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

Synthesis, ADME/T, and Carbonic Anhydrase Binding of Hydroxycarboxamide compounds

Chaired by DR. ALFREDO BERZAL-HERRANZ;
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pharmaceuticals MDPI

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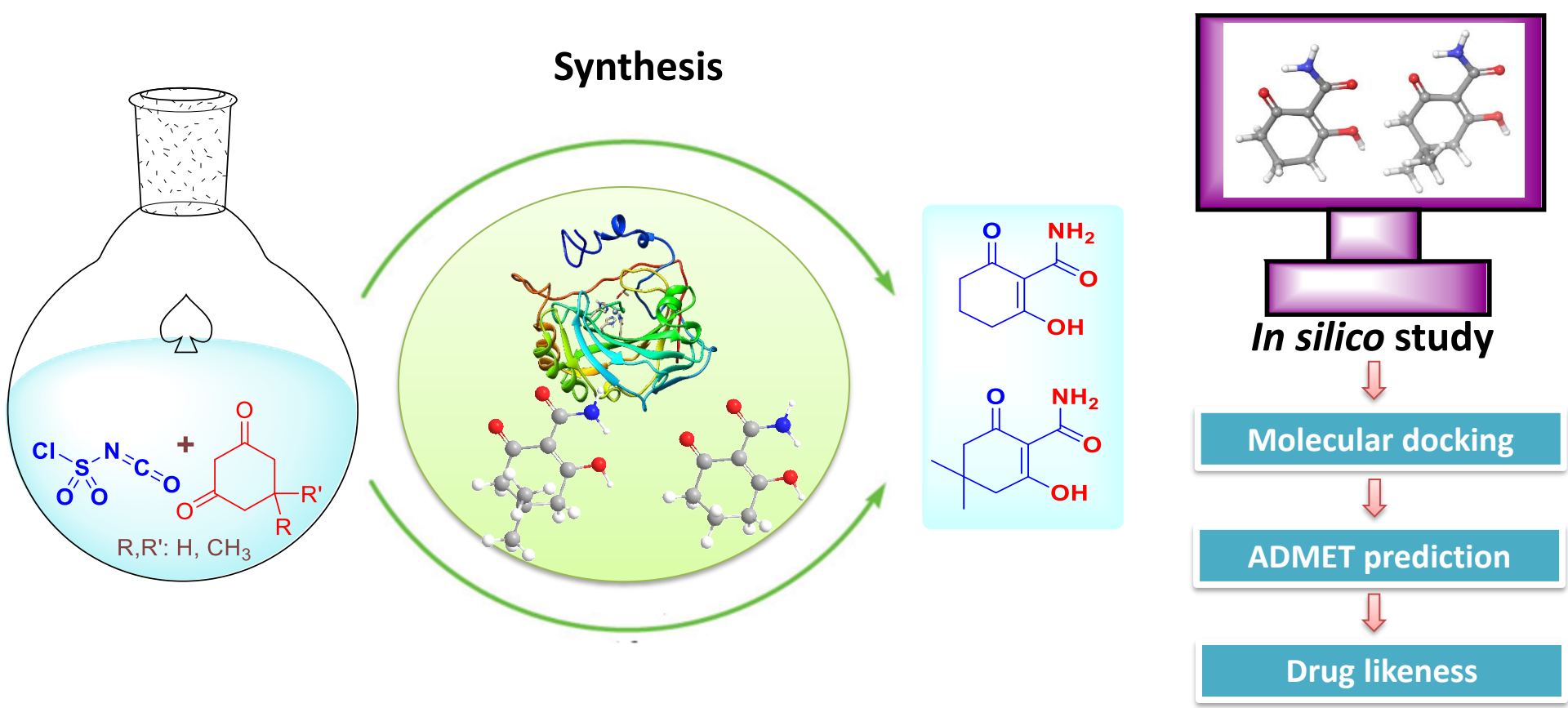
Graphical Abstract



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Abstract:

The interconversion of carbon dioxide and the bicarbonate ion is carried out by carbonic anhydrases (CA), which are ubiquitous metalloenzymes with Zn in their active site. Disorder of CA enzymes can cause several diseases such as glaucoma, epilepsy, obesity, and cancer. Many existing drugs have shown effective inhibition of CAs including: Acetazolamide, Dorzolamide, Methazolamide, and Valdecoxib.

In order to find new agents inhibiting CAs, two small molecules were synthesized and characterized by the usual spectroscopic methods. The prepared compounds are obtained by the condensation of dimedone and cyclohexanedione with CSI in the presence of methanol as proton donor.

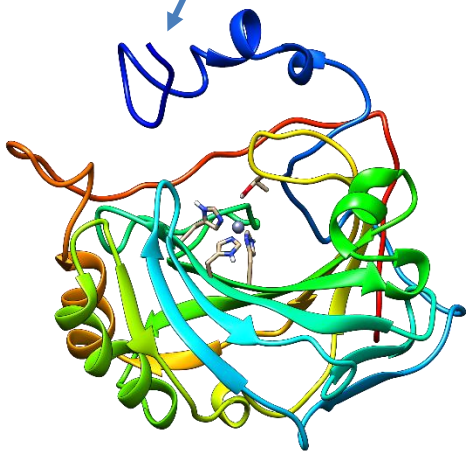
The synthesized derivatives contain a primary amide group ($CONH_2$) bio-isostere of the sulfonamide group (SO_2NH_2) which is present in the quasi-totality of CAs inhibitors. The interactions between our new synthesized molecules and the active site of CAII were determined using docking simulation (PDB: 2AW1), the results showed a great stability of these compounds inside the active site with the presence of metallic and hydrogen bonds similar to the ones present between CAII and the reference Valdecoxib. Pharmacokinetic properties and toxicity were predicted using *in silico* tool (SwissADME) and Molsoft.

Keywords: Carbonic anhydrase, Hydroxycarboxamide, Molecular docking, ADMET

Introduction

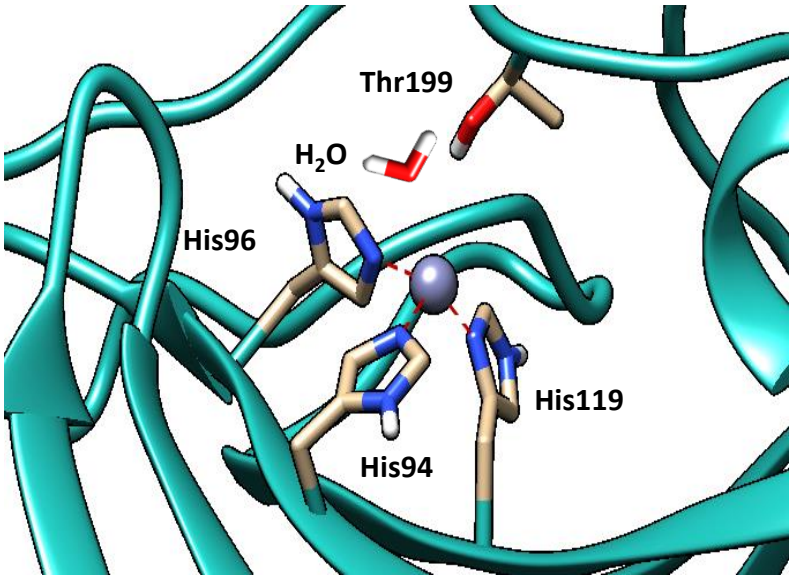
Carbonic anhydrases

Cytosol	External membrane	Metochondria	Secreted
CAI CAII CAIII CAVI CAXIII	CAIV CAIX CAXII CAXIV	CAV_A CAV_B	CAVI



Carbonic anhydrase II

- Cytoplasmic metalloenzyme.
- Most active isoform with 10^6 cycle per second.
- Present in erythrocytes, gastrointestinal tract, kidney, lung, eye, and brain.
- Catalyze the formation of H^+ and HCO_3^-



Active site

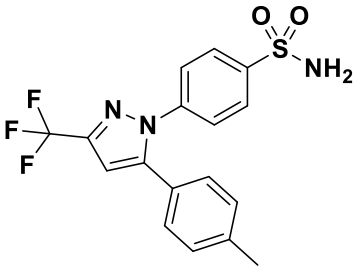
$$H_2O + CO_2 \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

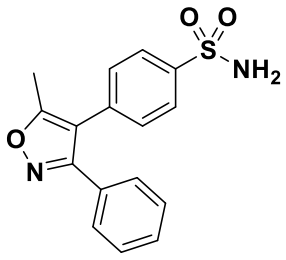
Highlights on carbonic anhydrase II

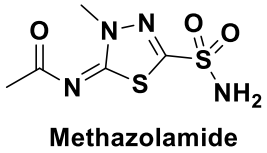
Zamanova S, Shabana AM, Mondal UK, Ilies MA. Expert Opin Ther Pat. 2019, 29, 509

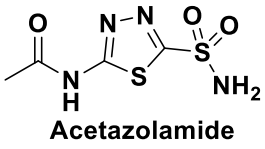
Introduction

Abnormal activity of carbonic anhydrase II can cause osteopetrosis, renal tubular acidosis, and cerebral calcification.

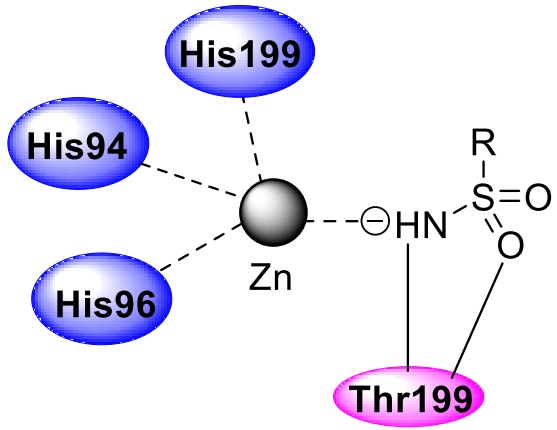




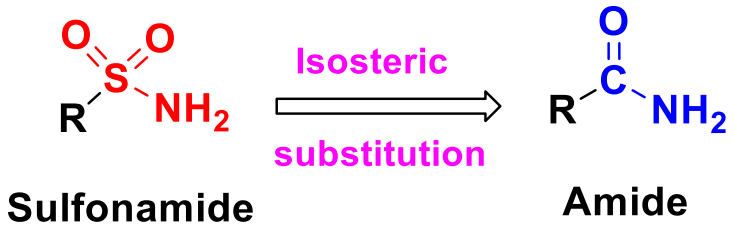




Many existing and novel sulfonamides were known for their inhibitory activities against CAs



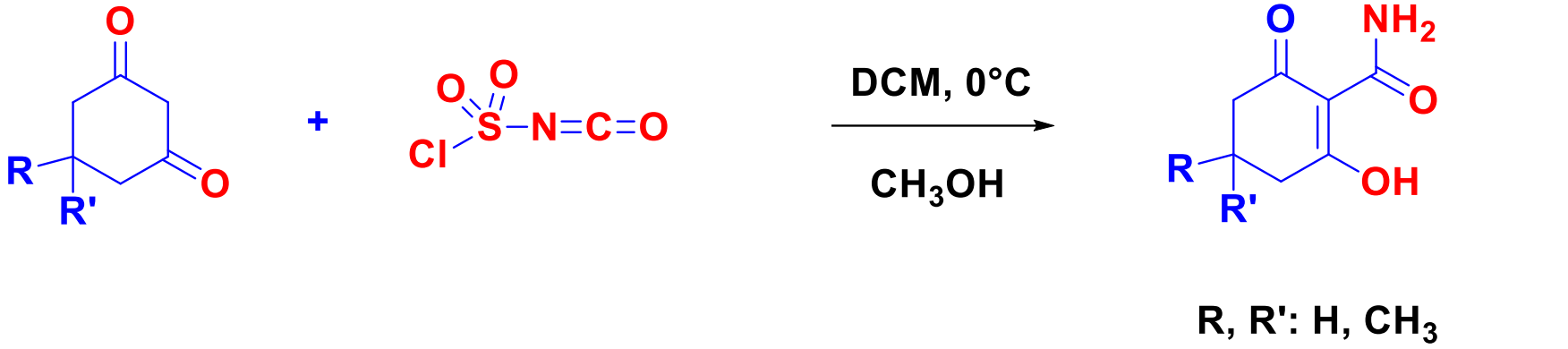
Key interactions between sulfonamides and CAII



Carta F, Supuran CT, Scozzafava A. Future Med Chem. 2014, 6, 1149

Results and discussion

Synthesis



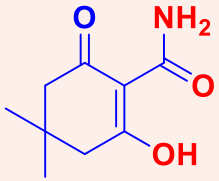
Hydroxycarboxamides

R, R': H, CH_3

- ✓ The synthesis of two hydroxycarboxamide derivatives is carried out in a *one pot* reaction by the condensation of chlorosulfonyl isocyanate with dimedone or cyclohexanedione in the presence of dichloromethane as solvent.
- ✓ Methanol is used in the end of the reaction as a proton donor
- ✓ The synthesized compounds are obtained with good yields

Results and discussion

Structural characterization

Code	Structure	Yields(%)
1		90
2		88

The structures of the prepared compounds **1** and **2** are confirmed by spectroscopic methods (^{1}H, ^{13}C) NMR, HMBC, HSQC, IR, and EA.

In ^{1}H NMR spectrum, the primary amide protons appeared as non-equivalent in the range of 5-6 ppm and 9-10 ppm respectively, which is due to hydrogen bonding.

In ^{13}C NMR spectrum, carbonyl groups appeared at 190, 200 ppm and carbonyl group of the amide function at 170, 173 ppm.

The FT-IR spectrum showed the characteristic bonds of the three functions, namely the amide NH stretching at 3344, 3335 cm^{-1} and its C=O stretching at 1649, 1644 cm^{-1}, the carbonyl of cyclohexanone at 1757, 1741 cm-1, and the enol group with its two signals OH stretching at 3210, 3205 cm^{-1} and the C=C stretching at 1571, 1565 cm^{-1}.

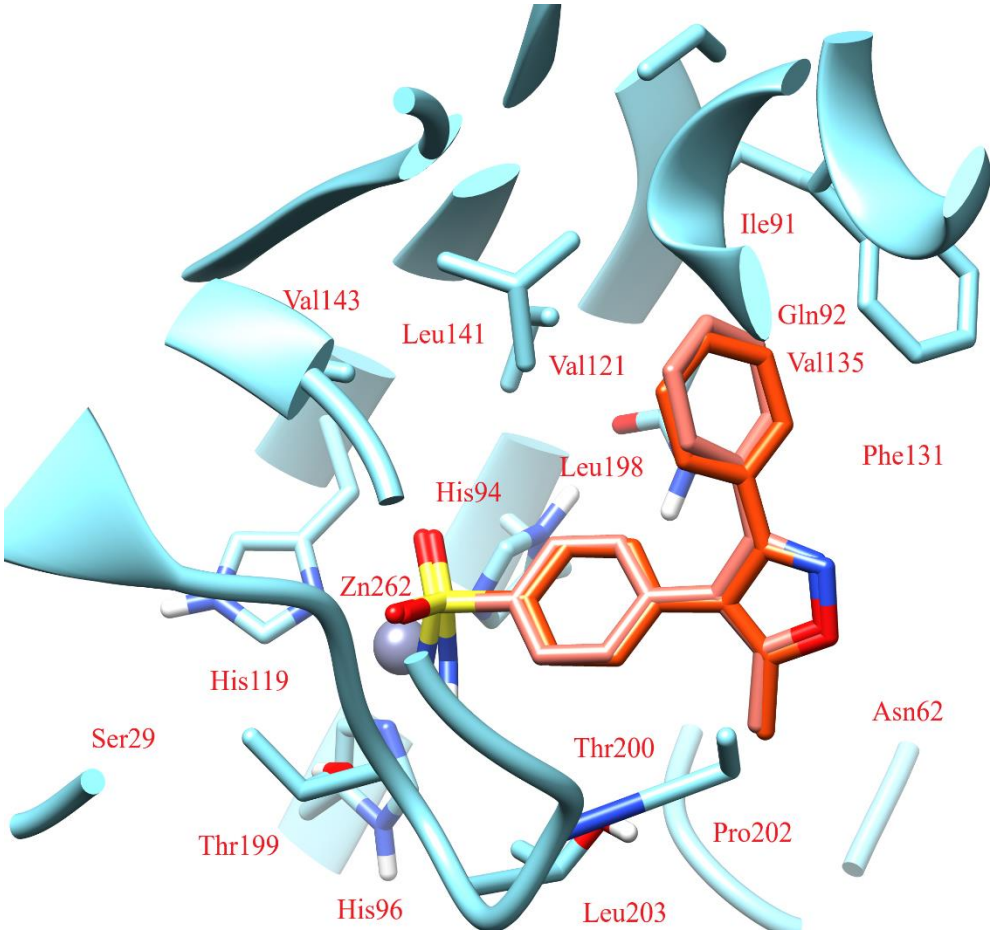
Results and discussion: *in silico* study

Molecular docking | **pdb: 2AW1**

Accuracy of docking protocol was examined by re-docking of **Valdecoxib** in the active site of Carbonic Anhydrase II (**CAII**).

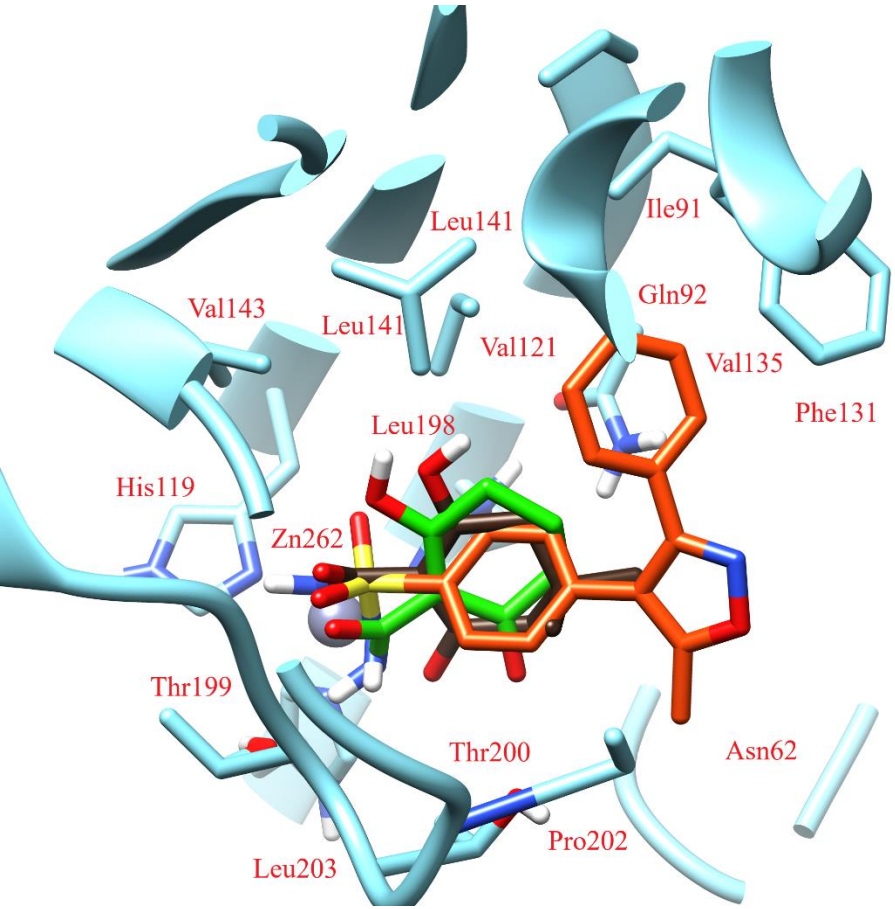
Molecular docking study was performed using *Schrodinger suite* (version 11.8) and *UCSF Chimera* (version 1.13.1) programs.

RMSD = 0.22 Å confirms validation of docking protocol using Extra Precision scoring function, in absence of water molecules.



Results and discussion: *in silico* study

Molecular docking | **pdb: 2AW1**

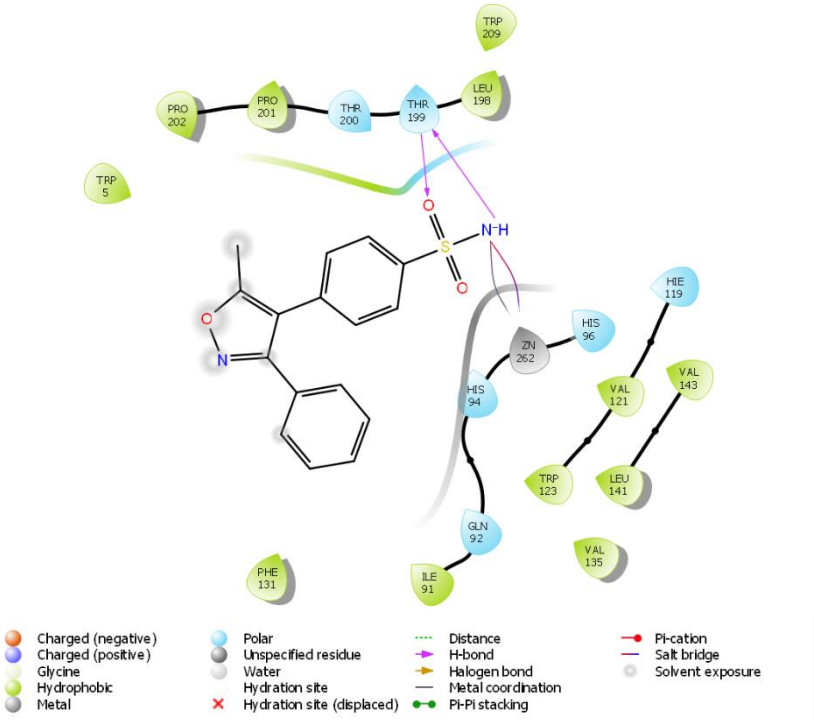


Superimposition of the synthesized hydroxycarboxamides and the co-crystallized ligand in the active site of CAII.
Results shows a moderate stability of the prepared compounds (**1**, **2**) inside the cavity compared with Valdecoxib.

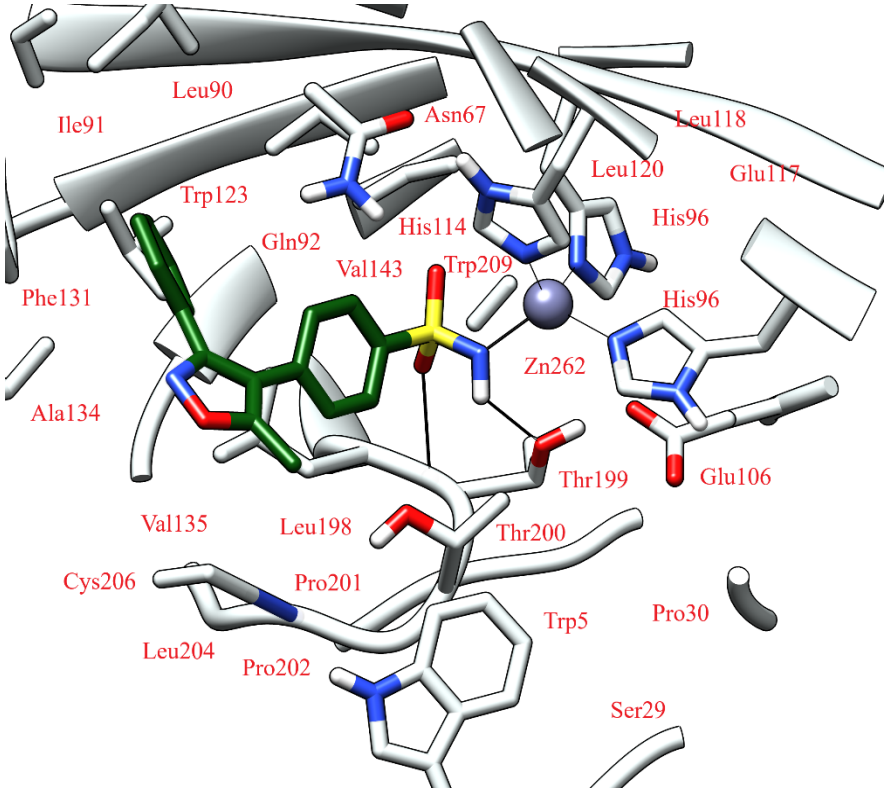
Compound code	Docking score	Binding energy
1	-5.90	-29.69
2	-5.40	-26.32
Valdecoxib	-9.00	-42.58

Results and discussion: *in silico* study

Molecular docking | **pdb: 2AW1**



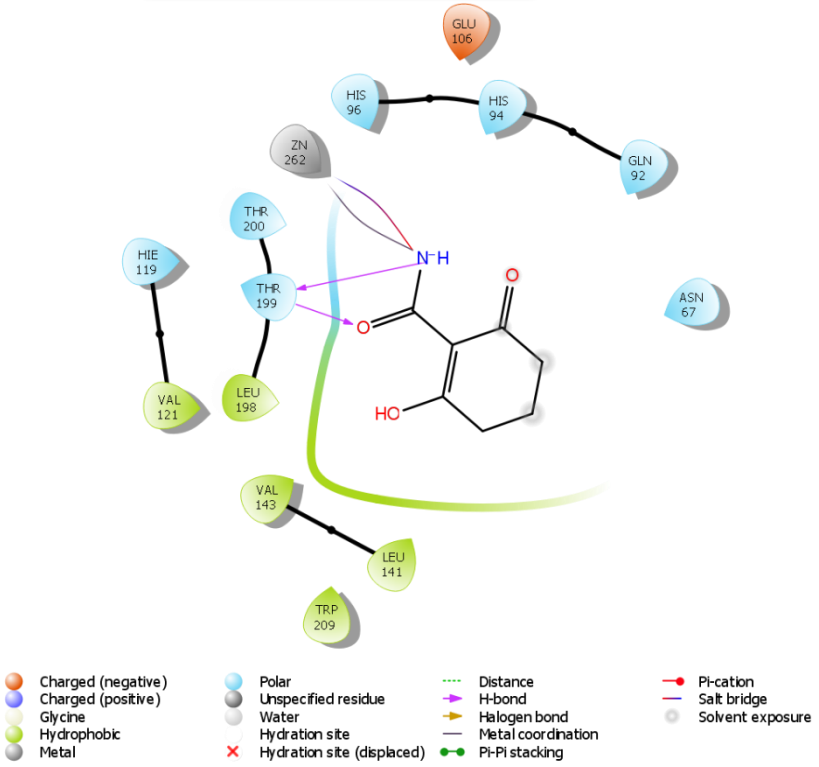
2D binding disposition of **Valdecoxib** in the active site of CAII.



3D binding disposition of **Valdecoxib** in the active site of CAII. The amino acid residues were shown as stick model and H bonds were shown as black lines. calculations

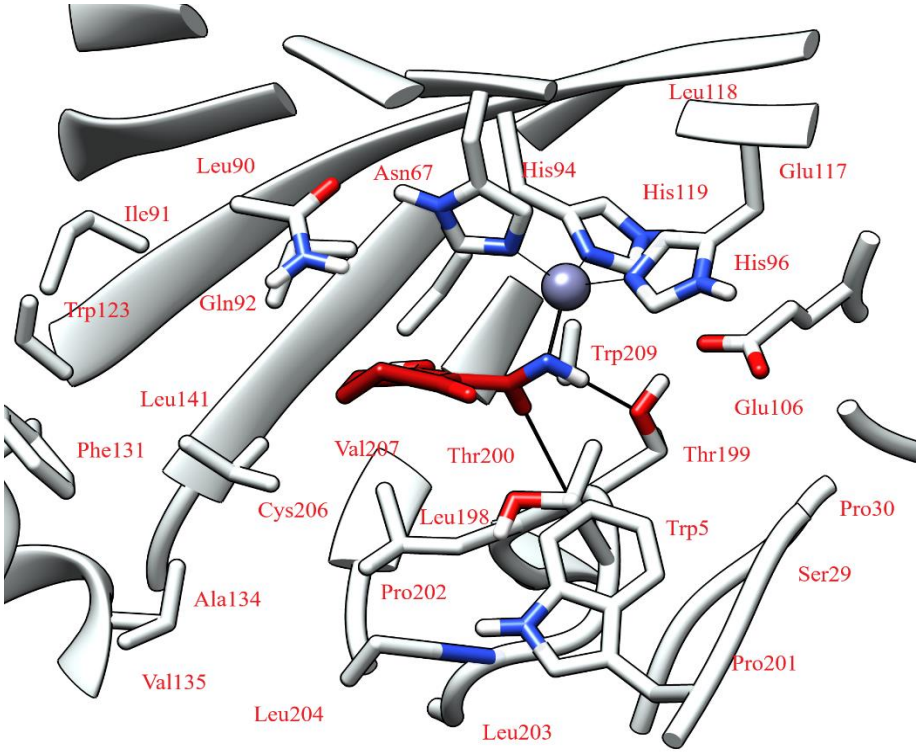
Results and discussion: *in silico* study

Molecular docking | **pdb: 2AW1**



2D binding disposition of compound **1** in the active site of CAII.

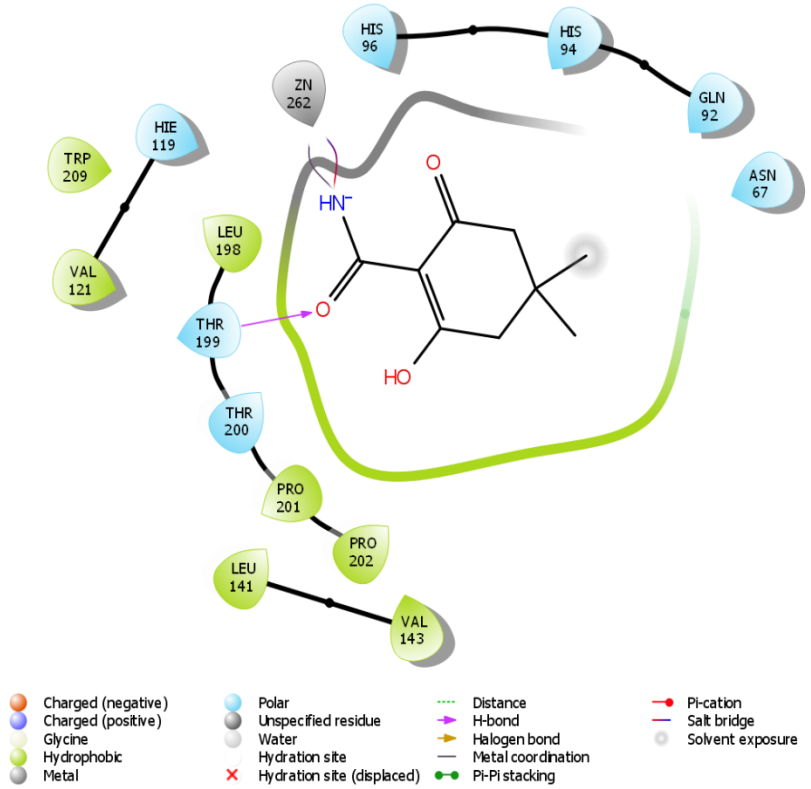
Hydroxycarboxamide as novel non classical CAII inhibitor



3D binding disposition of compound **1** in the active site of CAII. The amino acid residues were shown as stick model and H bonds were shown as black lines. calculations

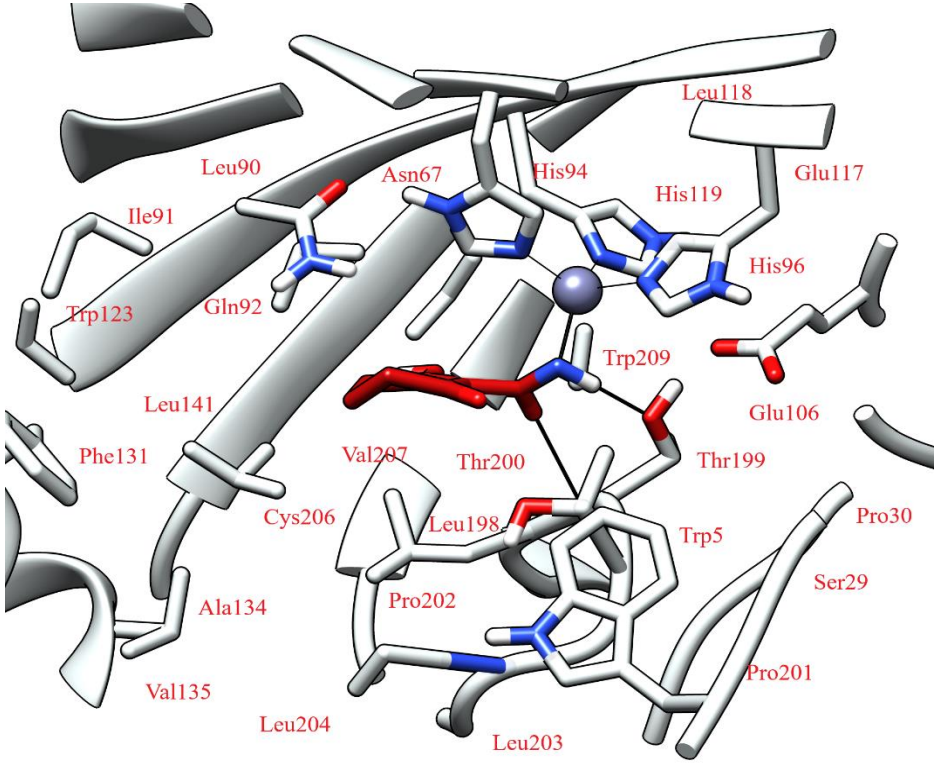
Results and discussion: *in silico* study

Molecular docking | **pdb: 2AW1**



2D binding disposition of compound **2** in the active site of CAII.

Hydroxycarboxamide as novel non classical CAII inhibitor



3D binding disposition of compound **2** in the active site of CAII. The amino acid residues were shown as stick model and H bonds were shown as black lines. calculations

Results and discussion: *in silico* study

Molecular docking

Comp code	Hydrogen bond	Hydrophobic interaction
1	Thr199-O of $CONH_2$ Thr199-NH of $CONH_2$	Val143, Leu141, Pro201, Pro202, Leu198, Val121, Trp209, Hie94
2	Thr199-O of $CONH_2$ Thr199-NH of $CONH_2$	Val143, Leu141, Pro201, Pro202, Leu198, Val121, Trp209, Hie94
Valdecoxib	Thr199-O of SO_2NH_2 Thr199-NH of SO_2NH_2	Val143, Leu141, Pro201, Pro202, Leu198, Val121, Trp209, Hie94, Trp123, Trp5, Val135, Ile91, ¨Phe131

Analysis of the molecular docking results showed that the interactions within the active site of CAII were attributed to hydrogen bonds with **Thr199** residue as the binding of the reference ligand (Valdecoxib) and metallic bond with **Zn262** which is required to the inhibitory activity against CAII. Moreover, the synthesized hydroxycarboxamides developed an important hydrophobic interactions.

Results and discussion: *in silico* study

ADMET study

Pharmacokinetic properties and toxicity were predicted using *in silico* tool (SwissADME) and Molsoft.

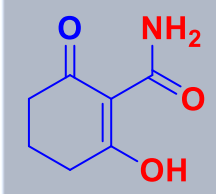
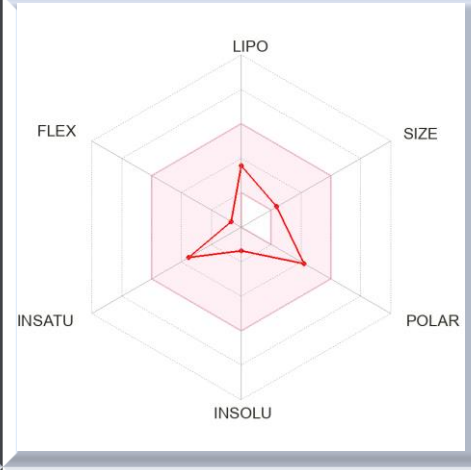
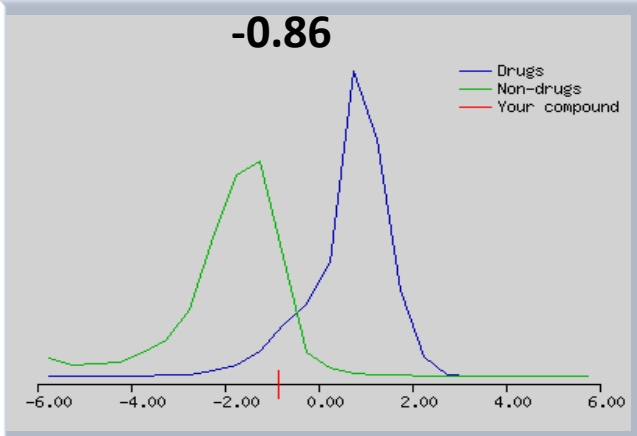
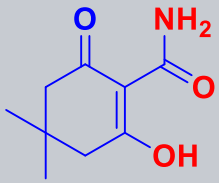
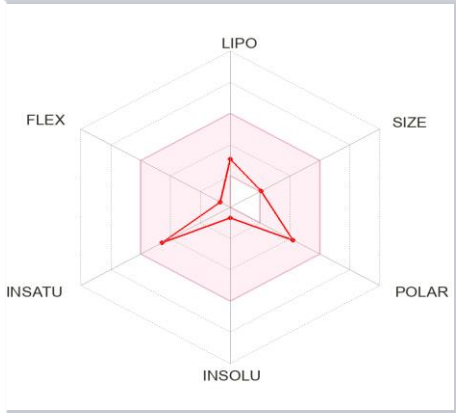
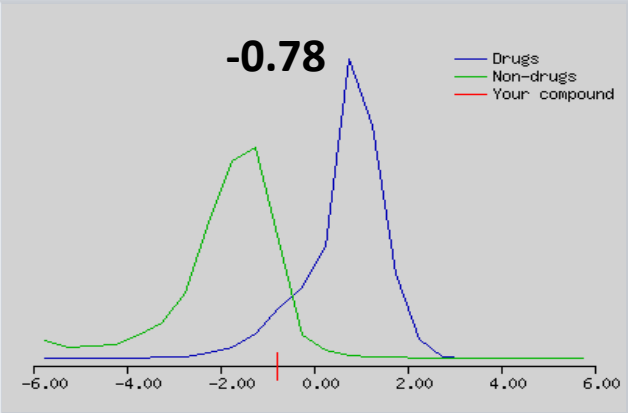
Property	Compound 1	Compound 2
Molecular weight (g/mole)	183.20	155.15
Rotatable Bonds	1	1
H-bond donor	2	2
H-bond acceptor	3	3
Log Po/W iLogP	0.81	0.45
Log S ESOL	-1.37	-0.67
GI	High	High
BBB	No	No
Log Kp (cm/s)	-6.90	-37.2
Bioavailability Score	0.56	0.56
TPSA (Å²)	80.39	80.39
P-gp substrate	No	No

Results and discussion: *in silico* study

SwissADME and MolSoft

The Hydroxycarboxamide (1, 2) are in the optimal range of flexibility, lipophilicity, solubility, polarity, and size.

The hydroxycarboxamides have physicochemical profiles that make them suitable for oral administration according to Lipinski, Ghose, Veber, and Egan.

	Bioavailability radar	Drug likeness
		
		

Conclusions

In conclusion, we have described the synthesis of two derivatives of hydroxycarboxamide. The synthesized compounds are obtained in good yields. The structures of these compounds have been confirmed using spectroscopic methods (IR, NMR, HMBC, HSQC, and EA).

The results of molecular docking study exhibited that hydroxycarboxamides interact with CAII in an effective and satisfactory manner. The two compounds formed an interesting Hydrogen bond with **Thr199** residue and metallic bond with **Zn 262**.

Also, we studied the prediction of absorption, distribution, properties of metabolism, excretion, and toxicity (ADMET) of the synthesized compounds.

This study showed that bioisosters ($CONH_2$) of sulfonamide group (SO_2NH_2) can be used as non classical CA inhibitors.

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).