

```

4JPS      PPPSSGELWGIHLMPPRILVECLLPNGMIVTLECLREATLITIKHELFKEARKYPLHQL
4JPS_model PPPSSGELWGIHLMPPRILVECLLPNGMIVTLECLREATLITIKHELFKEARKYPLHQL
*****

4JPS      LQDESSYIFVSVTQEAEREFFDETRRLCDLRLFQPFVKVIEPVGNREEKILNREIGFAI
4JPS_model LQDESSYIFVSVTQEAEREFFDETRRLCDLRLFQPFVKVIEPVGNREEKILNREIGFAI
*****

4JPS      GMPVCEFDVMKDPEVQDFRRNILNVCKEAVDLRDLNSPHSRAMYVYPNVESSPELPKHI
4JPS_model GMPVCEFDVMKDPEVQDFRRNILNVCKEAVDLRDLNSPHSRAMYVYPNVESSPELPKHI
*****

4JPS      YNKLDKGQIIIVVIWIVSPNNDKQKYTLKINHDCVPEQVIAEAIR-----
4JPS_model YNKLDKGQIIIVVIWIVSPNNDKQKYTLKINHDCVPEQVIAEAIRKKTRSMLLSSEQLKL
*****

4JPS      -KLEYQGKYILKVCGCDEYFLEKYPLSQYKYIRSCIMLGRMPNMLMAKESLSYQLPMD
4JPS_model CVLEYQGKYILKVCGCDEYFLEKYPLSQYKYIRSCIMLGRMPNMLMAKESLSYQLPMD
*****

4JPS      FTMPYSRRIS-----TKSLWVINSALRIKILCATYVNVNIRDIDKIYVRTGIY
4JPS_model FTMPYSRRISTATPYMNGETS:KSLWVINSALRIKILCATYVNVNIRDIDKIYVRTGIY
*****

4JPS      HGGEPLCDNVNTQRPVCSNPRWNEWLNVDIYIPDLPRARLCLISCSVKGRKGAKEEHCP
4JPS_model HGGEPLCDNVNTQRPVCSNPRWNEWLNVDIYIPDLPRARLCLISCSVKGRKGAKEEHCP
*****

4JPS      LAWGNINLFDYTDTLVSGKMALNLWPVPHGLEDLLNPIGVTGSNPNKETPCLELFDWFS
4JPS_model LAWGNINLFDYTDTLVSGKMALNLWPVPHGLEDLLNPIGVTGSNPNKETPCLELFDWFS
*****

4JPS      SVVKFPDMSVIEEHANE-----NDKEQLKAISTRDPLS
4JPS_model SVVKFPDMSVIEEHANWSVSREAGFSYSHAGLSNRLARDNELRENDKEQLKAISTRDPLS
*****

4JPS      EITEQEKDFLWSHRHYCVTIPEILPKLLSVKWNRSDEVAQMYCLVKDWPPIKPEQAMEL
4JPS_model EITEQEKDFLWSHRHYCVTIPEILPKLLSVKWNRSDEVAQMYCLVKDWPPIKPEQAMEL
*****

4JPS      LDCNYPDPMVRGFAVRCKEYLTDDKLSQYLQLVQLVQVLYEYLDNLLVRFLLKKALTNQ
4JPS_model LDCNYPDPMVRGFAVRCKEYLTDDKLSQYLQLVQLVQVLYEYLDNLLVRFLLKKALTNQ
*****

4JPS      RIGHFFFWHLKSEMHNKTVSQRFGLLLESYCRACGMYLKHLNRQVEAMEKLINLTDILKQ
4JPS_model RIGHFFFWHLKSEMHNKTVSQRFGLLLESYCRACGMYLKHLNRQVEAMEKLINLTDILKQ
*****

4JPS      EKKDETQKVQMKFLVEQMRRPDFMDALQGFLSPLNPAHQGNLRLIEECRIMSSAKRPLWL
4JPS_model EKKDETQKVQMKFLVEQMRRPDFMDALQGFLSPLNPAHQGNLRLIEECRIMSSAKRPLWL
*****

4JPS      NWENPDIMSELLFQNNIEIFKNGDDLQDDMLTLQIIRIMENIWQNQGLDLRMLPYGCLSI
4JPS_model NWENPDIMSELLFQNNIEIFKNGDDLQDDMLTLQIIRIMENIWQNQGLDLRMLPYGCLSI
*****

4JPS      GDCVGLIEVVRNSHTIMQIQCK-----FNSHTLHQWLKDNKNGEYDAAIDLFRSC
4JPS_model GDCVGLIEVVRNSHTIMQIQCKGGLKALQFNSHTLHQWLKDNKNGEYDAAIDLFRSC
*****

4JPS      AGYCVATFILGIGDRHNSNIMVKDDGQLFHIDFGHFLDHKKKKFGYKRERVPFVLTDQFL
4JPS_model AGYCVATFILGIGDRHNSNIMVKDDGQLFHIDFGHFLDHKKKKFGYKRERVPFVLTDQFL
*****

4JPS      IVISKGAQECTKTREFERFQEMCYKAYLAIRQHANLFINLSMMLGSGMPELQSFDDIAY
4JPS_model IVISKGAQECTKTREFERFQEMCYKAYLAIRQHANLFINLSMMLGSGMPELQSFDDIAY
*****

4JPS      IRKTLALDKTEQEALEYFMQMNDAAHGGWTTKMDWIFHTEWYWGDISREEVNEKLRDTA
4JPS_model IRKTLALDKTEQEALEYFMQMNDAAHGGWTTKMDWIFHTEWYWGDISREEVNEKLRDTA
*****

4JPS      DGTFLLVRDASTKDY---TLTLRKGGNNKLIKIFHR---GFSPLTFKLLYPVS-----
4JPS_model DGTFLLVRDASTKMHGDYTLTLRKGGNNKLIKIFHRDGKYGFSPLTFSSVVELINHYRNE
*****

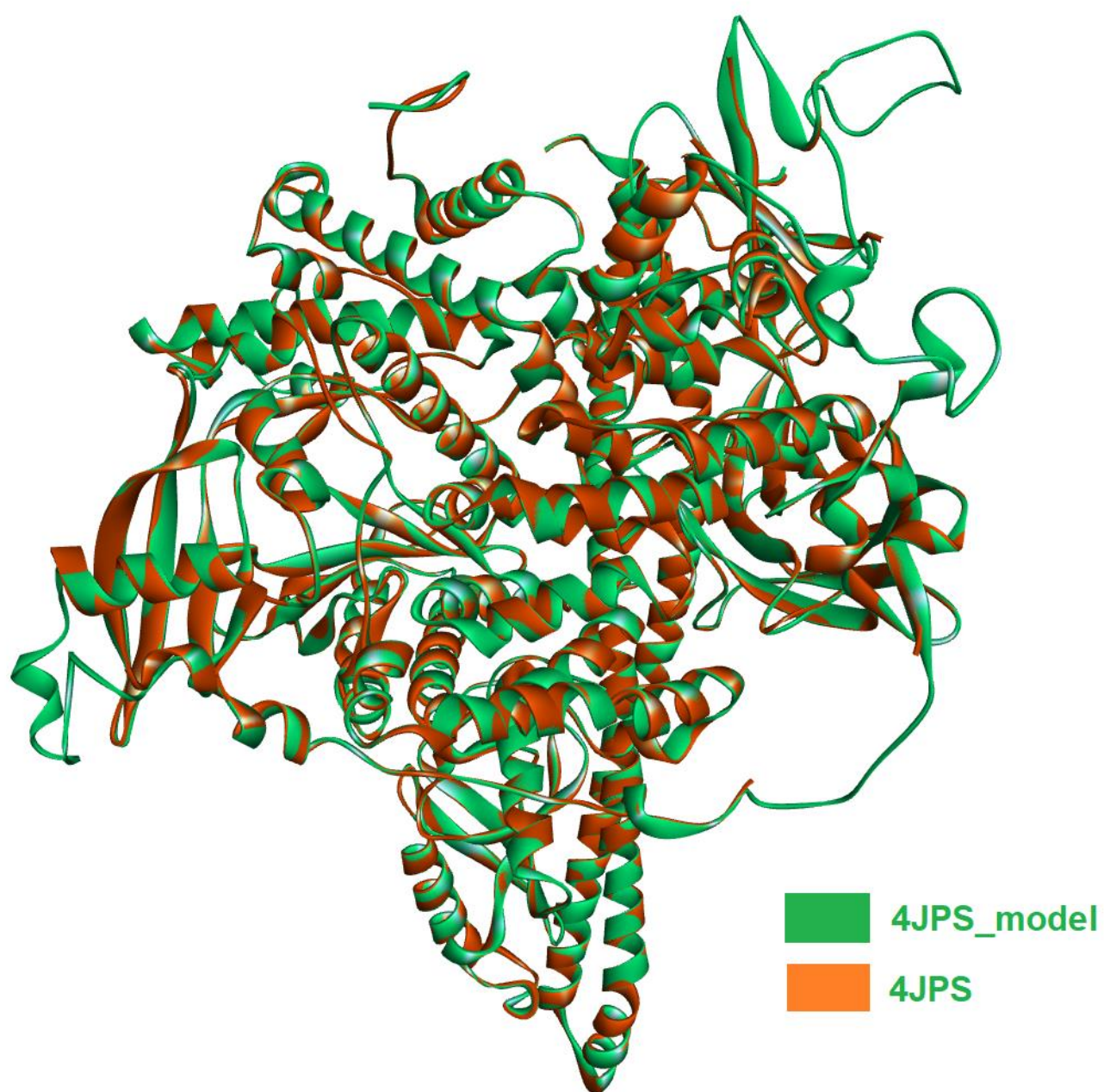
4JPS      -----KQVVKEDNIEAVGKKLHEYNTQFQEKREYDRLYEEYT
4JPS_model SLAQYNPKLDVKLLYPVSKYQDQVVKEDNIEAVGKKLHEYNTQFQEKREYDRLYEEYT
*****

4JPS      RTSQEIQMKRTAIEAFNETIKIFEEQCQTQERYSEYIEKFKREGNEKEIQRIMHNYDKL
4JPS_model RTSQEIQMKRTAIEAFNETIKIFEEQCQTQERYSEYIEKFKREGNEKEIQRIMHNYDKL
*****

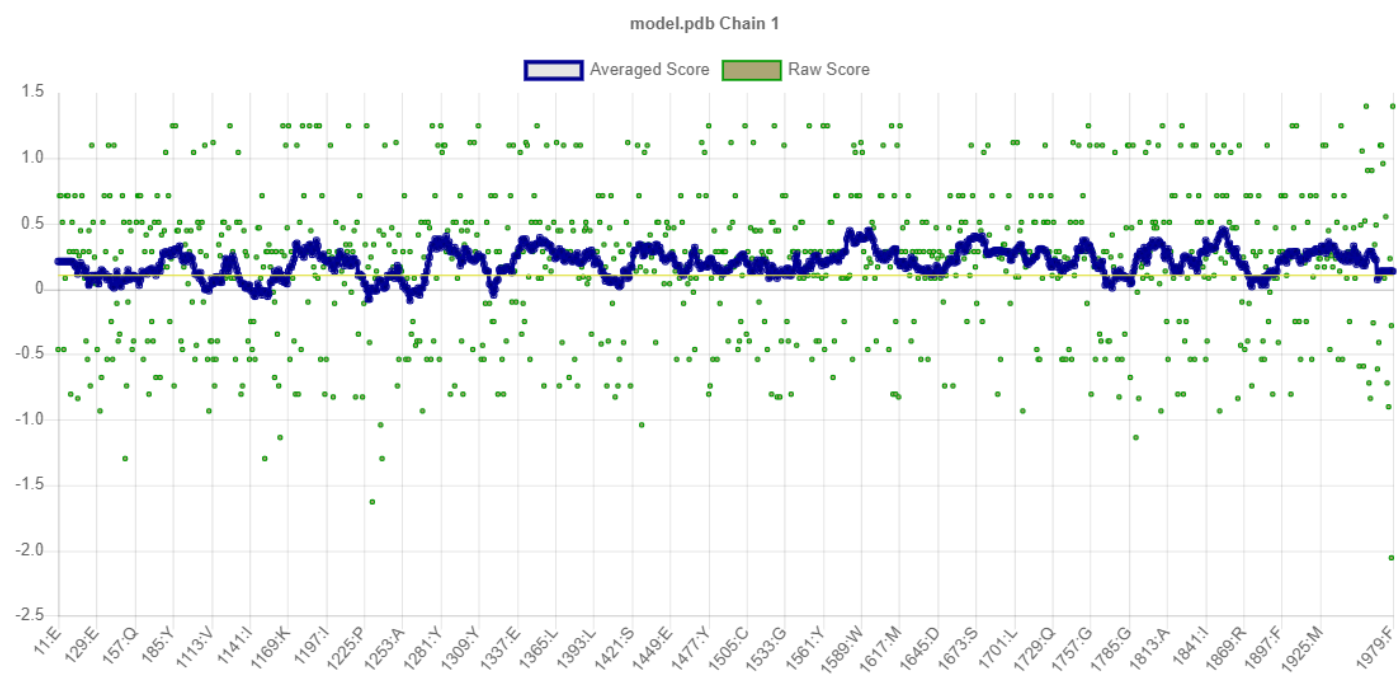
4JPS      KSRISEIIDSRRRLEEDLKKQAAEYREIDKRMNSIKPDLIQLRKTRDQYLMWLTKQGVRRQ
4JPS_model KSRISEIIDSRRRLEEDLKKQAAEYREIDKRMNSIKPDLIQLRKTRDQYLMWLTKQGVRRQ
*****

4JPS      K
4JPS_model K
*
```

**Supplementary Figure 1a:** CLUSTAL 2.1 Multiple Sequence Alignments of PDB ID: 4JPS (PIK3CA) with its model structure from the SwissModel.



**Supplementary Figure 1b:** Alignment (overlay) of 4JPS (orange) obtained from the RCSB PDB with model (green) obtained from the SwissModel.



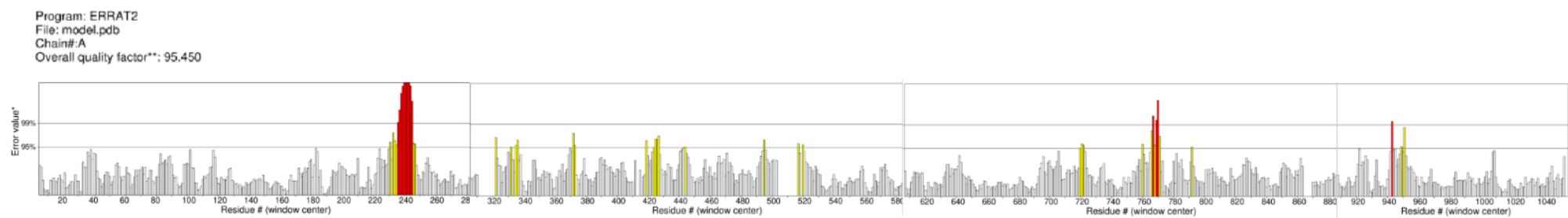
### VERIFY3D

82.33% of the residues have  
averaged 3D-1D score  $\geq 0.1$

**Pass**

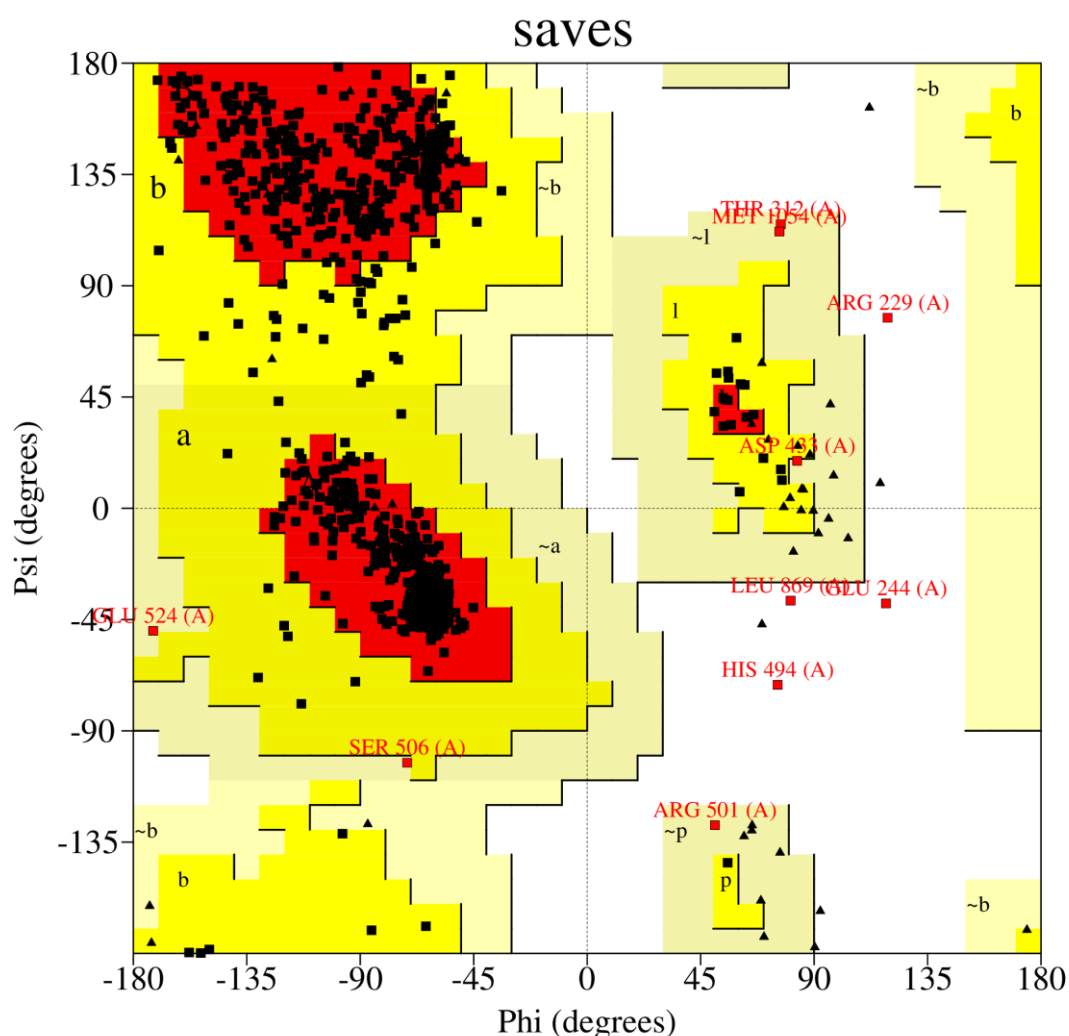
At least 80% of the amino acids have scored  $\geq 0.1$  in the 3D/1D profile.

**Supplementary Figure 1c:** Validation of 4JPS\_model using Verify3D.



**Supplementary Figure 1d:** Validation of 4JPS\_model using ERRAT2 showing 95.45% of quality factor.

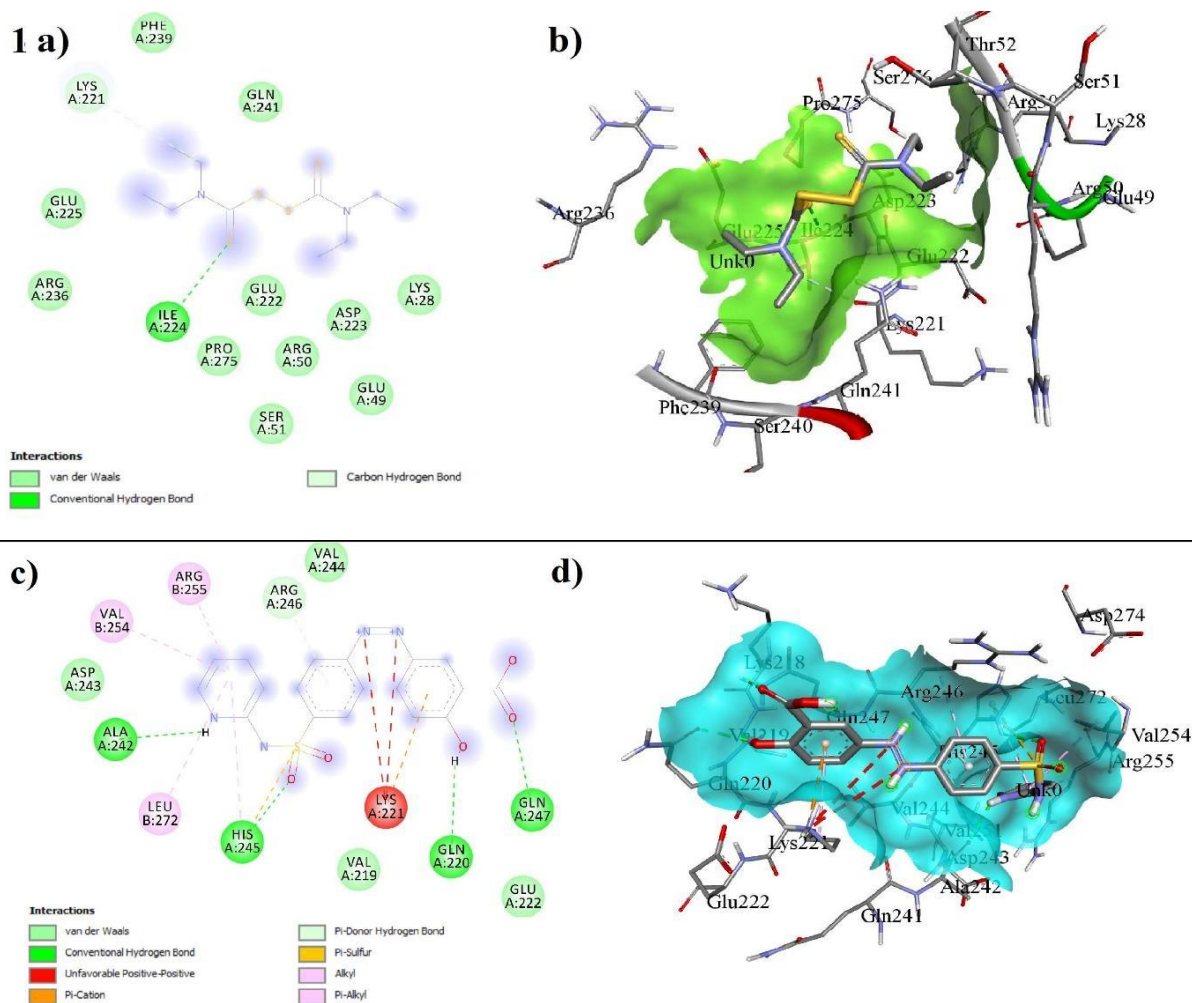
# Ramachandran Plot



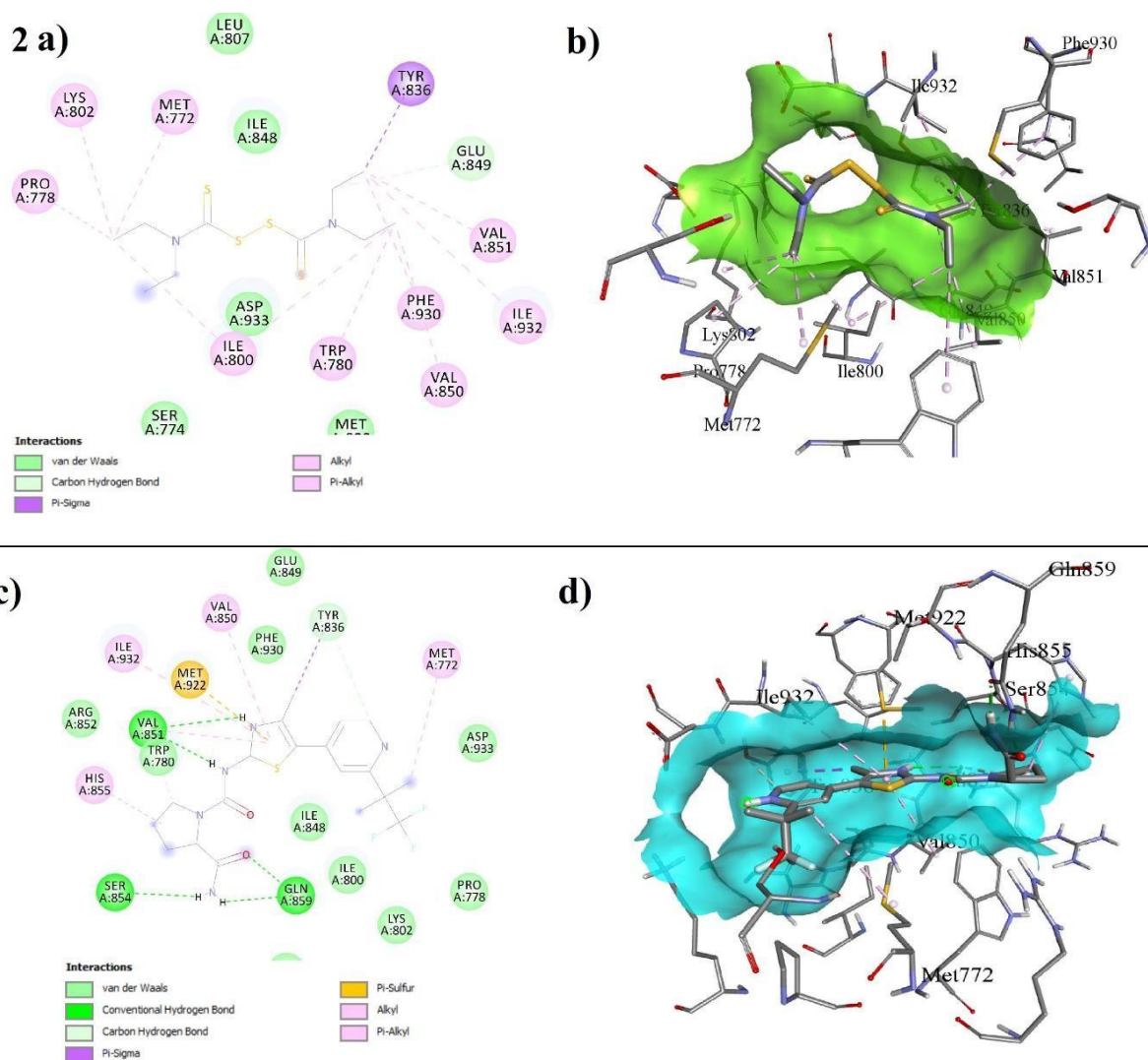
Residues in most favoured regions [A,B,L]	873	91.0%
Residues in additional allowed regions [a,b,l,p]	76	7.9%
Residues in generously allowed regions [~a,~b,~l,~p]	6	0.6%
Residues in disallowed regions	4	0.4%
	----	-----
Number of non-glycine and non-proline residues	959	100.0%
Number of end-residues (excl. Gly and Pro)	3	
Number of glycine residues (shown as triangles)	49	
Number of proline residues	51	
	----	
Total number of residues	1062	

**Supplementary Figure 1d:** Validation of 4JPS\_model using Ramachandran Plot showing about 98.9% residues in most favoured and additionally allowed region.

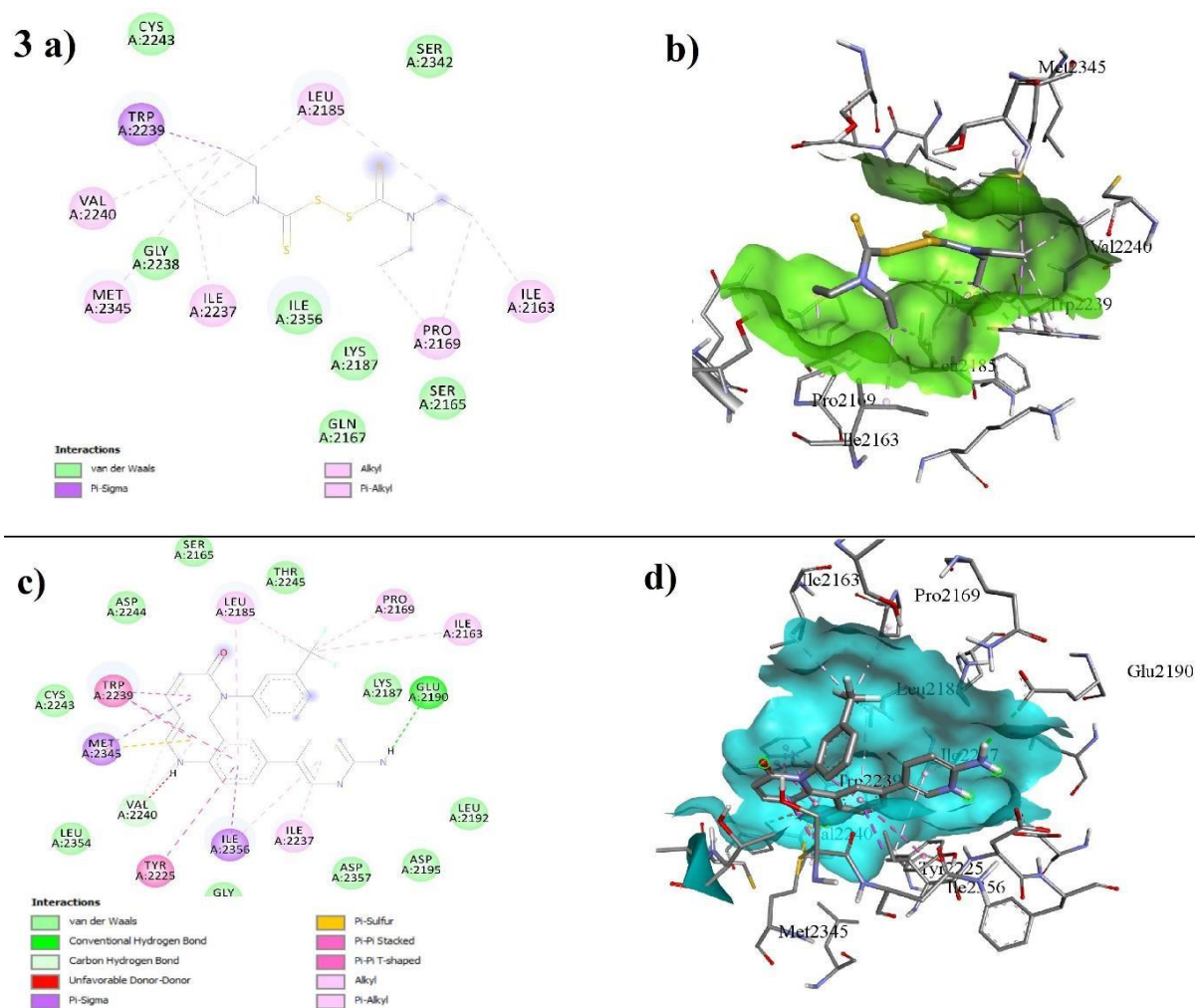




**Supplementary Figure S2:** 2D and 3D representation of Intermolecular interaction of DSF (a and b) and sulfasalazine (c and d) with NFKB. DSF formed one H-Bond with Ile224 and one hydrophobic bond with Lys221, whereas, sulfasalazine formed four H-Bond with Ala243, His245, Gln220, Gln247 and 6 hydrophobic bonds with Val254, Arg255, Leu272, His245 (2), Lys221.



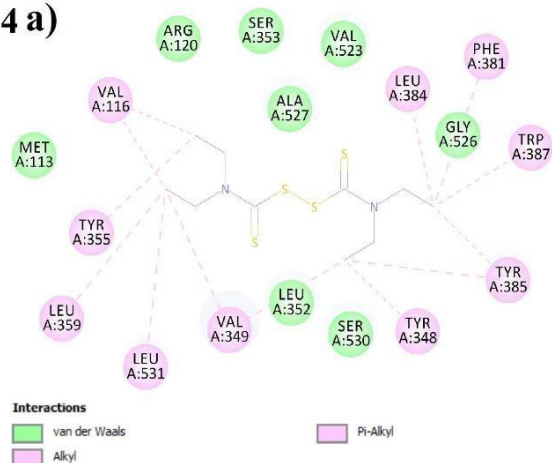
**Supplementary Figure S3:** 2D and 3D representation of Intermolecular interaction of DSF (a and b) and Alpelisib (c and d) with PIK3CA. DSF formed 11 hydrophobic bonds with Pro778, Lys802, Met772, Ile800, Trp780, Phe930, Val850, Ile932, Val851, Glu849, Tyr836, whereas, Alpelisib formed five H-Bond with Val851 (2), Ser854, Gln859 (2) and 11 hydrophobic bonds with His855, Val851 (4), Ile932, Met922, Val850, Tyr836 (2), Met772.



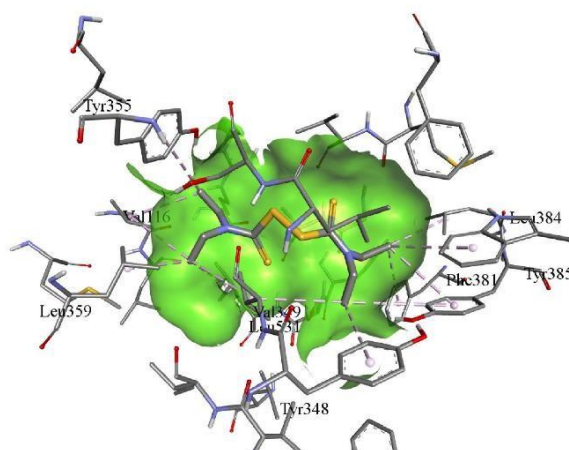
**Supplementary Figure S4:** 2D and 3D representation of Intermolecular interaction of DSF (a and b) and Torin- 2 (c and d) with MTOR. DSF formed 10 hydrophobic bonds with Leu2185 (2), Trp2239 (2), Val2240, Met2345, Ile2237, Pro2169 (2), Ile2163, whereas, Torin-2 formed one H-Bond with Glu2190 and 14 hydrophobic bonds with Ile2237, Ile2356 (2), Tyr2225, Val2240 (2), Met2345 (2), Trp2239 (2), Leu2185 (2), Pro2169, Ile2163.



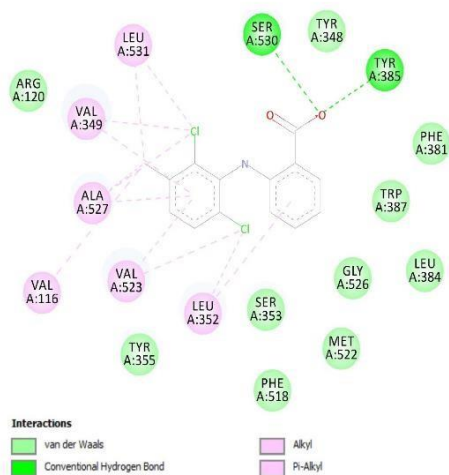
4 a)



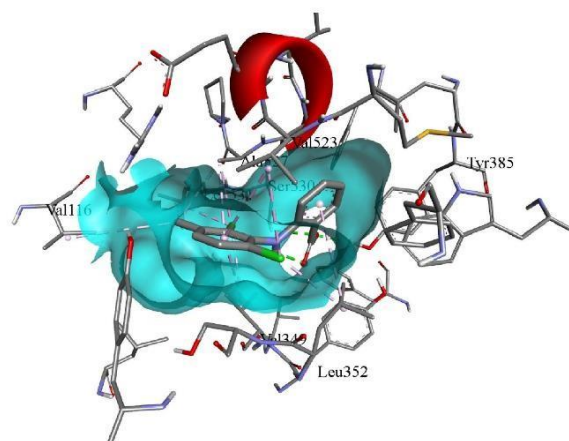
b)



c)

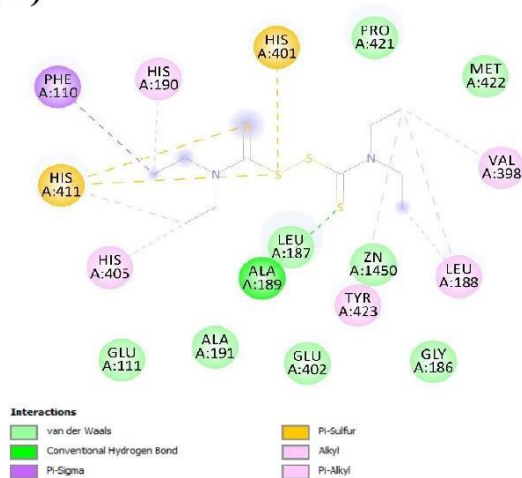


d)

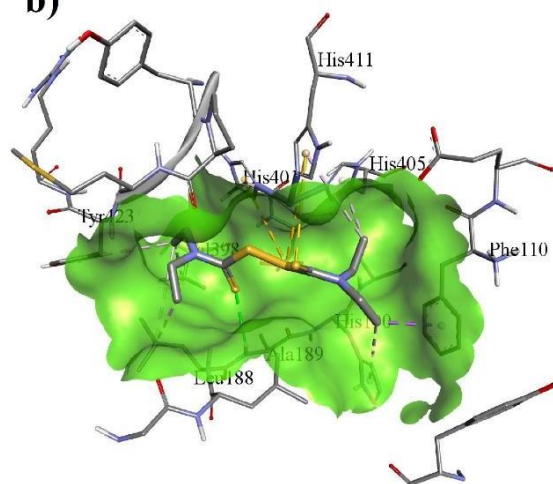


**Supplementary Figure S5:** 2D and 3D representation of Intermolecular interaction of DSF (a and b) and Meclofenamic acid (c and d) with PTGS2. DSF formed 13 hydrophobic bonds with Val116 (2), Tyr355, Leu359, Leu531, Val349 (2), Tyr348, Tyr385 (2), Trp387, Phe381, Leu384, whereas, meclofenamic acid formed 2 H-Bond with Ser530, Tyr385 and 11 hydrophobic bonds with Leu531 (2), Val341 (2), Ala527 (2), Val116, Val523 (2), Leu352 (2).

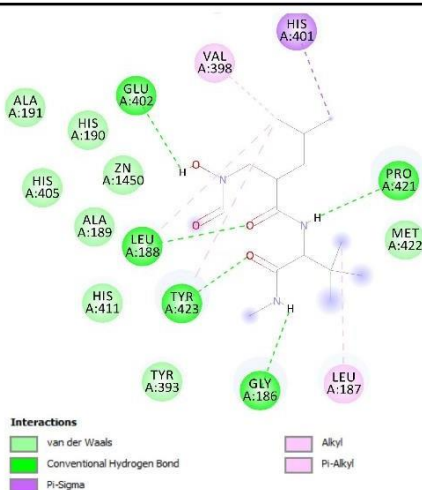
5 a)



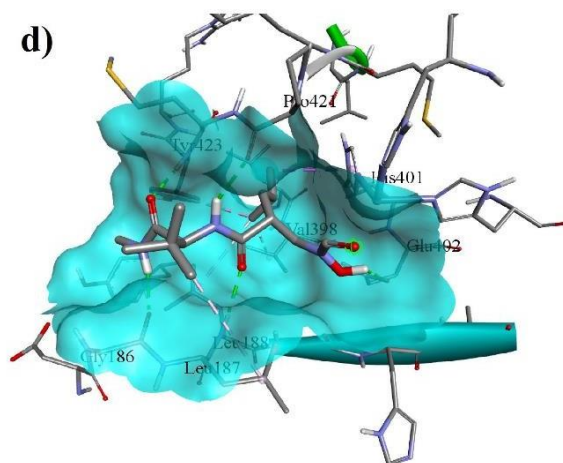
b)



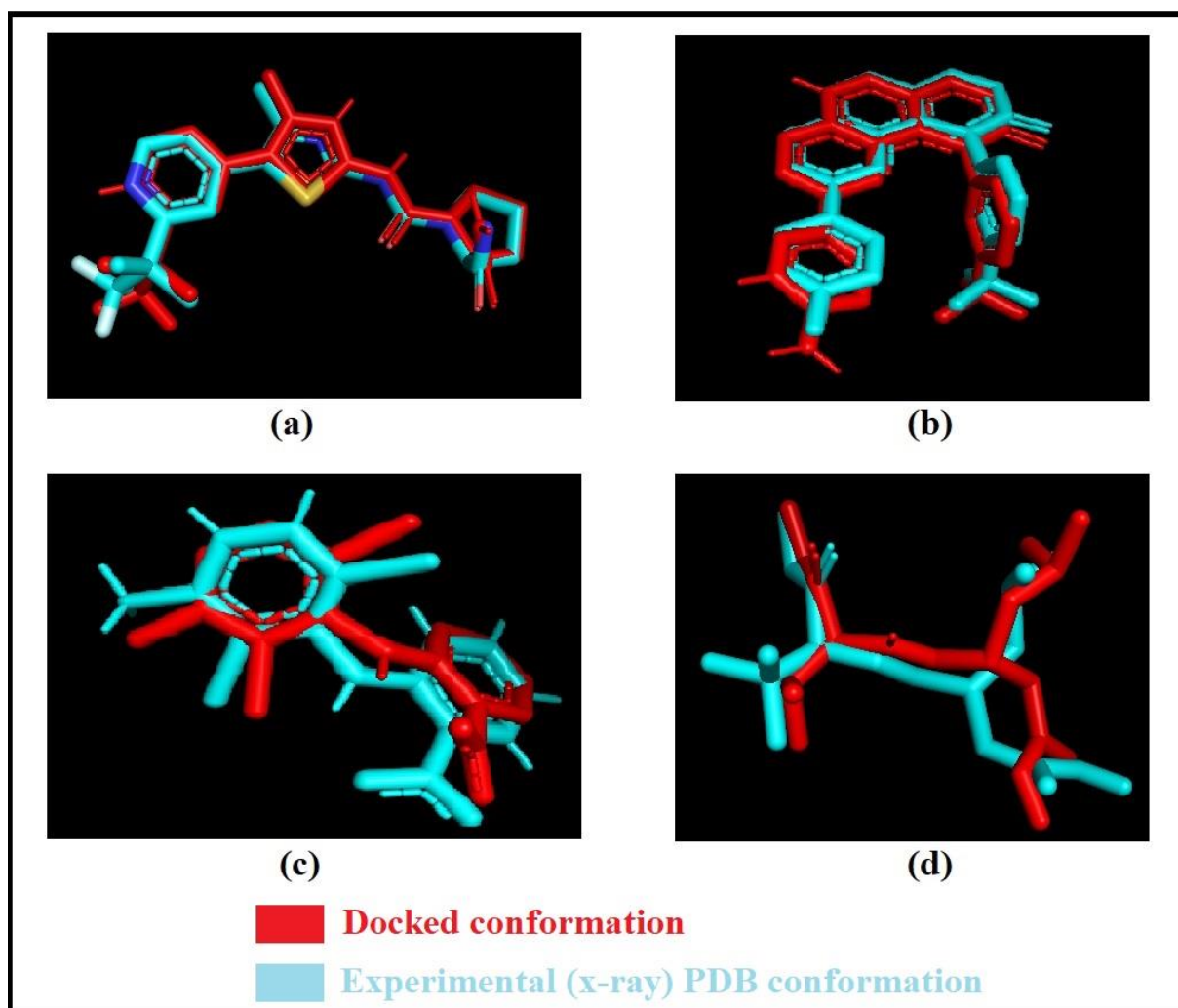
c)



d)



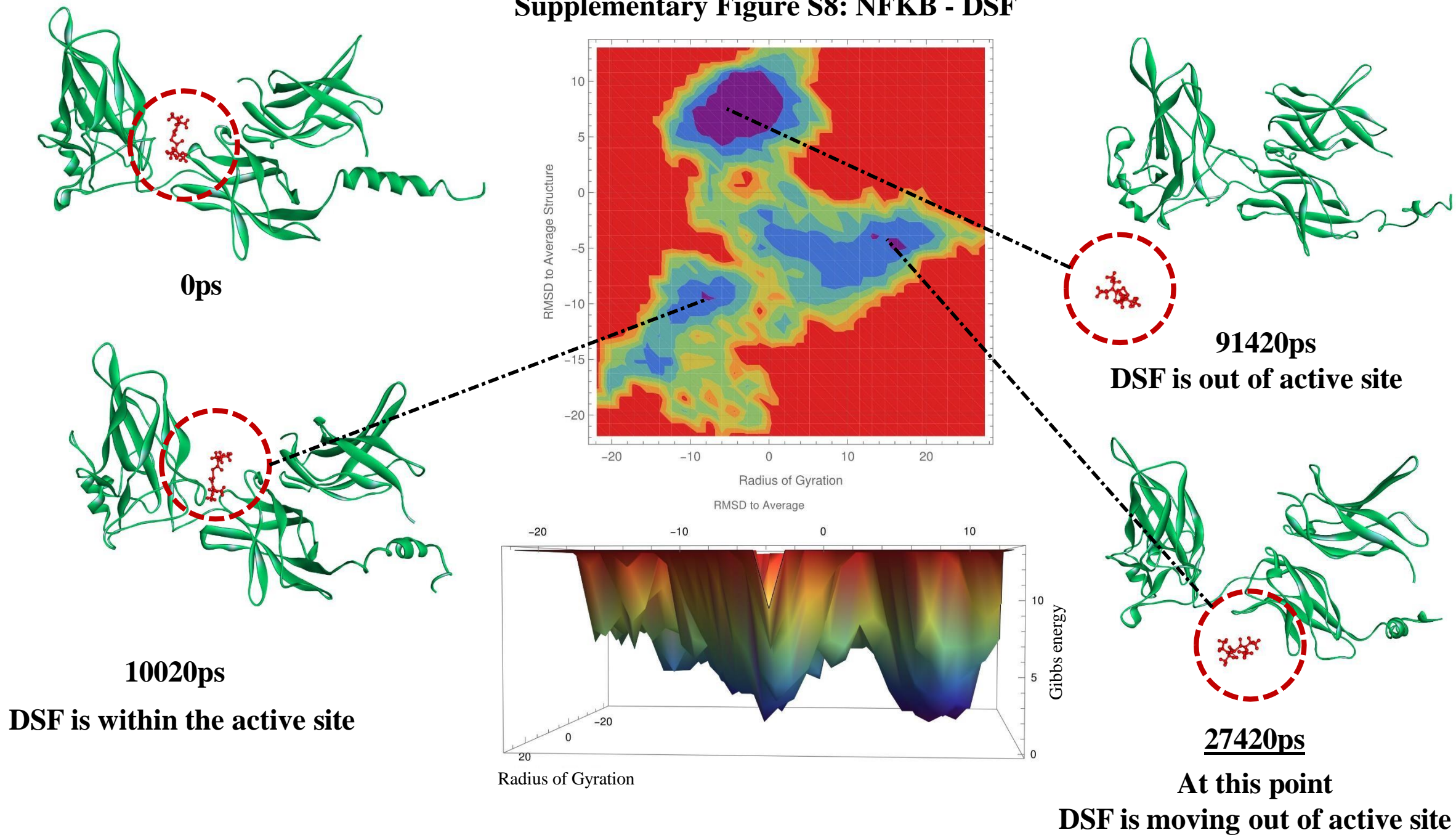
**Supplementary Figure S6:** 2D and 3D representation of Intermolecular interaction of DSF (a and b) and NFH (c and d) with MMP9. DSF formed 1 H-bond with Ala189 and 11 hydrophobic bonds with His411 (3), His405, Tyr423, Leu188 (2), Val398, His401, His190, Phe110, whereas, NFH formed 5 H-Bond with Glu402, Leu188, Tyr423, Gly186, Pro421 and 5 hydrophobic bonds with Leu188, Tyr423, Leu187, Val398, His401.



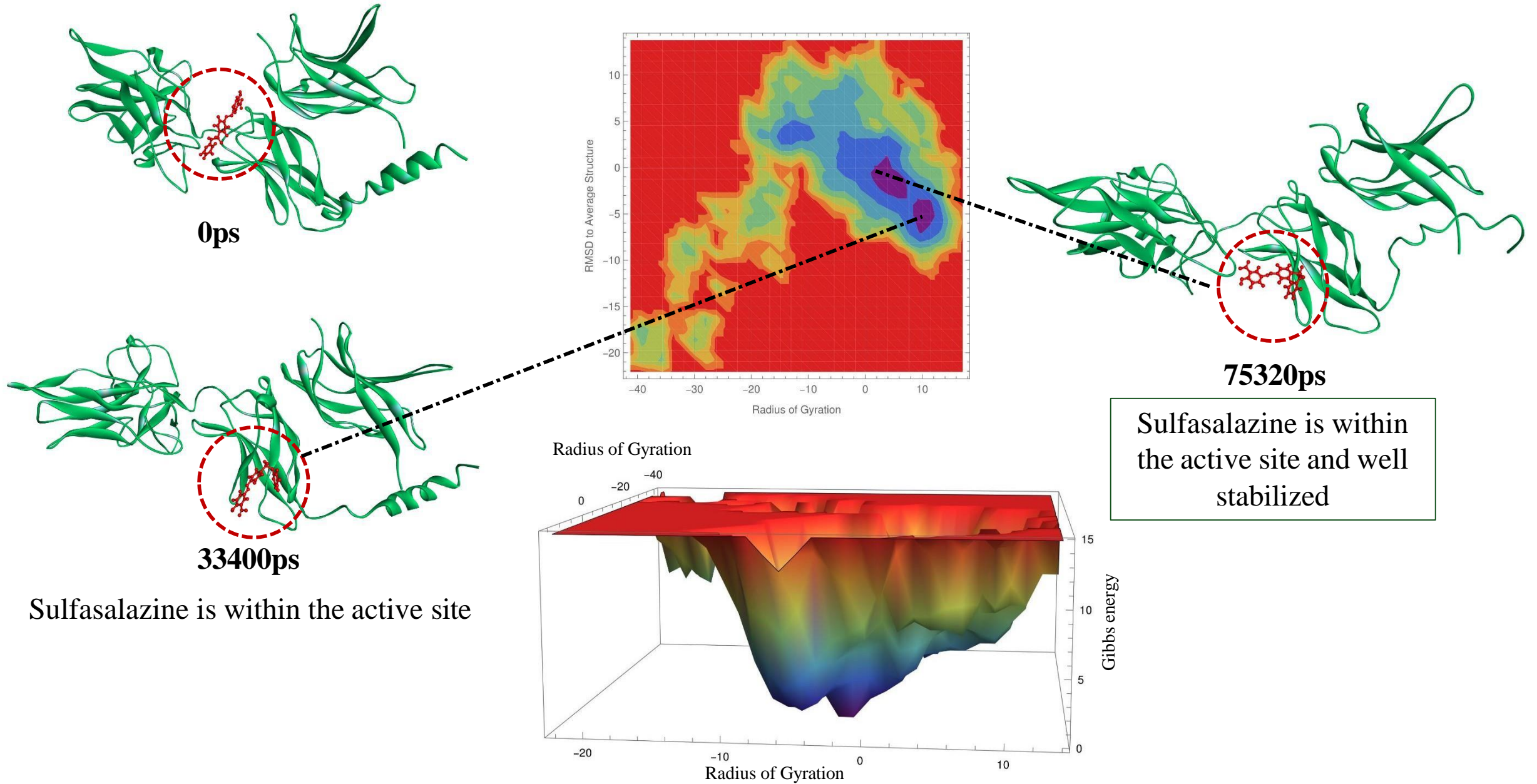
**Supplementary Figure S7:** Overlay of docked conformations (red) and experimental (X-ray) PDB conformations (cyan) for (a) Alpelisib (PIK3R1/PIK3CA), (b) Torin-2 (mTOR), (c) Meclofenamic acid (PTGS2), and (d) NFH (MMP9). The RMSD values between the conformations were found to be 0.498, 0.657, 0.625, and 1.336 Å, respectively, showing the accuracy of the docking protocol in predicting binding poses with close alignment to experimental structures.



**Supplementary Figure S8: NFkB - DSF**



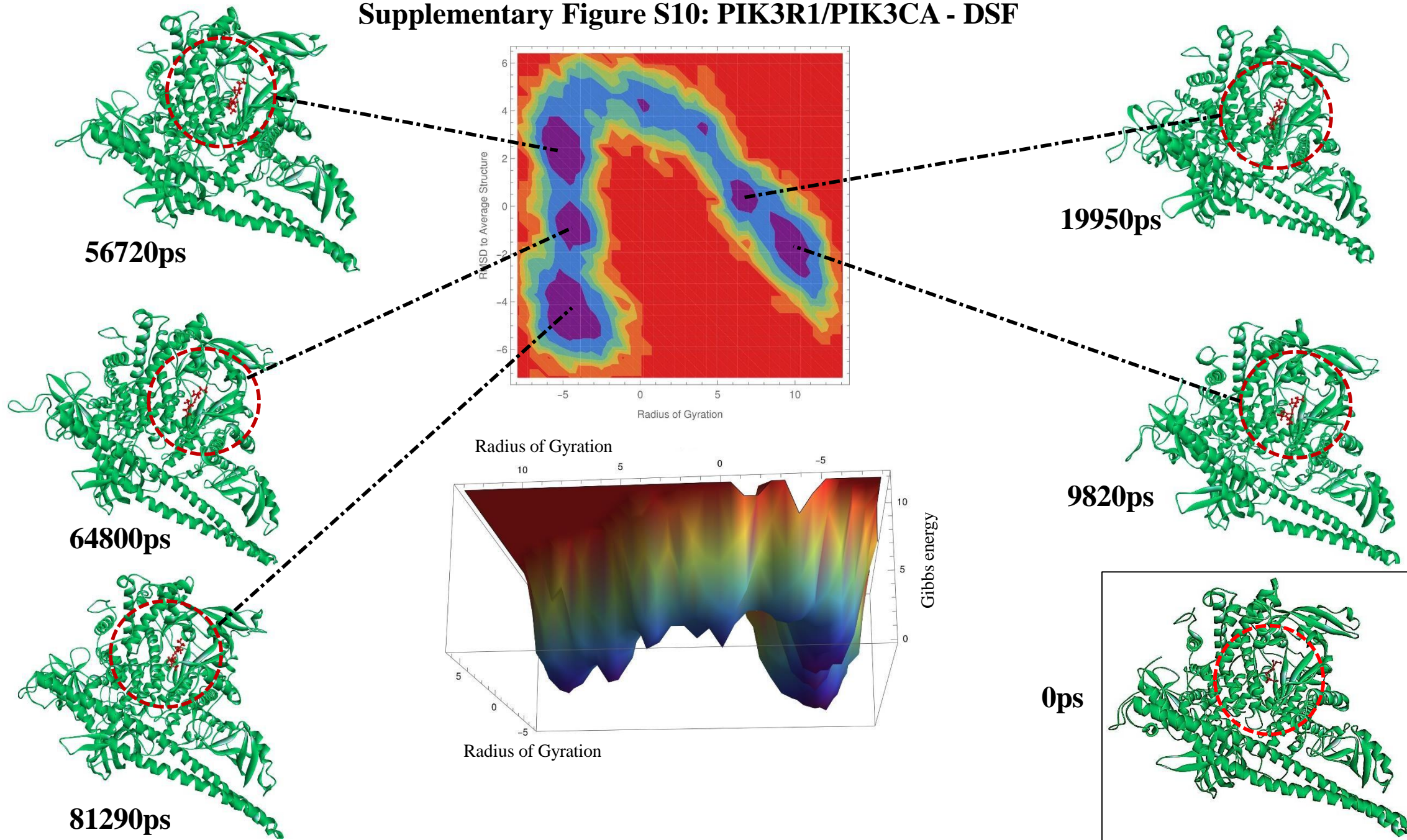
## Supplementary Figure S9: NFKB - Sulfasalazine





**Supplementary Figure S10: PIK3R1/PIK3CA - DSF**

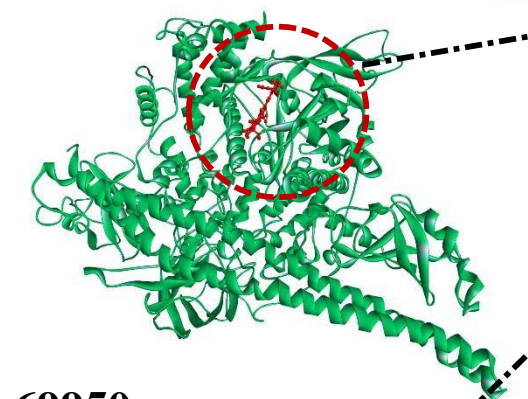
**PIK3 and DSF system stabilized after 50ns**



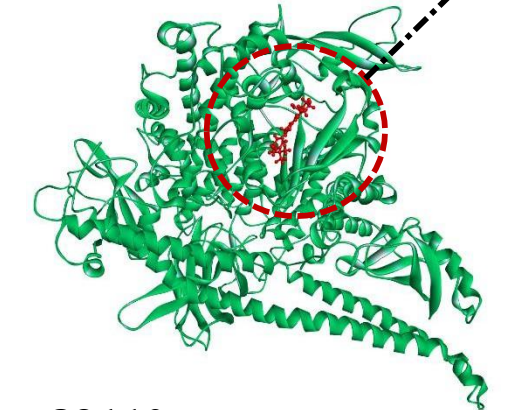


Supplementary Figure S11: PIK3R1/PIK3CA - Alpelisib

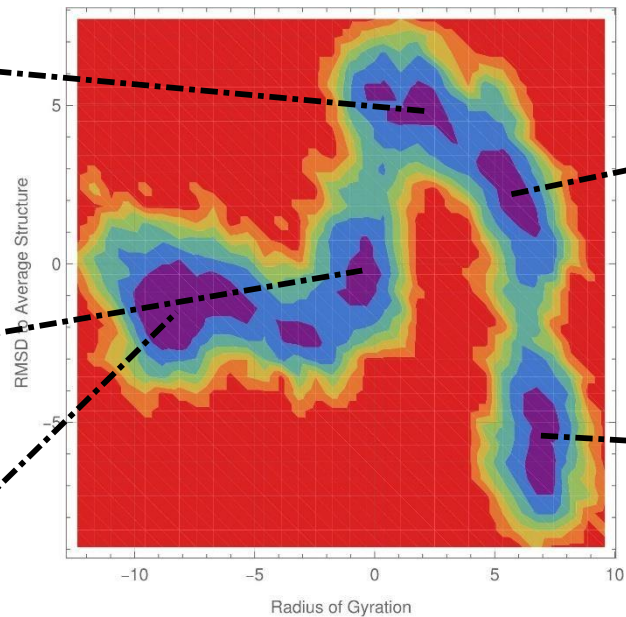
49810ps



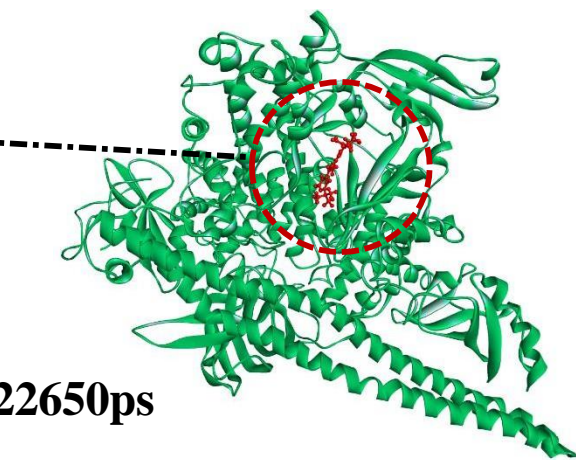
69950ps



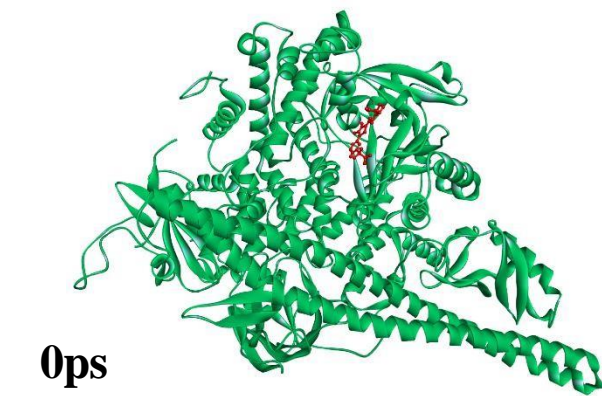
89110ps



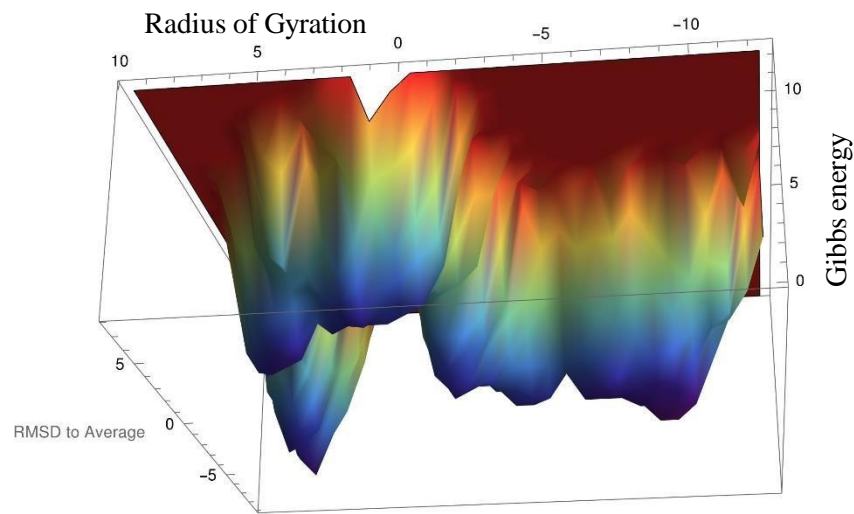
40470ps



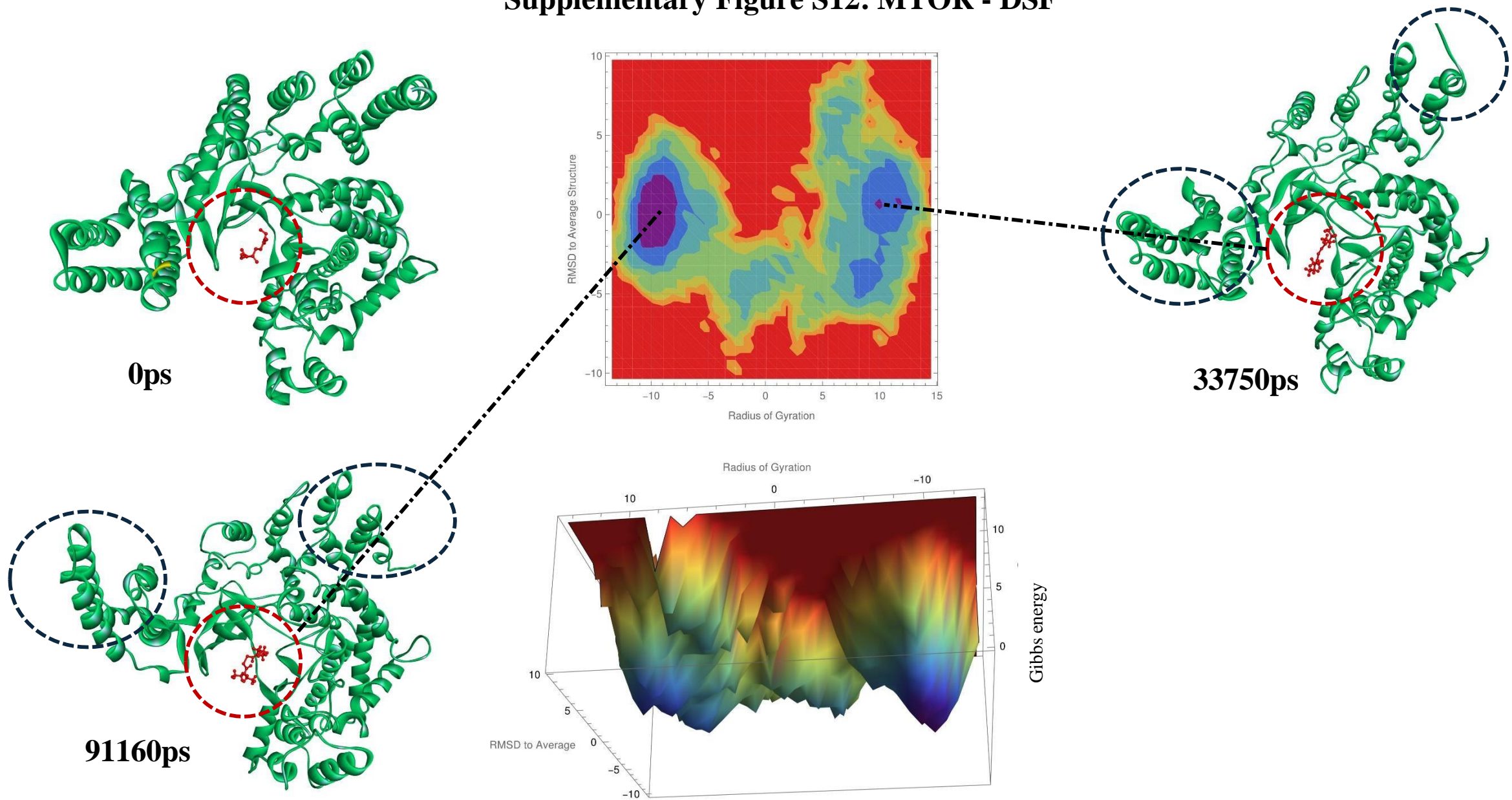
22650ps



0ps

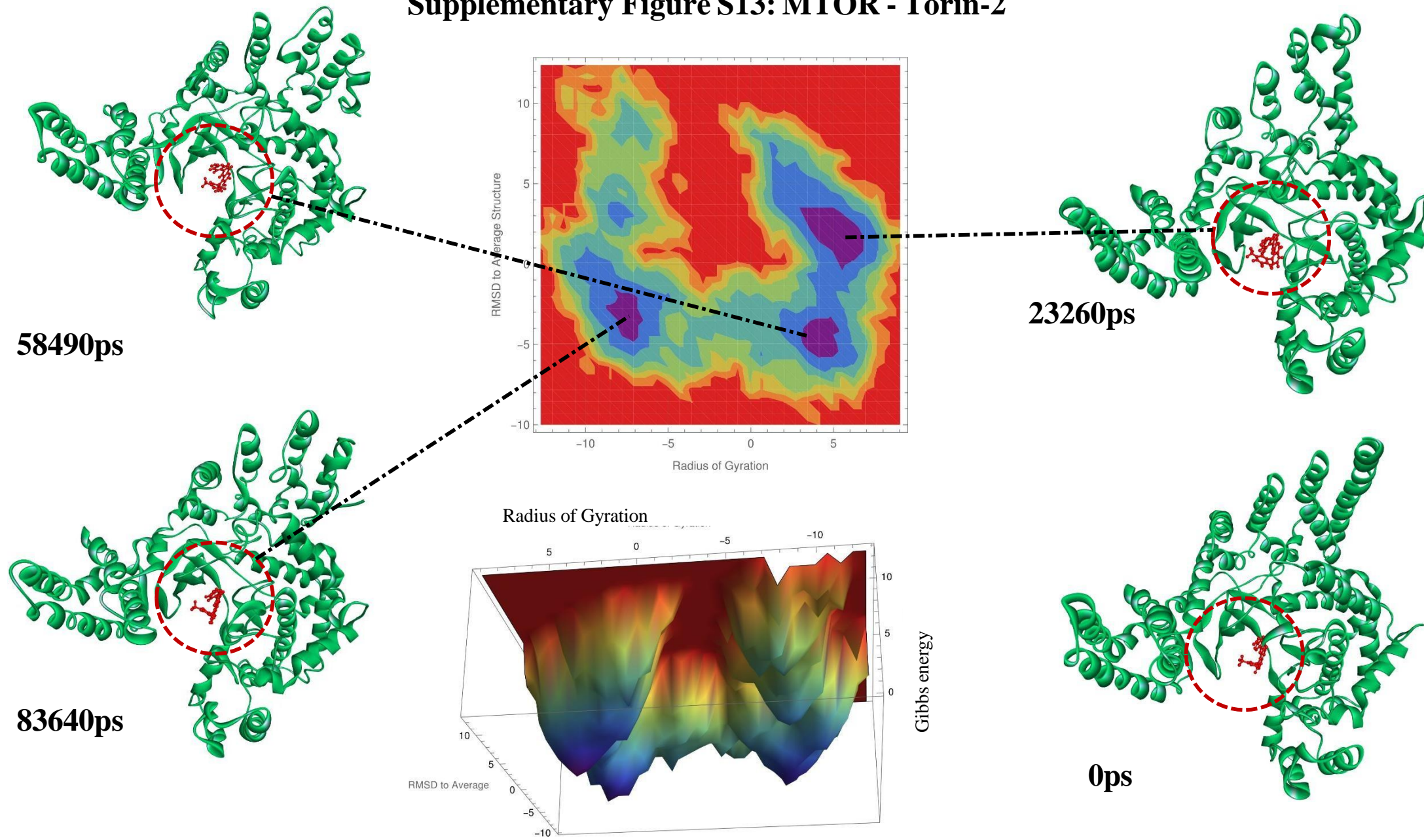


**Supplementary Figure S12: MTOR - DSF**

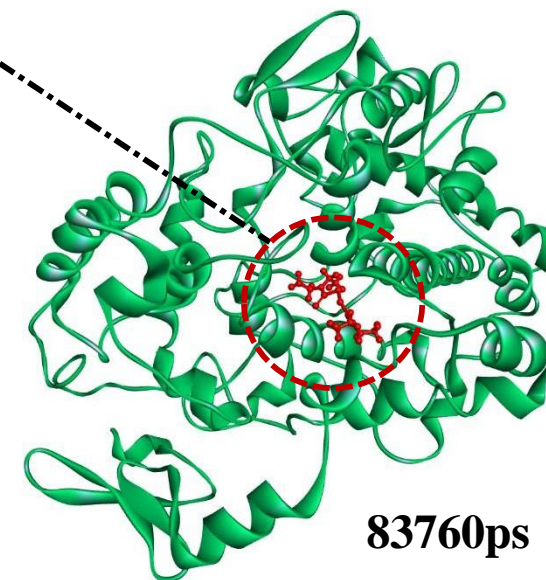
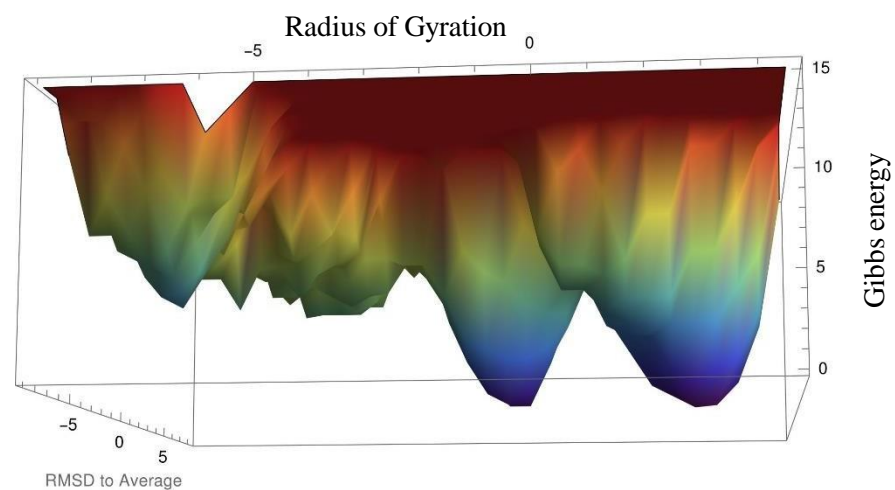
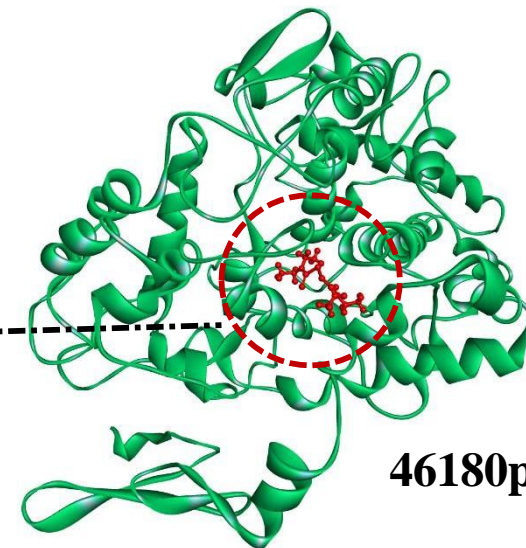
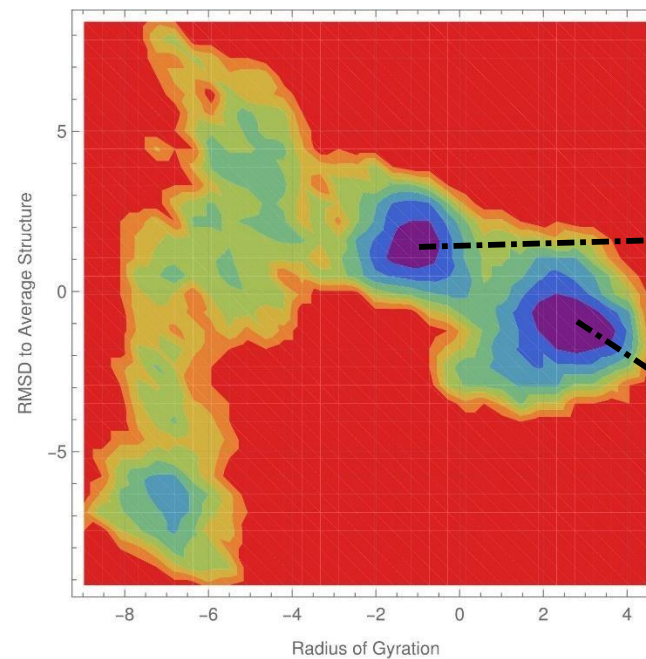
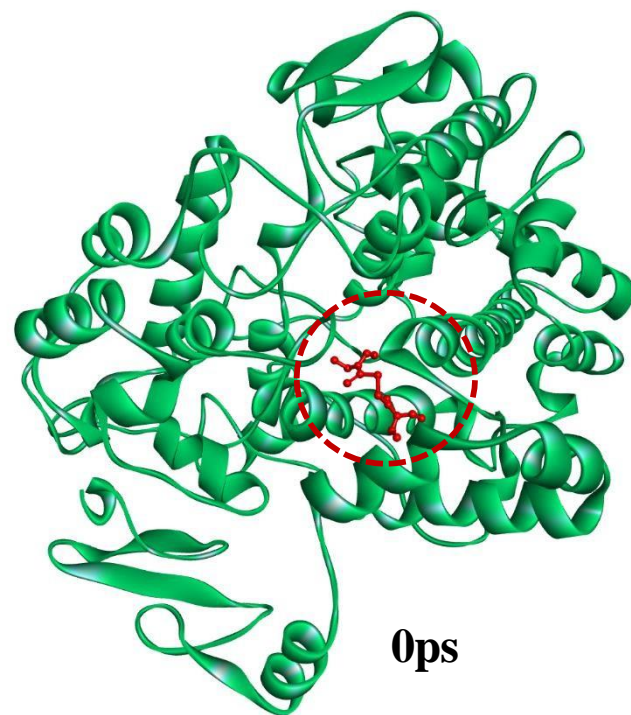




**Supplementary Figure S13: MTOR - Torin-2**

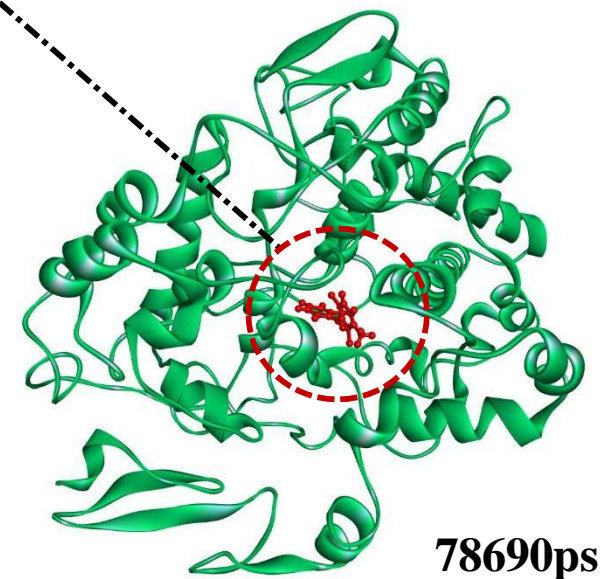
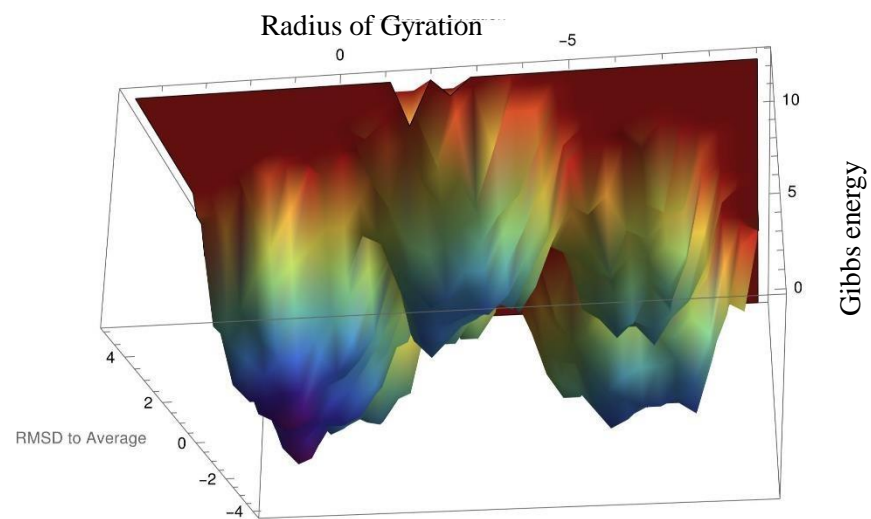
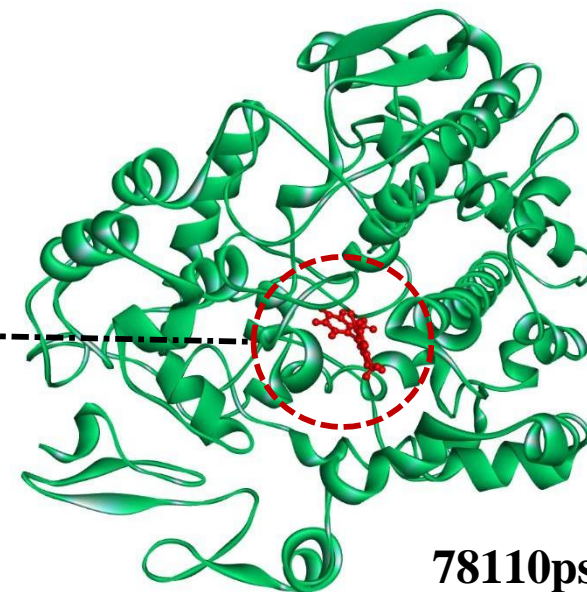
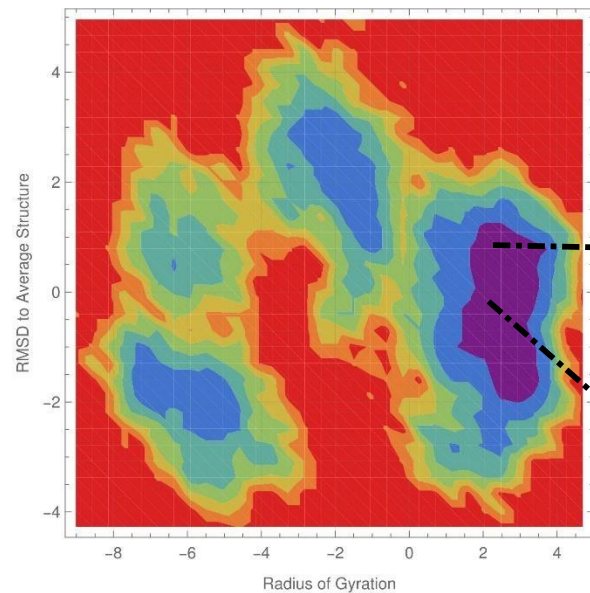
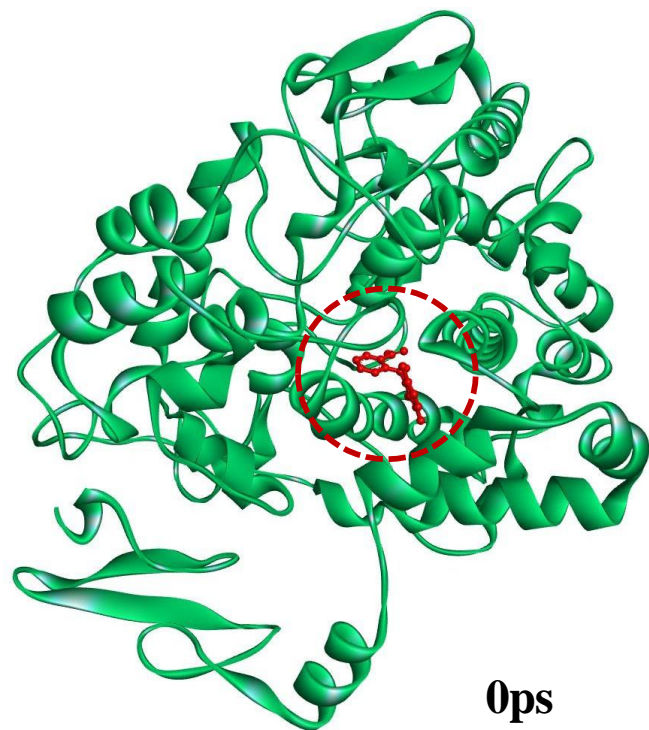


**Supplementary Figure S14: PTGS2 - DSF**

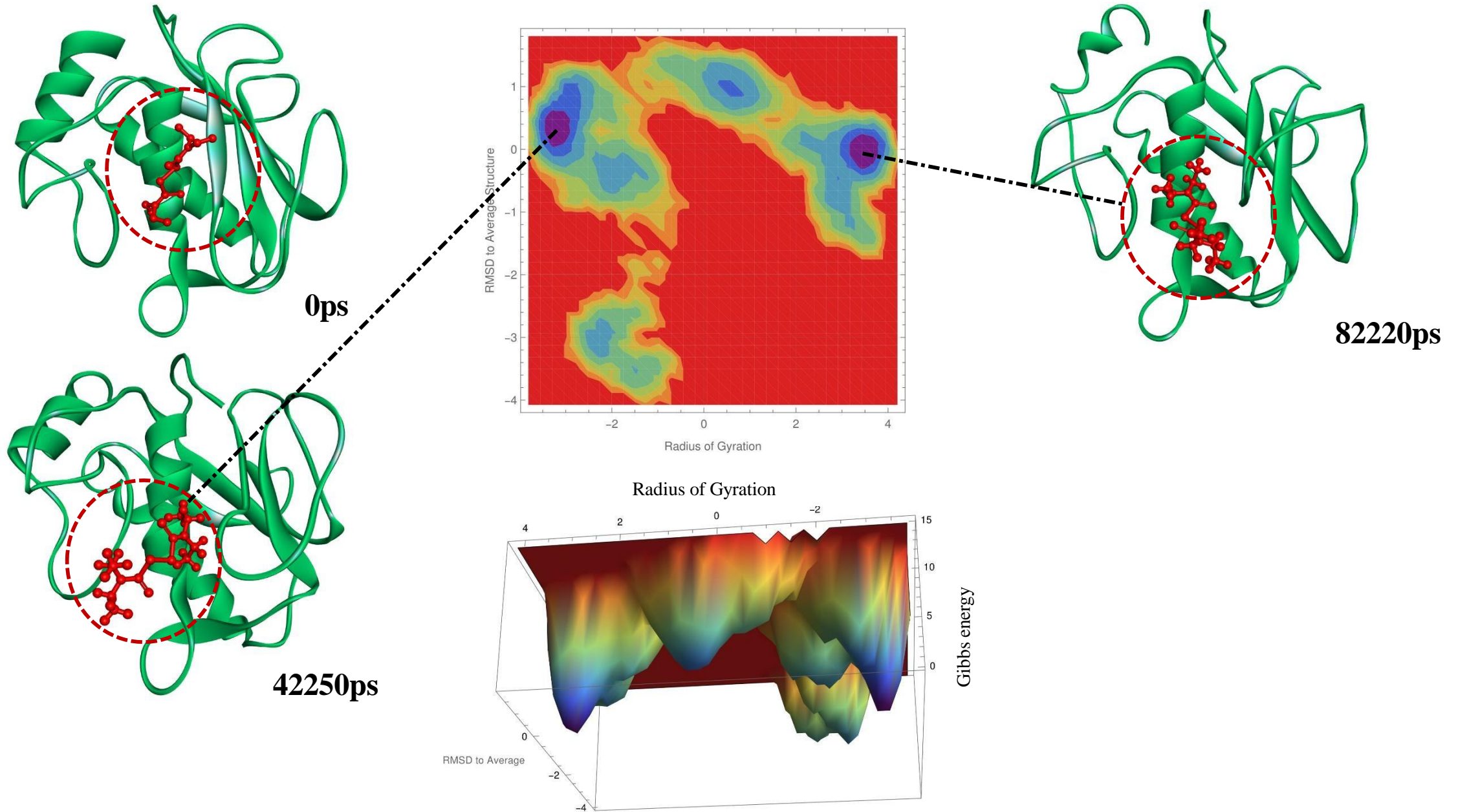




**Supplementary Figure S15: PTGS2 – Meclofenamic acid**



**Supplementary Figure S16: MMP9 – DSF**





**Supplementary Figure S17: MMP9 – NFH**

