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Supplementary Material

Conformers, Properties of the Anticancer Drug Plocabulin, and its Binding Mechanism with P-Glycoprotein: DFT and MD Studies

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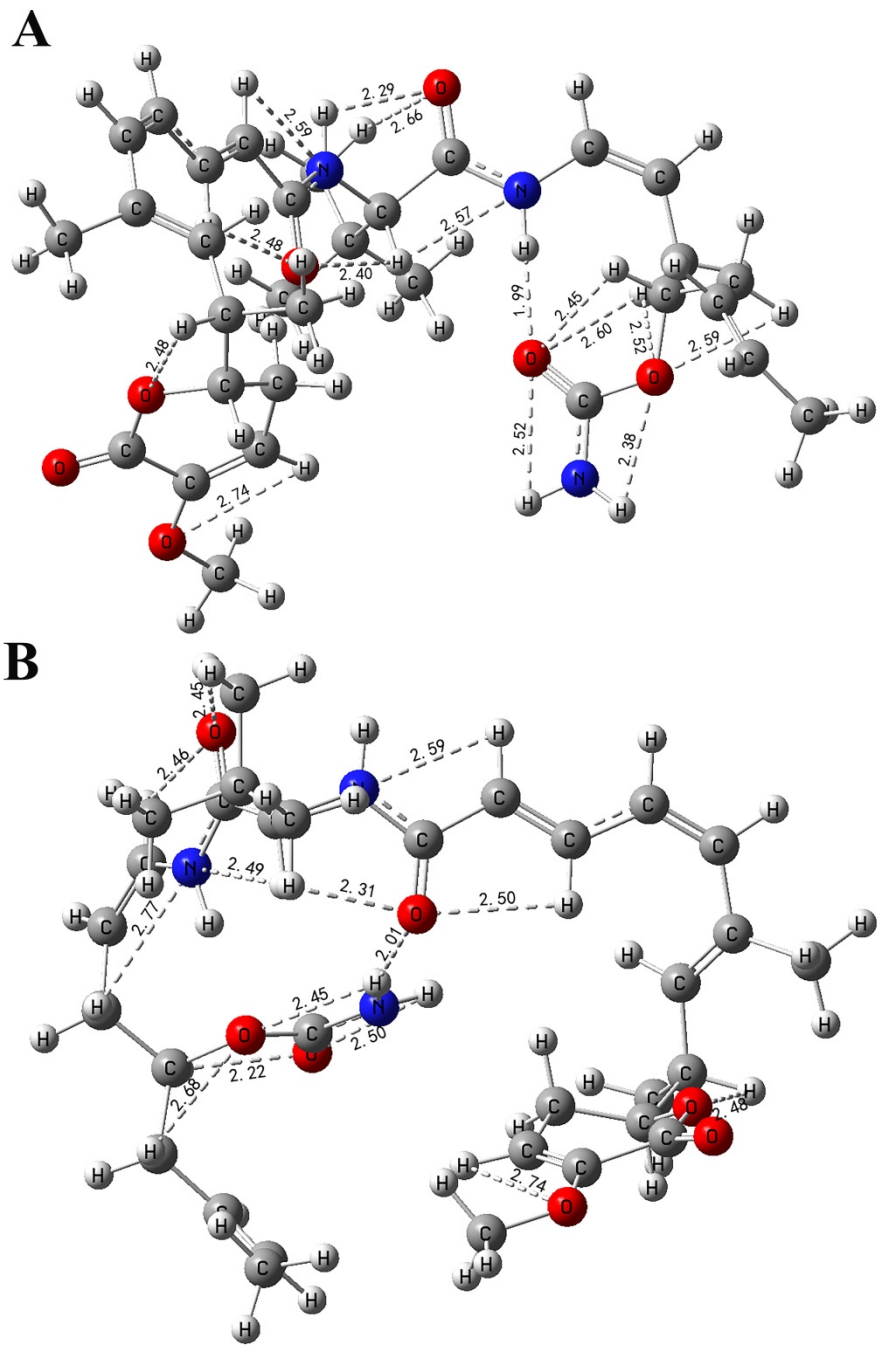

Figure S1 The conformations 2 and 3 of plocabulin.The important hydrogen bonds are represented by dotted lines.

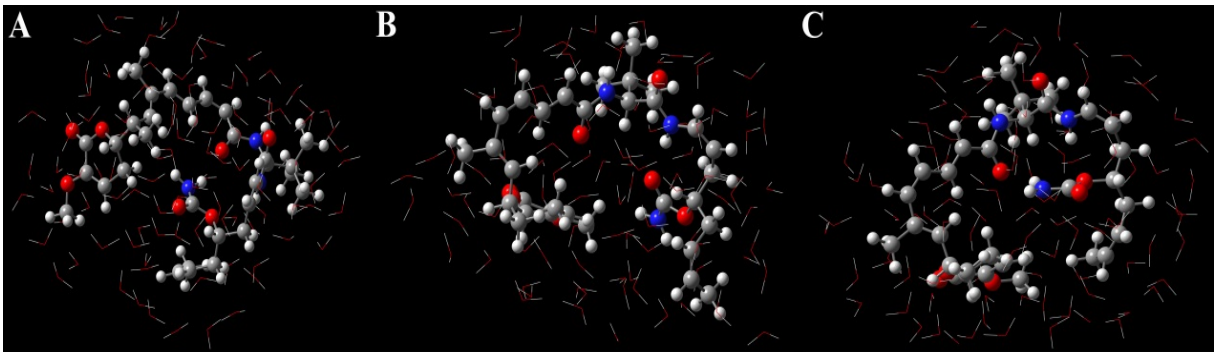

Figure S2 Explicit solvent model of conformer 1 (A), conformer 2 (B), and conformer 3 (C).

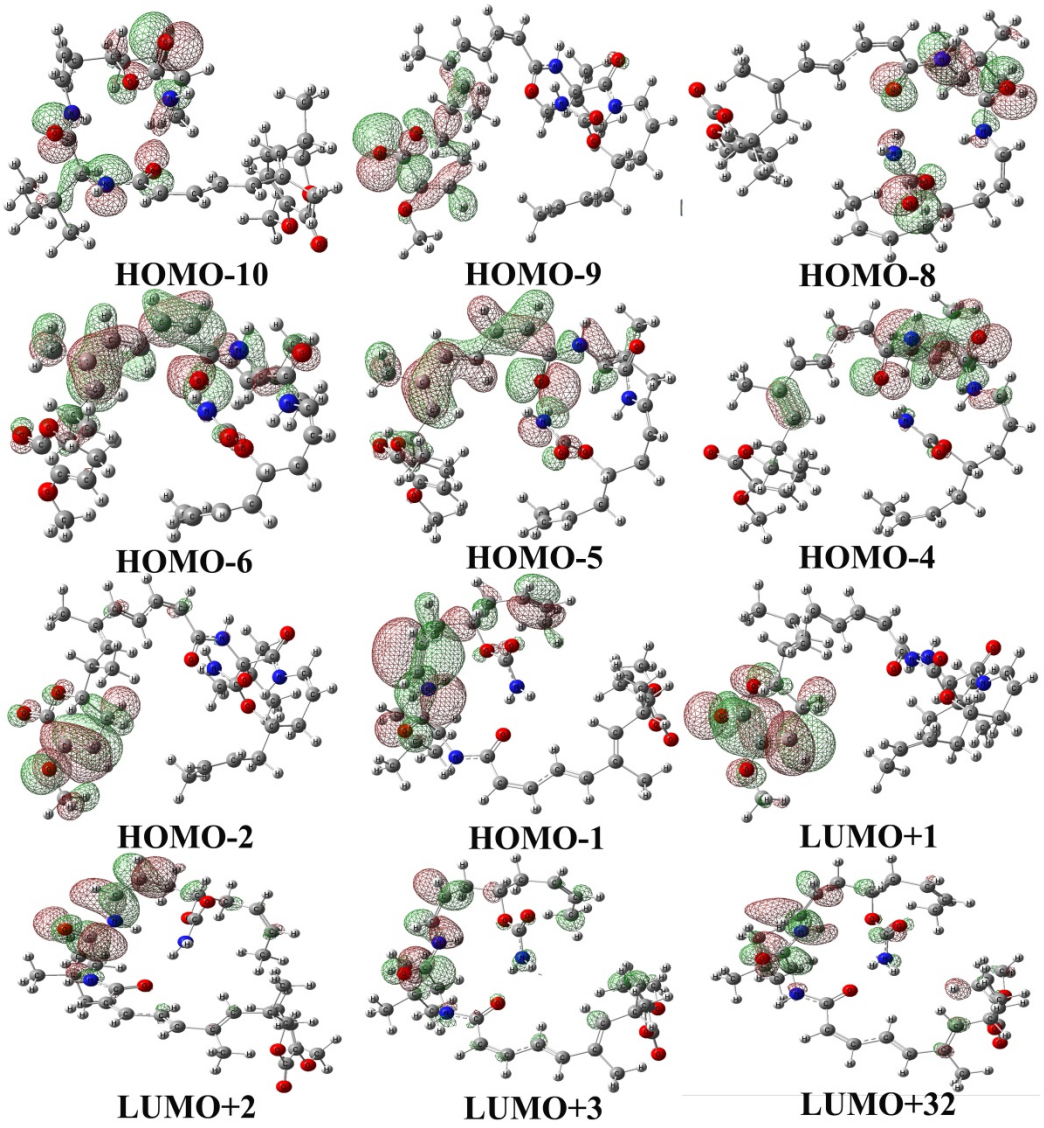

Figure S3 The orbitals involved (except for HOMO and LUMO) in the lowest five excited states for the most stable plocabulin conformation at the TD CAM-B3LYP/6-311+G(2df,p) level.

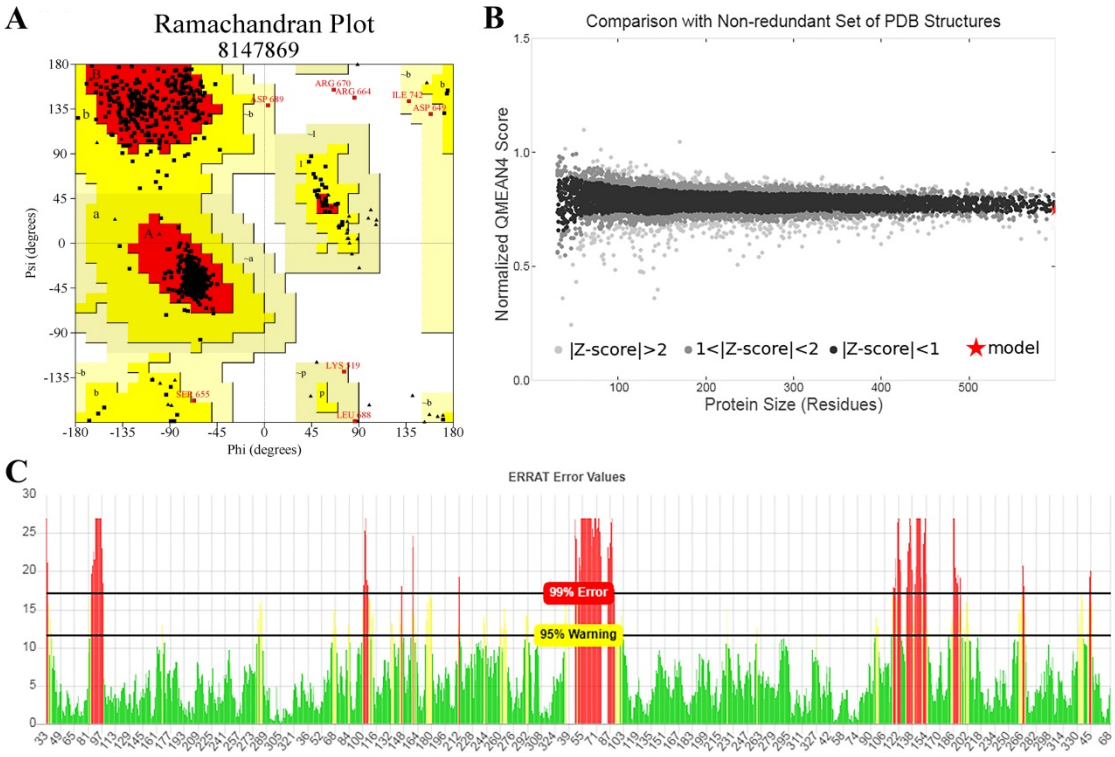

Figure S4 Quality assessment of p-glycoprotein homology model by PROCHECK (A), QMEAN (B) and ERRAT (C). **A:** A Ramachandran plot confirms good stereochemical quality of our model of p-glycoprotein. Results from PROCHECK: residues in most favoured regions: 93.9%; residues in additional allowed regions: 5.4%; residues in generously allowed regions: 0.5%; residues in disallowed regions: 0.2%. **B:** QMEAN is a composite scoring function which is able to derive both global and local absolute quality estimates on the basis of one single model. The QMEAN4 score of our model shown as a *red pentacle*, and the background is a score of high-quality crystal structures of similar size. **C:** ERRAT is a so-called "overall quality factor" for non-bonded atomic interactions. The calculated Error value of 82.3 confirms that our model is a high-quality model.

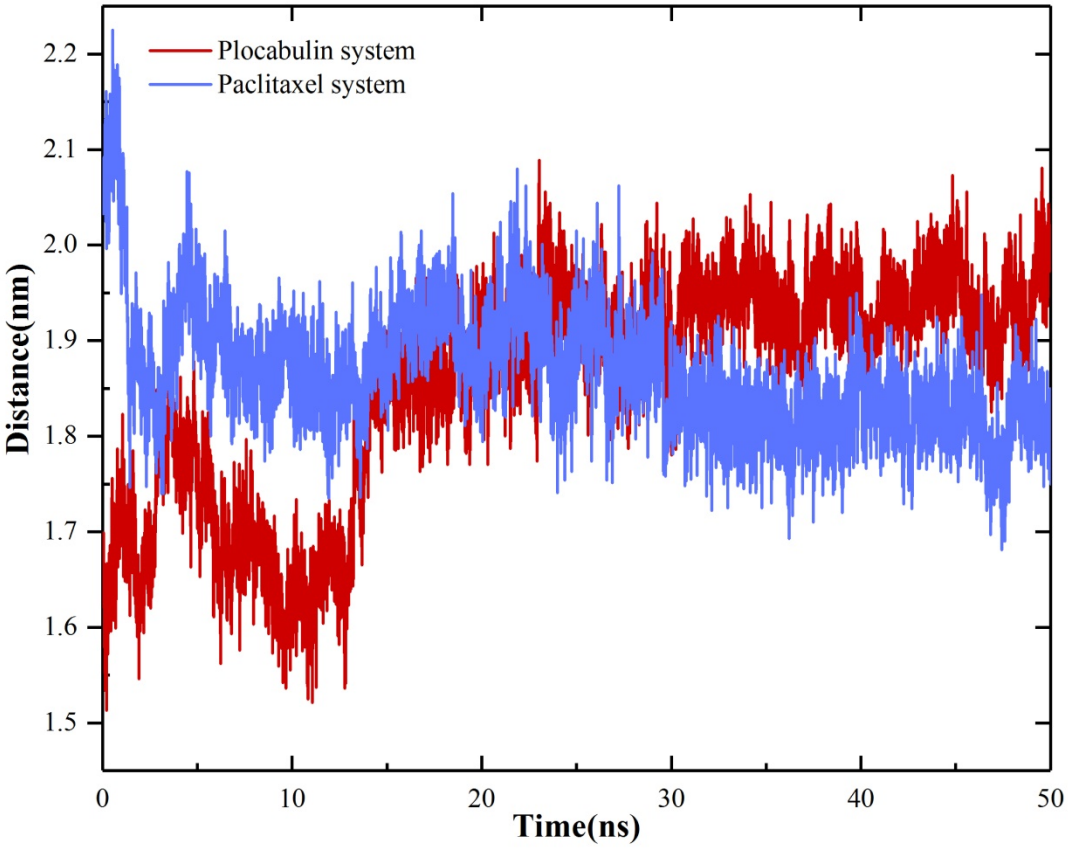

Figure S5 Plocabulin (*red*) and paclitaxel (*blue*) and THR76 centroid distance change graph with simulation time.During the whole process, PM060184 gradually moved away, and the change fluctuated greatly, and paclitaxel gradually approached, and the change was relatively mild.

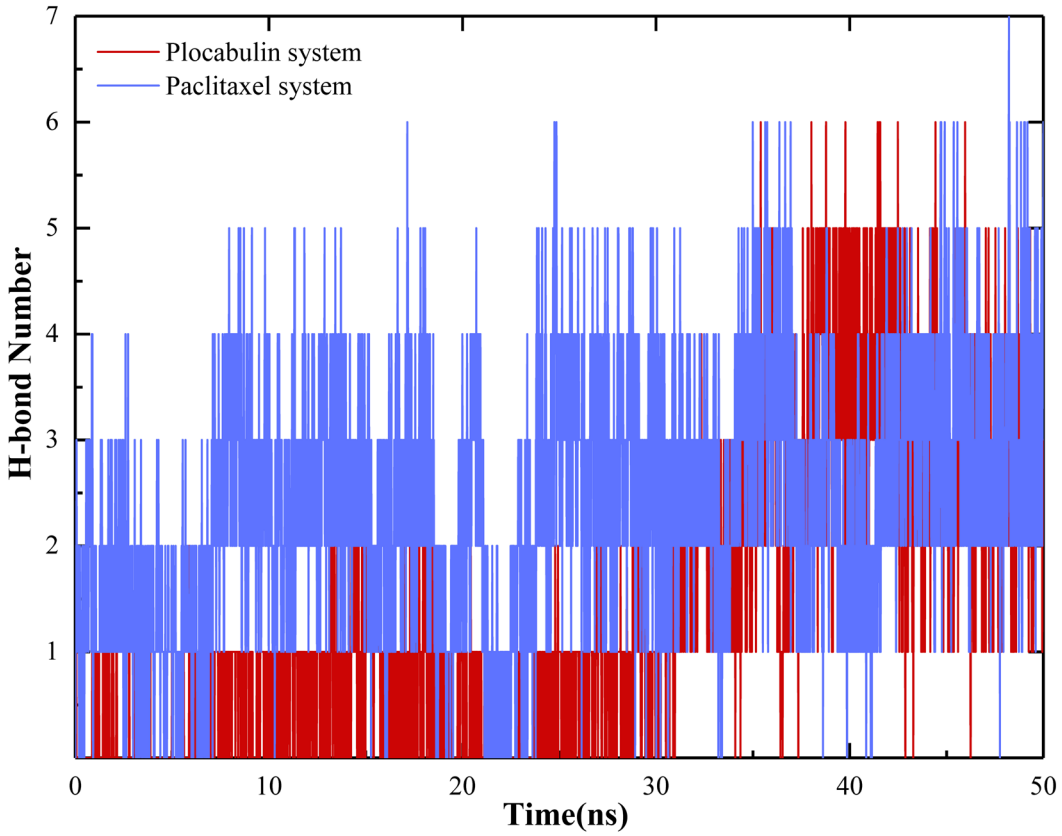

Figure S6 The number of hydrogen bonds formed between the ligand and P-glycoprotein varies with the simulation time. During the simulation, the number of hydrogen bonds between PM060184 (*red*) and protein is currently less than 1-2, and after 30ns, it gradually rises to 4-5; the number of hydrogen bonds between paclitaxel (*blue*) and protein has been maintained 4-5.

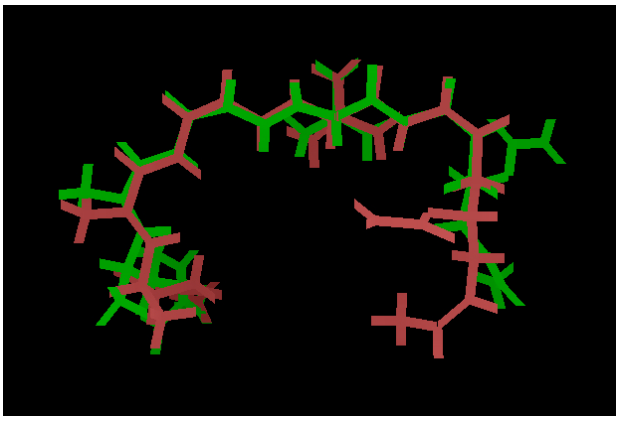

Figure S7 Comparison of the MD equilibrium conformation (green) with the global minimum of plocabulin (pink) predicted by the DFT.

Table S1 Harmonic vibrational frequencies (F; cm^{-1}) scaled by 0.96[28] and the infrared intensities (I; km/mol) for the typical vibrational modes of plocabulin conformers in aqueous solution.

Conformer	1		2		3	
Vibration mode	F	I	F	I	F	I
C11=C12	1657	220	1653	236	1642	212
C2=C3	1683	207	1685	200	1683	212
C13=O	1606	741	1606	576	1603	895
C18=C19	1728	114	1725	84	1726	98
C16=O	1677	548	1667	413	1677	197
C33=O	1697	837	1682	1184	1703	964
C1=O	1717	920	1716	910	1715	899
sym N34-H	3548	289	3595	227	3588	338
N17-H	3564	179	3611	76	3618	94
N14-H	3630	160	3615	127	3621	126
asym N34-H	3683	143	3714	117	3689	120

Table S2 Docking energy and the amino acids residue that interact in the 5 set docking regions and the hydrogen bonds formed.

region	conformation	Binding energy(kcal/mol)	Related amino acid residues						
			H-bond		Others				
1	1	-5.24	SER180	TYR920	ASP177	ARG148	LEU924	LEU890	GLU891
					LEU175	GLY894	LYS895	ASN172	THR898
					THR176	THR173			
	2	-4.16	SER180		ASP177	THR176	ASN172	THR898	LYS895
					GLY894	LYS887	GLU891	LEU890	
	3	-4.01	LYS887		LEU175	THR176	ASP177	GLU184	SER180
					VAL179	SER180	THR176		
	4	-4.42	ARG148		THR898	LYS895	GLU891	LEU890	ASN172
					THR173	LEU175	VAL179	SER180	THR176
	5	-3.63	ASN183		SER180	ASP177	THR176	ARG148	ASP886
					LEU890	LYS887	GLU891		
2	1	-6.33	TYR950		ALA985	ALA869	ILE868	MET949	GLY872
					THR945	GLN946	HIS61	PHE942	MET192
					GLN195				
	2	-5.99	GLN946		GLN347	SER344	SER196	MET192	GLN195
					THR199	THR945	MET949	LEU65	MET986
					ILE340	ILE868	VAL982		
	3	-5.83	GLN347		TYR950	MET949	TYR953	MET68	MET69
					LEU65	GLN195	THR199	ILE340	PHE343
					SER344				
	4	-6.36	GLN946	TYR950	VAL873	GLY872	ILE868	MET986	VAL982
			ALA869		LEU65				
	5	-5.8	GLN946	TYR950	MET876	GLU875	PHE938	ASP188	GLY872
					PHE942	GLN195	GLN946	HIS61	GLY62
					THR199	LEU65			
3	1	-5.05	GLN824	ASN820	ALA248	GLY251	TYR277	ARG789	TYR247
					GLU243	ALA823	ALA819	THR816	THR815
									MET101
	2	-5.25	ASN809	ASN820	ASP821	ALA813	ARG817	ILE1011	0
			HIS1007		LYS808	TRP803			
	3	-4.23	HIS1007		LYS808	ALA813	THR810	LEU814	ASN809
									MET101
					TRP803	ARG817	ILE1011	LYS1014	0
	4	-4.71	TRP803		THR816	ASN820	ASP821	ARG817	ALA813
									MET101
					HIS1007	ASN809	LYS1014	ILE1011	0
					LYS808				
	5	-4.43	HIS1007		met1010	LYS1014	ILE1011	TRP803	ASN809

					LEU814	ALA813	ARG817		
	1	-7.76	GLN725	GLN990	PHE770	PHE303	ILE306	TYR310	PHE732
					PHE983	SER979	ASN839	GLN838	PHE728
					ALA729	TYR307			
	2	-7.52	GLN990		MET986	ALA987	PHE983	VAL835	ASN839
					GLN725	PHE728	TYR310	SER979	ALA729
					PHE732	PHE759	TYR307	PHE303	ILE306
	3	-7.14	GLN990		VAL835	GLN838	PHE770	PHE303	ALA987
4					ASN842	GLN725	PHE303	PHE983	PHE728
					TYR307	PHE759	ILE306	TYR310	
	4	-6.78	GLN725		GLN990	MET986	PHE983	ALA729	PHE732
					TYR310	PHE759	ILE306	PHE303	
	5	-6.86	GLN725	GLN990	TYR310	ILE306	PHE303	TYR307	GLN725
			GLN990		PHE983	ASN725	GLN838	VAL835	ALA987
					MET986				
	1	-8.57	GLN725	GLN990	PHE72	MET69	TYR953	LEU975	PHE978
					ILE340	PHE336	PHE983	MET986	ALA987
					PHE303	TYR310	ILE306		
	2	-8.19	GLN725	TYR307	MET986	GLN347	PHE343	SER344	LEU339
					ILE340	PHE983	TYR310	PHE336	
	3	-7.75	GLN725	TYR307	TYR953	PHE978	ILE340	PHE336	MET986
5					PHE983	LEU339	TYR310	PHE728	
	4	-8.49	TYR310		ILE864	SER952	MET69	TYR953	PHE978
					VAL982	MET986	PHE983	PHE336	ILE340
					PHE728				
	5	-7.35	GLN725		THR199	SER344	ILE340	LEU65	MET69
					PHE336	PHE983	PHE728	TYR310	TYR307
					ILE306				