NEW HYDROXYAZOLES INHIBITORS OF AKR1C3 OBTAINED FROM NSAIDS BY SCAFFOLD HOPPING APPROACH AGAINST CASTRATE RESISTANT PROSTATE CANCER

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Prostate cancer (PCa) is the most commonly diagnosed cancer in men and the second leading cause of death in Western world. The resistance mechanisms occurring after the usual treatment with androgen deprivation therapy poses the urgent need of novel agents capable of targeting selectively the most critical features of resistance process. Since the overexpression of the steroidogenic enzyme Aldo-keto reductase 1C3 (AKR1C3) in castration resistant prostate cancer (CRPC) cells is one of the most effective acquired drug resistance mechanism, development of highly potent and AKR1C3-selective targeting inhibitors is a viable strategy for the treatment of CRPC and metastatic diseases. Flufenamic acid (FLU) and Indomethacin (INDO) have been shown to inhibit AKR1C3-dependent processes in human cell lines and murine xenografts. However, the potential therapeutic usefulness of these drugs in the context of CRPC is limited because of undesired side effects associated with chronic COX inhibition.

Since 2006, the authors have directed their efforts towards the investigation of hydroxylated pentatomic heterocyclic systems in order to create sophisticated tools able to bio(iso)sterically mimic the carboxyl group, as well as other acidic moieties. This bioisosteric tool, combined with a more general scaffold hopping approach, was applied to design innovative AKR1C3 inhibitors: starting from FLU and INDO scaffolds, we identified three classes of structurally different AKR1C3 inhibitors, two series deriving from FLU and one deriving from INDO. The best candidates will be presented and their in silico design, synthesis, chemico-physical properties and biological evaluation will be fully discussed. Worth of note, some compounds were more active than their leads FLU and INDO on AKR1C3, and none of them maintained activity on COX enzymes, suggesting these structures can be developed as future lead compounds against castrate resistant prostate cancer.

References