Electronic Supplementary Information

A Concise and Sequential Synthesis of Nitroimidazooxazole based Drug, Delamanid and related compound

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Figure S1: Synthesis of Delamanid developed by Otsuka pharmaceutical Ltd. (2004)³



Reagent and conditions: a) HNO₃, AcOH, Ac₂O, 5 °C, 2 h, and then at rt, 12 h, 69%; b) chloro benzene, 120-125 °C, 50 h, 95%; c) Conc. HCl, 90-95 °C, 12 h, 50%; d) Ti(OPr-i)₄, Di-*i*-*Pr*- D-tartrate, CH₂Cl₂, -35°C, cumene hydroperoxide, -35°C, DCM, 1h, -20 °C, 35 hrs.; e) P-nitrobenzoyl chloride, Et₃N, DCM, rt, 80%; f) Et₃N, AcOEt, 60-65 °C, 6 h, 87%; g) K₂CO₃, MeOH, rt, 2h, 97%; h) MsCl, pyridine, <15 °C, 2 h; i) DBU, AcOEt, rt, 2 h, 75%; j) Pyridinium-p-toluenensulfonate, overnight, rt, 96%; k) Pd(OAc)₂, *rac*-BINAP, Cs₂CO₃, toluene, reflux, 30 min, 64%; l) pyridinium p-toluenesulfonate, EtOH, 70 °C, 24 h, 94%; m) NaH, DMF, 50 °C, 2 h, 48%. $[\alpha]_D^{25}$ -8.0 ° (*c* 1, Chloroform).



Figure S2: Improved reported route for the synthesis of Delamanid⁵

Reagent and conditions: a) Ti(OPr-i)₄, di-i-Pr-D-tartrate, CH₂Cl₂, -35°C, cumene hydroperoxide, -35°C, DCM, 1h, -20 °C, 35 h, 82%; b) 10% aqueous. NaOH, toluene, 55 °C, 5 h, cooled overnight, 76%; c) NaOBu-*t*, Pd₂dba₃, *t*-BuXPhos, toluene, 110 °C, 3 h; d) MsCl, Et₃N, DCM, <15 °C, 2 h; e) DBU, AcOEt, rt, 2 h, 77%; f) *t*-BuOAc, NaOAc, 110 °C, 4 hrs. 73%.

Figure S3: Synthesis of key intermediate diole^{5, 6}



^{a,b} Reagent and conditions: a) Et₃N, ethyl acetate, 60 °C, 24 h, 92%; b) K_2CO_3 , MeOH, rt, 2h, 93%.

Figure S4: Synthesis of key intermediate 2-bromo-4-nitroimidazole 12⁷



^{*i*,*ii*}**Reagent and conditions:** i) compound S1 (88 mmol), bromine (211 mmol), NaHCO₃ (202 mmol), water (50 mL), 0 °C, 4h, 65 °C, 6 h, 88%; ii) compound S2 (85 mmol), KI (123 mmol), sodium sulfite (123 mmol), acetic acid, 120 °C, 16 h, 64%.

Table S1: Optimization table of coupling of 2-bromo-4-nitroimidazole 12 with compound 11



entry	Solvent	Base	Temp. °C	% Yield
1	Ethyl acetate	Et ₃ N	70	NR
2		Et ₃ N	80	Trace amount
3		DBU	100	NR
4	DMF	Cs ₂ CO ₃	100	Trace amount
5		DIPEA	115	89

"Reagent and Conditions: compound **12** (1 mmol), compound **11** (1 mmol), DIPEA (15 mmol), 115 °C, 12 h.

Figure S5: First reported route for the synthesis of VL-2098^{3, 8, 9}



Reagent and Conditions: a) Et₃N, AcOEt, 60-65 °C, 6 h, 87%; b) K₂CO₃, MeOH, rt, 2h, 97%; c) MsCl, pyridine, <15 °C, 2 h; d) DBU, AcOEt, rt, 2 h, 75%; e) NaH, DMF, 50 °C, 2 h, 48%.



Figure S5: Scalable reported route for the synthesis of VL-2098⁶

Reagent and conditions: i) $Ti(O-iPr)_4$, D(-)DIPT, TBHP, DCM, -25 °C to -30 °C,43% ii) K₂CO₃, 4-trifluromethoxyphenol, MeOH, rt-60 °C,; iii) Et₃N, 0 to -5 °C.; iv) Aqueous NaOH sol.,0 °C -15 °C, 92%; v) DIPEA, 110 °C -115 °C, 96%; vi) K₂CO₃ DMF, 90 °C, 51%.

¹H NMR of 1-iodo-4-((2-methylallyl)oxy)benzene 3:



¹³C NMR spectra of compound 3:



DEPT NMR spectra of compound 3:

08-Aug-radhika-c13 O-Allyl



GC-MS spectra of compound 3:



¹H NMR spectra of 1-(4-((2-methylallyl) oxy) phenyl) piperidin-4-ol (compound 5):



DEPT NMR spectra of compound 5:

H1 CN



c13-sumit CN

HRMS spectra of compound 5:

Qualitative Compound Report



¹H NMR spectra of 1-(4-((2-methylallyl) oxy) phenyl)-4-(4-(trifluoromethoxy) phenoxy) piperidine 8:



DEPT NMR of compound 8:



HRMS spectra of compound 8:

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¹H NMR spectra of (R)-2-methyl-3-(4-(4-(trifluoromethoxy)phenoxy) piperidin-1-yl)phenoxy)propane-1,2-diol R-(-)-9:



¹³C NMR spectra of compound R-(-)-9:



DEPT NMR of compound R-(-)-9:



HRMS spectra of compound R-(-)-9:

			Qualita	ative Com	pound Repor	t	
Data File Sample Type Instrument Nan Acq Method IRM Calibration Comment	ne Status	Dihydroxy. Sample Instrumen vishal_12-1 Success	d t 1 D1-13.m	Sample Name Position User Name Acquired Time DA Method	Dihydroxy Vial 11 28-05-2019 PM 1:22:16 Default.m		
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Compound Ta	ble				-	MEC DI#	
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L3	446.1942	446.1948	1.34	0.05	0.05	0.04	0.04



5957286

34202

Chiral HPLC spectra of compound R-(-)-9, S-(+)-9, RS-(±)-9:

2.

62.018

51.881

¹H NMR spectra of R)-1-(4-((2-methyloxiran-2-yl)methoxy)phenyl)-4-(4-trifluoromethoxy)phenoxy) 11:

 148

 148

 148



¹³C NMR spectra of R)-1-(4-((2-methyloxiran-2-yl)methoxy)phenyl)-4-(4-trifluoromethoxy)phenoxy) 11:



DEPT NMR of compound 11:



HRMS spectra of compound 11:

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¹H NMR spectra of 2-Bromo-4-nitro-1H-imidazole 12:



HRMS spectra of compound 12:

Data File Instrument Name (spectrum RM Calibration Status) NI-Br.d Sample Sample Instrument 1 Instrument I Instrument I I	Data File Sample Typ Instrument Acq Method								
Sample Group Requisition SW Person Infe. Scouseries TOF/6500 series Q-TOF B.05.01 (B5125) Compound Table RT Mass Formula MFG Formula Q 1: C3 H2 Br N3 O2 Olff OB Formula Q 1: C3 H2 Br N3 O2 Olff OB Formula Q 1: C3 H2 Br N3 O2 MFG Diff Oppoint DB Formula Q 1: C3 H2 Br N3 O2 MFG Diff Oppoint DB Formula Q 1: C3 H2 Br N3 O2 Olff DB Formula Q 1: C3 H2 Br N3 O2 MFG Diff Oppoint DB Formula Q 1: C3 H2 Br N3 O2 Mass Y10 4 0 50 0 50 0 50 0 50 0 50 0 50 0 50 0	Comment	e Name I Ition Status	NI-Br.c Sample Instrur vishal_ Succes	nent 1 12-01-13.m S	Sample Na Position User Nam Acquired T DA Metho	nme NI-Br Vial 25 e fime 19-07-201 d Default.m	9 PM 12:57:30		
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Image: Product of the bit of the	0.25 0 MS Spectr	150 200 rum Peak Li	st Form		Ion				
Instruction Instruction Instruction Instruction 194.9374 1 1018.41 C3 H3 Br N3 02 (M+H)+ Predicted Isotope Match Table ////////////////////////////////////	0.25 0 MS Specto m/z 191.940	150 200	st Form 7450.45 C3 H3 912.85 C3 H3	JIa Br N3 O2 Br N3 O2	Ion (M+H)+				
Interstelling in the second se	0.25 0 MS Spectr <i>m/z</i> 191.940 192.940	150 200 rum Peak Li z Abunc 02 1 1 07 1 1 38 1 1	st Form 7450.45 C3 H3 912.85 C3 H3 4996.04 C3 H3	ula Br N3 O2 Br N3 O2 Br N3 O2	Ion (M+H)+ (M+H)+ (M+H)+				
Isotope m/z Calc m/z Diff (ppm) Abund % Calc Abund % Abund Sum % Calc Abund Sum % 1 191.9402 191.9403 0.68 100 100 - 50.76 48.41	0.25 0 MS Spectr 191.940 193.93 194.932	150 200 rum Peak Li z Abunc 02 1 1 07 1 1 38 1 1 74 1 1	st Form 7450.45 C3 H3 912.85 C3 H3 4996.04 C3 H3 1018.41 C3 H3	ula Br N3 O2 Br N3 O2 Br N3 O2 Br N3 O2 Br N3 O2	Ion (M+H)+ (M+H)+ (M+H)+ (M+H)+				
1 191.9402 191.9403 0.68 100 100 - 50.76 48.41	0.25 0 MS Spectr m/z 191.940 192.940 193.93 194.937 Predicted	150 200 rum Peak Li Z Abunc 02 1 1 07 1 1 38 1 1 74 1 1 Isotope Mathematical Action of the second secon	st Form 7450.45 C3 H3 912.85 C3 H3 4996.04 C3 H3 1018.41 C3 H3 stch Table	ula Br N3 O2 Br N3 O2 Br N3 O2 Br N3 O2	Ion (M+H)+ (M+H)+ (M+H)+ (M+H)+				
	0.25 0 MS Spectr m/z 191.940 193.940 193.937 Predicted Isotope	150 200 rum Peak Li z Abunc 02 1 1 07 1	st Form 7450.45 C3 H3 912.85 C3 H3 4996.04 C3 H3 1018.41 C3 H3 atch Table Calc m/z	Ila Br N3 O2 Br N3 O2 Br N3 O2 Br N3 O2 Diff (ppm)	Ion (M+H)+ (M+H)+ (M+H)+ (M+H)+ (M+H)+ (M+H)+ (M+H)+	Calc Abund %	Abund Sum %	Calc Abund	Sum %
	0.25 0 m/z 191.940 193.93 194.937 Predicted Isotope	150 200 rum Peak Li z Abunc 02 1 1 07 1 - 138 1 1 174 1 - Isotope Ma m/z - 1 191.94 - 2 192.94 -	ist Formula 7450.45 C3 H3 912.85 C3 H3 4996.04 C3 H3 1018.41 C3 H3 atch Table Calc m/z 02 191.99 07 192.94	ula Br N3 O2 Br N3 O2 Br N3 O2 Br N3 O2 Br N3 O2 Diff (ppm) 03 0 22	Ion (M+H)+ (M+H)	Calc Abund % 100 4.45	Abund Sum % - 50.7/ 2.6/	Calc Abund	Sum % 48.41 2.15
3 193 938 193 9383 1.75 85.93 97.77 43.62 47.33	0.25 0 m/z 191.940 192.940 193.93 194.937 Predicted Isotope	150 200 z Abunc 02 1 107 1 38 1 174 1 Isotope Ma 1 191.94 2 192.94 3 192.94	Solution Formula 7450.45 C3 H3 912.85 C3 H3 4996.04 C3 H3 1018.41 C3 H3 atc Table Calc m/z 02 191.94 07 192.94	Jla Br N3 O2 Br N3 O2 Br N3 O2 Br N3 O2 Diff (ppm) 003 0 122 22 1	Ion (M+H)+ (M+H)	Calc Abund % 100 4.45 97.77	Abund Sum % - 50.7/ 2.6(43.6.	Calc Abund	Sum % 48.41 2.15 47.33

--- End Of Report ---





LC-MS spectra of compound 13:



¹H NMR spectra of 2-methyl-6-nitro-2-((4-(4-(trifluoromethoxy)phenoxy)piperidin-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole II, Delamanid:



¹³C NMR spectra of Delamanid II:



DEPT NMR of Delamanid II:



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HRMS spectra of compound Delamanid II:

oup 5W 6200 Q-Tr nd Table	0 series TOF/6 OF B.05.01 (B	1 500 series 5125)	Info.				
nd Table							
					I M	FG Diff	
ound Label	RT	Mass	Formula	м	FG Formula	(ppm) DB Fo	rmula
C25 H25 F3 N4 O6	0.3	534.1712	C25 H25 F3 N4	O6 C25	H25 F3 N4 O6	2.63 C25 H25	F3 N4 O6
150 200 25 trum Peak List	=3 N4 O6: +E 50 300 350 E Formu	ESI MFE Spo 0 400 450 Counts	500 550 600 vs. Mass-to-Charge) Frag=135.0V Of 650 700 750 8 e (m/z)	óo 860 900 950		
795 1 4139	08.19 C25 H2	6 F3 N4 O6	(M+H)+				
753 1 263	57.12 C25 H2	6 F3 N4 O6	(M+H)+				
d Isotope Mat	ch Table	1				10.1. 11	
m/z	Calc m/z	Diff (ppm	1) Abund % (Calc Abund %	Abund Sum %	Calc Abund Sum %	74.45
2 536.1802	2 536.1	83	5.11 31.38	29.03	22.78		21.61
3 537.1753	537.18	56 1	9.11 6.37	5.3	4.62		3.94
	nd Label 5 H25 F3 N4 O6 ectrum pd 7: C25 H25 I 150 200 21 trum Peak L13 x Abund 795 1 4139 802 1 1238 753 1 263 2 536.180 3 533.179	ad Label m/z 5 H25 F3 N4 O6 535.1795 setrum	ad Label m/z RT 5 H25 F3 N4 O6 535.1795 0.3 actrum	Ind Label m/z RT Algorithm 5 H25 F3 N4 06 535.1795 0.3 Find by Molecular scrum	Ind Label m/z RT Algorithm Mass 5 H25 F3 N4 O6 535.1795 0.3 Find by Molecular Feature 534.1713 sctrum	Ind Label m/z RT Algorithm Mass 5 H25 F3 N4 O6 535.1795 0.3 Find by Molecular Feature 534.1712 ectrum	Ind Label m/z RT Algorithm Mass 5 H25 F3 N4 06 535.1795 0.3 Find by Molecular Feature 534.1712 ectrum



¹H NMR spectra of 1-((2-methylallyl)oxy)-4-(trifluoromethoxy)benzene (14):

¹³C NMR spectra of 1-((2-methylallyl)oxy)-4-(trifluoromethoxy)benzene (14):







GC-MS spectra of compound 14:

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¹H NMR spectra of (R)-2-methyl-3-(4-(trifluoromethoxy)phenoxy)propane-1,2-diol *R*-(+)-15:



¹³C NMR spectra of (R)-2-methyl-3-(4-(trifluoromethoxy)phenoxy)propane-1,2-diol *R*-(+)-15::



-10 100 90 f1 (ppm) ò

DEPT NMR spectra of (R)-2-methyl-3-(4-(trifluoromethoxy)phenoxy)propane-1,2-diol *R*-(+)-15:



LC-MS spectra of compound *R*-(+)-15:



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¹H NMR spectra of (*R*)-1-(4-((2-methyloxiran-2-yl)methoxy)phenyl)-4-(4-trifluoromethoxy)phenoxy) (17):



LC-MS spectra of compound 17:



¹H NMR spectra of (R)-2-methyl-6-nitro-2-((4-(trifluoromethoxy)phenoxy)methyl)-2,3dihydroimidazo[2,1-b]oxazole (VL-2098, VII):



LC-MS spectra of compound VII (VL-2098):



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