International Symposium on
Setting their Table: Women and the Periodic Table of Elements
Feb. 11-12, 2019 - Murcia (Spain)

United Nations Educational, Scientific and Cultural Organization
2019 IYPT International Year of the Periodic Table of Chemical Elements

Zinc-containing enzyme; activation of β- and γ-carbonic anhydrases from pathogenic bacteria with tripeptides

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Topic: Old Elements, New Technologies: how to improve the quality of life.

Abstract:
Zinc is a chemical element with atomic number 30, turns out to be one of the essential elements present in living organisms.Zinc is located in the active site of CarbonicAnidrases (CA)and isresponsable of itscathalitycmechanism.To date, several isoforms of anhydrase are know, in particular α- β- γ- Carbonic Anhydrases are Zinc dependent and are very important in medicinalchemistry for their catalytic activity towards CO_2.[1]
In living organisms, the hydration of CO_2 and the dehydration of HCO_3^- take place in a very fast process, likeallprocessesconnected to transport / secretion. The mainmetabolicrole of CAsis the high efficiencycatalysis of CO_2hydration**(Figure1**).

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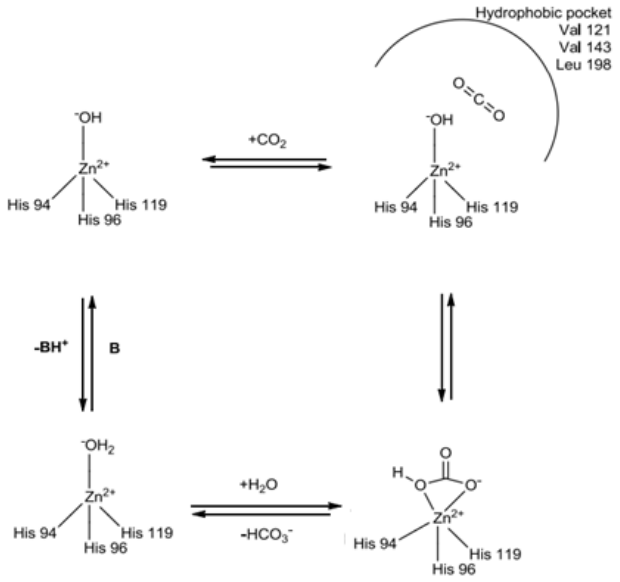

Figure 1. Interconvertionbetween carbon dioxide and bicarbonate.

CA inhibitors (CAIs) show pharmacologicapplications in pathologies in which the activity of theseenzymesisdysregulated (in humans), suchas edema, glaucoma,neurologicdiseases, obesity, and some tumors, and manysulphonamide or sulphamateCAIshavebeen in clinical use for decades.[2]
In contrast, investigation of activators of theseenzymes (CAAs) havebeenrelatively limited.[3]

However, no drug-design CAstudies are available for bacterial, β- and γ-CAs. Theseenzymeshaveonlyrecentlybeenstarted to be investigated for theiractivation with amines and amino acids.Bacterial β-CAs are active in bothdimeric and tetramericforms, with two or fouridenticalactivesites. Theirclosedconformationstructurepresents the catalyticZincionplaced in the terminal end of a channel, coordinatedtetrahedral with twocysteines, an histidine and an aspartic acid residue. The structure of the enzymesynthesized by *Vibriocholera* (VchCAβ)isparticularsinceitscatalyticactive site in the closedform, hasbeenisolatedatpHlowerthan 8.3 (**Figure 2**).In the inactiveform the bicarbonateestablishes bonds with the Zincion inside the closed pocket, howeveratpH> 8.3 the closedactive site assumes the open conformationbecause a residue of Asp, near the metal ion, moves to discover the Zincionwhich can coordinate with a water moleculeinvolved in catalytic activity.[4]

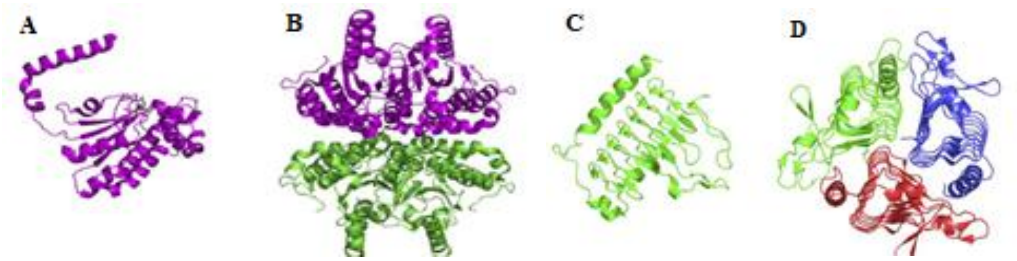

Figura 2 Rappresentation of **A** inactivemonomer,**B**activeterthramerof β-CA of *Vibrio colera*;**C**inactive and **D**activetrimer of the γ-CAenzymecoming from the bacterium*Methanosarcinathermophila*.

β-CA adoptsa 3-D conformationβ-helix and crystallizesas a tetramer withthreeactivesitescontainingZinc, each of whichisat the interfacebetweentwomonomers. The enzyme metal isactiveonlyin trimeric form.[5] Thisenzymaticclasspresentsa residues of glutamic acid in place of a histidine, whichactsas a protontransporter. The design of bioactivemoleculesthat modulate theseenzymesmay be useful for controlling the intraand extracellularpH of microorganisms, which can play crucialroles in the life cycles of pathogenicmicroorganisms.Thisis of greatinterestespecially to counter the problemassociated with the increase of resistancethatmicroorganismspresenttowardsconventionalantibiotics.In this work we report a study for investigating the capability of tripeptidesincorporating acid amico acid residues do show activatingeffectsagainst β- and γ- classCAs from pathogenicbacteriasuchas*VibrioCholerae, Mycobacteriumtubercolosis and Burkholderiapseudomallei.*Thesetripeptidesmay be usefulastools for investigating the role of theseenzymes in keybacterialprocesssuchasinvasion, colonization and payhogenicity, wich are currentlypoorly understood.[6]

References

1. C.T. Supuran. *Biochem. J.***2016**, 473, 2023–32.
2. C.T. Supuran.*Expert Opin Drug Discov***2017**, 12,61–88.
3. C.T. Supuran.*Nat Rev Drug Discov***2008**, 7,168–81.
4. S. Huang, T. Hainzl, C. Grundstrom, C.Forsman, G. Samuelsson, A. E. Sauer-Eriksson.*PLoS One***2011**, 6, E28458.
5. B.C. Tripp, J. G. Ferry. *Biochemistry***2000**, 39,9232–40.
6. A.Stefanucci, A.Angeli, M.P.Dimmito, G.Luisi, S. Del Prete, C.Capasso, W.A. Donald, A. Mollica& C. T. Supuran. *J. of Enz. Inhib. and Med. Chem*.**2018**, 33, 945–950.