Publication and conference presentation

Publication:

1. **Gaurav Sheth,** Shailesh R. Shah, Prabal Sengupta, Tushar Jarag, Sabbirhusen Chimanwala, Kalapatapu V.V.M. Sairam, Vaibhav Jain, Rashmi Talwar, Avinash Dhanave, Mehul Raviya and Trinadha Rao Chitturi. In the Quest for Potent and Selective Malic Enzyme 3 Inhibitors for the Treatment of Pancreatic Ductal Adenocarcinoma. *ACS Medicinal Chemistry Letters* **2023**, 14, 41-50. (Impact factor – 4.2)

Conference presentation:

1. **Gaurav Sheth**, Shailesh R. Shah and Trinadha Rao Chitturi. Development of potent and selective Malic enzyme 3 inhibitors for the treatment of pancreatic cancer. Oral presentation at 27th ISCB international conference on research and innovation in chemical, pharmaceutical and biological sciences held at Birla institute of technology, Ranchi on 16-19 Nov **2022**.

2. **Gaurav Sheth**, Shailesh R. Shah and Trinadha Rao Chitturi. Synthesis of novel irreversible inhibitors of Bruton Tyrosine Kinase (BTK) for treatment of Chronic Lymphocytic Leukemia (CLL). Poster presentation at national seminar on advances in chemistry of bioactive molecules held at Department of chemistry, M. S. University of Baroda, Vadodara on 17-18 Jan **2020**. (Additional work done during Ph. D. tenure which is not included as a part of the thesis)

ACS Medicinal Chemistry Letters

pubs.acs.org/acsmedchemlett

Letter

In the Quest for Potent and Selective Malic Enzyme 3 Inhibitors for the Treatment of Pancreatic Ductal Adenocarcinoma

Gaurav Sheth, Shailesh R. Shah,* Prabal Sengupta, Tushar Jarag, Sabbirhusen Chimanwala, Kalapatapu V. V. M. Sairam, Vaibhav Jain, Rashmi Talwar, Avinash Dhanave, Mehul Raviya, Soumya Menon, Shivangi Trivedi, and Trinadha Rao Chitturi*

Cite This: https://doi.org/10.1021/acsmedchemlett.2c00369

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The genome of pancreatic ductal adenocarcinoma (PDAC) is associated with frequent deletion of the tumor suppressor gene SMAD family member 4 (*SMAD4*) with collateral deletion of its chromosomal neighbor malic enzyme 2 (*ME2*). In *SMAD4*$^{-/-}$/*ME2*$^{-/-}$ PDAC cells, ME3 takes over the function of the ME2 enzyme, and hence therapeutic targeting of ME3 is expected to arrest tumor growth. Hitherto no selective small molecule inhibitor of ME3 has been reported in the context of PDAC. Based on the molecular docking studies and structure−activity relationships with the reported ME1 inhibitor, several analogues of 6-piperazin-1-ylpyridin-3-ol amides have been synthesized and screened for their ME inhibition activity. Among them, compound 16b is identified as the most potent and selective ME3 inhibitor with an IC_{50} of 0.15 μM on ME3, and with 15- and 9-fold selectivity over ME1 and ME2, respectively. In the cell viability assay, compound 16b exhibited an IC_{50} of 3.5 μM on ME2-null PDAC cells, *viz.*, BxPC-3.

KEYWORDS: *ME3 inhibitors, Anticancer compounds, PDAC, Collateral lethality, Malic enzyme, Molecular Docking*

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive pancreatic cancer originating from exocrine cells and accounts for more than 90% of pancreatic tumors.[1] PDAC patients remain asymptomatic at early stages, and a majority of them are diagnosed only at unresectable stages.[2] Due to its poor prognosis, it is one of the leading causes of cancer-related mortalities with a five year survival rate of less than 11%.[3] Chemotherapeutic combinations, viz., gemcitabine and paclitaxel or FOLFIRINOX (a combination of 5-fluorouracil, irinotecan, oxaliplatin, and folinic acid), are the current major standards of care for PDAC. However, there is an unmet clinical need for novel targeted therapies.[4]

Activating mutations in the Kirsten rat sarcoma virus (*KRAS*) oncogene is associated with more than 90% of PDAC cases along with subsequent deletion of tumor-suppressor genes like *INK4A/ARF*, tumor protein 53 (*TP53*), and SMAD family member 4 (*SMAD4*).[5] In PDAC, oncogenic *KRAS* mutation ($KRas^{G12D}$) driven activation of downstream signaling pathways like MAPK and PI3K-mTOR mobilizes uncontrolled proliferation and survival of cancer cells. Rapid proliferation of neoplastic cells requires an adequate supply of energy and biosynthetic precursors as cellular building blocks.[6] This enhanced energetic and anabolic requirement is satisfied through metabolically rewired processes which include aerobic glycolysis, glutaminolysis, and *de novo* fatty acid synthesis. Advancement of glycolysis and fatty acid synthesis is supported by bioprecursors like pyruvate and cofactors like nicotinamide adenine dinucleotide (NAD) phosphate NAD(P)$^+$ and NAD(P)H.

Expression of enzymes involved in the mitochondrial tricarboxylic acid (TCA) cycle is also upregulated in numerous cancers leading to metabolic alterations to meet the enhanced demand for bioenergy and biomass for chronic proliferation of cancer cells. In this context, malic enzymes (MEs) play a crucial role in catalyzing oxidative decarboxylation of L-malate to form pyruvate and CO_2 while simultaneously reducing NAD(P)$^+$ to NAD(P)H.[7] Both pyruvate and NADPH have an important role in energy production in cells, for the maintenance of redox balance and for the production of building blocks for biosynthesis. In mammalian context, three isoforms of malic enzyme have been identified. These are classified based on their cofactor specificities and subcellular

Received: August 7, 2022
Accepted: December 8, 2022

27th ISCB International Conference (ISCBC-2022)

OL-2

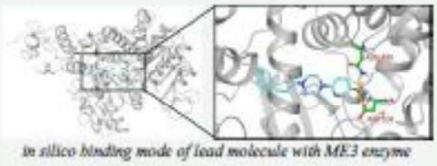
Development of potent and selective Malic enzyme 3 inhibitors for the treatment of pancreatic cancer

Gaurav Sheth[1,2], Shailesh R. Shah*[2,3] and Trinadha Rao Chitturi*[1]

[1] *Department of Medicinal Chemistry, Sun Pharma Advanced Research Company Ltd., Vadodara 390020, India*
[2] *Department of Chemistry, Faculty of Science, The M.S. University of Baroda, Vadodara 390002, India.*
[3] *Department of Chemistry, School of Sciences, Indrashil University, Rajpur 382740, India.*

Email: gaurav.sheth1981@gmail.com, shailesh-chem@msubaroda.ac.in, chitturi.rao@sparcmail.com

Abstract:
It is well documented that overexpression of Malic enzyme (ME) isoforms correlates with poor prognosis in diverse cancers [1-7]. ME plays a critical role in tumor development by catalyzing oxidative decarboxylation of L-malate into pyruvate and simultaneously reducing $NADP^+$ to NADPH. While pyruvate production helps in generation of cellular building blocks, NADPH is required for maintaining redox homeostasis and energy production [8].



in silico binding mode of lead molecule with ME3 enzyme

In pancreatic ductal adenocarcinoma (PDAC), tumor suppressor gene SMAD4 is deleted along with its neighboring gene ME2. Dey *et. al.*, through compelling in vitro and in vivo experiments, demonstrated that in this genetic event ME3 takes over the role of ME2 [8]. Hence, targeting ME3 could be a potential therapeutic strategy for PDAC patients with SMAD4 and ME2 deletions. Hitherto no selective small molecule inhibitor of ME3 has been reported in the context of PDAC. Through molecular docking studies and exploration of structure activity relationships, potent and selective ME3 inhibitors were designed and synthesized. These compounds were capable of engaging with ME3 in cell lysates and exhibited growth inhibition of $ME2^{-/-}$ PDAC cells viz. BxPC-3.

REFERENCES:

[1]Shi, Y. *et. al.*, Onco. Targets. Ther. 12, 2019, 5589-5599.
[2]Liao, R. *et. al.*, Sci. Rep. 8, 2018, 16743.
[3]Nakashima, C. *et. al.*, Cancer Sci. 109, 2018, 2036–2045.
[4]Ren, J. G. *et. al.*, Sci. Rep. 4, 2014, 5414.
[5]Yang, M. *et. al.*, Front. Oncol., 2021; DOI: 10.3389/fonc.2021.715593.
[6]Zhou, J. J. *et. al.*, Int. J. Med. Sci. 17, 2020, 799-806.
[7]Lee, Y. H. *et. al.*, Neoplasma 60, 2013, 607-616.
[8]Dey, P. *et. al.*, Nature 542, 2017, 119-123.

Poster presentation (P-13)

Synthesis of novel irreversible inhibitors of Bruton Tyrosine Kinase (BTK) for treatment of Chronic Lymphocytic Leukemia (CLL)

Gaurav Sheth[#*], Shailesh R. Shah[#], C. T. Rao*

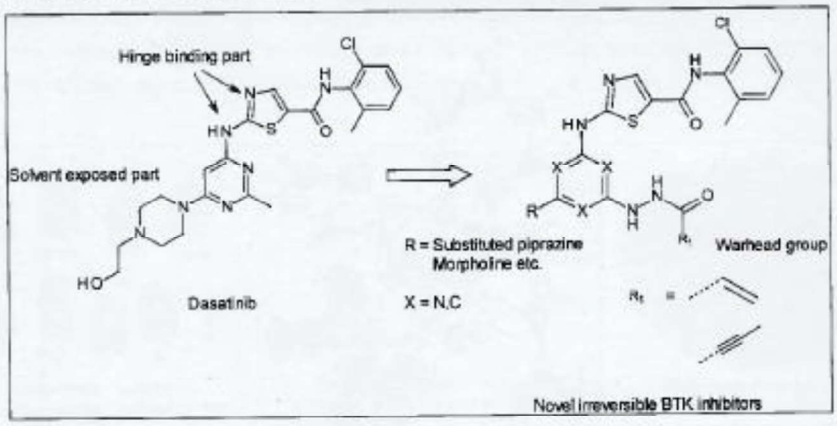
[#]**Department of Chemistry**

Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara-390002

***Sunpharma Advanced Research Company Ltd., Tandaja, Vadodara-390020**

Gaurav.sheth1981@gmail.com, shailesh-chem@msubaroda.ac.in,
Chitturi.Rao@sunpharma.com

Bruton's tyrosine kinase (BTK), a non-receptor tyrosine kinase, is a key downstream component of B cell receptor (BCR) signalling that functions as an important regulator of cell proliferation and cell survival in various B cell malignancies like chronic lymphocytic leukemia (CLL) and mantle-cell lymphoma (MCL) [1]. Ibrutinib and acalabrutinib are small molecule BTK inhibitors clinically approved for CLL and MCL. These drugs bind irreversibly through covalent binding with Cys481 within the ATP-binding pocket of the BTK enzyme[2]. Covalent binding of small molecules with Cys481 of BTK provide better target engagement and hence a sustainable pharmacological response. The present work describes in silico design and synthesis of novel covalent inhibitors of BTK (targeting Cys481) based on the dasatinib scaffold.



References

1. Rudi W. Hendriks, Saravanan Yuvaraj and Laurens P. Kil, *Nature Reviews Cancer*, 2014, **14**, 219-232.
2. Simar Pal Singh, Floris Dammeijer and Rudi W. Hendriks, *Molecular Cancer*, 2018, **17**, 57
3. Sengupta Prabal et al. WO 2017/168454.