Design, synthesis and biological evaluation of small molecule agonist of the Glucagon-Like Peptide-1 Receptor (GLP-1R) as an anti-diabetic agent

A

Thesis

For the Award of the Degree of

DOCTOR OF PHILOSOPHY

In

Science

Submitted

By

Khyati (Roll No.-D15016)

Under the supervision of

Dr. Prosenjit Mondal

(Assistant Professor)

School of Basic Sciences

Indian Institute of Technology Mandi

Mandi, Himachal Pradesh, India-175005

Declaration by the Research Scholar

I hereby declare that the entire work embodied in the thesis “Design, synthesis and biological evaluation of small molecule agonist of the Glucagon-Like Peptide-1Receptor (GLP-1R) as an antidiabetic agent” is the result of investigations carried out by me in the School of Basic Sciences, Indian Institute of Technology Mandi, under the supervision of Dr. Prosenjit Mondal, and that it has not been submitted elsewhere for any degree or diploma. In keeping with the general practice, due acknowledgements have been made wherever the work described is based on the finding of other investigators.

Place: Kamand, Mandi, (H.P), India. **Signature:**

Date: **Name**: Khyati

Declaration by the Research Advisor

I hereby certify that the entire work in this Thesis has been carried out by **Khyati (Roll No.-D15016)**, under my supervision in the **School of Basic Sciences**, Indian Institute of Technology Mandi, and that no part of it has been submitted elsewhere for any Degree or Diploma.

Signature:

Name of the Guide: Dr. Prosenjit Mondal

Date:

Dedicated to…

"My Beloved Family

and

Animal Life Sacrificed"

ACKNOWLEDGEMENT

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(Khyati)

PREFACE

Diabetes is a worldwide societal fiasco that pulverizes individual misery and has a high mortality rate across the globe. It is affecting individuals of all age groups, from children to individuals over 65 years of age. Diabetes mellitus is the condition of insufficient supply of insulin by β-cells or incapability of the body to use existing insulin (insulin resistant condition), thereby leading to hyperglycemia and eventually diabetes mellitus. The Glucagon-Like Peptide-1 (GLP-1), and GLP-1Receptor (GLP-1R) has been the focus of considerable research attention for their ability to reduce blood glucose level, body weight, protect β-cell mass and augmenting insulin secretion without causing hypoglycemia. Thus, GLP-1R has become a promising therapeutic target for the treatment of type 2 diabetes. However, GLP-1 is not available as therapeutics in the market, due to its very short half-life of 2 mins in the circulation. To overcome this limitation, researchers have introduced many stable analogs of GLP-1 such as Exendin-4 and Liraglutide.

Although available GLP-1 stable analogs like Exendin-4 and Liraglutide have more half-life than native GLP-1, they have several disadvantages like subcutaneous administration, belching, diarrhea, high cost, and low stability due to their peptidic nature. That represents an immense need of a small molecule GLP-1 analog as an anti-diabetic therapeutics. Thus, small-molecule agonists that target GLP-1R are preferable, but difficult to identify and develop, probably due to the large and open binding pocket of family B of G-protein-coupled receptors (GPCRs). This thesis work not only introduces a new strategy for the development of small-molecule agonist of GLP-1R but also presents the application of developed novel small molecule GLP-1R agonist in the treatment of diabetes.

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