Table S1. Cytotoxic Effect of Compound (4-6a,b) on MDA, and HepG2 Cell Lines expressed as Mean ± SD.

Concentration (µg/mL)	4a		4b	
	MDA	HepG2	MDA	HepG2
200	53.17 ± 3.15	60.54 ± 8.73	15.71 ± 2.86	20.26 ± 1.08
150	63.49 ± 3.88	63.21 ± 7.33	28.90 ± 3.74	32.29 ± 2.46
100	68.23 ± 1.94	74.73 ± 4.58	39.84 ± 2.26	38.23 ± 3.37
50	71.92 ± 3.38	78.70 ± 2.15	47.08 ± 2.04	43.99 ± 3.61
25	79.60 ± 7.05	81.24 ± 1.30	56.27 ± 0.84	46.23 ± 4.55
12.5	84.25 ± 3.08	83.84 ± 1.96	63.97 ± 1.66	51.51 ± 7.67
6.25	91.01 ± 4.85	90.16 ± 4.75	75.52 ± 3.57	79.13 ± 1.48
1	94.16 ± 0.98	93.68 ± 0.89	87.01 ± 1.76	91.16 ± 0.97

Concentration (µM)	5a		5b	
	MDA	HepG2	MDA	HepG2
200	9.53 ± 1.28	19.42 ± 3.68	7.96 ± 0.19	18.15 ± 4.52
150	11.27 ± 0.11	22.36 ± 0.90	9.74 ± 1.26	20.79 ± 3.25
100	12.03 ± 0.22	24.08 ± 0.23	10.37 ± 0.82	21.27 ± 3.48
50	45.88 ± 0.60	34.40 ± 0.49	31.26 ± 15.10	27.18 ± 8.65
25	53.89 ± 1.81	43.10 ± 0.49	51.96 ± 4.17	45.04 ± 0.99
12.5	61.54 ± 1.19	61.43 ± 4.31	62.99 ± 4.48	55.00 ± 3.60
6.25	74.79 ± 3.11	86.03 ± 1.07	79.20 ± 2.55	82.47 ± 1.43
1	87.76 ± 1.91	92.68 ± 1.63	84.97 ± 1.42	89.88 ± 1.23

Concentration (µg/mL)	6a		6b	
	MDA	HepG2	MDA	HepG2
200	7.24 ± 1.84	22.23 ± 0.82	41.72 ± 1.32	19.37 ± 0.96
150	10.27 ± 0.38	23.68 ± 0.50	48.13 ± 2.89	37.29 ± 3.25
100	12.01 ± 1.90	24.60 ± 0.23	52.01 ± 0.49	58.02 ± 1.36
50	50.51 ± 1.63	27.51 ± 1.47	56.52 ± 2.60	65.31 ± 1.23
25	58.91 ± 3.15	30.71 ± 0.97	58.12 ± 3.01	78.78 ± 1.47
12.5	62.31 ± 0.30	56.18 ± 11.13	68.77 ± 3.37	86.39 ± 2.50
6.25	67.89 ± 3.20	91.88 ± 5.77	78.51 ± 3.94	92.36 ± 1.47
1	80.86 ± 1.87	96.54 ± 0.99	87.35 ± 1.87	95.54 ± 0.98

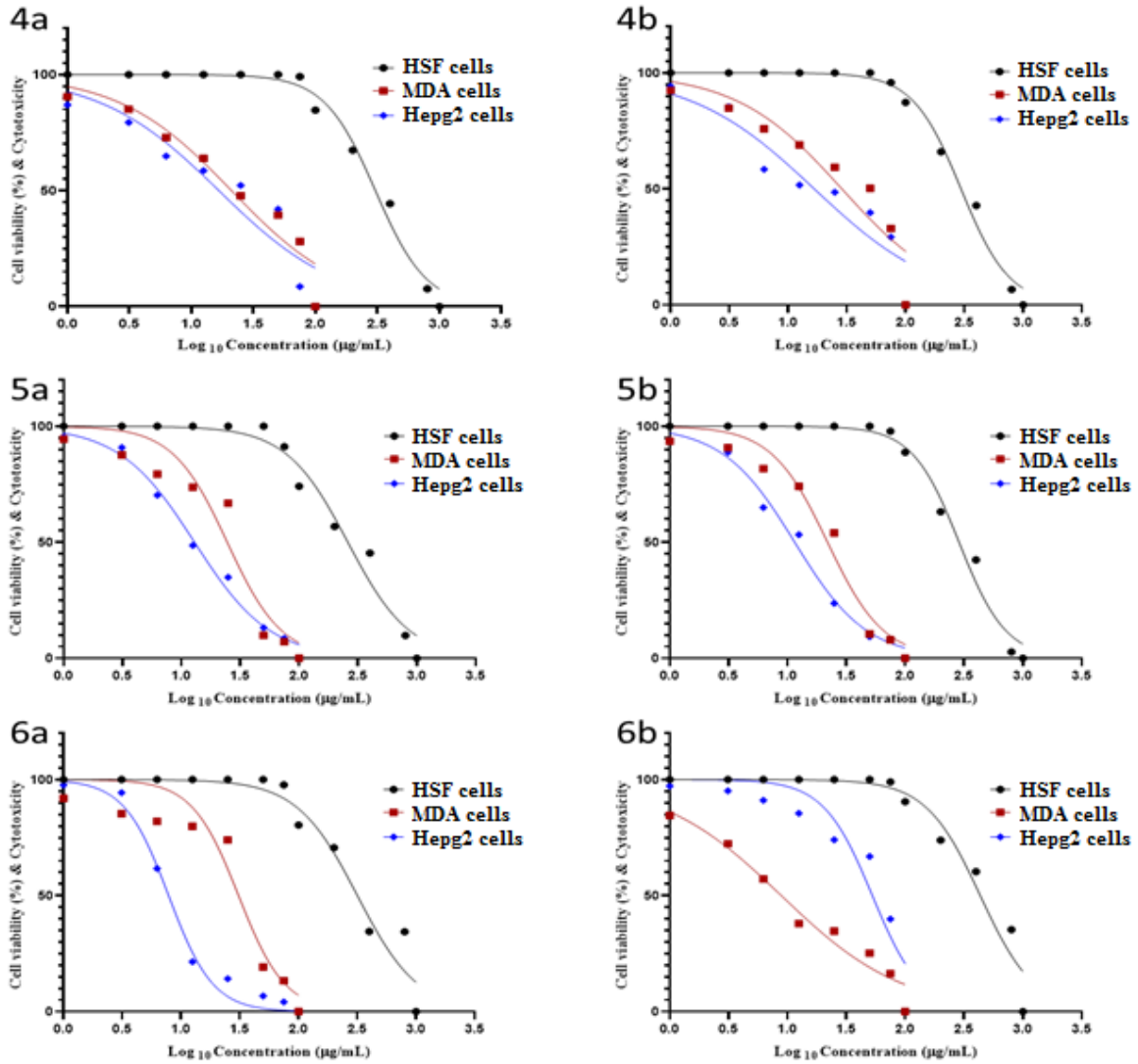


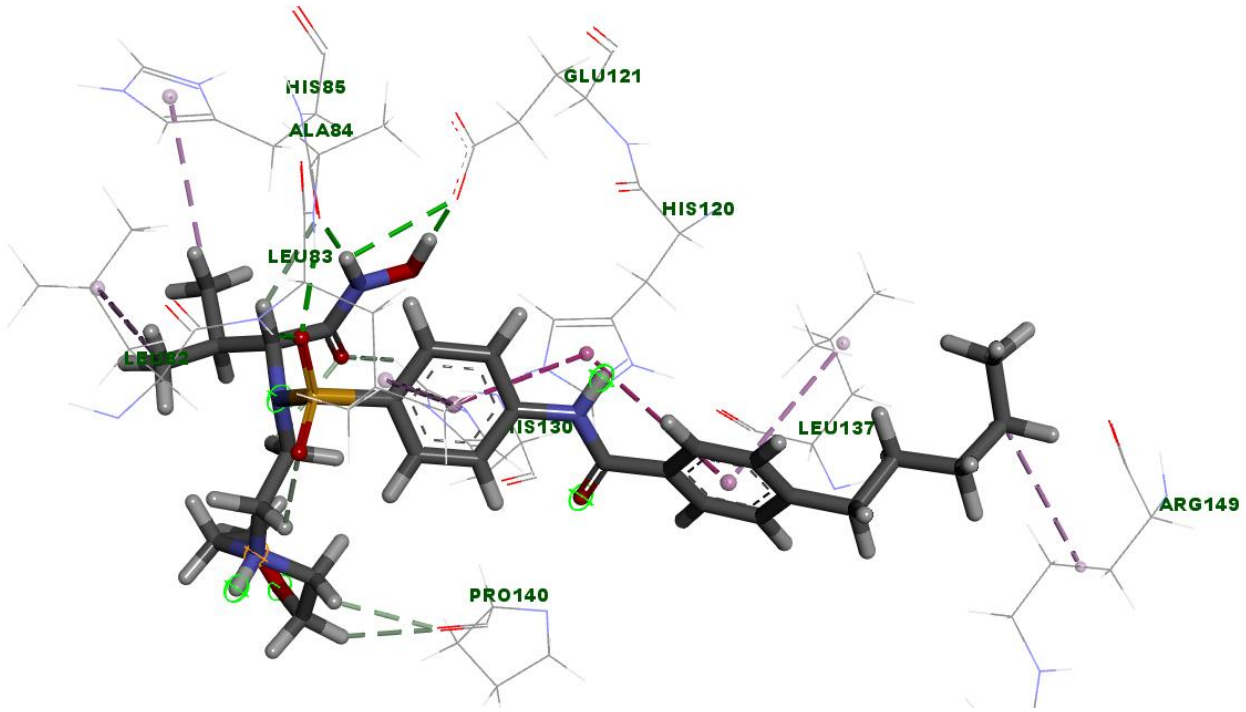
Figure S7: Cell viability and cytotoxicity of HSF, MDA, and HepG2 cell lines treated with different concentrations of synthetic compounds (**4-6*a, b***). The curves represent the dose-dependent response of each cell line to the compounds, illustrating cell viability (%) and cytotoxicity across a concentration gradient.

Molecular docking

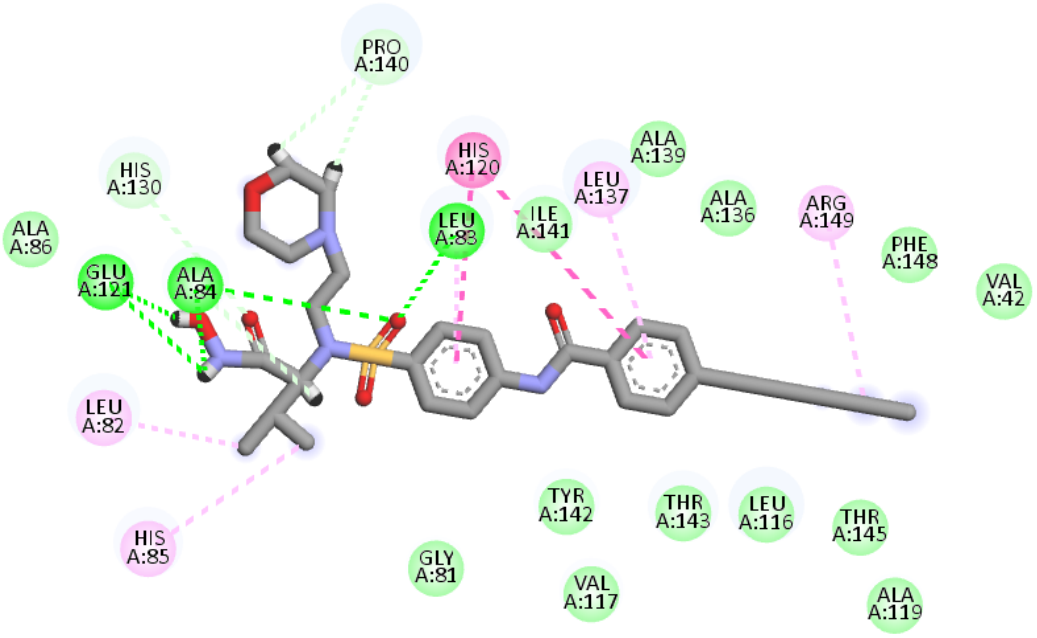
Molecular Operating Environment (MOE 2014) software was used to simulate the binding modes and calculate scores of the new candidates against two enzymes MMP-2 and MMP-9 in comparison to those of the co-crystallized ligand. The three-dimensional structure of the selected proteins were downloaded from the PDB website. The downloaded protein was prepared via three steps, firstly removal of water molecules downloaded with it. Secondly, protons were added and lastly the energy of the protein was minimized. The isolation of the pocket was then carried out. We isolated area of 4.5 A° around the crystallized ligand. Then

validation of the downloaded structure was confirmed by re-docking the crystallized ligand into the isolated pocket to ensure that RMSD is not more than 1.5. The preparation of the new antitumor derivatives for docking was carried out by the construction of the chemical structures at MOE. Protons were then added to the 3D structure. Finally, the energy was minimized using Force Field MMFF94x. The prepared structures were added to the created database. MOE conducted the docking of the newly synthesized compounds, calculated the binding energies, and provided the binding modes of all.

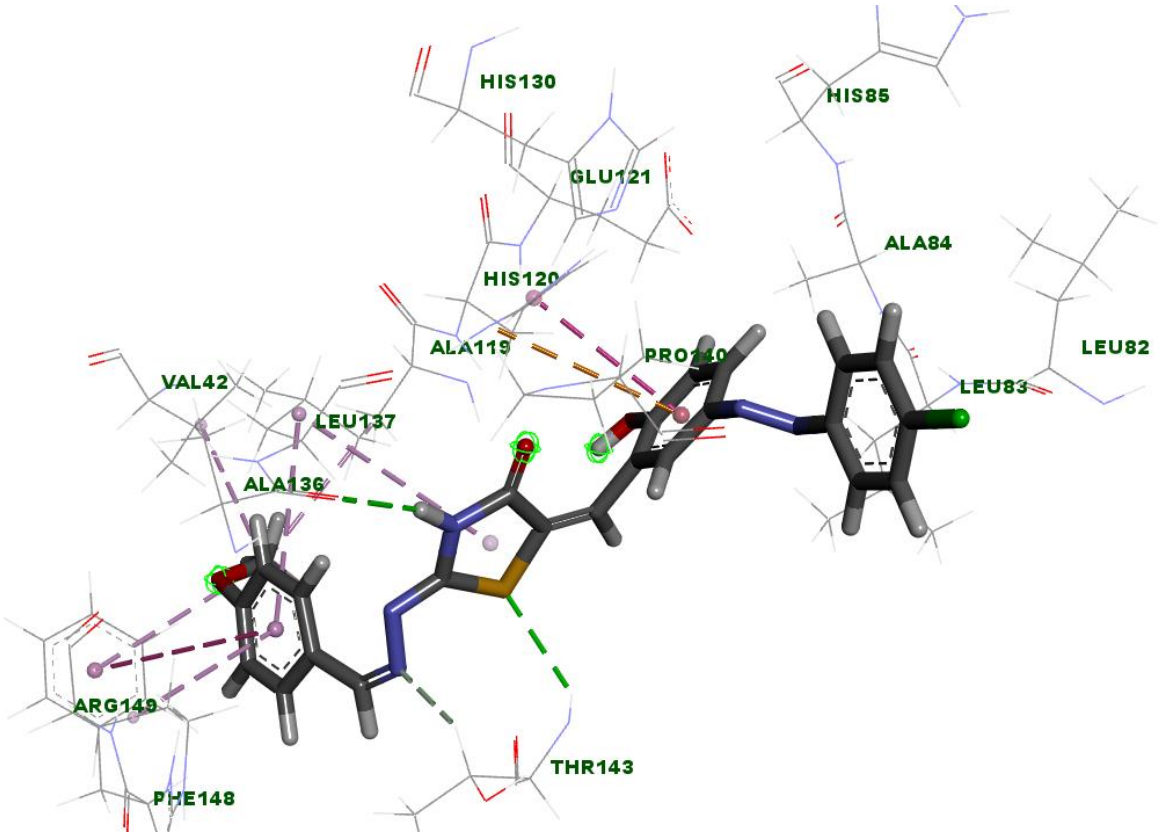
Here are illustrations for binding pattern of the new derivatives and co-crystallized ligand to MMP-2 and MMP-9 proteins.



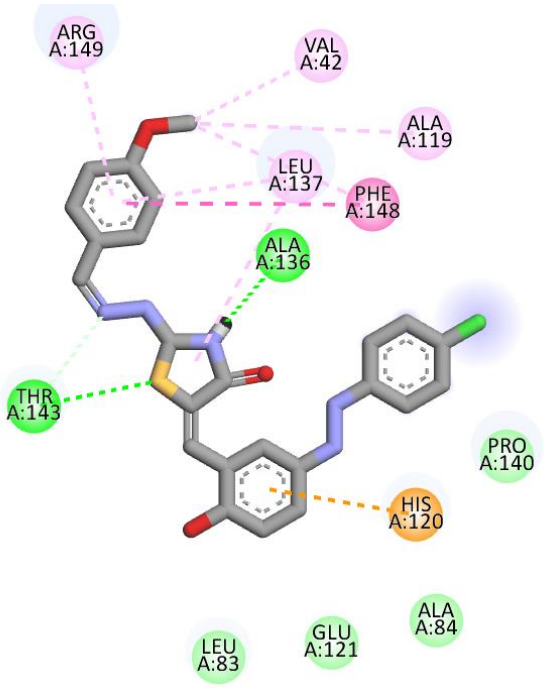
3D ligand interaction with MMP-2



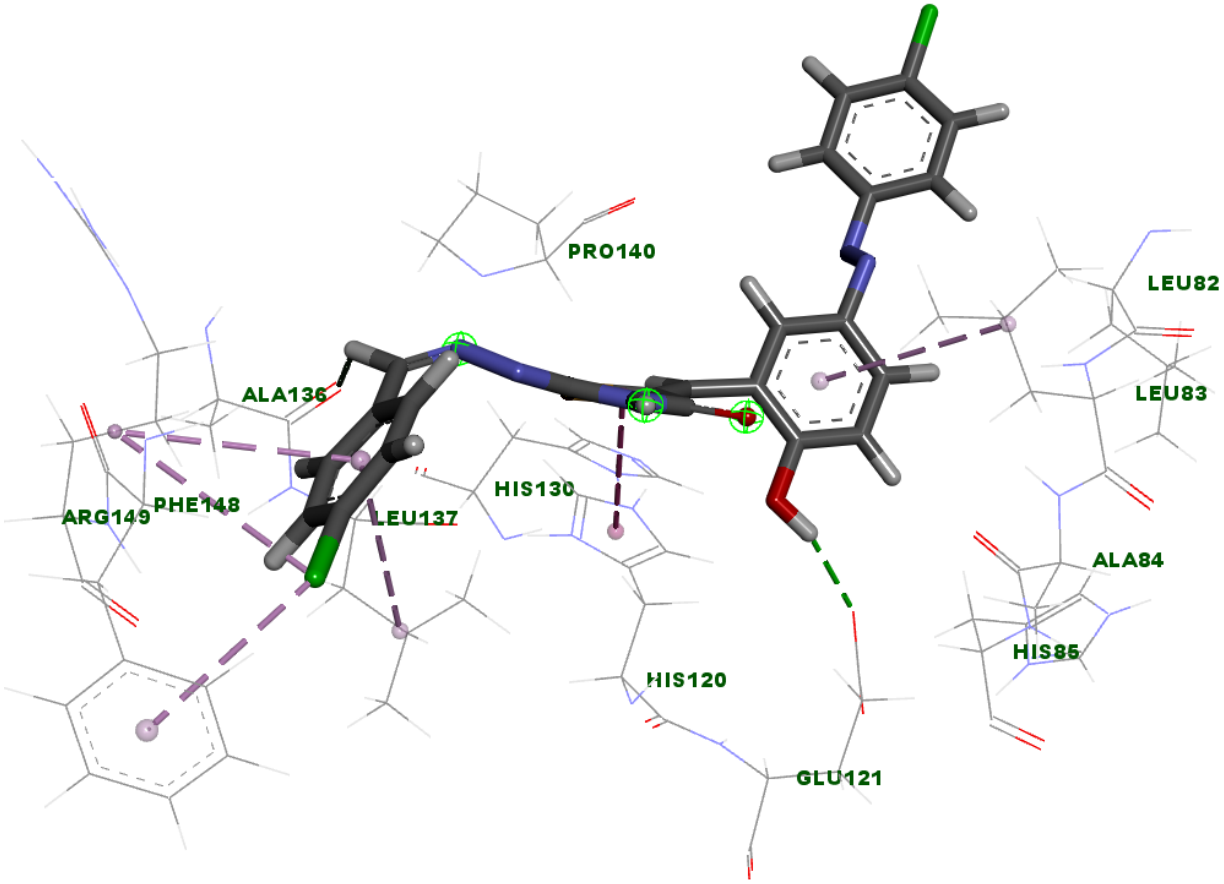
2D ligand interaction with MMP-2 pocket.



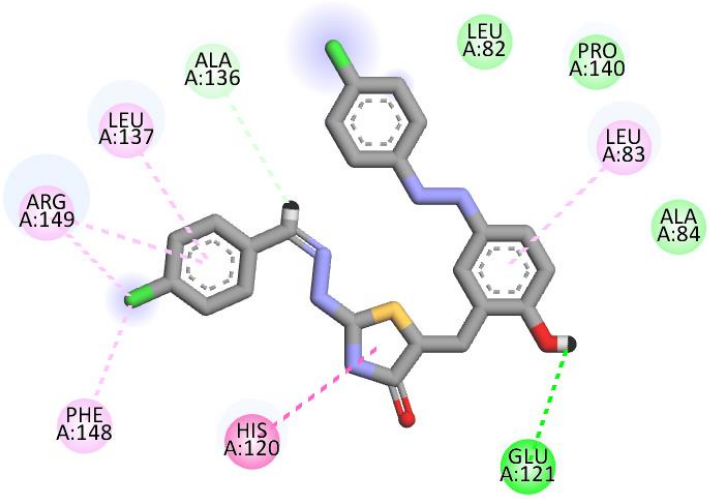
6a 3D binding mode to MMP-2



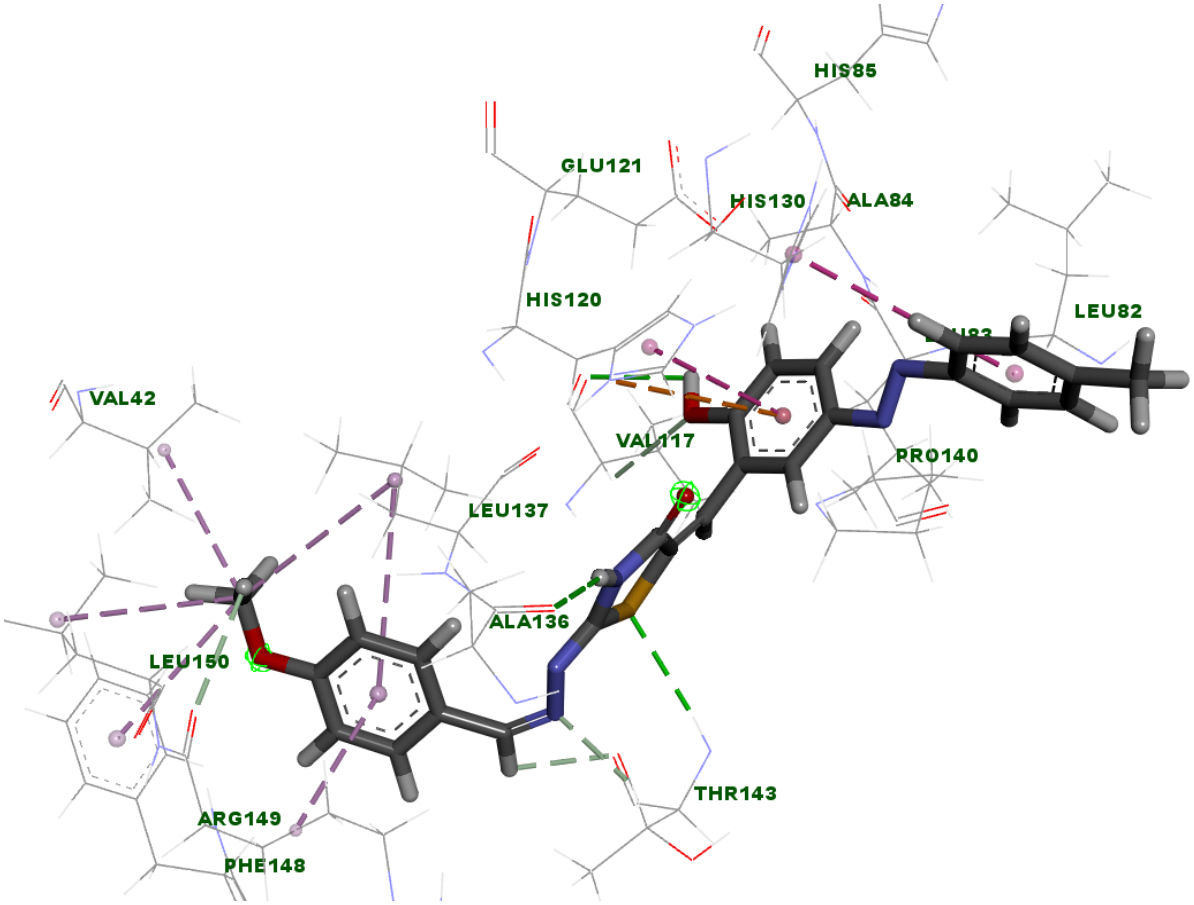
2D binding pattern of 6a to MMP-2



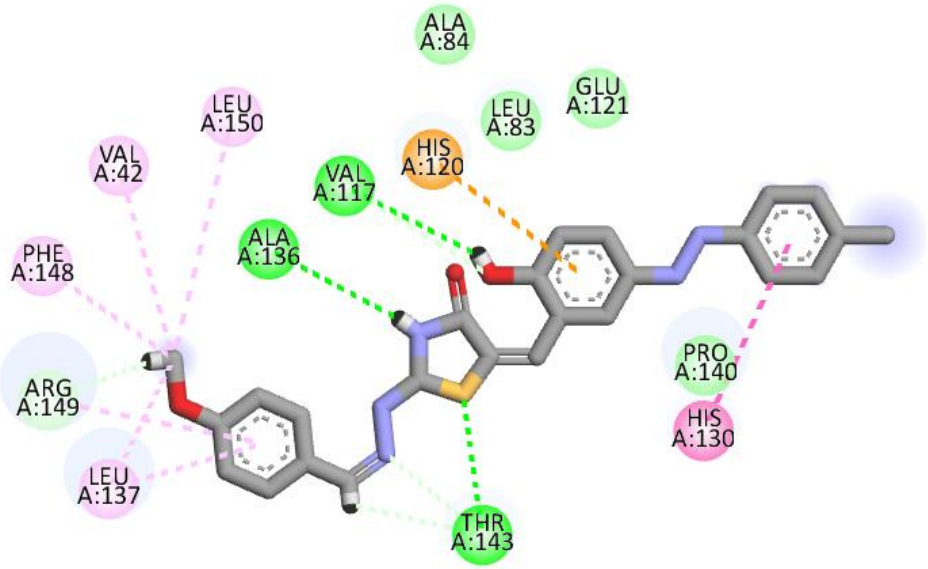
3D binding mode of 4a



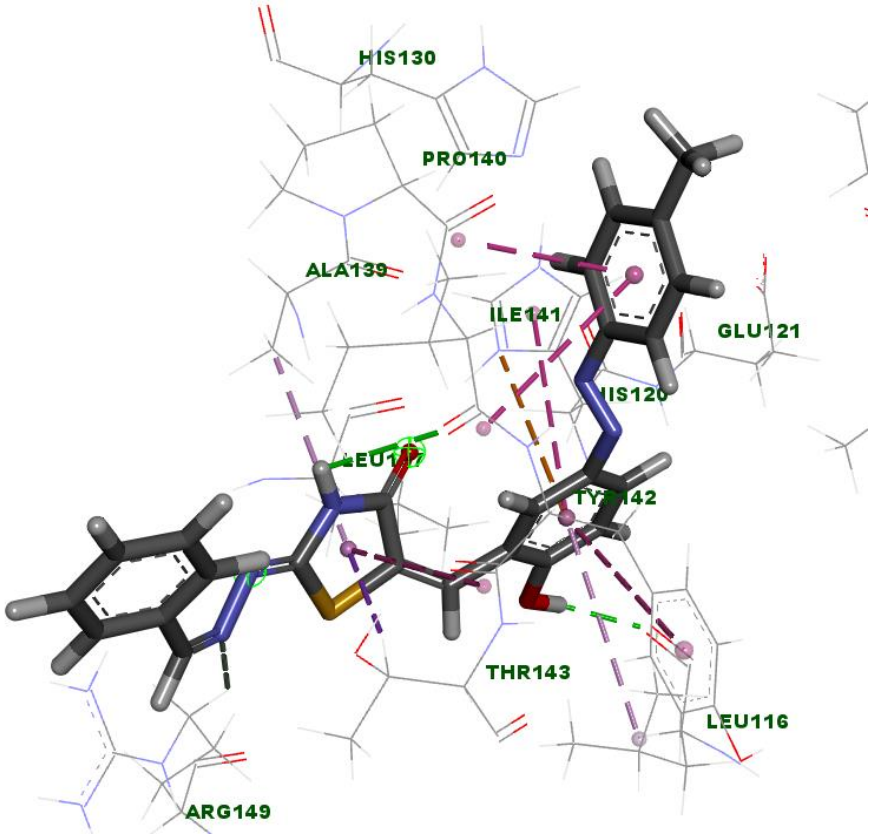
2D binding of 4a to MMP-2



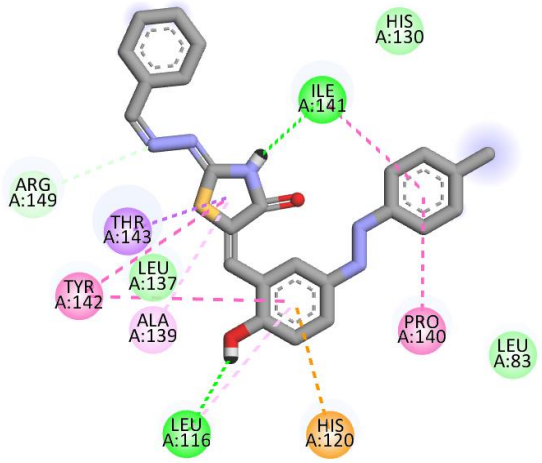
3D binding mode of 6b to MMP-2



2D binding of 6b to MMP-2



3D binding mode of 5b to MMP-2



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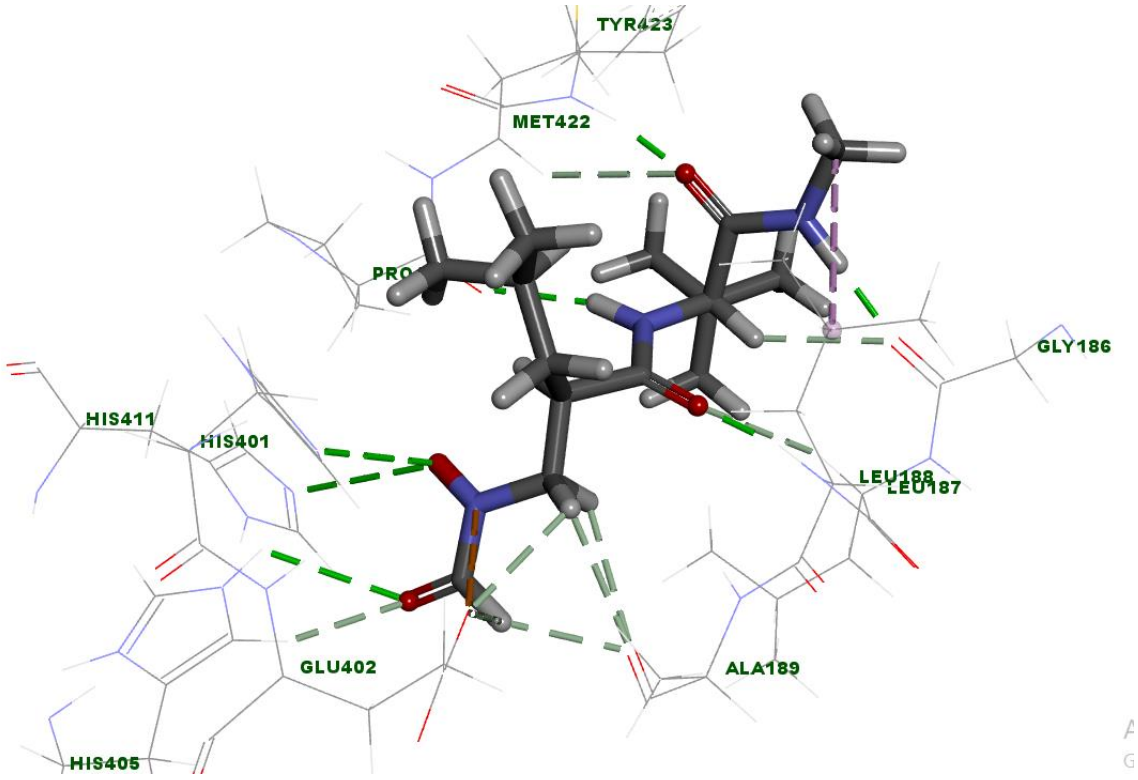
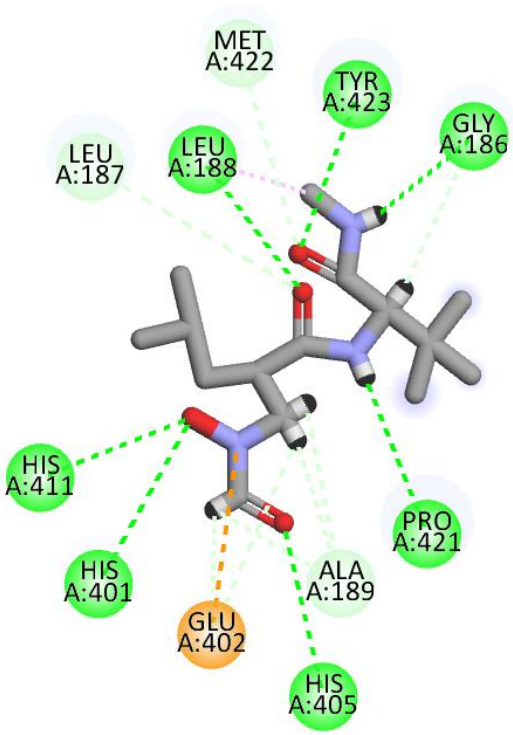
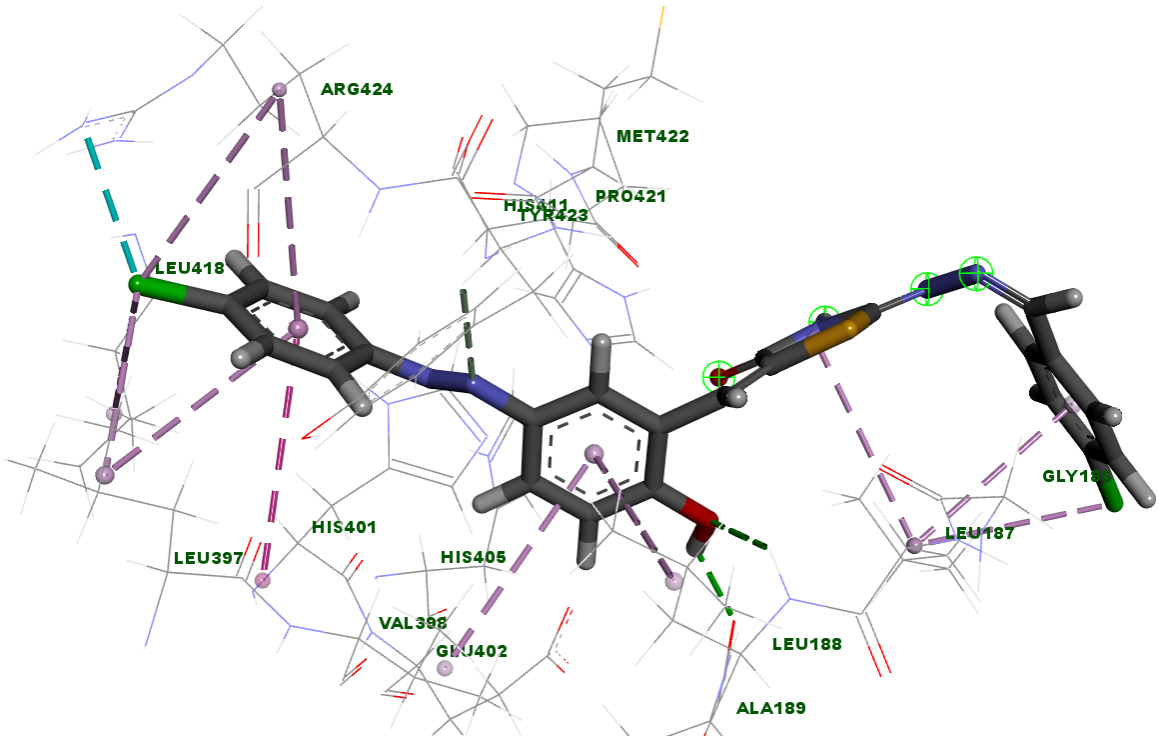


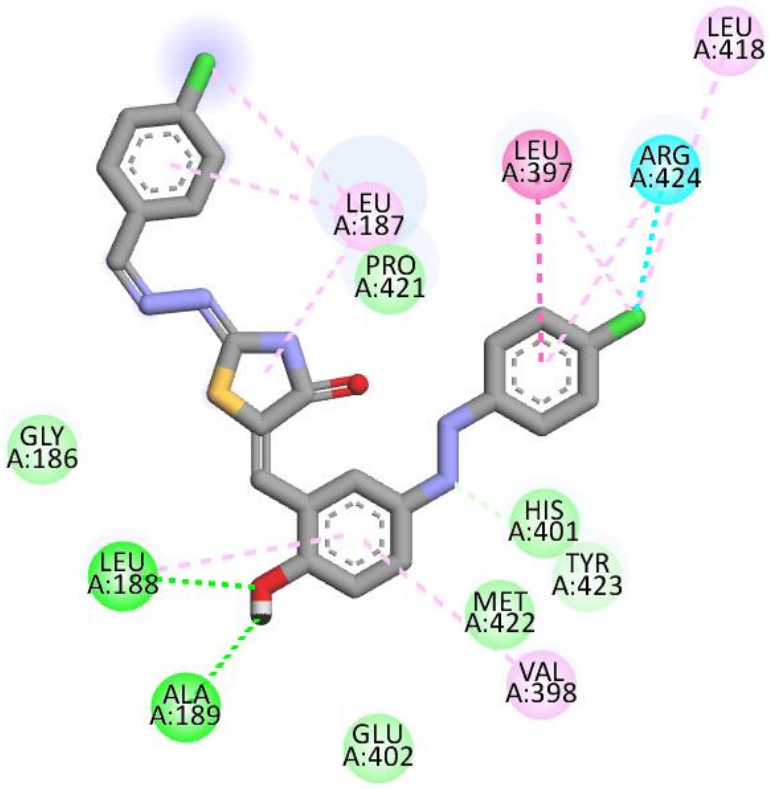
Ligand interaction mode with MMP-9 (3D)



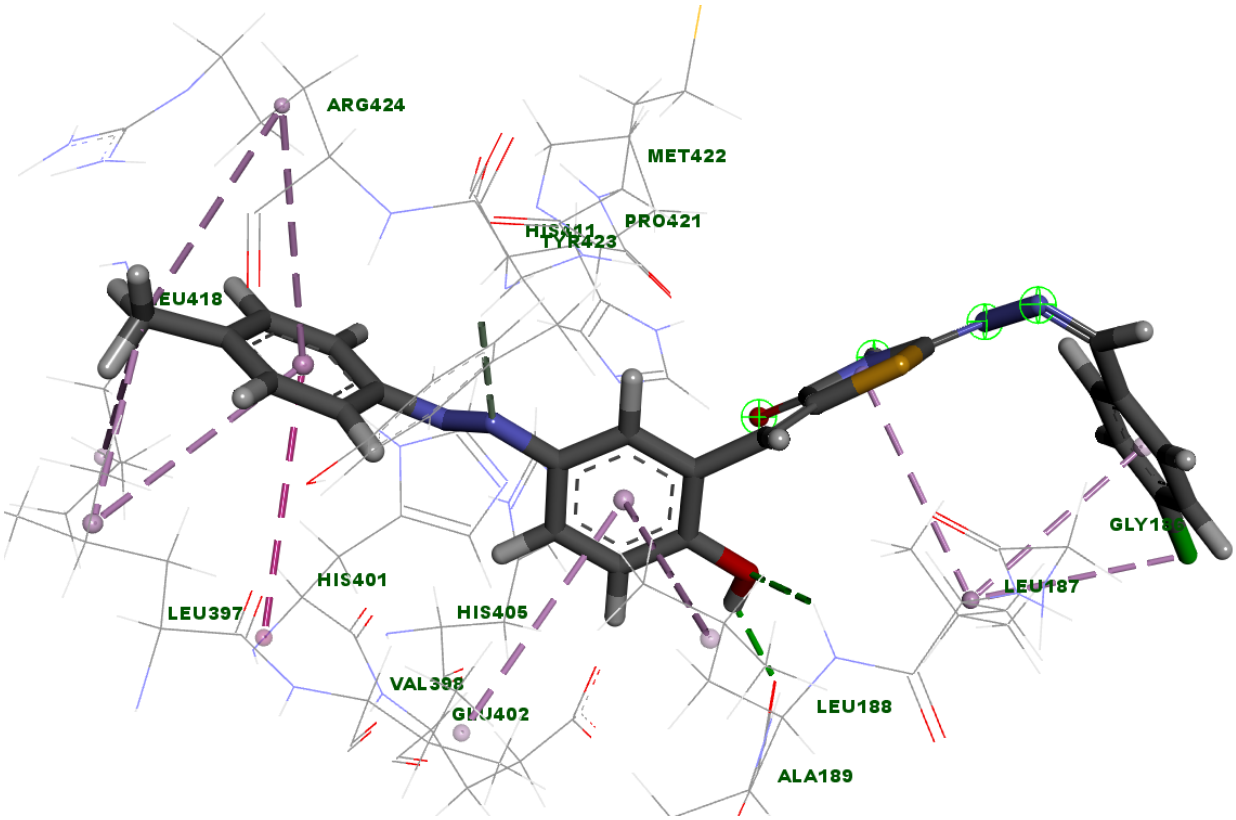
Ligand interaction mode with MMP-9 (2D)



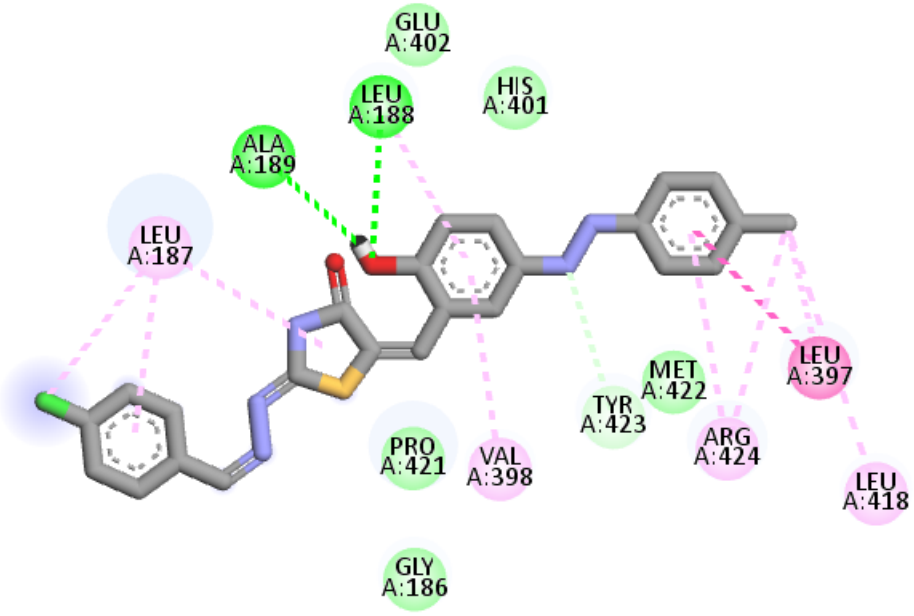
4a binding mode to MMP-9 (3D)



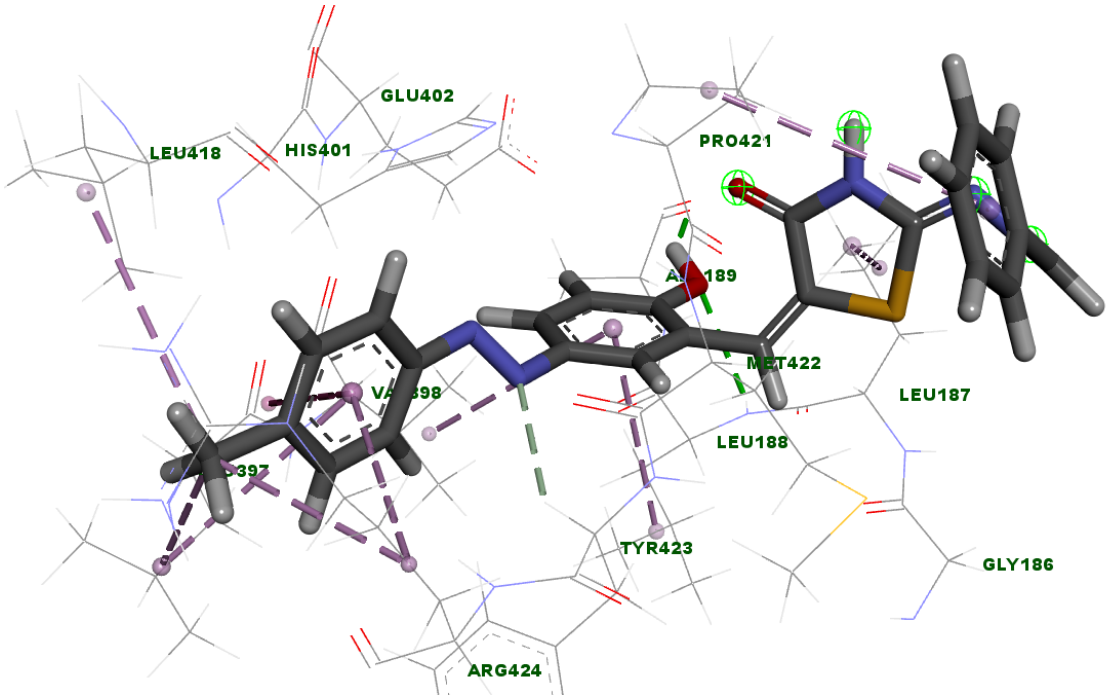
4a 2D binding mode to MMP-9



4b binding mode 3D to MMP-9



2D binding mode of 4b to MMP-9



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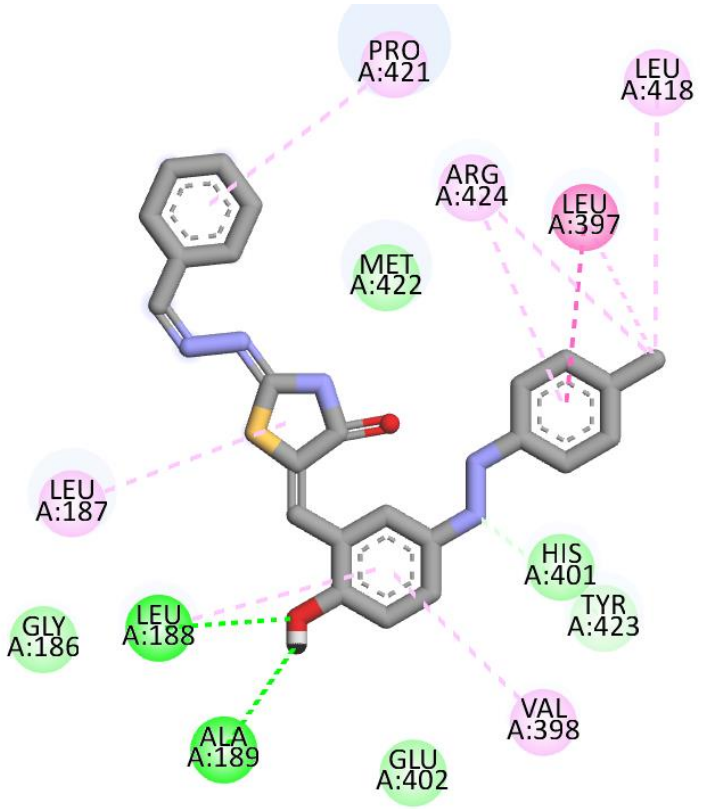
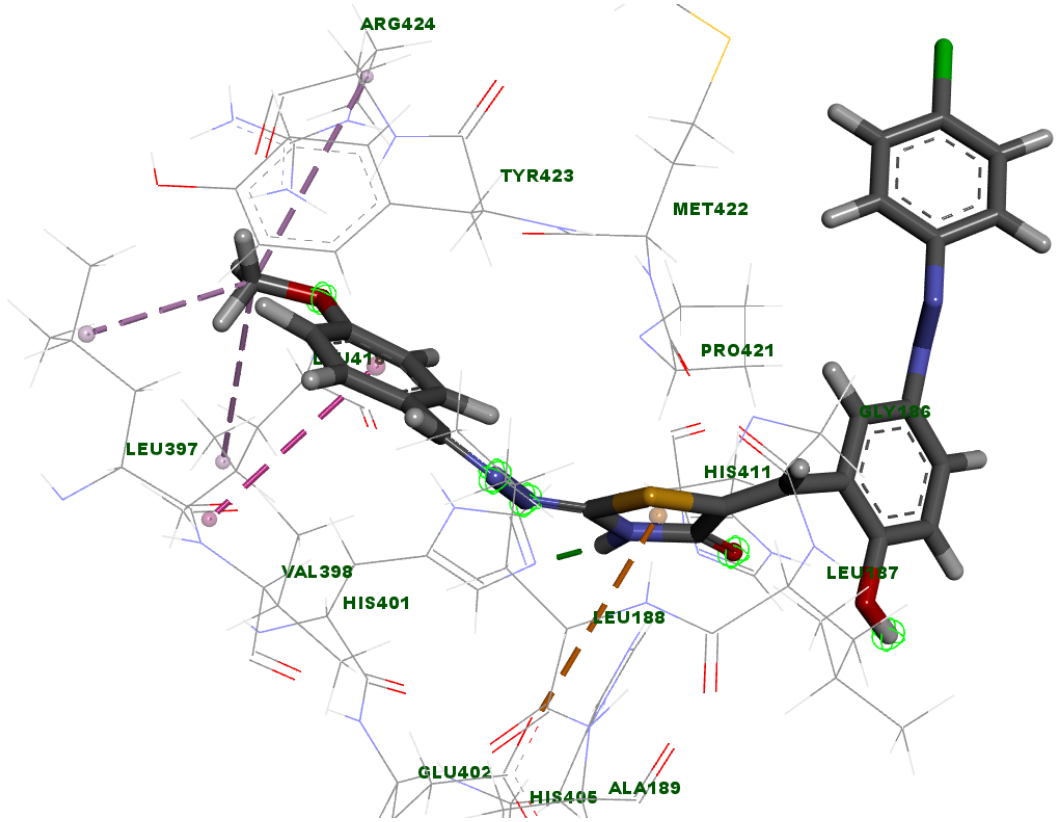
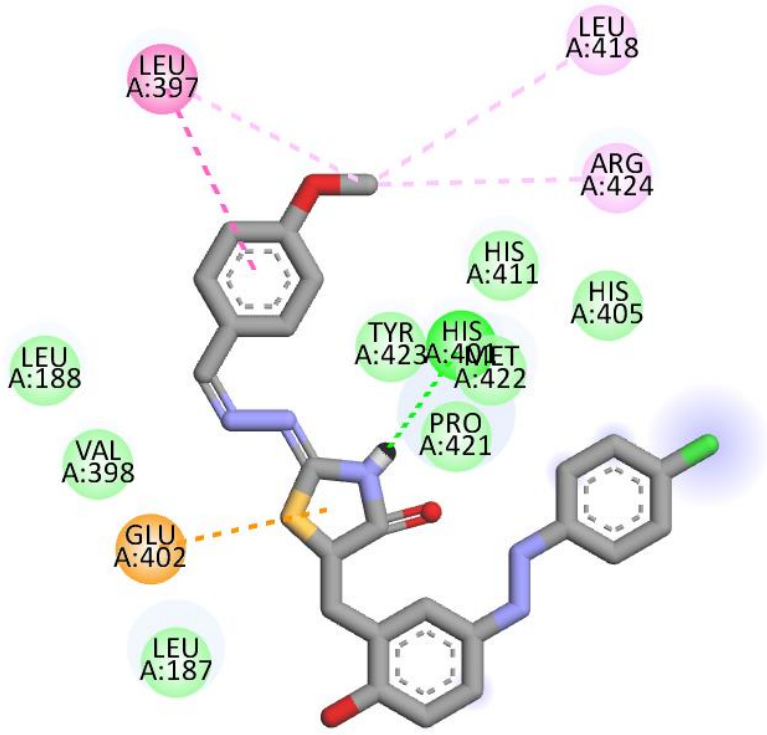


2D binding mode of 5b to MMP-9



6a 3D binding mode to MMP-9



6a 2D binding mode to MMP-9