Electronic Supplementary Information

Table 1

Chemical form	**Name of the compound**	**PubChem CID**	**MW (Da)**
Amino acid derivative	Mimosine	440473	198.17
	N-acetyl cysteine	12035	163.19
Alkaloids	Aristolochic acid	2236	341.27
	Ajamaline	2073	326.27
	Reserpine	5770	608.67
Flavonoids/terpenoids	Flavone	10680	222.23
	Querticin	15661826	300.26
	Myricetin	2581672	318.23
	Apigenin	5280443	270.23
	Kaempferol	5280863	286.23
	Luteolin	5280445	286.23
	Phloretin	4788	274.26
Antioxidant/polyphenols	Catechin	9064	290.26
	Ascorbic acid	54670067	176.16
	BHT	31404	220.35
	Nordihydroguaiaretic acid	4534	302.36
	Curcumin	969516	368.37
	N-propyl gallate	4947	212.19
	Chlorogenic acid	1794427	354.3
	Tannic acid	16129778	1701.19
Anti-inflammatory drugs	Dexamethasone	5743	392.46
	Indomethacin	3715	357.78
	Sodium cromoglycate	27503	512.33
	Salicylates	54675850	137.11
	Sodium aurothiomalate	22318	390.07

Text 1

1. Secondary structure details of EHY
   a) Helix regions: Corresponding residue numbers are given below
   α1:45-50, α2:100-103, α3:106-120, α4:140-143, α5:149-162, α6:168-197, α7:229-244, α8:261-281, α9:307-320, α10:337-369 & α11:415-424.
   b) β-sheets region:
   β1:37-41, β2:75-78, β3:129-132, β4:202-204 β5:291-294, β6:324-328, β7:374-378, β8:394-398, β9:407-411, β10:425-429.

Figure 1

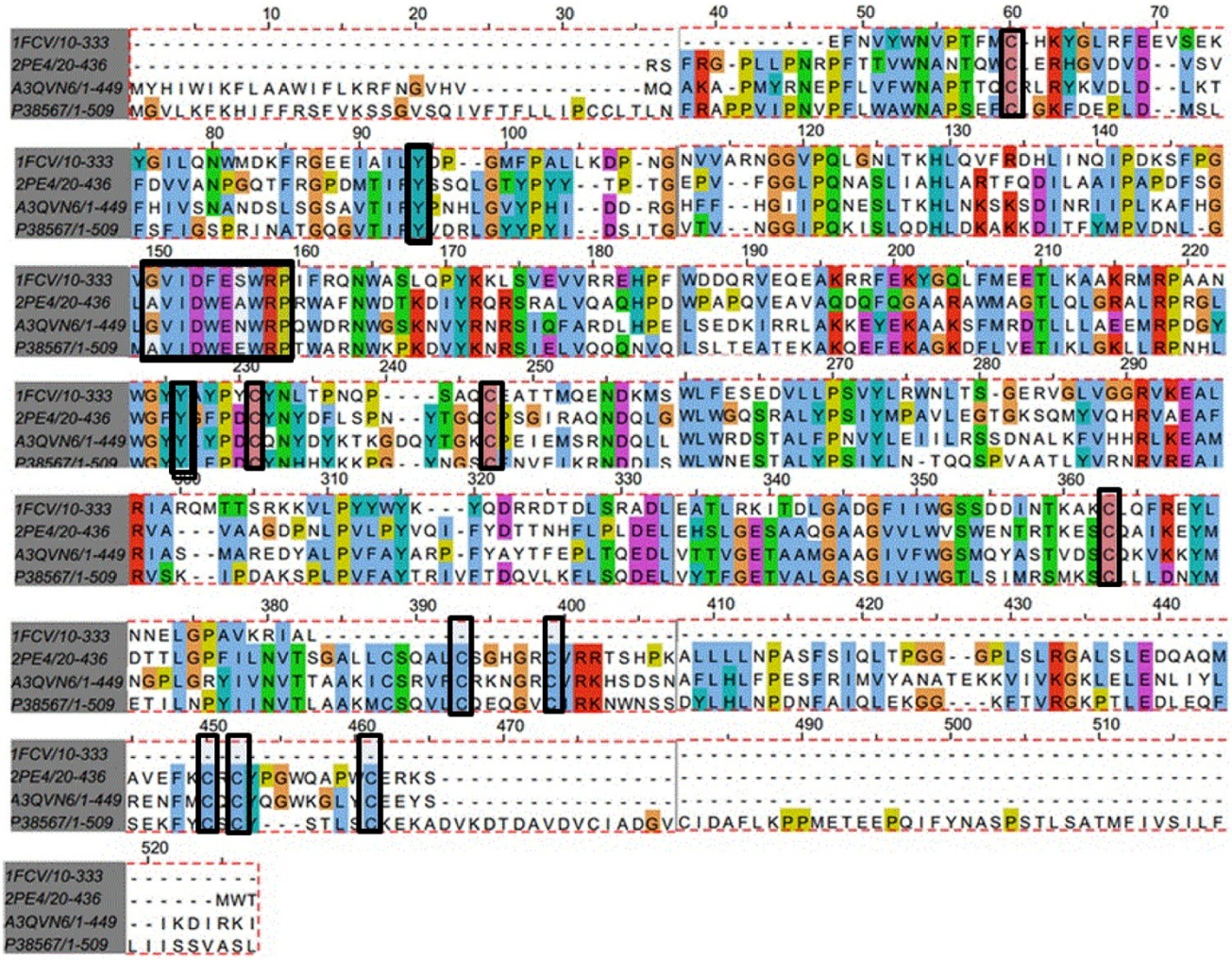

Fig.1 MSA of four Hyal sequences was performed using clustalX and captured image by JalView. The large rectangular box shows the conserved pattern nearby catalytic site region and conserved cysteine and tyrosine residues are also highlighted in vertical rectangular box.

Table 2

Ligand	Donor Hydrogen	Acceptor Hydrogen	Bond distance (Å)
1.Catechin	O4-H O5-H O6-H Lys148-N1HZ	Asp133-OD2 Asp91-OD1 Asp91-OD1 O6	2.7 2.6 2.5 3.1
2. Chlorogenic	O4H Tyr206OH Arg271N2H2 Arg271N2H2 Arg295N1H1 Arg295N2H2	Asp133OD2 O3 O5 O6 O9 O8	2.7 3.2 3.0 3.1 3.0 2.6
3. Kaempferol	O5-H Arg295-NH2 Arg271NH2	Asp133-OD2 O3 O6	2.7 3.1 2.9

4. Mimosine	Arg295NH2 N1H1 N2H2 Asn136NDZ	O3 Asp133OD2 Asp133OD1 O2	2.7 2.8 2.6 2.9
5.Myricetin	Asp251ND2 Tyr206-OH O2H O7H Asp136ND2 O6H Lys148NZH1 Lys148NZH2	O3 O4 Asp133OD2 Asp133OD1 O8 Asp91OD1 O8 O6	3.4 2.7 3.3 2.7 3.2 3.1 3.2 2.9

Table 3

	Atom 1	Atom 2	Distance (Å)	Atom1	Atom2	Distance (Å)
Chlorogenic acid (CGA)	CGA B 450 O5	HIS A 94 CB	3.38	**Myricetin (MYR)**		
	CGA B 450 O5	HIS A 94 CA	3.73	MYR B 450 O6	TYR A 300 CZ	3.76
	CGA B 450 C11	HIS A 94 N	3.88	MYR B 450 O6	TYR A 300 CE1	3.43
	CGA B 450 O6	GLY A 93 C	3.86	MYR B 450 O6	ALA A 299 C	3.67
	CGA B 450 O7	LEU A 70 CD1	3.52	MYR B 450 O6	ALA A 299 CB	3.47
	CGA B 450 O7	LEU A 70 CG	3.67	MYR B 450 O6	ALA A 299 CA	3.82
Mimosine (MIM)	MIM B 450 O3	TYR A 206 CZ	3.52	MYR B 450 C8	ARG A 295 NH1	3.59
	MIM B 450 O3	TYR A 206 CE2	3.68	MYR B 450 C3	ARG A 295 NH1	3.76
	MIM B 450 C3	GLU A 135 OE1	3.07	MYR B 450 C8	ARG A 295 CZ	3.76
	MIM B 450 C1	GLU A 135 OE1	3.70	MYR B 450 O5	TYR A 293 CE2	3.61
	MIM B 450 C3	GLU A 135 CD	3.87	MYR B 450 O5	TYR A 293 CD2	3.81
	MIM B 450 C1	GLU A 135 CD	3.74	MYR B 450 C5	TYR A 253 OH	3.67
	MIM B 450 C4	ASP A 133 OD2	3.19	MYR B 450 C6	TYR A 253 OH	3.71
	MIM B 450 C3	ASP A 133 OD2	3.53	MYR B 450 C1	TYR A 253 OH	3.58
	MIM B 450 C1	ASP A 133 OD2	3.05	MYR B 450 C1	TYR A 253 CZ	3.81
	MIM B 450 C1	ASP A 133 OD1	3.28	MYR B 450 C7	TYR A 253 CZ	3.71
	MIM B 450 C2	ASP A 133 OD1	3.86	MYR B 450 O3	TYR A 253 CE1	3.59
	MIM B 450 C4	ASP A 133 CG	3.70	MYR B 450 C7	TYR A 253 CE1	3.62

	MIM B 450 C1	ASP A 133 CG	3.38	MYR B 450 C12	TYR A 253 CD2	3.63
	MIM B 450 O2	PRO A 80 CD	3.23	MYR B 450 O5	TYR A 253 CD2	3.71
	MIM B 450 N2	PRO A 80 CG	3.58	MYR B 450 C11	TYR A 253 CD2	3.75
	MIM B 450 O2	PRO A 80 CG	3.66	MYR B 450 O3	TYR A 253 CD1	3.57
	MIM B 450 O2	TYR A 79 CD2	3.54	MYR B 450 C7	TYR A 253 CD1	3.74
				MYR B 450 C12	TYR A 253 CD1	3.70
				MYR B 450 C12	TYR A 253 CG	3.49
				MYR B 450 C12	TYR A 214 OH	3.50
				MYR B 450 O3	TYR A 214 CZ	3.13
				MYR B 450 O3	TYR A 214 CE1	3.15
				MYR B 450 C11	TYR A 206 OH	3.76

Figure 2

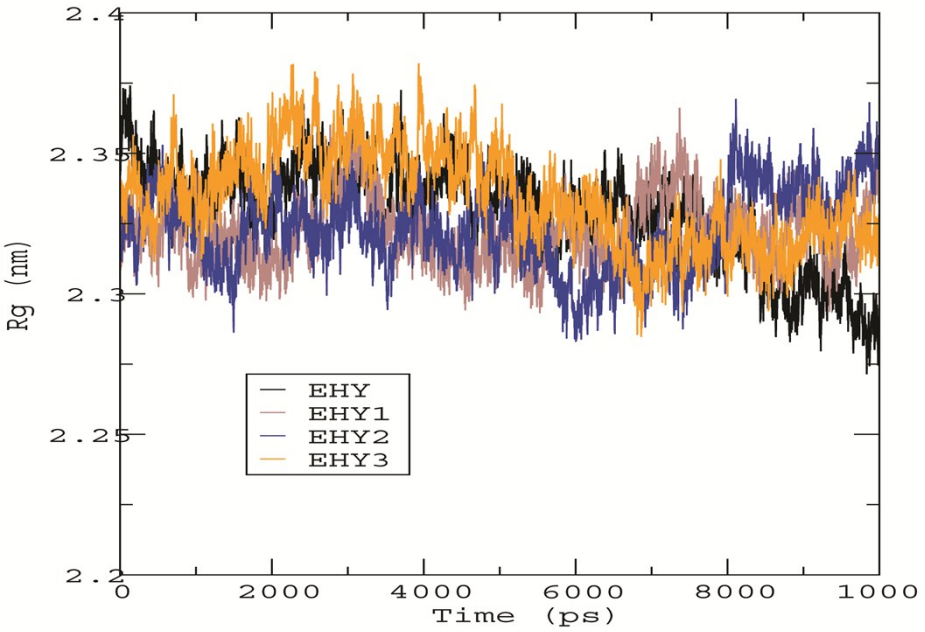

Fig.2: The radius of gyration of EHY (apo), EHY1 (with CGA), EHY2 (with MIM) and EHY3 (with MYR) were shown in figure. Color legend for each form is mentioned within small rectangular box.

Figure 3

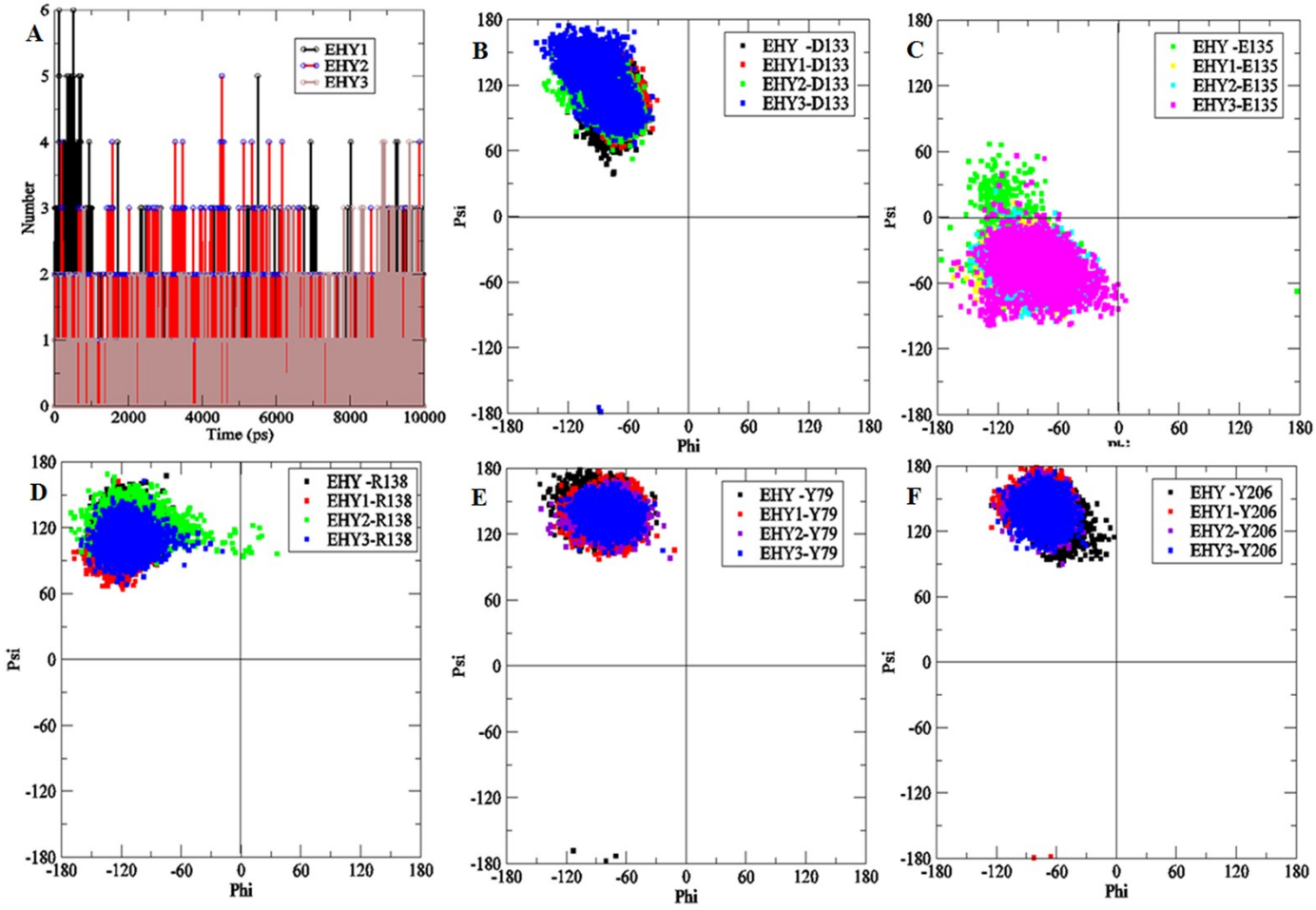

Fig.3. The Hydrogen bond occupancies (A) for the better binding plant compounds (EHY1 – with CGA, EHY2 – with MIM and EHY3 – with MYR) and Φ and ψ angle (in the range of -180 to +180) distribution of functionally important residues D133 (B), E135 (C), R138 (D), Y79 (E) and Y206 (F) are depicted in the above figure.

Text for Fig.3; B to F:

ASP133 residue dispersion was largely clustered in the core β-sheet region within the range of Φ=-150, -30 and ψ=+50, +175. The ASP133 in EHY1 and EHY2 was observed with less scattering reveals that CGA and MIM binding with this catalytic residue. When in fact, GLU135 in apo form was widely dispersed in helical region (Φ=+1, -165 and ψ=-100, +60) compared to the ligand bound forms. These observations extended that the ligand binding had made both ASP133 and GLU135 conformation rigid within the range of β-sheet. In MIM bound form, ARG138 was most widely scattered in the range of Φ=+25, -170 and ψ=+80, +170. Interestingly, the ARG138 distribution was very less in apo form in comparison with ligand bound forms. This states that ligand binding induces more conformational change of ARG138. The TYR79 and TYR206distributions were most restricted in EHY3 within the range of Φ=-10, -150 and ψ=+90, +160 due the strong hydrophobic interaction formed by MYR.

Figure 4

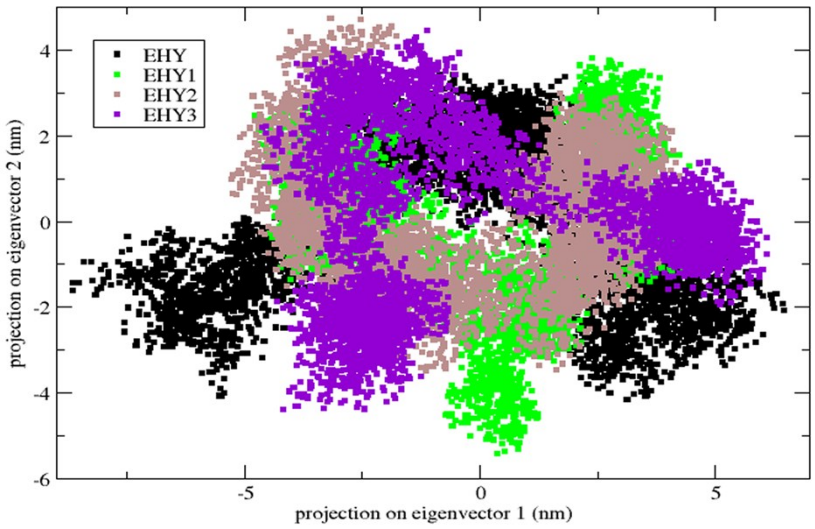

Fig.4: PCA based 2-D projection was plotted between PC1 and PC2 for apo (EHY) and ligand bound forms (EHY1, EHY2 and EHY3). Color representation for each form distribution was shown in square box shape and legend is mentioned within a rectangular box.

Figure 5

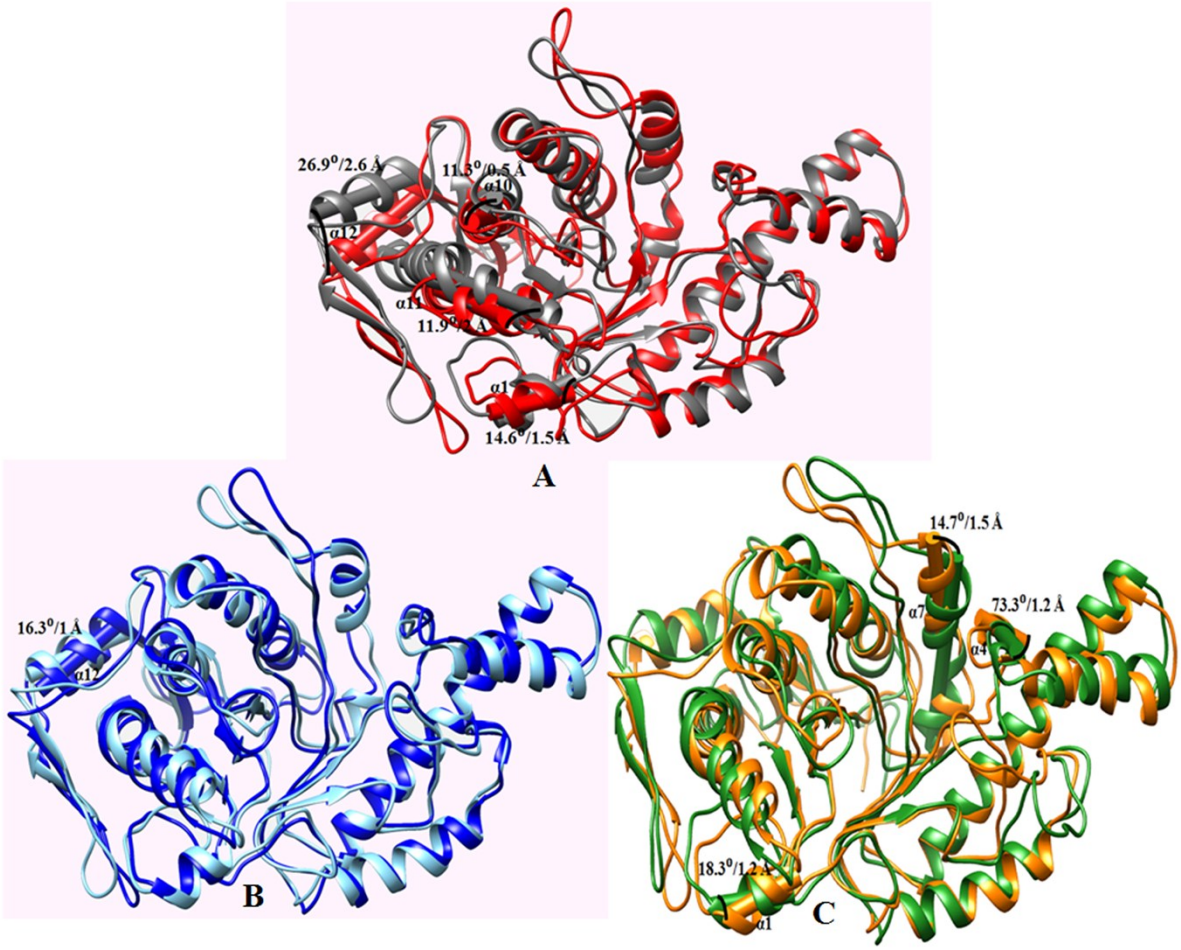

Fig.5.The conformational changes between docking to FEL poses are shown in the figure. The helical

axis (in degree and distance in angstrom) and loop changes of A) CGA, B) MIM and C) MYR bound are highlighted. Here light and dark colors are representing the dock and FEL conformations of EHY respectively.

Figure 6

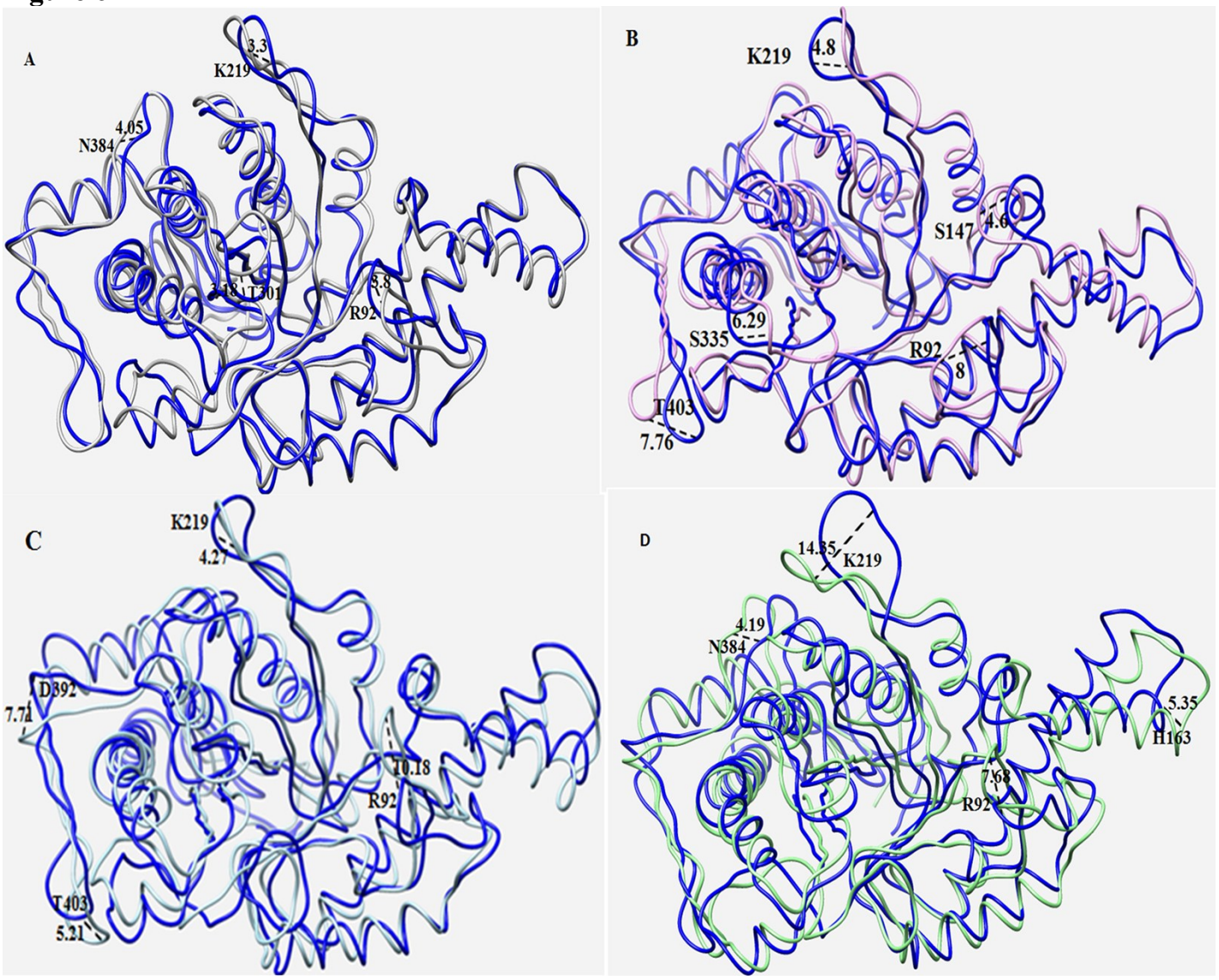

Fig.6 The structural dislocation and rearrangement of EHY in unligated and ligated forms are shown in this figure. The cut-off of the displacement is set as 4 Å. The residues involved in the large dislocations are highlighted and the distance of dislocation is denoted in angstrom. The light color ribbons are average conformation of A) apo, B) CGA, C) MIM and D) MYR bound forms and dark blue colors represent the large translocated conformation of EHY.

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Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.