UNIVERSITI TEKNOLOGI MARA

THE DISCOVERY OF A NOVEL SERIES OF BENZIMIDAZOLES AS A NEW PROSPECTIVE CLASS OF OCULAR HYPOTENSIVE AGENTS

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MSc

September 2019

AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the results of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

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Faculty	:	Medicine
Thesis Title	:	The Discovery of A Novel Series Of Benzimidazoles As A New Prospective Class Of Ocular Hypotensive Agents
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Date	:	September 2019

ABSTRACT

Ocular hypertension is believed to be involved in the etiology of primary open-angle glaucoma. Although many pharmaceutical agents have been shown to be effective for the reduction of intraocular pressure (IOP), a significant opportunity to improve glaucoma treatments remains. The aims of this study is to discover novel IOP lowering agents and thus, a total of 27 imidazo[1,2-a]- and pyrimido[1,2-a]benzimidazole compounds were screened for their IOP lowering activity in ocular normotensive and hypertensive rats. IOP lowering activity was determined by assessing maximum IOP decrease from baseline and control, duration of activities and area under the curve (AUC). During initial screening of 27 compounds, four compounds (RU-551, RU-555, RU-839), and RU-615 showed significant IOP lowering activities in ocular normotensive rats. Further screening for those four compounds was carried out in a single dose application in dexamethasone-induced ocular hypertensive rat and among the four compounds RU-615 was the most active in lowering IOP. RU-615 was similarly tested for dose-response relationship at 3 different concentrations (0.1%, 0.2% and 0.4%) in ocular hypertensive rats and this was followed by evaluation of ocular hypotensive effect after bilateral multiple drop administration with minimally effective concentration for 3-weeks. At the end of the 3-weeks chronic treatment, rats were subjected for retrograde labelling of retinal ganglion cells (RGC) to assess the effect of RU-615 on RGC survival and on retinal antioxidant markers. Both studies demonstrated the ability of RU-615 in providing antioxidant protection and preventing further retinal damages. In vitro part of this study explored the rho-kinase inhibitory activity of RU-615 using dexamethasone-treated HTMC as possible mechanism of action of its IOP lowering activity. Cell viability and CC_{50} showed that RU615 has a very good safety profile at 1 mM concentration, HTMC viability was slightly under 80%. The rho-kinase inhibitory activity of RU-615 was also compared with the effects of reference rho-kinase inhibitor compound, Y-27632. However, this study didn't show conventional rho-kinase inhibition by RU-615. For conclusion, RU-615, a novel N9-imidazobenzimidazole derivatives, exhibits significant IOP lowering effect in both ocular normotensive and ocular hypertensive rats. This IOP lowering activity together with antioxidant properties might be the factors that contributed to prevention of further RGC loss. It is noteworthy, that benzimidazoles have been shown to possess cholinomimetic, carbonic anhydrase inhibitory and adenosine A1 receptor agonist activities. Therefore, in the future studies it is important to identify the upstream targeted receptors for RU-615 and then delineate the involved intracellular signalling pathways which are likely to be other than rho-kinase inhibition.

ACKNOWLEDGEMENT

I would first like to thank my main supervisor Assoc. Prof. Dr. Igor Nikolayevich Iezhitsa of the Faculty of Medicine. His endless support and guidance throughout my research have shaped me to be a better researcher and person.

I also would like to give my thanks to both of my co-supervisor, Prof. Dr. Renu Agarwal for her much-needed advices and constructive criticism in my research and Prof. Dr. Nafeeza Mohd. Ismail for her support and advices. Not to forget Dr. Anna Krasilnikova who always was available to share her thoughts and advices. Special acknowledgment goes to Dr Norhafiza Razali for her contribution in experimental work and guidance in measurement of intraocular pressure.

We are extremely thankful to Dr. Tamara A. Orobinskaya, Dr. Tatiana A. Vakulina, Dr. Yuri K. Fomin, Dr. Svetlana V. Ivanovskaya, Dr. Leonid M. Kolomoytsev (Volgograd State Medical University, Volgograd, Russia) for their contribution in experimental work on hypotensive activity of imidazo[1,2-a]benzimidazole and pyrimido[1,2-a]benzimidazole compounds used for correlation analysis

This acknowledgment also goes to Dr. Olga Zhukovskaya and Prof. Dr. Vera Anisimova from Research Institute of Physical and Organic Chemistry, Rostov State Medical University (Rostov-on-Don, Russian Federation) for synthesis of imidazo[1,2-a]benzimidazole and pyrimido[1,2-a]benzimidazole compounds and to Prof. Dr. Alexander Spasov and Prof. Dr. Pavel Vassiliev from Research Institute of Pharmacology, Volgograd State Medical University (Volgograd, Russian Federation) for their significant contribution to study on relationship of hypotensive and IOP-lowering activities.

I also would like to acknowledge all my colleagues and senior fellows form Department of Pharmacology (Faculty of Medicine, UiTM) and Centre for Neuroscience Research (NeuRon) for their countless helps and advices without asking in return. I want to extend my gratitude to University Technology MARA, Sungai Buloh Campus for giving me the opportunity and accommodate me until the completion of my research. Not forgetting all the staffs from Institute of Medical Molecular Biotechnology (IMMB), and Laboratory Animal Care Unit (LACU) for their help and assistance during my laboratory experiments.

I gratefully acknowledge financial support from Research Acculturation Grant Scheme (RAGS) by the Ministry of Higher Education (MOHE) / Kementerian Pendidikan Tinggi (KPM) (Malaysia) under the project 600-RMI/RAGS 5/3 (46/2014). I would like to thank the Dean, Prof. Dr. Mohd Zamrin Dimon of Faculty of Medicine, Universiti Teknologi MARA for giving me an opportunity to carry out the research work through the esteemed University.

Finally, I would like to give my sincere thank you and gratitude towards all my family especially my parents for encouraging me in all of my pursuits, for their financial and moral support making the completion of this thesis possible. This Thesis is dedicated to them.

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