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Abstract

Exploring dihydroBenzoImidazoTriazineDione (BITD) Core to Generate Selective ALDH1A1 Inhibitors: A Scaffold Repositioning Approach†

Bianca Laura Bernardoni [1], Mattia Mori [2], Sonia Siragusa [3], Silvia Garavaglia [3], Ilaria D'Agostino [1,*] and Concettina La Motta [1]

[1] Department of Pharmacy, University of Pisa, 56126 Pisa, Italy; bianca.bernardoni@phd.unipi.it; ilaria.dagostino@unipi.it; concettina.lamotta@unipi.it
[2] Department of Biotechnology, Chemistry and Pharmacy, University of Siena, 53100 Siena, Italy; mattia.mori@unisi.it
[3] Department of Pharmaceutical Sciences, University of Piemonte Orientale, 28100 Novara, Italy; sonia.siragusa@uniupo.it; silvia.garavaglia@uniupo.it
* Correspondence: ilaria.dagostino@unipi.it
† Presented at the title, place, and date.

Cancer is a major challenge for Public Health, being one of the leading causes of death worldwide. The rise of multi-drug resistance and the generation of Cancer Stem Cells (CSCs) is seriously threatening the success of current chemotherapy and good prognosis. Aldehyde Dehydrogenase family (ALDH, EC: 1.2.1.3) has recently attracted the scientific community as a new valuable pharmacological target. ALDHs are detoxifying enzymes involved in the conversion of reactive aldehydes into the corresponding carboxylic acids. The 1A1 isoform (ALDH1A1) has been identified as a CSC biomarker and is associated with chemoresistance mechanisms and aggressive cancer phenotypes. Moreover, ALDH1A1 overexpression was found in several diseases like obesity, diabetes, and solid tumors, thus its inhibition may provide a potential therapeutic approach. In the last years, derivatives of the natural Isatin were reported to strongly inhibit ALDH enzymes. Interestingly, Isatin scaffold seems to share common chemical features with dihydroBenzoImidazoTriazineDione (BITD), a core previously investigated by us as a perspective inhibitor of aldose reductase. Therefore, we repositioned BITD nucleus and, based on the retrieved knowledge of ALDH enzymes, we designed new BITDs in order to allow the interaction with the target 1A1 enzyme. Through a microwave-assisted 3-step approach, a focused library of 2,10-disubstituted BITDs was synthesized. From enzymatic assays, one compound emerged as a selective inhibitor of ALDH1A1 over the 1A2 and 1A3 isoforms. Through i*n silico* studies, we rationalized the results, providing insights into the chemical features required for selectivity and the specific interaction networks for further optimization.

Keywords: Aldehyde dehydrogenase; ALDH1A1; benzoimidazotriazinedione; cancer; cancer stem cells; microwave; repositioning.

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