The 8th International Electronic Conference on Medicinal Chemistry (ECMC 2022)
01–30 NOVEMBER 2022 | ONLINE

Synthesis, molecular docking analysis, ADMET and drug likeness prediction of a benzenesulfonamide derivative analogue of SLC-0111

Chaired by DR. ALFREDO BERZAL-HERRANZ;
Co-Chaired by PROF. DR. MARIA EMÍLIA SOUSA

pharmaceuticals MDPI

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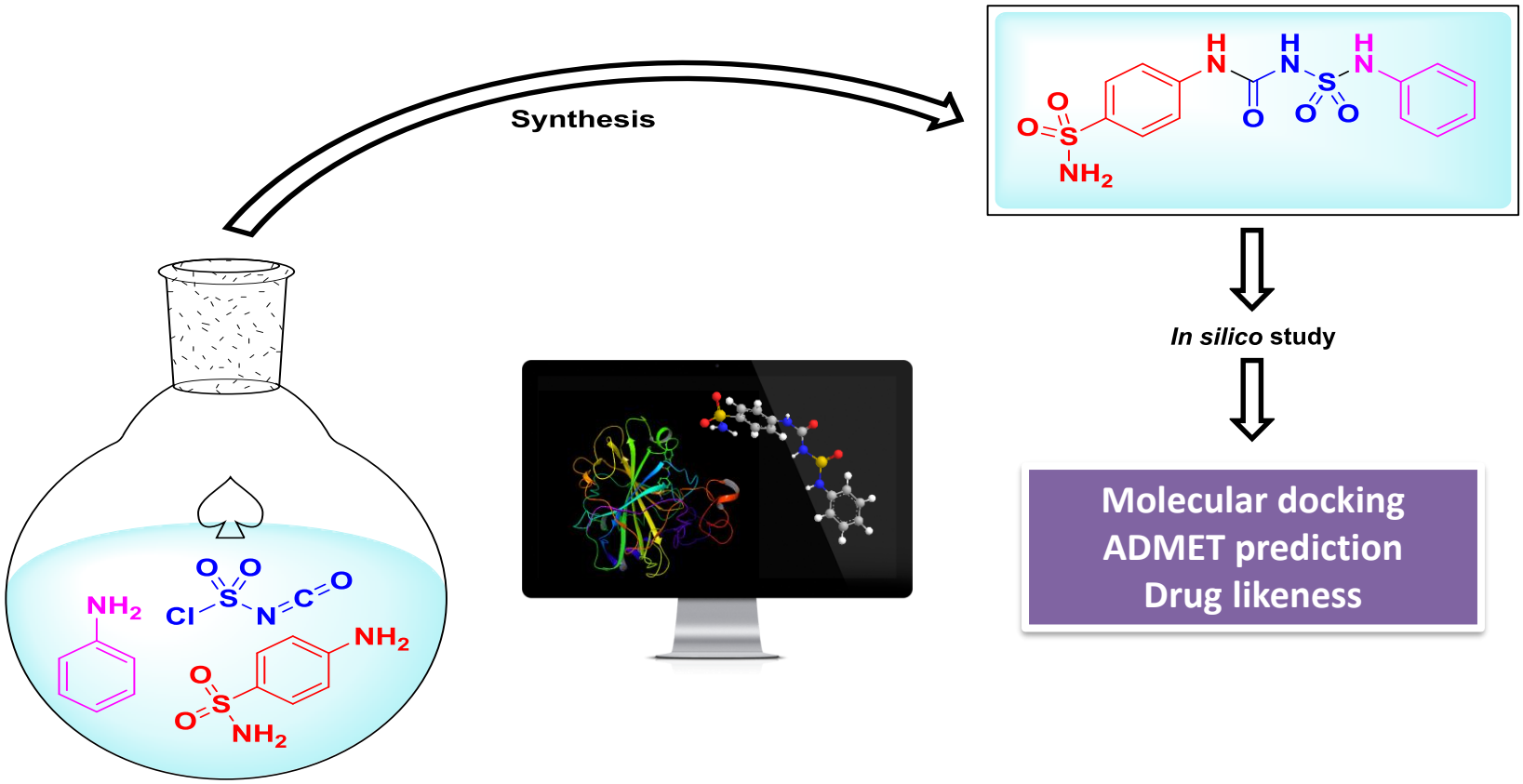
Graphical Abstract



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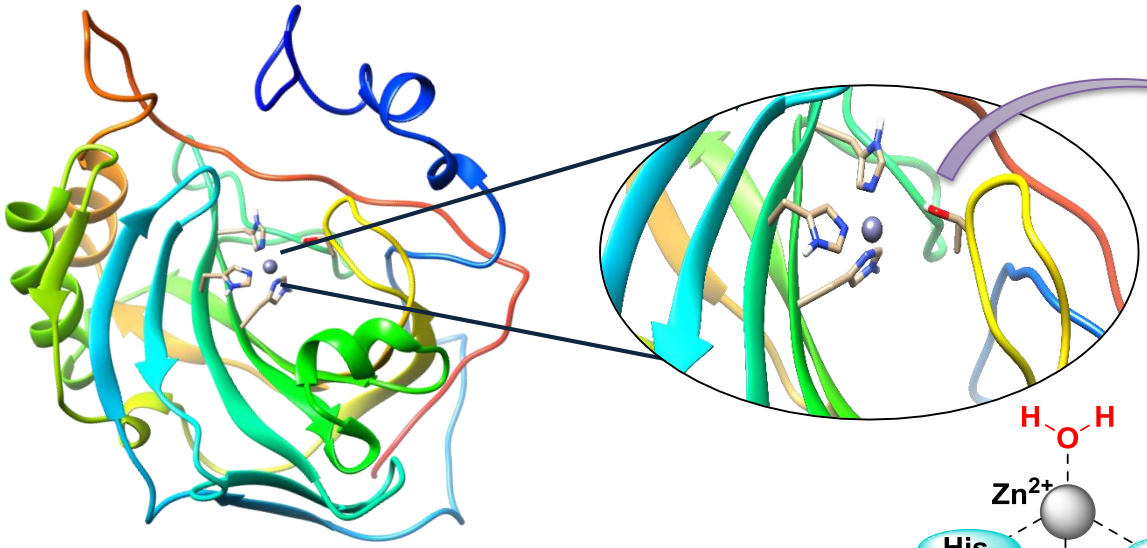
Abstract:

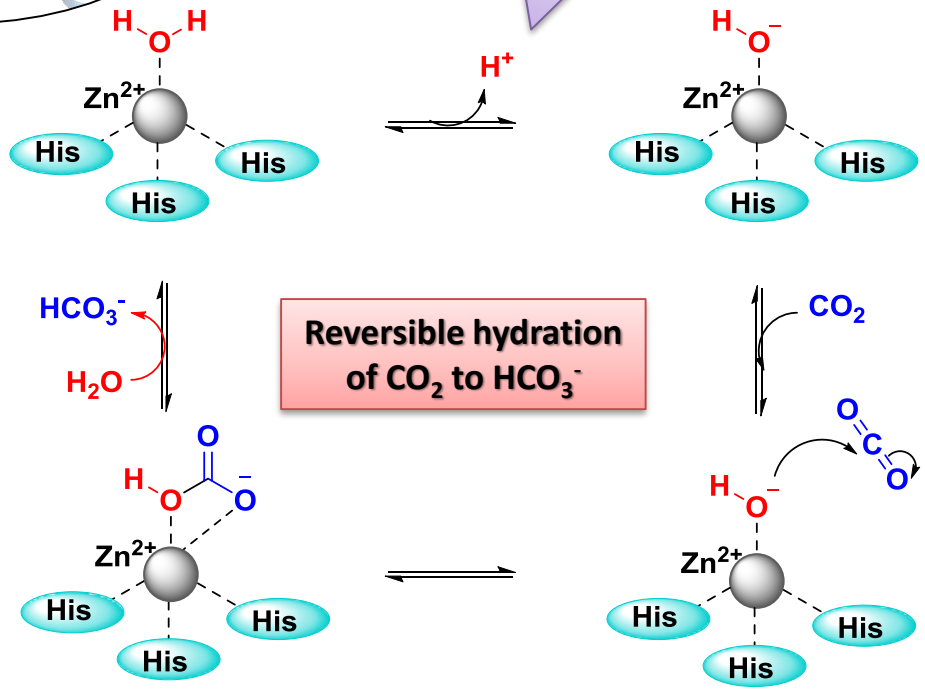
Carbonic anhydrases are metalloenzymes that regulate the interconversion of CO_2 and H_2CO_3, a reaction involved in many physiological processes. A disfunction of these enzymes is known to induce many diseases such as glaucoma, epilepsy and cancer. That's what increased the need to concept new target molecules with inhibitory effects on CAs. The most known compounds that inhibits CAs are sulfonamide-containing molecules, citing valdecoxib, acetazolamide and the antitumor agent lately introduced to phase II clinical trials; the SLC-0111. With an intention to obtain a new potential drug candidate, an analogue of the SLC-0111 compound was designed and synthesized using sulfanilamide, chlorosulfonyl isocyanate and aniline. IR, NMR spectroscopy and EA were used in the characterization of the structure. In order to explore the potentiality of our newly synthesized product to inhibit CAs, a docking simulation was performed on the binding pockets of both carbonic anhydrase II complexed with valdecoxib (pdb: 2AW1) and carbonic anhydrase IX-mimic complexed with SLC-0111 (pdb: 5JN3). The new derivative revealed an interesting stability inside the cavities of CA II and CA IX-mimic with docking scores of -9.782 and -7.466 respectively, and showed an efficient binding affinity in both cases through the formation of metal coordination with Zn and a hydrogen bond with the Thr199 which is known to be essential for the inhibition. Other significant extra interactions were observed as well with other residues in isoform II. Further, the pharmacokinetics properties and drug likeness were predicted using in silico tools; SwissADME and MolSoft online servers.

Keywords: molecular docking; carbonic anhydrase; benzenesulfonamide; SLC-0111; ADMET.

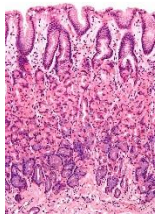
Introduction



Active site of the CA enzyme



Carbonic anhydrase is a zinc metalloprotein that catalyzes the reversible hydration of carbon dioxide to produce a bicarbonate ion and a proton.



Supuran CT. Biochem J. 2016,473, 2023

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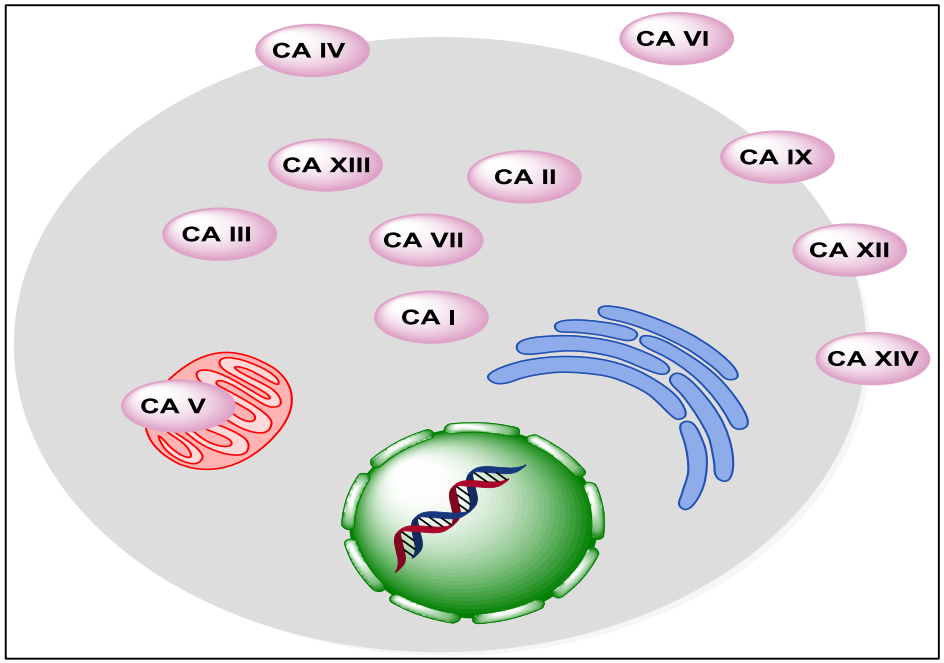
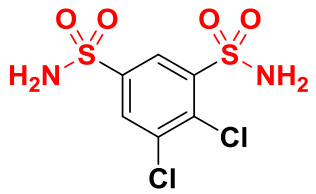
Introduction

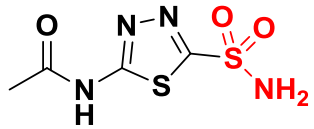


The fourteen isoforms of CAs located in the cell

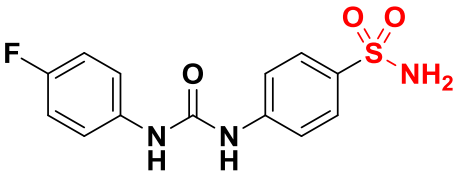
A disorder in the CAs can cause several diseases



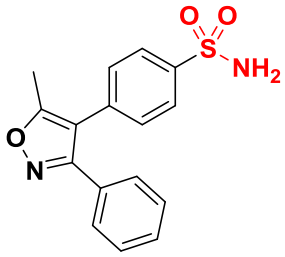
Dichlorophenamide



acetazolamide



SLC-0111



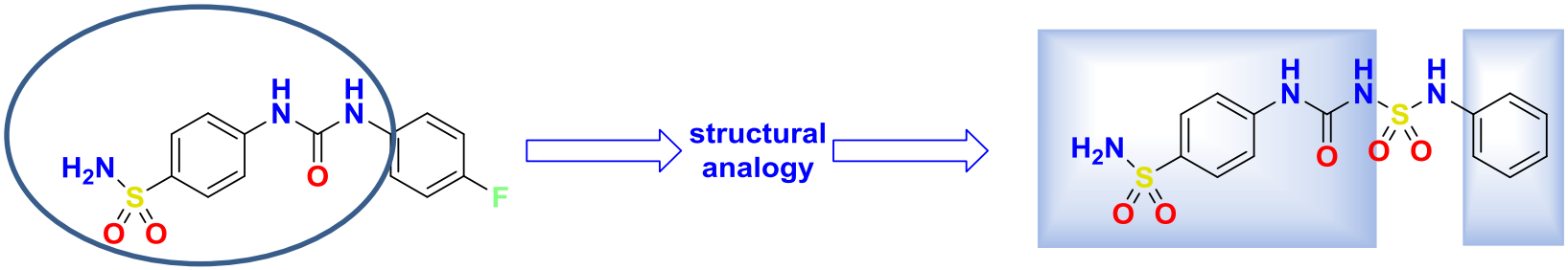
Valdecoxib

Some sulfonamide derivatives inhibitors of CAs

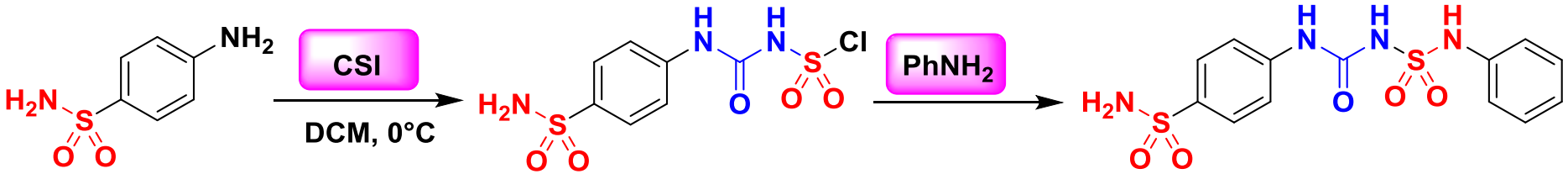
Singh S, Lomelino CL, Mboge MY, Frost SC, McKenna R. molecules. 2018, 23, 1045

Results and discussion

Synthesis



Synthetic route leading to the SLC-0111 analogue



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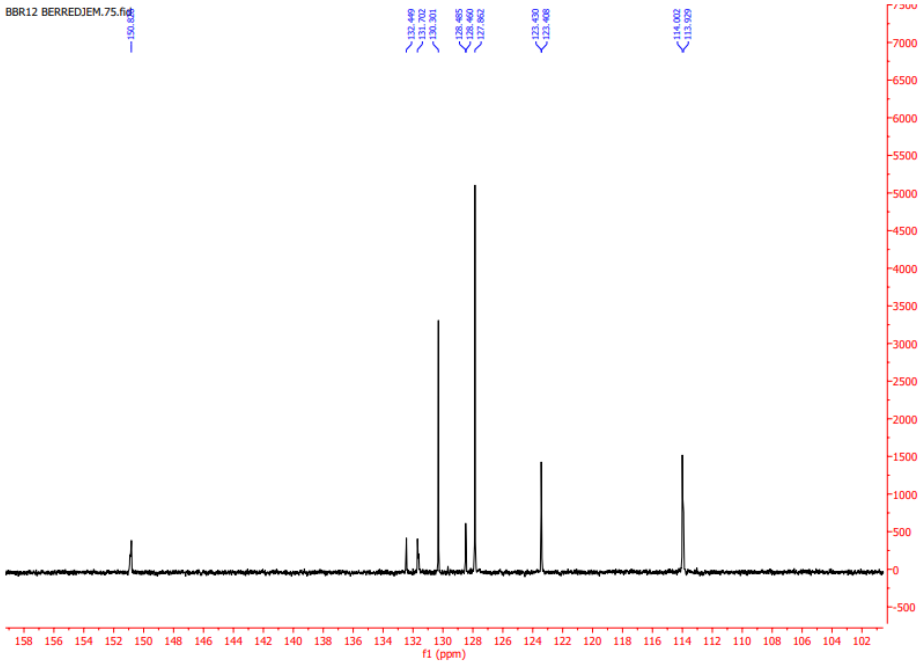
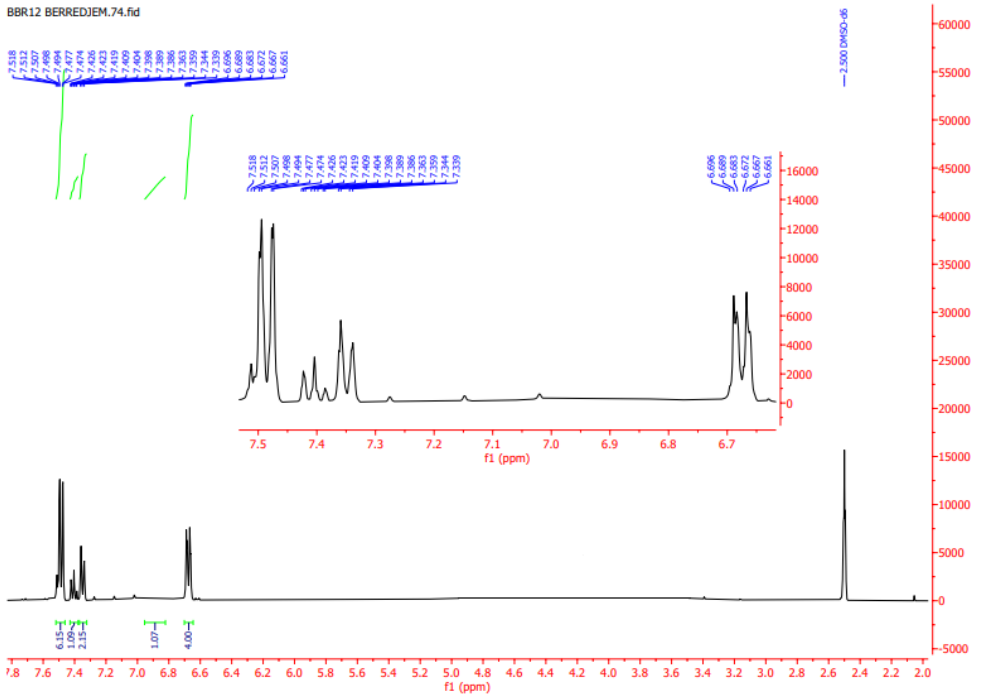
Results and discussion

Structural characterization



^{13}C NMR



^{1}H NMR

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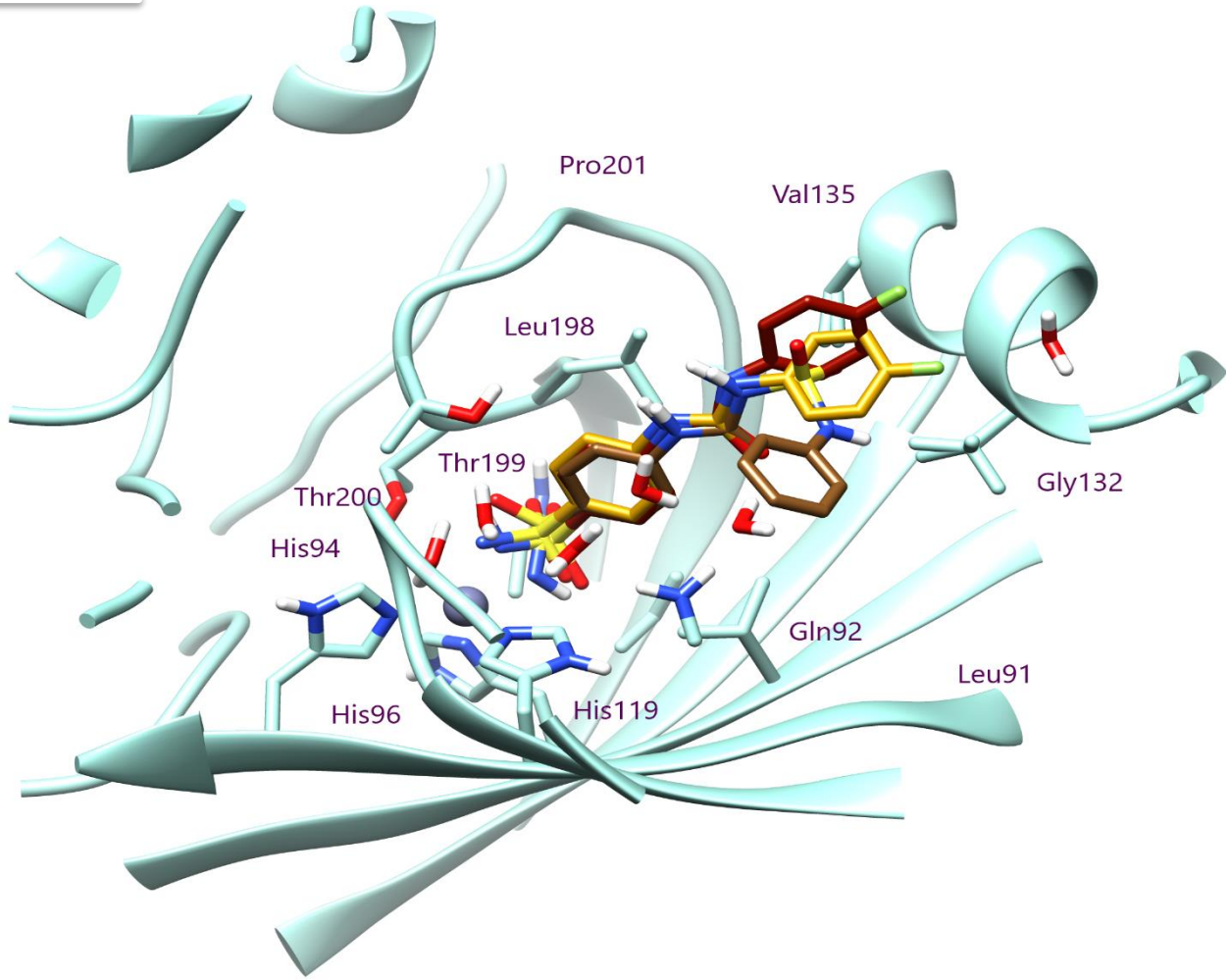
Docking

pdb: 5JN3

Superimposition of the synthesized molecule and the co-crystallized ligand in the active site.
Results shows a stability of the new compound inside the cavity.

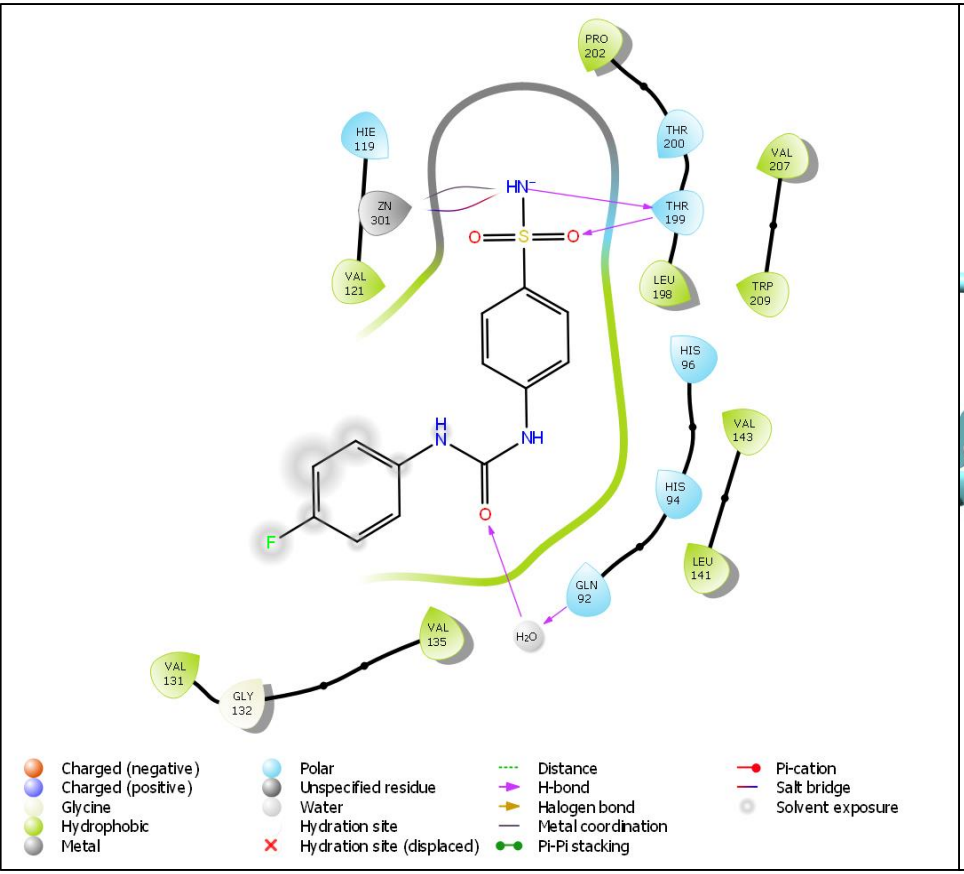
Ligand	Binding free energy (kcal.mol^{-1})
SLC-0111	-9.145
Synthesized ligand	-7.466

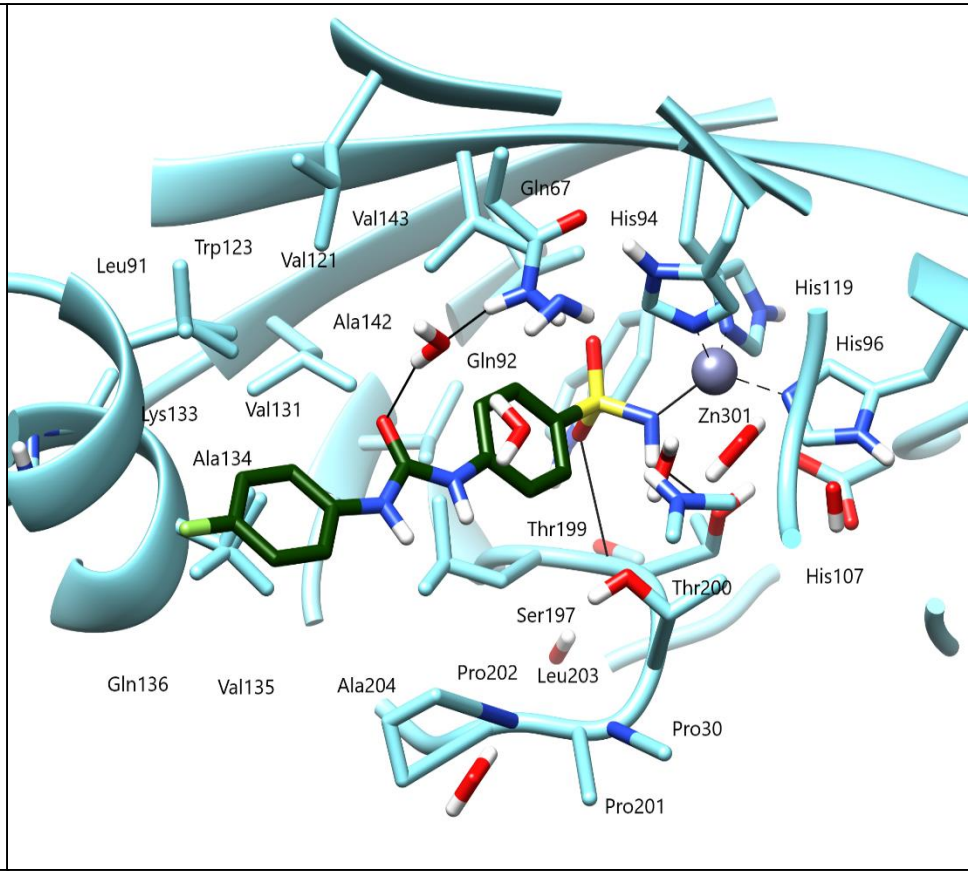


Results and discussion

Docking

pdb: 5JN3





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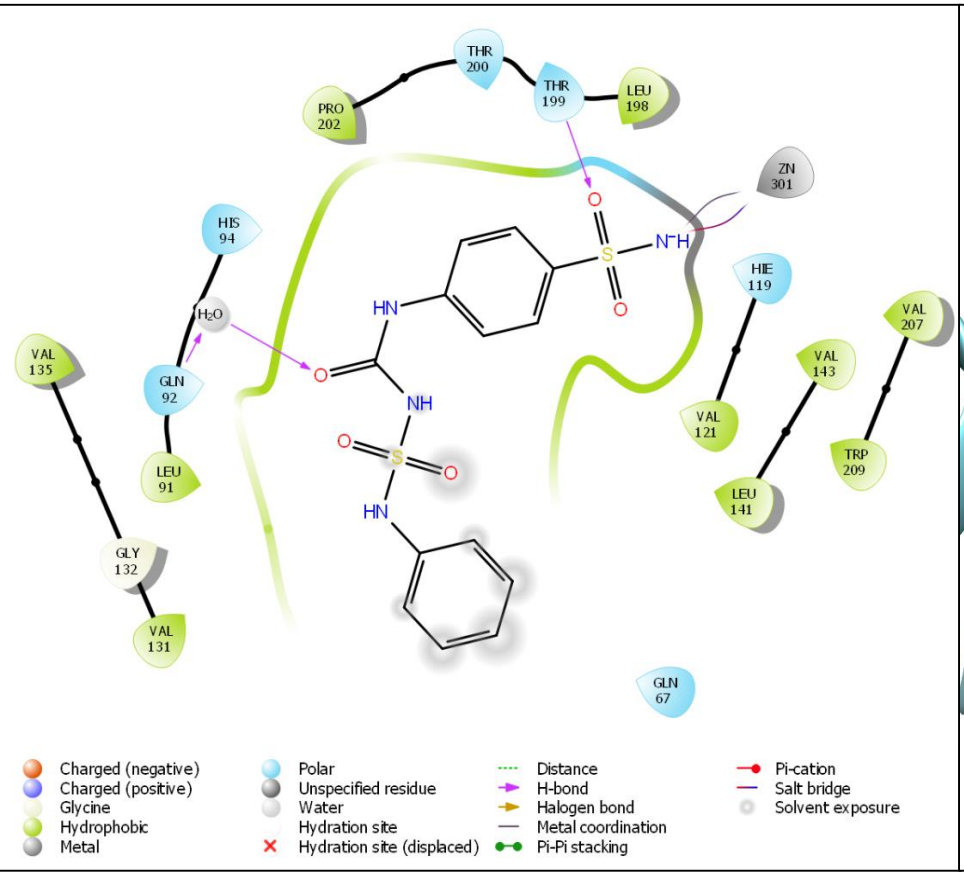

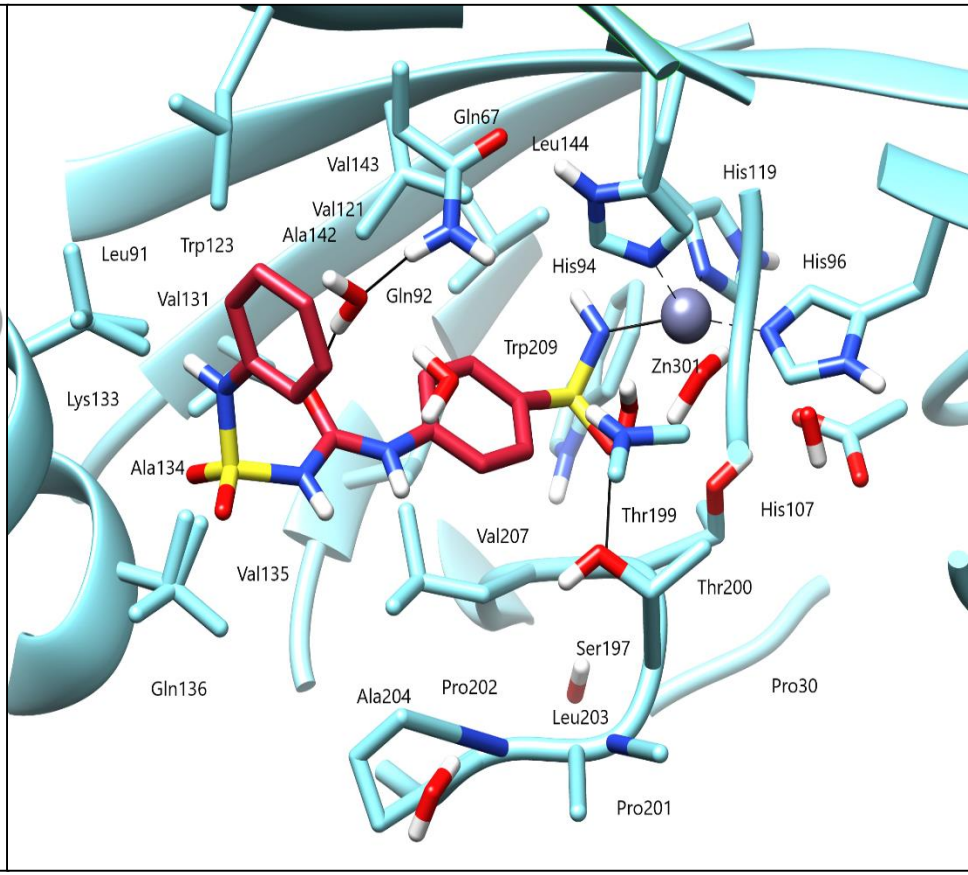

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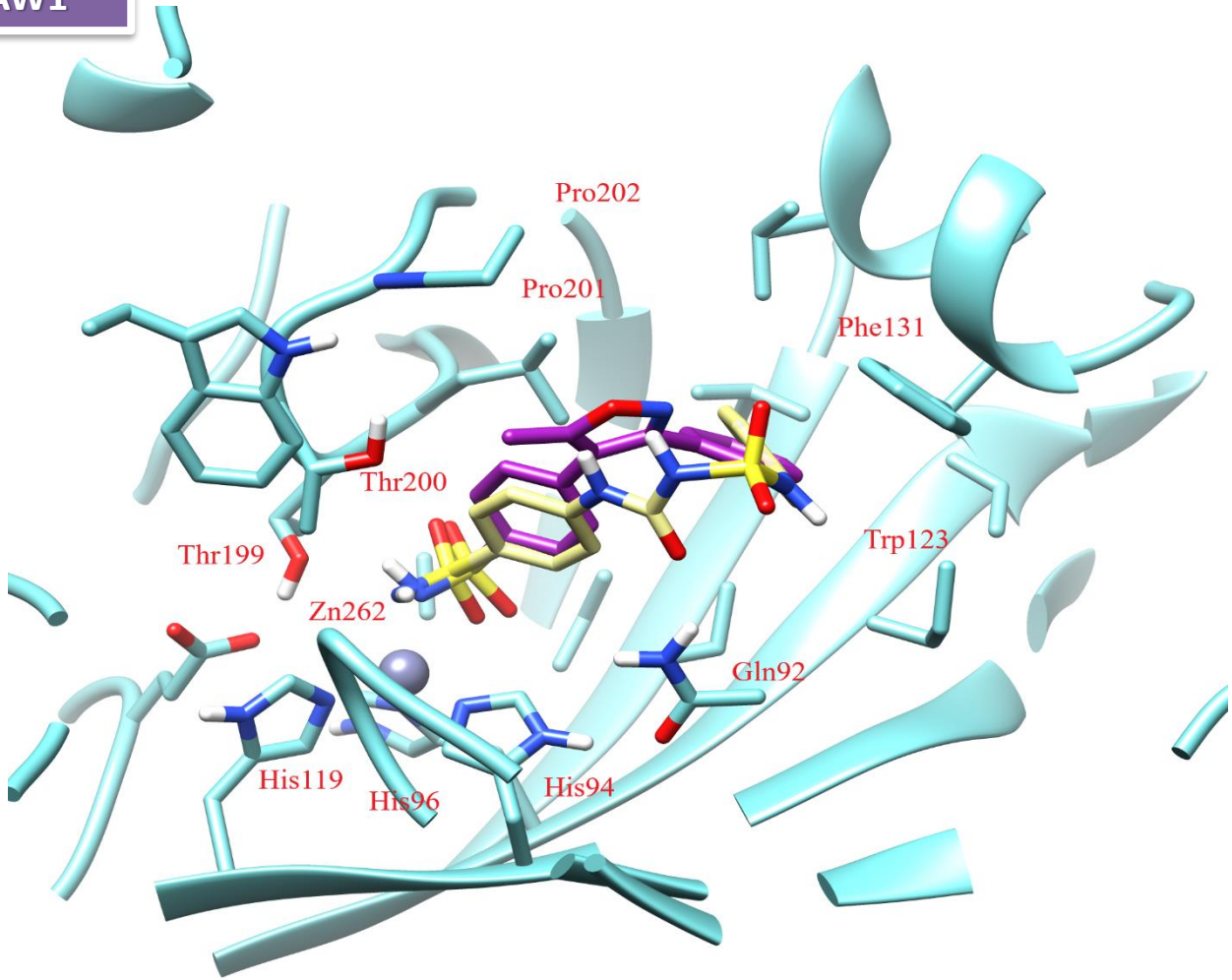
Docking

pdb: 2AW1

The synthesized compound is of a great stability since it have a binding energy lower that Valdecoxib.

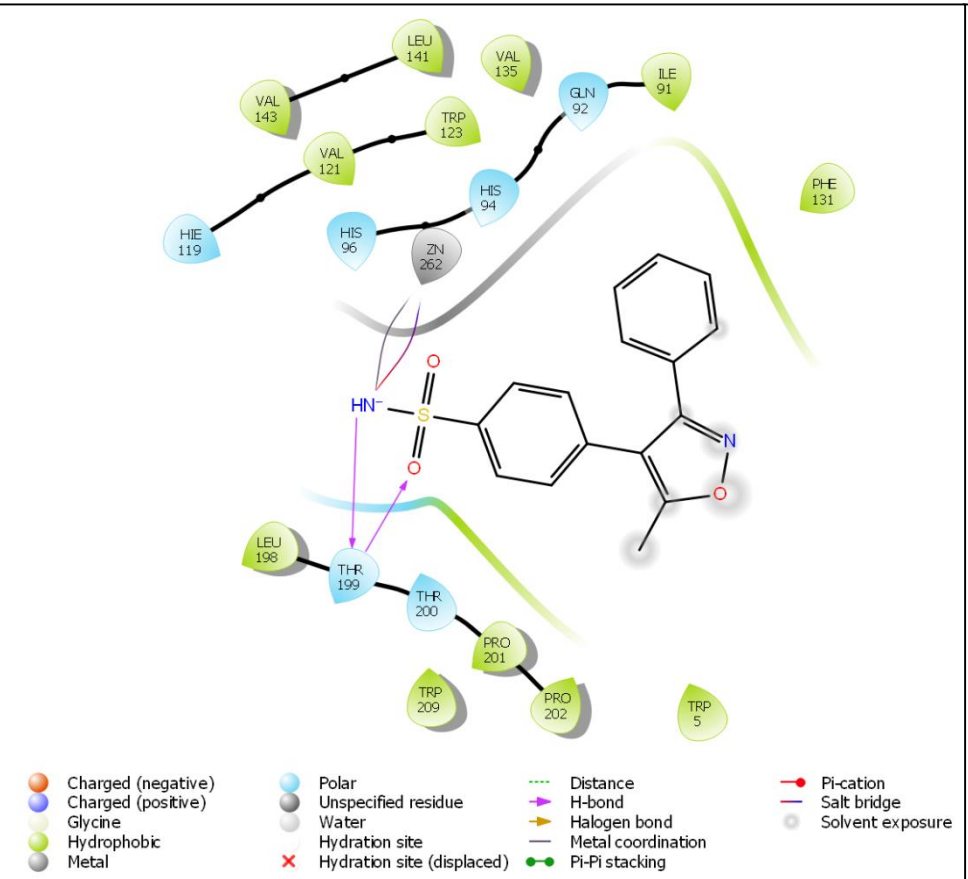
Ligand	Binding free energy (kcal.mol^{-1})
Valdecoxib	-9.006
Synthesized ligand	-9.782

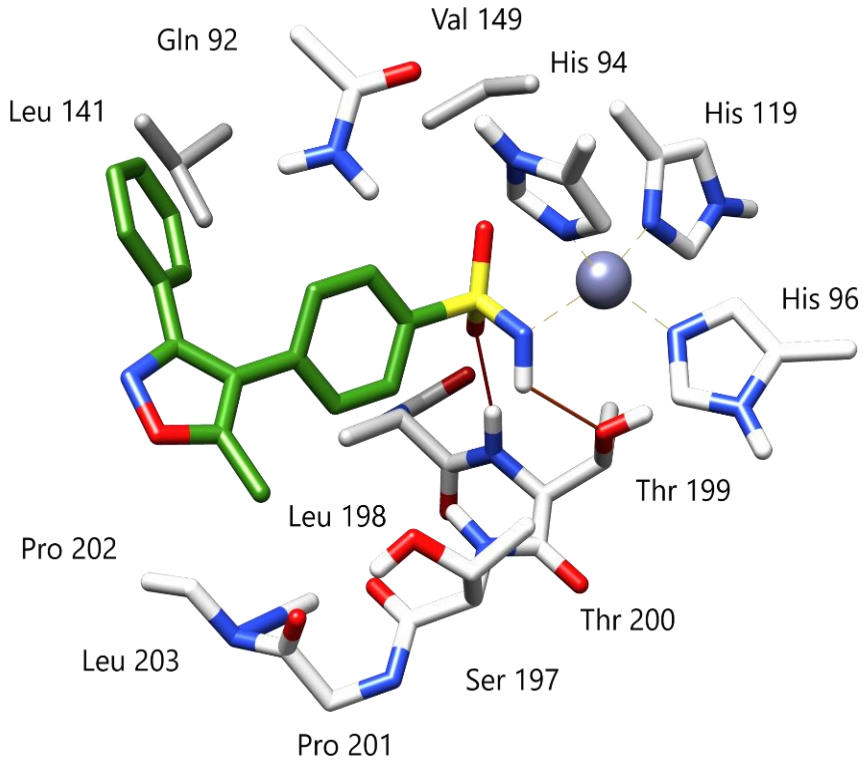


Results and discussion

Docking

pdb: 2AW1





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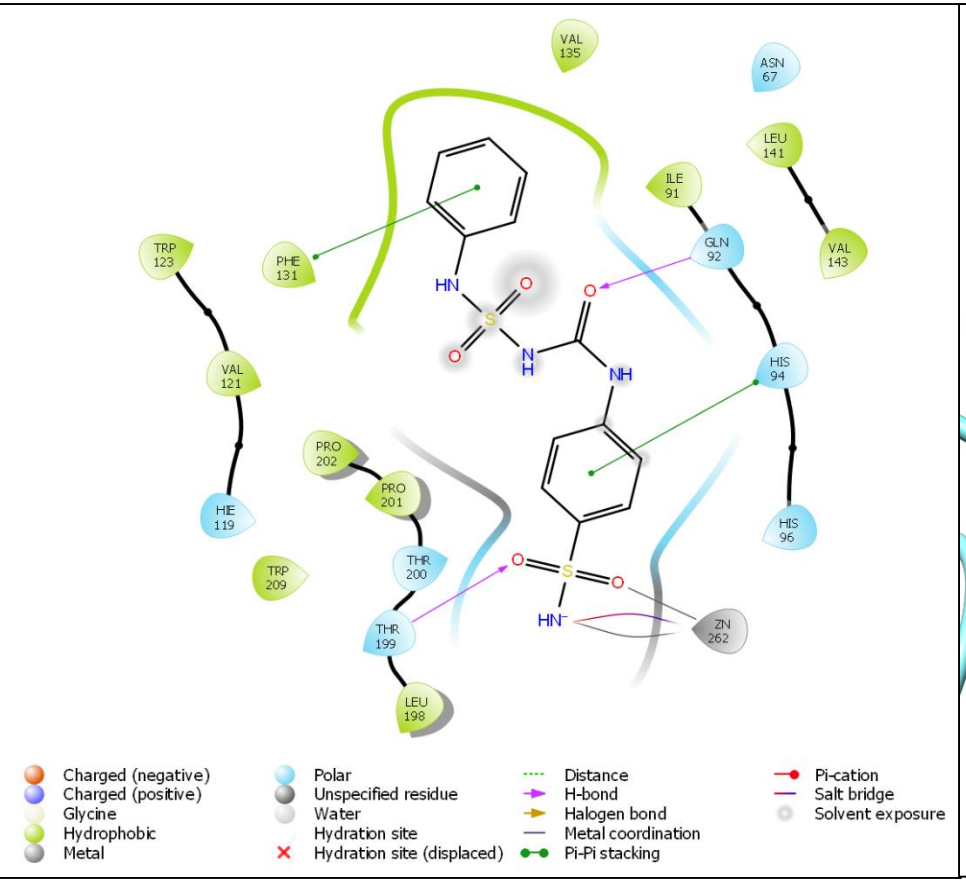
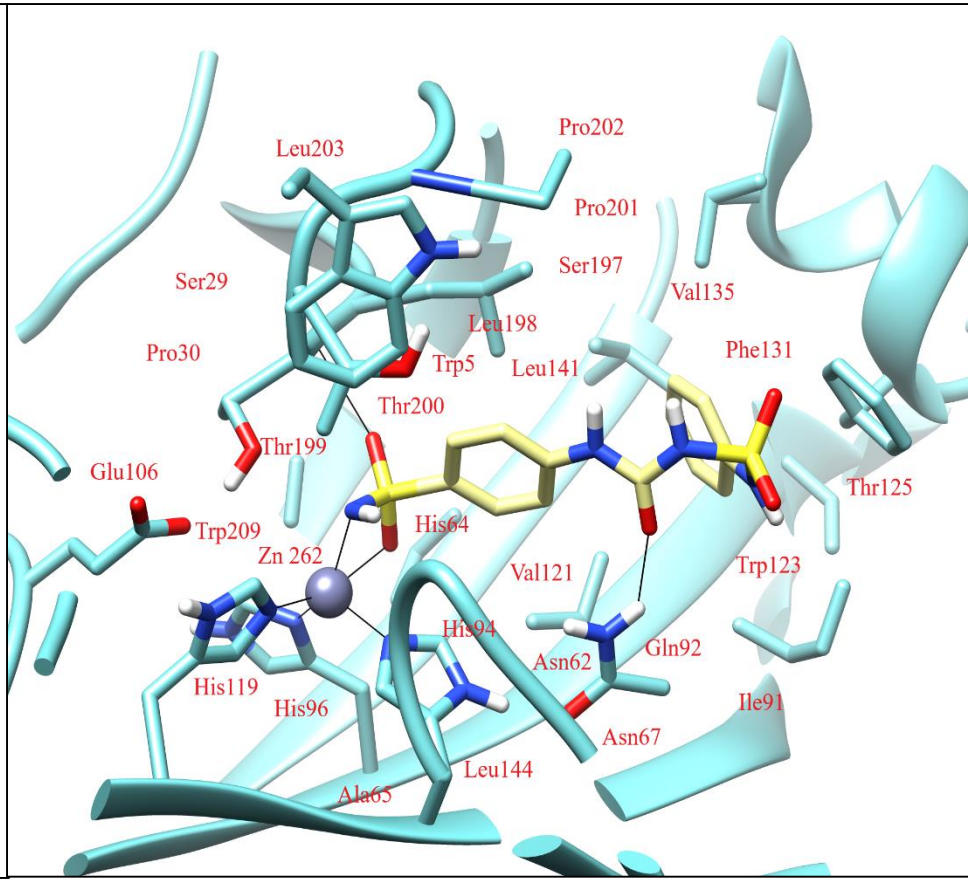
pdb: 2AW1





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Docking

Recapitulation

Interactions	5JN3	2AW1
H bonds	Thr199	Thr199, Gln92
Hydrophobic interactions	Val207, Trp209, Val143, Leu141, Val121, Leu198, Pro202, Leu91, Val135, Val131	Pro202, Pro201, Leu198, Trp209, Phe131, Ile91, Trp123, Val121, Val135, Leu141, Val143

Docking with pdb 5JN3

Synthesized compound formed a hydrogen bond with residue **Thr199** and a metallic bond with **Zn** which is required to the inhibitory activity against CAs.

Additional hydrophobic interactions occurred and were illustrated in the table above.

Docking with pdb 2AW1

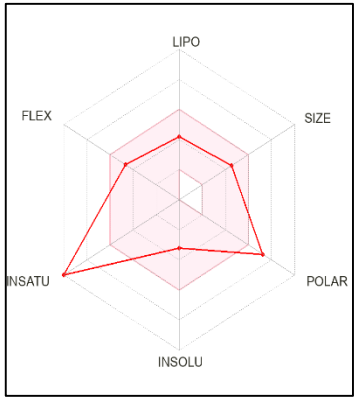
Synthesized compound formed two hydrogen bonds with residue **Thr199** and **Gln92**, a metallic bond with **Zn** is also noticed.

Other interactions were observed including many hydrophobic interactions and two π–π stacking with residues **Phe131** and **His94**.

Results and discussion

ADMET study

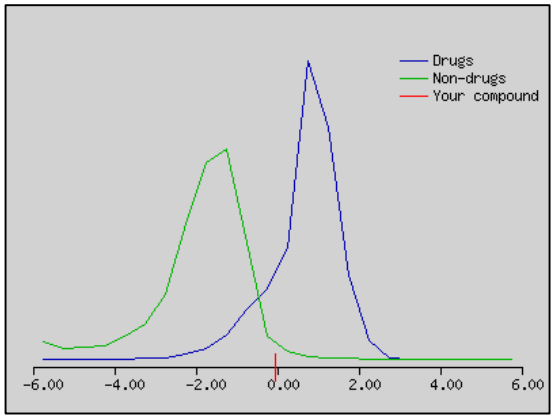
Using SwissADME and MolSoft



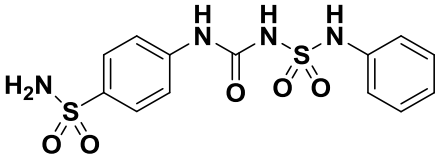
Bioavailability radar

The synthesized compound is in the optimal range of flexibility, lipophilicity, solubility, and size.

Property	Synthesized compound
Molecular weight (g/mole)	370.40 g/mol
Rotatable Bonds	7
H-bond donor	4
H-bond acceptor	6
Log Po/W iLogP	0.72
Log S ESOL	-3.20
GI	Low
BBB	No
Log Kp	-7.26 cm/s
Bioavailability Score	0.55
TPSA (Å²)	164.22 Å²
P-gp substrate	Yes
Brenk	0 alert



Drug likeness



It appears that the new SLC-0111 analogue is considered as drug-like according to Lipinski and Ghose

Conclusions

A new SLC-0111 analogue was synthesized and have been investigated for its binding mode to carbonic anhydrase enzyme. Results showed a great stability of the new compound inside the cavity of the enzyme for both pdb 2AW1 and 5JN3 with a good binding free energy (**-9.782** for pdb: 2AW1 and **-7.466** for pdb: 5JN3).

Results also indicated that the newly synthesized molecule did significant interactions with the residues of the active site and can be considered as a potential CA inhibitor.

ADMET and drug likeness were studied using SwissADME and MolSoft and it was assumed that our compound is considered as drug like according to Lipinski and Ghose's rules only. Further, its flexibility, lipophilicity, solubility, and size were in the norms but it appeared that the studied compound was too polar.

Drug likeness graph obtained using MolSoft showed that our compound is situated more in the range of drug-like than the non-drug range with a score near to 0.

Acknowledgments

This work was supported financially by The General Directorate for Scientific Research and Technological Development (DG-RSDT), Algerian Ministry of Scientific Research, Applied Organic Chemistry Laboratory (FNR 2000).