UNIVERSITI TEKNOLOGI MARA

ANTIVIRAL ACTIVITY OF N-SUBSTITUTED 5-(PHENYLAMINO)URACIL DERIVATIVES AGAINST CHIKUNGUNYA VIRUS

NOOR FARAH BINTI OMAR AHMAD

MSc

April 2018

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.

Name of Student	:	Noor Farah binti Omar Ahmad
Student I.D. No.	:	2014478508
Programme	:	Master of Medical Sciences (Biochemistry) - MD751
Faculty	:	Medicine
Thesis Title	:	Antiviral Activity of N-Substituted 5-(Phenylamino)Uracil Derivatives against Chikungunya Virus
Signature of Student	:	……
Date	:	April 2018

ABSTRACT

Chikungunya virus (CHIKV), is an arthropod-borne disease that causes Chikungunya fever. Currently, there is no available drug or vaccine to treat the infected CHIKV patients. Based on literature, novel N-substituted 5-(phenylamino)uracil derivatives exhibit inhibitory effects against HIV and Hepatitis C virus but not yet been tested on CHIKV. The half maximal cytotoxic concentration (CC_{50}) of six 5-substituted-(phenylamino) uracil and five 2,4-dioxo-3,4-dihydropyrimidine acetic acid compounds were at 200 µM and 800 µM respectively. Two compounds (Z214 and Z364) exhibited the best antiviral activity at concentration of 50 µM and 100 µM. Time-addition assay revealed that the inhibition was most efficient when Z214 (50 µM) and Z364 (100 µM) were added at 4 hour of post-infection (hpi) and at 6 hpi. This suggests that, these compounds have inhibitory effect as anti-CHIKV inhibitors at post-entry step of CHIKV replication cycle. Prophylactic treatment showed a decrease in number of CHIKV plaques when Z214 (50 µM) and Z364 (100 µM) were added 5 hours before infection by 100% and 71% ± 7.01 respectively. Z214 and Z354 exhibited a significant effect against CHIKV attachment and adsorption to the Vero cells at all tested concentrations (1.56 µM to 100 µM) as compared to the virus control. Both compounds exhibited inhibition against CHIKV internalization when the compounds (at all tested concentration ranging from 1.56 µM to 100 µM) were added during virus internalization. In conclusion, these compounds under novel N-substituted 5-(phenylamino)uracil derivatives exhibited promising antiviral activity for Chikungunya virus and it could be further studied.

ACKNOWLEDGEMENT

Firstly, I wish to thank to Allah S.W.T for giving me the opportunity to embark on my Master and for completing this long and challenging journey successfully. My gratitude and thanks go to my supervisor Dr. Wang Seok Mui, and co-supervisors, Assoc. Prof. Dr. Anna V. Krasilnikova and Prof. Dr. Shamala Devi Sekaran. Thank you for the support, patience and ideas in assisting me with this project. I also would like to express my gratitude to the staffs of Institute of Medical Molecular Biotechnology (IMMB) and Centre for Pathology Diagnostic and Research Laboratories (CPDRL) for providing the facilities, knowledge and assistance.

My appreciation goes to the Ministry of Higher Education (MoHE), Malaysia for giving us the Research Grant Scheme (RAGS) (600- RMI/RAGS 5/3 (93/2013) to conduct this research. Special thanks to my colleagues and friends for helping and giving me support to complete this project, sharing knowledge and experiences throughout my master project.

Finally, this thesis is dedicated to my dearest father and mother, Omar Ahmad bin Mahmuddin and Rahmah binti Ahmad and also my beloved husband, Muhammad Azroffi bin Mohammed Ariffin for the vision, support, courage and determination to educate me. This piece of victory is dedicated for all you. Alhamdullilah.

TABLE OF CONTENTS