ECMC 2023

MDPI

Abstract

Demethylation Leading to a Loss of Functional Activity: Searching for a New Target for a Promising Antiproliferative Diphenylimidazo[1,2-*a*]pyridine Derivative†

Ilaria D'Agostino, Bianca Laura Bernardoni, and Concettina La Motta*

Department of Pharmacy, University of Pisa, 56126 Pisa, Italy; ilaria.dagostino@unipi.it; bianca.bernardoni@phd.unipi.it; concettina.lamotta@unipi.it

* Correspondence: concettina.lamotta@unipi.it

† Presented at the 9th International Electronic Conference on Medicinal Chemistry, 2023.

Abstract: Chemical modifications of a compound-of-interest, such as an enzyme inhibitor, are at the basis of performing robust structure-activity relationships able to address synthetic efforts toward more and more potent ligands. In this context, substitution patterns on phenyl rings, e.g., introduction of electron-donor/withdrawing groups, are widely explored. Generation of derivatives is based on different approaches, including molecular modeling, the emerging artificial intelligence, or the more traditional organic chemistry strategy. The latter usually follows practical guidelines, e.g., the Topliss scheme, or the actual laboratory availability of chemicals. In the last decade, Prof. La Motta's group has been involved in the development of new anticancer agents targeting Aldehyde Dehydrogenases (ALDHs, EC: 1.2.1.3), enzymes involved in the detoxifying conversion of aldehydes into the safer corresponding carboxylic acids, recognized as Cancer Stem Cells biomarkers and overexpressed in solid tumors. Derivatives libraries containing the imidazo[1,2-*a*]pyridine scaffold have been proposed as ALDH inhibitors and isoform selectivity has been reached through different phenyl substitution patterns. In particular, a potent and selective ALDH1A3 inhibitor (**3q**, IC_{50} = 3.5 μM) endowed with three methoxy substituents in specific phenyl positions was previously reported. Thus, we enlarged the derivatives series of **3q**, also synthesizing its corresponding demethylated derivative (**1**). Unexpectedly, a complete loss of inhibitory activity was observed for **1**, still possessing a promising antiproliferative effect on a thyroid primary cell line. *In silico* analyses on ALDHs were performed to elucidate why such a small chemical modification severely affected the activity. Then, we investigated the actual antiproliferative mechanism of action of **1** by exploring in wet different possibilities, providing partial but interesting information.

Keywords:; chemical modification; imidazo[1,2-*a*]pyridine; aldehyde dehydrogenase; anticancer; antiproliferative effect; target investigation.

Citation: D'Agostino, I.; Berardoni, B.L.; La Motta, C.. Demethylation Leading to a Loss of Functional Activity: Searching for a New Target for a Promising Antiproliferative Diphenylimidazo[1,2-a]pyridine Derivative. *Med. Sci. Forum* **2023**, *2*, x. https://doi.org/10.3390/xxxxx

Academic Editor:

Published:

Supplementary Materials: a poster is available.

Author Contributions: Conceptualization, C.L.M.; methodology, I.D.A. and B.L.B.; data analysis, I.D.A. and C.L.M.. All authors have read and agreed to the published version of the manuscript

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The corresponding author can provide the data included in the present study upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

Acknowledgment: We thank all the collaborators for the assays and *in silico* studies.