Supplementary data

Design, synthesis, and molecular docking of novel urea linked 1,2,3-triazole-benzenesulfonamide hybrid as potential carbonic anhydrase inhibitors.

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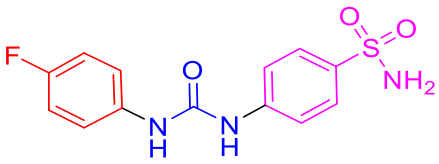
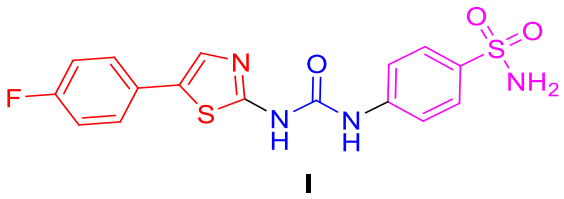


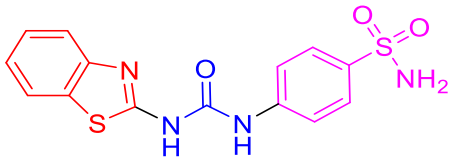
SLC-0111

*h*CA IX= 45 nM, *h*CA XII = 4.5 nM



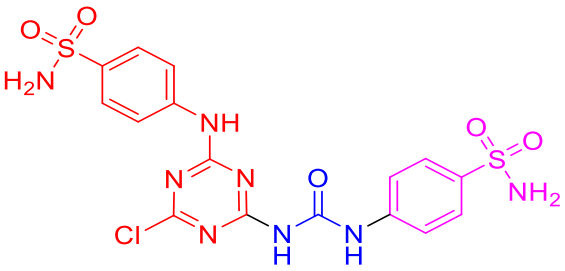
I

*h*CA IX=13.6 nM, *h*CA XII = 27.6 nM



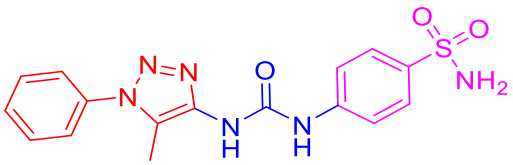
II

*h*CA IX= 31.5 nM, *h*CA XII = 29.3 nM



III

*h*CA IX= 11.8 nM, *h*CA XII = 39 nM



Target compound

Fig. 1. Chemical structures of SLC-0111, its reported analogues, and target compound.

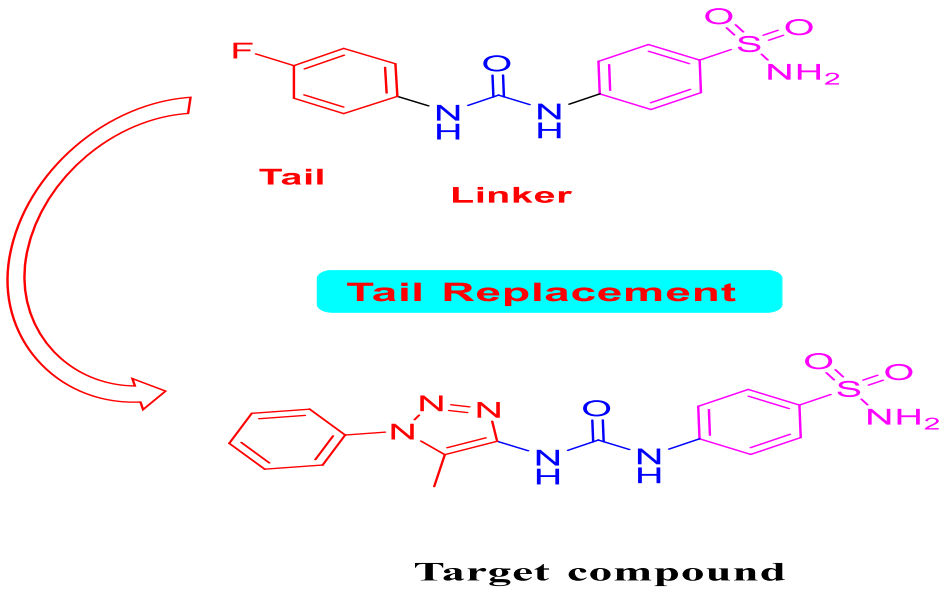


Fig. 2. Design of 4-(3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)ureido)benzenesulfonamide

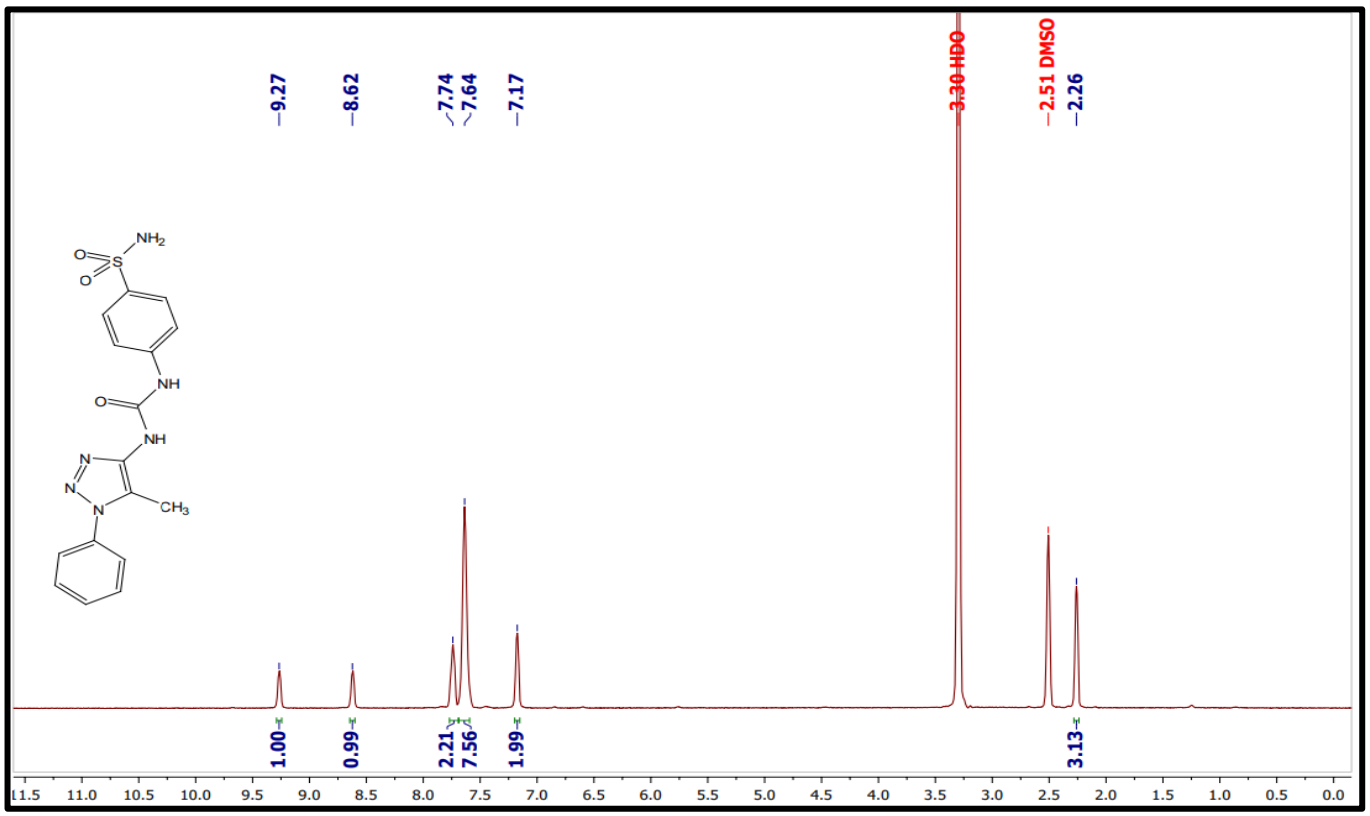


Fig.3 ^{1}H-NMR of compound 6

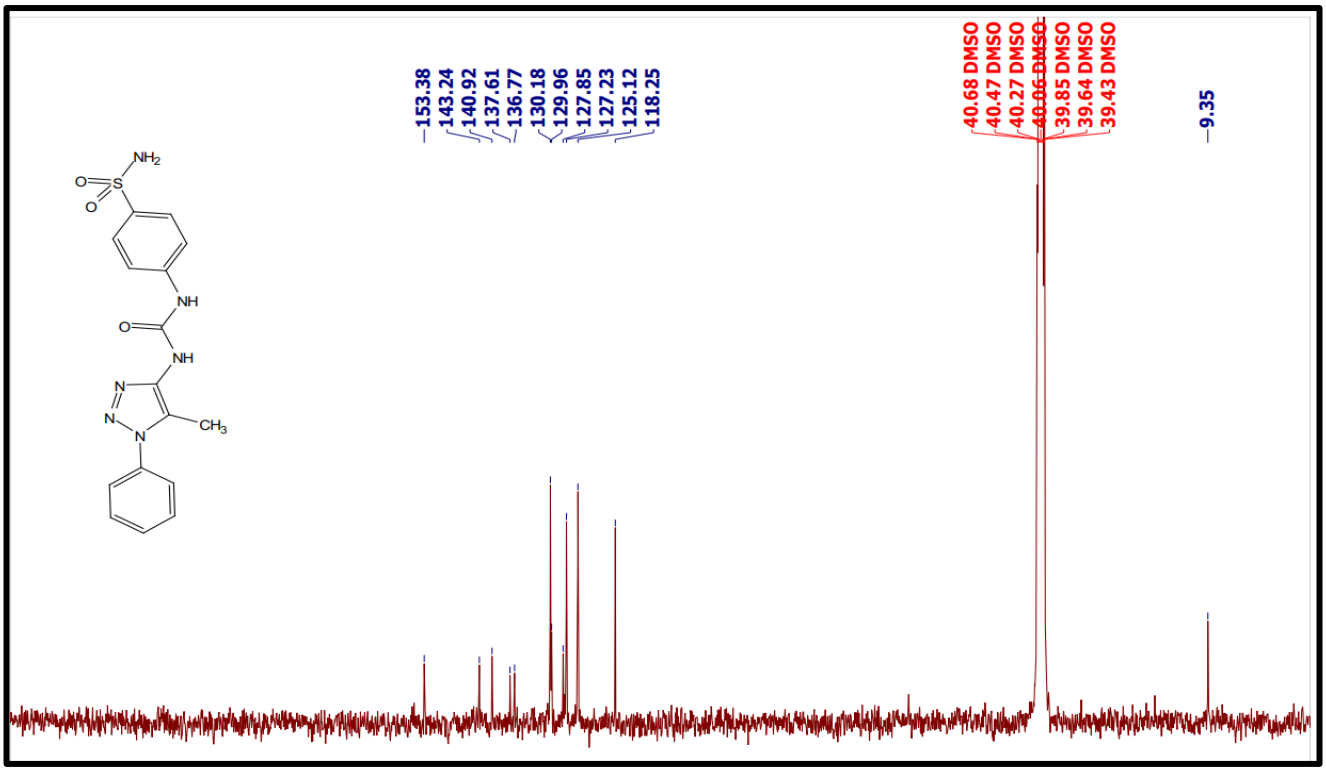


Fig.4 ^{13}C-NMR for compound 6

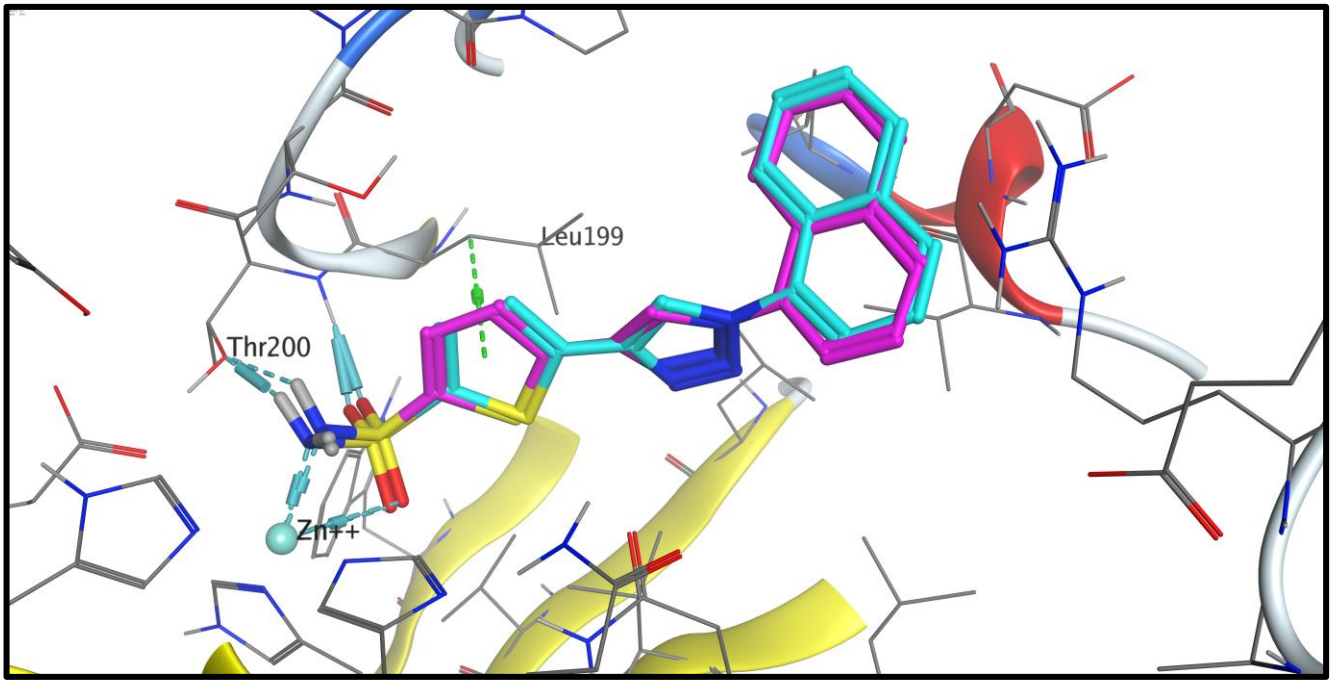


Fig.5 Self-redocking of the co-crystallized ligand in the active site of *h*CA IX.

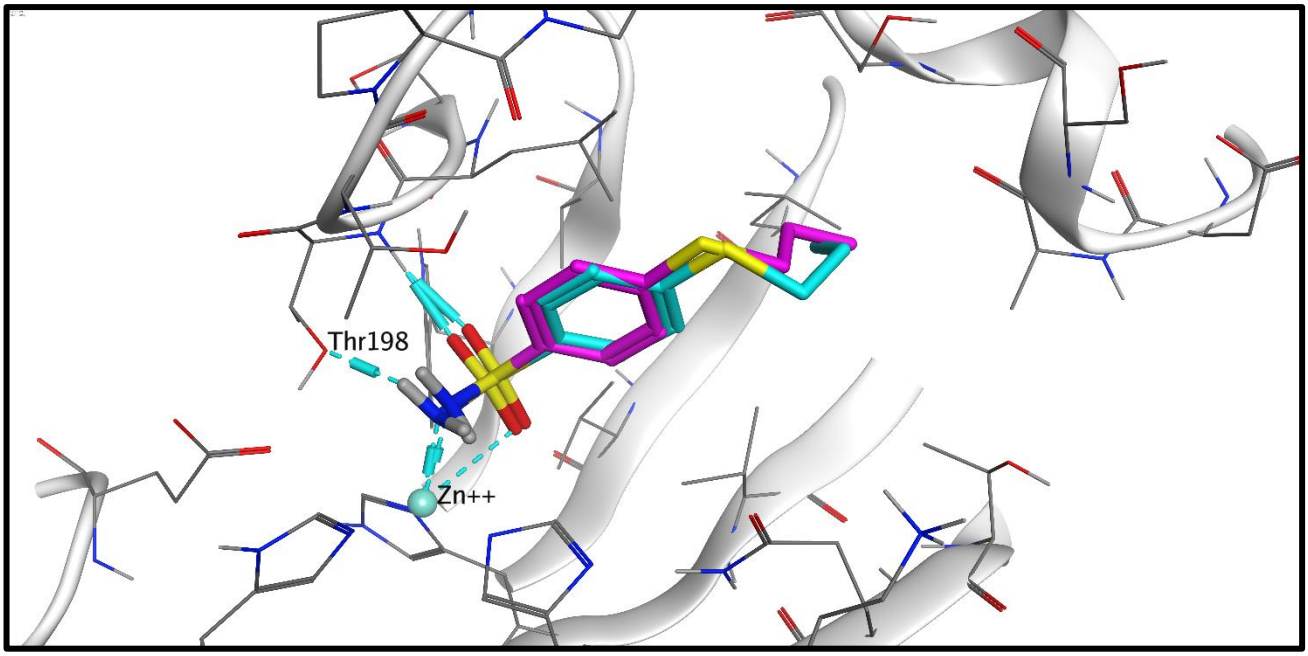


Fig.6 Self-redocking of the co-crystallized ligand in the active site of *h*CA XII.

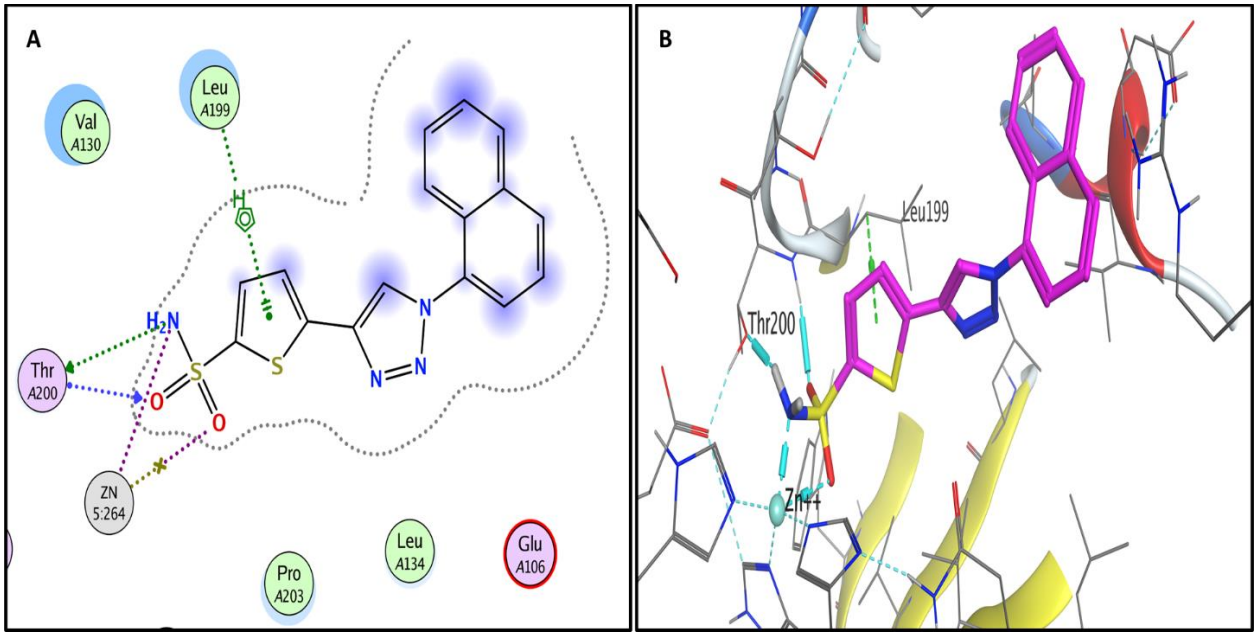


Fig. 7. (A) 2D binding interactions of the co-crystallized ligand in the active site of *h*CA IX. (B) 3D binding interactions of the co-crystallized ligand in the active site of *h*CA IX.

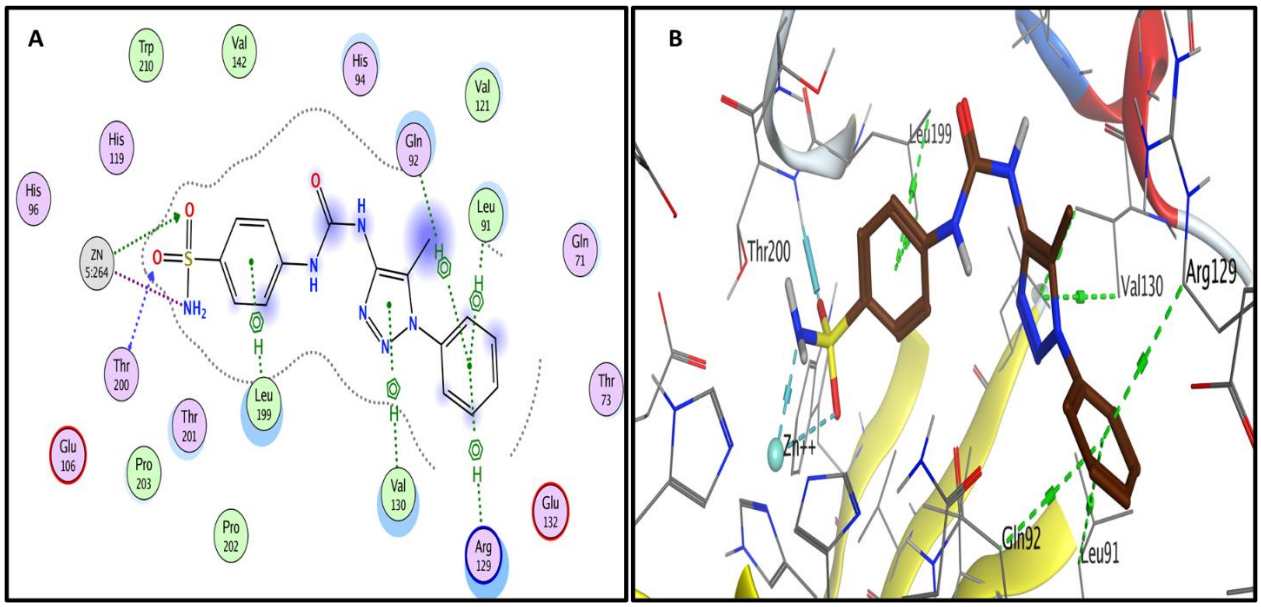


Fig. 8. (A) 2D interaction map of compound 6 in the active site of *h*CA IX. (B) 3D interaction map of compound 6 in the active site of *h*CA IX.

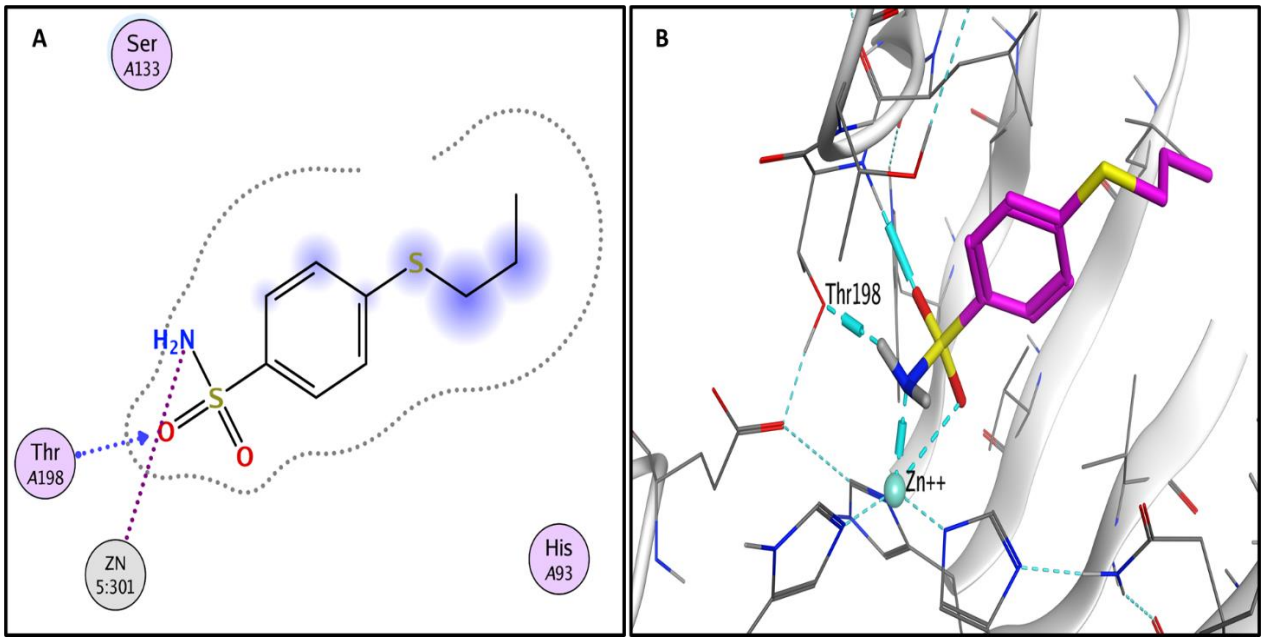


Fig. 9. (A) 2D binding interactions of the co-crystallized ligand in the active site of *h*CA XII. (B) 3D binding interactions of the co-crystallized ligand in the active site of *h*CA XII.

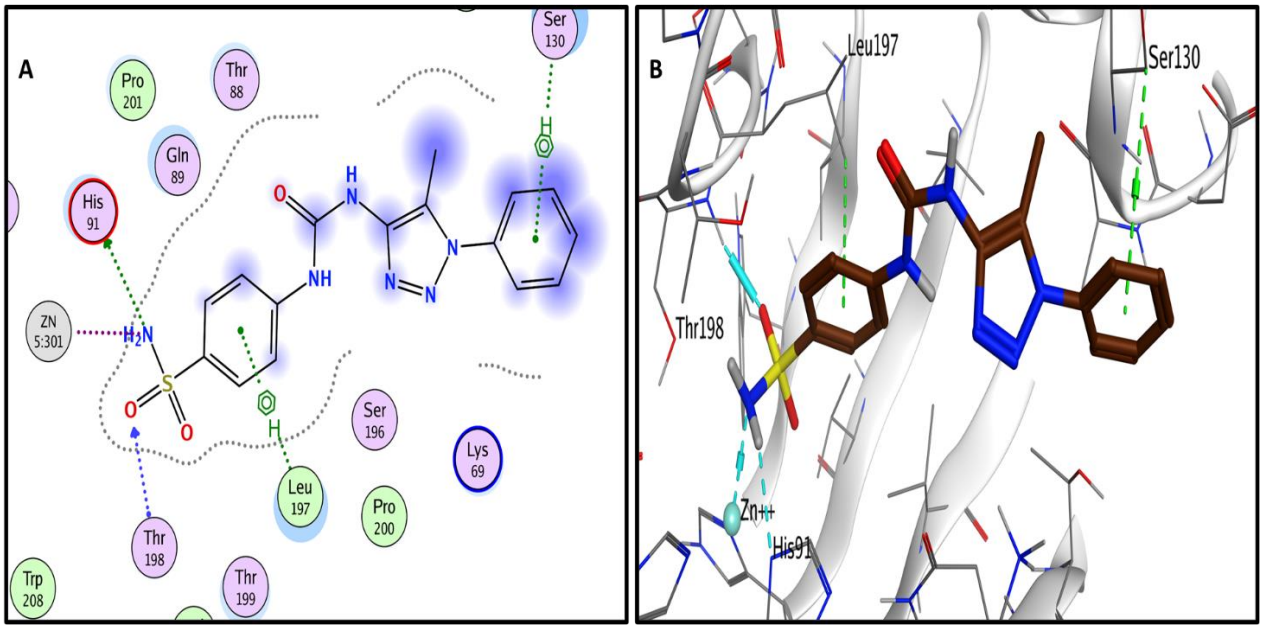


Fig. 10. (A) 2D interaction map of compound 6 in the active site of *h*CA XII. (B) 3D interaction map of compound 6 in the active site of *h*CA XII.

Docking studies

The process involved in the study consisted of several steps. Initially, compound 6 was copied from ChemBioOffice and transferred to Molecular Operating Environment (MOE 2014.0901) program. The energy of compound 6 was subsequently minimized using MOE default settings and partial charges were calculated automatically. For the molecular docking studies, both human carbonic anhydrases IX and XII proteins (PDB IDs: 5FL4 and 4WW8, respectively) were obtained from the RCSB Protein Data Bank. To prepare these proteins, the MOE LigX protocol was utilized. Compound **6** was docked into the binding sites of the target enzymes using MOE default settings. The number of generated poses was set to 10, and default settings were used for other parameters. The resulting docking poses were refined using the Forcefield approach and scored based on the affinity δG scoring system. To validate the docking protocol, the co-crystallized ligands were re-docked into the binding site of target enzymes. The resulting docking poses were visually examined, and the poses with the lowest binding free energy value and the most key interactions within the target protein's binding pocket were selected for further analysis in the docking studies.