Supplementary Material

Insights into the drug resistance induced by the BaDHPS mutations: molecular dynamic simulations and MM/GBSA studies

Drug resistance in the BaDHPS mutations

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Figure S1. The van der Waals binding free energy decomposition between the ligand DHP-STZ and the residues of wt (A), D184N (B) and K220Q (C). Important residues for the ligand binding are labeled in each figure.

Figure S2. The electrostatic binding free energy decomposition between the ligand DHP-STZ and the residues of wt (A), D184N (B) and K220Q (C). Important residues for the ligand binding are labeled in each figure.

Figure S3. SASA analyses for some hydrophobic residues around the binding site. The values of residues in wt, D184N and K220Q systems are colored black, magenta and blue, respectively.

Figure S4. Distances between the oxygen atom of Thr67 and the hydrogen atom of the ligand in the system wt (black), D184N (magenta) and K220Q (blue).

Table S1. Data of Hbonds during MD simulations between ligand DHP-STZ and protein wt (A), D184N (B) and K220Q (C), including the occupied percentage, distance, angle and lifetime. The hydrogen bonds that are resident for more than 30% of the simulation are chosen for the analyses. The ligand is labeled as residue 274 in all the three systems.

(A)

donor	acceptor H	acceptor	occupied (%)	distance (Å)	angle (°)	lifetime
:184@OD1	:274@H41	:274@N12	99.9	2.797	29.49	499.5
:120@OD1	:274@H32	:274@N12	99.8	2.876	20.4	332.7
:274@N10	:120@HD21	:120@ND2	99.7	2.914	21.02	249.2
:184@OD1	:274@H42	:274@N3	98.8	2.86	36.8	76
:184@OD2	:274@H42	:274@N3	59.2	3.248	28.86	2.9
:101@OD1	:274@H43	:274@N8	59	3.013	44.7	3.2
:101@OD2	:274@H43	:274@N8	54.5	3.198	18.06	2.9
:274@N12	:254@HE	:254@NE	51.7	3.233	37.19	2.1
:274@N5	:220@HZ3	:220@NZ	35	3.096	21.03	3.7
:274@N5	:220@HZ1	:220@NZ	31.8	3.093	21.27	3.2

(B)

donor	acceptor H	acceptor	occupied (%)	distance (Å)	angle (°)	lifetime
:184@OD1	:274@H42	:274@N3	99.4	2.919	19.87	142
:101@OD2	:274@H43	:274@N8	99.2	2.868	21.7	110.2
:274@N10	:120@HD21	:120@ND2	98.9	2.935	28.76	82.4
:274@N10	:254@HH12	:254@NH1	79	2.978	42.48	6.7
:120@OD1	:274@H32	:274@N12	75.5	2.888	16.12	31.5
:274@N5	:220@HZ1	:220@NZ	32.5	3.071	25.26	2.5

(C)

donor	acceptor H	acceptor	occupied (%)	distance (Å)	angle (°)	lifetime
:120@OD1	:274@H32	:274@N12	97.2	2.935	16.38	81
:67@O	:274@H44	:274@N14	96.7	2.882	17.47	74.4
:184@OD1	:274@H42	:274@N3	85.7	2.964	28.61	13
:274@N10	:120@HD21	:120@ND2	83.8	2.957	33.8	9.9
:184@OD1	:274@H41	:274@N12	57.9	2.871	31.83	34.1
:101@OD2	:274@H43	:274@N8	57.3	2.95	24.67	6.7
:101@OD1	:274@H43	:274@N8	56.9	2.964	30.92	4.9
:184@OD2	:274@H42	:274@N3	48.5	3.012	35.4	3.6
:184@OD2	:274@H41	:274@N12	40.9	2.885	32.36	19.5
:274@N10	:254@HH12	:254@NH1	34.9	3.039	38.53	5.5