Società Chimica Italiana
Sezione Sardegna

XII La Parola ai Giovani

27 Settembre 2013

Aula C Cittadella Universitaria di Monserrato

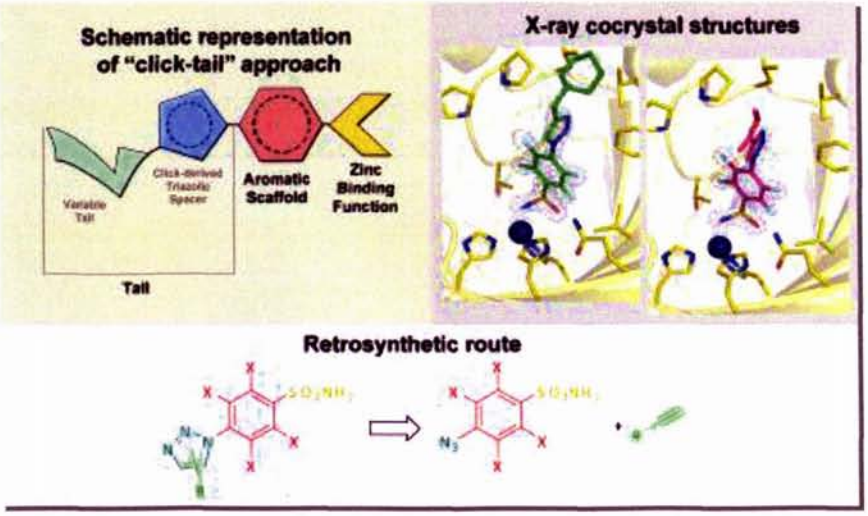
ABSTRACT BOOK

THE "CLICK-TAIL APPROACH" FOR THE DESIGN AND SYNTHESIS OF NOVEL CARBONIC ANHYDRASE INHIBITORS

Nicolino Pala[a], Laura Micheletto[a], Simone Ihm[a], Fabrizio Carta[b], Robert McKenna,[c] Claudiu T. Supuran[b], Mario Sechi[a] (nikpal@uniss.it)

a) Dipartimento di Chimica e Farmacia, Università di Sassari, via Vienna 2, 07100 Sassari, Italy; b) Università degli Studi di Firenze, Polo Scientifico, Laboratorio di Chimica Bioinorganica, Via della Lastruccia 3, 50019 Sesto Fiorentino (Firenze), Italy; c) Department of Biochemistry and Molecular Biology, College of Medicine, University of Florida, Box 100245, Gainesville, FL 32610, USA; d) Università degli Studi di Firenze, NEUROFARBA Dept., Sezione di Scienze Farmaceutiche, 50019 Sesto Fiorentino (Firenze), Italy.

The Carbonic Anhydrases (CAs) are a family of zinc enzymes deputed to the interconversion of carbonic dioxide to hydrogen carbonate. Factors such as primary sequence, localization, activity and tissue distribution concur to differentiate XVI mammalian isoforms. In human, CAs are involved in several physiopathological processes including respiration, acid/base homeostasis, calcification, gluconeogenesis, lipogenesis, glaucoma, high blood pressure, oedema, epilepsy, obesity, and cancer. In this context, CAs are emerged as important biological targets for several therapeutic applications.[1,2] To date, a plethora of compounds have been tested for their inhibitory activity against CAs[1-3] and, among them, the compounds bearing a substituted arylsulfonamide chemotype constitute the most important chemical class. Such chemical scaffold presents a well know pharmacophoric pattern constituted by an aromatic moiety bearing a Zinc Binding Function (ZBF) and a variable tail.[4] Herein, we report on a sustainable modular strategy, also called "click-tail approach",[5] used to obtain two series of 4-(4-substituted-1*H*-1,2,3-triazol-1-yl)benzenesulfonamides. Design and synthesis strategies, x-ray derived CA-ligand binding mode and enzyme-based inhibition results will be presented.



REFERENCES

[1] Supuran, C.T. Wiley Series in Drug Discovery and Development: Drug Design of Zinc-Enzyme Inhibitors. Wiley. A John Wiley & Sons, Inc., Publication, **2009**. [2] Supuran, C.T. *Nat. Rev. Drug Discov.* **2008**, *7*, 168-181. [3] Sechi, M. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5801–5806. [4] Pala, N. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2515-2520. [5] Lopez, M. *Current Pharmaceutical Design* **(2010)**, 16, 3277-3287.