2,6-Diphenyl-imidazopyridine derivatives as novel prototypes of anticancer agents targeting aldehyde dehydrogenases.

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Aldehyde dehydrogenase (ALDH) superfamily comprises 19 different enzyme types located in specific subcellular districts, including cytosol and mitocondria. Their main function is to oxidize endogenous and exogenous aldehydes produced in human cells. In particular, isoforms 1A1, 1A2 and 1A3 catalyze the transformation of retinal into retinoic acid, which is a potent differentiation tissue factor for cellular development. Overexpression of these three isoforms in cancer stem cells (CSC), underlined in recent studies, is to date extremely important in cancer field, as it offers the chance to use these proteins both as prognostic marker and as novel targets in the fight against cancer. Here we present a novel series of 2,6-diphenyl-imidazol[1,2-a]pyridines, designed as aldehyde dehydrogenase inhibitors by means of a structured-based optimizations of a previously developed lead, GA11. The novel compounds were evaluated in vitro for their activity and selectivity against the three isoforms of the ALDH1A family, and investigated through crystallization and modeling studies for their ability to interact with the catalytic site of the 1A3 isoform. Tested *in vitro* on different populations of CSCs, obtained from glioma, colorectal and prostate tissue specimens, they exhibited a relevant anti-proliferative efficacy, thus paving the way for treating cancer by means of the still untapped aldehyde dehydrogenases.