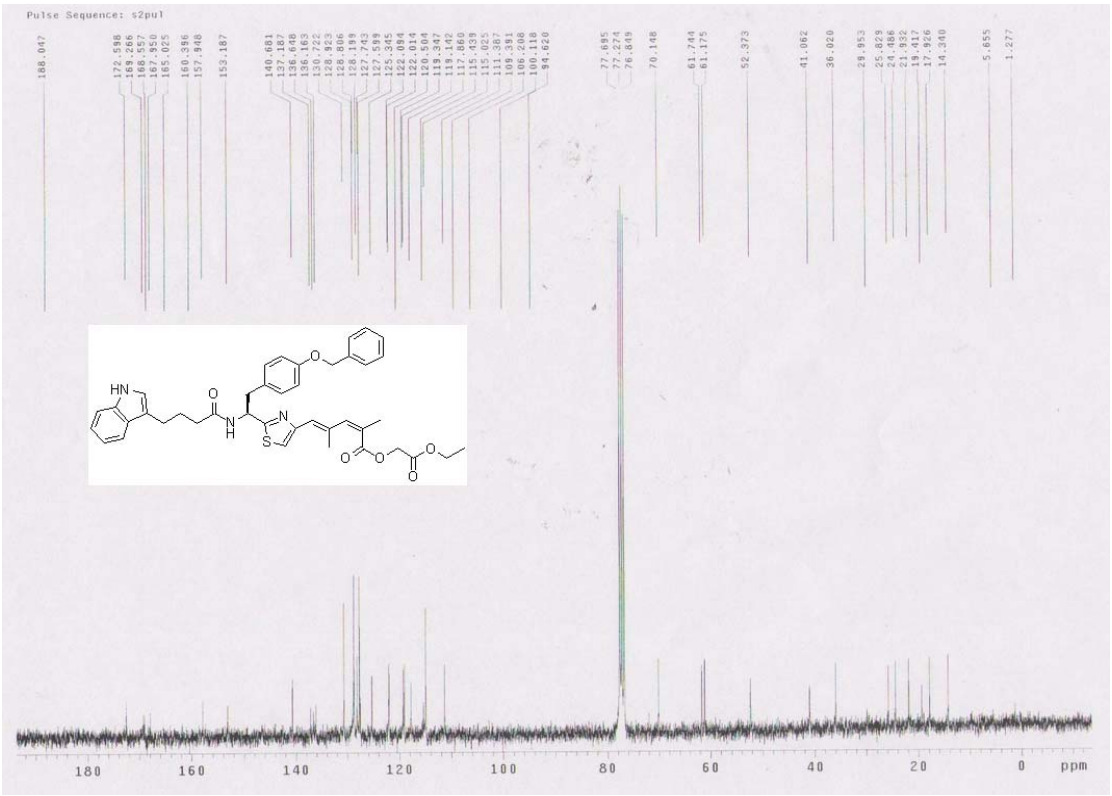


Figure S22 ^{13}C NMR (300 MHz, $CDCl_3$) spectrum of compound **12j**.

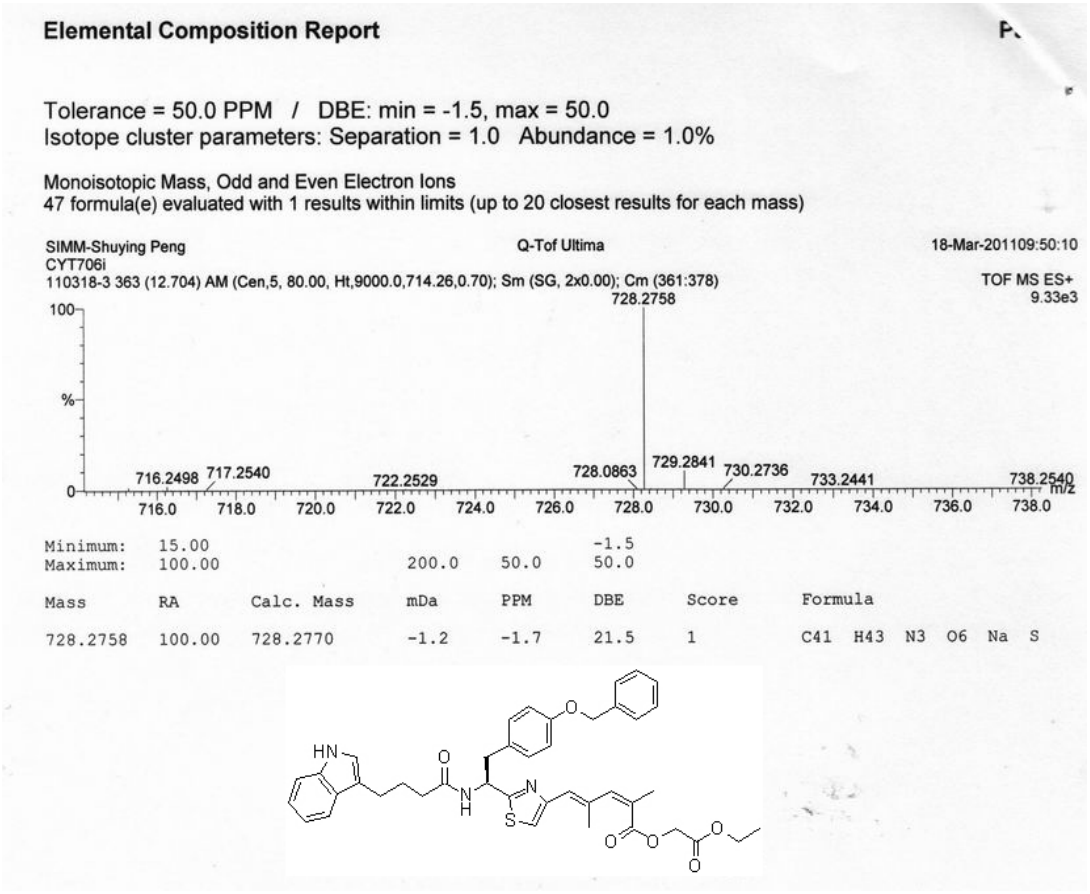


Figure S23 High resolution mass spectrum of compound 12**j**.

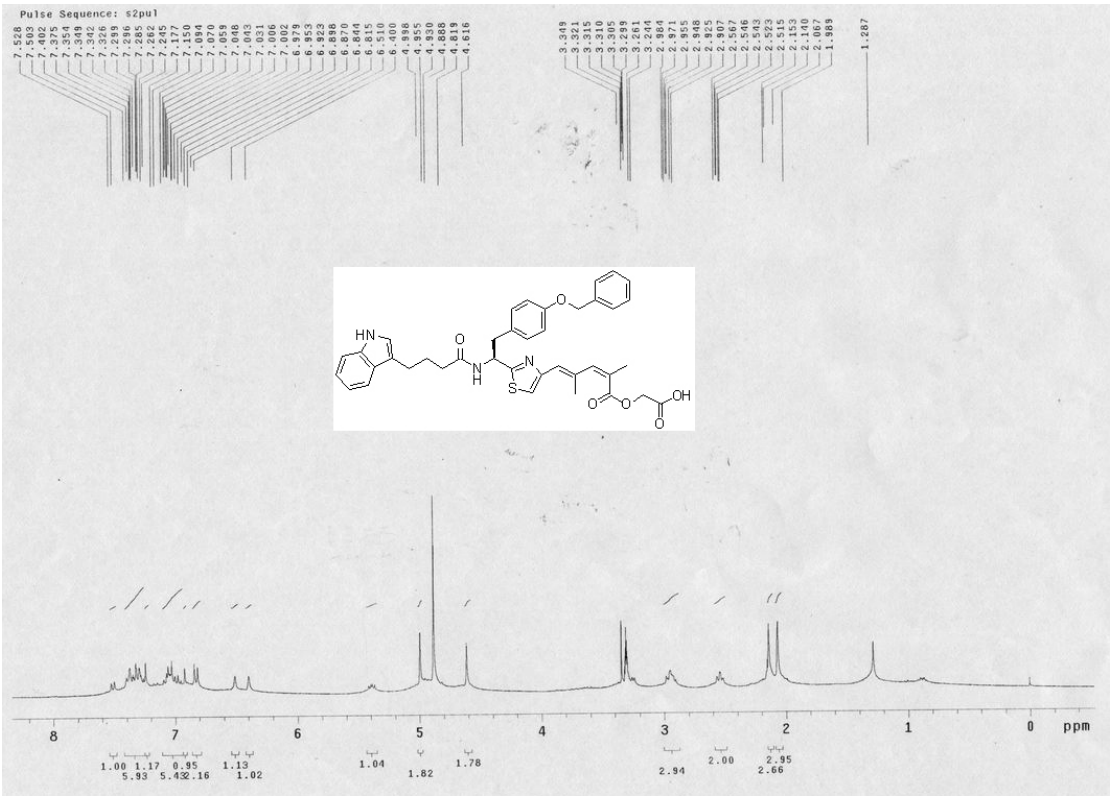


Figure S24 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **12k**.

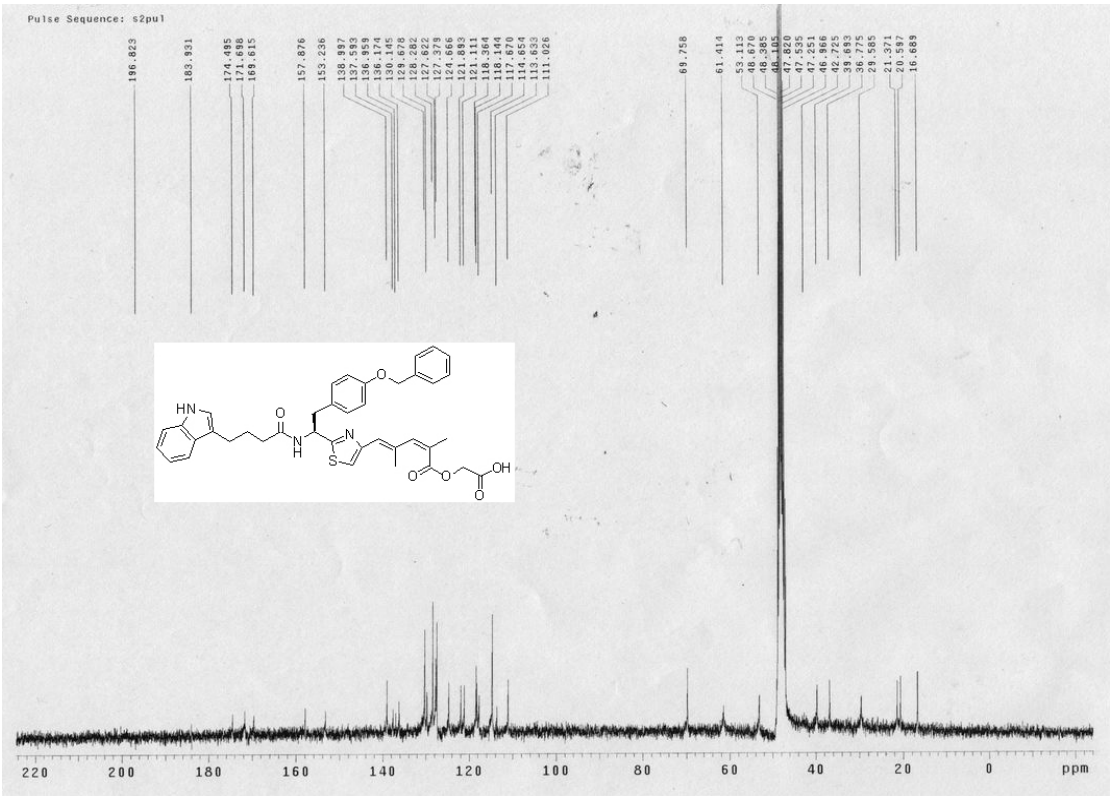


Figure S25 ^{13}C NMR (300 MHz, $CDCl_3$) spectrum of compound **12k**.

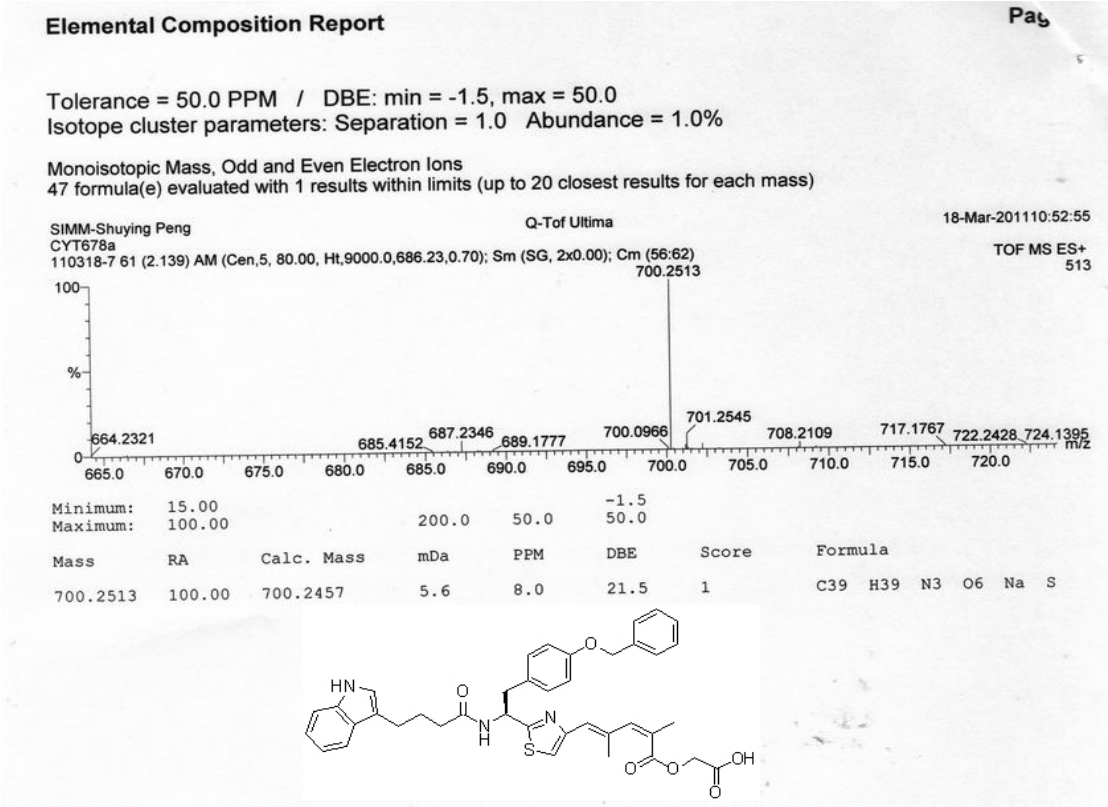
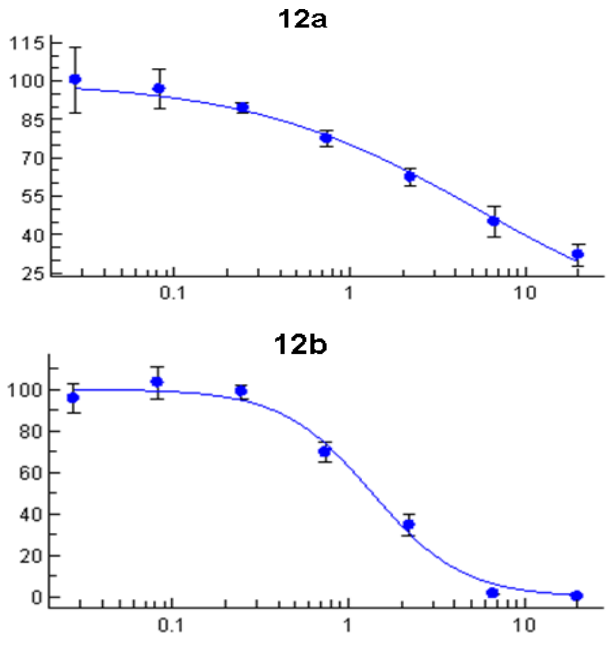
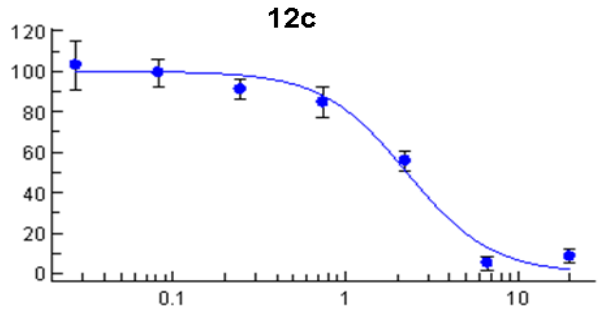
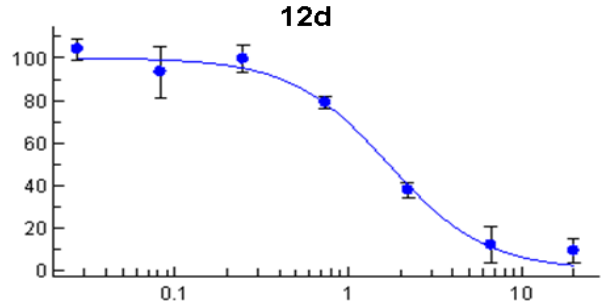


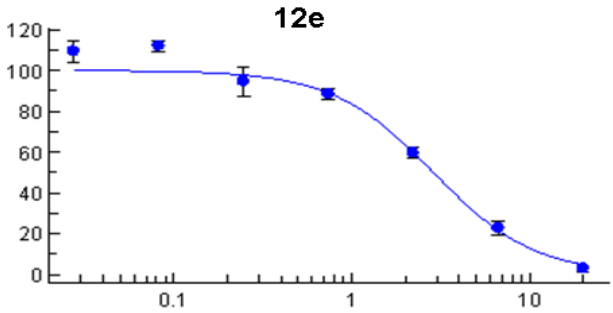
Figure S26 High resolution mass spectrum of compound **12k**.

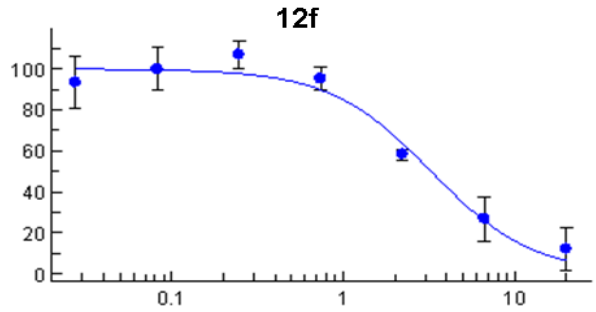
Diagrams of IC_{50} curves

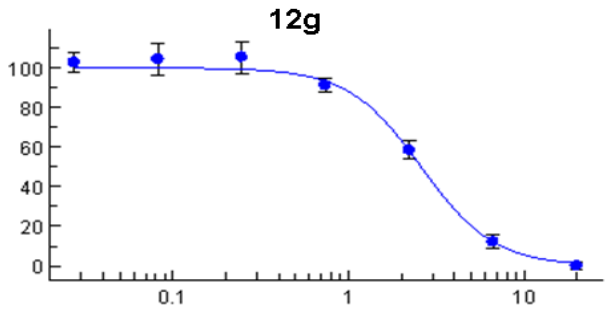


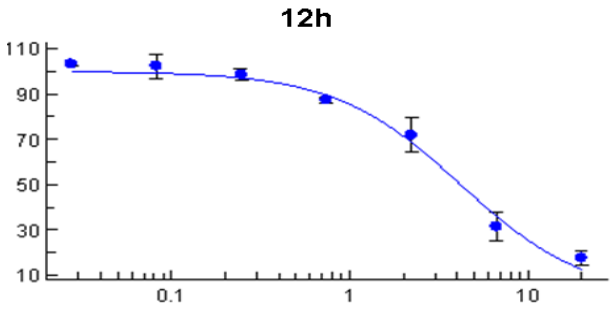


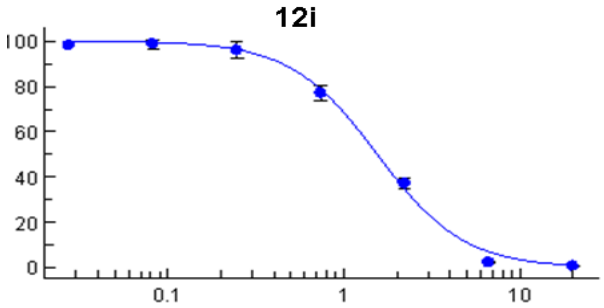


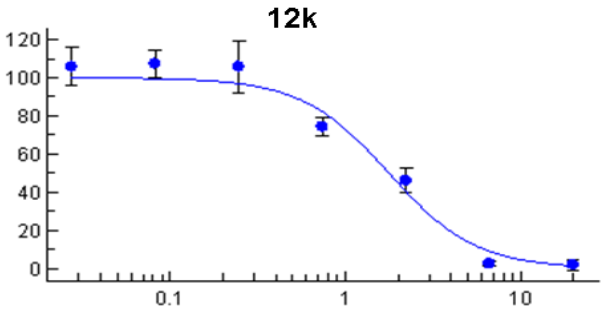












Reference for supporting information

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S2 Y.-N. Zhang, W. Zhang, D. Hong, L. Shi, Q. Shen, Y.-Y. Li, J. Li, L.-H. Hu,

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S3 S. Liu, Y.-M. Cui, F.-J. Nan, *Org. Lett.*, 2008, **10**, 3765.