Supplementary file 1

In-silico based discovery of potential Keap1 inhibitors using the strategies of pharmacophore screening, molecular docking, and MD simulation studies

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Statistical results of the top 10 pharmacophore hypotheses generated by HypoGenalgorithm.

Hypo. no	Total cost	Null Cost distance	RMSD	Correlation	Max. Fit	Features
1.	104.364	10.604	0.600368	0.936596	9.13981	HBA HBA HBA HYDROPHOBAromatic
2.	105.489	9.4790	0.697249	0.911059	8.42578	HBA HBA HBA HYDROPHOBAromatic
3.	106.023	8.9450	0.725229	0.903609	8.58790	HBA HBA HBA HYDROPHOBAromatic
4.	106.188	8.7800	0.728697	0.903109	8.80628	HBA HBA HBA HYDROPHOBAromatic

5.	106.511	8.4570	0.758513	0.893562	8.19845	HBA HBA HBA HYDROPHOBAromatic
6.	106.968	8	0.782225	0.886438	8.30334	HBA HBA HBA HYDROPHOBAromatic
7.	107.052	7.9160	0.788295	0.884439	8.06738	HBA HBA HBA HYDROPHOBAromatic
8.	107.373	7.5950	0.804100	0.879512	8.24711	HBA HBA HBA HYDROPHOBAromatic
9.	107.454	7.5140	0.807727	0.878365	7.69805	HBA HBA HBA HYDROPHOBAromatic
10.	107.5	7.4680	0.80841	0.878306	8.43267	HBA HBA HBA HYDROPHOBAromatic

Statistical results of the top 10 pharmacophore hypotheses generated by HypoGenalgorithm. (Supplementary data)

Hypo. no	Total cost	Null Cost distance	RMSD	Correlation	Max. Fit	Features
11.	104.364	10.604	0.600368	0.936596	9.13981	HBA HBA HBA HYDROPHOBAromatic
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16.	106.968	8	0.782225	0.886438	8.30334	HBA HBA HBA HYDROPHOBAromatic
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19.	107.454	7.5140	0.807727	0.878365	7.69805	HBA HBA HBA HYDROPHOBAromatic
20.	107.5	7.4680	0.80841	0.878306	8.43267	HBA HBA HBA HYDROPHOBAromatic

Costs and random hypothesis generated (Supplementary data)

Costs	Random1	Random2	Random3	Random4	Random5	Random6	Random7	Random8	Random9	Random10	Random11	Random12	Random13	Random14	Random15	Random16	Random17	Random18	Random19
104.364	114.968	114.968	113.793	114.968	114.968	114.968	114.968	114.968	114.968	114.968	114.968	114.968	114.968	114.968	114.968	114.968	112.377	114.968	114.618
105.489	122.084	120.418	114.429	123.786	117.555	126.755	120.963	122.929	133.174	130.296	120.634	131.188	126.736	117.534	119.627	116.82	113.231	119.717	114.968
106.023	122.75	120.492	114.968	129.772	117.744	127.078	128.8	123.169	134.381	131.153	121.514	131.505	127.148	117.623	122.342	117.058	114.968	120.694	115.819
106.188	123.579	120.806	116.339	130.832	117.907	127.742	129.223	124.242	134.639	131.536	122.585	131.754	127.739	117.708	124.227	117.361	115.356	120.823	117.471
106.511	123.681	120.444	116.852	131.839	118.215	128.385	129.842	124.619	134.746	131.845	122.642	132.643	127.888	118.886	124.838	117.517	117.79	120.824	118.407
106.968	123.774	120.716	117.138	132.74	118.306	128.525	129.825	126.395	134.873	131.873	123.361	133.093	129.188	118.994	124.964	117.673	118.517	121.227	118.417
107.052	123.864	120.777	117.491	132.749	118.406	128.503	129.909	126.952	134.891	131.874	123.394	133.099	129.395	119.074	125.616	118.955	118.595	121.733	120.334
107.373	124.128	120.805	118.038	132.915	118.553	128.701	130.016	127.234	134.939	132.153	123.728	133.569	129.443	119.231	125.956	119.074	118.778	121.923	121.674
107.454	124.134	120.837	118.091	132.921	118.561	128.701	130.022	127.237	134.939	132.153	123.728	133.569	129.443	119.231	125.956	119.074	118.778	121.923	121.674
107.5	124.161	120.828	118.177	132.943	118.533	128.769	130.047	127.473	134.973	132.223	123.924	133.765	129.495	119.452	126.156	119.274	119.316	122.507	122.482

ADMET properties of 3 top hit molecules (Supplementary data)

Compound	Aq. Sol (Log S)	GI absorption	BBB penetration	P-gp Inhibition	CYP450 inhibition					ADMET_Ext_Hepatotoxicity
					1A2	**2C19**	**2C9**	**2D6**	**3A4**	
Sulforaphane (Std)	-1.50	High	No	N	N	N	N	N	N	-1.7285
Hit_Asinex	-4.72	High	No	Y	N	N	Y	Y	Y	-1.3288
Hit_MiniMaybridge	-4.55	Low	No	N	N	N	N	N	N	-2.47373
Hit_Zinc	-4.38	high	No	N	Y	N	Y	Y	Y	-3.52324

Toxicity parameters of hit molecules(Supplementary data)

Compound	Female rat NTP prediction	Male rat NTP prediction	Skin irritancy	Aerobic biodegradability	Developmental toxicity potential	AMES prediction
Sulforaphane (Std)	Non-carcinogen	Non-carcinogen	Mild irritant	Non-degradable	Toxic	Non-mutagen
Hit_Asinex	Non-carcinogen	Non-carcinogen	Non-irritant	Non-degradable	Non-toxic	Non-mutagen
Hit_MiniMaybridge	Non-carcinogen	Non-carcinogen	Non-irritant	Non-degradable	Non-toxic	Non-mutagen
Hit_Zinc	Non-carcinogen	Non-carcinogen	Non-irritant	Non-degradable	Non-toxic	Non-mutagen

Drug likeness properties of 3 top hit molecules (Supplementary data)

Molecules	Mol Wt (g/mol	Alog P	H Bond donor	H bond acceptor	Lipinski's rule	Rotatable bonds	Total polar surface area	Molar refractivity	Verber's rule

	)						(Å^2)		
Sulforaphane (Std)	177.29	1.081	0	2	Yes	5	80.73	48.40	Yes
Hit_Asinex	489.02	2.906	3	6	Yes	8	125.88	139.28	Yes
Hit_MiniMaybridge	391.44	3.311	3	7	Yes	8	144.66	104.04	Yes
Hit_Zinc	382.41	4.066	3	6	Yes	8	100.91	106.22	Yes

Lipinski's rule**:** Mol wt ≤ 500 g/mol; ALog P ≤ 5 but not < 1; H-bond donors ≤ 5; H-bond acceptors ≤ 10; Verber's rule: Rotatable bonds ≤ 10; TPSA ≤ 140 Å^2

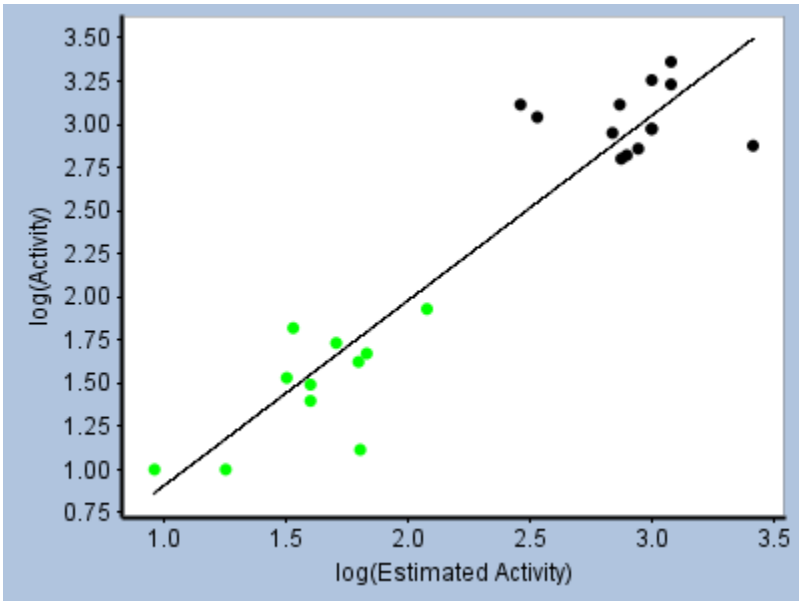
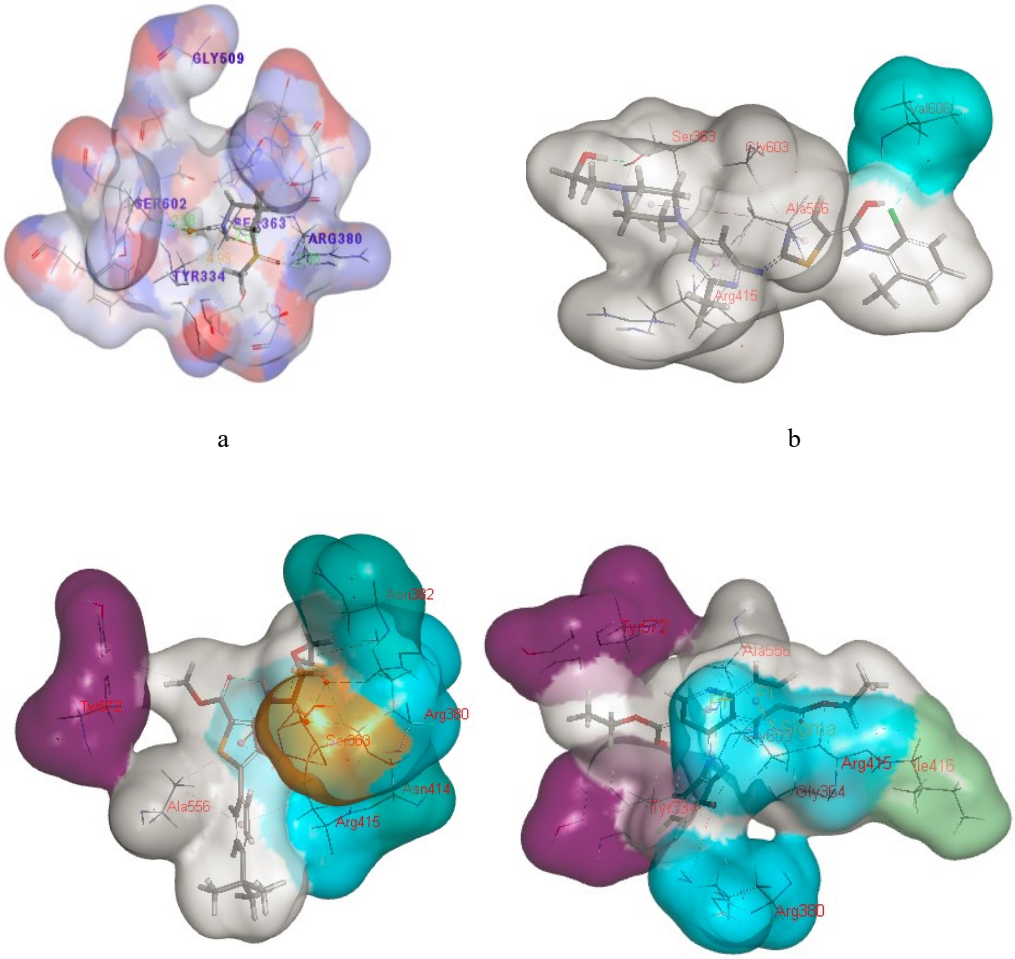


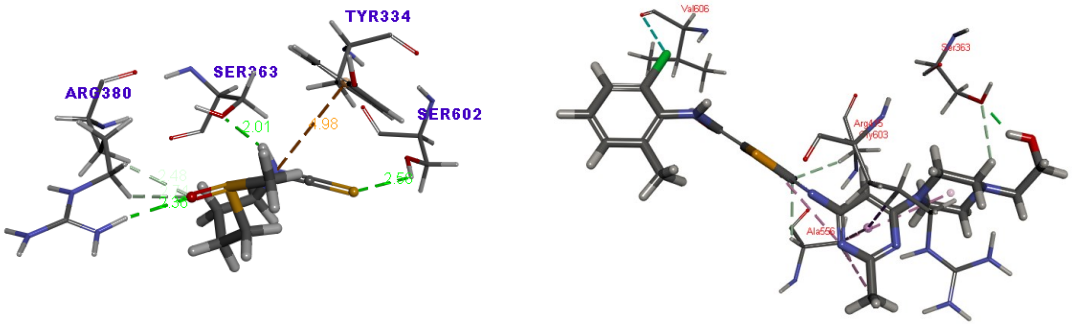
Fig. S1 Regression plot of hypothesis1. Green dots depict active molecules and black dots depict inactive molecules.



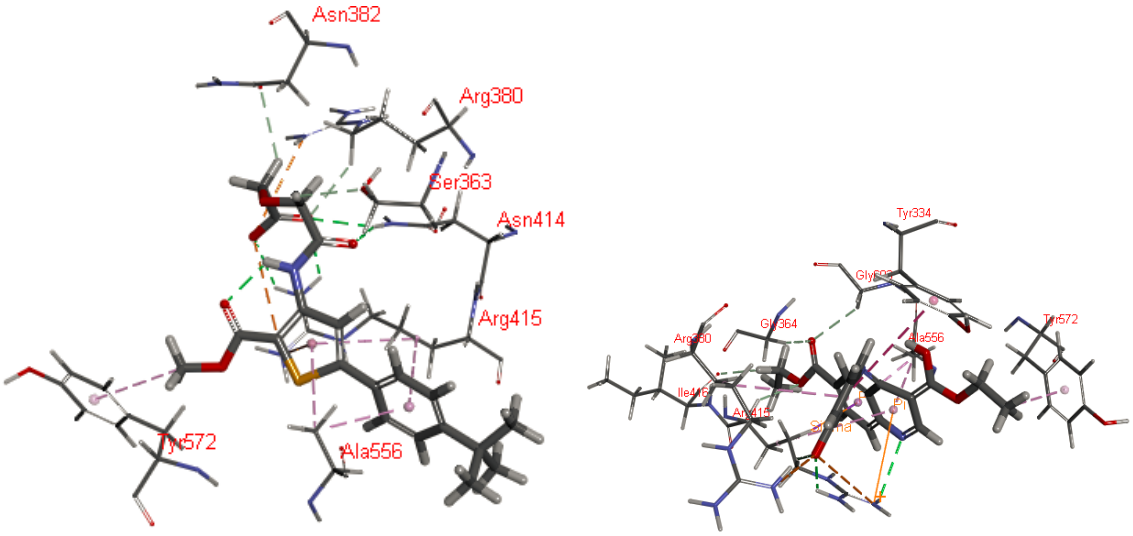
a b

c d

Fig. S2 (a) standard: sulforaphane, (b) Hit_Asinex (c) Hit_MiniMaybridge and (d) Hit_Zinc database



a b



c d

Fig. S3 Amino acid interactions (a) standard: sulforaphane (b) Hit_Asinex (c) Hit_MiniMaybridge and (d) Hit_zinc

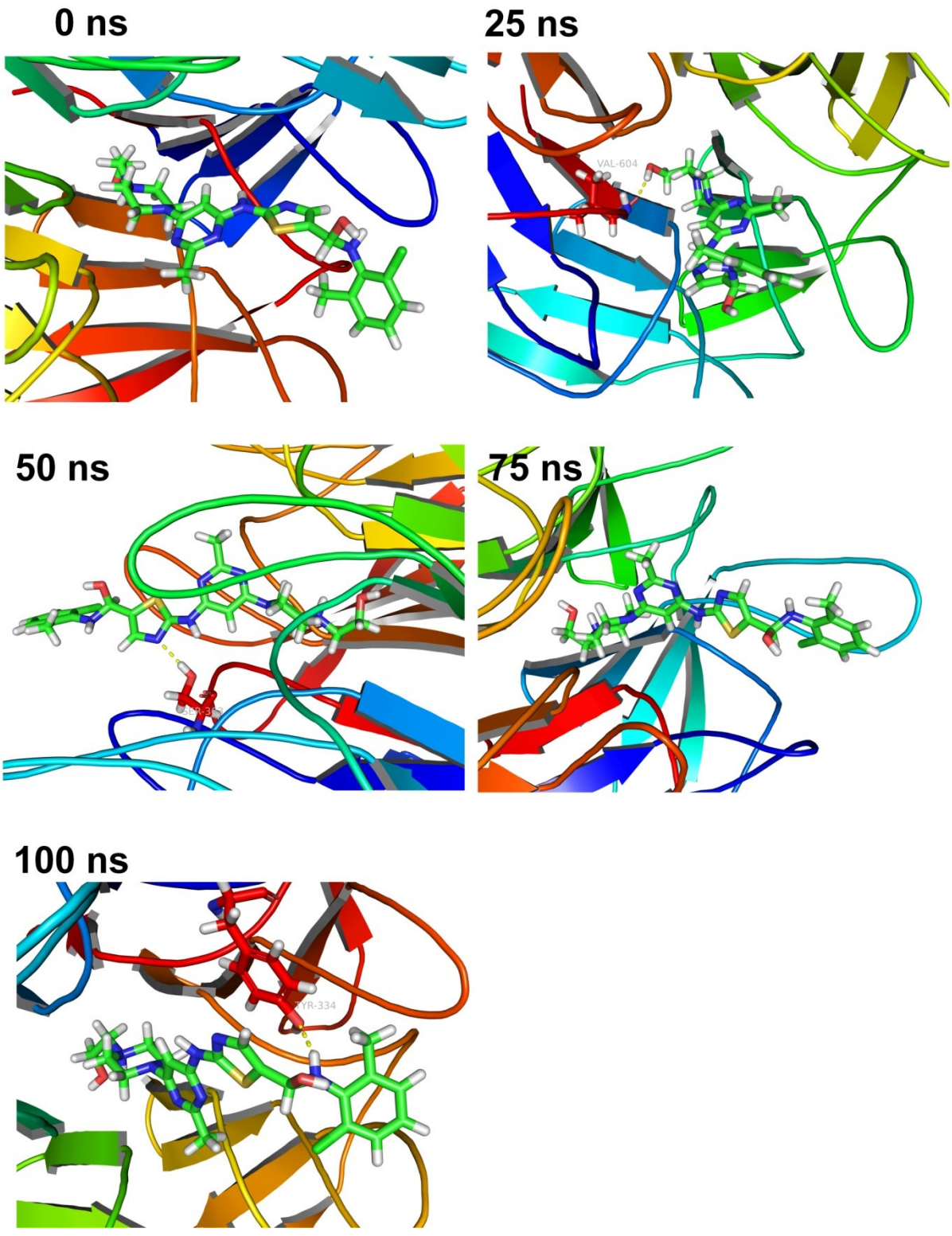


Fig. S4: Trajectories of protein-ligand (Hit-Asinex) complex extracted at different time interval of MDS

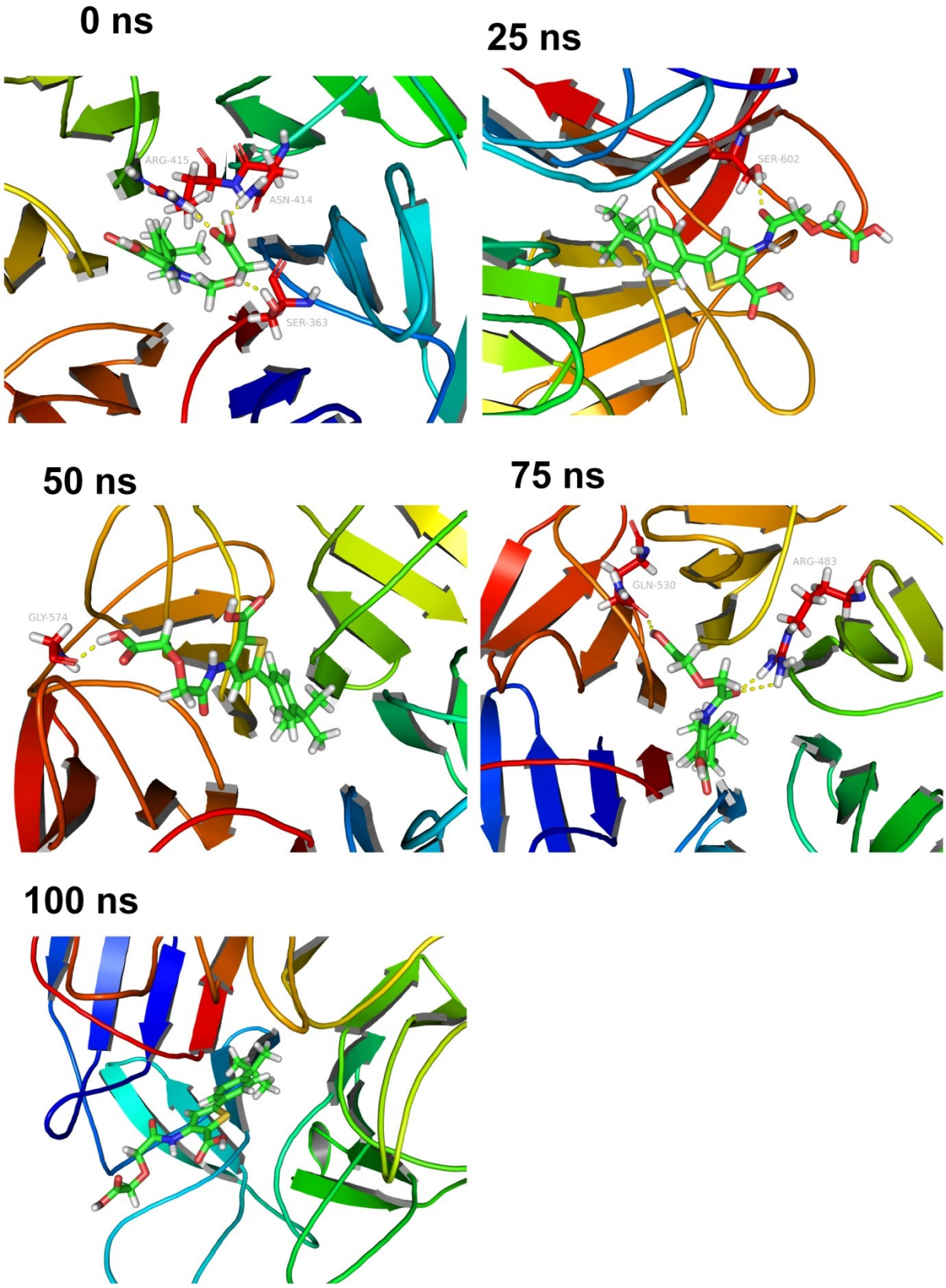


Fig. S5: Trajectories of protein-ligand (Hit-Maybridge) complex extracted at different time interval of MDS

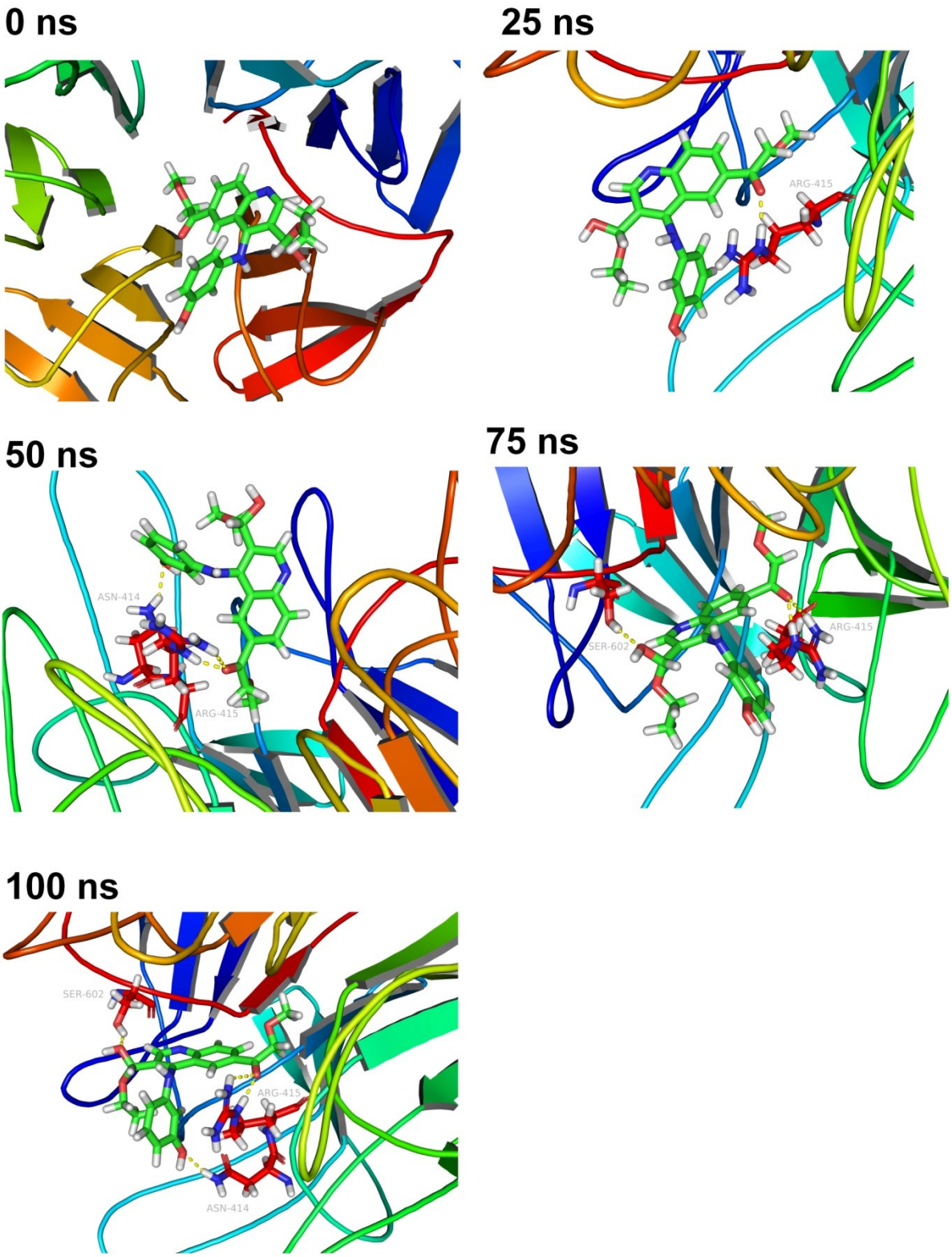


Fig. S6: Trajectories of protein-ligand (Hit-Zinc) complex extracted at different time interval of MDS

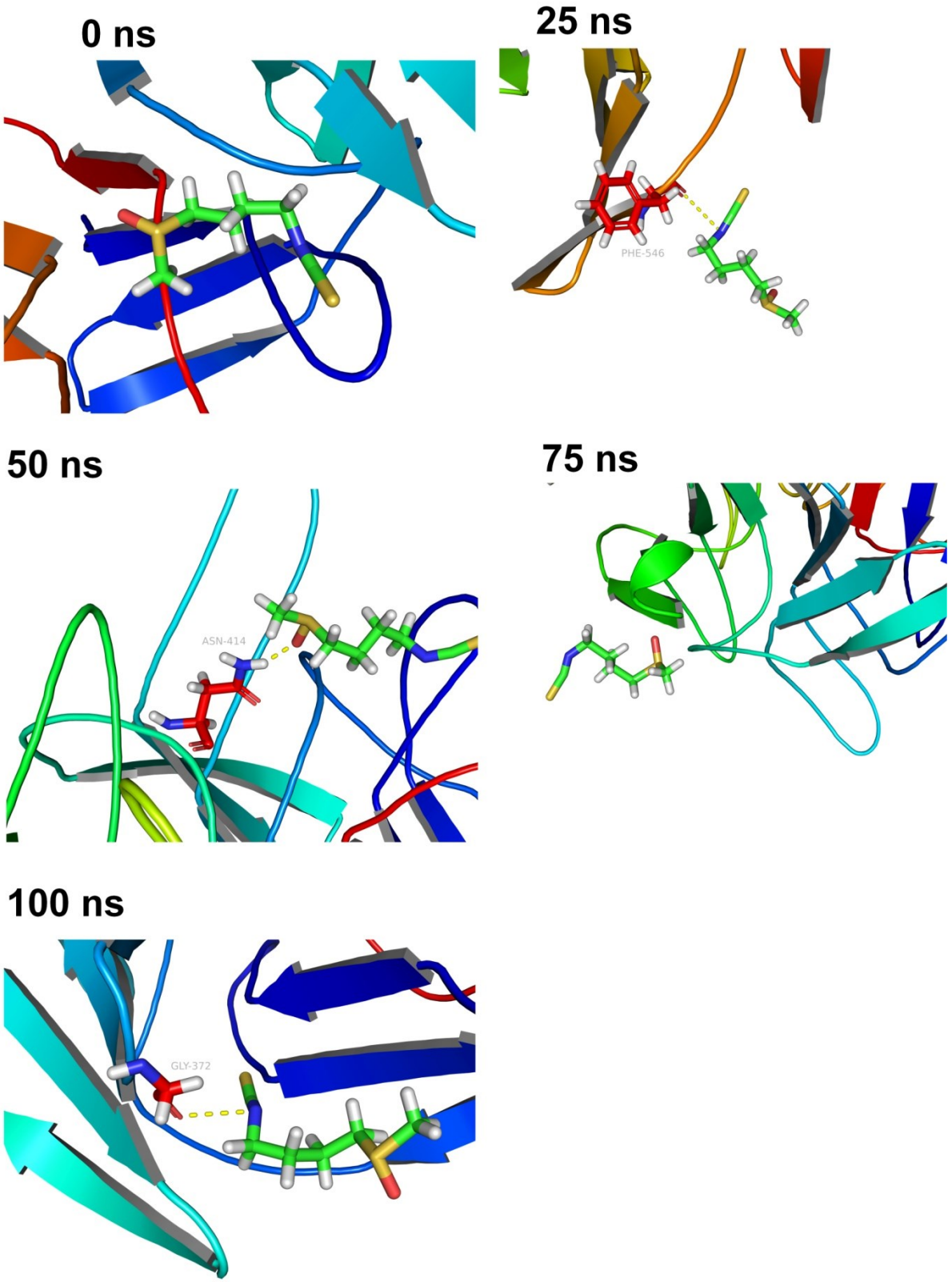


Fig. S7: Trajectories of protein-ligand (Standard Drug) complex extracted at different time interval of MDS