XXXV

Societa' Chimica Italiana

Convegno della Divisione di Chimica Organica

Dipartimento di Chimica e Farmacia
Università di Sassari
Istituto di Chimica Biomolecolare del CNR di Sassari

Comitato Scientifico:
Prof. Paolo Scrimin
Prof. Raffaele Riccio
Prof. Roberto Ballini
Prof. Valeria Conte
Prof. Marco D'Ischia
Prof. Gianluca Farinola
Prof. Francesco Sannicolò

Conferenze Plenarie:
Dott. Catia Bastioli, Matrìca/Novamont
Dott. Walter Cabri, Indena
Prof. Cinzia Chiappe, Uni Pisa
Prof. Antonella Dalla Cort, Uni Roma1
Prof. Bartolo Gabriele, Uni Calabria
Prof. Cesare Gennari, Uni Milano
Prof. Andrea Mazzanti, Uni Bologna
Dott. Alessandro Mordini, CNR Firenze
Prof. Carmen Nàjera, Uni Alicante
Dott. Vincenzo Palermo, ISOF CNR Bologna
Dott. Stefano Protti, Uni Pavia
Dott. Haymo Ross, EurJOCWiley
Prof. Claudio Trombini, Uni Bologna
Dott. Antonio Zanotti-Gerosa, JohnsonMatthey

Comitato Organizzatore:
Prof. Ugo Azzena
Dott. Massimo Carraro
Dott.ssa Giovanna Delogu
Dott.ssa Lidia De Luca
Dott. Davide Fabbri
Dott. Mauro Marchetti
Dott.ssa Luisa Pisano
Dott. Andrea Porcheddu
Dott.ssa Gloria Rassu
Dott. Pietro Spanu
Dott. Pietro Allegrini

Sassari, 9-13 Settembre 2013
Campus Universitario Via Vienna

Searching for Novel Carbonic Anhydrase Inhibitors: from Virtual Screening to the Lab Bench

[1]Nicolino Pala, [1]Roberta Cadoni, [1]Rino Weber, [1]Simone Ihm, [2]Roberto Dallocchio, [2]Alessandro Dessì, [3]Anna Maria Roggio, [4]Claudiu T. Supuran, [1]Mario Sechi.

[1]Department of Chemistry and Pharmacy, University of Sassari, Italy; [b]CNR-Istituto di Chimica Biomolecolare, Italia; [3]Porto Conte Ricerche, Alghero, Italy; [4]Laboratorio di Chimica Bioinorganica, Università degli Studi di Firenze, Italy
nikpal@uniss.it

Carbonic Anhydrases (CAs) are zinc metalloenzymes that catalyze the reversible hydration of carbon dioxide to bicarbonate both in prokaryotes and eukaryotes (1,2). To date, 16 mammalian CA isoforms (hCAs), which play crucial roles in several physiopathological processes, have been identified (2). All hCAs have an active site containing a metal cation cofactor [Zn(II)], which is essential for catalysis. Almost all known CA inhibitors (CAIs) act interacting with the zinc ion, and most potent inhibitors, such as sulfonamides and their bioisosteres, bear a zinc binding function (ZBF). Although this pharmacophore represents an important feature for effective CA inhibition, these sulfonamido-type inhibitors are affected by both toxicity and non-specificity. Thus, it is important to develop new classes of inhibitors containing different chemical scaffolds endowed with selectivity against particular isoforms, as well as a more favourable pharmacobiological profile.
In this context, Computer Aided Drug Design strategies have emerged as powerful tools in the modern drug discovery paradigm (3). In particular, using ligand- and pharmacophore-based virtual screening approaches, we identified novel chemical entities with original chemotypes, that showed an interesting and selective inhibitory activity in nanomolar/low micromolar range toward CA I and CAII, isoforms (4,5). Herein, we present the hit-to-lead optimization process for these prototypes.

(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) Wale, N.; Karypis, G.; Watson, I. A. *Comput. Syst. Bioinformatics Conf.* **2007**, *6*, 403-414.
(4) Pala, N.; Dallocchio, R.; Dessì, A.; Brancale, A.; Carta, F.; Ihm, S.; Innocenti, A.; Sechi, M.; Supuran, C.T. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2515-2520.
(5) Sechi, M.; Innocenti, A.; Pala, N.; Rogolino, D.; Carcelli, M.; Scozzafava, C.; Supuran, C.T. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5801–5806.