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, 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

INTRODUCTION

Chemical modifications of a compound of interest, such as an enzyme modulator, are at the basis of performing robust structure-activity relationships (**SARs**) able to address synthetic efforts towards more and more potent ligands. 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.

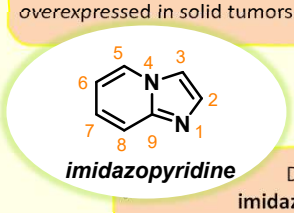
TEXT ME FOR INFO

Substitution patterns on (hetero)aromatic (*e.g.*, phenyl) rings are widely explored.

- electron-donor (ED) groups
- electron-withdrawing (EWG) groups
- isosters
- isomers
- bioisosters
- polysubstitution
- hydrophilic substituents
- hydrophobic substituents

BACKGROUND

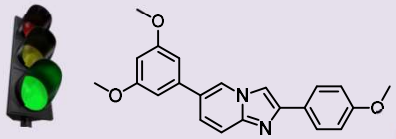
In the last decade, ***Prof. La Motta's group*** has been involved in the development of new anticancer agents targeting Aldehyde Dehydrogenases (**ALDHs**, EC: 1.2.1.3), enzymes involved in the detoxifying conversion of aldehydes into the safer corresponding carboxylic acids, recognized as ***Cancer Stem Cells*** biomarkers and overexpressed in solid tumors.



imidazopyridine

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.

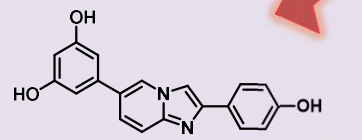
NEW EVIDENCE AND STUDIES



3q

Potent and selective ALDH1A3 inhibitor (IC_{50} = 3.5 µM)

*Chemical modifications of **3q** led to compound **1***

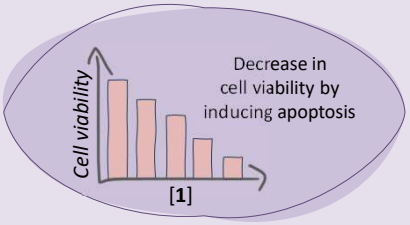


1

TOTALLY INACTIVE against ALDH1As

unexpected complete loss of inhibitory activity against ALDH1A enzymes

Cell-based assays



strong antiproliferative effect on thyroid cancer primary cells

... THUS, WHAT IS THE ACTUAL PHARMACOLOGICAL TARGET??

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INVESTIGATION

In silico studies to gain an insight into the binding mode of **1** in ALDH1A3

In wet assays to assess activity on different protein targets involved in cancer and antioxidant effects

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