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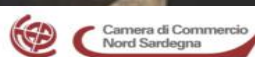
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Searching for Novel Carbonic Anhydrase Inhibitors: from Virtual Screening to the Lab Bench

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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.

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