Dedicated to

Shri. Dilip Sanghvi

Founder of Sun Pharmaceuticals

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Certificate

This is to certify that the thesis entitled **"Design and synthesis of molecules that inhibit cellular enzymes involved in glucose metabolism as anticancer agents"** submitted by **Gaurav Sheth** to the Maharaja Sayajirao University of Baroda, Vadodara, for the award of the degree of **Doctor of Philosophy in Chemistry**, is a bona fide record of the research work carried out by him under our supervision and guidance at Sun Pharma Advanced Research Company Ltd, Vadodara. The results embodied in this thesis have not been submitted to any other university or institute for the award of degree or diploma.

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Certificate

This is to certify that **Gaurav Sheth** (Reg. No.: FOS/2148, Date March 30, 2019) has published one research paper in *ACS medicinal chemistry letters* journal during his Ph.D. work.

1. **ACS Med. Chem. Lett. 2023, 14, 41-50**

"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 and Trinadha Rao Chitturi.

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This is to certify that **Gaurav Sheth** (Reg. No.: FOS/2148, Date March 30, 2019) has presented one oral presentation in conference during his Ph.D. work.

1. **Gaurav Sheth**, Shailesh R. Shah and Trinadha Rao. 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**.

Prof. S. R. Shah
Research supervisor

Declaration

To the best of my knowledge and belief the thesis entitled "**Design and synthesis of molecules that inhibit cellular enzymes involved in glucose metabolism as anticancer agents"** submitted here with to The Maharaja Sayajirao University of Baroda, Vadodara of the fulfillment for the award of the degree of **DOCTOR OF PHILOSOPHY IN CHEMISTRY** is the result of the work carried out by me in chemistry department at Sun Pharma Advanced Research Company Ltd. The results of this work have not been previously submitted for any degree/fellowship to any university or institute.

Date:

Place: Vadodara Gaurav Sheth

Preface

This thesis is the upshot of my Ph.D. study at Sun Pharma Advanced Research Company Ltd. and the department of Chemistry, The Maharaja Sayajirao University of Baroda, Vadodara, India. This study has been also a part of my job as principle research scientist at Sun Pharma Advanced Research Company Ltd., Vadodara, India to which I have been associated since July 2004.

The thesis consists of five major sections which cover the first in class development of Malic Enzyme 3 (ME3) inhibitors for the treatment of Pancreatic Ductal Adenocarcinoma (PDAC). A part of the thesis has been published in an international journal.

The '**Introduction**' section deals with the general information about pancreatic cancer. Detailed pathophysiology of the disease, the current treatment options and the un-met need in this area of PDAC were discussed. This was followed by detailed explanation of the role of ME3 in the context of PDAC patients with genetic deletion of *SMAD4* and *ME2* genes. Through systematic "HIT" finding exercise for ME3 as a target, five HITs were identified for the first time as ME3 inhibitors and one of them was selected for further optimization.

In the section titled **"Identification of pharmacophore for ME3 inhibition and study of structure activity relationship (SAR)"**, the strategies and rationale for HIT optimization of compound A are discussed. The structural elements critical for ME3 inhibition that have been identified which culminated in to a novel series of potent and cell active ME3 enzyme inhibitors.

In the section titled "**Selectivity enhancement for ME3 and in vivo preclinical evaluation"**, critical structural feature to achieve selectivity towards ME3 over other ME isoforms was identified. Systematic SAR study led to series of

compounds with improved isoform selectivity. This was followed by pre-clinical evaluation of one of the lead compound in *in vivo* xenograft model for PDAC.

In the section titled "**Design and synthesis of indole-piperazine carboxamide series and in vitro evaluation of tool compound in combination with trametinib",** further optimization of lead compound led to new series of compounds containing indole-piperazine carboxamides. This was followed by study of combination effect of one of the new lead with trametinib on cell growth inhibition of Hs766T PDAC cells.

In the section titled "**Design and synthesis of dual ME3-tubulin inhibitors for the treatment of PDAC",** diverse analogues with tricyclic aromatic rings were designed, synthesized and evaluated which led to new series of tricyclic compounds with potential of inhibiting two targets ME3 as well as tubulin. These compounds show sub nanomolar activity on pancreatic cancer cell lines.

In the last major section titled **"Comprehensive biological evaluation protocols of selected compounds for their mechanism of action, efficacy and safety"**. study protocols for biological evaluation of selected compounds were discussed.

I thoroughly enjoyed working on this research project and I found it to be a highly educational and rewarding experience. I felt a great sense of accomplishment upon completing this research on the use of ME3 inhibitors for the treatment of PDAC as its finding could be helpful in addressing an unmet need in this area. As a medicinal chemist, I am passionate about designing and developing ground breaking therapies that can address unmet medical needs and reduce human suffering.

Gaurav Sheth

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I would like to convey my heartfelt thanks to the H. R. and Admin Department of SPARC Ltd. and the teaching staff and the office staff of The M.S. University of Baroda for their timely help and support.

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Gaurav Sheth