UNIVERSITI PUTRA MALAYSIA

SYNTHESIS OF 2-ARYLDIHYDROBENZOFURAN NEOLIGNANS AND 2-ARYLBENZOFURAN NEOLIGNANS AND THEIR LARVICIDAL ACTIVITIES

SITI FADILAH JUHAN

FS 2018 33

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By

SITI FADILAH JUHAN

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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Chair: Siti Mariam Mohd Nor, PhD
Faculty: Science

2-Aryldihydrobenzofuran neolignans (tomentosanan A, ficusal, tomentosanan B) and 2-arylbenzofuran neolignans (zanthocapensole, zanthocapensate) have been isolated from the plants were synthesized and evaluated for their larvicidal activities against *Crocidolimia binotalis*. Two Heck coupling methods have been developed are using an activated C-I bond of iodovanillin or non-activated C-H bond of vanillin and alkene of cinnamic acid derivatives or methyl cinnamate derivatives. Heck coupling reaction between iodovanillin or vanillin with a series of cinnamic acid derivatives lead to the formation of eleven new compounds and four known compounds are 2-aryldihydrobenzofuran neolignan, 3-arylbenzofuran neolignans, 2-arylbenzofuran neolignans and stilbenes. The reaction involves a series of methyl cinnamate derivatives has resulted in the formation of five new compounds and three known compounds are lignans, neolignans, 2,3-diarylbenzofuran neolignan and coumarins. Both methods have been developed then have applied to the synthesis of five natural products of 2-arydihydrobenzofuran neolignans and 2-arylbenzofuran neolignans. All the targeted dihydrobenzofuran neolignans have synthesized as a single enantiomer form namely (+)-tomentosanan A, (+)-ficusal and (+)-tomentosanan B. Two routes have utilized to synthesize zanthocapensole and zanthocapensate and only their derivatives have been obtained from both routes. The selected compounds have been obtained from the Heck methods development and syntheses part have tested for larvicidal activity by using *Crocidolomia binotalis* larvae and azadirachtin as the commercial standard (LD_{50} = 2.818). The results indicate some of the compounds have significant activity such as dihydrobenzofuran neolignan, benzofuran neolignans, lignans, neolignans, stilbene and coumarin. Among all active compounds, (2*E*,3*E*)-dimethyl 2,3-bis(4-hydroxy-3,5-dimethoxybenzylidene)succinate (lignan) and methyl-3-(4-hydroxy-3-methoxyphenyl)-2-{2-methoxy-4[(*E*)-3-methoxy-3-oxo-prop-1-enyl]phenoxy}-prop-2-enoate (neolignan) have showed the strongest activity with LD_{50}=1.678 mg/L and LD_{50}=2.218 mg/L, respectively.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

SINTESIS BAGI 2-ARILDIHIDROBENZOFURAN NEOLIGNAN DAN 2-ARILBENZOFURAN NEOLIGNAN DAN AKTIVITI LARVASIDA MEREKA

Oleh

SITI FADILAH JUHAN

Januari 2018

Pengerusi: Siti Mariam Mohd Nor, PhD
Fakulti: Sains

2-Arildihidrobenzofuran neolignan (tomentosanan A, fikusal, tomentosanan B) dan 2-arilbenzofuran neolignan (zantokapensol, zantokapensat) yang telah diasingkan daripada tumbuh-tumbuhan telah disintesis dan dianalisis untuk aktiviti larvasida mereka terhadap Crocidolomia binotalis. Dua kaedah penggandingan Heck telah dibangunkan menggunakan ikatan aktif C-I yang diaktifkan daripada iodivanillin atau ikatan tidak aktif C-H daripada vanillin dan alkena dari terbitan asid sinamik atau terbitan metil sinamat. Tindak balas penggandingan Heck antara iodovanillin atau vanillin dengan siri terbitan asid sinamik membawa kepada pembentukan sebelas sebatian baharu dan empat sebatian diketahui iaitu 2-arildihidrobenzofuran neolignan, neolignan 3-arilbenzofuran, 2-arilbenzofuran neolignan dan stilben. Tindak balas yang melibatkan siri terbitan metil sinamat telah menghasilkan pembentukan lima sebation baharu dan tiga sebatian diketahui iaitu lignan, neolignan, 2,3-diarilbenzofuran neolignan dan kumarin. Kedua-dua kaedah yang telah dibangunkan kemudiannya telah digunakan dalam sintesis lima hasil semula jadi 2-arildihidrobenzofuran neolignan dan 2-arilbenzofuran neolignan. Semua sebatian sasaran dihidrobenzofuran neolignan telah disintesis sebagai enantiomer tunggal iaitu (+)-tomentosanan A, (+)-fikusal dan (+)-tomentosanan B. Dua laluan yang telah digunakan untuk mensintesis zantokapensol dan zantokapensat dan hanya terbitan mereka diperolehi daripada kedua-dua laluan. Sebatian terpilih yang telah diperolehi daripada pembangunan kaedah Heck dan bahagian sintesis telah diuji untuk aktiviti larvasida dengan menggunakan larva Crocidolomia binotalis dan azadiraktin sebagai piawai komersial (LD50 = 2.818). Hasilnya menunjukkan bahawa beberapa sebatian mempunyai aktiviti yang penting seperti neolignan dihidrobenzofuran, neolignan benzofuran, lignan, neolignan, stilben dan kumarin. Di antara semua sebatian aktif, (2E,3E)-dimethyl 2,3-bis(4-hydroxy-3,5-dimethoxybenzylidene)succinate (lignan) dan methyl-3-(4-hydroxy-3-methoxyphenyl)-2-{2-methoxy-4[(E)-3-methoxy-3-oxo-prop-1-enyl]phenoxy}-prop-2-enoate(neolignan) telah menunjukkan aktiviti terkuat dengan masing-masing LD50 = 1.678 mg/L dan LD50 = 2.218 mg/L.

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I certify that a Thesis Examination Committee has met on 30 January 2018 to conduct the final examination of Siti Fadilah binti Juhan on her thesis entitled "Synthesis of 2-Aryldihydrobenzofuran Neolignans and 2-Arylbenzofuran Neolignans and their Larvicidal Activities" 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 Doctor of Philosophy.

Members of the Thesis Examination Committee were as follows:

Tan Yen Ping, PhD
Senior Lecturer
Faculty of Science
Universiti Putra Malaysia
(Chairman)

Emilia binti Abd Malek, PhD
Senior Lecturer
Faculty of Science
Universiti Putra Malaysia
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Gwendoline Ee Cheng Lian, PhD
Professor
Faculty of Science
Universiti Putra Malaysia
(Internal Examiner)

Tirayut Vilaivan, PhD
Professor
Chulalongkorn University
Thailand
(External Examiner)

NOR AINI AB. SHUKOR, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 26 April 2018

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

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

Nur Kartinee Binti Kassim, PhD
Senior Lecturer
Faculty of Science
Universiti Putra Malaysia
(Member)

Siti Munirah Binti Mohd Faudzi, PhD
Senior Lecturer
Faculty of Science
Universiti Putra Malaysia
(Member)

Mohd Shukri Bin Mat Ali, PhD
Deputy Director and Principal Research Officer
Malaysian Agricultural Research and Development Institute
Malaysia
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LIST OF ABBREVIATIONS

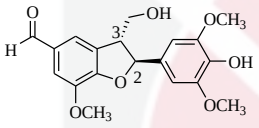
%	Percentage
α	Alpha
β	Beta
λ	Wavelength
br	Broad
δ	Chemical shift in ppm
c	Concentration
^{13}C	Carbon-13
COSY	Correlation Spectroscopy
CD	Circular dichrosim
d	Doublet
dd	Double of dublet
dt	Double of triplet
DI-MS	Direct Injection-Mass Spectrometry
EIMS	Electron Ionization Mass Spectrometry
EC_{50}	Half maximal effective concentration
FT-IR	Fourier Transform-Infrared Spectroscopy
GC-MS	Gas Chromatography-Mass Spectrometry
h	hour
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple Quantum Coherence
^{1}H	Proton-1
IR	Infrared
IC_{50}	Half maximal inhibitory concentration
LD_{50}	Lethal dose
LCMS	Liquid chromatography mass spectrometry
m	Multiplet
m/z	Mass per charge
M^+	Molecular ion
mp	Melting point
MS	Mass spectroscopy
NMR	Nuclear Magnetic Resonance
NEOSY	Nuclear Overhauser Effect Spectroscopy
q	Quartet
RT	Room temperature
R_f	Retention factor
s	Singlet
t	Triplet
TLC	Thin Layer Chromatography
QTOF	Quadrupole Time Of Flight
UV	Ultraviolet
UATR	Universal Attenuated Total Reflection
Hela	Cervical cancer
HepG2	Liver hepatocelular carcinoma
A375-S2	Human melanoma cells (skin cancer)
HT1080	Fibrosarcoma cell (tumor cancer)
HL60	Human promyelocytic leukemia cells

CHAPTER 1

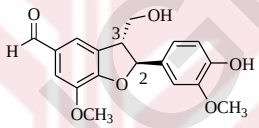
INTRODUCTION

1.1 Dihydrobenzofuran Neolignans and Benzofuran Neolignans

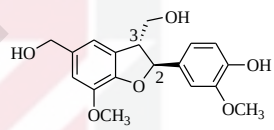
Dihydrobenzofuran and benzofuran neolignans are common compounds that are found in plants and appeared as a promising compound to study due to its potential bioactivity. Some of their activities are antimicrobial (Kirilmis *et al*., 2007), anti-inflammatory (Hwang *et al*., 2010; Tan *et al*., 2010; Lee *et al*., 2012), HIV integrase inhibitor (Abd-Elazem *et al*., 2002), antioxidant and anticancer (Rakotondramanana *et al*., 2007). Other reported biological activity of these compounds are insecticidal (González-Coloma *et al*., 2002), anti-complement (Luo *et al*., 2013), pesticidal (Cutillo *et al*., 2003) and antileishmanial (Miert *et al*., 2005). Five natural product compounds were studied in this research where three of them are dihydrobenzofuran neolignans, (-)-tomentosanan A (2*S*, 3*R*) (**1**), (-)-ficusal (2*S*, 3*R*) (**2**) and (-)-tomentosanan B (2*S*, 3*R*) (**3**) while the other two are benzofuran neolignans, zanthocapensole (**4**) and zanthocapensate (**5**) (**Figure 1.1**).



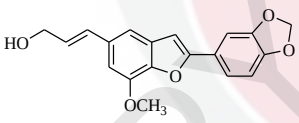
(-)-Tomentosanan A (2*S*, 3*R*) (**1**)



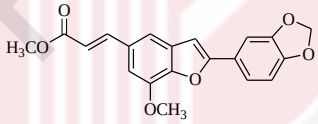
(-)-Ficusal (2*S*, 3*R*) (**2**)



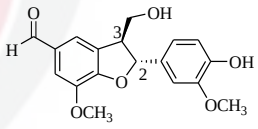
(-)-Tomentosanan B (2*S*, 3*R*) (**3**)



Zanthocapensole (**4**)



Zanthocapensate (**5**)



(+)-Ficusal (2*R*, 3*S*) (**6**)

Figure 1.1: Structure of targeted neolignans

2-Aryldihydrobenzofuran neolignans, (-)-tomentosanan A (**1**), (-)-ficusal (**2**) and (-)-tomentosanan B (**3**) were isolated from the seed of *Prunus tomentosa* (Liu *et al*., 2014). Compound **2** was reported to be isolated from several species such as leaves and stems of *Manglietia insignis* (Shang *et al*., 2013), *Acanthopanax senticosus* (Li *et al*., 2015) and the seed of *Crataegus pinnatifida* (Huang *et al*., 2015). Both **1** and **3** are in colorless oil meanwhile compound **2** was isolated as pale yellow oil. Compounds **1** and **3** were identified as new neolignans in 2014 by Liu and their co-worker. In contrast, its analog (+)-ficusal (2*R*, 3*S*) (**6**) was isolated from leaves of *Ficus microcarpa* L.f. (Moraceae) (Li and Kuo 2000), fruits of *Vitex agnus-castus* L (Chen *et al*., 2011), and *Metasequoia glyptostroboides* Hu *e*t Cheng (Taxodiaceae) (Zeng *et al*., 2013).

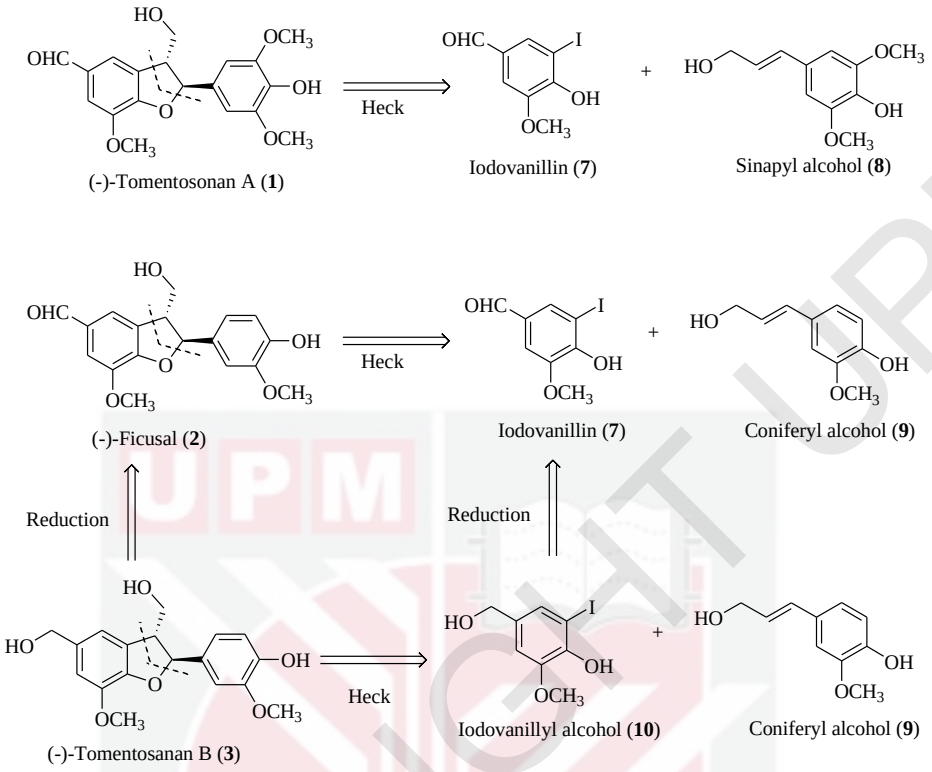
Compounds **1-3** shown strong antioxidant activity when tested against DPPH and ABTs radical. The compound also displayed strong anti-inflammatory activity on nitric oxide

(NO) production in murine microlia BV-2 with compound **2** gives the stronger activity (IC_{50}= 4.8 µM) compared to the standard drug used, minocycline (IC_{50}= 19.7 µM) (Liu *et al*., 2014). Some other activity that has been reported for compound **2** were antitumor when tested upon human tumor cell lines of HL-60, SMMC-7721, MCF-7 and SW480 (Shang *et al*., 2013), tumor necrosis factor α (TNF-α) production by the PLS-induced murine macrophage cell line RAW264.7 (Huang *et al*., 2015) and *in vitro* inhibitory activities against protein tyrosine phosphatase 1B(PTP1B), human vaccina H1 related protein (VHR) and protein phosphatase 1 (PP1) (Li *et al*., 2015). In addition, the enantiomer of **1** (compound **6**) found significantly inhibited MDA-MB-231 cells at 50 µM by 69.3% (Chung *et al*., 2012).

Zanthocapensole (**4**) and zanthocapensate (**5**) are 2-arylbenzofuran neolignans that were isolated from methanol extract of African *Zanthoxylum capense* root which have been ethnopharmacologically used to treat tuberculosis. They are analogs with the same appearance as white amorphous solid and have a good antibacterial activity against gram-positive (*Staphylococcus aureus* and *Enterococcus aureus*) and gram-negative (*Pseudomonas aeruginosa* and *Escherichia coli*). Compounds **4** and **5** were tested on human THP-1 macrophages and showed cytotoxicity at 72.3 µg/mol and 52.1 µg/mol, respectively (Luo *et al*., 2013). Both neolignans also have been tested on HCT116 cells and exhibited significant cytotoxicity activity.Compound **5** literally induced the highest percentage of apoptosis after 24 hours exposure at 20 M (Mansoor *et al*., 2013).

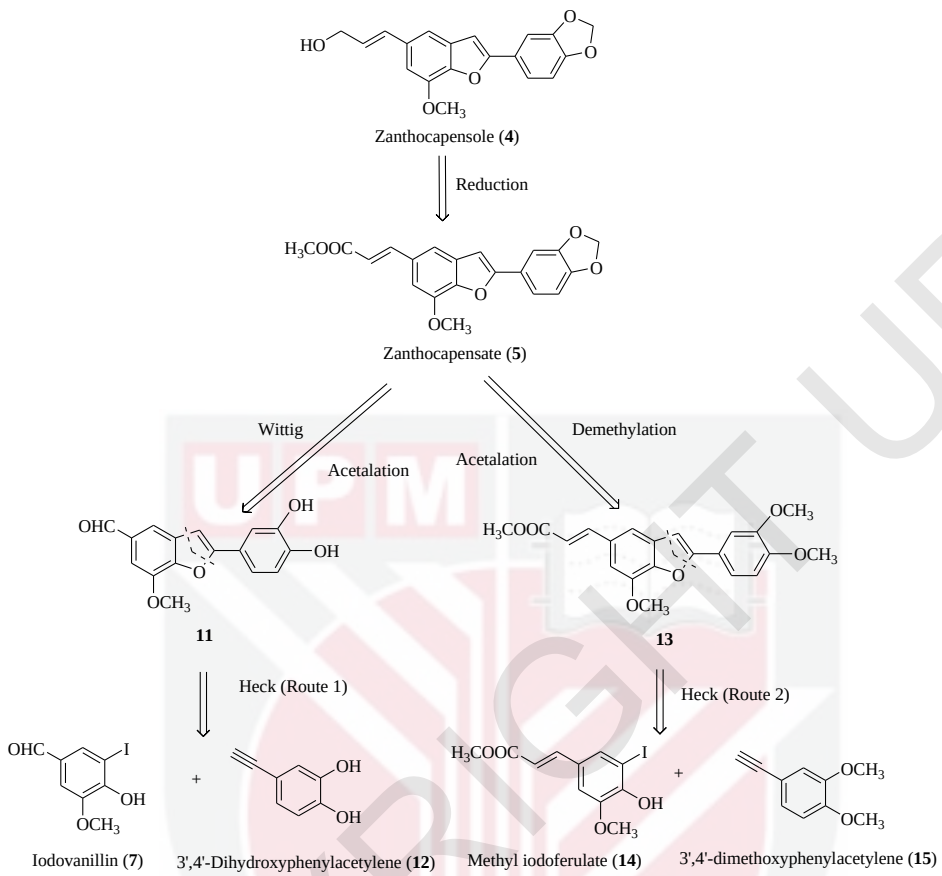
1.2 Retrosynthetic Analysis of Targeted Compounds

The retrosynthetic analysis showed that (-)-tomentosanan A (**1**) can be produced by coupling reaction between iodovanillin (**7**) and sinapyl alcohol (**8**) (**Scheme 1.1**). Meanwhile, the synthesis of (-)-ficusal (**2**) can be achieved by coupling between iodovanillin (**7**) with coniferyl alcohol (**9**) and further reduction resulted in production of (-)-tomentosanan B (**3**). The (-)-tomentosanan B (**3**) could as well be directly synthesized by coupling between iodovanilyl alcohol (**10**) with coniferyl alcohol (**9**).



Scheme 1.1: Retrosynthetic analysis of (-)-tomentosanan A, (-)-ficusal and (-)-tomentosanan B

The retrosynthetic analysis of zanthocapensole (**4**) and zanthocapensate (**5**) were proposed in two routes (**Scheme 1.2**). The first route is proposed by coupling of 3',4'-dihydroxyphenylacetelyne (**12**) with iodovanillin (**7**) to produce an intermediate of **11** before proceeding with acetalation and Wittig reactions to get zanthocapensate (**5**) and further reduce to obtain zanthocapensole (**4**). The second route was proposed by the reaction between methyl iodoferulate (**14**) and 3,4-dimethoxyphenylacetylene (**15**) to produce an intermediate of **13**, in which further demethylation and acetalation results in the synthesis of zanthocapensate (**5**).



Scheme 1.2: Retrosynthetic analysis of zanthocapensole and zanthocapensate

1.3 The Pesticidal/Insecticidal Activity of Lignans and Neolignans

Pesticides are essential to control pest and disease infestations in crop plantation or food production. However, resistance development of plant pathogens to conventional pesticide along with toxic effects initiated researcher's interest towards developing insecticide from natural origin. Pesticide mode of action is by targeting the systems or enzymes in the pest. The targeted enzymes or system might be identical or similar to the systems or enzymes in human beings thus, they pose risks to the human health and environment. Plant-derived compounds are believed to exert low-toxicity and high mortality target of insect population which would not cause ecosystem disturbance (Emberger, 2015). Various phytochemicals have been investigated for insecticidal, insect repellent and insect antifeedant activity such as diterpene ryanodanes and isoryanodanes from *Persea indica* (Lauraceae), lignans from *Machilus japonica* (Lauraceae) and diterpenoid alkaloids from *Delphinium cardiopetalum* (Ranunculaceae) (González-Coloma *et al*., 2002).

Crocidolomia binotalis (croci) is one of the agricultural pests that has been threatening crops plantation. Croci also known as cabbage head caterpillar have a life cycle completed depending on temperature and humidity approximately 28 days at a temperature of 26-33℃ or 30-41 days at lower temperature 16-22℃. They are almost exclusively found in hot humid highland tropics and constitute a more serious pest problem during the dry season since heavy rains can drown small larvae. The percentage of hatching could reach until 92% in each of their life cycles. If suitable control is not undertaken, especially in the dry season, the yield loss caused by this pest may reach up to 100% (Sastrosiswojo and Setiawati, 1992).

Croci is a serious pest in the highland area, especially for cabbage in Indonesia. The study conducted in Indonesia showed that hand-picking leaves with the egg masses and larvae were preferred to avoid the chemical spray (Shepard and Schellhorn 1994). However, this method can only be applied in a small plantation area. The adult moth can be killed by light traps, whereas its larva only can be killed by some type of commercial pesticides such as dust DDT (10%) or carbaryl (10%) malathion, monocrotophos and quinalphos. Some of the chemicals were already listed as the Persistent Organic Pollutants (POPs) pesticides and already banned by the Stockholm convention. Therefore, alternative methods to control insect pests through friendlier environment approach need to be done.

Based on the previous study, podophyllotoxin (**16**) is one of the most popular precursors that come from the lignan family that has potential as a pesticide. In 1978, Singh *et al.* isolated an active constituent, namely, peltatin methyl ether A (deoxpodophyllotoxin) which was toxic towards housefly (*Musca domestica*) and codling moth (*Laspayressia pomonella*). Further study on podophyllotoxin derivatives found that podophyllotoxin with pyridin ring (Di *et al*., 2007) and phenoxyanillin substituents (Liu *et al*., 2008) gave greater insecticidal activity against *Pieris rapae* than podophyllotoxin itself. An ester of 2-chloropodophyllotoxin (Xu and Xiao, 2009) and hydrazone derivatives of podophyllotoxin (Wang *et al*., 2014) also showed good insecticidal activities against the oriental armyworm, *Mythimna seperata.*

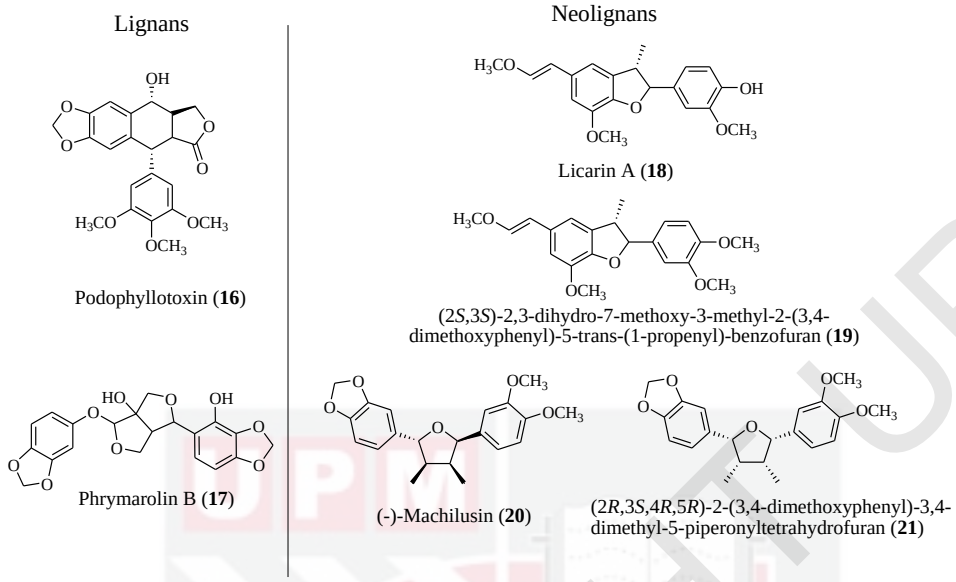


Figure 1.2: **Structure of potential pesticidal/insecticidal lignans and neolignans**

Phymarolin B (**17**), a furan type lignan which was isolated from *Phryma leptostachya* was evaluated for its insecticidal activity against the fourth instar larva of *Mythimna separata*. The compound exhibited moderate activity with LC_{50} of 502 µg/mL (Xiao *et al*., 2013). Another four furan type neolignans (**18**, **19**, **20** and **21**) from *Machilus japonica* were identified to have insecticidal activities against neonate *Spodoptera litura* larva with the significant EC_{50} of 0.20, 0.24, 0.19 and 0.13 µg/mL each by comparison to the positive control used, azadirachtin (0.25 µg/mL) thus further confirms that this specific group of compound have great potential as insecticide (González-Coloma *et al*., 2002).

To date, there are limited study focusing on dihydrobenzofuran neolignan and fewer investigations have been reported on benzofuran neolignan as pesticide. Therefore, it is a great need to study and identify the potential of lignans and neolignans as pesticides as the paradigm of agriculture needs.

1.4 Problem Statement and Hypothesis

Currently, the used of synthetic chemical pesticides is harmful towards human and environment which lead to the development of insecticide resistence in insects (Emberger, 2015), whereas the use of natural occurring pesticide from plant are eco-friendly and less toxic but comes with limited resources (González-Coloma *et al*., 2002). Therefore, it is important to study the synthetic chemical pesticide with the basic of potential natural dihydrobenzofuran neolignans and benzofuran neolignans to produce a more efficient, economical, safe and eco-friendly pesticides in Malaysia. *Crocidolomia binotalis* was chosen as the target pest in this study since it is one of the most popular pests other than *Plutella xylostella*, *Spodoptera litura* and *Hellula undalis* in Malaysia

(Lim *et al*., 1996). Besides, this pest is one of the most common cabbage pests identified in Cameron Highlands, Malaysia (Oii and Kelderman, 1979) and other crop plantation area in Indonesia (Sastrosiswojo and Setiawati, 1992; Shepard and Schellhorn 1994).

All pesticides or insecticides as mentioned in **1.3** (page 7) have similar structure with the targeted dihydrobenzofuran and benzofuran neolignans introduced in **1.1** (page 1). Evidently, the structure of active pesticide/insecticide compound consist a 5-membered heterocyclic; either dihydrofuran or tetrahydrofuran or two benzene rings. Furthermore, substituent such as hydroxyl, methyl or methoxy and the presence of double bond and acetal group also plays a significant role. All of these characteristics can be observed in the structure of tomentosanan A (**1**) and tomentosanan B (**3**), ficusal (**2** and **6**), zanthocapensole (**4**) and zanthocapensate (**5**). According to these facts, it can be deduced that the targeted compounds might display the same activity, and the presence of furan ring in their structures may enhance the insecticidal activity.

To the best of our knowledge, there are limited research on dihydrobenzofuran or benzofuran neolignans as pesticide or insecticide. This is the first research which focuses on the synthesis of neolignans **1-5**. The findings of this investigation provide a paradigm route to synthesize dihydrobenzofuran and benzofuran neolignans together with its derivatives as well as their insecticidal activity.

1.5 Objectives

The synthesis of neolignan especially dihydrobenzofuran and benzofuran are crucial in order to manufacture an efficient, safe and eco-friendly pesticides in Malaysia. This research project aimed to search insecticidal compounds which can lead to the discovery of insecticide candidates for *Crocidolomia binotalis* or for the future of agriculture research. Therefore, three objectives were proposed for this research:

1. To develop the Heck coupling method in the synthesis of neolignans *via* activated C-I bond of iodovanillin and non-activated C-H bond of vanillin.
2. To synthesize 2-aryldihydrobenzofuran and 2-arylbenzofuran neolignans and their derivatives *via* the developed Heck coupling reaction.
3. To determine the larvicidal activities of all the intermediate compounds and neolignans obtained.

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LIST OF PUBLICATIONS AND CONFERENCES

Publications

Juhan, S. F., Nor, S. M. M., Sukari, M. A. M., Azziz, S. S. S. A., Fah, W. F and Alimon, H. (2016). New Synthesized Aminoanthraquinone Derivatives and Its Antimicrobial and Anticancer Activities (Route II). *International Journal of Contemporary Applied Sciences* 3 (1) 18-33.

Nor, S. M. M., Sukari, M. A. M., Azziz, S. S. S. A., Fah, W. F., Alimon, H. and Juhan, S. F. (2013). Synthesis of New Cytotoxic Aminoanthraquinone Derivatives via Nucleophilic Substitution Reactions. *Molecules* 18: 8046-8062.

In Progress article:

1. 2-Aryldihydrobenzofuran neolignans: synthesis of ficusal and tomentosanan B (accepted for publication on 9 May 2018 in Der Chemica Sinica).
2. Chemical and Enzymatical Synthesis of Lignans and Neolignans derivatives and its larvicidal activities.
3. Synthesis of new derivatives of benzofuran neolignans and stilbenes *via* Heck coupling.
4. Synthesis of New Derivatives of Phenylcoumarins and Neolignans *via* Heck Coupling
5. Synthesis of (+)-Tomentosanan A *via* Heck Coupling Approach
6. Synthesis of zanthocapensole and zanthocapensate derivative using Heck coupling method.

Conferences

1. 29th The Malaysian Analytical Chemistry Symposium (SKAM 29) on 15 to 17 August 2016 at Bayview Beach Resort, Penang organized by Universiti Sains Malaysia. Participation as a poster presenter.

2. Fundamental Science Congress (FSC) on 12 to 13 November 2015 at Faculty of Science veterinary organized by Universiti Putra Malaysia. Participation as an oral presenter.

3. Fundamental Science Congress (FSC) on 20 to 21 August 2013 at Faculty of Science veterinary organized by Universiti Putra Malaysia. Participation as a poster presenter.

4. International Conference on Natural Products (ICNP2013) on 4 to 6 March 2013 at Shah Alam Convention Centre (SACC) organized by Universiti Teknologi MARA Shah Alam, Selangor and Malaysian Natural Product Society. Participation as an oral presenter

5. 2nd National Symposium in Organic Synthesis 2012 (New Frontiers in Organic Chemistry) on 16 and 17 July 2012 at Concorde Hotel Shah Alam organized by Institute of Science (IOS) Universiti Teknologi MARA Shah Alam, Selangor, Malaysia. Participation as a poster presenter.

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