UNIVERSITI TEKNOLOGI MARA

STYRYLLACTONES AND BIS-STYRYLLACTONES FROM THE STEMBARK OF *Goniothalamus lanceolatus* Miq. AND THEIR CYTOTOXIC ACTIVITY

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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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ABSTRACT

In the search for new bioactive compounds from plant of Malaysia, *Goniothalamus lanceolatus* Miq., an indigenous plant from Sarawak was investigated. This plant is used by the natives as a traditional medicine to treat various illnesses such as cancer, fever and skin diseases. Preliminary cytotoxic screening on the crude extracts against lung and colorectal cancer cell lines showed promising results from all parts with percentage of cell viability of less than 20% at concentration of 100 µg/mL. In view of the interesting ethno-medicinal and biological properties mentioned above, a detailed phytochemical study was conducted to provide scientific data for this plant. This study reported the isolation, structure elucidation, cytotoxic evaluation of pure compounds, and the plausible biogenetic route on the isolated compounds. The isolation and purification of compounds were accomplished by utilizing modern chromatographic techniques such as MPLC, HPLC and recycling HPLC. All structures were established through extensive 1D and 2D NMR analysis, whilst the absolute configurations were established by electronic circular dichroism data (ECD), supported by NOESY experiments and data comparison with literature values. Twelve styryllactones were isolated and identified as 6*S*-goniothalamin **1**, (6*S*,7*S*,8*S*)-goniodiol **2**, (6*S*,7*R*,8*S*)-8-chlorogoniodiol **3**, (6*S*,7*S*,8*S*)-goniodiol-7-monoacetate **4**, (6*S*,7*S*,8*S*)-goniodiol-8-monoacetate **5**, (6*S*,7*S*,8*S*)-(-)-*ent*-isogoniothalamin oxide **6**, (1*S*,5*S*,7*R*,8*R*)-3-*endo*, 7-*endo*-(-)-9-deoxygoniopypyrone **7**, (1*S*,5*S*,7*S*,8*R*)-3-*exo*, 7-*exo*-(+)-deoxygoniopypyrone B **8**, (1*S*,5*S*,7*R*,8*S*)-3-*endo*, 7-*endo*-(-)-8-*epi*-9-deoxygoniopypyrone **9**, (1*S*,5*S*,7*R*,8*S*)-3-*exo*, 7-*endo*-(+)-8-*epi*-9-deoxygoniopypyrone **10**, (1*S*,5*S*,7*R*,8*S*)-3-*endo*, 7-*endo*-(-)-8-*epi*-9-deoxygoniopypyrone acetate **11** and (1*S*,5*S*,7*S*,8*S*)-(-)-goniofupyrone B **12**. Interestingly, the styryllactones isolated from this plant possessed an α,β-unsaturated δ-lactone moiety with a 6*S* configuration, and δ-lactone moiety with a 1*S* configuration, which were a rare occurrence from nature. With the exception of **10**, all compounds are reported for the first time from the genus *Goniothalamus*. Seven new bis-styryllactones, named goniolanceolatins A-H **13-19** were also described. These goniolanceolatins comprised of either a pyranopyrone unit and a styrylpyrone unit, or two styrylpyrone units, which are linked by an ether bridge at positions C-8/C-8', C-8/C-7', or C-7/C-8'. The new compounds **13-19** were evaluated for their cytotoxicity against series of human lung and colorectal cancer cell lines, which revealed a promising cytotoxicity for **14** and **16** with IC_{50} values ranging from 2.2 to 7.8 µM, while sparing the human non-cancerous lung and colorectal cells. Docking studies of the active compounds **14** and **16** showed that they were able to bind with EGFR tyrosine kinase and cyclin-dependent kinase 2 through hydrogen bonding interactions with the important amino acids such as Lys721, Met769, Asn818, Arg157, Ile10, and Glu12.

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