Supporting Information

Design, Synthesis and Structure-Activity Relationships of Indoline-Based Kelch-like ECH Associated Protein 1-Nuclear Factor (Erythroid-derived 2)-like 2 (Keap1-Nrf2) Protein-Protein Interaction Inhibitors

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S1. Characterization of the Representative Intermediates.

2,4,6-trimethyl-*N*-(o-tolyl)benzenesulfonamide (20). To a solution of 2-nitrotoluene (412 mg, 3.0 mmol) in methanol (15 mL) was added Pd/C. The reaction mixture was stirred under hydrogen for 2 hours. The solution was filtered to remove the catalyst. The filtrate was concentrated under reduced pressure to give the gray oil and dissolved in toluene (10 mL). 2-mesitylenesulfonyl chloride (780 mg, 3.6 mmol) and pyridine (355 mg, 4.5 mmol) was added to the solution. The reaction mixture was stirred at 80 °C for 4 h under nitrogen. After cooling to room temperature, reaction mixture was then diluted in 40 mL of petroleum ether. After filtration, the solid was

collected and washed with 1 M hydrochloric acid. Purification by silica gel column chromatography afforded the compound **20** as the gray solid, yield 72%; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.43 (d, J = 8.1 Hz, 1H), 6.99 (s, 1H), 6.94 – 6.88 (m, 2H), 6.78 (ddd, J = 8.1, 2.2, 0.9 Hz, 1H), 6.42 (s, 1H), 2.61 (s, 6H), 2.31 (s, 6H); ESI-MS *m/z*: 299.1 $[M+H]^+$.

methyl *N*-(mesitylsulfonyl)-*N*-(o-tolyl) glycinate (21). To a solution of **20** (580 mg, 2.0 mmol) in DMF (5 mL) was added K_2CO_3 (415 mg, 3.0 mmol) followed by ethyl bromoacetate (460 mg, 3.0 mmol). After 2 h stirring at room temperature, the reaction mixture was then diluted in 30 mL of water and quenched with 2 M hydrochloric acid to pH 5. The crude product was obtained through filtration. Purification by silica gel column chromatography afforded the compound **21** as the white solid, yield 74%, ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.42 (s, 1H), 6.97 (t, *J* = 7.7 Hz, 1H), 6.90 (s, 2H), 6.79 (dd, *J* = 8.0, 2.3 Hz, 1H), 6.72 (t, *J* = 2.3 Hz, 1H), 4.42 (s, 2H), 3.82 (s, 3H), 2.41 (s, 6H), 2.29 (s, 3H), 2.11 (s, 3H); ESI-MS *m/z*: 362.1 $[M+H]^+$.

4-methyl-3-nitrophenyl trifluoromethanesulfonate (23a). To a solution of commercial **22a** (460 mg, 3.0 mmol) in DCM (20 mL), Et_3N (450 mg, 4.5 mmol) and Tf_2O (750 mg, 3.6 mmol) was added, and the reaction mixture was stirred for 2 h at room temperature. After the completion of the reaction monitored by TLC, the reaction mixture was extracted with EtOAc (×3). The combined organic extracts were washed with saturated $NaHCO_3$ solution, H_2O and saturated NaCl solution, then dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography provided the compound **23a**, yield 66%; ^{1}H NMR (300 MHz,

Chloroform-*d*) δ 7.96 (s, 1H), 7.03 (dd, *J* = 5.2, 3.0 Hz, 2H), 2.28 (s, 3H); ESI-MS *m/z*: 285.9 $[M+H]^+$.

***N*-(3-methoxyphenyl)-4-methyl-3-nitroaniline (24a).** A round bottomed flask was charged with 28.0 mg (0.12 mmol) of $Pd(AcO)_2$, 69.0 mg (0.12 mmol) of Xantphos, and 1.6 g (5.0 mmol) of $CsCO_3$ under a dry nitrogen atmosphere. The solid materials were suspended in 15 mL of toluene. **23a** (710 mg, 2.5 mmol) and 3-methoxyaniline (256.0 mg, 2.1 mmol) was dissolved in 5 mL of toluene and added to the flask. After heating at 100 °C for 12 h under nitrogen atmosphere, the resulting suspension was cooled to room temperature and filtered through a pad of Celite eluting with ethyl acetate, and the inorganic salts were removed. The solvent was evaporated and the crude residue was purified by silica gel chromatography, using n-hexane/EtOAc as eluent to provide the compound **24a**, yield 65%; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.71 – 7.66 (m, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 7.20 (s, 2H), 6.68 (ddd, *J* = 7.9, 2.2, 0.9 Hz, 1H), 6.64 (t, *J* = 2.3 Hz, 1H), 6.58 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1H), 5.83 (s, 1H), 3.81 (s, 3H), 2.53 (s, 3H); ESI-MS *m/z*: 259.1 $[M+H]^+$.

***N*-(5-((3-methoxyphenyl)amino)-2-methylphenyl)-2,4,6-trimethylbenzenesulfonamide (26a).** To a solution of **24a** (516 mg, 2.0 mmol) in methanol (15 mL) was added Pd/C. The reaction mixture was stirred under hydrogen for 2 hours. The solution was filtered to remove the catalyst. The filtrate was concentrated under reduced pressure to give the gray oil. The crude product, **25a**, was used without further purification. 2-mesitylenesulfonyl chloride (525 mg, 2.4 mmol) and pyridine (237 mg, 3.0 mmol) was added to the solution of toluene (10 mL) and **25a**. The reaction

mixture was stirred at 80 °C for 4 h under nitrogen. After cooling to room temperature, reaction mixture was then diluted in 40 mL of petroleum ether. After filtration, the solid was collected and washed with 1 M hydrochloric acid. The crude residue was purified by silica gel chromatography to provide the the gray solid **26a**, yield 50%; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.21 (s, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.06 (t, *J* = 8.1 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 3H), 6.90 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.58 (t, *J* = 2.2 Hz, 1H), 6.49 (dd, *J* = 7.8, 2.0 Hz, 1H), 6.37 (dd, *J* = 8.0, 2.3 Hz, 1H), 2.28 (s, 6H), 2.24 (s, 3H), 1.69 (s, 3H); ESI-MS *m/z*: 411.2 $[M+H]^+$.

methyl *N*-(mesitylsulfonyl)-*N*-(5-((3-methoxyphenyl)amino)-2-methylphenyl)glycinate (27a). To a solution of **26a** (615 mg, 1.5 mmol) in DMF (5 mL) was added K_2CO_3 (415 mg, 3.0 mmol) followed by ethyl bromoacetate (306 mg, 2.0 mmol). After 2 h stirring at room temperature, the reaction mixture was then diluted in 30 mL of water and quenched with 2 M hydrochloric acid to pH 5. The crude product was obtained through filtration. The crude residue was purified by silica gel chromatography to provide the the white solid **27a**, yield 78%; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.42 (s, 1H), 7.21 – 7.16 (m, 1H), 6.96 (t, *J* = 7.9 Hz, 1H), 6.90 (s, 2H), 6.79 (dd, *J* = 8.0, 2.3 Hz, 1H), 6.78 (t, *J* = 2.3 Hz, 1H), 6.69 (dd, *J* = 7.9, 1.0 Hz, 1H), 6.53 (dd, *J* = 8.0, 2.3 Hz, 1H), 4.50 (s, 2H), 3.82 (s, 3H), 3.72 (s, 3H), 2.41 (s, 6H), 2.29 (s, 6H). ESI-MS *m/z*: 483.2 $[M+H]^+$.

1-(3-methoxyphenyl)-4-nitro-1H-indole (30). To a solution of **28** (2.0 g, 12.3 mmol) and **29** (2.8 g, 18.5 mmol) in DCM (20 ml) was added 2 equiv of $Cu(OAc)_2$ and 2 equiv of triethylamine. The reaction mixture was stirring at room temperature for 24 hours, and then was concentrated

and the product **30** was purified by silica gel column chromatography (petroleumether/ethyl acetate = 20:1 to 2:1 v/v) to afford 2.9 g (70%) of desired product as light yellow solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.20 (dd, J = 8.0, 0.8 Hz, 1H), 7.85 (dt, J = 8.2, 0.9 Hz, 1H), 7.59 (d, J = 3.3 Hz, 1H), 7.51 – 7.42 (m, 2H), 7.32 (d, J = 8.1 Hz, 1H), 7.08 (dt, J = 7.9, 1.2 Hz, 1H), 7.00 (dq, J = 8.1, 1.2 Hz, 2H), 3.90 (s, 3H). ESI-MS *m/z*: 269.1 $(M+H)^+$.

1-(3-methoxyphenyl)-4-nitroindoline (31). To a solution of **30** (1.0 g, 3.7 mmol) and trifluoroacetic acid (6 ml) in DCM (20 ml) was added 4 equiv of sodium cyanoborohydride portionwise at 0 °C. After the addition was complete, the reaction mixture was stirring at room temperature for 12 hours, and then was diluted with saturated $NaHCO_3$. The organic layer was extracted and washed with 2 x 20 ml of brine followed by 2 x 20 ml of H_2O. The organics were dried over anhydrous Na_2SO_4 and crude material was purified by flash chromatography (petroleumether/ethyl acetate = 20:1 to 2:1 v/v) to afford 0.66 g (66%) of the desired product as a red solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.20 (d, J = 8.0 Hz, 1H), 6.93 (s, 1H), 6.90 - 6.85 (m, 2H), 6.77 (ddd, J = 8.3, 2.2, 0.9 Hz, 1H), 6.57 - 6.53 (m, 1H), 6.42 (s, 1H), 6.35 (dd, J = 6.8, 2.1 Hz, 1H), 3.91 (t, J = 8.5 Hz, 2H), 3.81 (s, 3H), 2.97 (t, J = 8.4 Hz, 2H), 2.62 (s, 6H), 2.32 (s, 3H); ESI-MS *m/z*: 271.1 $(M+H)^+$.

***N*-(1-(3-methoxyphenyl)indolin-4-yl)-2,4,6-trimethylbenzenesulfonamide (33a).** To a solution of **31** (540 mg, 2.0 mmol) in methanol (15 mL) was added Pd/C. The reaction mixture was stirred under hydrogen for 2 hours. The solution was filtered to remove the catalyst. The filtrate was concentrated under reduced pressure to give the gray oil. The crude product, **32**, was

used without further purification. 2-mesitylenesulfonyl chloride (525 mg, 2.4 mmol) and pyridine (237 mg, 3.0 mmol) was added to the solution of toluene (10 mL) and **32**. The reaction mixture was stirred at 80 °C for 4 h under nitrogen. After cooling to room temperature, reaction mixture was then diluted in 40 mL of petroleum ether. After filtration, the solid was collected and washed with 1 M hydrochloric acid. Recrystallization from acetonitrile gave the gray solid 532 mg, yield 63%; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.24 (d, J = 8.2 Hz, 1H), 6.96 (s, 2H), 6.95 – 6.90 (m, 2H), 6.79 (ddd, J = 8.1, 2.2, 0.9 Hz, 1H), 6.74 (t, J = 2.3 Hz, 1H), 6.57 – 6.53 (m, 1H), 6.42 (s, 1H), 6.35 (dd, J = 6.8, 2.1 Hz, 1H), 3.92 (t, J = 8.5 Hz, 2H), 3.82 (s, 3H), 2.98 (t, J = 8.4 Hz, 2H), 2.61 (s, 6H), 2.31 (s, 3H). ESI-MS *m/z*: 423.1 $[M+H]^+$.

methyl *N*-(mesitylsulfonyl)-*N*-(1-(3-methoxyphenyl)indolin-4-yl)glycinate (34a). To a solution of **33a** (630 mg, 1.5 mmol) in DMF (5 mL) was added K_2CO_3 (415 mg, 3.0 mmol) followed by ethyl bromoacetate (306 mg, 2.0 mmol). After 2 h stirring at room temperature, the reaction mixture was then diluted in 30 mL of water and quenched with 2 M hydrochloric acid to pH 5. The crude product was obtained through filtration. Recrystallization from ethyl acetate/nhexane gave the **34a** as a white solid 550 mg, yield 74%; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.22 (s, 1H), 7.11 – 7.06 (m, 1H), 6.99 (t, *J* = 7.9 Hz, 1H), 6.90 (s, 2H), 6.78 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.72 (t, *J* = 2.3 Hz, 1H), 6.68 (dd, *J* = 7.9, 1.0 Hz, 1H), 6.54 (dd, *J* = 8.0, 2.3 Hz, 1H), 4.52 (s, 2H), 3.82 (s, 3H), 3.75 (t, *J* = 8.4 Hz, 2H), 3.71 (s, 3H), 2.82 (t, *J* = 8.3 Hz, 2H), 2.41 (s, 6H), 2.29 (s, 3H). ESI-MS *m/z*: 493.2 $[M+H]^+$.

5-nitro-1,2,3,4-tetrahydroquinoline (36). To a solution of **35** (1.0 g, 5.7 mmol) in chloroform (20 ml) was added $Fe(OTf)_2$ (20 mg, 1 mol%) and diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (Hantzsch ester, 3.6 g , 14.2 mmol). After the addition was complete, the reaction mixture was stirring at 40 °C under nitrogen for 4 hours, and then was diluted with H_2O. The organic layer was extracted and washed with 2 x 20 ml of brine followed by 2 x 20 ml of H_2O. The organics were dried over anhydrous Na_2SO_4 and crude material was purified by flash chromatography (petroleumether/ethyl acetate = 40:1 to 20:1 v/v) to afford 608 mg (60%) of the desired product as a yellow solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.14 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.65 (dd, *J* = 7.9, 1.3 Hz, 1H), 4.23 (s, 1H), 3.34 (t, *J* = 5.5 Hz, 2H), 2.94 (t, *J* = 6.5 Hz, 2H), 1.98 – 1.87 (m, 2H); ESI-MS *m/z*: 179.1 $(M+H)^+$.

1-(3-methoxyphenyl)-5-nitro-1,2,3,4-tetrahydroquinoline (37). To a solution of **36** (890 g, 5.0 mmol) and 3-methoxybenzeneboronic acid (910 mg, 6.0 mmol) in DCM (20 ml) was added 2 equiv of $Cu(OAc)_2$ and 2 equiv of triethylamine. The reaction mixture was stirring at room temperature for 24 hours, and then was concentrated and the product **37** was purified by silica gel column chromatography (petroleumether/ethyl acetate = 40:1 to 10:1 v/v) to afford 780 mg (55%) of desired product as light yellow solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.36 – 7.30 (m, 1H), 7.18 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.99 (t, *J* = 8.2 Hz, 1H), 6.88 (dd, *J* = 8.4, 1.3 Hz, 1H), 6.82 (ddd, *J* = 7.9, 1.9, 1.0 Hz, 1H), 6.77 (tp, *J* = 2.5, 1.3 Hz, 2H), 3.82 (s, 3H), 3.68 – 3.62 (m, 2H), 3.04 (t, *J* = 6.5 Hz, 2H), 2.10 – 2.01 (m, 2H); ESI-MS *m/z*: 285.1 $(M+H)^+$.

***N*-(1-(3-methoxyphenyl)-1,2,3,4-tetrahydroquinolin-5-yl)-2,4,6-trimethylbenzenesulfonamide (39).** To a solution of **37** (568 mg, 2.0 mmol) in methanol (15 mL) was added Pd/C. The reaction mixture was stirred under hydrogen for 2 hours. The solution was filtered to remove the catalyst. The filtrate was concentrated under reduced pressure to give the gray oil. The crude product, **38**, was used without further purification. 2-mesitylenesulfonyl chloride (525 mg, 2.4 mmol) and pyridine (237 mg, 3.0 mmol) was added to the solution of toluene (10 mL) and **38**. The reaction mixture was stirred at 80 °C for 4 h under nitrogen. After cooling to room temperature, reaction mixture was then diluted in 40 mL of petroleum ether. After filtration, the solid was collected and washed with 1 M hydrochloric acid. Recrystallization from acetonitrile gave the gray solid 453 mg, yield 52%; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.25 (d, J = 8.0 Hz, 1H), 6.99 (s, 2H), 6.96 – 6.91 (m, 2H), 6.82 (ddd, J = 8.0, 2.2, 0.9 Hz, 1H), 6.76 (t, J = 2.3 Hz, 1H), 6.56 – 6.52 (m, 1H), 6.41 (s, 1H), 6.36 (dd, J = 6.8, 2.1 Hz, 1H), 3.82 (s, 3H), 3.67 – 3.60 (m, 2H), 3.03 (t, *J* = 6.5 Hz, 2H), 2.62 (s, 6H), 2.30 (s, 3H), 2.11 – 2.00 (m, 2H). ESI-MS *m/z*: 437.2 $[M+H]^+$.

methyl *N*-(mesitylsulfonyl)-*N*-(1-(3-methoxyphenyl)-1,2,3,4-tetrahydroquinolin-5-yl) glycinate (40). To a solution of **39** (654 mg, 1.5 mmol) in DMF (5 mL) was added K_2CO_3 (415 mg, 3.0 mmol) followed by ethyl bromoacetate (306 mg, 2.0 mmol). After 2 h stirring at room temperature, the reaction mixture was then diluted in 30 mL of water and quenched with 2 M hydrochloric acid to pH 5. The crude product was obtained through filtration. Recrystallization from ethyl acetate/nhexane gave the **40** as a white solid 548 mg, yield 72%; ^{1}H NMR (300 MHz,

Chloroform-*d*) δ 7.21 (s, 1H), 7.10 – 7.05 (m, 1H), 6.96 (t, *J* = 7.7 Hz, 1H), 6.91 (s, 2H), 6.76 (dd, *J* = 8.0, 2.1 Hz, 1H), 6.73 (t, *J* = 2.5 Hz, 1H), 6.67 (dd, *J* = 7.9, 1.0 Hz, 1H), 6.55 (dd, *J* = 8.0, 2.3 Hz, 1H), 4.51 (s, 2H), 3.85 (s, 3H), 3.74 (t, *J* = 8.4 Hz, 2H), 3.81 (s, 3H), 3.68 – 3.61 (m, 2H), 3.02 (t, *J* = 6.5 Hz, 2H), 2.61 (s, 6H), 2.31 (s, 3H), 2.12 – 2.00 (m, 2H). ESI-MS *m/z*: 509.2 $[M+H]^+$.

***tert*-butyl 4-nitro-1*H*-indole-1-carboxylate (41).** To a solution of **28** (5.0 g, 30.8 mmol) and triethylamine (3.7 g, 36.9 mmol) in DCM (50 mL) was added $(Boc)_2O$ (10.0 g, 45.7 mmol) dropwise at 0 °C and stirred for 2 h. Upon completion, the solution was concentrated under reduced pressure, and then the product **41** was purified by silica gel column chromatography (petroleumether/ethyl acetate = 40:1 to 10:1 v/v) to afford 5.7 g (71%) of desired product as white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.08 (s, 1H), 7.86 (t, *J* = 6.0 Hz, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 6.71 (d, *J* = 7.3 Hz, 1H), 6.38 (s, 1H), 2.01 (s, 9H); ESI-MS *m/z*: 263.1 $[M+H]^+$.

***tert*-butyl 4-((2,4,6-trimethylphenyl)sulfonamido)indoline-1-carboxylate (42).** To a solution of **41** (5.0 g, 19.1 mmol) in methanol (15 mL) was added Pd/C. The reaction mixture was stirred under hydrogen at 60 °C for 10 hours. The solution was filtered to remove the catalyst. The filtrate was concentrated under reduced pressure to give the gray oil without further purification. 2-mesitylenesulfonyl chloride (5.0 g, 22.9 mmol) and pyridine (237 mg, 28.6 mmol) was added to the solution of toluene (20 mL). The reaction mixture was stirred at 80 °C for 4 h under nitrogen. After cooling to room temperature, reaction mixture was then diluted in 40 mL of petroleum ether. After filtration, the solid was collected and washed with 1 M hydrochloric acid. Recrystallization from acetonitrile gave the gray solid 4.2 g, yield 53%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.12 (s,

1H), 7.22 (s, 2H), 6.98 (s, 1H), 6.84 (t, *J* = 8.0 Hz, 1H), 6.51 (d, *J* = 7.9 Hz, 1H), 3.80 (s, 2H), 3.12 (d, *J* = 8.5 Hz, 2H), 2.28 (s, 6H), 2.25 (s, 3H), 1.81 (s, 9H); ESI-MS *m/z*: 417.2 $[M+H]^+$.

***tert*-butyl 4-((N-(2-methoxy-2-oxoethyl)-2,4,6-trimethylphenyl)sulfonamido)indoline-1-carboxylate (43).** To a solution of **42** (4.0 g, 9.6 mmol) in DMF (10 mL) was added K_2CO_3 (2.0 g, 14.4 mmol) followed by ethyl bromoacetate (1.7 g, 11.5 mmol). After 2 h stirring at room temperature, the reaction mixture was then diluted in 30 mL of water and quenched with 2 M hydrochloric acid to pH 5. The crude product was obtained through filtration. Recrystallization from ethyl acetate/nhexane gave the **43** as a white solid 3.5 g, yield 75%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.12 (s, 1H), 7.22 (s, 2H), 6.98 (s, 1H), 6.84 (t, *J* = 8.0 Hz, 1H), 6.51 (d, *J* = 7.9 Hz, 1H), 4.32 (s, 2H), 3.84 (s, 3H), 3.80 (s, 2H), 3.12 (d, *J* = 8.5 Hz, 2H), 2.28 (s, 6H), 2.25 (s, 3H), 1.81 (s, 9H); ESI-MS *m/z*: 489.2 $[M+H]^+$.

methyl *N*-(indolin-4-yl)-*N*-(mesitylsulfonyl)glycinate (44): To a solution of **43** (3.0 g, 6.1 mmol) in DCM (10 mL) was added CF_3COOH (5 mL). After 1 h stirring at room temperature, the reaction mixture was concentrated under reduced pressure and quenched with 2 M $NaHCO_3$. The crude product was obtained through recrystallization from ethyl acetate/nhexane gave the **44** as a white solid 1.7 g, yield 75%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.98 (s, 2H), 6.86 (t, *J* = 8.0 Hz, 1H), 6.51 (d, *J* = 7.9 Hz, 1H), 6.41 (d, *J* = 7.5 Hz, 1H), 4.34 (s, 2H), 3.82 (s, 3H), 3.13 (d, *J* = 8.3 Hz, 2H), 2.29 (s, 6H), 2.25 (s, 3H). ESI-MS *m/z*: 389.1 $[M+H]^+$.

4-nitroindoline (45). To a solution of **28** (3.0 g, 18.5 mmol) and trifluoroacetic acid (6 ml) in DCM (20 ml) was added 4 equiv of sodium cyanoborohydride portionwise at 0 °C. After the

addition was complete, the reaction mixture was stirring at room temperature for 12 hours, and then was diluted with saturated $NaHCO_3$. The organic layer was extracted and washed with 2 x 20 ml of brine followed by 2 x 20 ml of H_2O. The organics were dried over anhydrous Na_2SO_4 and crude material was purified by flash chromatography (petroleumether/ethyl acetate = 20:1 to 4:1 v/v) to afford 2.4 g of the desired product as a red solid, yield 79%; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.14 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.65 (dd, *J* = 7.9, 1.3 Hz, 1H), 3.34 (t, *J* = 5.5 Hz, 2H), 2.94 (t, *J* = 6.5 Hz, 2H); ESI-MS *m/z*: 165.1 $(M+H)^+$.

methyl 2-bromo-2-(3-methoxyphenyl)acetate (47). I To a solution of **46** (3.0 g, 16.7 mmol) in CCl_4 (20 mL) was added NBS (2.9 g, 16.7 mmol) followed by AIBN (260 mg, 1.6 mmol). The reaction was heated to reflux for 6h under nitrogen. After cooling to room temperature, the reaction mixture was concentrated in vacuo and purified by silica gel column chromatography to give compound **47** as red oil, yield 56%; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.16 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.06 (t, *J* = 8.0 Hz, 2H), 6.68 (dd, *J* = 7.7, 1.5 Hz, 1H), 5.91 (s, 1H), 3.82 (s, 3H), 3.74 (s, 3H); ESI-MS *m/z*: 258.9 $(M+H)^+$.

methyl 2-(3-methoxyphenyl)-2-(4-nitroindolin-1-yl)acetate (48). To a solution of **45** (330 mg, 2.0 mmol) in DMF (5 mL) was added NaH (53 mg, 2.2 mmol) and **47** (567 mg, 2.2 mmol) at 0 °C, then the reaction mixture was stirred at 60 °C for 4 h under nitrogen. Upon completion, the solution was diluted in 30 mL of water and quenched with 2 M hydrochloric acid to pH 5. The crude product was obtained through filtration and purified by silica gel column chromatography, yield 59%; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.51 (d, *J* = 8.3 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.23 (t, *J* =

8.1 Hz, 1H), 7.02 - 6.92 (m, 3H), 6.66 (d, *J* = 7.9 Hz, 1H), 5.35 (s, 1H), 3.87 (d, *J* = 1.7 Hz, 3H), 3.83 (d, *J* = 1.7 Hz, 3H), 3.65 - 3.52 (m, 1H), 3.52 - 3.39 (m, 1H), 3.38 - 3.26 (m, 1H), 3.05 - 2.91 (m, 1H); ESI-MS *m/z*: 343.1 $(M+H)^+$.

2-(3-methoxyphenyl)-2-(4-nitroindolin-1-yl)acetic acid (49). To a solution of LiOH (1.0 g) in MeOH/H_2O (15/5 mL) was added **48** (343 mg, 1.0 mmol). The reaction mixture was stirring at room temperature overnight, then quenched with 2 M hydrochloric acid to pH 2 and diluted with 50 mL of water. Precipitate removed by filtration and washed with 5 × 10 mL water, then dried overnight in a vacuum desiccator, yielding **49** as a yellow solid, yield 84% ; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.52 (d, *J* = 8.5 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 8.1 Hz, 1H), 7.01 - 6.94 (m, 3H), 6.67 (d, *J* = 7.7 Hz, 1H), 5.35 (s, 1H), 3.82 (d, *J* = 1.7 Hz, 3H), 3.65 - 3.52 (m, 1H), 3.52 - 3.39 (m, 1H), 3.36 - 3.24 (m, 2H); ESI-MS *m/z*: 329.1 $(M+H)^+$.

2-(3-methoxyphenyl)-2-(4-nitroindolin-1-yl)-*N*-(phenylsulfonyl)acetamide (50a). 49 (328 mg, 1.0 mmol) was dissolved in 10 mL of distilled CH_2Cl_2. To this stirred solution, 2 equiv of EDCI and 2 equiv of DMAP and benzenesulfonamide (158 mg, 1.0 mmol) were added. The reaction was stirred for 4 hours at 40 °C. The organic layer was extracted and washed with 2 x 20 ml of brine followed by 2 x 20 ml of H_2O. The organics were dried over anhydrous Na_2SO_4 and crude material was purified by flash chromatography to afford the desired product as a yellow solid, yield 72%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.82 (s, 1H), 7.89 (d, *J* = 8.1 Hz, 2H), 7.63 (t, *J* = 7.8 Hz, 2H), 7.21 (s, 2H), 6.96 - 6.87 (m, 3H), 6.66 (s, 2H), 6.56 (d, *J* = 7.7 Hz, 1H), 5.17 (d, *J* = 8.5 Hz, 1H), 3.78 (s, 3H), 3.47 (s, 2H), 3.22 (s, 2H); ESI-MS *m/z*: 468.1 $(M+H)^+$.

2-(3-methoxyphenyl)-*N*-(phenylsulfonyl)-2-(4-((2,4,6-trimethylphenyl)sulfonamido)indolin-1-yl)acetamide (52a). 50a was synthesized according to the procedure of **42**, white solid, yield 51%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.40 (s, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.42 (t, J = 7.8 Hz, 2H), 7.26 (s, 2H), 6.97 - 6.87 (m, 3H), 6.61 (s, 2H), 6.52 (d, J = 7.3 Hz, 1H), 6.19 (d, J = 7.8 Hz, 1H), 5.19 (d, J = 8.7 Hz, 1H), 3.47 (s, 2H), 3.02 (s, 2H), 2.22 (dd, J = 13.0, 6.9 Hz, 9H); ESI-MS *m/z*: 620.2 $(M+H)^+$.

methyl *N*-(mesitylsulfonyl)-*N*-(1-(1-(3-methoxyphenyl)-2-oxo-2-(phenylsulfonamido)ethyl)indolin-4-yl)glycinate (53a). 53a was synthesized according to the procedure of **43**, white solid, yield 79%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.42 (s, 1H), 7.97 (d, J = 7.1 Hz, 2H), 7.72 (t, J = 8.6 Hz, 2H), 7.31 (s, 2H), 6.93 - 6.81 (m, 3H), 6.76 (s, 2H), 6.66 (d, J = 7.9 Hz, 1H), 6.29 (d, J = 7.8 Hz, 1H), 5.21 (d, J = 8.0 Hz, 1H), 4.28 (d, J = 8.2 Hz, 2H), 3.77 (s, 3H), 3.40 (s, 2H), 3.22 (s, 2H), 2.22 (dd, J = 13.0, 6.9 Hz, 9H); ESI-MS *m/z*: 692.2 $(M+H)^+$.

methyl 2-(4-((*N*-(2-methoxy-2-oxoethyl)-2,4,6-trimethylphenyl)sulfonamido)indolin-1-yl)-2-(3-methoxyphenyl)acetate (54). To a solution of **44** (776 mg, 2.0 mmol) in DMF (5 mL) was added NaH (53 mg, 2.2 mmol) and **47** (567 mg, 2.2 mmol) at 0 °C, then the reaction mixture was stirred at 60 °C for 4 h under nitrogen. Upon completion, the solution was diluted in 30 mL of water and quenched with 2 M hydrochloric acid to pH 5. The crude product was obtained through filtration and purified by silica gel column chromatography, yield 54%; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.06 (ddd, J = 16.8, 7.7, 1.7 Hz, 1H), 7.89 (dd, J = 7.6, 1.8 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.48 – 7.39 (m, 3H), 7.37 – 7.29 (m, 1H), 6.85 – 6.76 (m, 2H), 4.74 (d, J = 7.4 Hz,

1H), 4.47 (d, *J* = 17.7 Hz, 2H), 3.96 (s, 3H), 3.84 (s, 3H), 3.72 (s, 3H), 3.29 (t, *J* = 8.7 Hz, 2H), 3.20 (s, 2H), 2.35 (s, 6H), 2.22 (s, 3H); EI-MS m/z :567.2 $[M+H]^+$.

S2. Characterization of the Target Compounds.

***N*-(2,4,6-trimethylphenylsulfonyl)-*N*-(o-tolyl) glycine (9).** To a solution of LiOH (240 mg, 10.0 mmol) in MeOH/H_2O (5/5 mL) was added **21** (506 mg, 1.4 mmol). The reaction mixture was stirring at room temperature overnight, then quenched with 2 M hydrochloric acid to pH 2 and diluted with 50 mL of water. Precipitate removed by filtration and washed with 5 × 10 mL water, then dried overnight in a vacuum desiccator, yielding **9** as a white solid, yield 75%; mp: 164-166 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.82 (s, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.90 (d, *J* = 4.7 Hz, 3H), 6.81-6.71 (m, 1H), 4.30 (s, 2H), 2.15 (d, *J* = 2.9 Hz, 9H), 1.68 (s, 3H); HRMS (ESI): found 370.1191 ($C_{18}H_{21}NO_4S$, $[M+Na]^+$, requires 370.1198); HPLC (90:10 methanol:water): t_R= 6.72 min, 97.3%.

***N*-(mesitylsulfonyl)-*N*-(3-((3-methoxyphenyl) amino)-5-methylphenyl) glycine (10b). 10b** was synthesized according to the procedure of **10a**, white solid, yield 77%; mp: 172-174 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.63 (s, 1H), 8.10 (s, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.92 (s, 2H), 6.74 (t, *J* = 2.1 Hz, 1H), 6.61 (s, 1H), 6.42 (dd, *J* = 5.4, 3.0 Hz, 2H), 6.29 (ddd, *J* = 10.6, 7.9, 2.2 Hz, 2H), 4.29 (s, 2H), 2.30 (s, 6H), 2.15 (s, 3H), 2.05 (s, 3H); HRMS (ESI): found 469.1788 ($C_{25}H_{29}N_2O_5S$. $[M+H]^+$ requires 469.1791); HPLC (90:10 methanol:water): t_R= 6.11 min, 97.5%.

***N*-(mesitylsulfonyl)-*N*-(3-((3-methoxyphenyl) amino)-4-methylphenyl) glycine (10c). 10c** was synthesized according to the procedure of **10a**, white solid, yield 75%; mp: 136-138 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.63 (s, 1H), 8.10 (s, 1H), 6.96 (d, J = 8.1 Hz, 1H), 6.92 (s, 2H), 6.74 (t, J = 2.1 Hz, 1H), 6.61 (s, 1H), 6.42 (dd, J = 5.4, 3.0 Hz, 2H), 6.29 (ddd, J = 10.6, 7.9, 2.2 Hz, 2H), 4.29 (s, 2H), 2.30 (s, 6H), 2.15 (s, 3H), 2.05 (s, 3H); HRMS (ESI): found 469.1791 ($C_{25}H_{29}N_2O_5S$. $[M+H]^+$ requires 469.1791); HPLC (90:10 methanol:water): t_R= 6.05 min, 96.5%.

***N*-(mesitylsulfonyl)-*N*-(3-((3-methoxyphenyl) amino)-2-methylphenyl) glycine (10d). 10d** was synthesized according to the procedure of **10a**, white solid, yield 72%; mp: 158-160 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.63 (s, 1H), 8.10 (s, 1H), 6.96 (d, J = 8.1 Hz, 1H), 6.92 (s, 2H), 6.74 (t, J = 2.1 Hz, 1H), 6.61 (s, 1H), 6.42 (dd, J = 5.4, 3.0 Hz, 2H), 6.29 (ddd, J = 10.6, 7.9, 2.2 Hz, 2H), 4.29 (s, 2H), 2.30 (s, 6H), 2.15 (s, 3H), 2.05 (s, 3H); HRMS (ESI): found 469.1789 ($C_{25}H_{29}N_2O_5S$. $[M+H]^+$ requires 469.1791); HPLC (90:10 methanol:water): t_R= 6.14 min, 96.7%.

***N*-(mesitylsulfonyl)-*N*-(3-((3-methoxyphenyl) amino) phenyl) glycine (10e). 10e** was synthesized according to the procedure of **10a**, white solid, yield 83%; mp: 174-176 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.25 – 7.13 (m, 1H), 7.12 – 7.04 (m, 2H), 7.02 (d, J = 5.5 Hz, 2H), 6.89 (dd, J = 8.1, 2.3 Hz, 1H), 6.68 – 6.62 (m, 1H), 6.53 (t, J = 2.2 Hz, 1H), 6.40 (td, J = 8.1, 2.2 Hz, 2H), 4.41 (s, 2H), 3.71 (s, 3H), 2.37 (d, J = 3.8 Hz, 6H), 2.24 (s, 3H); HRMS (ESI): found 455.1635 ($C_{24}H_{27}N_2O_5S$. $[M+H]^+$ requires 455.1635); HPLC (90:10 methanol:water): t_R= 6.01 min, 95.7%.

***N*-(mesitylsulfonyl)-*N*-(3-((3-methoxyphenyl) amino)-4-(trifluoromethyl) phenyl) glycine (10f). 10g** was synthesized according to the procedure of **10a**, white solid, yield 71%; mp: 192-194 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.75 (s, 1H), 8.15 (s, 1H), 7.46 (d, J = 2.6 Hz, 1H), 7.16 (d, J = 8.2 Hz, 1H), 7.05 – 6.97 (m, 1H), 6.94 (d, J = 4.8 Hz, 2H), 6.83 (d, J = 7.9 Hz, 1H), 6.55 (t, J = 2.4 Hz, 1H), 6.47 (dd, J = 8.1, 2.0 Hz, 1H), 6.33 (dd, J = 8.0, 2.3 Hz, 1H), 4.38 (s, 2H), 3.70 (s, 3H), 2.34 (s, 6H), 2.24 (s, 3H); HRMS (ESI): found 523.1432 ($C_{25}H_{26}F_3N_2O_5S$. $[M+H]^+$ requires 523.1441); HPLC (90:10 methanol:water): t_R= 6.13 min, 96.4%.

***N*-(2-fluoro-3-((3-methoxyphenyl) amino) phenyl)-*N*-(mesitylsulfonyl) glycine (10g). 10g** was synthesized according to the procedure of **10a**, white solid, yield 73%; mp: 170-172 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.88 (s, 1H), 7.44 (s, 1H), 7.13 (d, J = 2.6 Hz, 3H), 7.04 – 6.96 (m, 3H), 6.35 – 6.26 (m, 2H), 6.15 (dd, J = 8.0, 2.0 Hz, 1H), 4.55 (d, J = 17.8 Hz, 1H), 4.26 (s, 1H), 3.77 (s, 3H), 2.24 (d, J = 3.7 Hz, 9H); HRMS (ESI): found 473.1539 ($C_{24}H_{26}FN_2O_5S$. $[M+H]^+$ requires 473.1541); HPLC (90:10 methanol:water): t_R= 6.21 min, 95.1%.

***N*-(mesitylsulfonyl)-*N*-(2-methoxy-3-((3-methoxyphenyl) amino) phenyl) glycine (10h). 10h** was synthesized according to the procedure of **10a**, white solid, yield 72%; mp: 140-142 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.87 (s, 1H), 7.57 (s, 1H), 7.24 (d, J = 2.8 Hz, 3H), 7.14 – 6.97 (m, 4H), 6.35 – 6.26 (m, 3H), 6.16 (dd, J = 8.2, 2.0 Hz, 1H), 4.55 (d, J = 18.0 Hz, 1H), 4.26 (s, 1H), 3.68 (s, 3H), 3.25 (s, 3H), 2.23 (d, J = 3.6 Hz, 9H); HRMS (ESI): found 485.1742 ($C_{25}H_{29}N_2O_6S$. $[M+H]^+$ requires 485.1740); HPLC (90:10 methanol:water): t_R= 6.12 min, 97.5%.

***N*-(mesitylsulfonyl)-*N*-(3-methoxy-4-((3-methoxyphenyl) amino) phenyl) glycine (10i).** **10i** was synthesized according to the procedure of **10a**, white solid, yield 82%; mp: 142-144 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.87 (s, 1H), 7.43 (s, 1H), 7.09 (dt, J = 8.1, 3.8 Hz, 2H), 7.00 (s, 2H), 6.75 (dd, J = 8.5, 2.3 Hz, 2H), 6.60 (ddt, J = 7.1, 2.1 Hz, 3H), 6.40 (dd, J = 8.0, 2.4 Hz, 1H), 3.68 (s, 3H), 2.36 (s, 6H), 2.24 (s, 3H); HRMS (ESI): found 455.1635 ($C_{24}H_{27}N_2O_5S$. $[M+H]^+$ requires 455.1635); HPLC (90:10 methanol:water): t_R= 6.15 min, 97.5%.

***N*-(1-(3-methoxyphenyl) indolin-4-yl)-*N*-((4-nitrophenyl) sulfonyl) glycine (11b). 11b** was synthesized according to the procedure of **11a**, white solid, yield 76%; mp: 137-139 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.76 (s, 1H), 8.31 (d, J = 10.1 Hz, 1H), 7.88 (d, J = 9.0 Hz, 1H), 7.53 (d, J = 10.3 Hz, 1H), 7.20 – 7.11 (m, 1H), 7.02 (d, J = 8.7 Hz, 1H), 6.93 (d, J = 17.1 Hz, 2H), 6.75 (s, 1H), 6.63 (s, 1H), 6.47 (d, J = 11.6 Hz, 1H), 6.26 – 6.14 (m, 1H), 4.28 (s, 1H), 4.15 (s, 1H), 3.76 (s, 3H), 3.74 (s, 2H), 3.67 (s, 3H), 2.98 (s, 2H); HRMS (ESI): found 484.1174 ($C_{23}H_{22}N_3O_7S$. $[M+H]^+$ requires 484.1173); HPLC (85:15 methanol:water): t_R= 4.23 min, 96.6%.

***N*-(1-(3-methoxyphenyl) indolin-4-yl)-*N*-((4- methoxyphenyl) sulfonyl) glycine (11c). 11c** was synthesized according to the procedure of **11a**, white solid, yield 74%; mp: 142-144 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.80 (s, 1H), 7.61 (s, 2H), 7.29 – 7.21 (m, 1H), 7.10 (s, 2H), 7.00 (d, J = 18.0 Hz, 2H), 6.84 (s, 1H), 6.73 (s, 1H), 6.55 (s, 1H), 6.25 (s, 1H), 4.25 (s, 1H), 3.86 (s, 3H), 3.84 (s, 1H), 3.76 (s, 3H), 3.05 (s, 2H); HRMS (ESI): found 469.1427 ($C_{24}H_{25}N_2O_6S$. $[M+H]^+$ requires 469.1428); HPLC (85:15 methanol:water): t_R= 4.23 min, 97.9%.

***N*-((4-acetamidophenyl) sulfonyl)-*N*-(1-(3-methoxyphenyl) indolin-4-yl) glycine (11d). 11d** was synthesized according to the procedure of **11a**, white solid, yield 79%; mp: 122-124 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.73 (s, 2H), 10.30 (s, 1H), 7.68 (d, J = 9.1 Hz, 2H), 7.52 (d, J = 9.3 Hz, 2H), 7.20 – 7.12 (m, 1H), 6.91 (d, J = 11.6 Hz, 2H), 6.70 (s, 1H), 6.63 (s, 1H), 6.46 (d, J = 9.4 Hz, 1H), 6.16 (d, J = 8.7 Hz, 1H), 4.16 (s, 2H), 3.77 (s, 2H), 3.67 (s, 3H), 2.97 (d, J = 2.7 Hz, 2H), 2.00 (s, 3H); HRMS (ESI): found 496.1552 ($C_{25}H_{26}N_3O_6S$. $[M+H]^+$ requires 496.1531); HPLC (85:15 methanol:water): t_R= 3.97 min, 98.5%.

***N*-(1-(3-methoxyphenyl) indolin-4-yl)-*N*-tosyl glycine (11e). 11e** was synthesized according to the procedure of **11a**, white solid, yield 80%; mp: 120-122 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.82 (s, 1H), 7.71 (s, 2H), 7.28 – 7.21 (m, 1H), 7.12 (s, 2H), 7.01 (d, J = 16.0 Hz, 2H), 6.85 (s, 1H), 6.71 (s, 1H), 6.56 (s, 1H), 6.24 (s, 1H), 4.24 (s, 1H), 3.82 (s, 3H), 3.80 (s, 1H), 3.04 (s, 2H), 2.36 (s, 3H); HRMS (ESI): found 453.1431 ($C_{24}H_{25}N_2O_5S$. $[M+H]^+$ requires 453.1415); HPLC (85:15 methanol:water): t_R= 4.25 min, 98.7%.

***N*-((4-fluorophenyl) sulfonyl)-*N*-(1-(3-methoxyphenyl) indolin-4-yl) glycine (11f). 11f** was synthesized according to the procedure of **11a**, white solid, yield 72%; mp: 151-153 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.73 (s, 1H), 8.36 (d, J = 10.3 Hz, 1H), 7.85 (d, J = 9.0 Hz, 1H), 7.63 (d, J = 10.7 Hz, 1H), 7.21 – 7.11 (m, 1H), 7.01 (d, J = 8.7 Hz, 1H), 6.92 (d, J = 15.1 Hz, 2H), 6.77 (s, 1H), 6.61 (s, 1H), 6.45 (d, J = 11.6 Hz, 1H), 6.27 – 6.16 (m, 1H), 4.27 (s, 1H), 4.14 (s, 1H), 3.72 (s, 3H), 3.72 (s, 2H), 3.66 (s, 3H), 2.99 (s, 2H); HRMS (ESI): found 457.1278 ($C_{23}H_{22}FN_2O_5S$. $[M+H]^+$ requires 457.1271); HPLC (85:15 methanol:water): t_R= 4.11 min, 95.4%.

***N*-(mesitylsulfonyl)-*N*-(1-(3-methoxyphenyl)-1H-indol-4-yl) glycine (12). 12** was synthesized according to the procedure of **11a**, white solid, yield 73%; mp: 186-188 ºC. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 12.80 (s, 1H), 7.64 (d, *J* = 3.3 Hz, 1H), 7.56 (p, *J* = 3.9 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.13 (d, *J* = 13.1 Hz, 3H), 7.09 (t, *J* = 2.2 Hz, 1H), 6.99 (s, 3H), 6.55 (d, *J* = 3.6 Hz, 1H), 4.51 (s, 2H), 3.83 (s, 3H), 2.36 (s, 6H), 2.22 (s, 3H); HRMS (ESI): found 479.1641 ($C_{26}H_{27}N_2O_5S$. $[M+H]^+$ requires 479.1635); HPLC (85:15 methanol:water): t_R= 4.26 min, 97.6%.

***N*-(mesitylsulfonyl)-N-(1-(3-methoxyphenyl)-1,2,3,4-tetrahydroquinolin-5-yl) glycine (13). 13** was synthesized according to the procedure of **11a**, white solid, yield 76%; mp: 149-151 ºC. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 12.82 (s, 1H), 7.28 (t, J = 8.2 Hz, 1H), 7.16 – 7.06 (m, 4H), 6.82 – 6.78 (m, 1H), 6.74 – 6.69 (m, 1H), 6.66 (d, J = 2.3 Hz, 1H), 6.54 (s, 1H), 4.42 (s, 2H), 3.75 (s, 3H), 3.70 (s, 2H), 2.70 (d, J = 8.3 Hz, 2H), 2.34 (d, J = 9.3 Hz, 6H), 2.22 (s, 3H), 2.10 – 2.00 (m, 2H); HRMS (ESI): found 495.1993 ($C_{27}H_{31}N_2O_5S$. $[M+H]^+$ requires 495.1991); HPLC (85:15 methanol:water): t_R= 4.11 min, 96.5%.

***N*-(mesitylsulfonyl)-*N*-(1-(3-methoxybenzoyl) indolin-4-yl) glycine (14a). 14a** was synthesized according to the procedure of **11a**, white solid, yield 62%; mp: 162-164 ºC. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 12.87 (s, 1H), 7.57 – 7.34 (m, 2H), 7.21 – 7.04 (m, 4H), 7.04 – 6.96 (m, 3H), 4.39 (s, 2H), 3.84 (t, *J* = 8.2 Hz, 2H), 3.80 (s, 3H), 2.85 (s, 2H), 2.30 (s, 6H), 2.26 (s, 3H); HRMS (ESI): found 509.1738 ($C_{27}H_{29}N_2O_6S$. $[M+H]^+$ requires 509.1740); HPLC (85:15 methanol:water): t_R= 4.02 min, 96.2%.

***N*-(mesitylsulfonyl)-*N*-(1-((4-methoxyphenyl) sulfonyl) indolin-4-yl) glycine (14b). 14b** was synthesized according to the procedure of **11a**, white solid, yield 62%; mp: 132-134 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.82 (s, 1H), 7.60 – 7.51 (m, 2H), 7.20 – 7.05 (m, 4H), 7.01 – 6.94 (m, 3H), 4.42 (s, 2H), 3.82 (t, J = 8.2 Hz, 2H), 3.80 (s, 3H), 2.84 (s, 2H), 2.32 (s, 6H), 2.24 (s, 3H); HRMS (ESI): found 545.1348 ($C_{26}H_{29}N_2O_7S_2$. $[M+H]^+$ requires 545.1350); HPLC (85:15 methanol:water): t_R= 3.89 min, 98.2%.

***N*-(mesitylsulfonyl)-*N*-(1-(4-methoxybenzyl) indolin-4-yl) glycine (14d). 14d** was synthesized according to the procedure of **11a**, white solid, yield 72%; mp: 161-163 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.17 (d, J = 8.2 Hz, 2H), 6.90 (s, 2H), 6.86 (dd, J = 8.2, 3.8 Hz, 3H), 6.51 (dd, J = 7.9, 5.9 Hz, 2H), 4.12 (s, 2H), 4.06 (s, 2H), 3.72 (s, 3H), 2.93 (t, J = 8.2 Hz, 2H), 2.27 (s, 6H), 2.20 (s, 3H) ; HRMS (ESI): found 495.1938 ($C_{27}H_{31}N_2O_5S$. $[M+H]^+$ requires 495.1947); HPLC (85:15 methanol:water): t_R= 4.12 min, 97.4%.

***N*-(mesitylsulfonyl)-*N*-(1-(4-methylbenzyl) indolin-4-yl) glycine (14e). 14e** was synthesized according to the procedure of **11a**, white solid, yield 77%; mp: 162-164 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.80 (s, 1H), 7.16 (d, J = 3.4 Hz, 1H), 7.14 – 7.09 (m, 3H), 6.95 (d, J = 10.3 Hz, 3H), 6.56 (td, J = 8.8, 7.4, 4.5 Hz, 2H), 4.35 (d, J = 13.8 Hz, 2H), 4.17 (d, J = 5.5 Hz, 2H), 2.98 (q, J = 8.3, 6.7 Hz, 2H), 2.27 (p, J = 8.7, 8.0 Hz, 10H), 2.20 (s, 3H); HRMS (ESI): found 479.1999 ($C_{27}H_{31}N_2O_4S$. $[M+H]^+$ requires 479.1999); HPLC (85:15 methanol:water): t_R= 4.21 min, 96.1%.

***N*-(mesitylsulfonyl)-*N*-(1-(4-(trifluoromethyl) benzyl) indolin-4-yl) glycine (14f). 14f** was synthesized according to the procedure of **11a**, white solid, yield 80%; mp: 181-183 ºC. ^{1}H NMR

(300 MHz, DMSO-d_6) δ 12.75 (s, 1H), 7.70 (s, 3H), 7.49 (s, 2H), 6.94 (s, 3H), 6.61 – 6.51 (m, 2H), 4.71 (d, J = 4.0 Hz, 0H), 4.49 (s, 1H), 4.34 (s, 3H), 3.06 (s, 2H), 2.37 (d, J = 4.1 Hz, 1H), 2.28 (s, 6H), 2.23 (s, 3H); HRMS (ESI): found 533.1713 ($C_{27}H_{28}F_3N_2O_4S$. $[M+H]^+$ requires 533.1716); HPLC (85:15 methanol:water): t_R= 4.17 min, 96.2%.

***N*-(1-(4-bromobenzyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (14g). 14g** was synthesized according to the procedure of **11a**, white solid, yield 74%; mp: 153-155 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.78 (s, 1H), 7.55 (s, 2H), 7.24 (s, 2H), 6.95 (s, 4H), 6.55 (d, J = 3.8 Hz, 1H), 4.56 (s, 1H), 4.33 (s, 2H), 4.20 (s, 2H), 3.00 (s, 2H), 2.37 (s, 2H), 2.27 (s, 6H), 2.22 (s, 3H) ; HRMS (ESI): found 543.0929 ($C_{26}H_{28}BrN_2O_4S$. $[M+H]^+$ requires 543.0947); HPLC (85:15 methanol:water): t_R= 4.12 min, 97.8%.

***N*-(1-(4-chlorobenzyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (14h). 14h** was synthesized according to the procedure of **11a**, white solid, yield 75%; mp: 145-147 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.81 (s, 1H), 7.31 (d, J = 7.0 Hz, 2H), 7.24 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.1 Hz, 3H), 6.55 (s, 2H), 4.34 (s, 2H), 4.22 (s, 2H), 3.05 – 2.94 (m, 2H), 2.44 (d, J = 8.9 Hz, 2H), 2.26 (s, 6H), 2.21 (s, 3H); HRMS (ESI): found 499.1453 ($C_{26}H_{28}ClN_2O_4S$. $[M+H]^+$ requires 499.1452); HPLC (85:15 methanol:water): t_R= 4.11 min, 95.3%.

***N*-(mesitylsulfonyl)-*N*-(1-(2-methoxybenzyl)indolin-4-yl)glycine (14i). 14i** was synthesized according to the procedure of **11a**, white solid, yield 72%; mp: 186-188 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.81 (s, 1H), 7.21 (d, J = 7.8 Hz, 1H), 6.93 (d, J = 7.7 Hz, 3H), 6.84 - 6.77 (m, 3H), 6.55 (t, J = 8.2 Hz, 2H), 4.35 (s, 2H), 4.21 (s, 2H), 3.72 (s, 3H), 3.69 (s, 1H), 2.47 (d, J = 6.3 Hz,

2H), 2.26 (s, 6H), 2.20 (s, 3H); HRMS (ESI): found 495.1937 ($C_{27}H_{31}N_2O_5S$. $[M+H]^+$ requires 495.1948); HPLC (85:15 methanol:water): t_R= 4.18 min, 97.2%.

***N*-(1-benzylindolin-4-yl)-*N*-(mesitylsulfonyl) glycine (14j). 14j** was synthesized according to the procedure of **11a**, white solid, yield 70%; mp: 166-168 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.81 (s, 1H), 7.31 (d, J = 7.0 Hz, 3H), 7.24 (d, J = 8.7 Hz, 3H), 6.93 (d, J = 8.1 Hz, 3H), 6.55 (s, 2H), 4.34 (s, 2H), 3.06 – 2.92 (m, 2H), 2.26 (s, 6H), 2.21 (s, 3H); HRMS (ESI): found 495.1834 ($C_{26}H_{29}N_2O_4S$. $[M+H]^+$ requires 465.1827); HPLC (85:15 methanol:water): t_R= 4.30 min, 98.8%.

***N*-(mesitylsulfonyl)-*N*-(1-(3-methylbenzyl) indolin-4-yl) glycine (14k). 14k** was synthesized according to the procedure of **11a**, white solid, yield 71%; mp: 125-127 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.83 (s, 1H), 7.24 (d, J = 7.9 Hz, 1H), 6.95 (d, J = 7.3 Hz, 3H), 6.83 – 6.76 (m, 3H), 6.53 (t, J = 8.0 Hz, 2H), 4.32 (s, 2H), 4.21 (s, 2H), 3.74 (s, 3H), 2.48 (d, J = 6.3 Hz, 2H), 2.26 (s, 6H), 2.22 (s, 3H), 2.01 (s, 3H); HRMS (ESI): found 479.1999 ($C_{27}H_{31}N_2O_4S$. $[M+H]^+$ requires 479.1999); HPLC (85:15 methanol:water): t_R= 4.31 min, 97.3%.

***N*-(mesitylsulfonyl)-*N*-(1-(3-(trifluoromethyl) benzyl) indolin-4-yl) glycine (14l). 14l** was synthesized according to the procedure of **11a**, white solid, yield 76%; mp: 173-175 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.81 (s, 1H), 7.21 (d, J = 7.7 Hz, 2H), 6.91 (d, J = 7.2 Hz, 2H), 6.81 – 6.72 (m, 4H), 6.52 (t, J = 8.4 Hz, 3H), 4.34 (s, 2H), 4.21 (s, 2H), 3.75 (s, 3H), 2.46 (d, J = 6.5 Hz, 2H), 2.28 (s, 6H), 2.21 (s, 3H), 2.01 (s, 3H); HRMS (ESI): found 533.1713 ($C_{27}H_{28}F_3N_2O_4S$. $[M+H]^+$ requires 533.1716); HPLC (85:15 methanol:water): t_R= 4.24 min, 97.9%.

***N*-(1-(3-bromobenzyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (14m). 14m** was synthesized according to the procedure of **11a**, white solid, yield 73%; mp: 136-138 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.80 (s, 1H), 7.65 (s, 2H), 7.25 (s, 2H), 6.98 (s, 3H), 6.56 (d, J = 3.8 Hz, 2H), 4.55 (s, 1H), 4.32 (s, 2H), 4.21 (s, 2H), 3.01 (s, 2H), 2.38 (s, 2H), 2.26 (s, 6H), 2.20 (s, 3H) ; HRMS (ESI): found 543.0929 ($C_{26}H_{28}BrN_2O_4S$. $[M+H]^+$ requires 543.0947); HPLC (85:15 methanol:water): t_R= 4.14 min, 95.6%.

***N*-(1-(3-chlorobenzyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (14n). 14n** was synthesized according to the procedure of **11a**, white solid, yield 72%; mp: 147-149 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.86 (s, 1H), 7.41 (s, 1H), 6.95 (s, 3H), 6.87 (s, 3H), 6.56 (s, 2H), 4.34 (s, 2H), 4.12 (s, 2H), 3.04 (s, 2H), 2.23 (s, 8H), 2.19 (s, 3H); HRMS (ESI): found 499.1453 ($C_{26}H_{28}ClN_2O_4S$. $[M+H]^+$ requires 499.1452); HPLC (85:15 methanol:water): t_R= 4.09 min, 96.2%.

***N*-(1-(3-cyanobenzyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (14o). 14o** was synthesized according to the procedure of **11a**, white solid, yield 72%; mp: 149-151 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.92 (s, 1H), 7.41 (s, 2H), 7.25 (s, 2H), 6.87 (s, 3H), 6.57 (s, 2H), 4.32 (s, 2H), 4.12 (s, 2H), 3.04 (s, 2H), 2.32 (s, 2H), 2.23 (s, 6H), 2.19 (s, 3H); HRMS (ESI): found 490.1753 ($C_{27}H_{28}N_3O_4S$. $[M+H]^+$ requires 490.1752); HPLC (85:15 methanol:water): t_R= 4.04 min, 97.2%.

***N*-(1-([1,1'-biphenyl]-3-ylmethyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (14p). 14p** was synthesized according to the procedure of **11a**, white solid, yield 73%; mp: 147-149 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.82 (s, 1H), 7.81 (s, 2H), 7.61 (d, J = 7.9 Hz, 2H), 7.59 (d, J = 7.4 Hz, 3H), 6.82 - 6.71 (m, 4H), 6.59 (t, J = 8.4 Hz, 2H), 6.52 (s, 1H), 4.33 (s, 2H), 4.12 (s, 2H), 3.05 (s,

2H), 2.35 (s, 2H), 2.21 (s, 6H), 2.18 (s, 3H); HRMS (ESI): found 541.2152 ($C_{32}H_{33}N_2O_4S$. $[M+H]^+$ requires 541.2155); HPLC (85:15 methanol:water): t_R= 4.32 min, 95.7%.

***N*-(1-(3-theoxybenzyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (14q). 14q** was synthesized according to the procedure of **11a**, white solid, yield 62%; mp: 121-123 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.81 (s, 1H), 7.25 (d, J = 7.1 Hz, 1H), 6.99 (d, J = 7.9 Hz, 2H), 6.87 – 6.79 (m, 4H), 6.54 (t, J = 8.4 Hz, 2H), 4.35 (s, 2H), 4.21 (s, 2H), 4.02 (s, 2H), 3.71 (s, 3H), 3.69 (s, 1H), 2.46 (d, J = 6.3 Hz, 2H), 2.27 (s, 6H), 2.22 (s, 3H), 1.54 (s, 3H); HRMS (ESI): found 509.2152 ($C_{28}H_{33}N_2O_5S$. $[M+H]^+$ requires 509.2154); HPLC (85:15 methanol:water): t_R= 4.20 min, 96.5%.

***N*-(1-(3-isopropoxybenzyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (14r). 14r** was synthesized according to the procedure of **11a**, white solid, yield 64%; mp: 124-126 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.82 (s, 1H), 7.27 (d, J = 6.9 Hz, 1H), 6.99 (d, J = 7.1 Hz, 1H), 6.89 – 6.77 (m, 5H), 6.53 (t, J = 8.2 Hz, 2H), 4.36 (s, 2H), 4.21 (s, 2H), 4.11 (s, 1H), 3.71 (s, 1H), 3.69 (s, 1H), 2.46 (d, J = 6.3 Hz, 2H), 2.27 (s, 6H), 2.22 (s, 3H), 1.46 (s, 6H); HRMS (ESI): found 525.2239 ($C_{29}H_{35}N_2O_5S$. $[M+H]^+$ requires 525.2247); HPLC (85:15 methanol:water): t_R= 4.18 min, 96.2%.

***N*-(mesitylsulfonyl)-*N*-(1-(3-nitrobenzyl) indolin-4-yl) glycine (14s). 14s** was synthesized according to the procedure of **11a**, white solid, yield 73%; mp: 142-144 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.90 (s, 1H), 8.14 (s, 2H), 7.74 (d, J = 7.8 Hz, 1H), 7.65 (t, J = 8.1 Hz, 1H), 6.96 (d, J = 7.7 Hz, 3H), 6.59 (t, J = 7.8 Hz, 2H), 4.37 (d, J = 12.3 Hz, 4H), 3.06 (t, J = 8.3 Hz, 2H), 2.39

(s, 2H), 2.24 (d, J = 17.6 Hz, 9H); HRMS (ESI): found 510.1692 ($C_{26}H_{28}N_3O_4S$. $[M+H]^+$ requires 510.1693); HPLC (85:15 methanol:water): t_R= 4.17 min, 96.8%.

***N*-(1-(3,5-dimethylbenzyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (14t). 14t** was synthesized according to the procedure of **11a**, white solid, yield 72%; mp: 146-148 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.82 (s, 1H), 7.92 – 7.82 (m, 2H), 7.56 – 7.39 (m, 2H), 6.95 (d, J = 9.3 Hz, 2H), 6.58 (t, J = 7.3 Hz, 2H), 4.32 (d, J = 12.7 Hz, 4H), 3.02 (t, J = 8.3 Hz, 2H), 2.46 (d, J = 9.3 Hz, 1H), 2.35 (s, 1H), 2.26 (s, 6H), 2.21 (s, 6H), 2.13 (s, 3H); HRMS (ESI): found 515.1989 ($C_{28}H_{32}N_2NaO_4S$. $[M+Na]^+$ requires 515.1975); HPLC (85:15 methanol:water): t_R= 4.21 min, 96.2%.

***N*-(1-(2,3-dimethylbenzyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (14u). 14u** was synthesized according to the procedure of **11a**, white solid, yield 62%; mp: 151-153 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.80 (s, 1H), 7.48 (d, J = 8.1 Hz, 3H), 7.33 (d, J = 7.2 Hz, 2H), 7.03 (d, J = 7.1 Hz, 2H), 6.69 (dd, J = 12.5, 7.7 Hz, 1H), 4.61 (s, 2H), 4.32 (s, 2H), 2.97 (t, J = 8.1 Hz, 2H), 2.34 (s, 6H), 2.19 (s, 3H), 2.03 (s, 6H); HRMS (ESI): found 515.1989 ($C_{28}H_{32}N_2NaO_4S$. $[M+Na]^+$ requires 515.1975); HPLC (85:15 methanol:water): t_R= 4.26 min, 97.3%.

***N*-(1-(3,5-dimethoxybenzyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (14v). 14v** was synthesized according to the procedure of **11a**, white solid, yield 60%; mp: 138-140 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.02 (s, 1H), 6.94 (s, 2H), 6.54 (dd, J = 12.1, 8.0 Hz, 2H), 6.40 (s, 2H), 6.21 (t, J = 2.1 Hz, 1H), 4.47 (s, 2H), 4.15 (s, 2H), 3.92 (s, 3H); 3.81 (s, 3H); 3.70 (s, 3H), 3.02 (t, J = 8.4 Hz, 2H), 2.46 (d, J = 8.3 Hz, 1H), 2.37 (s, 1H), 2.36 (s, 6H), 2.16 (s, 3H); HRMS (ESI):

found 525.2049 ($C_{28}H_{33}N_2O_6S$. $[M+H]^+$ requires 525.2053); HPLC (85:15 methanol:water): t_R= 4.23 min, 97.1%.

***N*-(1-(3-fluoro-5-methoxybenzyl)indolin-4-yl)-*N*-(mesitylsulfonyl)glycine (14w). 14w** was synthesized according to the procedure of **11a**, white solid, yield 64%; mp: 134-136 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.80 (s, 1H), 7.99 (s, 1H), 7.22 (s, 2H), 7.10 (s, 1H), 6.65 (dd, J = 10.1, 8.2 Hz, 2H), 6.42 (s, 1H), 6.21 (t, J = 2.1 Hz, 1H), 4.52 (s, 2H), 4.12 (s, 2H), 3.82 (s, 3H), 3.02 (t, J = 8.6 Hz, 2H), 2.47 (d, J = 8.5 Hz, 1H), 2.36 (s, 1H), 2.32 (s, 6H), 2.14 (s, 3H); HRMS (ESI): found 513.1845 ($C_{27}H_{30}FN_2O_5S$. $[M+H]^+$ requires 513.1853); HPLC (85:15 methanol:water): t_R= 4.15 min, 98.1%.

***N*-(1-(3,4-dimethoxybenzyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (14x). 14x** was synthesized according to the procedure of **11a**, white solid, yield 64%; mp: 148-150 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.84 (s, 1H), 7.52 (s, 1H), 7.34 (s, 2H), 6.55 (dd, J = 12.4, 8.7 Hz, 2H), 6.50 (s, 2H), 6.21 (t, J = 2.2 Hz, 1H), 4.45 (s, 2H), 4.28 (s, 2H), 3.82 (s, 3H); 3.71 (s, 3H), 3.05 (t, J = 8.6 Hz, 2H), 2.45 (d, J = 8.3 Hz, 1H), 2.37 (s, 1H), 2.34 (s, 6H), 2.14 (s, 3H); HRMS (ESI): found 525.2059 ($C_{28}H_{33}N_2O_6S$. $[M+H]^+$ requires 525.2053); HPLC (85:15 methanol:water): t_R= 4.15 min, 98.6%.

***N*-(1-(3-bromo-5-methoxybenzyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (14y). 14y** was synthesized according to the procedure of **11a**, white solid, yield 70%; mp: 151-153 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.80 (s, 1H), 7.52 (d, J = 8.6 Hz, 1H), 6.93 (s, 2H), 6.91 – 6.80 (m, 3H), 6.54 (d, J = 8.1 Hz, 1H), 6.39 (d, J = 7.8 Hz, 1H), 4.19 (s, 2H), 4.06 (s, 2H), 3.70 (s, 3H), 3.09 (t,

J = 8.4 Hz, 2H), 2.64 (d, *J* = 8.3 Hz, 1H), 2.37 (s, 1H), 2.34 (s, 6H), 2.14 (s, 3H); HRMS (ESI): found 573.1055 ($C_{28}H_{33}N_2O_6S$. $[M+H]^+$ requires 573.1046); HPLC (85:15 methanol:water): t_R= 4.04 min, 96.5%.

***N*-(mesitylsulfonyl)-*N*-(1-(3-methoxy-5-methylbenzyl) indolin-4-yl) glycine (14z). 14z** was synthesized according to the procedure of **11a**, white solid, yield 67%; mp: 162-164 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.72 (s, 1H), 6.90 (d, *J* = 13.3 Hz, 1H), 6.85 (s, 2H), 6.54 (d, *J* = 14.9 Hz, 3H), 6.44 (t, *J* = 7.8 Hz, 2H), 4.30 (d, *J* = 32.6 Hz, 2H), 4.05 (s, 2H), 3.61 (d, *J* = 3.8 Hz, 3H), 2.92 (t, *J* = 8.2 Hz, 2H), 2.24 (d, *J* = 11.1 Hz, 2H), 2.17 (d, *J* = 6.0 Hz, 9H), 2.11 (d, *J* = 11.1 Hz, 3H); HRMS (ESI): found 509.2045 ($C_{28}H_{33}N_2O_5S$. $[M+H]^+$ requires 509.2037); HPLC (85:15 methanol:water): t_R= 4.20 min, 95.3%.

2-(4-((*N*-(carboxymethyl)-2,4,6-trimethylphenyl) sulfonamido) indolin-1-yl)-2-(3-methoxyphenyl) acetic acid (15). To a solution of LiOH (1.0 g) in MeOH/H_2O (15/5 mL) was added **54** (560 mg, 1.0 mmol). The reaction mixture was stirring at room temperature overnight, then quenched with 2 M hydrochloric acid to pH 2 and diluted with 50 mL of water. Precipitate removed by filtration and washed with 5 × 10 mL water, then dried overnight in a vacuum desiccator, yielding **15** as a white solid, yield 76%; mp: 162-164 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.74 (s, 2H), 7.43 (d, *J* = 2.9 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 6.88 (d, *J* = 9.4 Hz, 2H), 6.83 (d, *J* = 4.1 Hz, 2H), 6.77 (d, *J* = 1.9 Hz, 1H), 6.46 (t, *J* = 7.6 Hz, 2H), 5.25 (s, 1H), 4.25 (d, *J* = 10.4 Hz, 2H), 3.65 (s, 3H), 3.29 (t, *J* = 8.7 Hz, 1H), 3.20 (s, 1H), 2.15 (s, 6H), 2.11 (s, 3H);

HRMS (ESI): found 538.1871 ($C_{28}H_{31}N_2O_7S$, $[M+H]^+$, requires 538.1875); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.01 min, 96.6%.

***N*-(mesitylsulfonyl)-*N*-(1-(1-(3-methoxyphenyl)-2-(methylsulfonamido)-2-oxoethyl) indolin-4-yl) glycine (16b). 16b** was synthesized according to the procedure of **15**, white solid, yield 68%; mp: 117-119 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.88 (s, 2H), 8.03 (s, 1H), 7.82 (d, J = 1.8 Hz, 1H), 7.49 (t, J = 7.9 Hz, 1H), 6.99 (d, J = 7.2 Hz, 1H), 6.91 (s, 1H), 6.74 (d, J = 10.5 Hz, 2H), 6.57 (d, J = 8.0 Hz, 1H), 6.25 (d, J = 7.7 Hz, 1H), 5.21 (s, 1H), 4.28 (s, 2H), 3.73 (s, 3H), 3.26 (d, J = 8.5 Hz, 1H), 2.94 (s, 3H), 2.67 (d, J = 8.2 Hz, 1H), 2.41 (s, 2H), 2.21 (s, 9H); HRMS (ESI): found 616.1735 ($C_{29}H_{34}N_3O_8S_2$. $[M+H]^+$ requires 616.1746); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.01 min, 95.8%.

***N*-(mesitylsulfonyl)-*N*-(1-(1-(3-methoxyphenyl)-2-oxo-2-((trifluoromethyl) sulfonamido) ethyl) indolin-4-yl) glycine (16c). 16c** was synthesized according to the procedure of **15**, white solid, yield 64%; mp: 105-107 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) 12.91 (s, 2H), δ 8.05 (s, 1H), 7.78 (d, J = 1.9 Hz, 1H), 7.29 (t, J = 7.9 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 6.90 (s, 1H), 6.70 (d, J = 10.3 Hz, 2H), 6.56 (d, J = 8.0 Hz, 1H), 6.23 (d, J = 7.9 Hz, 1H), 5.20 (s, 1H), 4.29 (s, 2H), 3.72 (s, 3H), 3.25 (d, J = 8.5 Hz, 1H), 2.66 (d, J = 8.2 Hz, 1H), 2.40 (s, 2H), 2.21 (s, 9H); HRMS (ESI): found 670.1422 ($C_{29}H_{31}F_3N_3O_8S_2$. $[M+H]^+$ requires 670.1412); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.08 min, 96.8%.

***N*-(mesitylsulfonyl)-*N*-(1-(1-(3-methoxyphenyl)-2-oxo-2-(pyridine-3-sulfonamido) ethyl) indolin-4-yl) glycine (16d). 16d** was synthesized according to the procedure of **15**, white solid,

yield 70%; mp: 121-123 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.82 (s, 2H), 8.90 (d, J = 4.1, 1.5 Hz, 1H), 8.42 (dd, J = 5.1, 1.4 Hz, 1H), 7.83 (d, J = 3.9 Hz, 1H), 7.27 (t, J = 8.3 Hz, 1H), 7.17 (t, J = 4.6 Hz, 1H), 6.91 (s, 3H), 6.67 (d, J = 6.3 Hz, 2H), 6.57 (d, J = 8.1 Hz, 1H), 6.15 (d, J = 7.7 Hz, 1H), 5.18 (s, 1H), 4.29 (s, 2H), 3.69 (s, 3H), 3.26 (d, J = 8.5 Hz, 1H), 2.69 - 2.60 (m, 1H), 2.24 (d, J = 6.4 Hz, 9H); HRMS (ESI): found 679.1879 ($C_{33}H_{35}N_4O_8S_2$. $[M+H]^+$ requires 679.1890); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 4.82 min, 98.3%.

***N*-(mesitylsulfonyl)-*N*-(1-(1-(3-methoxyphenyl)-2-oxo-2-(thiophene-2-sulfonamido) ethyl) indolin-4-yl) glycine (16e). 16e** was synthesized according to the procedure of **15**, white solid, yield 65%; mp: 98-100 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.73 (s, 2H), 8.05 (dd, J = 5.1, 1.4 Hz, 1H), 7.75 (d, J = 3.7 Hz, 1H), 7.26 (t, J = 8.1 Hz, 1H), 7.18 (t, J = 4.4 Hz, 1H), 6.90 (s, 3H), 6.66 (d, J = 6.1 Hz, 2H), 6.55 (d, J = 8.1 Hz, 1H), 6.19 (d, J = 7.9 Hz, 1H), 5.17 (s, 1H), 4.28 (s, 2H), 3.68 (s, 3H), 3.25 (d, J = 8.3 Hz, 1H), 2.68 - 2.60 (m, 1H), 2.20 (d, J = 6.4 Hz, 9H); HRMS (ESI): found 706.1316 ($C_{32}H_{33}N_3NaO_8S_3$. $[M+Na]^+$ requires 706.1322); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 4.89 min, 97.2%.

***N*-(mesitylsulfonyl)-*N*-(1-(1-(3-methoxyphenyl)-2-((4-methoxyphenyl) sulfonamido)-2-oxoethyl) indolin-4-yl) glycine (16f). 16f** was synthesized according to the procedure of **15**, white solid, yield 76%; mp: 112-114 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.39 (s, 2H), 7.80 (dt, J = 9.5, 5.8 Hz, 2H), 7.25 (q, J = 7.5 Hz, 1H), 7.16 - 7.06 (m, 2H), 6.91 (s, 4H), 6.62 (s, 2H), 6.21 - 6.10 (m, 1H), 5.15 (d, J = 7.6 Hz, 1H), 4.27 (d, J = 8.0 Hz, 2H), 3.87 - 3.79 (m, 3H), 3.25 (d, J = 8.6 Hz, 1H), 2.62 (s, 1H), 2.47 (s, 2H), 2.19 (d, J = 7.9 Hz, 9H); HRMS (ESI): found 708.2038

($C_{35}H_{38}N_3O_9S_2$. $[M+H]^+$ requires 708.2044); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 4.95 min, 99.0%.

***N*-(mesitylsulfonyl)-*N*-(1-(1-(3-methoxyphenyl)-2-((4-methylphenyl) sulfonamido)-2-oxoethyl) indolin-4-yl) glycine (16g). 16g** was synthesized according to the procedure of **15**, white solid, yield 77%; mp: 106-108 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.80 (s, 2H), 7.75 (s, 2H), 7.41 (s, 2H), 7.25 (d, J = 11.5 Hz, 2H),6.92 (s, 4H), 6.64 (d, J = 11.5 Hz, 2H), 6.17 (d, J = 8.1 Hz, 1H), 5.16 (s, 1H), 4.28 (s, 2H), 3.79 (s, 3H), 3.13 (s, 2H), 2.63 (s, 2H), 2.39 (s, 3H), 2.22 (d, J = 8.0 Hz, 9H); HRMS (ESI): found 692.2097 ($C_{35}H_{38}N_3O_8S_2$. $[M+H]^+$ requires 692.2094); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.22 min, 96.8%.

***N*-(1-(2-((4-fluorophenyl) sulfonamido)-1-(3-methoxyphenyl)-2-oxoethyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (16h). 16h** was synthesized according to the procedure of **15**, white solid, yield 76%; mp: 102-104 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.87 (s, 2H), 7.97 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.2 Hz, 2H), 7.27 (t, J = 8.2 Hz, 1H), 6.99 (d, J = 9.2 Hz, 1H), 6.92 (s, 2H), 6.87 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 7.6 Hz, 1H), 6.64 (s, 1H), 6.56 (d, J = 8.3 Hz, 1H), 6.18 (d, J = 7.8 Hz, 1H), 5.19 (s, 1H), 4.29 (s, 2H), 3.79 (s, 3H), 3.25 (d, J = 8.5 Hz, 1H), 2.64 (d, J = 7.8 Hz, 1H), 2.32 (d, J = 13.8 Hz, 2H), 2.20 (s, 9H); HRMS (ESI): found 696.1846 ($C_{34}H_{35}FN_3O_8S_2$. $[M+H]^+$ requires 696.1844); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 4.87 min, 97.8%.

***N*-(1-(2-((4-chlorophenyl) sulfonamido)-1-(3-methoxyphenyl)-2-oxoethyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (16i). 16i** was synthesized according to the procedure of **15**, white solid, yield 80%; mp: 105-107 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.69 (s, 2H), 7.87 (d, J =

8.6 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.28 (t, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 9.0 Hz, 1H), 6.91 (s, 2H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 7.4 Hz, 1H), 6.62 (s, 1H), 6.54 (d, *J* = 8.1 Hz, 1H), 6.18 (d, *J* = 7.8 Hz, 1H), 5.19 (s, 1H), 4.29 (s, 2H), 3.78 (s, 9H) 3.25 (d, *J* = 8.5 Hz, 1H), 2.64 (d, *J* = 7.8 Hz, 1H), 2.32 (d, *J* = 13.8 Hz, 2H), 2.20 (s, 9H); HRMS (ESI): found 712.1539 ($C_{34}H_{35}ClN_3O_8S_2$. $[M+H]^+$ requires 712.1548); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 4.91 min, 96.6%.

***N*-(1-(2-((4-bromophenyl) sulfonamido)-1-(3-methoxyphenyl)-2-oxoethyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (16j). 16j** was synthesized according to the procedure of **15**, white solid, yield 79%; mp: 108-110 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.80 (s, 1H), 12.57 (s, 1H), 7.88 (d, *J* = 7.7 Hz, 2H), 7.73 (t, *J* = 7.3 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 3H), 6.66 (d, *J* = 5.0 Hz, 2H), 6.55 (d, *J* = 8.1 Hz, 1H), 6.18 (d, *J* = 7.8 Hz, 1H), 5.17 (s, 1H), 4.29 (s, 2H), 3.69 (s, 3H), 3.23 (d, *J* = 8.5 Hz, 1H), 2.61 (t, *J* = 8.0 Hz, 1H), 2.28 (d, *J* = 10.1 Hz, 2H), 2.21 (s, 9H); HRMS (ESI): found 756.1045 ($C_{34}H_{35}BrN_3O_8S_2$. $[M+H]^+$ requires 756.1032); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 4.88 min, 98.5%.

***N*-(mesitylsulfonyl)-*N*-(1-(1-(3-methoxyphenyl)-2-oxo-2-((4-(trifluoromethyl) phenyl) sulfonamido) ethyl) indolin-4-yl) glycine (16k). 16k** was synthesized according to the procedure of **15**, white solid, yield 74%; mp: 94-96 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.91 (s, 2H), 8.08 (t, *J* = 6.8 Hz, 2H), 8.04 - 7.94 (m, 2H), 7.64 (s, 2H) 7.29 - 7.22 (m, 1H), 7.01 - 6.87 (m, 3H), 6.83 (d, *J* = 6.0 Hz, 1H), 6.67 (d, *J* = 7.0 Hz, 1H), 6.60 (s, 1H), 4.28 (d, *J* = 5.3 Hz, 2H), 3.73 - 3.62 (m, 3H), 3.25 (d, *J* = 8.7 Hz, 1H), 2.61 (s, 1H), 2.28 (d, *J* = 10.1 Hz, 2H), 2.31 - 2.08 (m, 9H); HRMS

(ESI): found 768.1632 ($C_{35}H_{34}F_3N_3NaO_8S_2$. $[M+Na]^+$ requires 768.1631); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 4.74 min, 98.1%.

***N*-(mesitylsulfonyl)-*N*-(1-(1-(3-methoxyphenyl)-2-((3-methylphenyl) sulfonamido)-2-oxoethyl) indolin-4-yl) glycine (16l). 16l** was synthesized according to the procedure of **15**, white solid, yield 79%; mp: 100-102 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.77 (s, 1H), 12.50 (s, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.61 (s, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.49 (d, J = 7.3 Hz, 1H), 7.26 (t, J = 8.2 Hz, 1H), 6.95 - 6.91 (m, 1H), 6.89 (s, 2H), 6.85 (d, J = 7.8 Hz, 1H), 6.69 - 6.62 (m, 2H), 6.54 (d, J = 8.1 Hz, 1H), 6.18 (d, J = 7.9 Hz, 1H), 5.15 (s, 1H), 4.27 (s, 2H), 3.68 (d, J = 4.8 Hz, 3H), 3.23 (d, J = 8.3 Hz, 1H), 2.62 (d, J = 7.9 Hz, 1H), 2.35 (s, 3H), 2.28 - 2.23 (m, 2H), 2.19 (d, J = 2.6 Hz, 9H); HRMS (ESI): found 692.2092 ($C_{35}H_{38}N_3O_8S_2$. $[M+H]^+$ requires 692.2094); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.16 min, 96.5%.

***N*-(mesitylsulfonyl)-*N*-(1-(1-(3-methoxyphenyl)-2-((2-methylphenyl) sulfonamido)-2-oxoethyl) indolin-4-yl) glycine (16m). 16m** was synthesized according to the procedure of **15**, white solid, yield 71%; mp: 102-104 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.63 (s, 2H), 7.95 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.42 (s, 1H), 7.36 (d, J = 7.5 Hz, 2H), 6.93 (s, 2H), 6.89 (s, 2H), 6.66 (s, 2H), 6.57 (d, J = 7.9 Hz, 1H), 6.26 (d, J = 7.9 Hz, 1H), 5.21 (s, 1H), 4.29 (s, 2H), 3.69 (s, 3H), 3.22 (d, J = 9.8 Hz, 2H), 2.28 (s, 2H), 2.20 (s, 9H), 2.03 (s, 3H); HRMS (ESI): found 714.1913 ($C_{35}H_{37}N_3NaO_8S_2$. $[M+Na]^+$ requires 714.1914); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.02 min, 98.5%.

***N*-(mesitylsulfonyl)-*N*-(1-(1-(3-methoxyphenyl)-2-((2-methoxyphenyl) sulfonamido)-2-oxoethyl) indolin-4-yl) glycine (16n). 16n** was synthesized according to the procedure of **15**, white solid, yield 69%; mp: 107-109 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.79 (s, 2H), 7.82 (d, J = 7.7 Hz, 1H), 7.66 (t, J = 7.7 Hz, 1H), 7.29 (t, J = 7.8 Hz, 2H), 7.19 - 7.11 (m, 2H), 6.91 (d, J = 7.0 Hz, 3H), 6.73 - 6.66 (m, 2H), 6.57 (d, J = 8.1 Hz, 1H), 6.26 (d, J = 7.8 Hz, 1H), 5.22 (s, 1H), 4.29 (s, 2H), 3.70 (s, 3H), 3.68 (s, 3H), 3.65 (s, 2H), 3.21 (dd, J = 17.6, 8.3 Hz, 2H), 2.24 (s, 3H), 2.19 (s, 6H); HRMS (ESI): found 708.2042 ($C_{35}H_{38}N_3O_9S_2$. $[M+H]^+$ requires 708.2044); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.09 min, 98.8%.

***N*-(mesitylsulfonyl)-*N*-(1-(2-((2-(2-methoxyethoxy) phenyl) sulfonamido)-1-(3-methoxyphenyl)-2-oxoethyl) indolin-4-yl) glycine (16o). 16o** was synthesized according to the procedure of **15**, white solid, yield 65%; mp: 121-123 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.76 (s, 2H), 7.83 (dd, J = 7.8, 1.6 Hz, 1H), 7.64 (s, 1H), 7.28 (d, J = 7.4 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 7.11 (s, 1H), 6.95 (d, J = 8.3 Hz, 2H), 6.88 (s, 2H), 6.67 (d, J = 8.9 Hz, 2H), 6.56 (d, J = 8.0 Hz, 1H), 6.32 (d, J = 7.8 Hz, 1H), 5.26 (s, 1H), 4.28 (s, 2H), 3.88 – 3.81 (m, 2H), 3.71 (d, J = 10.1 Hz, 3H), 3.63 – 3.51 (m, 2H), 2.27 (d, J = 13.2 Hz, 2H), 2.19 (s, 9H), 1.34 (s, 3H); HRMS (ESI): found 722.2158 ($C_{36}H_{40}N_3O_9S_2$. $[M+H]^+$ requires 722.2154); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.05 min, 98.1%.

***N*-(1-(2-((2-ethylphenyl)sulfonamido)-1-(3-methoxyphenyl)-2-oxoethyl)indolin-4-yl)-*N*-(mesitylsulfonyl)glycine (16p). 16p** was synthesized according to the procedure of **15**, white solid, yield 72%; mp: 105-107 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.65 (s, 2H), 7.98 (d, J = 8.1 Hz,

1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.40 (s, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 6.95 (s, 2H), 6.90 (s, 2H), 6.64 (s, 2H), 6.58 (d, *J* = 7.9 Hz, 1H), 6.27 (d, *J* = 7.7 Hz, 1H), 5.20 (s, 1H), 4.28 (s, 2H), 3.69 (s, 3H), 3.21 (d, *J* = 9.8 Hz, 1H), 2.65 (s, 2H), 2.28 (s, 2H), 2.21 (s, 9H), 1.28 (s, 3H); HRMS (ESI): found 722.2158 ($C_{36}H_{40}N_3O_9S_2$. $[M+H]^+$ requires 722.2154); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.26 min, 97.1%.

***N*-(1-(2-((2-fluorophenyl) sulfonamido)-1-(3-methoxyphenyl)-2-oxoethyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (16q). 16q** was synthesized according to the procedure of **15**, white solid, yield 74%; mp: 106-108 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.95 (s, 2H), 7.92 (t, *J* = 7.5 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 8.3 Hz, 2H), 7.30 (t, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 10.3 Hz, 2H), 6.90 (s, 2H), 6.71 (d, *J* = 7.7 Hz, 2H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.27 (d, *J* = 7.8 Hz, 1H), 5.24 (s, 1H), 4.29 (s, 2H), 3.72 (s, 3H), 3.23 (d, *J* = 8.6 Hz, 2H), 2.42 (d, *J* = 8.0 Hz, 2H), 2.20 (s, 3H), 2.18 (s, 6H); HRMS (ESI): found 718.1657 ($C_{34}H_{34}FN_3NaO_8S_2$. $[M+Na]^+$ requires 718.1663); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.67 min, 96.8%.

***N*-(1-(2-((2-chlorophenyl) sulfonamido)-1-(3-methoxyphenyl)-2-oxoethyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (16r). 16r** was synthesized according to the procedure of **15**, white solid, yield 75%; mp: 111-113 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.93 (s, 2H), 7.91 (t, *J* = 7.7 Hz, 1H), 7.79 (d, *J* = 7.3 Hz, 2H), 7.44 (t, *J* = 8.5 Hz, 2H), 7.31 (t, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 10.3 Hz, 2H), 6.91 (s, 1H), 6.72 (d, *J* = 7.9 Hz, 2H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.26 (d, *J* = 7.8 Hz, 1H), 5.23 (s, 1H), 4.28 (s, 2H), 3.71 (s, 3H), 3.235 (d, *J* = 8.6 Hz, 2H), 2.41 (d, *J* = 8.0 Hz, 2H),

2.21 (s, 3H), 2.18 (s, 6H); HRMS (ESI): found 734.1362 ($C_{34}H_{34}ClN_3NaO_8S_2$. $[M+Na]^+$ requires 734.1368); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.06 min, 98.9%.

***N*-(1-(2-((2-bromophenyl) sulfonamido)-1-(3-methoxyphenyl)-2-oxoethyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (16s). 16s** was synthesized according to the procedure of **15**, white solid, yield 78%; mp: 120-122 ºC. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 13.01 (s, 2H), 8.16 – 8.10 (m, 1H), 7.87 – 7.81 (m, 1H), 7.62 (d, *J* = 6.3 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 1H), 6.99 – 6.92 (m, 2H), 6.90 (d, *J* = 5.6 Hz, 2H), 6.76 – 6.69 (m, 2H), 6.57 (d, *J* = 8.1 Hz, 1H), 6.37 (d, *J* = 7.9 Hz, 1H), 5.32 (s, 1H), 4.29 (s, 2H), 3.71 (s, 3H), 3.67 (s, 2H), 3.23 (d, *J* = 8.7 Hz, 1H), 2.66 (d, *J* = 8.2 Hz, 1H), 2.20 (s, 3H), 2.18 (s, 6H); HRMS (ESI): found 756.1018 ($C_{34}H_{35}BrN_3O_8S_2$. $[M+H]^+$ requires 756.1043); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.21 min, 96.4%.

***N*-(mesitylsulfonyl)-*N*-(1-(1-(3-methoxyphenyl)-2-oxo-2-((2-(trifluoromethyl) phenyl) sulfonamido) ethyl) indolin-4-yl) glycine (16t). 16t** was synthesized according to the procedure of **15**, white solid, yield 69%; mp: 101-103 ºC. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 12.82 (s, 2H), 8.30 (s, 1H), 7.96 (d, *J* = 16.3 Hz, 3H), 7.27 (t, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 6.90 (d, *J* = 7.1 Hz, 3H), 6.70 – 6.62 (m, 2H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.27 (d, *J* = 7.7 Hz, 1H), 5.27 (s, 1H), 4.29 (s, 2H), 3.69 (d, *J* = 2.2 Hz, 3H), 3.25 (d, *J* = 9.0 Hz, 1H), 2.65 (d, *J* = 8.5 Hz, 1H), 2.27 (d, *J* = 12.4 Hz, 2H), 2.19 (d, *J* = 6.9 Hz, 9H); HRMS (ESI): found 746.1817 ($C_{35}H_{35}F_3N_3O_8S_2$. $[M+H]^+$ requires 746.1812); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.02 min, 96.9%.

***N*-(mesitylsulfonyl)-*N*-(1-(1-(3-methoxyphenyl)-2-oxo-2-((2-(trifluoromethoxy) phenyl) sulfonamido) ethyl) indolin-4-yl) glycine (16u). 16u** was synthesized according to the procedure

of **15**, white solid, yield 68%; mp: 90-92 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.94 (s, 2H), 8.06 (d, J = 8.0 Hz, 1H), 7.85 (t, J = 8.0 Hz, 1H), 7.58 (q, J = 8.5, 8.1 Hz, 2H), 7.30 (t, J = 7.9 Hz, 1H), 6.99 – 6.91 (m, 2H), 6.89 (s, 2H), 6.72 (t, J = 6.4 Hz, 2H), 6.57 (d, J = 8.0 Hz, 1H), 6.27 (d, J = 7.9 Hz, 1H), 5.26 (s, 1H), 4.29 (s, 2H), 3.72 (s, 3H), 3.69 (s, 2H), 3.24 (d, J = 8.6 Hz, 1H), 2.66 (d, J = 8.2 Hz, 1H), 2.19 (d, J = 5.1 Hz, 9H); HRMS (ESI): found 784.1574 ($C_{35}H_{34}F_3N_3NaO_9S_2$. $[M+Na]^+$ requires 784.1580); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.02 min, 97.8%.

***N*-(1-(2-((2,4-dimethylphenyl) sulfonamido)-1-(3-methoxyphenyl)-2-oxoethyl) indolin-4-yl)-*N*-(mesitylsulfonyl) glycine (16v). 16v** was synthesized according to the procedure of **15**, white solid, yield 69%; mp: 113-115 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.92 (s, 2H), 7.95 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 6.8 Hz, 1H), 7.37 – 7.27 (m, 2H), 7.08 (d, J = 9.9 Hz, 2H), 7.02 (s, 2H), 6.81 (d, J = 7.6 Hz, 1H), 6.77 – 6.66 (m, 2H), 6.40 (d, J = 7.9 Hz, 1H), 5.35 (s, 1H), 4.42 (s, 2H), 3.81 (s, 3H), 3.37 (d, J = 8.8 Hz, 1H), 2.80 – 2.74 (m, 1H), 2.54 (s, 2H), 2.33 (s, 9H), 2.12 (s, 6H); HRMS (ESI): found 706.2247 ($C_{36}H_{40}N_3O_8S_2$. $[M+H]^+$ requires 706.2251); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.31 min, 97.2%.

***N*-(1-(2-((2,4-dimethoxyphenyl)sulfonamido)-1-(3-methoxyphenyl)-2-oxoethyl)indolin-4-yl)-*N*-(mesitylsulfonyl)glycine (16x). 16x** was synthesized according to the procedure of **15**, white solid, yield 68%; mp: 101-103 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.91 (s, 2H), 7.93 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 6.8 Hz, 1H), 7.38 – 7.26 (m, 2H), 7.13 (d, J = 9.9 Hz, 2H), 7.04 (s, 2H), 6.80 (d, J = 7.6 Hz, 1H), 6.78 – 6.66 (m, 2H), 6.43 (d, J = 7.9 Hz, 1H), 5.34 (s, 1H), 4.41 (s, 2H), 3.95 (d, J = 3.3 Hz, 6H), 3.80 (s, 3H), 3.36 (d, J = 8.8 Hz, 1H), 2.81 – 2.73 (m, 1H), 2.53 (s,

2H), 2.35 (s, 9H); HRMS (ESI): found 760.1963 ($C_{36}H_{39}N_3NaO_{10}S_2$. $[M+H]^+$ requires 760.1969); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.20 min, 98.3%.

***N*-(1-(2-((3,5-dimethylphenyl)sulfonamido)-1-(3-methoxyphenyl)-2-oxoethyl)indolin-4-yl)-N-(mesitylsulfonyl)glycine (16y). 16y** was synthesized according to the procedure of **15**, white solid, yield 66%; mp: 102-104 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.93 (s, 2H), 7.96 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 6.4 Hz, 1H), 7.32 – 7.23 (m, 2H), 7.12 (d, J = 9.7 Hz, 2H), 7.06 (s, 2H), 6.80 (d, J = 7.6 Hz, 1H), 6.77 – 6.66 (m, 2H), 6.40 (d, J = 7.9 Hz, 1H), 5.35 (s, 1H), 4.41 (s, 2H), 3.82 (s, 3H), 3.36 (d, J = 8.6 Hz, 1H), 2.81 – 2.76 (m, 1H), 2.54 (s, 2H), 2.32 (s, 9H), 2.22 (s, 6H); HRMS (ESI): found 706.2247 ($C_{36}H_{40}N_3O_8S_2$. $[M+H]^+$ requires 706.2251); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.37 min, 98.4%.

***N*-(mesitylsulfonyl)-*N*-(1-(1-(3-methoxyphenyl)-2-(naphthalene-1-sulfonamido)-2-oxoethyl)indolin-4-yl)glycine (16z). 16z** was synthesized according to the procedure of **15**, white solid, yield 71%; mp: 100-102 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.86 (s, 2H), 8.32 (s, 2H), 7.96 (d, J = 16.7 Hz, 3H), 7.25 (t, J = 8.6 Hz, 2H), 6.99 (d, J = 8.5 Hz, 2H), 6.91 (d, J = 7.1 Hz, 3H), 6.72 - 6.62 (m, 2H), 6.58 (d, J = 8.0 Hz, 1H), 6.29 (d, J = 7.9 Hz, 1H), 5.26 (s, 1H), 4.28 (s, 2H), 3.79 (d, J = 2.2 Hz, 3H), 3.27 (s, 1H), 2.65 (s, 1H), 2.29 (d, J = 12.2 Hz, 2H), 2.18 (d, J = 6.9 Hz, 9H); HRMS (ESI): found 728.2095 ($C_{38}H_{38}N_3O_8S_2$. $[M+H]^+$ requires 728.2094); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 6.34 min, 99.2%.

***N*-((2-methoxy-4-methylphenyl)sulfonyl)-2-(3-methoxyphenyl)-2-(4-((4-methyl-*N*-(2-oxo-2-(phenylsulfonamido)ethyl)phenyl)sulfonamido)indolin-1-yl)acetamide (17c). 17c** was

synthesized according to the procedure of **17a**, white solid, yield 52%; mp: 188-190 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.84 (s, 2H), 7.79 (d, J = 8.9 Hz, 1H), 7.66 - 7.58 (m, 3H), 7.50 (d, J = 8.5 Hz, 2H), 7.38 (t, J = 7.4 Hz, 1H), 7.07 - 6.99 (m, 3H), 6.91 (t, J = 3.1 Hz, 3H), 6.83 (dd, J = 12.2, 7.3 Hz, 4H), 6.15 (d, J = 7.3 Hz, 1H), 6.00 (d, J = 8.1 Hz, 1H), 5.01 (s, 1H), 3.91 (d, J = 2.9 Hz, 2H), 3.84 (s, 3H), 3.72 (s, 3H), 3.64 (s, 2H), 2.82 - 2.72 (m, 1H), 2.37 (s, 6H); HRMS (ESI): found 833.1935 ($C_{40}H_{40}N_4O_{10}S_3$. $[M+H]^+$ requires 833.1928); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.43 min, 96.9%.

2-(4-((4-fluoro-*N*-(2-oxo-2-(phenylsulfonamido)ethyl)phenyl)sulfonamido)indolin-1-yl)-*N*-((2-methoxy-4-methylphenyl)sulfonyl)-2-(3-methoxyphenyl)acetamide (17d). 17d was synthesized according to the procedure of **17a**, white solid, yield 48%; mp: 211-213 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.58 (s, 2H), 7.78 (d, J = 7.1 Hz, 1H), 7.66 - 7.58 (m, 1H), 7.50 (d, J = 8.9 Hz, 2H), 7.35 (t, J = 7.9 Hz, 2H), 7.11 - 6.99 (m, 3H), 6.92 (dq, J = 10.4, 3.2, 3.1 Hz, 4H), 6.81 (dd, J = 15.2, 7.9Hz, 4H), 6.18 (d, J = 7.5 Hz, 1H), 6.08 (d, J = 8.3 Hz, 1H), 5.11 (s, 1H), 3.92 (d, J = 2.9 Hz, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.65 (s, 2H), 2.82 - 2.72 (m, 2H); HRMS (ESI): found 859.1541 ($C_{39}H_{37}FN_4NaO_{10}S_3$. $[M+Na]^+$ requires 859.1548); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.56 min, 97.3%.

2-(4-((4-acetamido-*N*-(2-oxo-2-(phenylsulfonamido)ethyl)phenyl)sulfonamido)indolin-1-yl)-*N*-((2-methoxy-4-methylphenyl)sulfonyl)-2-(3-methoxyphenyl)acetamide (17e). 17e was synthesized according to the procedure of **17a**, white solid, yield 43%; mp: 193-195 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.71 (s, 2H), 10.41 (s, 1H), 7.69 (d, J = 7.9 Hz, 2H), 7.63 - 7.59 (m, 2H),

7.52 (d, *J* = 8.9 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.14 - 7.05 (m, 2H), 6.91 (dd, *J* = 4.6, 3.3 Hz, 3H), 6.82 (dd, *J* = 12.3, 7.6 Hz, 4H), 6.15 (d, *J* = 7.9 Hz, 2H), 6.00 (d, *J* = 8.1 Hz, 1H), 5.01 (s, 1H), 3.92 (d, *J* = 2.1 Hz, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.64 (s, 2H), 2.81 - 2.72 (m, 2H), 2.37 (s, 3H), 2.02 (s, 3H); HRMS (ESI): found 898.2048 ($C_{41}H_{41}N_5NaO_{11}S_3$. $[M+Na]^+$ requires 898.2052); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.21 min, 98.3%.

***N*-((2-methoxy-4-methylphenyl)sulfonyl)-2-(4-((2-methoxy-*N*-(2-oxo-2-(phenylsulfonamido)ethyl)phenyl)sulfonamido)indolin-1-yl)-2-(3-methoxyphenyl)acetamide (17f). 17f** was synthesized according to the procedure of **17a**, white solid, yield 50%; mp: 223-225 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.33 (s, 2H), 7.86 (t, *J* = 9.1 Hz, 2H), 7.75 - 7.65 (m, 2H), 7.53 (d, *J* = 32.6 Hz, 6H), 7.36 - 7.27 (m, 2H), 7.22 (d, *J* = 6.1 Hz, 2H), 6.97 (t, *J* = 8.6 Hz, 2H), 6.81 (dd, *J* = 18.6, 9.0 Hz, 2H), 6.24 (d, *J* = 7.7 Hz, 1H), 5.09 (d, *J* = 19.7 Hz, 1H), 4.41 (s, 1H), 4.13 (s, 1H), 4.02 (s, 2H), 3.92 (d, *J* = 3.0 Hz, 3H), 3.74 (d, *J* = 2.9 Hz, 3H), 3.66 (d, *J* = 12.1 Hz, 3H), 3.20 (s, 2H), 2.40 (s, 3H); HRMS (ESI): found 871.1754 ($C_{40}H_{40}N_4NaO_{11}S_3$. $[M+Na]^+$ requires 871.1747); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.69 min, 97.5%.

***N*-((2-methoxy-4-methylphenyl)sulfonyl)-2-(4-((3-methoxy-*N*-(2-oxo-2-(phenylsulfonamido)ethyl)phenyl)sulfonamido)indolin-1-yl)-2-(3-methoxyphenyl)acetamide (17g). 17g** was synthesized according to the procedure of **17a**, white solid, yield 54%; mp: 207-209 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.76 (s, 2H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.73 - 7.66 (m, 2H), 7.59 (d, *J* = 8.9 Hz, 2H), 7.27 (t, *J* = 5.9 Hz, 2H), 7.12 - 7.04 (m, 3H), 6.91 (dq, *J* = 10.2, 3.6, 3.1 Hz, 3H), 6.82 (dd, *J* = 15.0, 7.5 Hz, 4H), 6.14 (d, *J* = 7.9 Hz, 1H), 6.00 (d, *J* = 8.1 Hz, 1H),

5.06 (s, 1H), 3.95 (d, *J* = 2.9 Hz, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.72 (s, 3H), 3.62 (s, 2H), 2.82 - 2.72 (m, 2H), 2.24 (s, 3H); HRMS (ESI): found 871.1754 ($C_{40}H_{40}N_4NaO_{11}S_3$. $[M+Na]^+$ requires 871.1747); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.48 min, 98.1%.

***N*-((2-methoxy-4-methylphenyl)sulfonyl)-2-(3-methoxyphenyl)-2-(4-(*N*-(2-oxo-2-(phenylsulfonamido)ethyl)phenylsulfonamido)indolin-1-yl)acetamide (17h). 17h** was synthesized according to the procedure of **17a**, white solid, yield 43%; mp: 231-233 ºC. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 12.51 (s, 2H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.27 (t, *J* = 5.3 Hz, 2H), 7.05 - 6.95 (m, 3H), 6.91 (m, 4H), 6.81 (dd, *J* = 12.2, 7.5 Hz, 4H), 6.17 (d, *J* = 7.7 Hz, 1H), 6.06 (d, *J* = 8.8 Hz, 1H), 5.12 (s, 1H), 3.99 (d, *J* = 2.5 Hz, 2H), 3.88 (s, 3H), 3.73 (s, 3H), 3.62 (s, 2H), 2.82 - 2.72 (m, 2H), 2.34 (s, 3H); HRMS (ESI): found 819.1829 ($C_{39}H_{39}N_4O_{10}S_3$. $[M+H]^+$ requires 819.1824); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.52 min, 97.5%.

2-(4-((*N*-(2-(cyclopropanesulfonamido)-2-oxoethyl)-4-methoxyphenyl)sulfonamido)indolin-1-yl)-N-((2-methoxy-4-methylphenyl)sulfonyl)-2-(3-methoxyphenyl)acetamide (18a). 18a was synthesized according to the procedure of **17a**, white solid, yield 51%; mp: 215-217 ºC. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 12.25 (s, 2H), 7.61 (dd, *J* = 8.0, 5.3 Hz, 3H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.90 (dd, *J* = 15.8, 8.8 Hz, 4H), 6.76 (t, *J* = 8.3 Hz, 2H), 6.22 (d, *J* = 7.8 Hz, 1H), 6.00 (d, *J* = 8.0 Hz, 1H), 4.79 (s, 1H), 3.93 (d, *J* = 3.5 Hz, 1H), 3.85 (s, 3H), 3.74 (s, 3H), 3.66 (s, 3H), 3.20 (s, 1H), 2.85 (d, *J* = 8.5 Hz, 2H), 2.66 - 2.57 (m, 1H), 2.34 (s, 3H), 0.73 (d, *J* = 4.5 Hz, 2H), 0.69 – 0.60 (m, 2H); HRMS (ESI): found

835.1746 ($C_{37}H_{40}N_4NaO_{11}S_3$. $[M+Na]^+$ requires 835.1747); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.42 min, 98.9%.

***N*-((2-methoxy-4-methylphenyl)sulfonyl)-2-(4-((4-methoxy-*N*-(2-(methylsulfonamido)-2-oxoethyl)phenyl)sulfonamido)indolin-1-yl)-2-(3-methoxyphenyl)acetamide (18b). 18b** was synthesized according to the procedure of **17a**, white solid, yield 45%; mp: 188-190 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.45 (s, 2H), 7.91 (d, J = 8.0 Hz, 3H), 7.65 (t, J = 7.6 Hz, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.10 (dd, J = 15.8, 8.8 Hz, 4H), 6.96 (t, J = 8.3 Hz, 2H), 6.21 (d, J = 7.8 Hz, 1H), 6.12 (d, J = 8.4 Hz, 1H), 4.88 (s, 1H), 3.95 (d, J = 3.7 Hz, 1H), 3.86 (s, 3H), 3.72 (s, 3H), 3.65 (s, 3H), 3.22 (s, 1H), 2.96 (s, 3H), 2.87 (d, J = 8.5 Hz, 2H), 2.66 - 2.56 (m, 1H), 2.32 (s, 3H); HRMS (ESI): found 787.1752 ($C_{35}H_{39}N_4O_{11}S_3$. $[M+H]^+$ requires 787.1748); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.28 min, 96.8%.

***N*-((2-methoxy-4-methylphenyl)sulfonyl)-2-(4-((4-methoxy-*N*-(2-oxo-2-((trifluoromethyl)sulfonamido)ethyl)phenyl)sulfonamido)indolin-1-yl)-2-(3-methoxyphenyl)acetamide (18c). 18c** was synthesized according to the procedure of **17a**, white solid, yield 46%; mp: 229-231 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.71 (s, 1H), 12.21 (s, 1H), 7.61 (t, J = 10.7 Hz, 3H), 7.26 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.6 Hz, 2H), 6.91 (s, 4H), 6.85 - 6.72 (m, 2H), 6.20 (d, J = 7.9 Hz, 1H), 6.04 (d, J = 7.9 Hz, 1H), 5.79 (s, 1H), 4.15 (s, 2H), 4.00 (s, 2H), 3.85 (s, 3H), 3.74 (s, 3H), 3.66 (s, 3H), 3.20 (s, 1H), 2.85 (d, J = 26.5 Hz, 1H), 2.36 (s, 3H); HRMS (ESI): found 863.1298 ($C_{35}H_{35}F_3N_4NaO_{11}S_3$. $[M+Na]^+$ requires 863.1308); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.16 min, 98.6%.

***N*-((2-methoxy-4-methylphenyl)sulfonyl)-2-(4-((4-methoxy-*N*-(2-oxo-2-(pyridine-3-sulfonamido)ethyl)phenyl)sulfonamido)indolin-1-yl)-2-(3-methoxyphenyl)acetamide (18d).** **18d** was synthesized according to the procedure of **17a**, white solid, yield 44%; mp: 196-198 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.57 (s, 2H), 7.78 (d, J = 7.1 Hz, 1H), 7.71 - 7.66 (m, 2H), 7.52 (d, J = 8.9 Hz, 2H), 7.29 (t, J = 7.9 Hz, 1H), 7.14 - 705 (m, 2H), 6.91 (s, 2H), 6.82 (dd, J = 15.0, 7.5 Hz, 4H), 6.14 (d, J = 7.9 Hz, 2H), 6.02 (d, J = 8.3 Hz, 2H), 5.01 (s, 1H), 3.91 (d, J = 2.9 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.71 (s, 3H), 3.64 (s, 2H), 2.82 (s, 2H), 2.37 (s, 3H); HRMS (ESI): found 872.1821 ($C_{39}H_{39}N_5NaO_{11}S_3$. $[M+Na]^+$ requires 872.1825); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.28 min, 97.8%.

***N*-((2-methoxy-4-methylphenyl)sulfonyl)-2-(4-((4-methoxy-*N*-(2-oxo-2-(thiophene-2-sulfonamido)ethyl)phenyl)sulfonamido)indolin-1-yl)-2-(3-methoxyphenyl)acetamide (18e).** **18e** was synthesized according to the procedure of **17a**, white solid, yield 43%; mp: 182-184 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.49 (s, 2H), 7.93 (d, J = 8.2 Hz, 3H), 7.69 (t, J = 7.6 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.10 (dd, J = 15.8, 8.8 Hz, 4H), 6.99 (t, J = 8.3 Hz, 3H), 6.21 (d, J = 7.8 Hz, 1H), 6.14 (d, J = 8.6 Hz, 2H), 4.99 (s, 1H), 3.98 (d, J = 3.9 Hz, 1H), 3.87 (s, 3H), 3.73 (s, 3H), 3.69 (s, 3H), 3.22 (s, 1H), 2.87 (d, J = 8.5 Hz, 2H), 2.66 - 2.56 (m, 1H), 2.32 (s, 3H); HRMS (ESI): found 877.1453 ($C_{38}H_{38}N_4NaO_{11}S_4$. $[M+Na]^+$ requires 877.1464); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.21 min, 95.8%.

***N*-((2-methoxy-4-methylphenyl)sulfonyl)-2-(4-((4-methoxy-*N*-(2-((4-methylphenyl)sulfonamido)-2-oxoethyl)phenyl)sulfonamido)indolin-1-yl)-2-(3-**

methoxyphenyl)acetamide (19b). 19b was synthesized according to the procedure of **17a**, white solid, yield 48%; mp: 224-226 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.41 (s, 2H), 7.83 (d, J = 7.9 Hz, 1H), 7.66 (dd, J = 8.6, 4.1 Hz, 3H), 7.36 (s, 1H), 7.23 (d, J = 8.7 Hz, 2H), 7.06 – 6.93 (m, 5H), 6.79 (d, J = 9.9 Hz, 3H), 6.48 (d, J = 7.8 Hz, 3H), 5.94 (d, J = 8.2 Hz, 2H), 4.93 (s, 1H), 4.46 (s, 1H), 3.96 (s, 1H), 3.85 (s, 3H), 3.79 (d, J = 2.1 Hz, 3H), 3.73 (s, 3H), 3.19 (d, J = 3.9 Hz, 1H), 2.88 (s, 2H), 2.35 (s, 6H); HRMS (ESI): found 885.1894 ($C_{41}H_{42}N_4NaO_{11}S_3$. $[M+Na]^+$ requires 885.1904); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.38 min, 96.8%.

2-(4-((*N*-(2-((4-fluorophenyl)sulfonamido)-2-oxoethyl)-4-methoxyphenyl)sulfonamido)indolin-1-yl)-*N*-((2-methoxy-4-methylphenyl)sulfonyl)-2-(3-methoxyphenyl)acetamide (19c). 19c was synthesized according to the procedure of **17a**, white solid, yield 43%; mp: 213-215 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.41 (s, 1H), 9.41 (s, 1H), 7.63 (t, J = 7.1 Hz, 3H), 7.56 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.0 Hz, 1H), 7.15 (t, J = 8.9 Hz, 2H), 7.03 (d, J = 8.5 Hz, 2H), 6.91 (s, 4H), 6.82 - 6.67 (m, 2H), 6.19 (d, J = 8.7 Hz, 1H), 5.93 (d, J = 8.1 Hz, 1H), 4.83 (s, 1H), 3.91 (s, 1H), 3.85 (d, J = 2.4 Hz, 3H), 3.80 (d, J = 11.4 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 2.82 (s, 2H), 2.35 (d, J = 6.4 Hz, 3H); HRMS (ESI): found 889.1651 ($C_{40}H_{39}N_4NaO_{11}S_3$. $[M+Na]^+$ requires 889.1653); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.45 min, 98.1%.

***N*-((2-methoxy-4-methylphenyl)sulfonyl)-2-(4-((4-methoxy-*N*-(2-oxo-2-((4-(trifluoromethyl)phenyl)sulfonamido)ethyl)phenyl)sulfonamido)indolin-1-yl)-2-(3-methoxyphenyl)acetamide (19d). 19d** was synthesized according to the procedure of **17a**, white

solid, yield 44%; mp: 223-225 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.41 (s, 2H), 7.68 (d, J = 7.8 Hz, 1H), 7.54 (dd, J = 8.6, 3.1 Hz, 3H), 7.23 (s, 1H), 7.13 (d, J = 8.5 Hz, 3H), 6.95 - 6.82 (m, 6H), 6.72 (d, J = 9.5 Hz, 2H), 6.28 (d, J = 7.8 Hz, 2H), 5.95 (d, J = 8.2 Hz, 1H), 4.83 (s, 1H), 4.42 (s, 1H), 3.88 (s, 1H), 3.84 (s, 3H), 3.72 (s, 3H), 3.66 (s, 3H), 3.16 (d, J = 3.9 Hz, 1H), 2.82 (s, 2H), 2.36 (s, 3H); HRMS (ESI): found 939.1741 ($C_{41}H_{39}N_4NaO_{11}S_3$. $[M+Na]^+$ requires 939.1743); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.56 min, 98.8%.

2-(4-((*N*-(2-((4-ethylphenyl)sulfonamido)-2-oxoethyl)-4-methoxyphenyl)sulfonamido)indolin-1-yl)-*N*-((2-methoxy-4-methylphenyl)sulfonyl)-2-(3-methoxyphenyl)acetamide (19e). 19e was synthesized according to the procedure of **17a**, white solid, yield 45%; mp: 217-219 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.51 (s, 2H), 8.23 (d, J = 7.3 Hz, 2H), 8.16 (dd, J = 8.6, 4.1 Hz, 2H), 7.86 (s, 1H), 7.73 (d, J = 8.7 Hz, 2H), 7.56 - 7.47 (m, 5H), 7.19 (d, J = 9.7 Hz, 3H), 6.88 (d, J = 7.8 Hz, 2H), 6.34 (d, J = 8.2 Hz, 2H), 4.99 (s, 1H), 4.56 (s, 1H), 4.02 - 4.09 (m, 2H), 3.96 (s, 1H), 3.85 (s, 3H), 3.77 (d, J = 2.1 Hz, 3H), 3.72 (s, 3H), 3.19 (d, J = 3.9 Hz, 1H), 2.88 (s, 2H), 2.35 (s, 3H), 1.34 - 1.25 (m, 3H); HRMS (ESI): found 899.2054 ($C_{42}H_{44}N_4NaO_{11}S_3$. $[M+Na]^+$ requires 899.2060); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.46 min, 98.3%.

2-(4-((*N*-(2-((4-hydroxyphenyl)sulfonamido)-2-oxoethyl)-4-methoxyphenyl)sulfonamido)indolin-1-yl)-*N*-((2-methoxy-4-methylphenyl)sulfonyl)-2-(3-methoxyphenyl)acetamide (19f). 19f was synthesized according to the procedure of **17a**, white solid, yield 45%; mp: 167-169 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.62 (s, 2H), 10.02 (s, 1H),

8.11 (d, J = 7.6 Hz, 2H), 8.15 (dd, J = 8.6, 4.1 Hz, 2H), 7.76 (s, 1H), 7.70 (d, J = 8.7 Hz, 2H), 7.59 - 7.48 (m, 5H), 7.18 (d, J = 7.7 Hz, 3H), 6.99 (d, J = 7.8 Hz, 2H), 6.64 (d, J = 8.2 Hz, 2H), 4.95 (s, 1H), 4.58 (s, 1H), 3.90 (s, 1H), 3.85 (s, 3H), 3.79 (d, J = 2.1 Hz, 3H), 3.74 (s, 3H), 3.19 (d, J = 3.9 Hz, 1H), 2.86 (s, 2H), 2.34 (s, 3H); HRMS (ESI): found 887.1862 ($C_{42}H_{44}N_4NaO_{11}S_3$. $[M+Na]^+$ requires 887.1864); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.02 min, 97.1%.

2-(4-((*N*-(2-((4-ethoxyphenyl)sulfonamido)-2-oxoethyl)-4-methoxyphenyl)sulfonamido)indolin-1-yl)-*N*-((2-methoxy-4-methylphenyl)sulfonyl)-2-(3-methoxyphenyl)acetamide (19g). 19g was synthesized according to the procedure of **17a**, white solid, yield 42%; mp: 199-201 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.51 (s, 2H), 8.13 (d, J = 8.6 Hz, 2H), 8.05 (dd, J = 8.4, 4.3 Hz, 2H), 7.86 (s, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.58 - 7.48 (m, 4H), 7.18 (d, J = 7.7 Hz, 3H), 6.99 (d, J = 7.8 Hz, 3H), 6.65 (d, J = 8.2 Hz, 2H), 4.97 (s, 1H), 4.57 (s, 1H), 4.04 - 4.08 (m, 2H), 3.91 (s, 1H), 3.88 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.23 (d, J = 3.9 Hz, 1H), 2.86 (s, 2H), 2.34 (s, 3H), 1.40 - 1.46 (m, 3H); HRMS (ESI): found 915.2131 ($C_{42}H_{44}N_4NaO_{12}S_3$. $[M+Na]^+$ requires 915.2134); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.43 min, 96.2%.

***N*-((2-methoxy-4-methylphenyl)sulfonyl)-2-(4-((4-methoxy-*N*-(2-((2-methoxyphenyl)sulfonamido)-2-oxoethyl)phenyl)sulfonamido)indolin-1-yl)-2-(3-methoxyphenyl)acetamide (19h). 19h** was synthesized according to the procedure of **17a**, white solid, yield 43%; mp: 201-203 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.27 (s, 1H), 9.10 (s, 1H), 7.71 - 7.49 (m, 3H), 7.36 (dd, J = 17.6, 8.5 Hz, 3H), 7.06 (dd, J = 17.8, 8.3 Hz, 5H), 6.89 (d, J =

18.4 Hz, 6H), 6.27 - 5.89 (m, 2H), 4.02 (d, *J* = 12.9 Hz, 1H), 3.88 - 3.82 (m, 3H), 3.79 - 3.71 (m, 3H), 3.68 (t, *J* = 5.8 Hz, 3H), 3.64 - 3.52 (m, 3H), 2.34 (d, *J* = 14.0 Hz, 3H); HRMS (ESI): found 879.2031 ($C_4H_{43}N_4O_{12}S_3$. $[M+H]^+$ requires 879.2034); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.53 min, 96.4%.

***N*-((2-methoxy-4-methylphenyl)sulfonyl)-2-(4-((4-methoxy-*N*-(2-((3-methoxyphenyl)sulfonamido)-2-oxoethyl)phenyl)sulfonamido)indolin-1-yl)-2-(3-methoxyphenyl)acetamide (19i). 19i** was synthesized according to the procedure of **17a**, white solid, yield 42%; mp: 184-186 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.65 (s, 1H), 12.21 (s, 1H), 7.84 (dd, *J* = 8.8, 3.1 Hz, 4H), 7.66 (d, *J* = 8.8 Hz, 4H), 7.46 (s, 1H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.90 - 6.80 (m, 6H), 6.77 (d, *J* = 9.5 Hz, 2H), 6.19 (d, *J* = 3.8 Hz, 2H), 5.97 (d, *J* = 8.2 Hz, 1H), 4.83 (s, 1H), 4.47 (s, 1H), 3.88 (s, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.73 (s, 3H), 3.66 (s, 3H), 3.23 (d, *J* = 3.9 Hz, 1H), 2.88 (s, 2H), 2.34 (s, 3H); HRMS (ESI): found 879.2031 ($C_4H_{43}N_4O_{12}S_3$. $[M+H]^+$ requires 879.2034); HPLC (85:15 methanol:water with 1‰ TFA): t_R = 5.74 min, 96.8%.

S3. Keap1 Kelch Domain Expression and Purification.

Keap1 Kelch domain was expressed and purified as previously described.[1] Briefly, the human Keap1 Kelch-DC (residues 321-609) was cloned into a pET-28a vector (Zoonbio Biotechnology) between a NcoI site and a XhoI site. The construct was expressed in *Escherichia coli* ArcticExpressTM (DE3), and the cells were then shaken until the optical density at 595 nm reached

0.4 to 0.6. The cells were next induced with a final concentration of 0.2 mM isopropyl-β-D-1-thiogalactopyranoside (IPTG) for another 4 h. Then the protein was purified on an ÄKTATM pure 25 system (GE Healthcare, Life Sciences) employing a Ni-NTA column (Novagen). Lastly, 10% SDS-PAGE was used for confirming the molecular weight of the purified protein.

S4. Fluoresce Polarization (FP) Competition Assay.

In vitro inhibitory activity of compounds on Keap1-Nrf2 PPI was carried out in the black non-binding surface Corning 3676 384-well plates by FP assay. The experimental procedure was detailedly described previously.[1] In brief, each well was added 40μL of assay solution, comprised of 10 μL of 4 nM FITC-9mer Nrf2 peptide amide, 10 μL of 12 nM Keap1 Kelch domain protein, 10 μL of HEPES buffer and 10 μL of diluted compounds in different concentrations. After 0.5 h incubation with slow shaking at room temperature, the fluorescence intensity was measured at λex 485 nm and λem 530 nm using a SpectraMax Multi-Mode Microplate Reader (Molecular Devices). The data were analyzed by GraphPad Prism 6.0 software.

S5. The Binding Mode of Compound 15 with Keap1.

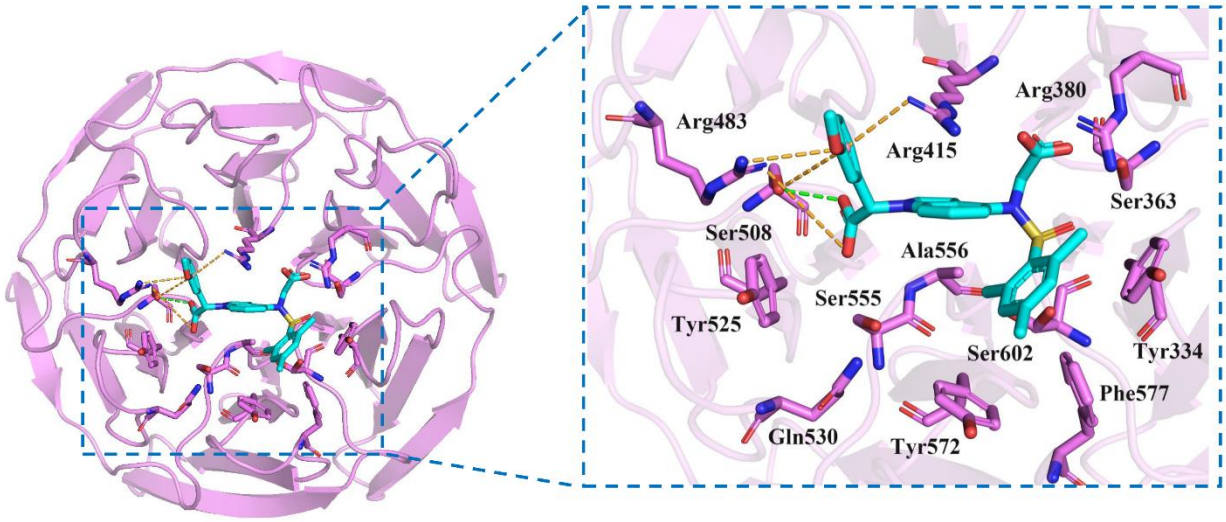
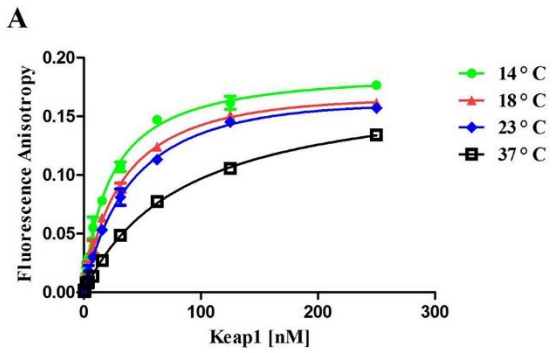


Figure S1. The binding mode of **15** with Keap1 using a docking method. The docking site was derived from the position of the small molecular ligand cocrystallized in the binding site of Keap1 (PDB 4XMB). The ligand is represented as sticks. Hydrogen bonds are represented by green dashed lines, and electrostatic interactions are represented by orange dashed lines. The π-π interactions are represented by pink dashed lines. The carbon atoms of small molecules and Keap1 residues are colored cyan and purple, respectively.

S6. Determination of Thermodynamics Data Based on a Tracer Displacement Assay.

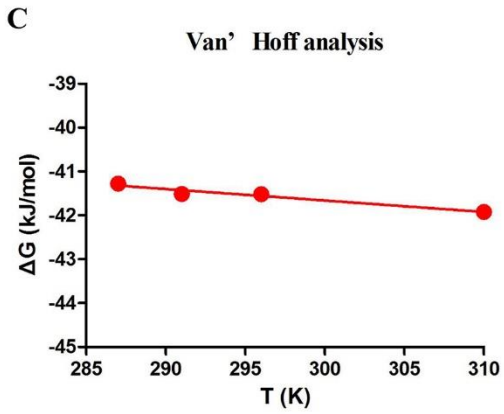
The thermodynamic data of test compounds were determined by a tracer displacement assay described in the literature.[2] The dissociation constants (K_d) of the Nrf2-derived peptide labeled with FITC (probe) against Keap1 were determined at different temperatures. The Keap1 concentration was increased in the presence of a fixed concentration of probe, resulting in the formation of Keap1: probe complex with an increase in observed fluorescence anisotropy readout (Figure S2A). By fitting the data to a one site total fit model, the K_d values were determined and

listed in Figure S2B. According to the equation ΔG = -RTln(1/K_d), the free binding energies (ΔG) were also determined and listed in Figure S2B. By plotting the free binding energies against the corresponding temperatures (Van't Hoff analysis; Figure S2C) the changes in enthalpy (ΔH, given by the y-intercept) and changes in entropy (ΔS, given by the slope) were determined (Figure S2D). The thermodynamics of binding of test compounds to Keap1 were determined as following procedure: First, the IC_{50} values of compounds were measured at different temperature and fitted using a variable slope four parameters fit. Determined IC_{50} values were converted to the corresponding dissociation constants according to Cheng-Prusoff-equation: K_i (compound) = IC_{50} (compound)/[1 + [probe]/$K_{d\ (probe)}$][3, 4]. Subsequently the ΔG is calculated and plotted against the associated temperatures.



B

T(° C)	14	18	23	37
T(K)	287	291	296	310
K_d (nM)	30.73±3.32	35.33±2.51	47.16±3.67	86.24±6.50
ΔG (kJ/mol)	-41.27	-41.51	-41.52	-41.92



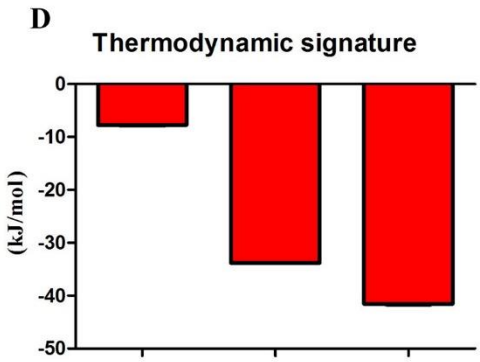


Figure S2. (A) Determination of K_d values for the interaction between Nrf2-derived FITC labeled peptide (probe) and Keap1 at various temperatures. Increasing Keap1 concentrations were incubated with the probe at different temperatures. (B) K_d and ΔG values of probe-Keap1 interactions at various temperatures. (C) Van' Hoff analysis of probe-Keap1 interactions. (D) Thermodynamic profiling of probe-Keap1 interactions.

S7. Isothermal Titration Calorimetry (ITC) Assay.

According to the previous method,[1] ITC assay was carried out at 25 °C with the ITC200 system (MicroCal). Both the protein sample and the compound were dissolved in 10 mM HEPES buffer (pH 7.4). 2 μL aliquots of indicated concentrations of compounds dissolved in 10 mM HEPES buffer (pH 7.4) were injected 19 times at 2.5 min intervals from a stirring syringe (750 rpm) into the sample cell containing 220 μl of corresponding concentrations of Keap1 Kelch domain (dissolved in the same HEPES buffer). The data were analyzed using the Origin 7.0 software (MicroCal).

S8. Biolayer Interferometry (BLI) Assay.

The BLI assay was performed as previously described.[1] The Keap1 Kelch domain protein was biotinylated in 20 mM HEPES buffer (pH 7.0). Octet Red 96 instrument (FortéBio Inc.) was used to evaluated the interaction between the ligand and the protein at 30 °C. First, the sensor SSA

(Super Streptavidin Biosensors tips, FortéBio, Inc., Menlo Park, CA) were prewetted with buffer (FortéBio) to construct a baseline. Then the biotinylated Keap1 protein was immobilized onto sensors. After that, this detection contained five steps: (a) baseline acquisition; (b) protein loading onto the sensor; (c) second baseline acquisition; (d) association of the ligand for the measurement of k_{on}; (e) dissociation of the ligands for the measurement of k_{dis}. Four concentrations of compound **19a** were used for test. The association and dissociation plot and kinetic constants were obtained with FortéBio data analysis software. Equilibrium dissociation constant (K_d) was calculated by the ratio of k_{dis} to k_{on}.

S9. ARE-Luciferase Activity Assay.

This assay was performed according to previous procedure reported previously.[5] HepG2-ARE-C8 cells were plated in 96-well plates (4×10^4 cells/well) and incubated overnight. The cells were exposed to different concentrations of **19a**, with the luciferase cell culture lysis reagent as a blank, SFN serving as a positive control and DMSO as a negative control. After 12 h of treatment, the medium was removed, and 100 μL of cold PBS was added to each well. Then, the cells were harvested using the luciferase cell culture lysis reagent. After centrifugation, 20 μL of the supernatant from the lysate was used to measure luciferase activity according to the manufacturer's protocol (Promega, Madison, WI). The luciferase activity was determined by a Luminoskan Ascent

(Thermo Scientific, USA). The data were obtained in triplicate and shown as a fold induction over the control.

S10. Cell Viability Assay.

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was performed to evaluate the cytotoxicity of **19a** in the H9c2 cells. In brief, cells were seeded into 96-well plates for overnight, treated with test compound **19a** at various concentrations (0-100 μM) for 24 h. Subsequently, 20 μL of MTT (5 mg/mL) was added to each well. After incubation at 37°C for 4 h, MTT solution was removed and DMSO (150 μL) was added to each well. The absorbance values were determined by Multiskan Spectrum Microplate Reader (Thermo, USA) at 570 nm and 630 nm. Each concentration was tested in triplicate wells and data were analyzed as described previously. The data in Figure S3 showed that the survival rate remained higher than approximately 90% under 100 μM, indicating no apparent cytotoxicity for the treatment of **19a**.

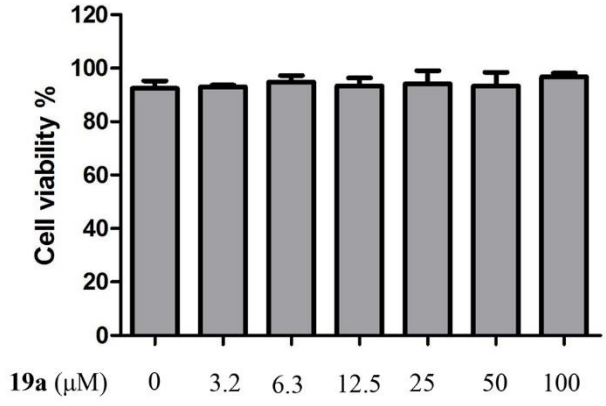


Figure S3. The cytotoxicity of **19a** against the H9c2 cells using the MTT assay.

S11. RNA Extraction and qRT-PCR Analysis.

The quantitative real-time (qRT)-PCR was performed as reported previously.[6] Total RNA of H9c2 cells was extracted from the treated cells using TRIzol reagent (Invitrogen). Then the RNA was converted to cDNA by reverse transcriptase (PrimeScript RT reagent kit) according to the manufacturer's instructions. qRT-PCR analysis of Nrf2, HO-1, NQO1, and GCLM were carried out using the StepOne System Fast real-time PCR system (Applied Biosystems). The values are shown as the fold of the control. All genes' mRNA expression was normalized against GAPDH expression. Primers used for qRT-PCR are listed as follows: Nrf2 (Sense primer: AACCACCCTGAAAGCACGC, Antisense primer: TGAAATGCCGGAGTCAGAATC); HO-1 (Sense primer: ATGGCCTCCCTGTACCACATC, Antisense primer: TGTTGCGCTCAATCTCCTCCT); NQO1 (Sense primer: CGCAGACCTTGTGATATTCCAG Antisense primer: CGTTTCTTCCATCCTTCCAGG); GCLM (Sense primer: TTGGAGTTGCACAGCTGGATTC, Antisense primer: TGGTTTTACCTGTGCCCACTG).

S12. Western Blot Analysis.

Anti-Nrf2 (16396-1-AP), Anti-HO-1 (10701-1-AP), Anti-NQO1 (11451-1-AP), and anti-GCLM (14241-1-AP) antibodies were purchased from Proteintech Group, Inc. Anti-β-actin (AP0060) was purchased from Bioworld (Bioworld, USA). The detailed procedure was described previously.[1] Generally, the protein extracts were separated by SDS-PAGE and then blotted onto PVDF

membranes (PerkinElmer, Northwalk, CT, USA). After being blocked with 1% BSA for 2 h, the membranes were incubated with the primary antibodies at 4 °C overnight. Then they were washed and treated with a DyLight 800 labeled secondary antibody at room temperature for 2 h. The membranes were screened through the odyssey infrared imaging System (LI-COR, Lincoln, Nebraska, USA).

S13. IL-1β, IL-6, and TNF-α Production.

Inflammatory cytokines consisting of IL-1β (IL-1β (Rat) ELISA kit, EK0393, Boster), IL-6 (IL-6 (Rat) ELISA kit, EK0412, Boster), and TNF-α (TNF-α (Rat) ELISA kit, EK0526, Boster) were assessed using sandwich ELISA method according to the manufacturer's instructions.

S14. Evaluation of GSH/GSSG Ratio.

The ratio of GSH/GSSG (GSH and GSSG Assay Kit, S0053, Beyotime, China) was measured evaluated in H9c2 cells using commercially available kit according to the manufacturer manual.

S15. Detection of ROS Level.

H9c2 cells were seeded in 6-well plates at the density of 70-80% confluence per well for overnight incubation. Then the cells were treated with test compounds for indicated time. After treatment, cells were washed once with 2 mL of 10% PBS and stained with 10 mM cH2DCF-DA

(S0033, Reactive Oxygen Species Assay Kit, Beyotime, China) in the dark at 37 °C for 20 min in DMEM medium free with FBS. Analysis was done with a fluorescence microscope (OLYMPUS DP72, Japan) equipped with a U-RFL-T power supply.

S16. Animal Experiments.

Histopathological Examination. The heart samples fixed with 10% buffered formalin were embedded in paraffin. Each section (4 μm) was stained with H&E. The fixed sections were examined by light microscopy for the presence of lesions. Histological evaluation of the severity of inflammation was performed using a scoring system, by a pathologist who was blinded to the treatment. The histologic inflammatory score was shown in Figure S4.

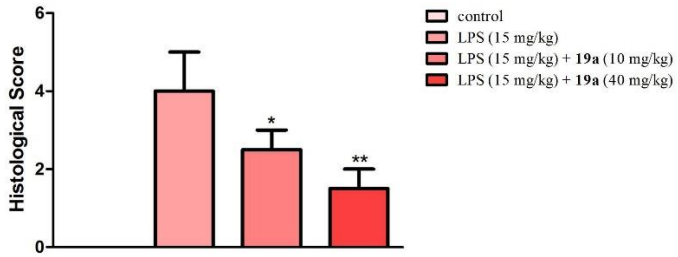


Figure S4. Histologic inflammatory score. The results are expressed as the means ± SEM (n = 8 mice/group). *p < 0.05, **p < 0.01 and ***p < 0.001, one-way ANOVA with Tukey-Kramer posttest.

Immunohistochemical Analysis. The dissected cardiac tissues were prepared for immunohistochemical (IHC) analysis of the expression patterns of Nrf2, HO-1, NQO1 and GCLM. This analysis was performed as reported previously.[1] Briefly, the slides were deparaffinized and

heated by using microwave and boiled twice for 6 min in 10 mM citrate buffer (pH 6.0) for antigen retrieval. Each section was treated with 5% hydrogen peroxide and 4% peptone casein blocking solution for 15 min to diminish nonspecific staining. The slides were incubated with primary antibodies (Proteintech Group, Inc) at room temperature for 40 min in Tris-buffered saline containing 0.05% Tween 20, and then developed using respective horseradish peroxidase (HRP)-conjugated secondary antibodies (rabbit or mouse) EnVisionTM System (Dako). The peroxidasebinding sites were detected by staining with 3,3'-diaminobenzidine tetrahydrochloride (Dako). Finally, counterstaining was performed using Mayer's hematoxylin.

IL-1β, IL-6 and TNF-α Production. Freshly collected blood samples were kept at room temperature for 20 min and centrifuged at 3000 × g for 10 min at 4 °C, and the supernatant was used for detection and analysis. The secretion of IL-1β, IL-6 and TNF-α in mouse serum samples was measured by double-antibody sandwich ELISA according to the manufacturer's instructions of these commercially available kits ((IL-1β (m) ELISA kit, EK0394, Boster), IL-6 (IL-6 (m) ELISA kit, EK0411, Boster), and TNF-α (TNF-α (m) ELISA kit, EK0527, Boster).

Evaluation of ROS and GSH/GSSG ratio. The ratio of GSH/GSSG (GSH and GSSG Assay Kit, S0053, Beyotime, China) and ROS level (S0033, Reactive Oxygen Species Assay Kit, Beyotime, China) were measured in the heart homogenate using commercially available kits according to the manufacturer's instructions.

S17. Statistical Analysis.

Results are expressed as the means ± SEM. Statistical tests were performed using GraphPad Prism 6.0 software. For multiple comparisons between groups, a one-way ANOVA was performed to detect statistical differences. Differences within the ANOVA were determined using a Tukey'sposthoc test.

S18. References.

(1) Lu, M. C.; Zhang, X.; Wu, F.; Tan, S. J.; Zhao, J.; You, Q. D.; Jiang, Z. Y. Discovery of a Potent Kelch-Like ECH-Associated Protein 1-Nuclear Factor Erythroid 2-Related Factor 2 (Keap1-Nrf2) Protein-Protein Interaction Inhibitor with Natural Proline Structure as a Cytoprotective Agent against Acetaminophen-Induced Hepatotoxicity. *J. Med. Chem.* **2019**, 62, 6796-6813.

(2) Nasiri, H. R.; Linge, S.; Ullmann, D. Thermodynamic profiling of inhibitors of Nrf2:Keap1 interactions. *Bioorg. Med. Chem. Lett.* **2016**, 26, 526-529.

(3) Cheng, Y.Prusoff, W. H. Relationship between the inhibition constant (K1) and the concentration of inhibitor which causes 50 per cent inhibition (I50) of an enzymatic reaction. *Biochem Pharmacol.* **1973**, 22, 3099-3108.

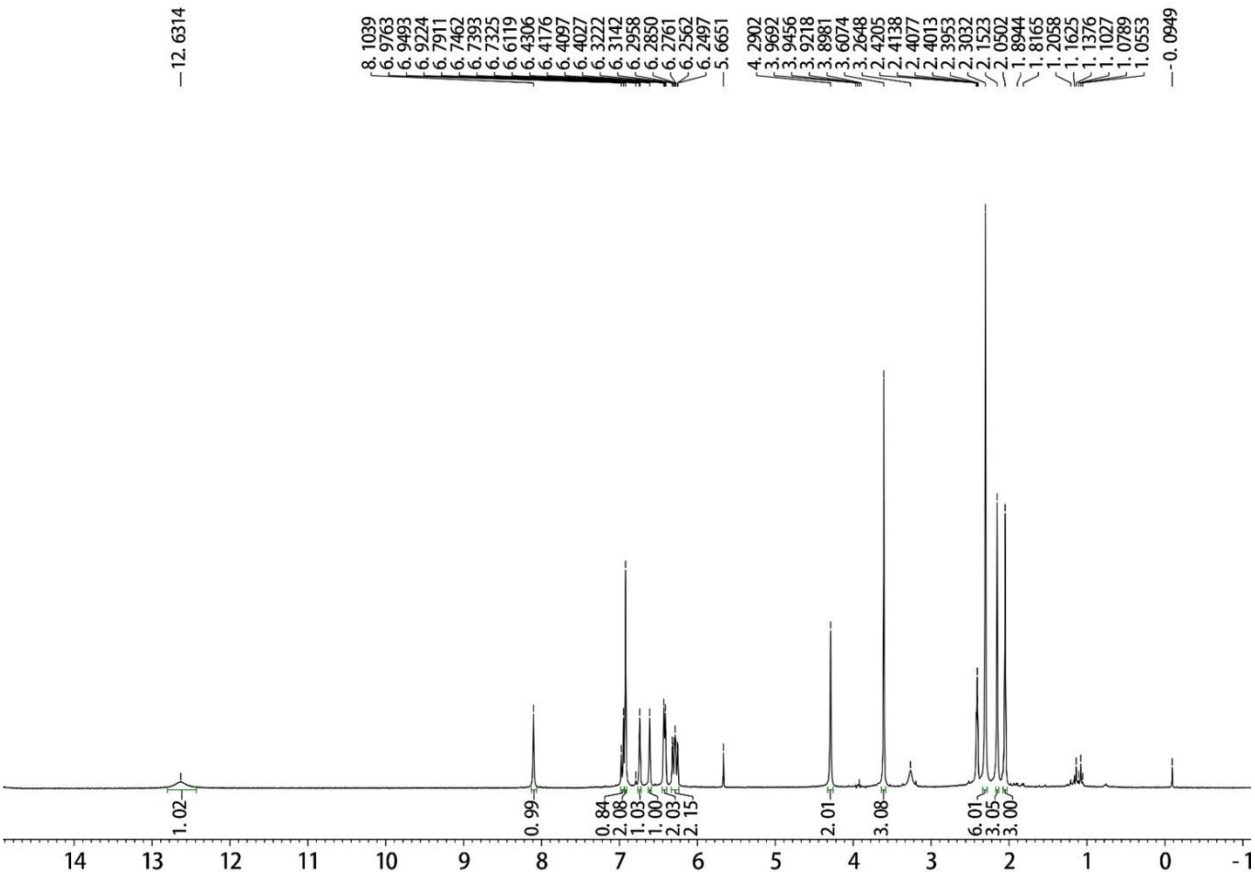
(4) Munson, P. J.Rodbard, D. An exact correction to the "Cheng-Prusoff" correction. *J Recept Res.* **1988**, 8, 533-546.

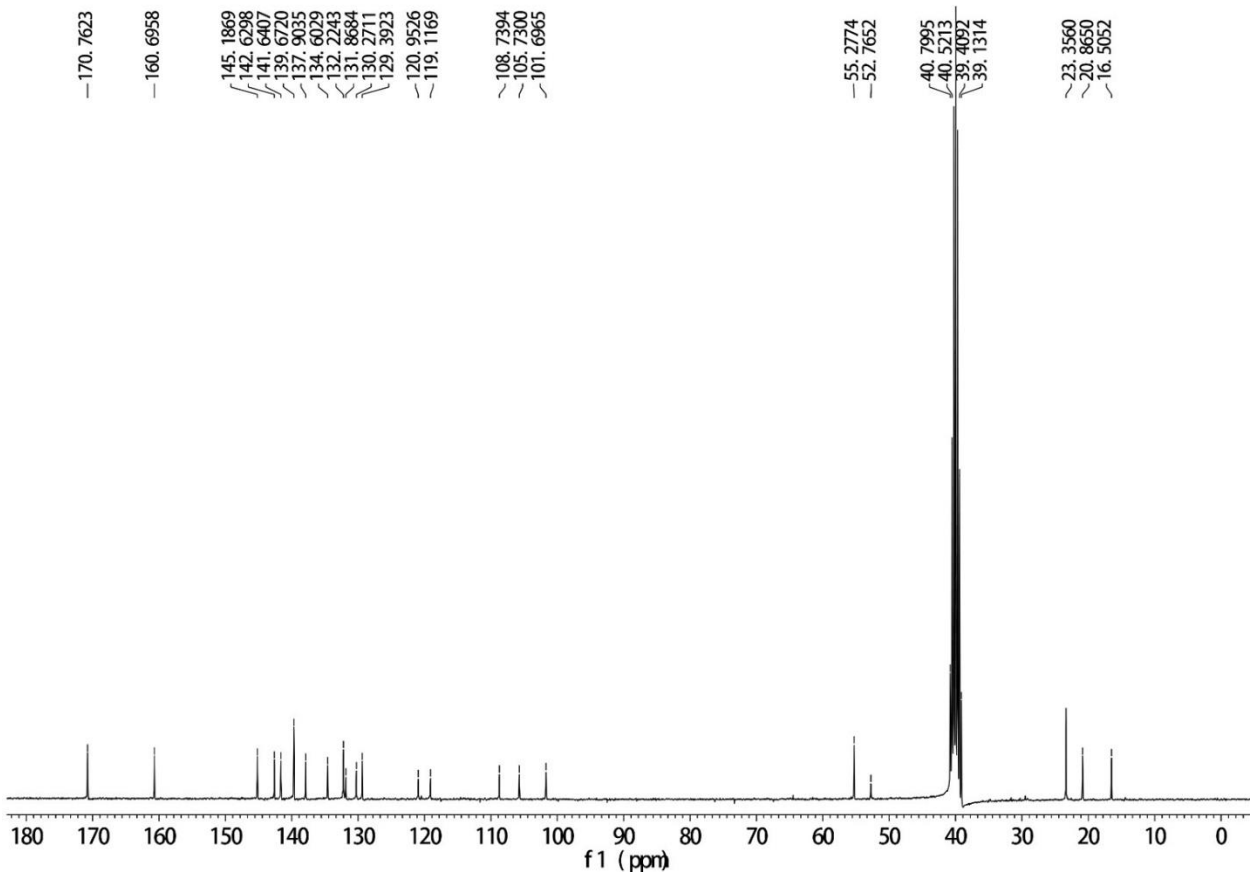
(5) Jiang, Z. Y.; Lu, M. C.; Xu, L. L.; Yang, T. T.; Xi, M. Y.; Xu, X. L.; Guo, X. K.; Zhang, X. J.; You, Q. D.; Sun, H. P. Discovery of potent Keap1-Nrf2 protein-protein interaction inhibitor based on molecular binding determinants analysis. *J. Med. Chem.* **2014**, 57, 2736-2745.

(6) Lu, M.-C.; Ji, J.-A.; Jiang, Y.-L.; Chen, Z.-Y.; Yuan, Z.-W.; You, Q.-D.; Jiang, Z.-Y. An inhibitor of the Keap1-Nrf2 protein-protein interaction protects NCM460 colonic cells and alleviates experimental colitis. *Sci Rep.* **2016**, 6, 26585.

S19. ^{1}H-NMR, ^{13}C-NMR, HRMS and HPLC Spectra for Representative Target Compounds.

1. ^{1}H-NMR, ^{13}C-NMR, HRMS and HPLC Spectra for 10a

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129. 3923
120. 9526
119. 1169
108. 7394
105. 7300
101. 6965
55. 2774
52. 7652
40. 7995
40. 5213
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16. 5052
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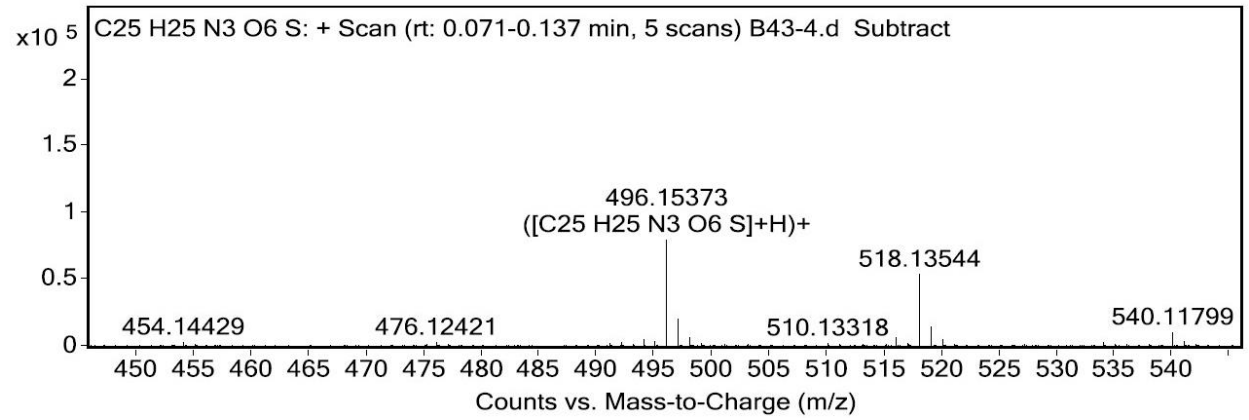
f1 (ppm)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1.5
1
0.5
0
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([C25 H25 N3 O6 S]+H)+
518.13544
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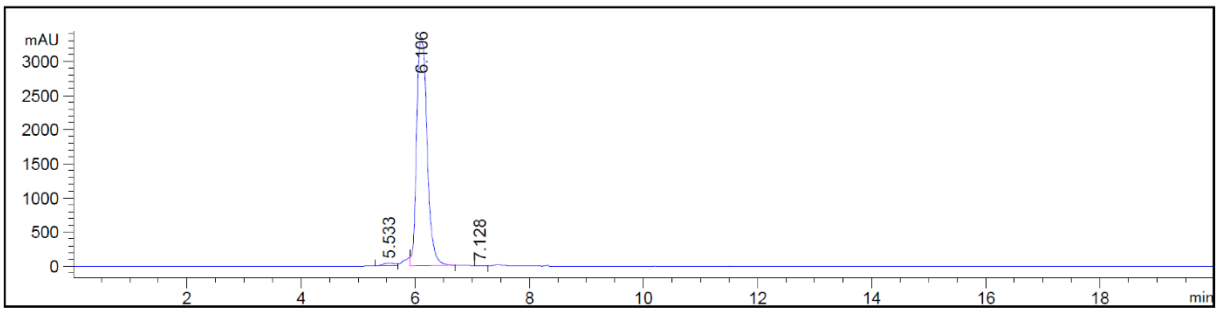
450 455 460 465 470 475 480 485 490 495 500 505 510 515 520 525 530 535 540
Counts vs. Mass-to-Charge (m/z)



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2	6.106	VB	0.2038	4.25499e4	3270.56055	98.5270
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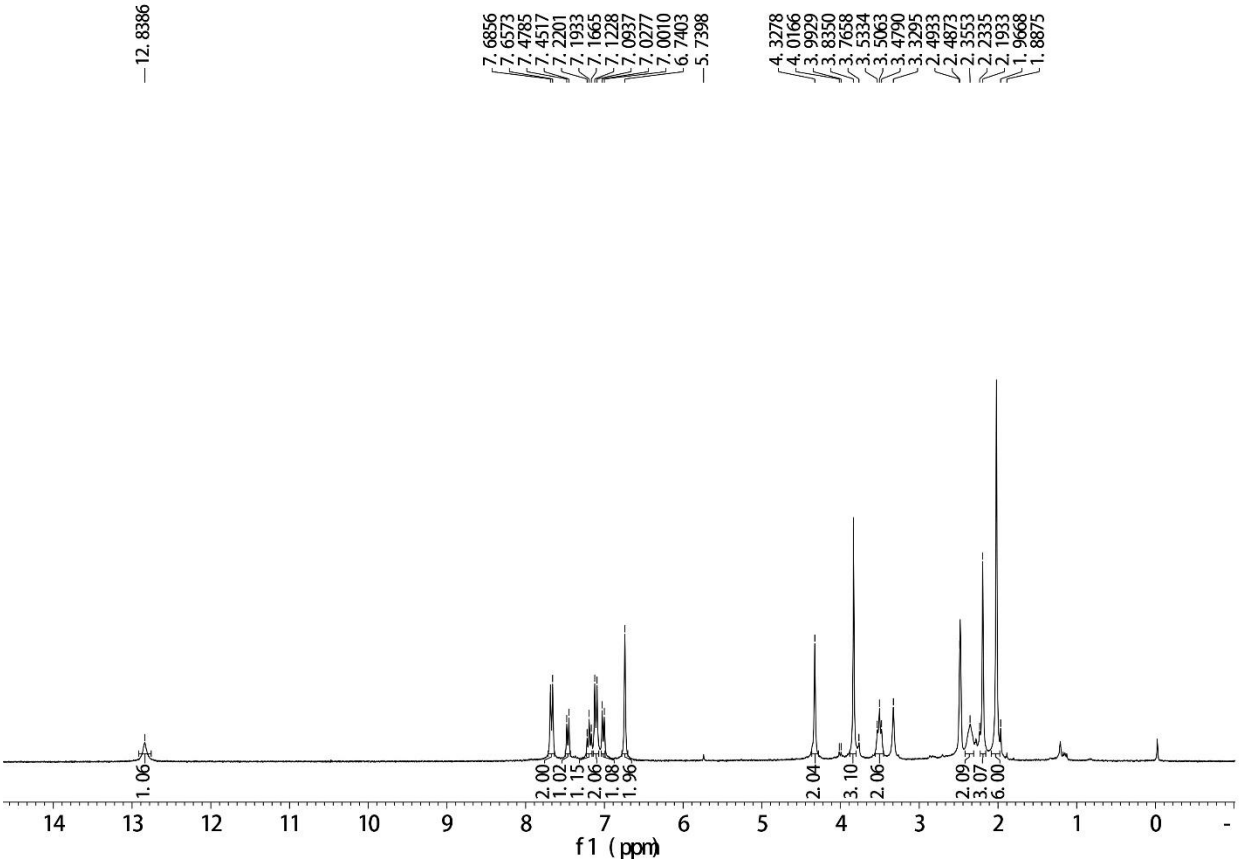
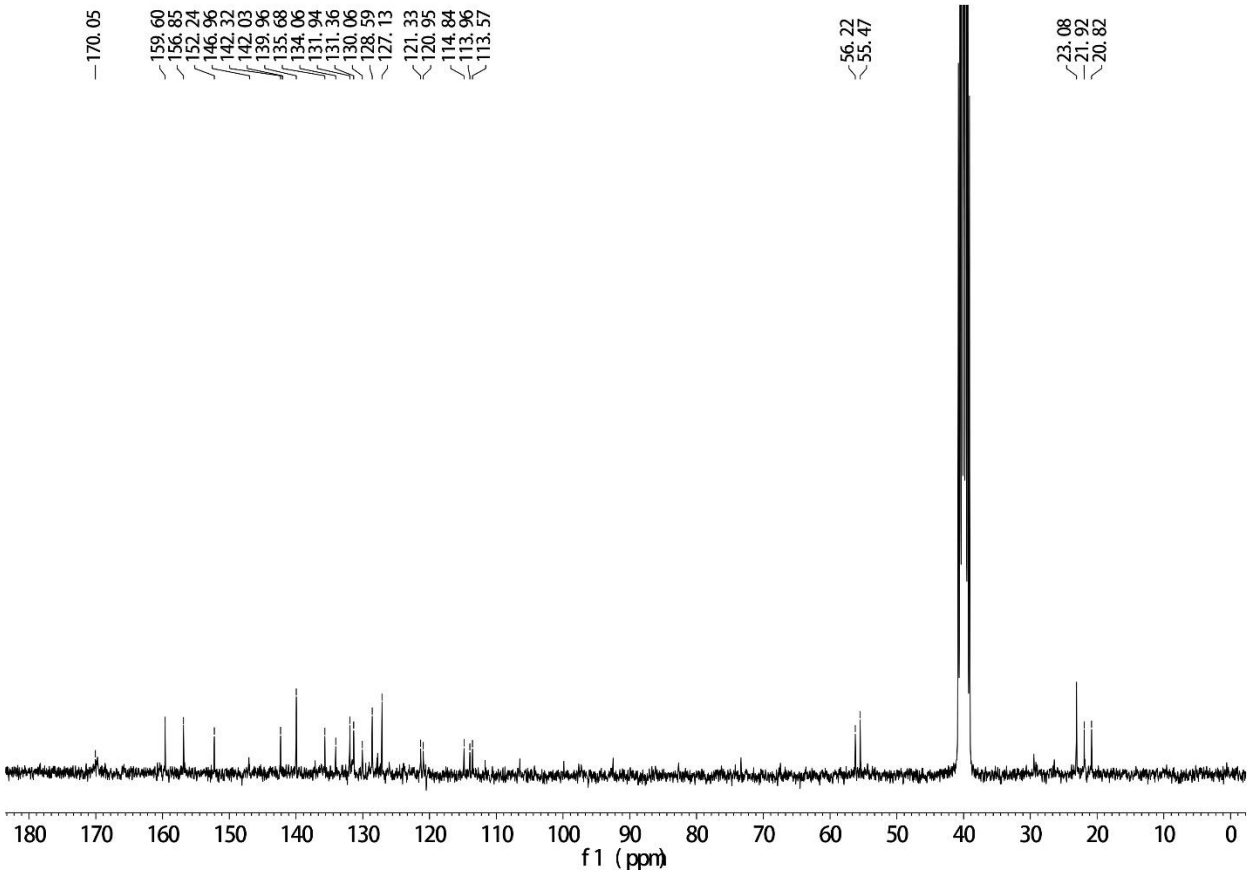
2. ^{1}H-NMR, ^{13}C-NMR, HRMS and HPLC Spectra for 11a

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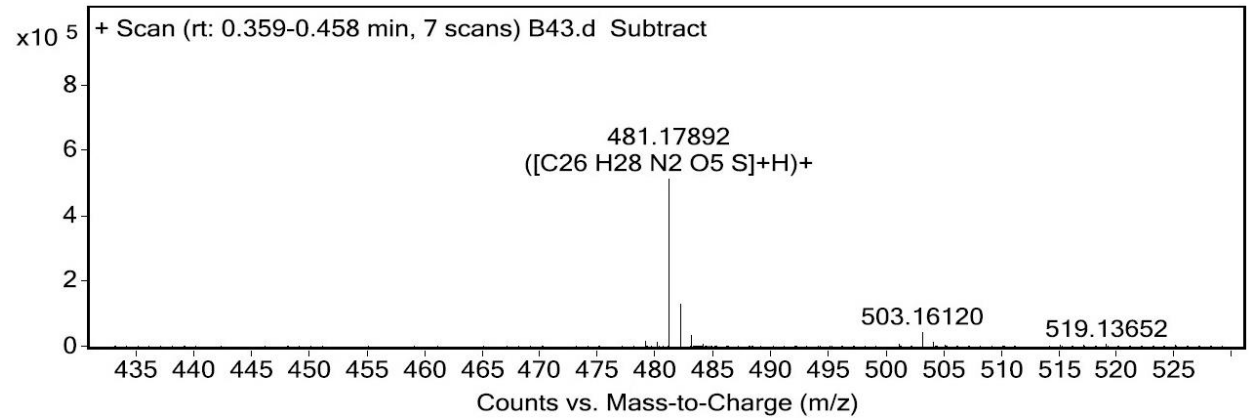
f1 (ppm)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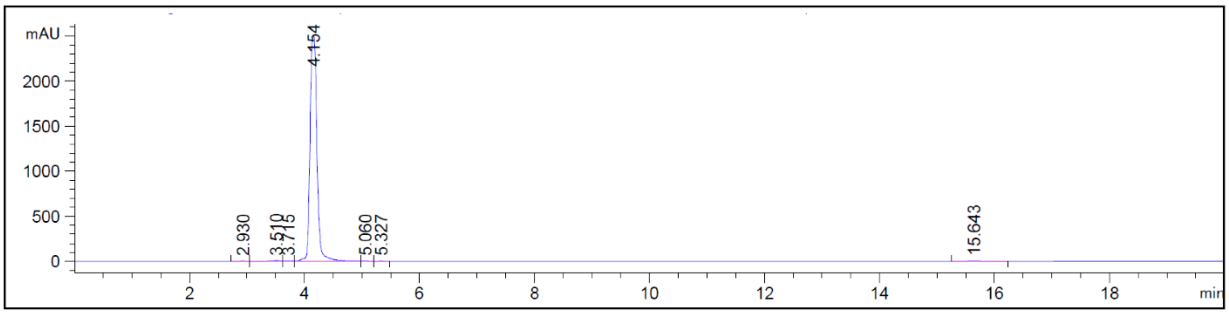
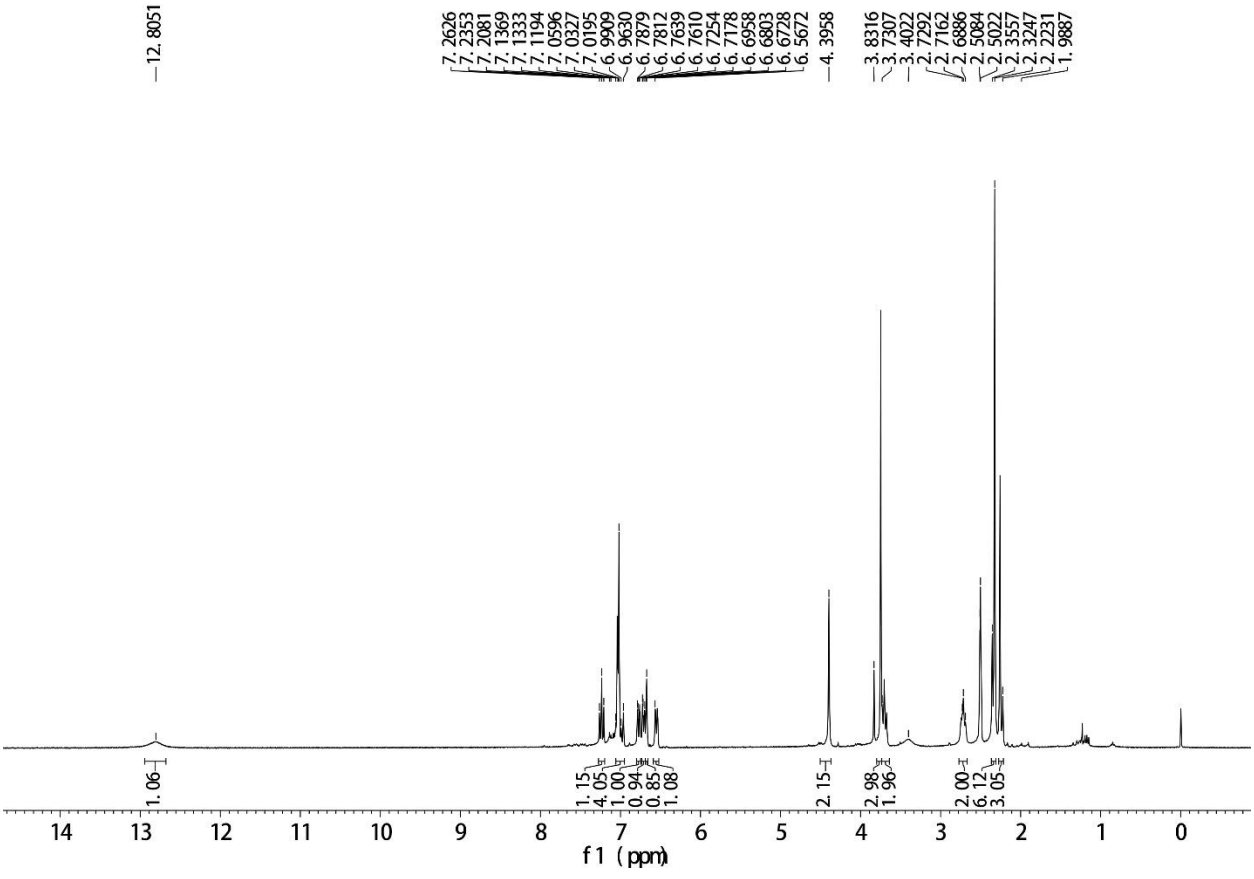
2
4
6
8
435 440 445 450 455 460 465 470 475 480 485 490 495 500 505 510 515 520 525
Counts vs. Mass-to-Charge (m/z)

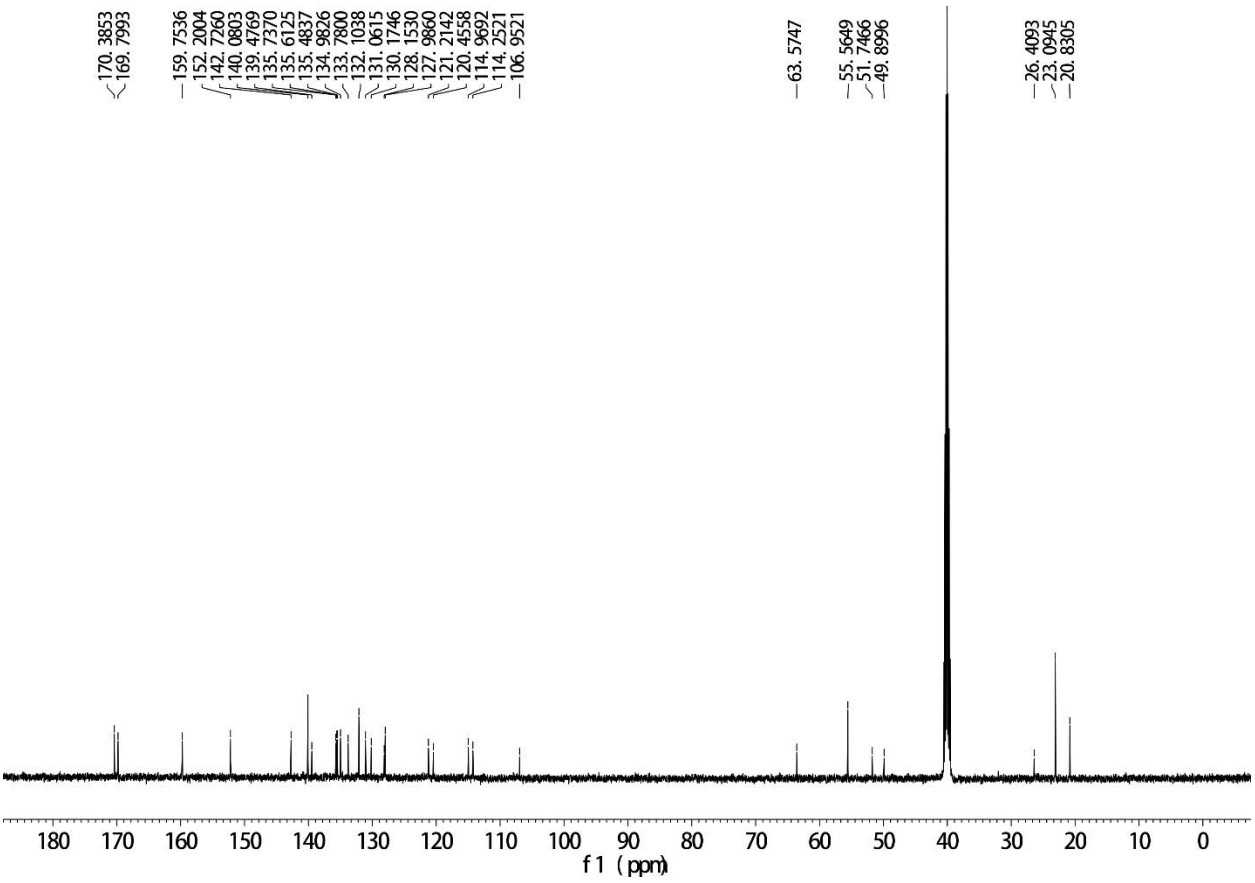


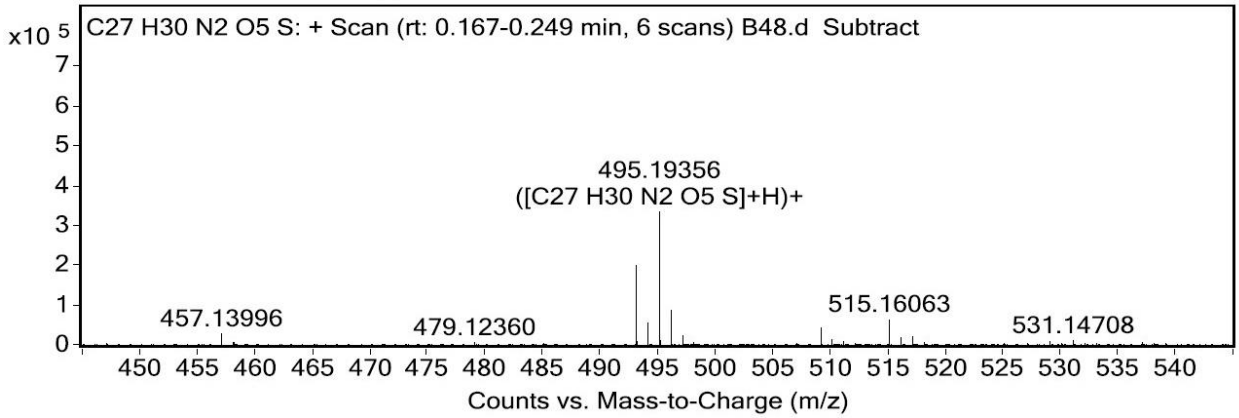
Signal: DAD1 A, Sig=254,4 Ref=360,100

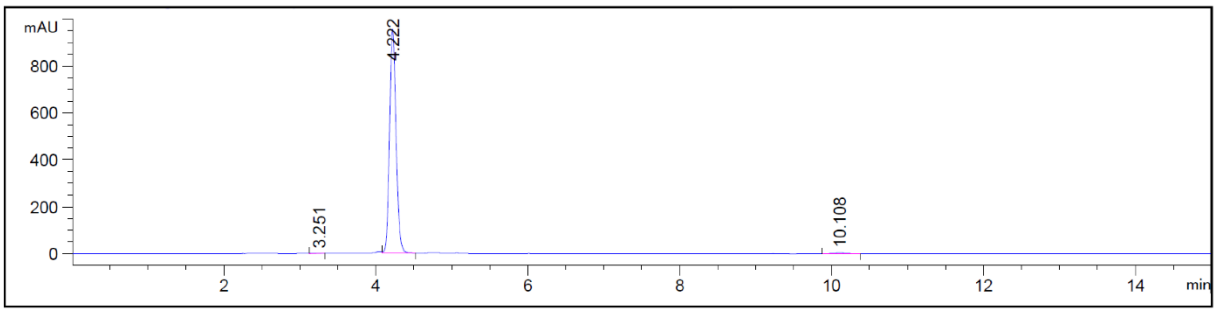
Peak	Retention Time min	Type	Width min	Area mAU*s	Height mAU	Relative Area %
1	3.715	VV	0.1536	33.42636	3.26164	0.1573
2	4.154	VV	0.1317	2.10018e4	2506.84570	98.8172
3	5.060	VV	0.1297	20.64192	2.36692	0.0971
4	5.327	VB	0.1330	14.30538	1.68589	0.0673
5	15.643	BB	0.2865	70.92972	3.85815	0.3337

3. ^{1}H-NMR, ^{13}C-NMR, HRMS and HPLC Spectra for 14c




170.3853
169.7993
159.7536
152.2004
142.7260
140.0803
139.4769
135.7370
135.6125
135.4837
134.9826
133.7800
132.1038
131.0615
130.1746
128.1530
127.9860
121.2142
120.4558
114.9692
114.2521
106.9521
63.5747
55.5649
51.7466
49.8996
26.4093
23.0945
20.8305
f1 (ppm)

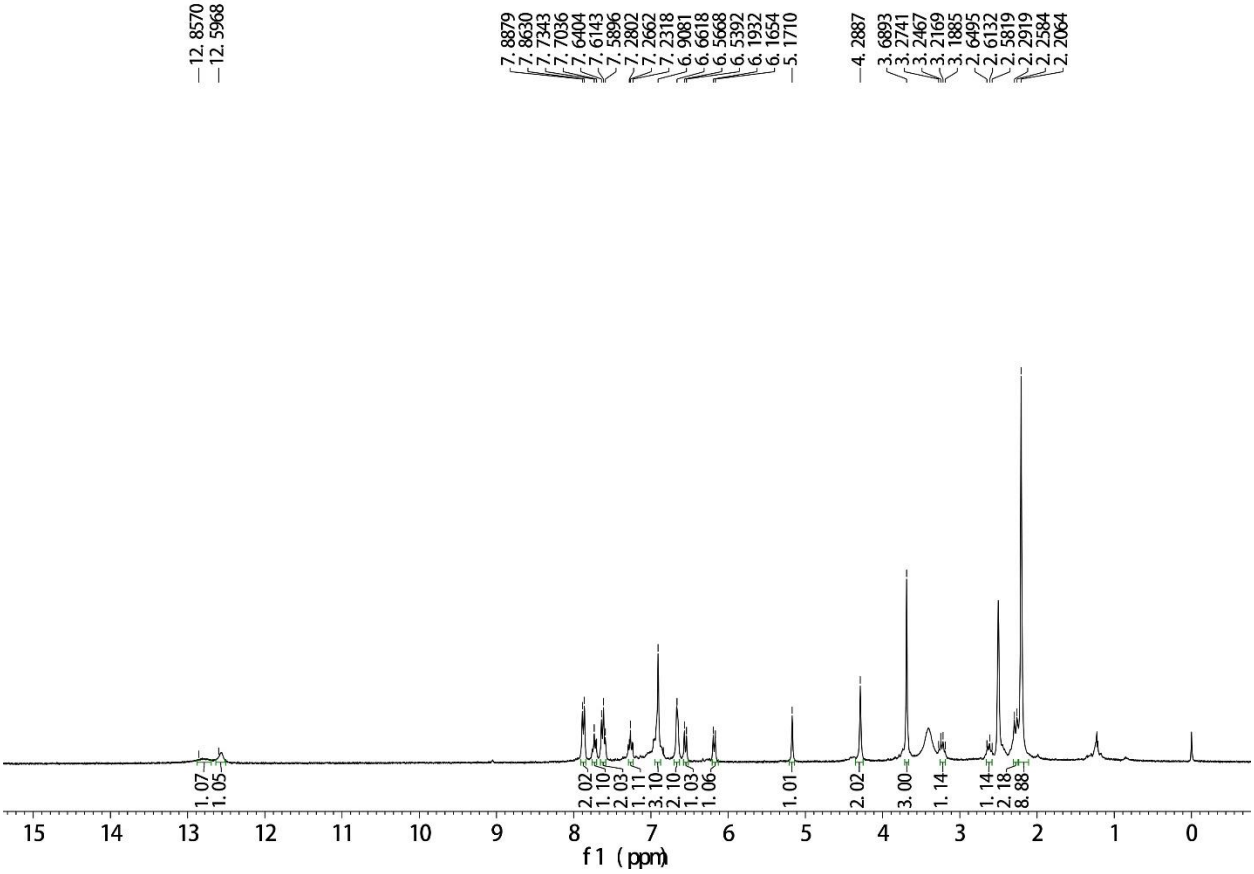

C27 H30 N2 O5 S: + Scan (rt: 0.167-0.249 min, 6 scans) B48.d Subtract
x10 5
495.19356
([C27 H30 N2 O5 S]+H)+
457.13996
479.12360
515.16063
531.14708
Counts vs. Mass-to-Charge (m/z)

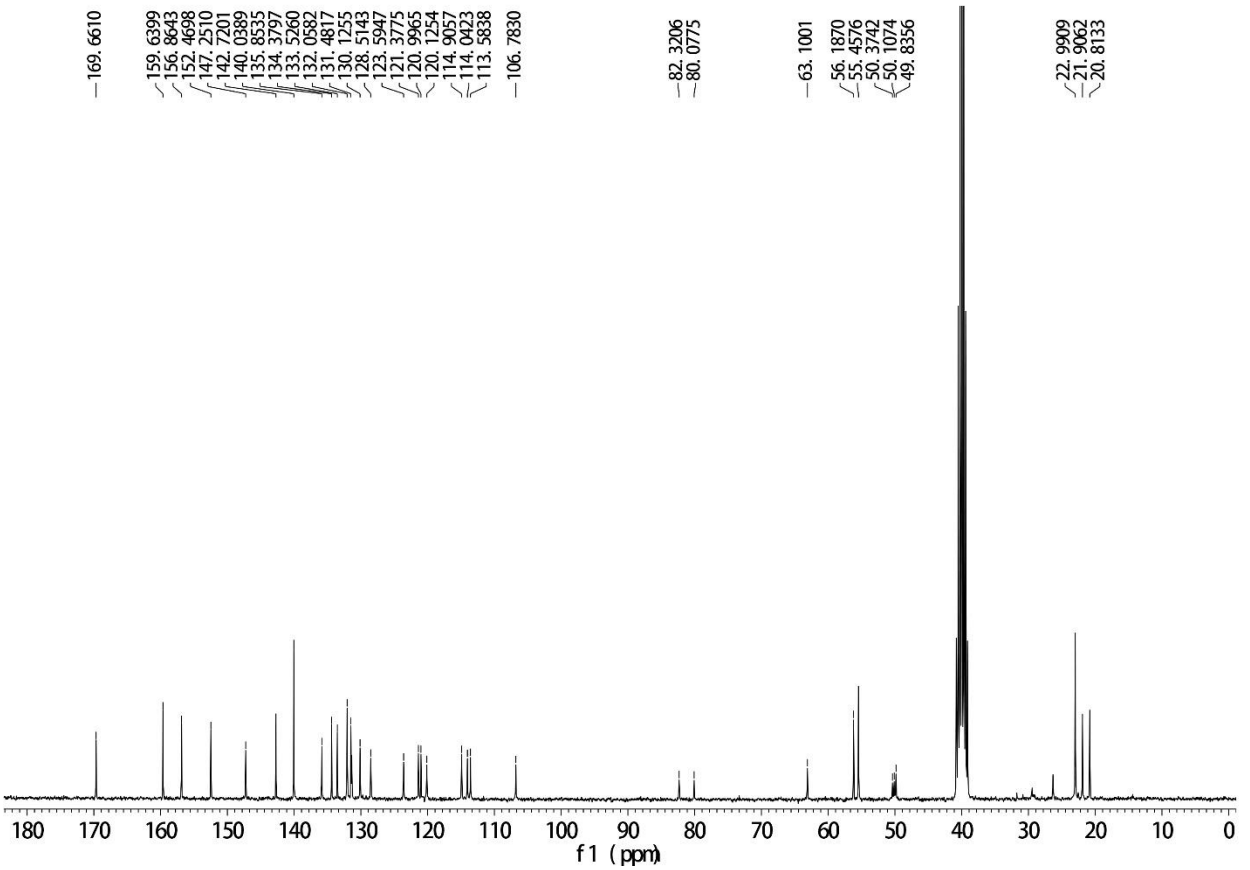


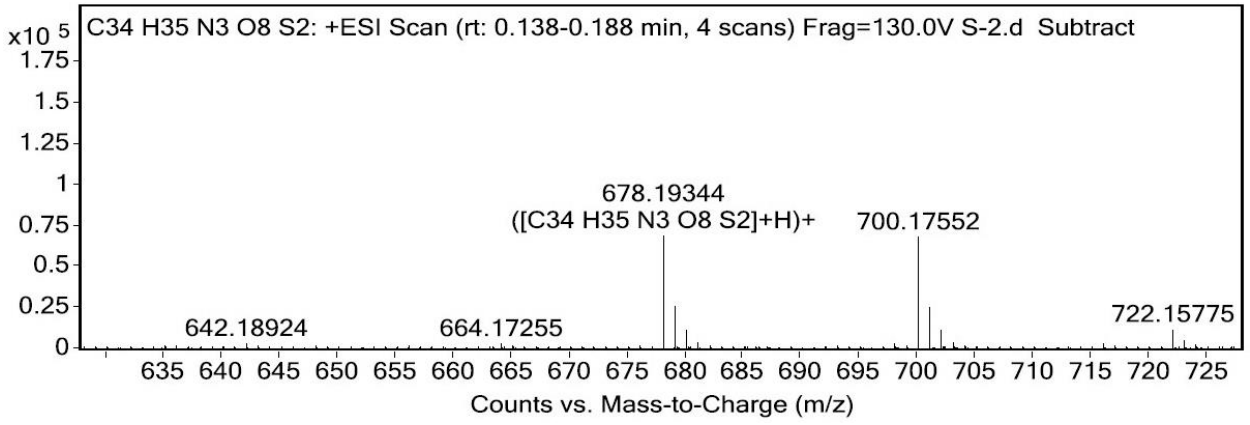
Signal: DAD1 A, Sig=254,4 Ref=360,100

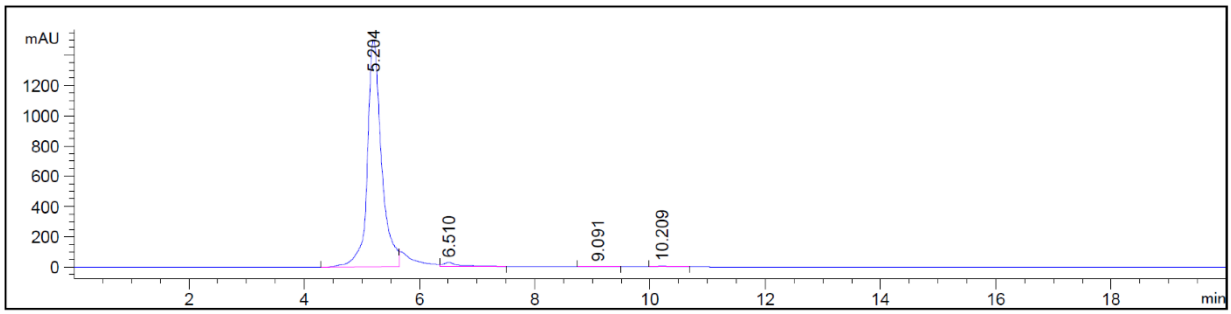
Peak	Retention Time min	Type	Width min	Area mAU*s	Height mAU	Relative Area %
1	3.251	VB	0.0899	10.97695	1.73233	0.1966
2	4.222	VB	0.0896	5536.50293	955.38245	99.1850
3	10.108	BB	0.1668	34.51756	3.27991	0.6184

4. ^{1}H-NMR, ^{13}C-NMR, HRMS and HPLC Spectra for 16a




169.6610
159.6399
156.8643
152.4698
147.2510
142.7201
140.0389
135.8535
134.3797
133.5260
132.0582
131.4817
130.1255
128.5143
123.5947
121.3775
120.9965
120.1254
114.9057
114.0423
113.5838
106.7830
82.3206
80.0775
63.1001
56.1870
55.4576
50.3742
50.1074
49.8356
22.9909
21.9062
20.8133
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

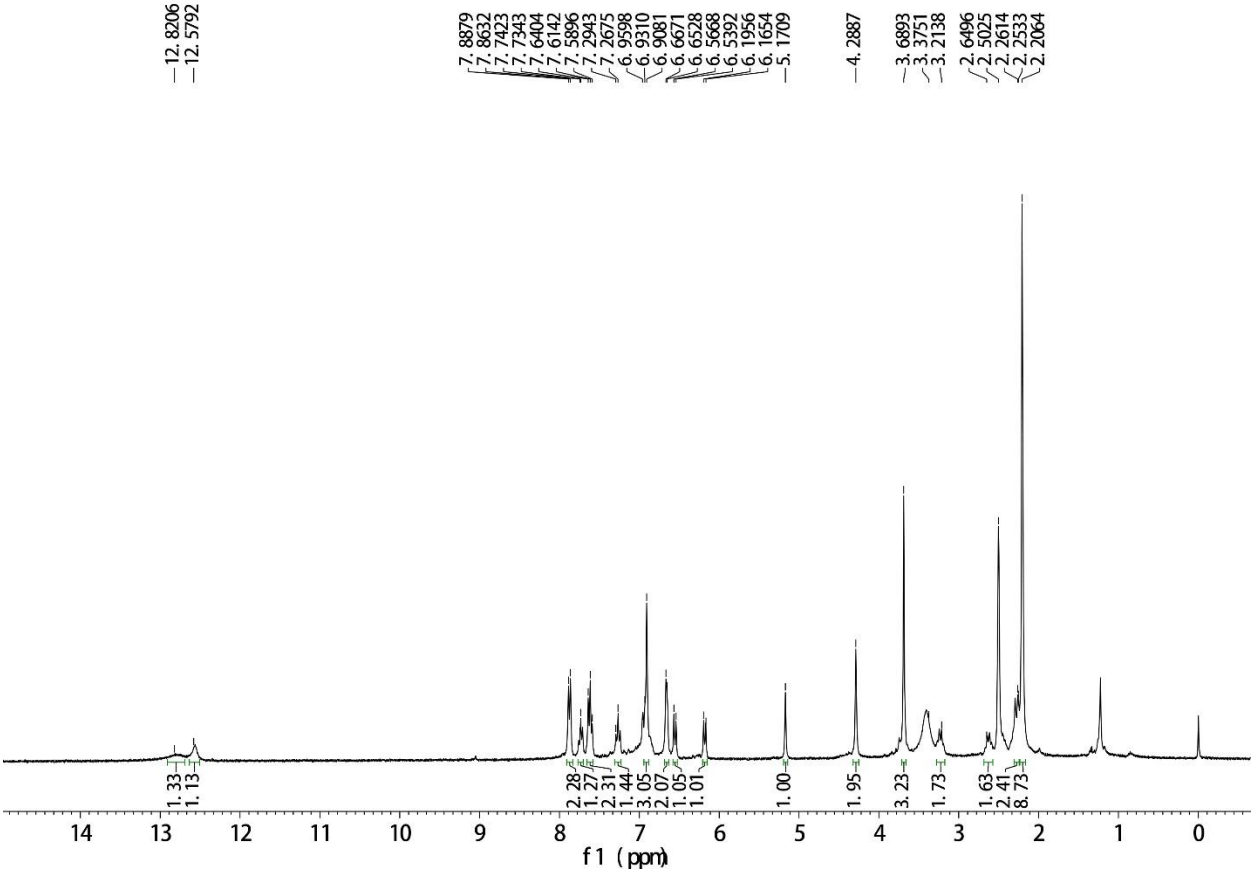

C34 H35 N3 O8 S2: +ESI Scan (rt: 0.138-0.188 min, 4 scans) Frag=130.0V S-2.d Subtract
x10 5
1.75
1.5
1.25
1
0.75
0.5
0.25
0
678.19344
([C34 H35 N3 O8 S2]+H)+
700.17552
642.18924
664.17255
722.15775
635 640 645 650 655 660 665 670 675 680 685 690 695 700 705 710 715 720 725
Counts vs. Mass-to-Charge (m/z)

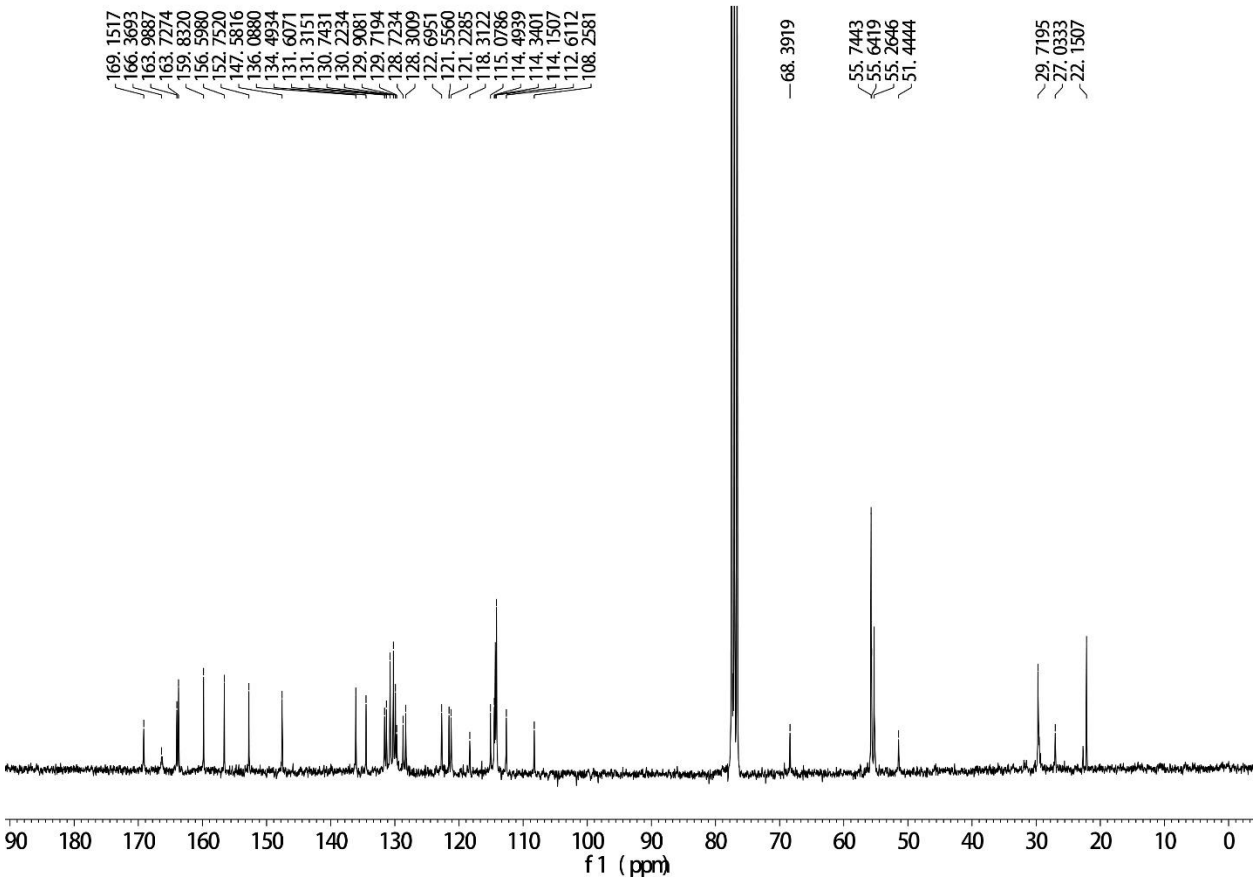


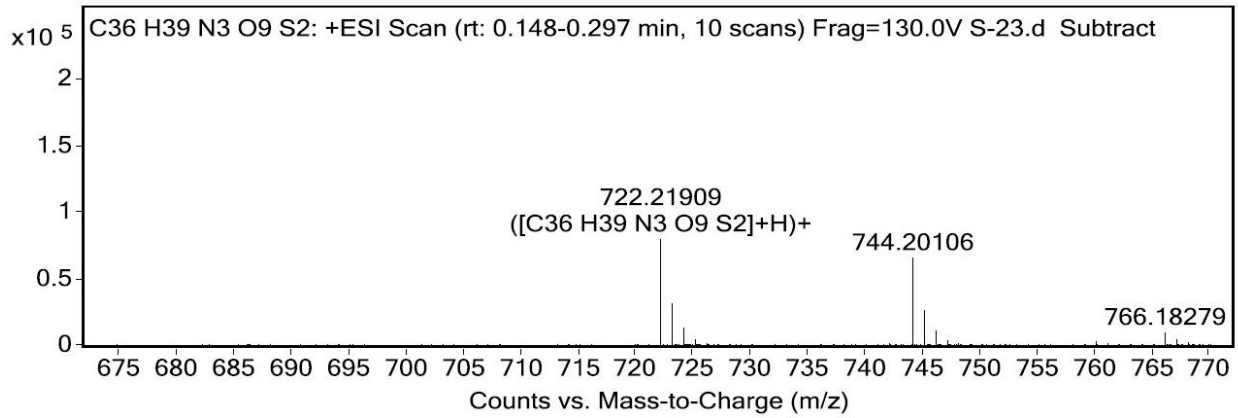
Signal: DAD1 A, Sig=254,4 Ref=360,100

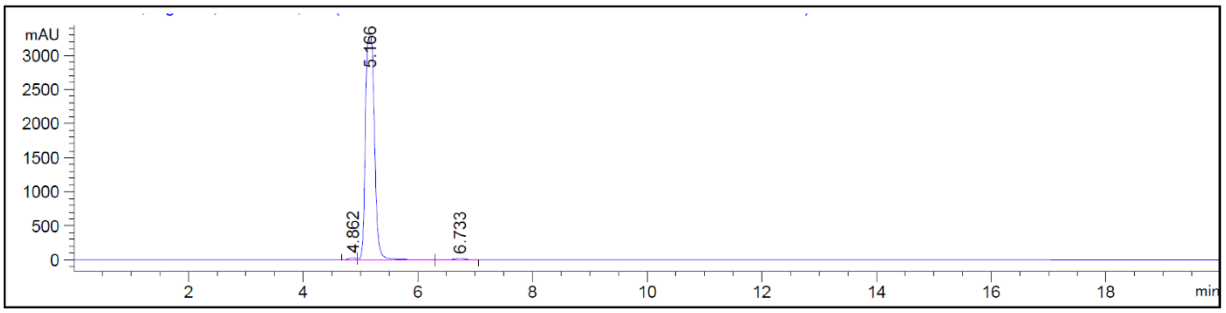
Peak	Retention Time min	Type	Width min	Area mAU*s	Height mAU	Relative Area %
1	5.204	BV	0.2498	2.56136e4	1495.27893	97.5315
2	6.510	VB	0.2616	571.93182	29.57635	2.1778
3	9.091	BB	0.1723	22.71348	1.97347	0.0865
4	10.209	BB	0.1935	53.63646	4.07553	0.2042

5. ^{1}H-NMR, ^{13}C-NMR, HRMS and HPLC Spectra for 16w




169. 1517
166. 3693
163. 9887
163. 7274
159. 8320
156. 5980
152. 7520
147. 5816
136. 0880
134. 4934
131. 6071
131. 3151
130. 7431
130. 2234
129. 9081
129. 7194
128. 7234
128. 3009
122. 6951
121. 5560
121. 2285
118. 3122
115. 0786
114. 4939
114. 3401
114. 1507
112. 6112
108. 2581
68. 3919
55. 7443
55. 6419
55. 2646
51. 4444
29. 7195
27. 0333
22. 1507
90 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

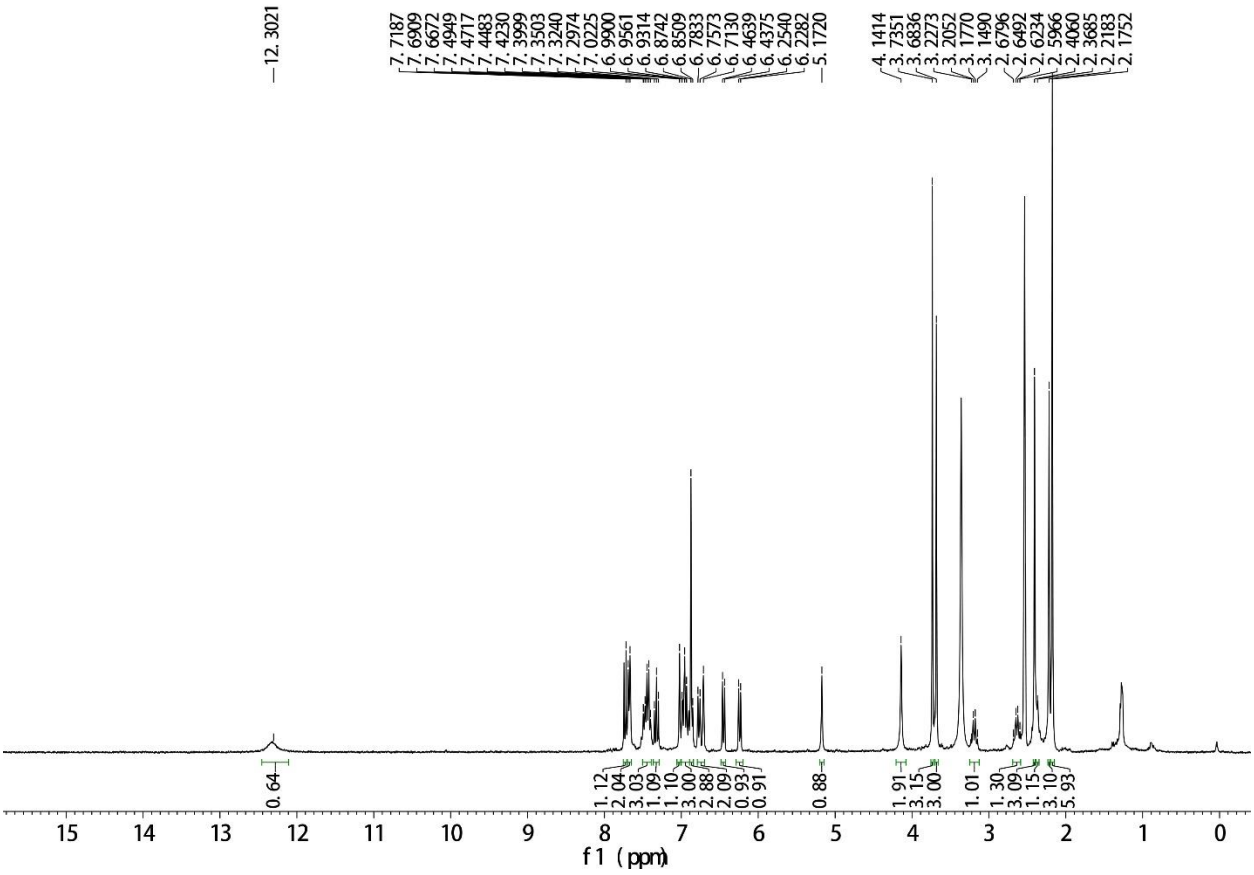

x10 5
C36 H39 N3 O9 S2: +ESI Scan (rt: 0.148-0.297 min, 10 scans) Frag=130.0V S-23.d Subtract
2
1.5
1
0.5
0
722.21909
([C36 H39 N3 O9 S2]+H)+
744.20106
766.18279
675 680 685 690 695 700 705 710 715 720 725 730 735 740 745 750 755 760 765 770
Counts vs. Mass-to-Charge (m/z)

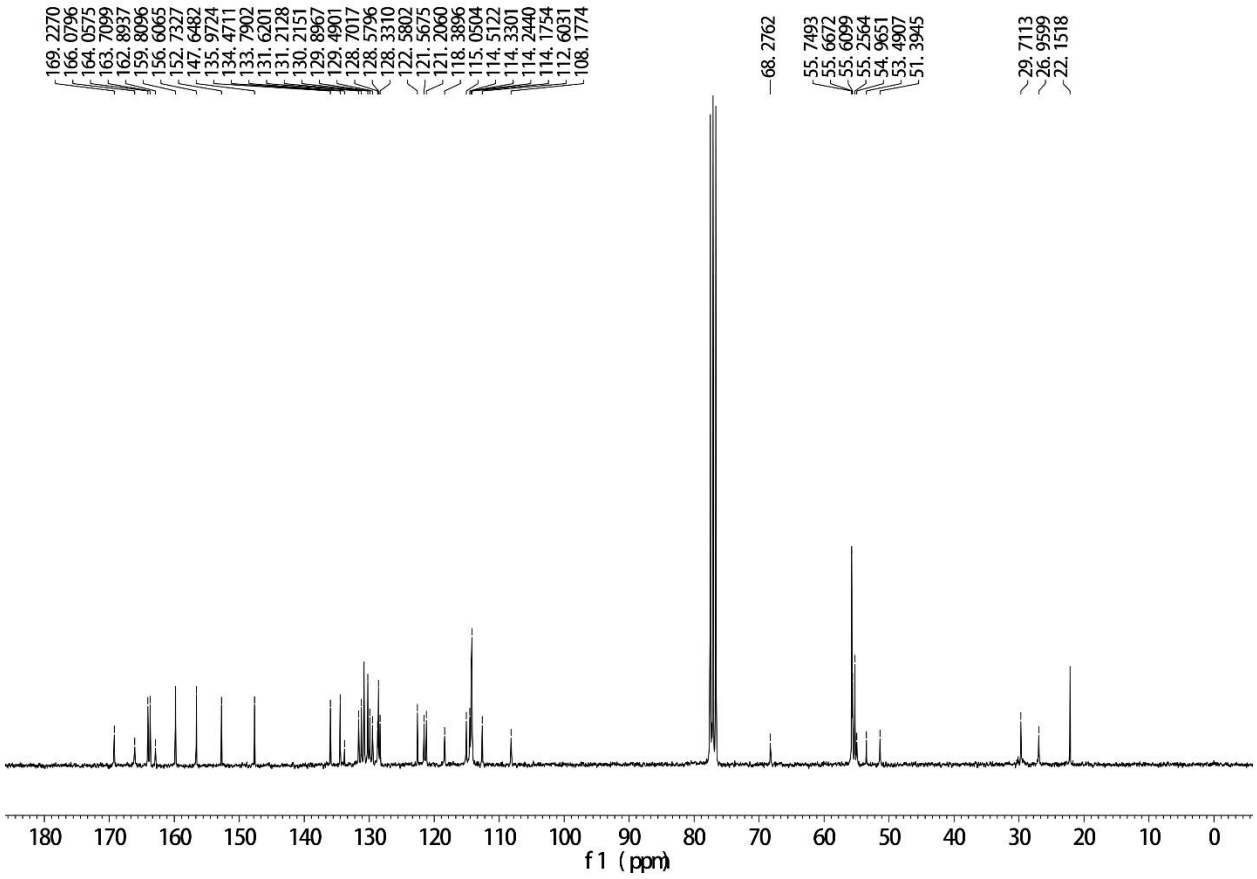


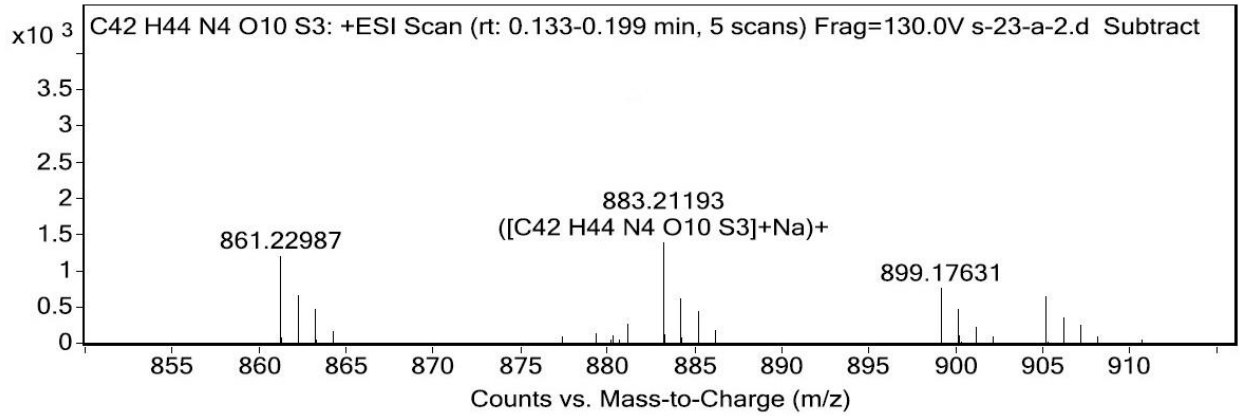
Signal: DAD1 A, Sig=254,4 Ref=360,100

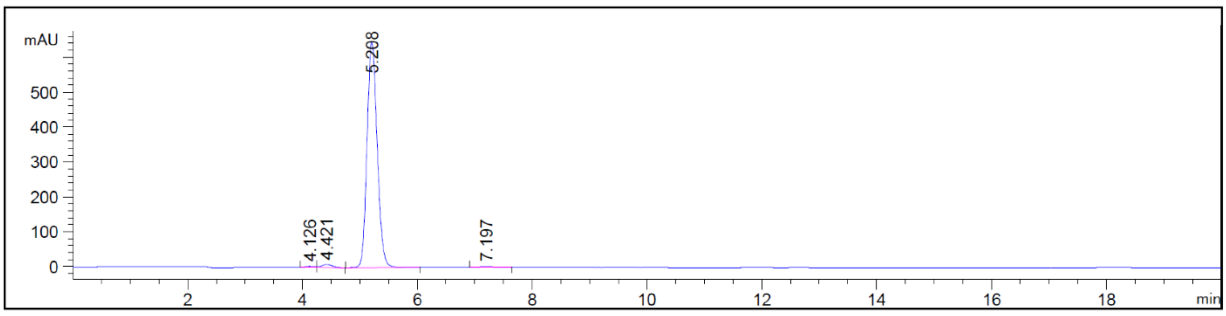
Peak	Retention Time min	Type	Width min	Area mAU*s	Height mAU	Relative Area %
1	4.862	BV	0.1219	242.13307	30.74068	0.6710
2	5.166	VB	0.1727	3.55795e4	3276.26611	98.5927
3	6.733	BB	0.1598	265.72113	25.86738	0.7363

6. ^{1}H-NMR, ^{13}C-NMR, HRMS and HPLC Spectra for 17a




169. 2270
166. 0796
164. 0575
163. 7099
162. 8937
159. 8096
156. 6065
152. 7327
147. 6482
135. 9724
134. 4711
133. 7902
131. 6201
131. 2128
130. 2151
129. 8967
129. 4901
128. 7017
128. 5796
128. 3310
122. 5802
121. 5675
121. 2060
118. 3896
115. 0504
114. 5122
114. 3301
114. 2440
114. 1754
112. 6031
108. 1774
68. 2762
55. 7493
55. 6672
55. 6099
55. 2564
54. 9651
53. 4907
51. 3945
29. 7113
26. 9599
22. 1518
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

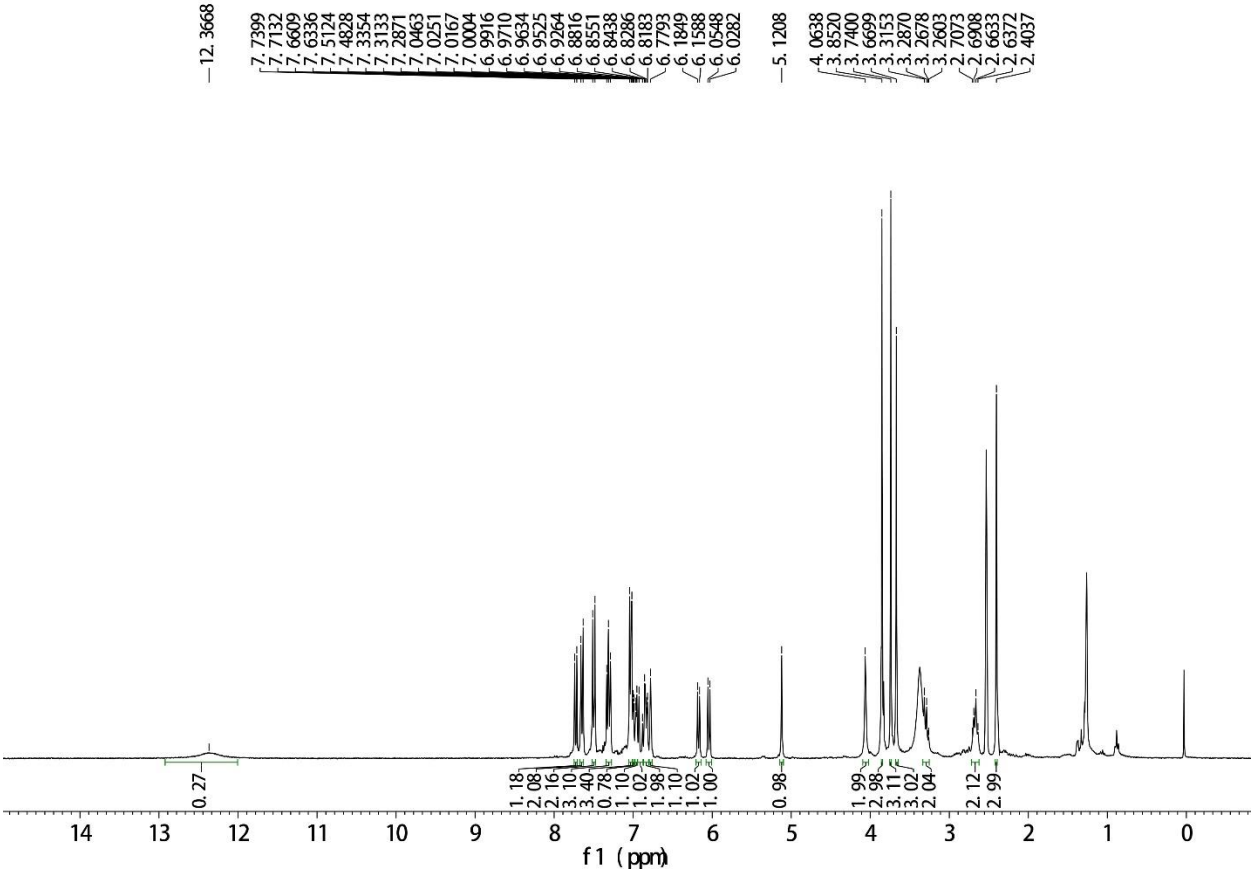

C42 H44 N4 O10 S3: +ESI Scan (rt: 0.133-0.199 min, 5 scans) Frag=130.0V s-23-a-2.d Subtract
x10 3
3.5
3
2.5
2
1.5
1
0.5
0
861.22987
883.21193
([C42 H44 N4 O10 S3]+Na)+
899.17631
855 860 865 870 875 880 885 890 895 900 905 910
Counts vs. Mass-to-Charge (m/z)

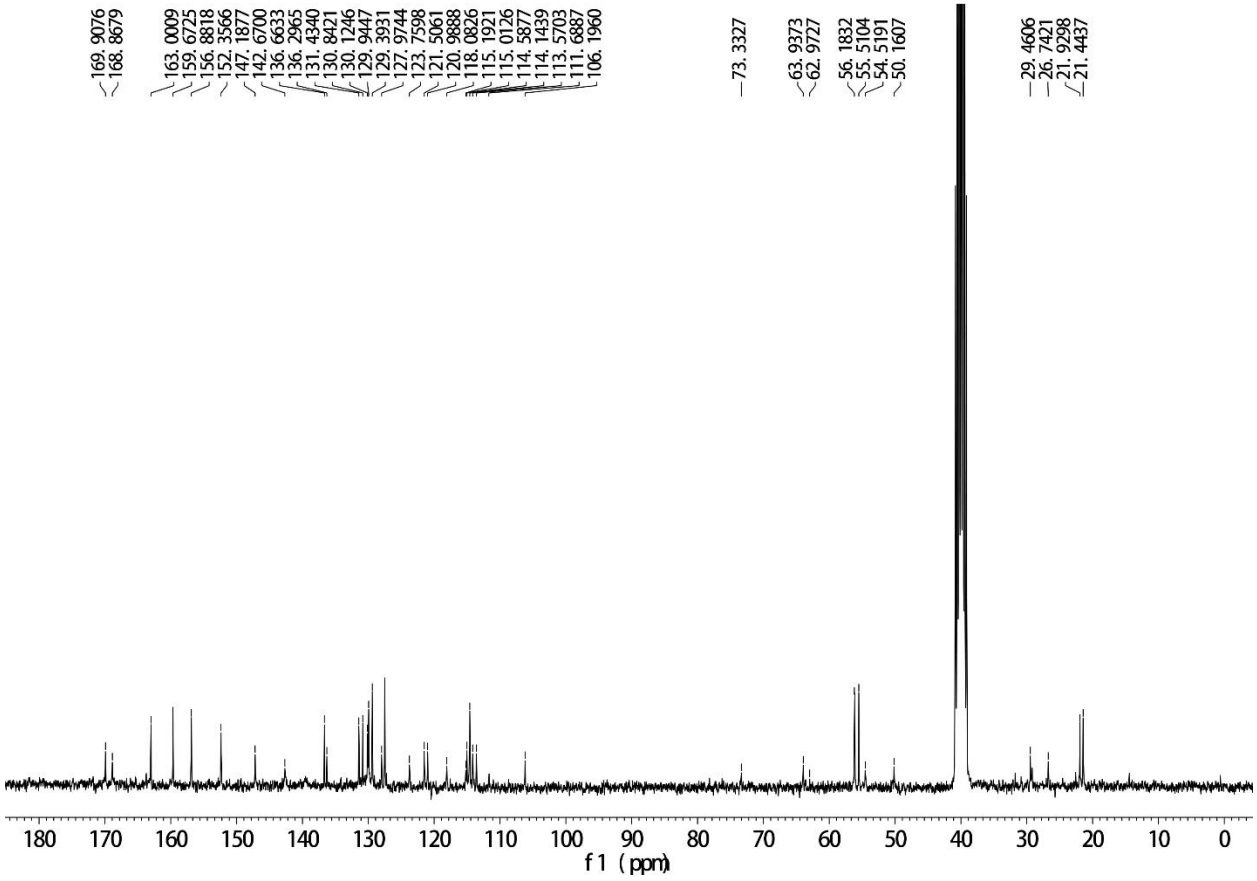


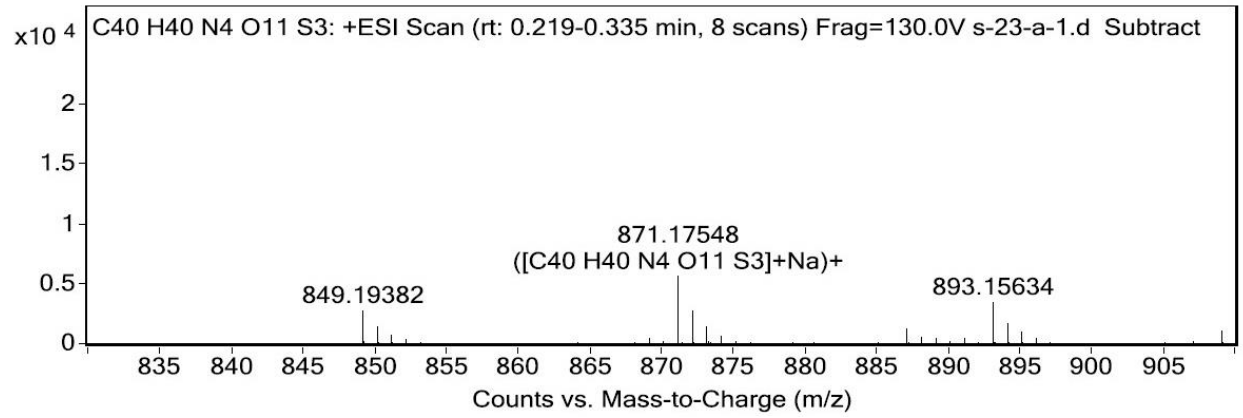
Signal: DAD1 A, Sig=254,4 Ref=360,100

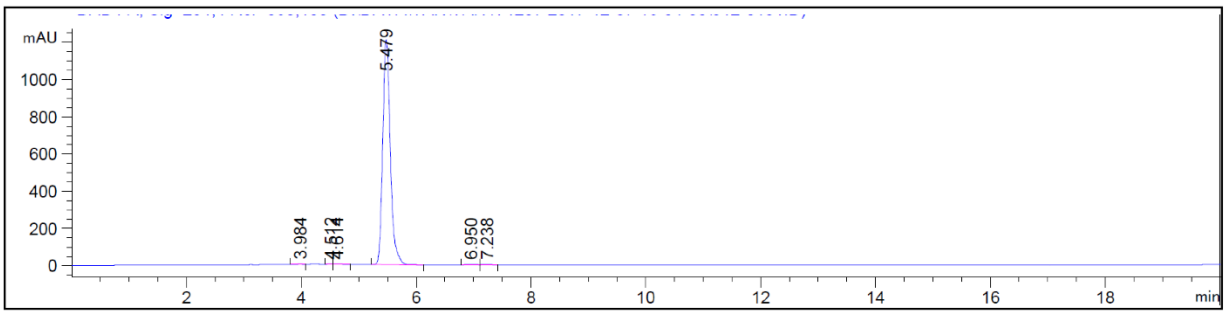
Peak	Retention Time min	Type	Width min	Area mAU*s	Height mAU	Relative Area %
1	4.126	BV	0.1553	28.81402	2.86510	0.3556
2	4.421	VB	0.1862	105.06260	8.74292	1.2968
3	5.208	BB	0.1911	7926.56494	646.05945	97.8361
4	7.197	BB	0.2167	41.44003	2.93472	0.5115

7. ^{1}H-NMR, ^{13}C-NMR, HRMS and HPLC Spectra for 17b




169.9076
168.8679
163.0009
159.6725
156.8818
152.3566
147.1877
142.6700
136.6633
136.2965
131.4340
130.8421
130.1246
129.9447
129.3931
127.9744
123.7598
121.5061
120.9888
118.0826
115.1921
115.0126
114.5877
114.1439
113.5703
111.6887
106.1960
73.3327
63.9373
62.9727
56.1832
55.5104
54.5191
50.1607
29.4606
26.7421
21.9298
21.4437
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

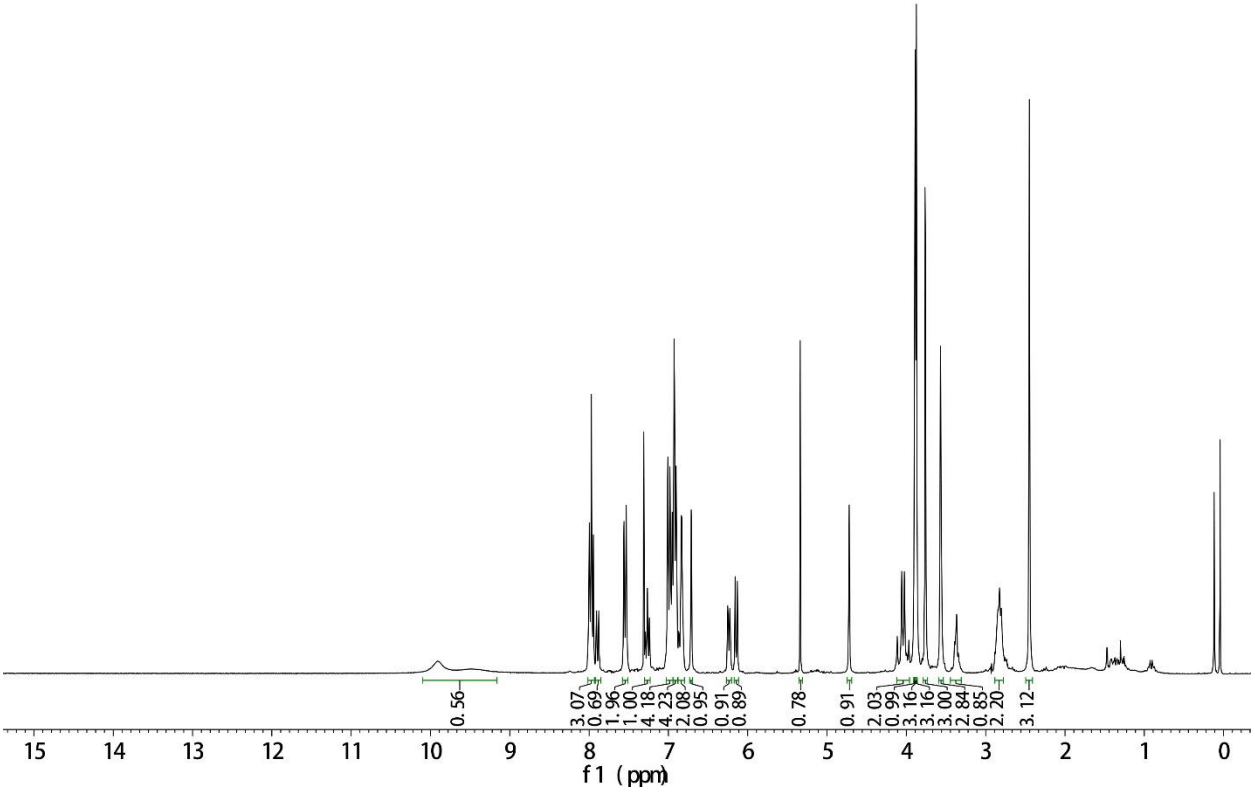

x10 4
C40 H40 N4 O11 S3: +ESI Scan (rt: 0.219-0.335 min, 8 scans) Frag=130.0V s-23-a-1.d Subtract
2
1.5
1
0.5
0
871.17548
([C40 H40 N4 O11 S3]+Na)+
849.19382
893.15634
835 840 845 850 855 860 865 870 875 880 885 890 895 900 905
Counts vs. Mass-to-Charge (m/z)

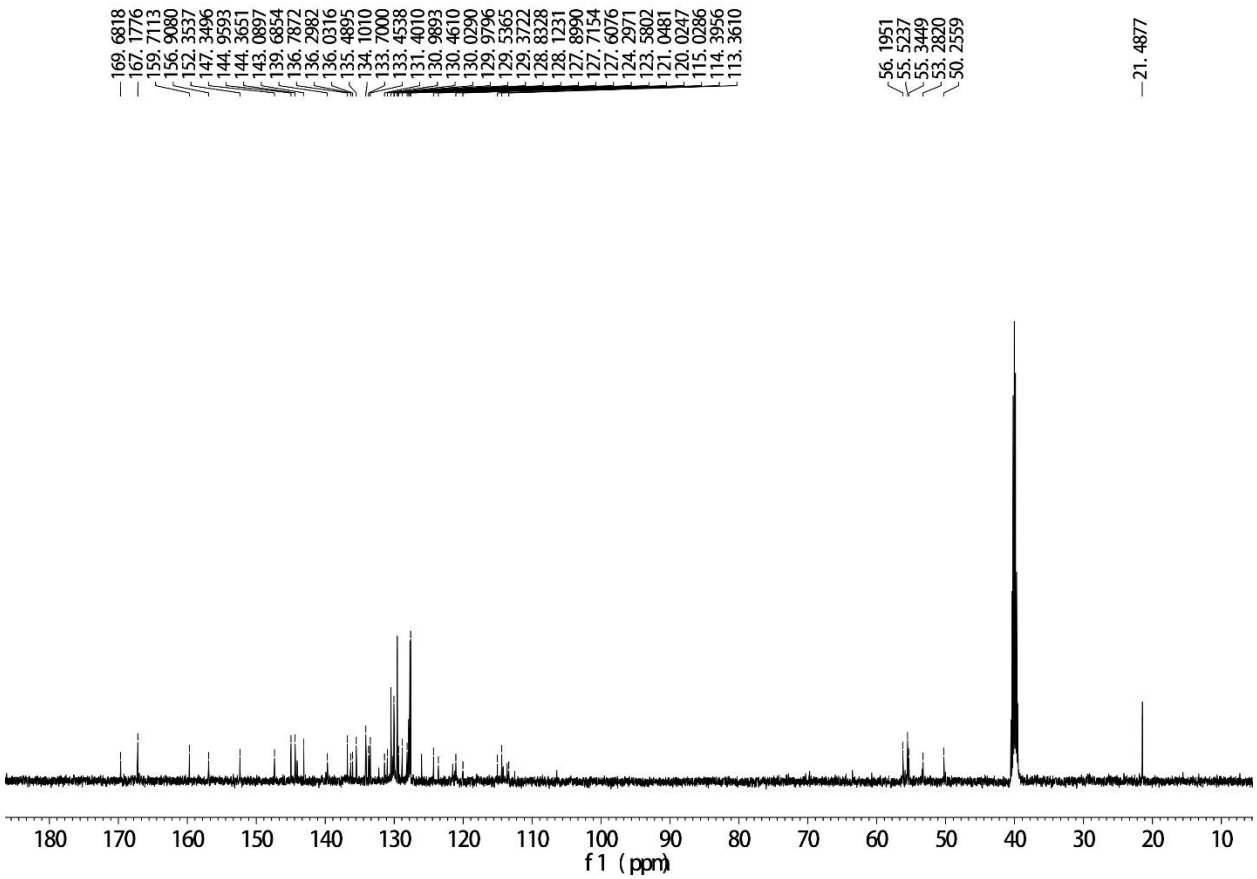


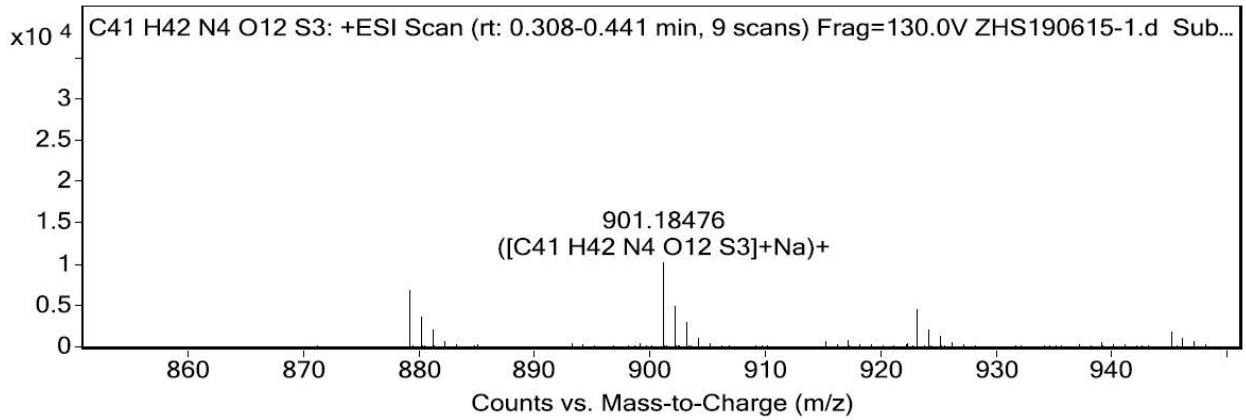
Signal: DAD1 A, Sig=254,4 Ref=360,100

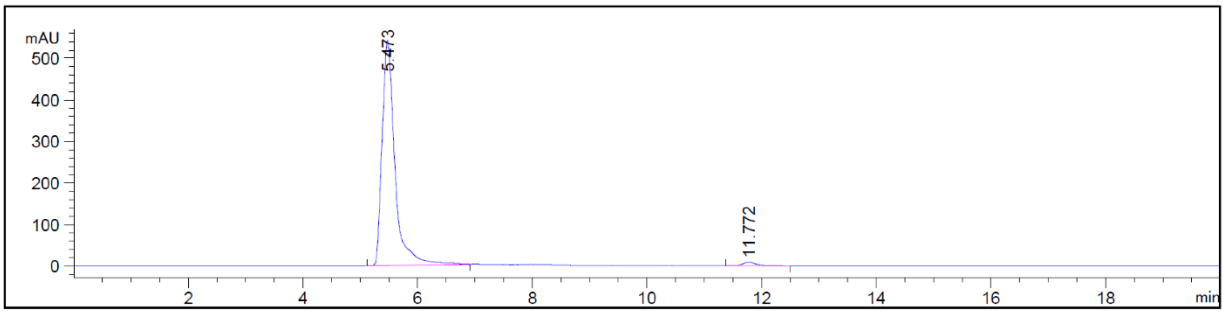
Peak	Retention Time min	Type	Width min	Area mAU*s	Height mAU	Relative Area %
1	4.614	VB	0.1207	29.64063	3.65058	0.2660
2	5.479	BB	0.1408	1.10545e4	1207.91138	99.1993
3	6.950	BV	0.1585	23.67913	2.37081	0.2125
4	7.238	VB	0.1483	15.80267	1.67212	0.1418

8. ^{1}H-NMR, ^{13}C-NMR, HRMS and HPLC Spectra for 19a




169.6818
167.1776
159.7113
156.9080
152.3537
147.3496
144.9593
144.3651
143.0897
139.6854
136.7872
136.2982
136.0316
135.4895
134.1010
133.7000
133.4538
131.4010
130.9893
130.4610
130.0290
129.9796
129.5365
129.3722
128.8328
128.1231
127.8990
127.7154
127.6076
124.2971
123.5802
121.0481
120.0247
115.0286
114.3956
113.3610
56.1951
55.5237
55.3449
53.2820
50.2559
21.4877
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


x10 4
C41 H42 N4 O12 S3: +ESI Scan (rt: 0.308-0.441 min, 9 scans) Frag=130.0V ZHS190615-1.d Sub...
3
2.5
2
1.5
1
0.5
0
901.18476
([C41 H42 N4 O12 S3]+Na)+
860 870 880 890 900 910 920 930 940
Counts vs. Mass-to-Charge (m/z)



Signal: DAD1 A, Sig=254,4 Ref=360,100

Peak	Retention Time min	Type	Width min	Area mAU*s	Height mAU	Relative Area %
1	5.473	BB	0.2248	8399.07617	542.07520	98.3931
2	11.772	BB	0.2432	137.16754	8.54921	1.6069