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Investigation of pyrazoline-based aromatic sulfamates as carbonic anhydrase isoforms I, II, IX and XII inhibitors.

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pharmaceuticals MDPI

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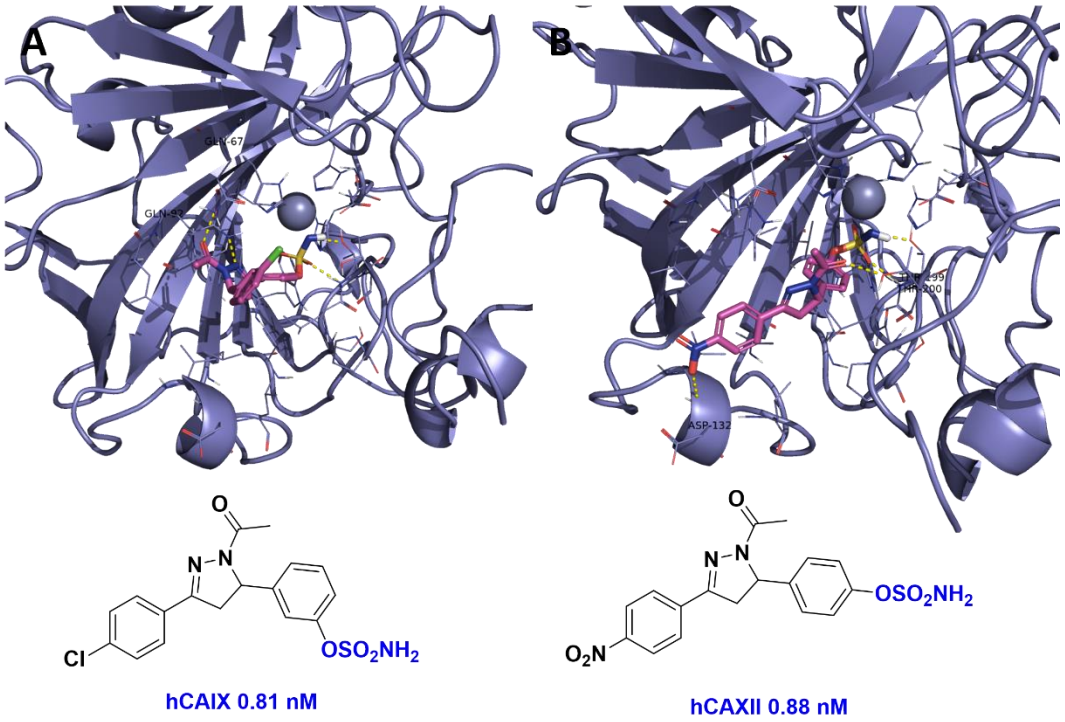
Investigation of pyrazoline-based aromatic sulfamates as Carbonic Anhydrase isoforms I, II, IX and XII inhibitors.



hCAIX 0.81 nM

hCAXII 0.88 nM

Abstract: Pyrazolines are biologically privileged scaffolds, endowed with versatile biological activity, such as an anti-proliferative action. Four new series of aromatic sulfamates were synthesized and investigated for the inhibition of four human (h) isoforms of zinc enzyme carbonic anhydrase, hCA I, II, IX, and XII. The reported derivatives, obtained by a sulfamoylation reaction of the corresponding phenolic precursors, bear 3,5-diarylpyrazoline moieties as spacers between the benzenesulfamate fragment which binds the zinc ion of the CA active site, and the tail of the inhibitor. The derivatives were tested for the inhibition of the cytosolic, hCA I and II (off target isoforms) and the trans-membrane, tumor-associated hCA IX and XII enzymes (anti-cancer drug targets). Generally, hCA I was not effectively inhibited, whereas many low nanomolar inhibitors were evidenced against hCA II (KIs in the range of 0.42–90.1 nM), IX (KIs in the range of 0.72–63.6 nM), and XII (KIs in the range of 0.88–85.2 nM). The best substitution fragments at the pyrazoline ring included for CA II a 4-sulfamic group on the 3-aryl ring and halogens on the 5-aryl ring or a methoxyl group on the 3-aryl ring and a 4-sulfamate group on the 5-aryl ring; for CA IX and CA XII they included the sulfamic group on the 3- or 4-position of the 5-aryl ring and an electronwithdrawing group on the 4-postion of the 3-aryl ring

Keywords: Pyrazolines, Aryl Sulfamates, Carbonic Anhydrase, Enzyme inhibition,

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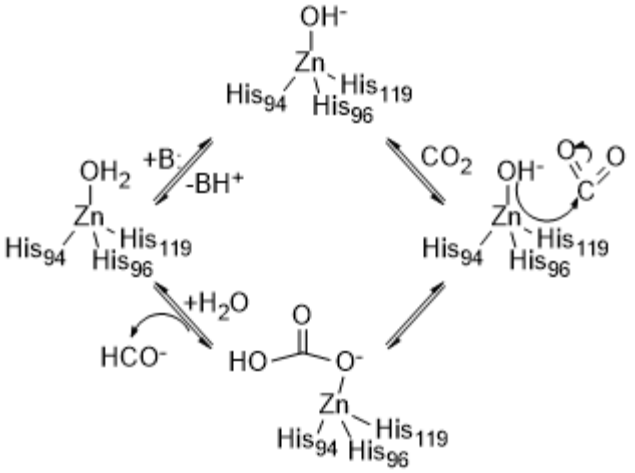
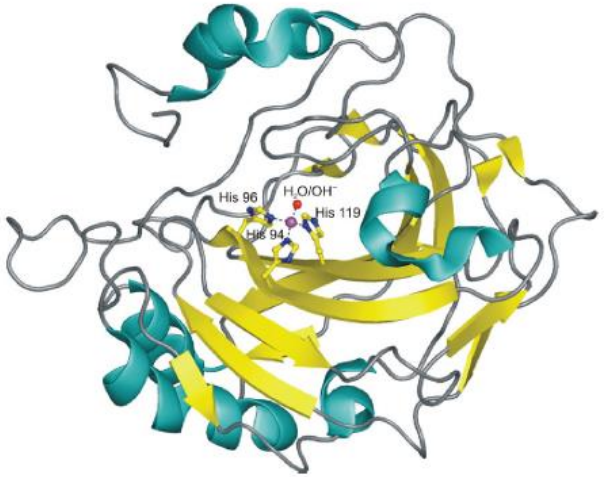
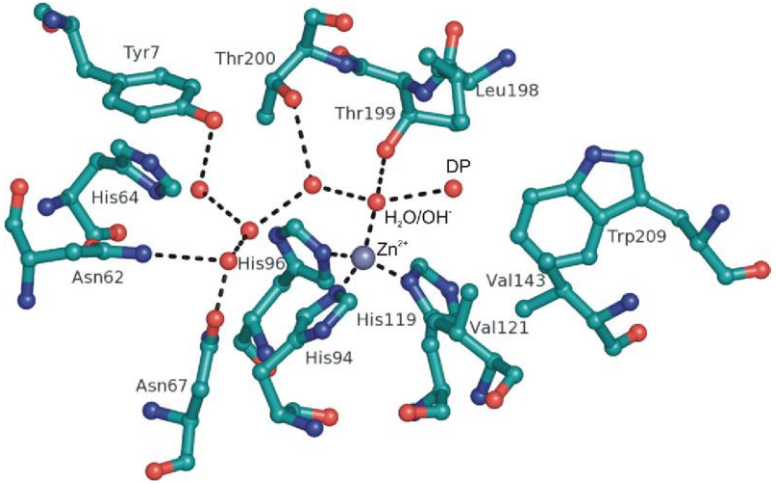
Human Carbonic Anhydrase

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





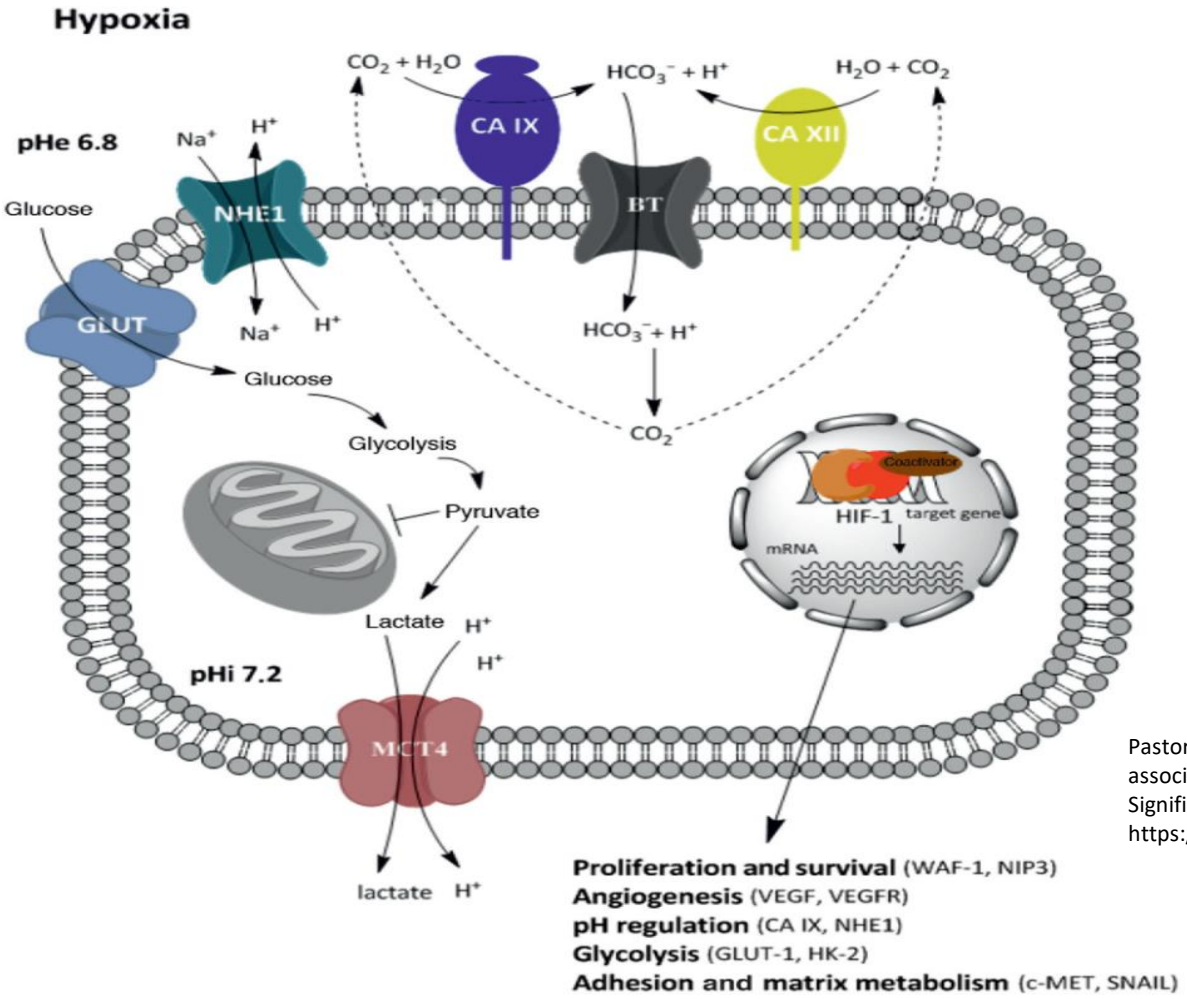


Supuran, C. T. (2008). Carbonic anhydrases: Novel therapeutic applications for inhibitors and activators. Nature Reviews Drug Discovery, 7, 168–181. https://doi.org/10.1038/nrd2467

*h*CAs tissue distribution

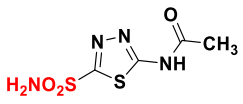
Isoform	Organ/tissue distribution	Subcellular localization	Diseases in which is involved
hCAI	Erythrocytes, eye, gastrointestinal tract	Cytosol	Retinal/cerebral edema
hCAII	Erythrocytes, eye, brain, bone, kidney lung, etc	Cytosol	Glaucoma, edema, epilepsy, altitude sickness
hCAIII	Skeletal muscle, adipocytes	Cytosol	Oxidative stress
hCAIV	kidney, lung, pancreas, brain capillaries, colon, heart muscle, eye	Membrane-bound	Glaucoma, retinitis pigmentosa, stroke
hCAVa	Liver	Mitochondria	Obesity
hCAVb	Heart and skeletal muscle, pancreas, kidney, spinal cord, gastrointestinal tract	Mitochondria	Obesity
hCAVI	Salivary and mammary glands	Secreted into saliva and milk	Cariogenesis
hCAVII	CNS	Cytosol	Epilepsy, oxidative stress
hCAIX	Tumors, gastrointestinal mucosa	Transmembrane	Cancer
hCAXII	Renal, intestinal, reproductive epithelia, eye, tumors	Transmembrane	Cancer, glaucoma
hCAXIII	Kidney, brain, lung, gut, reproductive tract	Cytosol	Sterility
hCAXIV	Brain, liver, eye, skeletal muscle	Transmembrane	Epilepsy, retinopathies

*h*CA IX/XII as target

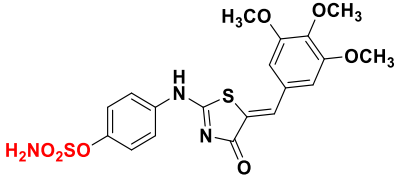


Pastorekova, S., Parkkila, S., & Zavada, J. (2006). Tumor-associated Carbonic Anhydrases and Their Clinical Significance. Advances in Clinical Chemistry, 42, 167-216. https://doi.org/10.1016/S0065-2423(06)42005-9

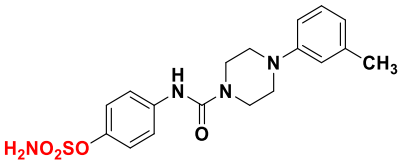
Design of N^1-acetyl-3,5-diarylpyrazoline sulfamates



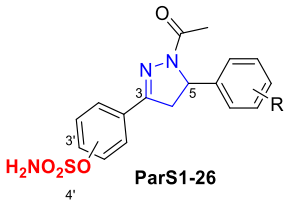
Acetozolamide
CA IX Ki 25.0 nM



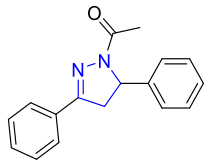
CA IX Ki 17.6 nM

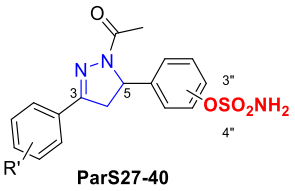


CA IX Ki 0.91 nM

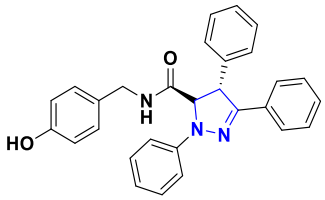


ParS1-26

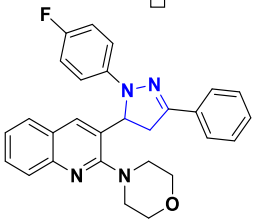




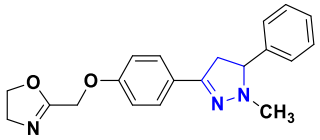
ParS27-40



Antiproliferative activity



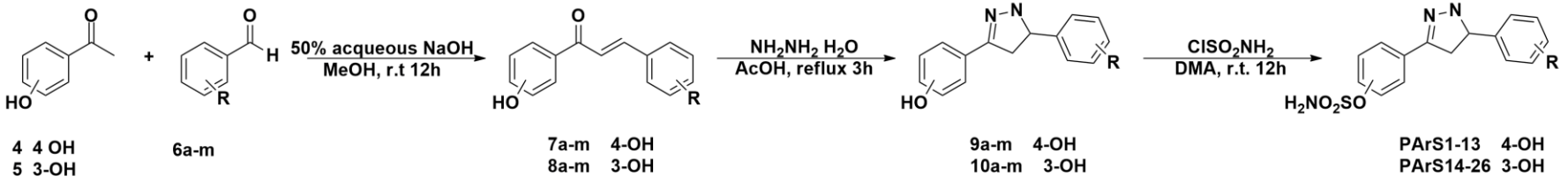
Antitubercolosis activity



Antimalarial activity

Nocentini, A., Moi, D., Balboni, G., Salvadori, S., Onnis, V., & Supuran, C. T. (2018). Bioorg.Chem., 77, 21. Moi, D., Nocentini, A., Deplano, A., Balboni, G., Supuran, C. T., & Onnis, V. (2019) Eur. J. Med. Chem., 182, 111638; Nocentini, A., Moi, D., Deplano, A., Osman, S.M., AlOthman, Z.A., Balboni, G., Suèpuran, C.T., Onnis, V. (2020), Eur. J. Med. Chem, 186, 111896.

Synthesis of N^1-acetyl-3,5-diarylpyrazoline sulfamates



4 4 OH
5 3-OH

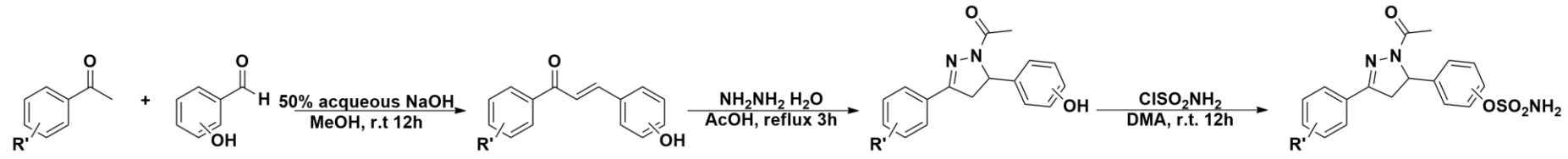
6a-m

7a-m 4-OH
8a-m 3-OH

9a-m 4-OH
10a-m 3-OH

PArS1-13 4-OH
PArS14-26 3-OH

a R= H
b R= 4-CH_3
c R= 4-OCH_3
d R= 4-NO_2
e R= 4-CF_3
f R= 4-F
g R= 2-Cl
h R= 3-Cl
i R= 4-Cl
j R= 2,4-Cl_2
k R= 2,5-Cl_2
l R= 2,6-Cl_2
m R= naphtyl



11a-g

12 4-OH
13 3-OH

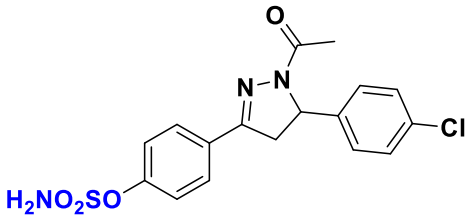
14a-g 4-OH
15a-g 3-OH

16a-g 4-OH
17a-g 3-OH

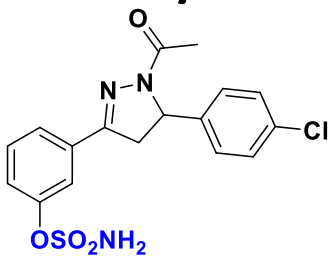
PArS27-33 4-OH
PArS34-40 3-OH

a R= H
b R= 4-CH_3
c R= 4-OCH_3
d R= 4-NO_2
e R= 4-Cl
f R= 2,4-Cl_2
g R= 3,4-Cl_2

Results from biological assay

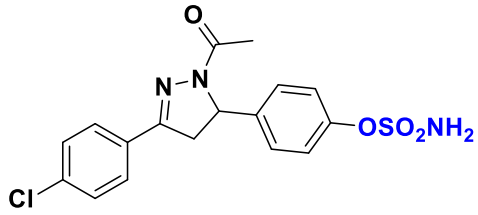


hCAI 1137.1 nM
hCAII 6.0 nM
hCAIX 6.9 nM
hCAXII 27.3 nM

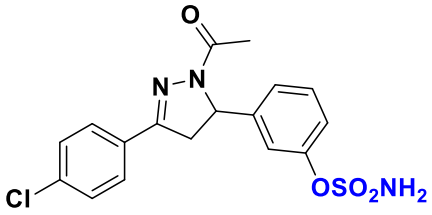


hCAI 437.7 nM
hCAII 14.7 nM
hCAIX 6.9 nM
hCAXII 9.3 nM

Nocentini, A., Moi, D., Balboni, G., Salvadori, S., Onnis, V., & Supuran, C. T. (2018). Bioorg.Chem., 77, 21. Moi, D., Nocentini, A., Deplano, A., Balboni, G., Supuran, C. T., & Onnis, V. (2019) Eur.J. Med. Chem., 182, 111638

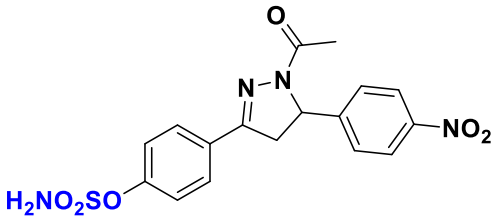


hCAI 970.2 nM
hCAII 19.5 nM
hCAIX 8.3 nM
hCAXII 29.5 nM

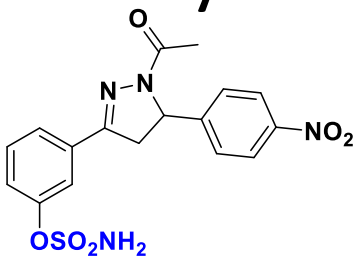


hCAI 2104.9 nM
hCAII 32.7 nM
hCAIX 0.81 nM
hCAXII 22.3 nM

Results from biological assay

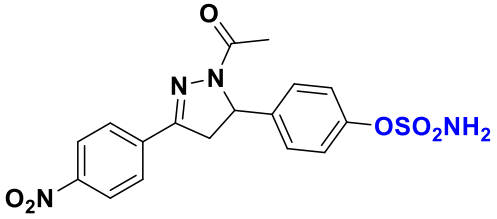


hCAI 3208.5 nM
hCAII 1.2 nM
hCAIX 74.3 nM
hCAXII n.d.

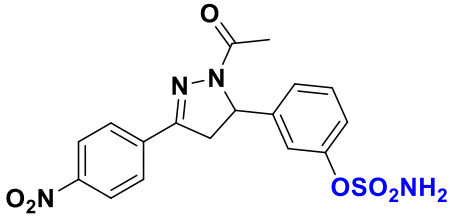


hCAI 1458.2 nM
hCAII 133.9 nM
hCAIX 10.1 nM
hCAXII 20.8 nM

Nocentini, A., Moi, D., Balboni, G., Salvadori, S., Onnis, V., & Supuran, C. T. (2018). Bioorg.Chem., 77, 21. Moi, D., Nocentini, A., Deplano, A., Balboni, G., Supuran, C. T., & Onnis, V. (2019) Eur.J. Med. Chem., 182, 111638

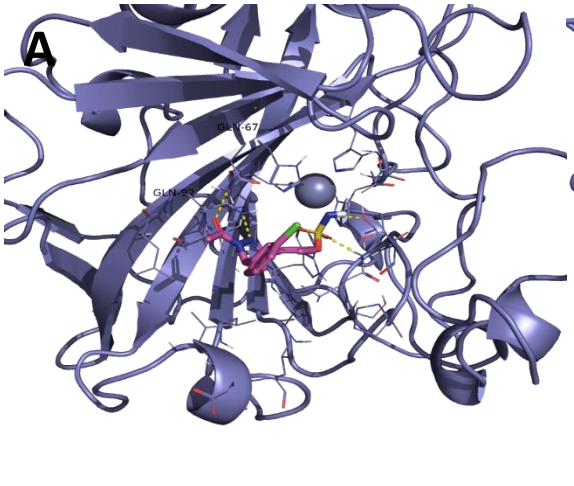


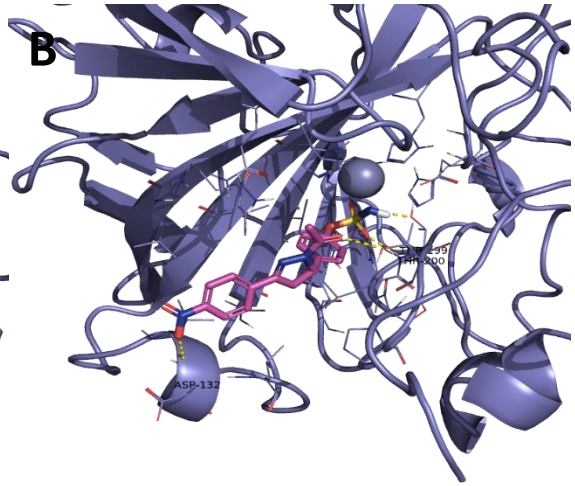
hCAI 3818.1 nM
hCAII 9.5 nM
hCAIX 15.0 nM
hCAXII 0.88 nM

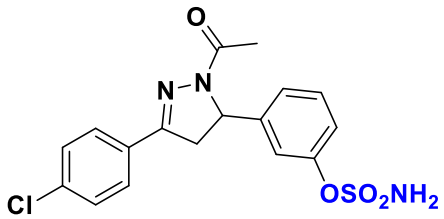


hCAI 2546.8 nM
hCAII 22.9 nM
hCAIX 9.4 nM
hCAXII 20.5 nM

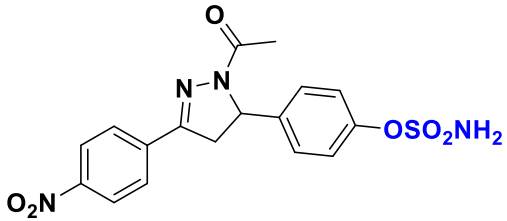
Molecular docking







hCAIX 0.81 nM



hCAXII 0.88 nM

Nocentini, A., Moi, D., Balboni, G., Salvadori, S., Onnis, V., & Supuran, C. T. (2018). Bioorg.Chem., 77, 21. Moi, D., Nocentini, A., Deplano, A., Balboni, G., Supuran, C. T., & Onnis, V. (2019) Eur.J. Med. Chem., 182, 111638

Conclusions

- Small library of N1-acetyl-3,5-diarylpyrazoline sulfamates were synthetized and tested for the inhibition of hCAI, hCAII, hCAIX and hCAXII
- The benzenesulfamate fragment were positioned at meta or para position on the 3-aryl or 5-aryl of the 4,5-dihydropyrazole ring
- Correlation between the position of sulfamate moiety on 5 or 3-aryl ring and the inhibitory activity
- SAR analysis showed that the sulfamic group on the 3- or 4- position of the 5-aryl with an electron-withdrawing group on the 4-postion of the 3-aryl ring is necessary for the inhibition of hCAIX and hCAXII

Acknowledgments

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- Department of Life Sciences and Biotechnology, University of Ferrara

Thank you for your attention