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Vanillin derivatives as highly selective inhibitors of the cancer associated carbonic anhydrase isoforms IX and XII

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GICAR GRUPO DE INVESTIGACIÓN EN CARBOHIDRATOS CEDECOR (CIC-UNLP)

COMISIÓN DE INVESTIGACIONES CIENTÍFICAS

CONICET

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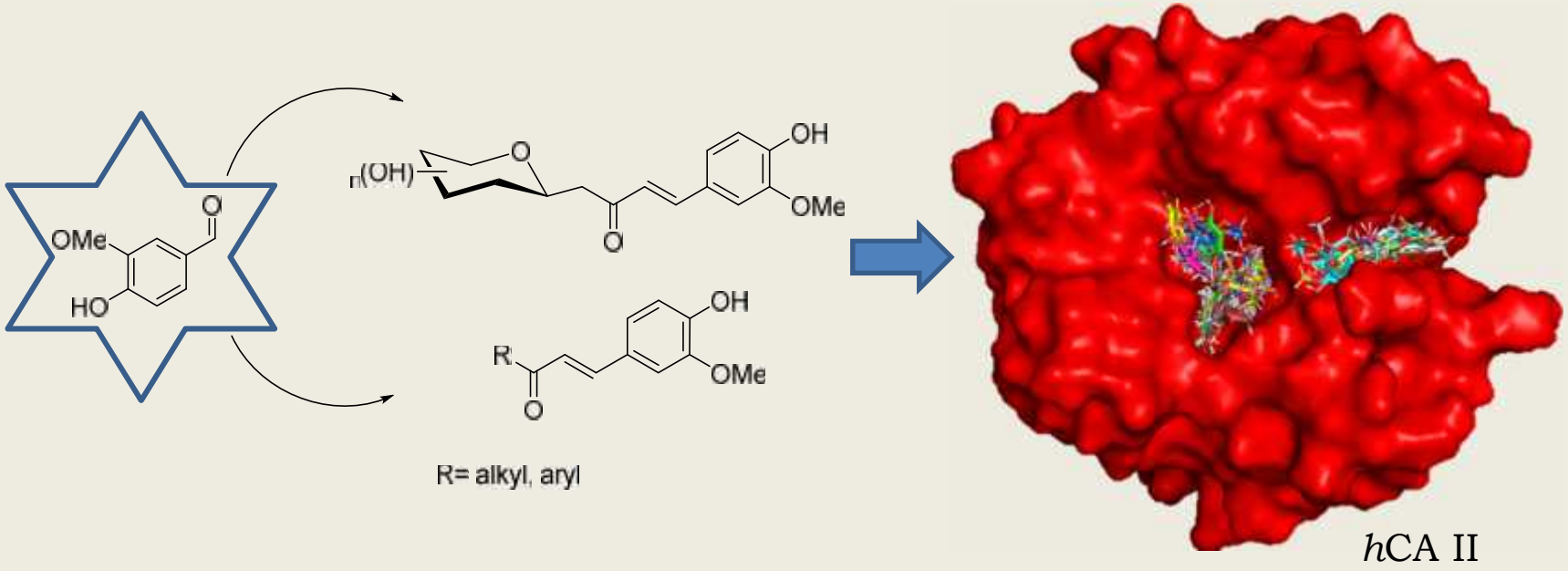


Abstract

Relationship between carbonic anhydrase (CA) and cancer has been known for more than 20 years but only recently two isozymes (IX and XII) overexpressed in solid tumor have been identified, cloned and sequenced. Membrane-bound *h*CA isozymes IX and XII are expressed at high levels and with a high prevalence in different tumor tissues, whose normal counterparts do not contain these proteins. Thus, specifically targeting the tumor associated isoforms *h*CA IX and XII over the main off target isoforms *h*CA I and II, which have a physiological relevance, using specific inhibitors is a promising strategy in the cancer therapy.

[6]-Paradol, a pungent phenolic compound present in certain Zingiberaceae plants (ginger, etc.), is known to have cytotoxicity activity against human leukemia cells. Also other ingredients of ginger like [6]-shogaol showed to inhibit non-small cell lung cancer cells. All these compounds contain the 4-hydroxy-3-methoxyphenyl moiety also found in vanillin. Recently our group showed that attachment of carbohydrate tails to phenoxy moiety leads to highly selective CA IX inhibitors. The aim of the present work is to study new *C*-glycoside incorporating the 4-hydroxy-3-methoxyphenyl moiety as selective inhibitor of tumor associated CA isoforms. We present the *h*CA (I, II, IX and XII) inhibition profile of the carbohydrate derivatives and also other ones prepared by aldol reaction of alkyl and aryl ketones. Docking analysis is discussed showing that the high selectivity could be explained in terms of a binding pocket out of the CA active site. Thus, discovery of these selective IX and XII inhibitors will be a promising step in the strategy for an effective cancer therapy.

Keywords: cancer; carbonic anhydrase; enzyme inhibition; vanillin.

Introduction

Cancer

- Cancer is the second cause of death globally.
- In the last years “targeted therapies” have emerged as an alternative to traditional treatments.
- Two isozymes overexpressed in solid tumor have been identified, cloned and sequenced: CA IX and XII.
- Both of these enzymes are associated with cancer progression, metastasis, and impaired therapeutic response.

Carbonic Anhydrase (CA)

- Metalloenzymes family that contains Zn^{2+} in the active site.
- There are five families: α-, β-, γ-, δ-, ε-CAs.
- α-CAs present in mammals (16 isoforms). Some are intracellular (CA I and II) and others are transmembrane (CA IX and XII).
- β-CAs present in bacteria and algae.
- CAs catalyze a simple but important reaction:

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

Reversible hydration of CO_2

CA inhibitors

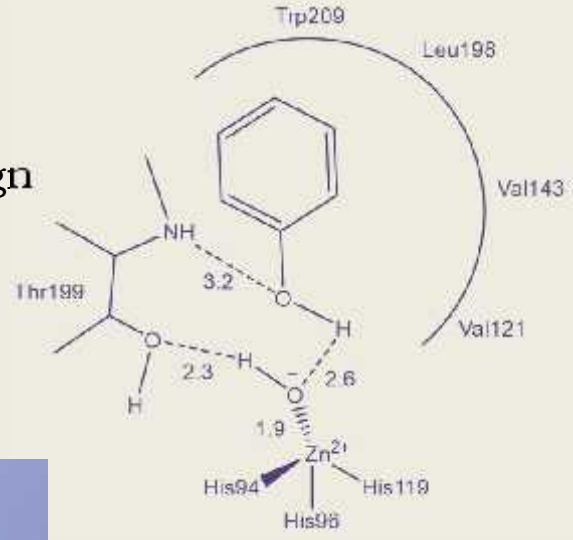
- Design of specific inhibitors of CA IX and XII is considered to be a promising strategy in the cancer therapy.

- Problem to solve!: target the tumor associated isoforms hCA IX and XII over the main off target isoforms hCA I and II, which have a physiological relevance.

- Some CA pharmacophores are :

  - Phenols: OH binds through hydrogen bonds with the water molecule/hydroxyl ion attached to Zn (II).
  - Methoxyaryl: They bind within the enzymatic active site without interaction with the zinc ion and through different interactions with amino acid residues and water molecules.

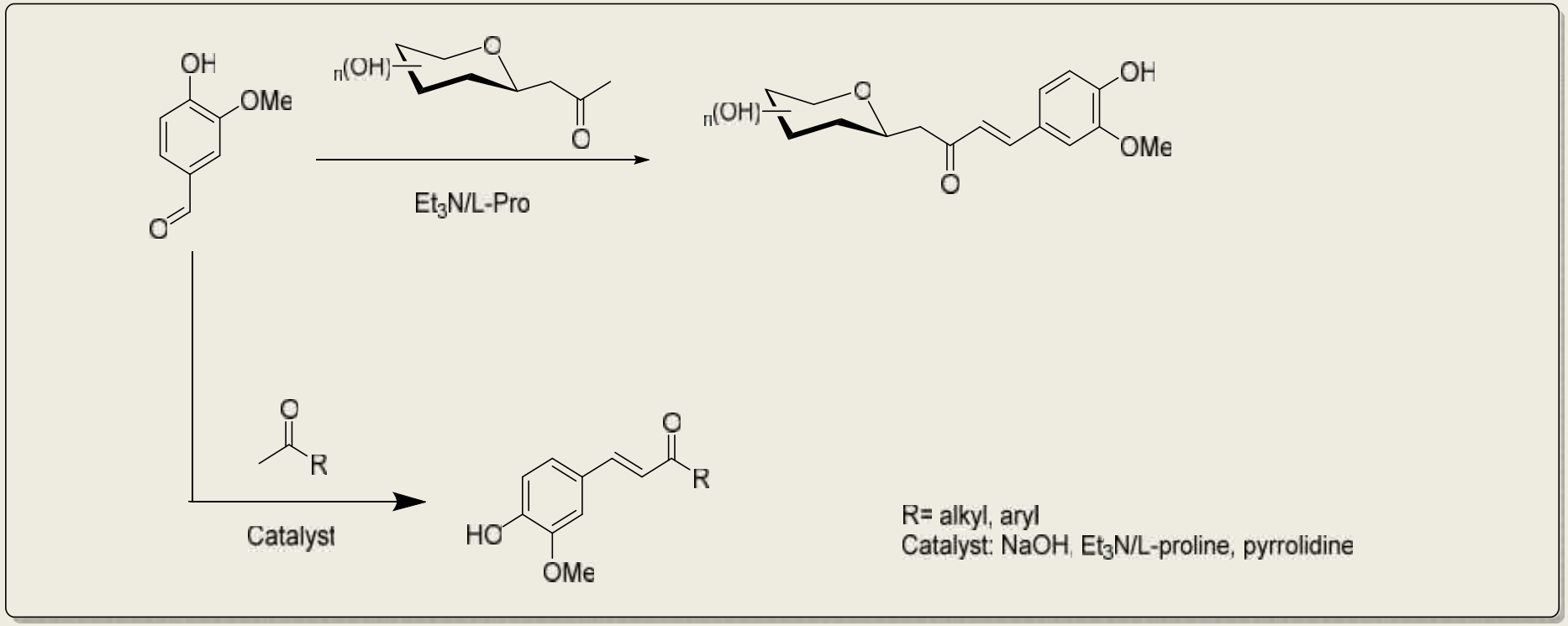
- We studied the attachment of carbohydrate and alkyl and aryl chains to the vanillin moiety in order to design selective CA inhibitors.



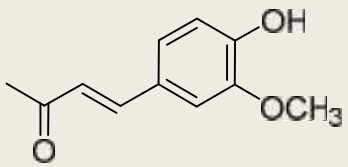
Phenol-*h*CA II adduct

Results and discussion

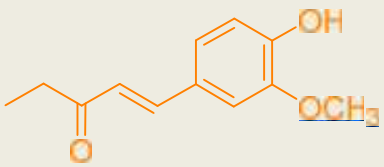
Preparation of vanillin derivatives



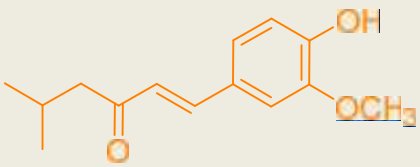
Vanillin derivatives and inhibitory activity



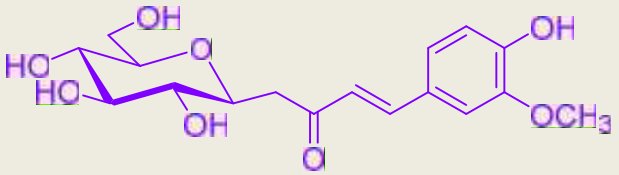
1
I/IX=3.6
II/IX>416
I/XII=27.0
II/XII>3125



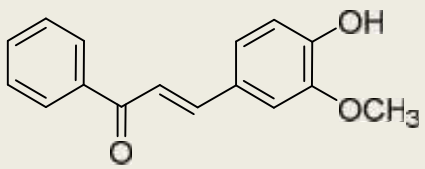
2
I/IX>312
II/IX>312
I/XII>4000
II/XII>4000



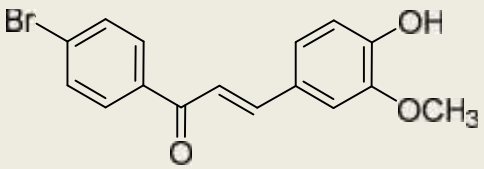
3
I/IX>380
II/IX>380
I/XII>5882
II/XII>5882



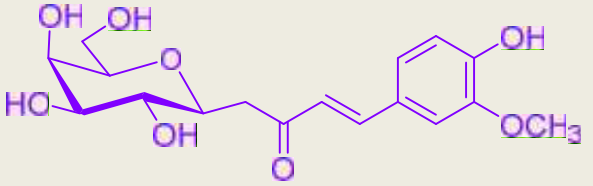
6
I/IX=2.3
II/IX>325
I/XII=15.0
II/XII>2083



4
I/IX=2.6
II/IX=3.3
I/XII=121.1
II/XII=153.0



5
I/IX<0.009
II/IX<0.008
I/XII=14.5
II/XII=12.8

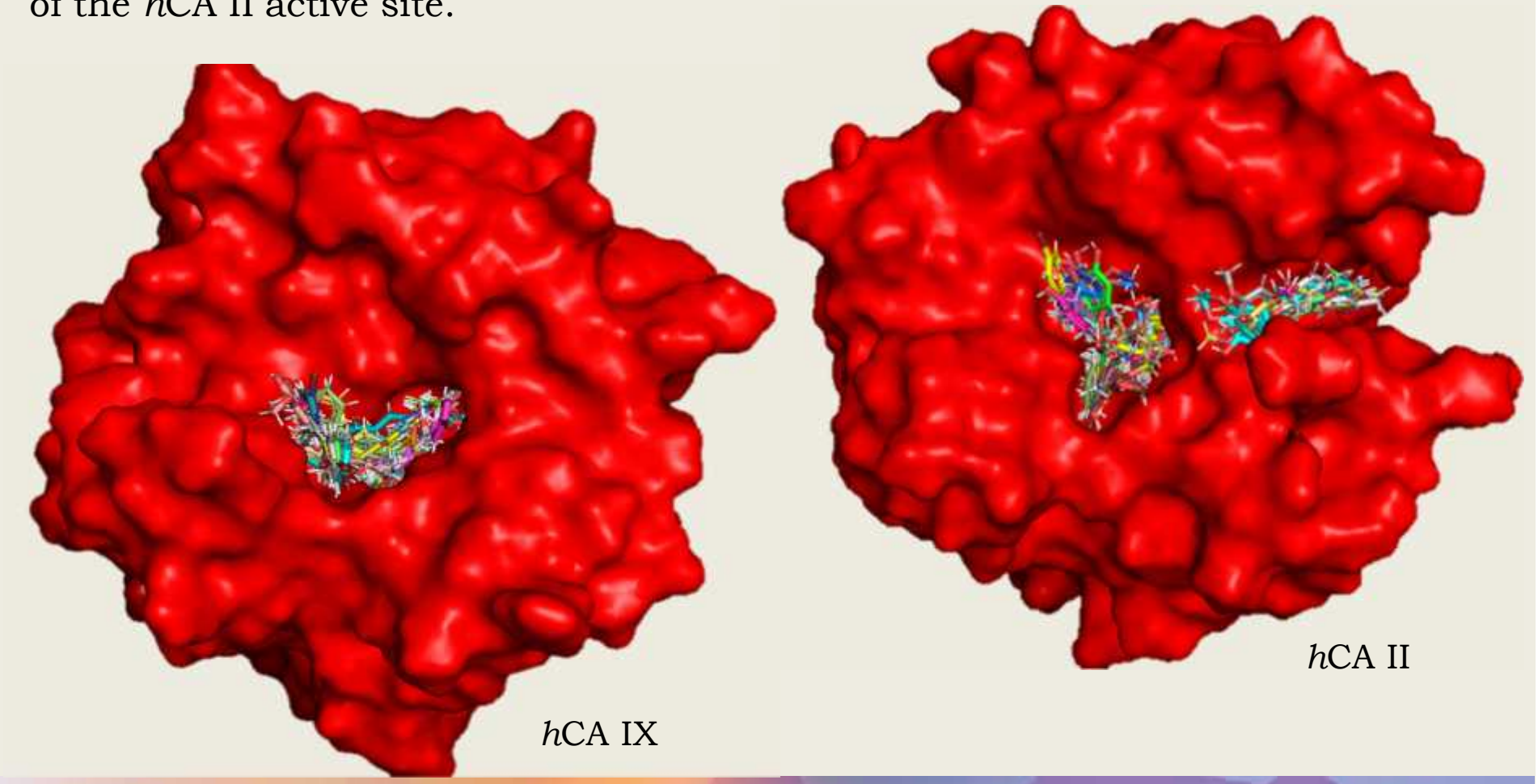


7
I/IX=3.9
II/IX>480
I/XII=32.2
II/XII>4000

A/B = selectivity
A= CA I, CA II
B= CA IX, CA XII
1-5 = Dehydroparadol
6 and **7** = *C*-glycoside

Docking snapshots

The frames show the arrangement of the lower energy poses of the vanillin derivatives inside of the *h*CAIX active site and some inside of binding pocket out of the *h*CA II active site.



*h*CA IX

*h*CA II

Conclusions

- The compounds showed better activity profile against *h*CA IX and XII over I and II which is highly desirable when only the tumor-associated isoforms would be targeted.

- Dehydroparadol **2** and **3** were the most effective and selective inhibitors to *h*CA IX and XII over I and II.

- *C*-glycosides **6** and **7** were the most effective and selective inhibitors to *h*CA IX and XII over II.

- The high selectivity could be explained in terms of a binding pocket out of the CA active site.

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