UNIVERSITI TEKNOLOGI MARA

ALKALOIDS, STYRYL LACTONES, AND ACETOGENIN FROM THE ROOTS OF *Goniothalamus lanceolatus* Miq. AND THEIR ANTIPROLIFERATIVE ACTIVITY

NURULFAZLINA EDAYAH BINTI RASOL

Thesis submitted in fulfilment
of the requirement for degree of
Doctor of Philosophy
(Science)

Faculty of Applied Sciences

April 2020

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 other degree or qualification.

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

Name of Student	:	Nurulfazlina Edayah Binti Rasol
Student I.D No	:	2014696076
Programme	:	Doctor of Philosophy (Science) - AS 950
Faculty	:	Applied Sciences
Thesis Title	:	Alkaloids, Styryl lactones, and Acetogenin from the Roots of *Goniothalamus lanceolatus* Miq. and Their Antiproliferative Activity
Signature of Student	:	.....
Date	:	April 2020

ABSTRACT

Goniothalamus lanceolatus Miq., locally known as selukai or getimang is an ethnomedicinal plant indigenous to Sarawak. It is used traditionally to treat cancer. Phytochemical investigation on the roots of *G. lanceolatus* Miq. was conducted with the objective of comprehensively analyse the chemical constituents present in the roots of *G. lanceolatus*, especially the ones potentially active as antiproliferative agents. The roots of *G. lanceolatus* Miq. was extracted successively using hexane, dichloromethane, and methanol. The hexane and dichloromethane extracts showed antiproliferative activity against colorectal and lung cancer cell lines with percentage viability of cell less than 15%. Among the two extracts, the HPLC-DAD profile of the dichloromethane extract revealed the presence of more active UV components, and thus selected for further investigation. Mass-based dereplication strategy using in-house and online mass database system successfully identified 24 constituents comprising of styryl lactones, alkaloids, and acetogenins in the dichloromethane extract. Isolation and purification from the active antiproliferative fractions, M2 to M7 led to characterization of ten styryl lactones, five alkaloids, and one acetogenin, where six dereplicated compounds were verified. All the structures were elucidated using 1D- and 2D-NMR spectroscopy. Absolute configurations of the styryl lactones were established by ECD analysis through comparison of the experimental and theoretically calculated ECD spectra, while stereochemistry of the alkaloids were established using the single X-ray crystallography data. The known *S*-goniothalamin and parvistone D, are reported for the first time from *Goniothalamus* genus. Two new styryl lactones 5*R*,6*R*-5-hydroxy-6-styryltetrahydropyrane-2-one and goniolanceolatin E, and five new styryl lactone diastereomers, 5*R*,6*R*-5-acetylgoniothalamin, 5*R*,6*R*-5-hydroxygoniothalamin, goniofupyrone B, deoxygoniopypyrone B, and goniolanceolatin A, along with a known pyrano-pyrone, 1*S*,5*S*,7*R*,8*S*,3-*exo*,7-*endo*-(+)-8-*epi*-9-deoxygoniopypyrone are described. The 6*S*/1*S*- styryl lactones isolated in this work are new discoveries in *Goniothalamus* species. Biogenesis pathway of these 6*S*/1*S* styryl lactones are proposed. In addition, two new alkaloids, (-)-goniolanceolactam and 2-acetyl-3-amino-1,4-naphthoquinone were also identified along with the known alkaloids, 2-acetyl-3-amino-5-hydroxy-1,4-naphthoquinone, cleistopholine and liriodenine, and the acetogenin, annonacin. *S*-Goniothalamin, (-)-goniolanceolactam and annonacin exhibited potential antiproliferative activity against all tested cancer cell lines with the IC_{50} values of less than 10.0 μM. The alkaloids, 2-acetyl-3-amino-1,4-naphthoquinone and 2-acetyl-3-amino-5-hydroxy-1,4-naphthoquinone, as well as liriodenine demonstrated antiproliferative against HCT116, A549, and NCI-H23 cell lines with IC_{50} values ranging between 4.5 to 10.3 μM. 5*R*,6*R*-5-hydroxygoniothalamin showed selective activity against lung cancer cell lines, A549, and NCI-H1299, with the IC_{50} values of 8.0 and 8.9 μM, respectively. Other styryl lactones exhibited only weak activity. All isolated compounds were non-toxic to normal cell lines except for annonacin.

ACKNOWLEDGEMENT

بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

"In the name of Allah, The Most Gracious, and The Most Merciful"

Alhamdulillah, all praises to Allah and salam to our Prophet Muhammad s.a.w, Who bestowed me the strength and knowledge, and His blessing to embark and complete this Ph.D. journey.

Foremost, I wish to express my deepest gratitude to my supervisor, Professor Dr. Nor Hadiani Ismail, for giving me the opportunity to do the research and providing me a constant motivation, guidance, advice and immense knowledge. Her invaluable help of constructive comments and suggestions throughout the time of research and writing of the thesis have contributed to the success of this journey. Without her guidance, this study would not have been possible. It was a great privilege and honor to work under her supervision. My appreciation also goes to my co-supervisor, Professor Dr. Fasihuddin Badruddin Ahmad for his support, idea, and knowledge regarding the scope of my study.

Appreciation is dedicated to my mother, Suhaiyati binti Baki, for her continuous prayers and support throughout completing the study. Thank you for allowing me to make my dream come true and letting me be an independent person. Indeed, this achievement is a gift that I made special for herself. My gratitude also goes to my beloved siblings; Ain, Amirrull and Afiqah, and my lovely nephew and niece; Umar and Mardhiah for cheering me along the journey.

Special thanks go to all of the staffs and fellows at Atta-ur-Rahman Institute for Natural Product Discovery (AuRIns) for their opinions and knowledge sharing which assists me to open my mind on other perspective area when it comes to building up my career. Also, my heartfelt thanks go to our collaborator Dr. Dhaval Patel (WATERS Corporation), for assisting me in the dereplication study using NPAS UNIFI software. It was a meaningful experience to learn about the advanced technique for handling high-end instrument of LCMS in the identification of natural product during my research.

To all my lab mates in Chemical Marker Laboratory; Najah, Halimatun, Noraini, Vicky, Fauziah, Ann, Sarwana, Nadhirah, and all my friends at AuRIns, thank you for your ideas and being my supporter along this journey.

Last but not least, I would like to extend my gratitude to the Universiti Teknologi Mara and Ministry of Higher Education Malaysia for awarding me the 'Program Ahli Sains dan Penyelidikan Muda' (PSPM) scholarship and the supported grant FRGS/1/2016/STG01/UiTM/01/1 for the five years of my study. May Allah bless all of you, who are directly and indirectly involved in my Ph.D. journey.

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