ACS Medicinal Chemistry Letters

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Patent Highlight

Inhibitors of Interleukin 4 Induced Protein 1 (IL4I1) as Potential Treatment for Cancer

Ahmed F. Abdel-Magid*

Cite This: ACS Med. Chem. Lett. 2023, 14, 127−128

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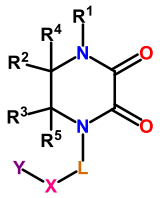
ABSTRACT: The invention in this patent application relates to piperazine-2,3-dione derivatives represented generally by formula 1. These compounds show activities as selective interleukin 4 induced protein 1 (IL4I1) inhibitors and may potentially be useful in preventing and treating IL4Il-related diseases, such as endometrial, ovarian, and triple negative breast cancers.

Important Compound Classes.



Title. IL4I1 Inhibitors and Methods of Use

URL. https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2022227015&_cid=P10-LAGZH1-09942-1

Patent Publication Number. WO 2022/227015 A1

Publication Date. November 3, 2022

Priority Application. PCT/CN 2021/091534

Priority Date. April 30, 2021

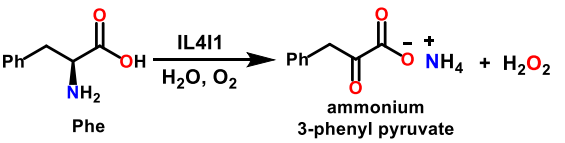
Inventors. Giambasu, G. M.; Haidle, A. M.; Hopkins, B. A.; Jewell, J. P.; Larsen, M. A.; Lesburg, C. A.; Liu, P.; Pu, Q.; Sanyal, S.; Siliphaivanh, P.; Tudor, M.; White, C. M.; Yan, X.; Zhao, L.; Zheng, X.-M.

Assignee Company. Merck Sharp & Dohme Corp., 770 Sumneytown Pike, West Point, Pennsylvania 19486, USA; MSD R&D Co., Ltd. [CN/CN], SF, Building A, Zongbuyuan Erqi, No. 1582 Gumei Road, Xuhui District, Shanghai 200233, China

Disease Area. Cancer, including endometrial, ovarian, and triple negative breast cancer

Biological Target. Interleukin 4 induced protein 1 (IL4I1)

Summary. The glycosylated protein interleukin 4 induced protein 1 (IL4I1) is a member of the L-amino acid oxidase (LAAO) family of flavin adenine dinucleotide (FAD)-bound enzymes. It is expressed in myeloid cells as well as T and B lymphocytes. IL4I1 performs primarily the oxidative deamination of phenylalanine (Phe) in the presence of H_2O and O_2 to produce ammonium 3-phenylpyruvate and H_2O_2 according to the following equation:



Note: the initial products (3-phenyl pyruvic acid and NH_3) react to form ammonium 3-phenyl pyruvate salt

This activity has given this enzyme the name L-phenylalanine oxidase. However, it also shows activity toward catalyzing the oxidative deamination of other L-α-amino acids containing aromatic residues, including tyrosine (Tyr) and tryptophan (Trp), to produce 3-(4-hydroxyphenyl)pyruvate and indole-3-pyruvate, respectively. In addition, IL4I1 shows weaker activity toward the oxidative deamination of L-arginine.

IL4I1 is highly produced in cells of myeloid origin (monocytes/macrophages and dendritic cells) of the human immune system. Its production is particularly elevated as a result of stimulation by inflammatory and T helper type 1 (Th1) stimuli. Accordingly, IL4I1 is strongly produced by dendritic cell and macrophage populations from chronic Th1 granulomas of sarcoidosis and tuberculosis, but not Th2 granulomas (schistosomiasis). It is also strongly produced by tumor-infiltrating macrophages from various histological types of tumors.

The oxidative deamination activity of IL4I1 causes the depletion of essential amino acids while liberating several toxic metabolites that may block the actions of anti-tumor effector T cells. Researchers have observed the expression of IL4I1 in the tumor-associated macrophage (TAM) population of many types of tumors, and it was also detected in tumor cells of several B lymphoma subtypes. The presence of IL4I1-producing cells in the tumor cell microenvironment inhibits the anti-tumor immune response either directly by limiting the proliferation

Published: January 17, 2023

and functionality of cytotoxic T cells and Th1 cells or indirectly by facilitating the accumulation of T_{reg} cells. Analyses of biopsy samples of human tumor and normal tissues have identified increased expression of both IL4I1 mRNA and protein in tumor-infiltrating myeloid cells.

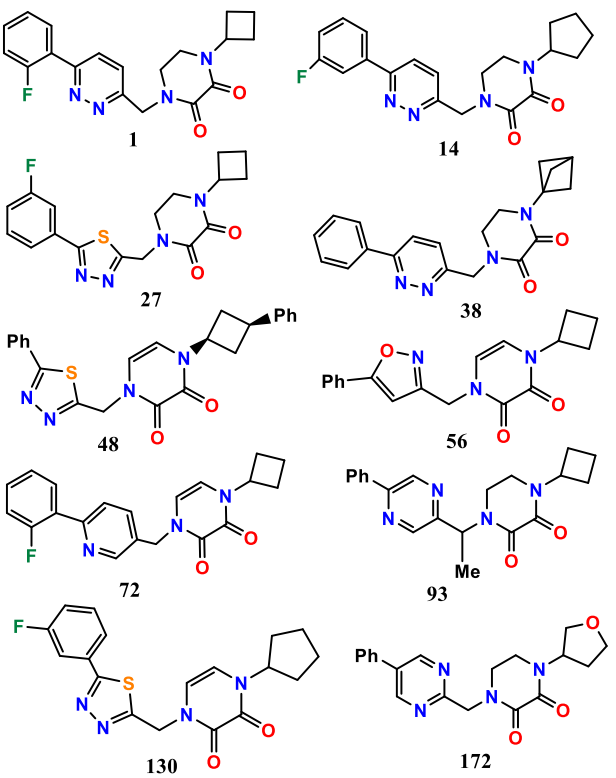
The Cancer Genome Atlas (TCGA) indicates that, among solid tumors, endometrial carcinoma contains the highest levels of IL4I1 mRNA expression, followed by serious ovarian and triple negative breast cancers. Additionally, elevated levels of phenylpyruvic acid (the product of oxidative deamination of phenylalanine by IL4I1) were detected in endometrial and ovarian tumor samples compared to matched adjacent tissues obtained from the same patients. Furthermore, the accumulation of detectable levels of phenylpyruvic acid in tumor samples is dependent on the presence of IL4I1 itself.

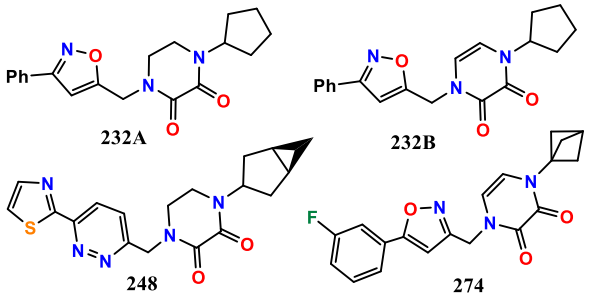
The above data point to the inhibition of IL4I1 as a potentially useful biological target for the treatment of cancer indications where IL4I1 is most expressed and/or active, including endometrial, ovarian, and triple negative breast cancers.

Therefore, there is a need for specific inhibitors of IL4I1. Currently, however, there are no available specific inhibitors of IL4I1, and while researchers have identified some molecules capable of inhibiting related LAAOs found in snake venom, they were generally non-selective, with little activity against IL4I1.

The compounds of formula 1 described in this patent application have displayed specific activities against IL4I1 and may potentially provide useful treatment of cancer indications where IL4I1 is most expressed and/or active, including endometrial, ovarian, and triple negative breast cancers.

Key Structures. The inventors reported the structures and methods of synthesis of 278 examples of formula 1, including the following representative examples:





Biological Assay. IL4I1 Enzymatic Assay

Biological Data. The inhibitory effect of the compounds of formula 1 (EC_{50}) on IL4I1 was assessed by measuring the effectiveness of these compounds in inhibiting the production of H_2O_2. The data obtained from testing the above representative examples by this assay are outlined in the following table:

Example	IL4I1 inhibition EC_{50} (nM) (240 min)
1	10
14	6
27	5
38	23
48	2
56	1
72	2
93	20
130	1
172	68
232A	2
232B	1
248	23
274	2

Recent Review Articles. See refs 1−3.

AUTHOR INFORMATION

Corresponding Author

Ahmed F. Abdel-Magid − *Therachem Research Medilab, LLC, Chelsea, Alabama 35043, United States;* orcid.org/0000-0001-7438-1414; Email: afmagid@comcast.net

Complete contact information is available at: https://pubs.acs.org/10.1021/acsmedchemlett.2c00525

Notes

The author declares no competing financial interest.

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https://doi.org/10.1021/acsmedchemlett.2c00525
ACS Med. Chem. Lett. 2023, 14, 127−128