Faculty of Resource Science and Technology

Pharmacophore Modelling Analysis and Synthesis of Vanillin Derivatives as Neuraminidase Inhibitors of Influenza Virus and 3CL^{pro} Inhibitors of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)

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DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Malaysia Sarawak. Except where due acknowledgements have been made, the work is that of the author alone. The thesis has not been accepted for any degree and is not concurrently submitted in candidature of any other degree.

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ABSTRACT

Influenza remain as global threat and public health concern over the years. For the past century, there were a number of significant influenza pandemics recorded, which were H1N1 Spanish flu (1918), the H2N2 Asian flu (1957), the H3N2 Hong Kong flu (1968), and the H1N1 swine flu (2009). Despite the fact that licensed drugs were available, antigenic drifts and shifts of influenza virus resulted in mutation of the virus, therefore the virus possess resistance towards available drugs. Thus, research in discovering more effective drugs or inhibitors against influenza virus is continuously necessary. Focus is given particularly to the discovery of neuraminidase inhibitors (NAIs) of influenza virus due to the important role of neuraminidase in facilitating the spread of virus. At the same time, severe acute respiratory syndrome coronavirus (SARS-CoV) also remain as a global threat due to the high rate of mutation and recombination. There were no licensed drugs available for SARS-CoV despite the numerous research being conducted, hence discovery of potent drugs or inhibitors for SARS-CoV become necessarily important. Focus is given particularly to the finding of $3CL^{pro}$ inhibitors of SARS-CoV for the importance of $3CL^{pro}$ in viral polyproteins processing and replicase complex activity controlling. Vanillin was reported in research for its biological activities, whereby the most important activity is the antiviral activity against NA. Research related to vanillin as NAIs are very potential and interesting, but considerably limited. Therefore, in this research, a list of Schiff base vanillin derivatives were evaluated and analysed for their potential as NAIs and $3CL^{pro}$ inhibitors *via* computer-aided drug design (CADD), particularly ligand-based pharmacophore modelling, virtual screening and structure-based molecular docking. As a result, 7 out of 9 vanillin derivatives, labelled as A1 to A7, were concluded to possess potential as both NAIs and $3CL^{pro}$ inhibitors. The 7 vanillin

derivatives successfully synthesized and characterized by Fourier Transform-Infrared spectroscopy (FT-IR).

Keywords: Coronavirus, docking, influenza, pharmacophore, vanillin

Analisis Pemodelan Farmakofor dan Pembuatan Derivatif Vanillin Sebagai Perencat Neuraminidase Virus Influenza dan Perencat 3CL^{pro} Koronavirus Sindrom Pernafasan Akut Teruk (SARS-CoV)

ABSTRAK

Influenza kekal sebagai ancaman global dan keprihatinan kesihatan dari awam untuk beberapa tahun. Pada abad yang lalu, terdapat beberapa pandemik influenza yang ketara direkodkan, termasuk Selesema Sepanyol H1N1 (1918), Selesema Asia H2N2 (1957), Selesema Hong Kong H3N2 (1968), dan Selesema babi H1N1 (2009). Walaupun ubat berdaftar tersedia, pergeseran antigenik virus influenza menyebabkan mutasi virus tersebut, oleh yang demikian virus tersebut mempunyai rintangan terhadap ubat yang ada. Oleh itu, penyelidikan dalam mencari ubat atau perencat yang lebih berkesan terhadap virus influenza adalah diperlukan secara berterusan. Fokus diberi khususnya kepada pencarian perencat neuraminidase (NAIs) virus influenza disebabkan oleh kepentingan peranan neuraminidase dalam membantu penyebaran virus. Pada masa yang sama, sindrom pernafasan akut teruk (SARS-CoV) juga kekal sebagai ancaman global disebabkan oleh kadar mutasi dan rekombinasi yang tinggi. Tiada ubat berdaftar tersedia untuk SARS-CoV walaupun banyak penyelidikan telah dijalankan, dengan itu pencarian ubat atau perencat yang berkesan untuk SARS-CoV menjadi amat penting. Fokus diberi khususnya kepada pencarian perencat 3CL^{pro} SARS-CoV disebabkan oleh kepentingan 3CL^{pro} dalam pemprosesan poliprotein viral dan pengawalan aktiviti kompleks replika. Vanillin telah dilaporkan dalam penyelidikan dari segi aktiviti biologikalnya, di mana aktiviti yang paling penting adalah aktiviti antivirus terhadap NA. Penyelidikan berkaitan dengan vanillin sebagai NAIs adalah berpotensi dan menarik, tetapi dikira terhad. Oleh itu, dalam penyelidikan ini, satu senarai derivatif vanillin Schiff base telah dinilai dan dianalisis dari segi potensi sebagai perencat NA dan 3CL^{pro} melalui reka bentuk ubat berbantukan

komputer (CADD), khususnya pemodelan farmakofor berasaskan ligan, saringan maya, dan dok molekul berasaskan struktur. Akibatnya, 7 daripada 9 derivatif vanillin, dilabel sebagai A1 ke A7, disimpulkan sebagai perencat NA dan 3CL^{pro} yang berpotensi. 7 derivatif vanillin tersebut berjaya disintesis dan dicirikan dengan Spektroskopi Inframerah-Transformasi Fourier.

Kata kunci: *Koronavirus, dok, influenza, farmakofor, vanillin*

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LIST OF ABBREVIATIONS

2D	2 Dimensional
$3CL^{pro}$	3C-like Protease
3D	3 Dimensional
CADD	Computer-Aided Drug Design
CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus Disease 2019
FT-IR	Fourier Transform-Infrared Spectroscopy
HA	Hemagglutinin
HBA	Hydrogen Bond Acceptor
HBD	Hydrogen Bond Donor
LBDD	Ligand-based Drug Design
NA	Neuraminidase
NAIs	Neuraminidase Inhibitors
NI	Negative Ionisable Area
PI	Positive Ionisable Area
PL^{pro}	Papain-like Protease
PM	Pharmacophore Model
SARS-CoV	Severe Acute Respiratory Syndrome
SBDD	Structure-based Drug Design
TLC	Thin Layer Chromatography
WHO	World Health Organization