

Supporting Information

A Perspective on Medicinal Chemistry Approaches for Targeting Pyruvate Kinase M2

Sahil Arora¹, Gaurav Joshi,^{1,2} Anuhar Chaturvedi,³ Michael Heuser,³ Santoshkumar Patil,⁴ Raj Kumar^{1*}

¹Laboratory for Drug Design and Synthesis, Department of Pharmaceutical Sciences and Natural Products, Central University of Punjab, Bathinda, 151401 India;

²School of Pharmacy, Graphic Era Hill University, Dehradun, Uttarakhand, 248171 India

³Department of Hematology, Hemostasis, Oncology, and Stem Cell Transplantation, Hannover Medical School, Hannover, 30625, Germany

⁴Discovery Services, Syngene International Ltd., Biocon Park, SEZ, Bommasandra Industrial Area-Phase-IV, Bommasandra-Jigani Link Road, Bengaluru, Karnataka 560099, India

*Corresponding author (R. Kumar; Email: raj.khunger@gmail.com; raj.khunger@cup.edu.in)

Table of content

1. Scheme S1. Sequence alignment.....	S2
2. Table S1. Homology between PK isoforms.....	S3
3. Scheme S2. Phylogenetic analysis.....	S4
4. Figure S1 (1-75). Binding poses of PKM2 inhibitor/activator within the drug binding pocket of PKM2.....	S5 onwards

Supporting Information

4IP7_1 Chains	-----MEGPAGY-LRRADVAQLTQELGTAFFQQQLPAAMADTFLEHLCLLDIDSEPV	37
2VGB_1 Chains	-----LTQELGTAFFQQQLPAAMADTFLEHLCLLDIDSEPV	37
3SRF_1 Chains	MGSSHHHHHHSSGLVPRGSHMSKPHSEAGTAFIQTQQLHAAMADTFLEHMCRLDIDSPP	60
3BJF_1 Chains	-----QTQQLHAAMADTFLEHMCRLDIDSPP	27
	* *** *****:***:*****:***:*****:***:*****:***:*****:	
4IP7_1 Chains	AARSTSIIATIGPASRSVERLKE ^M KAGMNIARLNFSHGSHEYHAESIANVREAVESFAG	112
2VGB_1 Chains	AARSTSIIATIGPASRSVERLKE ^M KAGMNIARLNFSHGSHEYHAESIANVREAVESFAG	97
3SRF_1 Chains	TARNTGIIC ^T IGPASRSVETLKEMIKSGMNVARLNFSHGTHEYHAETIKNVRTATESFAS	120
3BJF_1 Chains	TARNTGIIC ^T IGPASRSVETLKEMIKSGMNVARLNFSHGTHEYHAETIKNVRTATESFAS	87
	:***:***:*****:***:*****:***:*****:***:*****:***:*****:	
4IP7_1 Chains	SPLSYRPVAIALDTKGPEIRTGILQGGPESEVELVKGSQVLVTVDPAFRTRGNANTVW	172
2VGB_1 Chains	SPLSYRPVAIALDTKGPEIRTGILQGGPESEVELVKGSQVLVTVDPAFRTRGNANTVW	157
3SRF_1 Chains	DPILYRPVAVALDTKGPEIRTGLIKSGTAEV ^E VELKKGATLKITLDNAYMEKCDENLWLD	180
3BJF_1 Chains	DPILYRPVAVALDTKGPEIRTGLIKSGTAEV ^E VELKKGATLKITLDNAYMEKCDENLWLD	147
	:***:*****:*****:***:*****:***:*****:***:*****:***:*****:	
4IP7_1 Chains	YPNIVRWPVGRIYIDDGLISLVWQKIGPEGLVQVENGGVLGSRKGVNLPGAQVDLPG	232
2VGB_1 Chains	YPNIVRWPVGRIYIDDGLISLVWQKIGPEGLVQVENGGVLGSRKGVNLPGAQVDLPG	217
3SRF_1 Chains	YKNICKVVEVGSKIYVDDGLISLQVKQKGADFLVTEVENGGSLGSKKGVNLPGAQVDLPA	240
3BJF_1 Chains	YKNICKVVEVGSKIYVDDGLISLQVKQKGADFLVTEVENGGSLGSKKGVNLPGAQVDLPA	207
	:***:***:***:*****:***:***:*****:***:*****:***:*****:*****:	
4IP7_1 Chains	LSEQDVRDLRFGVEHGVDIVFASFVRKASDVAAVRAALGPEGHGIKIISKIENHEGVKR	292
2VGB_1 Chains	LSEQDVRDLRFGVEHGVDIVFASFVRKASDVAAVRAALGPEGHGIKIISKIENHEGVKR	277
3SRF_1 Chains	VSEKDIQDLKFGEVQDVMVFASFIRKASDVHEVRKVLGEKGKNIKISKIENHEGVRRF	300
3BJF_1 Chains	VSEKDIQDLKFGEVQDVMVFASFIRKASDVHEVRKVLGEKGKNIKISKIENHEGVRRF	267
	:***:***:***:***:*****:***:***:*****:***:*****:***:*****:	
4IP7_1 Chains	DEILEVSDGIMVAR ^D LGIEIPA ^E KVFLAQKNNIIGRCNLAGKPVVCATQML ^E SMITKPR	352
2VGB_1 Chains	DEILEVSDGIMVAR ^D LGIEIPA ^E KVFLAQKNNIIGRCNLAGKPVVCATQML ^E SMITKPR	337
3SRF_1 Chains	DEILEASDGIMVAR ^D LGIEIPA ^E KVFLAQKNNIIGRCN ^R AGKPVVCATQML ^E SMIKKPR	360
3BJF_1 Chains	DEILEASDGIMVAR ^D LGIEIPA ^E KVFLAQKNNIIGRCN ^R AGKPVVCATQML ^E SMIKKPR	327
	:***:*****:*****:*****:*****:*****:*****:*****:*****:*****:	
4IP7_1 Chains	TRAETSDVANAVLDGADCIMLSGETAKGNFPVEAVKMHQHAIAREAEAAVYHRQLFEELRR	412
2VGB_1 Chains	TRAETSDVANAVLDGADCIMLSGETAKGNFPVEAVKMHQHAIAREAEAAVYHRQLFEELRR	397
3SRF_1 Chains	TRAEGSDVANAVLDGADCIMLSGETAKGDYPLEAVRMQH ^L IAREAEAA ^F HRLKLFEE ^L RR	420
3BJF_1 Chains	TRAEGSDVANAVLDGADCIMLSGETAKGDYPLEAVRMQ ^N L ^I AREAEAA ^I YHQLFEELRR	387
	:***:*****:*****:*****:*****:*****:*****:*****:*****:*****:	
4IP7_1 Chains	AAPL ^S RDPTEVTAIGAVEAAFKCCAA ^I IVLTTTGRSAQLLSRYR ^P RAAVIAVTRSAQAA	472
2VGB_1 Chains	AAPL ^S RDPTEVTAIGAVEAAFKCCAA ^I IVLTTTGRSAQLLSRYR ^P RAAVIAVTRSAQAA	457
3SRF_1 Chains	ASSHSTDLM ^E AMAMGS ^V EASYKCLAA ^L IVL ^T ESGRSAHQVARYR ^P APIIAVTRNPQTA	480
3BJF_1 Chains	LAPITS ^D PTEATAVGAVEASF ^K CCSGAI ^I VLTKSGR ^A HQVARYR ^P APIIAVTRNPQTA	447
	: : * . ***:***:***:***:***:***:*****:*****:*****:*****:***:	
4IP7_1 Chains	RQVHLCRGV ^F PLL ^Y REPPEAIWADDVDRRVQFGIESGKL ^R GFLRVGDLVIVWTGNRP ^G SG	532
2VGB_1 Chains	RQVHLCRGV ^F PLL ^Y REPPEAIWADDVDRRVQFGIESGKL ^R GFLRVGDLVIVWTGNRP ^G SG	517
3SRF_1 Chains	RQAHLYRGIFPV ^L CKD ^P VQEA ^W AED ^V DLRVNFAMNV ^G KARGFFKKGDVV ^V LTGNRP ^G SG	540
3BJF_1 Chains	RQAHLYRGIFPV ^L CKD ^P VQEA ^W AED ^V DLRVNFAMNV ^G KARGFFKKGDVV ^V LTGNRP ^G SG	507
	:***:***:***:***:***:***:***:***:***:***:***:*****:*****:	
4IP7_1 Chains	YTNIMRVL ^S IS 543	
2VGB_1 Chains	YTNIMRVL ^S IS 528	
3SRF_1 Chains	FTNTMRVVPVP 551	
3BJF_1 Chains	FTNTMRVVPVP 518	
	:***:***:***:	

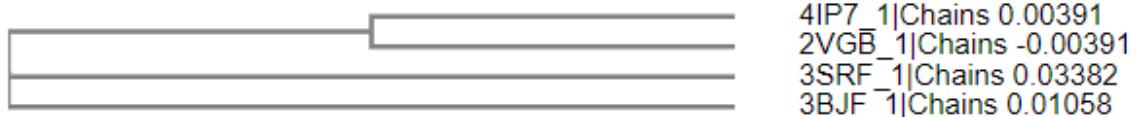
Scheme S1. Amino acids sequence alignment of PK isoforms, namely PKL (PDB ID: 41P7); PKR (PDB ID: 2VGB); PKM1 (PDB ID: 3SRF) and PKM2 (PDB ID: 3BJF)

Supporting Information

Table S1. Percentage similarity (homology) of various PK isoforms namely PKL (PDB ID: 4IP7); PKR (PDB ID: 2VGB); PKM1 (PDB ID: 3SRF) in comparison, with PKM2 (PDB ID: 3BJF)

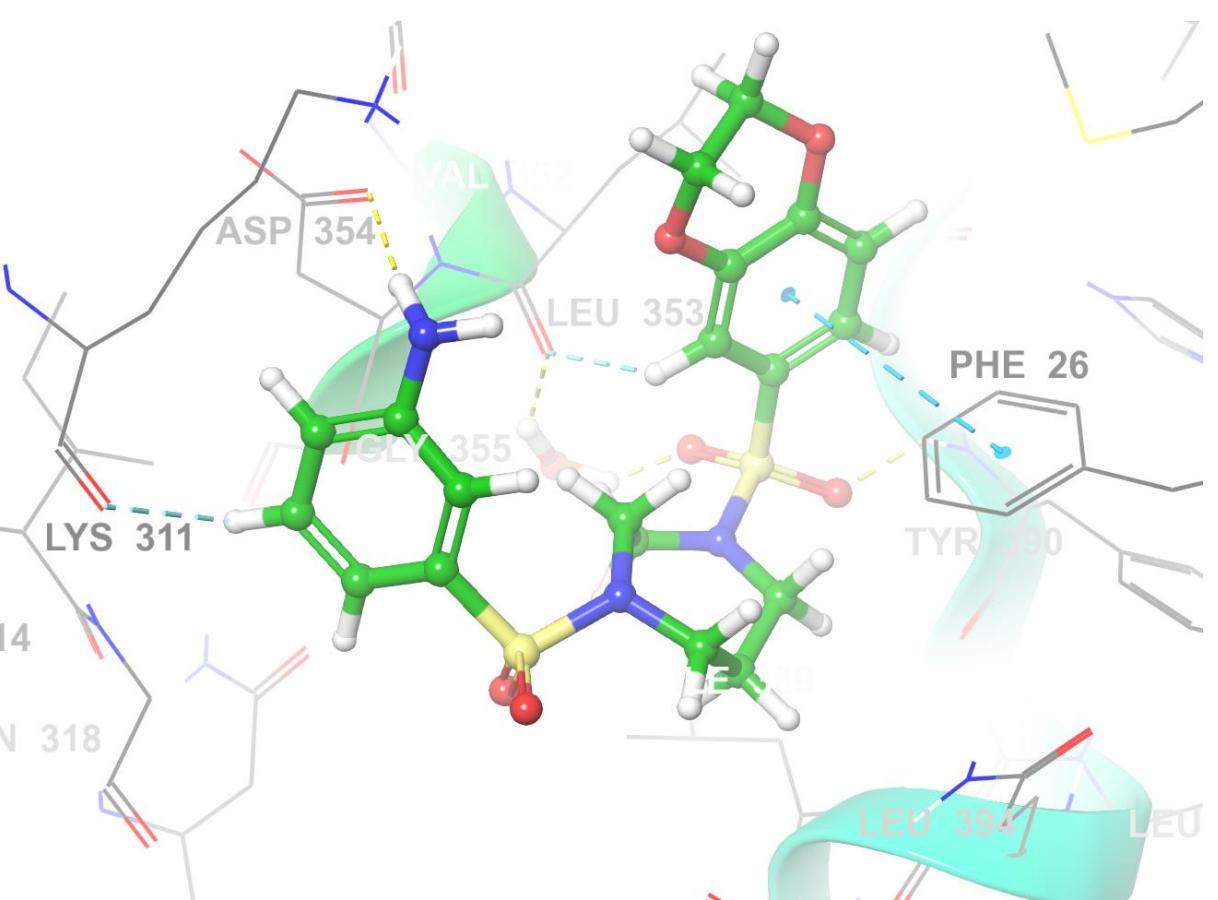
Sr No	Protein Code	% Similarity with PKM2 (PDB ID: 3BJF)
1	PDB ID:3SRF (PKM1)	95.56%
2	PDB ID:2VGB (PKR)	71 – 72%
3	PDB ID: 4IP7 (PKL)	71 – 72%

Supporting Information

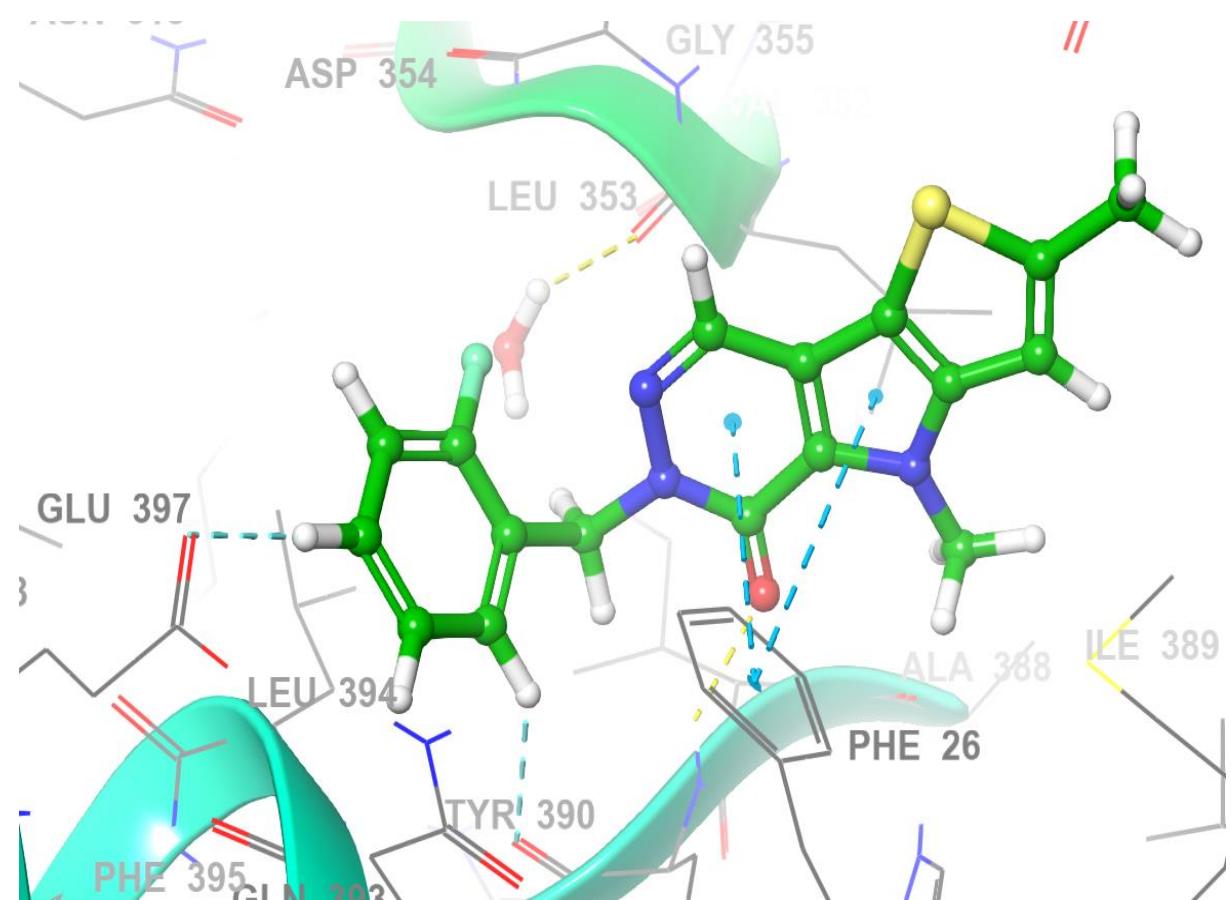


Scheme S2. Phylogenetic tree of the PK isoforms deduced from their amino acids' sequences

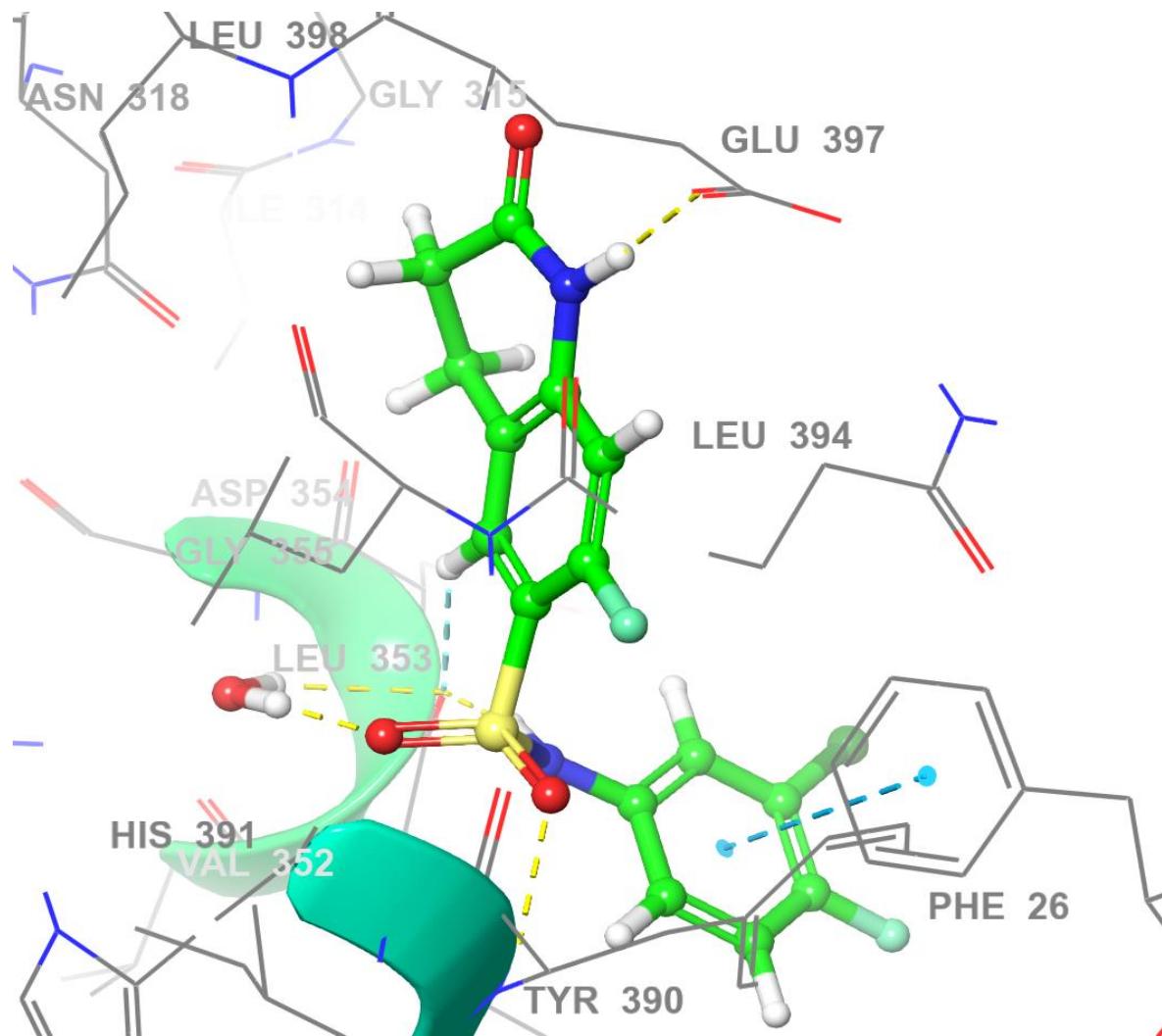
Figure S1 (1-75). Binding poses of PKM2 inhibitors/activators within the drug-binding pocket of PKM2



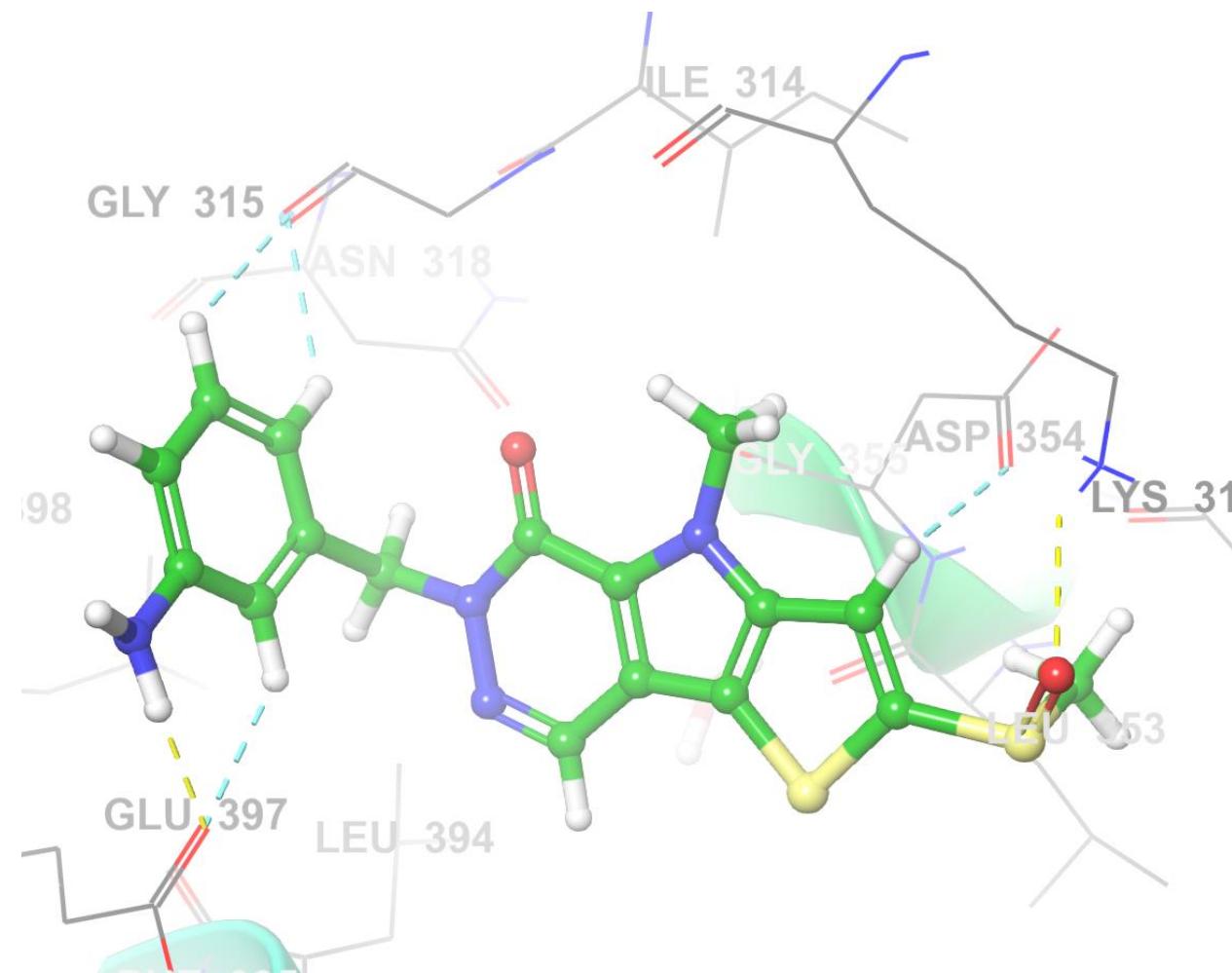
1



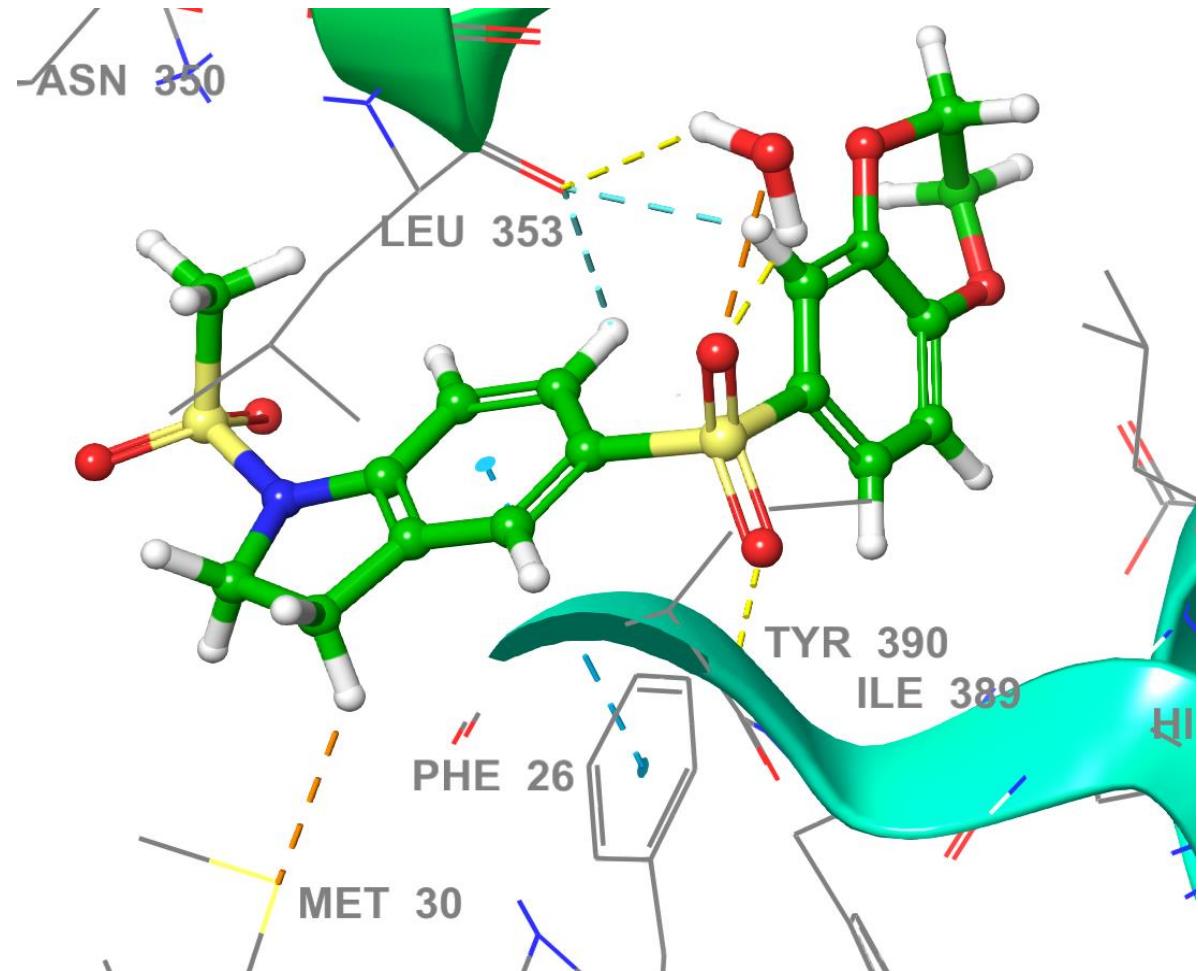
2



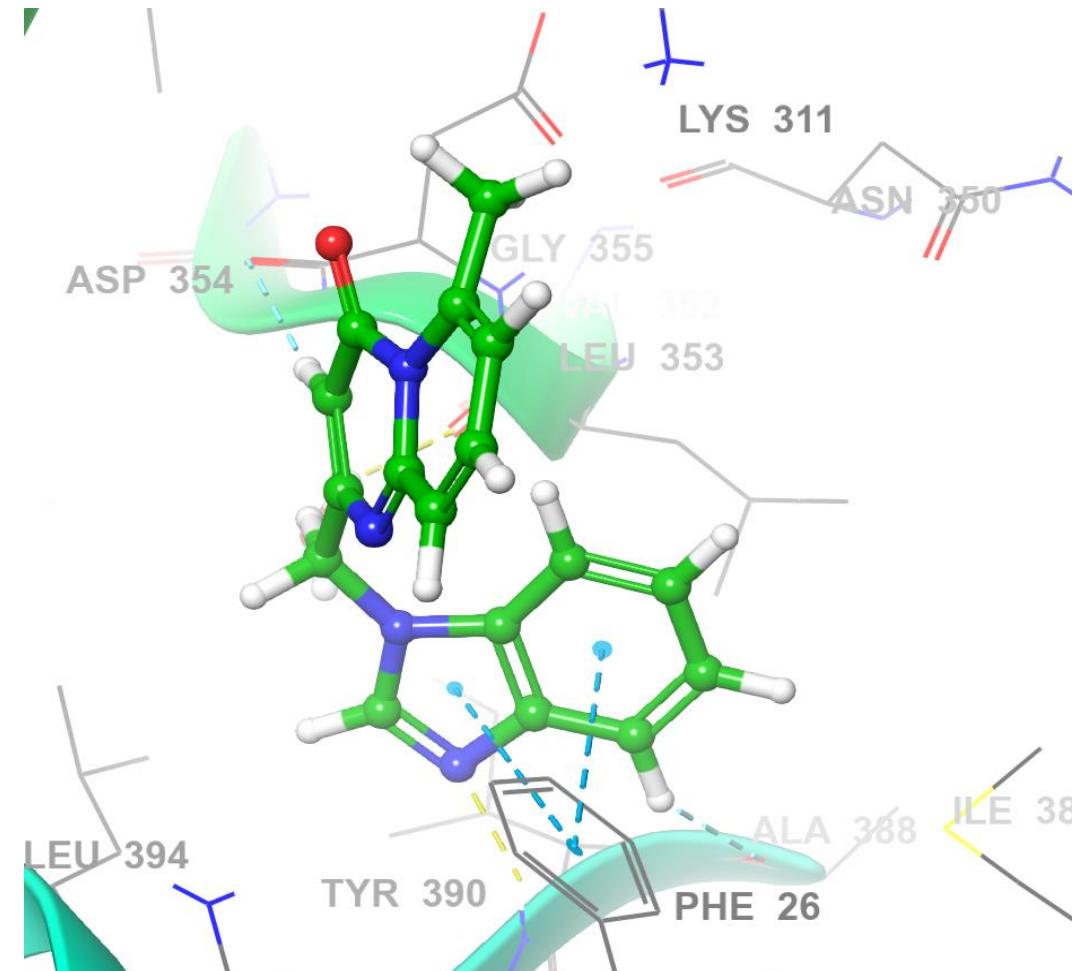
3



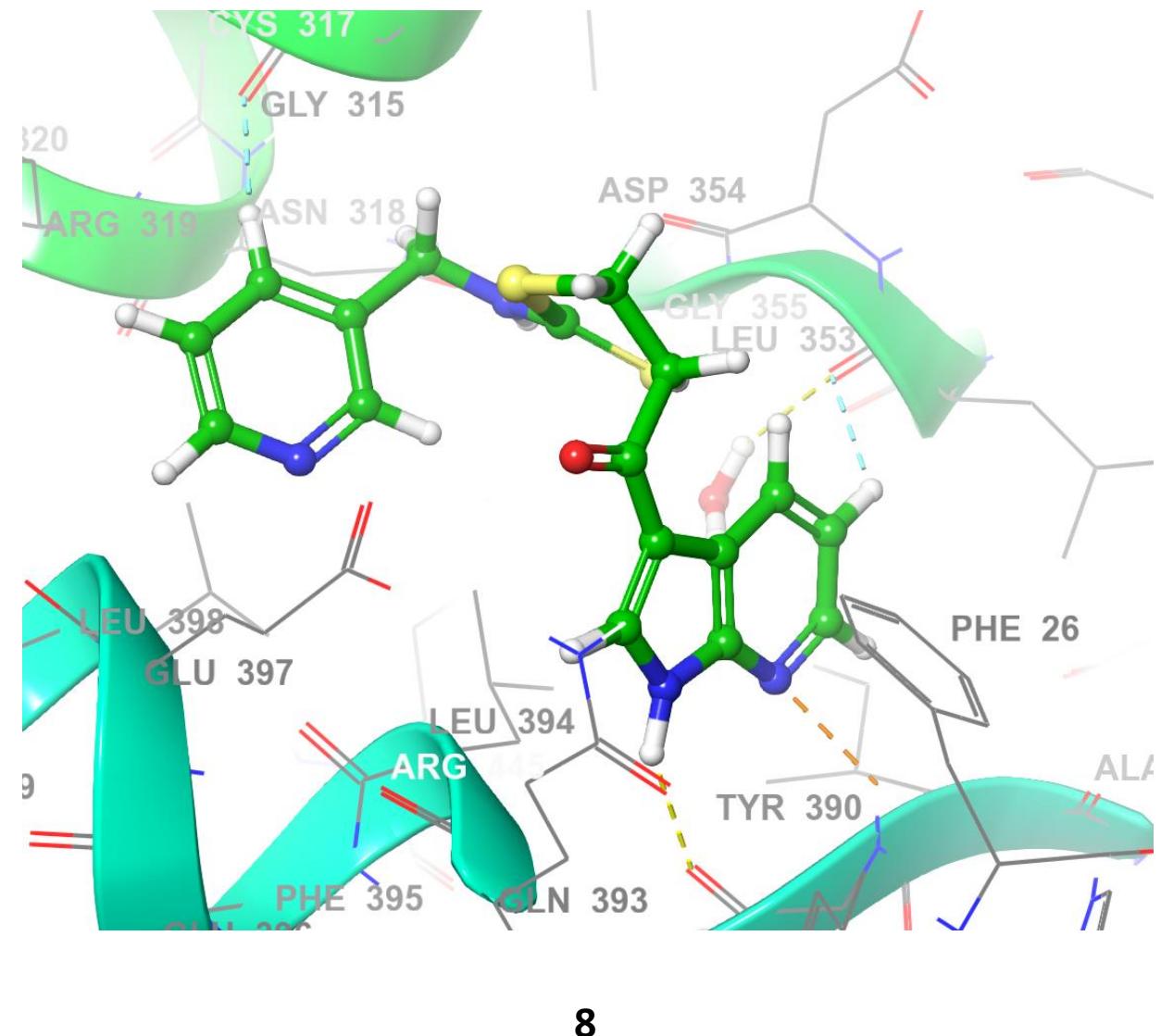
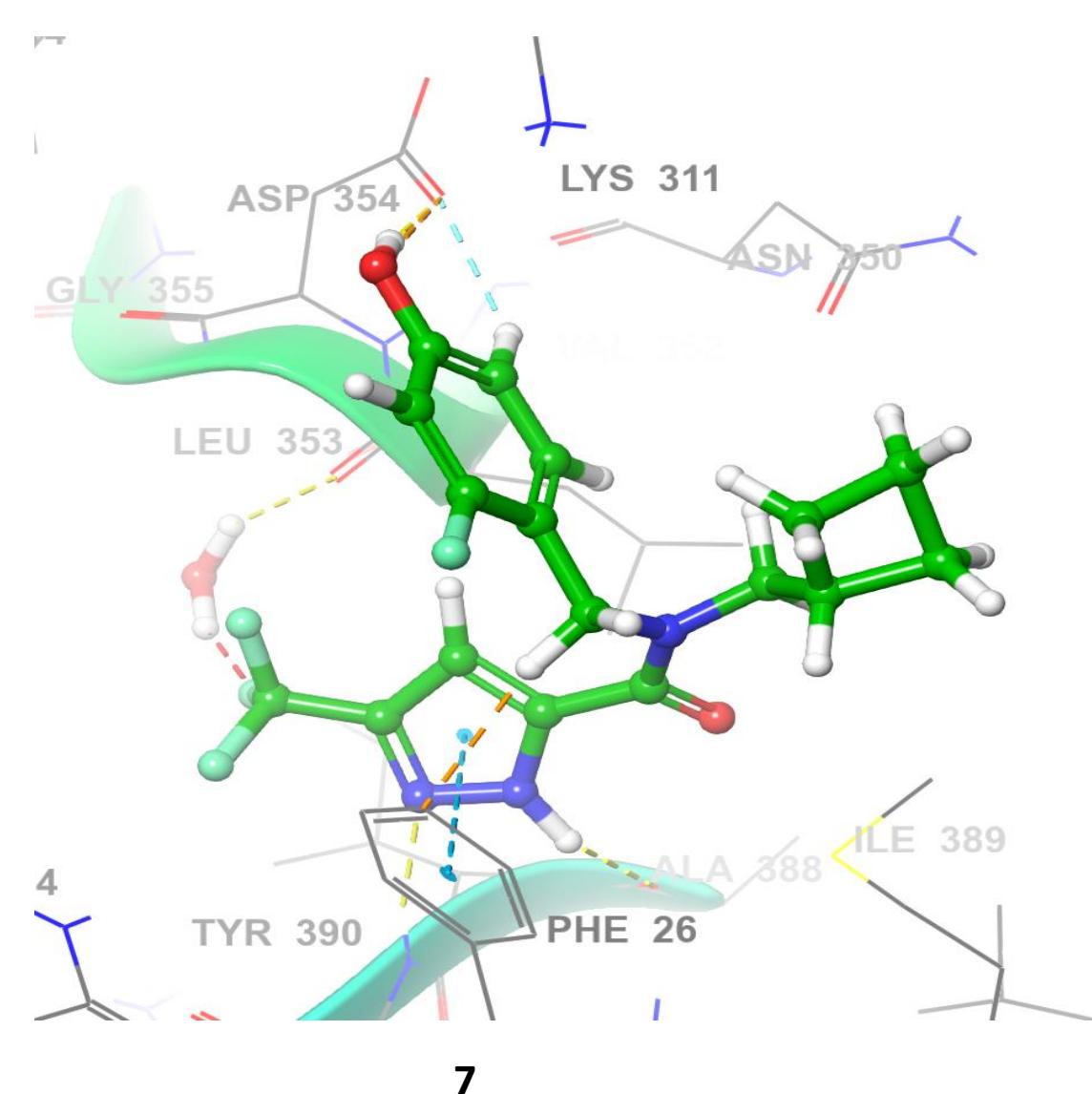
4

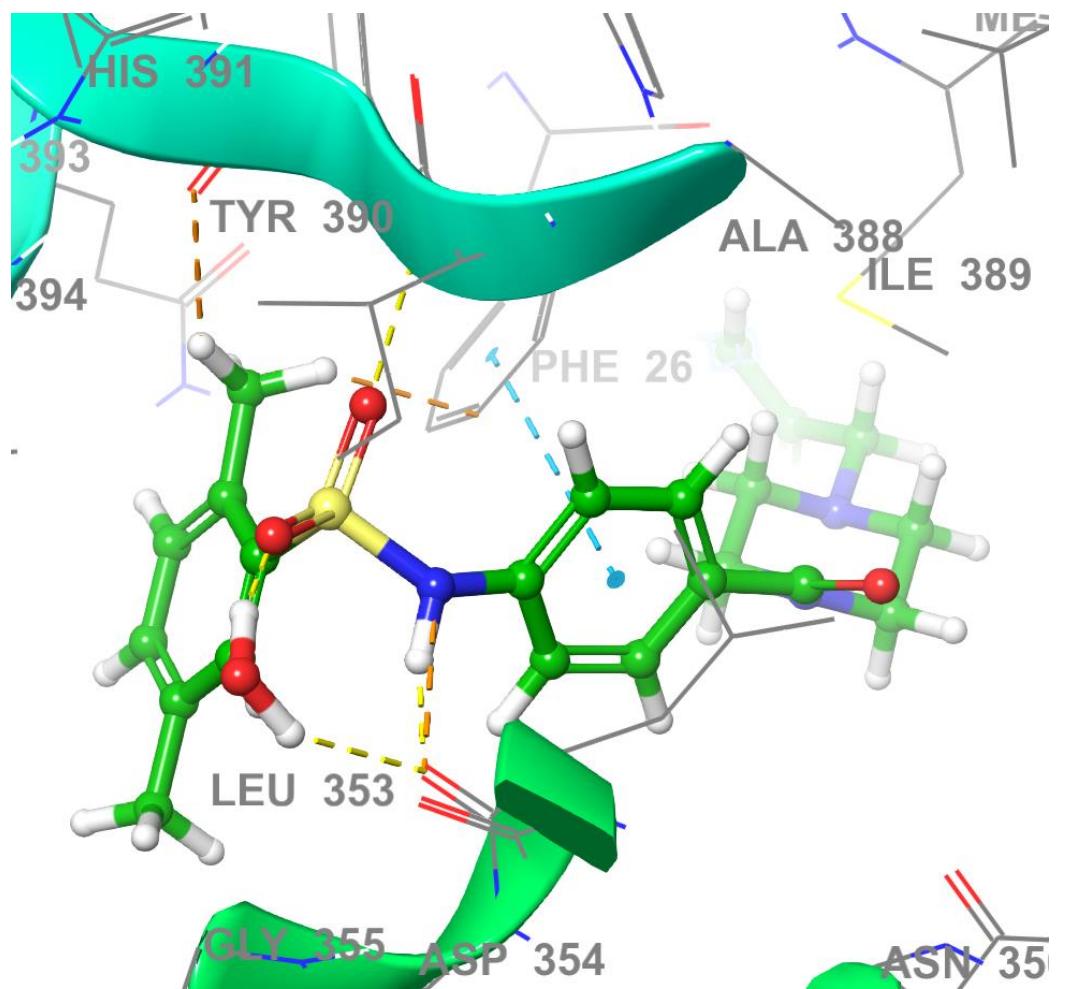


5

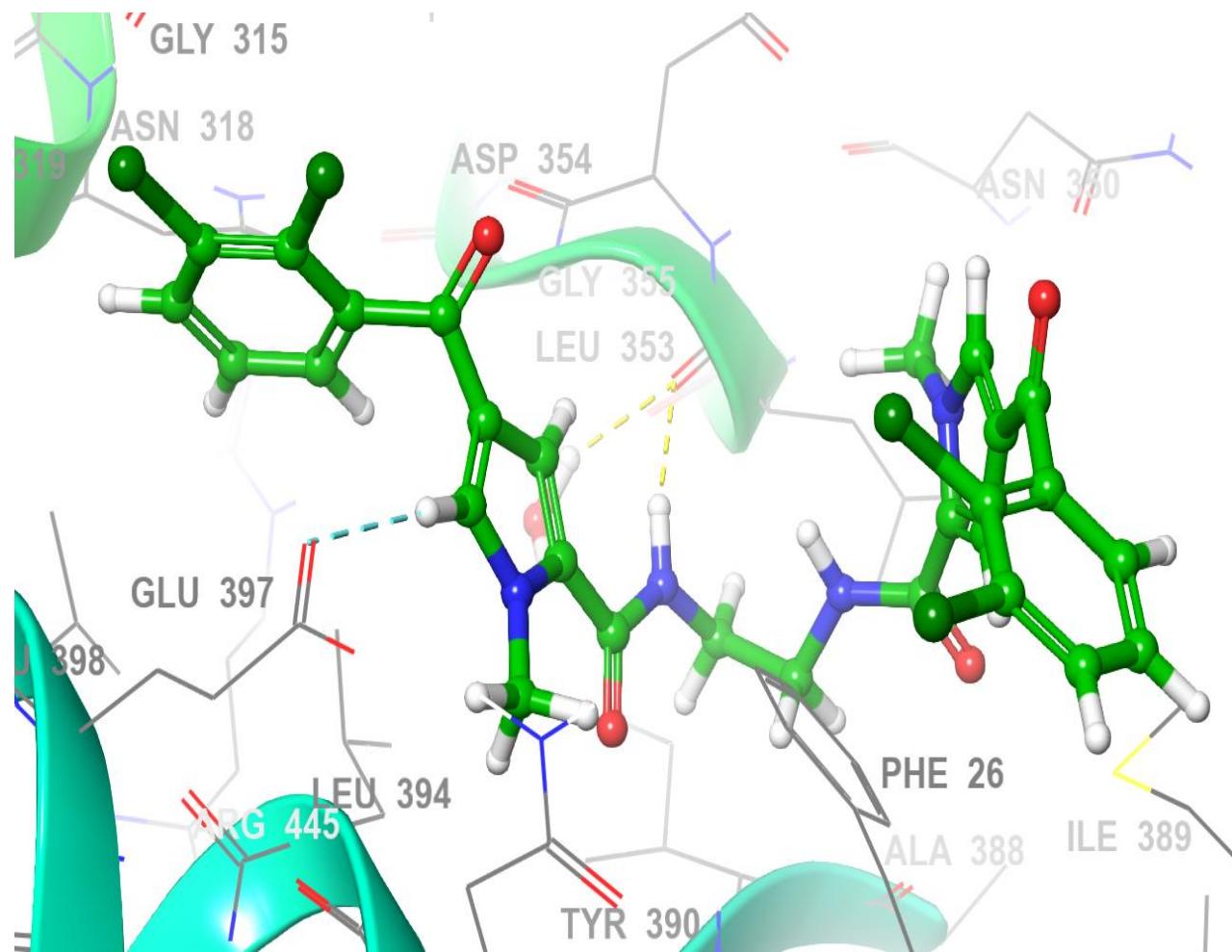


6

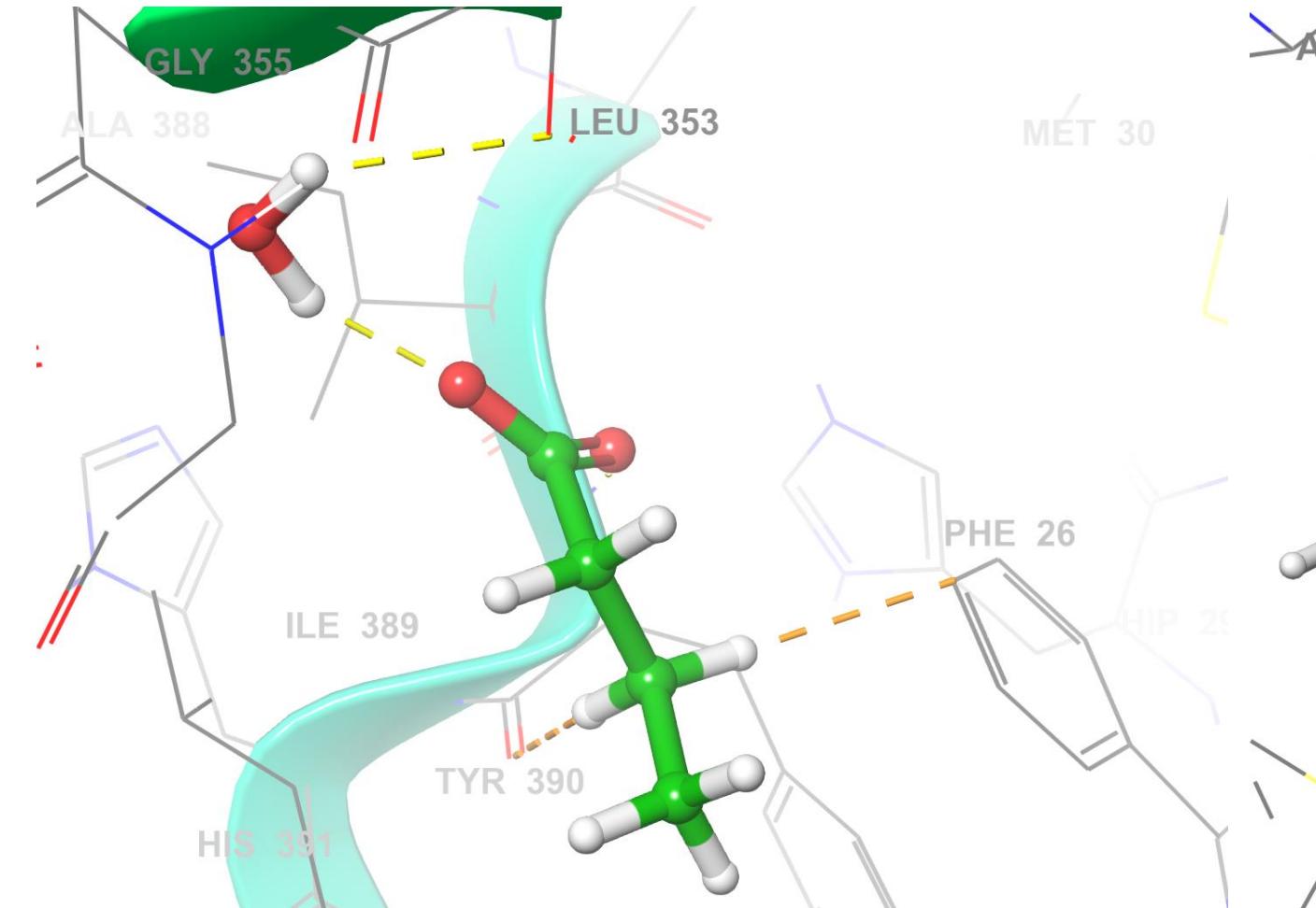




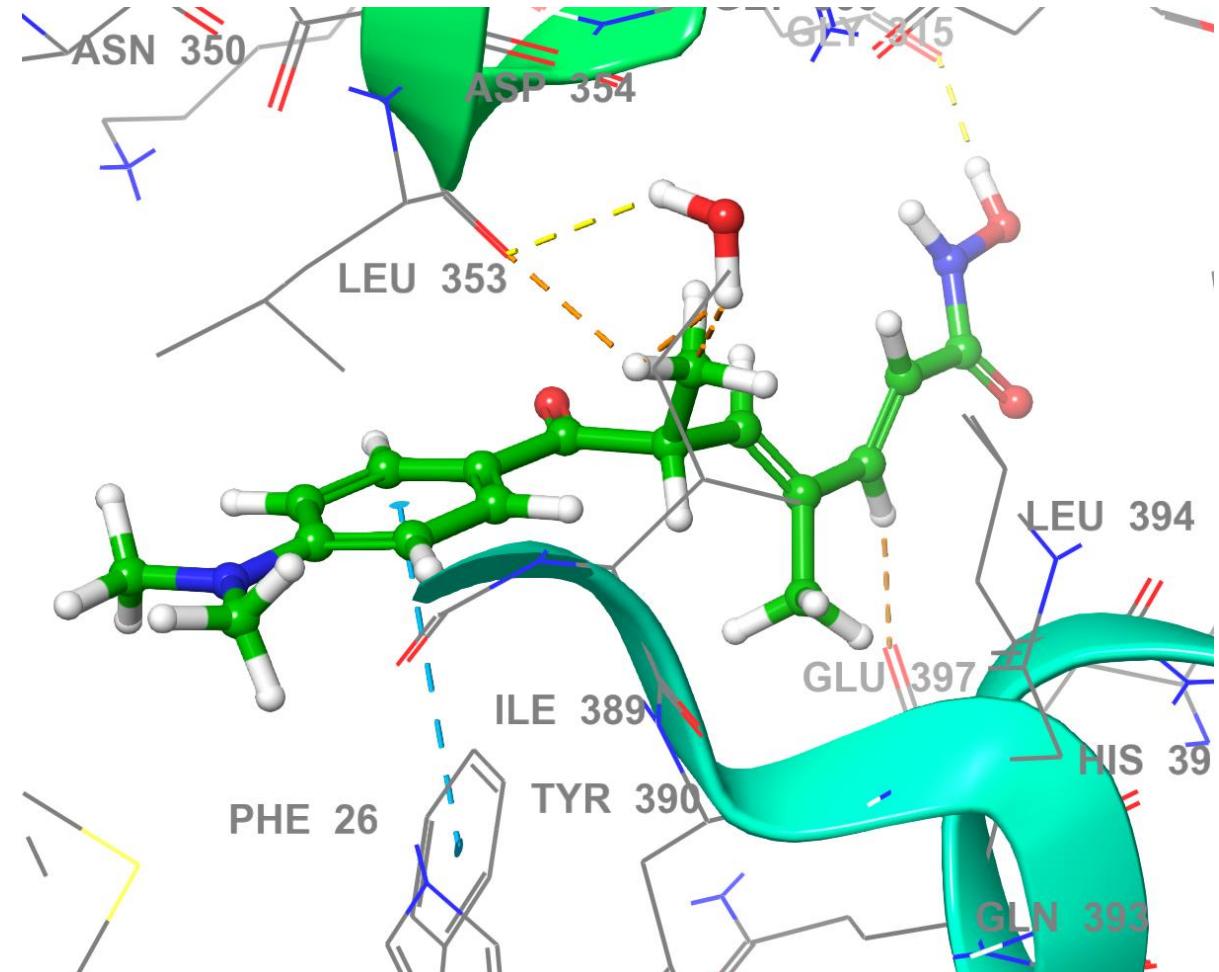
9



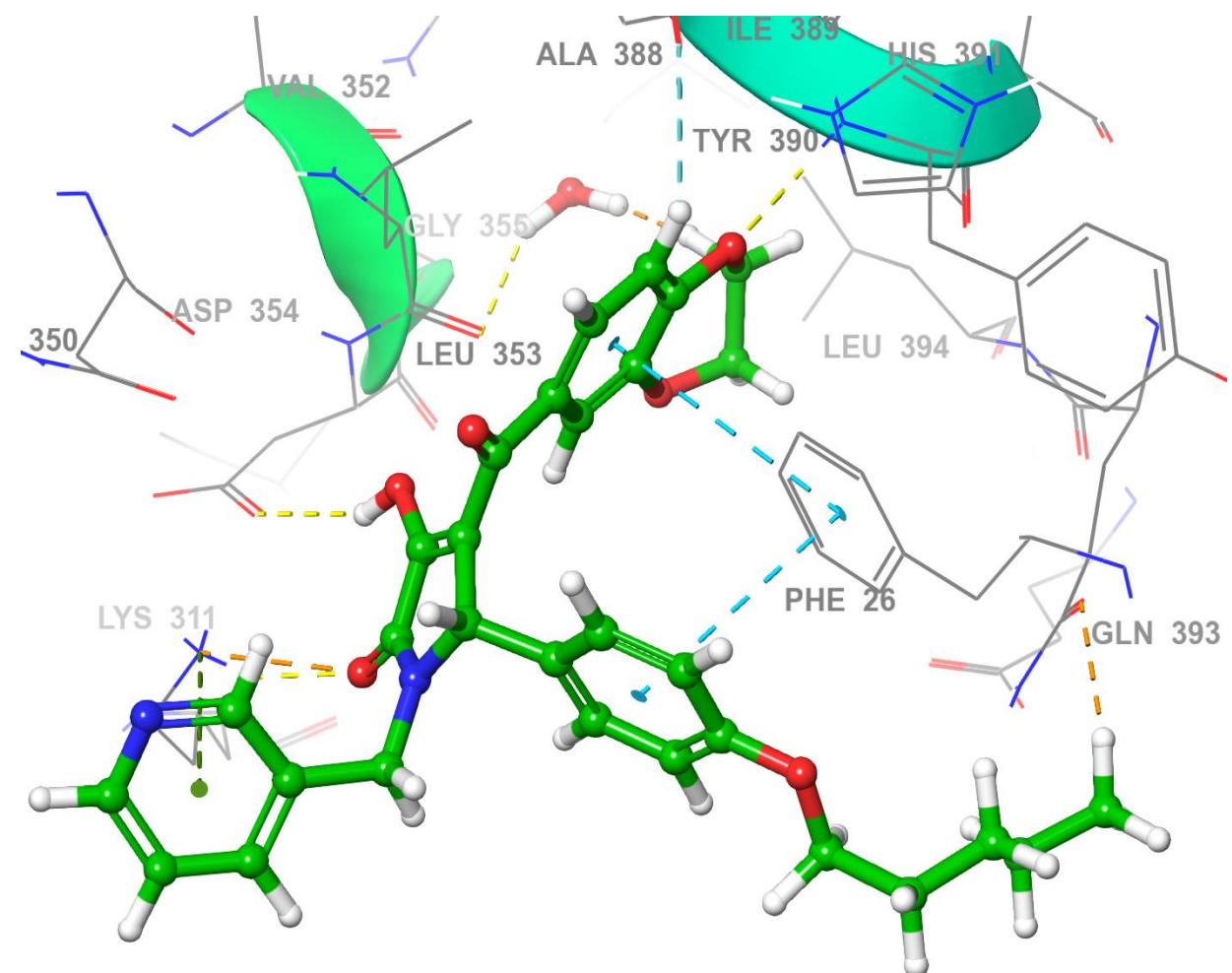
10



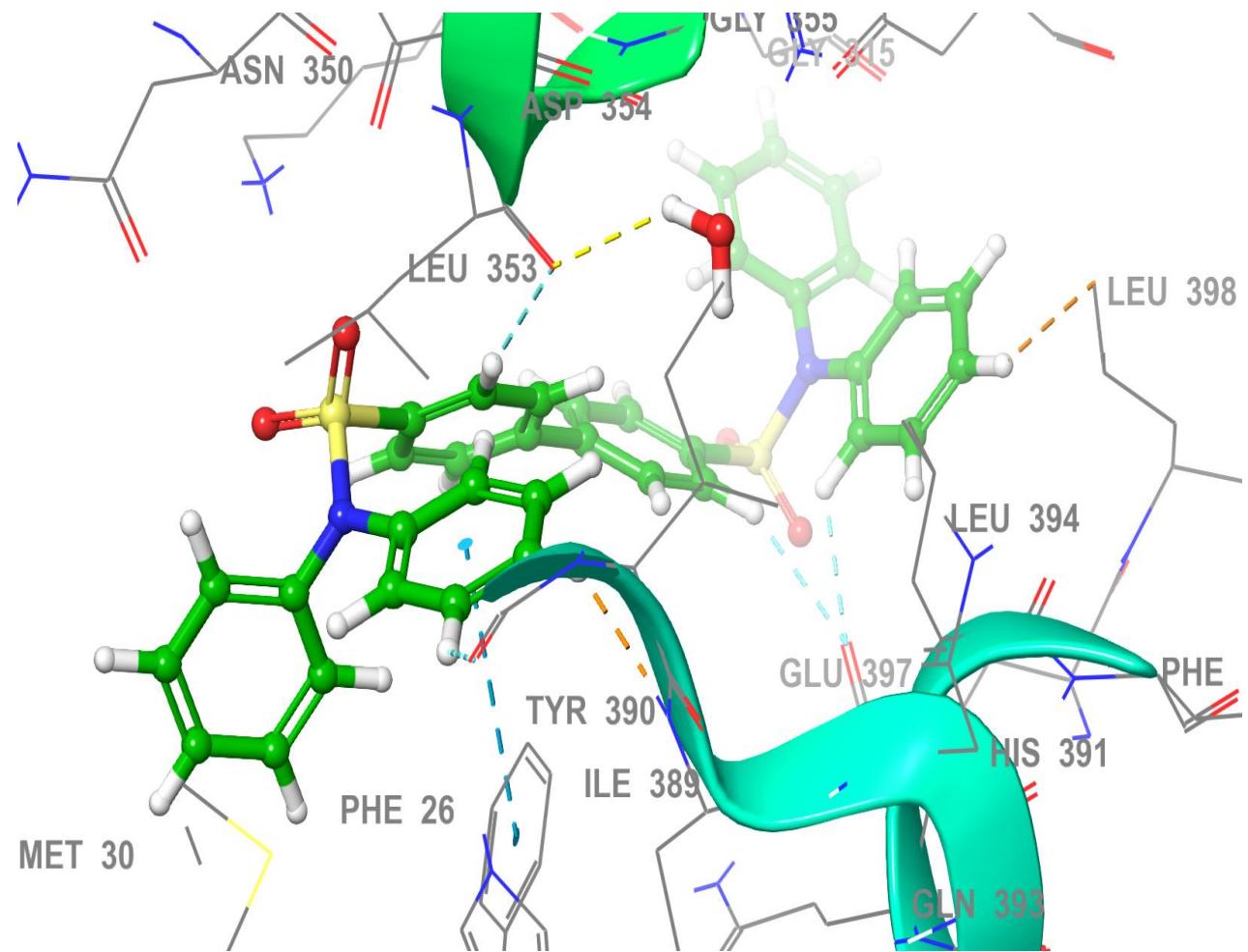
11



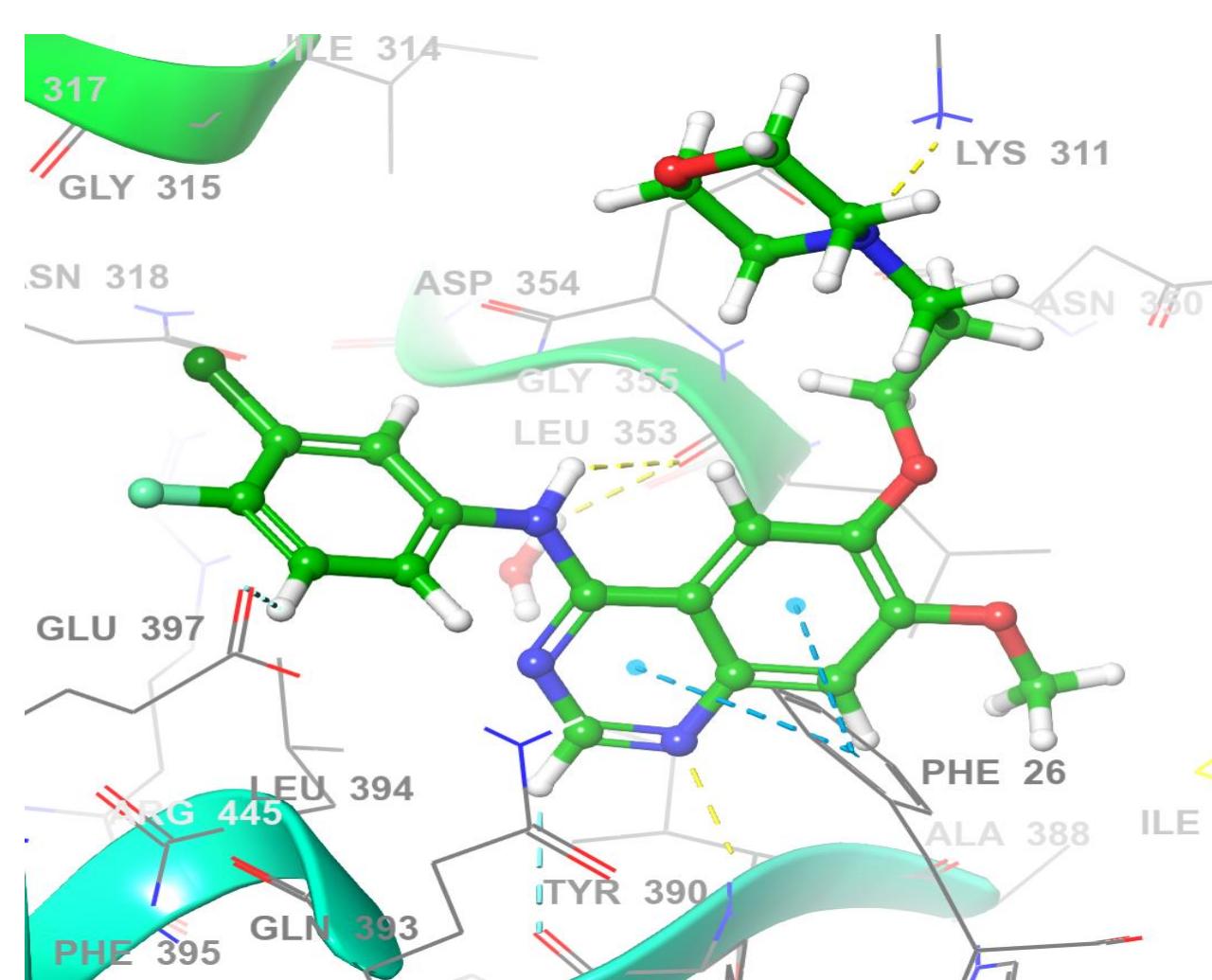
12



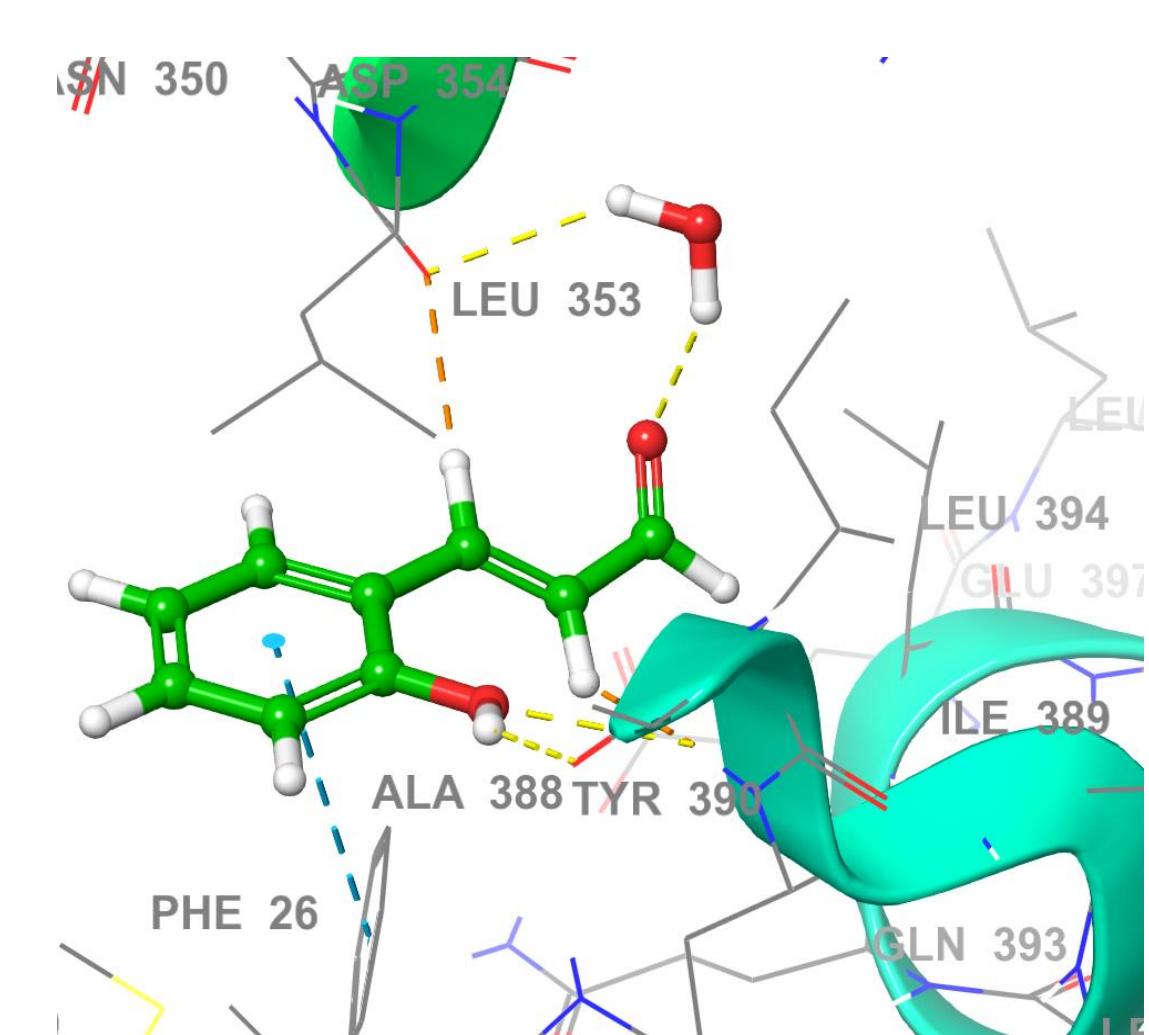
13



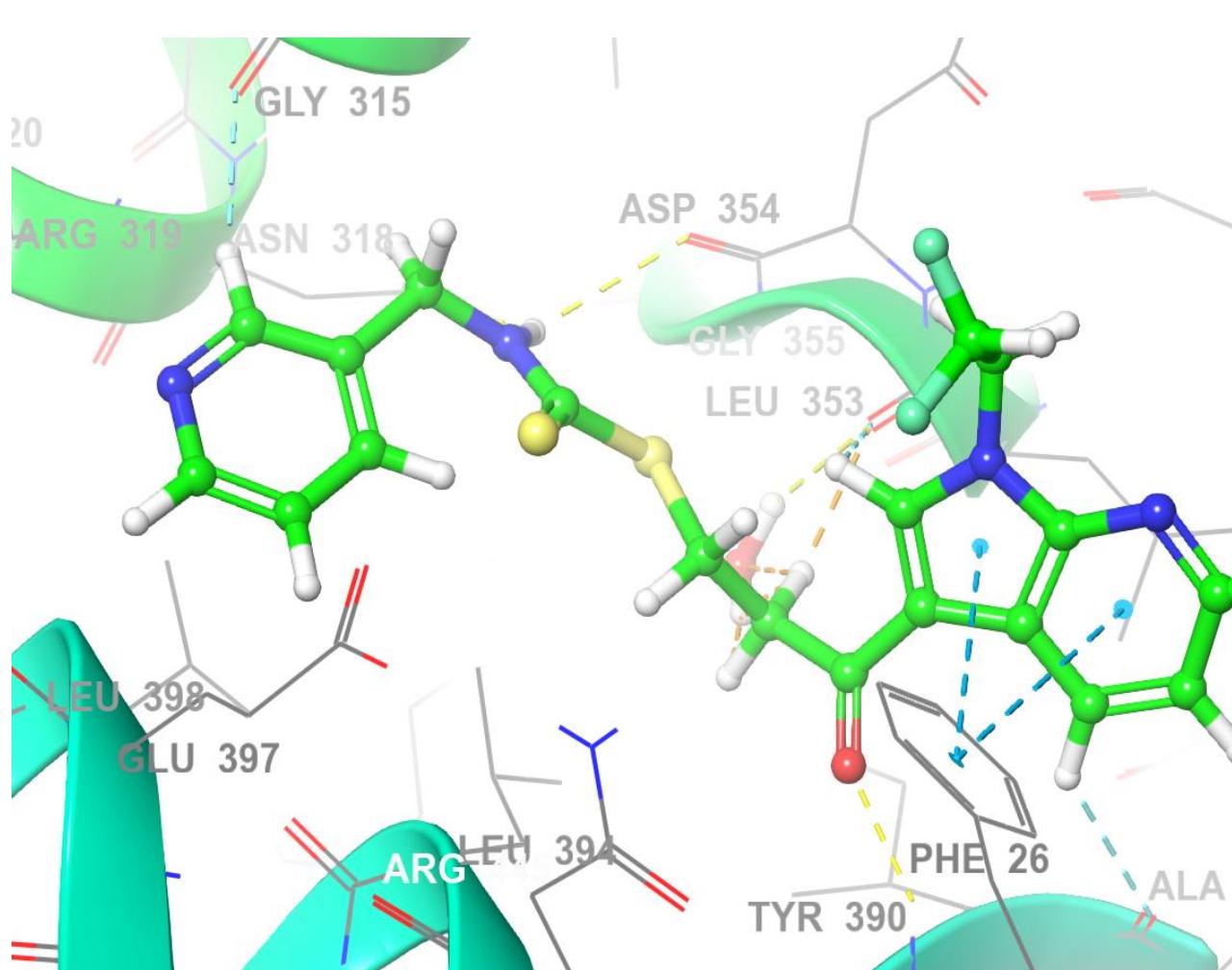
14



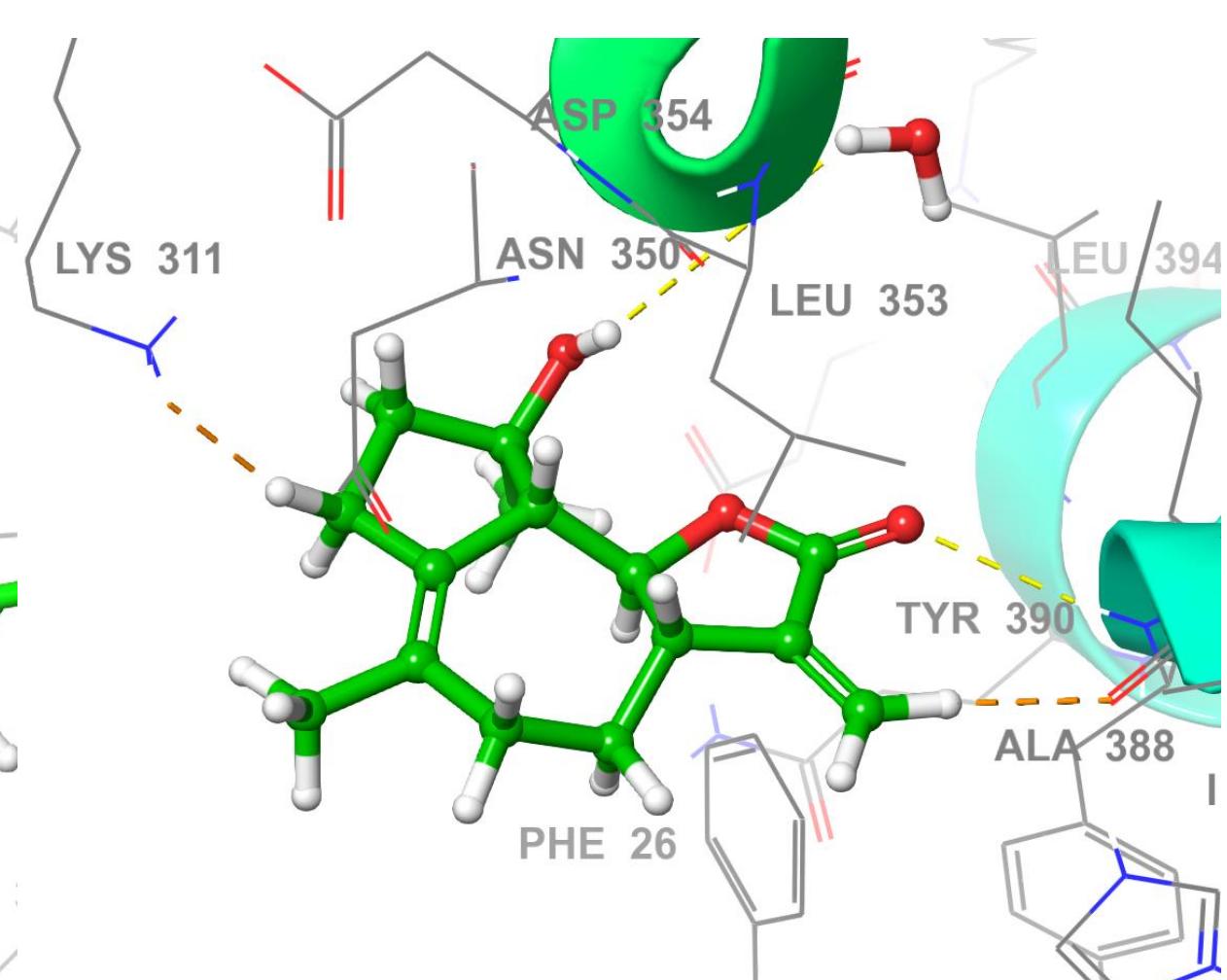
15



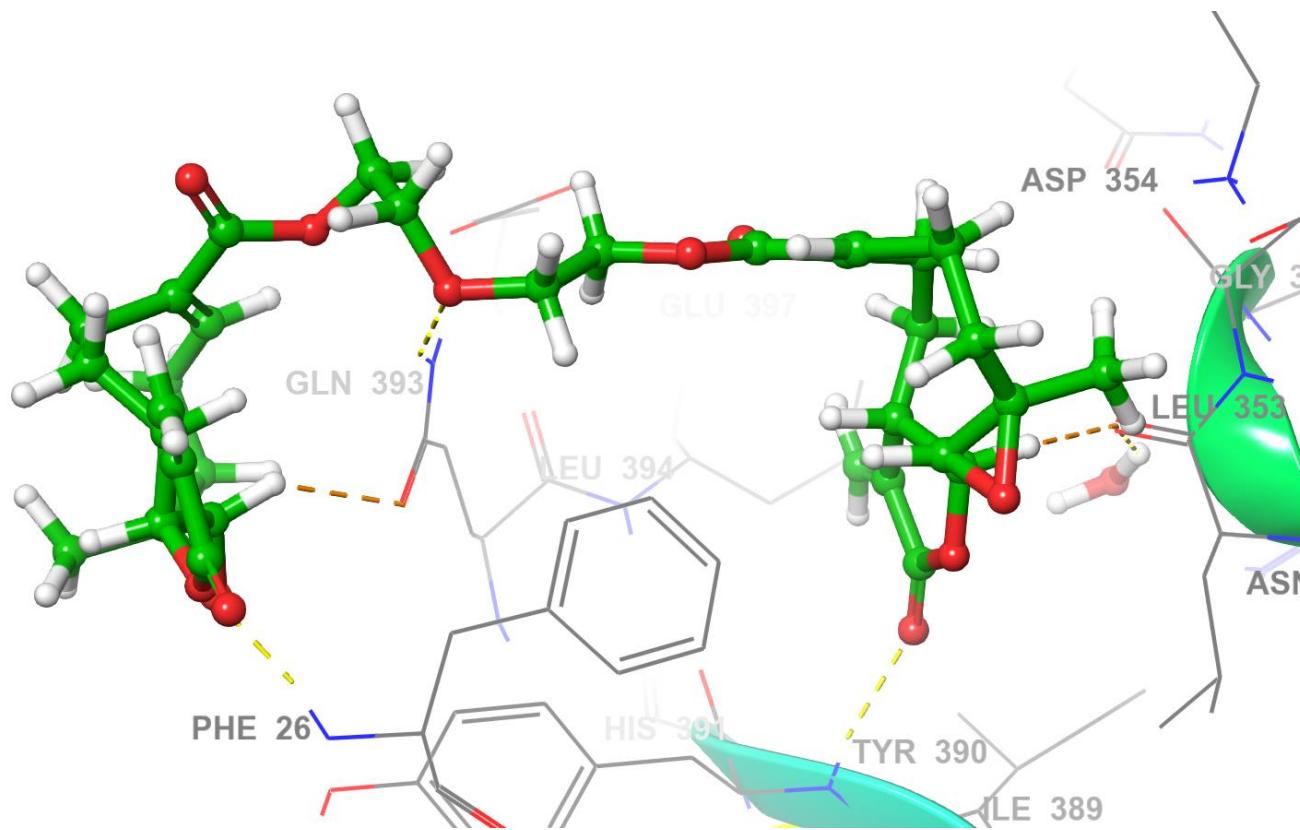
16



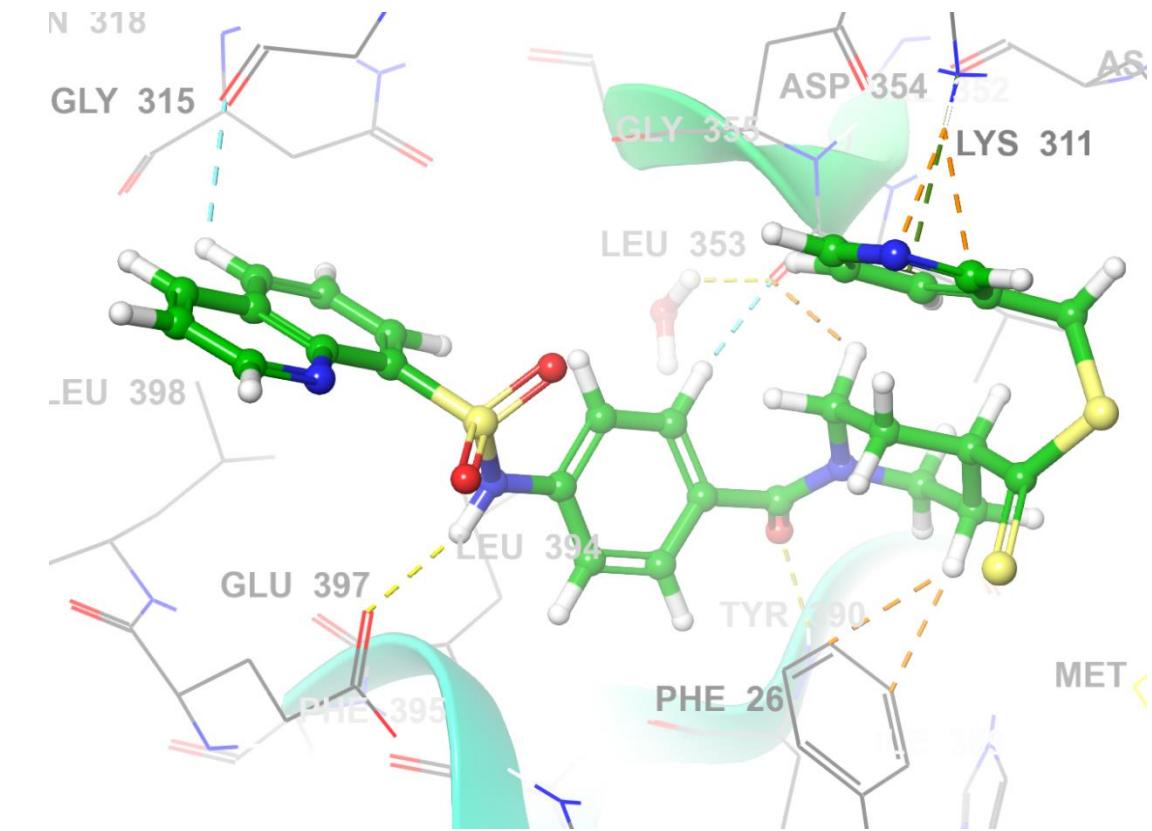
17



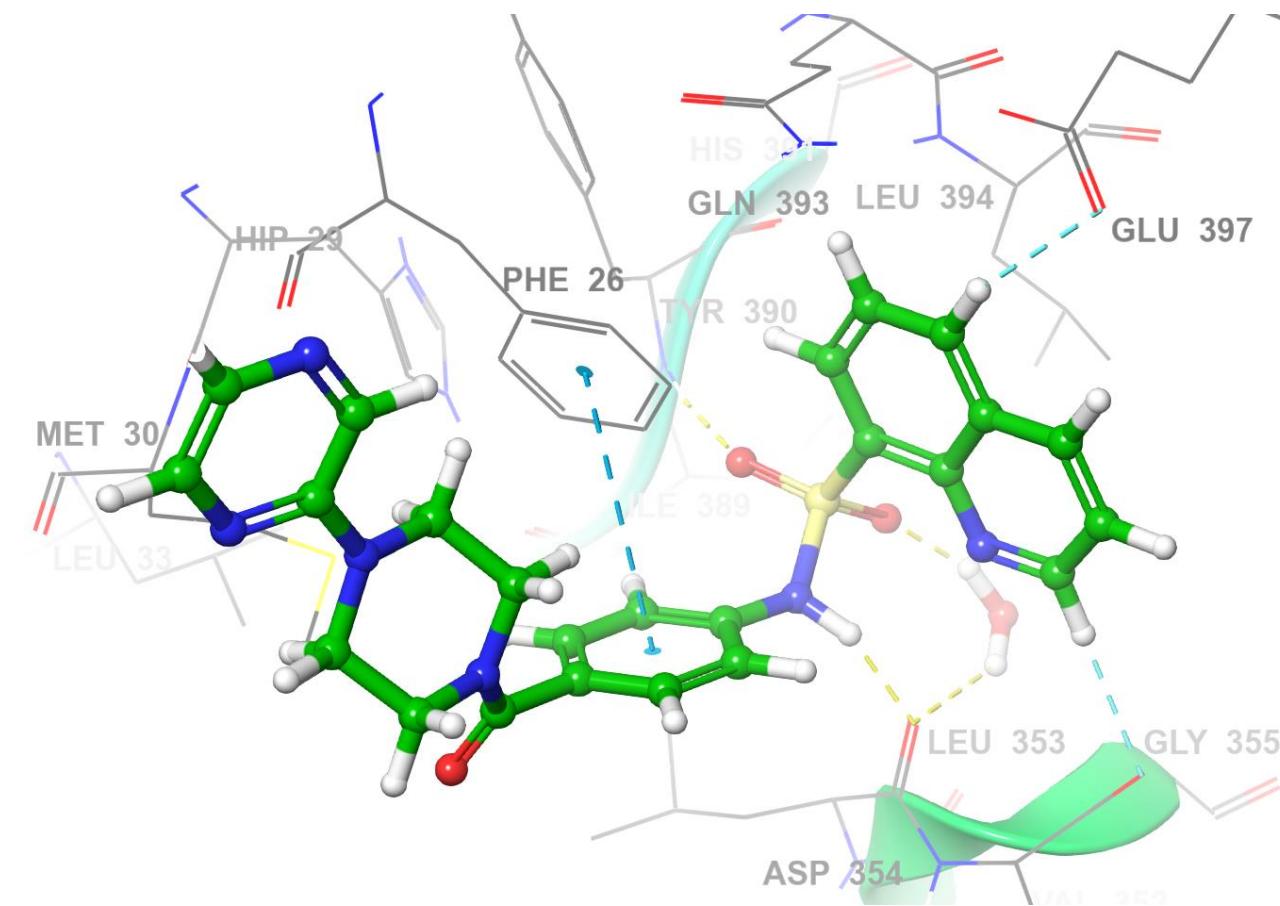
18



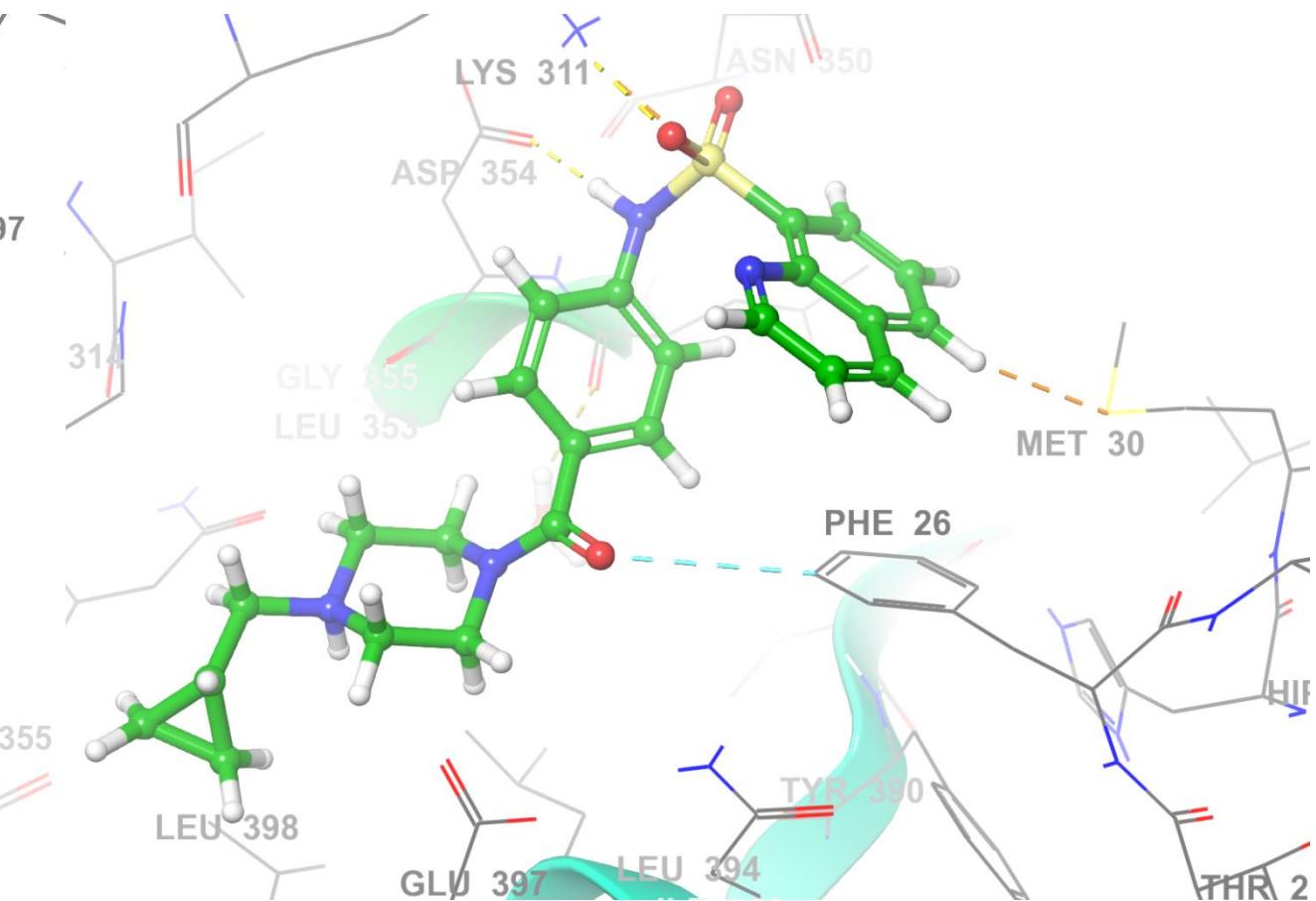
19



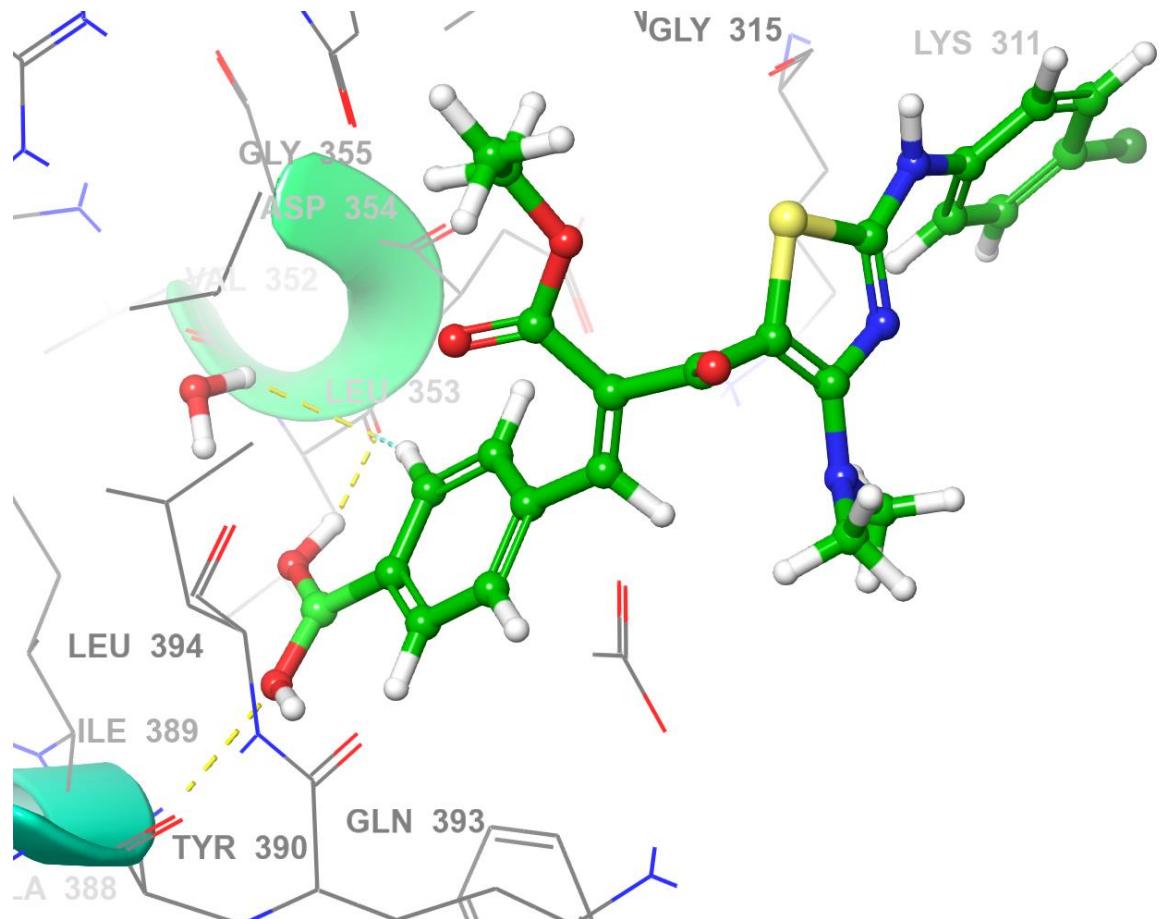
20



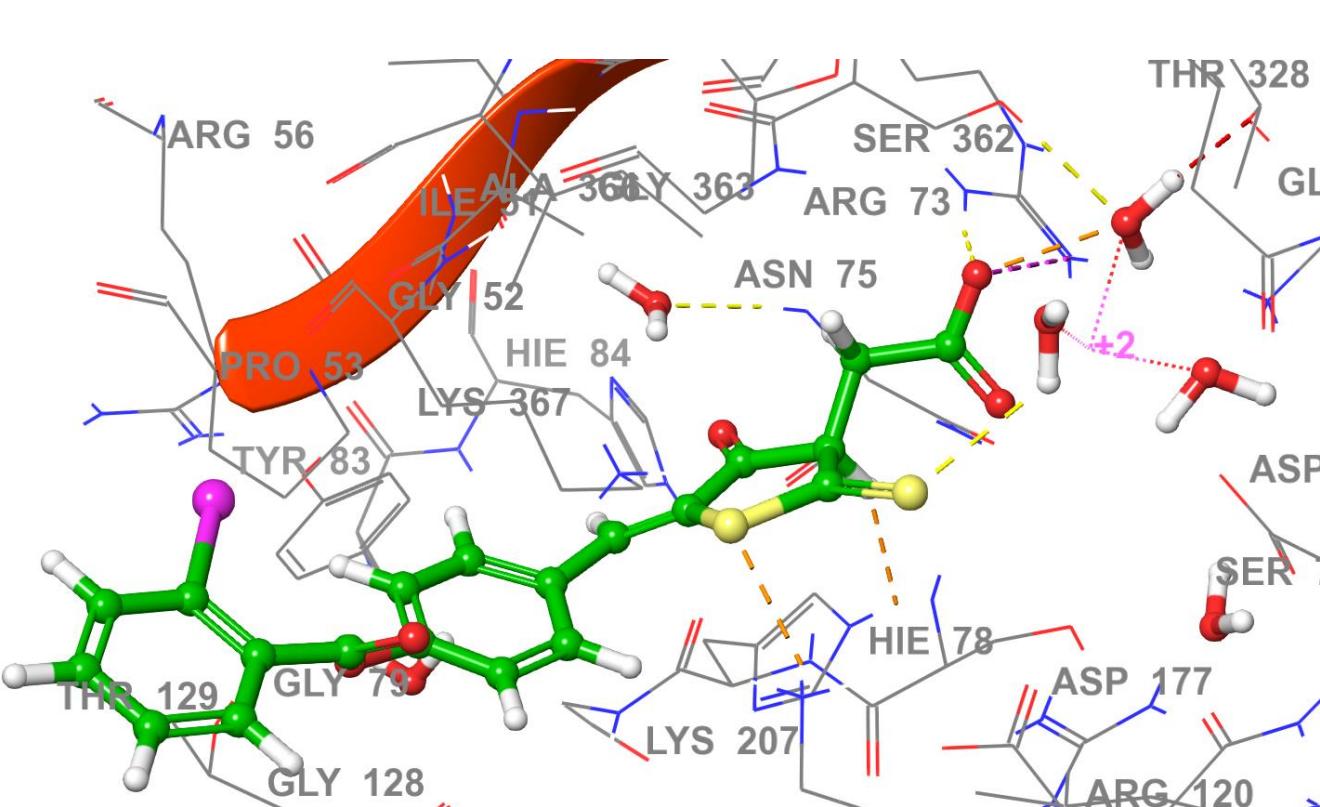
21



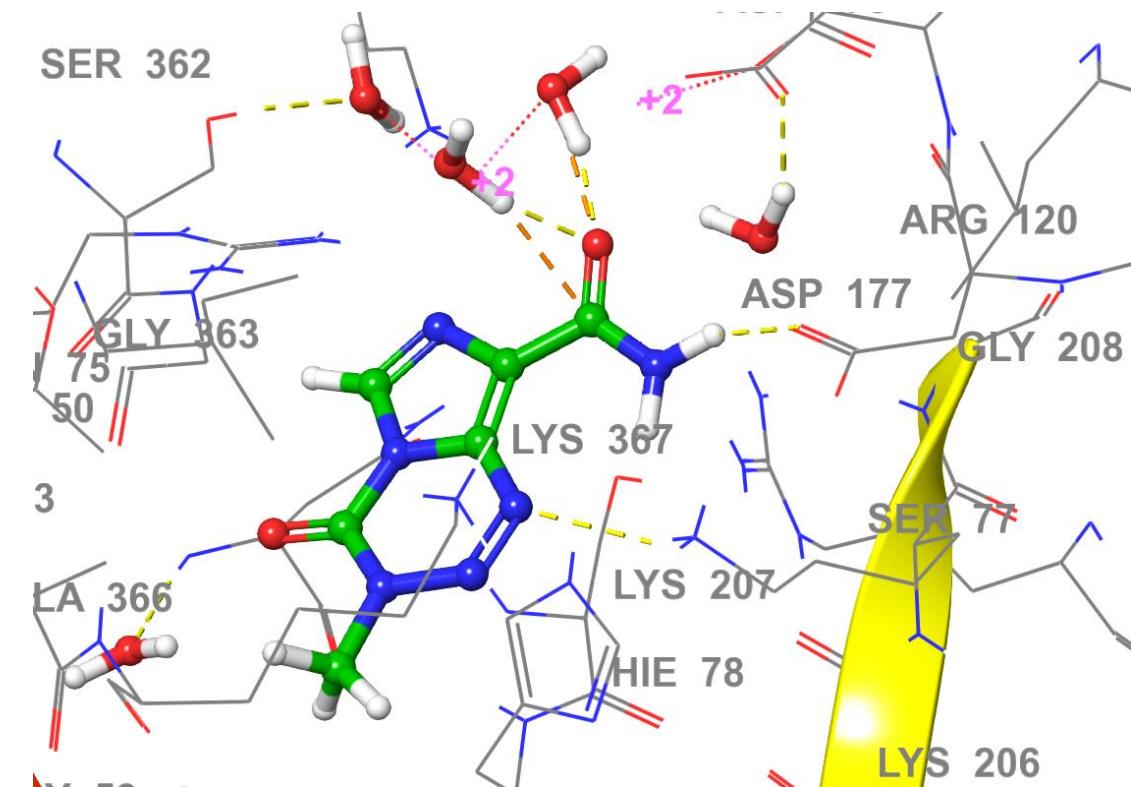
22



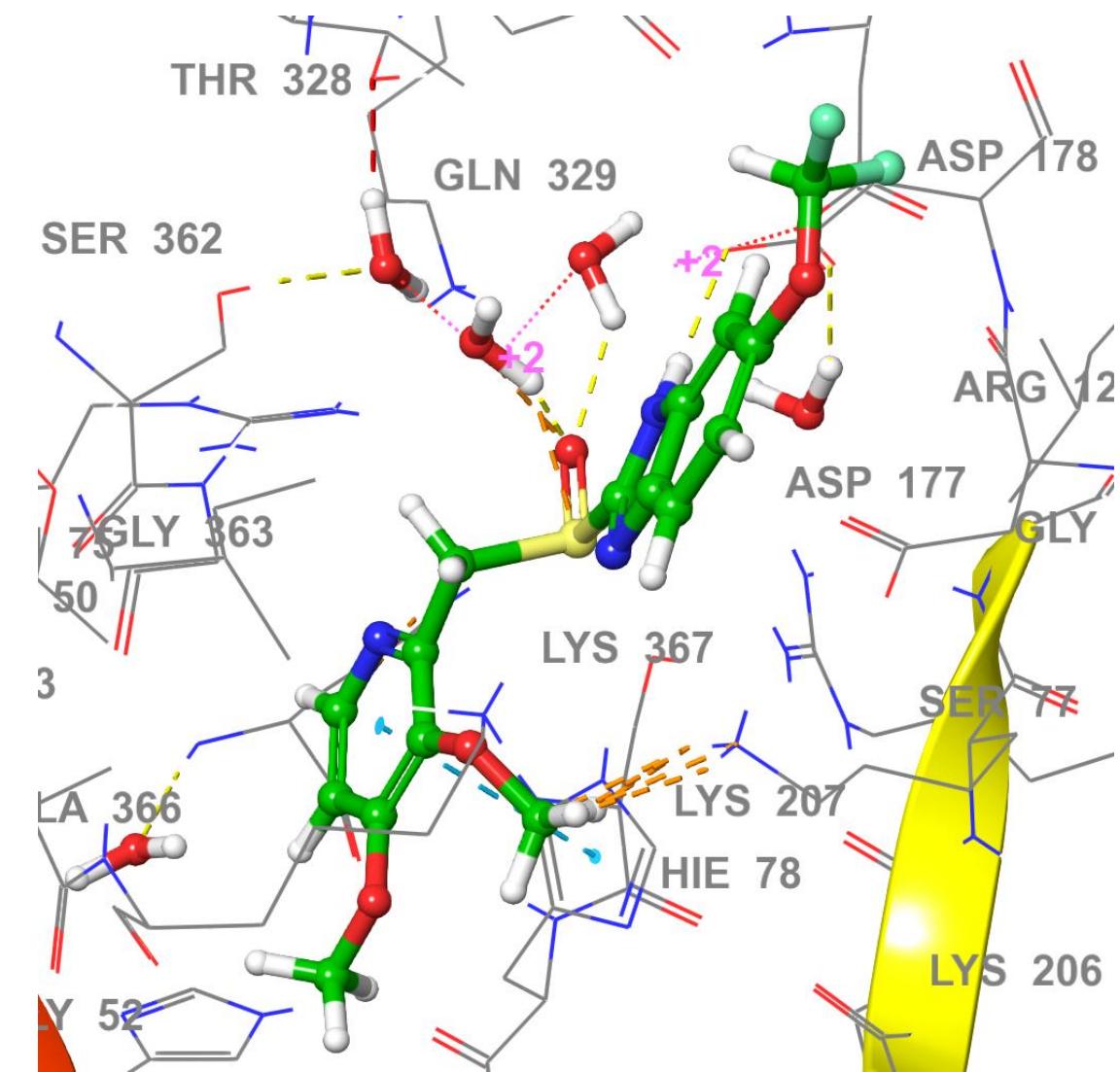
23



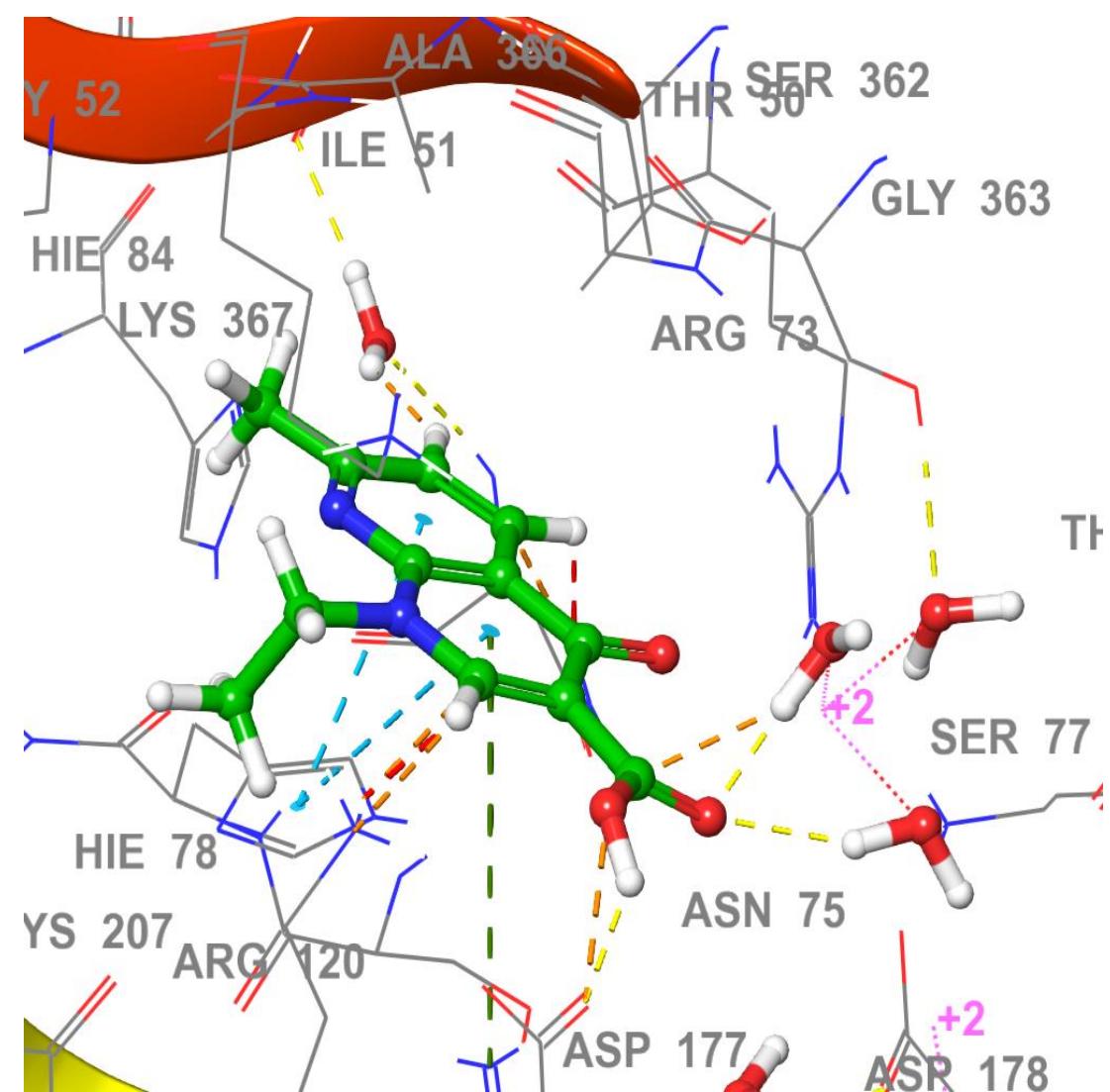
24



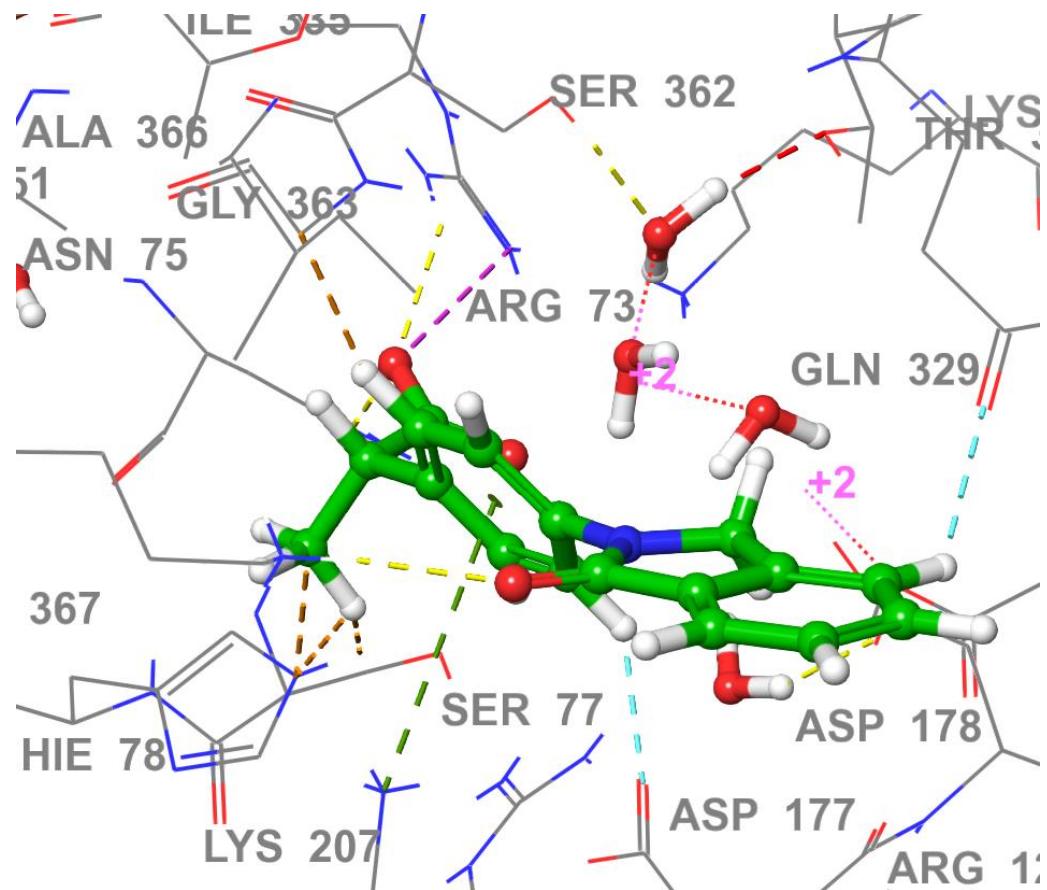
25



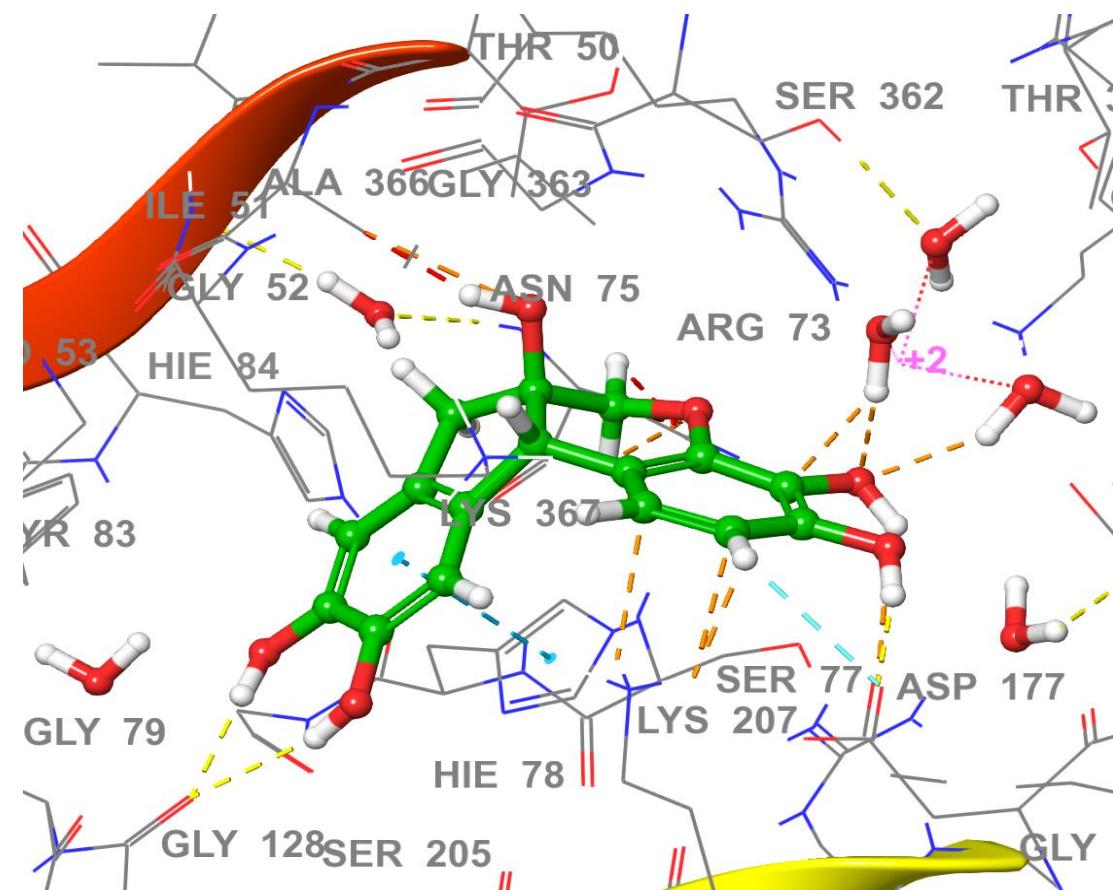
26



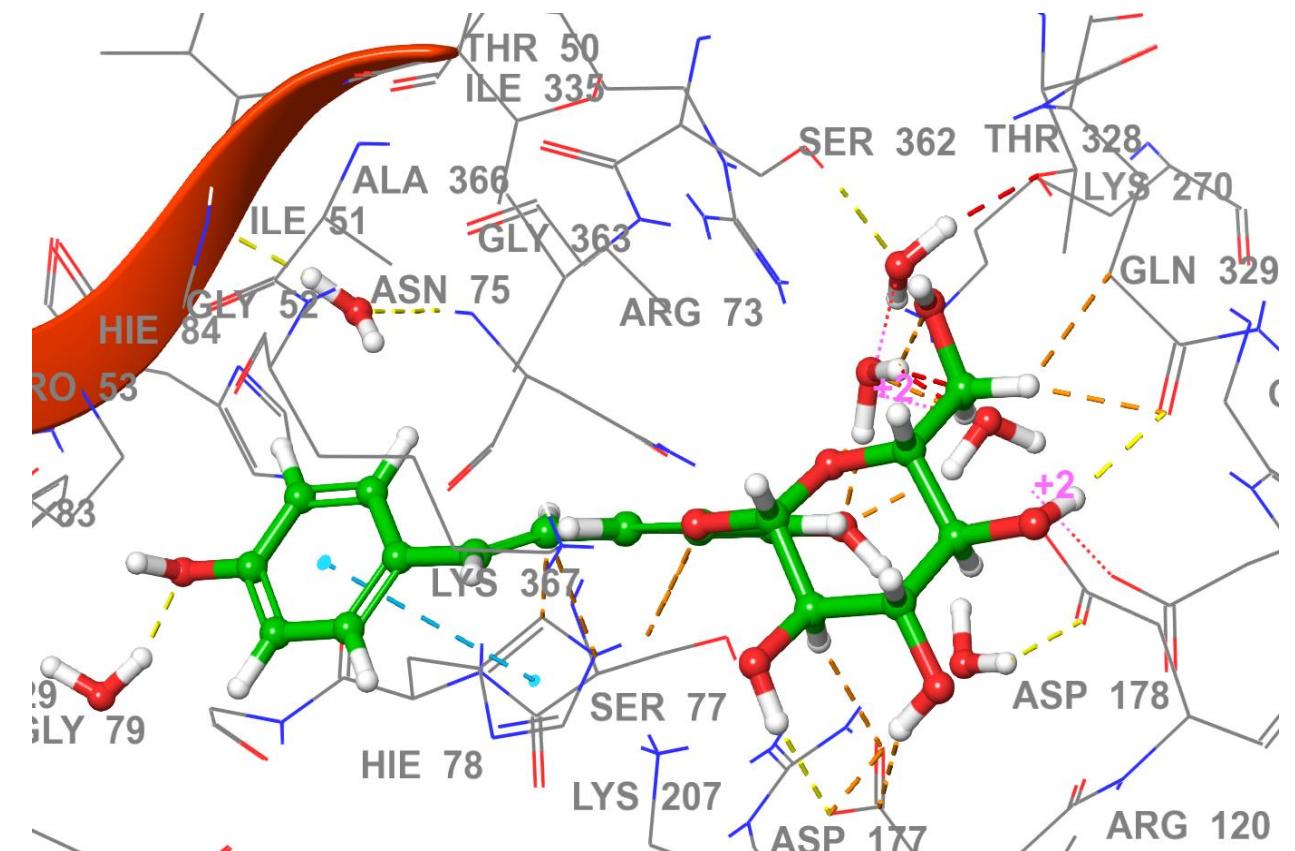
27



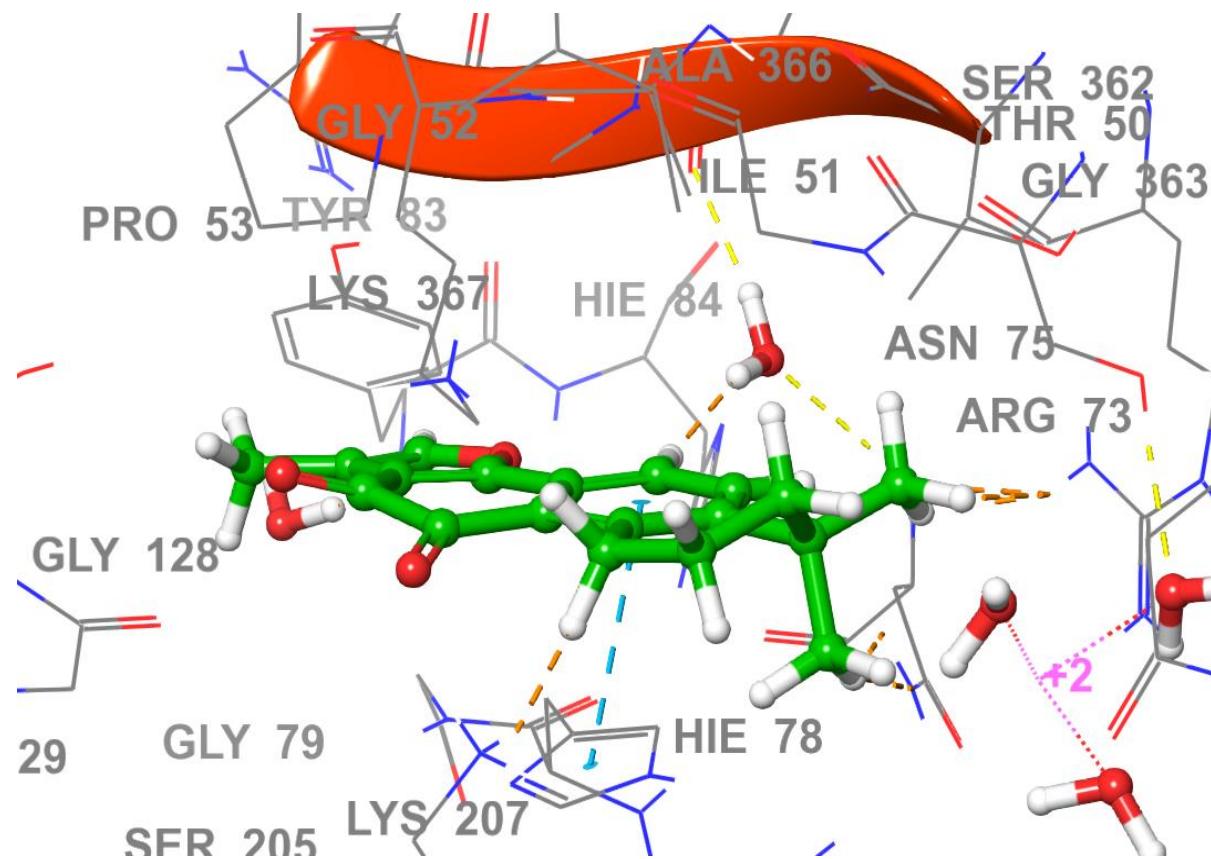
28



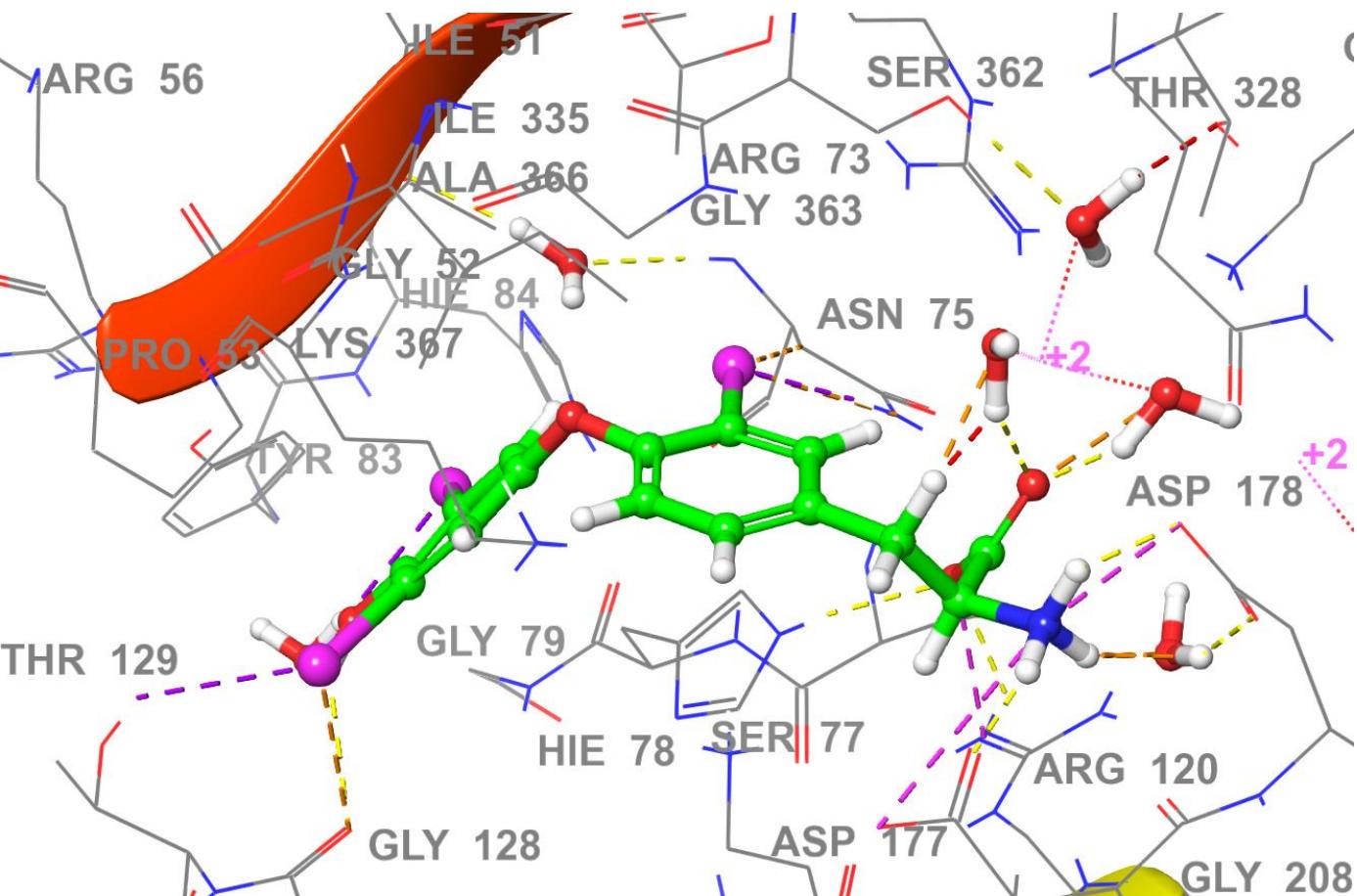
29



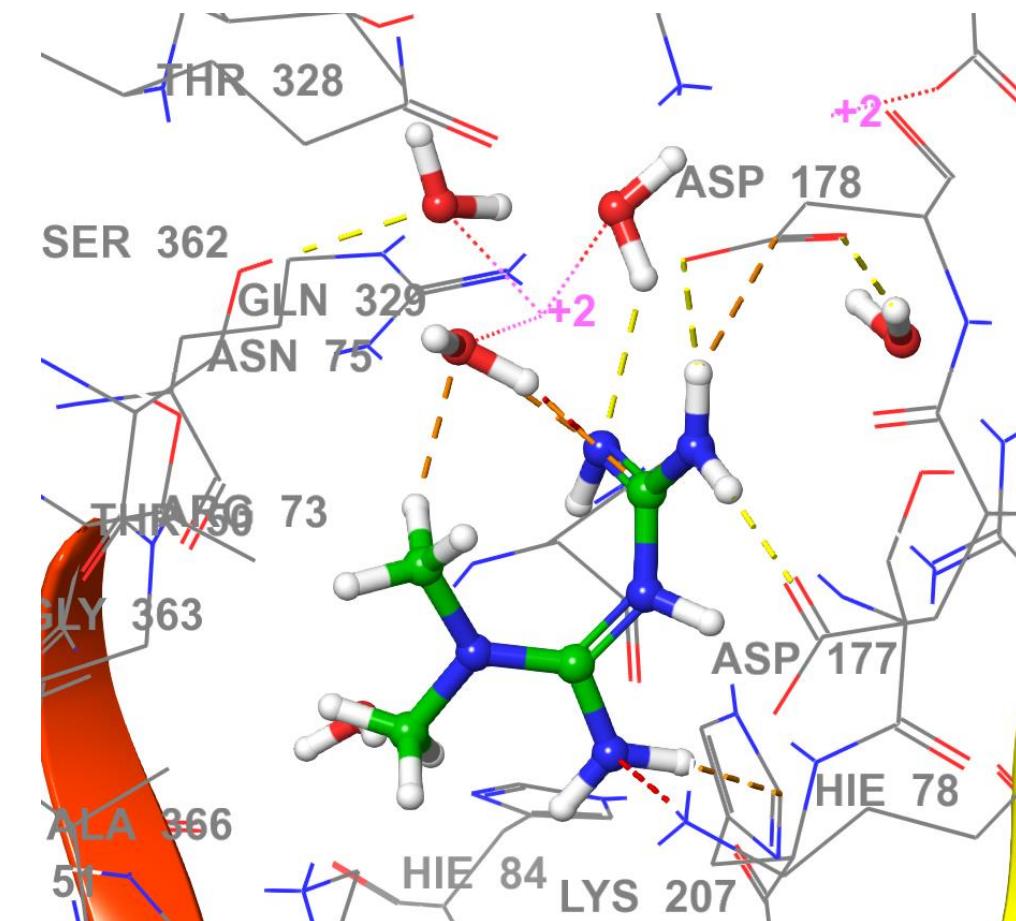
30



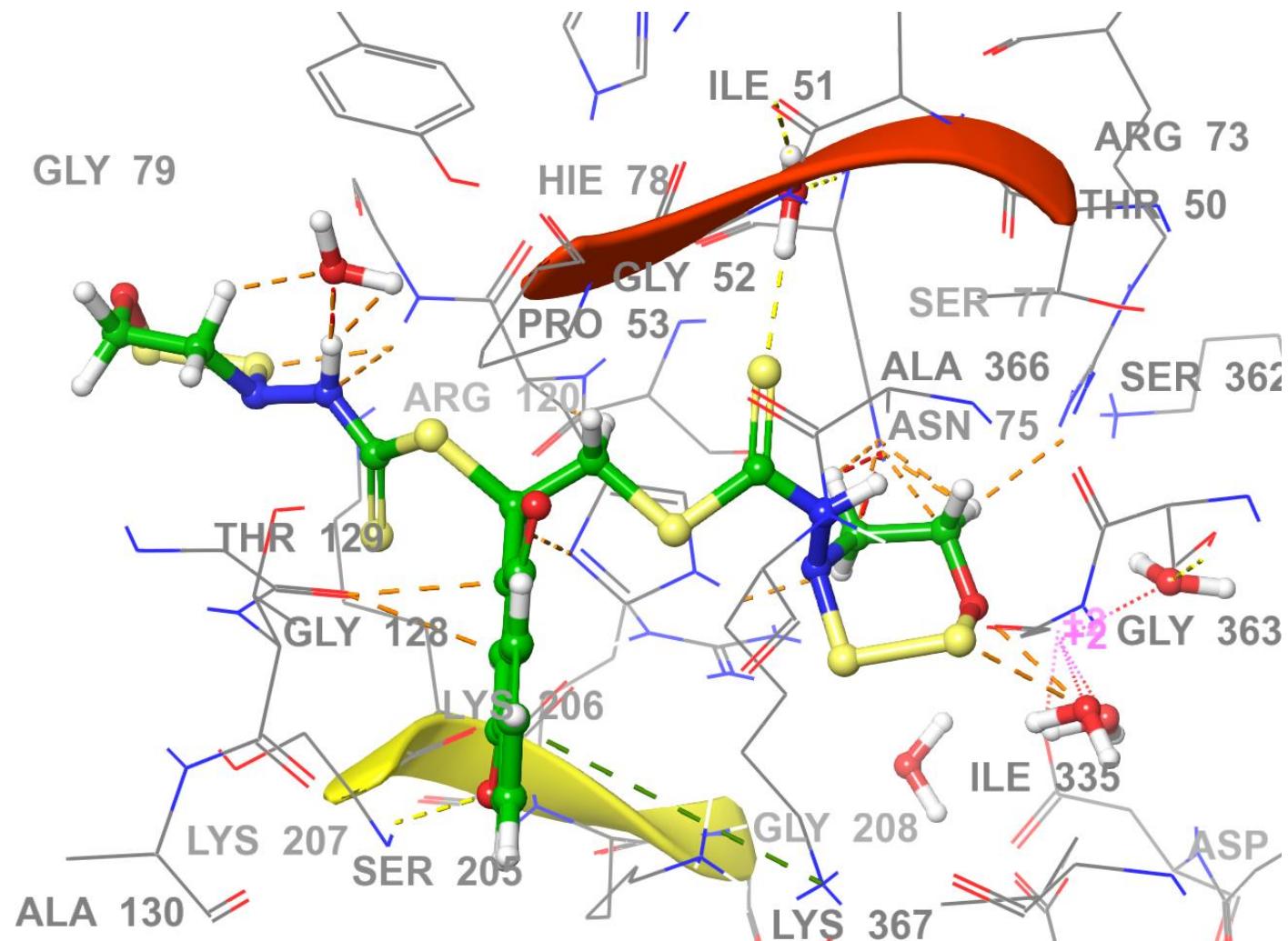
31



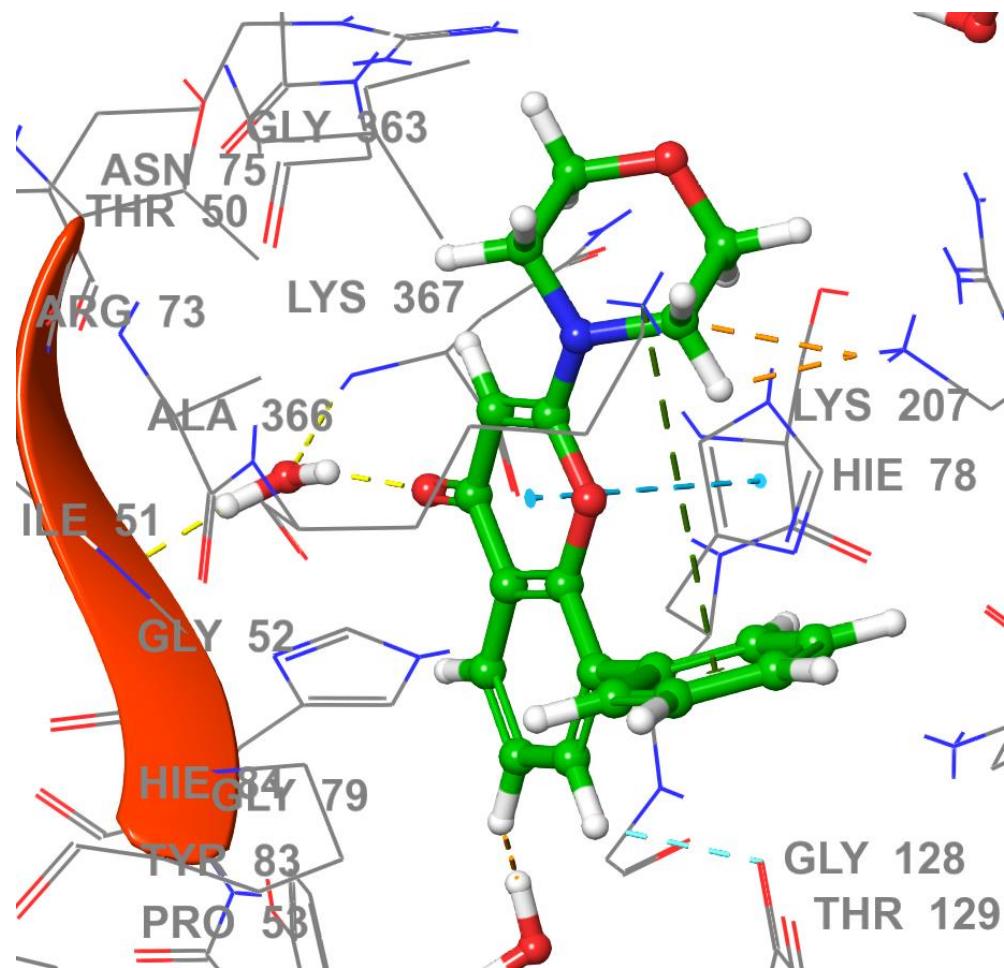
32



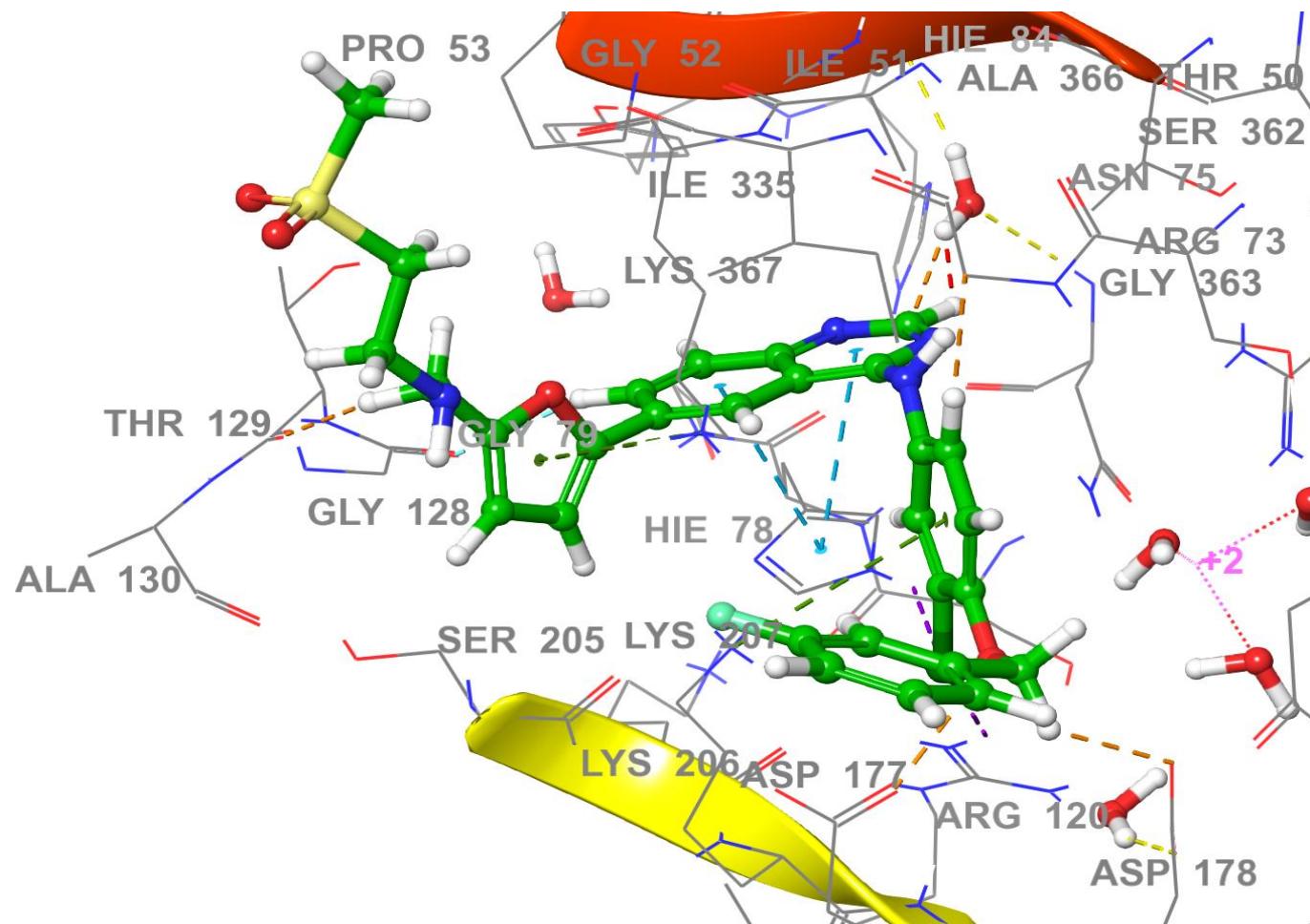
33



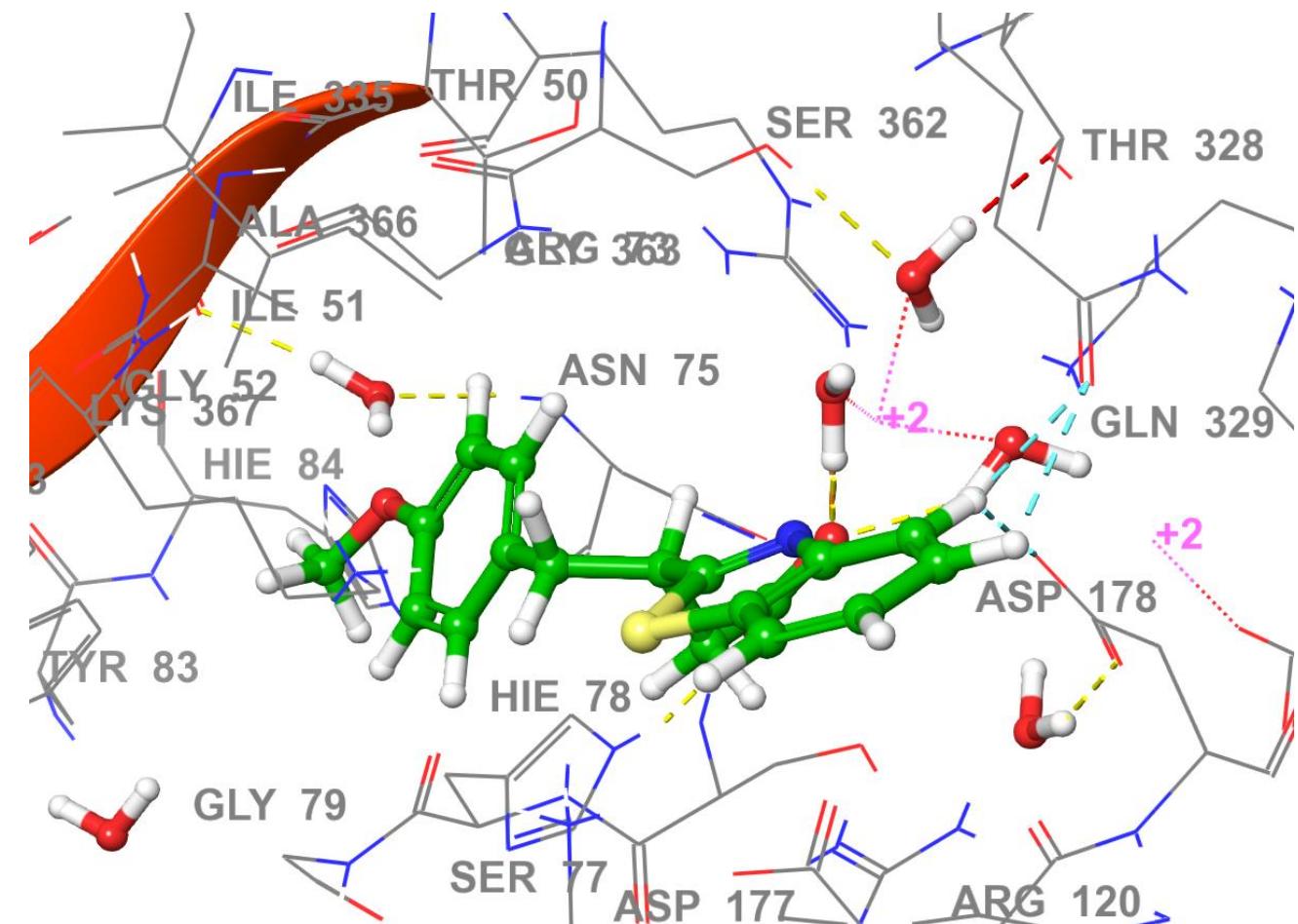
35



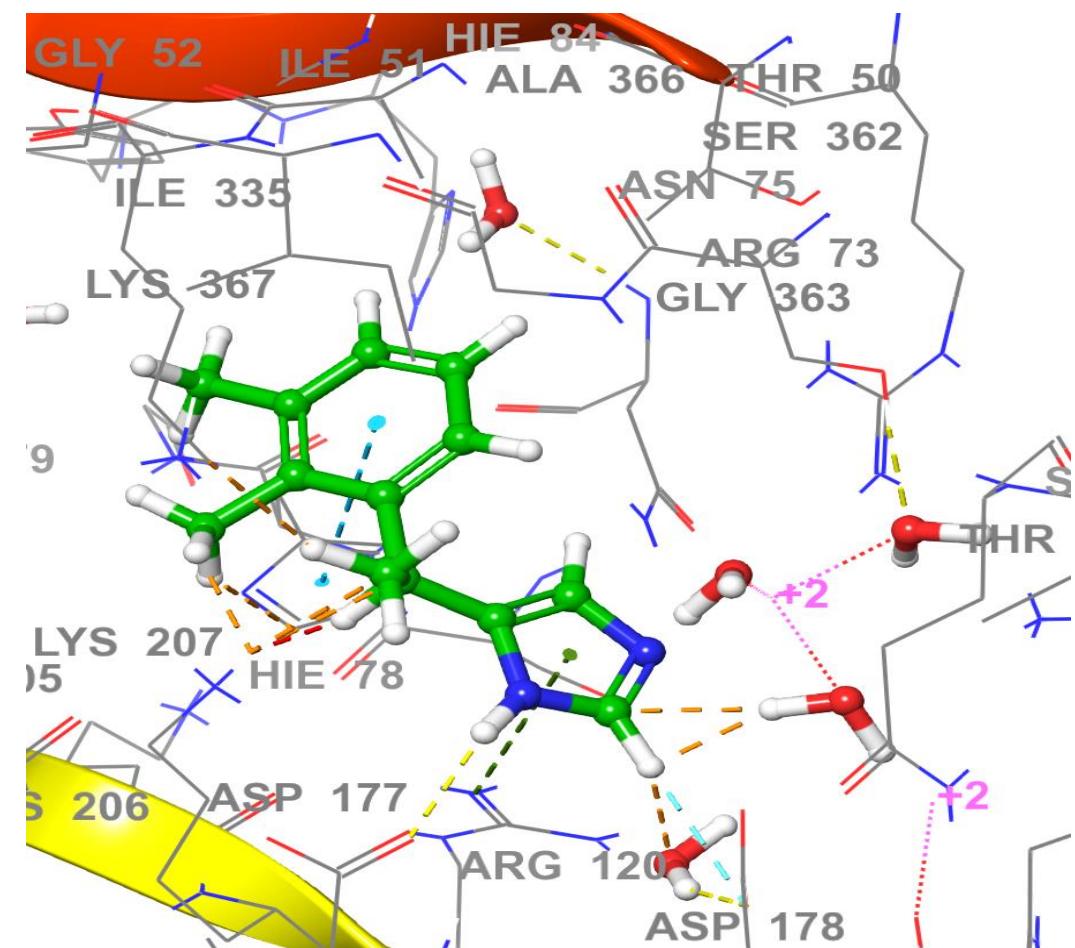
36



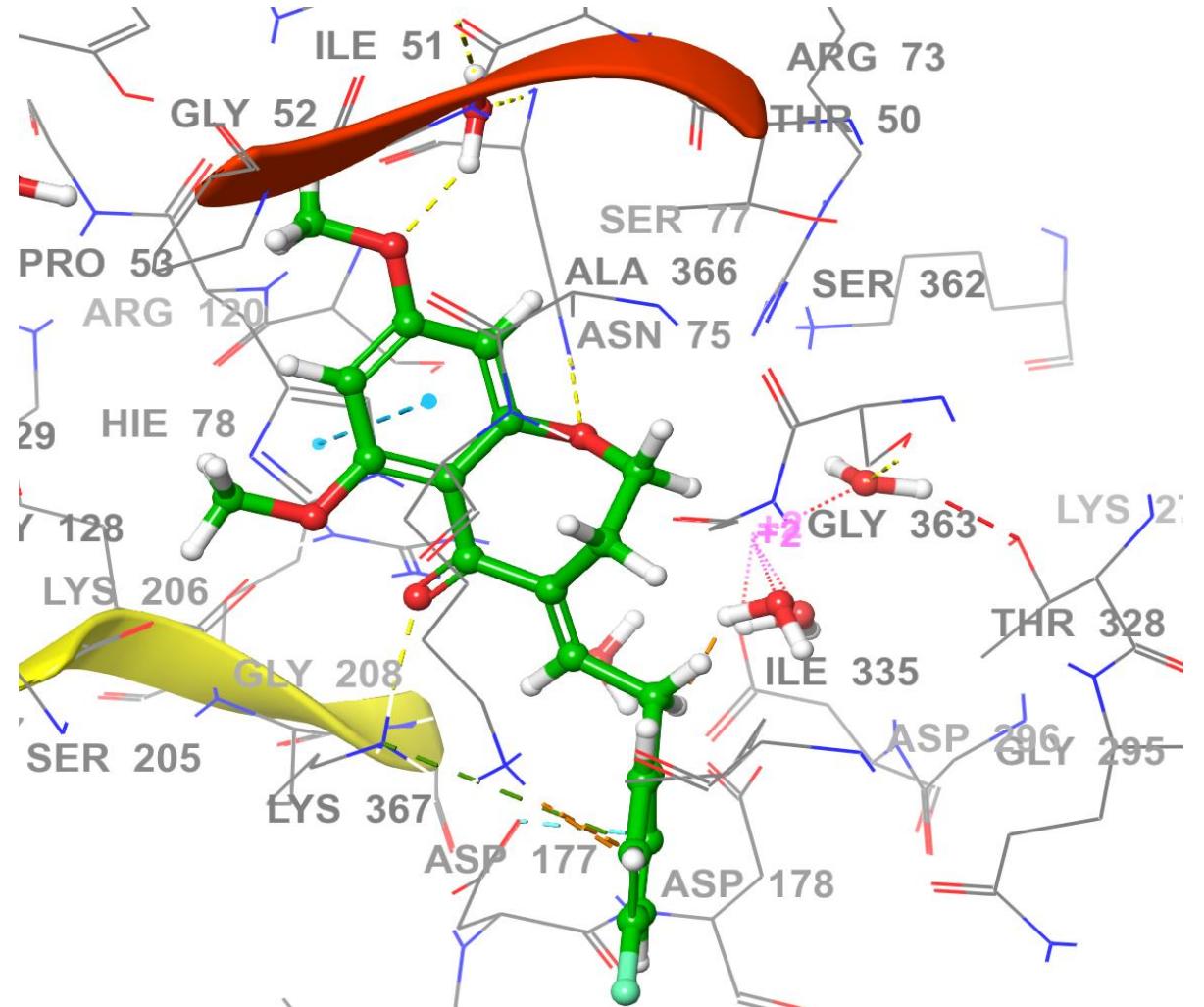
37



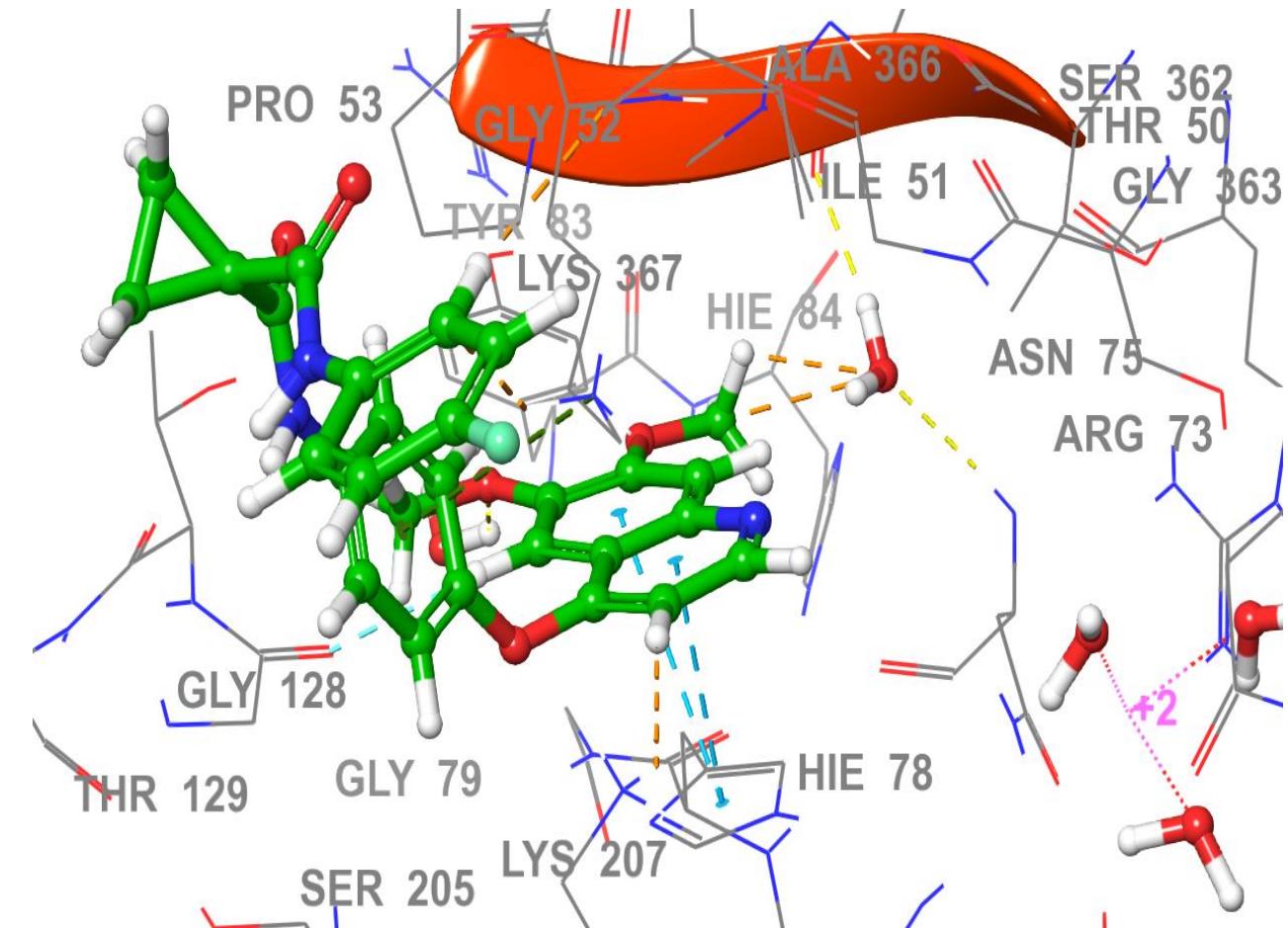
38



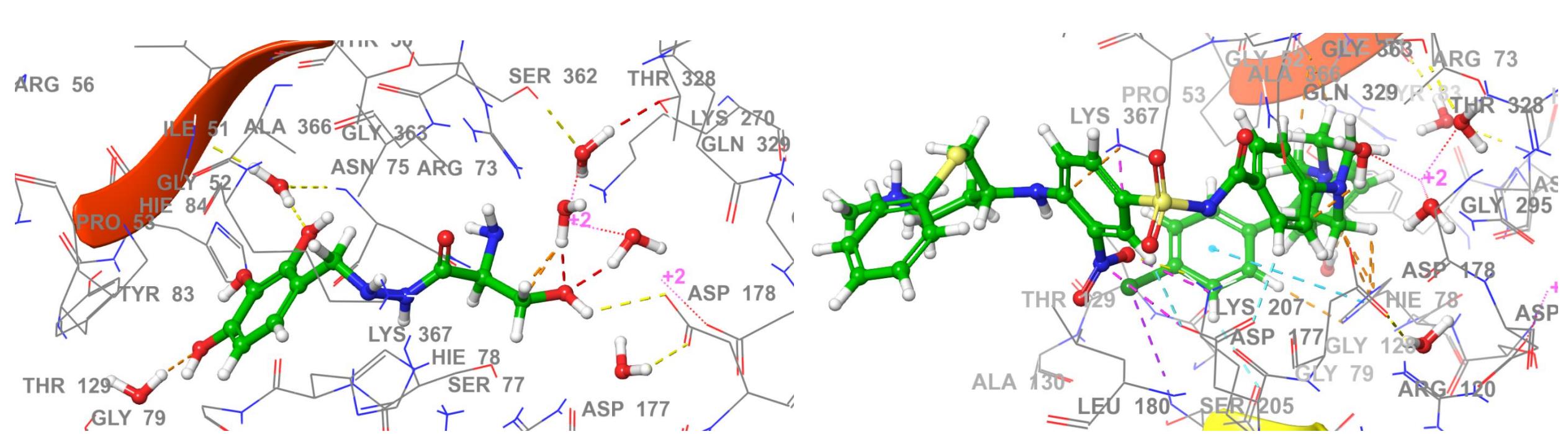
39



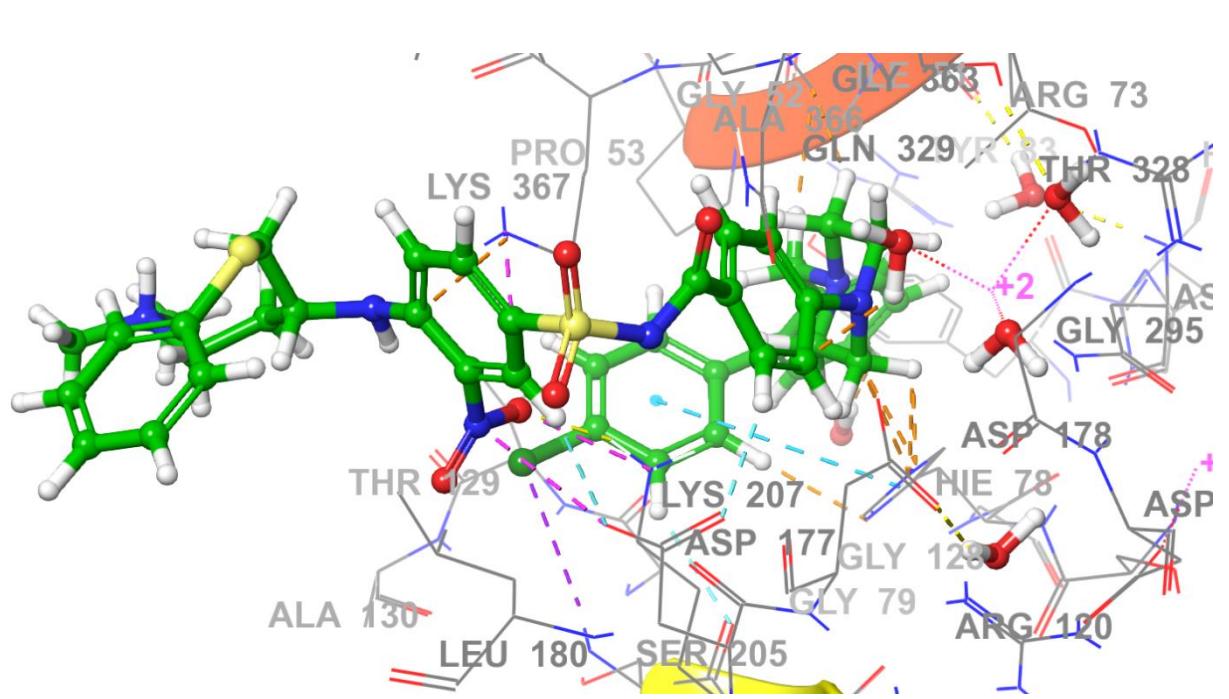
40



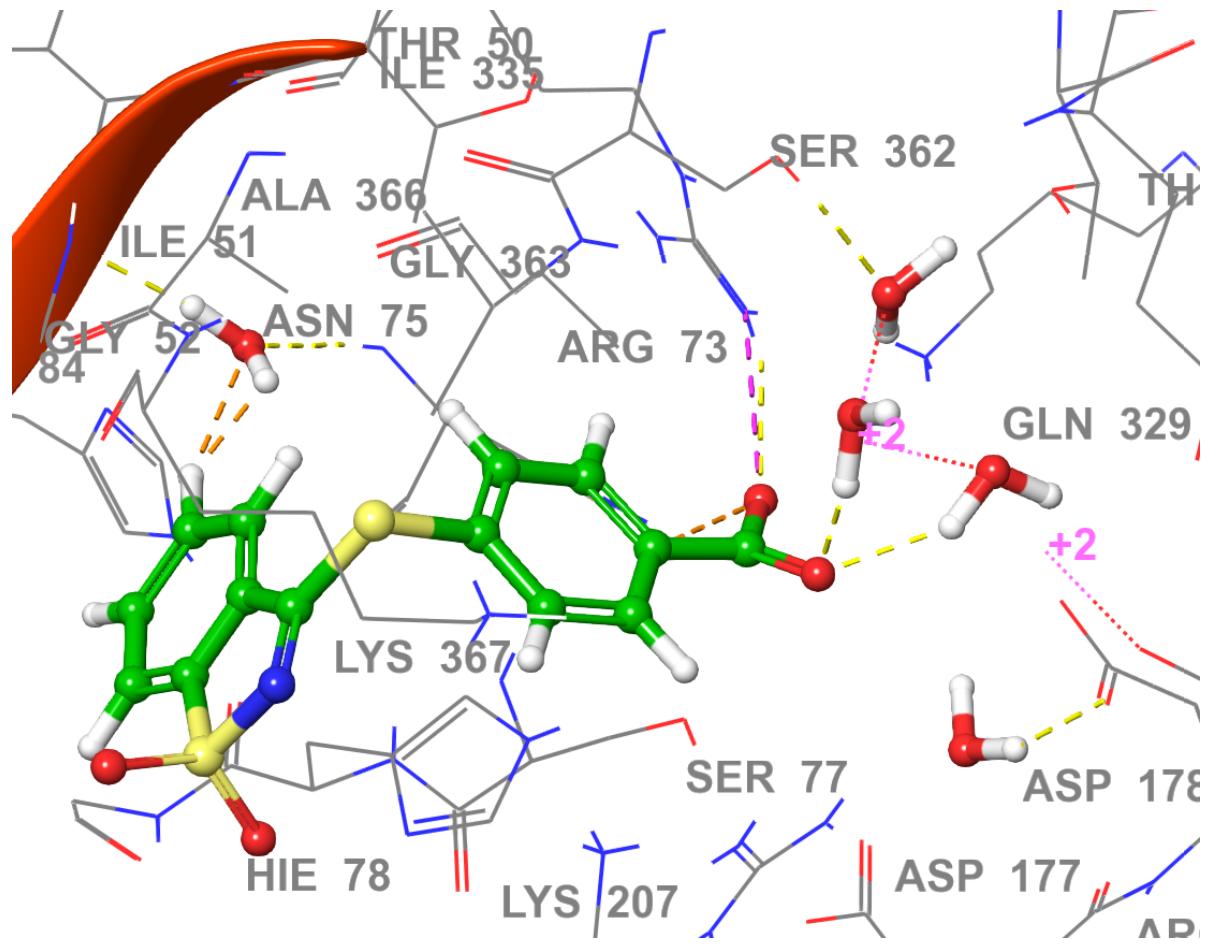
41



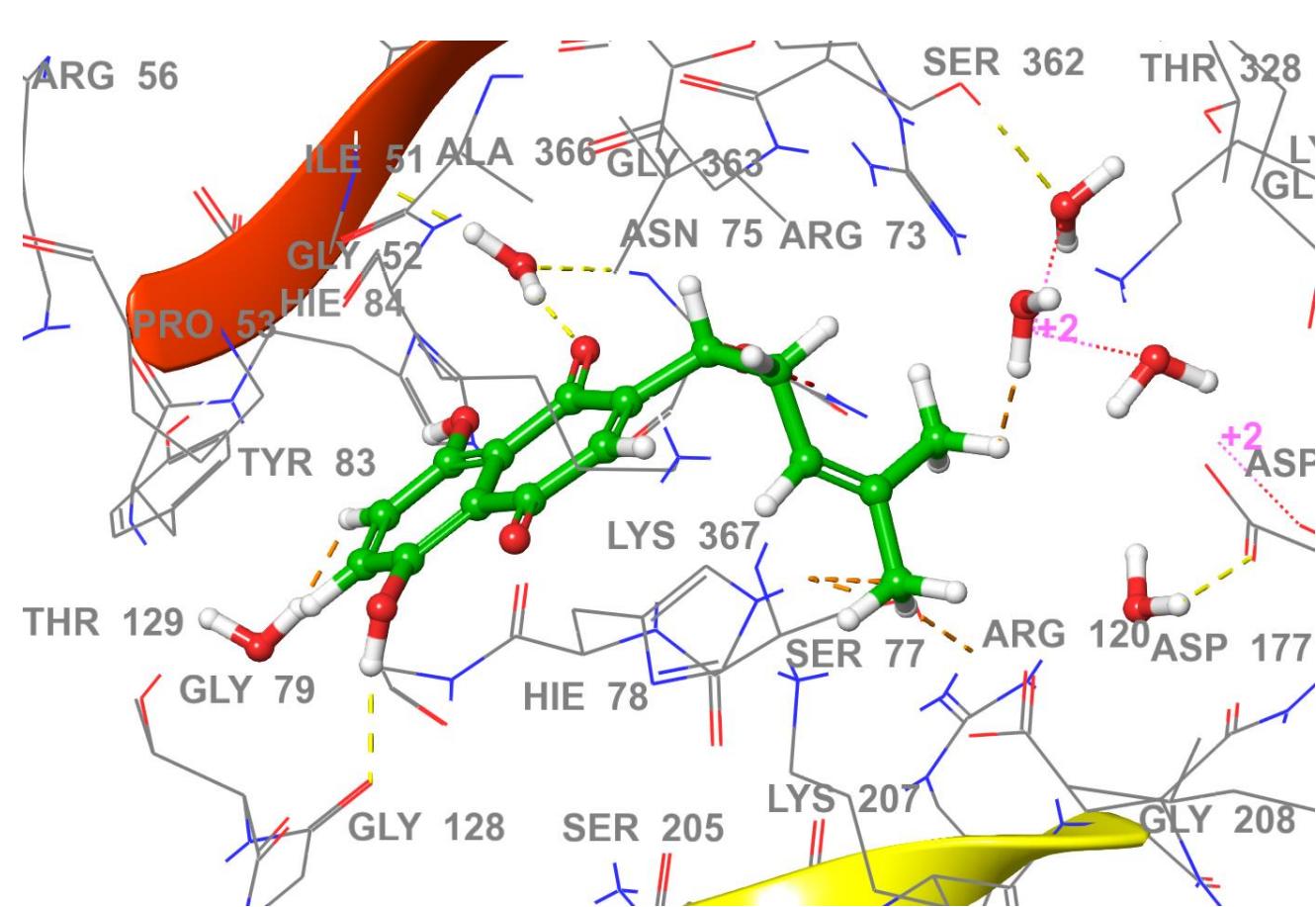
42



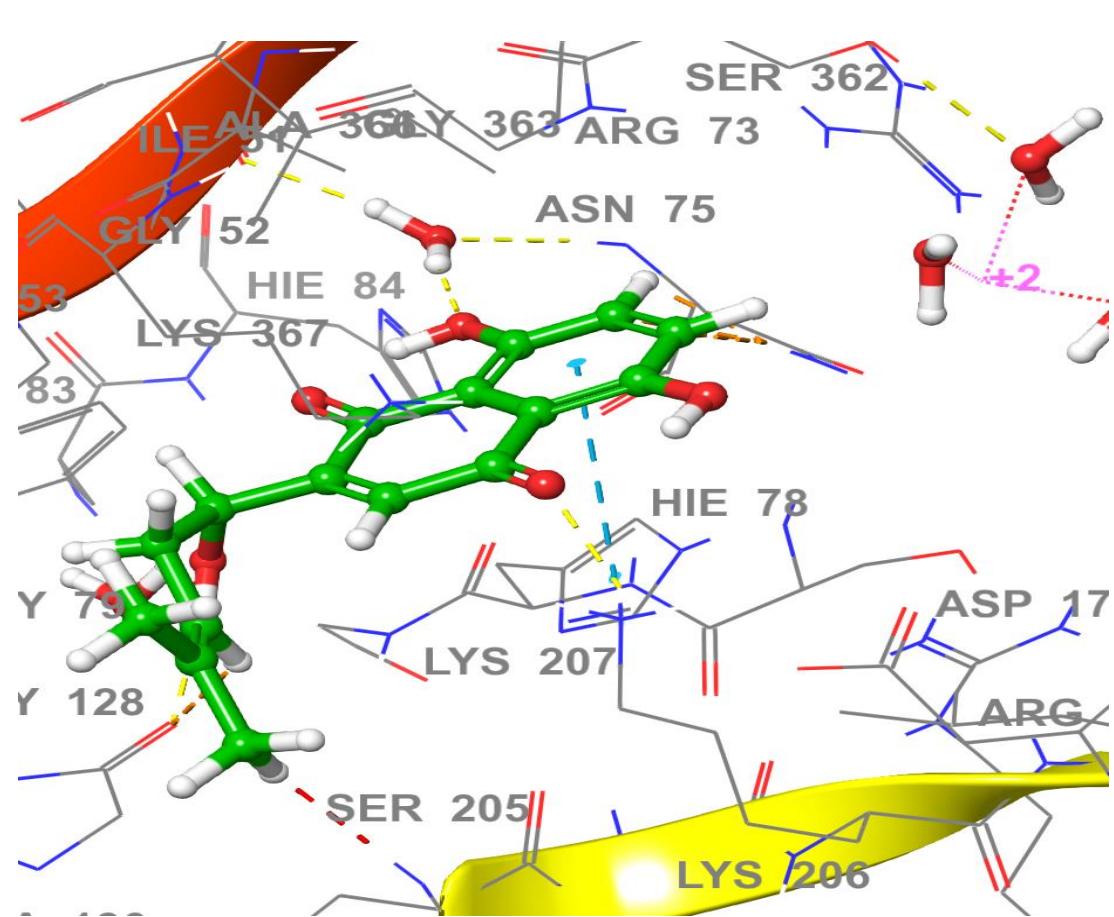
43



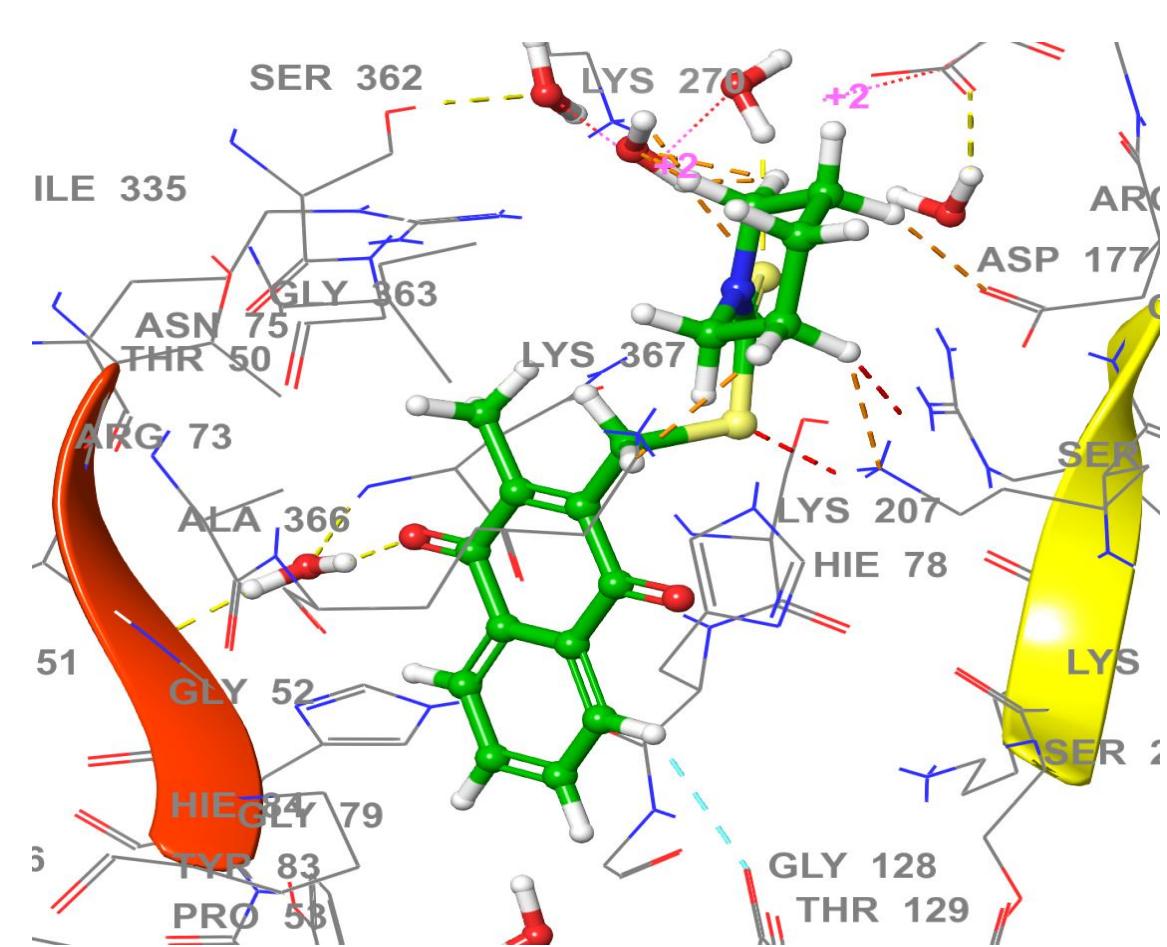
44



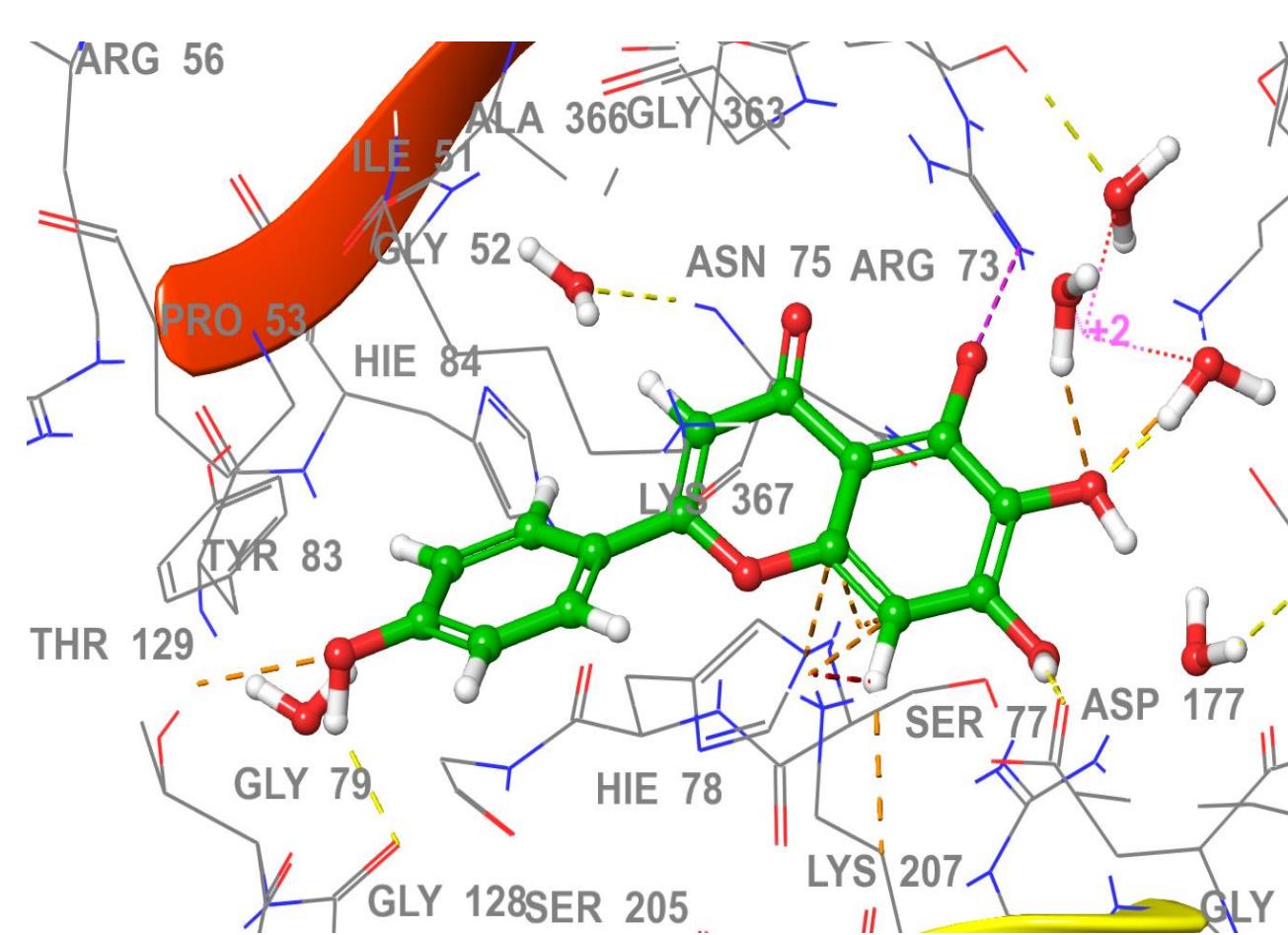
46



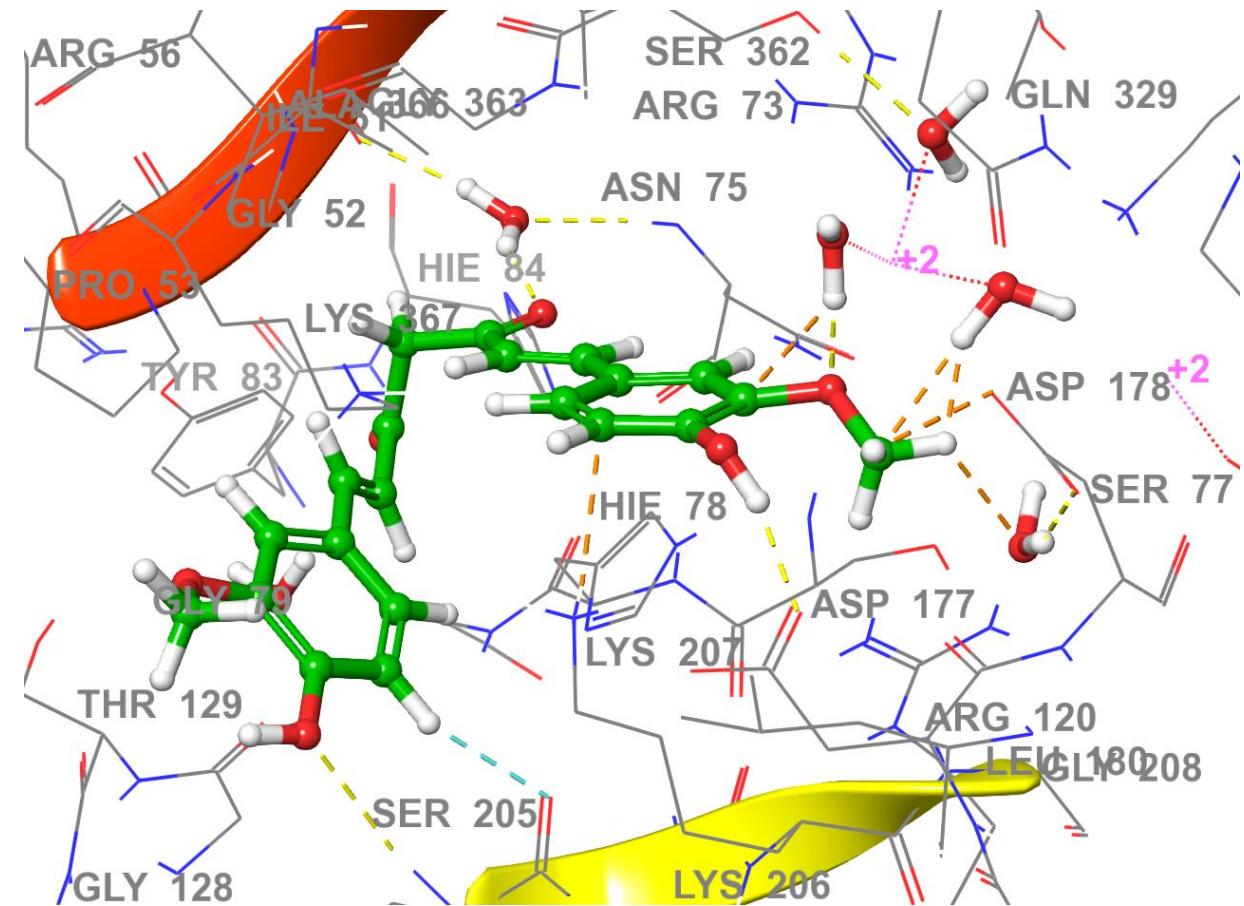
47



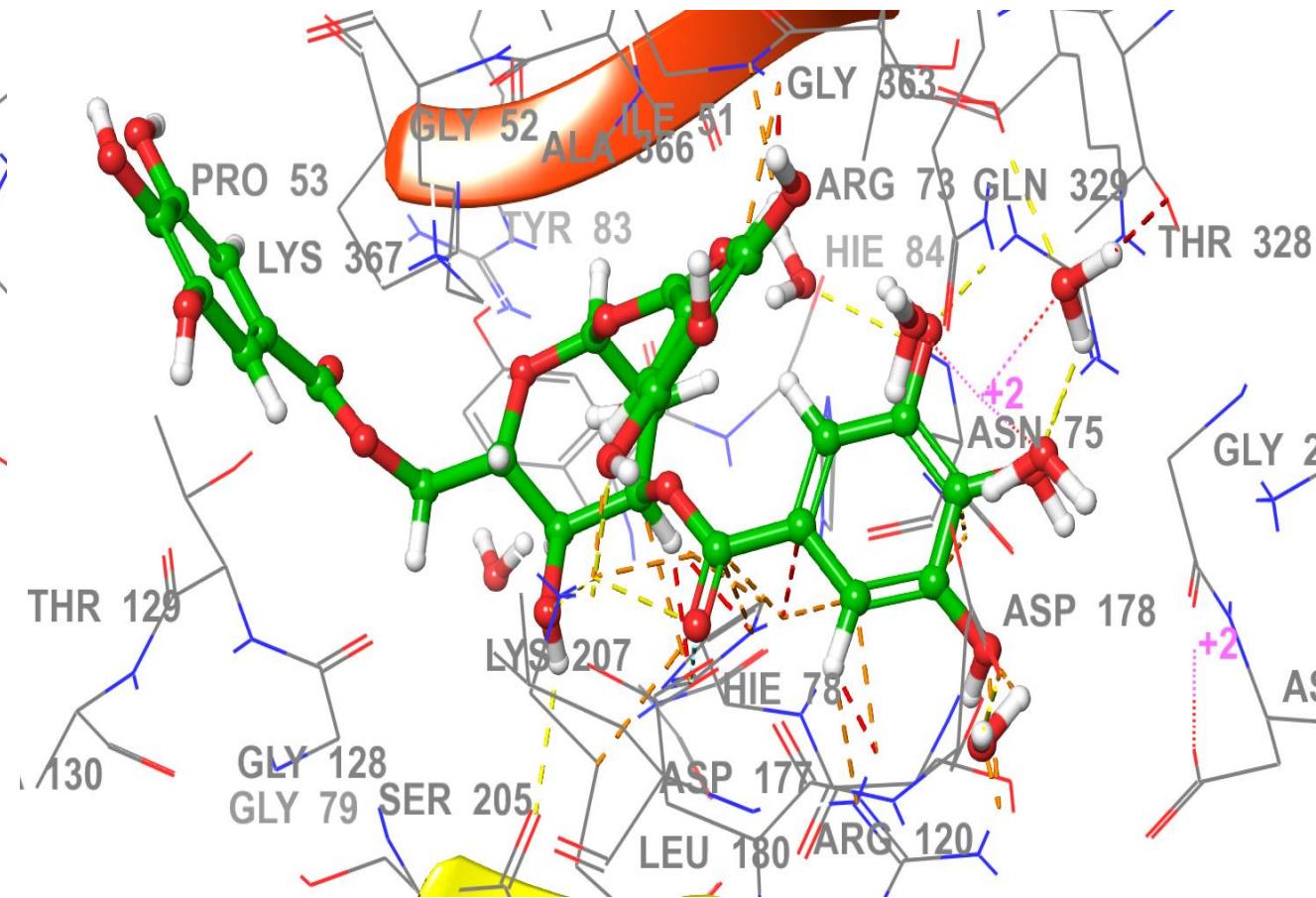
48



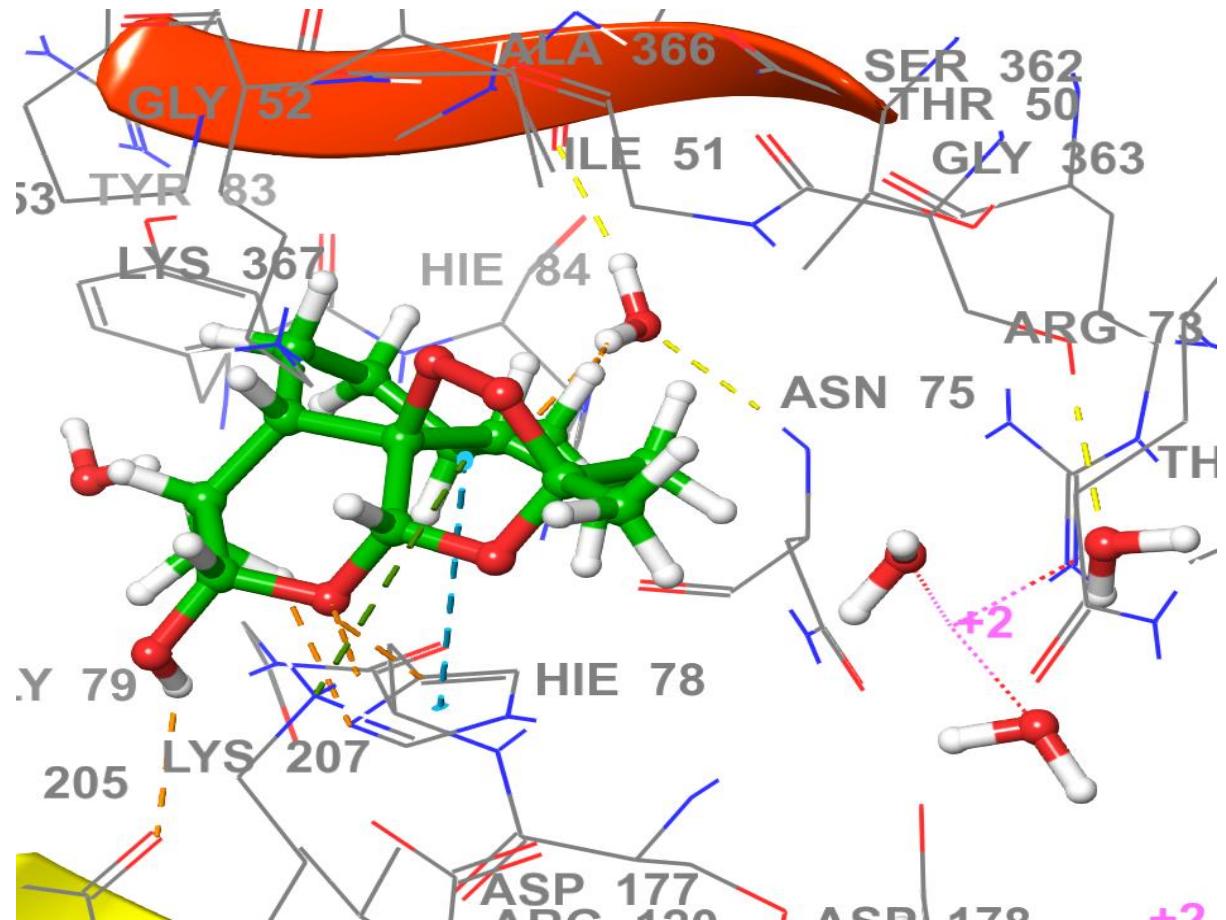
51



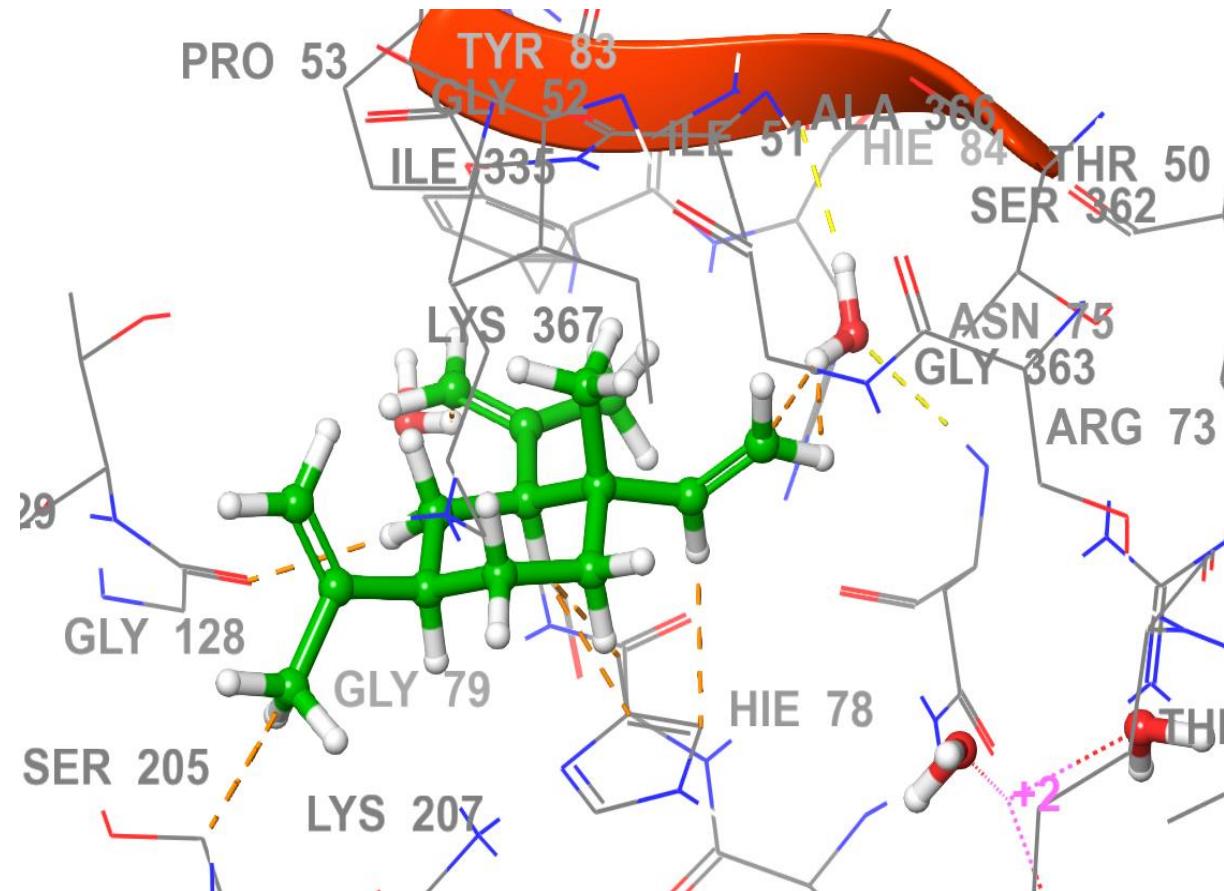
52



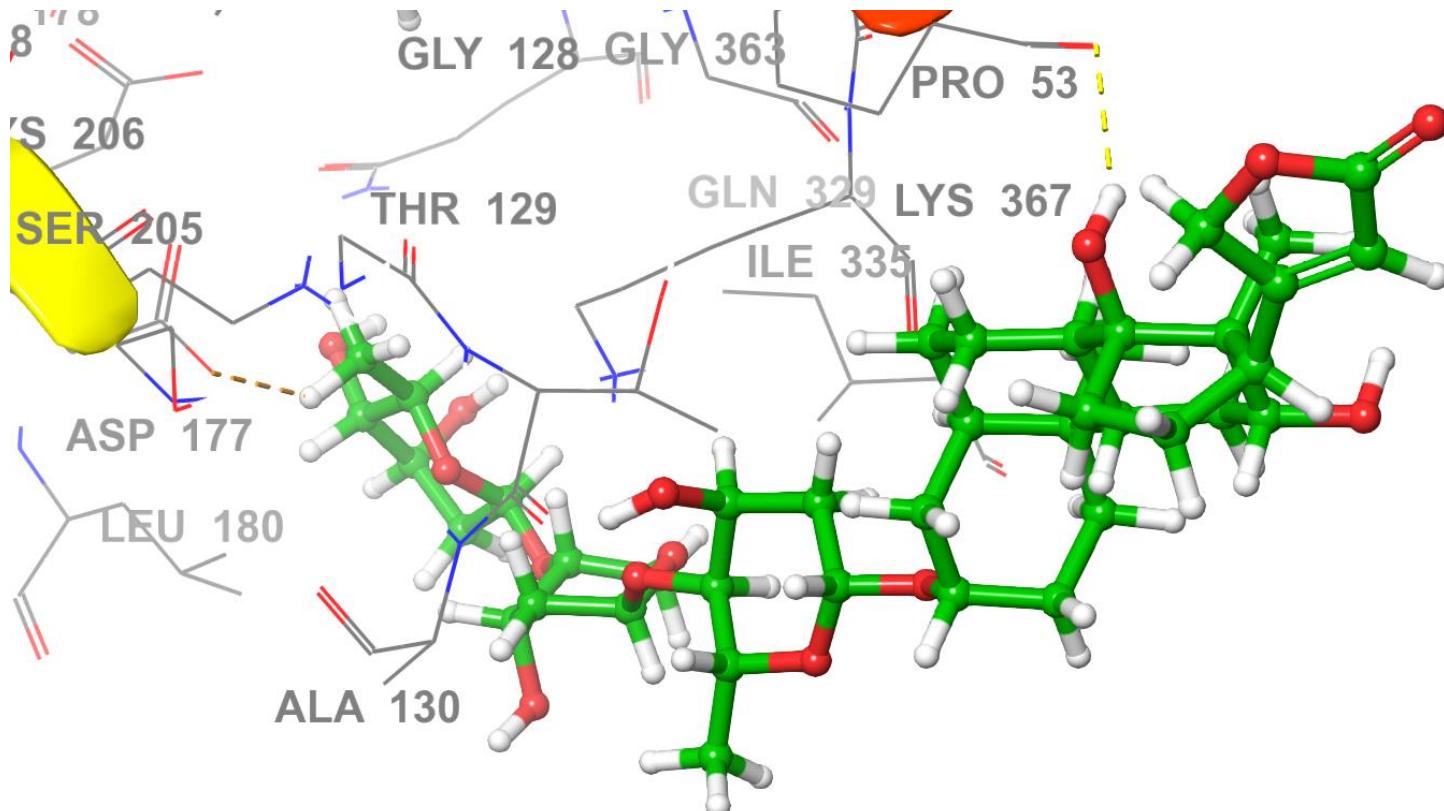
53



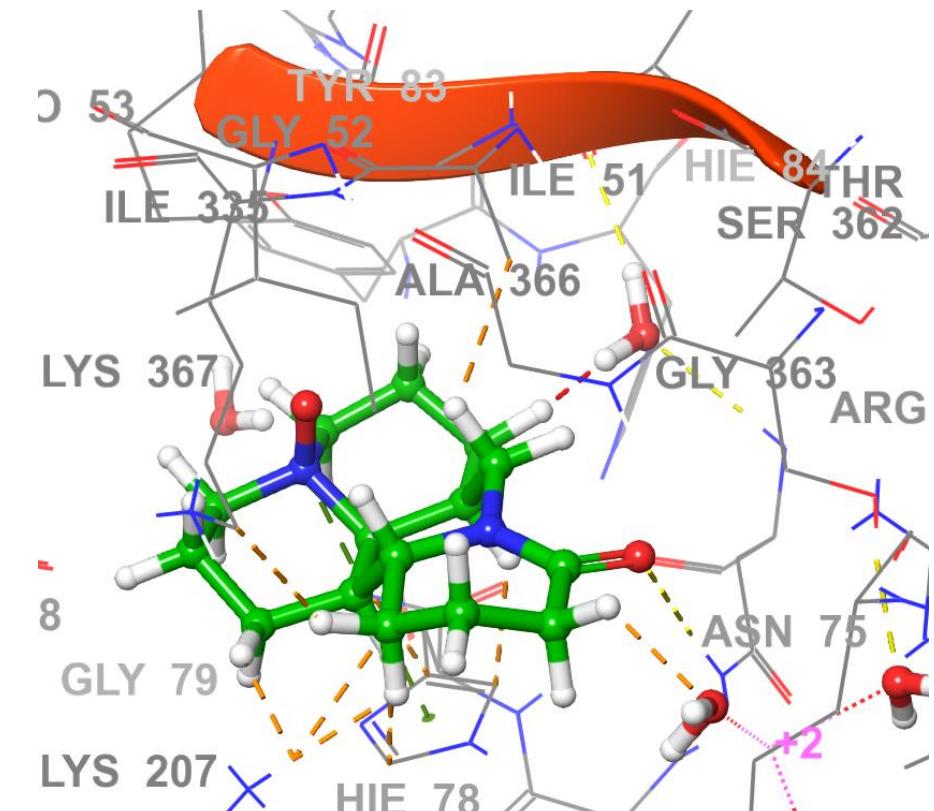
54



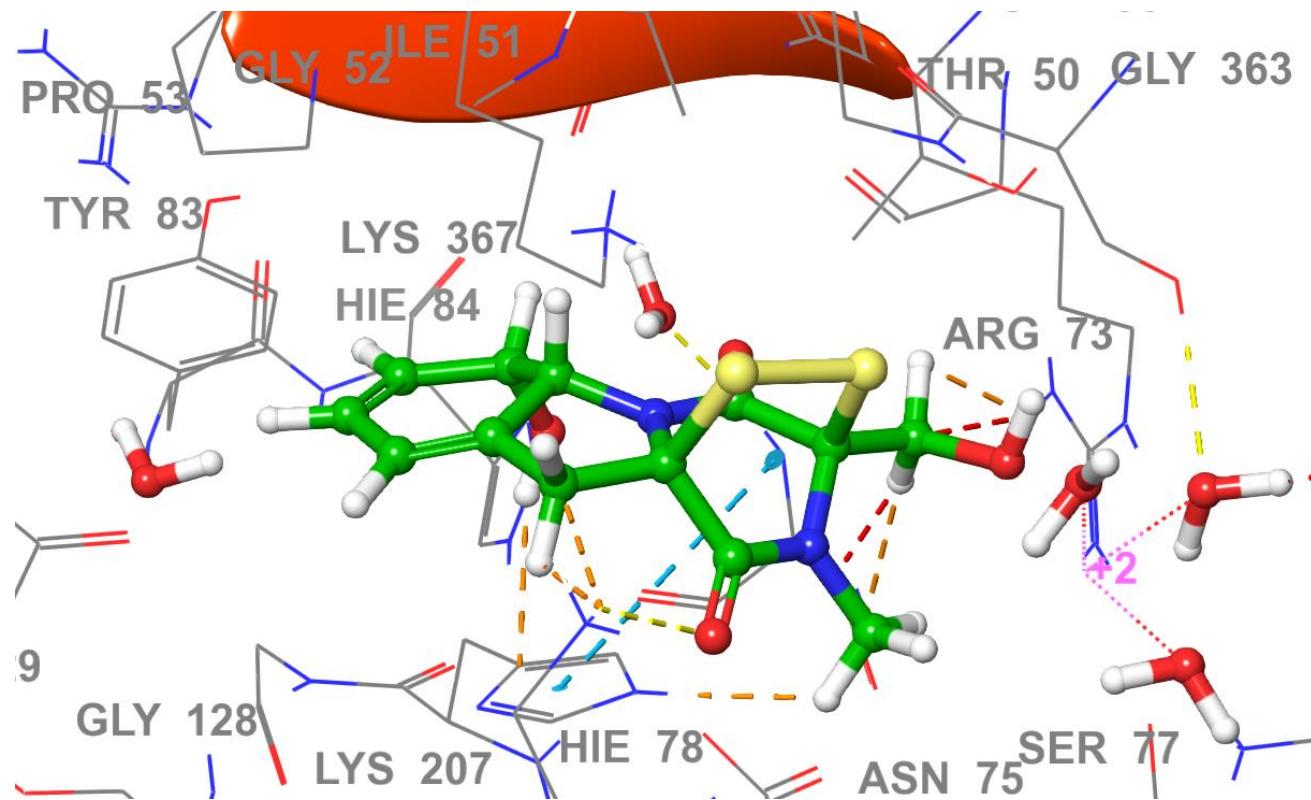
55



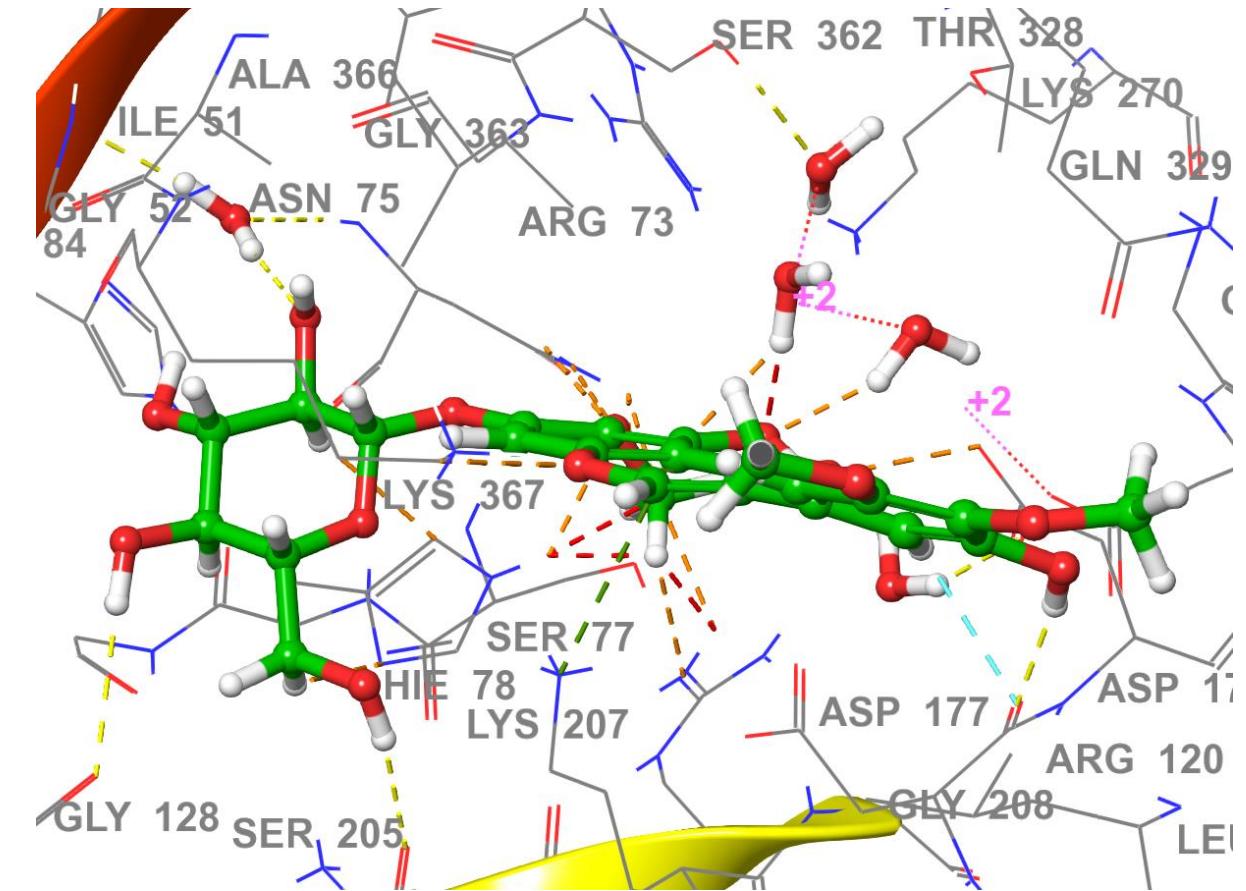
56



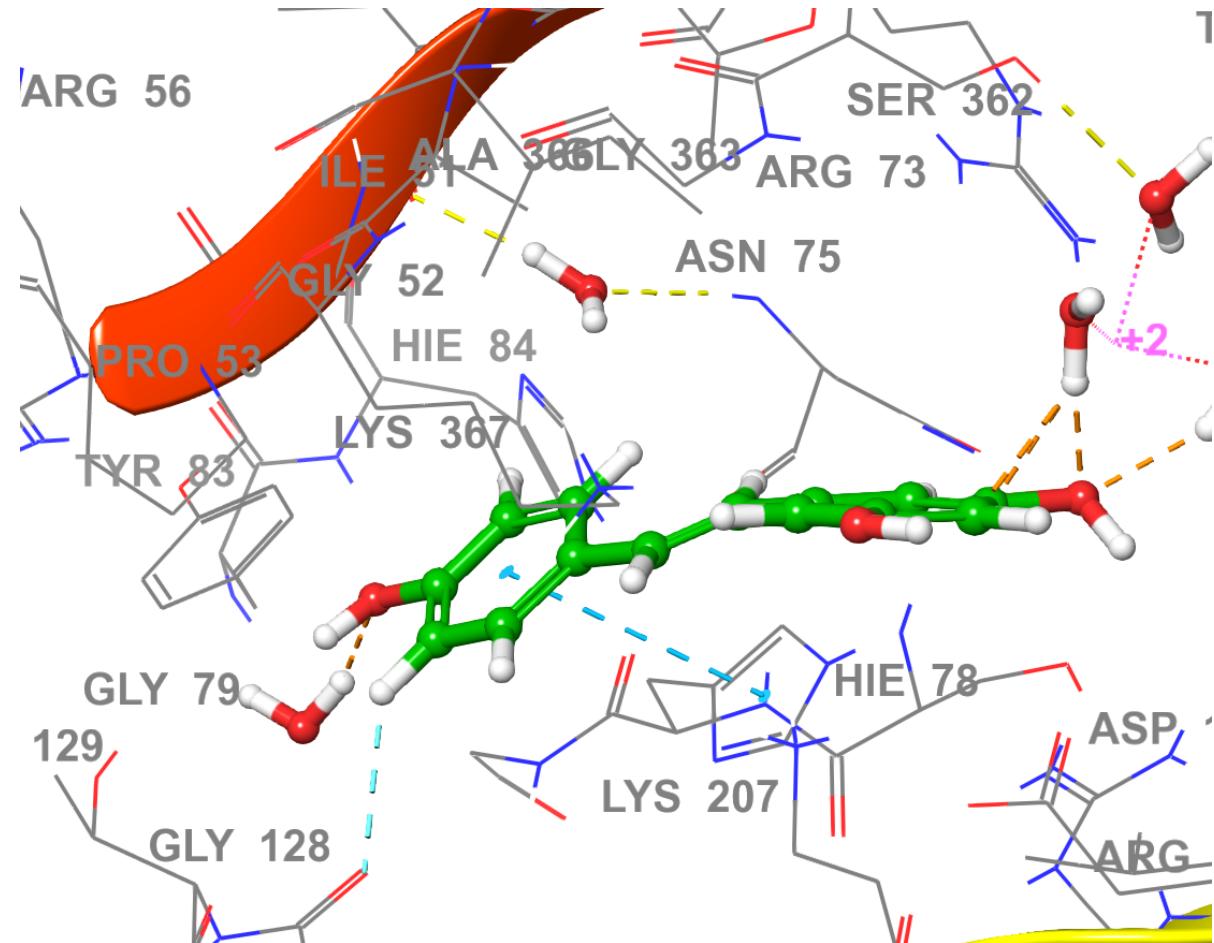
57



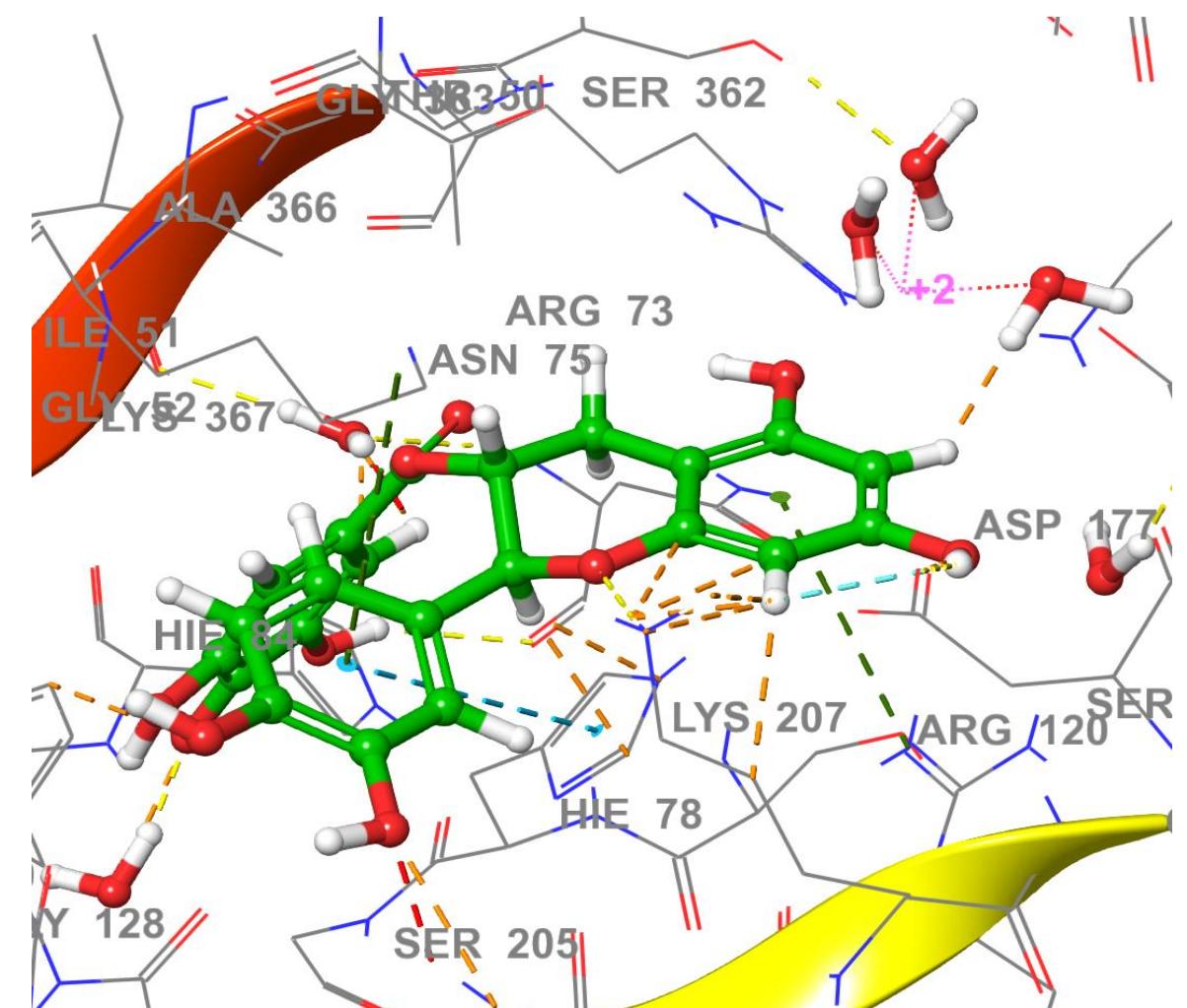
58



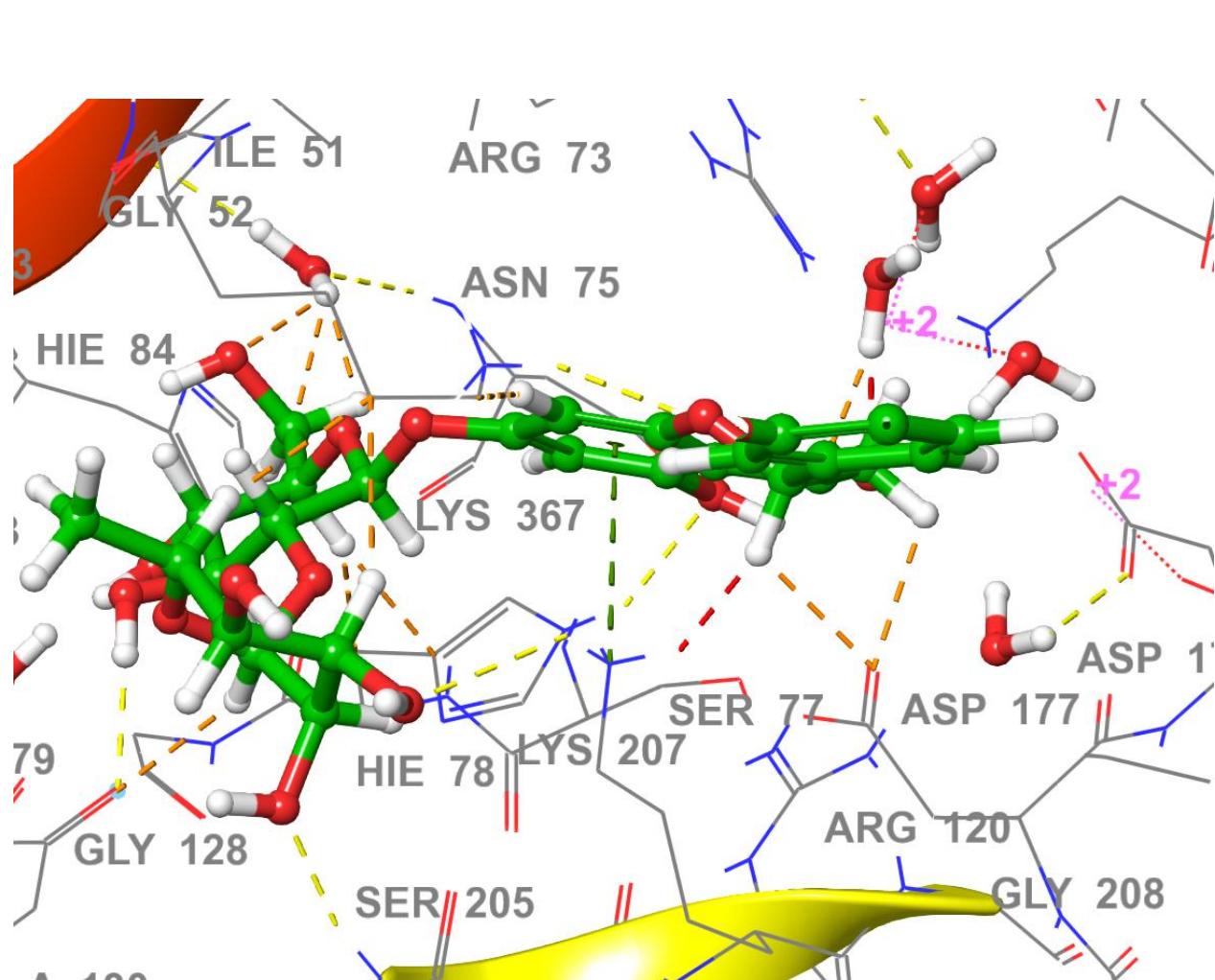
60



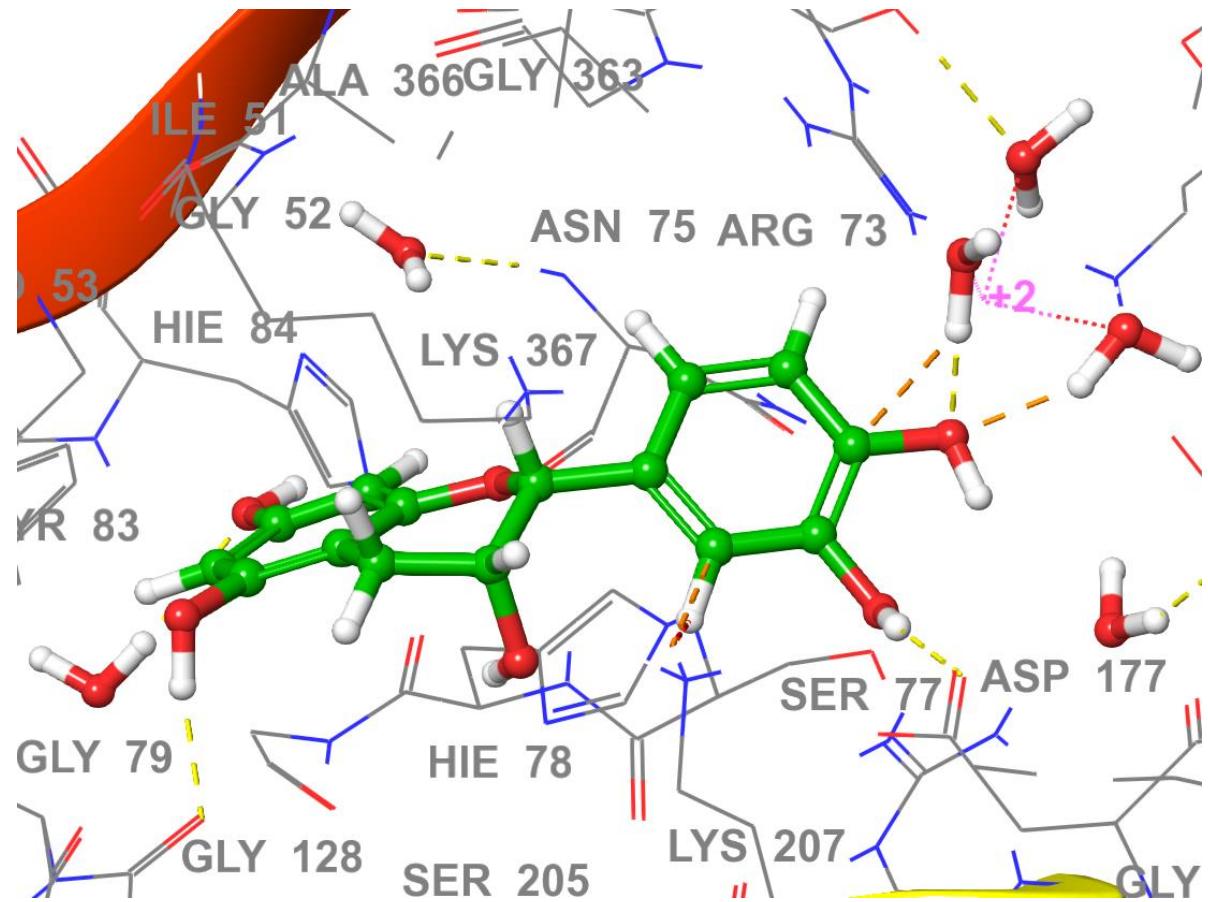
61



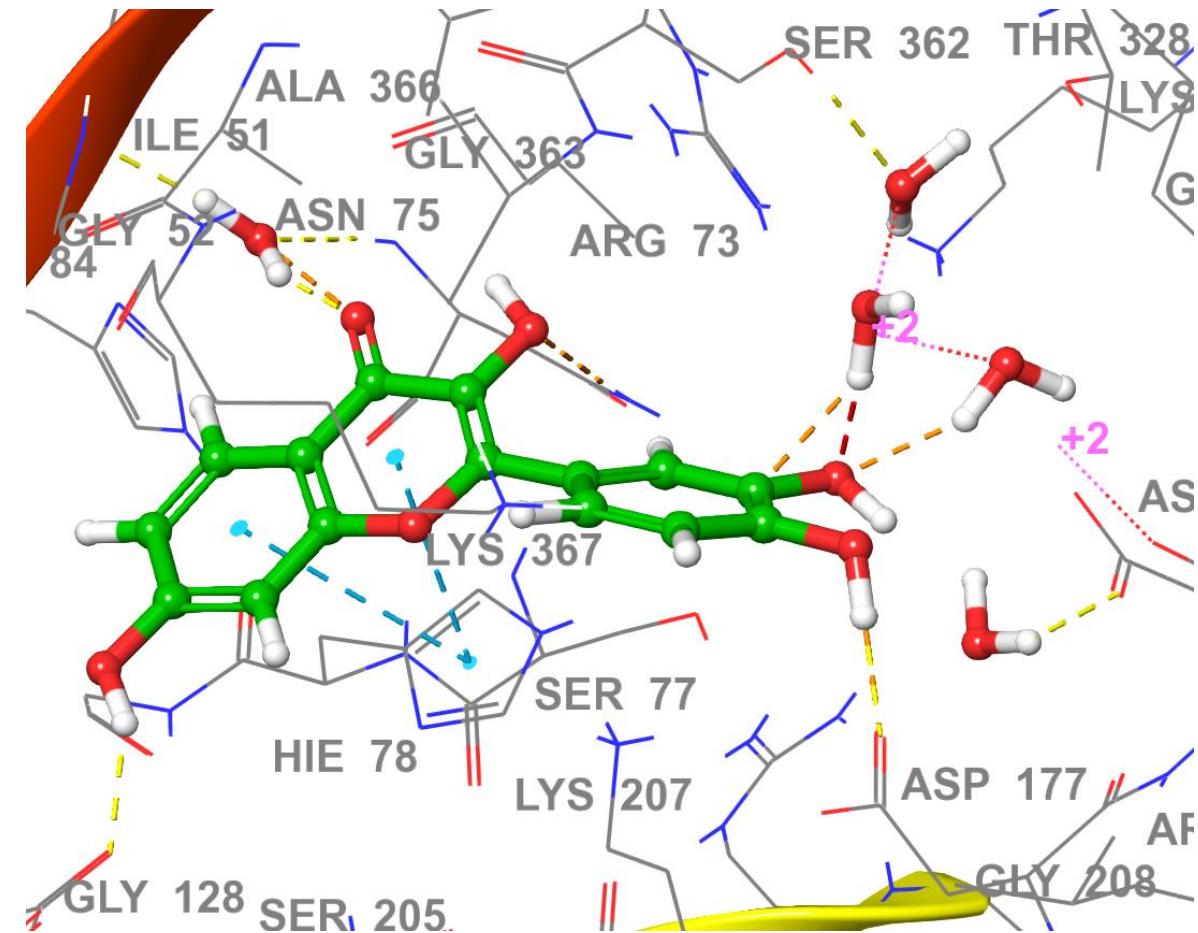
62



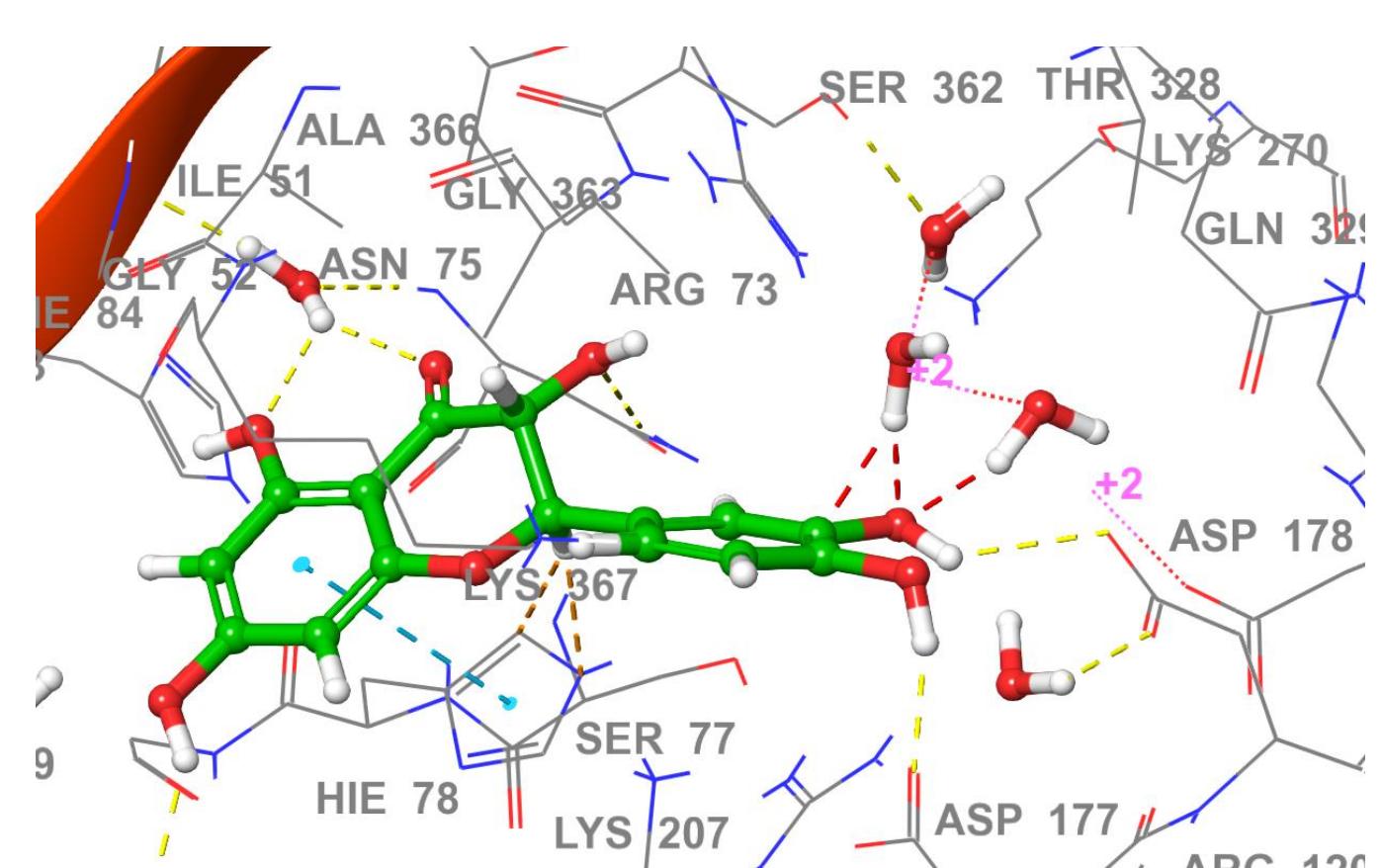
63



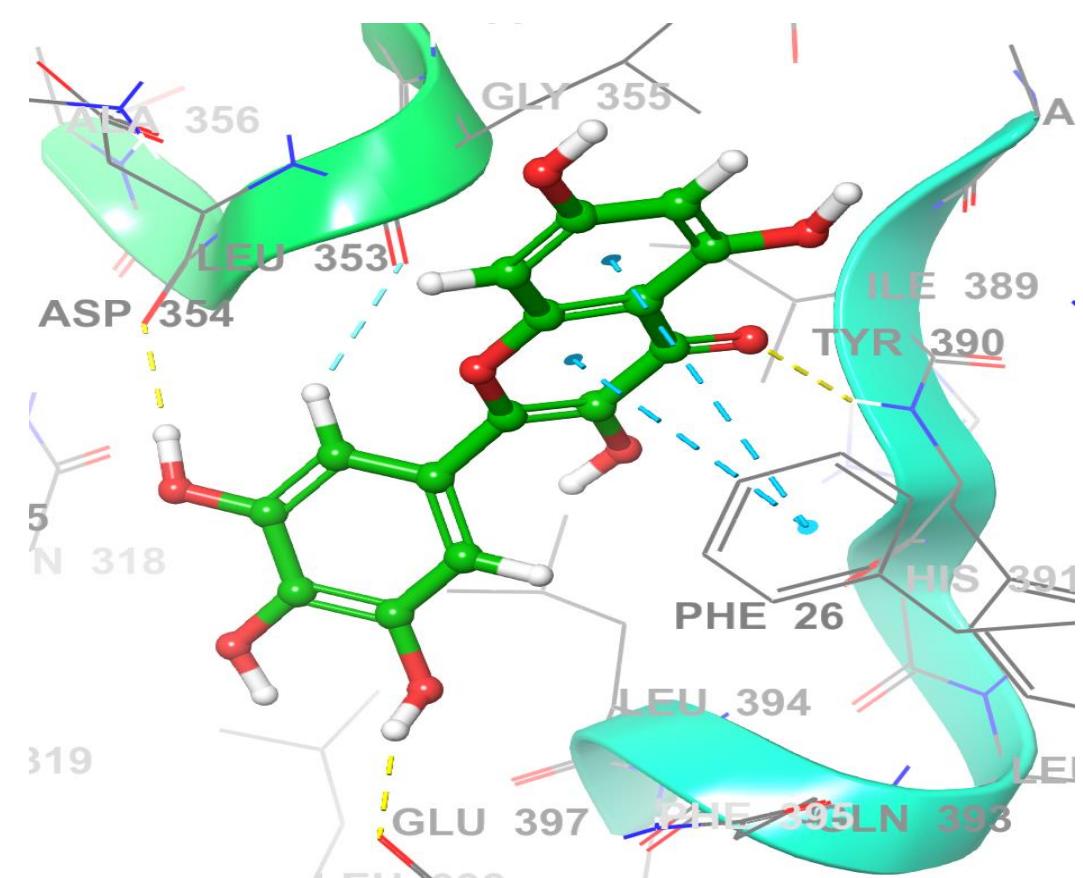
64



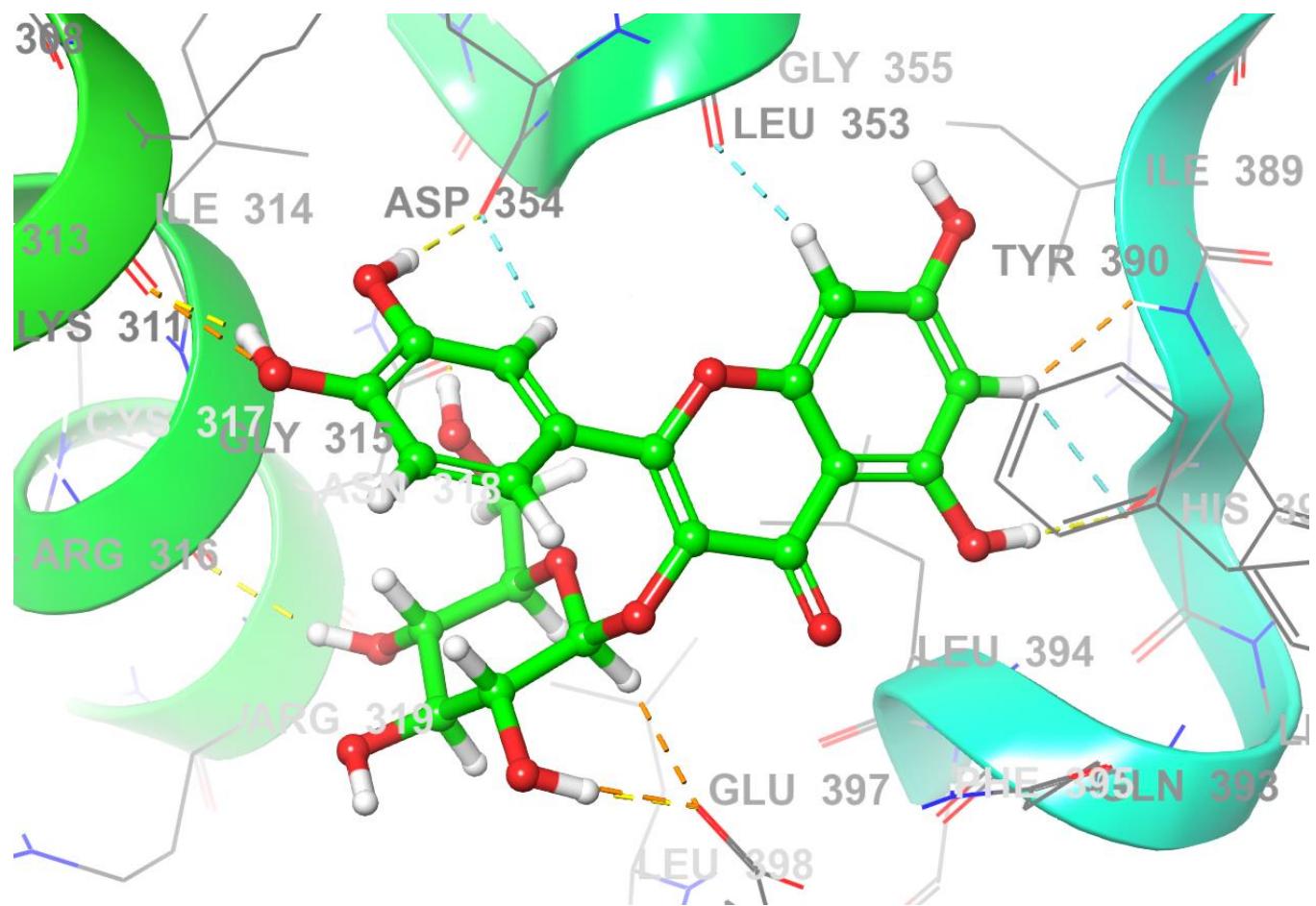
65



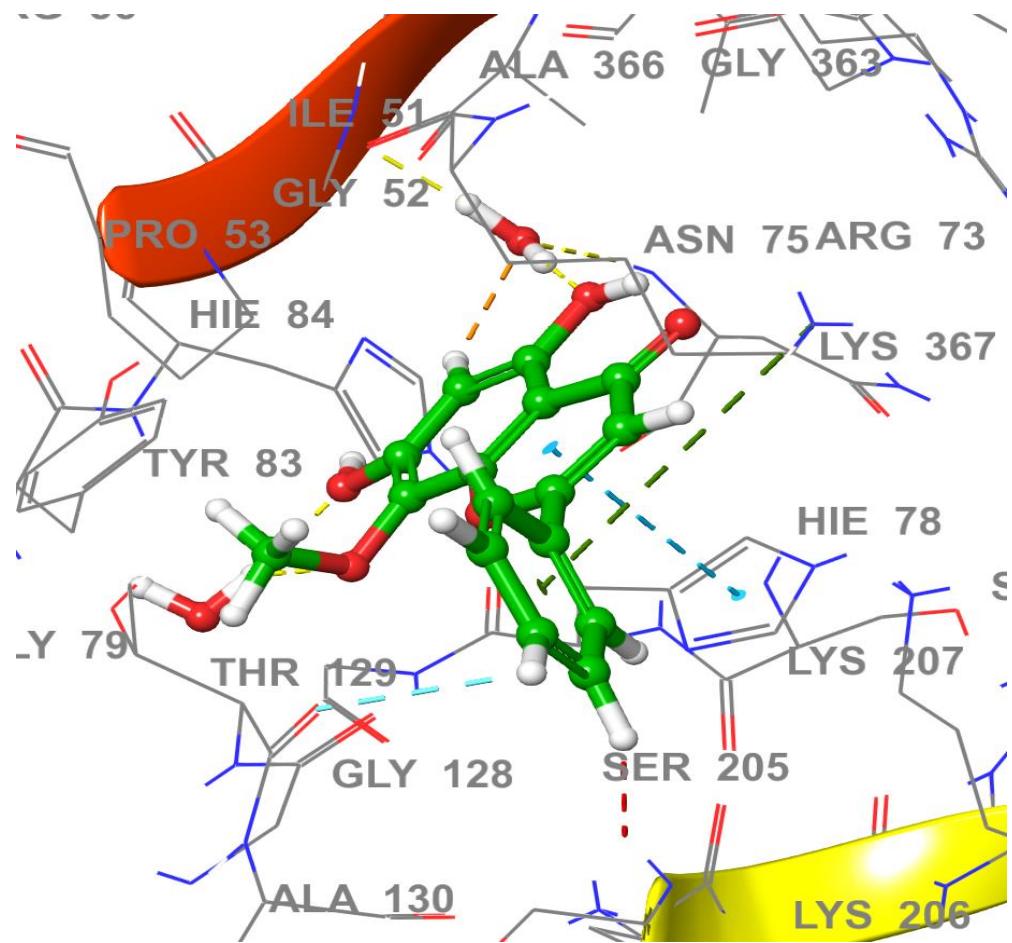
66



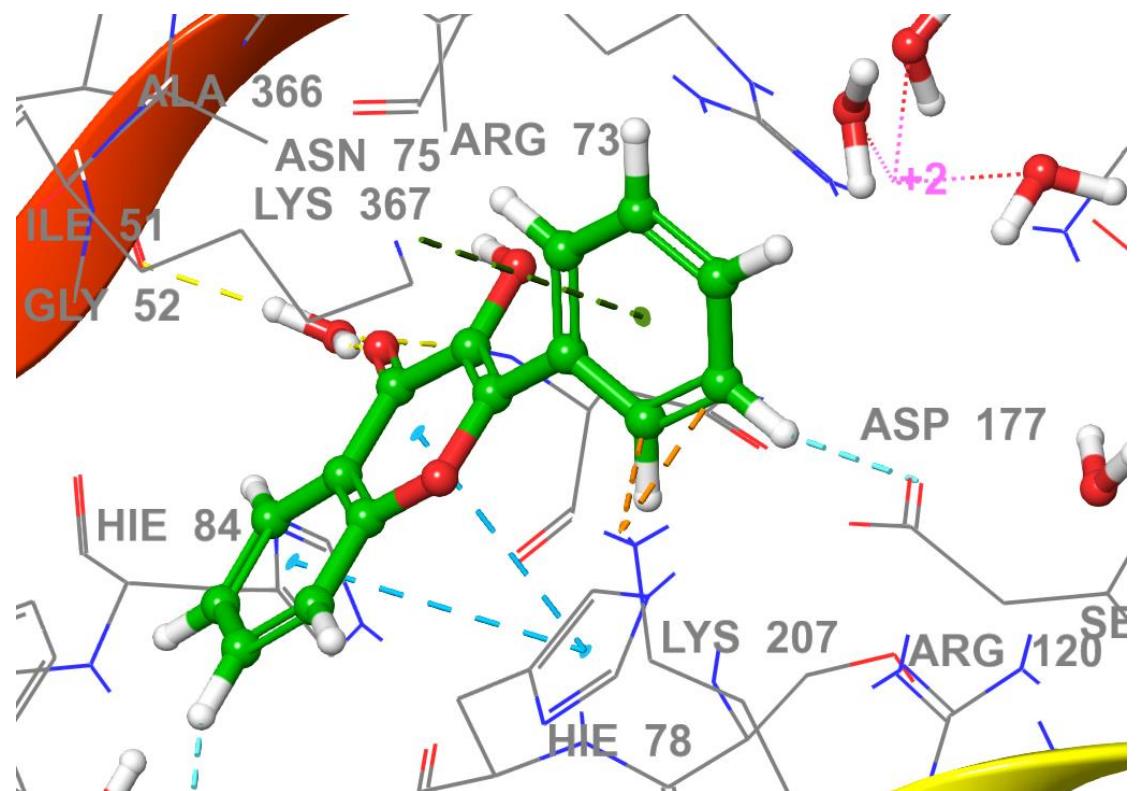
67



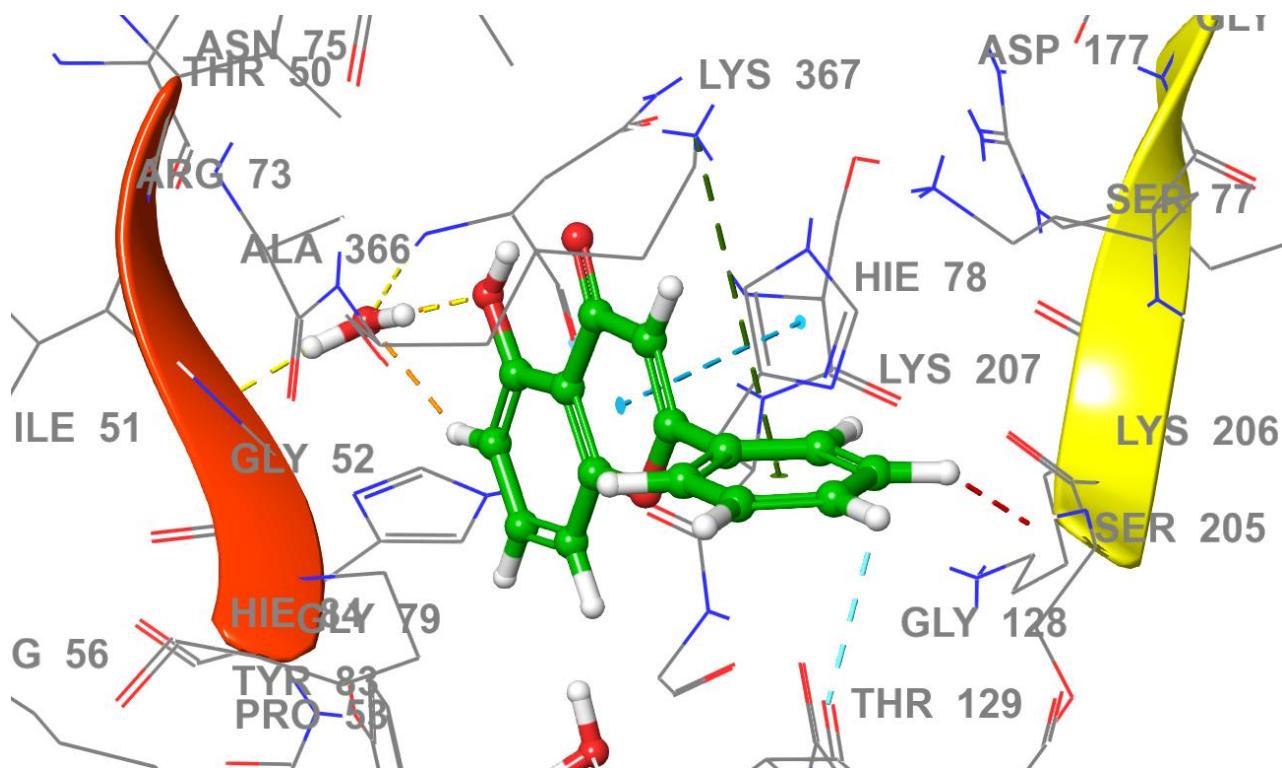
68



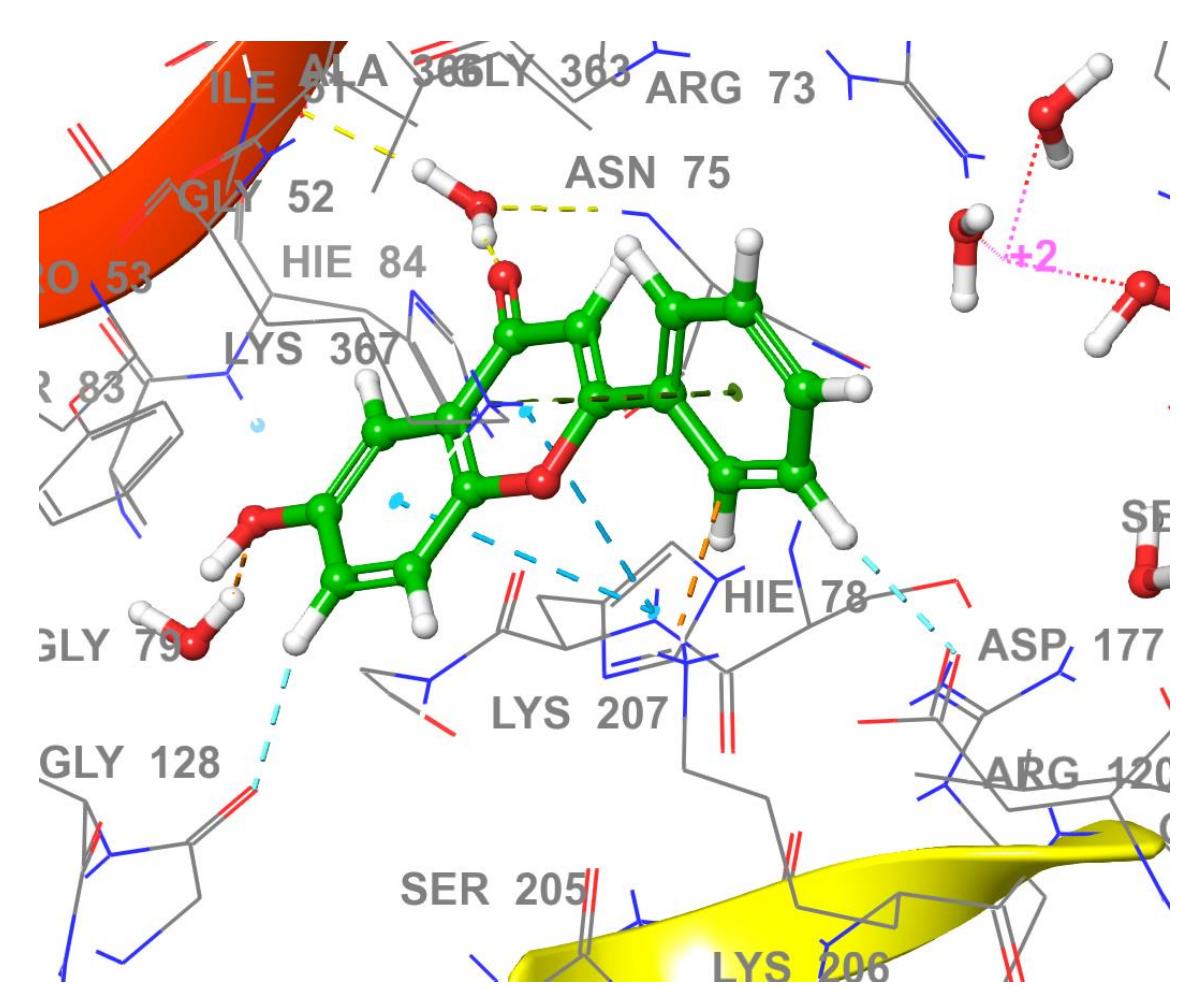
69



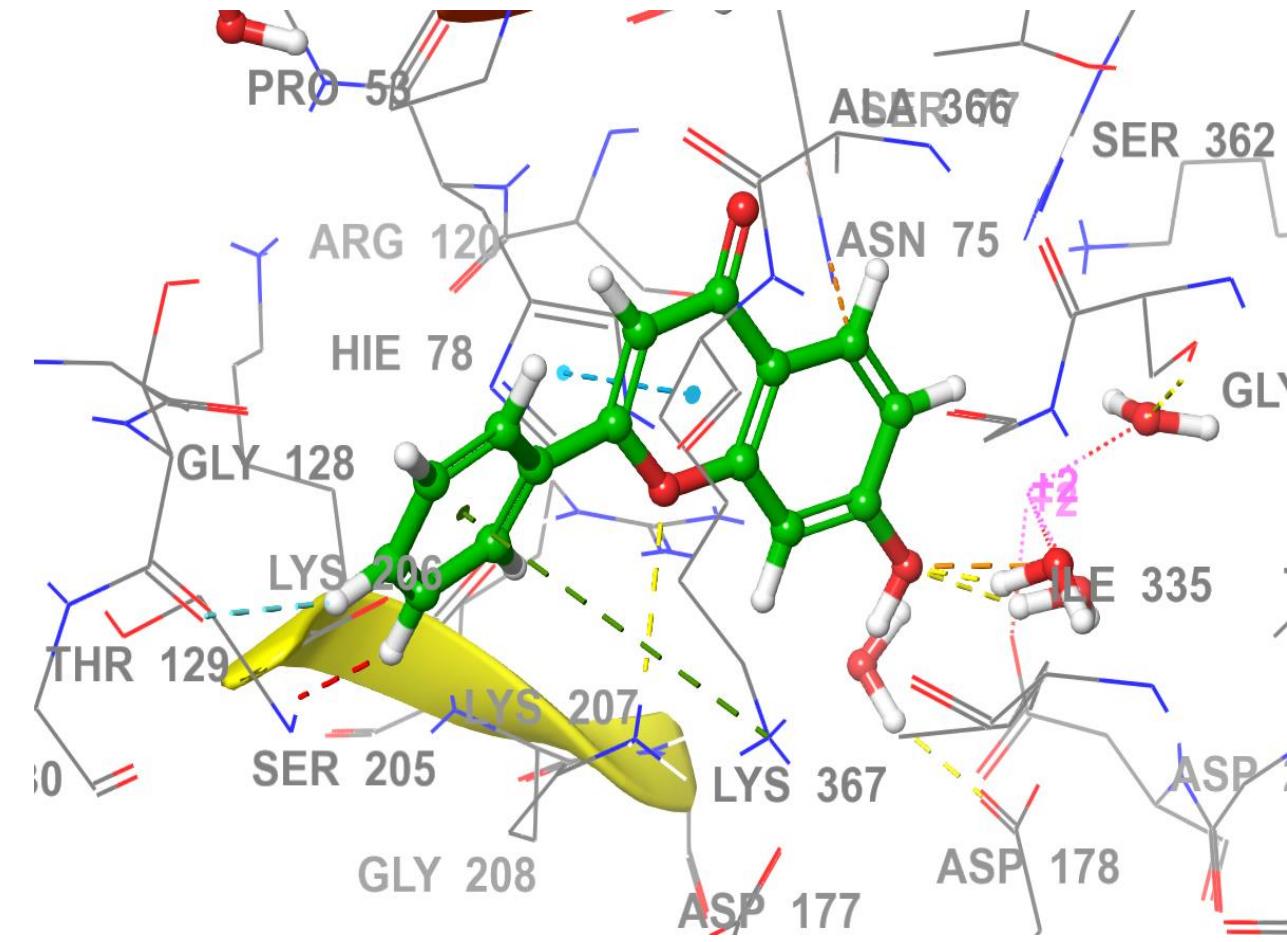
70



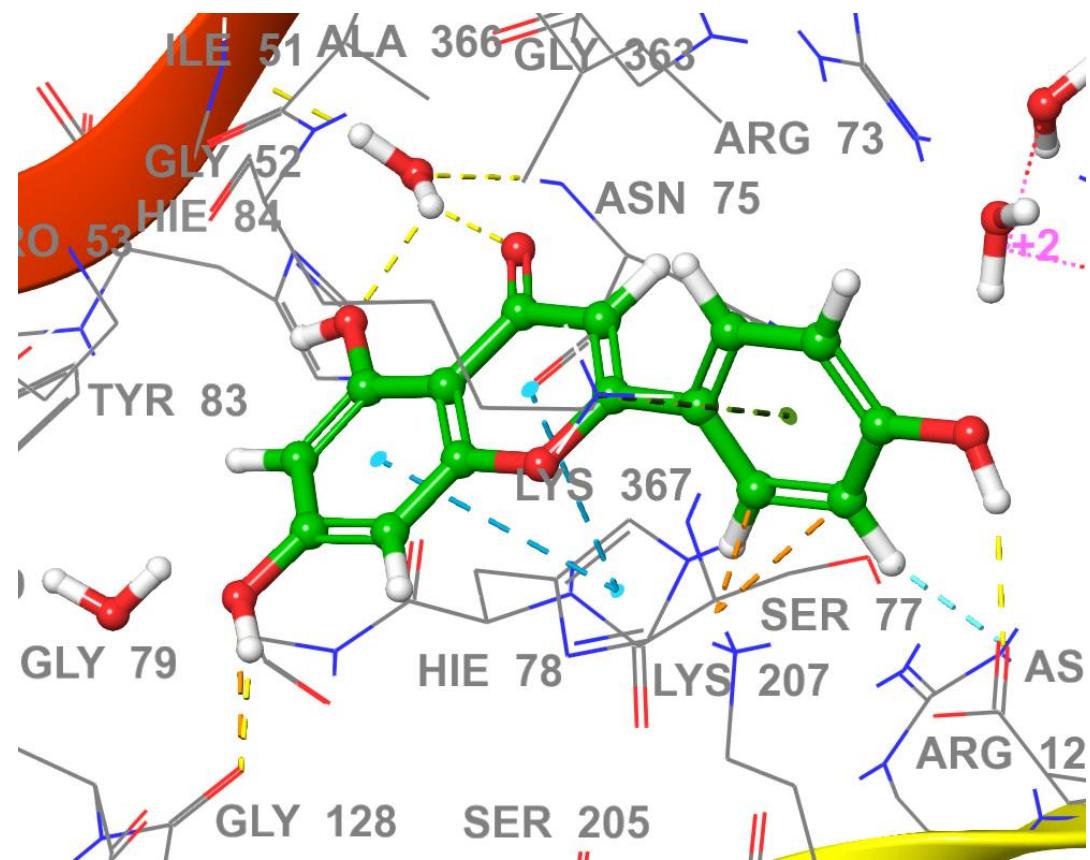
71



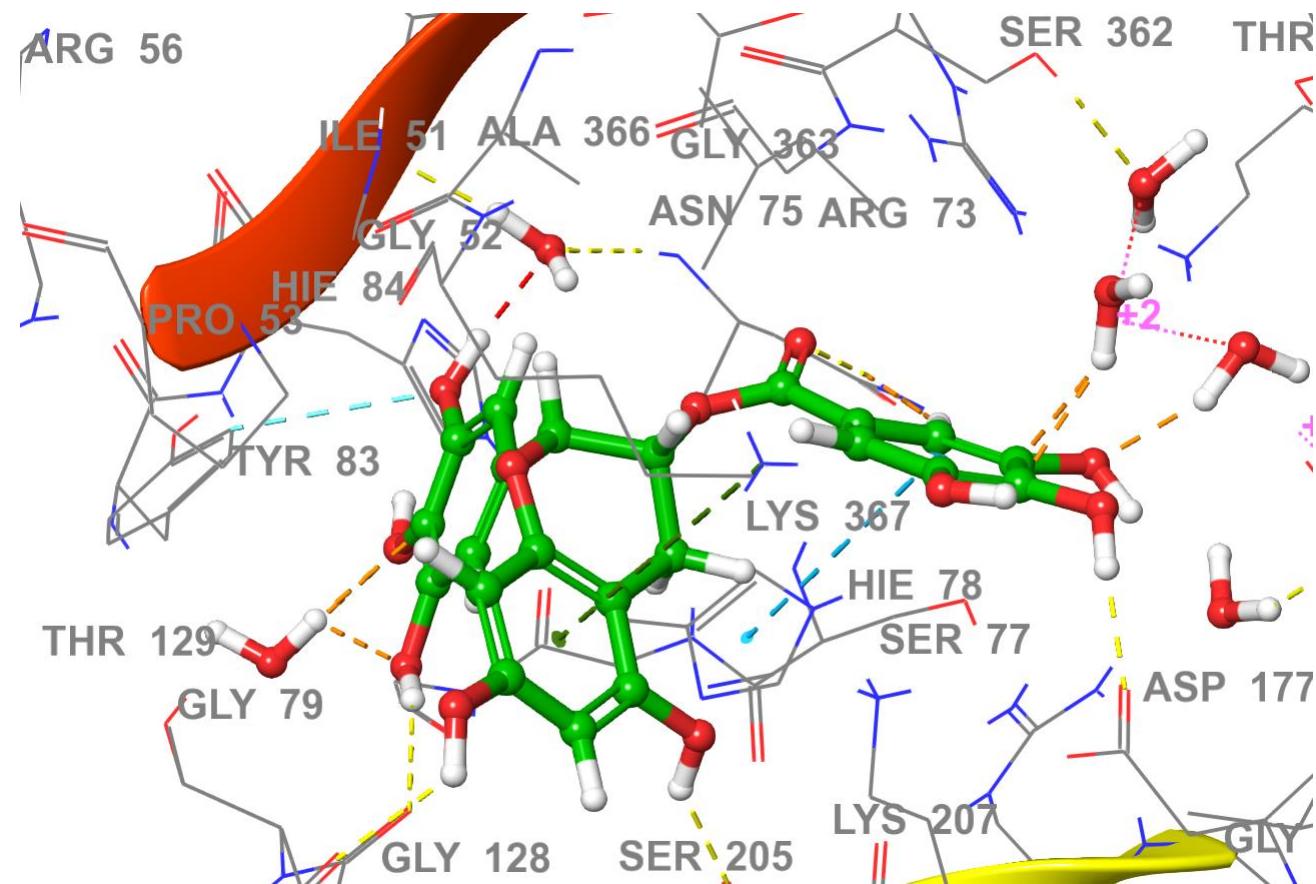
72



73



74



75