UNIVERSITI PUTRA MALAYSIA

SYNTHESIS OF γ-LACTONE AND δ-LACTONE ANALOGUES OF ATRANONE F VIA RADICAL CYCLISATION APPROACH

NAWWAR FATHIAH BINTI MOHD FAUZI

FS 2013 26

SYNTHESIS OF *γ*-LACTONE AND *δ*-LACTONE ANALOGUES OF ATRANONE F VIA RADICAL CYCLISATION APPROACH

NAWWAR FATHIAH BINTI MOHD FAUZI

MASTER OF SCIENCE
UNIVERSITI PUTRA MALAYSIA

2013

SYNTHESIS OF γ-LACTONE AND δ-LACTONE ANALOGUES OF ATRANONE F VIA RADICAL CYCLISATION APPROACH

By

NAWWAR FATHIAH BINTI MOHD FAUZI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Master of Science

May 2013

COPYRIGHT

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science.

SYNTHESIS OF *γ*-LACTONE AND *δ*-LACTONE ANALOGUES OF ATRANONE F VIA RADICAL CYCLISATION APPROACH

By

NAWWAR FATHIAH BINTI MOHD FAUZI

May 2013

Chairperson : Siti Mariam Mohd Nor, PhD
Faculty : Science

Radical cyclisation is a method have been reported to successfully cyclise either C=C (alkene) or alkyne (C≡C) in the attempt of making heterocyclic compounds. New approach has been done in this research where nitrile group (C≡N) proved to cyclise the desired lactones. Atranone F which is a natural product that was isolated from toxigenic fungus named *Stachybotrys chartarum* was chosen for the synthesis of lactones analogues in this research. Atranone F contains both 5-membered ring (*γ*) and 6-membered ring (*δ*) lactones which have many applications in medicines and agricultures. Analogue structures of both *γ*- and *δ*-lactones were prepared from their corresponding cyanohydrins *via* 2 steps of reactions; 1) acylation and 2) radical cyclisation. For the acylation reaction, three *α*-cyanobromoesters; 1-cyanoethyl 2-bromopropanoate (**75e**), 1-cyanocyclohexyl 2-bromopropanoate (**75f**) and 1-cyanoethyl 2-bromoethanoate (**75g**) together with four *β*-cyanobromoesters; 1-cyanopropan-2-yl 2-bromopropanoate (**77e**),

1-cyano-2-methylpropan-2-yl 2-bromopropanoate (**77f**), 1-cyanopropan-2-yl 2-bromoethanoate (**77g**) and 1-cyano-2-methylpropan-2-yl 2-bromoethanoate (**77h**) have been successfully synthesized. In total, five new esters have been produced including (**75f**), (**75g**), (**77e**), (**77f**) and (**77g**). All esters products were cyclised to lactones using radical chemistry under the treatment with tris(trimethylsilyl)silane (TTMSH) and azobisisobutyronitrile (AIBN) in toluene. Three analogue structures of γ-lactone; 4-amino-3,5-dimethylfuran-2-one (**78e**), 4-amino-5-cyclohexyl-3-methyl-3-ene-2-one (**78f**, new compound) and 4-imino-5-methylfuran-2-one (**78g**, new compound) were obtained. Meanwhile, four analogue of δ-lactone have been synthesized (all new compounds); 4-imino-5-hydro-3,6-dimethylpyran-2-one (**79e**), 4-amino-5-hydro-3,6,6-trimethylpyran-2-one (**79f**), 4-imino-3,5-dihydro-6-methylpyran-2-one (**79g**) and 4-imino-3,5-dihydro-6,6-dimethylpyran-2-one (**79h**). Two types of biological activities have been carried out on the cyanobromoesters and the lactones produced in order to determine their activities; 1) Ichthyotoxic test and 2) Cytotoxic assays. Esters **75e**, **75f**, **75g** and **77g** showed strong ichthyotoxic activity with TL_M values of 6.26, 4.00, 2.85 and 4.00 ppm respectively. For the cytotoxic test, esters **75f**, **75g**, **77e**, **77g**, **77h** and lactone **79h** showed good to moderate activity against HL60 cell lines (% viability: 7.1-40.1)

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

SINTESIS ANALOG *γ*-LAKTON DAN *δ*-LAKTON DARI ATRANONE F MELALUI PENDEKATAN PENSIKLIKAN RADIKAL

Oleh

NAWWAR FATHIAH BINTI MOHD FAUZI

Mei 2013

Pengerusi : Siti Mariam Mohd Nor, PhD

Fakulti : Sains

Pensiklikan radikal adalah kaedah yang telah dilaporkan berjaya mengsiklik sama ada C=C (alkena) atau alkuna (C≡C) dalam usaha untuk membuat sebatian heterosiklik. Pendekatan baru telah dilakukan dalam kajian ini di mana kumpulan nitril (C≡N) terbukti membentuk lakton yang dikehendaki. Atranon F merupakan produk sebatian semulajadi yang telah diasingkan daripada kulat toksigenik yang dinamakan *Stachybotrys chartarum* telah dipilih untuk mensintesis analog lakton di dalam kajian ini. Atranon F mengandungi kedua-dua cincin 5-ahli: (*γ*) dan cincin 6-ahli: (*δ*) lakton yang mempunyai banyak aplikasi dalam ubat-ubatan dan industri pertanian. Struktur analog kedua-dua *γ*- dan *δ*-lakton telah disediakan daripada sianohidrin masing-masing melalui 2 langkah tindak balas iaitu; 1) pengasilan dan 2) pengsiklikan radikal. Untuk tindak balas pengasilan, tiga *α*-sianobromoester; 1-sianoetil 2-bromopropanoat (**75e**), 1-

sianosikloheksil 2-bromopropanoat (**75f**) dan 1-sianoetil 2-bromoetanoat (**75g**) bersama empat *β*-sianobromoester; 1-sianopropan-2-il 2-bromopropanoat (**77e**), 1-siano-2-metilpropan-2-il 2-bromopropanoat (**77f**), 1-sianopropan-2-il 2-bromoetanoat (**77g**) dan 1-siano-2-metilpropan-2-il 2-bromoetanoat (**77h**) telah berjaya disintesis. Secara keseluruhan, lima ester baru telah berjaya dihasilkan termasuk (**75f**), (**75g**), (**77e**), (**77f**) dan (**77g**). Semua produk ester telah digunakan untuk membentuk lakton melalui kaedah kimia radikal dengan tris(trimetilsilil)silan (TTMSH) dan azobisisobutironitril (AIBN) dalam toluena. Tiga struktur analog *γ*-lakton; 4-amino-3,5-dimetilfuran-2-on (**78e**), 4-amino-5-sikloheksil-3-metilfuran-2-on (**78f**, sebatian baru) dan 4-imino-5-metilfuran-2-on (**78g**, sebatian baru) telah diperolehi. Manakala, empat analog *δ*-lakton telah disintesis (semua sebatian baru) 4-imino-5-hidro-3,6-dimetilpiran-2-on (**79e**), 4-amino-5-hidro-3,6,6-trimetilpiran-2-on (**79f**), 4-imino-3,5-dihidro-6-metilpiran-2-on (**79g**) dan 4-imino-3,5-dihidro-6,6-dimetilpiran-2-on (**79h**). Dua jenis aktiviti biologi yang telah dijalankan ke atas sianobromoester dan lakton yang terhasil untuk menentukan keaktifan sebatian-sebatian tersebut; 1) ujian ichtiotoksik dan 2) ujian sitotoksik. Ester **75e**, **75f**, **75g** dan **77g** telah menunjukkan aktiviti ichtiotoksik yang tinggi dengan nilai TL_M masing-masing 6.26, 4.00, 2.85 dan 4.00 ppm. Untuk ujian sitotoksik, ester **75f**, **75g**, **77e**, **77g**, **77h** dan lakton **79h** telah menunjukkan aktiviti yang baik atau sederhana terhadap sel kanser HL60 (% keberkesanan: 7.1-40.1).

ACKNOWLEDGEMENTS

Bismillah. Ar-Rahman, Ar-Rahim. Alhamdulillah, all praises to Allah S.W.T for the strength, the courage, the time, the opportunity and the chance to go through everything while finishing this research. There are so many obstacles to go through but somehow, with His guidance I managed to overcome everything.

The most supportive, cool and motivated supervisor, Dr. Siti Mariam binti Mohd Nor, thank you so much for your time, concern and guidance throughout the research. All the knowledge will forever be in mind and InsyaAllah, I will use it again and again in the future. To my co-supervisor, Dr. Intan Safinar binti Ismail, thank you so much for the guide, the time and concern throughout the research.

To my parents, Haji Mohd Fauzi bin Haji Abdul Wahab and Hajah Norizan binti Haji Jaafar, both are the coolest, bestest and most understanding parents in the universe! Thank you is not enough to describe how much I appreciate all of the sacrifices and encouragements that have been the strength for me all of these times. Thank you so much Buyah and Ummi. Not to forget, my dearest siblings: Nawwar Aqilah, Nawwar Syahirah, Hassan Din, Muhammad Luqman and Isyraf Imran. I love you guys so much and you guys rock!

To my best friends, Sheda, Ana, Yuyu, Anis, Mieza, Ed and Lily thank you for being there for me whenever I needed u guys the most. Thank you for being the shoulder to cry on and thank you for listening to me for all of these times. To my labmates, Kak Ya and Dila, thanks to both of you for the help and the best buddies to me in the lab!

Not to forget, I would like to thank Universiti Putra Malaysia for the financial support that kept my stomach and my fuel full! Also, to the government for their excellent idea on the "MyBrain15" program that supports my tuition fees for all of these semesters.

Last but not least, I would like to thank my dear Muhammad Naqib bin Mohd Ramli for the love, care, support and motivations. You have been one of the reasons for me to finish this research and the person who always reminded me to always keep on track. Thank you so much dear. To those I've forgot to mention your name here, you know who you are and thank you!!!!! Alhamdulillah!! Finally, I graduated!!!

I certify that a Thesis Examination Committee has met on 28th May 2013 to conduct the final examination of **Nawwar Fathiah Binti Mohd Fauzi** on her thesis entitled "**Synthesis of *γ*-Lactone and *δ*-Lactone Analogues of Atranone F *via* Radical Cyclisation Approach**" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the **Master of Science**.

Members of the Thesis Examination Committee were as follows:

Mohd Aspollah bin Hj Md Mohd Sukari, PhD
Professor
Faculty of Science
Universiti Putra Malaysia
(Chairman)

Emilia binti Abd Malek, PhD
Senior Lecturer
Faculty of Science
Universiti Putra Malaysia
(Internal Examiner)

Khozirah binti Shaari, PhD
Professor
Faculty of Science
Universiti Putra Malaysia
(Internal Examiner)

Kartini binti Ahmad, PhD
Senior Lecturer
Faculty of Science and Mathematic
Universiti Pendidikan Sultan Idris
Perak, Malaysia
(External Examiner)

_____
NORITAH OMAR, PhD
Assoc. Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 2 August 2013

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

Siti Mariam Mohd Nor, PhD
Senior Lecturer
Faculty of Science
Universiti Putra Malaysia
(Chairman)

Intan Safinar Ismail, PhD
Senior Lecturer
Faculty of Science
Universiti Putra Malaysia
(Member)

_____
BUJANG BIN KIM HUAT, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

DECLARATION

I declare that the thesis is my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.

_____

NAWWAR FATHIAH BINTI MOHD FAUZI

Date: 28th May 2012

TABLE OF CONTENTS