STRUCTURAL INSIGHT INTO LIGAND BINDING INTERACTIONS WITH DEN2 AND DEN3 PROTEASES

PRATHEEV ALAGAPPAN

(SGJ 100015)

SUBMITTED TO

INSTITUTE OF BIOLOGICAL SCIENCES

FACULTY OF SCIENCE

UNIVERSITY OF MALAYA

IN PARTIAL FULFILMENT

OF THE REQUIREMENTS FOR

THE DEGREE OF MASTER OF BIOINFORMATICS

2012

UNIVERSITI MALAYA

ORIGINAL LITERARY WORK DECLARATION

Name of Candidate: PRATHEEV ALAGAPPAN (830831015151)

Registration/Matric No: SGJ 100015

Name of Degree: MASTER OF BIOINFORMATICS

TITLE ("this Work"): STRUCTURAL INSIGHT INTO LIGAND BINDING INTERACTIONS WITH DEN2 AND DEN3 PROTEASES

Field of Study: BIOINFORMATICS

I do solemnly and sincerely declare that:

(1) I am the sole author/writer of this Work;
(2) This Work is original;
(3) Any use of any work in which copyright exists was done by way of fair dealing and for permitted purposes and any excerpt or extract from, or reference to or reproduction of any copyright work has been disclosed expressly and sufficiently and the title of the Work and its authorship have been acknowledged in this Work;
(4) I do not have any actual knowledge nor do I ought reasonably to know that the making of this work constitutes an infringement of any copyright work;
(5) I hereby assign all and every rights in the copyright to this Work to the University of Malaya ("UM"), who henceforth shall be owner of the copyright in this Work and that any reproduction or use in any form or by any means whatsoever is prohibited without the written consent of UM having been first had and obtained;
(6) I am fully aware that if in the course of making this Work I have infringed any Copyright whether intentionally or otherwise, I may be subject to legal action or any other action as may be determined by UM.

Candidate's Signature Date:

Subscribed and solemnly declared before,

Witness's Signature Date:

Name:

Designation:

ABSTRAK

Denggi adalah satu penyakit yang serius yang merupakan beban kepada kesihatan global. Pada masa ini, satu-satunya kaedah yang dipraktikkan untuk mengawal penyakit ini adalah dengan kawalan vektor. Penyebaran wabak denggi yang meluas telah memberi penekanan kepada kepentingan penyelidikkan ubatan dengan strategi yang cekap dan kos efektif supaya dapat mengenal pasti inhibitor yang berpotensi and berkesan menangani wabak ini. Dalam menyokong keperluan ini, beberapa pendekatan dalam proses penyelidikan telah digunakan dalam bidang penyelidikkan ubat-ubatan ini. Perbandingan struktur antara model homologi 'DEN2' dan struktur kristal 'DEN3' dalam kajian molekul dok inhibitor merujuk kepada 'DENV serine protease NS2B/NS3' telah dijalankan. Inhibitor rujukan terdiri daripada inhibitor yang dilaporkan sebagai inhibitor berdaya-saing dan bukan berdaya-saing ('4 hydroxypanduratin A', 'alpinetin', 'pinocembrin', 'pinostrobin' dan 'cardamonin'). Projek kajian ini telah dilaksanakan dengan beberapa objektif mengenai interaksi inhibitor dan perbandingan antara model homologi 'DEN2' dan struktur kristal 'DEN3' dengan mengenalpasti beberapa perbezaan dalam interaksi molekul untuk mengenalpasti interaksi mutlak untuk menghalang 'protease'.

ABSTRACT

Dengue is a serious disease which has re-emerged to become a global health burden. Currently, the only method deployed to manage this disease is by vector control. The increasing spread and severity of the dengue virus infection give emphasis to the importance of drug discovery strategies that could efficiently and cost-effectively identify potent drugs for development. In support of this requirement, several computational approaches were applied in this work. Initially structural comparison between the DEN2 homology model and DEN3 crystal structures and molecular docking studies of reference ligands to the DENV NS2B/NS3 serine protease were carried out. These reference ligands consist of reported competitive inhibitors and non-competitive inhibitors (4-hydroxypanduratin A, alpinetin, pinocembrin, pinostrobin and cardamonin). This study has provided some insights on possible binding interactions and comparison between the DEN2 homology model and DEN3 crystal structures where several differences with the interactions with the ligand binding residues have shown to be important for the protease inhibition.

ACKNOWLEDGEMENT

I would like to sincerely thank my supportive supervisor, Dr. Rozana Othman for providing me the access to the computational laboratory workstations, valuable advices and continuous guidance to complete the research project. I would also like to thank Dr. Saharuddin for his guidance. I want to also thank Heh Choon Han, Yap Beow Keat and Chin Sek Peng for their helpful assistance with troubleshooting and knowledge sharing regarding the computational tools and its usage. Lastly, I thank my family and friends who was a great source of motivation and inspiration. Thank you.

LIST OF FIGURES

corresponding amino acid residues are labelled in yellow. Atom colours: red = 0, white = H, grey = C and blue =N.

Figure 10: Ligplot 2D representations of the binding modes of 4-hydroxypandurratin A (4-HPA) on (a) 2FOMP7 , (b) 3U1J, (c) 3U1I_1, (d) 3U1I_2, NS2B-NS3 serine proteases. A 2D representation of ligand binding interaction model showing the ligand in purple, residues involved in hydrogen bonding with the ligand in brown with the corresponding hydrogen bond in dotted green line and residues involved in hydrophobic interactions with red spikes.

Figure 11: Ligplot 2D representations of the binding modes of alpinetin on (a) 2FOMP7 , (b) 3U1J, (c) 3U1I_1, (d) 3U1I_2, NS2B-NS3 serine proteases A 2D representation of ligand binding interaction model showing the ligand in purple, residues involved in hydrogen bonding with the ligand in brown with the corresponding hydrogen bond in dotted green line and residues involved in hydrophobic interactions with red spikes.

Figure 12: Ligplot 2D representations of the binding modes of pinocembrin on (a) 2FOMP7 , (b) 3U1J, (c) 3U1I_1, (d) 3U1I_2, NS2B-NS3 serine proteases. A 2D representation of ligand binding interaction model showing the ligand in purple, residues involved in hydrogen bonding with the ligand in brown with the corresponding hydrogen bond in dotted green line and residues involved in hydrophobic interactions with red spikes

Figure13: Ligplot 2D representations of the binding modes of pinostrobin on (a) 2FOMP7 , (b) 3U1J, (c) 3U1I_1, (d) 3U1I_2, NS2B-NS3 serine proteases. A 2D representation of ligand binding interaction model showing the ligand in purple, residues involved in hydrogen bonding with the ligand in brown with the corresponding hydrogen bond in dotted green line and residues involved in hydrophobic interactions with red spikes.

Figure 14: Ligplot 2D representations of the binding modes of cardamonin on (a) 2FOMP7 , (b) 3U1J, (c) 3U1I_1, (d) 3U1I_2, NS2B-NS3 serine proteases. A 2D representation of ligand binding interaction model showing the ligand in purple, residues involved in hydrogen bonding with the ligand in brown with the corresponding hydrogen bond in dotted green line and residues involved in hydrophobic interactions with red spikes.

LIST OF TABLES

LIST OF APPENDICES