Synthesis of human carbonic anhydrase inhibitors with structure of 4-substituted pyridine-3-sulfonamide

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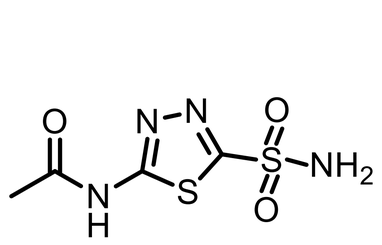
Introduction

Carbonic Anhydrase (hCA) **[1]**

- A metalloenzyme that catalyses the hydration of carbon dioxide.
- 15 isoforms specific for different tissues.
- Main role: breathing and maintaining acid-base equlibrum.
- Non-selective inhibitors - diuretics and anti-glaucoma drugs.

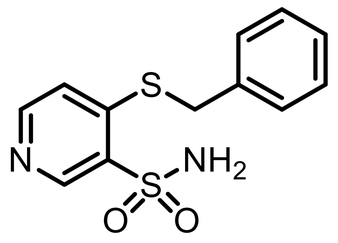
Isoform IX (hCAIX)

- Not very common in healthy tissues but highly expressed in tumor tissues.
- Associated with tumor hypoxia = increasing of expansion, malignancy progression, resistance to therapy.
- hCAIX inhibition = increased effectiveness of chemotherapy, reduction of tumor metastasis.
- Need for high selectivity for hCAIX over common isoforms (mainly hCAII).

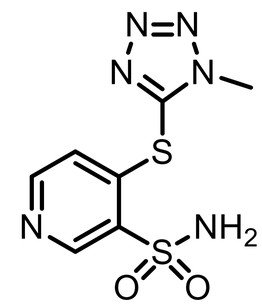


acetazolamid - clinically used

hCA II hCA IX
K*i* = 12 nM 25 nM



hCA II hCAI X
K*i* = 10 nM 30 nM

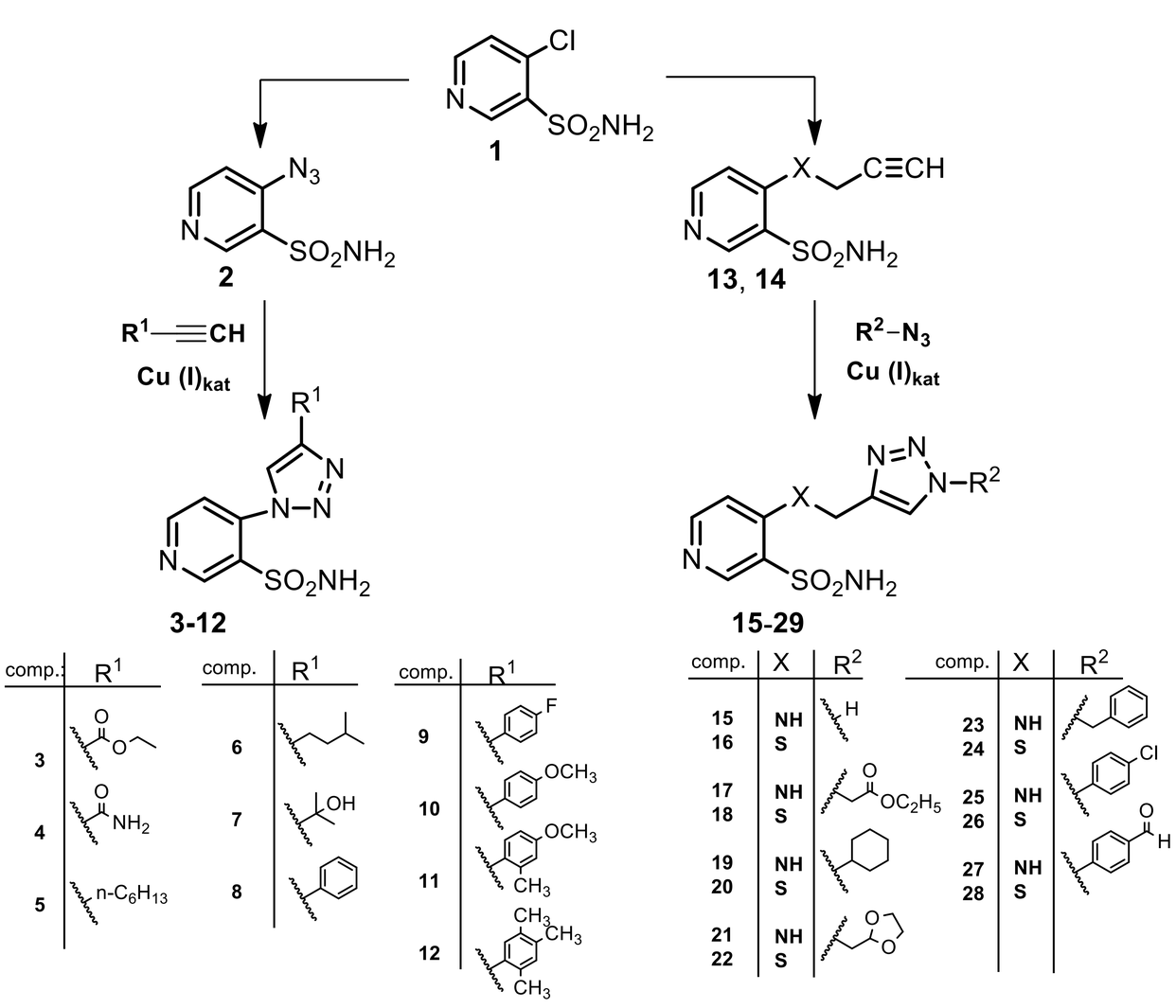


hCA II hCA IX
K*i* = 46 nM 5 nM

Our previous CA inhibitors [2-5]

Synthesis:

Planed compounds **3**-**29** were synthesized starting from 4-chloropyridine-3-sulfonamide (**1**) by introducion of an azide (**2**) or alkyne (**13**, **14**) moiety in the position 4. Next, using the Cu(I) catalyzed azide-alkyne cycloaddition reaction (CuAAC Huisgen reaction), compounds **3**-**12** and **15**-**28,** containing a 1,2,3-triazole ring in the position 4 of the pyridine scaffold, were obtained . The structure of the new compounds was confirmed using spectroscopic methods: IR, ^{1}H NMR, and elemental analysis (C, H, N).



comp.	R^1
3	
4	
5	

comp.	R^1
6	
7	
8	

comp.	R^1
9	
10	
11	
12	

comp.	X	R^2
15	NH	
16	S	
17	NH	
18	S	
19	NH	
20	S	
21	NH	
22	S	

comp.	X	R^2
23	NH	
24	S	
25	NH	
26	S	
27	NH	
28	S	

ADME calculation:

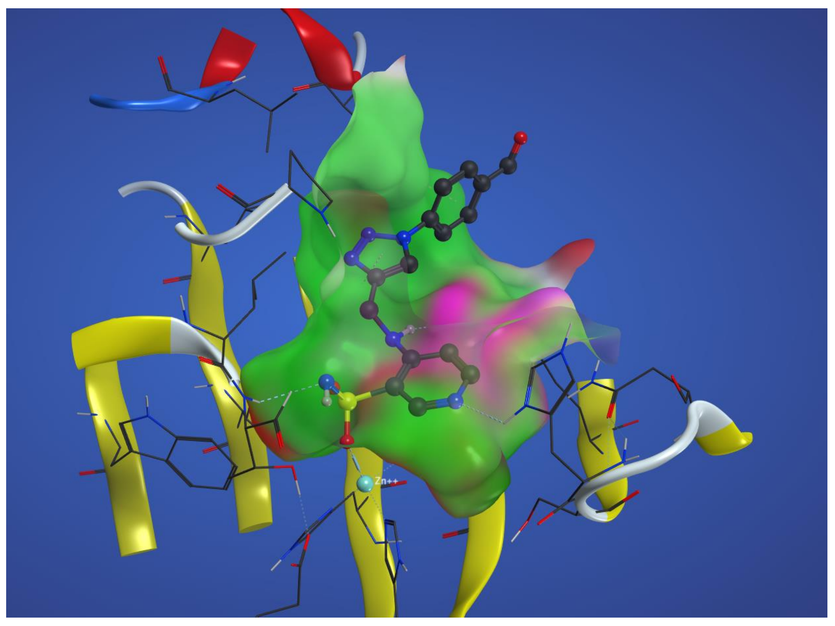
Pharmacokinetic properties and ADME parameters were determined using the SwissAdme tool (Swiss Institute of Bioinformatics.)

- All compounds meets Lipiński's rules, and the vast majority also meet the rules of Veber and Ghose.
- They show good or moderate solubility.
- No penetration of the blood-brain barrier.
- Predominantly high gastrointestinal absorption with the exception of derivatives containing a thiomethylene linker (X = S) (**16**, **18**, **20**, **22**, **26** and **28**).
- Lack of inhibition of cytochrome P450 (CYP) enzymes.

Docking studies:

Using the Molecular Operating Environment (MOE 2019.01) software the structures of the obtained compounds were docked to tumor-associated isozyme IX (PDB 5FL4) and ubiquitous isozyme II (PDB: 5DRS) of human carbonic anhydrase. The binding energy of individual compounds is in the range of 7.4-8.3 kcal / mol for isozyme IX and 5.2-8.3 kcal / mol for isozyme II. Only 3 compounds (**12**, **21**, **22**) show a higher affinity for hCAII (difference 0.2-0.1 kcal / mol), while the remaining ones show higher interaction energy with isozyme IX (difference 0.1-2.6 kcal / mol) .

The zinc cation and His68, Leu91, Gln 92, His 94, Val 121, Val 130 and Thr 200 are responsible for the interaction of the compounds with the hCAIX active site.



*Arrangement of the compound **27** in the hCAIX active center (S = -8.06 kcal / mol)*

Cytotoxicity:

Compounds **7**, **8**, **18**, **22** and **24** were tested for cytostatic activity against 3 human cancer cell lines: breast cancer (MCF-7), colon cancer (HCT-116) and cervical cancer (HeLa) using the MTT test. The tested compounds showed high values of the IC_{50} parameter (IC_{50}> 120 μM), which proves the weak in vitro antitumor properties not related to the inhibition of carbonic anhydrase.

Literature:

[1] J. Y. Winum, et all. (2009) *Anti-cancerAgents in Med. Chem*. 9, 693-702
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The 7th International Electronic Conference on Medicinal Chemistry
01–30 NOVEMBER 2021 | ONLINE