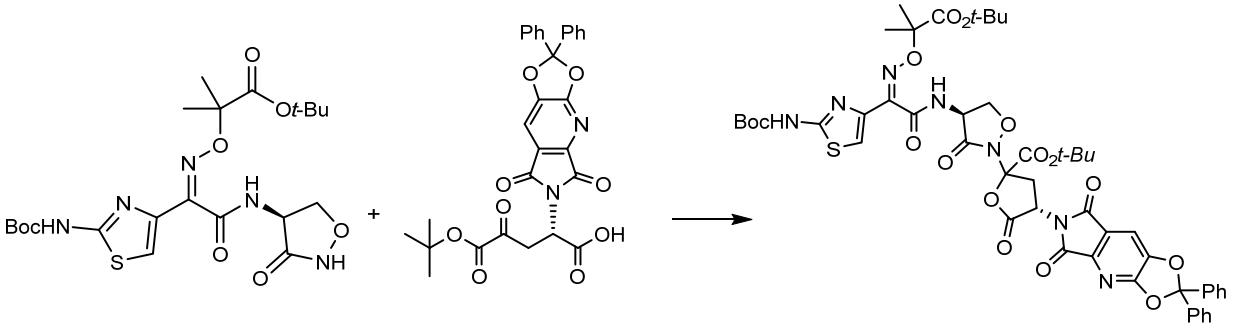
[0365] To (2*S*)-2-amino-5-*tert*-butoxy-4,5-dioxopentanoic acid hydrochloride **70** (2.03 g, 7.68 mmol, prepared as described in *J. Med. Chem*. 2014, *57*, 3845-3855) was added a solution of 2,2-diphenyl-2*H*-[1,3]dioxolo[4,5-*b*]furo[3,4-*e*]pyridine-5,7-dione **69** (crude, 1.27 g, 3.68 mmol) in anhydrous pyridine (25 mL) at room temperature. The reaction mixture was stirred and heated at 90 °C for 2.5 h, then cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in DCM (10 mL) and water (120 mL) was added. The mixture was extracted with ethyl acetate and the combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using a gradient of 0 to 16% acetonitrile in DCM to afford (2*S*)-5-*tert*-butoxy-2-(5,7-dioxo-2,2-diphenyl-5,7-dihydro-2*H*,6*H*-[1,3]dioxolo[4,5-*b*]pyrrolo[3,4-*e*]pyridin-6-yl)-4,5-dioxopentanoic acid **71** (390 mg, 19%) as a brown foam.

[0366] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.57-7.53 (m, 4H), 7.51-7.47 (m, 6H), 5.19-5.16 (m, 1H), 3.71-3.62 (m, 1H), 3.37-3.34 (m, 1H), 1.44 (s, 9H).

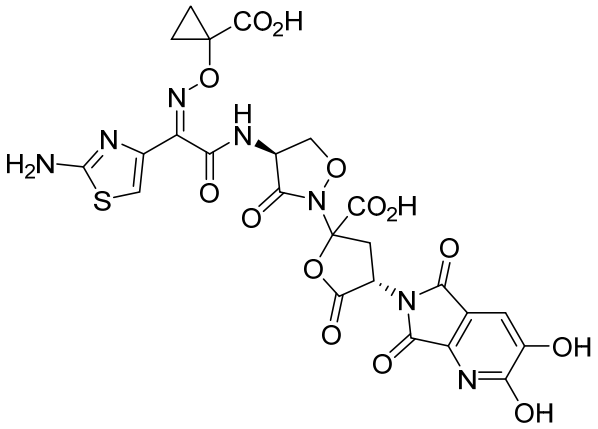
[0367] MS (ESI) m/z: $[M+1]^+$ 545.2

[0368] Step 5: *tert*-butyl (4*S*)-2-[(4*S*)-4-{[(2*Z*)-2-{2-[(*tert*-butoxycarbonyl)amino]-1,3-thiazol-4-yl}-2-{[(1-*tert*-butoxy-2-methyl-1-oxopropan-2-yl)oxy]imino}acetyl]amino}-3-oxo-1,2-oxazolidin-2-yl]-4-(5,7-dioxo-2,2-diphenyl-5,7-dihydro-2*H*,6*H*-[1,3]dioxolo[4,5-*b*]pyrrolo[3,4-*e*]pyridin-6-yl)-5-oxooxolane-2-carboxylate (**73**)



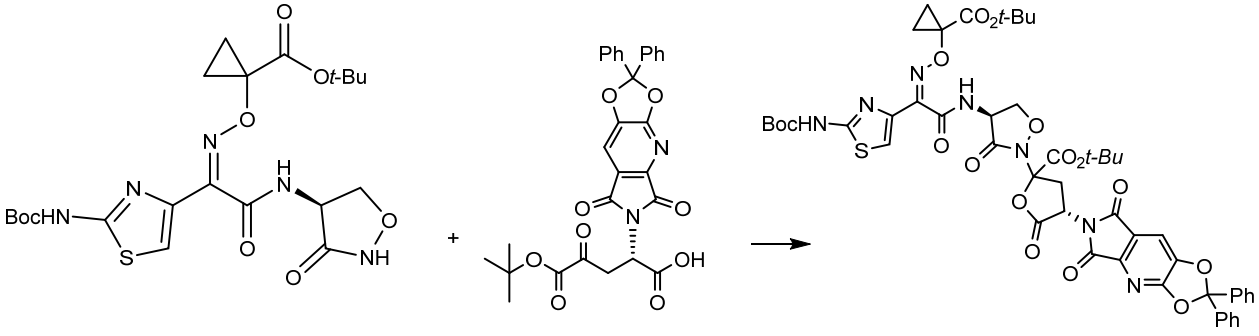
72 **71** **73**

[0369] To a mixture of (2*S*)-5-*tert*-butoxy-2-(5,7-dioxo-2,2-diphenyl-5,7-dihydro-2*H*,6*H*-[1,3]dioxolo[4,5-*b*]pyrrolo[3,4-*e*]pyridin-6-yl)-4,5-dioxopentanoic acid **71** (390 mg, 0.72 mmol)



Compound 3

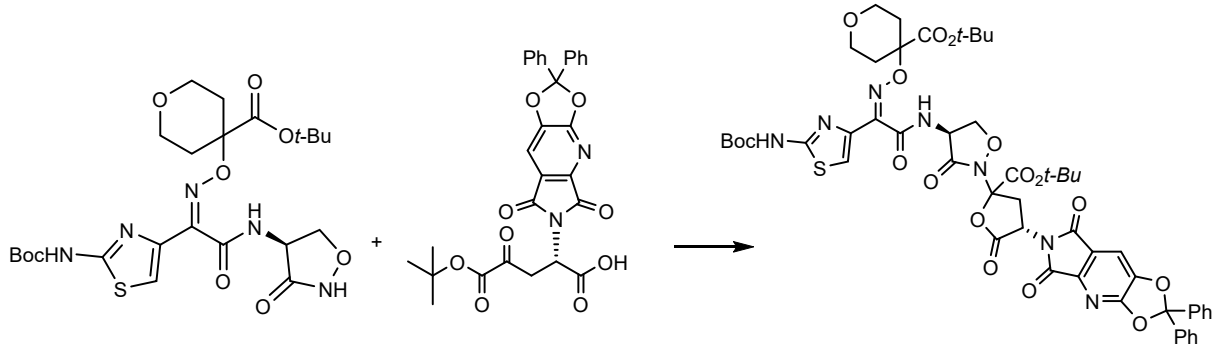
[0376] Step 1: *tert*-butyl (4*S*)-2-[(4*S*)-4-{[(2*Z*)-2-{2-[(*tert*-butoxycarbonyl)amino]-1,3-thiazol-4-yl}-2-({[1-(*tert*-butoxycarbonyl)cyclopropyl]oxy}imino)acetyl]amino}-3-oxo-1,2-oxazolidin-2-yl]-4-(5,7-dioxo-2,2-diphenyl-5,7-dihydro-2*H*,6*H*-[1,3]dioxolo[4,5-*b*]pyrrolo[3,4-*e*]pyridin-6-yl)-5-oxooxolane-2-carboxylate (**74**)



5 **71** **74**

[0377] To a mixture of (2*S*)-5-*tert*-butoxy-2-(5,7-dioxo-2,2-diphenyl-5,7-dihydro-2*H*,6*H*-[1,3]dioxolo[4,5-*b*]pyrrolo[3,4-*e*]pyridin-6-yl)-4,5-dioxopentanoic acid **71** (105 mg, 0.2 mmol, prepared as described in Example 10, Step 4) and *tert*-butyl 1-{[(*Z*)-(1-{2-[(*tert*-butoxycarbonyl)amino]-1,3-thiazol-4-yl}-2-oxo-2-{[(4*S*)-3-oxo-1,2-oxazolidin-4-yl]amino}ethylidene)amino]oxy}cyclopropane-1-carboxylate **5** (100 mg, 0.2 mmol, prepared as described in Example 1, Step 4) in anhydrous THF (2 mL) was added DMAP (5 mg, 0.04 mmol), followed by DCC (56 mg, 0.27 mmol) at 0 °C. The reaction mixture was allowed to gradually warm up to room temperature and stirring was continued for 18 h. The reaction mixture was then concentrated under reduced pressure and the residue was triturated with 25% DCM in

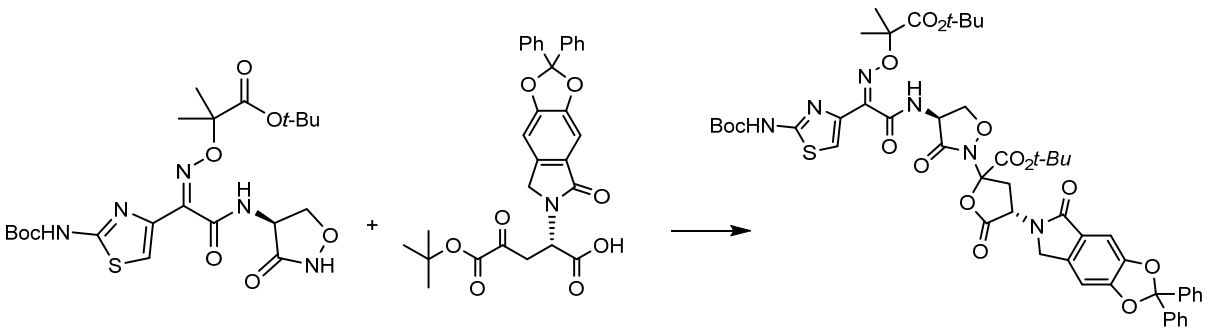
b]pyrrolo[3,4-*e*]pyridin-6-yl)-5-oxooxolan-2-yl]-3-oxo-1,2-oxazolidin-4-yl}amino)-2-oxoethylidene]amino}oxy)oxane-4-carboxylate (**75**)



37 **71** **75**

[0385] To a mixture of *tert*-butyl 4-{[(*Z*)-(1-{2-[(*tert*-butoxycarbonyl)amino]-1,3-thiazol-4-yl}-2-oxo-2-{[(4*S*)-3-oxo-1,2-oxazolidin-4-yl]amino}ethylidene)amino]oxy}oxane-4-carboxylate **71** (316 mg, 0.58 mmol, prepared as described in Example 5, Step 7) and (2*S*)-5-*tert*-butoxy-2-(5,7-dioxo-2,2-diphenyl-5,7-dihydro-2*H*,6*H*-[1,3]dioxolo[4,5-*b*]pyrrolo[3,4-*e*]pyridin-6-yl)-4,5-dioxopentanoic acid **37** (293 mg, 0.53 mmol, prepared as described in Example 10, Step 4) in anhydrous THF (9 mL) was added DMAP (14 mg, 0.11 mmol), followed by DCC (153 mg, 0.74 mmol) at 0 °C. The reaction mixture was allowed to slowly warm up to room temperature and stirred for 18 h. The mixture was then concentrated, and the residue was treated with 30% DCM in hexanes and the precipitated solids were removed by filtration. The filtrate was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography using a gradient of 10 to 40% ethyl acetate in hexanes to afford *tert*-butyl 4-({(*Z*)-[1-{2-[(*tert*-butoxycarbonyl)amino]-1,3-thiazol-4-yl}-2-({(4*S*)-2-[(4*S*)-2-(*tert*-butoxycarbonyl)-4-(5,7-dioxo-2,2-diphenyl-5,7-dihydro-2*H*,6*H*-[1,3]dioxolo[4,5-*b*]pyrrolo[3,4-*e*]pyridin-6-yl)-5-oxooxolan-2-yl]-3-oxo-1,2-oxazolidin-4-yl}amino)-2-oxoethylidene]amino}oxy)oxane-4-carboxylate **75** (238 mg, 42%) as a light brown foam.

[0386] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26-8.01 (m, 2H), 7.59-7.56 (m, 4H), 7.46-7.42 (m, 7H), 7.37-7.34 (m, 1H), 5.46-4.88 (m, 3H), 4.39-4.21 (m, 1H), 3.89-3.33 (m, 5H), 2.91-2.77 (m, 1H), 2.26-2.12 (m, 4H), 1.60-1.57 (m, 9H), 1.56-1.51 (m, 9H), 1.49-1.42 (m, 9H).



72 **86** **87**

[0430] To a mixture of (2*S*)-5-*tert*-butoxy-4,5-dioxo-2-(5-oxo-2,2-diphenyl-5,7-dihydro-2*H*,6*H*-[1,3]dioxolo[4,5-*f*]isoindol-6-yl)pentanoic acid **86** (112 mg, 0.21 mmol) and *tert*-butyl 2-{[(*Z*)-(1-{2-[(*tert*-butoxycarbonyl)amino]-1,3-thiazol-4-yl}-2-oxo-2-{[(4*S*)-3-oxo-1,2-oxazolidin-4-yl]amino}ethylidene)amino]oxy}-2-methylpropanoate **72** (109 mg, 0.21 mmol) in anhydrous THF (4 mL) was added DMAP (6 mg, 0.049 mmol), followed by DCC (62 mg, 0.30 mmol) at 0 °C. The reaction mixture was allowed to gradually warm up to room temperature and was stirred for 18 h. The mixture was then concentrated, and the residue was treated with 25% DCM in hexanes and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography using a gradient of 10 to 40% ethyl acetate in hexanes to afford *tert*-butyl (4*S*)-2-[(4*S*)-4-{[(2*Z*)-2-{2-[(*tert*-butoxycarbonyl)amino]-1,3-thiazol-4-yl}-2-{[(1-*tert*-butoxy-2-methyl-1-oxopropan-2-yl)oxy]imino}acetyl]amino}-3-oxo-1,2-oxazolidin-2-yl]-5-oxo-4-(5-oxo-2,2-diphenyl-5,7-dihydro-2*H*,6*H*-[1,3]dioxolo[4,5-*f*]isoindol-6-yl)oxolane-2-carboxylate **87** (132 mg, 61%) as a white foam.

[0431] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21-8.18 (m, 1H), 7.57-7.52 (m, 4H), 7.41-7.34 (m, 7H), 7.30-7.29 (m, 1H), 6.92-6.90 (m, 1H), 5.47-5.39 (m, 1H), 5.20-4.85 (m, 2H), 4.34-4.21 (m, 3H), 3.51-3.31 (m, 1H), 2.93-2.49 (m, 1H), 1.61-1.58 (m, 6H), 1.55-1.52 (m, 18H), 1.43 (s, 9H).

[0432] Step 10: (4*S*)-2-[(4*S*)-4-{[(2*Z*)-2-(2-amino-1,3-thiazol-4-yl)-2-{[(2-carboxypropan-2-yl)oxy]imino}acetyl]amino}-3-oxo-1,2-oxazolidin-2-yl]-4-(5,6-dihydroxy-1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)-5-oxooxolane-2-carboxylic acid (**Compound 35**)