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SYNTHESIS OF AMINOANTHRAQUINONE DERIVATIVES FROM QUINIZARIN

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By

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Thesis submitted to the School of Graduate Studies, Universiti Putra Malaysia, in fulfillment of the Requirement for Degree of Master of Science

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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 AMINOANTHRAQUINONE DERIVATIVES FROM QUINIZARIN

By

SITI FADILAH BINTI JUHAN

October 2013

Chairman: Siti Mariam Bte Mohd Nor, Phd

Faculty : Science

Amino derivatives of anthraquinone have been known to have a wide range of reactivities as anticancer agents, where modifications such as reduction, alkylation, or acylation to the anthraquinones also play important roles to increase their bioactivities. Twelve aminoanthraquinones including eight new aminoanthraquinones were synthesized *via* two different routes that consisted of two-step reactions. In the first route, quinizarin (**6**) was subjected to reduction, alkylation and acylation separately, thus giving an intermediate of 4-hydroxyanthracene-1,10-dione (**82**), 1-hydroxy-4-methoxyanthracenedione (**49**) and 4-hydroxy-9,10-dioxo-9,10-dihydroanthracene-1-yl acetate (**84**) before further reacting to produce anthracene-1,4-dione (**83**), 1,4-dimethoxyanthracene-9,10-dione (**50**) and 9,10-dioxo-9,10-dihydroanthracene-1,4-diyl diacetate (**85**) in excellent yields. These three products were then treated with butyamine ($BuNH_2$) in the presence of iodobenzene-diacetate ($PhI(OAc)_2$) as a catalyst to produce aminoanthraquinones 2-(butylamino)anthracene-1,4-dione (**83a**), 2-(butylamino)-4-methoxyanthracene-9,10-dione (**50a**), 2,3-(dibutylamino)anthracene-9,10-dione (**50b**), 1-(butylamino)-4-methoxyanthacene-9,10-dione (**50c**), 1,4-(dibutylamino)anthracene-9,10-dione (**50d**) and 2-(butylamino)-1,4-dihydroxyanthracene-9,10-dione (**86**). In the second route, compound **6** first underwent amination to give 2-(butylamino)-1,4-dihydroxyanthracene-9,10-dione (**86**) (major product) and 1-(butylamino)-4-hydroxyanthracene-9,10-dione (**87**, minor product). Compound **86** was then subjected to reduction, alkylation and acylation separately. Reduction of compound **86** resulted in the compound **83a** which is the same compound produced in the first route whereas methylation gave a mixture of 2-(butyamino)-1-hydroxy-4-methoxyanthracene-9,10-dione (**86a**) and 2-(butyamino)-1,4-dimethoxyanthracene-9,10-dione (**86b**). The acylation produced a mixture of 3-(butylamino)-4-hydroxy-9,10-dioxo-9,10-dihydroanthracene-1-yl acetate (**86c**), 2-(butylamino)-4-hydroxy-9,10-dioxo-9,10-dihydroanthracene-1-yl acetate (**86d**) and 2-(butylamino)-9,10-dioxo-9,10-dihydroanthracene-1,4-diyl diacetate (**86e**). The products were characterised *via* a variety of physico-chemical and spectroscopic techniques, including melting point measurements, Fourier Transform Infrared Spectroscopy (FT-IR), Direct Injection Mass Spectrometry (DI-MS), Gas Chromatography Mass Spectrometry (GCMS) and also Nuclear Magnetic Resonance spectroscopy (NMR). Compound **86e** exhibited strong antimicrobial activities toward *Methicillin-resistant Staphylococcus aureus*

(MRSA), *Pseudomonas aeruginosa*, *Candida albicans* and *Escherichia coli (MIC values of 0.1 - 0.5 mg/mL). Meanwhile, compounds* ***83a***, ***50a***, ***50c***, ***86a***, ***86b*** *and* ***86e*** *showed strong activities against both* human estrogen receptor positive breast cancer *(MCF-7) (IC_{50} 1.1 - 11.0 μg/mL) and* human hepatocarcinoma *(Hep-G2) (IC_{50} 1.1 - 14.0 μg/mL) cell lines.*

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

SINTESIS BAGI TERBITAN AMINOANTRAKUINON DARIPADA KUINIZARIN

Oleh

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Terbitan aminoantrakuinon telah diketahui mempunyai lingkungan luas aktiviti sebagai agen anti-kanser , manakala pengubahsuaian seperti penurunan, pengalkilan dan pengasilan terhadap antrakuinon juga memainkan peranan penting bagi meningkatkan bioaktivitinya. Duabelas aminoantrakuinon termasuk lapan aminoantrakuinon baru telah disintesis melalui dua laluan yang berbeza yang terdiri daripada dua langkah tindak balas. Dalam laluan pertama, kuinizarin (**6**) telah mengalami penurunan, pengalkilan dan pengasilan secara berasingan , sekali gus memberi perantaraan 4-hidroksiantrasin-1,10-dion (**82**), 1-hidroksi-4-metoksiantrasin-9,10-dion (**49**) dan 4-hidroksi-9,10-dioxo-9,10 hidroksiantrasin-1-il asetat (**84**) sebelum bertindak balas lagi untuk menghasilkan antrasin-1,4-dion (**83**), 1,4-dimetoksiantrasin-9 ,10-dion (**50**) dan 9,10-dioxo-9, 10-dihidroantrasin-1,4-diil diasetat (**85**) dengan hasil yang sangat baik. Kesemua tiga produk kemudian ditindak balas dengan butilamin ($BuNH_2$) dengan kehadiran iodobenzena-diasetat ($PhI(OAc)_2$) sebagai pemangkin untuk menghasilkan aminoantrakuinon untuk menghasilkan 2-(butilamino)antrasin-1,4-dion (**83a**), 2-(butilamino)-4-metoksiantrasin-9,10-dion (**50a**) dan 2,3-(dibutilamino)antrasin-9,10-dion (**50b**), 1-(butilamino)-4-metoksiantrasin-9,10-dion (**50c**) dan 1,4-(dibutilamino)antrasin-9,10-dion (**50d**) dan 2-(butilamino)-1,4-dihidroksiantrasin-9,10-dion (**86**). Dalam laluan yang kedua, sebation **6** terdahulu melalui pengaminan untuk menghasilkan 2-(butilamino)-1,4-dihidroksiantrasin-9,10-dion (**86**) (produk utama) dan 2-(butilamino)-1,4-dihidroksiantrasin-9,10-dion (**87**, produk kecil). Sebation **86** kemudian diikuti dengan samada penurunan, pengalkilan dan pengasilan secara berasingan. Penurunan sebation **86** menghasilkan sebatian yang sama daripada laluan pertama (**86a**), manakala pengmetilan memberikan campuran 2-(butilamino)-1-hidroksi-4-metoksiantrasin-9,10-dion (**86a**) dan 2-(butilamino)-1,4-dimetoksiantrasin-9,10-dion (**86b**). Pengasilan telah menghasilkan campuran 3-(butilamino)-4-hidroksi-9,10-dioxo-9,10-dihidroantrasin-1-il asetat (**86c**), 2-(butilamino)-4-hidroksi-9,10-dioxo-9,10-dihidroantrasin-1-il asetat (**86d**) dan 2-(butilamino)-9,10-dioxo-9,10-dihidroantrasin-1,4-diil diacetat (**86e**). Produk telah dicirian melalui pelbagai kaedah fizikal-kimikal dan spektoskopik termasuk takat lebur, Spektroskopi Jelmaan Fourier Inframerah (FT-IR), Suntikan Terus Spektrometri Jisim (DIMS), Kromatogafi Gas Spektrometri Jisim (GCMS) dan juga Resonan Magnetik Nuklear spektroskopi (NMR). Sebatian **86e** menunjukkan aktiviti antimikrob yang kuat ke atas *Methicillin-resistant Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Candida albicans* dan *Escherichia*

coli (bacaan MIC 0.1 - 0.5 mg/mL). Manakala Sebatian **83a**, **50a**, **50c**, **86a**, **86b** dan **86e** telah menunjukkan aktiviti yang kuat terhadap kedua-dua sel kanser reseptor estrogen manusia kanser payudara positive (MCF-7) *(IC_{50} 1.1 - 11.0* μg/mL) *dan hepatokarsinoma manusia (Hep-G2) (IC_{50} 1.1 - 14.0* μg/mL).

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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:

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DECLARATION

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

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SITI FADILAH JUHAN

Date: 9th October 2013

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LIST OF ABBREVIATIONS

Ac_2O	Acetic anhydride
%	Percentage
α	Alpha
β	Beta
br	Broad
δ	Chemical shift in ppm
d	Doublet
dd	Double of dublet
dt	Double of triplet
CC	Column Chromatography
COSY	Correlation Spectroscopy
DI-MS	Direct Injection-Mass Spectrometry
DEPT	Distortionless Enhancement by Polarization Transfer
EIMS	Electron Ionization Mass Spectrometry
EtOAc	Ethyl acetate
FT-IR	Fourier Transform-Infrared Spectroscopy
GC-MS	Gas Chromatography-Mass Spectrometry
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple Quantum Coherence
IR	Infrared
IC_{50}	Half maximal inhibitory concentration
m	Multiplet
m/z	Mass per charge
M^+	Molecular ion
Me_2CO	Acetone
MeOH	Methanol
mp	Melting point
MIC	Minimum inhibition concentration

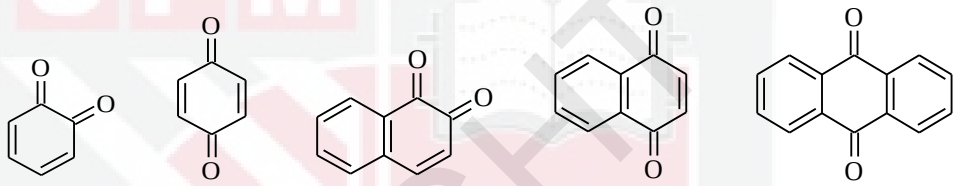
MS	Mass spectroscopy
NMR	Nuclear Magnetic Resonance
q	Quartet
RT	Room temperature
R_f	Retention factor
s	Singlet
t	Triplet
TLC	Thin Layer Chromatography
UV	Ultraviolet
UATR	Universal Attenuated Total Reflection

CHAPTER 1

INTRODUCTION

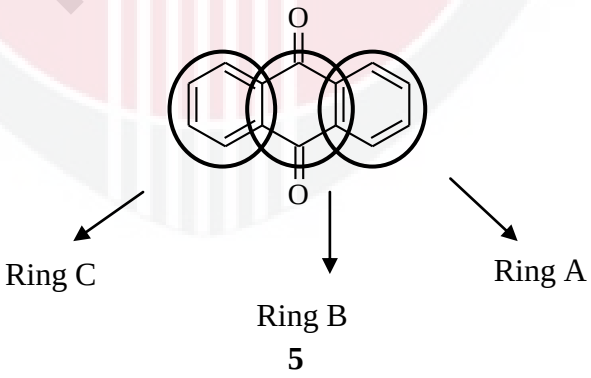
1.1 Anthraquinone family

A quinone a cyclic organic compound containing two carbonyl groups either adjacent or separated by a vinylene group in a six-membered unsaturated ring. In some types of quinones, the carbonyl groups are located in different rings. Quinones occur as biochromes, which includes the benzoquinones (1,2-benzoquinone (**1**), 1,4-benzoquinone (**2**)), naphthoquinones (1,2-naphthoquinone (**3**), 1,4-naphthoquinone (**4**)), anthraquinones (9,10-anthraquinone (**5**)), and polycyclic quinines. The quinones are mostly found in bacteria, in certain fungi, and in various higher plant forms, but only in a few animals (Jakob and Elmadfa, 1995).



1 **2** **3** **4** **5**

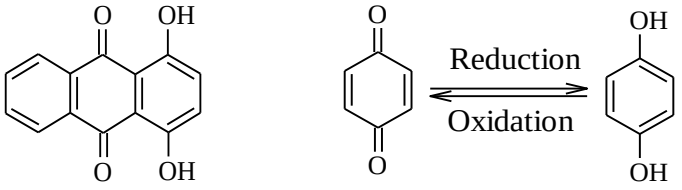
Anthraquinones, also called anthracenedione or dioxoanthracene are formally derived from aromatic compounds. The basic structure of an anthraquinone contains at least three rings and two ketone groups either on the same ring or adjacent to each other (**Figure 1.1**). There are many types of anthraquinones found in nature and they have found application in industries and drug development.



5

Figure 1.1: Basic structure of anthraquinone

Quinizarin (**6**) is one of the common types of anthraquinones found naturally in plants. This compound, also known as 1,4-dihydroxyanthraquinone or 1,4-dihydroxyanthracene-9,10-dione, has a molecular formula of $C_{14}H_8O_4$ and a molecular weight of 240.21 g/mol. The melting point of quinizarin (**6**) is 191-193°C and it exists as an orange powder at room temperature.



6 **7** **8**

The interesting features of the quinizarin is that it contains both benzoquinone (**7**) and hydroquinone (**8**) groups where compound **8** can be easily oxidized to **7** using mild oxidation. Benzoquinone (**7**) is commonly used as a dehydrogenation reagent or can act as a dienophile in a Diels-Alder reaction whereas hydroquinone (**8**) is used as a reducing agent that is soluble in water which finds its used in the cosmetic industry, where it is being used as a whitening agent with no carcinogenic effects on humans.

Quinizarin (**6**) is largely used as an intermediate in the synthesis of drugs that have high potential antitumor activity (Hua *et al*., 2004). It is also used as a starting material for coloring compound (Sokolyuk *et al*., 1993 and Matsuako *et al*., 1980), antioxidants, (Yen *et al*., 2000) and polymerization inhibitors (Surkau *et al*., 2010). Quinizarin (**6**) derived synthetic polymer can also be used in photo imaging and in fluorescence chemosensors (Ahn *et al*., 2009). Quinizarin (**6**) itself is already used in industry as dyes for gasoline and several types of heating oil. There are few reports on anthraquinones with regard to their cytotoxic properties as the benzene ring in the structure has a high potential for redox reactions (Klüpfel, 2009).

1.2 General reaction

Quinizarin (**6**) possesses several functional groups that can be modified including the reduction of ketone group (Hua *et al*., 2004), substitutions on aromatic ring, and alkylation (Sugimoto *et* al., 2002) or acylation (Wilson *et al*., 2006) of hydroxyl groups. All the reactions play an important role to increase the bioactive potential of certain compounds as will be discussed in the literature review.

Aminoantraquinones are known to be one of the most popular anthraquinone derivatives that has a wide range of anticancer and antitumor activities (Rautier *et al*., 1996; Shchekotikin *et al*., 2006 and Jin *et al*., 2011). It is believed that the presence of the amino group on quinizarin (**6**) could enhance the activity agaist several types of microbes and cancer cell lines.

Lithium aluminium hydride ($LiAlH_4$) is the common reducing agent used in reduction especially to reduce carboxylic acids, amides and also esters. Another mild reducing agent is sodium borohydride ($NaBH_4$). The use of $NaBH_4$ is preferred due to its versatility and it is less hazardous compared to $LiAlH_4$. $LiAlH_4$ is known as a strong reducing agent and can also reduce carbon-carbon double bonds thus resulting in more side products (Slaugh, 1966).

Methylation or alkylation is a reaction that involve the addition of a methyl group to a substrate and the common reagent used is dimethyl sulfate $(CH_3)_2SO_4$ or methyl iodide (CH_3I). Dimethyl sulfate easily methylates alcohols (Camara *et al*., 2001), phenols, amine (Sugimoto *et al*., 2002) and carboxylic acids (Kuran *et al*., 2008) in high yields (Camara *et al*., 2001) and typically occurs by S_N2 mechanism.

Acylation is defined as the simple chemical reaction to produce esters. In general, esters can be prepared from the reaction of alcohols with either carboxylic acids or acid chlorides or acid anhydrides in the presence of a catalyst. For the acylation of quinizarin (**6**) in this work, acetic acid anhydride was used since the reaction involves a tertiary alcohol.

An aromatic reaction occurs when a compound contains a cyclic conjugated system. Two reactions are involved either the electrophilic or nucleophilic aromatic substitution. It is possible to conduct this aromatic substitution on quinizarin (**6**) due to the existence of polycyclic aromatic hydrocarbon in the structure. Electrophilic aromatic substitution is one of the most common aromatic reactions where the π-bond in aromatic ring acts as a nucleophile and reacts with the incoming electrophile. In order to produce amino derivatives of anthraquinone, butylamine was chosen as a substituent group based on previous study that claimed the usage of a shorter amine would result in lower cytotoxic effect (Teich *et al*., 2004) whereas the use of diamine or longer-chain amine could produce side products due to its reactive properties and an easily be oxidized (Jin *et al*., 2011).

Iodobenzene-diacetate, $PhI(OAc)_2$ is the catalyst used for this aromatic reaction. It has already been applied in the oxidation reaction of phenols (Pelter and Elgendy, 1988), oligomerization of trifluoromethanesulfonic acid (Kitamura *et al*., 1999) and oxidation of primary and secondary alcohols to the respective carbonyl compounds (Yusubov *et al.*, 2006). It was reported that the use of $PhI(OAc)_2$ in the amination reaction of quinizarin (**6**) could give selectivity on the substitution of the benzene ring (Shchekotikhin *et al*., 2006).

1.3 Biological Activity

Bioassay studies were conducted to show that the compound synthesised in this study have their own biological potential including antimicrobial and cytotoxic activities (MTT assay). The antimicrobial activity was carried out by two methods, disc diffusion test and minimum inhibition concentration (MIC). The test involved four different types of microbes which are *Methicillin-resistant Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa, Candida albicans and Escherichia coli.* All four microbes used are commonly found in daily life and are usually responsible for different diseases among humans.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a type of staph bacteria that commonly cause infections *via* skin contact. This bacteria is also known as a major cause of bloodstream infections (BSIs) by Seybold *et al.* (2006). In hospital, the usage of antibiotics such as oxacillin, penicillin, and amoxicillin are widely applied but these antibiotics have their own side effecst such as fever, itching, yellow skin and eyes, dark urine, bloody diarrhea and are also not suitable for asthma patients.

Pseudomonas aeruginosa is a kind of bacteria that could cause diseases to animals and also to humans. It commonly found in soil and water or on the surface of plants and animals. In medicine, this bacteria is resistant to most antibiotics resulted by the permeability barrier afforded by its Gram-negative outer membrane and also by its potential to colonize in a biofilm form thus making the cells uninfluenced by the

therapeutic concentration of antibiotics. The patients that are infected by this bacterium are more likely to develop multiple organ failure and die (Martino *et al*., 2002). It also can cause chronic infection to people that have cystric fibrosis (CF) or to patients of severe burn wounds (Komor *et al*., 2012).

Candida albicans is a diploid fungus that grows both as yeast and filamentous cells and known are to be the most pathogenic Candida species (Naglik *et al*., 2011). This type of fungus can cause a wide range of infections on the oral mucosa called candidiasis (Yang *et al*., 2012). *Candida albicans* is the main type of fungi that is able to form biofilms, which causes superficial skin and mucous membrane infections as well as deep-seated mycoses, particularly in immune-compromised patients. In these patients, invasive infections are often associated with high morbidity and mortality. Furthermore, the increase in antifungal resistance has decreased the efficacy of conventional therapies (Gonzales and Maisch, 2012).

Escherichia coli is the name of a germ, or bacterium that lives in the digestive tracts of humans and animals. *E. coli* were first recognized as a cause of diarrhea and septicemia in calves more than 115 years ago (Gay and Besser, 1994). The people who are infected with this type of bacterium may have vomiting, stomach cramps, nausea or even bloody diarrhea. In some cases *E. coli* may also cause severe anaemia or kidney failure, which can lead to death. The infection is more risky to people who have a weaker immune system such as children, older or pregnant women. It can easily spread through food, water or contact.

The cytotoxic activity was carried out on two different cancer cell lines, which are human estrogen receptor positive breast cancer cells (MCF-7) and human hepatocarcinoma cells (Hep-G2). Breast cancer is one of the most popular types of cancer among woman instead of cervical cancer whereas Hep-G2 is a well known genetic disease in the world.

Breast cancer is a disease in which malignant (cancer) cells form in the tissues of the breast. Even though breast cancer usually happens to women, but it still possible to occur in men. According to the National Breast Cancer Foundation (INC), each year it is estimated that over 220,000 women in the United States will be diagnosed with breast cancer and more than 40,000 will die whereas, an estimated 2,150 men will be diagnosed with breast cancer and approximately 410 will die each year. Current treatments used for breast cancer such as radiation, anti-hormonal therapy, surgery and chemotherapy using synthetic drugs, have been reported to produce various side effects (Natarajan *et al*., 2011). Besides that, breast cancer, especially for human estrogen receptor positive breast cancer cells (MCF-7) can subsequently gain resistance thus survive the treatment (Yang *et al*., 2006). Therefore, the studies on finding of the new drugs to treat breast cancer is of importance.

Hep-G2 is a perpetual liver cancer cell line which is derived from the liver tissue and can cause morbidity and mortality. The liver is particularly susceptible to toxicants since the portal vein brings blood to this organ after intestinal absorption. The absorbed drugs and xenobiotics in a concentrated form can cause reactive oxygen species and free radical-mediated damage that may result in inflammatory and fibrotic processes (Jaeschke *et al*., 2002). There are more than two billion people in this world who have been infected with hepatitis B virus (HBV) and approximately

360 million are chronically infected. This virus could cause chronic sickness with starting symptoms such as weakness, vomiting, loss of appetite, abdominal pain, joint pain, dark urine, skin rashes and jaundice (Rots *et al*., 2010).

1.4 Objectives of the study

Derivatives of anthraquinone especially the aminoanthraquinones have attracted attention due to their biological properties. This aminoanthraquinones can offer scope in biomedical research and have potential as pharmaceuticals or in drug discovery. It was interesting to produce new aminoanthraquinones using two different routes that consist of two reaction steps that differ in sequence, either reduction or methylation or acylation then followed by amination or *vice versa*. There are several parameters that were studied such as the effect of catalyst, heat, time of reaction and also some reactant equivalence.

The main targets of this study are stated below:

1. To synthesize and characterise new derivatives of aminoanthraquinone from quinizarin.
2. To determine the antimicrobial and cytotoxic properties of the derivatives of aminoanthraquinone produced.

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