# Supporting Information

**Discovery of Novel Pyridone-Conjugated Monosulfactams as Potent and Broad-Spectrum Antibiotics for Multidrug-Resistant Gram-Negative Infections**

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**I. Table S1. Individual MIC Data of tested compounds**

| Bacterial strain | β-lactamase | MIC (mg/L) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | BAL[a] | AZT[b] | MER[c] | CEF[d] | **8** | **9** | **10** | **11** | **12a** |
| *Escherichia coli* | | | | | | | | | | |
| 208687 | ESBLs | 0.25 | 32 | 0.5 | 2 | 8 | 1 | 2 | 1 | 0.06 |
| 212648 | | 1 | 2 | 8 | 1 | 4 | 2 | 2 | 4 | 0.06 |
| 209285 | | 0.25 | 16 | 1 | 2 | 32 | 4 | 8 | 64 | 0.25 |
| 106342 | | 0.5 | 4 | 8 | 1 | 4 | 2 | 2 | >64 | 0.06 |
| 210737 | non-ESBLs | 0.25 | 0.5 | 0.125 | 0.5 | 4 | 0.25 | 1 | 1 | 0.06 |
| *Klebsiella pneumoniae* | | | | | | | | | | |
| 212423 | KPC-2 | 64 | >64 | 64 | 64 | >64 | 64 | 64 | 64 | 64 |
| 209632 | | >64 | >64 | 32 | 32 | >64 | 64 | 64 | 64 | 64 |
| 209735 | | >64 | >64 | >64 | 64 | >64 | >64 | 64 | 64 | 64 |
| 212232 | | 0.25 | >64 | >64 | >64 | 32 | 4 | 16 | 8 | 0.03 |
| 212229 | | >64 | >64 | >64 | 32 | >64 | >64 | 64 | 64 | 64 |
| *Acinetobacter baumannii* | | | | | | | | | | |
| 210278 | OXA-23 | 0.5 | 64 | 64 | >64 | 16 | 4 | 16 | 8 | 0.5 |
| 211606 | | 0.5 | 64 | 64 | >64 | 16 | 8 | 16 | 8 | 0.5 |
| 208995 | | 1 | >64 | 64 | >64 | 32 | 8 | 32 | 16 | 1 |
| 207200 | | 0.5 | >64 | 64 | >64 | 64 | 4 | 16 | 8 | 0.5 |
| 211137 | | >64 | >64 | 64 | 32 | 16 | 64 | 64 | 64 | 64 |
| *Pseudomonas aeruginosa* | | | | | | | | | | |
| 212886 | IMP-4 | 1 | 64 | 64 | >64 | >64 | 64 | 64 | 64 | 0.5 |
| 209471 | | 2 | 32 | 32 | >64 | 64 | 64 | 64 | 64 | 1 |
| 208247 | | 1 | 32 | 64 | >64 | 64 | 64 | 64 | 64 | 0.25 |
| 209321 | | 2 | 32 | 64 | >64 | >64 | 64 | 16 | 64 | 1 |
| 207272 | | 4 | 4 | 32 | >64 | >64 | 64 | 32 | 64 | 8 |

**Table S1—Continued**

| Bacterial strain | β-lactamase | MIC (mg/L) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **12b** | **12c** | **12d** | **12e** | **13a** | **13b** | **13c** | **14a** | **14b** |
| *Escherichia coli* | | | | | | | | | | |
| 208687 | ESBLs | 0.25 | <0.03 | 0.06 | <0.03 | <0.03 | <0.03 | <0.03 | 0.5 | 0.25 |
| 212648 | | 2 | 0.06 | 0.125 | <0.03 | <0.03 | 0.125 | <0.03 | 0.125 | 1 |
| 209285 | | 0.5 | 0.25 | 4 | 0.125 | 0.06 | 0.25 | 0.125 | 1 | 1 |
| 106342 | | 2 | 0.125 | 2 | <0.03 | <0.03 | 0.06 | <0.03 | 1 | 0.25 |
| 210737 | non-ESBLs | 0.25 | <0.03 | 2 | 0.06 | 0.06 | 0.25 | <0.03 | 4 | 0.25 |
| *Klebsiella pneumoniae* | | | | | | | | | | |
| 212423 | KPC-2 | 4 | 0.25 | 2 | 16 | 4 | 16 | 1 | 1 | 2 |
| 209632 | | 2 | 0.5 | 2 | >64 | 8 | 8 | 4 | 1 | 2 |
| 209735 | | 1 | 0.5 | 2 | 8 | 8 | 8 | 2 | 1 | 2 |
| 212232 | | 0.03 | <0.03 | 0.06 | <0.03 | <0.03 | 0.06 | <0.03 | 0.25 | 0.25 |
| 212229 | | >64 | 0.5 | 64 | >64 | 2 | 8 | 8 | 1 | 2 |
| *Acinetobacter baumannii* | | | | | | | | | | |
| 210278 | OXA-23 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 0.5 | 1 |
| 211606 | | 1 | 0.5 | 1 | 0.5 | 1 | 1 | 1 | 0.5 | 0.5 |
| 208995 | | 2 | 1 | 2 | 1 | 2 | 2 | 2 | 0.5 | 1 |
| 207200 | | 1 | 0.5 | 1 | 2 | 2 | 1 | 2 | 0.5 | 1 |
| 211137 | | 0.25 | 0.125 | 0.5 | 0.25 | 0.5 | 0.5 | 0.5 | 0.5 | 1 |
| *Pseudomonas aeruginosa* | | | | | | | | | | |
| 212886 | IMP-4 | 0.5 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 1 |
| 209471 | | 0.5 | 0.5 | 1 | 1 | 1 | 1 | 2 | 4 | 2 |
| 208247 | | 0.125 | 0.25 | 0.25 | 0.5 | 0.5 | 0.5 | 1 | 1 | 1 |
| 209321 | | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 1 |
| 207272 | | 4 | 1 | 4 | 1 | 1 | 2 | 1 | 4 | 4 |

**Table S1—Continued**

| Bacterial strain | β-lactamase | MIC (mg/L) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **14c** | **15a** | **15b** | **15c** | **16a** | **16b** | **16c** | **17** | **18** |
| *Escherichia coli* | | | | | | | | | | |
| 208687 | ESBLs | 0.06 | 0.06 | <0.03 | <0.03 | <0.03 | <0.03 | <0.03 | 0.06 | 0.125 |
| 212648 | | 0.125 | 0.125 | 0.125 | 0.25 | 0.125 | <0.03 | 0.25 | 0.25 | 0.5 |
| 209285 | | 0.5 | 0.25 | 0.25 | 0.25 | 0.25 | 0.125 | 0.25 | 0.25 | 1 |
| 106342 | | 1 | 0.25 | 0.25 | 0.125 | 0.03 | <0.03 | 2 | 0.25 | 0.5 |
| 210737 | non-ESBLs | 4 | 4 | <0.03 | 0.06 | <0.03 | 0.06 | 0.06 | <0.03 | <0.03 |
| *Klebsiella pneumoniae* | | | | | | | | | | |
| 212423 | KPC-2 | 2 | 32 | 2 | 64 | 0.5 | 0.5 | 1 | 1 | 64 |
| 209632 | | 2 | >64 | 2 | >64 | 0.5 | 0.5 | 1 | 1 | 64 |
| 209735 | | 2 | 8 | 2 | >64 | 1 | 0.5 | 0.5 | 1 | 64 |
| 212232 | | 0.25 | 0.25 | 0.06 | 0.25 | <0.03 | 0.06 | 0.06 | 0.06 | 0.25 |
| 212229 | | 2 | >64 | 2 | >64 | 1 | 1 | 2 | 1 | 64 |
| *Acinetobacter baumannii* | | | | | | | | | | |
| 210278 | OXA-23 | 0.5 | 0.5 | 0.5 | 2 | 0.5 | 1 | 2 | 1 | 2 |
| 211606 | | 0.25 | 0.5 | 0.125 | 1 | 0.5 | 1 | 2 | 1 | 2 |
| 208995 | | 1 | 2 | 1 | 2 | 1 | 2 | 2 | 2 | 2 |
| 207200 | | 0.5 | 0.5 | 0.25 | 8 | 0.5 | 2 | 2 | 1 | 2 |
| 211137 | | 1 | 1 | 1 | 2 | 0.125 | 0.25 | 0.25 | 0.25 | 64 |
| *Pseudomonas aeruginosa* | | | | | | | | | | |
| 212886 | IMP-4 | 4 | 1 | 1 | 2 | 0.5 | 2 | 4 | 0.5 | 2 |
| 209471 | | 4 | 2 | 4 | 2 | 0.5 | 0.5 | 8 | 1 | 2 |
| 208247 | | 4 | 0.25 | 1 | 0.5 | 0.125 | 0.25 | 1 | 0.5 | 0.5 |
| 209321 | | 4 | 2 | 2 | 8 | 1 | 1 | 8 | 0.5 | 4 |
| 207272 | | 4 | 16 | 4 | 8 | 1 | 4 | 32 | 4 | 64 |

**Table S1—Continued**

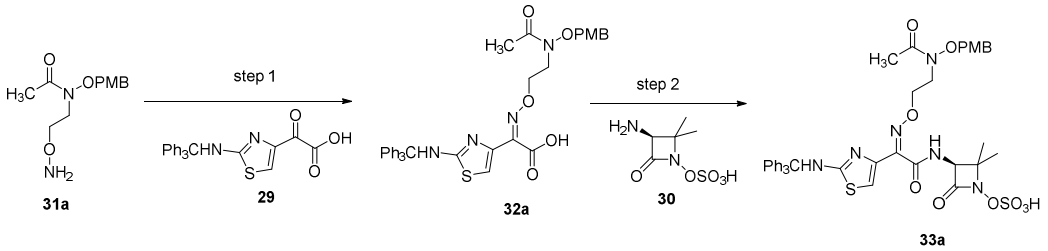
| Bacterial strain | β-lactamase | MIC (mg/L) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** | **27** | **28** |
| *Escherichia coli* | | | | | | | | | | | |
| 208687 | ESBLs | 0.06 | 0.125 | 0.125 | 0.06 | 0.125 | 0.25 | 1 | 2 | <0.03 | <0.03 |
| 212648 | | 0.06 | 0.06 | 0.125 | 0.25 | 0.5 | 0.5 | 1 | 1 | <0.03 | 0.125 |
| 209285 | | 0.25 | 1 | 0.125 | 2 | 1 | 1 | 1 | 2 | 0.25 | 0.5 |
| 106342 | | 0.25 | 2 | 0.25 | 2 | 0.5 | 1 | 2 | 8 | <0.03 | <0.03 |
| 210737 | non-ESBLs | 1 | 1 | 0.06 | 0.25 | 0.06 | 0.125 | 0.5 | 0.5 | 0.06 | 0.06 |
| *Klebsiella pneumoniae* | | | | | | | | | | | |
| 212423 | KPC-2 | 0.25 | 1 | 1 | 0.25 | 0.5 | 2 | 4 | 2 | >64 | 0.5 |
| 209632 | | 0.25 | 1 | 1 | 0.5 | 0.5 | 1 | 4 | 2 | >64 | 0.5 |
| 209735 | | 0.125 | 1 | 1 | 0.5 | 0.25 | 1 | 4 | 1 | >64 | 0.5 |
| 212232 | | 0.06 | 0.06 | 0.125 | 0.06 | 0.5 | 0.5 | 1 | 0.5 | 0.06 | 0.125 |
| 212229 | | 0.5 | 1 | 1 | 0.25 | 0.5 | 1 | 4 | 2 | >64 | 0.5 |
| *Acinetobacter baumannii* | | | | | | | | | | | |
| 210278 | OXA-23 | 1 | 4 | 1 | 4 | 0.5 | >64 | 2 | 32 | 1 | 2 |
| 211606 | | 1 | 2 | 1 | 4 | 0.5 | 32 | 2 | 16 | 0.5 | 1 |
| 208995 | | 2 | 4 | 1 | 32 | 1 | >64 | 4 | 64 | 1 | 2 |
| 207200 | | 2 | 4 | 2 | 64 | 1 | 64 | 4 | 64 | 1 | 2 |
| 211137 | | 0.06 | 0.5 | 1 | 0.25 | 0.5 | 0.25 | 1 | 0.5 | 4 | 0.5 |
| *Pseudomonas aeruginosa* | | | | | | | | | | | |
| 212886 | IMP-4 | 1 | 1 | 0.25 | 1 | 1 | 1 | 2 | 2 | 1 | 4 |
| 209471 | | 2 | 4 | 1 | 2 | 1 | 2 | 2 | 4 | 1 | 2 |
| 208247 | | 0.25 | 0.5 | 0.125 | 1 | 0.06 | 0.5 | 1 | 1 | 0.5 | 1 |
| 209321 | | 4 | 2 | 1 | 2 | 1 | 4 | 2 | 4 | 1 | 8 |
| 207272 | | 8 | 32 | 0.5 | 4 | 1 | 2 | 2 | 4 | 2 | 4 |

[a]BAL: BAL30072; [b]AZT: aztronam; [c]MER: meropenem; [d]CEF: ceftizoxime sodium.

## II. Experimental Procedures

**General**. All solvents and chemicals were used as purchased without further purification. Inert atmosphere operations were conducted under argon in flame-dried glassware. Room temperature refers to 20–25 °C. All reaction mixtures were monitored using thin-layer chromatography (TLC) on silica gel F-254 TLC plates. Column chromatography was carried out using silica gel (200–300 mesh). Melting points (uncorrected) were determined on an X-4 melting point apparatus. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker 400 NMR or a Bruker 500 NMR spectrometer using solvent residue as the internal standards. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are reported in Hertz (Hz). EI-MS spectra were obtained on a Finnigan MAT95 spectrometer and ESI-MS spectra were obtained on a Krats MS 80 mass spectrometer. Purity of all final compounds was determined by analytical HPLC (PLATISIL ODS 250 × 4.6 mm, particle size 5μm) with methanol/buffer (0.1% $CF_3COOH$ and 0.1% $NH_4OH$ in water, pH 3.5) as the mobile phase. The *ee* values were determined using chiral HPLC (CHIRALPAK AD-H column 250 × 4.6 mm, particle size 5μm or CHIRALCEL OD-H column 250 × 4.6 mm, particle size 5μm) with ethanol/*n*-hexane as the mobile phase. A purity of >95% was achieved for all tested compounds.

**Preparation of intermediate 33a.**

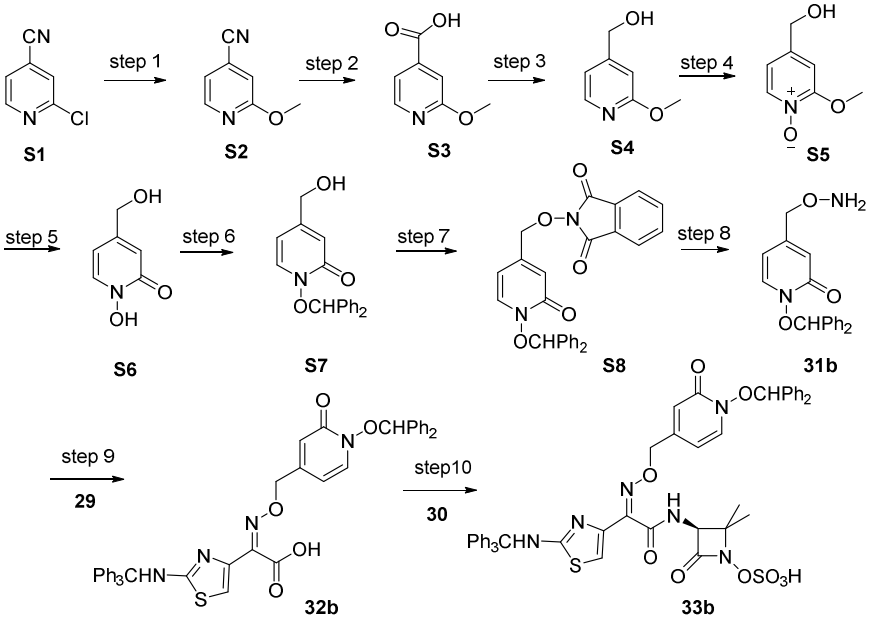



**(*Z*)-3-Acetyl-1-(4-methoxyphenyl)-8-(2-(tritylamino)thiazol-4-yl)-2,6-dioxa-3,7-diazanon -7-en-9-oic Acid (32a).** A solution of **31a** (520 mg, 2.05 mmol) in anhydrous ethanol and dichloromethane (1:1, 20 mL) was treated with **29** (805 mg, 1.94 mmol), the resulting mixture was stirred at room temperature for 4 h. For synthesis of **31a**, see Myoung, G. K. et al., *Bioorg. Med. Chem. Lett.* **1996**, *17*, 2077 – 2080. For synthesis of **29**, see Sakagami, K. et al., *Chem. Pharm. Bull.* **1990**, *38*, 3476 – 3479. After completion of the reaction, the solvent was removed in vacuo and the residue was purified by chromatography on silica gel with dichloromethane/methanol to afford **32a** as a light yellow solid (530 mg, 40%). mp: 95 – 97 °C.$^{1}H$ NMR (400 MHz, DMSO-$d_6$) δ 8.85 (s, 1H), 7.39 – 7.26 (m, 15H), 7.25 – 7.20 (m, 2H), 6.96 – 6.89 (m, 2H), 6.83 (s, 1H), 4.78 (s, 2H), 4.15 (t, *J* = 5.8 Hz, 2H), 3.81 (t, *J* = 5.7 Hz, 2H), 3.75 (s, 3H), 1.95 (s, 3H). $^{13}C$ NMR (126 MHz, DMSO) δ 167.95, 167.91, 164.18, 159.97, 153.86, 144.17(4C), 131.71(2C), 129.43(6C), 128.20(6C), 127.99, 127.34(3C), 114.21(2C), 113.95, 75.58, 71.86, 63.43, 55.48, 20.77. HRMS (ESI) *m/z* calcd for

$C_{36}H_{33}N_4O_6S$ [M − H] $^-$ 649.2126, found 649.2118.

**(*S*,*Z*)-3-(3-Acetyl-1-(4-methoxyphenyl)-8-(2-(tritylamino)thiazol-4-yl)-2,6-dioxa-3,7-diazanon-7-en-9-amido)-2,2-dimethyl-4-oxoazetidin-1-yl Hydrogen Sulfate (33a).** For synthesis of **30**, see James, E. D. et al., *J. Org. Chem.* **2003**, *68*, 177 – 179 and Slusarchyk, W.A. et al., *Tetrahedron Letters* **1986**, *27*, 2789–2792. A solution of **32a** (500 mg, 0.77 mmol) in DMSO (20 mL) was treated with HATU (351 mg, 0.92 mmol), $NaHCO_3$ (194 mg, 2.31 mmol) and **30** (242 mg, 1.15 mmol), and then the reacting mixture was stirred at room temperature overnight. After completion of the reaction, water (30 mL) was added and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel with dichloromethane/methanol to afford **33a** as a light yellow solid (400 mg, 62%). mp: 156 – 158 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.10 (s, 1H), 8.88 (s, 1H), 7.38 – 7.20 (m, 21H), 6.95 (s, 1H), 6.92 (s, 1H), 6.71 (s, 1H), 4.79 (s, 2H), 4.51 (d, $J$ = 7.8 Hz, 1H), 4.15 (t, $J$ = 5.8 Hz, 2H), 3.82 (t, $J$ = 5.8 Hz, 2H), 3.76 (s, 3H), 1.96 (s, 3H), 1.39 (s, 3H), 1.20 (s, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 168.06, 163.09, 162.05, 160.02, 150.09, 144.10(4C), 142.02, 131.73(2C), 129.44(6C), 128.24(6C), 127.39(3C), 127.14, 114.26(2C), 111.97, 75.82, 71.79, 70.60, 68.17, 61.21, 60.21, 55.57, 23.92(2C), 20.71. HRMS (ESI) *m/z* calcd for $C_{41}H_{41}N_6O_{10}S_2$ [M − H] $^-$ 841.2331, found 841.2329.

**Preparation of intermediate 33b.**




**2-Methoxyisonicotinonitrile (S2).** A solution of 2-chloroisonicotinonitrile (3.0 g, 21.66 mmol) in 1,4-dioxane (25 mL) was treated with sodium methanolate (6.5 mL, 32.49 mmol). The reaction mixture was heated at reflux for 4 h, and then cooled to room temperature. The resulting precipitate was filtered and washed with methanol. The filtrate was concentrated down to about 20 mL, and water (40 mL) was added. The solid which precipitated out was

filtered off and purified by chromatography on silica gel with petroleum/ethyl acetate to afford **S2** as a white solid (1.0 g, 34%). mp: 92 – 93 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 5.3 Hz, 1H), 8.01 (dd, *J* = 5.4, 1.4 Hz, 1H), 7.94 (s, 1H), 4.06 (s, 3H). MS (EI): *m/z* 134 $[M]^+$

**2-Methoxyisonicotinic Acid (S3).** A solution of **S2** (1.1 g, 8.21 mmol) in ethanol (20 mL) was treated with 10 *M* aqueous sodium hydroxide solution (10 mL) and heated to reflux. After 1 h, the mixture was cooled to room temperature and diluted with water. Concentrated hydrochloric acid was added to attain pH = 4, and the resulting precipitate was isolated by filtration. The material was washed with water and dried in vacuo to provide **S3** as a white solid (1.1 g, 88%). mp: 184 – 187 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.65 (s, 1H), 8.33 (dd, *J* = 5.2, 0.8 Hz, 1H), 7.39 (dd, *J* = 5.2, 1.4 Hz, 1H), 7.20 –7.16 (m, 1H), 3.89 (s, 3H). HRMS (ESI) *m/z* calcd for $C_7H_8NO_3$ $[M + H]^+$ 154.0499, found 14.0497.

**(2-Methoxypyridin-4-yl)methanol (S4).** To a solution of **S3** (500 mg, 3.27 mmol) in THF (30 mL) was added slowly borane dimethyl sulfide (3.3 mL, 6.60 mmol). The resulting solution was stirred at reflux overnight and then quenched by slowly adding 2 *M* aqueous hydrogen chloride (10 mL). The solution was extracted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated in vacuo. The resulting residue was purified by chromatography on silica gel with petroleum/ethyl acetate to afford **S4** as an oil (335 mg, 74%). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 5.3 Hz, 1H), 6.86 (dd, *J* = 5.2, 1.4 Hz, 1H), 6.78 – 6.74 (m, 1H), 4.69 (d, *J* = 1.1 Hz, 2H), 3.94 (s, 3H). MS (ESI): *m/z* 140 $[M + H]^+$.

**4-(Hydroxymethyl)-2-methoxypyridine 1-Oxide (S5).** A solution of **S4** (340 mg, 2.45 mmol) in dichloromethane (10 mL) was cooled to 0 °C in an ice bath, and then treated with *m*-CPBA (976 mg, 4.81 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was diluted with dichloromethane, and then washed with water, saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$and brine, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated. The resulting residue was purified by chromatography on silica gel with dichloromethane/methanol to afford **S5** as an oil (300 mg, 80%). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.15 (d, *J* = 6.6 Hz, 1H), 7.11 (d, *J* = 2.2 Hz, 1H), 6.95 (dd, *J* = 6.7, 2.2 Hz, 1H), 5.53 (t, *J* = 5.7 Hz, 1H), 4.49 (d, *J* = 5.6 Hz, 2H), 3.95 (s, 3H). HRMS (ESI) *m/z* calcd for $C_7H_{10}NO_3$ $[M + H]^+$ 156.0655, found 156.0654.

**1-Hydroxy-4-(hydroxymethyl)pyridin-2(1*H*)-one (S6).** A solution of **S5** (300 mg, 1.93 mmol) in dry dichloromethane (5 mL) and DMF (5 mL) was cooled to −10 °C, and then a solution of boron trichloride in *n*-hexane (2 mL, 2.00 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1 h, then the reaction was allowed to heated to 50 °C and stirred overnignt. The reaction mixture was quenched by slow addition of methanol (5 mL) and stirred for 10 min. The solution was concentrated in vacuo to afford **S6** as a crude oil, which was used next step without purification.

**Diphenyldiazomethane.** A suspension of benzophenone hydrazone (45.0 g, 0.23 mol) in

petroleum (250 mL) was treated with activated manganese dioxide (60.0 g, 0.69 mol). The resulting mixture was heated to 40 °C and stirred for 45 min. The reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo to give diphenyldiazomethane as red oil (43.0 g, 96.6%), which was used next step without purification. .

**1-(Benzhydryloxy)-4-(hydroxymethyl)pyridin-2(1*H*)-one (S7).** The crude material **S6** from the former step was dissolved in methanol (10 mL) and cooled to 0 °C, then a solution of diphenyldiazomethane (1.1 g, 5.67 mmol) in dichloromethane (5 mL) was added dropwise. After addition, the reaction mixture was allowed to warm to room temperature and stirred for 3 h. Then the solution was concentrated and the residue was purified by chromatography on silica gel with dichloromethane/methanol to afford **S7** as a white solid (200 mg, 34% by two steps). mp: 107 – 108 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.32 (m, 10H), 6.89 (d, *J* = 7.3 Hz, 1H), 6.68 – 6.63 (m, 1H), 6.57 (s, 1H), 5.76 (dd, *J* = 7.3, 2.2 Hz, 1H), 4.44 (s, 2H), 3.39 (s, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 159.31, 153.57, 137.63(2C), 136.40, 128.75(2C), 128.56(4C), 128.53(4C), 117.59, 102.79, 87.99, 62.87. HRMS (ESI) *m/z* calcd for $C_{19}H_{17}NNaO_3$ $[M + Na]^+$ 330.1101, found 330.1097.

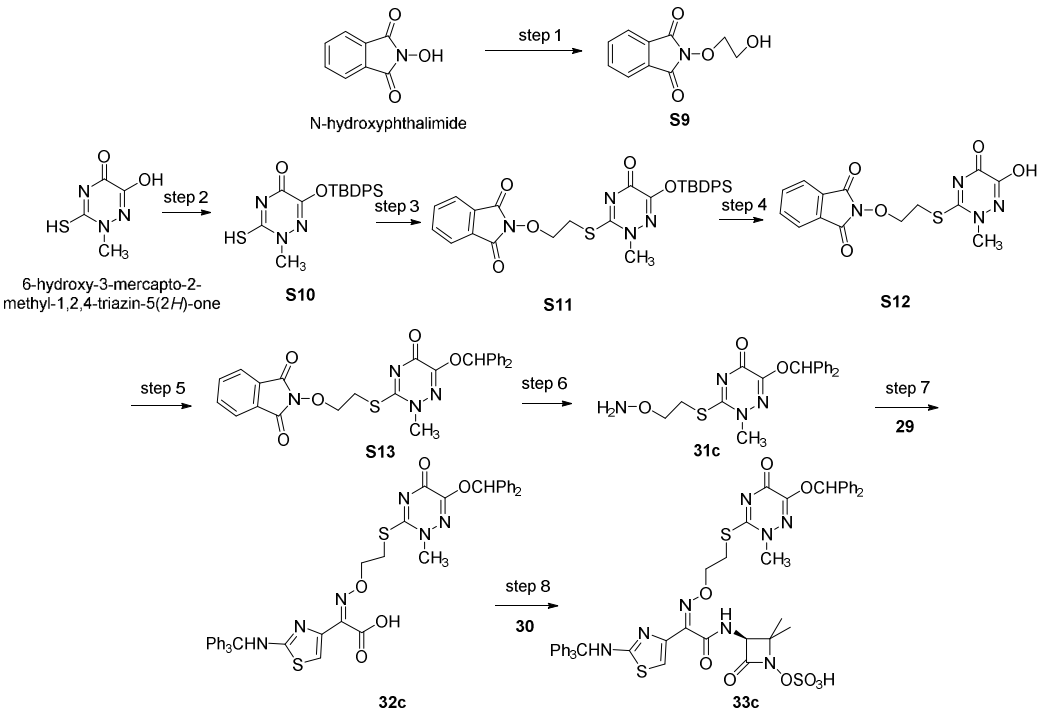
**2-((1-(Benzhydryloxy)-2-oxo-1,2-dihydropyridin-4-yl)methoxy)isoindoline-1,3-dione (S8).** A solution of **S7** (220 mg, 0.72 mmol) in dry THF (10 mL) was treated with *N*-hydroxyphthalimide (137 mg, 0.84 mmol) and $PPh_3$ (377 mg, 1.44 mmol) under argon atmosphere, then the mixture was cooled to 0 °C. A solution of DEAD (0.22 mL, 1.44 mmol) in dry THF (3 mL) was added dropwise. After addition, the resulting mixture was allowed to warm to room temperature and stirred for 30 min before being quenched by addition of water. The solution was extracted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated in vacuo. The resulting residue was purified by chromatography on silica gel with petroleum/ethyl acetate to give **S8** as a white solid (280 mg, 88%). mp: 182 – 183 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.72 (m, 4H), 7.48 – 7.31 (m, 10H), 6.99 (d, *J* = 7.3 Hz, 1H), 6.67 (dt, *J* = 2.1, 0.7 Hz, 1H), 6.59 (s, 1H), 6.12 (dd, *J* = 7.4, 2.3 Hz, 1H), 4.96 (d, *J* = 0.9 Hz, 2H). HRMS (ESI) *m/z* calcd for $C_{27}H_{20}NaN_2O_5$ $[M + Na]^+$ 475.1264, found 475.1261.

**4-((Aminooxy)methyl)-1-(benzhydryloxy)pyridin-2(1*H*)-one (31b).** To a solution of **S8** (330 mg, 0.73 mmol) in ethanol (10 mL) was added 85% hydrazine hydrate (0.05 mL, 0.87 mmol), and the resulting mixture was allowed to stirred at room temperature for 20 min. Water (10mL) was added, and the mixture was extracted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated in vacuo. The crude was purified by chromatography on silica gel with dichloromethane/methanol to give **31b** as a colorless oil (165 mg, 70%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.32 (m, 10H), 6.95 (d, *J* = 7.3 Hz, 1H), 6.66 – 6.56 (m, 2H), 5.75 (dd, *J* = 7.3, 2.2 Hz, 1H), 5.53 (s, 2H), 4.45 (s, 2H). HRMS (ESI) *m/z* calcd for $C_{19}H_{19}N_2O_3$ $[M + H]^+$ 323.1390, found 323.1396.

**(*Z*)-2-(((1-(Benzhydryloxy)-2-oxo-1,2-dihydropyridin-4-yl)methoxy)imino)-2-(2-(tritylamino)thiazol-4-yl)acetic Acid (32b).** Compound **32b** (160 mg, 60%) was prepared from **31b** (120 mg, 0.37 mmol) and **29** (153 mg, 0.37 mmol) in the same manner as described for **32a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.60 (s, 1H), 7.52 (s, 1H), 7.52 – 7.19 (m, 25H), 6.64 – 6.53 (m, 2H), 6.50 (s, 1H), 5.94 (d, $J$ = 7.2 Hz, 1H), 4.76 (s, 2H). MS (ESI): *m/z* 717 [M − H]$^-$.

**(*S*,*Z*)-3-(2-(((1-(Benzhydryloxy)-2-oxo-1,2-dihydropyridin-4-yl)methoxy)imino)-2-(2-(tritylamino)thiazol-4-yl)acetamido)-2,2-dimethyl-4-oxoazetidin-1-yl Hydrogen Sulfate (33b).** Compound **33b** (115 mg, 57%) was prepared from **32b** (160 mg, 0.22 mmol) and **30** (69 mg, 0.33 mmol) in the same manner as described for **33a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.55 (d, $J$ = 7.9 Hz, 1H), 8.91 (s, 1H), 7.60 – 7.18 (m, 25H), 6.70 (s, 1H), 6.61 (s, 1H), 6.50 – 6.44 (m, 1H), 5.90 (dd, $J$ = 7.4, 2.2 Hz, 1H), 4.88 (s, 2H), 4.55 (d, $J$ = 7.8 Hz, 1H), 1.40 (s, 3H), 1.14 (s, 3H). MS (ESI): *m/z* 909 [M − H] $^-$.

**Preparation of intermediate 33c.**




**2-(2-Hydroxyethoxy)isoindoline-1,3-dione (S9).** A solution of *N*-hydroxyphthalimide (4.4 g, 27.03 mmol) in DMF (50 mL) was treated with potassium carbonate (4.5 g, 32.61 mmol), the resulting mixture was stirred at room temperature for 30 min. Then, 2-bromoethanol (1.92 mL, 27.03 mmol) was added and the mixture was heated to 80 °C. After 2 h, the mixture was cooled to room temperature and poured into ice water. The resulting precipitate was isolated by filtration and washed with water, dried in vacuo to provide **S9** as a white solid (3.82 g, 68%). mp: 75 – 77 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.77 (m, 4H), 4.36 – 4.30 (m, 2H), 3.83 (dt, $J$ = 6.8, 4.2 Hz, 2H), 3.53 (t, $J$ = 7.0 Hz, 1H). MS (ESI): *m/z* 208 [M + H] $^+$.

**6-((*tert*-Butyldiphenylsilyl)oxy)-3-mercapto-2-methyl-1,2,4-triazin-5(2*H*)-one (S10).** A solution of 6-hydroxy-3-mercapto-2-methyl-1,2,4-triazin-5(2*H*)-one (1.0 g, 6.28 mmol) in dry THF (50 mL) was treated with triethylamine (1.0 mL, 7.54 mmol) and *tert*-butyldiphenylsilyl chloride (1.95 mL, 7.54 mmol). The resulting mixture was stirred at room temperature for 1 h and then quenched with water (30 mL). The solution was extracted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated in vacuo. The resulting residue was purified by chromatography on silica gel with petroleum/ethyl acetate to give **S10** as a white solid (1.96 g, 78%). mp: 125 – 128 °C.$^1$H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.75 – 7.35 (m, 10H), 3.48 (s, 3H), 1.17 (s, 9H). HRMS (ESI) *m/z* calcd for $C_{20}H_{22}N_3O_2SSi$ $[M - H]^-$ 396.1207, found 396.1202.

**2-(2-((6-((*tert*-Butyldiphenylsilyl)oxy)-2-methyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)thio)ethoxy)isoindoline-1,3-dione (S11).** Compound **S11** (516 mg, 52%) was prepared from **S9** (347 mg, 1.68 mmol), **S10** (800 mg, 2.01 mmol), $PPh_3$ (661 mg, 2.52 mmol) and DEAD (0.4 mL, 2.52 mmol) in the same manner as described for **S8**. mp: 69 – 70 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.80 (m, 4H), 7.75 – 7.34 (m, 10H), 4.44 (t, *J* = 5.4 Hz, 2H), 3.61 (t, *J* = 5.4 Hz, 2H), 3.39 (s, 3H), 1.15 (s, 9H). HRMS (ESI) *m/z* calcd for $C_{30}H_{31}N_4O_5SSi$ $[M + H]^+$ 587.1779, found 587.1770.

**2-(2-((6-Hydroxy-2-methyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)thio)ethoxy)isoindoline-1,3-dione (S12).** A solution of **S11** (550 mg, 0.94 mmol) in dry THF (30 mL) was treated with tetrabutylammonium fluoride (0.94 mL, 0.94mmol). The resulting mixture was stirred at room temperature for 0.5 h and then quenched with 3 *M* methanol hydrochloride solution (0.33 mL). Then petroleum (20 mL) was added to form precipitate. The precipitate was isolated by filtration and washed with petroleum and dried in vacuo to give **S12** as a white solid, which was used next step without purification.

**2-(2-((6-(Benzhydryloxy)-2-methyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)thio)ethoxy)isoindoline-1,3-dione (S13).** Compound **S13** (240 mg, 50% by two steps) was prepared from crude material **S12** from the former step and diphenyldiazomethane (547 mg, 2.82 mmol) in the same manner as described for **S7**. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.48 – 7.29 (m, 10H), 6.78 (s, 1H), 4.46 (t, *J* = 5.3 Hz, 2H), 3.69 (s, 3H), 3.65 (t, *J* = 5.3 Hz, 2H). MS (ESI): *m/z* 514 $[M]^+$.

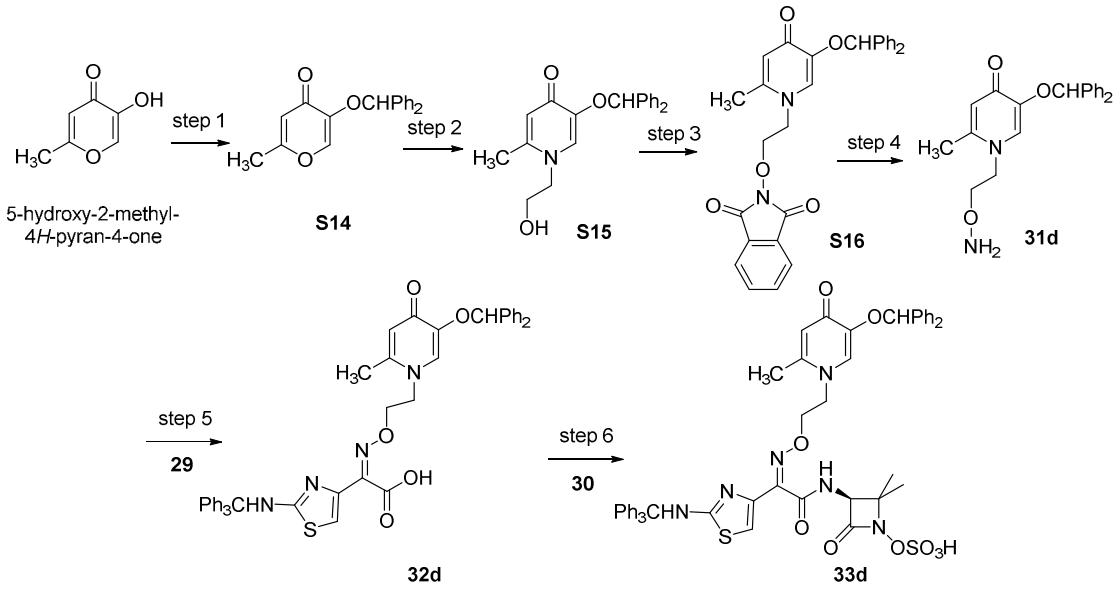
**3-((2-(Aminooxy)ethyl)thio)-6-(benzhydryloxy)-2-methyl-1,2,4-triazin-5(2*H*)-one (31c).** Compound **31c** (162 mg, 90%) was prepared from **S13** (240 mg, 0.47 mmol) and 85% hydrazine hydrate (0.03 mL, 0.51 mmol) in the same manner as described for **31b**. MS (ESI): *m/z* 385 $[M + H]^+$.

**(*Z*)-2-((2-((6-(Benzhydryloxy)-2-methyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)thio)ethoxy)imino)-2-(2-(tritylamino)thiazol-4-yl)acetic Acid (32c).** Compound **32c** (251 mg, 76%) was prepared from **31c** (160 mg, 0.42 mmol) and **29** (174 mg, 0.42 mmol) in the same manner as described for **32a**. mp: 163 – 167 °C.$^1$H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.44 – 7.23

(m, 25H), 6.73 (s, 1H), 6.66 (s, 1H), 4.40 (t, $J$ = 5.9 Hz, 2H), 3.55 (t, $J$ = 5.9 Hz, 2H), 3.50 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{43}H_{35}N_6O_5S_2$ $[M - H]^-$ 779.2116, found 779.2122.

**(*S*,*Z*)-3-(2-((2-((6-(Benzhydryloxy)-2-methyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)thio)ethoxy)imino)-2-(2-(tritylamino)thiazol-4-yl)acetamido)-2,2-dimethyl-4-oxoazetidin-1-yl Hydrogen Sulfate (33c).** Compound **33c** (154 mg, 83%) was prepared from **32c** (150 mg, 0.19 mmol) and **30** (61 mg, 0.29 mmol) in the same manner as described for **33a**. mp: 155 °C decomp. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.38 (d, $J$ = 7.7 Hz, 1H), 8.87 (s, 1H), 7.51 – 7.15 (m, 25H), 6.79 (s, 1H), 6.71 (s, 1H), 4.51 (d, $J$ = 7.7 Hz, 1H), 4.23 (t, $J$ = 5.7 Hz, 2H), 3.56 (s, 3H), 3.41 (t, $J$ =5.7 Hz, 2H), 1.40 (s, 3H), 1.23 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{48}H_{43}N_8O_9S_3$ $[M - H]^-$ 971.2321, found 971.2320.

**Preparation of intermediate 33d.**




**5-(Benzhydryloxy)-2-methyl-4*H*-pyran-4-one (S14).** Compound **S14** (2.33 g, 35%) was prepared from commercial material 5-hydroxy-2-methyl-4*H*-pyran-4-one (2.9 g, 23.00 mmol) and diphenyldiazomethane (6.7 g, 34.50 mmol) in the same manner as described for **S7**. mp: 123 – 125 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.29 (m, 11H), 6.40 (s, 1H), 6.22 (q, $J$ = 0.7 Hz, 1H), 2.21 (d, $J$ = 0.7 Hz, 3H). HRMS (ESI) *m/z* calcd for $C_{19}H_{16}NaO_3$ $[M + Na]^+$ 315.0992, found 315.0987.

**5-(Benzhydryloxy)-1-(2-hydroxyethyl)-2-methylpyridin-4(1*H*)-one (S15).** A suspension of **S14** (1.8 g, 6.15 mmol) in methanol (5 mL) was treated with ethanolamine (18.4 mL, 307.50 mmol). The resulting mixture was heated to 60 °C and stirred for 12 h. The reaction mixture was cooled to room temperature and water (30 mL) was added. The solution was extracted with ethyl acetate, washed with brine, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated in vacuo. The resulting residue was purified by chromatography on silica gel with dichloromethane/methanol to afford **S15** (0.62 g, 30%), mp: 209 – 210 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.19 (m, 10H), 6.92 (s, 1H), 6.31 (s, 1H), 6.01 (s, 1H),

3.72 (dd, *J* = 5.6, 3.7 Hz, 2H), 3.59 (dd, *J* = 5.5, 3.6 Hz, 2H), 2.00 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{21}H_{22}NO_3$ $[M + H]^+$ 336.1594, found 336.1601.

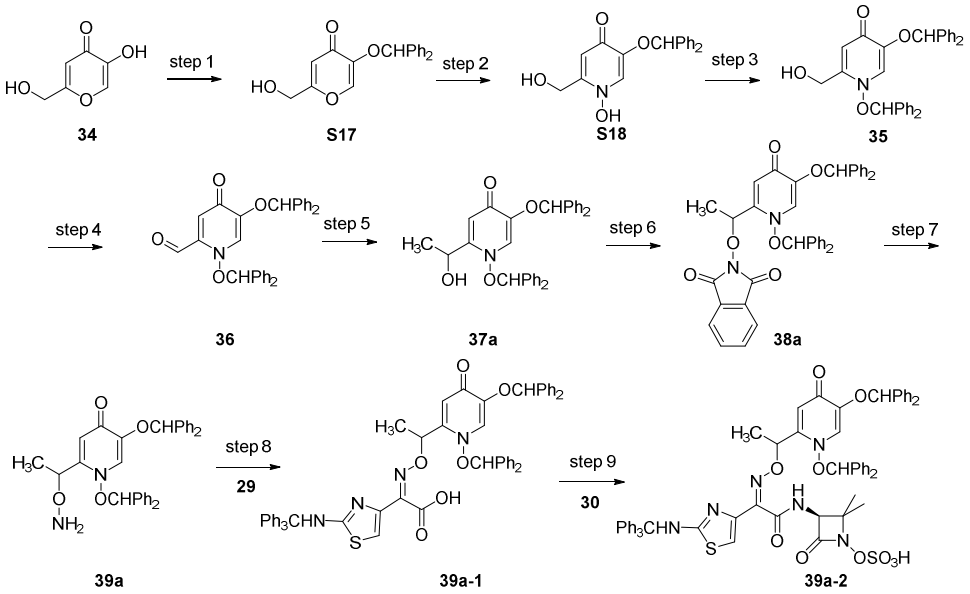
**2-(2-(5-(Benzhydryloxy)-2-methyl-4-oxopyridin-1(4*H*)-yl)ethoxy)isoindoline-1,3-dione (S16).** Compound **S16** (720 mg, 75%) was prepared from **S15** (670 mg, 1.99 mmol), *N*-hydroxyphthalimide (489 mg, 2.99 mmol), $PPh_3$ (1.56 g, 5.99 mmol) and DEAD (0.94 mL, 5.99 mmol) in the same manner as described for **S8**. mp: 114 – 116 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.76 (m, 4H), 7.49 – 7.09 (m, 11H), 6.56 (s, 1H), 6.34 (s, 1H), 4.22 (t, *J* = 5.3 Hz, 2H), 4.06 (t, *J* = 5.3 Hz, 2H), 2.25 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{29}H_{25}N_2O_5$ $[M + H]^+$ 481.1758, found 481.1766.

**1-(2-(Aminooxy)ethyl)-5-(benzhydryloxy)-2-methylpyridin-4(1*H*)-one (31d).** Compound **31d** (190 mg, 30%) was prepared from **S16** (850 mg, 1.77 mmol) and 85% hydrazine hydrate (0.11 mL, 1.95 mmol) in the same manner as described for **31b**. mp: 169 – 171 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.25 (m, 10H), 6.97 (s, 1H), 6.58 (s, 1H), 6.35 (s, 1H), 3.86 (t, *J* = 5.0 Hz, 2H), 3.68 (t, *J* = 5.0 Hz, 2H), 2.22 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{21}H_{23}N_2O_3$ $[M + H]^+$ 351.1703, found 351.1711.

**(*Z*)-2-((2-(5-(Benzhydryloxy)-2-methyl-4-oxopyridin-1(4*H*)-yl)ethoxy)imino)-2-(2-(tritylamino)thiazol-4-yl)acetic Acid (32d).** Compound **32d** (300 mg, 79%) was prepared from **31d** (178 mg, 0.51 mmol) and **29** (200 mg, 0.48 mmol) in the same manner as described for **32a**. mp: 165 – 167 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.87 (s, 1H), 7.40 – 7.17 (m, 25H), 6.85 (s, 1H), 6.55 (s, 1H), 6.04 (s, 1H), 5.76 (s, 1H), 4.16 (t, *J* = 5.0 Hz, 2H), 3.96 (t, *J* = 5.1 Hz, 2H), 2.14 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{45}H_{39}N_4O_5S$ $[M + H]^+$ 747.2636, found 747.2649.

**(*S*,*Z*)-3-(2-((2-(5-(Benzhydryloxy)-2-methyl-4-oxopyridin-1(4H)-yl)ethoxy)imino)-2-(2-(tritylamino)thiazol-4-yl)acetamido)-2,2-dimethyl-4-oxoazetidin-1-yl Hydrogen Sulfate (33d).** Compound **33d** (200 mg, 53%) was prepared from **32d** (300 mg, 0.40 mmol) and **30** (126 mg, 0.60 mmol) in the same manner as described for **33a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.44 (d, *J* = 7.9 Hz, 1H), 8.86 (s, 1H), 7.43 – 7.19 (m, 25H), 6.73 (s, 1H), 6.61 (s, 1H), 6.02 (s, 1H), 4.53 (d, *J* = 7.9 Hz, 1H), 4.10 (t, *J* = 5.4 Hz, 2H), 3.94 (t, *J* = 5.4 Hz, 2H), 2.14 (s, 3H), 1.38 (s, 3H), 1.15 (s, 3H).

**Preparation of intermediate 39a-2.**




**5-(Benzhydryloxy)-2-(hydroxymethyl)-4*H*-pyran-4-one (S17).** A suspension of kojic acid **34** (17 g, 0.12 mol) in ethanol (350 mL) was treated with diphenyldiazomethane (46 g, 0.24 mol). The mixture was stirred at 40 °C for 20 h and concentrated in vacuo to remove ethanol. The resulting residue was taken up in petroleum/toluene/water (5/3/2, 500 mL) to precipitate. The light yellow solid was filtered and suspended in *tert*-butyl methyl ether (100 mL) and then filtered to afford **S17** as a white solid (23.5 g, 64%). mp: 126 – 128 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.41 – 7.28 (m, 10H), 6.48 (s, 1H), 6.34 (s, 1H), 4.39 (d, $J$ = 6.5 Hz, 2H), 2.88 (t, $J$ = 6.6 Hz, 1H). MS (ESI): *m/z* 331 [M + Na] $^+$.

**5-(Benzhydryloxy)-1-hydroxy-2-(hydroxymethyl)pyridin-4(1*H*)-one (S18).** A suspension of **S17** (21.0 g, 68.10 mmol) in a mixture of ethanol (75 mL) and water (75 mL) was treated with hydroxylamine hydrochloride (47.0 g, 0.68 mol) and sodium acetate trihydrate (92.5 g, 0.68 mol). The resulting mixture was heated to 70 °C and stirred for 18 h. The reaction mixture was cooled to room temperature and filtered to give white solid. The solid was washed sequentially with water, ethanol and *tert*-butyl methyl ether and dried in vacuo to provide **S18** as a white solid (10.0 g, 46%). mp: 222 – 224 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.71 (s, 1H), 7.97 (s, 1H), 7.55 – 7.23 (m, 10H), 6.94 (s, 1H), 6.65 (s, 1H), 5.49 (d, $J$ = 6.8 Hz, 1H), 4.39 (d, $J$ = 3.2 Hz, 2H). MS (ESI): *m/z* 324 [M + H] $^+$.

**1,5-Bis(benzhydryloxy)-2-(hydroxymethyl)pyridin-4(1*H*)-one (35).** A suspension of **S18** (9.0 g, 27.8 mmol) in DMSO (150 mL) was heated to 85 °C to dissolve the compound. The reaction mixture was cooled to room temperature and treated with potassium carbonate (5.8 g, 41.70 mmol), sodium iodide (6.1 g, 41.70 mmol) and chlorodiphenylmethane (7.2 mL, 41.70 mmol). The mixture was stirred at room temperature for 20 h and then treated with ice cold water. The yellow solid was filtered, washed with water and suspended in ethyl acetate (100 mL) and petroleum (50 mL), collected by filtration and washed with ethyl acetate to afford **9** as a light yellow solid (13.5 g, 99%). mp: 123 – 125 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ

7.60 (s, 1H), 7.41 – 7.22 (m, 20H), 6.41 (s, 1H), 6.33 (s, 1H), 6.02 (s, 1H), 5.49 (t, $J$ = 6.0 Hz, 1H), 4.11 (d, $J$ = 5.8 Hz, 2H). MS (ESI): *m/z* 490 $[M + H]^+$.

**1,5-Bis(benzhydryloxy)-4-oxo-1,4-dihydropyridine-2-carbaldehyde (36).** A suspension of **35** (15.0 g, 30.64 mmol) in dichloromethane (210 mL) was added DMSO (70 mL) to dissolve the compound. The resulting mixture was then cooled to 0 °C, and triethylamine (27 mL) was added followed by sulfur trioxide pyridine complex (24.4 g, 0.15 mol). The solution was allowed to stir at 0 °C for 6 h, and then the reaction was concentrated in vacuo to remove dichloromethane and redissolved in ethyl acetate (200 mL). The mixture was washed with water and brine, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated in vacuo. The resulting residue was purified by chromatography on silica gel with dichloromethane/methanol to give **36** as a white solid (12.0 g, 80%). mp: 127 – 128 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.42 – 7.30 (m, 16H), 7.13 – 7.08 (m, 5H), 6.65 (s, 1H), 6.42 (s, 1H), 5.80 (s, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 181.08, 172.27, 148.76, 140.02(2C), 138.84, 135.80(2C), 129.76(2C), 129.03(4C), 128.65(4C), 128.14(2C), 127.94(4C), 127.36(4C), 126.83, 116.34, 93.49, 82.40. HRMS (EI) *m/z* calcd for $C_{32}H_{25}NO_4$ $[M]^+$ 487.1784, found 487.1775.

**1,5-Bis(benzhydryloxy)-2-(1-hydroxyethyl)pyridin-4(1*H*)-one (37a).** A solution of **36** (1.66 g, 3.40 mmol) in dry THF (20 mL) under argon atmosphere was cooled to −20 °C, and then a solution of methylmagnesium bromide in THF (3.4 mL, 10.20 mmol) was added dropwise to keep the reaction mixture below 10 °C. After addition, the resulting mixture was allowed to warm to room temperature and stirred for 3 h before quenched by slow addition of saturated aqueous $NH_4Cl$. The solution was extracted with ethyl acetate, washed with brine, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated in vacuo. The resulting residue was purified by chromatography on silica gel with petroleum/ethyl acetate to afford **37a** as a white solid (1.56 g, 91%). mp: 87 – 90 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.11 (m, 20H), 6.67 (s, 1H), 6.56 (s, 1H), 6.01 (s,1H), 5.94(s,1H), 4.75 (q, $J$ = 6.5 Hz, 1H), 1.36 (d, $J$ = 6.5 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.77, 152.15, 144.86, 140.51, 140.41, 137.77, 137.38, 129.16, 129.00, 128.74(2C), 128.56(2C), 128.50(2C), 128.45(2C), 127.84, 127.81, 127.20(4C), 126.98(4C), 126.82, 112.45, 92.51, 82.14, 63.23, 22.36. HRMS (ESI) *m/z* calcd for $C_{33}H_{30}NO_4$ $[M + H]^+$ 504.2169, found 504.2182.

**2-(1-(1,5-Bis(benzhydryloxy)-4-oxo-1,4-dihydropyridin-2-yl)ethoxy)isoindoline-1,3-dion e (38a).** Compound **38a** (1.03 g, 67%) was prepared from **37a** (1.2 g, 2.38 mmol), *N*-hydroxyphthalimide (0.47 g, 2.86 mmol), $PPh_3$ (0.94 g, 3.58 mmol) and DEAD (0.56 mL, 3.58 mmol) in the same manner as described for **S8**. mp: 100 – 102 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, $J$ = 5.4, 3.2 Hz, 2H), 7.78 (dd, $J$ = 5.4, 3.2 Hz, 2H), 7.48 – 7.30 (m, 20H), 6.82 (s, 1H), 6.44 (s, 1H), 6.36 (s, 1H), 5.98 (s, 1H), 5.28 (q, $J$ = 6.8 Hz, 1H), 1.41 (d, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.33, 163.89(2C), 146.08, 143.68, 140.33, 140.18, 137.43, 137.29, 134.72(2C), 129.43, 129.06(2C), 128.87(2C), 128.81, 128.77(2C), 128.64, 128.56(2C), 128.50(2C), 127.93, 127.87, 127.44(2C), 127.06(2C), 126.98(2C), 126.43,

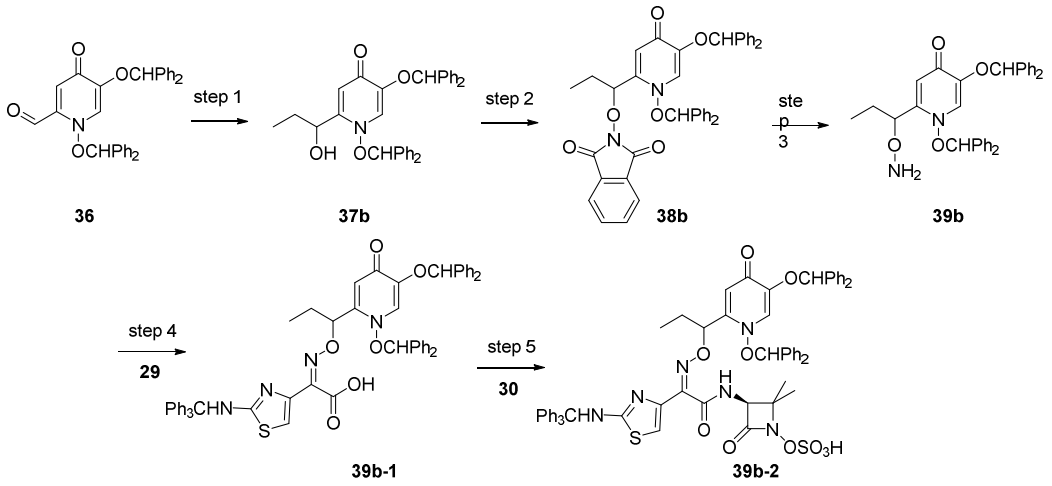
123.79(2C), 114.52, 92.10, 82.05, 77.75, 17.23. HRMS (ESI) *m/z* calcd for $C_{41}H_{33}N_2O_6$ [M + H] $^+$ 649.2333, found 649.2348.

**2-(1-(Aminooxy)ethyl)-1,5-bis(benzhydryloxy)pyridin-4(1*H*)-one (39a).** Compound **39a** (800 mg, 97%) was prepared from **38a** (1.03 g, 1.59 mmol) and 85% hydrazine hydrate (0.10 mL, 1.75 mmol) in the same manner as described for **31b**. mp: 70 – 71 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.21 (m, 20H), 6.60 (s, 1H), 6.47 (s, 1H), 6.15 (s, 1H), 5.79 (s, 1H), 5.39 (s, 2H), 4.73 (q, *J* = 6.6 Hz, 1H), 1.28 (d, *J* = 6.6 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.75, 148.87, 145.69, 140.49, 140.18, 137.66, 137.48, 129.55, 129.17(2C), 128.84(2C), 128.82(2C), 128.75, 128.56(2C), 128.43(2C), 127.84(2C), 127.38(2C), 126.99(2C), 126.66(2C), 125.68, 111.64, 92.16, 82.15, 75.45, 19.88. HRMS (ESI) *m/z* calcd for $C_{33}H_{31}N_2O_4$ [M + H] $^+$ 519.2278, found 519.2291.

**(*Z*)-2-((1-(1,5-Bis(benzhydryloxy)-4-oxo-1,4-dihydropyridin-2-yl)ethoxy)imino)-2-(2-(tritylamino)thiazol-4-yl)acetic Acid (39a-1).** Compound **39a-1** (1.12 g, 79%) was prepared from **39a** (800 mg, 1.54 mmol) and **29** (605 mg, 1.46 mmol) in the same manner as described for **32a**. mp: 157 – 159 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.48 (s, 1H), 7.47–7.17 (m,35H), 6.68 (s, 1H), 6.49 (s, 1H), 6.13 (s, 1H), 6.11 (s, 1H), 5.04 (q, *J* = 6.6 Hz, 1H), 1.21 (d, *J* = 6.6 Hz, 3H). $^{13}$C NMR (126 MHz, DMSO) characteristic peaks: δ 171.37, 167.76, 163.66, 149.62, 147.93, 145.29, 144.20, 141.19, 141.12, 140.66, 137.50, 137.35, 129.57, 129.39, 129.31, 129.22, 129.04, 129.00, 128.45, 128.25, 128.15, 127.84, 127.27, 127.17, 127.05, 126.35, 111.67, 110.93, 90.95, 81.12, 74.59, 71.91, 19.32. HRMS (ESI) *m/z* calcd for $C_{57}H_{47}N_4O_6S$ [M + H] $^+$ 915.3211, found 915.3221.

**(3*S*)-3-((*Z*)-2-((1-(1,5-Bis(benzhydryloxy)-4-oxo-1,4-dihydropyridin-2-yl)ethoxy)imino)-2-(2-(tritylamino)thiazol-4-yl)acetamido)-2,2-dimethyl-4-oxoazetidin-1-yl Hydrogen Sulfate (39a-2).** Compound **39a-2** (a mixture of diastereomer (approximately 1:1), 670 mg, 92%) was prepared from **39a-1** (600 mg, 0.66 mmol) and **30** (206 mg, 0.98 mmol) in the same manner as described for **33a**. mp: 170 °C decomp. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.46 (d, *J* = 7.7 Hz, 1H), 8.72 (s, 1/2H), 8.69 (s, 1/2H), 7.72 (s, 1/2H), 7.69 (s, 1/2H), 7.46 – 7.18 (m, 35H), 6.70 (s, 1/2H), 6.68 (s, 1/2H), 6.39 (s, 1/2H), 6.38 (s, 1/2H), 6.29 (s, 1/2H), 6.16 (s, 1/2H), 5.15 – 5.01 (m, 1H), 4.50 (d, *J* = 7.8 Hz, 1/2H), 4.46 (d, *J* = 7.5 Hz, 1/2H), 1.40 (s, 3/2H), 1.38 (s, 3/2H), 1.18 – 1.10 (m, 6H). $^{13}$C NMR (126 MHz, DMSO, most carbons show two peaks because of diastereomers) characteristic peaks: δ 170.78, 167.87, 162.90 and 162.76, 162.05 and 161.91, 158.74 and 158.47, 150.90 and 150.81, 148.50 and 148.42, 148.21, 146.15, 145.17 and 145.10, 144.04, 141.69 and 141.63, 140.80, 137.36 and 137.31, 137.27 and 137.24, 129.76, 129.39, 129.29, 129.26, 129.10, 129.09, 129.06, 128.71, 128.63, 128.48, 128.37, 128.24, 127.96, 127.66, 127.60, 127.37, 127.16, 127.14, 127.05, 126.91, 126.83, 126.65, 112.18 and 112.00, 111.85 and 111.75, 91.54 and 91.50, 81.53 and 81.48, 74.35 and 73.92, 71.75, 68.37 and 68.22, 61.44 and 61.18, 23.94, 20.82 and 20.69, 19.33 and 19.18. HRMS (ESI) *m/z* calcd for $C_{62}H_{53}N_6O_{10}S_2$ [M − H] $^-$ 1105.3270, found 1105.3274.

**Preparation of intermediate 39b-2.**




**1,5-Bis(benzhydryloxy)-2-(1-hydroxypropyl)pyridin-4(1*H*)-one (37b).** Compound **37b** (720 mg, 68%) was prepared from **36** (1.0 g, 2.05 mmol) and ethylmagnesium bromide (10.0 mL, 10.00 mmol) in the same manner as described for **37a**. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.48 (s, 1H), 7.45 – 7.20 (m, 20H), 6.32 (s, 1H), 6.27 (s, 1H), 6.05 (s, 1H), 5.36 (d, $J$ = 6.0 Hz, 1H), 4.26 (dt, $J$ = 6.7, 6.0 Hz, 1H), 1.43 – 1.33 (m, 2H), 0.70 (t, $J$ = 7.3 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.69, 151.42, 144.77, 140.53, 140.45, 137.86, 137.47, 129.10, 128.99, 128.71(2C), 128.49(2C), 128.46(2C), 128.43(2C), 127.83, 127.77, 127.25(4C), 126.96(2C), 126.94(2C), 126.92, 113.14, 92.43, 82.12, 68.33, 29.71, 9.97. HRMS (ESI) *m/z* calcd for $C_{34}H_{32}NO_4$ $[M + H]^+$ 518.2326, found 518.2327.

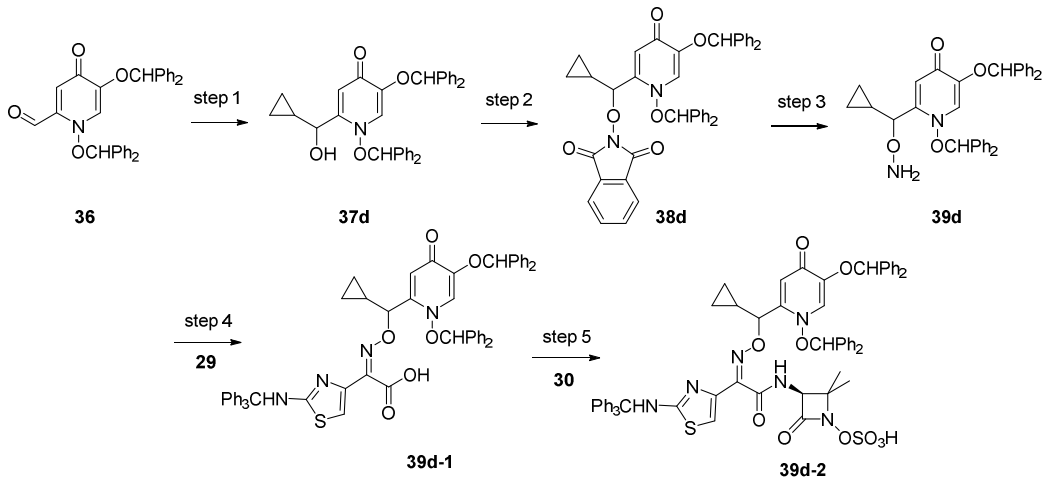
**2-(1-(1,5-Bis(benzhydryloxy)-4-oxo-1,4-dihydropyridin-2-yl)propoxy)isoindoline-1,3-dione (38b).** Compound **38b** (160 mg, 62%) was prepared from **37b** (200 mg, 0.39 mmol), *N*-hydroxyphthalimide (78 mg, 0.46 mmol), $PPh_3$ (254.4 mg, 0.97 mmol) and DEAD (0.15 mL, 0.97 mmol) in the same manner as described for **S8**. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.68 (m, 4H), 7.36 – 7.12 (m, 20H), 6.72 (s, 1H), 6.37 (s, 1H), 6.28 (s, 1H), 5.87 (s, 1H), 4.89 (t, $J$ = 7.1 Hz, 1H), 1.61 – 1.40 (m, 2H), 0.86 (t, $J$ = 7.4 Hz, 3H). MS (ESI): *m/z* 663 $[M + H]^+$.

**2-(1-(Aminooxy)propyl)-1,5-bis(benzhydryloxy)pyridin-4(1*H*)-one (39b).** Compound **39b** (110 mg, 86%) was prepared from **38b** (160 mg, 0.24 mmol) and 85% hydrazine hydrate (0.02 mL, 0.36 mmol) in the same manner as described for **31b**. MS (ESI): *m/z* 533 $[M + H]^+$.

**(*Z*)-2-((1-(1,5-Bis(benzhydryloxy)-4-oxo-1,4-dihydropyridin-2-yl)propoxy)imino)-2-(2-(tritylamino)thiazol-4-yl)acetic Acid (39b-1).** Compound **39b-1** (300 mg, 69%) was prepared from **39b** (250 mg, 0.47 mmol) and **29** (195 mg, 0.47 mmol) in the same manner as described for **32a**. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 8.73 (s, 1H), 7.54 (s, 1H), 7.47 – 7.18 (m, 35H), 6.81 (s, 1H), 6.29 (s, 1H), 6.27 (s, 1H), 5.93 (s, 1H), 4.81 (m, 1H), 1.33 – 1.19 (m, 2H), 0.67 (t, $J$ = 7.3 Hz, 3H). MS (ESI): *m/z* 929 $[M + H]^+$.

**(3*S*)-3-((*Z*)-2-((1-(1,5-Bis(benzhydryloxy)-4-oxo-1,4-dihydropyridin-2-yl)propoxy)imino)-2-(2-(tritylamino)thiazol-4-yl)acetamido)-2,2-dimethyl-4-oxoazetidin-1-yl Hydrogen Sulfate (39b-2).** Compound **39b-2** (a mixture of diastereomer (approximately 1:1), 250 mg, 70%) was prepared from **39b-1** (300 mg, 0.32 mmol) and **30** (95 mg, 0.45 mmol) in the same manner as described for **33a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.50 (d, $J$ = 7.9 Hz, 1/2H), 9.46 (d, $J$ = 7.5 Hz, 1/2H), 8.65 (s, 1/2H), 8.62 (s, 1/2H), 7.43 – 7.19 (m, 35H), 6.71 (s, 1/2H), 6.69 (s, 1/2H), 6.33 (s, 1H), 6.18 (s, 1/2H), 6.17 (s, 1/2H), 6.07 (s, 1/2H), 5.95 (s, 1/2H), 4.85 (dd, $J$ = 8.1, 4.7 Hz, 1/2H), 4.77 (dd, $J$ = 8.6, 4.4 Hz, 1/2H), 4.52 (d, $J$ = 7.8 Hz, 1/2H), 4.48 (d, $J$ = 7.5 Hz, 1/2H), 1.99 (dt, $J$ = 13.2, 7.0 Hz, 2H), 1.40 (s, 3/2H), 1.38 (s, 3/2H), 1.17 (s, 3H), 0.67 (t, $J$ = 7.3 Hz, 3H). MS (ESI): *m/z* 1119 [M − H] $^-$.

**Preparation of intermediate 39d-2.**




**1,5-Bis(benzhydryloxy)-2-(cyclopropyl(hydroxy)methyl)pyridin-4(1*H*)-one (37d).** Compound **37d** (477 mg, 73%) was prepared from **36** (600 mg, 1.23 mmol) and cyclopropylmagnesium bromide (9.6 mL, 4.80 mmol) in the same manner as described for **37a**. $^1$H NMR(400 MHz, DMSO-$d_6$) δ 7.56 (s, 1H), 7.43 – 7.12 (m, 20H), 6.33 (s, 1H), 6.28 (s, 1H), 6.11 (s, 1H), 5.43 (d, $J$ = 6.2 Hz, 1H), 3.92 (t, $J$ = 6.2 Hz, 1H), 0.94 – 0.83 (m, 1H), 0.39 – 0.31 (m, 1H), 0.30 – 0.23 (m, 1H), 0.22 – 0.15 (m, 1H), –0.03 ~ –0.12 (m, 1H). MS (ESI): *m/z* 530 [M + H] $^+$.

**2-((1,5-Bis(benzhydryloxy)-4-oxo-1,4-dihydropyridin-2-yl)(cyclopropyl)methoxy)isoindoline-1,3-dione (38d).** Compound **38d** (290 mg, 48%) was prepared from **37d** (477 mg, 0.90 mmol), *N*-hydroxyphthalimide (440 mg, 2.70 mmol), $PPh_3$ (708 mg, 2.70 mmol) and DEAD (0.42 mL, 2.70 mmol) in the same manner as described for **S8**. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.74 (m, 4H), 7.42 – 7.19 (m, 20H), 6.81 (s, 1H), 6.54 (s, 1H), 6.42 (s, 1H), 5.91 (s, 1H), 4.22 (d, $J$ = 9.7 Hz, 1H), 0.95 – 0.82 (m, 1H), 0.72 – 0.61 (m, 1H), 0.54 – 0.41 (m, 2H), –0.11 ~ –0.22 (m, 1H). MS (ESI): *m/z* 675 [M + H] $^+$.

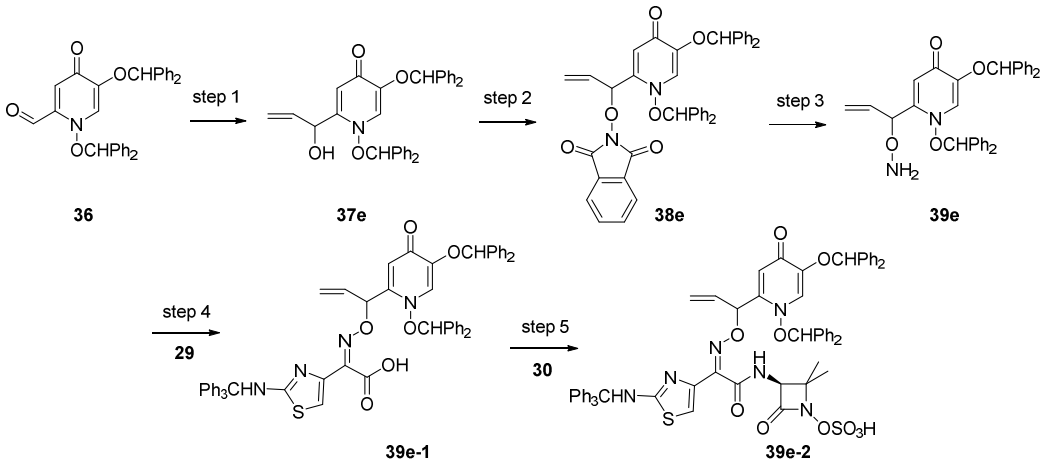
**2-((Aminooxy)(cyclopropyl)methyl)-1,5-bis(benzhydryloxy)pyridin-4(1*H*)-one (39d).** Compound **39d** (200 mg, 92%) was prepared from **38d** (270 mg, 0.40 mmol) and 85%

hydrazine hydrate (0.03 mL, 0.44 mmol) in the same manner as described for **31b**. MS (ESI): *m/z* 545 $[M + H]^+$.

**(*Z*)-2-(((1,5-Bis(benzhydryloxy)-4-oxo-1,4-dihydropyridin-2-yl)(cyclopropyl)methoxy)imino)-2-(2-(tritylamino)thiazol-4-yl)acetic Acid (39d-1).** Compound **39d-1** (390 mg, 65%) was prepared from **39d** (350 mg, 0.64 mmol) and **29** (265 mg, 0.64 mmol) in the same manner as described for **32a**. $^1$H NMR (400 MHz, $CD_3OD$) δ 8.20 (s, 1H), 6.67 (s, 1H), 6.63 (s, 1H), 6.24 (s, 1H), 5.98 (s, 1H), 4.40 (d, *J* = 7.9 Hz, 1H), 1.07 (d, *J* = 11.7 Hz, 1H), 0.48 (s, 1H), 0.36 (s, 1H), 0.28 (d, *J* = 8.6 Hz, 1H), 0.03 (s, 1H). MS (ESI): *m/z* 941 $[M + H]^+$.

**(3*S*)-3-((*Z*)-2-(((1,5-Bis(benzhydryloxy)-4-oxo-1,4-dihydropyridin-2-yl)(cyclopropyl)methoxy)imino)-2-(2-(tritylamino)thiazol-4-yl)acetamido)-2,2-dimethyl-4-oxoazetidin-1-yl Hydrogen Sulfate (39d-2).** Compound **39d-2** (a mixture of diastereomer (approximately 1:1), 340 mg, 73%) was prepared from **39d-1** (390 mg, 0.41 mmol) and **30** (126 mg, 0.60 mmol) in the same manner as described for **33a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.45 (d, *J* = 7.7 Hz, 1H), 8.63 (d, *J* = 3.3 Hz, 1H), 7.43 – 7.13 (m, 35H), 6.73 (s, 1/2H), 6.70 (s, 1/2H), 6.34 (s, 1/2H), 6.31 (s, 1/2H), 6.20 (s, 1/2H), 6.16 (s, 1/2H), 6.13 (s, 1/2H), 6.12 (s, 1/2H), 4.53 (d, *J* = 7.8 Hz, 1/2H), 4.48 (d, *J* = 7.6 Hz, 1/2H), 4.39 (d, *J* = 8.1 Hz, 1/2H), 4.32 (d, *J* = 7.9 Hz, 1/2H), 1.37 (s, 3H), 1.14 (s, 3/2H), 1.12 (s, 3/2H), 0.90 – 0.83 (m, 1H), 0.53 – 0.44 (m, 1H), 0.42 – 0.32 (m,1H), 0.30 – 0.24 (m, 1/2H), 0.23 – 0.16 (m, 1/2H), −0.04 ~ −0.17 (m,1H). MS (ESI): *m/z* 1131 $[M - H]^-$.

**Preparation of intermediate 39e-2.**




**1,5-Bis(benzhydryloxy)-2-(1-hydroxyallyl)pyridin-4(1*H*)-one (37e).** Compound **37e** (800 mg, 76%) was prepared from **36** (1.0 g, 2.05 mmol) and vinylmagnesium bromide (10.0 mL, 10.00 mmol) in the same manner as described for **37a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.58 (s, 1H), 7.45 – 7.17 (m, 20H), 6.35 (s, 1H), 6.32 (s, 1H), 5.93 (s, 1H), 5.78 (d, *J* = 6.0 Hz, 1H), 5.58 (m, 1H), 5.15 – 5.11 (m, 1H), 5.11 – 5.06 (m, 1H), 4.85 (t, *J* = 5.5 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.55, 149.23, 145.02, 140.44, 140.36, 137.68, 137.45, 136.17, 129.15, 128.99, 128.77(2C), 128.60(2C), 128.51(2C), 128.47(2C), 127.88, 127.81, 127.20(2C), 127.11(2C), 127.04, 126.91(4C), 116.95, 113.96, 92.58, 82.17, 67.83. HRMS (ESI) *m/z* calcd

for $C_{34}H_{30}NO_4$ $[M + H]^+$ 516.2169, found 516.2171.

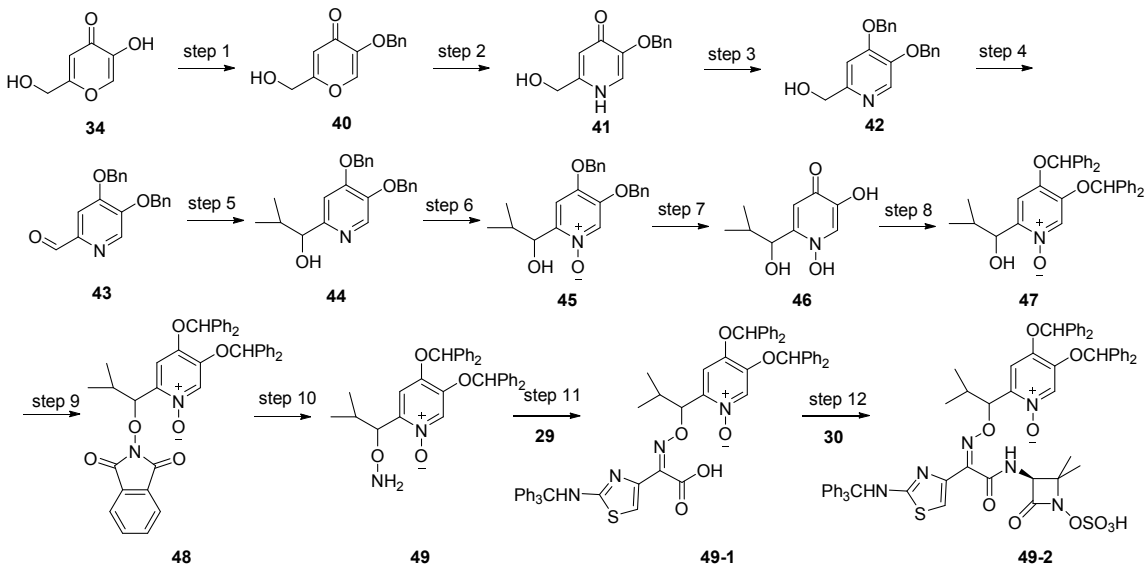
**2-((1-(1,5-Bis(benzhydryloxy)-4-oxo-1,4-dihydropyridin-2-yl)allyl)oxy)isoindoline-1,3-dione (38e).** Compound **38e** (661 mg, 65%) was prepared from **37e** (800 mg, 1.55 mmol), *N*-hydroxyphthalimide (310 mg, 1.90 mmol), $PPh_3$ (839 mg, 3.20 mmol) and DEAD (0.50 mL, 3.20 mmol) in the same manner as described for **S8**. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.73 (m, 4H), 7.40 – 7.22 (m, 20H), 6.77 (s, 1H), 6.58 (s, 1H), 6.28 (s, 1H), 5.96 (dd, *J* = 10.2, 8.0 Hz, 1H), 5.92 (s, 1H), 5.55 (d, *J* = 8.0 Hz, 1H), 5.29 (dd, *J* = 17.2, 10.2 Hz, 1H), 5.10 (d, *J* = 17.2 Hz, 1H). MS (ESI): *m/z* 661 $[M + H]^+$.

**2-(1-(Aminooxy)allyl)-1,5-bis(benzhydryloxy)pyridin-4(1*H*)-one (39e).** Compound **39e** (479 mg, 90%) was prepared from **38e** (660 mg, 1.0 mmol) and 85% hydrazine hydrate (0.06 mL, 1.05 mmol) in the same manner as described for **31b**. MS (ESI): *m/z* 531 $[M + H]^+$.

**(*Z*)-2-(((1-(1,5-Bis(benzhydryloxy)-4-oxo-1,4-dihydropyridin-2-yl)allyl)oxy)imino)-2-(2-(tritylamino)thiazol-4-yl)acetic Acid (39e-1).** Compound **39e-1** (480 mg, 61%) was prepared from **39e** (450 mg, 0.85 mmol) and **29** (352 mg, 0.85 mmol) in the same manner as described for **32a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.45 (s, 1H), 7.52 – 7.15 (m, 35H), 6.66 (s, 1H), 6.52 (s, 1H), 6.11 (s, 1H), 6.04 (s, 1H), 5.68 (t, *J* = 12.6 Hz, 1H), 5.45 (d, *J* = 5.4 Hz, 1H), 5.26 – 5.14 (m, 2H). MS (ESI): *m/z* 927 $[M + H]^+$.

**(3*S*)-3-((*Z*)-2-(((1-(1,5-Bis(benzhydryloxy)-4-oxo-1,4-dihydropyridin-2-yl)allyl)oxy)imino)-2-(2-(tritylamino)thiazol-4-yl)acetamido)-2,2-dimethyl-4-oxoazetidin-1-yl Hydrogen Sulfate (39e-2).** Compound **39e-2** (a mixture of diastereomer (approximately 1:1), 300 mg, 52%) was prepared from **39e-1** (480 mg, 0.52 mmol) and **30** (164 mg, 0.78 mmol) in the same manner as described for **33a**. mp: 153 °C decomp. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.52 (t, *J* = 8.3 Hz, 1H), 8.79 (s, 1/2H), 8.73 (s, 1/2H), 7.53 – 7.12 (m, 35H), 6.72 (s, 1/2H), 6.70 (s, 1/2H), 6.32 (s, 1/2H), 6.31 (s, 1/2H), 6.22 (s, 1/2H), 6.18 (s, 1/2H), 5.98 (s, 1/2H), 5.92 (s, 1/2H), 5.69 (ddd, *J* = 17.2, 10.7, 5.3 Hz, 1/2H), 5.58 (ddd, *J* = 17.5, 10.7, 5.4 Hz, 1/2H), 5.47 (dt, *J* = 5.4, 1.4 Hz, 1/2H), 5.44 – 5.41 (m, 1/2H), 5.34 – 5.08 (m, 2H), 4.52 (d, *J* = 7.9 Hz, 1/2H), 4.48 (d, *J* = 7.5 Hz, 1/2H), 1.37 (s, 3/2H), 1.35 (s, 3/2H), 1.06 (s, 3/2H), 1.03 (s, 3/2H). MS (ESI): *m/z* 1117 $[M - H]^-$.

**Preparation of intermediate 49-2.**




**5-(Benzyloxy)-2-(hydroxymethyl)-4*H*-pyran-4-one (40).** A suspension of **34** (100 g, 0.70 mol) in methanol (350 mL) was treated with 2.3 *M* aqueous sodium hydroxide (300 mL, 0.70 mol). Benzyl chloride (89 mL, 0.77 mol) was added to the mixture, and then the solution was heated to 60 °C and stirred 6 h. The reaction mixture was cooled to room temperature and concentrated, filtered, and the resulting precipitate was washed with water and ethyl acetate to give **40** as a white solid (149.3 g, 91 %). mp: 124 – 126 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.44 – 7.32 (m, 5H), 6.54 (t, *J* = 0.9 Hz, 1H), 5.07 (s, 2H), 4.46 (dd, *J* = 6.6, 0.9 Hz, 2H), 3.31 (s, 1H). MS (ESI): *m/z* 233 $[M + H]^+$.

**5-(Benzyloxy)-2-(hydroxymethyl)pyridin-4(1*H*)-one (41).** A suspension of **40** (78 g, 0.34 mol) in MeOH (150 mL) was treated with aqueous ammonium hydroxide (400 mL, 4.44 mol). The resulting mixture was heated to 55 °C and stirred overnight, then cooled to room temperature, the resulting precipitate was collected by filtration and washed with water, followed by ethyl acetate to afford **41** as a white solid (70 g, 90%). mp: 218 – 220 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.11 (s, 1H), 7.44 – 7.27 (m, 6H), 6.08 (s, 1H), 5.59 (d, *J* = 6.0 Hz, 1H), 4.98 (s, 2H), 4.32 (d, *J* = 5.7 Hz, 2H). MS (ESI): *m/z* 232 $[M + H]^+$.

**(4,5-Bis(benzyloxy)pyridin-2-yl)methanol (42).** A suspension of **41** (10 g, 43.29 mmol) in DMSO (50 mL) was treated with potassium carbonate (7.1 g, 51.90 mmol) and benzyl chloride (6.0 mL, 51.90 mmol). The resulting mixture was stirred at room temperature overnight and then heated to 50 °C for 2 h. After cooling to room temperature, the mixture was poured into water (100 mL). The solution was extracted with ethyl acetate, washed with water and brine, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated in vacuo. The resulting residue was purified by chromatography on silica gel with dichloromethane/methanol to afford **42** as a yellow solid (6.0 g, 43%). mp: 80 – 82 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.09 (s, 1H), 7.50 – 7.27 (m, 10H), 7.17 (s, 1H), 5.31 (t, *J* = 5.7 Hz, 1H), 5.21 (s, 2H), 5.15 (s, 2H), 4.41 (d, *J* = 5.7 Hz, 2H). MS (ESI): *m/z* 322 [M + H]

$^{+}$.

**4,5-Bis(benzyloxy)picolinaldehyde (43).** Compound **43** (25.5 g, 95 %) was prepared from **42** (27 g, 0.08 mol) and sulfur trioxide pyridine complex (33.3 g, 0.21 mol) in the same manner as described for **36**. mp: 79 – 81 °C.$^{1}$H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.31 (s, 1H), 7.57 (s, 1H), 7.49 – 7.31 (m, 10H), 5.32 (s, 2H), 5.27 (s, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 192.39, 155.14, 148.34, 148.33, 136.15, 135.72, 135.23, 128.79(2C), 128.76(2C), 128.48, 128.43, 127.38(2C), 127.34(2C), 105.85, 71.74, 70.66. HRMS (EI) *m/z* calcd for $C_{20}H_{17}NO_3$ [M] $^{+}$ 319.1208, found 319.1211.

**1-(4,5-Bis(benzyloxy)pyridin-2-yl)-2-methylpropan-1-ol (44).** Compound **44** (9.5 g, 68%) was prepared from **43** (12.3 g, 38.56 mmol) and isopropylmagnesium bromide (25.7 mL, 77.10 mmol) in the same manner as described for **37a**. mp: 61 – 63 °C.$^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.48 – 7.30 (m, 10H), 6.75 (s, 1H), 5.21 (s, 2H), 5.18 (s, 2H), 4.40 (d, *J* = 3.2 Hz, 1H), 3.98 (s, 1H), 1.95 – 1.85 (m, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.72 (d, *J* = 6.7 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 156.36, 155.60, 144.24, 136.61, 135.69, 135.62, 128.72(2C), 128.59(2C), 128.29, 128.14, 127.54(2C), 127.24(2C), 105.57, 77.15, 72.40, 70.40, 35.11, 19.33, 16.14. HRMS (ESI) *m/z* calcd for $C_{23}H_{26}NO_3$ [M + H] $^{+}$ 364.1907, found 364.1914.

**4,5-Bis(benzyloxy)-2-(1-hydroxy-2-methylpropyl)pyridine 1-Oxide (45).** Compound **45a** (8.0 g, 81%) was prepared from **44** (9.5 g, 26.09 mmol) and *m*-CPBA (15.9 g, 78.32 mmol) in the same manner as described for **S5**. mp: 176 – 178 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.44 – 7.27 (m, 10H), 6.64 (s, 1H), 6.25 (s, 1H), 5.25 – 5.15 (m, 2H), 5.11 (s, 2H), 4.21 (d, *J* = 8.1 Hz, 1H), 2.32 (m, 1H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.73 (d, *J* = 6.7 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 148.90, 145.43, 145.35, 135.01, 128.84(2C), 128.82(2C), 128.63, 128.58, 128.52, 127.47(2C), 127.31(2C), 109.04, 77.24, 72.20, 71.37, 31.54, 19.65, 18.23. HRMS (ESI) *m/z* calcd for $C_{23}H_{26}NO_4$ [M + H] $^{+}$ 380.1856, found 380.1850.

**1,5-Dihydroxy-2-(1-hydroxy-2-methylpropyl)pyridin-4(1*H*)-one (46).** Compound **46** (crude material) was prepared from **45** (8.0 g, 21.11 mmol) and boron trichloride in *n*-hexane (52.7 mL, 52.70 mmol) in the same manner as described for **S6**, which was used in the next step without purification.

**4,5-Bis(benzhydryloxy)-2-(1-hydroxy-2-methylpropyl)pyridine 1-Oxide (47).** Compound **47** (4.3 g, 38% by two steps) was prepared from **46** (crude material) and diphenyldiazomethane (20.4 g, 105.15 mmol) in the same manner as described for **S7**. mp: 149 – 151 °C.$^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.45 – 7.27 (m, 20H), 6.55 (s, 1H), 6.27 (s, 1H), 6.23 (d, *J* = 8.7 Hz, 1H), 6.18 (s, 1H), 4.03 (t, *J* = 8.5 Hz, 1H), 2.25 – 2.12 (m, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.53 (d, *J* = 6.7 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 150.48, 147.14, 146.74, 141.71, 141.63, 141.53, 141.50, 132.97, 130.79 (4C), 130.74 (4C), 130.29 (2C), 130.27 (2C), 128.63 (2C), 128.53 (2C), 128.50 (2C), 128.43 (2C), 113.60, 86.49, 85.36, 79.90, 33.03, 21.43, 20.23. HRMS (ESI) *m/z* calcd for $C_{35}H_{34}NO_4$ [M + H] $^{+}$ 532.2482, found 532.2490.

**4,5-Bis(benzhydryloxy)-2-(1-((1,3-dioxoisoindolin-2-yl)oxy)-2-methylpropyl)pyridine 1-Oxide (48).** Compound **48** (2.9 g, 56%) was prepared from **47** (4.1 g, 7.71 mmol), *N*-hydroxyphthalimide (1.51 g, 9.26 mmol), $PPh_3$ (3.04 g, 11.6 mmol) and DIAD (2.27 mL, 11.6 mmol) in the same manner as described for **S8**. mp: 191 – 193 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 5.6, 3.1 Hz, 2H), 7.73 (s, 1H), 7.70 (dd, *J* = 5.6, 3.1Hz, 2H), 7.59 (s, 1H), 7.59 – 7.55 (m, 4H), 7.46 – 7.27 (m, 16H), 6.72 (s, 1H), 6.15 (s, 1H), 5.88 (d, *J* =6.8 Hz, 1H), 2.11 (h, *J* = 6.9 Hz, 1H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.64 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.64(2C), 147.46, 145.49, 142.83, 140.66, 140.11(2C), 140.04, 134.48(2C), 130.34(2C), 128.99(2C), 128.94, 128.80(2C), 128.72(2C), 128.53(2C), 128.29, 128.20, 128.17, 127.95, 126.79(2C), 126.77(2C), 126.73(2C), 126.61(2C), 123.49(2C), 111.50, 85.90, 84.39, 82.83, 31.02, 18.95, 15.66. HRMS (ESI) *m/z* calcd for $C_{43}H_{37}N_2O_6$ [M + H] $^+$ 677.2646, found 677.2662.

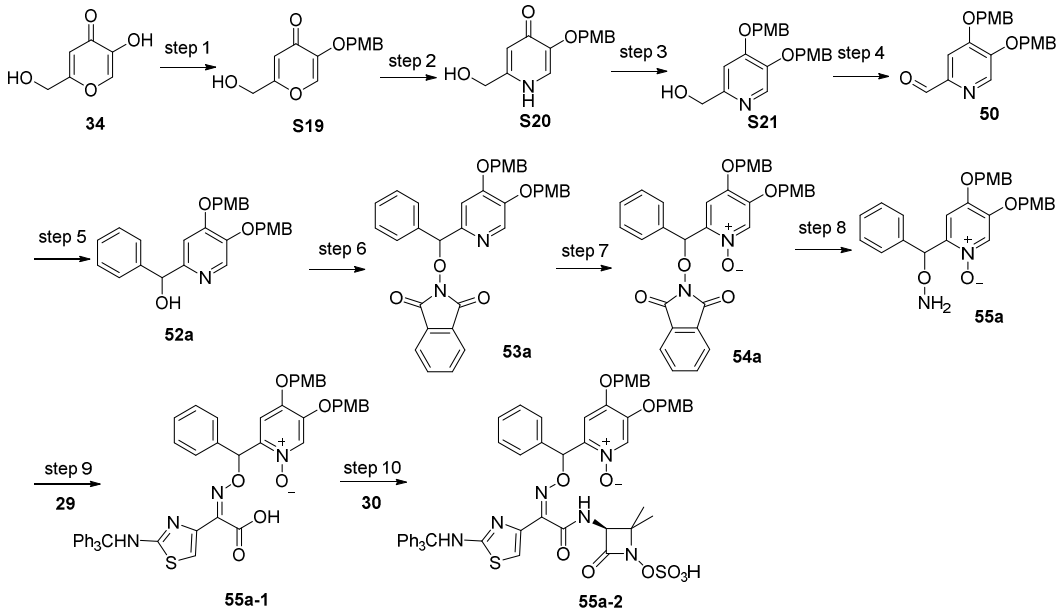
**2-(1-(Aminooxy)-2-methylpropyl)-4,5-bis(benzhydryloxy)pyridine 1-Oxide (49).** Compound **49** (2.1 g, 79%) was prepared from **48** (3.3 g, 4.88 mmol) and 85% hydrazine hydrate (0.30 mL, 5.40 mmol) in the same manner as described for **31b**. mp: 71 – 73 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.97 (s, 1H), 7.64 – 7.22 (m, 20H), 6.88 (s, 1H), 6.82 (s, 1H), 6.69 (s, 1H), 5.95 (s, 2H), 4.68 (d, J = 3.7 Hz, 1H), 1.87 – 1.76 (m, 1H), 0.82 (d, J = 6.9 Hz, 3H), 0.36 (d, J = 7.0 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 147.74, 145.70, 145.41, 140.04, 140.02, 139.96, 139.80, 130.87, 128.89(2C), 128.81(2C), 128.79(2C), 128.77(2C), 128.31(2C), 128.25(2C), 126.73(4C), 126.68(4C), 110.29, 84.58, 84.48, 83.14, 30.41, 19.00, 16.59. HRMS (ESI) *m/z* calcd for $C_{35}H_{35}N_2O_4$ [M + H] $^+$ 547.2591, found 547.2600.

**(*Z*)-4,5-Bis(benzhydryloxy)-2-(1-(((carboxy(2-(tritylamino)thiazol-4-yl)methylene)amino)oxy)-2-methylpropyl)pyridine 1-Oxide (49-1).** Compound **49-1** (236 mg, 65%) was prepared from **49** (210 mg, 0.38 mmol) and **29** (141 mg, 0.34 mmol) in the same manner as described for **32a**. mp: 160 – 162 °C.$^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.90 (s, 1H), 7.99 (s, 1H), 7.62 – 7.15 (m, 35H), 6.96 (s, 1H), 6.90 (s,1H), 6.69 (s, 1H), 6.54 (s, 1H), 5.28 (d, *J* = 3.2 Hz, 1H), 2.12 – 2.00 (m, 1H), 0.90 (d, *J* = 7.0 Hz, 3H),0.43 (d, *J* = 7.0 Hz, 3H). $^{13}$C NMR (126 MHz, DMSO) characteristic peaks:δ 167.84, 164.35, 145.66, 145.08, 144.14, 143.87, 141.10, 140.86, 140.62, 140.60, 140.52, 129.40, 129.25, 129.21, 129.17, 129.00, 128.48, 128.40, 128.33, 128.16, 127.28, 126.80, 126.74, 126.69, 111.61, 111.39, 83.21, 81.78, 81.62, 71.85, 29.15, 19.62, 16.05. HRMS (ESI) *m/z* calcd for $C_{59}H_{49}N_4O_6S$ [M − H] $^-$ 941.3378, found 941.3379.

**4,5-Bis(benzhydryloxy)-2-(1-((((*Z*)-2-(((*S*)-2,2-dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxo-1-(2-(tritylamino)thiazol-4-yl)ethylidene)amino)oxy)-2-methylpropyl)pyridine 1-Oxide (49-2).** Compound **49-2** (a mixture of diastereomer (approximately 1:1), 294 mg, 94%) was prepared from **49-1** (260 mg, 0.27 mmol) and **30** (86 mg, 0.41 mmol) in the same manner as described for **33a**. mp: 186 °C decomp. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.77 (d, *J* = 7.7 Hz, 1/2H), 9.68 (d, *J* = 7.0 Hz, 1/2H), 8.90 (s, 1H), 8.02 (s, 1/2H), 7.99 (s, 1/2H), 7.63 – 7.16 (m, 35H), 7.04 (s, 1/2H), 6.87 (s, 1/2H), 6.79 (s, 1/2H), 6.77 (s, 1/2H), 6.74 (s, 1/2H),

6.73 (s, 1/2H), 6.72 (s, 1/2H), 6.70 (s, 1/2H), 5.32 (d, $J$ = 3.2 Hz, 1/2H), 5.26 (d, $J$ = 3.7 Hz, 1/2H), 4.81 (d, $J$ = 7.8 Hz, 1/2H), 4.65 (d, $J$ = 7.1 Hz, 1/2H), 2.05 – 1.93 (m, 1H), 1.57 (s, 3/2H), 1.52 (s, 3/2H), 1.37 (s, 3/2H), 1.34 (s, 3/2H), 0.87 (d, $J$ = 6.9 Hz, 3/2H), 0.82 (d, $J$ = 7.0 Hz, 3/2H), 0.36 (d, $J$ = 7.0 Hz, 3/2H), 0.32 (d, $J$ = 7.1 Hz, 3/2H). $^{13}$C NMR (126 MHz, DMSO, most carbons show two peaks because of diastereomers) characteristic peaks: δ 168.23 and 168.17, 163.68 and 163.63, 162.07 and 161.88, 151.28 and 150.93, 145.72 and 145.67, 144.94 and 144.87, 144.30 and 144.10, 143.93, 141.75 and 141.71, 141.21, 141.10, 140.98, 140.80 and 140.54, 129.40, 129.26, 129.23, 129.05, 129.02, 128.48, 128.44, 128.26, 128.19, 127.44, 126.85, 126.75, 126.72, 126.64, 112.97 and 112.72, 111.75 and 111.65, 83.27 and 83.09, 81.60 and 81.57, 81.44 and 81.26, 71.62, 68.01 and 67.89, 61.58 and 61.22, 29.57 and 29.12, 24.02 and 23.97, 21.17 and 21.07, 19.46 and19.37, 16.22 and 15.99. HRMS (ESI) *m/z* calcd for $C_{64}H_{57}N_6O_{10}S_2$ $[M - H]^-$ 1133.3583, found 1133.3608.

**Preparation of intermediate 55a-2.**




**2-(Hydroxymethyl)-5-((4-methoxybenzyl)oxy)-4*H*-pyran-4-one (S19).** A suspension of **34** (10.0 g, 70.40 mmol) in DMF (60 mL) was treated with potassium carbonate (11.6 g, 84.05 mmol) and *p*-methoxybenzyl chloride (10.5 mL, 77.42 mmol). The resulting mixture was heated to 80 °C and stirred overnight, then cooled to room temperature and poured into ice water (200 mL), and then the resulting suspension was stirred for 0.5 h. The precipitate was collected by filtration and washed with water, followed by ethyl acetate to afford **S19** as a yellow solid (13.3 g, 73%). mp: 122 – 123 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.15 (s, 1H), 7.34 (d, $J$ = 8.6 Hz, 2H), 6.95 (d, $J$ = 8.6 Hz, 2H), 6.31 (s, 1H), 5.69 (t, $J$ = 6.1 Hz, 1H), 4.85 (s, 2H), 4.29 (d, $J$ = 6.1 Hz, 2H), 3.76 (s, 3H). MS (ESI): *m/z* 285 $[M + Na]^+$.

**2-(Hydroxymethyl)-5-((4-methoxybenzyl)oxy)pyridin-4(1*H*)-one (S20).** Compound **S20** (12.4 g, 78%) was prepared from **S19** (16.0 g, 61.07 mmol) and aqueous ammonium hydroxide (82 mL, 910 mmol) in the same manner as described for **41**. mp: 213 – 216 °C. $^1$H

NMR (400 MHz, DMSO-$d_6$) δ 11.12 (s, 1H), 7.32 (d, $J$ = 8.2 Hz, 2H), 7.26 (s, 1H), 6.92 (d, $J$ = 8.2 Hz, 2H), 6.08 (s, 1H), 5.60 (s, 1H), 4.91 (s, 2H), 4.32 (d, $J$ = 4.7 Hz, 2H), 3.74 (s, 3H). MS (ESI): *m/z* 262 $[M + H]^+$.

**(4,5-Bis((4-methoxybenzyl)oxy)pyridin-2-yl)methanol (S21).** Compound **S21**(6.4 g, 35%) was prepared from **S20** (12.4 g, 47.51 mmol) and *p*-methoxybenzyl chloride (8.2 mL, 60.41 mmol) in the same manner as described for **42**. mp: 103 – 105 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.07 (s, 1H), 7.39 (d, $J$ = 8.3 Hz, 2H), 7.32 (d, $J$ = 8.3 Hz, 2H), 7.18 (s, 1H), 6.96 (d, $J$ = 8.2 Hz, 2H), 6.91 (d, $J$ = 8.2 Hz, 2H), 5.31 (t, $J$ = 5.7 Hz, 1H), 5.12 (s, 2H), 5.05 (s, 2H), 4.43 (d, $J$ = 5.7 Hz, 2H), 3.76 (s, 3H), 3.74 (s, 3H). MS (ESI): *m/z* 382 $[M + H]^+$.

**4,5-Bis((4-methoxybenzyl)oxy)picolinaldehyde (50).** Compound **50** (5.5 g, 86%) was prepared from **S21** (6.4 g, 16.79 mmol) and sulfur trioxide pyridine complex (8.0 g, 50.39 mmol) in the same manner as described for **36**. mp: 85 – 87 °C.$^1$H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.30 (s, 1H), 7.56 (s, 2H), 7.36 (d, $J$ = 8.7 Hz, 2H), 7.34 (d, $J$ = 8.7 Hz, 2H), 6.93 – 6.87 (m, 4H), 5.22 (s, 2H), 5.17 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 192.44, 159.77, 159.73, 155.23, 148.36, 148.24, 136.42, 129.27(2C), 129.23(2C), 127.74, 127.22, 114.16(2C), 114.12(2C), 105.91, 71.65, 70.53, 55.30(2C). HRMS (EI) *m/z* calcd for $C_{22}H_{21}NO_5$ $[M]^+$ 379.1420, found 379.1419.

**(4,5-Bis((4-methoxybenzyl)oxy)pyridin-2-yl)(phenyl)methanol (52a).** Compound **52a** (3.9 g, 92%) was prepared from **50** (3.5 g, 9.26 mmol) and phenylmagnesium chloride (14.0 mL, 28.00 mmol) in the same manner as described for **37a**. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.37 – 7.30 (m, 5H), 7.31 – 7.19 (m, 4H), 6.90 – 6.83(m, 4H), 6.65 (s, 1H), 5.60 (s, 1H), 5.07 (s, 2H), 5.04 – 4.96 (m, 2H), 3.81 (s, 3H), 3.81 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 159.60, 159.55, 155.96, 155.75, 144.44, 143.32, 135.52, 129.31(2C), 129.20(2C), 128.62, 128.54(2C), 127.74, 127.51, 126.97(2C), 114.04(2C), 113.97(2C), 105.87, 74.85, 72.21, 70.20, 55.29(2C). HRMS (ESI) *m/z* calcd for $C_{28}H_{28}NO_5$ $[M + H]^+$ 458.1962, found 458.1951.

**2-((4,5-Bis((4-methoxybenzyl)oxy)pyridin-2-yl)(phenyl)methoxy)isoindoline-1,3-dione (53a).** Compound **53a** (4.1 g, 80%) was prepared from **52a** (3.9 g, 8.53 mmol), *N*-hydroxyphthalimide (1.7 g, 10.29 mmol), $PPh_3$ (3.4 g, 12.80 mmol) and DEAD (2.0 mL, 12.80 mmol) in the same manner as described for **S8**. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.76 (dd, $J$ = 5.6, 3.0 Hz, 2H), 7.70 (dd, $J$ = 5.6, 3.0Hz, 2H), 7.45 – 7.40 (m, 4H), 7.32 – 7.28 (m, 5H), 6.93 (d, $J$ = 8.7 Hz, 2H), 6.84 (d, $J$ = 8.7 Hz, 2H), 6.47(s, 1H), 5.36 – 5.22 (m, 2H), 5.05 (s, 2H), 3.83 (s, 3H), 3.78 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.59(2C), 159.58, 159.51, 155.61, 152.39, 144.86, 136.93, 136.56, 134.40(2C), 129.41(2C), 129.32(2C), 128.91, 128.86, 128.60, 128.42(2C), 128.25(2C), 127.98, 126.95, 123.48(2C), 114.06(2C), 113.94(2C), 107.48, 90.40, 71.98, 70.34, 55.31, 55.27. HRMS (ESI) *m/z* calcd for $C_{36}H_{31}N_2O_7$ $[M + H]^+$ 603.2126, found 603.2122.

**2-(((1,3-Dioxoisoindolin-2-yl)oxy)(phenyl)methyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (54a).** Compound **54a** (3.7 g, 88%) was prepared from **53a** (4.07 g, 6.75 mmol)

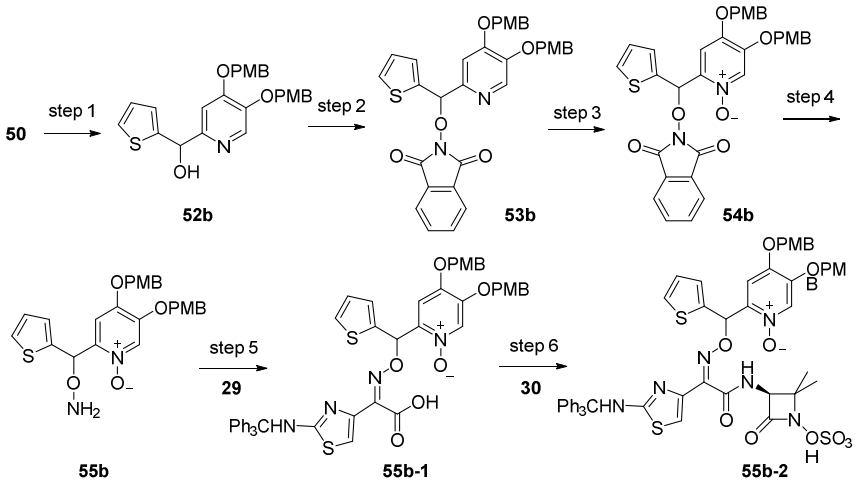
and *m*-CPBA (4.11 g, 20.26 mmol) in the same manner as described for **S5**. mp: 76 – 78 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.84 (s, 1H), 7.78 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.47 – 7.41 (m, 4H), 7.33 – 7.26 (m, 5H), 7.07 (s, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.86(d, *J* = 8.7 Hz, 2H), 5.45 – 5.29 (m, 2H), 4.98 (s, 2H), 3.83 (s, 3H), 3.78 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.51(2C), 159.81, 159.79, 149.20, 146.23, 142.38, 134.59(2C), 134.48, 132.87, 132.14, 132.07, 131.97, 131.95, 129.59, 129.39, 128.83, 128.56(2C), 128.46(2C), 128.00, 127.44, 123.62(2C), 114.17(2C), 114.15(2C), 108.52, 83.34, 71.96, 71.27, 55.34, 55.28. HRMS (ESI) *m/z* calcd for $C_{36}H_{31}N_2O_8$ $[M + H]^+$ 619.2075, found 619.2065.

**2-((Aminooxy)(phenyl)methyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (55a).** Compound **55a** (230 mg, 55%) was prepared from **54a** (530 mg, 0.86 mmol) and 85% hydrazine hydrate (0.07 mL, 1.22 mmol) in the same manner as described for **31b**. mp: 175 – 178 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.40 – 7.29 (m, 9H), 6.98 (s, 1H), 6.93 – 6.89 (m, 4H), 6.26 (s, 1H), 5.48 (s, 2H), 5.16 (s, 2H), 5.01 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 159.84, 159.76, 148.14, 145.93, 144.50, 137.36, 129.32(2C), 129.28(2C), 128.49(2C), 128.42, 128.38, 127.58(2C), 127.33, 127.23, 114.20(2C), 114.16(2C), 107.52, 81.55, 71.97, 71.15, 55.32(2C). HRMS (ESI) *m/z* calcd for $C_{28}H_{29}N_2O_6$ $[M + H]^+$ 489.2020, found 489.2011.

**(*Z*)-2-((((Carboxy(2-(tritylamino)thiazol-4-yl)methylene)amino)oxy)(phenyl)methyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (55a-1).** Compound **55a-1** (570 mg, 70%) was prepared from **55a** (448 mg, 0.92 mmol) and **29** (344 mg, 0.83 mmol) in the same manner as described for **32a**. mp: 140 – 142 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.89 (s, 1H), 8.07 (s, 1H), 7.41 – 7.15 (m, 24H), 6.97 – 6.84 (m, 5H)，6.56 (s, 1H), 5.14 (s, 2H), 5.05 (s, 2H), 3.74 (s, 3H), 3.73 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{52}H_{43}N_4O_8S$ $[M - H]^-$ 883.2807, found 883.2807.

**2-(((((*Z*)-2-(((*S*)-2,2-Dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxo-1-(2-(tritylamino)thiazol-4-yl)ethylidene)amino)oxy)(phenyl)methyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (55a-2).** Compound **55a-2** (a mixture of diastereomer (approximately 1:1), 240 mg, 66%) was prepared from **55a-1** (300 mg, 0.34 mmol) and **30** (92.6 mg, 0.44 mmol) in the same manner as described for **33a**. mp: 177 °C decomp. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.71 (d, *J* = 7.6 Hz, 1/2H), 9.65 (d, *J* = 8.0 Hz, 1/2H), 8.94 (s, 1/2H), 8.93 (s, 1/2H), 8.07 (s, 1/2H), 8.05 (s, 1/2H), 7.39 – 7.09 (m, 24H), 6.96 (s, 1H), 6.94 (s, 1H), 6.93 (s, 1/2H), 6.91 (s, 1/2H), 6.88 (s, 1/2H), 6.86 (s, 1/2H), 6.82 (s, 1/2H), 6.78 (s, 1/2H), 6.54 (s, 1H), 5.30 – 5.17 (m, 2H), 5.10 – 5.04 (m, 2H), 4.60 (dd, *J* = 7.6, 3.5 Hz, 1H), 3.75 – 3.73 (m, 6H), 1.40 (s, 3/2H), 1.36 (s, 3/2H), 1.11 (s, 3/2H), 0.88 (s, 3/2H). HRMS (ESI) *m/z* calcd for $C_{57}H_{51}N_6O_{12}S_2$ $[M - H]^-$ 1075.3012, found 1075.3008.

**Preparation of intermediate 55b-2.**




**(4,5-Bis((4-methoxybenzyl)oxy)pyridin-2-yl)(thiophen-2-yl)methanol (52b).** Under argon atmosphere, a solution of thiophene (2.1 mL, 26.30 mmol) in dry THF (10 mL) was cooled to −78 °C, a solution of *n*-butyllithium in *n*-hexane (3.3 mL, 7.92 mmol) was added dropwise to keep the reaction mixture below −70 °C. After addition, the resulting mixture was stirred for 30 min. After which time, a solution of **50** (1.0 g, 2.63 mmol) in dry THF (10 mL) was added dropwise and stirred for 3 h. The reaction was allowed to warm to 0 °C and quenched by slow addition of saturated aqueous $NH_4Cl$. The solution was extracted with ethyl acetate, washed with brine, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated in vacuo. The resulting residue was purified by chromatography on silica gel with petroleum/ethyl acetate to afford **52b** as a light yellow oil (0.99 g, 81%). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.32 (d, *J* = 8.8 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 2H), 7.24 (dd, *J* = 4.5, 1.8 Hz, 1H), 6.95 – 6.92 (m, 2H), 6.91 – 6.85 (m, 4H), 6.81 (s, 1H), 5.88 (s, 1H), 5.08 (s, 2H), 5.05 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 159.61, 159.53, 156.02, 154.83, 147.47, 144.63, 135.49, 129.29(2C), 129.16(2C), 128.51, 127.47, 126.51, 125.46, 124.93, 114.05(2C), 113.95(2C), 105.73, 72.15, 70.72, 70.27, 55.27(2C). HRMS (ESI) *m/z* calcd for $C_{26}H_{26}NO_5S$ $[M + H]^+$ 464.1526, found 464.1514.

**2-((4,5-Bis((4-methoxybenzyl)oxy)pyridin-2-yl)(thiophen-2-yl)methoxy)isoindoline-1,3-dione (53b).** Compound **53b** (2.91 g, 82%) was prepared from **52b** (2.7 g, 5.82 mmol), *N*-hydroxyphthalimide (2.85 g, 17.48 mmol) , $PPh_3$ (4.55 g, 17.48 mmol) and DIAD (3.4 mL, 17.48 mmol) in the same manner as described for **S8**. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.78 – 7.75 (m, 2H), 7.72 (s, 1H), 7.72 – 7.69 (m, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 7.35 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.99 (m, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.93 – 6.90 (m, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.63 (d, *J* = 0.7 Hz, 1H), 5.33 (d, *J* = 11.7 Hz, 1H), 5.26 (d, *J* = 11.7 Hz, 1H), 5.07 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H).

**2-(((1,3-Dioxoisoindolin-2-yl)oxy)(thiophen-2-yl)methyl)-4,5-bis((4-methoxybenzyl)oxy) pyridine 1-Oxide (54b).** Compound **54b** (1.6 g, 54%) was prepared from **53b** (2.91 g, 4.78 mmol) and *m*-CPBA (1.94 g, 9.56 mmol) in the same manner as described for **S5**. mp: 77 –

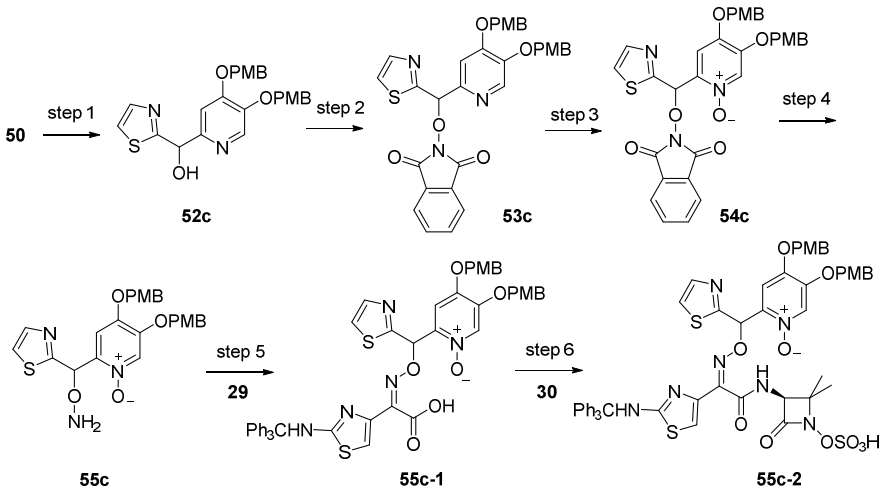
78 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.85 (m, 2H), 7.81 – 7.78 (m, 2H), 7.76 –7.71 (m, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.35 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.31 – 7.27 (m, 3H), 7.08 – 7.05 (m, 1H), 6.96 – 6.92 (m, 3H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.39 (d, *J* = 11.6 Hz, 1H), 5.30 (d, *J* = 11.6 Hz, 1H), 5.00 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H). MS (ESI): *m/z* 625 $[M + H]^+$.

**2-((Aminooxy)(thiophen-2-yl)methyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (55b).** Compound **55b** (0.98 g, 83%) was prepared from **54b** (1.5 g, 2.45 mmol) and 85% hydrazine hydrate (0.15 mL, 2.57 mmol) in the same manner as described for **31b**. mp: 152 – 153 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.35 – 7.31 (m, 4H), 7.29 (dd, J = 5.1, 0.9 Hz, 1H), 7.05 (dt, J = 3.6, 0.9 Hz, 1H), 7.02 (s, 1H), 6.96 (dd, J = 5.1, 3.5 Hz, 1H), 6.93 – 6.89 (m, 4H), 6.52 (s, 1H), 5.52 (s, 2H), 5.16 (s, 2H), 5.03 (s, 2H), 3.83 (s, 6H). MS (ESI): *m/z* 495 $[M + H]^+$.

**(*Z*)-2-((((Carboxy(2-(tritylamino)thiazol-4-yl)methylene)amino)oxy)(thiophen-2-yl)methyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (55b-1).** Compound **55b-1** (474 mg, 58%) was prepared from **55b** (450 mg, 0.91 mmol) and **29** (339 mg, 0.81 mmol) in the same manner as described for **32a**. mp: 165 – 167 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.90 (s, 1H), 8.12 (s, 1H), 7.54 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.36 – 7.24 (m, 18H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.99 – 6.90 (m, 4H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.77 (s, 1H), 5.15 – 5.04 (m, 4H), 3.75 (s, 3H), 3.73 (s, 3H). MS (ESI): *m/z* 889 $[M - H]^-$.

**2-(((((*Z*)-2-(((*S*)-2,2-Dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxo-1-(2-(tritylamino)thiazol-4-yl)ethylidene)amino)oxy)(thiophen-2-yl)methyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (55b-2).** Compound **55b-2** (a mixture of diastereomer (approximately 1:1), 500 mg, 91%) was prepared from **55b-1** (450 mg, 0.51 mmol) and **30** (160 mg, 0.76 mmol) in the same manner as described for **33a**. mp: 179 °C decomp. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.72 (d, *J* = 7.7 Hz, 1/2H), 9.69 (d, *J* = 7.7 Hz, 1/2H), 8.95 (s, 1H), 8.13 (s, 1/2H), 8.10 (s, 1/2H), 7.53 (dd, *J* = 5.1, 1.2 Hz, 1/2H), 7.51 (dd, *J* = 5.1, 1.3 Hz, 1/2H), 7.40 – 7.26 (m, 18H), 7.25 – 7.21 (m, 2H), 7.11 (s, 1/2H), 6.98 – 6.93 (m, 2H), 6.92 (s, 1/2H), 6.90 (s, 1/2H), 6.88 (s, 1/2H), 6.87 – 6.84 (m, 1H), 6.83 (d, *J* = 0.7 Hz, 1/2H), 6.79 (d, *J* = 0.7 Hz, 1/2H), 6.78 (s, 1/2H), 6.75 (d, *J* = 0.8 Hz, 1/2H), 5.29 – 5.14 (m, 2H), 5.09 (d, *J* = 7.4 Hz, 2H), 4.62 (d, *J* = 7.7 Hz, 1/2H), 4.59 (d, *J* = 7.6 Hz, 1/2H), 3.75 (d, *J* = 1.3 Hz, 3H), 3.74 (d, *J* = 1.1 Hz, 3H), 1.40 (s, 3/2H), 1.39 (s, 3/2H), 1.16 (s, 3/2H), 0.99 (s, 3/2H). MS (ESI): *m/z* 1081 $[M - H]^-$.

**Preparation of intermediate 55c-2.**




**(4,5-Bis((4-methoxybenzyl)oxy)pyridin-2-yl)(thiazol-2-yl)methanol (52c).** A solution of **50** (2.5 g, 6.59 mmol) in dry THF (20 mL) was treated with 2-bromothiazole (3.6 mL, 39.54 mmol), and then the solution was cooled to −78 °C. Under argon atmosphere, a solution of *n*-butyllithium in *n*-hexane (2.7 mL, 6.48 mmol) was added dropwise to keep the reaction mixture below −70 °C. After addition, the resulting mixture was stirred for 1 h. The reaction mixture was allowed to warm to 0 °C and quenched by slow addition of saturated aqueous $NH_4Cl$. The solution was extracted with ethyl acetate, washed with brine, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated in vacuo. The resulting residue was purified by chromatography on silica gel with petroleum/ethyl acetate to give **52c** as a light yellow oil (1.68 g, 55%). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.74 (d, *J* = 3.3 Hz, 1H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 3.3 Hz, 1H), 7.24 (s, 1H), 6.88 (t, *J* = 8.7 Hz, 4H), 5.96 (s, 1H), 5.11 (s, 2H), 5.07 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H). $^{13}$C NMR (126 MHz, CDCl3) δ 159.63, 159.52, 156.35, 151.97, 144.96, 142.51, 135.13, 130.88, 129.35(2C), 129.23(2C), 128.42, 127.40, 119.26, 114.00(2C), 113.95(2C), 105.84, 72.10, 70.35, 55.25(2C). HRMS (ESI) *m/z* calcd for $C_{25}H_{25}N_2O_5S$ $[M + H]^+$ 465.1479, found 465.1482.

**2-((4,5-Bis((4-methoxybenzyl)oxy)pyridin-2-yl)(thiazol-2-yl)methoxy)isoindoline-1,3-dione (53c).** Compound **53c** (0.8 g, 36%) was prepared from **52c** (1.68 g, 3.61 mmol), *N*-hydroxyphthalimide (1.77 g, 10.85 mmol), $PPh_3$ (4.73 g, 18.05 mmol) and DEAD (2.83 mL, 18.05 mmol) in the same manner as described for **S8**. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.77 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.74 (d, *J* = 3.2 Hz, 1H), 7.71 (dd, *J* = 5.6, 3.0 Hz, 3H), 7.61 (s, 1H), 7.44 (d, *J* = 3.0 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.62 (s, 1H), 5.24 (d, *J* = 11.5 Hz, 1H), 5.21 (d, *J* = 11.5 Hz, 1H), 5.08 (s, 2H), 3.82 (s, 3H), 3.78 (s, 3H). MS (ESI): *m/z* 610 $[M + H]^+$.

**2-(((1,3-Dioxoisoindolin-2-yl)oxy)(thiazol-2-yl)methyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (54c).** Compound **54c** (328 mg, 40%) was prepared from **53c** (800 mg, 1.31

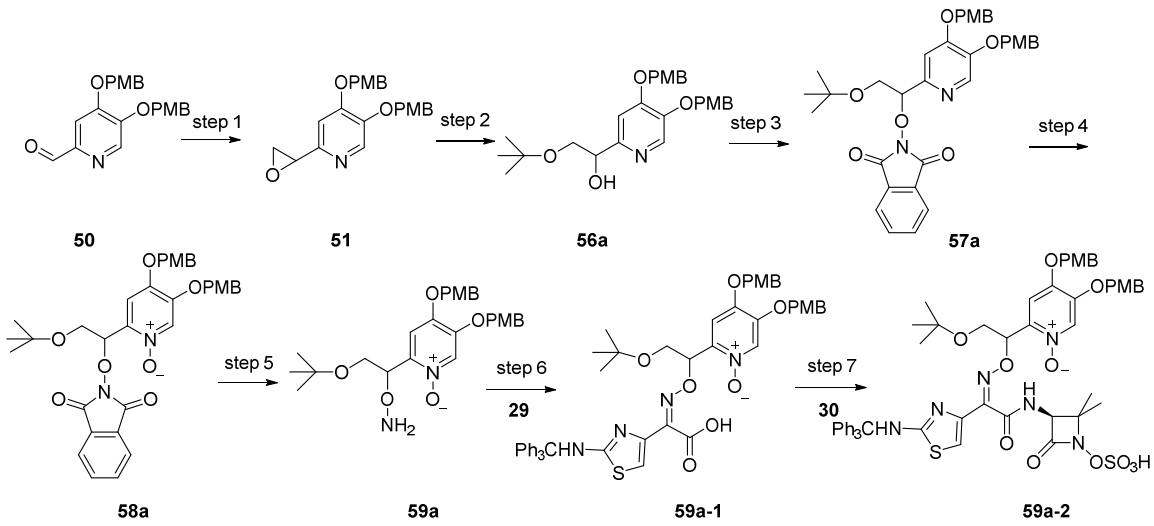
mmol) and *m*-CPBA (798 mg, 3.93 mmol) in the same manner as described for **S5**. mp: 75 – 76 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.87 (s, 1H), 7.82 (dd, *J* = 5.5, 3.1 Hz, 1H), 7.80 (d, *J* = 3.2 Hz, 1H), 7.75 (dd, *J* = 5.5, 3.1 Hz, 1H), 7.46 (d, *J* = 3.2 Hz, 1H), 7.43 (d, *J* = 8.6 Hz, 1H), 7.29 – 7.26 (m, 3H), 6.93 (d, *J* = 8.6 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 5.37 – 5.22 (m, 1H), 5.01 (s, 1H), 3.83 (s, 3H), 3.79 (s, 3H). MS (ESI): *m/z* 626 $[M + H]^+$.

**2-((Aminooxy)(thiazol-2-yl)methyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (55c).** Compound **55c** (176 mg, 65%) was prepared from **54c** (340 mg, 0.54 mmol) and 85% hydrazine hydrate (0.04 mL, 0.69 mmol) in the same manner as described for **31b**. mp: 127 – 129 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.77 (d, J = 3.3 Hz, 1H), 7.33 (d, J = 3.3 Hz, 1H), 7.32 – 7.27 (m, 4H), 7.07 (s, 1H), 6.90 – 6.86 (m, 4H), 6.57 (s, 1H), 5.73 (s, 2H), 5.16 – 5.06 (m, 2H), 5.01 (s, 2H), 3.80 (s, 3H), 3.80 (s, 3H). MS (ESI): *m/z* 496 $[M + H]^+$.

**(*Z*)-2-((((Carboxy(2-(tritylamino)thiazol-4-yl)methylene)amino)oxy)(thiazol-2-yl)methyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (55c-1).** Compound **55c-1** (400 mg, 45%) was prepared from **55c** (495 mg, 1.0 mmol) and **29** (373 mg, 0.90 mmol) in the same manner as described for **32a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.69 (s, 1H), 8.05 (s, 1H), 7.79 – 7.74 (m, 1H), 7.42 – 7.20 (m, 20H), 6.96 – 6.91 (m, 2H), 6.86 – 6.80 (m, 2H), 6.75 (s, 1H), 6.70 (s, 1H), 5.35 – 5.10 (m, 2H), 5.07 (s, 2H), 3.75 (s, 3H), 3.73 (s, 3H). MS (ESI): *m/z* 890 $[M - H]^-$.

**2-(((((*Z*)-2-(((*S*)-2,2-Dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxo-1-(2-(tritylamino)thiazol-4-yl)ethylidene)amino)oxy)(thiazol-2-yl)methyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (55c-2).** Compound **55c-2** (a mixture of diastereomer (approximately 1:1), 230 mg, 47%) was prepared from **55c-1**(400 mg, 0.45 mmol) and **30** (141 mg, 0.67 mmol) in the same manner as described for **33a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.73 (t, *J* = 7.0 Hz, 1H), 8.94 (d, *J* = 2.2 Hz, 1H), 8.14 (s, 1/2H), 8.12 (s, 1/2H), 7.82 – 7.76 (m, 2H), 7.39 – 7.15 (m, 20H), 6.97 – 6.92 (m, 2H), 6.92 – 6.87 (m, 2H), 6.86 – 6.82 (m, 2H), 5.25 – 5.05 (m, 4H), 4.57 (d, *J* = 7.6 Hz, 1/2H), 4.54 (d, *J* = 7.6 Hz, 1/2H), 3.74 (s, 3H), 3.72 (s, 3H), 1.35 (s, 3H), 1.07 (s, 3/2H), 0.88 (s, 3/2H). MS (ESI): *m/z* 1082 $[M - H]^-$.

**Preparation of intermediate 59a-2.**




**4,5-Bis((4-methoxybenzyl)oxy)-2-(oxiran-2-yl)pyridine (51).** A solution of trimethylsulfoxonium iodide (6.4 g, 29.00 mmol) in DMSO (60 mL) was cooled to 0 °C, then sodium hydride 60 pecent dispersion in oil (1.16 g, 29.00 mmol) was added and stirred at 0 °C for 0.5 h. Compound **50** (10.0 g, 26.46 mmol) was dissolved in DMSO (40 mL), which was added dropwise to the reaction mixture at the same temperature. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Reaction was monitored by TLC, after completion of the reaction, the reaction mixture was quenched by addition of water (10 mL) in an ice bath and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated in vacuo. The resulting residue was purified by chromatography on silica gel with petroleum/ethyl acetate to afford **51** as a white solid (4.7 g, 45%). mp: 76 – 78 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.10 (s, 2H), 5.07 (s, 2H), 3.91 (dd, *J* = 4.1, 2.5 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.11 (dd, *J* = 5.6, 4.1 Hz, 1H), 2.79 (dd, *J* = 5.7, 2.5 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 159.67, 159.54, 156.25, 152.10, 144.74, 137.80, 129.37(2C), 129.18(2C), 128.59, 127.67, 114.08(2C), 113.95(2C), 104.07, 72.29, 70.23, 55.31, 52.88, 50.34(2C). HRMS (ESI) *m/z* calcd for $C_{23}H_{24}NO_5$ $[M + H]^+$ 394.1649, found 394.1657.

**1-(4,5-Bis((4-methoxybenzyl)oxy)pyridin-2-yl)-2-(*tert*-butoxy)ethan-1-ol (56a).** A solution of **51** (1.5 g, 3.82 mmol) in *tert*-butanol (15 mL) was treated with potassium *tert*-butanolate (2.13 g, 19.10 mmol), and the reaction mixture was heated to 50 °C and stirred overnight. After completion of the reaction, the reaction mixture was cooled to room temperature and diluted with water (30 mL). The resulting solution was extracted with ethyl acetate twice. The combined organic layers were washed with brine solution, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated in vacuo. The resulting residue was purified by chromatography on silica gel with petroleum/ethyl acetate to afford **56a** as an oil (600mg,

34%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.36 (d, *J* = 8.6 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.10 (s, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.13 (s, 2H), 5.07 (s, 2H), 4.73 – 4.67 (m, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.56 (dd, *J* = 9.0, 4.9 Hz, 1H), 3.44 (dd, *J* = 9.0, 7.4 Hz, 1H), 1.16 (s, 9H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 159.63, 159.50, 155.94, 155.20, 144.15, 136.87, 129.37(2C), 129.17(2C), 128.77, 127.86, 114.06(2C), 113.92(2C), 105.76, 73.44, 72.62, 72.38, 70.16, 66.45, 55.31(2C), 27.57(3C). HRMS (ESI) *m/z* calcd for $C_{27}H_{34}NO_6$ $[M + H]^+$ 468.2381, found 468.2379.

**2-(1-(4,5-Bis((4-methoxybenzyl)oxy)pyridin-2-yl)-2-(*tert*-butoxy)ethoxy)isoindoline-1,3-dione (57a).** Compound **57a** (600 mg, 77%) was prepared from **56a** (600 mg, 1.28 mmol), *N*-hydroxyphthalimide (314 mg, 1.92 mmol), $PPh_3$ (499 mg, 1.92 mmol) and DIAD (0.24 mL, 1.92 mmol) in the same manner as described for **S8**. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.80 –7.78 (m, 2H), 7.72 – 7.69 (m, 2H), 7.52 (s, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.52 – 5.48 (m, 1H), 5.28 – 5.18 (m, 2H), 5.07 (s, 2H), 3.90 – 3.88 (m, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 1.02 (s, 9H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.51(2C), 159.62, 159.50, 155.74, 150.76, 144.85, 136.47, 134.24(2C), 129.42(2C), 129.35(2C), 129.09(2C), 128.55, 127.93, 123.35(2C), 114.03(2C), 113.92(2C), 108.20, 88.63, 73.49, 72.05, 70.40, 64.12, 55.26(2C), 27.13(3C). HRMS (ESI) *m/z* calcd for $C_{35}H_{37}N_2O_8$ $[M + H]^+$ 613.2544, found 613.2528.

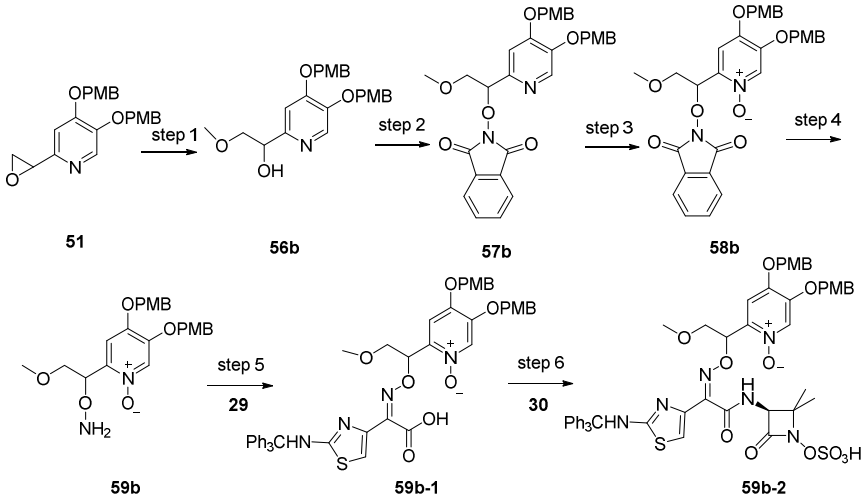
**2-(2-(*tert*-Butoxy)-1-((1,3-dioxoisoindolin-2-yl)oxy)ethyl)-4,5-bis((4-methoxybenzyl)oxy) pyridine 1-Oxide (58a).** Compound **58a** (540 mg, 88%) was prepared from **57a** (600 mg, 0.98 mmol) and *m*-CPBA (604 mg, 2.94 mmol) in the same manner as described for **S5**. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.80 – 7.78 (m, 2H), 7.77 (s, 1H), 7.74 – 7.71 (m, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 3H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.09 (dd, *J* = 4.6, 2.3 Hz, 1H), 5.40 – 5.28 (m, 2H), 5.06 – 4.97 (m, 2H), 4.11 (dd, *J* = 11.5, 2.4 Hz, 1H), 3.87 (dd, *J* = 11.5, 4.6 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 1.04 (s, 9H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.38(2C), 159.78, 159.73, 148.69, 145.90, 140.77, 134.52(2C), 129.48(2C), 129.35(2C), 128.91(2C), 127.96, 127.67, 127.21, 123.55(2C), 114.12(2C), 114.10(2C), 109.65, 82.95, 73.89, 71.99, 71.18, 61.17, 55.29(2C), 27.16(3C). HRMS (ESI) *m/z* calcd for $C_{35}H_{36}N2O_9$ $[M + H]^+$ 629.2494, found 629.2492.

**2-(1-(Aminooxy)-2-(*tert*-butoxy)ethyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (59a).** Compound **59a** (415 mg, 99%) was prepared from **58a** (530 mg, 0.84 mmol) and 85% hydrazine hydrate (0.05 mL, 0.87 mmol) in the same manner as described for **31b**. mp: 118 – 120 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 6.95 (s, 1H), 6.94 – 6.89 (m, 4H), 5.41 (s, 2H), 5.32 (dd, J = 5.4, 2.4 Hz, 1H), 5.23 – 5.10 (m, 2H), 5.05 (s, 2H), 3.86 – 3.84 (m, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.60 (dd, J = 10.8, 5.4 Hz, 1H), 1.11 (s, 9H). $^{13}$C NMR (126 MHz, DMSO) δ 159.66(2C), 147.23, 145.29, 143.06, 130.14(2C), 130.10(2C), 128.31, 128.24, 127.95, 114.35(4C), 108.34, 80.98, 73.05, 71.10, 70.65, 61.30, 55.52(2C), 27.61(3C). HRMS (ESI) *m/z* calcd for $C_{27}H_{35}N_2O_7$ $[M + H]^+$ 499.2439, found 499.2426.

**(*Z*)-2-(2-(*tert*-Butoxy)-1-(((carboxy(2-(tritylamino)thiazol-4-yl)methylene)amino)oxy)ethyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (59a-1).** Compound **59a-1** (584 mg, 80%) was prepared from **59a** (408 mg, 0.82 mmol) and **29** (323 mg, 0.78 mmol) in the same manner as described for **32a**. mp: 137 – 139 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.88 (s, 1H), 8.10 (s, 1H), 7.35 – 7.14 (m, 19H), 7.04 (s, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.91 (s, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.60 (dd, *J* = 6.5, 2.1 Hz, 1H), 5.11 – 4.97 (m, 4H), 3.74 (s, 3H), 3.71 (s, 3H), 3.66 (dd, *J* = 11.1, 2.1 Hz, 1H), 3.50 (dd, *J* = 11.2, 6.6 Hz, 1H), 1.03 (s, 9H). HRMS (ESI) *m/z* calcd for $C_{51}H_{49}N_4O_9S$ [M − H] $^-$ 893.3226, found 893.3233.

**2-(2-(*tert*-Butoxy)-1-((((*Z*)-2-(((*S*)-2,2-dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxo-1-(2-(tritylamino)thiazol-4-yl)ethylidene)amino)oxy)ethyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (59a-2).** Compound **59a-2** (a mixture of diastereomer (approximately 1:1), 600 mg, 92%) was prepared from **59a-1** (540 mg, 0.60 mmol) and **30** (190 mg, 0.90 mmol) in the same manner as described for **33a**. mp: 110 – 112 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.71 (d, *J* = 7.6 Hz, 1/2H), 9.68 (d, *J* = 7.8 Hz, 1/2H), 8.91 (s, 1H), 8.12 (s, 1/2H), 8.08 (s, 1/2H), 7.37 – 7.25 (m, 15H), 7.24 – 7.17 (m, 4H), 7.08 (s, 1/2H), 6.97 (s, 1/2H), 6.93 (dd, *J* = 8.7, 1.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 6.79 (s, 1/2H), 6.72 (s, 1/2H), 5.63 (dd, *J* = 5.9, 2.2 Hz, 1/2H), 5.57 (dd, *J* = 5.9, 2.4 Hz, 1/2H), 5.29 – 5.19 (m, 1H), 5.11 – 4.98 (m, 3H), 4.64 (d, *J* = 7.8 Hz, 1/2H), 4.60 (d, *J* = 7.6 Hz, 1/2H), 3.74 (s, 3/2H), 3.73 (s, 3/2H), 3.72 (s, 3/2H), 3.71 (s, 3/2H), 3.62 – 3.57 (m, 1H), 3.54 – 3.47 (m, 1H), 1.47 (s, 3/2H), 1.44 (s, 3/2H), 1.34 (s, 3/2H), 1.33 (s, 3/2H), 0.99 (s, 9/2H), 0.97 (s, 9/2H). HRMS (ESI) *m/z* calcd for $C_{56}H_{57}N_6O_{13}S_2$ [M − H] $^-$ 1085.3431, found 1085.3429.

**Preparation of intermediate 59b-2.**




**1-(4,5-Bis((4-methoxybenzyl)oxy)pyridin-2-yl)-2-methoxyethan-1-ol (56b).** A solution of **51** (2.47 g, 6.28 mmol) in methanol (20 mL) was treated with sodium methanolate (12.5 mL, 62.80 mmol), and then the reaction mixture was stirred at room temperature overnight. After completion of the reaction, the reaction mixture was diluted with water and extracted with

ethyl acetate twice. The combined organic layers were washed with brine solution, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated in vacuo. The resulting residue was purified by chromatography on silica gel with petroleum/ethyl acetate to afford **56b** as an oil (1.87 g, 70%). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.36 (d, *J* = 8.6 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.01 (s, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.13 (s, 2H), 5.07 (s, 2H), 4.78 (dd, *J* = 7.0, 4.8 Hz, 1H), 3.97 (d, *J* = 7.7 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.60 (dd, *J* = 9.8, 4.5 Hz, 1H), 3.53 (dd, *J* = 9.8, 6.8 Hz, 1H), 3.38 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 159.65, 159.53, 156.05, 154.33, 144.35, 136.62, 129.33(2C), 129.21(2C), 128.70, 127.76, 114.07(2C), 113.95(2C), 105.52, 72.31, 71.83, 70.24, 59.20, 55.32, 55.29. HRMS (ESI) *m/z* calcd for $C_{24}H_{28}NO_6$ $[M + H]^+$ 426.1911, found 426.1916.

**2-(1-(4,5-Bis((4-methoxybenzyl)oxy)pyridin-2-yl)-2-methoxyethoxy)isoindoline-1,3-dion e (57b).** Compound **57b** (2.0 g, 80%) was prepared from **56b** (1.87 g, 4.40 mmol), *N*-hydroxyphthalimide (861 mg, 5.28 mmol), $PPh_3$ (1.73 g, 6.60 mmol) and DIAD (0.91 mL, 6.60 mmol) in the same manner as described for **S8**. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.81 – 7.76 (m, 2H), 7.73 – 7.70 (m, 2H), 7.56 (s, 1H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.55 (dd, *J* = 7.0, 3.2 Hz, 1H), 5.29 – 5.19 (m, 2H), 5.05 (s, 2H), 3.95 (dd, *J* = 11.5, 7.0 Hz, 1H), 3.86 (dd, *J* = 11.5, 3.2 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.39 (s, 3H). MS (ESI): *m/z* 571 $[M + H]^+$.

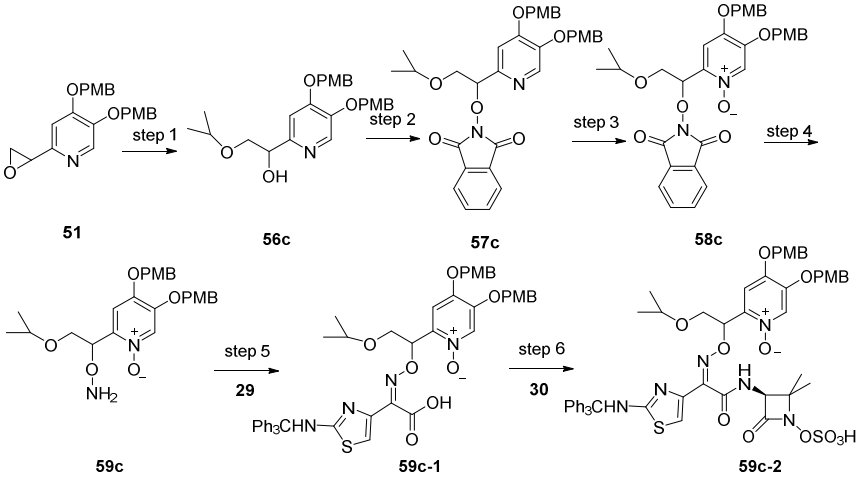
**2-(1-((1,3-Dioxoisoindolin-2-yl)oxy)-2-methoxyethyl)-4,5-bis((4-methoxybenzyl)oxy)pyri dine 1-Oxide (58b).** Compound **58b** (1.72 g, 84%) was prepared from **57b** (2.0 g, 3.51 mmol) and *m*-CPBA (2.13 g, 10.49 mmol) in the same manner as described for **S5**. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.81 (dd, *J* = 5.6, 3.1 Hz, 2H), 7.77 (s, 1H), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.23 (dd, *J* = 5.0, 2.5 Hz, 1H), 5.40 – 5.27 (m, 2H), 5.05 – 4.98 (m, 2H), 4.04 – 3.92 (m, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 3.44 (s, 3H). MS (ESI): *m/z* 587 $[M + H]^+$.

**2-(1-(Aminooxy)-2-methoxyethyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (59b).** Compound **59b** (1.02 g, 76%) was prepared from **58b** (1.72 g, 2.93 mmol) and 85% hydrazine hydrate (0.18 mL, 3.22 mmol) in the same manner as described for **31b**. mp: 108 – 110 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.36 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 6.95 – 6.88 (m, 5H), 5.43 (s, 2H), 5.40 (dd, J = 5.6, 2.5 Hz, 1H), 5.23 – 5.10 (m, 2H), 5.04 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.78 (dd, J = 10.8, 2.5 Hz, 1H), 3.65 (dd, J = 10.8, 5.7 Hz, 1H), 3.37 (s, 3H). MS (ESI): *m/z* 457 $[M + H]^+$.

**(*Z*)-2-(1-(((Carboxy(2-(tritylamino)thiazol-4-yl)methylene)amino)oxy)-2-methoxyethyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (50b-1).** Compound **59b-1** (810 mg, 85%) was prepared from **59b** (510 mg, 1.12 mmol) and **29** (440 mg, 1.06 mmol) in the same manner as described for **32a**. mp: 158 – 160 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.89 (s, 1H), 8.12 (s, 1H), 7.34 – 7.23 (m, 15H), 7.21 – 7.15 (m, 4H), 7.06 (s, 1H), 6.95 – 6.91 (m, 3H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.72 (dd, *J* = 6.3, 2.3 Hz, 1H), 5.06 (s, 2H), 5.03 (s, 2H), 3.74 (s, 3H), 3.71 (s, 3H), 3.69 – 3.57 (m, 2H), 3.25 (s, 3H). MS (ESI): *m/z* 851 $[M - H]^-$.

**2-(1-((((*Z*)-2-(((*S*)-2,2-Dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxo-1-(2-(trityl amino)thiazol-4-yl)ethylidene)amino)oxy)-2-methoxyethyl)-4,5-bis((4-methoxybenzyl)ox y)pyridine 1-Oxide (59b-2).** Compound **59b-2** (a mixture of diastereomer (approximately 1:1), 450 mg, 89%) was prepared from **59b-1** (410 mg, 0.48 mmol) and **30** (151 mg, 0.72 mmol) in the same manner as described for **33a**. mp: 161 °C decomp. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.78 (d, $J$ = 7.3 Hz, 1/2H), 9.73 (d, $J$ = 7.7 Hz, 1/2H), 8.94 (s, 1/2H), 8.93 (s, 1/2H), 8.21 (s, 1/2H), 8.19 (s, 1/2H), 7.39 – 7.26 (m, 15H), 7.24 – 7.18 (m, 4H), 7.13 (s, 1/2H), 7.06 (s, 1/2H), 6.94 (d, $J$ = 8.6 Hz, 2H), 6.89 (d, $J$ = 8.6 Hz,1H), 6.85 (d, $J$ = 8.6 Hz, 1H), 6.82 (s, 1/2H), 6.78 (s, 1/2H), 5.73 (dd, $J$ = 6.2, 2.3 Hz, 1/2H), 5.69 (dd, $J$ = 6.2, 2.4 Hz, 1/2H), 5.28 – 5.06 (m,4H), 4.66 (d, $J$ = 7.7 Hz, 1/2H), 4.59 (d, $J$ = 7.3 Hz, 1/2H), 3.74 (d, $J$ = 1.2 Hz, 3H), 3.72 (s, 3H), 3.69 – 3.47 (m, 2H), 3.24 (s, 3/2H), 3.20 (s, 3/2H), 1.47 (s, 3/2H), 1.44 (s, 3/2H), 1.34 (s, 3/2H), 1.31 (s, 3/2H). MS (ESI): *m/z* 1043 [M − H] $^-$.

**Preparation of intermediate 59c-2.**




**1-(4,5-Bis((4-methoxybenzyl)oxy)pyridin-2-yl)-2-isopropoxyethan-1-ol (56c).** A solution of isopropanol (2.9 mL, 38 mmol) in THF (30 mL) was cooled to 0 °C and treated with sodium hydride 60 pecent dispersion in oil (1.5 g, 38 mmol). The resulting mixture was stirred at 0 °C for 30 min, and then a solution of **51** (1.5 g, 3.8 mmol) in THF (10 mL) was added dropwise. After addition, the mixture was heated to 50 °C and stirred overnight. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine solution, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel with petroleum/ethyl acetate to afford **56c** as an oil (880 mg, 51%). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.35 (d, $J$ = 8.6 Hz, 2H), 7.31 (d, $J$ = 8.6 Hz, 2H), 7.08 (s, 1H), 6.91 (d, $J$ = 8.6 Hz, 2H), 6.86 (d, $J$ = 8.6 Hz, 2H), 5.12 (s, 2H), 5.07 (s, 2H), 4.75 (dd, $J$ = 7.2, 4.7 Hz, 1H), 3.89 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.66 – 3.57 (m, 2H), 3.51 (dd, $J$ = 9.5, 7.3 Hz, 1H), 1.15 (d, $J$ = 2.1 Hz, 3H), 1.14 (d, $J$ = 2.1 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 159.64, 159.51, 156.01, 154.88, 144.22, 136.78, 129.36(2C),

129.18(2C), 128.74, 127.82, 114.07(2C), 113.93(2C), 105.62, 72.62, 72.36, 72.30, 72.21, 70.19, 55.31, 55.28, 22.15, 22.06. HRMS (ESI) *m/z* calcd for $C_{26}H_{32}NO_6$ $[M + H]^+$ 454.2224, found 454.2214.

**2-(1-(4,5-Bis((4-methoxybenzyl)oxy)pyridin-2-yl)-2-isopropoxyethoxy)isoindoline-1,3-dione (57c).** Compound **57c** (1.0 g, 86%) was prepared from **56c** (880 mg, 1.94 mmol), *N*-hydroxyphthalimide (475 mg, 2.91 mmol), $PPh_3$ (763 mg, 2.91 mmol) and DIAD (0.36 mL, 2.91 mmol) in the same manner as described for **S8**. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.80 – 7.77 (m, 2H), 7.72 – 7.69 (m, 2H), 7.53 (s, 1H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.54 (dd, *J* = 6.6, 3.4 Hz, 1H), 5.31 – 5.17 (m, 2H), 5.06 (s, 2H), 3.99 – 3.89 (m, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.60 (p, *J* = 6.1 Hz, 1H), 1.06 (d, *J* = 6.1 Hz, 3H), 1.00 (d, *J* = 6.1 Hz, 3H). MS (ESI): *m/z* 599 $[M + H]^+$.

**2-(1-((1,3-Dioxoisoindolin-2-yl)oxy)-2-isopropoxyethyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (58c).** Compound **58c** (900 mg, 88%) was prepared from **57c** (1.0 g, 1.67 mmol) and *m*-CPBA (1.02 g, 5.01 mmol) in the same manner as described for **S5**. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.81 – 7.77 (m, 2H), 7.75 (s, 1H), 7.74 – 7.71 (m, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.16 (dd, *J* = 5.2, 2.3 Hz, 1H), 5.40 – 5.24 (m, 2H), 5.07 – 4.95 (m, 2H), 4.12 – 4.06 (m, 1H), 3.88 (dd, *J* = 12.0, 5.3 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.73 – 3.62 (m, 1H), 1.15 (d, *J* = 6.1 Hz, 3H), 1.01 (d, *J* = 6.1 Hz, 3H). MS (ESI): *m/z* 615 $[M + H]^+$.

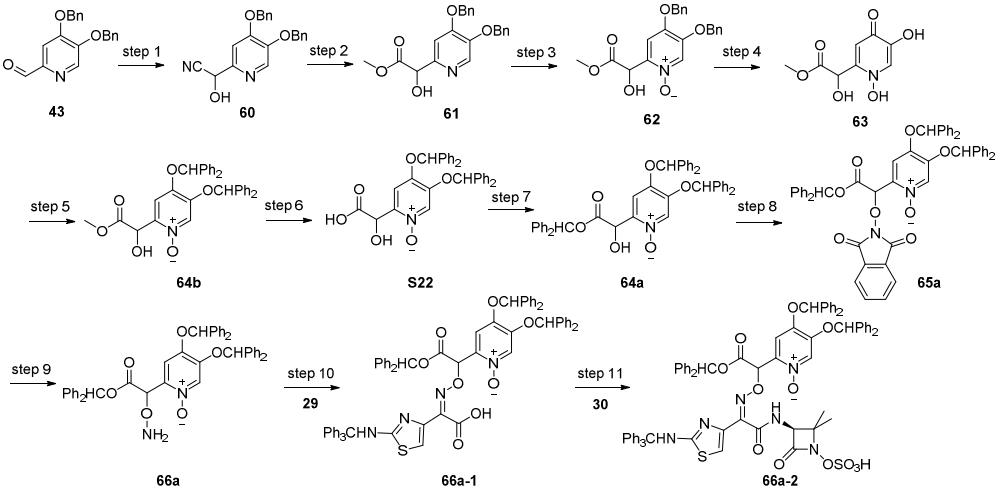
**2-(1-(Aminooxy)-2-isopropoxyethyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (59c).** Compound **59c** (590 mg, 83%) was prepared from **58c** (900 mg, 1.46 mmol) and 85% hydrazine hydrate (0.09 mL, 1.61 mmol) in the same manner as described for **31b**. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.35 – 7.29 (m, 4H), 6.92 (s, 1H), 6.91 – 6.87 (m, 4H), 5.41 (s, 2H), 5.34 (dd, J = 5.8, 2.4 Hz, 1H), 5.19 – 5.07 (m, 2H), 5.02 (s, 2H), 3.84 (dd, J = 11.1, 2.4 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.61 – 3.53 (m, 2H), 1.15 (d, J = 6.1 Hz, 3H), 1.04 (d, J = 6.1 Hz, 3H). MS (ESI): *m/z* 485 $[M + H]^+$.

**(*Z*)-2-(1-(((Carboxy(2-(tritylamino)thiazol-4-yl)methylene)amino)oxy)-2-isopropoxyethyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (59c-1).** Compound **50c-1** (990 mg, 92%) was prepared from **59c** (590 mg, 1.22 mmol) and **29** (479 mg, 1.16mmol) in the same manner as described for **32a**. mp: 131 – 133 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.66 (s, 1H), 8.04 (s, 1H), 7.75 (s, 1H), 7.39 – 7.18 (m, 19H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.72 (s, 1H), 5.59 – 5.53 (m, 1H), 5.28 (d, *J* = 11.8 Hz, 1H), 5.09 (d, *J* = 11.9 Hz, 1H), 5.05 (s, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 3.70 – 3.63 (m, 1H), 3.62 – 3.55 (m, 1H), 3.47 – 3.41 (m, 1H), 1.07 (d, *J* = 6.1 Hz, 3H), 1.00 (d, *J* = 6.0 Hz, 3H). MS (ESI): *m/z* 879 $[M - H]^-$.

**2-(1-((((*Z*)-2-(((*S*)-2,2-Dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxo-1-(2-(tritylamino)thiazol-4-yl)ethylidene)amino)oxy)-2-isopropoxyethyl)-4,5-bis((4-methoxybenzyl)oxy)pyridine 1-Oxide (59c-2).** Compound **59c-2** (a mixture of diastereomer (approximately

1:1), 525 mg, 88%) was prepared from **59c-1** (490 mg, 0.56 mmol) and **30** (174 mg, 0.83 mmol) in the same manner as described for **33a**. mp: 169 °C decomp. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.75 (d, $J$ = 7.4 Hz, 1/2H), 9.70 (d, $J$ = 7.8 Hz, 1/2H), 8.91 (d, $J$ = 2.9 Hz, 1H), 8.11 (s, 1/2H), 8.09 (s, 1/2H), 7.37 – 7.16 (m, 19H), 7.09 (s, 1/2H), 6.99 (s, 1/2H), 6.96 – 6.91 (m, 2H), 6.89 (d, $J$ = 8.7 Hz, 1/2H), 6.85 (d, $J$ = 8.7 Hz, 1/2H), 6.80 (d, $J$ = 0.7 Hz, 1/2H), 6.74 (d, $J$ = 0.7 Hz, 1/2H), 5.67 (dd, $J$ = 6.5, 2.1 Hz, 1/2H), 5.62 (dd, $J$ = 6.1, 2.3 Hz, 1/2H), 5.25 – 5.01 (m, 4H), 4.65 (d, $J$ = 7.7 Hz, 1/2H), 4.60 (d, $J$ = 7.4 Hz, 1/2H), 3.74 (d, $J$ = 1.6 Hz, 3H), 3.71 (s, 3H), 3.70 – 3.61 (m, 1H), 3.58 – 3.43 (m, 2H), 3.17 (s, 3/2H), 3.16 (s, 3/2H), 1.47 (s, 3/2H), 1.45 (s, 3/2H), 1.33 (s, 3/2H), 1.31 (s, 3/2H), 1.01 (dd, $J$ = 6.1, 3.1 Hz, 3H), 0.95 (d, $J$ = 6.1 Hz, 3/2H), 0.93 (d, $J$ = 6.2 Hz, 3/2H). MS (ESI): *m/z* 1071 [M − H] $^-$.

**Preparation of intermediate 66a-2.**




**2-(4,5-Bis(benzyloxy)pyridin-2-yl)-2-hydroxyacetonitrile (60).** A solution of **43** (31.8 g, 99.96 mmol) in THF (120 mL) and water (350 mL) was treated with $NaHSO_3$ (15.5 g, 149.97 mmol), the reaction mixture was cooled to 0 °C and stirred for 1 h. After which time, sodium cyanide (7.5 g, 150.96 mmol) was added in one portion and the solution was stirred at 0 °C overnight. The resulting precipitate was collected by filtration and washed with water, followed by petroleum to afford **60** as a light yellow solid (33 g, 96%). mp: 114 – 117 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.50 – 7.34 (m, 10H), 7.06 (s, 1H), 5.48 (s, 1H), 5.27(s, 2H), 5.24 (s, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 156.59, 147.00, 145.79, 135.97, 135.37, 135.02, 128.85(2C), 128.71(2C), 128.58, 128.36, 127.44(2C), 127.38(2C), 118.68, 105.50, 72.18, 70.87, 62.20.

**Methyl 2-(4,5-bis(benzyloxy)pyridin-2-yl)-2-hydroxyacetate (61).** Compound **60** (5.0 g, 14.4 mmol) was dissolved in 2 *M* methanol hydrochloride solution (40 mL). The resulting mixture was stirred at room temperature for 10 h and then concentrated in vacuo to remove methanol. Then the residue was treated with water (50 mL) and extracted with dichloromethane twice. The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated in vacuo. The resulting

residue was purified by chromatography on silica gel with dichloromethane/methanol to afford **61** as a light oil (5.1 g, 93%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.50 – 7.28 (m, 10H), 7.08 (s, 1H) , 5.26 (s, 2H), 5.23(s, 1H), 5.21 (s, 2H), 3.73 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.70, 155.97, 150.21, 145.19, 136.35, 135.68, 135.48, 128.74(2C), 128.64(2C), 128.36, 128.22, 127.45(2C), 127.31(2C), 106.08, 72.83, 72.20, 70.54, 52.80. MS (ESI): *m/z* 380 $[M + H]^+$.

**4,5-Bis(benzyloxy)-2-(1-hydroxy-2-methoxy-2-oxoethyl)pyridine 1-Oxide (62).** Compound **62** (3.79 g, 72%) was prepared from **61** (5.1 g, 13.46 mmol) and *m*-CPBA (5.46 g, 26.92 mmol) in the same manner as described for **S5**. mp: 156 – 158 °C.$^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.46 – 7.35 (m, 10H), 6.96 (s, 1H), 5.25 (q, $J$ = 12.0 Hz, 2H), 5.16 (s, 2H), 5.14 (s, 1H), 3.78 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 170.60, 149.22, 146.52, 141.01, 134.87, 134.85, 128.88(4C), 128.70, 128.68, 127.89, 127.41(2C), 127.35(2C), 109.51, 72.25, 71.56, 71.37, 52.94. HRMS (ESI) *m/z* calcd for $C_{22}H_{22}NO_6$ $[M + H]^+$ 396.1442, found 396.1442.

**Methyl 2-(1,5-dihydroxy-4-oxo-1,4-dihydropyridin-2-yl)-2-hydroxyacetate (63).** Compound **63** (crude material) was prepared from **62** (2.5 g, 6.32 mmol) and boron trichloride in *n*-hexane (19.0 mL, 19.00 mmol) in the same manner as described for **S6**. Compound **63** was used in the next step without purification.

**4,5-Bis(benzhydryloxy)-2-(1-hydroxy-2-methoxy-2-oxoethyl)pyridine 1-Oxide (64b).** Compound **64b** (2.12 g, 61% by two steps) was prepared from **63** (crude material) and diphenyldiazomethane (6.13 g, 31.6 mmol) in the same manner as described for **S7**. mp: 92 – 94 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.46 – 7.28 (m, 20H), 6.78 (s, 1H), 6.30 (s, 1H), 6.19(s, 1H), 4.93 (s, 1H) , 3.68 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 170.39, 149.43, 146.30, 141.37, 139.69, 139.61, 139.56, 139.51, 130.08, 129.00(2C), 128.90(2C), 128.87(2C), 128.84(2C), 128.51, 128.46, 128.44, 128.39, 126.65(4C), 126.51(4C), 111.72, 84.67, 83.86, 71.24, 52.88. HRMS (ESI) *m/z* calcd for $C_{34}H_{30}NO_6$ $[M + H]^+$ 548.2068, found 548.2084.

**4,5-Bis(benzhydryloxy)-2-(carboxy(hydroxy)methyl)pyridine 1-Oxide (S22).** A solution of **64b** (2.0 g, 3.65 mmol) in mixed solvent of THF (25 mL) and water (25 mL) was cooled to 0 °C, then lithium hydrate (306 mg, 7.30 mmol) was added in one portion. The resulting mixture was allowed to warm to room temperature and stirred for 1 h, and then the pH of solution was adjusted to 5 with 1 *M* aqueous hydrogen chloride. The resulting solution was extracted with ethyl acetate (60 mL × 2). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated in vacuo to afford **S22** (1.85 g, 95%) as a light yellow solid, which was used in the next step without purification. MS (ESI): *m/z* 532 $[M - H]^-$.

**4,5-Bis(benzhydryloxy)-2-(2-(benzhydryloxy)-1-hydroxy-2-oxoethyl)pyridine 1-Oxide (64a).** Compound **64a** (2.15 g, 84% by two steps) was prepared from **S22** (1.85 g, 3.47 mmol) and diphenyldiazomethane (2.12 g, 10.95 mmol) in the same manner as described for **S7**. mp: 85 – 88 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.52 – 7.02 (m, 30H), 6.88 (s, 1H),

6.76 (s, 1H), 6.22 (s, 1H), 6.17 (s, 1H), 4.94 (s, 1H). HRMS (ESI) *m/z* calcd for $C_{46}H_{38}NO_6$ $[M + H]^+$ 700.2694, found 700.2700.

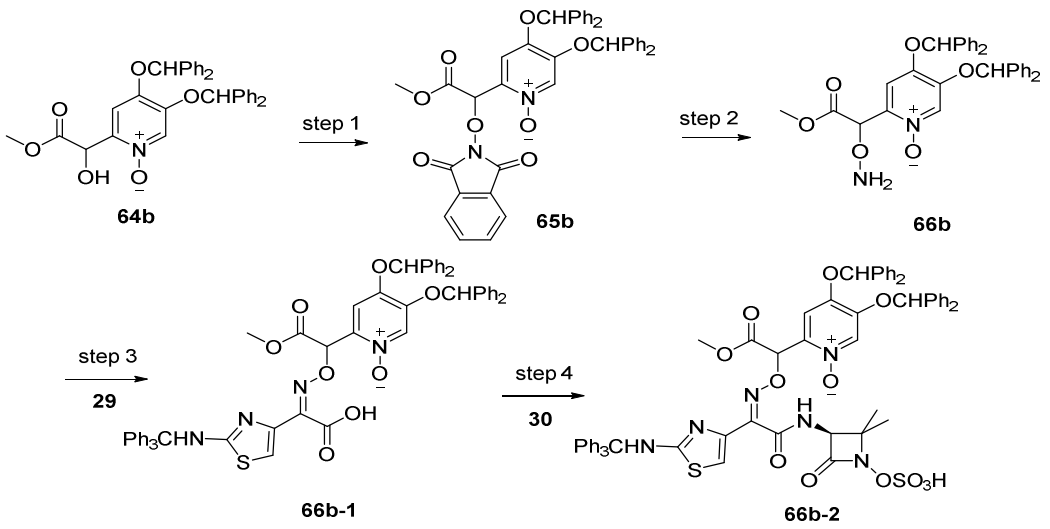
**4,5-Bis(benzhydryloxy)-2-(2-(benzhydryloxy)-1-((1,3-dioxoisoindolin-2-yl)oxy)-2-oxoethyl)pyridine 1-Oxide (65a).** Compound **65a** (1.2 g, 46%) was prepared from **64a** (2.15 g, 3.08 mmol), *N*-hydroxyphthalimide (1.51 g, 9.23 mmol), $PPh_3$ (2.42 g, 9.23 mmol) and DIAD (1.81 mL, 9.23 mmol) in the same manner as described for **S8**. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.73 – 7.70 (m, 4H), 7.46 – 7.15 (m, 30H), 6.83 (s, 1H), 6.39 (s, 1H), 6.26 (s, 1H), 6.18 (s, 1H), 5.35 (s, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) characteristic peaks: δ 168.93, 148.83, 146.27, 141.20, 139.61, 139.60, 139.57, 139.54, 139.52, 130.15, 128.94, 128.88, 128.47, 128.45, 128.40, 128.34, 128.04, 127.84, 127.27, 126.87, 126.68, 126.65, 126.53, 111.82, 84.64, 83.79, 78.03, 71.82. MS (ESI): *m/z* 845 $[M + H]^+$.

**2-(1-(Aminooxy)-2-(benzhydryloxy)-2-oxoethyl)-4,5-bis(benzhydryloxy)pyridine 1-Oxide (66a).** Compound **66a** (340 mg, 34%) was prepared from **65a** (1.2 g, 1.42 mmol) and 85% hydrazine hydrate (0.09 mL, 1.56 mmol) in the same manner as described for **31b**.

**(*Z*)-4,5-Bis(benzhydryloxy)-2-(2-(benzhydryloxy)-1-(((carboxy(2-(tritylamino)thiazol-4-yl)methylene)amino)oxy)-2-oxoethyl)pyridine 1-Oxide (66a-1).** Compound **66a-1** (370 mg, 70%) was prepared from **66a** (340 mg, 0.48 mmol) and **29** (199 mg, 0.48 mmol) in the same manner as described for **32a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.63 (s, 1H), 8.24 (s, 1H), 8.03 (s, 1H), 7.60 – 7.13 (m, 45H), 7.02 – 6.97 (m, 1H), 6.83 (s, 1H) , 6.72 (s, 1H), 6.70 (s, 1H), 5.72 (s, 1H). MS (ESI): *m/z* 1111 $[M + H]^+$.

**4,5-Bis(benzhydryloxy)-2-(2-(benzhydryloxy)-1-((((*Z*)-2-(((*S*)-2,2-dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxo-1-(2-(tritylamino)thiazol-4-yl)ethylidene)amino)oxy)-2-oxoethyl)pyridine 1-Oxide (66a-2).** Compound **66a-2** (a mixture of diastereomer (approximately 1:1), 321 mg, 76%) was prepared from **66a-1**(360 mg, 0.32 mmol) and **30** (101 mg, 0.48 mmol) in the same manner as described for **33a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.80 (d, *J* = 7.5 Hz, 1/2H), 9.73 (d, *J* = 7.2 Hz, 1/2H), 8.96 (s, 1/2H), 8.92 (s, 1/2H), 8.15 (s, 1/2H), 8.11 (s, 1/2H), 7.64 – 7.09 (m, 35H), 6.91 (s, 1/2H), 6.83 (s, 1/2H), 6.77 (s, 1H), 6.76 (s, 1/2H), 6.73 (s, 1/2H), 6.69 (s, 1/2H), 6.67 (s, 1/2H), 5.86 (s, 1H), 4.63 (d, *J* = 7.5 Hz, 1/2H), 4.56 (d, *J* = 7.2 Hz, 1/2H), 1.37 (s, 3H), 1.07 (s, 3/2H), 1.02 (s, 3/2H). MS (ESI): *m/z* 1301 $[M - H]^-$.

**Preparation of intermediate 66b-2.**



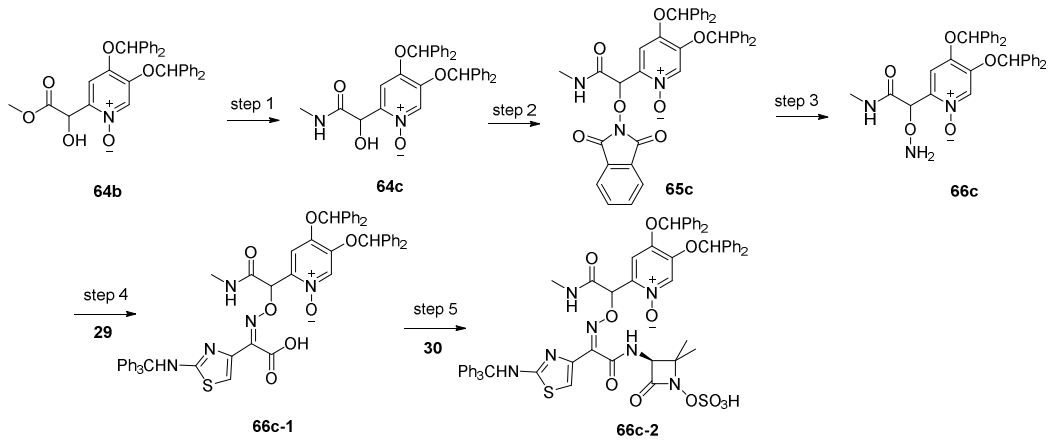

**4,5-Bis(benzhydryloxy)-2-(1-((1,3-dioxoisoindolin-2-yl)oxy)-2-methoxy-2-oxoethyl)pyridine 1-Oxide (65b).** Compound **65b** (1.5 g, 67%) was prepared from **64b** (1.79 g, 3.26 mmol), *N*-hydroxyphthalimide (1.6 g, 9.78 mmol), $PPh_3$ (2.57 g, 9.78 mmol) and DIAD (1.92 mL, 9.78 mmol) in the same manner as described for **S8**. mp: 79 – 81 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.84 – 7.74 (m, 4H), 7.52 – 7.26 (m, 21H), 6.50 (s,1H) , 6.21 (s, 1H), 6.09 (s, 1H), 3.72 (s, 3H). MS (ESI): *m/z* 693 $[M + H]^+$.

**2-(1-(Aminooxy)-2-methoxy-2-oxoethyl)-4,5-bis(benzhydryloxy)pyridine 1-Oxide (66b).** Compound **66b** (324 mg, 80%) was prepared from **65b** (500 mg, 0.72 mmol) and 85% hydrazine hydrate (0.04 mL, 0.72 mmol) in the same manner as described for **31b**. MS (ESI): *m/z* 563 $[M + H]^+$.

**(*Z*)-4,5-Bis(benzhydryloxy)-2-(1-(((carboxy(2-(tritylamino)thiazol-4-yl)methylene)amino)oxy)-2-methoxy-2-oxoethyl)pyridine 1-Oxide (66b-1).** Compound **66b-1** (200 mg, 41%) was prepared from **66b** (286 mg, 0.51 mmol) and **29** (211 mg, 0.51 mmol) in the same manner as described for **32a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.64 (s, 1H), 8.20 (s, 1H), 7.95 (s, 1H), 7.62 – 7.13 (m, 35H), 6.96 (s,1H), 6.84 (s, 1H), 6.68 (s, 1H), 5.55 (s, 1H), 3.60 (s, 3H). MS (ESI): *m/z* 957 $[M - H]^-$.

**4,5-Bis(benzhydryloxy)-2-(1-((((*Z*)-2-(((*S*)-2,2-dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxo-1-(2-(tritylamino)thiazol-4-yl)ethylidene)amino)oxy)-2-methoxy-2-oxoethyl)pyridine 1-Oxide (66b-2).** Compound **66b-2** (a mixture of diastereomer (approximately 1:1), 140 mg, 36%) was prepared from **66b-1** (320 mg, 0.33 mmol) and **30** (105 mg, 0.50 mmol) in the same manner as described for **33a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.84 (d, $J$ = 7.4 Hz, 1/2H), 9.67 (d, $J$ = 7.3 Hz, 1/2H), 8.97 (s, 1/2H), 8.91 (s, 1/2H), 8.05 (s, 1H), 7.62 – 7.03 (m, 35H), 6.94 (s, 1/2H), 6.86 (s, 1/2H), 6.79 – 6.64 (m, 2H), 5.73 (s, 1/2H), 5.69 (s, 1/2H), 4.65 (d, $J$ = 7.4 Hz, 1/2H), 4.60 (d, $J$ = 7.4 Hz, 1/2H), 3.53 (s, 3/2H), 3.52 (s, 3/2H), 1.46 (s, 3/2H), 1.45 (s, 3/2H), 1.19 – 1.12 (m, 3H). MS (ESI): *m/z* 1149 $[M - H]^-$.

**Preparation of intermediate 66c-2.**




**4,5-Bis(benzhydryloxy)-2-(1-hydroxy-2-(methylamino)-2-oxoethyl)pyridine 1-Oxide (64c).** A solution of **64b** (930 mg, 1.70 mmol) in methanol (10 mL) was treated with methylamine in methanol (4.5 mL, 34.00 mmol), and the resulting mixture was stirred at room temperature for 1 h. After which time, the solution was extracted with ethyl acetate twice. The combined organic layers were washed with brine solution, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel with petroleum/ethyl acetate to afford **64c** as a white solid (553 mg, 60%). mp: 78 – 80 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.35 (d, *J* = 4.8 Hz, 1H), 7.79 (s, 1H), 7.47 – 7.27 (m, 20H), 7.12(s, 1H), 6.33 (s, 1H), 6.19 (s, 1H), 5.45 (d, *J* = 4.1 Hz, 1H), 4.91 (d, *J* = 4.1 Hz, 1H), 2.75 (d, *J* = 4.8 Hz,3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 170.41, 150.37, 145.49, 144.41, 139.75, 139.70, 139.68, 139.65, 130.37, 128.88(4C), 128.85(4C), 128.41(2C), 128.39(2C), 126.75(2C), 126.69(2C), 126.59(4C), 108.44, 84.66, 83.44, 66.63, 26.48. HRMS (ESI) *m/z* calcd for $C_{34}H_{31}N_2O_5$ $[M + H]^+$ 547.2227, found 547.2234.

**4,5-Bis(benzhydryloxy)-2-(1-((1,3-dioxoisoindolin-2-yl)oxy)-2-(methylamino)-2-oxoethyl )pyridine 1-Oxide (65c).** Compound **65c** (420 mg, 62%) was prepared from **64c** (535 mg, 0.98 mmol), *N*-hydroxyphthalimide (480 mg, 2.94 mmol), $PPh_3$ (771 mg, 2.94 mmol) and DIAD (0.58 mL, 2.94 mmol) in the same manner as described for **S8**. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.20 (q, *J* = 4.8 Hz, 1H), 7.81 – 7.75 (m, 4H), 7.75 (s, 1H), 7.57 – 7.28 (m, 20H), 6.68 (s, 1H), 6.30 (s, 1H), 6.15 (s, 1H), 3.89 (s, 1H), 2.75 (d, *J* = 4.8 Hz, 3H). MS (ESI): *m/z* 692 $[M + H]^+$.

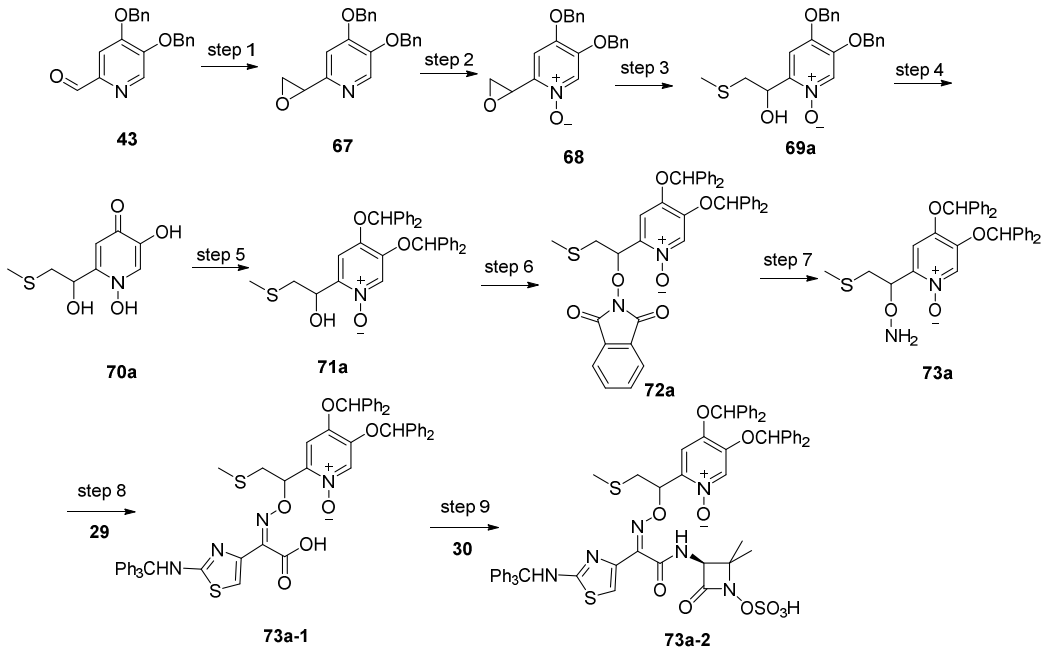
**2-(1-(Aminooxy)-2-(methylamino)-2-oxoethyl)-4,5-bis(benzhydryloxy)pyridine 1-Oxide (66c).** Compound **66c** (256 mg, 49%) was prepared from **65c** (640 mg, 0.93mmol) and 85% hydrazine hydrate (0.06 mL, 1.11mmol) in the same manner as described for **31b**. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 4.8 Hz, 1H), 7.82 (s, 1H), 7.48 – 7.28 (m, 20H), 6.93 (s, 1H), 6.34 (s, 1H), 6.19 (s, 1H), 5.58 (s, 1H), 5.47 (s, 2H), 2.70 (d, J = 4.8 Hz, 3H). MS (ESI): *m/z* 562 $[M + H]^+$.

**(*Z*)-4,5-Bis(benzhydryloxy)-2-(1-(((carboxy(2-(tritylamino)thiazol-4-yl)methylene)amino )oxy)-2-(methylamino)-2-oxoethyl)pyridine 1-Oxide (66c-1).** Compound **66c-1** (160 mg,

19%) was prepared from **66c** (500 mg, 0.89 mmol) and **29** (278 mg, 0.67 mmol) in the same manner as described for **32a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.70 (s, 1H), 8.65 (s, 1H), 7.95 (s, 1H), 7.72 (s, 1H), 7.46 – 7.00 (m,35H), 6.79 (s, 1H), 6.66 (s, 1H), 5.70 (s, 1H), 2.55 (d, $J$ = 4.5 Hz, 3H). MS (ESI): *m/z* 956 $[M - H]^-$.

**4,5-Bis(benzhydryloxy)-2-(1-((((*Z*)-2-(((*S*)-2,2-dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxo-1-(2-(tritylamino)thiazol-4-yl)ethylidene)amino)oxy)-2-(methylamino)-2-oxoethyl)pyridine 1-Oxide (66c-2).** Compound **66c-2** (a mixture of diastereomer (approximately 1:1), 120 mg, 62%) was prepared from **66c-1** (160 mg, 0.17 mmol) and **30** (53 mg, 0.25 mmol) in the same manner as described for **33a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.71 (d, $J$ = 7.8 Hz, 1/2H), 9.67 (d, $J$ = 7.7 Hz, 1/2H), 8.96 (s, 1/2H), 8.92 (s, 1/2H), 8.25 (q, $J$ = 4.8 Hz, 1/2H), 8.17 (q, $J$ = 4.9 Hz, 1/2H), 8.06 (s, 1/2H), 8.04 (s, 1/2H), 7.59 – 7.07 (m, 35H), 6.88 (s, 1/2H), 6.84 (s, 1/2H), 6.76 (s, 1/2H), 6.75 (s, 1/2H), 6.73 (s, 1/2H), 6.70 (s, 1/2H), 5.85 (s, 1H), 4.66 (dd, $J$ = 7.7, 3.9 Hz, 1H), 2.54 (t, $J$ = 4.5 Hz, 3H), 1.46 (s, 3/2H), 1.45 (s, 3/2H), 1.20 (s, 3/2H), 1.15 (s, 3/2H). MS (ESI): *m/z* 1148 $[M - H]^-$.

**Preparation of intermediate 73a-2.**




**4,5-Bis(benzyloxy)-2-(oxiran-2-yl)pyridine (67).** Compound **67** (1.89 g, 57%) was prepared from **43** (3.2 g, 10.00 mmol) and trimethylsulfoxonium iodide (2.42 g, 11.00 mmol) in the same manner as described for **51**. mp: 73 – 74 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.46 – 7.29 (m, 10H), 6.78 (s, 1H), 5.20 (s, 2H), 5.18(s, 2H), 3.91 (dd, $J$ = 4.2, 2.5 Hz, 1H), 3.11 (dd, $J$ = 5.7, 4.2 Hz, 1H), 2.78 (dd, $J$ = 5.7, 2.5 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 156.08, 152.18, 144.80, 137.37, 136.51, 135.66, 128.72(2C), 128.59(2C), 128.32, 128.15, 127.53(2C), 127.32(2C), 104.02, 72.38, 70.40, 52.86, 50.34. HRMS (ESI) *m/z* calcd for $C_{21}H_{20}NO_3$ $[M + H]^+$ 334.1438, found 334.1442.

**4,5-Bis(benzyloxy)-2-(oxiran-2-yl)pyridine 1-Oxide (68).** Compound **68** (3.2 g, 80%) was

prepared from **67** (3.8 g, 11.41 mmol) and *m*-CPBA (7.05 g, 34.23 mmol) in the same manner as described for **S5**. mp: 135 – 137 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.45 – 7.32 (m, 10H), 6.73 (s, 1H), 5.21 – 5.13 (m, 2H), 5.12 (s, 2H), 4.48 (dd, *J* = 4.2, 2.4 Hz, 1H), 3.25 (dd, *J* = 5.6, 4.2 Hz, 1H), 2.62 (dd, *J* = 5.6, 2.4 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 148.89, 145.89, 141.96, 135.05, 135.03, 128.82(2C), 128.78(2C), 128.60, 128.57, 128.44, 127.48(2C), 127.38(2C), 105.20, 72.16, 71.32, 50.28, 47.71. HRMS (ESI) *m/z* calcd for $C_{21}H_{20}NO_4$ $[M + H]^+$ 350.1387, found 350.1387.

**4,5-Bis(benzyloxy)-2-(1-hydroxy-2-(methylthio)ethyl)pyridine 1-Oxide (69a).** A solution of **68** (3.0 g, 8.58 mmol) in dioxane (20 mL) was treated with 20 percent aqueous sodium methanethiolate (29.8 mL, 85.80 mmol) and stirred at room temperature overnight. Then the resulting precipitate was collected by filtration and washed with water, followed by petroleum to afford **69a** as a white solid (1.43 g, 42%). mp: 190 – 193 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.46 – 7.33 (m, 10H), 6.88 (s, 1H), 5.93 (d, *J* = 7.4 Hz, 1H), 5.22 (s, 2H), 5.12 (s, 2H), 4.83 (q, *J* = 7.0 Hz, 1H), 3.21 (dd, *J* = 13.7, 7.0 Hz, 1H), 2.85 (dd, *J* = 13.7, 6.5 Hz, 1H), 2.01 (s, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 147.43, 146.29, 145.36, 136.43, 136.41, 129.00(2C), 128.98(2C), 128.67, 128.65, 128.28(2C), 128.22(2C), 127.81, 107.87, 71.40, 70.87, 67.81, 38.26, 16.35. HRMS (ESI) *m/z* calcd for $C_{22}H_{24}NO_4S$ $[M + H]^+$ 398.1421, found 398.1421.

**1,5-Dihydroxy-2-(1-hydroxy-2-(methylthio)ethyl)pyridin-4(1*H*)-one (70a).** Compound **70a** (crude material) was prepared from **69a** (7.2 g, 18.11 mmol) and boron trichloride in *n*-hexane (45.3 mL, 45.27 mmol) in the same manner as described for **S6**, which was used in the next step without purification.

**4,5-Bis(benzhydryloxy)-2-(1-hydroxy-2-(methylthio)ethyl)pyridine 1-Oxide (71a).** Compound **71a** (4.3 g, 43% by two steps) was prepared from **70a** (crude material) and diphenyldiazomethane (21.1 g, 108.70 mmol) in the same manner as described for **S7**. mp: 67 – 69 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.45 – 7.28 (m, 20H), 6.82 (s, 1H), 6.31 (s, 1H), 6.20 (s, 1H), 5.96 (s, 1H), 4.69 (t, *J* = 6.5 Hz, 1H), 3.04 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.76 (dd, *J* = 13.7, 5.9 Hz, 1H), 1.83 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 148.99, 145.52, 144.00, 139.71(2C), 139.68(2C), 130.91, 128.89(2C), 128.87(2C), 128.84(2C), 128.83(2C), 128.40(4C), 126.72(2C), 126.70(2C), 126.63(2C), 126.59(2C), 110.83, 84.60, 83.51, 70.62, 37.57, 15.93. HRMS (ESI) *m/z* calcd for $C_{34}H_{32}NO_4S$ $[M + H]^+$ 550.2047, found 550.2053.

**4,5-Bis(benzhydryloxy)-2-(1-((1,3-dioxoisoindolin-2-yl)oxy)-2-(methylthio)ethyl)pyridin e 1-Oxide (72a).** Under argon atmosphere, a solution of **71a** (3.1 g, 5.64 mmol) in dry THF (40 mL) was treated with *N*-hydroxyphthalimide (4.6 g, 28.2 mmol) and $PBu_3$ (3.84 mL, 16.92 mmol), then the mixture was cooled to −10 °C. A solution of DIAD (2.1 mL, 16.92 mmol) in dry THF (5 mL) was added dropwise. After addition, the resulting mixture was stirred at the same temperature overnight. After completion of the reaction, the reaction was quenched by addition of water. The solution was extracted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $Na_2SO_4$, filtered and then the

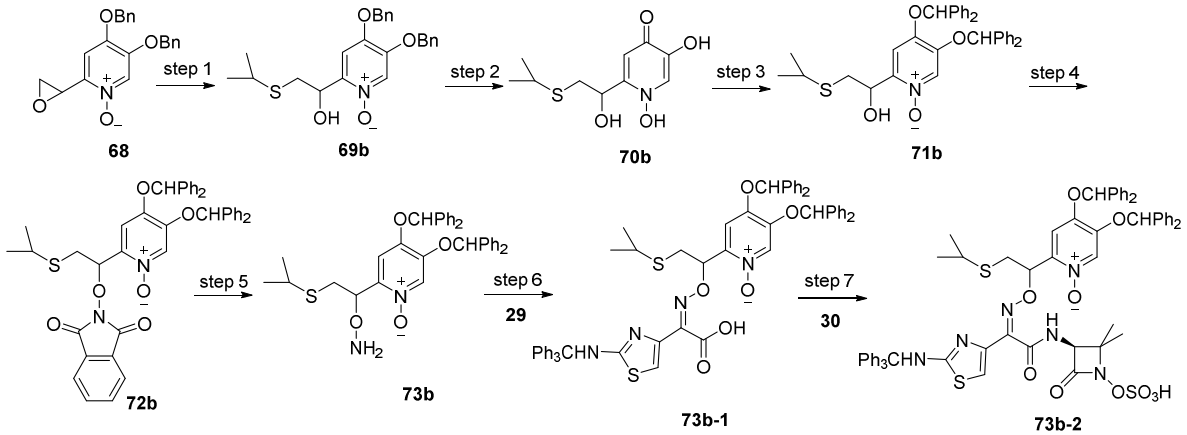
filtrate was concentrated in vacuo. The resulting residue was purified by chromatography on silica gel with petroleum/ethyl acetate to afford **72a** as a yellow solid (2.0 g, 51%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.81 – 7.77 (m, 3H), 7.76 – 7.70 (m, 2H), 7.63 – 7.27 (m, 20H), 6.73 (s, 1H), 6.18 (s, 1H), 6.14 (dd, *J* = 5.8, 3.5 Hz, 1H), 3.16 (dd, *J* = 14.9, 3.5 Hz, 1H), 2.90 (dd, *J* = 14.9, 5.8 Hz, 1H), 1.88 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.47(2C), 148.36, 145.84, 141.89, 140.61, 140.00, 139.92, 139.87, 134.68(2C), 130.07, 128.97(2C), 128.82(2C), 128.80(2C), 128.75(2C), 128.54(2C), 128.30, 128.25, 128.24, 127.97, 126.87(2C), 126.74(2C), 126.73(2C), 126.67(2C), 123.68(2C), 110.92, 84.32, 82.93, 81.70, 35.67, 16.70. HRMS (ESI) *m/z* calcd for $C_{42}H_{35}N_2O_6S$ $[M + H]^+$ 695.2210, found 695.2222.

**2-(1-(Aminooxy)-2-(methylthio)ethyl)-4,5-bis(benzhydryloxy)pyridine 1-Oxide (73a).** Compound **73a** (206 mg, 69%) was prepared from **72a** (366 mg, 0.53 mmol) and 85% hydrazine hydrate (0.04 mL, 0.53 mmol) in the same manner as described for **31b**. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.48 – 7.26 (m, 20H), 6.80 (s, 1H), 6.32 (s, 1H), 6.19 (s, 1H), 5.20 (dd, J = 7.3, 3.1 Hz, 1H), 5.06 (s, 2H), 2.96 (dd, J = 14.2, 3.1 Hz, 1H), 2.63 (dd, J = 14.2, 7.3 Hz, 1H), 2.01 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 147.95, 145.60, 144.43, 140.01, 139.94(2C), 139.87, 130.80, 128.97(2C), 128.83(2C), 128.79(2C), 128.74(2C), 128.35(2C), 128.28(2C), 126.81(2C), 126.77(2C), 126.66(2C), 126.64(2C), 109.72, 84.51, 83.22, 79.91, 35.52, 16.54. HRMS (ESI) *m/z* calcd for $C_{34}H_{33}N_2O_4S$ $[M + H]^+$ 565.2156, found 565.2160.

**(*Z*)-4,5-Bis(benzhydryloxy)-2-(1-(((carboxy(2-(tritylamino)thiazol-4-yl)methylene)amino)oxy)-2-(methylthio)ethyl)pyridine 1-Oxide (73a-1).** Compound **73a-1** (380 mg, 77%) was prepared from **73a** (290 mg, 0.51 mmol) and **29** (191 mg, 0.46 mmol) in the same manner as described for **32a**. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 8.77 (s, 1H), 7.94 (s, 1H), 7.60 – 7.08 (m, 35H), 7.05 (s, 1H), 6.85 (s, 1H), 6.66 (s, 1H), 5.48 (d, *J* = 7.0 Hz, 1H), 3.00 – 2.90 (m, 1H), 2.66 (dd, *J* = 14.9, 7.1 Hz, 1H), 1.96 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{58}H_{49}N_4O_6S_2$ $[M + H]^+$ 961.3088, found 961.3091.

**4,5-Bis(benzhydryloxy)-2-(1-((((*Z*)-2-(((*S*)-2,2-dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxo-1-(2-(tritylamino)thiazol-4-yl)ethylidene)amino)oxy)-2-(methylthio)ethyl)pyridine 1-Oxide (73a-2).** Compound **73a-2** (a mixture of diastereomer (approximately 1:1), 310 mg, 66%) was prepared from **73a-1** (380 mg, 0.40 mmol) and **30** (124 mg, 0.59 mmol) in the same manner as described for **33a**. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 9.81 (d, *J* = 7.8 Hz, 1/2H), 9.78 (d, *J* = 7.7 Hz, 1/2H), 8.92 (s, 1/2H), 8.89 (s, 1/2H), 8.02 (s, 1/2H), 8.01 (s, 1/2H), 7.60 – 7.18 (m, 35H), 6.83 (s, 1/2H), 6.83 (s, 1/2H), 6.80 (s, 1/2H), 6.77 (s, 1/2H), 6.72 – 6.70 (m, 1H), 5.57 (td, *J* = 6.8, 3.2 Hz, 1H), 4.76 (d, *J* = 7.7 Hz, 1/2H), 4.65 (d, *J* = 7.7 Hz, 1/2H), 2.84 (ddd, *J* = 15.0, 7.0, 3.2 Hz, 1H), 2.60 (dt, *J* = 14.7, 7.4 Hz, 1H), 1.87 (s, 3/2H), 1.73 (s, 3/2H), 1.54 (s, 3/2H), 1.52 (s, 3/2H), 1.36 (s, 3/2H), 1.32 (s, 3/2H). HRMS (ESI) *m/z* calcd for $C_{63}H_{55}N_6O_{10}S_3$ $[M - H]^-$ 1151.3147, found 1151.3147.

**Preparation of intermediate 73b-2.**




**4,5-Bis(benzyloxy)-2-(1-hydroxy-2-(isopropylthio)ethyl)pyridine 1-Oxide (69b).** A solution of 2-propanethiol (2.66 mL, 28.60 mmol) in dioxane (20 mL) was cooled to 0 °C and treated with sodium hydride 60 pecent dispersion in oil (1.14 g, 28.60 mmol). The resulting mixture was stirred at 0 °C for 30 min, then a solution of **68** (2.0 g, 5.72 mmol) in dioxane (10 mL) was added dropwise. After addition, the mixture was warm to room temperature and stirred for 1 h. After completion of the reaction, water was added, and then the resulting precipitate was filtered and washed sequentially with water and petroleum and dried in vacuo to provide **69b** as a white solid (1.3 g, 53%). mp: 132 – 134 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.48 – 7.32 (m, 10H), 6.90 (s, 1H), 5.89 (d, $J$ = 6.9 Hz, 1H), 5.23 (s, 2H), 5.14 (s, 2H), 4.85 (q, $J$ = 6.7 Hz, 1H), 3.32 (dd, $J$ = 13.5, 6.9 Hz, 1H), 2.95 – 2.83 (m, 2H), 1.26 (d, $J$ = 6.7 Hz, 3H), 1.24 (d, $J$ = 6.7 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 149.05, 145.70, 144.18, 135.07, 135.02, 128.83(4C), 128.62, 128.59, 128.42, 127.41(4C), 108.28, 72.22, 71.41, 70.57, 35.52, 34.30, 23.49(2C). HRMS (ESI) *m/z* calcd for $C_{24}H_{28}NO_4S$ $[M + H]^+$ 426.1734, found 426.1741.

**1,5-Dihydroxy-2-(1-hydroxy-2-(isopropylthio)ethyl)pyridin-4(1*H*)-one (70b).** Compound **70b** (crude material) was prepared from **69b** (2.17 g, 5.10 mmol) and boron trichloride in *n*-hexane (12.70 mL, 12.70 mmol) in the same manner as described for **S6**, which was used in the next step without purification.

**4,5-Bis(benzhydryloxy)-2-(1-hydroxy-2-(isopropylthio)ethyl)pyridine 1-Oxide (71b).** Compound **71b** (1.03 g, 35% by two steps) was prepared from **70b** (crude material) and diphenyldiazomethane (5.94 g, 30.62 mmol) in the same manner as described for **S7**. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.47 – 7.28 (m, 20H), 6.81 (s, 1H), 6.30 (s, 1H), 6.18 (s, 1H), 4.68 (t, $J$ = 6.8 Hz, 1H), 3.13 (dd, $J$ = 13.6, 7.1 Hz, 1H), 2.83 – 2.71 (m, 2H), 1.16 (d, $J$ = 6.7 Hz, 3H), 1.14 (d, $J$ = 6.8 Hz, 3H). MS (ESI): *m/z* 578 $[M + H]^+$.

**4,5-Bis(benzhydryloxy)-2-(1-((1,3-dioxoisoindolin-2-yl)oxy)-2-(isopropylthio)ethyl)pyridine 1-Oxide (72b).** Compound **72b** (641 mg, 50%) was prepared from **71b** (1.03 g, 1.78 mmol), *N*-hydroxyphthalimide (873 mg, 5.35 mmol), $PBu_3$ (1.34mL, 5.35 mmol) and DIAD (1.05 mL, 5.35 mmol) in the same manner as described for **72a**. $^{1}$H NMR (400 MHz, $CDCl_3$)

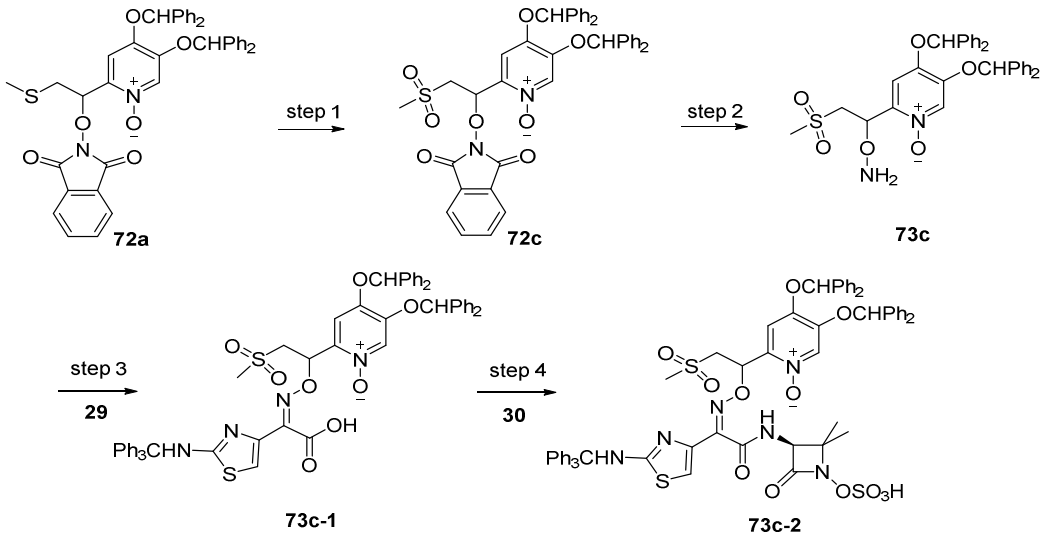
δ 7.81 – 7.76 (m, 3H), 7.75 – 7.71 (m, 3H), 7.63 – 7.28 (m, 20H), 6.73 (s, 1H), 6.15 (s, 1H), 6.09 (dd, *J* = 6.2, 3.5 Hz, 1H), 3.25 (dd, *J* = 14.7, 3.6 Hz, 1H), 2.92 – 2.81 (m, 2H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 3H). HRMS (ESI) *m/z* calcd for $C_{44}H_{39}N_2O_6S$ $[M + H]^+$ 723.2523, found 723.2520.

**2-(1-(Aminooxy)-2-(isopropylthio)ethyl)-4,5-bis(benzhydryloxy)pyridine 1-Oxide (73b).** Compound **73b** (314 mg, 66%) was prepared from **72b** (580 mg, 0.81 mmol) and 85% hydrazine hydrate (0.05 mL, 0.86 mmol) in the same manner as described for **31b**. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.48 – 7.27 (m, 20H), 6.78 (s, 1H), 6.31 (s, 1H), 6.18 (s, 1H), 5.14 (dd, J = 7.8, 3.1 Hz, 1H), 5.04 (s, 2H), 3.05 (dd, J = 14.0, 3.1 Hz, 1H), 2.88 (h, J = 6.6 Hz, 1H), 2.61 (dd, J = 14.0, 7.8 Hz, 1H), 1.21 (d, J = 6.7 Hz, 3H), 1.17 (d, J = 6.7 Hz, 3H). MS (ESI): *m/z* 593 $[M + H]^+$.

**(*Z*)-4,5-Bis(benzhydryloxy)-2-(1-(((carboxy(2-(tritylamino)thiazol-4-yl)methylene)amino)oxy)-2-(isopropylthio)ethyl)pyridine 1-Oxide (73b-1).** Compound **73b-1** (390 mg, 77%) was prepared from **73b** (305 mg, 0.51 mmol) and **29** (203 mg, 0.49 mmol) in the same manner as described for **32a**. mp: 147 – 149 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.92 (s, 1H), 8.01 (s, 1H), 7.60 – 7.03 (m, 35H), 6.93 (s, 1H), 6.70 (s, 1H), 6.57 (s, 1H), 5.48 (dd, *J* = 7.3, 2.9 Hz, 1H), 3.00 (dd, *J* = 14.7, 2.9 Hz, 1H), 2.84 (p, *J* = 6.7 Hz, 1H), 2.69 (dd, *J* = 14.7, 7.3 Hz, 1H), 1.06 (d, *J* = 6.6 Hz, 3H), 1.02 (d, *J* = 6.7 Hz, 3H). MS (ESI): *m/z* 987 $[M - H]^-$.

**4,5-Bis(benzhydryloxy)-2-(1-((((*Z*)-2-(((*S*)-2,2-dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxo-1-(2-(tritylamino)thiazol-4-yl)ethylidene)amino)oxy)-2-(isopropylthio)ethyl)pyridine 1-Oxide (73b-2).** Compound **73b-2** (a mixture of diastereomer (approximately 1:1), 400 mg, 93%) was prepared from **73b-1** (362 mg, 0.37 mmol) and **30** (116 mg, 0.55 mmol) in the same manner as described for **33a**. mp: 157 °C decomp.$^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.86 – 9.78 (m, 1H), 8.95 (s, 1/2H), 8.91 (s, 1/2H), 8.04 (s, 1/2H), 8.03 (s, 1/2H), 7.62 – 7.15 (m, 35H), 6.85 (s, 1/2H), 6.83 (s, 1/2H), 6.81 (s, 1/2H), 6.80 (s, 1/2H), 6.72 (d, *J* = 4.0 Hz, 1H), 5.57 – 5.47 (m, 1H), 4.76 (d, *J* = 7.7 Hz, 1/2H), 4.61 (d, *J* = 7.7 Hz, 1/2H), 2.93 – 2.79 (m, 2H), 2.67 – 2.57 (m, 1H), 1.56 (s, 3/2H), 1.53 (s, 3/2H), 1.38 (s, 3/2H), 1.33 (s, 3/2H), 1.02 (d, *J* = 6.8 Hz, 3/2H), 0.99 (dd, *J* = 6.7, 2.2 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3/2H). MS (ESI): *m/z* 1179 $[M - H]^-$.

**Preparation of intermediate 73c-2.**




**4,5-Bis(benzhydryloxy)-2-(1-((1,3-dioxoisoindolin-2-yl)oxy)-2-(methylsulfonyl)ethyl)pyridine 1-Oxide (72c).** Compound **72c** (1.90 g, 91%) was prepared from **72a** (2.0 g, 2.88 mmol) and *m*-CPBA (2.34 g, 11.52 mmol) in the same manner as described for **S5**. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.80 (m, 2H), 7.79 (s, 1H), 7.78 – 7.74 (m, 2H), 7.65 (s, 1H), 7.57 – 7.27 (m, 20H), 6.62 (s, 1H), 6.20 – 6.16 (m, 2H), 3.64 – 3.49 (m, 2H), 3.10 (s, 3H). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 163.34(2C), 149.80, 146.37, 140.26, 140.11, 139.58, 139.56(2C), 134.94(2C), 130.16, 129.07(2C), 128.88(2C), 128.80(2C), 128.65(2C), 128.63(2C), 128.51, 128.45, 128.36, 128.16, 126.78(2C), 126.72(2C), 126.69(2C), 126.67(2C), 123.90(2C), 109.71, 84.32, 83.18, 77.95, 56.16, 41.72. HRMS (ESI) *m/z* calcd for $C_{42}H_{35}N_2O_8S$ $[M + H]^+$ 727.2109, found 727.2114.

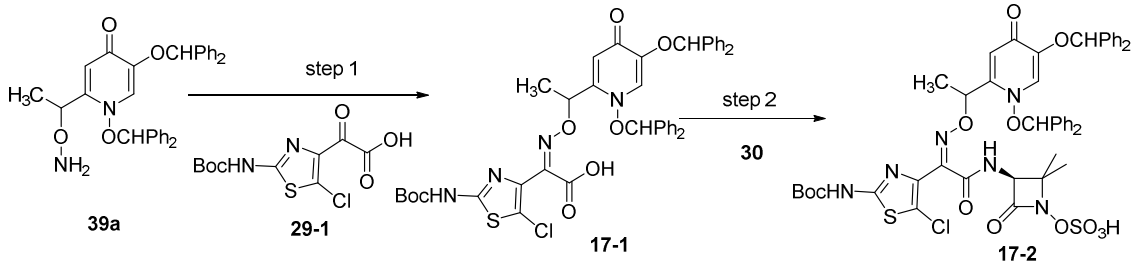
**2-(1-(Aminooxy)-2-(methylsulfonyl)ethyl)-4,5-bis(benzhydryloxy)pyridine 1-Oxide (73c).** Compound **73c** (980 mg, 63%) was prepared from **72c** (1.89 g, 2.61 mmol) and 85% hydrazine hydrate (0.16 mL, 2.87 mmol) in the same manner as described for **31b**. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.52 – 7.29 (m, 20H), 6.84 (s, 1H), 6.34 (s, 1H), 6.21 (s, 1H), 5.32 (dd, J = 9.0, 2.2 Hz, 1H), 3.64 (dd, J = 15.0, 2.2 Hz, 1H), 3.10 (dd, J = 14.9, 8.9 Hz, 1H), 3.00 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{34}H_{33}N_2O_6S$ $[M + H]^+$ 597.2054, found 597.2052.

**(*Z*)-4,5-Bis(benzhydryloxy)-2-(1-(((carboxy(2-(tritylamino)thiazol-4-yl)methylene)amino)oxy)-2-(methylsulfonyl)ethyl)pyridine 1-Oxide (73c-1).** Compound **73c-1** (1.07 g, 76%) was prepared from **73c** (850 mg, 1.42 mmol) and **29** (560 mg, 1.35 mmol) in the same manner as described for **32a**. mp: 166 – 168 °C. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 8.97 (s, 1H), 8.09 (s, 1H), 7.62 – 6.89 (m, 36H), 6.72 (s, 1H), 6.56 (s, 1H), 5.71 (dd, *J* = 9.3, 3.2 Hz, 1H), 3.69 – 3.52 (m, 2H), 3.01 (s, 3H). MS (ESI): *m/z* 991 $[M - H]^-$.

**4,5-Bis(benzhydryloxy)-2-(1-((((Z)-2-(((S)-2,2-dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxo-1-(2-(tritylamino)thiazol-4-yl)ethylidene)amino)oxy)-2-(methylsulfonyl)ethyl)pyridine 1-Oxide (73c-2).** Compound **73c-2** (a mixture of diastereomer (approximately

1:1), 960 mg, 75%) was prepared from **73c-1** (1.07 g, 1.08 mmol) and **30** (340 mg, 1.62 mmol) in the same manner as described for **32a**. mp: 183 °C decomp. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.84 (d, $J$ = 7.3 Hz, 1/2H), 9.82 (d, $J$ = 7.7 Hz, 1/2H), 8.94 (s, 1/2H), 8.93 (s, 1/2H), 8.08 (s, 1/2H), 8.07 (s, 1/2H), 7.60 – 7.05 (m, 35H), 6.93 (s, 1/2H), 6.91 (s, 1/2H), 6.89 (s, 1/2H), 6.75 (s, 1/2H), 6.72 (s, 1H), 5.80 (dd, $J$ = 9.7, 2.2 Hz, 1/2H), 5.76 (dd, $J$ = 9.7, 2.2 Hz, 1/2H), 4.74 (d, $J$ = 7.7 Hz, 1/2H), 4.69 (d, $J$ = 7.3 Hz, 1/2H), 3.52 – 3.37 (m, 2H), 3.03 (s, 3/2H), 3.01 (s, 3/2H), 1.52 (s, 3/2H), 1.51 (s, 3/2H), 1.34 (s, 3/2H), 1.31 (s, 3/2H). MS (ESI): *m/z* 1183 [M − H] $^-$.

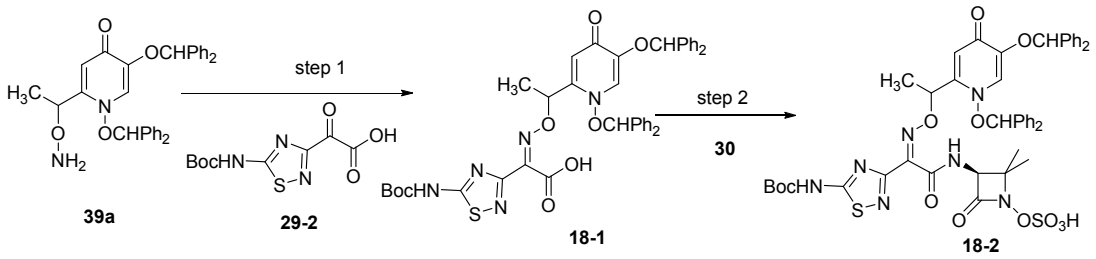
**Preparation of intermediate 17-2.**




**(*Z*)-2-((1-(1,5-Bis(benzhydryloxy)-4-oxo-1,4-dihydropyridin-2-yl)ethoxy)imino)-2-(2-((*tert*-butoxycarbonyl)amino)-5-chlorothiazol-4-yl)acetic Acid (17-1).** Compound **17-1** (348 mg, 66%) was prepared from **39a** (340 mg, 0.65 mmol) and **29-1** (191 mg, 0.62 mmol) in the same manner as described for **32a**. For synthesis of **29-1**, see Yamawaki, K. et al., *Bioorg. Med. Chem.* **2007**, *15*, 6716 – 6732. mp: 154 – 157 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.05 (s, 1H), 7.63 (s, 1H), 7.49 – 7.08 (m, 20H), 6.33 (s, 1H), 6.28 (s, 1H), 6.05 (s, 1H), 5.19 (q, $J$ = 6.6 Hz, 1H), 1.46 (s, 9H), 1.17 (d, $J$ = 6.6 Hz, 3H). HRMS (ESI) *m/z* calcd for $C_{43}H_{38}ClN_4O_8S$ [M − H] $^-$ 805.2104, found 805.2112.

**(3*S*)-3-((*Z*)-2-((1-(1,5-Bis(benzhydryloxy)-4-oxo-1,4-dihydropyridin-2-yl)ethoxy)imino)-2-(2-((*tert*-butoxycarbonyl)amino)-5-chlorothiazol-4-yl)acetamido)-2,2-dimethyl-4-oxoazetidin-1-yl Hydrogen Sulfate (17-2).** Compound **17-2** (a mixture of diastereomer (approximately 1:1), 333 mg, 81%) was prepared from **17-1** (330 mg, 0.41 mmol) and **30** (122 mg, 0.58 mmol) in the same manner as described for **33a**. mp: 172 °C decomp. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.60 (dd, $J$ = 7.7, 3.2 Hz, 1H), 7.60 (s, 1H), 7.45 – 7.02 (m, 20H), 6.32 (s, 1H), 6.26 (s, 1/2H), 6.25 (s, 1/2H), 6.15 (s, 1/2H), 6.03 (s, 1/2H), 5.24 – 5.08 (m, 1H), 4.56 (d, $J$ = 8.3 Hz, 1/2H), 4.52 (d, $J$ = 7.6 Hz, 1/2H), 1.46 (s,9H), 1.41 (s, 3/2H), 1.39 (s, 3/2H), 1.18 (s, 3/2H), 1.17 (s, 3/2H), 1.10 (d, $J$ = 6.0 Hz, 3/2H), 1.03 (d, $J$ = 6.1 Hz, 3/2H). HRMS (ESI) *m/z* calcd for $C_{48}H_{46}ClN_6O_{12}S_2$ [M − H] $^-$ 997.2309, found 997.2304.

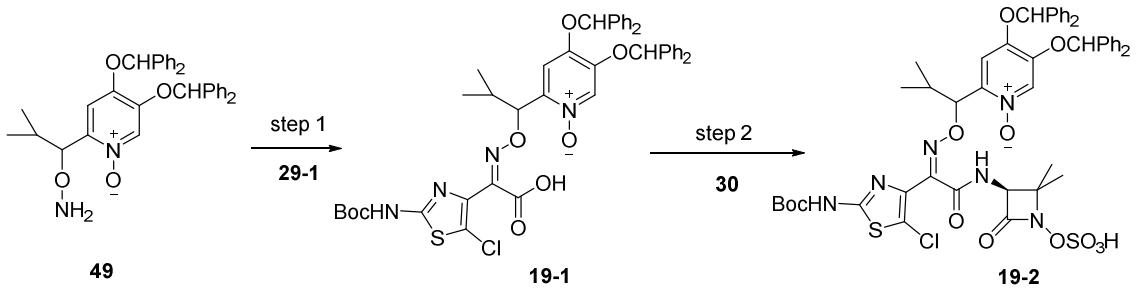
**Preparation of intermediate 18-2.**




**(*Z*)-2-((1-(1,5-Bis(benzhydryloxy)-4-oxo-1,4-dihydropyridin-2-yl)ethoxy)imino)-2-(5-((*tert*-butoxycarbonyl)amino)-1,2,4-thiadiazol-3-yl)acetic Acid (18-1).** Compound **18-1** (188 mg, 32%) was prepared from **39a** (387 mg, 0.75 mmol) and **29-2** (136 mg, 0.50 mmol) in the same manner as described for **32a**. For synthesis of **29-2**, see Yamawaki, K., et al., *Bioorg. Med. Chem.* **2007**, *15*, 6716 – 6732. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.59 (s, 1H), 7.44 (s, 1H), 7.42 – 7.32 (m, 20H), 6.42 (s, 1H), 6.20 (s, 1H), 6.09 (s, 1H), 5.21 (q, $J$ = 6.9 Hz, 1H), 1.50 (s, 9H), 1.24 (d, $J$ = 6.9 Hz, 3H).

**(3*S*)-3-((*Z*)-2-((1-(1,5-Bis(benzhydryloxy)-4-oxo-1,4-dihydropyridin-2-yl)ethoxy)imino)-2-(5-((*tert*-butoxycarbonyl)amino)-1,2,4-thiadiazol-3-yl)acetamido)-2,2-dimethyl-4-oxoazetidin-1-yl Hydrogen Sulfate (18-2).** Compound **18-2** (a mixture of diastereomer (approximately 1:1), 200 mg, 88%) was prepared from **18-1** (183 mg, 0.24 mmol) and **30** (75.6 mg, 0.36mmol) in the same manner as described for **33a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.61 (s, 1H), 9.62 (d, $J$ = 7.7 Hz, 1H), 7.52 (s, 1/2H), 7.47 (s, 1/2H), 7.42 – 7.11 (m, 20H), 6.31 (s, 1H), 6.23 (s, 1/2H), 6.20 (s, 1/2H), 6.09 (s, 1/2H), 6.00 (s, 1/2H), 5.25 – 5.08 (m, 1H), 4.57 (d, $J$ = 8.0 Hz, 1/2H), 4.54 (d, $J$ = 7.7 Hz, 1/2H), 1.46 (s, 9H), 1.38 (s, 3/2H), 1.37 (s, 3/2H), 1.20 – 1.16 (m, 3H), 1.14 (s, 3/2H), 1.13 (s, 3/2H). MS (ESI): *m/z* 964 $[M - H]^-$.

**Preparation of intermediate 19-2.**

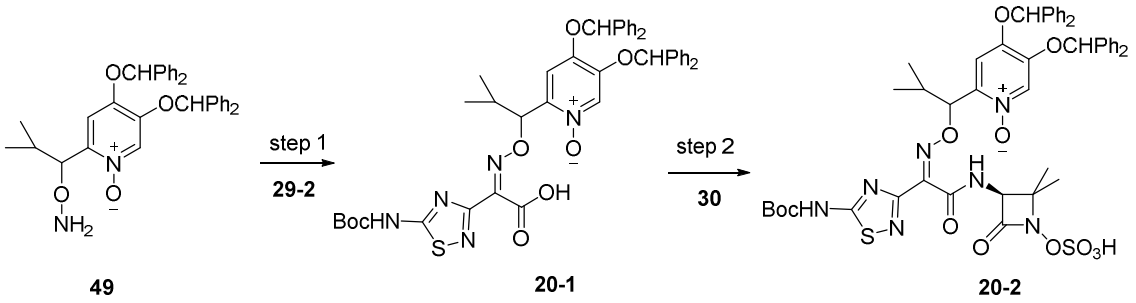



**(*Z*)-4,5-Bis(benzhydryloxy)-2-(1-((((2-((*tert*-butoxycarbonyl)amino)-5-chlorothiazol-4-yl)(carboxy)methylene)amino)oxy)-2-methylpropyl)pyridine 1-Oxide (19-1).** Compound **19-1** (770 mg, 92%) was prepared from **49** (550 mg, 1.01 mmol) and **29-1** (293 mg, 0.96 mmol) in the same manner as described for **32a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.06 (s, 1H), 8.01 (s, 1H), 7.64 – 7.18 (m, 20H), 7.01 (s, 1H), 6.70 (s, 1H), 6.58 (s, 1H), 5.36 (d, $J$ = 3.6 Hz, 1H), 2.11 (td, $J$ = 7.0, 3.9 Hz, 1H), 1.46 (s, 9H), 0.90 (d, $J$ = 6.9 Hz, 3H), 0.49 (d, $J$ = 7.0 Hz, 3H). HRMS (ESI) *m/z* calcd for $C_{45}H_{42}ClN_4O_8S$ $[M - H]^-$ 833.2417, found

833.2411.

**4,5-Bis(benzhydryloxy)-2-(1-((((*Z*)-1-(2-((*tert*-butoxycarbonyl)amino)-5-chlorothiazol-4-yl)-2-(((*S*)-2,2-dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropyl)pyridine 1-Oxide (19-2).** Compound **19-2** (a mixture of diastereomer (approximately 1:1), 750 mg, 79%) was prepared from **19-1** (770 mg, 0.92 mmol) and **30** (290 mg, 1.38 mmol) in the same manner as described for **33a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.06 (s, 1/2H), 12.03 (s, 1/2H), 9.90 (d, $J$ = 8.0 Hz, 1/2H), 9.78 (d, $J$ = 7.7 Hz, 1/2H), 8.01 (s, 1/2H), 7.98 (s, 1/2H), 7.63 – 7.19 (m, 20H), 7.09 (s, 1/2H), 6.94 (s, 1/2H), 6.77 (s, 1/2H), 6.74 (s, 1/2H), 6.72 (s, 1/2H), 6.69 (s, 1/2H), 5.40 (d, $J$ = 3.4 Hz, 1/2H), 5.33 (d, $J$ = 4.2 Hz, 1/2H), 4.87 (d, $J$ = 8.0 Hz, 1/2H), 4.73 (d, $J$ = 7.6 Hz, 1/2H), 2.10 – 1.88 (m, 1H), 1.59 (s, 3/2H), 1.54 (s, 3/2H), 1.45 (d, $J$ = 1.2 Hz, 9H), 1.42 (s, 3/2H), 1.40 (s, 3/2H), 0.89 (d, $J$ = 6.9 Hz, 3/2H), 0.82 (d, $J$ = 6.8 Hz, 3/2H), 0.45 (d, $J$ = 6.9 Hz, 3/2H), 0.38 (d, $J$ = 7.0 Hz, 3/2H). HRMS (ESI) *m/z* calcd for $C_{50}H_{50}ClN_6O_{12}S_2$ [M − H] $^-$ 1025.2622, found 1025.2638.

**Preparation of intermediate 20-2.**

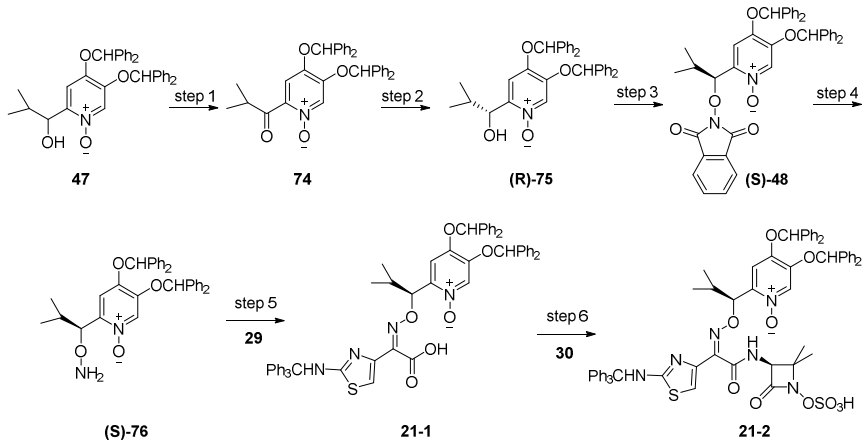



**(*Z*)-4,5-Bis(benzhydryloxy)-2-(1-((((5-((*tert*-butoxycarbonyl)amino)-1,2,4-thiadiazol-3-yl)(carboxy)methylene)amino)oxy)-2-methylpropyl)pyridine 1-Oxide (20-1).** Compound **20-1** (68 mg, 16 %) was prepared from **49** (300 mg, 0.55 mmol) and **29-2** (149 mg, 0.54 mmol) in the same manner as described for **32a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.54 (s, 1H), 8.04 (s, 1H), 7.63 – 7.06 (m, 20H), 6.89 (s, 1H), 6.71 (s, 1H), 6.55 (s, 1H), 5.43 (d, $J$ = 3.8 Hz, 1H), 2.15 – 2.02 (m, 1H), 1.49 (s, 9H), 0.90 (d, $J$ = 6.8 Hz, 3H), 0.52 (d, $J$ = 6.9 Hz, 3H). HRMS (ESI) *m/z* calcd for $C_{44}H_{42}N_5O_8S$ [M − H] $^-$ 800.2760, found 800.2751.

**4,5-Bis(benzhydryloxy)-2-(1-((((*Z*)-1-(5-((*tert*-butoxycarbonyl)amino)-1,2,4-thiadiazol-3-yl)-2-(((*S*)-2,2-dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropyl)pyridine 1-Oxide (20-2).** Compound **20-2** (a mixture of diastereomer (approximately 1:1), 57 mg, 75%) was prepared from **20-1** (62 mg, 0.08 mmol) and **30** (24 mg, 0.12 mmol) in the same manner as described for **33a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.54 (s, 1H), 9.93 (d, $J$ = 7.7 Hz, 1/2H), 9.86 (d, $J$ = 7.2 Hz, 1/2H), 8.05 (s, 1/2H), 8.03 (s, 1/2H), 7.63 – 7.16 (m, 20H), 6.99 (s, 1/2H), 6.89 (s, 1/2H), 6.76 (s, 1/2H), 6.73 (s, 1H), 6.71 (s, 1/2H), 5.47 (d, $J$ = 3.4 Hz, 1/2H), 5.41 (d, $J$ = 4.2 Hz, 1/2H), 4.91 (d, $J$ = 7.7 Hz, 1/2H), 4.74 (d, $J$ = 7.2 Hz, 1/2H), 2.08 – 1.86 (m, 1H), 1.61 (s, 3/2H), 1.57 (s, 3/2H), 1.48 (s, 9H), 1.46 (s, 3/2H), 1.42 (s, 3/2H), 0.89 (d, $J$ = 6.9 Hz, 3/2H), 0.83 (d, $J$ = 6.9 Hz, 3/2H), 0.46 (d, $J$

= 6.9 Hz, 3/2H), 0.38 (d, *J* = 6.9 Hz, 3/2H). HRMS (ESI) *m/z* calcd for $C_{49}H_{50}N_7O_{12}S_2$ [M − H] $^-$ 992.2964, found 992.2962.

**Preparation of intermediate 21-2.**




**4,5-Bis(benzhydryloxy)-2-isobutyrylpyridine 1-Oxide (74).** Compound **74** (3.58 g, 65%) was prepared from **47** (5.5 g, 10.36 mmol) and sulfur trioxide pyridine complex (4.94 g, 31.08 mmol) in the same manner as described for **36**. mp: 140 – 142 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.45 – 7.29 (m, 20H), 7.05 (s, 1H), 6.32 (s, 1H), 6.23 (s, 1H), 3.85 (p, *J* = 6.9 Hz, 1H), 1.06 (d, *J* = 6.9 Hz, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 201.50, 148.19, 147.45, 140.38, 139.73(2C), 139.50(2C), 130.57, 128.92(4C), 128.84(4C), 128.49(2C), 128.35(2C), 126.65(4C), 126.61(4C), 112.29, 84.29, 83.46, 39.09, 18.07(2C). HRMS (ESI) *m/z* calcd for $C_{35}H_{32}NO_4$ [M + H] $^+$ 530.2326, found 530.2327.

**(*R*)-4,5-Bis(benzhydryloxy)-2-(1-hydroxy-2-methylpropyl)pyridine 1-Oxide ((*R*)–75).** The catalyst for the reaction was freshly prepared by mixing together in solution in DMF (20 mL), dichloro(*p*-cymene)ruthenium(II) dimer (49.9 mg, 0.08 mmol), (1*S*, 2*S*)-(+)-*N*-(4-toluenesulphonyl)-1,2-ethane diamine (59.8 mg, 0.16 mmol) and triethylamine (24.2 mg, 0.24 mmol). The mixture was stirred at room temperature under argon for 1 h. In parallel, a mixture of formic acid/triethylamine 5:2 [(1.4 mL, 37.1 mmol):(2.1 mL, 15.1 mmol)] was prepared. To this formic acid/trimethylamine solution was added **74** (2.55 g, 4.81 mmol) dissolved in *tert*-Butyl methyl ether (20 mL). The preformed catalyst solution was then added to *tert*-Butyl methyl ether solution and the reaction mixture stirred at room temperature for 14 h. Water (20 mL) was added and the effervescent solution stirred for a further 20 min. The reaction mixture was extracted with ethyl acetate (50 mL × 2). The combined organic layers were washed with brine solution, dried over anhydrous $Na_2SO_4$, filtered and then the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel with petroleum/ethyl acetate to afford (*R*)–**75** as a white solid (2.45 g, 96%). After recrystallization in ethyl acetate, the *ee* value was raised to 98.1%. Chiral HPLC retention time 6.68 min; column: CHIRALCEL OD-H column (250 × 4.6 mm, 5μm); column temperature 30 °C; flow rate 0.5 mL/min; detection UV 254 nm; mobile phase:

solvent A = ethanol (40%), solvent B= *n*-hexane (60%); total run time 15.0 min. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.45 – 7.27 (m, 20H), 6.55 (s, 1H), 6.27 (s, 1H), 6.23 (d, *J* = 8.7 Hz, 1H), 6.18 (s, 1H), 4.03 (t, *J* = 8.5 Hz, 1H), 2.25 – 2.12 (m, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.53 (d, *J* = 6.7 Hz, 3H). HRMS (ESI) *m/z* calcd for $C_{35}H_{34}NO_4$ $[M + H]^+$ 532.2482, found 532.2484.

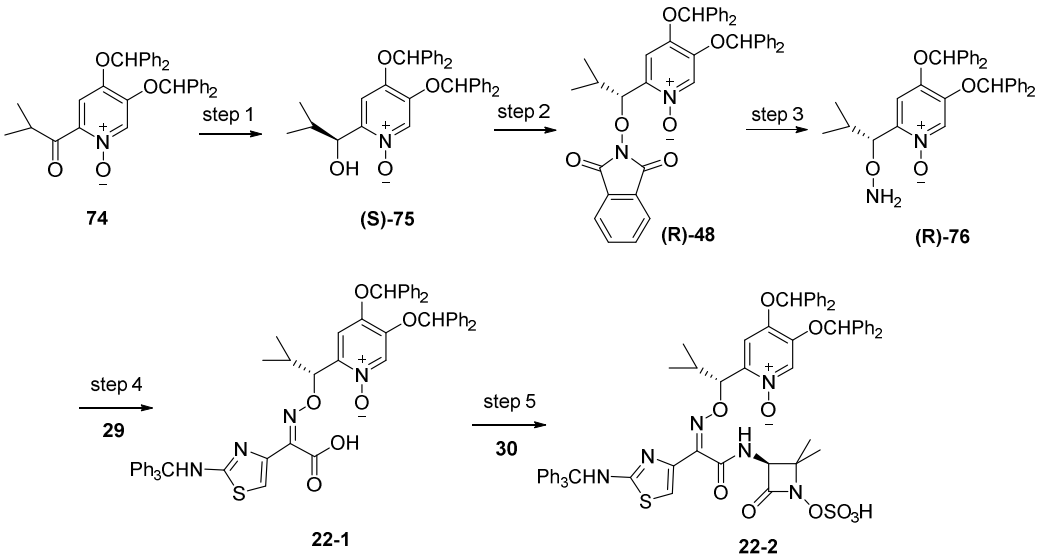
**(*S*)-4,5-Bis(benzhydryloxy)-2-(1-((1,3-dioxoisoindolin-2-yl)oxy)-2-methylpropyl)pyridine 1-Oxide ((*S*)–48).** Compound (*S*)–**48** (2.5 g, 71%) was prepared from (*R*)–**75** (2.75 g, 5.17 mmol), *N*-hydroxyphthalimide (844 mg, 5.17 mmol), $PBu_3$ (1.94 mL, 7.75 mmol) and DIAD (1.52 mL, 7.75 mmol) in the same manner as described for **72a**. After recrystallization in ethyl acetate, the *ee* value of (*S*)–**48** was raised to 99.7%. Chiral HPLC retention time 9.13 min; column: CHIRALCEL OD-H column (250 × 4.6 mm, 5μm); column temperature 30 °C; flow rate 0.5 mL/min; detection UV 254 nm; mobile phase: solvent A = ethanol (40%), solvent B= *n*-hexane (60%); total run time 20.0 min. mp: 86 – 88 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.74 (m, 2H), 7.72 (s, 1H), 7.72 – 7.68 (m, 2H), 7.59 (s, 1H), 7.58 – 7.26 (m, 20H), 6.71 (s, 1H), 6.14 (s, 1H), 5.88 (d, *J* = 4.3 Hz, 1H), 2.10 (pd, *J* = 7.0, 4.3 Hz, 1H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.63 (d, *J* = 7.0 Hz, 3H). HRMS (ESI) *m/z* calcd for $C_{43}H_{37}N_2O_6$ $[M + H]^+$ 677.2646, found 677.2645.

**(*S*)-2-(1-(Aminooxy)-2-methylpropyl)-4,5-bis(benzhydryloxy)pyridine 1-Oxide ((S)–76).** Compound (*S*)–**76** (2.36 g, 83%) was prepared from (*S*)–**48** (3.54 g, 5.32 mmol) and 85% hydrazine hydrate (0.33 mL, 5.75 mmol) in the same manner as described for **31b**. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.48 – 7.27 (m, 20H), 6.69 (s, 1H), 6.32 (s, 1H), 6.19 (s, 1H), 4.93 (d, *J* = 4.7 Hz, 1H), 1.99 (pd, *J* = 6.9, 4.7 Hz, 1H), 0.92 (d, J = 6.9 Hz, 3H), 0.66 (d, *J* = 6.9 Hz, 3H). HRMS (ESI) *m/z* calcd for $C_{35}H_{35}N_2O_4$ $[M + H]^+$ 547.2591, found 547.2596.

**(*S*,*Z*)-4,5-Bis(benzhydryloxy)-2-(1-(((carboxy(2-(tritylamino)thiazol-4-yl)methylene)amino)oxy)-2-methylpropyl)pyridine 1-Oxide (21-1).** Compound **21-1** (683 mg, 83%) was prepared from (*S*)–**76** (480 mg, 0.88 mmol) and **29** (327 mg, 0.79 mmol) in the same manner as described for **32a**. mp: 170 – 171 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.63 (s, 1H), 7.89 (s, 1H), 7.61 – 7.10 (m, 37H), 6.76 (s, 1H), 6.63 (s, 1H), 5.21 (d, J = 2.9 Hz, 1H), 2.15 – 2.05 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H), 0.45 (d, J = 6.9 Hz, 3H). MS (ESI): *m/z* 941 $[M - H]^-$.

**4,5-Bis(benzhydryloxy)-2-((*S*)-1-((((*Z*)-2-(((*S*)-2,2-dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxo-1-(2-(tritylamino)thiazol-4-yl)ethylidene)amino)oxy)-2-methylpropyl)pyridine 1-Oxide (21-2).** Compound **21-2** (740 mg, 93%) was prepared from **21-1** (663 mg, 0.70 mmol) and **30** (221 mg, 1.05 mmol) in the same manner as described for **33a**. mp: 179 °C decomp. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.78 (d, *J* = 7.8 Hz, 1H), 8.91 (s, 1H), 8.00 (s, 1H), 7.64 – 7.17 (m, 35H), 7.05 (s, 1H), 6.79 (s, 1H), 6.77 (s, 1H), 6.71 (s, 1H), 5.32 (d, *J* = 3.3 Hz, 1H), 4.81 (d, *J* = 7.8 Hz, 1H), 2.03 – 1.90 (m, 1H), 1.57 (s, 3H), 1.35 (s, 3H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.32 (d, *J* = 7.0 Hz, 3H). MS (ESI): *m/z* 1133 $[M - H]^-$.

**Preparation of intermediate 22-2.**




**(*S*)-4,5-Bis(benzhydryloxy)-2-(1-hydroxy-2-methylpropyl)pyridine 1-Oxide ((*S*)–75).** Compound (*S*)–**75** (2.55 g, 85%) was prepared from **74** (2.99 g, 5.66 mmol), dichloro(*p*-cymene)ruthenium(II) dimer (55.7 mg, 0.09 mmol) and (1*R*, 2*R*)-(+)-*N*-(4-toluenesulphonyl)-1,2-ethane diamine (66.0 mg, 0.18 mmol) in the same manner as described for (*R*)–**75**. After recrystallization in ethyl acetate, the *ee* value of (*S*)–**75** was raised to 99.0%. Chiral HPLC retention time 8.49 min; column: CHIRALCEL OD-H column (250 × 4.6 mm, 5μm); column temperature 30 °C; flow rate 0.5 mL/min; detection UV 254 nm; mobile phase: solvent A = ethanol (40%), solvent B= *n*-hexane (60%); total run time 15.0 min. mp: 93 – 95 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.44 – 7.28 (m, 20H), 6.54 (s, 1H), 6.27 (s, 1H), 6.22 (d, *J* = 8.7 Hz, 1H), 6.18 (s, 1H), 4.02 (t, *J* = 8.3 Hz, 1H), 2.25 – 2.12 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.53 (d, *J* = 6.7 Hz, 3H). HRMS (ESI) *m/z* calcd for $C_{35}H_{34}NO_4$ $[M + H]^+$ 532.2482, found 532.2484.

**(*R*)-4,5-Bis(benzhydryloxy)-2-(1-((1,3-dioxoisoindolin-2-yl)oxy)-2-methylpropyl)pyridin e 1-Oxide ((*R*)–48).** Compound (*R*)–**48** (1.57 g, 71%) was prepared from (*S*)–**75** (1.75 g, 3.29 mmol), *N*-hydroxyphthalimide (537 mg, 3.29 mmol), $PBu_3$ (1.24 mL, 4.94 mmol) and DIAD (1.03 mL, 5.24 mmol) in the same manner as described for **72a**. After recrystallization in ethyl acetate, the *ee* value of (*R*)–**48** was raised to 97.9%. Chiral HPLC retention time 12.29 min; column: CHIRALCEL OD-H column (250 × 4.6 mm, 5μm); column temperature 30 °C; flow rate 0.5 mL/min; detection UV 254 nm; mobile phase: solvent A = ethanol (40%), solvent B= *n*-hexane (60%); total run time 20.0 min. mp: 87 – 89 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.74 (m, 2H), 7.73 (s, 1H), 7.72 – 7.69 (m, 2H), 7.59 (s, 1H), 7.58 – 7.25 (m, 20H), 6.72 (s, 1H), 6.15 (s, 1H), 5.88 (d, *J* = 4.3 Hz, 1H), 2.11 (pd, *J* = 7.0, 4.3 Hz, 1H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.63 (d, *J* = 6.9 Hz, 3H). HRMS (ESI) *m/z* calcd for $C_{43}H_{37}N_2O_6$ $[M + H]^+$ 677.2646, found 677.2644.

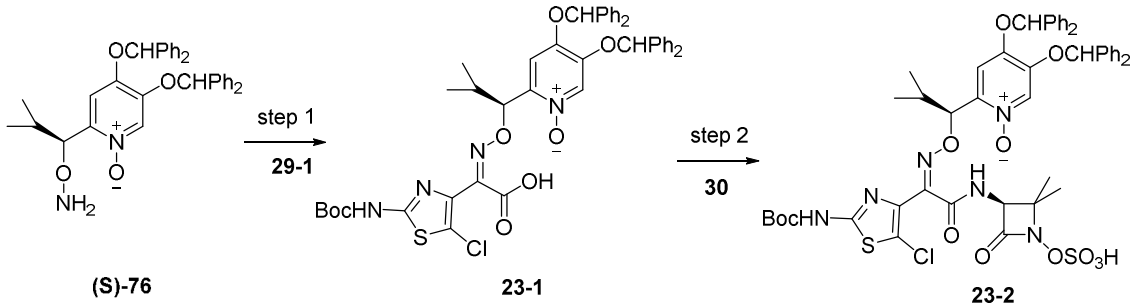
**(*R*)-2-(1-(Aminooxy)-2-methylpropyl)-4,5-bis(benzhydryloxy)pyridine 1-Oxide ((*R*) –76).**

Compound (*R*)–**76** (600 mg, 89%) was prepared from (*R*)–**48** (840 mg, 1.24 mmol) and 85% hydrazine hydrate (0.08 mL, 1.36 mmol) in the same manner as described for **31b**. mp: 72 – 74 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.48 – 7.27 (m, 21H), 6.69 (s, 1H), 6.31 (s, 1H), 6.19 (s, 1H), 4.93 (d, *J* = 4.7 Hz, 1H), 1.99 (pd, *J* = 6.9, 4.7 Hz, 1H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.66 (d, *J* = 6.9 Hz, 3H). HRMS (ESI) *m/z* calcd for $C_{35}H_{35}N_2O_4$ [M + H] $^+$ 547.2591, found 547.2594.

**(*R*,*Z*)-4,5-Bis(benzhydryloxy)-2-(1-(((carboxy(2-(tritylamino)thiazol-4-yl)methylene)amino)oxy)-2-methylpropyl)pyridine 1-Oxide (22-1).** Compound **22-1** (500 mg, 72%) was prepared from (*R*)–**76** (400 mg, 0.73 mmol) and **29** (245 mg, 0.59 mmol) in the same manner as described for **32a**. mp: 170 – 172 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.90 (s, 1H), 7.99 (s, 1H), 7.62 – 7.16 (m, 35H), 6.95 (s, 1H), 6.90 (s, 1H), 6.69 (s, 1H), 6.54 (s, 1H), 5.28 (d, *J* = 3.2 Hz, 1H), 2.12 – 2.00 (m, 1H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.43 (d, *J* = 6.8 Hz, 3H). MS (ESI): *m/z* 941 [M − H]$^-$.

**4,5-Bis(benzhydryloxy)-2-((*R*)-1-((((*Z*)-2-(((*S*)-2,2-dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxo-1-(2-(tritylamino)thiazol-4-yl)ethylidene)amino)oxy)-2-methylpropyl)pyridine 1-Oxide (22-2).** Compound **22-2** (520 mg, 90%) was prepared from **22-1** (480 mg, 0.51 mmol) and **30** (160 mg, 0.76 mmol) in the same manner as described for **33a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.68 (d, *J* = 7.1 Hz, 1H), 8.91 (s, 1H), 8.03 (s, 1H), 7.63 – 7.17 (m, 35H), 6.87 (s, 1H), 6.75 (s, 1H), 6.74 (s, 1H), 6.73 (s, 1H), 5.26 (d, *J* = 3.8 Hz, 1H), 4.65 (d, *J* = 7.1 Hz, 1H), 1.94 – 1.84 (m, 1H), 1.53 (s, 3H), 1.37 (s, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.36 (d, *J* = 6.9 Hz, 3H). MS (ESI): *m/z* 1133 [M − H] $^-$.

**Preparation of intermediate 23-2.**

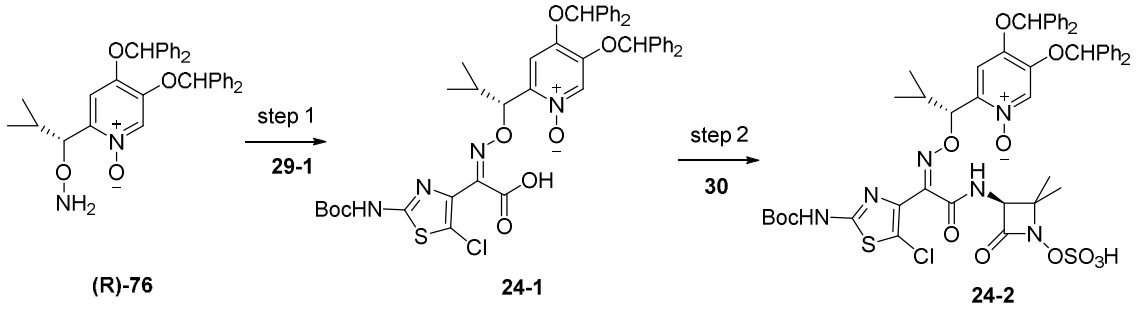



**(*S*,*Z*)-4,5-Bis(benzhydryloxy)-2-(1-((((2-((*tert*-butoxycarbonyl)amino)-5-chlorothiazol-4-yl)(carboxy)methylene)amino)oxy)-2-methylpropyl)pyridine 1-Oxide (23-1).** Compound **23-1** (595 mg, 82%) was prepared from (*S*)–**76** (475 mg, 0.87 mmol) and **29**-1(239 mg, 0.78 mmol) in the same manner as described for **32a**. mp: 161 – 162 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.00 (s, 1H), 7.96 (s, 1H), 7.68 – 7.16 (m, 22H), 6.68 (s, 1H), 5.31 (d, *J* = 6.3 Hz, 1H), 2.17 – 2.06 (m, 1H), 1.46 (s, 9H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.47 (d, *J* = 6.8 Hz, 3H). MS (ESI): *m/z* 833 [M − H] $^-$.

**4,5-Bis(benzhydryloxy)-2-((*S*)-1-((((*Z*)-1-(2-((*tert*-butoxycarbonyl)amino)-5-chlorothiazol-4-yl)-2-(((*S*)-2,2-dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropyl)pyridine 1-Oxide (23-2).** Compound **23-2** (640 mg, 90%) was

prepared from **23-1** (580 mg, 0.69 mmol) and **30** (219 mg, 1.04 mmol) in the same manner as described for **33a**. mp: 165 °C decomp. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.07 (d, $J$ = 3.9 Hz, 1H), 9.90 (d, $J$ = 8.0 Hz, 1H), 7.98 (s, 1H), 7.64 – 7.21 (m, 20H), 7.09 (s, 1H), 6.77 (s, 1H), 6.69 (s, 1H), 5.40 (d, $J$ = 3.4 Hz, 1H), 4.87 (d, $J$ = 8.0 Hz, 1H), 2.03 (td, $J$ = 7.0, 3.6 Hz, 1H), 1.59 (s, 3H), 1.45 (s, 9H), 1.40 (s, 3H), 0.89 (d, $J$ = 6.9 Hz, 3H), 0.38 (d, $J$ = 7.0 Hz, 3H). MS (ESI): *m/z* 1025 [M − H] $^-$.

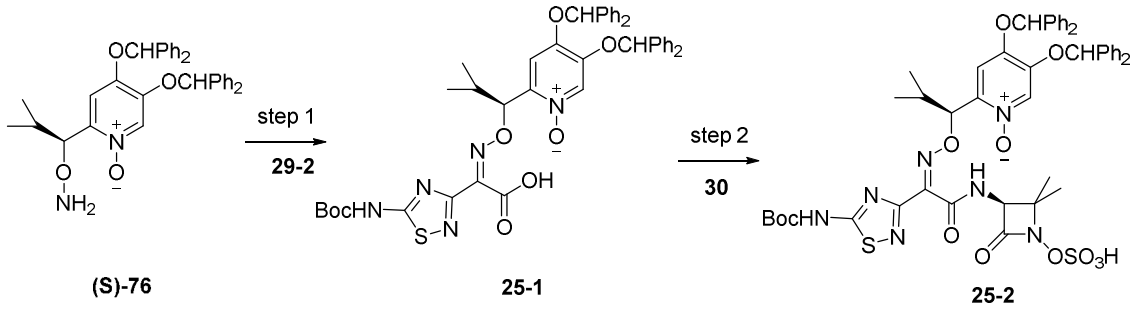
**Preparation of intermediate 24-2.**




**(*R*,*Z*)-4,5-Bis(benzhydryloxy)-2-(1-((((2-((*tert*-butoxycarbonyl)amino)-5-chlorothiazol-4-yl)(carboxy)methylene)amino)oxy)-2-methylpropyl)pyridine 1-Oxide (24-1).** Compound **24-1** (510 mg, 81%) was prepared from (*R*)–**76** (415 mg, 0.76 mmol) and **29**-1 (209 mg, 0.68 mmol) in the same manner as described for **32a**. mp: 159 – 162 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.92 (s, 1H), 7.88 (s, 1H), 7.67 – 7.19 (m, 22H), 6.64 (s, 1H), 5.23 (s, 1H), 2.12 (s, 1H), 1.45 (s, 9H), 0.96 (d, $J$ = 6.9 Hz, 3H), 0.47 (d, $J$ = 7.0 Hz, 3H). MS (ESI): *m/z* 833 [M − H] $^-$.

**4,5-Bis(benzhydryloxy)-2-((*R*)-1-((((*Z*)-1-(2-((*tert*-butoxycarbonyl)amino)-5-chlorothiazol-4-yl)-2-(((*S*)-2,2-dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropyl)pyridine 1-Oxide (24-2).** Compound **24-2** (567 mg, 90%) was prepared from **24-1** (510 mg, 0.61 mmol) and **30** (193 mg, 0.92 mmol) in the same manner as described for **33a**. mp: 171 °C decomp. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.03 (s, 1H), 9.79 (d, $J$ = 7.7 Hz, 1H), 8.01 (s, 1H), 7.62 – 7.19 (m, 22H), 6.94 (s, 1H), 6.74 (s, 1H), 6.72 (s, 1H), 5.33 (d, $J$ = 4.2 Hz, 1H), 4.73 (d, $J$ = 7.7 Hz, 1H), 1.98 – 1.90 (m, 1H), 1.54 (s, 3H), 1.45 (s, 9H), 1.42 (s, 3H), 0.82 (d, $J$ = 6.8 Hz, 3H), 0.45 (d, $J$ = 6.9 Hz, 3H). MS (ESI): *m/z* 1025 [M − H] $^-$.

**Preparation of intermediate 25-2.**

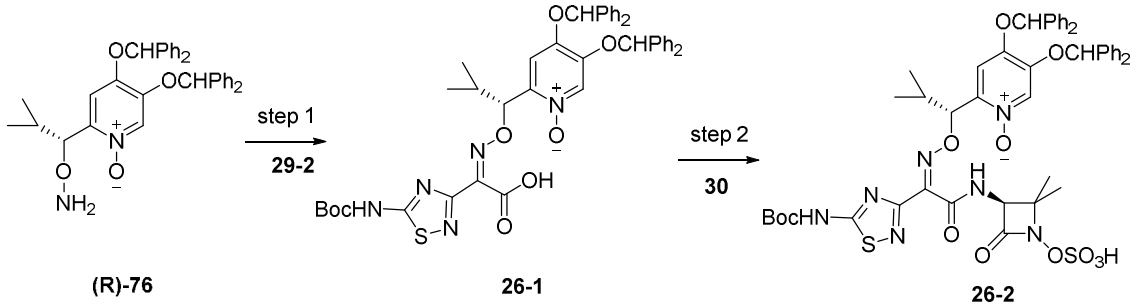



**(*S*,*Z*)-4,5-Bis(benzhydryloxy)-2-(1-((((5-((*tert*-butoxycarbonyl)amino)-1,2,4-thiadiazol-3-**

**yl)(carboxy)methylene)amino)oxy)-2-methylpropyl)pyridine 1-Oxide (25-1).** Compound **25-1** (560 mg, 85%) was prepared from (*S*)–**76** (450 mg, 0.82 mmol) and **29**-2 (224 mg, 0.82 mmol) in the same manner as described for **32a**. mp: 182 – 184 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.54 (s, 1H), 8.04 (s, 1H), 7.61 – 7.06 (m, 20H), 6.89 (s, 1H), 6.71 (s, 1H), 6.54 (s, 1H), 5.43 (d, $J$ = 3.8 Hz, 1H), 2.14 – 2.03 (m, 1H), 1.49 (s, 9H), 0.90 (d, $J$ = 6.8 Hz, 3H), 0.52 (d, $J$ = 6.9 Hz, 3H). MS (ESI): *m/z* 800 [M − H]$^-$.

**4,5-Bis(benzhydryloxy)-2-((*S*)-1-((((*Z*)-1-(5-((*tert*-butoxycarbonyl)amino)-1,2,4-thiadiazol-3-yl)-2-(((*S*)-2,2-dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropyl)pyridine 1-Oxide (25-2).** Compound **25-2** (545 mg, 86%) was prepared from **25-1** (510 mg, 0.64 mmol) and **30** (200 mg, 0.95 mmol) in the same manner as described for **33a**. mp: 182 °C decomp. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.52 (s, 1H), 9.92 (d, $J$ = 7.7 Hz, 1H), 8.02 (s, 1H), 7.65 – 7.18 (m, 20H), 6.98 (s, 1H), 6.76 (s, 1H), 6.71 (s, 1H), 5.47 (d, $J$ = 3.5 Hz, 1H), 4.90 (d, $J$ = 7.7 Hz, 1H), 2.06 – 1.92 (m, 1H), 1.60 (s, 3H), 1.48 (s, 9H), 1.41 (s, 3H), 0.88 (d, $J$ = 6.8 Hz, 3H), 0.38 (d, $J$ = 6.9 Hz, 3H). MS (ESI): *m/z* 992 [M − H]$^-$.

**Preparation of intermediate 26-2.**

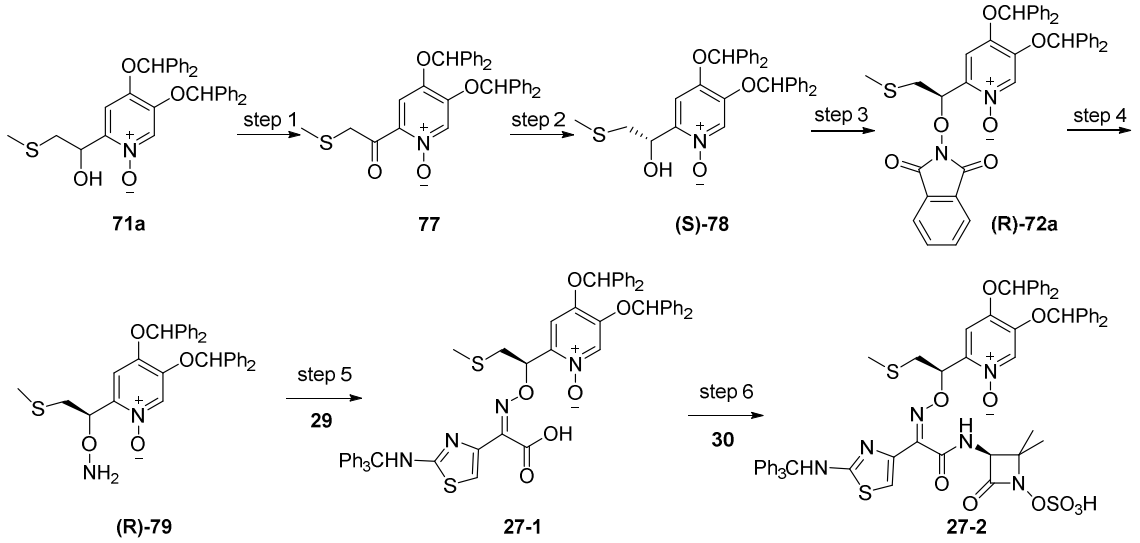



(R)-76 26-1 26-2

**(*R*,*Z*)-4,5-Bis(benzhydryloxy)-2-(1-((((5-((*tert*-butoxycarbonyl)amino)-1,2,4-thiadiazol-3-yl)(carboxy)methylene)amino)oxy)-2-methylpropyl)pyridine 1-Oxide (26-1).** Compound **26-1** (533 mg, 76%) was prepared from (*R*)-**76** (480 mg, 0.88 mmol) and **29**-2 (240 mg, 0.88 mmol) in the same manner as described for **32a**. mp: 184 – 186 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.54 (s, 1H), 8.04 (s, 1H), 7.61 – 7.06 (m, 20H), 6.89 (s, 1H), 6.71 (s, 1H), 6.54 (s, 1H), 5.43 (d, $J$ = 3.8 Hz, 1H), 2.14 – 2.02 (m, 1H), 1.49 (s, 9H), 0.90 (d, $J$ = 6.8 Hz, 3H), 0.52 (d, $J$ = 6.9 Hz, 3H). MS (ESI): *m/z* 800 [M − H]$^-$.

**4,5-Bis(benzhydryloxy)-2-((*R*)-1-((((*Z*)-1-(5-((*tert*-butoxycarbonyl)amino)-1,2,4-thiadiazol-3-yl)-2-(((*S*)-2,2-dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxoethylidene)amino)oxy)-2-methylpropyl)pyridine 1-Oxide (26-2).** Compound **26-2** (520 mg, 82%) was prepared from **26-1** (513 mg, 0.64 mmol) and **30** (202 mg, 0.96 mmol) in the same manner as described for **33a**. mp: 181 °C decomp. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.52 (s, 1H), 9.84 (d, $J$ = 7.2 Hz, 1H), 8.04 (s, 1H), 7.64 – 7.19 (m, 20H), 6.88 (s, 1H), 6.73 (s, 1H), 6.72 (s, 1H), 5.40 (d, $J$ = 4.3 Hz, 1H), 4.73 (d, $J$ = 7.2 Hz, 1H), 2.04 – 1.84 (m, 1H), 1.56 (s, 3H), 1.49 (s, 9H), 1.45 (s, 3H), 0.82 (d, $J$ = 6.9 Hz, 3H), 0.45 (d, $J$ = 6.9 Hz, 3H). MS (ESI): *m/z* 992 [M − H]$^-$.

**Preparation of intermediate 27-2.**




**4,5-Bis(benzhydryloxy)-2-(2-(methylthio)acetyl)pyridine 1-Oxide (77).** Compound **77** (2.57 g, 48%) was prepared from **71a** (5.4 g, 9.84 mmol) and sulfur trioxide pyridine complex (4.69 g, 29.52 mmol) in the same manner as described for **36**. mp: 115 – 116 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.48 – 7.27 (m, 21H), 6.35 (s, 1H), 6.23 (s, 1H), 4.01 (s, 2H), 1.91 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 188.37, 148.93, 147.26, 139.71(2C), 139.39(2C), 138.95, 130.39, 128.95(4C), 128.85(4C), 128.54(2C), 128.35(2C), 126.65(4C), 126.56(4C), 112.84, 84.31, 83.38, 44.17, 15.14. HRMS (ESI) *m/z* calcd for $C_{34}H_{30}NO_4S$ $[M + H]^+$ 548.1890, found 548.1900.

**(*S*)-4,5-Bis(benzhydryloxy)-2-(1-hydroxy-2-(methylthio)ethyl)pyridine 1-Oxide ((*S*)–78).** Compound (*S*)–**78** (1.56 g, 86%) was prepared from **77** (1.8 g, 3.29 mmol), dichloro(*p*-cymene)ruthenium(II) dimer (31.1 mg, 0.05 mmol) and (1*S*, 2*S*)-(+)-*N*-(4-toluenesulphonyl)-1,2-ethane diamine (37.3 mg, 0.10 mmol) in the same manner as described for (*R*)–**75**. After recrystallization in ethyl acetate, the *ee* value of (*S*)–**78** was raised to 97.9%. Chiral HPLC retention time 11.97 min; column: CHIRALCEL OD-H column (250 × 4.6 mm, 5μm); column temperature 30 °C; flow rate 0.5 mL/min; detection UV 254 nm; mobile phase: solvent A = ethanol (40%), solvent B= *n*-hexane (60%); total run time 15.0 min. mp: 75 – 77 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.45 – 7.28 (m, 20H), 6.80 (s, 1H), 6.30 (s, 1H), 6.19 (s, 1H), 5.98 (d, *J* = 7.6 Hz, 1H), 4.73 – 4.63 (m, 1H), 3.04 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.77 (dd, *J* = 13.8, 6.3 Hz, 1H), 1.82 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{34}H_{32}NO_4S$ $[M + H]^+$ 550.2047, found 550.2048.

**(*R*)-4,5-Bis(benzhydryloxy)-2-(1-((1,3-dioxoisoindolin-2-yl)oxy)-2-(methylthio)ethyl)pyridine 1-Oxide ((*R*)–72a).** Compound (*R*)–**72a** (341 mg, 42%) was prepared from (*S*)–**78** (640 mg, 1.16 mmol), *N*-hydroxyphthalimide (1.89 g, 11.60 mmol), $PBu_3$ (1.74 mL, 6.96 mmol) and DIAD (1.36 mL, 6.96 mmol) in the same manner as described for **72a**. After recrystallization in ethyl acetate, the *ee* value of (*R*)–**72a** was raised to 97.1%. Chiral HPLC

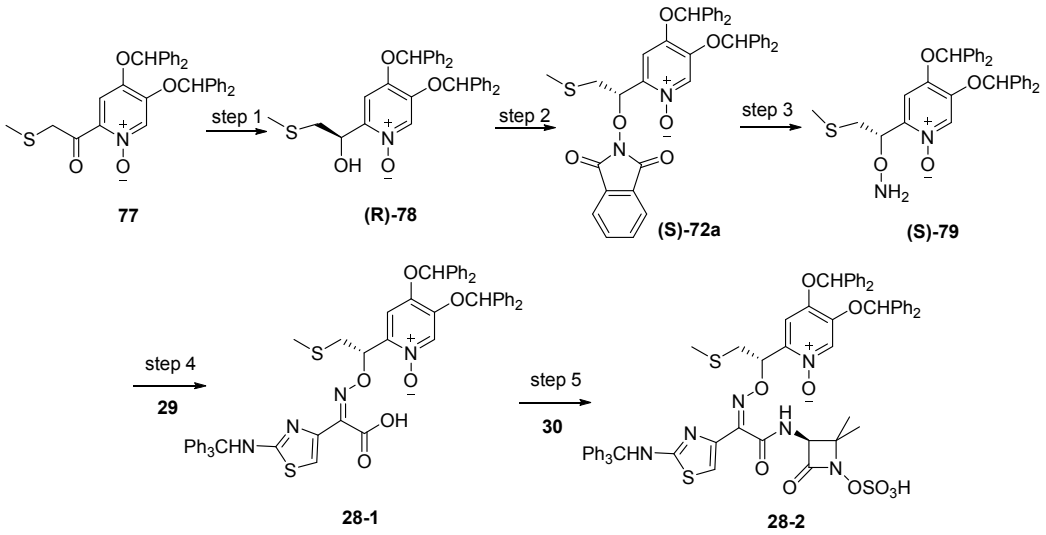
retention time 24.42 min; column: CHIRALPAK AD-H column (250 × 4.6 mm, 5μm); column temperature 30 °C; flow rate 0.5 mL/min; detection UV 254 nm; mobile phase: solvent A = ethanol (30%), solvent B= *n*-hexane (70%); total run time 30.0 min. mp: 77 – 79 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.81 – 7.78 (m, 2H), 7.74 (s, 2H), 7.74 – 7.72 (m, 2H), 7.63 – 7.27 (m, 20H), 6.73 (s, 1H), 6.17 (s, 1H), 6.13 (dd, *J* = 5.8, 3.5 Hz, 1H), 3.15 (dd, *J* = 14.9, 3.5 Hz, 1H), 2.90 (dd, *J* = 14.9, 5.8 Hz, 1H), 1.88 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{42}H_{35}N_2O_6S$ $[M + H]^+$ 695.2210, found 695.2211.

**(*R*)-2-(1-(Aminooxy)-2-(methylthio)ethyl)-4,5-bis(benzhydryloxy)pyridine 1-Oxide ((*R*)–79).** Compound (*R*)–**79** (287 mg, 81%) was prepared from (*R*)–**72a** (439 mg, 0.63 mmol) and 85% hydrazine hydrate (0.04 mL, 0.67 mmol) in the same manner as described for **31b**. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.49 – 7.27 (m, 21H), 6.80 (s, 1H), 6.32 (s, 1H), 6.18 (s, 1H), 5.19 (dd, *J* = 7.3, 3.1 Hz, 1H), 5.05 (s, 2H), 2.95 (dd, *J* = 14.2, 3.1 Hz, 1H), 2.62 (dd, *J* = 14.2, 7.3 Hz, 1H), 2.01 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{34}H_{33}N_2O_4S$ $[M + H]^+$ 565.2156, found 565.2153.

**(*R*,*Z*)-4,5-Bis(benzhydryloxy)-2-(1-(((carboxy(2-(tritylamino)thiazol-4-yl)methylene)amino)oxy)-2-(methylthio)ethyl)pyridine 1-Oxide (27-1).** Compound **27-1** (371 mg, 76%) was prepared from (*R*)–**79** (287 mg, 0.51 mmol) and **29** (199 mg, 0.48 mmol) in the same manner as described for **32a**. mp: 188 – 190 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.89 (s, 1H), 7.97 (s, 1H), 7.60 – 7.04 (m, 35H), 6.92 (s, 1H), 6.66 (s, 1H), 6.57 (s, 1H), 5.53 (dd, *J* = 6.6, 3.0 Hz, 1H), 2.96 (dd, *J* = 14.8, 3.0 Hz, 1H), 2.71 (dd, *J* = 14.8, 6.7 Hz, 1H), 1.91 (s, 3H). MS (ESI): *m/z* 959 $[M - H]^-$.

**4,5-Bis(benzhydryloxy)-2-((*R*)-1-((((*Z*)-2-(((*S*)-2,2-dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxo-1-(2-(tritylamino)thiazol-4-yl)ethylidene)amino)oxy)-2-(methylthio)ethyl)pyridine 1-Oxide (27-2).** Compound **27-2** (335 mg, 83%) was prepared from **27-1** (336 mg, 0.35 mmol) and **30** (109 mg, 0.52 mmol) in the same manner as described for **33a**. mp: 184 °C decomp. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.82 (d, *J* = 7.7 Hz, 1H), 8.94 (s, 1H), 8.02 (s, 1H), 7.66 – 7.05 (m, 35H), 6.84 (s, 1H), 6.83 (s, 1H), 6.72 (s, 1H), 5.59 (dd, *J* = 6.6, 3.0 Hz, 1H), 4.76 (d, *J* = 7.7 Hz, 1H), 2.85 (dd, *J* = 14.6, 3.0 Hz, 1H), 2.61 (dd, *J* = 14.6, 6.6 Hz, 1H), 1.73 (s, 3H), 1.55 (s, 3H), 1.33 (s, 3H). MS (ESI): m/z 1151 $[M - H]^-$.

**Preparation of intermediate 28-2.**




**(*R*)-4,5-bis(benzhydryloxy)-2-(1-hydroxy-2-(methylthio)ethyl)pyridine 1-Oxide ((*R*)–78).** Compound (*R*)–**78** (780 mg, 68%) was prepared from **77** (1.14 g, 2.08 mmol), dichloro(*p*-cymene)ruthenium(II) dimer (18.7 mg, 0.03 mmol) and (1*R*, 2*R*)-(+)-*N*-(4-toluenesulphonyl)-1,2-ethane diamine (22.4 mg, 0.06 mmol) in the same manner as described for (*R*)–**75**. After recrystallization in ethyl acetate, the *ee* value of (*R*)–**78** was raised to 96.7%. Chiral HPLC retention time 9.26 min; column: CHIRALCEL OD-H column (250 × 4.6 mm, 5μm); column temperature 30 °C; flow rate 0.5 mL/min; detection UV 254 nm; mobile phase: solvent A = ethanol (40%), solvent B= *n*-hexane (60%); total run time 15.0 min. mp: 73 – 75 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.45 – 7.29 (m, 20H), 6.80 (s, 1H), 6.30 (s, 1H), 6.19 (s, 1H), 5.97 (d, *J* = 7.8 Hz, 1H), 4.72 – 4.61 (m, 1H), 3.04 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.77 (dd, *J* = 13.8, 6.2 Hz, 1H), 1.83 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{34}H_{32}NO_4S$ $[M + H]^+$ 550.2047, found 550.2046.

**(*S*)-4,5-bis(benzhydryloxy)-2-(1-((1,3-dioxoisoindolin-2-yl)oxy)-2-(methylthio)ethyl)pyridine 1-Oxide ((*S*)–72a).** Compound (*S*)–**72a** (648 mg, 61%) was prepared from (*R*)–**78** (848 mg, 1.54 mmol), *N*-hydroxyphthalimide (2.51 g, 15.40 mmol), $PBu_3$ (2.31 mL, 9.24 mmol) and DIAD (1.81 mL, 9.24 mmol) in the same manner as described for **72a**. After recrystallization in ethyl acetate, the ee value of (*S*)–**72a** was raised to 94.9%. Chiral HPLC retention time 21.67min; column: CHIRALPAK AD-H column (250 × 4.6 mm, 5μm); column temperature 30 °C; flow rate 0.5 mL/min; detection UV 254 nm; mobile phase: solvent A = ethanol (30%), solvent B= *n*-hexane (70%); total run time 30.0 min. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.77 (m, 3H), 7.76 – 7.71 (m, 3H), 7.62 – 7.27 (m, 20H), 6.73 (s, 1H), 6.16 (s, 1H), 6.13 (dd, *J* = 5.7, 3.5 Hz, 1H), 3.16 (dd, *J* = 14.9, 3.5 Hz, 1H), 2.90 (dd, *J* = 14.9, 5.8 Hz, 1H), 1.88 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{42}H_{35}N_2O_6S$ $[M + H]^+$ 695.2210, found 695.2209.

**(*S*)-2-(1-(aminooxy)-2-(methylthio)ethyl)-4,5-bis(benzhydryloxy)pyridine 1-Oxide ((*S*)–79).** Compound (*S*)–**79** (390 mg, 82%) was prepared from (*S*)–**72a** (583 mg, 0.84 mmol) and

85% hydrazine hydrate (0.05 mL, 0.87 mmol) in the same manner as described for **31b**. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.47 – 7.28 (m, 20H), 6.80 (s, 1H), 6.32 (s, 1H), 6.18 (s, 1H), 5.19 (dd, *J* = 7.3, 3.1 Hz, 1H), 5.05 (s, 2H), 2.96 (dd, *J* = 14.2, 3.1 Hz, 1H), 2.62 (dd, *J* = 14.2, 7.3 Hz, 1H), 2.01 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{34}H_{33}N_2O_4S$ $[M + H]^+$ 565.2156, found 565.2156.

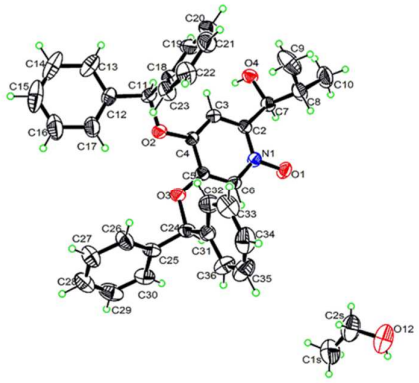
**(*S*,*Z*)-4,5-Bis(benzhydryloxy)-2-(1-(((carboxy(2-(tritylamino)thiazol-4-yl)methylene)amino)oxy)-2-(methylthio)ethyl)pyridine 1-Oxide (28-1).** Compound **28-1** (522 mg, 85%) was prepared from (*S*)–**79** (360 mg, 0.64 mmol) and **29** (265 mg, 0.64 mmol) in the same manner as described for **32a**. mp: 185 – 187 °C.$^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.93 (s, 1H), 8.00 (s, 1H), 7.63 – 7.05 (m, 35H), 6.94 (s, 1H), 6.70 (s, 1H), 6.57 (s, 1H), 5.54 (d, *J* = 6.5 Hz, 1H), 2.97 (d, *J* = 14.3 Hz, 1H), 2.71 (dd, *J* = 14.9, 6.9 Hz, 1H), 1.93 (s, 3H). MS (ESI): *m/z* 959 $[M - H]^-$.

**4,5-Bis(benzhydryloxy)-2-((S)-1-((((Z)-2-(((S)-2,2-dimethyl-4-oxo-1-(sulfooxy)azetidin-3-yl)amino)-2-oxo-1-(2-(tritylamino)thiazol-4-yl)ethylidene)amino)oxy)-2-(methylthio)ethyl)pyridine 1-Oxide (28-2).** Compound **28-2** (505 mg, 92%) was prepared from **28-1** (460 mg, 0.48 mmol) and **30** (151 mg, 0.72 mmol) in the same manner as described for **33a**. mp: 180 °C decomp. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.79 (d, *J* = 7.3 Hz, 1H), 8.90 (s, 1H), 8.02 (s, 1H), 7.63 – 7.18 (m, 35H), 6.80 (s, 1H), 6.77 (s, 1H), 6.71 (s, 1H), 5.56 (dd, *J* = 6.8, 3.2 Hz, 1H), 4.65 (d, *J* = 7.3 Hz, 1H), 2.82 (dd, *J* = 14.8, 3.2 Hz, 1H), 2.58 (dd, *J* = 14.8, 6.8 Hz, 1H), 1.86 (s, 3H), 1.51 (s, 3H), 1.35 (s, 3H). MS (ESI): *m/z* 1151 $[M - H]^-$.

## III. Spectral data of BAL30072

**(*S*,*Z*)-3-(2-(2-Aminothiazol-4-yl)-2-(((1,5-dihydroxy-4-oxo-1,4-dihydropyridin-2-yl)methoxy)imino)acetamido)-2,2-dimethyl-4-oxoazetidin-1-yl Hydrogen Sulfate (BAL30072).** $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.66 (d, *J* = 7.8 Hz, 1H), 8.26 (s, 1H), 7.15 (s, 1H), 6.89 (s, 1H), 5.33(s, 2H), 4.66 (d, *J* = 7.8 Hz, 1H), 1.45 (s, 3H), 1.25 (s, 3H).$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ169.47, 162.27, 161.92, 157.61, 150.72, 145.07, 142.86, 139.81, 128.15, 111.68, 111.15, 69.24, 68.31, 61.24, 23.87, 20.86. HRMS (ESI) *m/z* calcd for $C_{16}H_{17}N_6O_{10}S_2$ $[M - H]^-$ 517.0453, found 517.0462.

## IV. X-ray structure of (*S*)–75




## V. HPLC analysis for tested compounds

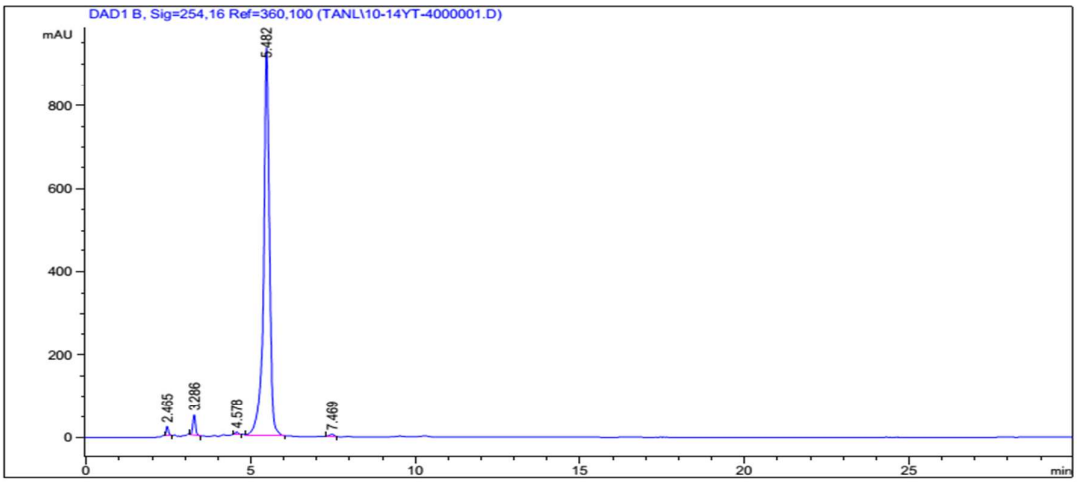
Method: PLATISIL ODS (250 × 4.6 mm, particle size 5μm); mobile phase: eluent A, methanol; eluent B, buffer solution (0.1% $CF_3COOH$ and 0.1% $NH_4OH$ in water, pH 3.5); isocratic (30:70) with a flow rate of 1 mL $min^{-1}$ and detection at 254 nm; column temperature, 30 ℃.

**Table S2.** HPLC analysis for tested compounds

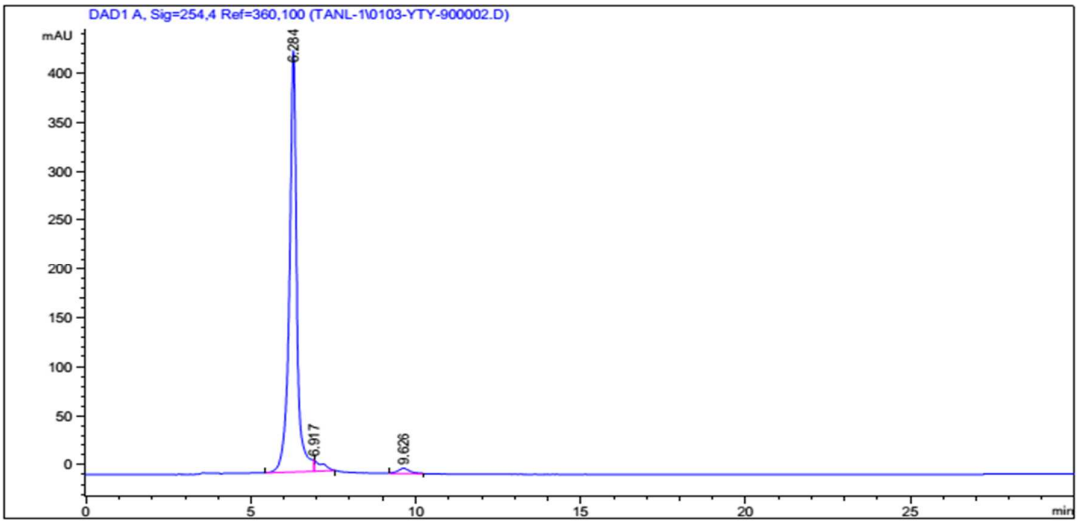
| Compd | Purity | Compd | Purity | Compd | Purity |
|---|---|---|---|---|---|
| **8** | 95.8% | **14a** | 98.2% | **20** | 95.7% |
| **9** | 95.7% | **14b** | 98.0% | **21** | 96.1% |
| **10** | 95.4% | **14c** | 96.6% | **22** | 95.9% |
| **11** | 95.2% | **15a** | 96.8% | **23** | 96.4% |
| **12a** | 97.6% | **15b** | 96.4% | **24** | 96.8% |
| **12b** | 97.1% | **15c** | 98.3% | **25** | 98.3% |
| **12c** | 96.4% | **16a** | 95.6% | **26** | 98.2% |
| **12d** | 95.1% | **16b** | 95.4% | **27** | 97.2% |
| **12e** | 99.3% | **16c** | 96.2% | **28** | 97.4% |
| **13a** | 95.1% | **17** | 95.1% | BAL30072 | 98.7% |
| **13b** | 96.0% | **18** | 95.8% | | |
| **13c** | 95.2% | **19** | 95.5% | | |

## HPLC Traces of Representative Compounds

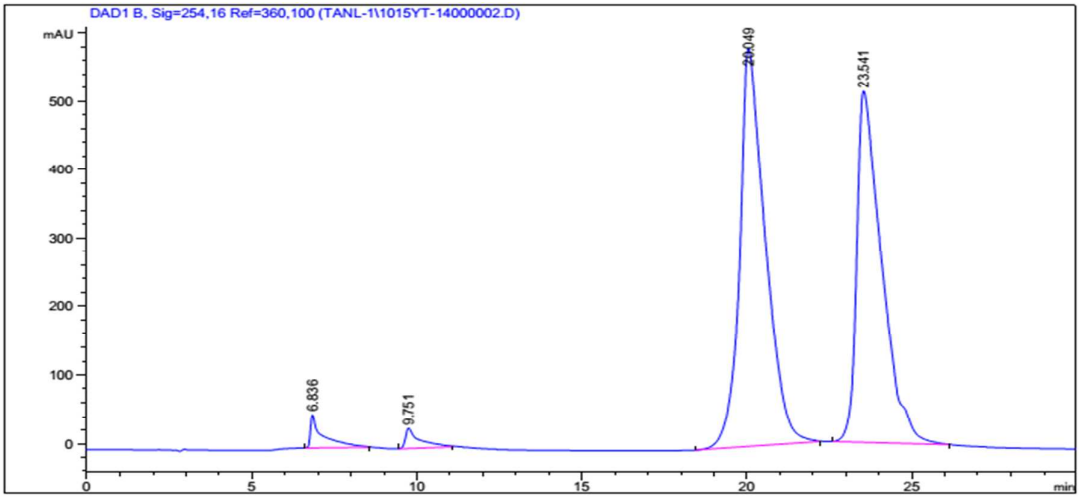
**8**



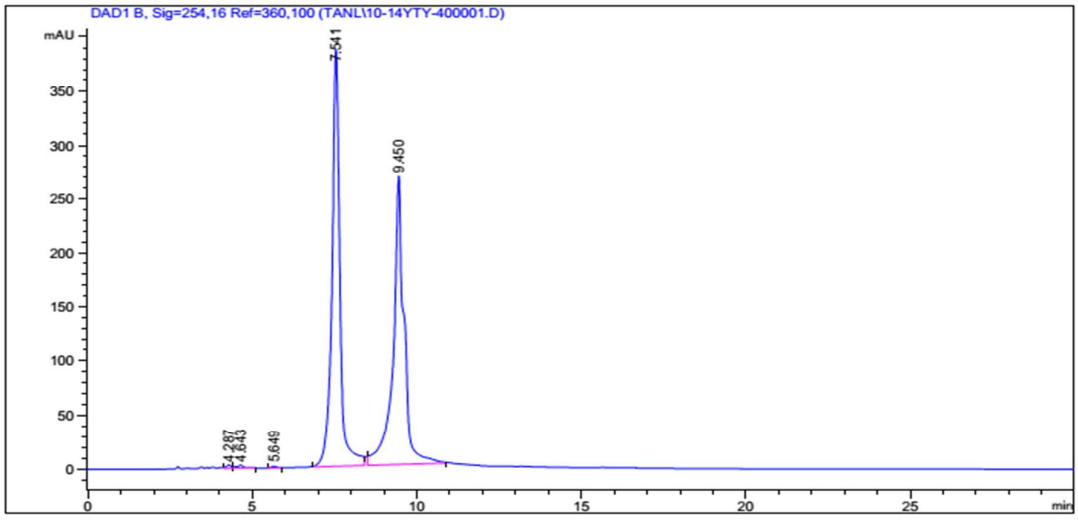

**10**



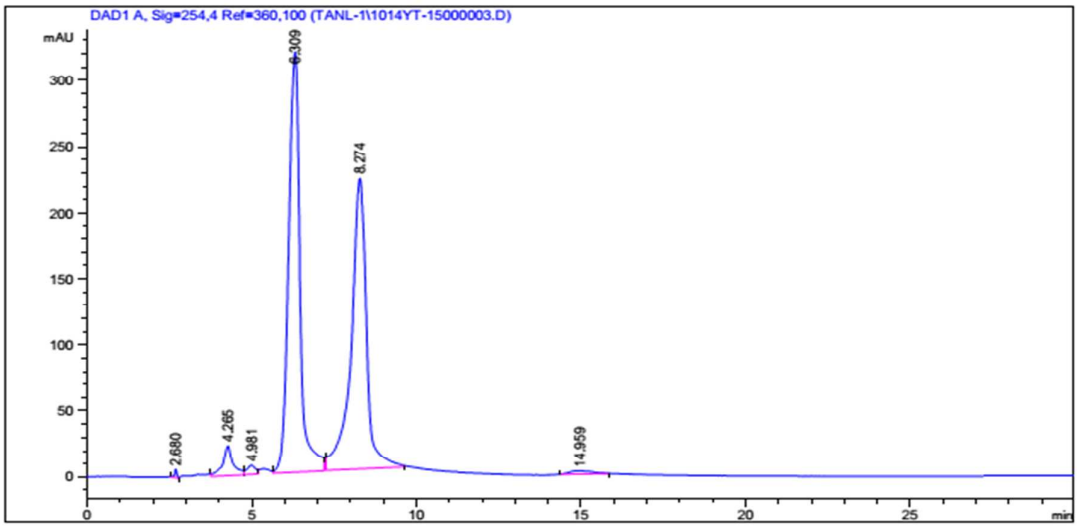

**12c**



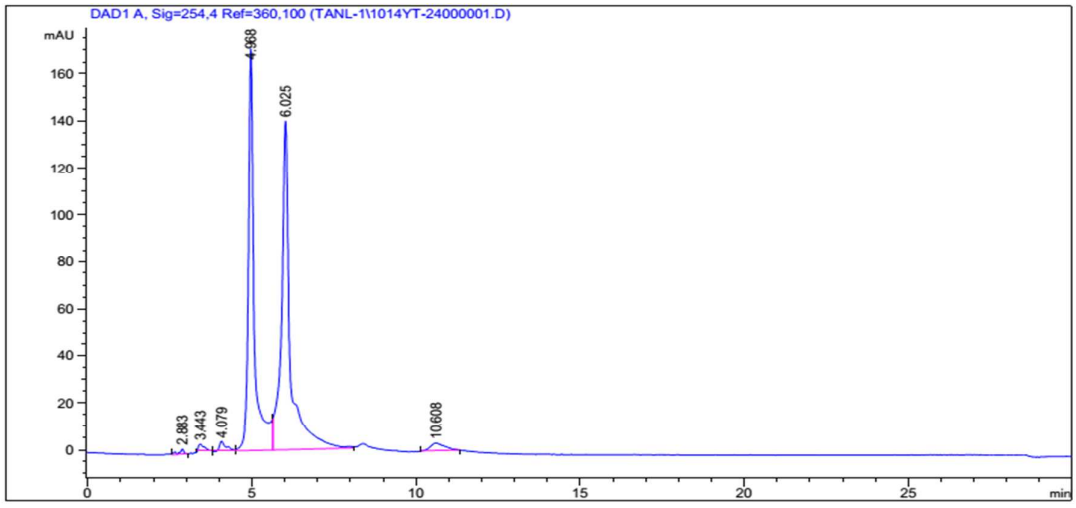
**12e**



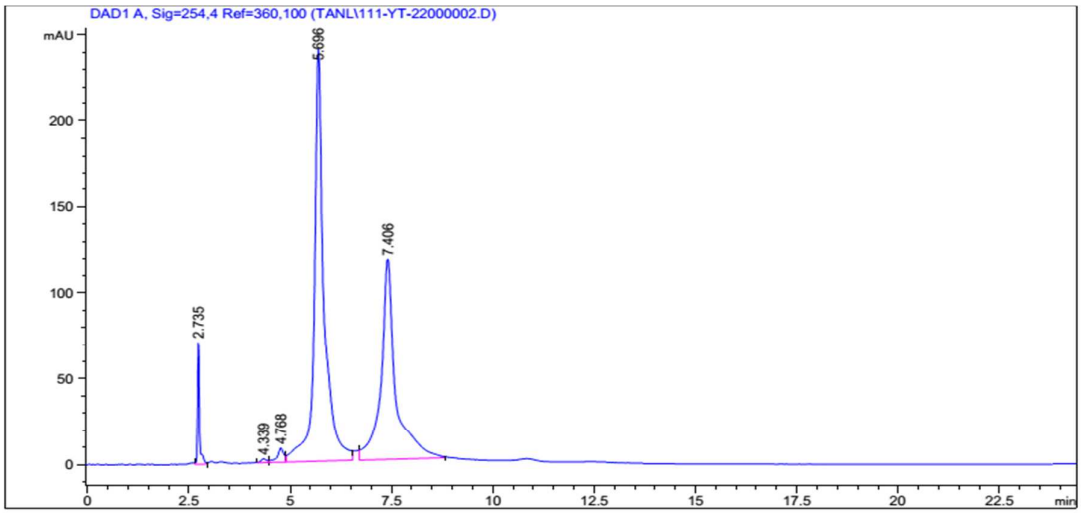

**13a** (eluent A / eluent B 40/60)



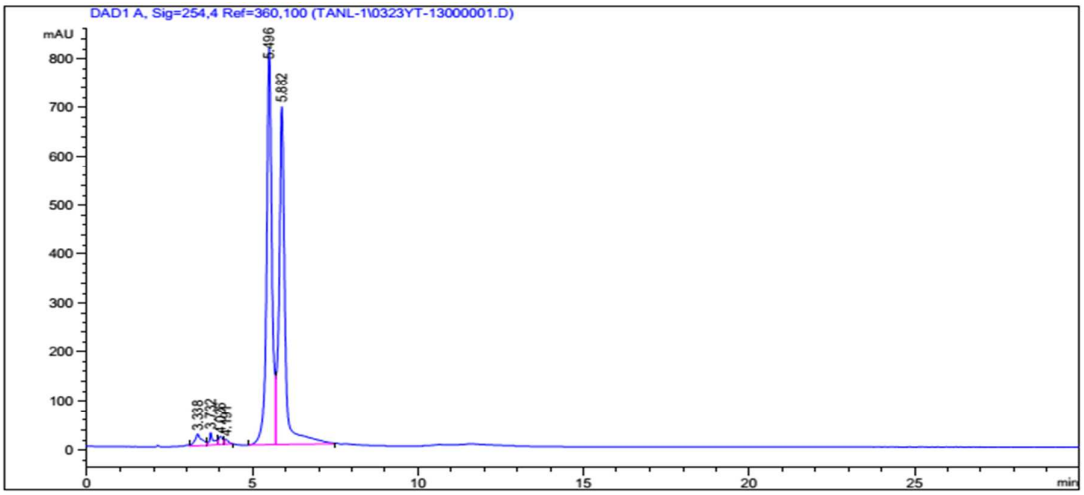

**13b** (eluent A / eluent B 40/60)



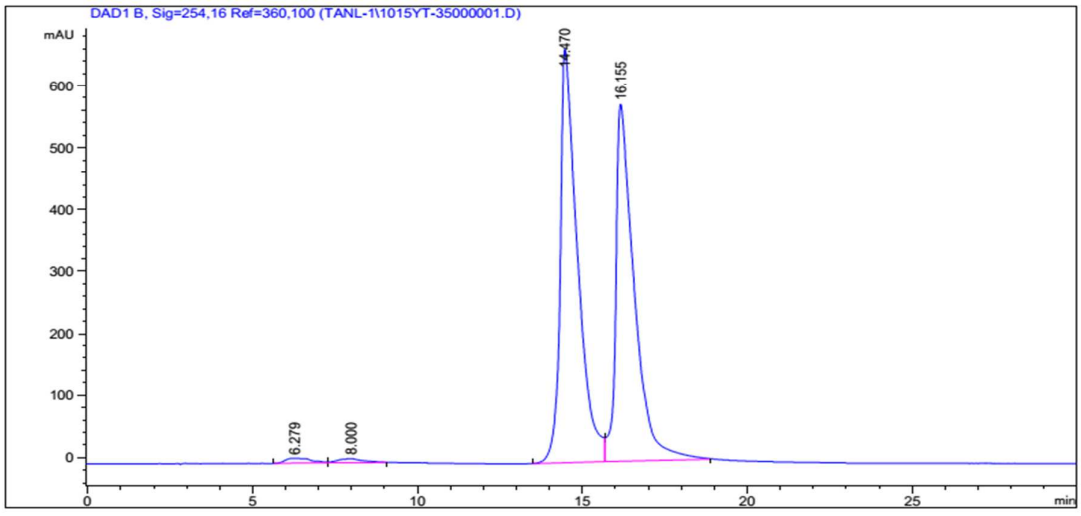
**13c**


DAD1 A, Sig=254,4 Ref=360,100 (TANL\111-YT-22000002.D)
mAU
2.735
4.339
4.768
5.696
7.406
min

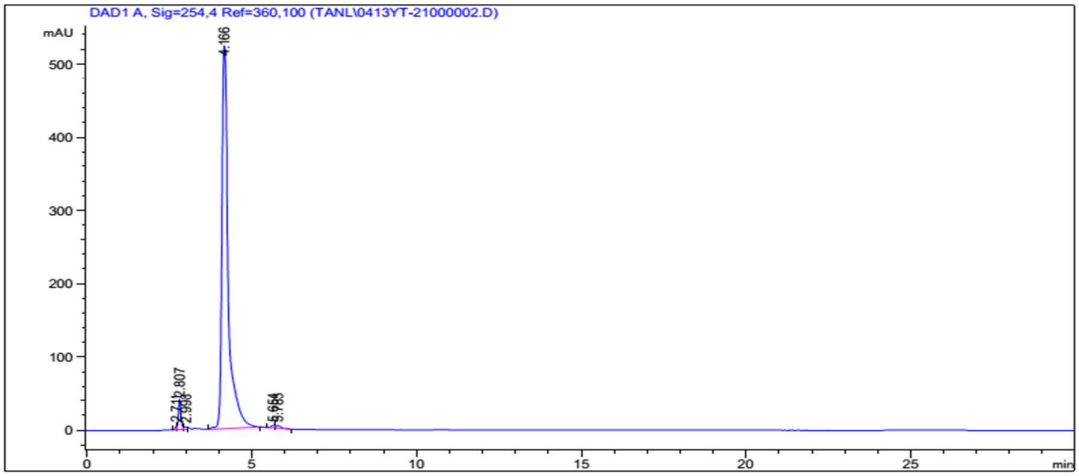
**15b**


DAD1 A, Sig=254,4 Ref=360,100 (TANL-1\0323YT-13000001.D)
mAU
5.496
5.682
min

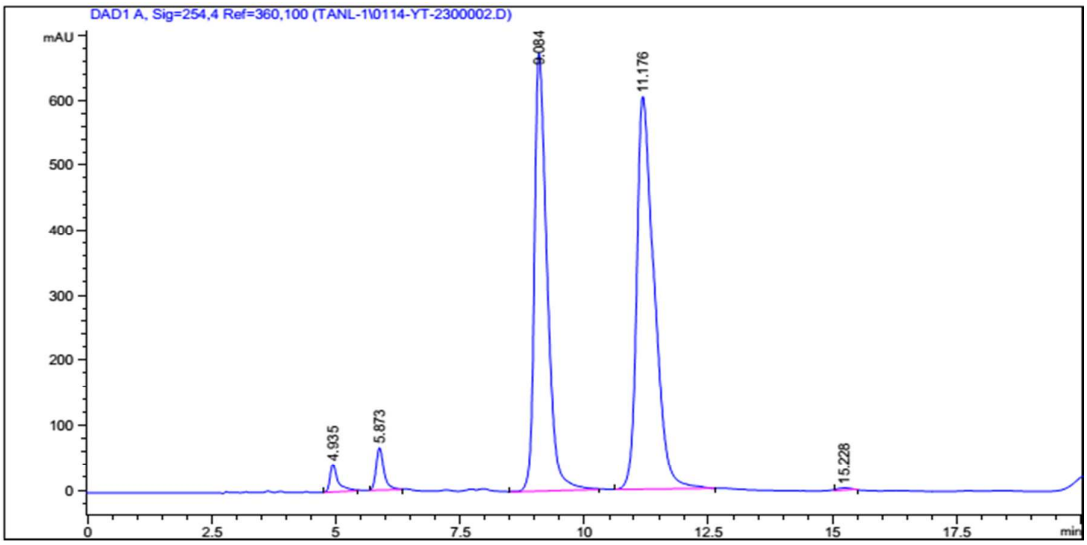
**15c**


DAD1 B, Sig=254,16 Ref=360,100 (TANL-1\1015YT-35000001.D)
mAU
6.279
8.000
14.470
16.155
min

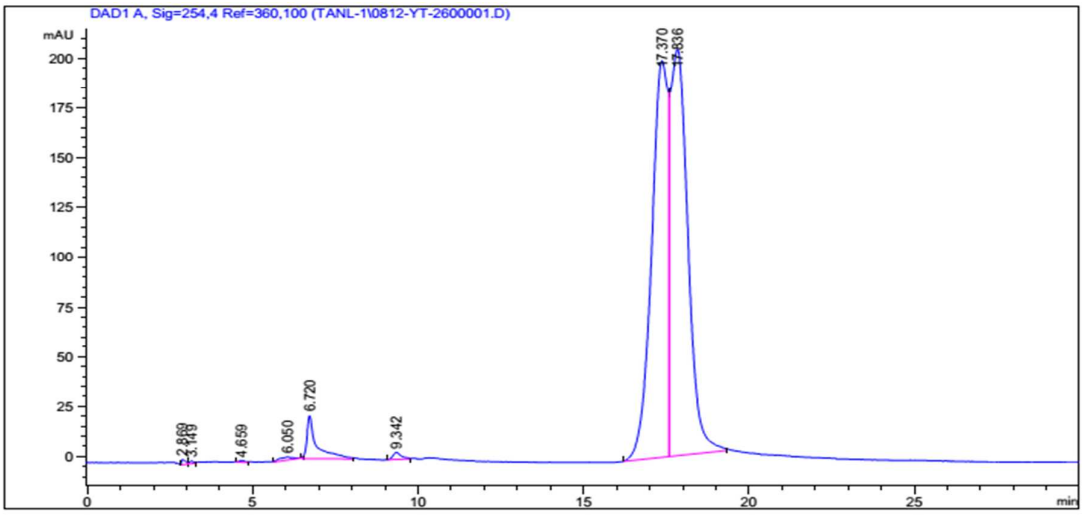
**16c**



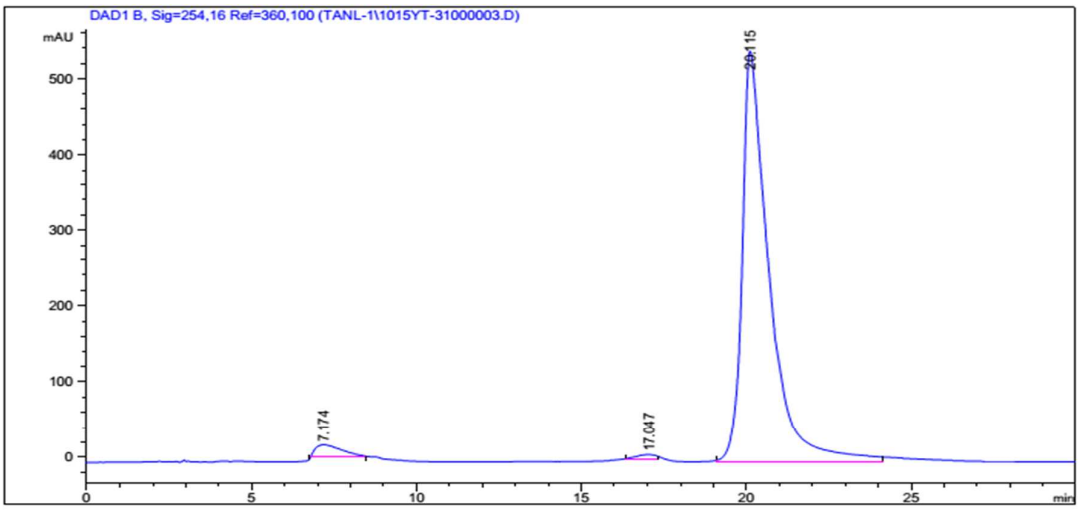

**19** (eluent A / eluent B 40/60)



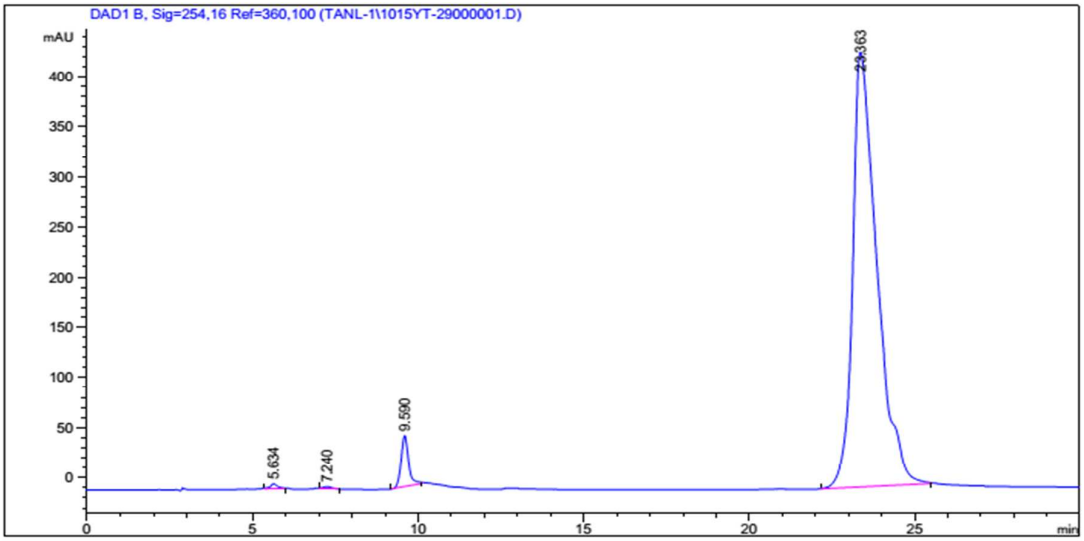

**20**



**21**




**22**




**BAL30072**