Supporting Information:

Characterization of the core ribosomal binding region for the oxazolidone family of antibiotics using Cryo-EM

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Table S1. CryoEM Structure collection statistics.

Data Collection	Tedizolid	Tedizolid -isomer	Radezolid	Contezolid	T145
Micrographs	3037	1019	1687	2410	1288
Particles (Final map)	140k	77.5k	250k	127k	207k
Pixel size (Å)	1.14	0.97	l.14	0.895	1.14
Defocus range (μm)	0.4-1.6	0.9-1.9	0.4-1.6	0.4-1.6	0.4-1.6
Voltage (kV) G = Glacios A = Artica	200 (G)	200 (A)	200 (G)	200 (G)	200 (G)
Electron dose (e/Å^2)	47	50	47	47	47
Resolution (0.143 FSC) (Å)	3.2	3.1	3.1	2.9	3.1
Refinement					
CC_{map_model}	0.84	0.83	0.77	0.85	
Model Quality					
RMSD					
Bond length (Å) / Bond angles (°)	0.008/0.679	0.008/0.797	0.002/0.364	0.003/0.486	
Ramachandran					
Favoured (%)	91.1	88.8	95.9	97.10	
Outliers (%)	0	0	0	0	
Rotamer outliers (%)	0.09	0.04	0.04	2.31	
C-Beta deviations (%)	0	0	0	0.12	
Clashscore	4.32	4.44	3.37	9.01	

Figure S1. Fourier Shell Correlation (FSC) curves for the 50S:antibiotic complexes.

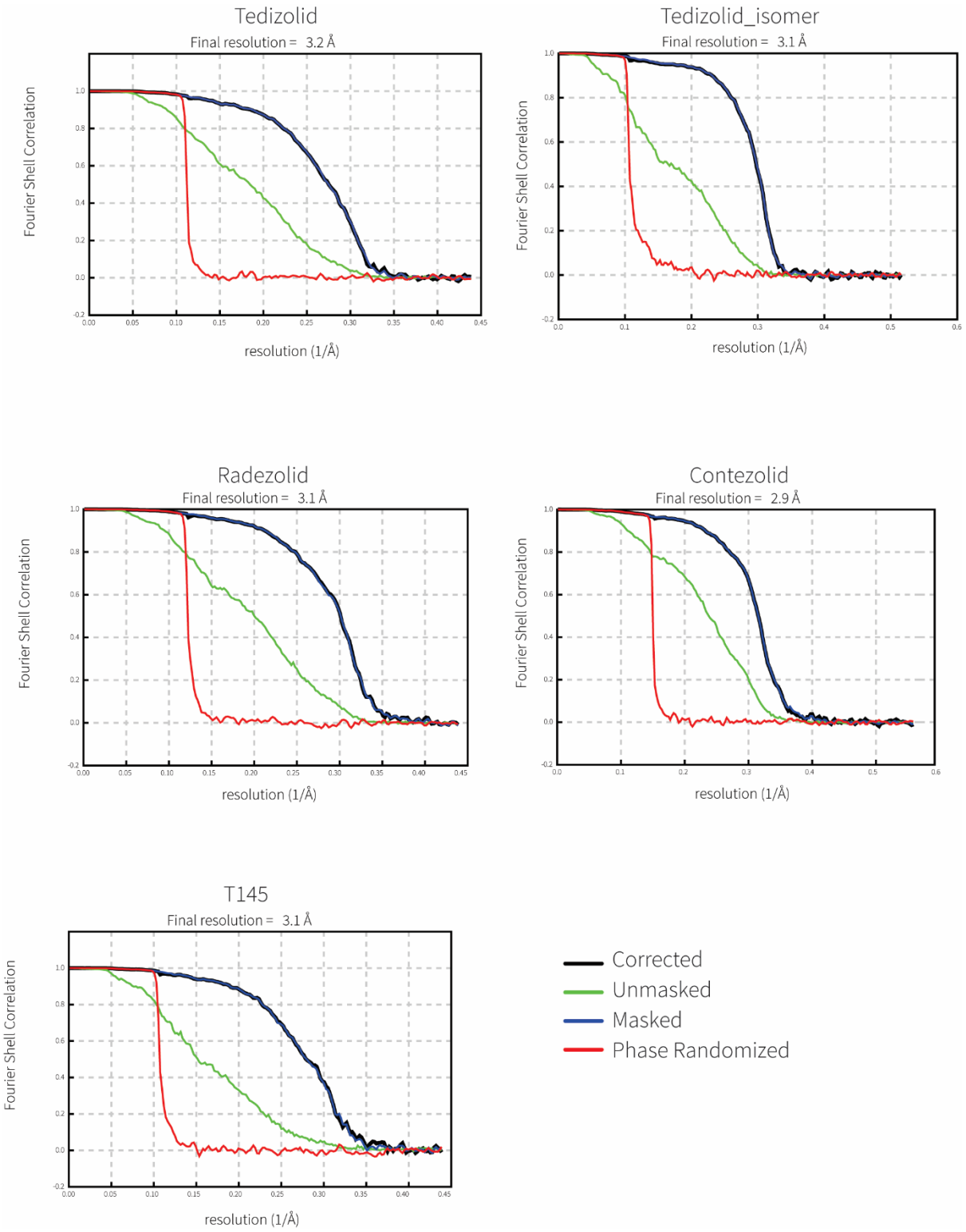


Figure S2. Calculated densities around the antibiotic binding site. a) Contezolid b) Radezolid c) Tedizolid d) Tedizolid-isomer e) T145. All density is drawn at 4 σ and the binding site is drawn from the same relative ribosome orientation. Note, the density around T145 poorly encapsulates the binding pose of the antibiotic.

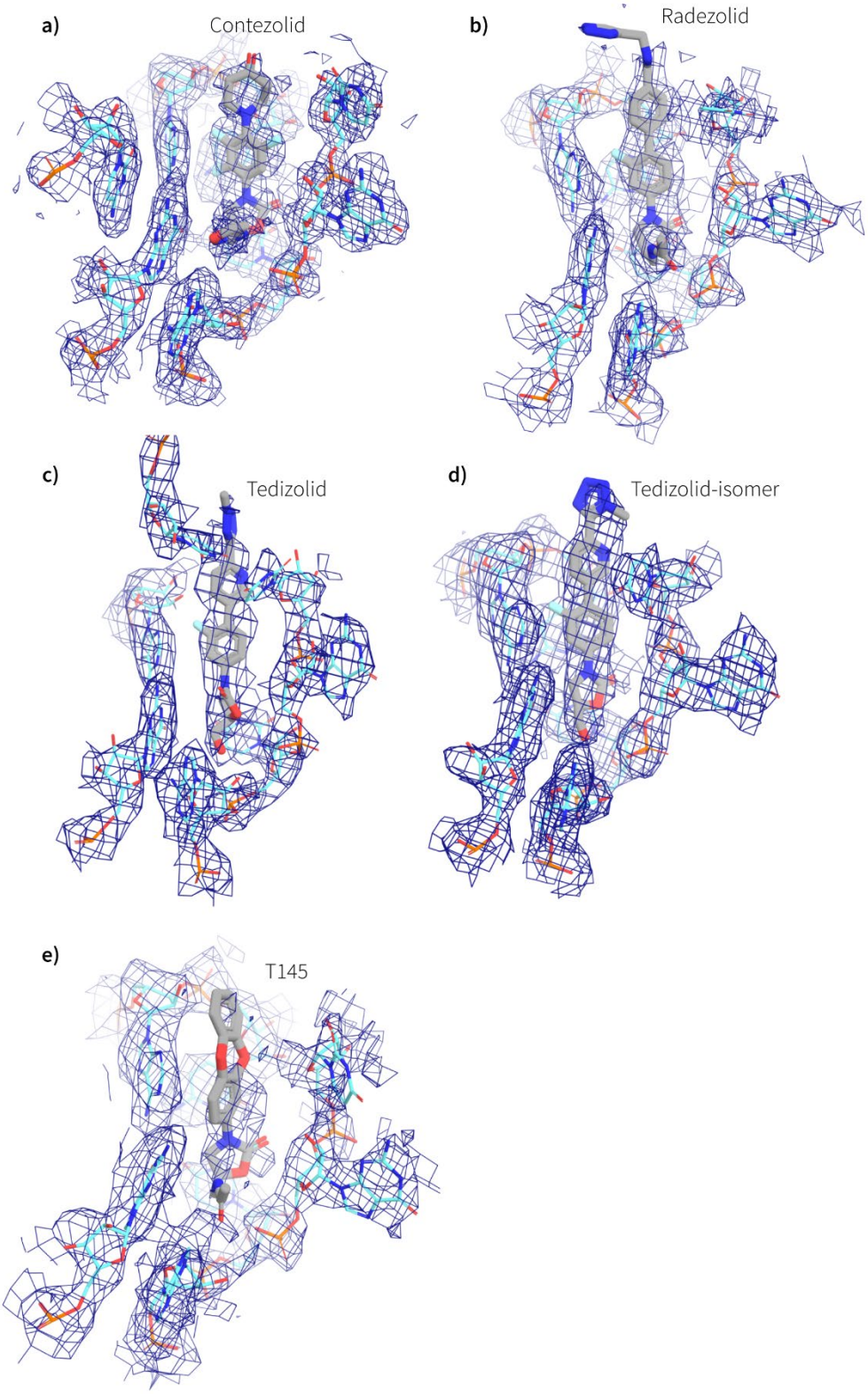
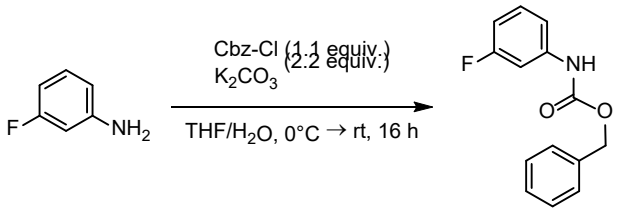


Table S2. X-ray structure statistics

Identification code	Tedizolid-isomer	Tedizolid
Empirical formula	$C_{17}H_{15}FN_6O_3$	$C_{17}H_{15}FN_6O_3$
Formula weight	370.35	370.35
Temperature/K	123.00(10)	293(2)
Crystal system	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P2_1$
a/Å	7.3378(2)	4.8421(4)
b/Å	12.2910(4)	14.8955(13)
c/Å	17.3809(5)	11.2667(8)
α/°	90	90
β/°	90	94.172(7)
γ/°	90	90
Volume/Å^3	1567.56(8)	810.46(11)
Z	4	2
ρ_{calc}g/cm^3	1.569	1.518
μ/mm^{-1}	1.017	0.984
F(000)	768	384
Radiation	Cu Kα (λ = 1.54184)	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.812 to 154.192	7.868 to 155.04
Index ranges	$-7 \le h \le 9$, $-15 \le k \le 15$, $-21 \le l \le 21$	$-5 \le h \le 5$, $-18 \le k \le 18$, $-14 \le l \le 14$
Reflections collected	15449	11672
Independent reflections	3241 [R_{int} = 0.1520, R_{sigma} = 0.0890]	3152 [R_{int} = 0.2174, R_{sigma} = 0.1305]
Data/restraints/parameters	3241/0/247	3152/1/247
Goodness-of-fit on F^2	1.057	1.067
Final R indexes [I>=2σ (I)]	R_1 = 0.0901, wR_2 = 0.2418	R_1 = 0.0975, wR_2 = 0.2416
Final R indexes [all data]	R_1 = 0.1008, wR_2 = 0.2534	R_1 = 0.1103, wR_2 = 0.2724
Largest diff. peak/hole / e Å^{-3}	1.46/-0.54	0.51/-0.47
Flack parameter	0.2(3)	-0.1(3)

Tedizolid Synthesis

(3-fluorophenyl)carbamate



To a solution of 3-fluoroanaline (2.60 mL, 27.00 mmol) and K_2CO_3 (7.46 g, 54.00 mmol) in a 1:1 mixture of THF/H_2O (120 mL) was added Cbz-Cl (4.29 mL, 29.70 mmol) dropwise at 0°C. The reaction was left to reach ambient temperature over 16 h. The mixture was extracted with ethyl acetate and the organics washed with water, then brine, dried over $MgSO_4$ and reduced in vacuo. The resulting residue was dissolved in ether and titrated out with hexane to afford benzyl(3-fluorophenyl)carbamate (6.28 g, 25.61 mmol, yield 95%) as colorless crystals.

R_f: 0.28 (10 % EtOAc in Hexanes)

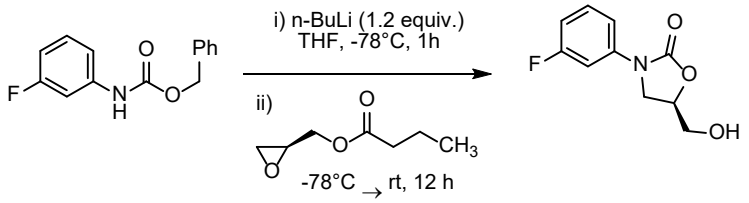
^{1}H-NMR (400 MHz, DMSO): δ 7.37 (m, 5H), 7.23 (m, 1H), 7.02 (dd, J = 8.2, 2.1 Hz, 1H), 6.85 (bs, 1H), 6.77 (tdd, J = 8.3, 2.5, 1.0 Hz, 1H) 5.21 (s, 2H)

^{13}C-NMR (151 MHz, DMSO): δ 163.60, 162.00, 153.71, 141.44 (d, J = 10.5 Hz), 136.84, 130.87 (d, J = 9.0 Hz), 128.92, 128.64, 128.58, 114.40, 109.29 (d, J = 21.0 Hz), 105.28 (d, J = 27.0 Hz), 66.44

IR: 3358, 2959, 1703, 1600, 1523, 1492, 1445, 1266, 1224, 1148, 1042

LRMS: Found: [M + H^+], 245.9, $C_{14}H_{12}FNO_2$ requires [M + H^+], 246.1

(R)-3-(3-fluorophenyl)-5-(hydroxymethyl)oxazolidin-2-one



To a solution of benzyl(3-fluorophenyl)carbamate (10.00 g, 40.70 mmol) in THF (100 mL) was added n-BuLi (1.6M, 28.0 mL, 44.7 mmol) dropwise at -78 °C. After stirring for 1 h (R)-glycidyl butyrate (5.12 mL, 36.36 mmol) was added at keeping the temperature at -78 °C, once addition was complete the mixture was allowed to reach ambient temperature over 12 h. The mixture was quenched with NH_4Cl and the organic layer separated, washed with water, then brine, dried over $MgSO_4$ and reduced in vacuo. The resulting residue was heated in ether and the solid precipitate filtered to give the desired (R)-3-(3-fluorophenyl)-5-(hydroxymethyl)oxazolidin-2-one (7.30g, 34.56 mmol, yield 94%) as a white powder.

R_f: 0.29 (50 % EtOAc in Hexanes)

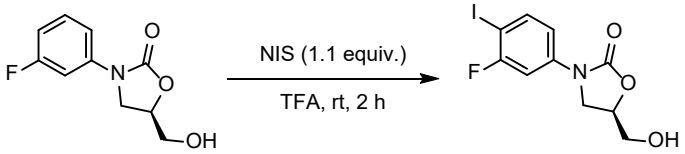
^{1}H-NMR (400 MHz, DMSO): δ 7.45 (dt, J = 11.2, 2.3 Hz, 1H), 7.33 (m, 1H), 7.27 (m, 1H), 6.85 (tdd, J = 8.2, 2.4, 1.0 Hz, 1H), 4.77 (m, 1H), 4.00 (m, 3H), 3.78 (ddd, J = 12.6, 7.3, 4.0 Hz, 1H)

^{13}C-NMR (151 MHz, DMSO): δ 163.56, 161.96, 154.81, 140.73 (d, J = 10.5 Hz), 131.00 (d, J = 9.0 Hz), 113.79, 110.16 (d, J = 21.0 Hz), 105.18 (d, J = 27.0 Hz), 73.77, 62.07, 46.45

IR: 3516, 3110, 2927, 1711, 1610, 1588, 1492, 1453, 1418, 1324, 1194

LRMS: Found: [M + H^+], 211.9 $C_{10}H_{10}FNO_3$ requires [M + H^+], 212.1

(R)-3-(3-fluoro-4-iodophenyl)-5-(hydroxymethyl)oxazolidin-2-one



To a solution of (R)-3-(3-fluoro-4-iodophenyl)-5-(hydroxymethyl)oxazolidin-2-one (2.96 g, 14.02 mmol) in TFA (30 ml) was added NIS (3.32 g, 14.74 mmol) at room temperature and left to stir for 2 h. The resulting solution was reduced under pressure and the residue taken up in EtOAc, the organic layer was washed with water, then brine, dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by flash column chromatography (20 % EtOAc : Hexanes) to afford the desired product (4.20 g, yield 89 %) as white crystals.

R_f: 0.30 (50 % EtOAc in Hexanes)

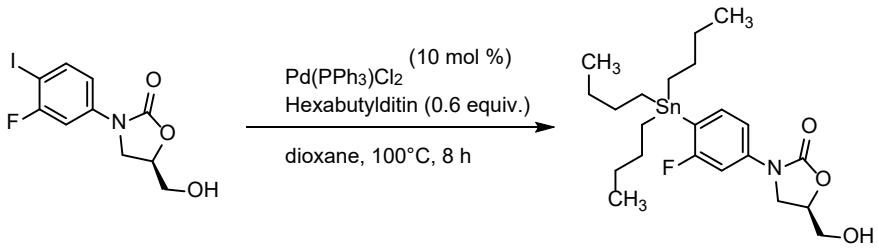
^{1}H-NMR (400 MHz, DMSO): δ 7.48 (dd, J = 8.7, 7.5 Hz, 1H), 7.60 (dd, J = 11.0, 2.5 Hz, 1H), 7.32 (dd, J = 11.0, 2.5 Hz, 1H), 5.23 (s, 1H), 4.74 (m, 1H), 4.09 (t, 1H), 3.84 (dd, J = 8.9, 6.1 Hz, 1H)

^{13}C NMR (151 MHz, DMSO): δ 179.85, 162.45, 160.86, 154.70, 140.97 (d, J = 28 Hz), 139.50, 115.87, 105.60, 73.86, 62.02, 29.99

IR: 3516, 3110, 2927, 1711, 1610, 1588, 1492, 1453, 1418, 1324, 1194

LRMS: Found: [M + H^+], 337.6 $C_{10}H_9FINO_3$ requires [M + H^+], 338.0

(R)-3-(3-fluoro-4-(tributylstannyl)phenyl)-5-(hydroxymethyl)oxazolidin-2-one



To a solution of (R)-3-(3-fluoro-4-iodophenyl)-5-(hydroxymethyl)oxazolidin-2-one (1.00 g, 2.97 mmol) dissolved in dioxane (30mL) was added palladium-bis-[triphenylphosphine]dichloride (0.20 g, 10 mol%) and hexabutylditine (1.80 mL). The reaction was heated to 100 °C for 8 h before being filtered through celite. The residue was dissolved in EtOAc, washed with water 3x, then brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue purified by flash column chromatography (0-5% MeOH : dichloromethane) to afford the desired product as a light yellow oil (0.790 g, 53% yield)

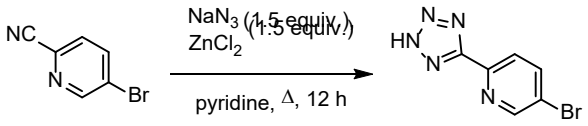
(Due to the toxic nature of the product only proton and carbon NMR data were collect)

R_f: 0.28 (50 % EtOAc in Hexanes)

^{1}H-NMR (400 MHz, DMSO): δ 7.38-7.29 (m, 2H), 7.23 (dd, J = 7.9, 2.1 Hz, 1H), 4.47 (m, 1H), 3.99 (m, 2H), 3.74 (m, 1H), 1.51 (m, 6H), 1.32 (m, 6H), 1.09 (m, 6H), 0.88 (t, 9H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.77, 166.45, 154.63, 140.01 (d, J = 11.1 Hz), 137.56 (d, J = 18.2 Hz), 132.05 (d, J = 11.1 Hz), 128.60 (d, J = 12.1 Hz), 122.01, 121.55, 113.66, 104.82, 104.47, 73.01, 62.72, 46.27, 28.98, 27.25, 13.66, 9.90.

5-bromo-2-(2*H*-tetrazol-5-yl)pyridine



To a solution of Zinc chloride (8.38 g, 61.48 mmol) in pyridine (40 mL) was added sodium azide (2.66 g, 61.48 mmol) and 5-bromopicolinonitrile (7.50 g, 41.00 mmol). The mixture was heated to reflux for 12 h and then quenched with water. The organics were extracted with EtOAc, washed with water 3 x, then brine, dried over $MgSO_4$ and concentrated in vacuo. The resulting precipitate was washed with ether to afford the desired compound (8.53g, yield 92%) as a white solid.

R_f: 0.14 (10 % MeOH in CH_2Cl_2)

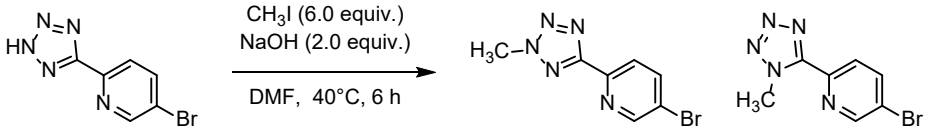
^{1}H NMR (600 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.33 (dd, J = 8.4, 2.3 Hz, 1H), 8.15 (d, J = 8.5 Hz, 1H).

^{13}C NMR (151 MHz, DMSO) δ 154.89, 151.37, 143.07, 141.31, 124.55, 122.92.

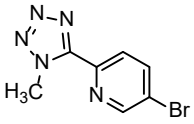
IR: 3062, 2728, 2465, 1598, 1554, 1470, 1424, 1355, 1247, 1165, 1097, 1024

LRMS: Found: [M + H^+], 226.0 $C_6H_4BrN_5$ requires [M + H^+], 226.0

5-bromo-2-(2-methyl-tetrazol-5-yl)pyridine (regioisomers)



To a solution of 5-bromo-2-(2*H*-tetrazol-5-yl)pyridine (5.00 g, 22.12 mmol) and NaOH (1.77 g, 44.24 mmol) in DMF was added CH_3I (8.50 mL, 132.72 mmol) dropwise at 0 °C degrees. The mixture was allowed to reach ambient temperature over 6 h, before being quenched with water. The desired product was extracted with EtOAc, the organic layer washed with water 3 x, then brine and dried over $MgSO_4$. The solution was reduced in vacuo and purified by flash column chromatography (1-10% MeOH : CH_2Cl_2) to afford the desired product (4.04 g, yield 76%) as a white solid in a 1:1 mixture.



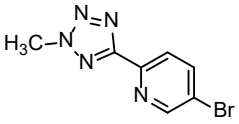
R_f: 0.66 (50 % EtOAc in Hexanes)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (d, J = 2.3 Hz, 1H), 8.34 (dd, J = 8.4, 2.4 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 4.38 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.70, 155.81, 148.26, 146.01, 130.93, 127.73, 41.86.

IR: 3091, 1453, 1420, 1354, 1285, 1234, 1124, 1090, 992

LRMS: Found: [M + H^+], 240.0 $C_7H_6BrN_5$ requires [M + H^+], 240.0



R_f: 0.38 (50 % EtOAc in Hexanes)

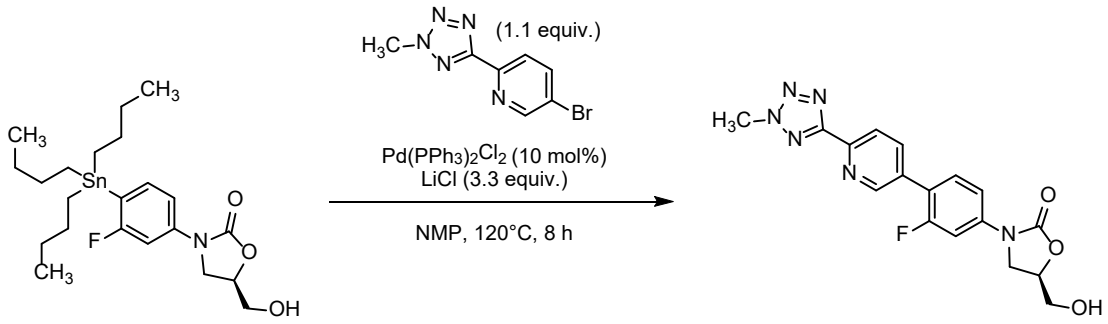
^{1}H NMR (600 MHz, DMSO-d_6) δ 8.88 (dd, J = 2.4, 0.7 Hz, 1H), 8.27 (dd, J = 8.4, 2.4 Hz, 1H), 8.08 (dd, J = 8.4, 0.8 Hz, 1H), 4.46 (s, 3H).

^{13}C NMR (151 MHz, DMSO) δ 163.84, 151.43, 145.39, 140.76, 124.31, 122.17, 40.34.

IR: 2923, 1441, 1380, 1286, 1235, 1119, 1051, 1003

LRMS: Found: [M + H^+], 240.0 $C_7H_6BrN_5$ requires [M + H^+], 240.0

Tedizolid



To a solution of (R)-3-(3-fluoro-4-(tributylstannyl)phenyl)-5-(hydroxymethyl)oxazolidin-2-one

(380 mg, 0.76 mmol) dissolved in NMP (20 mL) was added lithium chloride (117 mg, 2.50 mmol), palladium-bis-[triphenylphosphine]dichloride (70 mg, 10 mol%) and tetrazole (200 mg, 0.83 mmol). The mixture was heated to 120 °C under an inert atmosphere for 8 h. The resulting solution was filtered through celite and the filtrate washed with MeOH 3 x times. The organic layer was extracted, dried with brine, $MgSO_4$, reduced in vacuo and purified by flash column chromatography (0-10% MeOH : dichloromethane) to afford Tedizolid (67.23 mg, yield 24%) after recrystallization as a white solid.

R_f: 0.16 (5 % MeOH in CH_2Cl_2)

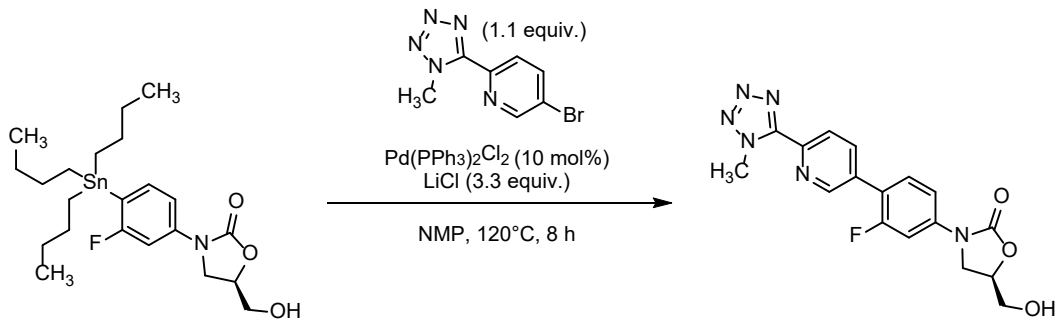
^{1}H NMR (600 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.27 – 8.17 (m, 2H), 7.78 – 7.68 (m, 2H), 7.53 (dd, *J* = 8.6, 2.2 Hz, 1H), 5.25 (t, *J* = 5.6 Hz, 1H), 4.77 (m, 1H), 4.48 (s, 3H), 4.16 (t, *J* = 9.0 Hz, 1H), 3.91 (dd, *J* = 8.9, 6.1 Hz, 1H), 3.71 (ddd, *J* = 12.3, 5.4, 3.3 Hz, 1H), 3.59 (ddd, *J* = 12.3, 5.8, 4.0 Hz, 1H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 164.33, 160.61, 158.98, 154.80, 149.92, 145.52, 141.02 (d, J = 11.3 Hz), 137.64 (d, J = 3.7 Hz), 132.11, 131.41, 122.56, 119.04 (d, J = 13.5 Hz), 114.46 (d, J = 3.2 Hz), 105.83 (d, J = 28.4 Hz), 73.94, 62.06, 46.46.

IR: 3567, 1743, 1624, 1516, 1474, 1416, 1360, 1331, 1229, 1203, 1148, 1110, 1098, 1032, 1011, 990

HRMS: Found: [M + H$^+$], 371.1247 $C_{17}H_{15}FN_6O_3$ requires [M + H$^+$], 371.1262

Tedizolid Regioisomer



To a solution of (R)-3-(3-fluoro-4-(tributylstannyl)phenyl)-5-(hydroxymethyl)oxazolidin-2-one

(260 mg, 0.52 mmol) dissolved in NMP (20 mL) was added lithium chloride (80 mg, 1.89 mmol), palladium-bis-[triphenylphosphine]dichloride (48 mg, 10 mol%) and 5-bromo-2-(1-methyl-1*H*-tetrazol-5-yl)pyridine (137 mg, 0.57 mmol). The mixture was heated to 120 °C and left to stir under Schleck conditions for 8 h. The resulting solution was filtered through celite and the filtrate washed with water 3 times. The organic layer was extracted, dried with brine, $MgSO_4$, reduced in vacuo and purified by flash column chromatography (0-10% MeOH : dichloromethane) to afford the tedizolid isomer (80.84 mg, yield 42%) as a white solid

R_f: 0.24 (5 % MeOH in CH_2Cl_2)

^{1}H-NMR (400 MHz, DMSO): δ 9.04 (bs, 1H), 8.33 (m, 2H), 7.77 (m, 2H), 7.57 (dd, J = 8.6,

2.3 Hz, 1H), 5.27 (t, 1H), 4.79 (m, 1H), 4.48, (s, 3H), 4.18 (t, 1H), 3.93 (dd, J = 9.0, 6.0 Hz, 1H) 3.73 (m, 1H), 3.61 (m, 1H)

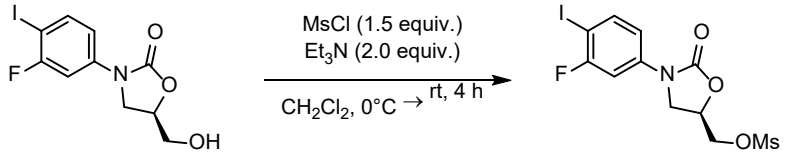
^{13}C NMR (151 MHz, DMSO): δ 160.66, 159.03, 154.80, 152.23, 149.44, 149.41, 143.53, 141.21, 138.05, 138.03, 132.66, 132.64, 131.49, 131.46, 124.45, 118.71, 118.62, 114.50, 114.49, 105.92, 105.73, 73.96, 62.06, 46.45, 37.14.

IR: 3252, 1745, 1620, 1473, 1408, 1377, 1327, 1220, 1195, 1148, 1103, 1043, 1015, 992

HRMS: Found: [M + H^+], 371.1232 $C_{17}H_{15}FN_6O_3$ requires [M + H^+], 371.1262

Radezolid Synthesis

(3-(3-fluoro-4-iodophenyl)-2-oxooxazolidin-5-yl)methyl methanesulfonate



To a solution of (R)-3-(3-fluoro-4-iodophenyl)-5-(hydroxymethyl)oxazolidin-2-one (1.50 g, 4.45 mmol) and trimethylamine (1.24 mL, 8.90 mmol) in CH_2Cl_2 (30 mL) was added methansulfonyl chloride (0.52 ml, 6.68 mmol) dropwise at 0 °C degrees. The mixture was warmed to room temperature over 4 h before being quenched with water. The organics were extracted using EtOAc, washed with water 3 x, then brine and dried over $MgSO_4$. The crude residue reduced in vaccuo and purified using flash chromatography (75% EtOAc : Hexanes) to afford the desired product (1.44 g yield 78%) as a white solid.

R_f: 0.58 (75 % EtOAc in Hexanes)

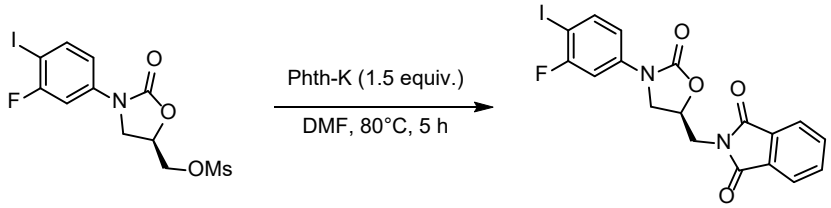
^{1}H-NMR (400 MHz, DMSO): δ 7.83 (m, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 5.03 (m, 1H), 4.50 (m, 2H), 4.18 (t, 1H), 3.83 (t, 1H), 3.25 (s, 3H)

^{13}C NMR (151 MHz, DMSO): δ 162.45, 160.85, 154.02, 140.55 (d, J = 9.0 Hz), 139.58 (d, J = 4.5), 116.14, 105.99, 105.79, 74.90 (d, J = 26.0 Hz), 70.68, 70.07, 46.22, 37.28

IR: 3100, 3014, 1750, 1597, 1480, 1419, 1331, 1166, 1005

LRMS: Found: [M + H$^+$], 415.5 $C_{11}H_{11}FINO_5S$ requires [M + H$^+$], 416.0

2-((3-(3-fluoro-4-iodophenly-2-oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione



A mixture of (3-(3-fluoro-4-iodophenyl)-2-oxooxazolidin-5-yl)methyl methanesulfonate (1.40 g, 3.37 mmol) and potassium phthalimide (0.70 g, 3.78 mmol) was dissolved in DMF (40 mL) and then heated to 80 °C for 5 h. The reaction was quenched with water and the oganics extracted with EtOAc, washed with water 3 x, then brine and dried over $MgSO_4$. The solution was reduced in vacuo and washed with ether to afford the desired product (1.15 g, yield 73%) as a white solid.

R_f: 0.71 (2 % MeOH in CH_2Cl_2)

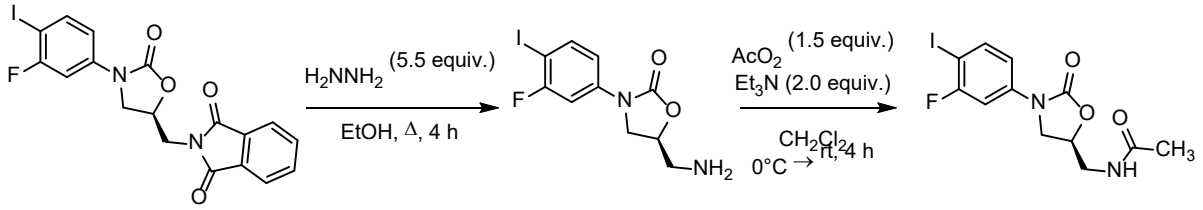
^{1}H-NMR (400 MHz, DMSO): δ 7.92-7.80 (m, 5H), 7.51 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 4.98 (m, 1H), 4.21 (t, 1H), 4.18 (t, 1H), 4.02 (dd, J = 4 Hz, 1H), 3.93 (m, 2H)

^{13}C NMR (151 MHz, DMSO): δ 168.23, 162.39, 160.80, 154.03, 140.74 (d, J = 11.0 Hz), 139.52 (d, J = 3.0 Hz), 135.04, 131.95, 123.69, 116.11, 105.95, 105.75, 74.84, 74.67, 70.78, 48.07, 40.83

IR: 1743, 1709, 1601, 1489, 1433, 1383, 1233, 1129, 1044

LRMS: Found: [M + H$^+$], 466.5 $C_{18}H_{12}FIN_2O_4$ requires [M + H$^+$], 467.0

(S)-*N*-((3-(3-fluoro-4-iodophenyl)-2-oxooazolidin-5-yl)methylacetamide



To a solution of 2-((3-(3-fluoro-4-iodophenly-2-oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione

(1.28g, 2.75 mmol) dissolved in ethanol was added hydrazine hydrate 80% in water (0.83 mL 13.75 mmol) and the mixture heated to reflux for 4 h. The reaction was quenched with water upon formation of a white precipitate and extracted with ethyl acetate. The organic layer was washed with water 3 x, then brine, dried over $MgSO_4$ and reduced in vacuo. To a solution of the crude residue in CH_2Cl_2 and trimethylamine (0.77 mL, 5.50 mmol) was added acetic anhydride (0.39 mL, 4.13 mmol) at 0°C degrees. The reaction was warmed to room temperature over 4 h and quenched with ammonium chloride. The organics were extracted using EtOAc which was washed with water 3 x, then brine and dried over $MgSO_4$. The solvent was reduced in vaccuo and the residue washed in ether and filtered to afford the desired product (0.820 g, yield 82% *over two steps)*

R_f: 0.63 (10 % MeOH in CH_2Cl_2)

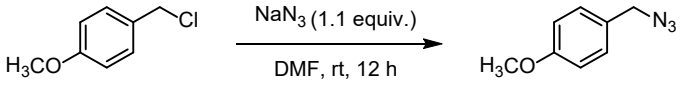
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (t, 1H), 7.82 (dd, J = 8.6, 7.6 Hz, 1H), 7.55 (dd, J = 10.9, 2.5 Hz, 1H), 7.18 (dd, J = 8.6, 2.5 Hz, 1H), 4.78 – 4.70 (m, 1H), 4.11 (t, 1H), 3.73 (dd, J = 9.1, 6.4 Hz, 1H), 3.41 (t, 2H), 1.83 (s, 3H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 170.45, 162.43, 160.84, 154.35, 140.85 (d, J = 10.2 Hz), 139.53 (d, J = 3.4 Hz), 116.07 (d, J = 3.0 Hz), 105.80 (d, J = 29.7 Hz), 72.24, 47.59, 41.82, 22.90.

IR: 3408, 1747, 1670, 1596, 1526, 1478, 1428, 1412, 1336, 1274, 1226, 1200, 1113, 1040

LRMS: Found: [M + H^+], 378.6 $C_{12}H_{12}FIN_2O_3$ requires [M + H^+], 379.0

1-(azidomethyl)-4-methoxybenzene



To a solution of 4-methoxybenzyl chloride (11.30 mL, 83.00 mmol) in DMF was added sodium azide (5.50 g, 84.00 mmol) and the resulting mixture stirred at room temperature for 12 h. The reaction mixture was quenched with water and the organics extracted with ethyl acetate. The organic extracts were washed with water (3x) and brine, dried over $MgSO_4$ and concerntrated in vacuo. The desired product was obtained without further purification as a colorless oil (14.37g, yield 99%)

R_f: 0.73 (15 % EtOAc in Hexanes)

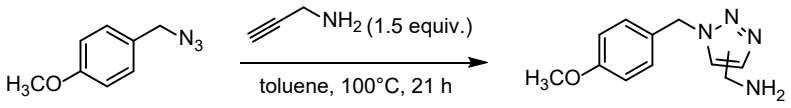
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.20 (s, 2H), 3.75 (s, 3H)

^{13}C NMR (151 MHz, $CDCl_3$) δ 159.67, 129.78, 127.44, 114.22, 55.28, 54.40

IR: 2936, 2089, 1611, 1511, 1458, 1242, 1174, 1031, 810

LRMS: Found: [M + H^+], 136.0 C_8H_9NO requires [M + H^+], 136.1

(1-(4-methoxybenzyl)-1,2,3-triazol-5-yl)methanamine



To a solution of 4-methoxybenzylazide (6.00 g, 36.77 mmol) in toluene (120 mL) was added propargylamine (3.53 mL, 55.15 mmol), the mixture was heated to 100°C for 21 h. The reaction was cooled to room temperature and concentrated in vacuo to remove toluene. The resulting residue was taken up in ethyl acetate, washed with water (x3), then brine and dried over $MgSO_4$ and reduced in vacuo. The crude mixture was purified by flash column chromatography (2-5-10% MeOH : CH_2Cl_2) to afford both regiosomers 1:1 (7.96 g, yield 92%).

High Isomer

R_f: 0.18 (5 % MeOH in CH_2Cl_2)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (s, 1H), 7.18 (d, J = 8.3 Hz, 2H), 6.92 (d, J = 8.3 Hz, 2H), 5.53 (s, 2H), 3.74 (s, 3H), 3.71 (s, 2H), 1.86 (s, 2H)

^{13}C NMR (101 MHz, DMSO): δ 159.37, 139.69, 132.58, 129.40, 128.27, 114.56, 55.58, 50.59, 35.05.

IR: 3338, 3279, 3196, 2958, 2912, 2839, 1612, 1512, 1442, 1371, 1282, 1238, 1173, 1080, 1025

LRMS: Found: [M + H^+], 219.1 $C_{11}H_{14}N_4O$ requires [M + H^+], 219.1

Low Isomer

R_f: 0.08 (5 % MeOH in CH_2Cl_2)

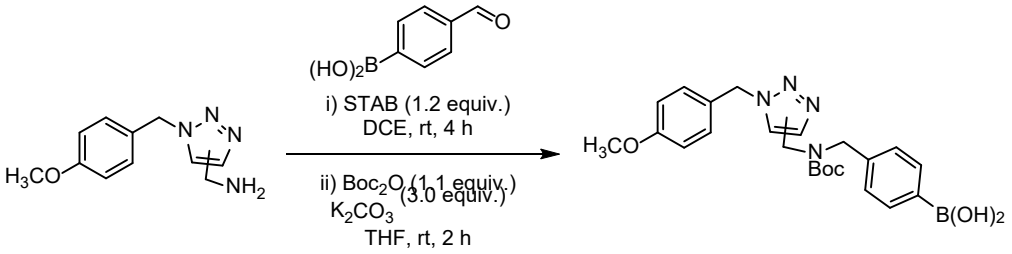
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, J = 6.9 Hz, 1H), 7.29 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 5.47 (s, 2H), 4.67 (s, 2H), 4.15 (s, 1H), 3.74 (s, 4H).

^{13}C NMR (101 MHz, DMSO): δ 159.37, 139.69, 132.58, 129.40, 128.27, 114.56, 55.58, 50.59, 35.05.

IR: 3274, 3065, 2957, 2896, 1605, 1510, 1443, 1349, 1244, 1174, 1126, 1029

LRMS: Found: [M + H^+], 219.1 $C_{11}H_{14}N_4O$ requires [M + H^+], 219.1

(4-(((*tert*-butoxycarbonyl)((1-(4-methoxybenzyl)-1,2,3-triazol-5-yl)methyl)amino)methyl)phenyl)boronic acid



To a solution of regioisomers (1.00 g, 4.58 mmol) and 4-formylphenylboronic acid (0.70g, 4.58 mmol) in DCE (40 mL) was slowly added sodium triacetoxyborohydride (STAB) (1.46 g, 6.87 mmol) in three portions over 30 minutes. The mixture was left to stir for 4 h at room temperature before quenching the reaction with water. The organics were extracted with CH_2Cl_2, washed with water 3 x, then brine and dried over $MgSO_4$. The solution was reduced in vacuo and then dissolved in THF/H_2O to which potassium carbonate (1.90 g, 13.75 mmol) and Boc_2O (1.00 mL, 4.35 mmol) was added and the reaction left at ambient temperature for 2 h. The organics were extracted with ethyl acetate, washed with water 3 x, then brine, dried over $MgSO_4$ and reduced in vacuo. The crude residue was purified by flash column (0-10 % MeOH in CH_2Cl_2) to afford the desired regioisomers with a combined yield of (1.31 g, yield: 63% *over two steps*)

R_f: 0.21 (2 % MeOH in CH_2Cl_2)

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 1H), 7.07 (d, J = 8.2 Hz, 2H), 6.92 (dd, J = 20.6, 8.6 Hz, 4H), 6.68 (d, J = 8.5 Hz, 2H), 5.47 (s, 2H), 4.38 (s, 2H), 4.15 (s, 2H), 3.73 (s, 3H), 1.34 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ ^{13}C NMR (151 MHz, DMSO) δ 159.40, 155.12, 146.67, 140.00, 139.29, 135.85, 134.77, 134.12, 129.09, 128.02, 126.88, 114.57, 80.36, 55.57, 50.64, 50.62, 50.13, 28.28.

IR: 2976, 2934, 1687, 1611, 1514, 1458, 1400, 1366, 1245, 1148, 1115, 1067, 1031

LRMS: Found: [M + H^+], 452.8 $C_{23}H_{30}BN_4O_5$ requires [M + H^+], 453.2

R_f: 0.55 (10 % MeOH in CH_2Cl_2)

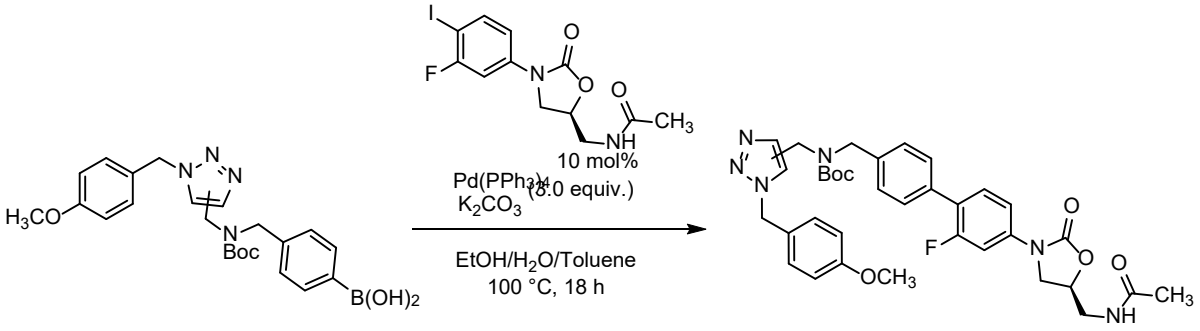
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (s, 2H), 7.74 (d, J = 7.6 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 7.16 (s, 2H), 6.95 – 6.89 (m, 2H), 5.48 (s, 2H), 4.34 (m, 4H), 3.73 (s, 3H), 1.36 (s, 9H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 159.55, 155.17, 144.46 (d, J = 53.3 Hz), 140.32, 134.73, 133.25, 129.94, 128.46, 126.75 (d, J = 46.4 Hz), 123.43 (d, J = 73.0 Hz), 114.54, 79.77, 55.60, 52.72, 49.98 (d, J = 61.3 Hz), 41.81 (d, J = 46.7 Hz), 28.42.

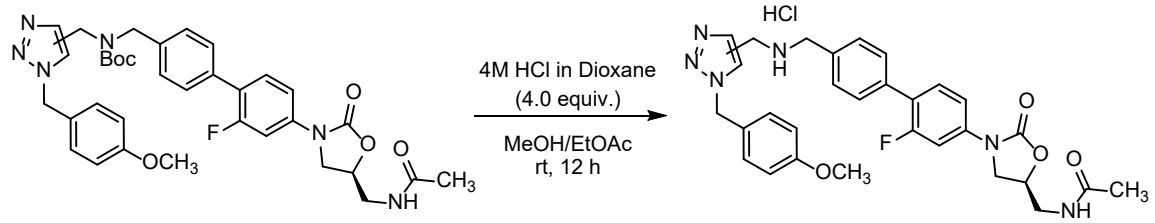
IR: 3340, 3134, 2979, 1673, 1611, 1515, 1474, 1403, 1339, 1306, 1251, 1159, 1063, 1032

LRMS: Found: [M + H^+], 452.8 $C_{23}H_{30}BN_4O_5$ requires [M + H^+], 453.2

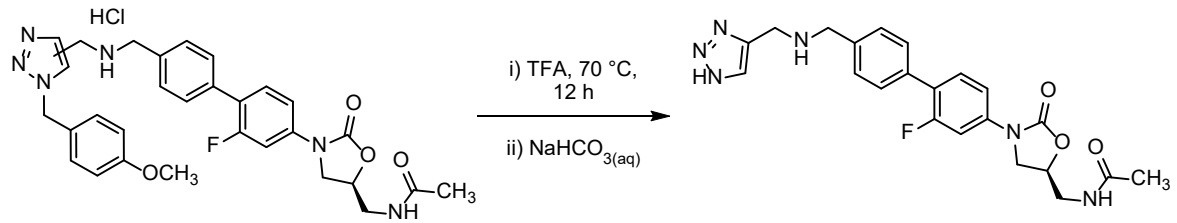
Radezolid



To a flame dried Schleck was added boronic acid (0.600 g, 1.32 mmol), oxazolidinone (0.500 g 1.32 mmol), potassium carbonate (0.55 g, 4.00 mmol) and $Pd(PPh_3)_4$ (153 mg, 10 mol%). The mixture was dissolved in degassed toluene (15 mL), ethanol (5 mL) and water (5 mL) before being warmed to gentle reflux at 100°C for 18 h. The mixture was extracted with EtOAc and the organics washed with water 3 x, then brine and dried over $MgSO_4$. The solution was reduced in vacuo and the residue purified by flash column chromatography (5-10% MeOH : CH_2Cl_2).



The isolated residue was taken up in EtOAc (5 mL) and MeOH (25 mL) and 4N hydrogen chloride in dioxane (2.65 mL, 10.56 mmol) added at room temperature and left for 12 h. The mixture was concentrated in vacuo and the crude residue which was washed with EtOAc to



afford Radezolid-PMP Hydrochloride (0.692 g, yield 88% *over two steps*) as the hydrochloride salt, white solid.

The remaining solid was dissolved in TFA (10 mL) and the mixture heated to 70 °C for 12 h. The reaction was quenched with water, the organics extracted with EtOAc and the aqueous layer collected. The aqueous layer was left at room temperature and after 1 h a white precipitate was observed and collected via filtration. The precipitate was washed in ethyl acetate to afford the desired product Radezolid as an off-white solid yield (342 mg, yield 67%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 14.79 (bs, 1H), 8.26 (t, J = 5.9 Hz, 1H), 7.73 (s, 1H), 7.65 – 7.36 (m, 7H), 4.77 (m, 1H), 4.17 (t, J = 9.0 Hz, 1H), 3.84 – 3.68 (m, 5H), 3.44 (t, J = 5.5 Hz, 2H), 1.85 (s, 3H).

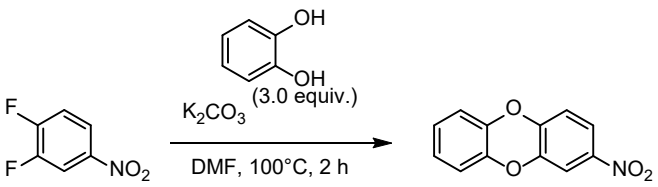
^{13}C NMR (151 MHz, DMSO) δ 170.50, 160.26, 158.64, 154.47, 140.55, 139.61, 139.54, 133.38, 128.76, 123.34, 123.25, 114.44, 114.42, 106.12, 105.93, 72.22, 52.32, 47.67, 43.19, 41.87, 22.92.

IR: 3343, 2938, 2734, 2590, 2430, 2324, 1743, 1656, 1625, 1523, 1500, 1439, 1408, 1360, 12240, 1194, 1152, 1088, 1041, 803

HRMS: Found: [M + H$^+$], 439.1881 $C_{22}H_{23}FN_6O_3$ requires [M + H$^+$],439.1888

T145 Synthesis

2-nitrodibenzodioxine



To a solution of 3,4-difluoronitrobenzene (5.00 mL, 45.20 mmol) in DMF (100mL) was added potassium carbonated (12.00 g, 136.35 mmol). The mixture was heated to reflux and catechol (5.00 g, 45.20 mmol) was added in small portions over 30 minutes. Once addition was complete, the reaction was left to stir at 100°C for 2 h. The reaction was poured into ice water giving a yellow precipitate, which was collected and washed with water upon filtration to afford the desired product (9.55g, 92% yield) as a yellow solid.

R_f: 0.67 (15 % EtOAc in Hexanes)

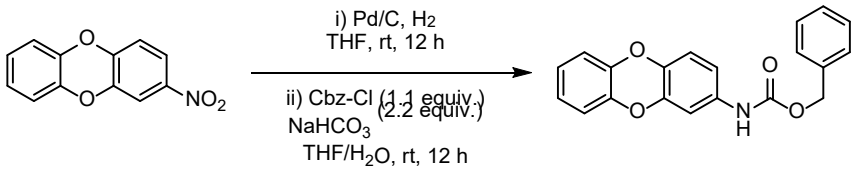
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (dd, J = 8.9, 2.7 Hz, 1H), 7.78 (d, J = 2.7 Hz, 1H), 7.20 (d, J = 8.9 Hz, 1H), 7.08 – 7.01 (m, 4H)

^{13}C NMR (151 MHz, DMSO-d_6) δ 147.39, 143.71, 141. 86, 140.71 (d, J = 4.5 Hz), 125.86, 125.48, 120.94, 117.42, 117.14, 116.99, 112.35.

IR: 2115, 1515, 1480, 1426, 1330, 1287, 1272, 1204, 1123, 1100

LRMS: Found: [M + H^+], 229.8 $C_{12}H_7NO_4$ requires [M + H^+], 230.0

Benzyl dibenzodioxin-2-ylcarbamate



To a solution of 2-nitrodibenzodioxine (1.80 g, 7.85 mmol) in THF (20 mL) was added 10 mol% Pd/C (0.300 g). Hydrogen gas was bubbled through the mixture for 12 h at ambient temperature. The mixture was filtered through celite and the filtrate concentrated in vacuo. The product was purified by column chromatography (15-20% EtOAc : Hexane). The residue was dissolved in THF/H_2O, $NaHCO_3$ (1.46 g, 17.27 mmol) was added followed by the slow addition of Cbz-Cl at 0°C. The reaction was allowed to reach ambient temperature, after 12 h the reaction was quenched and the organics extracted with ethyl acetate. The organic layer was washed with water (3x) and brine, dried over $MgSO_4$ and reduced in vacuo to afford the desired product without further purification (1.98 g, yield 76% over two steps) as white crystals.

R_f: 0.32 (20 % EtOAc in Hexanes)

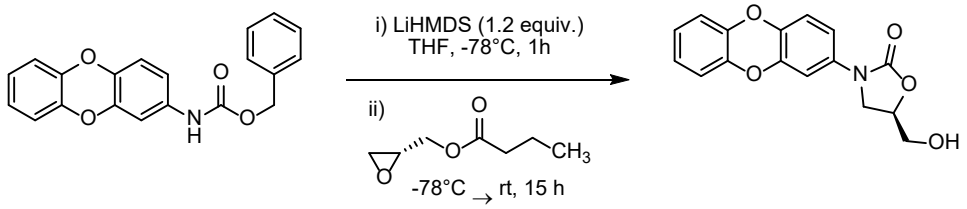
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 (s, 1H), 7.44 – 7.33 (m, 5H), 7.16 (d, J = 2.4 Hz, 1H), 7.03 (dd, J = 8.7, 2.5 Hz, 1H), 6.99 – 6.89 (m, 5H), 5.14 (s, 2H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 153.73, 141.93, 141.55 (d, J = 7.6 Hz) 136.94, 136.78, 135.92, 128.91, 128.62, 128.54, 124.82, 124.58, 116.92, 116.82 (d, J = 6.0 Hz) 113.90, 106.70, 66.33

IR: 3338, 1701, 1531, 1495, 1255, 1225, 1211, 1048

LRMS: Found: [M + H^+], 333.8 $C_{20}H_{15}NO_4$ requires [M + H^+], 334.1

(R)-3-(dibenzodioxin-2-yl)-5-(hydroxymethyl)oxazolidin-2-one



To a solution of benzyl dibenzodioxin-2-ylcarbamate (1.85 g, 5.55 mmol) in THF (40 mL) was added LiHMDS (1.06M, 6.8 mL, 6.66 mmol) dropwise at -78°C. Once addition was complete the reaction was left to stir for 1 h before (R)-glycidyl butyrate (0.40 mL, 5.55 mmol) was added dropwise at -78°C. The mixture was left to warm to ambient temperature over 15 h. The crude residue was washed in hot ether to afford the desired product (1.30 g, yield 78%) as a white solid.

R_f: 0.56 (2 % MeOH in CH_2Cl_2)

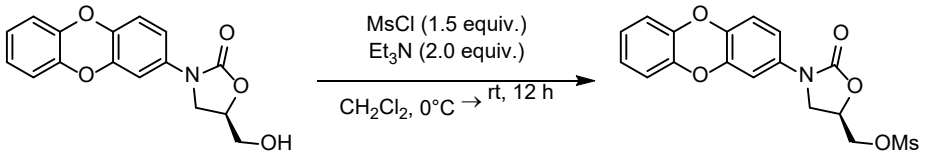
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 (d, J = 2.5 Hz, 1H), 7.10 (dd, J = 8.9, 2.7, Hz, 1H), 7.05 – 6.94 (m, 5H), 5.22 (t, J = 5.6 Hz, 1H), 4.69 (m, 1H), 4.06 (t, 1H), 3.83 – 3.76 (m, 1H), 3.61 (m, 2H)

^{13}C NMR (101 MHz, DMSO) δ 154.83, 141.79, 141.64, 141.44, 137.47, 135.32, 124.91, 124.71, 116.92, 116.84, 113.55, 106.65, 73.60, 62.10, 46.51.

IR: 3541, 1717, 1515, 1492, 1482, 1410, 1294, 1268, 1100

LRMS: Found: [M + H^+], 299.8 $C_{16}H_{13}NO_5$ requires [M + H^+], 300.1

(*R*)-3-(dibenzodioxin-2-yl)-2-oxooxazolidin-5-yl)methyl methanesulfonate



To a solution of (*R*)-3-(dibenzodioxin-2-yl)-5-(hydroxymethyl)oxazolidin-2-one (0.800 g, 2.67 mmol) and Et_3N (0.75 mL, 5.35 mmol) in CH_2Cl_2 (25.0mL) was added methanesulfonyl chloride (0.31mL, 4.00 mmol) dropwise at 0°C. The mixture was left to warm to ambient temperature over 4 h and was quenched with ice water. The organics were extracted with CH_2Cl_2 and washed with water 3x, then brine and dried over $MgSO_4$. The residue was reduced in vaccuo to afford a crude residue that was recrystalised in ether to give the desired product (1.01g yield 79%) as a white solid.

R_f: 0.41 (2 % MeOH in CH_2Cl_2)

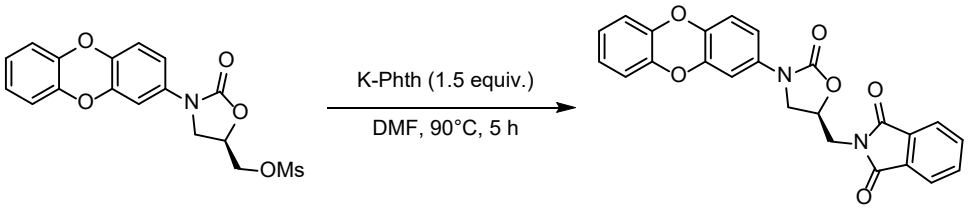
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30 (d, *J* = 2.6 Hz, 1H), 7.08 (dd, *J* = 8.9, 2.7, Hz, 1H), 7.03 – 6.95 (m, 5H), 4.99 (m, 1H), 4.49 (m, 2H), 4.15 (t, 1H), 3.80 (dd, 1H *J* = 9.2, 6.2 Hz, 1H), 3.26 (s, 3H)

^{13}C NMR (101 MHz, DMSO) δ 154.15, 141.74, 141.67, 141.40, 137.78, 134.84, 124.93, 124.74, 116.89, 113.95, 107.03, 70.42, 70.18, 46.39, 37.27.

IR: 3019, 1743, 1518, 1493, 1354, 1292, 1264, 1170, 1117

LRMS: Found: [M + H^+], 377.7 $C_{17}H_{15}NO_7S$ requires [M + H^+], 378.0

(*S*)-2-((3-(dibenzodioxin-2-yl)-2-2oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione



(*R*)-3-(dibenzodioxin-2-yl)-2-oxooxazolidin-5-yl)methyl methanesulfonate (1.00 g, 2.65 mmol) and potassium phthalimide (0.736 g, 3.95 mmol) was dissolved in DMF (25 mL) and heated to 90°C for 5 h. The mixture was poured into water and extracted with ethyl acetate 3 x, washed with water 3 x, then brine and dried over dried over $MgSO_4$. The solution was reduced in vacuo to afford a crude residue that was recrystalised in ether to give the desired product (0.372g yield 33%) as a white solid.

R_f: 0.64 (2 % MeOH in CH_2Cl_2)

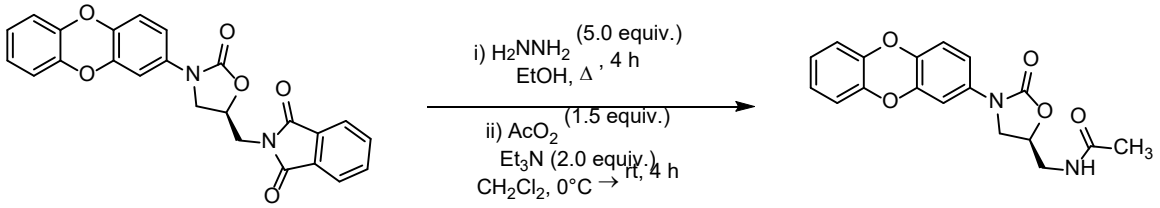
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 – 7.83 (m, 4H), 7.24 (d, J = 2.3 Hz, 1H), 7.06 – 6.96 (m, 6H), 4.93 (m, 1H), 4.17 (t, J = 9.0 Hz, 1H), 4.00 (dd, J = 14.6, 7.1 Hz, 1H), 3.94 – 3.85 (m, 2H).

^{13}C NMR (151 MHz, DMSO) 168.26, 154.21, 141.77, 141.66, 141.42, 137.75, 135.07, 131.97, 125.00, 124.81, 123.71, 116.96, 116.92, 116.90, 114.06, 107.08, 70.50, 48.29.

IR: 1748, 1706, 1520, 1496, 1396, 1305, 1266, 1216, 1133, 1092, 1041

LRMS: Found: [M + H^+], 429.0 $C_{24}H_{16}N_2O_6$ requires [M + H^+], 429.1

(*S*)-N-((3-(dibenzo[b,e][1,4]dioxin-2-yl)-2-oxooxazolidin-5-yl)methyl)acetamide (T145)



To a solution of (*S*)-2-((3-(dibenzodioxin-2-yl)-2-2oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione (330 mg, 0.77 mmol) in ethanol (20 mL) was added hydrazine hydrate 80% in water (0.23 mL, 3.85 mmol) and the mixture heated to reflux for 4 h. The reaction was quenched with water upon formation of a white precipitate and extracted with EtOAc. The orangic layer was washed with water 3 x, then brine, dried over $MgSO_4$ and reduced in vaccuo. To a solution of the crude residue 3in CH_2Cl_2 (20 mL) and trim$_{et}$hylamine (0.22 mL, 1.54 mmol) was added acetic anhydride (0.11 mL, 1.16 mmol) at 0 °C degrees. The reaction was warmed to room temperature over 4 h and quenched with sat NH_4Cl. The organics were extracted using EtOAc, washed with water 3 x, then brine and dried over $MgSO_4$. The solvent was reduced in vacuo and the residue washed in ether and filtered to afford the desired product (205 mg, yield 78%) as a white solid.

R_f: 0.33 (5 % MeOH in CH_2Cl_2)

^{1}H NMR (400 MHz, DMSO-d_6) ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 – 7.83 (m, 4H), 7.24 (d, J = 2.3 Hz, 1H), 7.06 – 6.96 (m, 6H), 4.93 (m, 1H), 4.17 (t, J = 9.0 Hz, 1H), 4.00 (dd, J = 14.6, 7.1 Hz, 1H), 3.94 – 3.85 (m, 2H).

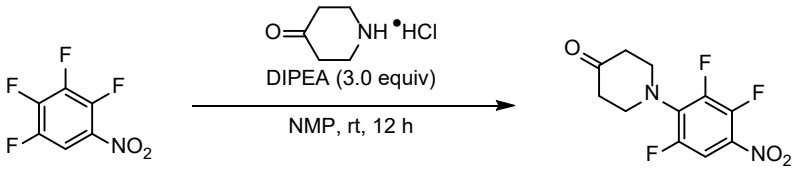
^{13}C NMR (101 MHz, DMSO): δ 170.46, 154.51, 141.77, 141.65, 141.42, 137.63, 135.18, 124.99, 124.79, 116.95, 116.90, 113.88, 106.94, 71.99, 47.75, 41.88, 22.92.

IR: 3288, 3092, 2922, 1728, 1643, 1557, 1510, 1426, 1295, 1232, 1216, 1078, 1032

HRMS: Found: [M + H^+], 341.1090 $C_{18}H_{16}N_2O_5$ requires [M + H^+], 341.1132

Contezolid Synthesis

1-(2,3,6-trifluoro-4-nitrophenyl)piperidin-4-one



To a solution of tetrafluoronitrobenzene (4.00 mL, 33.09 mmol) and piperidinone·HCl (4.70 g, 34.57 mmol) in NMP (35 mL) was added Hunigs base (11.41 mL, 49.63 mmol) dropwise at 0 °C. The reaction was allowed to reach ambient temperature over 12 h. The mixture was then poured into ice water which gave a yellow precipitate that was collected by filtration to give the desired product (8.00 g, yield 88%)

R_f: 0.23 (20 % EtOAc in Hexanes)

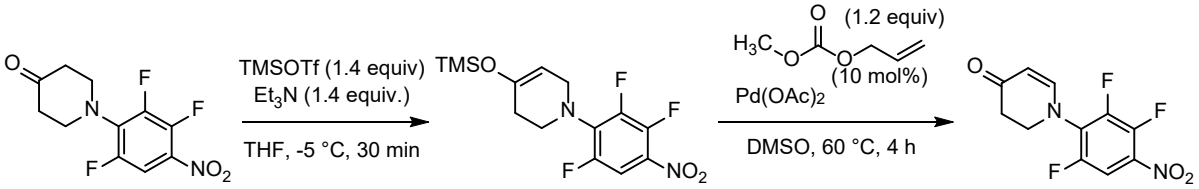
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (ddd, *J* = 12.0, 6.7, 2.2 Hz, 1H), 3.70 (t, *J* = 6.2 Hz, 3H), 2.62 (t, *J* = 6.1 Hz, 4H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 206.19, 149.80 (ddd, *J* = 246.2, 6.3, 2.8 Hz), 145.04 (ddd, *J* = 249.3, 14.3, 7.4 Hz), 143.96 (ddd, *J* = 265.6, 15.6, 3.4 Hz), 134.99 (dd, *J* = 13.7, 9.3 Hz), 129.57, 108.59 (d, *J* = 28.0 Hz), 50.26, 42.07.

IR: 1712, 1612, 1515, 1471, 1411, 1299, 1228, 1155, 1120, 1025

HRMS: Found: [M + H^+], 275.0 $C_{18}H_{16}N_2O_5$ requires [M + H^+], 275.1

1-(2,3,6-trifluoro-4-nitrophenyl)-4-((trimethylsilyl)oxy)-1,2,3,6-tetrahydropyridine



To a solution of 1-(2,3,6-trifluoro-4-nitrophenyl)piperidin-4-one (2.50 g 9.12 mmol) and Et_3N (1.65 mL, 11.86 mmol) in THF (45 mL) was added TMSOTf (2.15 mL 11.86 mmol) dropwise at -5 °C . The reaction was monitored via TLC and once all starting material has been consumed (~30min) the reaction was quenched with water. The organics were extracted with EtOAc, washed with water 2 x, then brine and dried with $MgSO_4$. The solution was reduced in vacuo to afford a red oil which was used without further purification. The crude residue was dissolved in dry DMSO (40 mL) to which palladium acetate (205 mg, 10 mol%) and allylmethylcarbonate (1.45 mL, 12.77 mmol) were added. The mixture was heated to 60 °C and left stirring for 5 h. The reaction was quenched with water and extracted with EtOAc, the organics were washed with water 3 x, then brine and dried with $MgSO_4$. The resulting solution was reduced in vacuo to afford a yellow oil which solidified upon standing to give the desired product (2.06 g, yield 83% *over two steps*)

R_f: 0.48 (50 % EtOAc in Hexanes)

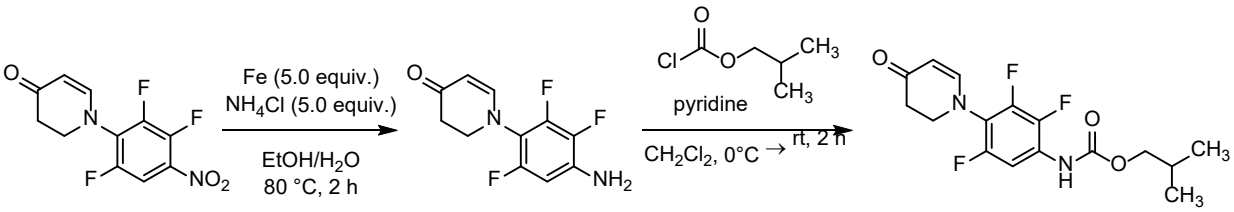
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (ddd, J = 11.1, 6.7, 2.0 Hz, 1H), 7.54 (dd, J = 7.9, 2.2 Hz, 1H), 5.22 (d, J = 7.9 Hz, 1H), 4.10 – 3.93 (m, 2H), 2.58 – 2.52 (m, 2H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 190.96, 150.73, 145.52 (ddd, J = 251.4, 14.4, 5.8 Hz), 142.52 (ddd, J = 262.4, 15.1, 4.0 Hz), 132.75 (s), 129.34 (dd, J = 15.7, 11.0 Hz), 109.02 (dd, J = 27.7, 3.3 Hz), 104.10, 48.97, 36.08.

IR: 1654, 1579, 1531, 1499, 1482, 1458, 1339, 1304, 1283, 1230, 1197, 1175, 1117, 1103, 1033

LRMS: Found: [M + H^+], 273.0 $C_{18}H_{16}N_2O_5$ requires [M + H^+], 273.0

Isobutyl (2,3,5-trifluoro-4-(4-oxo-3,4-dihydropyridine-1-yl)phenylcarbamate



To a solution of 1-(2,3,6-trifluoro-4-nitrophenyl)-2,3-dihydropyidine-4-one (1.00 g 3.67 mmol) in EtOH (20 mL) and H_2O (20 mL) was added iron powder (1.03 g, 18.37 mmol) and ammonium chloride (1.18 g, 22.02 mmol). The mixture was refluxed for 2 h and then filtered through celite and reduced in vacuo. The aqueous solution was extracted with EtOAc washed with water 3 x, then brine and dried with $MgSO_4$. The solution was reduced in vacuo to afford the desired amine (0.830 g) which was used without further purification. The amine was dissolved in CH_2Cl_2 (50 mL) and pyridine (0.34 mL, 4.11 mmol) before adding isobutylchloroformate (0.51 mL, 3.77 mmol) dropwise at 0 °C. The mixture was left to reach ambient temperature over 2 h and was quenched with water. The organics were extracted using EtOAc, washed with water 3 x, then brine and dried over $MgSO_4$. The resulting solution was reduced in vacuo and the residue purified by flash column (30 % EtOAc : hexanes) to give the desired product (0.906 g, yield: 73% *over two steps*)

R_f: 0.54 (50 % EtOAc in Hexanes)

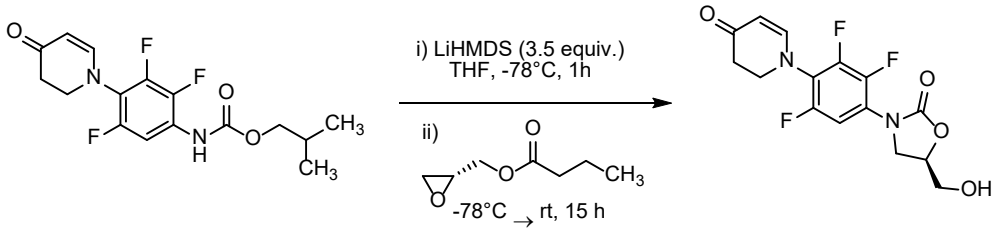
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 7.59 (ddd, J = 12.6, 6.8, 2.3 Hz, 1H), 7.44 (d, J = 7.7 Hz, 1H), 5.03 (d, J = 7.7 Hz, 1H), 3.91 (d, J = 6.7 Hz, 2H), 3.83 (t, J = 7.4 Hz, 2H), 2.49 – 2.46 (t, 2H), 1.93 (dt, J = 13.4, 6.7 Hz, 1H), 0.93 (d, J = 6.7 Hz, 6H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 190.96, 154.13, 153.03, 152.70, 146.49 (ddd, J = 247.4, 12.9, 7.4 Hz), 139.52 (dd, J = 246.5, 14.2 Hz), 127.02 (ddd, J = 13.2, 9.9, 3.3 Hz), 118.65 (dd, J = 17.4, 12.4 Hz), 105.20 (d, J = 26.9 Hz), 101.99, 71.38, 49.68, 36.44, 27.96, 19.26.

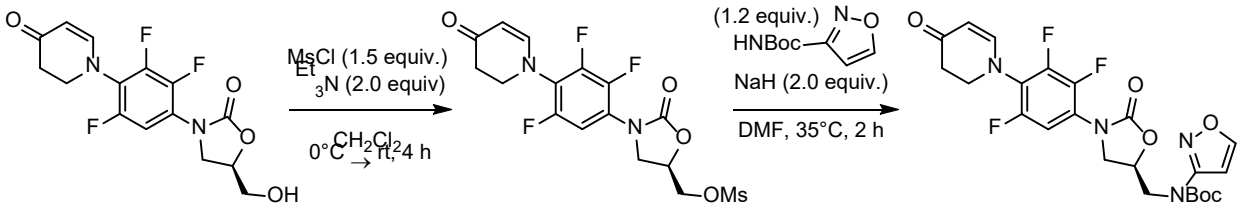
IR: 2964, 1721, 1581, 1544, 1509, 1469, 1305, 1251, 1213, 1175, 1102, 1036, 1010

LRMS: Found: [M + H$^+$], 343.1 $C_{16}H_{17}F_3N_2O_3$ requires [M + H$^+$], 343.1

(*S*)-5-((isoxazol-5-ylamino)methyl)-3-(2,3,5-trifluoro-4-(4-oxo-3,4-dihydropyridin-1-(*2H*)-yl)phenyl)oxazolidin-2-one (Contezolid)



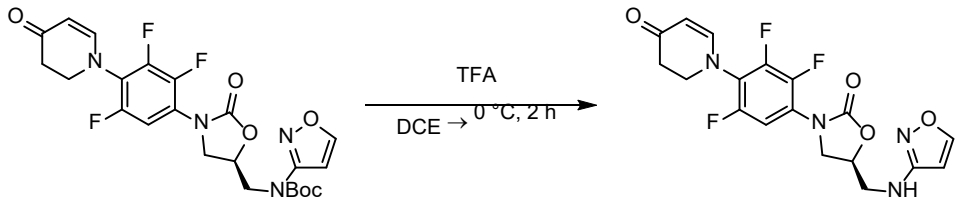
To a solution of 1-(2,3,6-trifluoro-4-nitrophenyl)-4-((trimethylsilyl)oxy)-1,2,3,6-tetrahydropyridine (0.500 g, 1.46 mmol) in THF (20 mL) was added LiHMDS (5.11 mL, 1M in THF) dropwise at -78 °C. The mixture was left to stir for 1 h before adding (R)-glycidyl butyrate (0.22 mL, 1.61 mmol) dropwise at -78 °C. The reaction mixture was allowed to reach ambient over 15 h at which point it was quenched with water. The organics were extracted using EtOAc, washed with water 3 x, then brine and dried over $MgSO_4$. The solution was reduced in vacuo to afford the desired product with several inseparable impurities (~ 0.200 g)



which was used without further purification.

To the crude (*R*)-5-(hydrpxymethyl)-3-(2,3,5-trifluoro-4-(4-oxo-3,4-dihydropyridine-1(2*H*)-yl)phenyl)oxazolidin-2-one (0.200 g, 0.58 mmol) in CH_2Cl_2 (30 mL) and Et_3N (0.16 mL , 1.17

mmol] in was added MsCl (0.07 mL, 0.87 mmol) dropwise at 0 °C. The reaction was allowed to reach ambient temperature over 4 h and was quenched with water. The organics were extracted using EtOAc, washed with water 3 x, then with brine and dried over $MgSO_4$. The solvent was evaporated and the crude residue was dissolved in DMF (20 mL) to which NaH [xx, mmol] was added at 0 °C. After the evolution of H_2 ceased Bocisoxazole [xx, mmol] was added dropwise at ambient. Once addition was complete the mixture was heated to 35 °C for 2 h. The reaction was quenched with water and extracted with EtOAc, washed with water 6 x, then brine and dried with $MgSO_4$. The solution was reduced in vacuo and the residue purified by flash column (1-5 % MeOH : CH_2Cl_2) to give crude [xx].



The residue was dissolved in dry DCE (20 mL) and TFA [xx] was added dropwise at 0 °C. The mixture was allowed to warm to ambient over 2 h at which point all volatiles were removed under reduced pressure. The residue was taken up in EtOAc, washed with $NaHCO_3$ 3 x, then brine and dried over $MgSO_4$. The solvent was reduced in vacuo and purified using PrepHPLC to afford the desired product

(42mg, 7% *over 5 steps*)

R_f: 0.08 (10 % MeOH in CH_2Cl_2)

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.05 (d, *J* = 1.8 Hz, 1H), 7.30 (ddd, *J* = 11.4, 6.6, 2.2 Hz, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 5.89 (d, *J* = 1.8 Hz, 1H), 5.25 (d, *J* = 7.8 Hz, 1H), 4.99 (ddt, *J* = 8.7, 6.3, 4.9 Hz, 1H), 4.80 (s, 1H), 4.17 (td, *J* = 8.8, 1.3 Hz, 1H), 3.95 (ddd, *J* = 9.0, 6.5,

1.3 Hz, 1H), 3.87 (t, *J* = 7.4 Hz, 2H), 3.71 (ddd, *J* = 14.7, 6.8, 3.5 Hz, 1H), 3.63 (dt, *J* = 14.6, 6.0 Hz, 1H), 2.67 – 2.63 (m, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 191.77, 163.63, 158.41 (d, *J* = 16.7 Hz), 155.03, 152.35 (dt, *J* = 247.9, 3.8 Hz), 151.22, 146.62 (ddd, *J* = 252.2, 13.8, 6.7 Hz), 142.21 (ddd, *J* = 251.4, 13.9, 4.1 Hz), 124.79 (ddd, *J* = 12.1, 9.1, 2.8 Hz), 121.72 (dd, *J* = 16.6, 11.8 Hz), 108.19, 103.27 (d, *J* = 22.4 Hz), 96.44 (d, *J* = 13.3 Hz), 72.95 (d, *J* = 21.3 Hz), 49.66 (t), 49.01 (dt), 46.44 (t, *J* = 15.6 Hz), 36.19 (t).

IR: 3327, 2920, 1753, 1648, 1586, 1515, 1414, 1385, 1305, 1234, 1178, 1128, 1032

HRMS: Found: [M + H^+], 409.1156 $C_{18}H_{15}F_3N_4O_4$ requires [M + H^+], 409.1118