Electronic Supplementary Material (ESI) for Chemical Communications

Sulfo-click Reaction via *in situ* Generated Thioacids and its Application in Kinetic Target-Guided Synthesis.

Niranjan Kumar Namelikonda and Roman Manetsch*

Department of Chemistry, University of South Florida,

4202 East Fowler Avenue, Tampa, Florida 33620, USA.

manetsch@usf.edu

SUPPORTING INFORMATION

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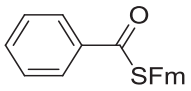
General: All reagents and solvents were purchased from commercial sources and used without further purification. All reactions were run under an argon atmosphere unless otherwise indicated. Prior to use of solvents in reactions, they were purified by passing the degassed solvents through a column of activated alumina and transferred by an oven-dried syringe or cannula. Thin layer chromatography was performed on Merck TLC plates (silica gel 60 F_{254}). ^{1}H NMR and ^{13}C NMR were recorded on a Varian Inova 400 (400 MHz) or a Bruker Avance DPX-250 (250 MHz) instrument. The purification of designated compounds was carried out using reverse phase HPLC system (Waters Prep LC 4000 system with Waters 996 photo-diode array detector, Agilent column Eclipse XDB-C18, 5 μm, 9.4 mm × 250 mm). Compounds were eluted using a gradient elution of A: B (80:20 to 0:100) over 40 min at a flow rate of 5.0 mL/min, where solvent A was H_2O (0.05% TFA) and solvent B was CH_3CN (0.05% TFA). The HRMS data were measured on an Agilent 6210 Series MSD/TOF with electrospray ionization. The LC/MS data were measured on an Agilent 1100 LC/MSD-VL with electrospray ionization.

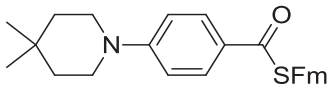
1. Preparation of 9-fluorenylmethyl thioesters: All the 9-fluorenylmethyl thioesters were prepared from the corresponding carboxylic acids[1] according to the literature procedure.[2] All the products were purified by silica gel column chromatography.

1.1 **Thiobenzoic acid *S*-(9*H*-fluoren-9-ylmethyl) ester (1a):**



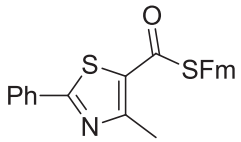
Yield: 91%. R_f = 0.6 (9:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.42 Hz, 2H), 7.74 (t, *J* = 7.0 Hz, 4H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.45-7.35 (m, 4H), 7.32 (t, *J* = 7.4 Hz, 2H), 4.26 (t, *J* = 6.0 Hz, 1H), 3.67 (d, *J* = 6.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.78, 145.74, 141.18, 137.14, 133.51, 128.71, 127.84, 127.37, 127.27, 124.89, 120.05, 46.95, 32.78. HRMS (ESI) calcd for $C_{21}H_{16}OS$ $[M + Na]^+$: 339.08141, Found: 339.08104.

1.2 **4-(4,4-Dimethyl-piperidin-1-yl)-thiobenzoic acid *S*-(9*H*-fluoren-9-ylmethyl) ester (1b):**



Yield: 89%. R_f: 0.5 (9:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 9.0 Hz, 2H), 7.77 (t, *J* = 7.8 Hz, 4H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.1 Hz, 2H), 6.83 (d, *J* = 9.0 Hz, 2H), 4.24 (t, *J* = 6.2 Hz, 1H), 3.61 (d, *J* = 6.3 Hz, 2H), 3.40 – 3.28 (m, 4H), 1.53 – 1.43 (m, 4H), 1.00 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.47, 154.67, 146.14, 141.11, 129.44, 127.69, 127.19, 125.98, 125.01, 119.95, 113.11, 47.31, 44.15, 38.05, 32.51, 28.80, 27.90. HRMS (ESI) calcd for $C_{28}H_{29}NOS$ $[M + Na]^+$: 450.18621, Found: 450.18753.

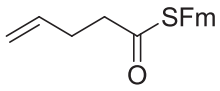
1.3 **4-Methyl-2-phenyl-thiazole-5-carbothioic acid *S*-(9*H*-fluoren-9-ylmethyl) ester (1c):**



Yield: 89%. R_f: 0.4 (9:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.1 Hz, 2H), 7.80 – 7.70 (m, 4H), 7.50 – 7.38 (m, 5H), 7.34 (t, *J* = 7.4 Hz, 2H), 4.27 (t, *J* = 6.0 Hz, 1H), 3.68 (d, *J* = 6.1 Hz, 2H), 2.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.99, 169.71, 158.58,

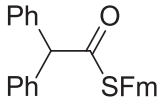
145.52, 141.17, 132.82, 131.35, 129.20, 127.92, 127.29, 127.06, 124.87, 120.08, 46.95, 33.80, 18.52. HRMS (ESI) calcd for $C_{25}H_{19}NOS_2$ $[M + H]^+$: 414.09808, Found: 414.09889.

1.4 **Pent-4-enethioic acid S-(9*H*-fluoren-9-ylmethyl) ester (1d):**



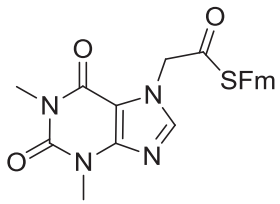
Yield: 93%. R_f: 0.7 (9:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.5 Hz, 2H), 7.67 – 7.62 (m, 2H), 7.39 (dd, *J* = 10.8, 4.1 Hz, 2H), 7.31 (td, *J* = 7.5, 1.2 Hz, 2H), 5.78 – 5.64 (m, 1H), 4.98 (ddd, *J* = 12.2, 10.2, 1.5 Hz, 2H), 4.16 (s, 1H), 3.54 (d, *J* = 5.8 Hz, 2H), 2.57 (dd, *J* = 8.2, 6.7 Hz, 2H), 2.38 – 2.28 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.20, 145.36, 141.06, 135.99, 127.62, 127.03, 124.60, 119.80, 115.73, 46.73, 43.11, 32.04, 29.35. HRMS (ESI) calcd for $C_{19}H_{18}OS$ $[M + Na]^+$: 317.09706, Found: 317.09689.

1.5 **Diphenyl-thioacetic acid S-(9*H*-fluoren-9-ylmethyl) ester (1e):**



Yield: 84%. R_f: 0.7 (9:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.6, 0.6 Hz, 2H), 7.63 – 7.57 (m, 2H), 7.43 – 7.36 (m, 2H), 7.32 – 7.21 (m, 8H), 7.14 (ddd, *J* = 7.6, 1.4, 0.7 Hz, 4H), 5.11 (s, 1H), 4.20 (t, *J* = 5.6 Hz, 1H), 3.60 (dd, *J* = 5.6, 1.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.24, 145.19, 141.18, 138.07, 128.71, 128.52, 127.63, 127.30, 127.05, 124.68, 119.79, 65.05, 46.71, 32.44**.** HRMS (ESI) calcd for $C_{28}H_{22}OS$ $[M + K]^+$: 445.10229, Found: 445.10238.

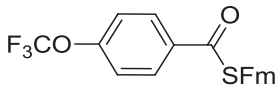
1.6 **(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-yl)-thioacetic acid S-(9*H*-fluoren-9-ylmethyl) ester (1f):**



Yield: 82%. R_f: 0.6 (9:1 DCM:methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.6 Hz, 2H), 7.50 – 7.45 (m, 2H), 7.37 (s, 1H), 7.33 – 7.26 (m, 2H), 7.20 (td, *J* = 7.5, 1.0 Hz, 2H), 5.02

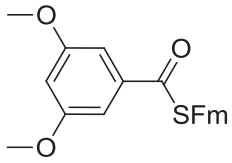
(s, 2H), 4.08 (t, *J* = 5.7 Hz, 1H), 3.52 (d, *J* = 5.7 Hz, 2H), 3.49 (s, 3H), 3.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.89, 155.15, 151.66, 148.58, 144.85, 142.01, 141.18, 127.97, 127.26, 124.66, 120.02, 107.03, 54.38, 46.46, 32.56, 29.90, 28.00. HRMS (ESI) calcd for $C_{23}H_{20}N_4O_3S$ $[M + H]^+$: 433.13289, Found: 433.13334.

1.7 **4-Trifluoromethoxy-thiobenzoic acid S-(9*H*-fluoren-9-ylmethyl) ester (1g):**



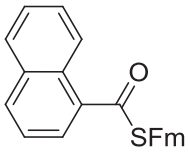
Yield: 89%. R_f: 0.7 (9:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.91 (m, 2H), 7.76 (d, *J* = 7.51 Hz, 2H), 7.71 (d, *J* = 7.48 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.36 – 7.29 (m, 2H), 7.27 – 7.18 (m, 2H), 4.26 (t, *J* = 5.8 Hz, 1H), 3.71 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.26, 152.90, 145.50, 141.21, 135.32, 129.29, 127.91, 127.29, 124.80, 120.51, 120.38 (q, *J* = 259.82 Hz), 120.08, 46.80, 32.86. HRMS (ESI) calcd for $C_{22}H_{15}F_3O_2S$ $[M + H]^+$: 401.08176, Found: 401.08228.

1.8 **3,5-Dimethoxy-thiobenzoic acid S-(9*H*-fluoren-9-ylmethyl) ester (1h):**



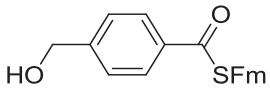
Yield: 83%. R_f: 0.4 (9:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (t, *J* = 8.3 Hz, 4H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.09 (d, *J* = 2.3 Hz, 2H), 6.65 (t, *J* = 2.3 Hz, 1H), 4.26 (t, *J* = 6.1 Hz, 1H), 3.82 (s, 6H), 3.66 (d, *J* = 6.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.70, 160.95, 145.74, 141.18, 139.10, 127.85, 127.28, 124.89, 120.06, 105.91, 105.14, 55.77, 46.96, 33.00. HRMS (ESI) calcd for $C_{23}H_{20}O_3S$ $[M + Na]^+$: 399.10254, Found: 399.10423.

1.9 **Naphthalene-1-carbothioic acid S-(9*H*-fluoren-9-ylmethyl) ester (1i):**



Yield: 65%. R_f: 0.6 (9:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.85 (dd, *J* = 7.3, 1.2 Hz, 2H), 7.80 – 7.75 (m, 4H), 7.59 – 7.49 (m, 2H), 7.46 – 7.39 (m, 3H), 7.36 (td, *J* = 7.4, 1.2 Hz, 2H), 4.37 (t, *J* = 5.7 Hz, 1H), 3.82 (d, *J* = 5.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.10, 145.63, 141.39, 135.83, 133.79, 132.74, 129.24, 128.37, 127.95, 127.86, 127.39, 127.27, 126.71, 125.32, 124.96, 124.53, 120.05, 47.10, 33.23. HRMS (ESI) calcd for $C_{25}H_{18}OS$ $[M + Na]^+$: 389.09706, Found: 389.09708.

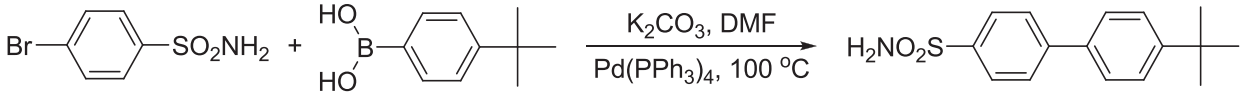
1.10 **4-Hydroxymethyl-thiobenzoic acid S-(9*H*-fluoren-9-ylmethyl) ester (1j):**



Yield: 59%. R_f: 0.3 (7:3 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.78 – 7.71 (m, 4H), 7.40 (t, *J* = 7.9 Hz, 4H), 7.33 (td, *J* = 7.4, 1.0 Hz, 2H), 4.75 (s, 2H), 4.26 (t, *J* = 6.0 Hz, 1H), 3.68 (d, *J* = 6.1 Hz, 2H), 1.85 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.45, 146.65, 145.72, 141.19, 136.35, 127.85, 127.65, 127.28, 126.74, 124.89, 120.05, 64.72, 46.94, 32.77. HRMS (ESI) calcd for $C_{22}H_{18}O_2S$ $[M + Na]^+$: 369.09197, Found: 369.09108.

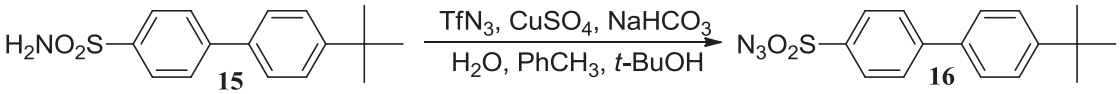
2. Synthesis of sulfonyl azides:[1,5]

2.1 4'- *tert*-Butyl-biphenyl-4-sulfonyl azide (16):



13 14 15

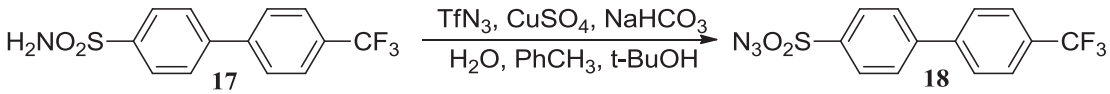
Biaryl **15** was synthesized following the literature procedure[3] starting from commercially available sulfonamide **13** (300 mg, 1.27 mmol) and boronic acid **14** (271.5 mg, 1.52 mmol) in 95% yield (349 mg). R_f: 0.65 (1:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, DMSO) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.84 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.39 (s, 1H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 150.91, 143.22, 142.66, 135.81, 126.85, 126.67, 126.26, 125.86, 34.31, 31.02. HRMS (ESI) calcd for $C_{16}H_{19}NO_2S$ $[M + H]^+$: 290.12093, Found: 290.12074.



15 16

Sulfonylazide **16** was synthesized by following the literature procedure[4] starting from sulfonamide **15** (250 mg, 0.864 mmol) in 97% yield (263 mg). R_f: 0.8 (4:1 hexanes: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.99 (m, 2H), 7.84 – 7.78 (m, 2H), 7.62 – 7.51 (m, 4H), 1.39 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.51, 147.84, 136.67, 135.84, 128.14, 128.08, 127.22, 126.31, 34.85, 31.38. HRMS (ESI) calcd for $C_{16}H_{17}N_3O_2S$ $[M + Na]^+$: 338.09337, Found: 338.09325.

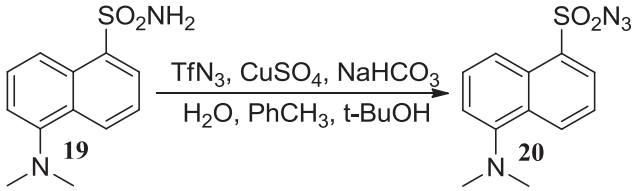
2.2 4'- trifluoromethyl-biphenyl-4-sulfonyl azide (18):



17 18

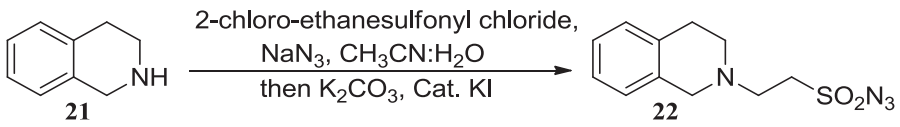
Sulfonylazide **18** was synthesized following the literature procedure[4] starting from corresponding sulfonamide[3] **17** (250 mg, 0.829 mmol) in 96% yield (261 mg). R_f: 0.75 (4:1 Hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.04 (m, 2H), 7.86 – 7.80 (m, 2H), 7.80 - 7.72 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.36, 142.34, 138.04, 131.11 (q, *J* = 33.07 Hz), 128.63, 128.33, 127.96, 126.27 (q, *J* = 3.73 Hz), 124.08 (q, *J* = 272.33 Hz). HRMS (ESI) calcd for $C_{13}H_8F_3N_3O_2S$ $[M + Na]^+$: 350.01815, Found: 350.01937.

2.3 **5-Dimethylamino-naphthalene-1-sulfonyl azide (20):**



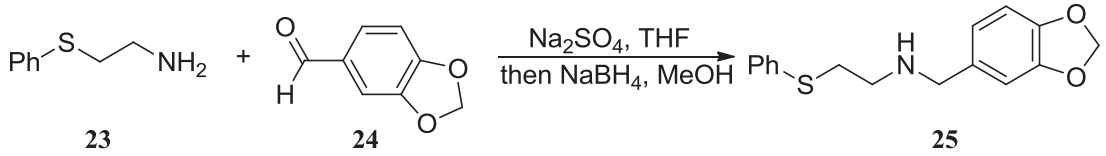
Sulfonylazide **20** was prepared by following the procedure described for the synthesis of compound **18** starting from commercially available dansylamide **19** (100 mg, 0.4 mmol) in 75% (82 mg) yield. R_f: 0.5 (4:1 Hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (dt, *J* = 8.5, 1.1 Hz, 1H), 8.34 (dd, *J* = 7.4, 1.3 Hz, 1H), 8.20 (dt, *J* = 8.7, 0.9 Hz, 1H), 7.66 – 7.56 (m, 2H), 7.24 (dd, *J* = 7.7, 0.8 Hz, 1H), 2.90 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 152.16, 133.66, 132.74, 130.12, 130.03, 129.62, 129.29, 122.96, 118.70, 115.85, 45.38. HRMS (ESI) calcd for $C_{12}H_{12}N_4O_2S$ $[M + Na]^+$: 299.05732, Found: 299.05785.

2.4 **2-(3,4-Dihydro-1*H*-isoquinolin-2-yl)-ethanesulfonyl azide (22):**



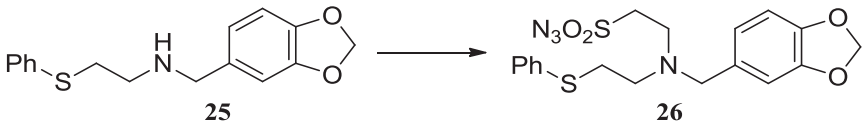
2-Chloro-ethanesulfonyl chloride (195.6 mg, 1.2 mmol) in 5 mL of acetonitrile was added sodium azide (78 mg, 1.2 mmol) dissolved in 1 mL of water slowly. After 3 hours K_2CO_3 (331 mg, 2.4 mmol) and KI (2 mol%) were added followed by the amine **21** (159 mg, 1.2 mmol) dissolved in 2 mL of acetonitrile. After three hours water was added and the reaction mixture was extracted with DCM, combined organic layers were dried over Na_2SO_4 and crude product was purified by flash chromatography to provide the desired sulfonylazide **22** in 59% (188 mg) yield. R_f: 0.4 (4:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, CD_3OD) δ 7.18 – 6.99 (m, 4H), 3.81 (t, *J* = 6.5 Hz, 2H), 3.71 (s, 2H), 3.04 (t, *J* = 6.5 Hz, 2H), 2.91 (t, *J* = 5.8 Hz, 2H), 2.82 (t, *J* = 5.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.77, 133.75, 128.77, 126.58, 126.55, 125.95, 55.55, 54.10, 51.94, 50.87, 28.88. HRMS (ESI) calcd for $C_{11}H_{14}N_4O_2S$ $[M + Na]^+$: 289.07297, Found: 289.07271.

2.5 **2-[Benzo[1,3]dioxol-5-ylmethyl-(2-phenylsulfanyl-ethyl)-amino]-ethanesulfonyl azide (26):**



23 **24** **25**

Amine **23**[1] (1 g, 6.5 mmol) and aldehyde **24** (980 mg, 6.5 mmol) were taken in anhydrous THF (25 mL) and dry Na_2SO_4 (2 g) was added to the reaction mixture and stirred for three hours. Then the reaction mixture was filtered and solvent was evaporated under reduced pressure. The residue was taken in anhydrous methanol (25 mL) and at 0 ^oC $NaBH_4$ (296 mg, 7.8 mmol) was added portion wise and the reaction mixture was stirred for an hour. The reaction was quenched with solid ammonium chloride, methanol was removed under reduced pressure, diluted with water , extracted with EtOAc, combined extracts were dried over Na_2SO_4 and solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography to yield the required secondary amine **25** in 54% (1.01 g) yield. R_f: 0.3 (1:1 hexanes:EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.10 (m, 2H), 7.08 – 7.02 (m, 2H), 6.99 – 6.93 (m, 1H), 6.59 (s, 1H), 6.51 (d, J = 1.9 Hz, 2H), 5.70 (s, 2H), 3.47 (s, 2H), 2.85 (t, J = 6.5 Hz, 2H), 2.61 (t, J = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.81, 146.62, 135.89, 134.20, 129.80, 129.01, 126.30, 121.25, 108.71, 108.15, 100.97, 53.31, 47.44, 34.35. HRMS (ESI) calcd for $C_{16}H_{17}NO_2S$ $[M + Na]^+$: 288.10528, Found: 288.10452.



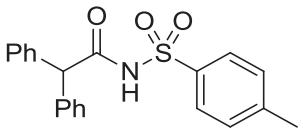
25 **26**

Sulfonylazide **26** was prepared starting from amine **25** (200 mg, 0.7 mmol) following the procedure described for the synthesis of compound **22** in 57% (166 mg) yield. R_f: 0.6 (2:1 hexanes:EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.14 (m, 4H), 7.14 – 7.05 (m, 1H), 6.73 (s, 1H), 6.67 – 6.59 (m, 2H), 5.86 (s, 2H), 3.47 (s, 2H), 3.33 – 3.25 (m, 2H), 3.02 – 2.88 (m, 4H), 2.73 – 2.64 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.97, 147.11, 135.95, 131.55, 129.29, 129.07, 126.25, 122.05, 109.20, 108.13, 101.11, 58.36, 53.89, 53.06, 47.84, 31.35. HRMS (ESI) calcd for $C_{18}H_{20}N_4O_4S_2$ $[M + Na]^+$: 443.08182, Found: 443.08216.

3. General procedure for the amidation reaction between thioesters and sulfonylazides with DBU:

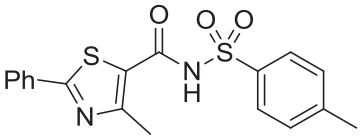
All the reactions were performed at 20-30 mg scale. The 9-fluorenylmethyl thioester was taken in a 1.5 mL eppendorf and 3.5% DBU/dry DMF solution was added (per 1 μmol of thioester, 4.7 μL of 3.5% DBU/dry DMF solution was added) and the reaction was stirred for a minute. Then the sulfonylazide (1 eq to thioester) was added to the reaction mixture and immediately bubbling was observed. After the reaction was completed in a minute, (monitored by LC-MS) water (200 μL) was added and the pH was adjusted to 7.0 using 1M HCl solution. The reaction mixture was extracted with DCM until there is no product in the aqueous layer (checked by TLC or LC-MS). The product was purified by flash chromatography.

3.1 ***N*-Diphenylacetyl-4-methyl-benzenesulfonamide (3a):**



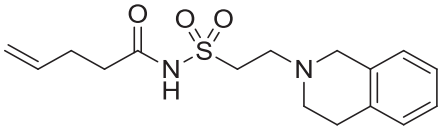
Yield: 85%. R_f: 0.4 (7:3 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.4 Hz, 2H), 7.34 – 7.20 (m, 8H), 7.13 – 6.90 (m, 4H), 4.87 (s, 1H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.45, 145.16, 137.07, 135.06, 129.50, 128.94, 128.75, 128.55, 127.79, 58.70, 21.69. HRMS (ESI) calcd for $C_{21}H_{19}NO_3S$ $[M + H]^+$: 366.11584, Found: 366.115823.2

3.2 **4-Methyl-*N*-(4-methyl-2-phenyl-thiazole-5-carbonyl)-benzenesulfonamide (3b):**



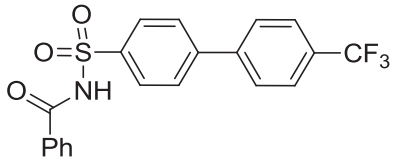
Yield: 81%. R_f: 0.3 (9:1 DCM:methanol). ^{1}H NMR (400 MHz, DMSO) δ 7.95 – 7.84 (m, 2H), 7.74 (d, J = 8.1 Hz, 2H), 7.47 (m, 3H), 7.24 (d, J = 8.5 Hz, 2H), 2.58 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 165.12, 164.69, 154.88, 142.28, 140.17, 133.08, 130.29, 129.14, 128.27, 126.98, 126.00, 20.89, 16.90. HRMS (ESI) calcd for $C_{18}H_{16}N_2O_3S_2$ $[M + H]^+$: 373.06751, Found: 373.06703.

3.3 **2-(3,4-Dihydro-1*H*-isoquinolin-2-yl)-ethanesulfonic acid pent-4-enoyl-amide (3C):**



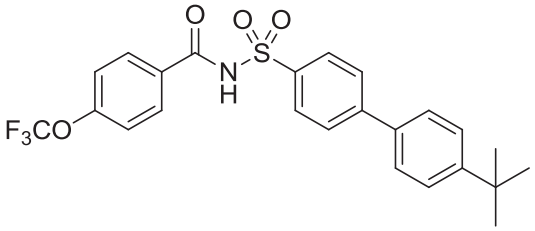
Yield: 78%. R_f: 0.5 (9:1 DCM:methanol). ^{1}H NMR (400 MHz, DMSO) δ 7.22 – 6.87 (m, 4H), 5.67 (ddt, *J* = 16.6, 10.3, 6.3 Hz, 1H), 5.01 – 4.80 (m, 2H), 3.66 – 3.53 (m, 4H), 2.86 (t, *J* = 6.8 Hz, 2H), 2.80 (t, *J* = 5.5 Hz, 2H), 2.70 (t, *J* = 5.8 Hz, 2H), 2.26-2.1 (m, 2H), 2.18 – 2.04 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 172.24, 136.90, 134.22, 133.70, 128.34, 126.29, 126.01, 125.47, 115.32, 54.90, 51.33, 50.05, 48.96, 34.67, 28.36, 27.75. HRMS (ESI) calcd for $C_{16}H_{22}N_2O_3S$ [M + Na]$^+$: 345.12433, Found: 345.12469.

3.4 **4'-Trifluoromethyl-biphenyl-4-sulfonic acid benzoylamide (3d):**



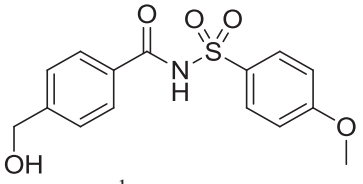
Yield: 90%. R_f: 0.4 (1:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, DMSO) δ 8.05 – 7.99 (m, 2H), 7.97 – 7.89 (m, 4H), 7.85 (m, 4H), 7.50 – 7.44 (m, 1H), 7.42 – 7.35 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 168.11, 143.51, 143.07, 141.16, 136.17, 131.18, 128.38 (q, *J* = 32.25 Hz), 128.35, 127.94, 127.82, 126.91, 125.84 (q, *J* = 3.73 Hz), 124.25 (q, *J* = 271.84 Hz). HRMS (ESI) calcd for $C_{20}H_{14}F_3NO_3S$ [M + H]$^+$: 406.07193, Found: 406.07267.

3.5 **4'-tert-Butyl-biphenyl-4-sulfonic acid 4-trifluoromethoxy-benzoylamide (3e):**



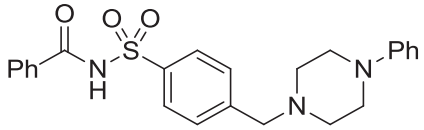
Yield: 88%. R_f: 0.4 (1:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, DMSO) δ 8.02 (d, *J* = 8.8 Hz, 2H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 166.04, 150.85, 150.68, 143.48, 140.80, 135.96, 133.99, 130.71, 127.98, 126.70, 126.45, 125.84, 120.21, 119.9 (q, *J* = 258.0 Hz), 34.30, 31.01. HRMS (ESI) calcd for $C_{24}H_{22}F_3NO_4S$ [M + Na]$^+$: 500.11138, Found: 500.11239.

3.6 ***N*-(4-Hydroxymethyl-benzoyl)-4-methoxy-benzenesulfonamide (3f):**



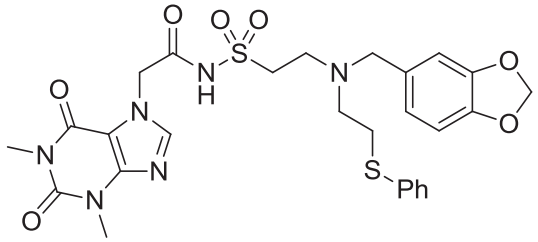
Yield: 87%. R_f: 0.7 (9:1 DCM:methanol). ^{1}H NMR (400 MHz, DMSO) δ 7.81 (d, *J* = 6.5 Hz, 2H), 7.79 (d, *J* = 6.1 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 5.21 (br s, 1H), 4.48 (s, 2H), 3.77 (s, 3H), 2.46 (br s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 167.49, 161.55, 146.06, 129.34, 128.21, 125.63, 113.35, 62.52, 55.48. HRMS (ESI) calcd for $C_{15}H_{15}NO_5S$ [M + Na]$^+$: 344.05631, Found: 344.05767.

3.7 ***N*-Benzoyl-4-(4-phenyl-piperazin-1-ylmethyl)-benzenesulfonamide (3g):**



Yield: 80%. R_f: 0.5 (9:1 DCM:methanol). ^{1}H NMR (400 MHz, DMF) δ 8.11 (d, *J* = 8.3 Hz, 2H), 8.07 – 7.98 (m, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.63 (t, *J* = 6.9 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.24 (dd, *J* = 8.6, 7.4 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.81 (t, *J* = 7.3 Hz, 1H), 3.80 (s, 2H), 3.29 – 3.19 (m, 4H), 2.74 – 2.65 (m, 4H). ^{13}C NMR (101 MHz, DMF) δ 167.25, 152.44, 144.59, 140.98, 134.14, 133.92, 130.43, 130.06, 129.58, 129.56, 129.20, 128.71, 120.17, 116.75, 115.01, 62.51, 53.99, 49.51. HRMS (ESI) calcd for $C_{24}H_{25}N_3O_3S$ [M + Na]$^+$: 458.15088, Found: 458.15182.

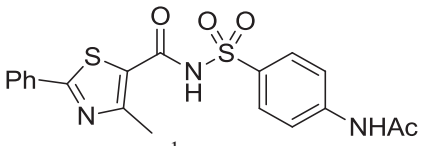
3.8 **2-[Benzo[1,3]dioxol-5-ylmethyl-(2-phenylsulfanyl-ethyl)-amino]-ethanesulfonic acid [2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-yl)-acetyl]-amide (3h):**



Yield: 73%. R_f: 0.4 (9:1 DCM:methanol). ^{1}H NMR (400 MHz, DMSO) δ 7.95 (s, 1H), 7.24 – 7.15 (m, 4H), 7.13 – 7.07 (m, 1H), 6.87 (d, *J* = 1.4 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.74 (dd, *J* = 7.9, 1.5 Hz, 1H), 5.98 (s, 2H), 4.91 (s, 2H), 3.56 (s, 2H), 3.40 (s, 3H), 3.36 – 3.26 (m, 2H), 3.13 (s, 3H), 3.05 – 2.99 (m, 2H), 2.95 – 2.88 (m, 2H), 2.67 – 2.60 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 169.34, 154.40, 150.93, 147.71, 147.17, 146.22, 143.44, 136.04, 132.18, 128.85,

127.46, 125.25, 121.84, 108.94, 107.75, 106.49, 100.75, 56.89, 51.39, 49.88, 48.33, 47.36, 29.36, 29.22, 27.34. HRMS (ESI) calcd for $C_{27}H_{30}N_6O_7S_2$ $[M + H]^+$: 615.16902, Found: 615.17159.

3.9 ***N*-{4-[(4-Methyl-2-phenyl-thiazole-5-carbonyl)-sulfamoyl]-phenyl}-acetamide (3i):**



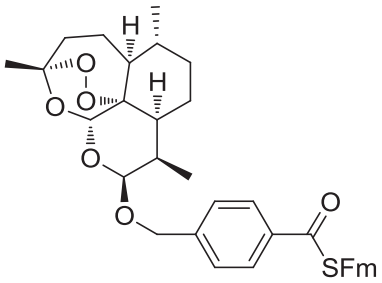
Yield: 60%. R_f: 0.45 (4:1 DCM:methanol). ^{1}H NMR (400 MHz, DMSO) δ 10.15 (s, 1H), 7.90 (dd, *J* = 5.6, 2.2 Hz, 2H), 7.77 – 7.70 (m, 2H), 7.59 (d, *J* = 7.6 Hz, 2H), 7.51 – 7.42 (m, 3H), 2.58 (d, *J* = 1.3 Hz, 3H), 2.06 (d, *J* = 1.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 168.51, 165.42, 164.64, 154.19, 140.69, 140.12, 133.25, 132.64, 130.11, 129.10, 127.67, 125.92, 117.62, 24.03, 16.82. HRMS (ESI) calcd for $C_{19}H_{17}N_3O_4S_2$ $[M + H]^+$: 416.07332, Found: 416.07350.

4. General procedure for amidation with Cs_2CO_3:

All the reactions were performed at 20-30 mg scale. The 9-fluorenylmethyl thioester was taken in a 1.5 mL eppendorf in dry DMF, (per 1 µmol of thioester, 4.7 µL of DMF was added) 5 equivalents of solid Cs_2CO_3 was added and the reaction was stirred for a 90 minutes at room temperature. Then the sulfonylazide (1 eq w.r.t. thioester) was added to the reaction mixture and stirred for 30 minutes. After the reaction was complete, (monitored by LC-MS) water (200 µL) was added and the pH was adjusted to 7.0 using 1M HCl solution. The reaction mixture was extracted with DCM until there was no product in aqueous layer (checked by TLC or LC-MS). The product was purified by flash chromatography.

5. Synthesis of fluorescent artemisinin derivative:

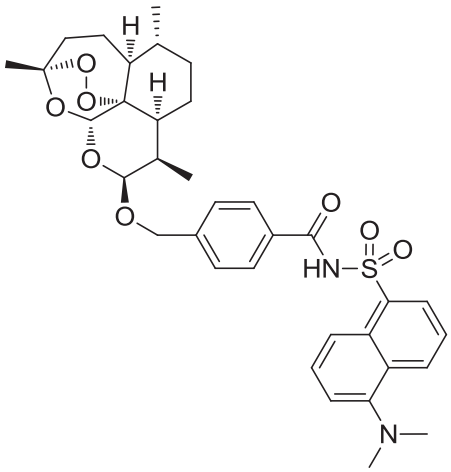
5.1 **Thioester of artelinic acid (6):**



Dihydroartemisinin[6] (200 mg, 0.7 mmol) was dissolved in anhydrous diethyl ether (25 mL) under N_2. $BF_3.Et_2O$ (106 µL, 0.84 mmol) was added to the solution, followed by the addition of alcohol **1j** (243.6 mg, 0.7 mmol). The reaction mixture was allowed to stir for 32 hours at room temperature and then the reaction was quenched with water. The organic phase was washed with Na_2SO_4 solution (30% W/V), dried over Mg_2SO_4, filtered and the solvent was removed under reduced pressure to give the crude product. Purification by chromatography gave the product in 46% yield (200 mg) along with a trace amount of the other diastereomer. R_f: 0.5 (4:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.4, 1.8 Hz, 2H), 7.75 (t, *J* = 7.7 Hz, 4H), 7.45 – 7.29 (m, 6H), 5.45 (s, 1H), 4.95 (d, *J* = 13.3 Hz, 1H), 4.92 (d, *J* = 3.18 Hz, 1H), 4.56 (d, *J* = 13.3 Hz, 1H), 4.26 (t, *J* = 6.0 Hz, 1H), 3.68 (d, *J* = 6.0 Hz, 2H), 2.76 – 2.64 (m, 1H), 2.39 (td, *J* = 14.0, 4.1 Hz, 1H), 2.10 – 1.99 (m, 1H), 1.94 – 1.76 (m, 3H), 1.69 – 1.59 (m, 1H), 1.58 – 1.18 (m, 5H), 1.46 (s, 3H), 0.97 (d, *J* = 7.4 Hz, 3H), 0.95 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.30, 145.69, 144.35, 141.14, 136.18, 127.80, 127.44, 127.35, 127.22,

127.07, 124.84, 120.00, 104.28, 101.76, 88.13, 81.14, 69.22, 52.64, 46.91, 44.43, 37.52, 36.51, 34.68, 32.71, 31.00, 26.26, 24.77, 24.63, 20.41, 13.19.

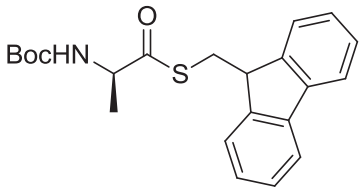
5.2 **Acylsulfonamide (8):**



The acylsulfonamide of artemisinin **8** was prepared by following the general procedure using DBU, starting from the thioester **6** (66 mg, 0.107 mmol) and dansyl azide (29.7 mg, 0.107 mmol). The product was initially purified by column chromatography (using 9:1 DCM: methanol, R_f: 0.5) to enrich the sample for the preparative HPLC. After the separation of 10β diastereomer from the mixture by preparative HPLC, water and acetonitrile as elutant system, 50 mg (71%) product **8** was obtained. ^{1}H NMR (400 MHz, DMSO) δ 12.79 (s, 1H), 8.54 (d, *J* = 8.5 Hz, 1H), 8.42 – 8.32 (m, 2H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.72 (dd, *J* = 8.5, 7.4 Hz, 1H), 7.65 – 7.58 (m, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.22 (m, 1H), 5.38 (s, 1H), 4.80 (d, *J* = 3.4 Hz, 1H), 4.80 (d, *J* = 13.3 Hz, 1H), 4.48 (d, *J* = 13.3 Hz, 1H), 2.82 (s, 6H), 2.48 – 2.39 (m, 1H), 2.18 (td, *J* = 14.0, 4.1 Hz, 1H), 2.06 - 1.96 (m, 1H), 1.86 – 1.62 (m, 3H), 1.57 – 1.49 (m, 1H), 1.44 – 1.10 (m, 5H), 1.29 (s, 3H), 0.87 (d, *J* = 7.5 Hz, 3H), 0.87 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 164.94, 151.50, 144.02, 134.30, 131.28, 130.74, 130.29, 128.84, 128.38, 128.14, 126.93, 125.26, 123.55, 117.99, 115.20, 103.33, 100.64, 87.01, 80.42, 68.37, 52.00, 45.02, 43.70, 36.52, 35.98, 34.00, 30.45, 25.58, 24.18, 23.96, 20.08, 12.76. HRMS (ESI) calcd for $C_{35}H_{42}N_2O_8S$ $[M + H]^+$: 651.27346, Found: 651.27427.

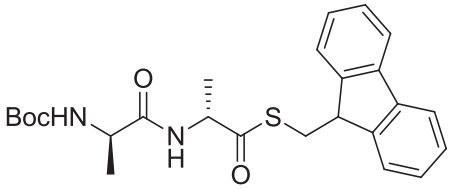
6. Synthesis of peptidic acylsulfonamide:

6.1 **(R)-S-((9*H*-fluoren-9-yl)methyl) 2-((tert-butoxycarbonyl)amino)propanethioate (9):**



To the mixture of Boc-Ala-OH (280 mg, 1.5 mmol) and FmSH (314 mg, 1.5 mmol) in anhydrous DCM (4 mL) was added EDCI (297.4 mg, 1.57 mmol) and DMAP (5 mol %) and the reaction mixture was stirred at room temperature for an hour. Water (10 mL) was added and the reaction mixture was extracted with DCM. The combined organic layers were mixed and dried over Na_2SO_4 and purified by flash chromatography to yield 79% (450 mg) of thioester **9**. R_f: 0.55 (1:4 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.6 Hz, 2H), 7.64 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.30 (tdd, *J* = 7.4, 2.3, 1.1 Hz, 2H), 5.00 (d, *J* = 7.2 Hz, 1H), 4.37 – 4.26 (m, 1H), 4.17 (t, *J* = 5.7 Hz, 1H), 3.59 – 3.44 (m, 2H), 1.46 (s, 9H), 1.20 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.73, 154.92, 145.35, 141.20, 127.73, 127.10, 124.79, 119.87, 80.23, 56.40, 46.78, 32.02, 28.39, 18.60. HRMS (ESI) calcd for $C_{22}H_{25}NO_3S$ $[M + H]^+$: 384.16279, Found: 384.16095.

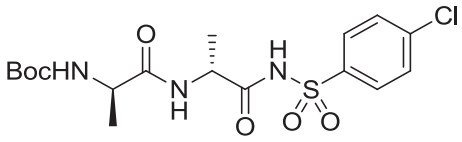
6.2 **(R)-S-((9*H*-fluoren-9-yl)methyl) 2-((R)-2-((tert-butoxycarbonyl)amino)propanamido) propanethioate (10):**



The thioester **9** (236 mg, 0.616 mmol) was stirred with 1:3 TFA:DCM (3 mL) for 20 min at room temperature. Then the volatiles were removed under reduced pressure and the flask was kept under high vacuum for couple of hours to get rid of any trace amount of left over TFA. In the same flask Boc-Ala-OH **9** (119 mg, 0.629 mmol), HATU (239 mg, 0.629 mmol) and DIPEA (223 µL, 1.38 mmol) were added in DMF (4 mL) was stirred for 90 min at room temperature. Water (10 mL) was added, the reaction mixture was extracted with DCM, combined extracts were dried over Na_2SO_4 and purified by flash column chromatography to obtain the dipeptide **10** in 88% (245 mg) yield. R_f: 0.5 (3:2 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* =

7.5 Hz, 2H), 7.63 – 7.57 (m, 2H), 7.41 – 7.34 (m, 2H), 7.32 - 7.26 (m, 2H), 6.70 (br s, 1H), 5.05 (br s, 1H), 4.65 – 4.46 (m, 1H), 4.20 – 4.09 (m, 2H), 3.57 – 3.45 (m, 2H), 1.43 (s, 9H), 1.32 (d, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.58, 172.43, 155.76, 145.31, 141.27, 127.86, 127.21, 124.84, 119.98, 80.56, 55.18, 49.88, 46.81, 32.14, 28.43, 18.61, 18.08. HRMS (ESI) calcd for $C_{25}H_{30}N_2O_4S$ $[M + H]^+$: 455.19990, Found: 455.20203.

6.3 **tert-butyl ((R)-1-(((R)-1-(4-chlorophenylsulfonamido)-1-oxopropan-2-yl)amino)-1-oxopropan-2-yl)carbamate (11):**



The sulfonamide **11** was prepared following the general procedure using DBU, starting from the thioester **10** (40 mg, 0.088 mmol) in 76% (29 mg) yield. R_f: 0.4 (4:1 DCM:methanol). ^{1}H NMR (400 MHz, DMSO) δ 12.33 (s, 1H), 8.01 (d, *J* = 6.8 Hz, 1H), 7.94 – 7.87 (m, 2H), 7.74 – 7.67 (m, 2H), 6.88 (d, *J* = 7.5 Hz, 1H), 4.24 – 4.13 (m, 1H), 3.96 – 3.86 (m, 1H), 1.35 (s, 9H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.09 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.68, 171.60, 155.00, 138.60, 137.90, 129.35, 129.27, 77.97, 49.21, 48.51, 28.15, 17.88, 16.77. HRMS (ESI) calcd for $C_{17}H_{24}ClN_3O_6S$ $[M + H]^+$: 434.11471, Found: 434.11613 (error m/z = 3.27 ppm).

7. Kinetic target-guided synthesis experiments:

7.1 Generation of thioacids with 5% piperidine/DMF prior to the kinetic TGS, LC/MS analysis:

All the thioacids were generated according to the following general procedure. In a 500 µL eppendorf, 1-2 mg of thioester was taken and treated with 5% piperidine/DMF solution (for 1 µmol of thioester, 4.7 µL of 5% piperidine/dry DMF) at room temperature. After complete consumption of the thioester in two minutes (monitored by LC-MS), the reaction mixture was diluted with HPLC grade MeOH to obtain 2 mM stock solution, which was immediately used for the TGS screening studies without further purification. The kinetic TGS incubation procedures were previously reported.[1]

7.2 Gradient systems for LC/MS analysis:

The gradient systems used for the LC/MS-SIM were as follows.

Gradient System 1:

Time (min)	Eluent B %	Flow rate (mL/min)
0	10	0.7
2	10	0.7
8	100	1.0
11.50	100	1.0
13.00	10	0.7

Eluent A: H_2O (0.05% TFA), Eluent B: CH_3CN (0.05% TFA)

Gradient System 2:

Time (min)	Eluent B %	Flow rate (mL/min)
0	10	0.7
2	10	0.7
10	100	1.0
11.50	100	1.0
13.00	10	0.7

Eluent A: H_2O (0.05% TFA), Eluent B: CH_3CN (0.05% TFA)

7.3 **Kinetic TGS incubations of SZ4 with conventionally synthesized and purified TA2 and the one with *in situ* deprotected thioester TA2' with 5% piperidine/DMF targeting wildtype Bcl-X_L.**

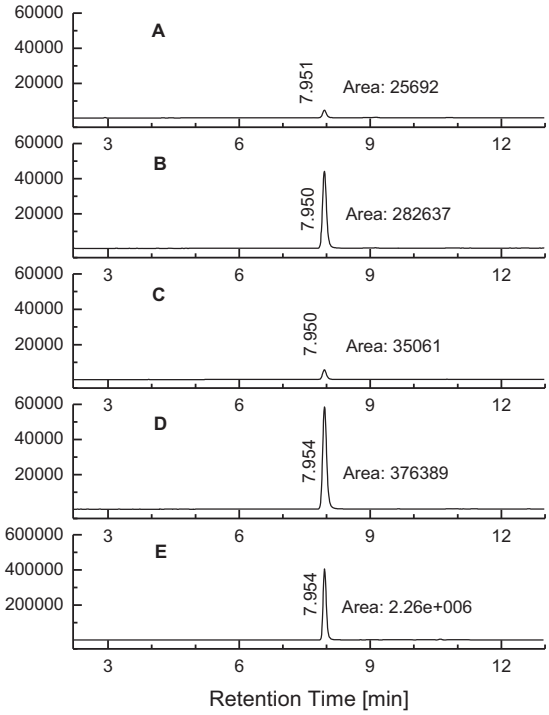


Figure S1: LC/MS-SIM analysis of kinetic TGS incubations with fragments SZ4 and TA2 targeting wildtype Bcl-X_L. The samples were incubated at 37 °C for 6 h and subjected to LC/MS-SIM analysis with gradient system 1. (A) Incubation sample containing fragments **SZ4** and conventionally synthesized **TA2** in the absence of wildtype Bcl-X_L. (B) Incubation sample containing fragments **SZ4** and conventionally synthesized **TA2** in the presence of 2 μM wildtype Bcl-X_L. (C) Incubation sample containing fragments **SZ4** and **TA2** derived from Fm thioester **TA2'** in the absence of wildtype Bcl-X_L. (D) Incubation sample containing fragments **SZ4** and **TA2** derived from Fm thioester **TA2'** in the presence of 2 μM wildtype Bcl-X_L. (E) Synthetic **SZ4TA2** as reference compound.

7.4 **Incubation experiments to determine the formation of piperidine amide during kinetic TGS with thioacid TA2 generated by deprotection of thioester TA2' with 5% piperidine/DMF:**

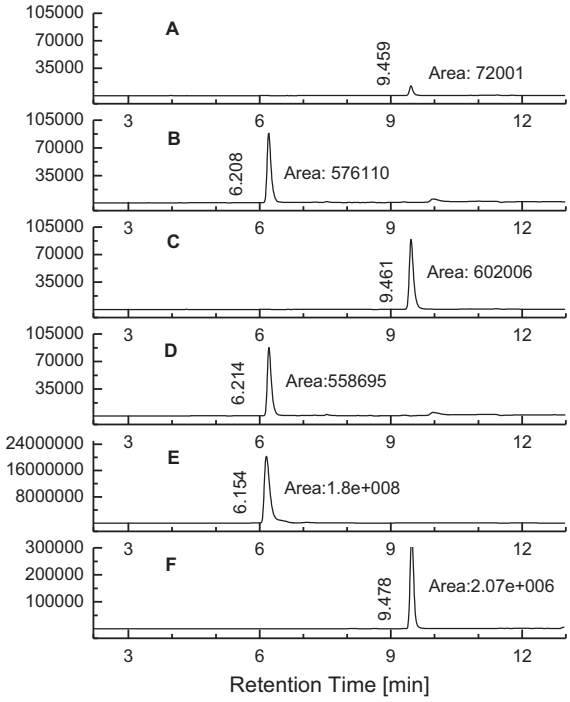


Figure S2: LC/MS-SIM analysis of kinetic TGS incubations with Bcl-X_L and fragments SZ4 and TA2 derived from Fm thioester TA2'. The samples were incubated with thioacid TA2 derived from Fm thioester TA2' at 37 ^{o}C for 6 hours and subjected to LC/MS-SIM analysis with gradient system 2. (A) Detection of **SZ4TA2** in incubation sample containing fragments **SZ4** and **TA2** in absence of wildtype Bcl-X_L. (B) Detection of piperidine amide in the incubation sample containing fragments **SZ4** and **TA2** in absence of wildtype Bcl-X_L. (C) Detection of **SZ4TA2** in the incubation sample containing fragments **SZ4** and **TA2** in presence of 2 μM wildtype Bcl-X_L. (D) Detection of piperidine amide in the incubation sample containing fragments **SZ4** and **TA2** in presence of 2 μM wildtype Bcl-X_L. (E) Synthetic piperidine amide as the reference compound. (F) Synthetic **SZ4TA2** as the reference.

7.5 **Kinetic TGS incubation experiments with SZ4 and TA2 derived from Fm thioester TA2' with wildtype Bcl-X_L, mutant Bcl-X_L, and bovine erythrocyte carbonic anhydrase II (bCAII):** Similar to the initial proof-of-concept study, control experiments were conducted to demonstrate that the templation effect occurs only if the active site of the Bcl-X_L protein is available. When **TA2** derived from thioester **TA2'** was incubated along with sulfonylazide **SZ4** with either mutant Bcl-X_L, concavalin A, or a mixture of Bcl-X_L and Bim BH3 peptide (see section 7.6), the formation of **SZ4TA2** was significantly decreased the amounts detected for the incubations with wildtype Bcl-X_L. These results clearly demonstrate, that the control incubations previously developed to assess whether the templation reaction occurs at the desired protein's active site, are reproducible with **TA2** derived from thioester **TA2'**.

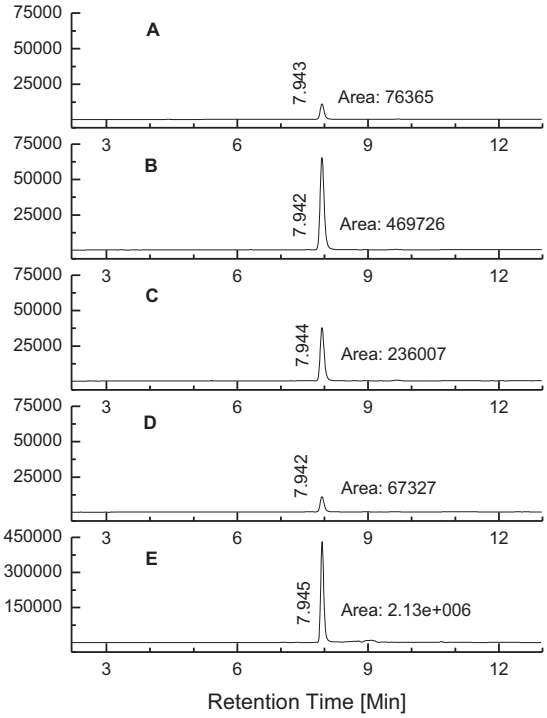


Figure S3: LC/MS-SIM analysis of kinetic TGS incubations with fragments SZ4 and TA2 derived from Fm thioester TA2' using wildtype Bcl-X_L, mutant Bcl-X_L, and bCAII as templates. All samples were incubated with **SZ4** and thioacid **TA2** derived from Fm thioester **TA2'** at 37 ^{o}C for 6 hours and subjected to LC/MS-SIM analysis with gradient system 1. (A) Incubation sample containing fragments **SZ4** and **TA2** in absence of wildtype Bcl-X_L. (B) Incubation sample containing fragments **SZ4** and **TA2** in presence of 2 µM wildtype Bcl-X_L. (C) Incubation sample containing fragments **SZ4** and **TA2** in presence of 2 µM mutant Bcl-X_L. (D) Incubation sample containing fragments **SZ4** and **TA2** in presence of 2 µM bovine erythrocyte carbonic anhydrase II (bCAII). (E) Synthetic **SZ4TA2** as reference.

7.6 **Kinetic TGS incubation experiments with SZ4 and TA2 derived from Fm thioester TA2' with wildtype Bcl-X_L and Bim BH3 peptide:**

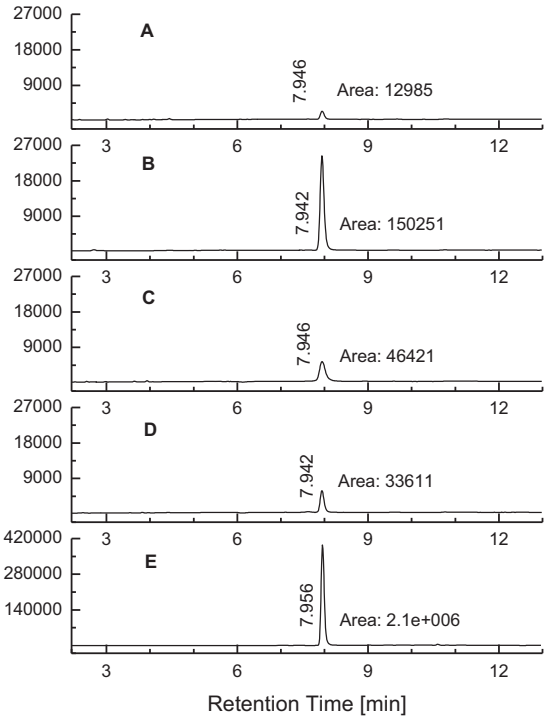


Figure S4: Suppression of the Bcl-X_L-templated incubation with Bim BH3 peptide. The protein samples were incubated with **SZ4** and **TA2** derived from Fm thioester **TA2'** for six hours at 37 °C and subjected to LC/MS-SIM analysis with gradient system 1. A) Incubation of **SZ4** and **TA2** without Bcl-X_L. B) Incubation of **SZ4** and **TA2** with 2 μM Bcl-X_L.C) Incubation of **SZ4** and **TA2** with 2 μM Bcl-X_L and 20 μM Bim BH3 peptide. D) Incubation of **SZ4** and **TA2** with 20 μM Bim BH3 peptide. E) Synthetic **SZ4TA2** as reference.

8. References:

1. All the carboxylic acids used for the synthesis of thioesters are commercially available except those correspond to the synthesis of **1b** and **1c**. We reported the Synthesis of these two carboxylic acids before. The synthesis of sulfonyl azides used for the synthesis of compounds **3a**, **3g** was also reported in the same paper. Hu, X.; sun, J.; Wang, H. G.; Manetsch, R. *J. Am. Chem. Soc.* **2008**, *130* (42), 13820-13821.
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3. Parrish, C.A. *et. al. J. Med. Chem.* **2007,** *50***,** 4939 – 4952**.**
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