Supporting Information:

Benzodioxane-benzamides as FtsZ inhibitors: effects of linker's functionalization on Gram-positive antimicrobial activity.

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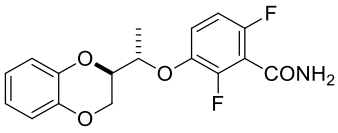
Summary

Erythro 3-[1-(1,4-benzodioxan-2yl)ethyl-1-oxy]-2,6-difluorobenzamide (FZ104)



^{1}H-NMR (DMSO-d_6):

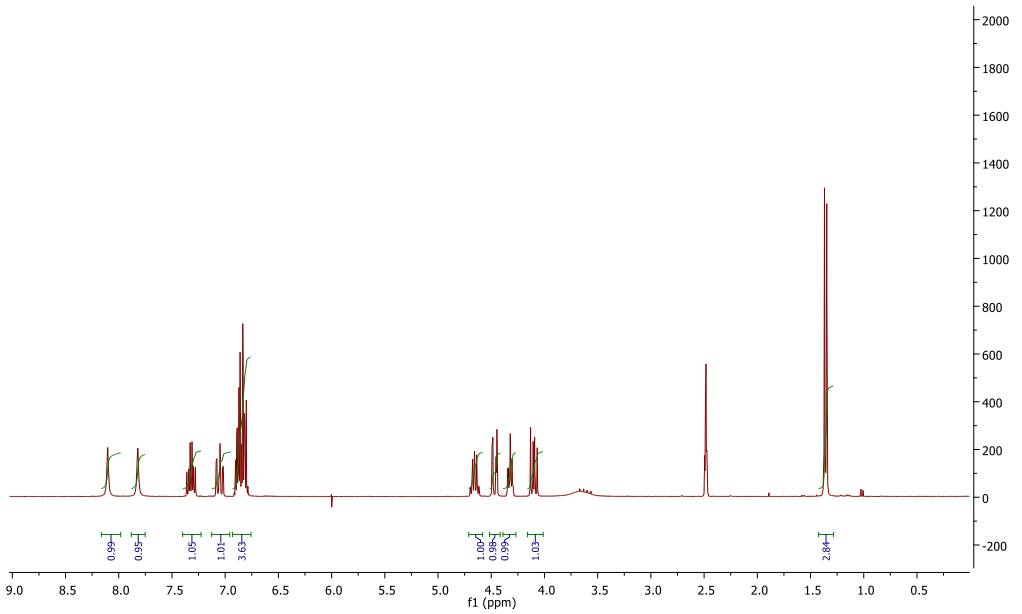


Figure S1: ^{1}H-NMR spectrum of Compound FZ104

^{13}C-NMR (DMSO-d_6):

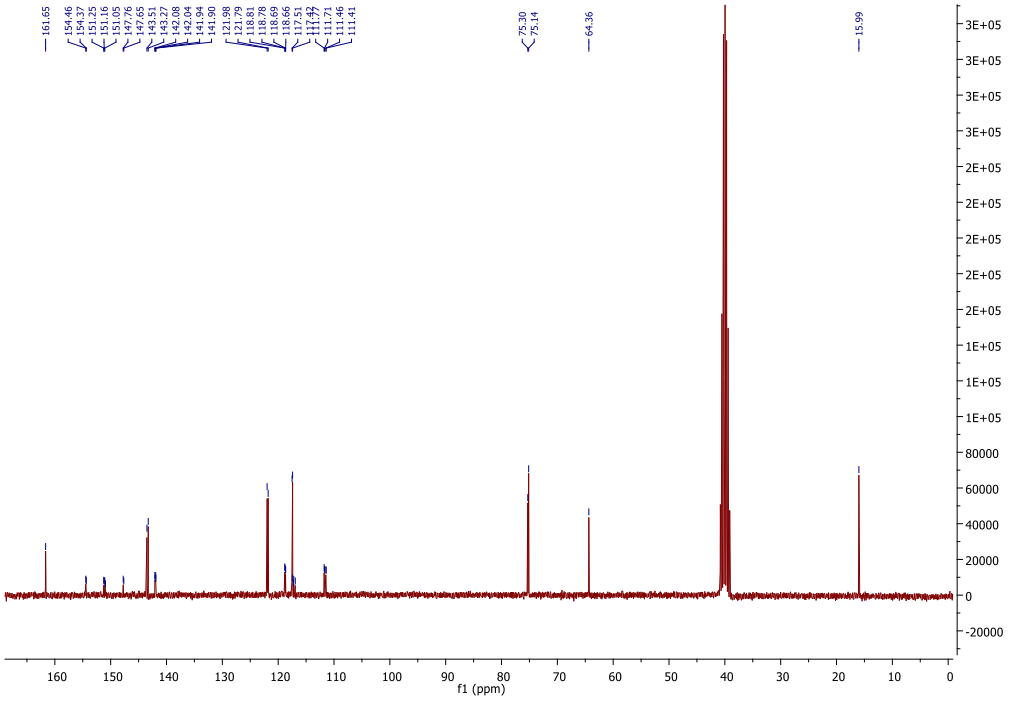


Figure S2: ^{13}C-NMR spectrum of Compound FZ104

HPLC:

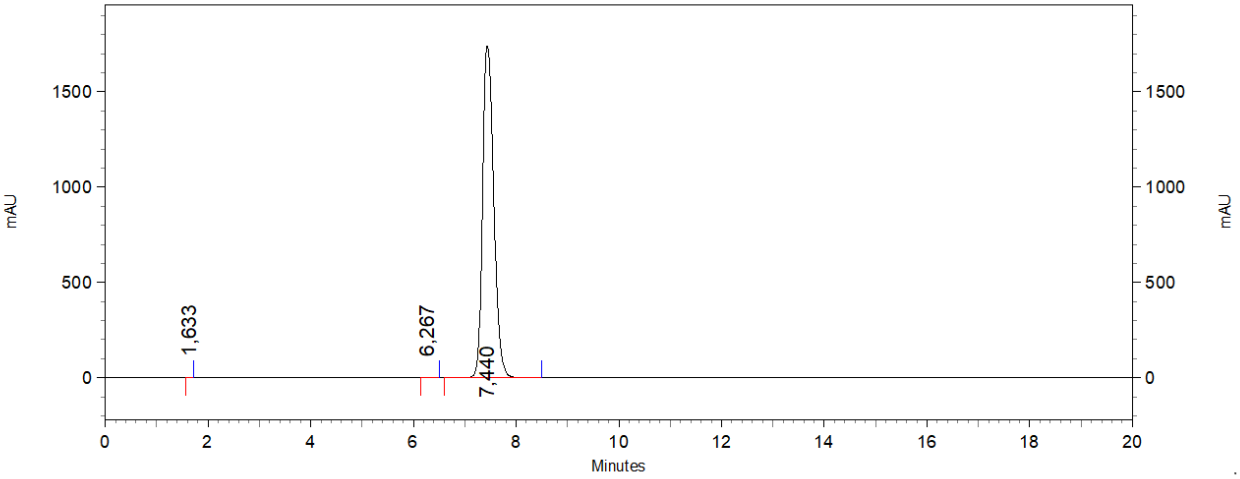
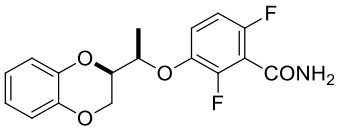


Figure S3: HPLC chromatogram of Compound FZ104

Threo 3-[1-(1,4-benzodioxan-2yl)ethyl-1-oxy]-2,6-difluorobenzamide (FZ105)



^{1}H-NMR (DMSO-d_6):

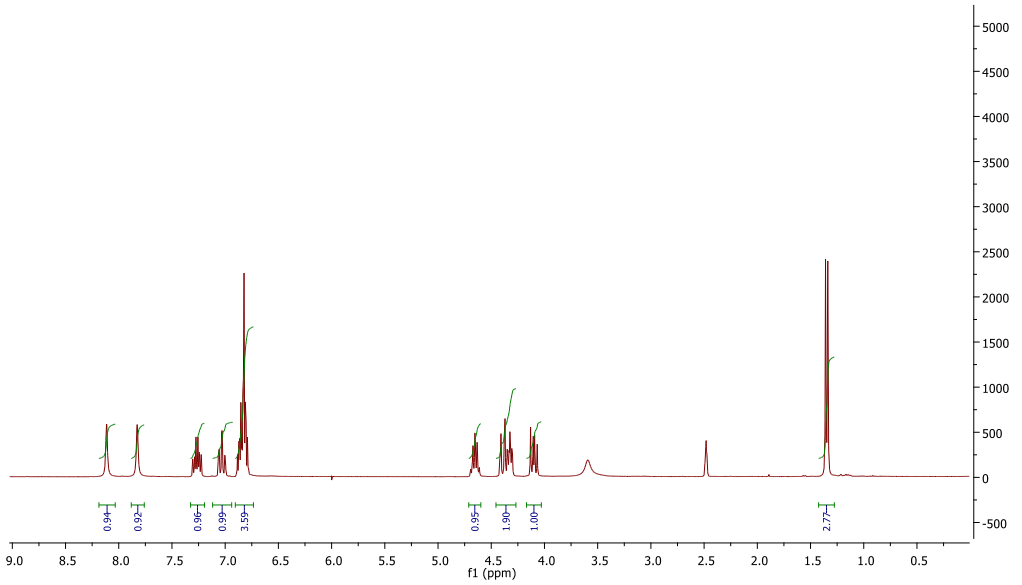


Figure S4: ^{1}H-NMR spectrum of Compound FZ105

^{13}C-NMR (DMSO-d6):

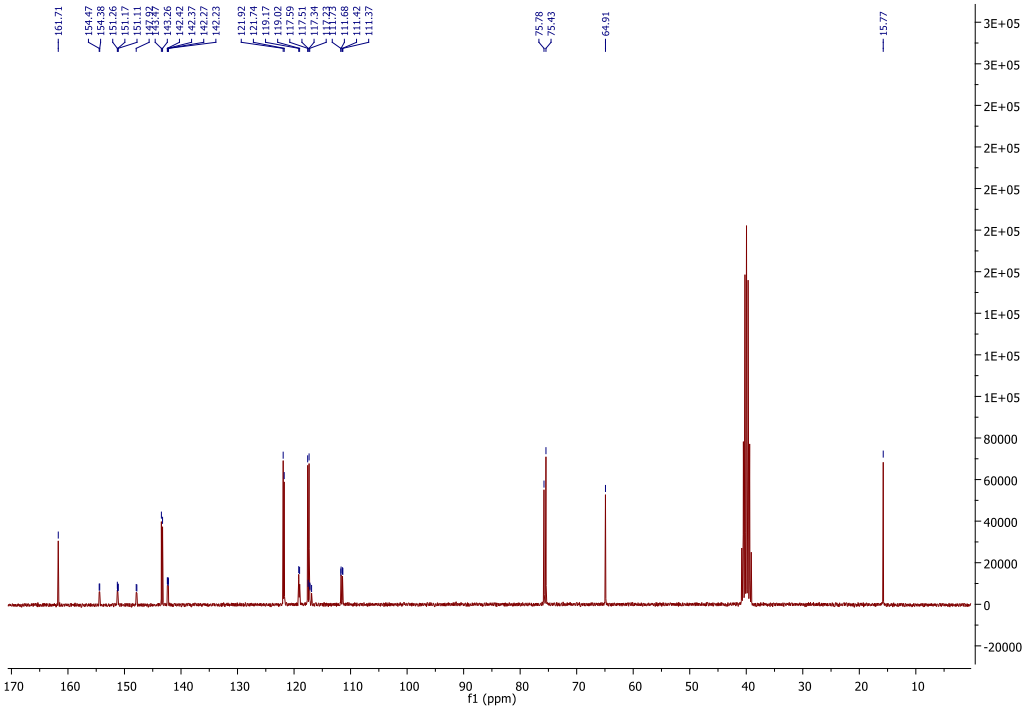


Figure S5: ^{13}C-NMR spectrum of Compound FZ105

HPLC:

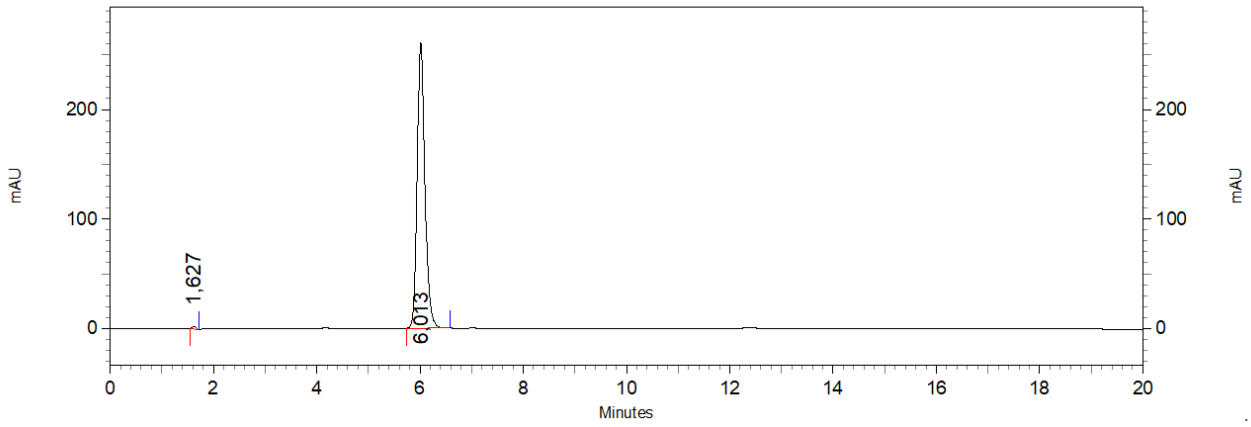
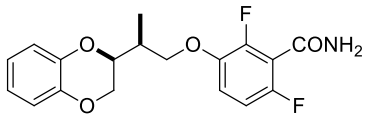


Figure S6: HPLC chromatogram of Compound FZ105

Erythro 3-(2-(1,4-benzodioxan-2-yl)-1-propyloxy)-2,6-difluorobenzamide (FZ98)



^{1}H-NMR (DMSO-d_6):

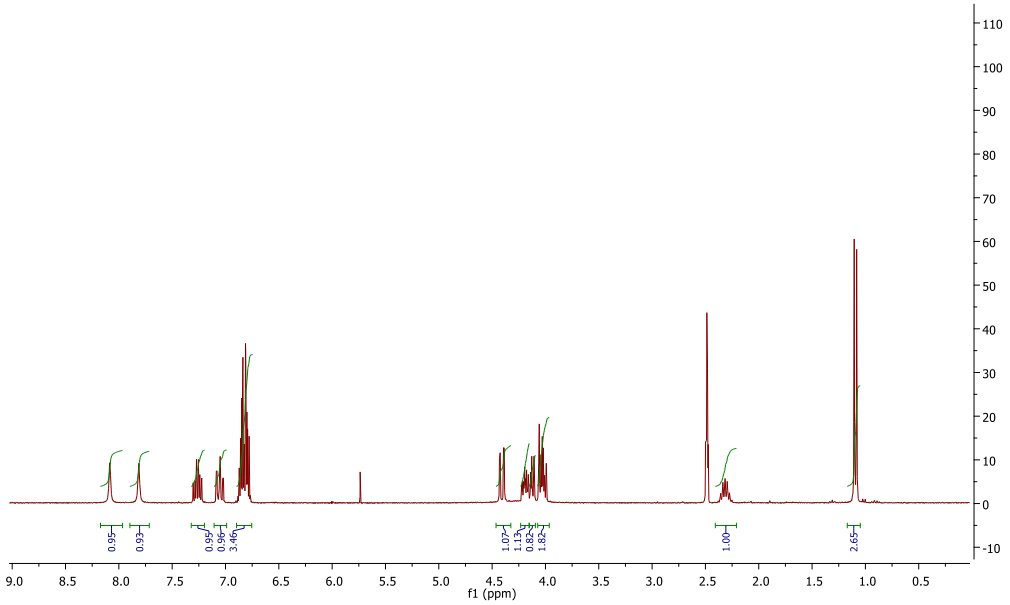


Figure S7: ^{1}H-NMR spectrum of Compound FZ98

^{13}C-NMR (DMSO-d_6):

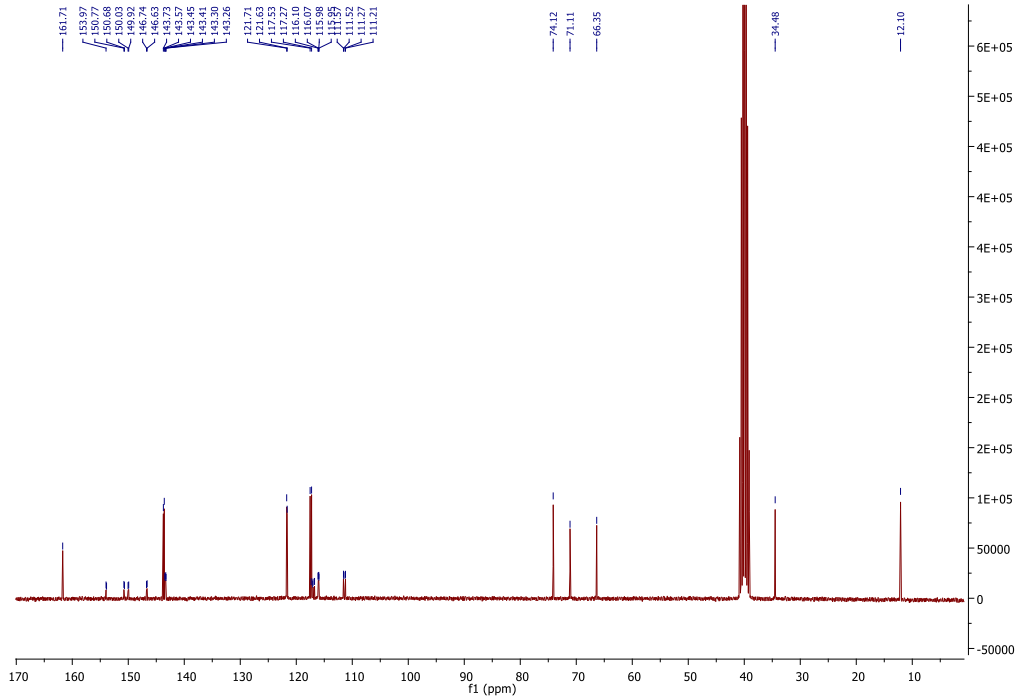


Figure S8: ^{13}C-NMR spectrum of Compound FZ98

HPLC:

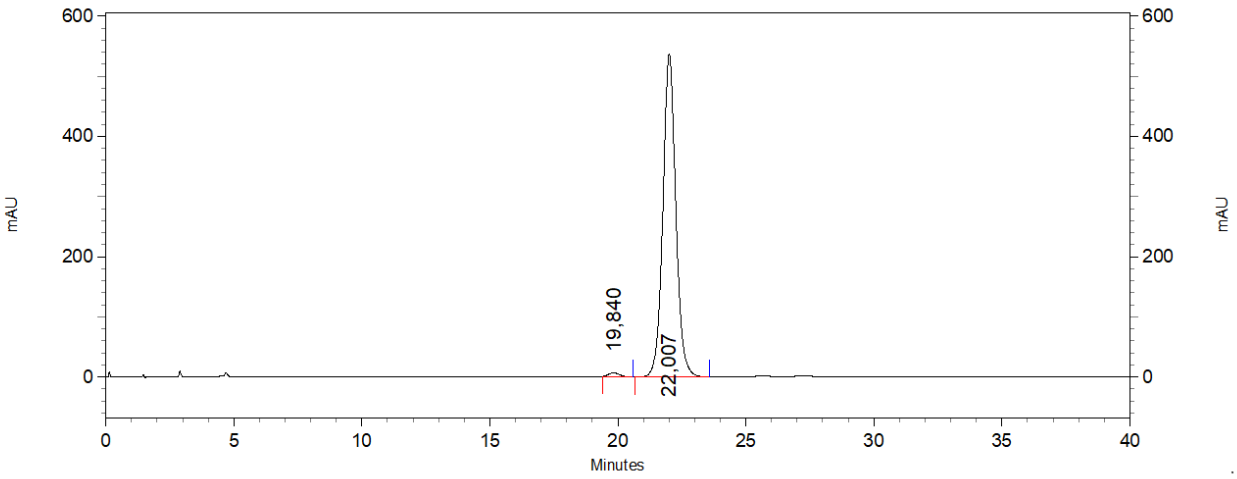
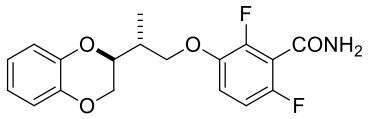


Figure S9: HPLC chromatogram of Compound FZ98

Threo 3-(2-(1,4-benzodioxan-2-yl)-1-propyloxy)-2,6-difluorobenzamide (FZ97)



^{1}H-NMR (DMSO-d_6):

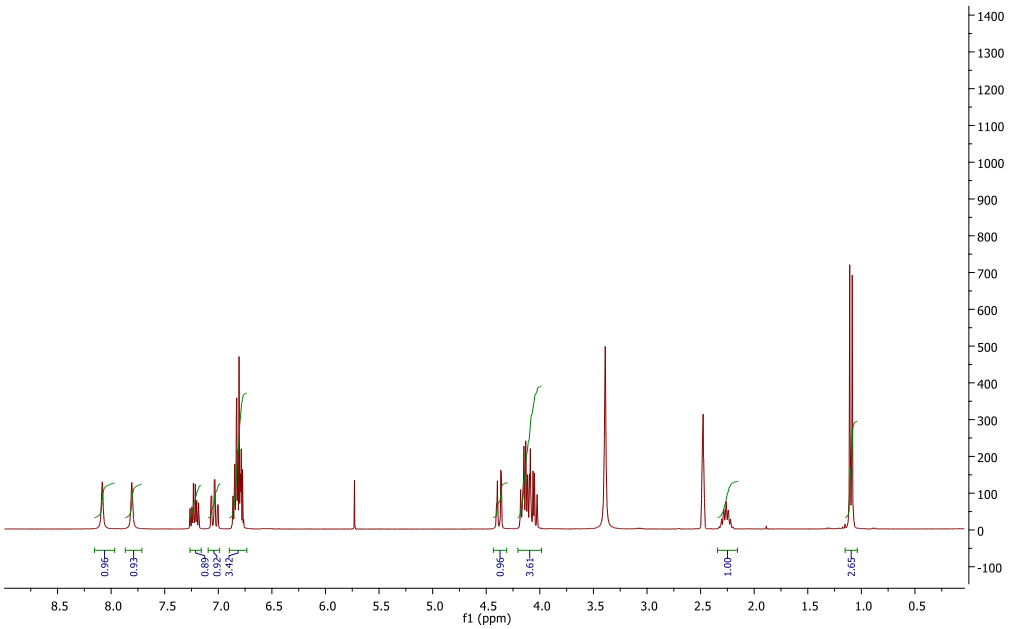


Figure S10: ^{1}H-NMR spectrum of Compound FZ97

^{13}C-NMR (DMSO-d_6):

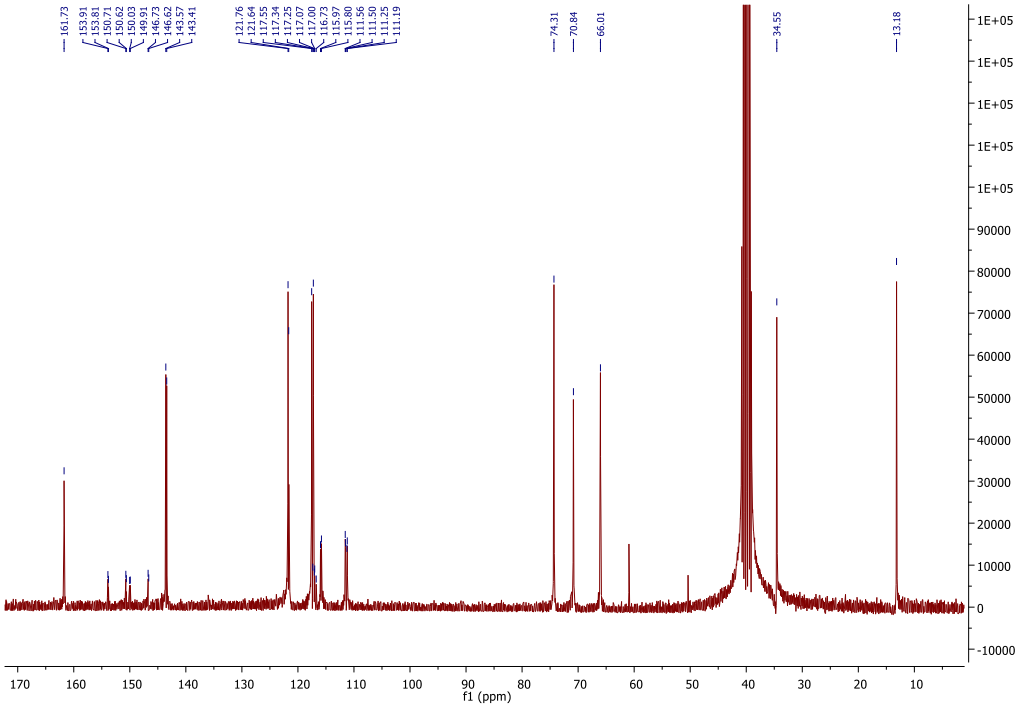


Figure S11: ^{13}C-NMR spectrum of Compound FZ97

HPLC:

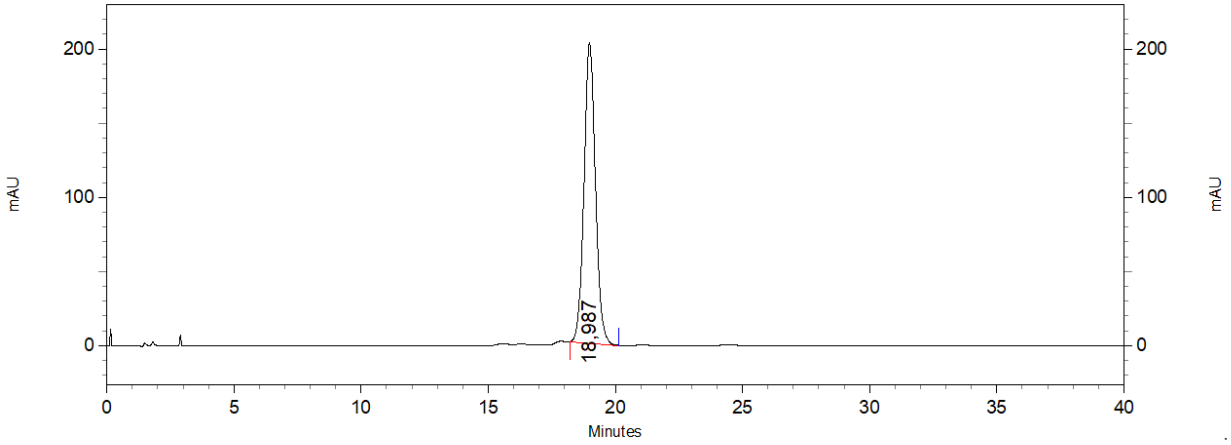
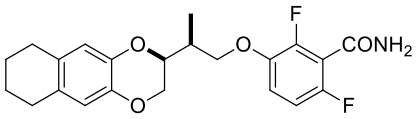


Figure S12: HPLC chromatogram of Compound FZ97

Erythro 3-(2-(5,6,7,8-Tetrahydro-1,4-naphthodioxan-2-yl)prop-1-yloxy)-2,6-difluorobenzamide (FZ118)



^{1}H-NMR (DMSO-d_6):

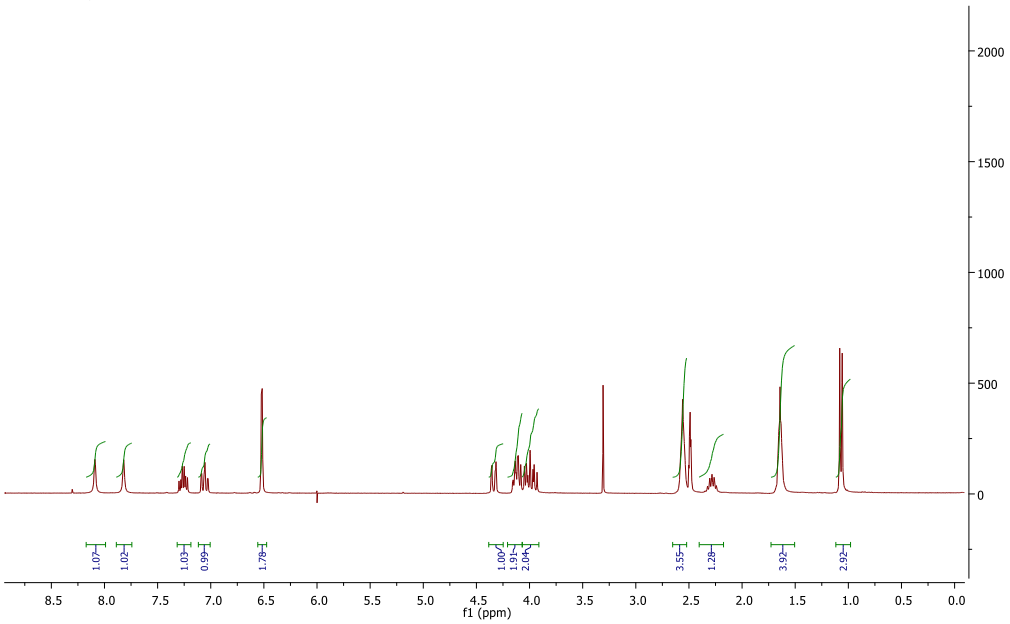


Figure S13: ^{1}H-NMR spectrum of Compound FZ118

^{13}C-NMR (DMSO-d_6):

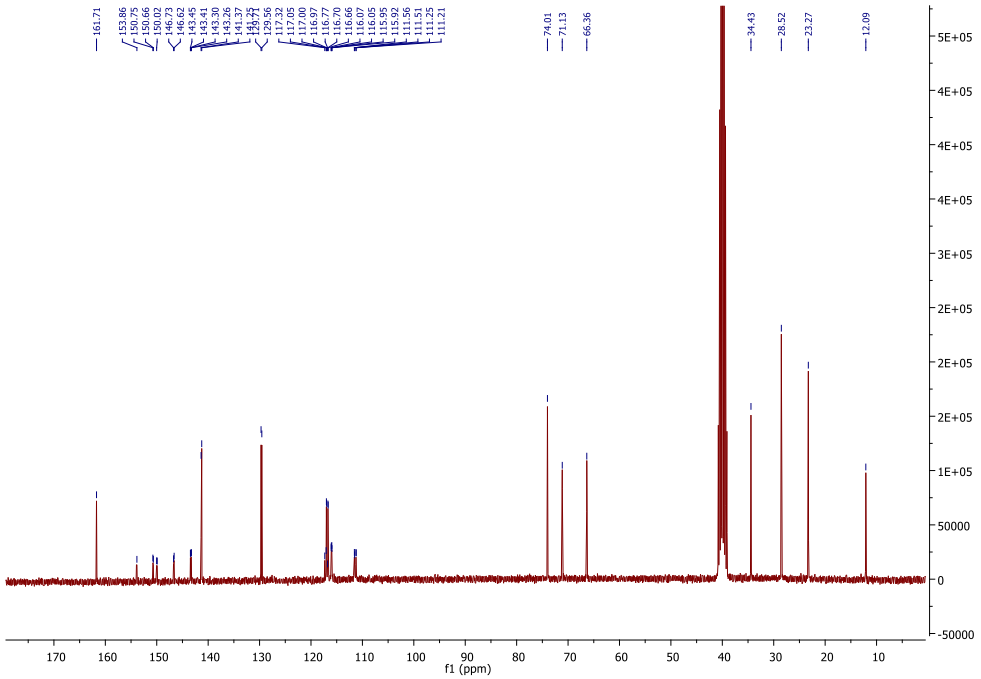


Figure S14: ^{13}C-NMR spectrum of Compound FZ118

HPLC:

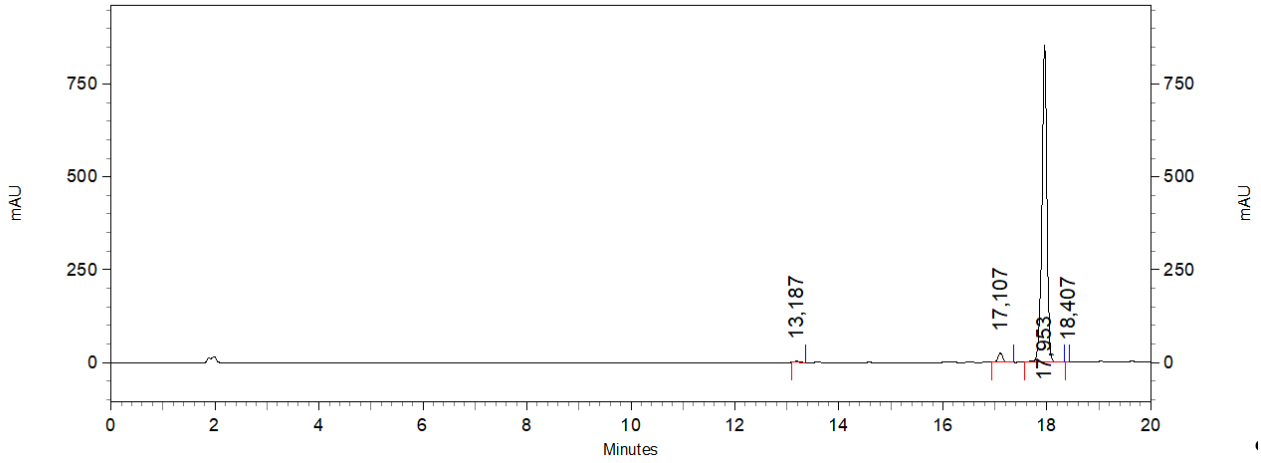
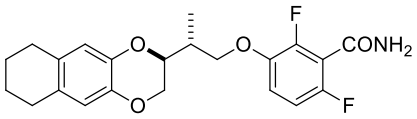


Figure S15: HPLC chromatogram of Compound FZ118

Threo 3-(2-(5,6,7,8-Tetrahydro-1,4-naphthodioxan-2-yl)prop-1-yloxy)-2,6-difluorobenzamide (FZ119)



^{1}H-NMR (DMSO-d_6):

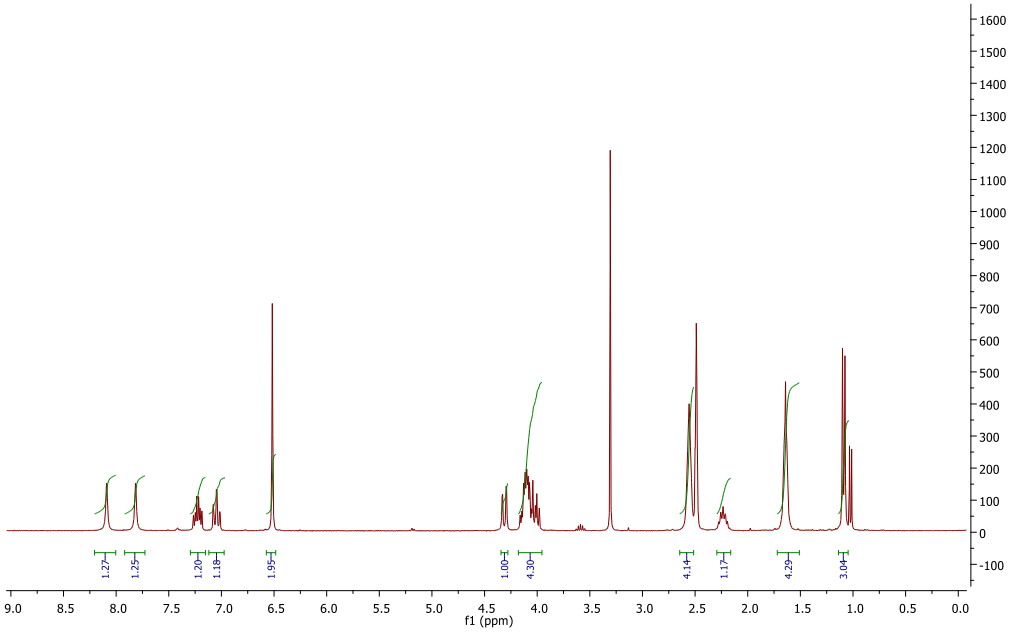


Figure S16: ^{1}H-NMR spectrum of Compound FZ119

^{13}C-NMR (DMSO-d_6):

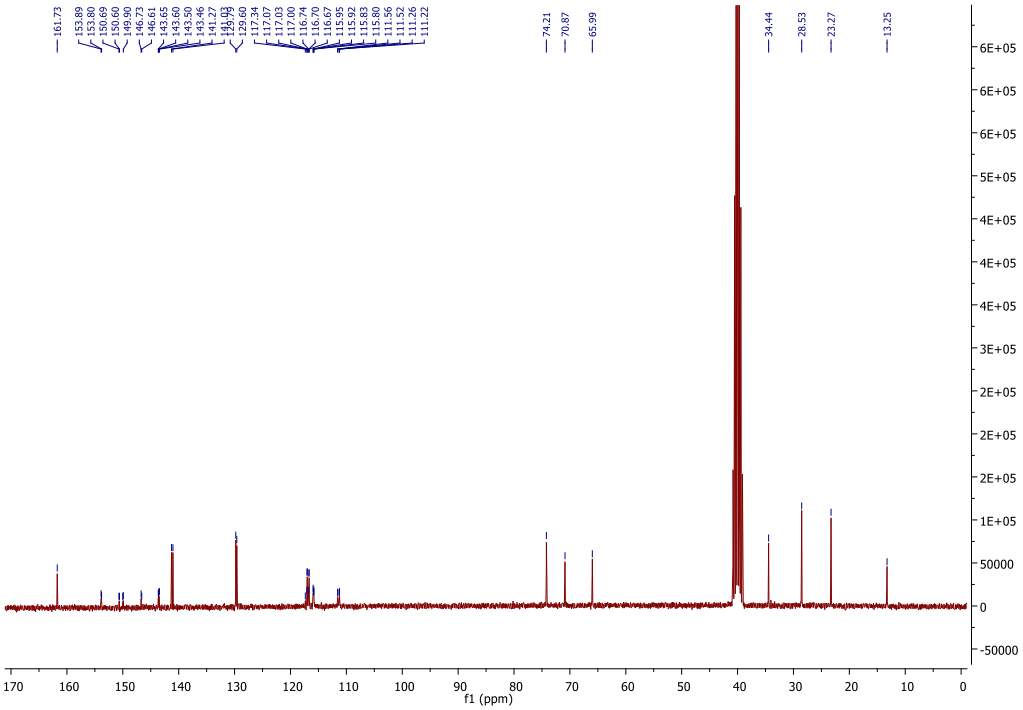


Figure S17: ^{13}C-NMR spectrum of Compound FZ119

HPLC:

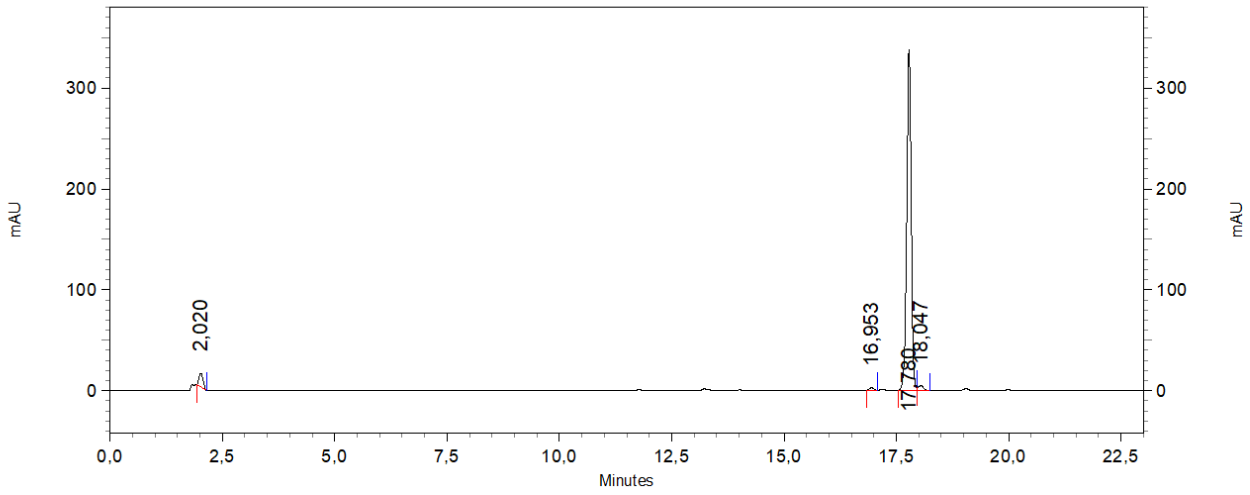


Figure S18: HPLC chromatogram of Compound FZ119

Docking studies

*Table S1: Docking range scores (*kcal/ mol) of the new inhibitors (considering the best and the worst docking poses maintaining the three key hydrogen bonds), correlated to the relative antimicrobial activity towards S. aureus.*

Compound (pose number)	Docking range scores*	MIC *vs S. aureus* (μM)	Compound (pose number)	Docking range scores*	MIC *vs S. aureus* (μM)
FZ104_*S'R* (4)	**(-11.468, -8.607)**	**23.9**	**FZ112_*S'R* (14)**	**(-13.364, -10.932)**	**364.4**
FZ104_*R'S* (5)	**(-10.935, -9.614)**		**FZ112_*R'S* (15)**	**(-12.904, -9.683)**	
FZ105_*S'S* (13)	**(-11.778, -8.269)**	**190.9**	**FZ113_*S'S* (17)**	**(-12.814, -10.783)**	**364.4**
FZ105_*R'R* (14)	**(-11.198, -9.519)**		**FZ113_*R'R* (14)**	**(-13.177, -10.887)**	
FZ97_*R'S* (17)	**(-11.645, -10.710)**	**366.4**	**FZ116_*S'R* (15)**	**(-14.221, -10.870)**	**4.9**
FZ97_*S'R* (13)	**(-11.325, -9.555)**		**FZ116_*R'S* (14)**	**(-14.666, -12.334)**	
FZ98_*R'R* (11)	**(-12.295, -10.552)**	**91.6**	**FZ117_*S'S* (13)**	**(-15.470, -11.972)**	**19.7**
FZ98_*S'S* (16)	**(-12.754, -10.250)**		**FZ117_*R'R* (12)**	**(-13.790, -11.048)**	
FZ118_*R'R* (19)	**(-13.305, -11.611)**	**9.9**			
FZ118_*S'S* (12)	**(-15.596, -11.541)**				
FZ119_*R'S* (14)	**(-12.803, -11.386)**	**9.9**			
FZ119_*S'R* (16)	**(-14.200, -11.170)**				

Root-Mean-Square Deviation (RMSD)

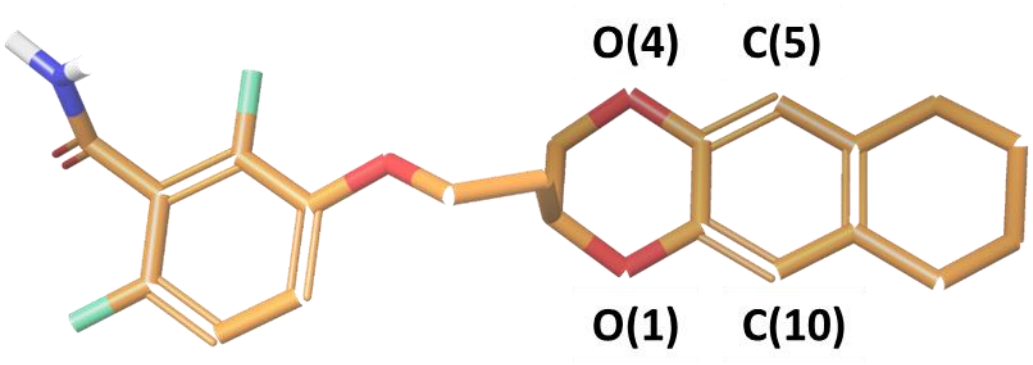


Figure S19: Legenda for O(1), O(4), C(5) and C(10) labeling, to calculate the RMSD in the superposition FZ100-novel compounds

Table S2: RMSD for atom pairs between O(1), O(4), C(5) and C(10) using FZ100 as reference structure

Inhibitor Pose	**RMSD O(4) (Å)**	**RMSD O(1) (Å)**	**RMSD C(5) (Å)**	**RMSD C(10) (Å)**	**180º rotation**
1_FZ104_*R'S*	0.883	0.865	0.773	0.807	not
2_FZ116_*R'S*	0.515	0.148	0.572	0.256	yes
7_FZ117_*S'S*	0.581	0.606	0.809	0.881	yes
10_FZ117_*S'S*	0.744	0.917	0.36	0.847	yes
2_FZ118_*R'R*	0.169	0.129	0.816	0.941	yes
3_FZ119_*R'S*	0.332	0.384	0.530	0.557	yes
4_FZ119_*R'S*	0.400	0.305	0.514	0.668	yes

IFD scores

Table S3

Title	*docking score*
1_FZ104_R'S	*-10.935*
1_FZ104_R'S	-10.988
1_FZ104_R'S	-10.985
1_FZ104_R'S	-10.294
1_FZ104_R'S	-9.614
1_FZ104_S'R	-11.468
1_FZ104_S'R	-10.571
1_FZ104_S'R	-9.293
1_FZ104_S'R	-8.607
2_FZ105_R'R	-11.198
2_FZ105_R'R	-11.378
2_FZ105_R'R	-10.998
2_FZ105_R'R	-10.72
2_FZ105_R'R	-10.701
2_FZ105_R'R	-11.009
2_FZ105_R'R	-11.298
2_FZ105_R'R	-10.548
2_FZ105_R'R	-10.42
2_FZ105_R'R	-10.59
2_FZ105_R'R	-10.78
2_FZ105_R'R	-10.661
2_FZ105_R'R	-10.172
2_FZ105_R'R	-9.519
2_FZ105_S'S	-11.778
2_FZ105_S'S	-11.254
2_FZ105_S'S	-10.863
2_FZ105_S'S	-10.693
2_FZ105_S'S	-10.352
2_FZ105_S'S	-11.348
2_FZ105_S'S	-10.381
2_FZ105_S'S	-9.818
2_FZ105_S'S	-10.122
2_FZ105_S'S	-9.208
2_FZ105_S'S	-9.951
2_FZ105_S'S	-9.315
2_FZ105_S'S	-8.269
3_FZ97_R'S	-11.645
3_FZ97_R'S	-11.446
3_FZ97_R'S	-11.194
3_FZ97_R'S	-11.631
3_FZ97_R'S	-10.775
3_FZ97_R'S	-11.139
3_FZ97_R'S	-11.326
3_FZ97_R'S	-10.719
3_FZ97_R'S	-11.063
3_FZ97_R'S	-11.552
3_FZ97_R'S	-11.298
3_FZ97_R'S	-11.347
3_FZ97_R'S	-10.87
3_FZ97_R'S	-10.924
3_FZ97_R'S	-10.945
3_FZ97_R'S	-10.185
3_FZ97_R'S	-10.71
3_FZ97_S'R	-11.325
3_FZ97_S'R	-11.25
3_FZ97_S'R	-10.745
3_FZ97_S'R	-11.164
3_FZ97_S'R	-10.889
3_FZ97_S'R	-11.762
3_FZ97_S'R	-10.88
3_FZ97_S'R	-11.236
3_FZ97_S'R	-11.125
3_FZ97_S'R	-11.136
3_FZ97_S'R	-11.039
3_FZ97_S'R	-10.823
3_FZ97_S'R	-9.555
4_FZ98_R'R	-12.295
4_FZ98_R'R	-12.051
4_FZ98_R'R	-12.181
4_FZ98_R'R	-12.072
4_FZ98_R'R	-11.59
4_FZ98_R'R	-11.63
4_FZ98_R'R	-11.021
4_FZ98_R'R	-11.307
4_FZ98_R'R	-11.022
4_FZ98_R'R	-10.863
4_FZ98_R'R	-10.552
4_FZ98_S'S	-12.754
4_FZ98_S'S	-11.747
4_FZ98_S'S	-11.661
4_FZ98_S'S	-11.655
4_FZ98_S'S	-12.197
4_FZ98_S'S	-12
4_FZ98_S'S	-10.641
4_FZ98_S'S	-11.39
4_FZ98_S'S	-11.01
4_FZ98_S'S	-11.05
4_FZ98_S'S	-10.705
4_FZ98_S'S	-10.632
4_FZ98_S'S	-10.445
4_FZ98_S'S	-10.767
4_FZ98_S'S	-10.577
4_FZ98_S'S	-10.25
5_FZ112_R'S	-12.904
5_FZ112_R'S	-13.132
5_FZ112_R'S	-12.821
5_FZ112_R'S	-12.788
5_FZ112_R'S	-12.105
5_FZ112_R'S	-12.268
5_FZ112_R'S	-11.986
5_FZ112_R'S	-12.135
5_FZ112_R'S	-11.681
5_FZ112_R'S	-11.826
5_FZ112_R'S	-11.057
5_FZ112_R'S	-10.773
5_FZ112_R'S	-10.39
5_FZ112_R'S	-10.312
5_FZ112_R'S	-9.683
5_FZ112_S'R	-13.364
5_FZ112_S'R	-13.738
5_FZ112_S'R	-12.656
5_FZ112_S'R	-12.474
5_FZ112_S'R	-13.215
5_FZ112_S'R	-11.885
5_FZ112_S'R	-12.884
5_FZ112_S'R	-12.383
5_FZ112_S'R	-11.897
5_FZ112_S'R	-11.879
5_FZ112_S'R	-11.073
5_FZ112_S'R	-11.236
5_FZ112_S'R	-10.903
5_FZ112_S'R	-10.932
6_FZ113_R'R	-13.177
6_FZ113_R'R	-13.212
6_FZ113_R'R	-12.148
6_FZ113_R'R	-12.877
6_FZ113_R'R	-13.413
6_FZ113_R'R	-12.544
6_FZ113_R'R	-12.31
6_FZ113_R'R	-12
6_FZ113_R'R	-11.694
6_FZ113_R'R	-11.35
6_FZ113_R'R	-11.336
6_FZ113_R'R	-11.092
6_FZ113_R'R	-10.675
6_FZ113_R'R	-10.887
6_FZ113_S'S	-12.814
6_FZ113_S'S	-11.957

6_FZ113_S'S	-11.803	*8_FZ117_R'R*	-13.79	*9_FZ118_S'S*	-15.596
6_FZ113_S'S	-13.147	*8_FZ117_R'R*	-13.941	*9_FZ118_S'S*	-13.581
6_FZ113_S'S	-12.217	*8_FZ117_R'R*	-13.863	*9_FZ118_S'S*	-14.049
6_FZ113_S'S	-11.752	*8_FZ117_R'R*	-14.278	*9_FZ118_S'S*	-13.534
6_FZ113_S'S	-11.621	*8_FZ117_R'R*	-14.045	*9_FZ118_S'S*	-13.213
6_FZ113_S'S	-11.8	*8_FZ117_R'R*	-13.667	*9_FZ118_S'S*	-12.668
6_FZ113_S'S	-11.749	*8_FZ117_R'R*	-13.425	*9_FZ118_S'S*	-12.475
6_FZ113_S'S	-11.598	*8_FZ117_R'R*	-13.471	*9_FZ118_S'S*	-12.303
6_FZ113_S'S	-11.583	*8_FZ117_R'R*	-13.021	*9_FZ118_S'S*	-12.371
6_FZ113_S'S	-11.634	*8_FZ117_R'R*	-12.784	*9_FZ118_S'S*	-12.316
6_FZ113_S'S	-11.393	*8_FZ117_R'R*	-12.525	*9_FZ118_S'S*	-11.804
6_FZ113_S'S	-11.551	*8_FZ117_R'R*	-11.048	*9_FZ118_S'S*	-11.541
6_FZ113_S'S	-11.406	*8_FZ117_S'S*	-15.47	*10_FZ119_R'S*	-12.803
6_FZ113_S'S	-11.501	*8_FZ117_S'S*	-14.841	*10_FZ119_R'S*	-12.656
6_FZ113_S'S	-10.783	*8_FZ117_S'S*	-14.968	*10_FZ119_R'S*	-13.023
7_FZ116_R'S	-14.666	*8_FZ117_S'S*	-13.518	*10_FZ119_R'S*	-12.869
7_FZ116_R'S	-14.631	*8_FZ117_S'S*	-13.303	*10_FZ119_R'S*	-13.176
7_FZ116_R'S	-14.165	*8_FZ117_S'S*	-13.605	*10_FZ119_R'S*	-12.827
7_FZ116_R'S	-13.899	*8_FZ117_S'S*	-13.438	*10_FZ119_R'S*	-12.429
7_FZ116_R'S	-13.926	*8_FZ117_S'S*	-13.559	*10_FZ119_R'S*	-12.698
7_FZ116_R'S	-12.833	*8_FZ117_S'S*	-12.733	*10_FZ119_R'S*	-12.44
7_FZ116_R'S	-13.598	*8_FZ117_S'S*	-12.537	*10_FZ119_R'S*	-12.558
7_FZ116_R'S	-13.678	*8_FZ117_S'S*	-12.415	*10_FZ119_R'S*	-12.27
7_FZ116_R'S	-13.823	*8_FZ117_S'S*	-12.191	*10_FZ119_R'S*	-12.517
7_FZ116_R'S	-13.366	*8_FZ117_S'S*	-11.972	*10_FZ119_R'S*	-11.913
7_FZ116_R'S	-12.694	*9_FZ118_R'R*	-13.305	*10_FZ119_R'S*	-11.386
7_FZ116_R'S	-12.896	*9_FZ118_R'R*	-12.865	*10_FZ119_S'R*	-14.2
7_FZ116_R'S	-13.312	*9_FZ118_R'R*	-13.127	*10_FZ119_S'R*	-13.369
7_FZ116_R'S	-12.334	*9_FZ118_R'R*	-13.32	*10_FZ119_S'R*	-13.256
7_FZ116_S'R	-14.221	*9_FZ118_R'R*	-13.584	*10_FZ119_S'R*	-13.533
7_FZ116_S'R	-13.397	*9_FZ118_R'R*	-12.741	*10_FZ119_S'R*	-13.357
7_FZ116_S'R	-13.12	*9_FZ118_R'R*	-13.254	*10_FZ119_S'R*	-13.32
7_FZ116_S'R	-13.38	*9_FZ118_R'R*	-12.9	*10_FZ119_S'R*	-13.396
7_FZ116_S'R	-13.506	*9_FZ118_R'R*	-13.026	*10_FZ119_S'R*	-13.411
7_FZ116_S'R	-13.383	*9_FZ118_R'R*	-12.777	*10_FZ119_S'R*	-13.012
7_FZ116_S'R	-12.29	*9_FZ118_R'R*	-12.697	*10_FZ119_S'R*	-12.475
7_FZ116_S'R	-12.791	*9_FZ118_R'R*	-11.861	*10_FZ119_S'R*	-12.478
7_FZ116_S'R	-13.289	*9_FZ118_R'R*	-12.418	*10_FZ119_S'R*	-12.541
7_FZ116_S'R	-12.848	*9_FZ118_R'R*	-12.093	*10_FZ119_S'R*	-12.885
7_FZ116_S'R	-12.773	*9_FZ118_R'R*	-12.328	*10_FZ119_S'R*	-12.368
7_FZ116_S'R	-12.308	*9_FZ118_R'R*	-11.838	*10_FZ119_S'R*	-12.87
7_FZ116_S'R	-11.716	*9_FZ118_R'R*	-12.286	*10_FZ119_S'R*	-11.17
7_FZ116_S'R	-11.338	*9_FZ118_R'R*	-11.572		
7_FZ116_S'R	-10.87	*9_FZ118_R'R*	-11.611		