Rational design of carbonic anhydrase VII inhibitors. Synthesis of new candidates with the sulfamide scaffold

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Introduction

Human carbonic anhydrase VII (hCA VII) constitutes a promising molecular target for the treatment of epileptic seizures and other central nervous system disorders (such as neuropathic pain) due to its almost exclusive expression in neurons.[1]

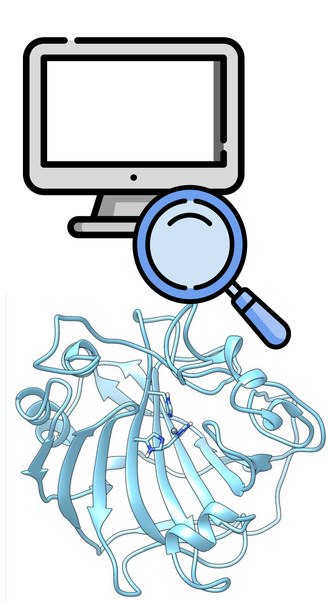
hCA VII, like all catalytically active anhydrases, is a metalloenzyme characterized by a zinc ion in the active site.[1] These enzymes catalyze the carbon dioxide to bicarbonate reversible hydration reaction[1]:

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

Aim

Here we present the application of a fully validated molecular docking protocol[1] for the rational selection of the most promising N,N'-disubstituted sulfamides derivatives to be synthesized as potential new hCAVII inhibitors.

Inhibitor design



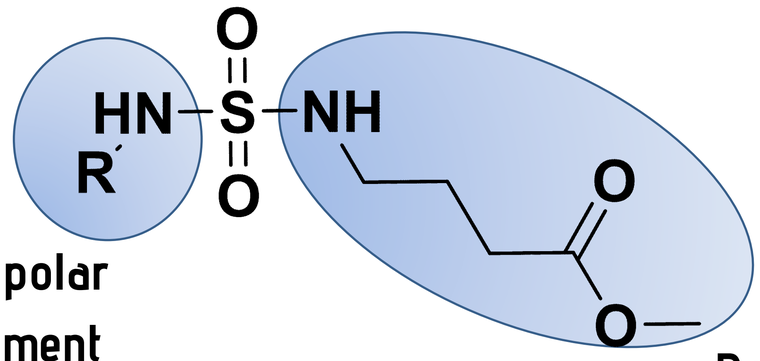
Docking analysis

- Score
- Pose (visual inspection)
- Docking ligand efficiency

Rational sulfamides selection

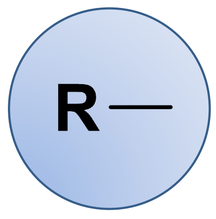
Chemical synthesis

General features of the candidates



Non polar Fragment

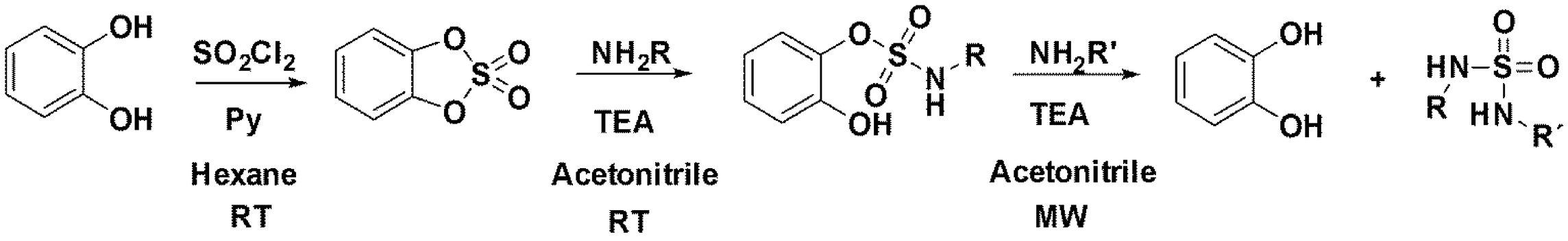
Polar Fragment



Alkyl, Cycloalkyl, Aromatic

GABA methyl ester

Organic Synthesis[2]



Biological Assays

In vitro

Inhibition assay against hCAVII

In vivo

Acute models of epilepsy in mice

References

1) Gantner, M. E etal. Identification of New Carbonic Anhydrase VII Inhibitors by Structure-Based Virtual Screening. *J. Chem. Inf. Model.* 2022, 62 (19), 4760–4770. https://doi.org/10.1021/acs.jcim.2c00910.

2) Villalba, M. L et al *Bioorganic & Medicinal Chemistry* 2016, *24* (4), 894–901. https://doi.org/10.1016/j.bmc.2016.01.012.

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