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2009 : March 2009 - New Hot Papers : Claudiu T. Supuran

NEW HOT PAPERS - 2009

March 2009



Claudiu T. Supuran talks with *ScienceWatch.com* and answers a few questions about this month's New Hot Paper in the field of Pharmacology & Toxicology.



Article Title: Carbonic anhydrases: novel therapeutic applications for inhibitors and activators

Authors: Supuran, CT

Journal: NAT REV DRUG DISCOV

Volume: 7

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Page: 168-181

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SW: Why do you think your paper is highly cited?

The carbonic anhydrases (CAs, EC 4.2.1.1) are widespread enzymes all over the phylogenetic tree, from very simple organisms, such as bacteria and microscopic fungi or protozoa, to plants and animals. They constitute interesting targets for the design of pharmacological agents useful in the treatment or prevention of a variety of disorders such as glaucoma, acid-base disequilibria, epilepsy, and various other neuromuscular diseases, altitude sickness, edema, and obesity. They have been used for many years as diuretics.

CA inhibitors (CAIs) were recently shown to be useful in the management (imaging and treatment) of hypoxic tumors, since at least two CA isozymes of the 16 presently known in mammals, i.e., CA IX and XII, are predominantly found in tumor cells and are lacking from normal tissues. The involvement of these enzymes, which catalyze the simplest physiological reaction, CO₂ hydration to bicarbonate and a proton, in many physiological/pathological processes—as well as the fact that generally different isoforms of the 16 mentioned above are involved in such particular processes—allows for the development of diverse medicinal chemistry applications of their inhibitors.

Thus, CA IX and XII are the targets for the development of novel antitumor therapies, CA II and XII for the development of antiglaucoma drugs, CA Va and CA Vb for the design of new anti-obesity agents, CA VII for the development of anticonvulsant/antiepileptic drugs; whereas non-vertebrate CAs, such as for example the α -CA present in *Plasmodium falciparum* may lead to novel types of antimalaria drugs.

Recently cloned and purified/characterized were many such enzymes (generally belonging to the β -CA class) from many pathogenic organisms such as the bacteria *Mycobacterium tuberculosis* and

Helicobacter pylori, or the fungi *Candida albicans* and *Cryptococcus neoformans*. Inhibition of these enzymes may lead to a new generation of anti-infectives.

Activation of different CA isoforms was mainly investigated by our group, and has recently been shown to constitute a novel therapeutic approach for the enhancement of synaptic efficacy, which may constitute an excellent means for the treatment of Alzheimer's disease, aging, and other conditions in need of achieving spatial learning and memory therapy.

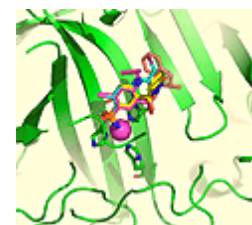
Thus, one may modulate the activity of CAs either by inhibiting or by activating these enzymes with specific agents, the mechanisms of actions which have begun to be ultimately understood in greater detail.

Furthermore, I predict that many other families of CAs will be discovered in the future in addition to the five such families presently known (the a-z -CAs), since these enzymes deal with a critical compound—carbon dioxide—important for biosynthetic processes involving one carbon atom, and which probably has already played important roles in the primordial stages of life on earth.

Nowadays, over-production of carbon dioxide in the atmosphere and its involvement in the global warming processes might also be dealt with by using some of the enzymes which efficiently convert this pollutant to bicarbonate, which is non-toxic, water soluble, and has no global warming effects.

It should be mentioned that over the last few years we have also reported the X-ray crystal data of many CAs with various drugs, such as, among others, the diuretics indapamide, chlorthalidone, furosemide, and triflumethiazide (shown in the Figure).

Figure 1:



+ [View larger image & details](#)

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

This is a review article, presenting the state of the art in the field of CA inhibitors and activators, as well as their applications in therapy. It presents diverse methodologies useful in the drug design of different pharmacological agents based on CAIs and CA activators (CAAs). This paper represents a thorough review of all these novel applications of CAIs/CAAs, updated with the latest developments in the field.

SW: Could you summarize the significance of your paper in layman's terms?

Compounds belonging to the CAIs may lead to better drugs useful to treat glaucoma, a chronic eye disease leading to blindness, which is rather diffused, and for which no optimal cure is available at this moment. On the other hand, since several CAs are predominantly found in tumors—and more precisely in hypoxic tumors—compounds of this type seem very promising for discovering novel antitumor therapies as well as for imaging purposes of diverse cancers.

Finally, some CAIs seem to be useful for developing novel anti-obesity drugs. Thus, at least three conditions in need of pharmacological treatment, i.e., glaucoma, cancer, and obesity, may benefit from drugs belonging to this class. It should also be stressed that the isozymes responsible for the three pathologies examined here are different: CA II and XII for glaucoma, CA IX and XII for cancer and CA V for anti-obesity drugs.

The CAAs, on the other hand, may lead to the development of agents useful in the treatment of Alzheimer's disease or other conditions in need of achieving spatial learning and memory therapy. The important progress done ultimately in deciphering the structure, catalytic and inhibition mechanisms of CAs from pathogenic organisms, may lead to the development of antifungal or antibacterial drugs possessing a new mechanism of action.

SW: How did you become involved in this research?

My interest in CA research dates back to 1987. Since then, our group at the University of Florence, in Italy, was involved in several research projects on CA inhibitors and activators, financed either by the European Union or from private drug companies. Our group has achieved international recognition due to the fact that many important discoveries related to the field have been performed here. As a consequence, our laboratory is financed by the EU as well as by some of the most important drug companies interested in the development of novel therapies based on such compounds.

We are currently participating in several such programs, aimed at the development of anti-glaucoma, anti-cancer, anti-obesity, and anti-infective drugs, as well as research leading to a better understanding of the interactions of such compounds with enzymes, which we study using a variety of modern methods. We are collaborating for such purposes with many excellent research groups in Europe, the

USA, Japan, Australia, and Turkey, a factor which may also help explain our successes and the priorities in CA research as reviewed in the paper.

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Figure 1:

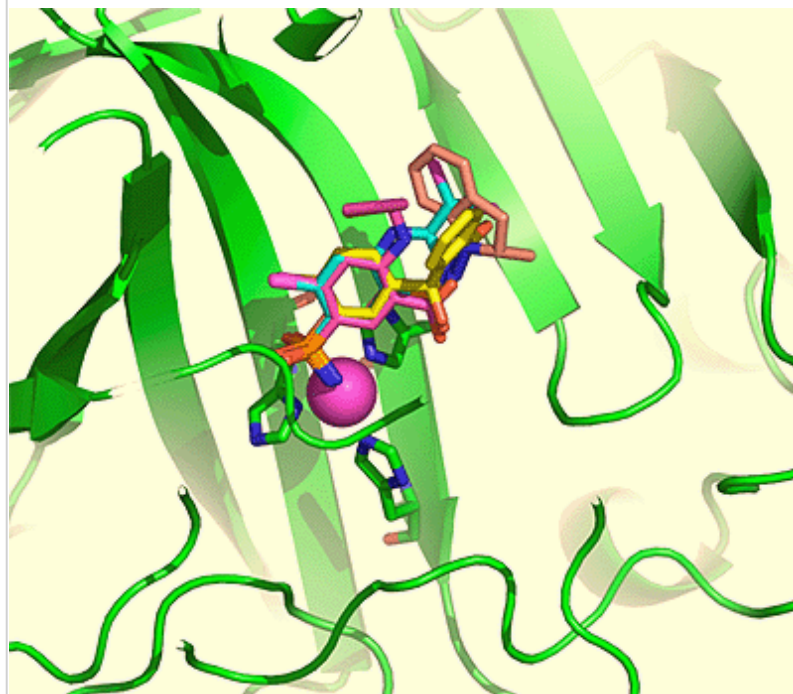


Figure 1:

Superposition of X-ray crystal structures of the human carbonic anhydrase II (hCA II) – clortalidone (yellow), hCA II – indapamide (wheat), hCA II – trichlorometiazide (sky) and hCA II – furosemide (magenta) adducts. The histidine ligands coordinating the zinc ion (violet sphere) and protein backbones (green) in all four complexes are entirely superposable. The four compounds are widely used diuretic drugs. (cf. Temperini *et al.*, *Bioorg. Med. Chem Lett.* 2009, 17, 1214-1221).

KEYWORDS: PRESSURE-LOWERING PROPERTIES; CYTOSOLIC ISOZYME-I; RAY CRYSTALLOGRAPHIC STRUCTURE; CELL LUNG-CANCER; X-RAY; ACTIVE-SITE; HETEROCYCLIC SULFONAMIDES; SULFAMATE INHIBITORS; HYPOXIC TUMORS; ISOFORM-II.

More commentary by Claudiu T. Supuran: [New Hot Paper](#) (July 2004), and [New Hot Paper](#) (September 2005).



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