Relative Binding Energies Predict Crystallographic Binding Modes of Ethionamide Booster Lead Compounds

Natalie J. Tatum et al.

Supplementary Charts

Chart S1: Chemical structures of compounds **3**, **10**, **85** and **BDM31343**.

Supplementary Figures

Figure S1: Close-up of the compound **3** hydrogen bonding to EthR.

Figure S2: Close-up of the compound **85** hydrogen bonding to EthR.

Figure S3: Graphed energy (electrostatic in red, van der Waals in blue) over the course of the simulation for each compound pose in complex with EthR, per 20 ps.

Figure S4: Ligand poses for all four replicas clustered by pose (left, pose 1; right, pose 2), for **(a)** compound 3, **(b)** compound 85, **(c)** compound **10**, **(d)** BDM31343.

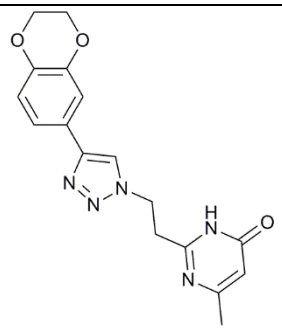
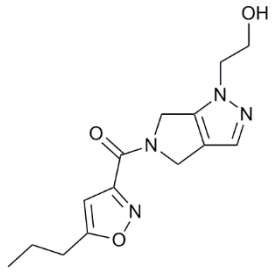
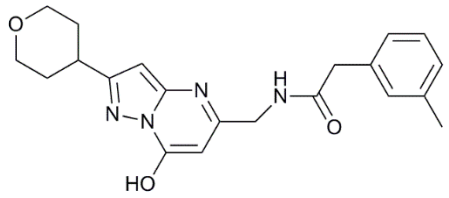
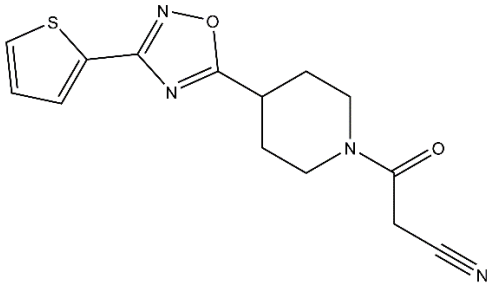
Supplementary Tables

Table S1: Data collection and refinement statistics for EthR-**3** and EthR-**85**.

Table S2: Tabulated electrostatic contributions per residue.

Table S3: Tabulated van der waals contributions per residue.

Chart S1

Name	**Structure**
Compound **3**	
Compound **10**	
Compound **85**	
BDM31343	

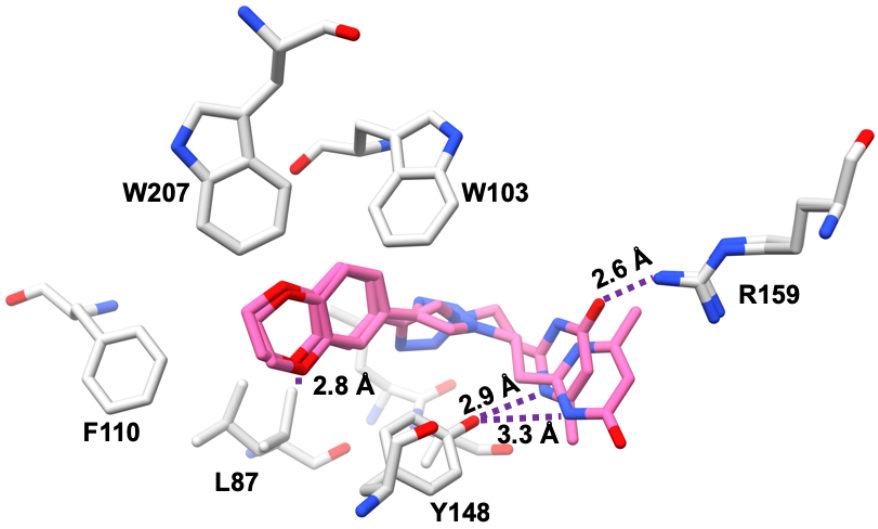


Figure S1: Close-up of the compound **3** hydrogen bonding to EthR.

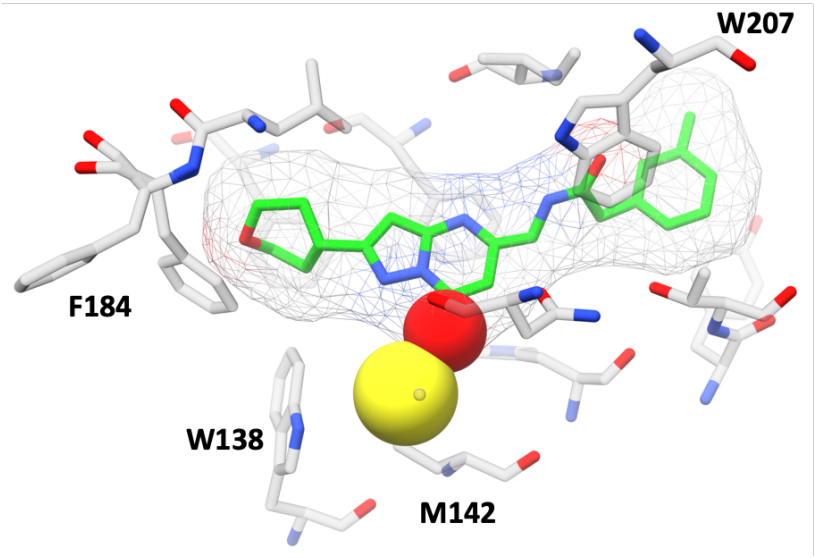


Figure S2: Close-up of the compound **85** hydrogen bonding to EthR. Van der Waals spheres are shown for M142 sulphur and ligand O2 shown to demonstrate overlap.

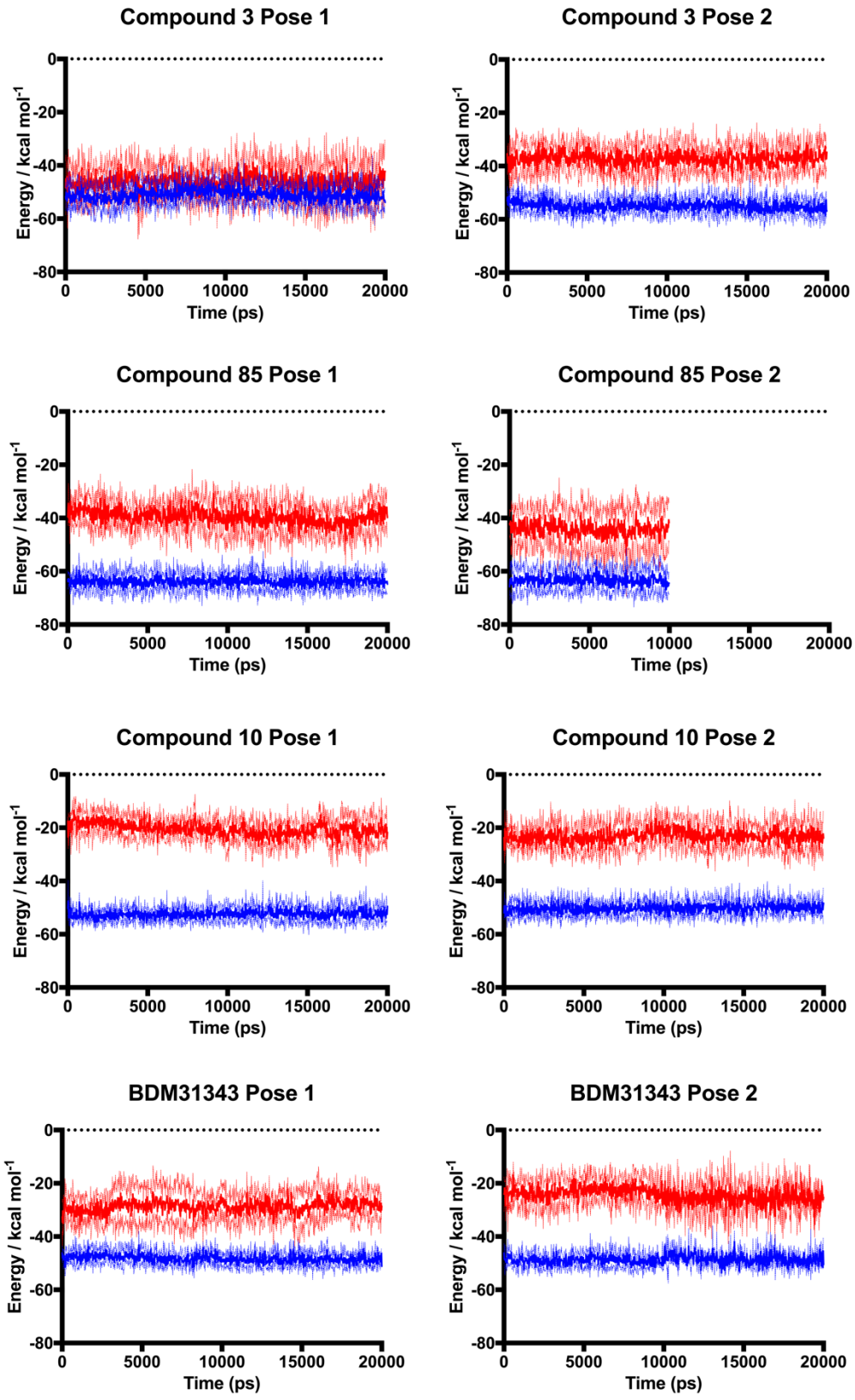


Figure S3: Graphed energy (electrostatic in red, van der Waals in blue) over the course of the simulation for each compound pose in complex with EthR, per 20 ps. Mean of four replicas presented as solid line with dashed line representing standard deviation from the mean. Graphs prepared in Graphpad Prism 7.

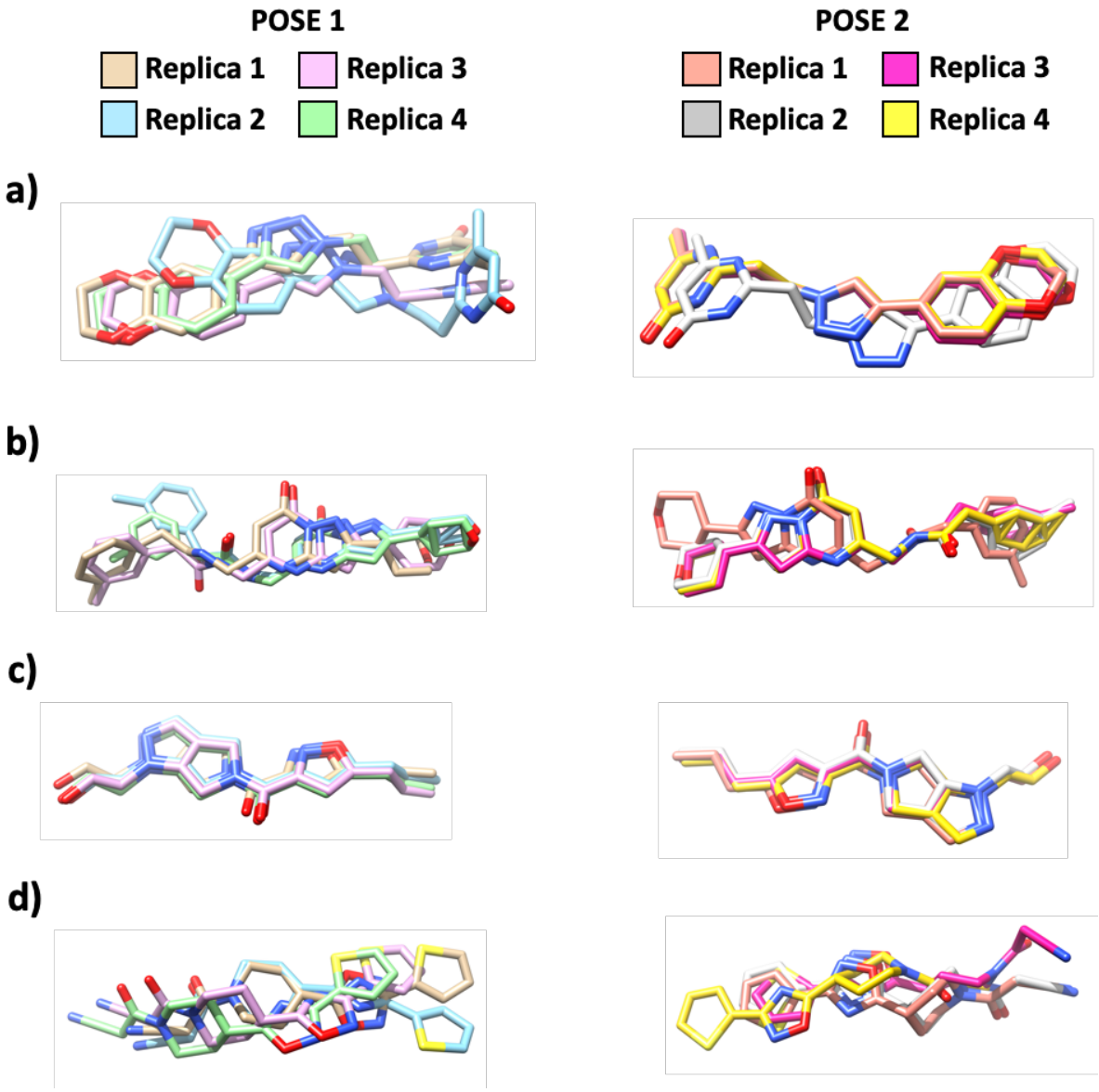


Figure S4: Ligand poses for all four replicas clustered by pose (left, pose 1; right, pose 2), for **(a)** compound 3, **(b)** compound 85, **(c)** compound **10**, **(d)** BDM31343.

Table S1: Data collection and refinement statistics for EthR-**3** and EthR-**85**.

Structure	**3**	**85**
DLS Beamline	I03	I04-1
Wavelength [Å]	0.96000	0.91741
a, b [Å]	121.76	120.89
c [Å]	33.63	33.68
α=β=γ [°]	90	90
Space group	$P4_12_12$	$P4_12_12$
Resolution range	86.10-1.80	85.48-1.80
No. of refl.	44875	43521
Multiplicity	7.09	7.12
Wilson B [$Å^2$]	32.1	36.0
I/sigma[#]	21.3 (4.2)	14.9 (3.1)
Rmerge [%]*	6.0 (52.8)	7.2 (61.3)
Completeness [%]*	99.6 (98.1)	98.4 (95.8)
Rwork [%]	18.42	20.53
Rfree [%]	21.39	25.68
No of residues	193	192
No of water	69	25
Protein B [$Å^2$]	32.80	35.34
Ligand B [$Å^2$]	72.64	60.70
Water [$Å^2$]	37.75	37.39
Rmsd bond lengths [Å]	0.0142	0.0716
Rmsd angles [°]	1.7263	1.5975
Ramach. Ouliers	2 (1.11%)	2 (1.08%)
PDB code		

* calculated by XDS, Friedel pairs not merged

numbers in brackets refer to last shell

Table S2: Tabulated electrostatic contributions per residue. Where no interactions/contacts are made, values are not given. Graphed as figure 3.

		Compound 85				BDM31343				Compound 10 (Pose A)				Compound 10 (Pose B)				Compound 3			
		REPLICA1	REPLICA2	REPLICA3	REPLICA4	REPLICA1	REPLICA2	REPLICA3	REPLICA4	REPLICA1	REPLICA2	REPLICA3	REPLICA4	REPLICA1	REPLICA2	REPLICA3	REPLICA4	REPLICA1	REPLICA2	REPLICA3	REPLICA4
Asp	**84**	1.94	2.16	2.14	2.14																
Leu	**87**	-0.30	-0.34	-0.36	-0.31	-0.01	0.14	0.17	0.09	-0.19	-0.21	-0.24	-0.23	0.00	0.00	-0.01	0.00	-0.34	-0.34	-0.37	-0.30
Leu	**90**	0.15	0.11	0.18	0.15	-0.15	-0.29	-0.12	-0.02	-0.03		-0.08	-0.14					0.61	-0.14	0.18	-0.41
Ala	**91**	-0.02	-0.02	0.02	-0.03					-0.01		-0.05	-0.09					-0.07	0.16	-0.03	0.00
Pro	**94**																	-1.21	0.05	-0.51	-0.70
Ala	**95**																	-1.06	-0.08	-0.51	-0.52
Glu	**100**						-0.05	-0.09	-0.01												
Met	**102**	-0.02	0.03	-0.17	-0.06	0.14	0.22	-0.29	-0.25	0.09	0.17	0.15	0.13					1.15	-0.30	0.19	0.32
Trp	**103**	-0.80	-0.59	-0.67	-0.71	0.07	0.36	0.13	-0.21	-0.14	-0.19	-0.21	-0.21	0.03	-0.07	0.04	0.11	-0.8	0.23	0.18	0.19
Arg	**104**													-0.29	-0.29	-0.30	-0.30				
Thr	**105**																	-0.7	-0.09	-0.26	-0.42
Gly	**106**	0.92	0.15	1.12	1.07	-0.46	-0.85	-0.15	0.15	-0.79	-0.87	-0.85	-0.83	-0.51	-0.51	-0.52	-0.52	-1.45	-1.01	-1.1	-1.26
Ile	**107**	0.18	-0.06	0.23	0.32	0.36	0.40	0.02	0.00	0.12	0.21	0.19	0.19	-0.13	-0.25	-0.25	-0.26	-0.27	-0.02	-0.26	-0.26
Phe	**110**	-0.50	0.34	-0.10	-0.30	-1.56	-1.56	-1.03	-0.72	-0.15	-0.27	-0.17	-0.01	-0.95	-0.59	-0.65	-0.78	-0.39	0.04	-0.72	-0.54
Phe	**114**	-0.12	-0.09	-0.13	-0.13									-0.37	-0.34	-0.32	-0.32				
Trp	**138**	-0.15	-0.41	-0.22	-0.13					-0.16	-0.41	-0.39	-0.19	0.19	0.10	0.13	0.16				
Met	**142**	-0.10	0.33	0.13	-0.16	-1.61	-1.21	-0.23	-0.63	0.14		-1.19	-1.51	-0.07	0.09	-0.04	0.25				
Lys	**144**	-1.39	-1.64	-1.77	-2.03		0.75	1.46	1.33					0.23	0.24	0.25	0.25				
Trp	**145**	1.21	1.22	1.05	1.10	0.19	-0.24	0.01	0.51	0.11	0.91	0.78	0.91	0.16	0.10	0.06	0.06	-0.22	-0.01	-0.18	-0.13
Tyr	**148**	-1.29	-1.5	-1.44	-1.43	-0.22	0.23	-0.47	-0.71	-0.89	-1.37	-1.24	-1.47	-0.15	-0.25	-0.27	-0.16	-0.87	-1.33	-1.22	-1.01
Thr	**149**	-1.70	-1.45	-1.79	-1.72	-0.86	-0.52	-0.65	-1.02	-0.54	-1.65	-1.63	-1.75	-0.21	-0.26	-0.2	-0.21	0.33	0.39	0.24	0.21
Val	**152**	-0.08	-0.1	-0.07	-0.05	-0.08	-0.04	-0.10		0.13	0.09	0.07	0.04					0.04	0.21	0.20	0.11
Asn	**176**	-4.17	-3.35	-4.44	-4.22	-1.58	-1.33	0.27	-1.08	-0.92	-1.56	-1.85	-1.61	0.24	0.02	-0.14	-0.83	-2.18	-0.15	-1.9	-0.36
Asn	**179**	-4.29	-4.61	-2.85	-3.50	-1.91	-1.37	-3.95	-3.34	0.49	0.17	0.37	0.63	-1.94	-4.75	-4.42	-2.85	0.81	-0.32	0.22	0.60
Glu	**180**	-0.02	-0.17	-0.11	-0.08	0.16	0.20	0.10	0.69	-0.07	0.02	0.15	0.20	-1.78	-0.15	-0.38	-0.30				
Leu	**183**	-0.08	-0.12	-0.07	-0.06					-0.05	-0.09	-0.08	-0.07	0.07	0.14	0.12	0.08				
Phe	**184**													0.07	0.07	0.09	0.08				
Phe	**187**													0.12	0.11	0.11	0.10				
Trp	**207**	-0.39	-0.06	-0.29	-0.21	-0.11	-0.18	-0.07	0.07	-0.03	-0.04	-0.02	-0.04	-0.10	-0.16	-0.13	-0.13	0.14	-0.39	-0.01	0.09

Table S3: Tabulated van der waals contributions per residue. Where no interactions/contacts are made, values are not given. Graphed as figure 3.

		Compound 85				BDM31343				Compound 10 (Pose A)				Compound 10 (Pose B)				Compound 3			
		REPLICA 1	REPLICA 2	REPLICA 3	REPLICA 4	REPLICA 1	REPLICA 2	REPLICA 3	REPLICA 4	REPLICA 1	REPLICA 2	REPLICA 3	REPLICA 4	REPLICA 1	REPLICA 2	REPLICA 3	REPLICA 4	REPLICA 1	REPLICA 2	REPLICA 3	REPLICA 4
Asp	**84**	-0.14	-0.18	-0.16	-0.15																
Leu	**87**	-3.48	-4.39	-4.16	-3.71	-2.59	-3.16	-3.29	-3.03	-3.07	-3.06	-3.27	-3.28	-2.16	-2.03	-2.08	-2.29	-3.16	-2.29	-3.38	-3.15
Leu	**90**	-1.90	-2.04	-2.03	-1.74	-1.29	-2.38	-0.98	-0.32	-0.57		-1.10	-1.45					-3.64	-3.99	-4.38	-3.87
Ala	**91**	-1.15	-1.05	-1.19	-1.26					-0.19		-0.74	-1.02					-2.93	-1.64	-2.14	-2.22
Pro	**94**																	-1.66	-0.40	-1.5	-1.37
Ala	**95**																	-0.47	-0.19	-1.5	-0.52
Glu	**100**						-1.42	-1.12	-0.16												
Met	**102**	-1.90	-1.63	-2.15	-1.95	-1.96	-0.79	-1.37	-0.87	-1.58	-1.89	-2.11	-2.09					-4.07	-3.6	-3.91	-4.04
Trp	**103**	-3.85	-3.24	-3.54	-3.83	-4.02	-2.97	-4.77	-3.17	-3.82	-4.28	-4.13	-4.09	-1.68	-1.45	-1.66	-1.78	-4.87	-4.38	-4.47	-5.35
Arg	**104**													-0.13	-0.12	-0.13	-0.13				
Thr	**105**																	-1.49	-0.4	-0.45	-0.56
Gly	**106**	-2.49	-2.01	-2.05	-2.08	-2.55	-2.13	-1.10	-1.25	-2.42	-2.18	-2.17	-2.15	-1.68	-1.47	-1.39	-1.86	-2.14	-1.92	-1.87	-2.23
Ile	**107**	-1.58	-0.68	-1.88	-1.79	-2.84	-2.87	-1.04	-1.47	-3.54	-3.38	-3.36	-3.05	-3.14	-2.84	-3.16	-2.82	-1.41	-1.52	-2.49	-2.74
Phe	**110**	-7.81	-5.46	-7.26	-7.63	-5.40	-5.30	-3.47	-3.53	-6.02	-5.87	-5.89	-5.55	-6.86	-7.31	-7.26	-7.10	-1.60	-0.79	-2.23	-2.34
Phe	**114**	-2.88	-2.43	-2.52	-2.80									-2.92	-2.99	-3.04	-2.92				
Trp	**138**	-1.62	-2.57	-1.72	-1.56					-0.71	-0.27	-0.30	-0.32	-1.37	-1.22	-1.30	-1.30				
Met	**142**	-1.63	-2.49	-1.70	-1.60	-1.29	-0.96	-0.50	-1.30	-0.43		-0.90	-0.78	-0.43	-0.85	-0.61	-1.41				
Lys	**144**	-0.19	-0.25	-0.22	-0.24		-0.14	-0.19	-0.20					-0.20	-0.18	-0.19	-0.21				
Trp	**145**	-3.85	-5.18	-4.07	-4.10	-3.47	-3.31	-4.69	-4.79	-3.58	-4.14	-4.12	-4.25	-4.97	-4.69	-4.9	-4.95	-2.65	-0.47	-2.02	-1.20
Tyr	**148**	-1.07	-2.99	-2.66	-2.16	-2.12	-2.11	-2.17	-2.47	-2.65	-2.94	-2.52	-2.51	-2.01	-1.9	-1.92	-2.03	-3.08	-3.76	-4.05	-3.30
Thr	**149**	-2.10	-2.37	-2.10	-2.21	-2.3	-2.47	-2.33	-1.96	-1.82	-2.13	-2.14	-2.24	-1.86	-2.04	-1.95	-2.20	-1.87	-1.80	-1.85	-1.49
Val	**152**	-1.71	-1.40	-1.55	-1.60	-1.94	-2.21	-1.32		-1.27	-1.40	-1.44	-1.50					-3.30	-5.33	-2.74	-3.00
Asn	**176**	-3.27	-3.96	-3.06	-2.84	-1.97	-1.95	-2.90	-3.35	-2.16	-3.15	-3.27	-3.38	-0.90	-3.17	-2.84	-3.27	-1.56	-1.21	-1.21	-0.66

Asn	**179**	-1.02	-1.12	-2.13	-1.45	-0.95	-1.17	-0.46	-1.43	-3.05	-2.13	-2.36	-2.37	-1.20	-1.76	-1.71	-1.08	-0.96	-0.83	-1.11	-1.25
Glu	**180**	-4.01	-4.07	-4.11	-4.08	-1.05	-0.49	-2.29	-2.72	-1.72	-1.63	-1.56	-1.37	-3.19	-3.29	-3.42	-3.17				
Leu	**183**	-1.98	-0.96	-1.89	-2.00					-1.26	-0.75	-0.68	-0.36	-2.29	-2.10	-2.03	-2.03				
Phe	**184**													-1.02	-0.97	-0.91	-0.82				
Phe	**187**													-1.00	-0.85	-0.82	-0.79				
Trp	**207**	-2.55	-2.46	-2.87	-2.81	-2.21	-2.09	-2.01	-2.50	-3.14	-3.30	-3.35	-3.33	-1.97	-2.55	-2.51	-2.04	-3.40	-2.26	-2.27	-2.50