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Synthesis of a Water Soluble Resveratrol Derivative as a Potential Anti-Cancer Drug.

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by

Augustine Foster Essel

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ABSTRACT

Synthesis of a Water Soluble Resveratrol Derivative as a Potential Anti-Cancer Drug

by

Augustine Foster Essel

Research on development of water soluble anti-cancer drugs is one of the great challenges of modern medicinal chemistry. Resveratrol (Res) is one of the many phytoalexins producing stilbenoids present in several medicinal plants, grape skin, peanuts, and red wine. It has been found to exhibit anti-cancer, anti-inflammatory, and anti-oxidant properties. Water solubility and bioavailability are some of the setbacks of this interesting compound. In view of this, effort has been made to synthesize amino acid derivative of resveratrol to improve its bioavailability and solubility in water. Methyl 4-{-[(1E)-2-(3, 5-dihydroxyphenyl)-ethenyl] - phenoxy} butyrate (**7**), a novel ester intermediate, has been synthesized and could be subjected to further chemical transformations to obtain amino acid derivatives.

DEDICATION

This thesis is dedicated to my Dad, Rev.Moses K Essel, my wife Amada Essel, and to my unborn baby Gabriella.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

DNA	Deoxyribonucleic acid
COX	Cyclooxygenase
Fig	Figure
UV	Ultra Violet
CoA	Co enzyme
DMF	Dimethylformamide
AC	Acetyl
Gly	Glycine
Hrs	Hours
Temp	Temperature
DMSO	Dimethyl Sulfoxide
M.p	Melting Point
IR	Infra red
Lit	Literature
NMR	Nuclear Magnetic Resonance
THF	Tetrahydrofuran

CHAPTER 1

INTRODUCTION

Research on development of water soluble anti-cancer drugs is one of the great challenges of modern medicinal chemistry. In view of this, effort has been made to synthesize water soluble resveratrol derivatives.

Biology of Cancer

Naturally, our body cells are programmed to divide, grow, and die. Damage to DNA can cause cells to experience uncontrolled growth and, therefore, damage to the genes involved in cell division. The four key types of genes which are responsible for the cell division process are: oncogene, which tell cells when to divide, tumor suppressor genes tell cells when not to divide, suicide genes control apoptosis and tell the cell to kill itself if something goes wrong, and DNA-repair genes instruct a cell to repair damaged DNA [1] . Cancer occurs when a cell's gene mutations make the cell unable to correct DNA damage and unable to commit suicide [1].

Carcinogens are a group of substances that cause damage to DNA, promoting or aiding cancer. Tobacco, asbestos, arsenic, radiation such as gamma and x-rays, the sun, and compounds in car exhaust fumes are all examples of carcinogens [1]. When our bodies are exposed to carcinogens, free radicals are produced that in turn react with other molecules in the body. There are five broad groups that are used to classify cancer [1].

1. Carcinomas are characterized by cells that cover internal and external parts of the body such as lung, breast, and colon cancer.
2. Sarcomas are characterized by cells that are located in bone, cartilage, fat, connective tissue, muscle, and other supportive tissues.
3. Lymphomas are cancers that begin in the lymph nodes and immune system tissues.
4. Leukemia is cancers that begin in the bone marrow and often accumulate in the bloodstream.
5. Adenomas are cancers that arise in the thyroid, the pituitary gland, the adrenal gland, and other glandular tissues.

Cancer Treatment

One of the following six categories can be used as a treatment method for cancer: surgery, radiation, chemotherapy, immunotherapy, hormone therapy, and gene therapy.

Surgery

This kind of cancer treatment is useful at the onset of the cancer cells when they have not spread to other part of the body. In this case it is possible to completely cure a patient by surgically removing the cancer from the body. This is often seen in the removal of the prostate or a breast or testicle. After the disease has spread, however, it is nearly impossible to remove all of the cancer cells. Surgery may also be instrumental in helping to control symptoms such as bowel obstruction or spinal cord compression [1].

Radiotherapy

Radiation treatment also known as radiotherapy kills cancer cells by using or exposing high-energy rays on the cancer cells. High energy rays causes damage to the molecules that make up the cancer cells and lead them to commit suicide. Radiotherapy uses high-energy gamma-rays that are emitted from metals such as radium or high-energy x-rays that are created in a special machine. Early radiation treatments caused severe side-effects because the energy beams damage normal, healthy tissue, but technologies have improved so that beams can be more accurately targeted. Radiotherapy is used as a standalone treatment to shrink a tumor or destroy cancer cells (including those associated with leukemia and lymphoma), and it is also used in combination with other cancer treatments [1].

Immunotherapy

Immunotherapy aims to get the body's immune system to fight the tumor. Systemic immunotherapy treats the whole body by administering an agent such as the protein interferon alpha that can shrink tumors. Immunotherapy can also be considered non-specific if it improves cancer-fighting abilities by stimulating the entire immune system, and it can be considered targeted if the treatment specifically tells the immune system to destroy cancer cells. These therapies are relatively young, but researchers have had success with treatments that introduce antibodies to the body that inhibit the growth of breast cancer cells. Bone marrow transplantation (hematopoietic stem cell transplantation) can also be considered immunotherapy because the donor's immune cells will often attack the tumor or cancer cells that are present in the host [1].

Gene Therapy

The objective of gene therapy is to replace damaged genes with ones that work to remove a root cause of cancer, damage to DNA. Interesting research are been done to replace the damaged gene that signals cells to stop dividing (the p53 gene) with a copy of a working gene.

Other gene-based therapies focus on further damaging cancer cell DNA to the point where the cell commits suicide [1].

Chemotherapy

Chemist plays an important role when it comes to chemotherapy and intense research is being done to develop potent chemotherapeutic drugs. Chemotherapy uses chemicals that interfere with the cell division process - damaging proteins or DNA - so that cancer cells will commit suicide. These treatments target any rapidly dividing cells (not necessarily just cancer cells), but normal cells usually can recover from any chemical-induced damage while cancer cells cannot. Chemotherapy is generally used to treat cancer that has spread or metastasized because the medicines travel throughout the entire body. It is a necessary treatment for some forms of leukemia and lymphoma. Chemotherapy treatment occurs in cycles so the body has time to heal between doses. However, there are still common side effects such as hair loss, nausea, fatigue, and vomiting. Combination therapies often include multiple types of chemotherapy or chemotherapy combined with other treatment options [1].

Natural Compounds with Health Benefits

Polyphenols

Polyphenols are naturally occurring compounds that have been found to affect cancer cell growth and they have attracted great research attention. Initial evidence came from epidemiologic studies suggesting that a diet that includes regular consumption of fruits and vegetables (rich in polyphenols) significantly reduces the risk of many cancers [2]. The anti-cancer properties of polyphenols can be attributed to their ability to act as anti-oxidants, and also to their ability to interact with basic cellular mechanisms. These cellular interactions include interference with membrane and intracellular receptors, modulation of signaling cascades, interaction with the basic enzymes involved in tumor promotion and metastasis, interaction with oncogene, and oncoproteins [2]. Their great properties could be significantly exploited in the field of oncology.

Classification and Nomenclature of Polyphenols

Polyphenols are classified by the presence of more than one phenol unit or building block per molecule. Generally, they are divided into hydroxylable tannins, phenylpropanoid such as lignin, and flavonoids as shown in Figure 1 [3].

Hydroxybenzoic acids
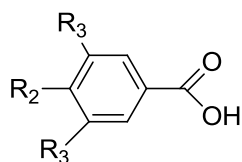
$R_1 = R_2 = OH$, $R_3 = H$: Protocatechuic acid
$R_1 = R_2 = R_3 = OH$: Gallic acid

Hydroxycinnamic acids
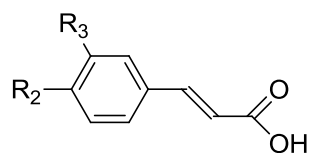
$R_1 = OH$: Coumaric acid
$R_1 = R_2 = OH$: Caffeic acid
$R_1 = OCH_3$, $R_2 = OH$

Flavanoids
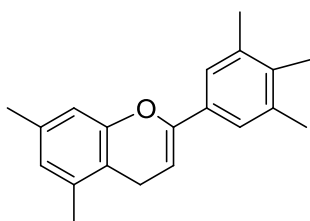
see Figure. 3
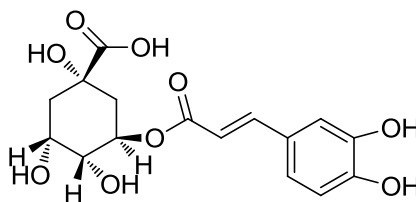
Chlorogenic acid

Stilbenes
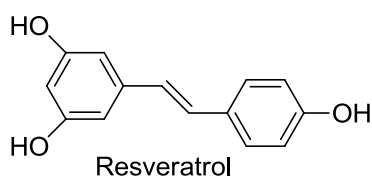
Resveratrol

Lignans
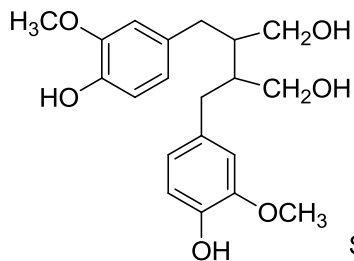
Secolsotariciresinol

Figure 1. Classification of polyphenols

The type of phenonic subcomponent could also be used as a basis for classifying Polyphenols. More than one subcomponent can be present on a given Polyphenols. Examples are shown Figure 2 [3].

Hydroquinone   Resorcinol

(Juglone)   (Resveratrol)
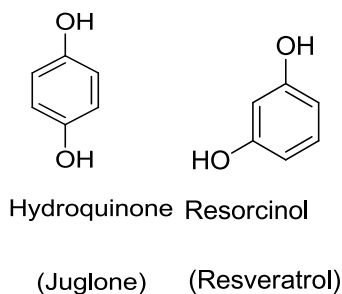
Figure 2. Nomenclature of polyphenols based on phenolic subcomponent

Selected Natural Compounds with Anti-Cancer Properties

Naphthoquinones
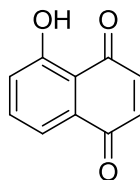
2

In recent years, some naphthoquinone derivatives such as Juglone **2** have been found to exhibit anti-bacterial, anti-fungal, and anti-viral properties and they could be used as anti-cancer agent because they can provoke cell apoptosis [4].

5-hydroxy-1,4-naphthalenedione (Juglone) is a naphthoquinone pigment that occurs as a natural product in the roots, leaves, nut, bark, and wood of black walnut (Junglans, nigra) and European Walnut (Junlars ,regia) and butter nut (Junglans, cinerea) [5].

Juglone is an allelopathic compound, meaning it is synthesized by one plant and affect the growth of another. In the case of Juglone it is toxic or growth-stunting to plants. Landscapers have long known that gardening underneath or near black walnut tree can be difficult. Juglone exerts it effect by inhibiting certain enzymes needed for metabolic functions. Nonetheless, a number of plants are resistant to Juglone, example fagus, Acer, and others [6].

Crushed unripe walnut hulls have been used for generation in various types of folk medicine. The hulls are made into poultices and robbed into the skin to treat bacterial or fungal infections such as herpes or warts. External application of black walnut also kills ring worm, and Chinese herbalist use this substance to kill tape worm. Juglone, due to its ability to create dark

orange-brown stains, has been used as coloring agent for foods and cosmetics such as hair dye. It is known in food industry as C.I Natural Brown 7 or C.I 75500. Traditionally Juglone has been used as natural dye for clothing and fabrics, particularly wool. It has also been used as Ink [5].

Between 1976 and 1999, 73 patent involving Juglone were obtained in the United State (Us patent and Trademark office, 1999). These patents demonstrated a variety of potential uses for juglone, for example to prepare antiviral naphthoquinone derivatives useful for AIDs treatment (Kurtz et al, 1996, Boyd et al, 1999).

Flavonoids

Flavonoids are group of natural occuring polyphenols that have also atrracted great research attention. They include several thausand compounds such as those shown in Figure 3 [6]. Flavonoids constitute a group of natural compounds that occur in fruits and vegetables, wine, and tea[7]. Scientists in the fields of nutritional biochemistry and medicinal chemistry have gained much interst in these compunds.The centre of attraction of these compounds could be attributed to the following reasons; first, these polyphenols exert potent anti-oxidants actions in numerous in vitro systems[7,12]. Second, the dietry intake of flavonoids and similar polyphenols exceeds that of anti-oxidative vitamins and provitamins. In epidemiologic studies, increase intake of flavonoids was associated with reduced risk of major cardiac events [9,10]. The health benefits of flavanoids are mainly attributed to their free radical scavenging properties thus counterreacting conditions of oxidative stress that accompany disorders such as coronary artery disease, and their vascular diseases, stroke, inflamatory diseases, and cancer [9].

Flavonols

Flavones

R_2 = OH; R_1 = R_3 = H: Kaempferol
R_1 = R_2 = OH; R_3 = H: Quercetin R_1 = H; R_2 = OH: Apigenin
R_1 = R_2 = R_3 = OH: Myricetin R_1 = R_2 = OH: Luteolin
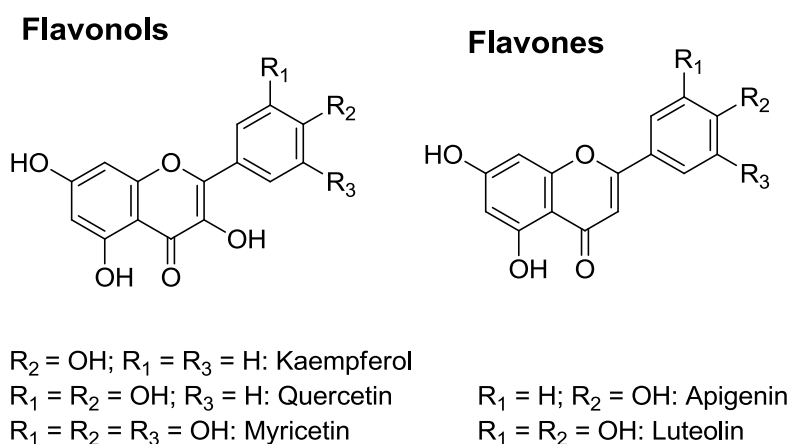
Figure 3. Flavonoids continued on next page
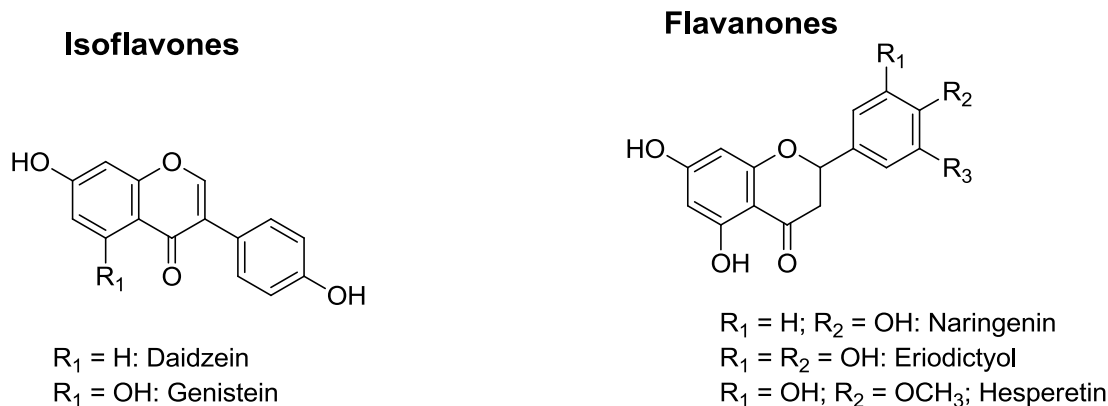
Figure 3. Flavonoids

Resorcinol

The chemistry of resorcinol is of great interest to bioorganic or natural product scientists due to its structural significant. The OH groups on resorcinol form hydrogen bonds to target molecules, holding them in a proper orientation for reaction. Research has indicated that most food supplements containing resorcinol moiety have potential anti-inflammatory, anti-oxidant, and anti- tumor properties. Some examples of natural occurring polyphenols with resorcinol moiety are quercetin, kaempferol, genistein, and resveratrol as shown in Figure 4.

Quercetin

Quercetin is a food supplements and it exhibit anti-inflammatory activities by inhibiting both manufacture of and release of Histamine and other allergic and inflammatory mediators. It also exerts potential anti-oxidant and vitamin C- sparing action [10]. Recent studies have supported that quercetin may help men with chronic prostatitis and both men and women with interstitial cystitis, possibly because of its action as mast cell inhibitor [11, 12].

Kaempferol

Kaempferol is another interesting natural flavanoid that has been isolated from tea, broccoli, grapefruits, apples, and other plant sources. Kaempferol consumption in tea and broccoli has been associated with reduced risk of heart disease [13].

Genistein

Genistein and other flavones have been found to have anti-angiogenic effects (blocking formation of new blood vessels) and may block the uncontrolled cell growth associated with cancer, most likely by inhibiting the activity of substances in the body that regulate cell division and cell survival (growth factors) [14]. Various studies have found moderate doses of Genistein

to have inhibitory effects on cancers of the prostate, cervical, brain, breast, and colon [14].

University Of Califonia, Los Angeles (UCLA) cancer researchers have found that study participants who ate foods containing certain flavanoid seemed to be protected from developing lung cancer. Dr. Zuo-Feng Zhang of the UCLA's Jonsson Cancer Center and a professor of public health and epidemiology at the UCLA School of Public Health said the flavonoids that appeared to be the most protective included catechins found in strawberries and green and black teas; Kaempferol, found in brussel sprouts and apples; and quercetin, found in beans, onions , and apples [15].

Quercetin Kaempferol Genistein

Resveratrol Resorcinol Daidzein
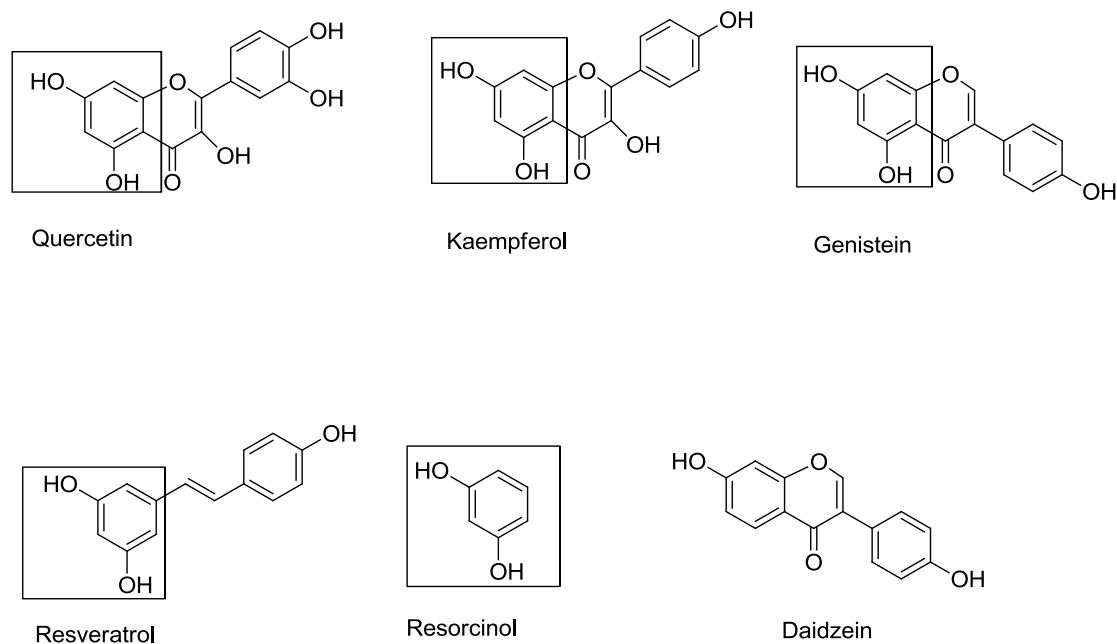
Figure 4. Compounds containing resorcinol moiety

Chemistry of Resveratrol and Its Derivatives
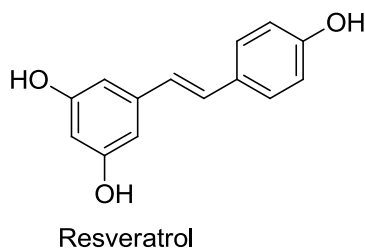
Resveratrol

Resveratrol (Res) is one of the many phytoalexin producing stilbenoid present in several medicinal plants, grape skin, peanuts, and red wine [16]. In addition to its phytoalexin effect, it is also believed that it protects the plant against oxidative stress and UV radiation [17]. Biosynthesis of resveratrol occurs by the action of key enzyme, stilbene synthase (StSy) that

converts one molecule of P-coumarol-CoA and three molecules of malonyl CoA into resveratrol [18]. Malonyl CoA is derived by elongation of acetyl CoA units, while P-Coumaroyl-CoA from phenylalanine which in plants can be synthesize from sugars via Shikimate pathway [19].

The properties of resveratrol cannot be well understood without considering the chemistry of Stilbenes. Stilbenes are diarylethene and basically they are hydrocarbons consisting of trans or cis-ethane double bond substituted with phenyl groups on both carbon atoms of the double bond. They exist in two isomeric forms: The first isomer is trans-1, 2-diphenylethylene also known as (E)-stilbene. The second isomer is cis-1, 2-diphenylethylene commonly referred to as (Z)-stilbene. The Z isomer is sterically hindered and less stable because the steric interactions forces the aromatic rings out of plane and prevent conjugation. Cis-stilbene has melting point of 5-6°C, while the trans-stilbene melts around 125°C [20].

<center>Derivatives of Stilbene</center>

Many stilbene derivatives, chemically referred to as stilbenoid are present naturally in plants and are known to act as phytoalexins that help to improve the plant's defensive mechanism against pathogens [21]. Resveratrol and its cousin pterostilbene are examples of stilbenoid. Other examples that are suggested to have varied health benefits include piceatannol and pinosylvin .The chemistry of each mention above is discussed briefly.

Pterostilbene

Pterostilbene is chemically related to resveratrol and it is thought to be the key compound found predominantly in blueberries (as well as grapes) that exhibit anti-cancer (breast cancer), hypercholesterolemia, anti-hypertriglycridemia properties as well as fight off and reverse cognitive decline. It is believed that the compound also has anti-diabetic properties but so far very little has been studied on this issue [22].

Unlike resveratrol, which is found in red wine, pterostilbene is not present in wine because it is not stable in light and air. It is also believed that pterostilbene metabolizes slowly as compared with resveratrol [22].
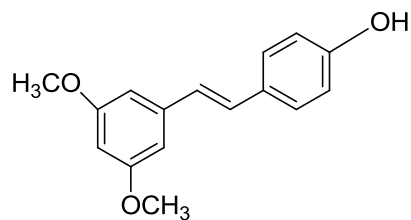
Pterostilbene

Piceatannol

3, 4, 3', 5'-tetrahydroxy-trans-stilbene, commonly known as piceatannol, is a phenol stilbenoid. It is the metabolite of resveratrol found in red wine. LMP2A, a viral protein-tyrosinekinase implicated in leukemia, Non-Hodgkin's Lymphoma, and other diseases associated with Epstein-Barr virus (EBV) also called human herpesVirus4 (HHV-4), was found to be blocked by piceatannol in vivo. These preliminary studies on piceatannol have attracted a lot of research attention as a potential anti-cancer and anti-EBV drug [23].
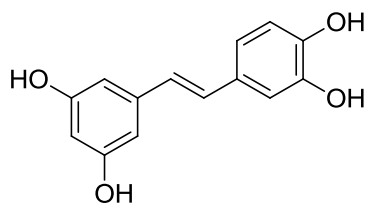
Piceatannol

Pinosylvin

Pinosylvin is a pre-infectious stilbenoid toxin (synthesized prior to infection) contrary to phytoalexins which are synthesized during infection. It is a fungi-toxin protecting the wood from fungal infection [24]. In 2005 S.K.Lee et al. reported that pinosylvin could exhibit more potent growth inhibitory activities against *Candida albicans* and *Sacchraromyces* cerevisiae compared to resveratrol [25]. Derivatives of pinosylvin have been reported to exhibit anti-cancer properties [26].

Pinosylvin

20
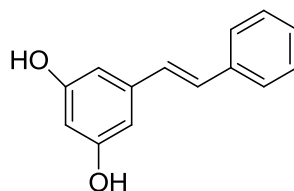
Early Discovery and History of Resveratrol

It is believed that resveratrol was first mentioned in Japanese article in 1939 by M.Takaoka, who isolated it from the poisonous but medicinal *Veratrum album* [27]. The name is presumed to have 'coined' from resorcinol (the fact that it is resorcinol derivative) and *Veratrum* species (the plant it was first isolated from) [27]. Until today it is believed that resveratrol has also been isolated from roughly 70 different plant species, most important of which is the skin and seeds of red grapes [28].

Recent Studies and Applications

Within the past decade, it has become increasingly clear that resveratrol posses significant health benefits to humans and could be potent chemo-preventative agent for several different health related problems including cancer, cardiovascular diseases, ischemia, and aging [29, 30].

Anti-Aging/Life Extension

The fact that Res could be used as anti-aging agent attracted enormous attention worldwide. Here are some of captured 'Res making headlines'

- "The belief that aging is still an unsolved problem is longer true" - Hayflick, San Francisco School of Medicine. 2007
- "The most phenomenon discovery since antibiotics" - Sinclair   Harvard University, 2003
- "Aging as we know it may not be inevitable" - Newsweek Magazine Dec 4, 2006
- "We may all soon be taking a pill that could give as extra decade or two of healthy old age" - CBS News (60 minutes), May 25, 2009
- "Living well past 100 could actually be possible" - Barbara Walters, CBS NEWS (Live to 150) May 13, 2009

The notion that aging requires treatment is because aging is a negative term that connotes deterioration, approaching pathology, and death [31].

In 2003 the groups of Howitz and Sinclair reported in the journal Nature that Res significantly extends the life of the yeast S*acchraromyces cerevisiae* [32]. Sinclair later conducted some studies that showed Res could also prolonged the lifespan of the worm C*aenorhabdities elegans* and the fruit fly *Drosophila melanogaster* [33].

In 2007 Sinclair's result was reproduced by a different group of scientists using C.*elegans* [34]. Unfortunately, a third group of researches could not achieve consistent increases in lifespan of D.*melanogaster* or C.*elegans* [35]. The first positive result of Res supplementation in a vertebrate was obtained by Italian scientists in 2006. A Short-lived fish N*othobrachius furzeri,* with a median life span of nine weeks was used .They found that a maximal dose of Res increased the median lifespan by 56%. The studies showed that the fish supplemented with Res showed significant higher general swimming activity and better learning to avoid an unpleasant stimulus [36].

Resveratrol as Anti-Cancer Compound

Trans-Res have been reported to have multiple health related benefits to humans. Such health benefits include anti-inflammatory and cancer chemo-preventative potentials [37]. For the past few years scientists have devoted much time and resources to research the biological activity of Res, especially the anti-oxidant activity because free radical-induced peroxidation of membrane lipids and oxidative damage of DNA have been considered to be associated with a wide variety of chronic health problems such as cancer, atherosclerosis, and aging and gene transcription can be regulated by oxidants, anti-oxidants, and other determinants of the intracellular redox state[38,39,40].

It has also been reported that Res is a good anti-oxidant against the peroxidation of low-density lipoprotein (LDL), liposome [41]. Research has also proven the anti-oxidant activity of Res is related to its hydroxyl (OH) groups which can scavenge free radicals produced in vivo [41]. It has also been revealed that Res has potential inhibitory effects on cyclooxygenase [37], rat liver mitochondrial ATPase [42], Human F1 ATPase [43, 44], and tyrosinase [45]. It is believed that Res is currently in clinical phase II trials as an anti-cancer drug for treatment of human colon cancer [46]. In addition to the above studies, Res has been shown to inhibit the activation of the oncogene transcription factor NF-kB by various inflammatory agents [46]. In 1997, Jang reported that topical Res applications prevented skin cancer development in mice treated with a carcinogen [37]. It has been reported that in vitro Res interacts with multiple molecular targets and damaged cells of breast, skin, gastric, colon, esophageal, prostate , and pancreatic cancer and leukemia [48].

The study of pharmacokinetics of Res in humans revealed that even high doses of Res might be insufficient to achieve Res concentration required for the systemic prevention of cancer

[49]. This result was consistent with the results from the animal cancer models, which indicated that the *in vivo* effectiveness of Res is limited by its poor systemic bioavailability [50, 51].

<div align="center">Other Suggested Applications</div>

Researchers at the Weil Medical College of Cornell University came up with a report in 2006 which indicated that dietary supplementation with Res significantly reduced plaque formation in animal brains, a component of Alzheimer and other Neurodegenerative diseases [52]. The results explained that in mice oral Res produced large reductions in brain plaque in the hypothalamus (-90%), striatum (-89%), and medial cortex (-48%) sections of the brain [53]. Researchers have come up with the theory that one mechanism for plaque eradication is the ability of resveratrol to chelate copper [54].

Anti-Inflammatory Effect

Resveratrol (Res) is also believed to posses anti-inflammatory effects and this has been demonstrated in several studies using animal models. In a rat model of carrageenan-induced paw edema, Res inhibited both acute and chronic phases of the inflammatory process [55].

Cardio-Protective Effect

Epidemiological studies have shown that cardiovascular and cerebrovascular ischemic events are decreased by moderate wine consumption [57]. This study is consistent with the fact that red wine is the most important dietary source of Res [57], and it has been suggested that Res is at least partly responsible for the so-called 'French paradox', which refers to the reduced incidence of cardiovascular diseases in region of French where saturated fats are consumed in even larger quantity than in US where red wine are consumed in far larger quantity [58]. It achieves the effects by the following functions: (1) Inhibition of vascular cell adhesion molecules expression, (2) Inhibition of vascular smooth muscles cell proliferation, (3) Stimulation of endolethelial nitric oxide synthase (eNOS) activity, (4) Inhibition of platelet aggregation, (5) Inhibition of LDL peroxidation [54, 55].

Anti-Diabetic Effect

Studies have shown that resveratrol possesses hypoglycemic and hypolipidemic effects in both streptozotocin (STZ)-induced diabetes rats and STZ-nicotinamide-diabetes rats. Res ameliorate common diabetes symptoms such as polyphagia, polydipsia, and body weight loss. In human clinical trials, resveratrol has lowered blood sugar levels in both Phases 1b and Phase IIa,

conducted by Sirtris Pharmaceutical, Inc[58].

Anti-Viral Effect

Studies show that resveratrol inhibits herpes simplex virus (HSV) types 1 and 2 replication by inhibition of an early step in the virus replication cycle. *In vivo* studies in mice show Res inhibits or reduces HSV replication in the virgina and limits extra-virginal diseas.The skin of resveratrol-treated animals showed no apparent dermal toxicity such as erythema, scaling crusting, lichenification, or excoriation. Studies also show that resveratrol inhibits varicella-zoster virus, certain influenza virus, respiratory viruses, and human cytomegalovirus [59].

Pharmacokinetics of Resveratrol

Resveratrol seems to provide an important lead as a cancer chemo-preventative or chemo-therapeutic agent but pharmacokinetics studies have revealed a number of setbacks in relation to its absorption, metabolism, and bioavailability. Experimental results have revealed that one way of administering resveratrol in humans appears to be buccal delivery (without swallowing) by direct absorption through the inside of the mouth. This study showed that when one mg of Res in 50 mL solution was retained in the mouth for one min before swallowing, 37ng/ml of free Res were measured in plasma two minutes later. It was further explained that all resveratrol that enters the blood circulation would be converted to molecules such as glucuronated and sulfate as it passes through the liver [60]. It also believed that about 70% of the resveratrol dose given orally as a pill was absorbed; but oral bioavailability of resveratrol was low because it was rapidly metabolized in intestines and liver into conjugated forms:glucuronate and sulfonate.The most abundant resveratrol metabolites observed in humans, rats, and mice are trans-resveratrol-3-O-glucuronide and trans-resveratrol-3-sulfate [61]. Walle suggested sulfate conjugates are the primary source of activity [62]. Wang et al. (2008) also suggested the glucuronides, and Boocock et al. (2007) also emphasized the need for further study of the effects of the metabolites.

Mechanism of Action

The ability of resveratrol to enhance life extension are not fully understood, but scientists believed that the compound appear to mimic several of the biochemical effects of calorie restriction. Some studies indicate that resveratrol activates Sirtuin 1(SIRT1) and PGC-1α and improve functioning of the mitochondria [62]. The mechanism may include direct quenching of reactive oxygen species, inhibition of enzymes, formation of chelates, activation of anti-oxidant

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enzymes, etc. Scientists in the field of computational chemistry have proposed two main mechanisms responsible for free radical scavenging processes of chain-breaking anti-oxidant ArOH:

a)   H-atom transfer (1) , (b) One electron transfer (2)

$$ArOH \ + \ R^{\bullet} \longrightarrow RH \ + ArO^{\bullet} \qquad 1$$

$$ArOH \ + \ R^{\bullet} \longrightarrow R^{-} + ArOH^{\bullet +} \qquad 2$$
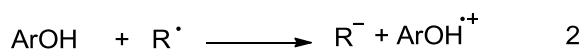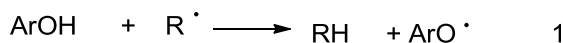
Scheme 1. Free radical scavenging mechanism

Both mechanisms are important for the scavenging activity of reactive species by an ArOH in a certain chemical or biological systems and may occur at the same time [63]. It is important to note that, in the second mechanism (one electron transfer) the Hydrogen bonding is normally retained as in the parent molecule contributing to a further stabilization. Resveratrol also acts as an anti-inflammatory agent by inhibiting cyclooxygenase (COX) activity [64] and by releasing cytokines from macrophages in chronic obstructive pulmonary disease (COPD). Other data from cell culture and animal experiments suggest that it plays a role in cancer chemoprevention during initiation, promotion, and progression of carcinogenesis. Resveratrol also inhibited the enzymes CYP1A1, CYP1A2, and CYP1B1 in tumor cells [65].

Derivatives of Resveratrol

Since the discovery of resveratrol in 1939, there has been intense research about this stilbenoid that has revealed some setbacks about the potency of this compound as chemo preventative agent. Studies have revealed that because of the many targets known to interact with Res, it is very difficult to pinpoint which targets is most important for a given disease state [66]. For this reason scientists are developing resveratrol derivatives that could exhibit selectivity for only one target. Another documented setback of resveratrol is its lack of potency and the need for high dosage administration; hence, there is the need to modify this compound to increase its potency. The problem of resveratrol having limited bioavailability has also been documented. It is believed that circulating resveratrol has a serum half-life of 8-14 min because it is rapidly metabolized by sulfation and glucuronation [67]. Res 3-sulfate and res 3-glucuronide, the two primary metabolites of resveratrol, have both been shown to exhibit far lower affinity for COX-1 and COX-2 [68].

It is been suggested that for resveratrol to be effectively used as a chemotherapeutic agent, modified analogues with comparable activity that lack the hydroxyl groups and hence could not be sulfated or glucuronated must be synthesized [69].

Aliphatic acids and their ester or ether derivatives of resveratrol have been found to possess good water solubility and increased bioavailability as shown in Figure 5. Jiang reported that compounds 1a and 1b did not show any improved solubility when measured in either water or phosphate buffer compared to their aliphatic acids 2a and 2b which showed improved water solubility (PH 7). Jiang also reported that the binding affinity of compound 2a and 2b for Human serum albumin (HSA) was higher than that of Res and as the number of chain of the aliphatic acid group increases so as the binding affinity [70].
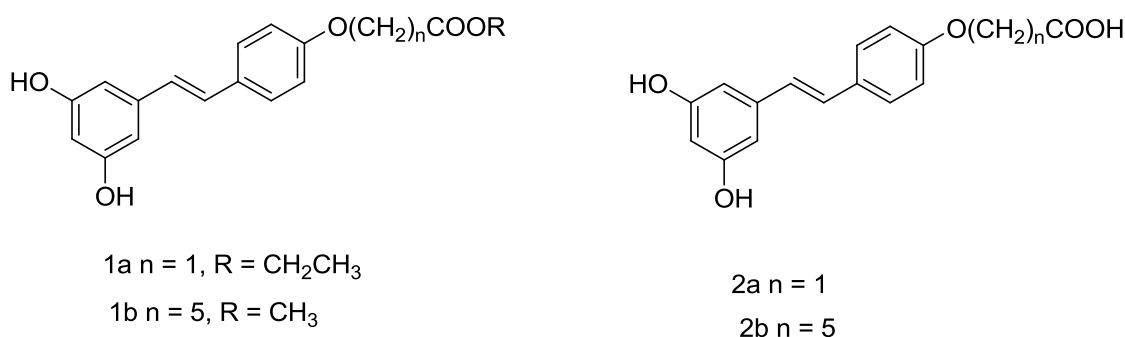

$$1a\ n = 1, R = CH_2CH_3$$
$$1b\ n = 5, R = CH_3$$

$$2a\ n = 1$$
$$2b\ n = 5$$

Figure 5. Derivatives of resveratrol by Jiang [70]

In 2007 Huang et al. reported that methylation of three hydroxyl groups of trans-Res could improve the anti-tumor activity .They suggested the increased cytotoxic activities of the modified Res could be attributed to the increased lipophilic activity of these compounds, which might increase the permeability of the cell membranes, Figure 6 .They also concluded that compound with alkyl ring amino side chains 3a and 3b showed better cytotoxic activities than those containing aromatic ring, 3c. Compound 3d was found to show the highest anti-tumor activity but they could not explain this observation [71].
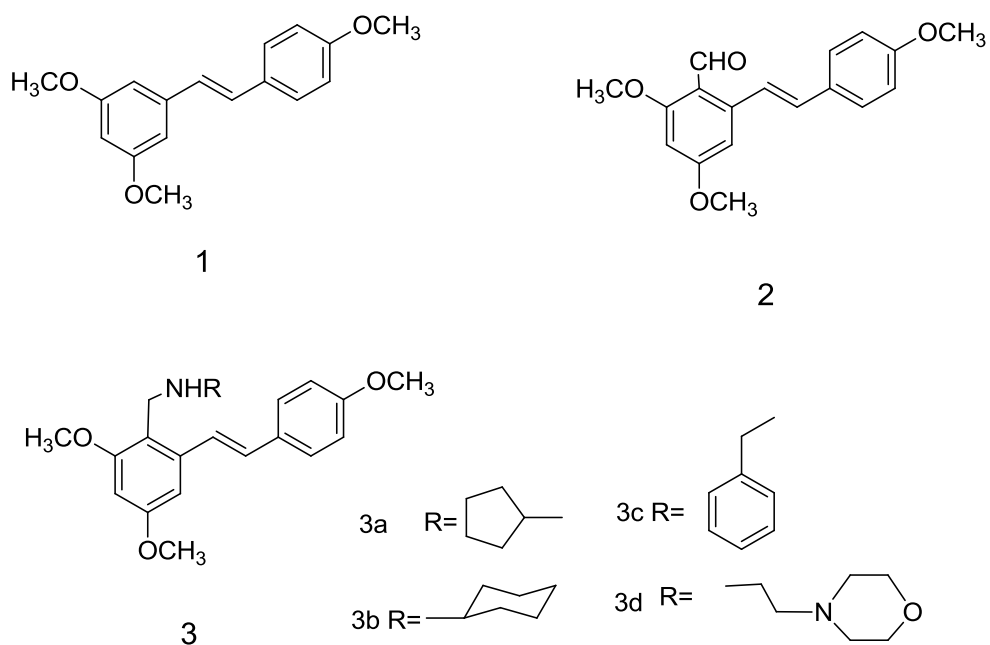
**Figure 6**. Derivatives of resveratrol by Huang et al. [71]

Chemical Synthesis of Resveratrol

Most medicinally important polyphenols occurs naturally in plants and effort to isolate them in their natural form is a problem due to insufficient and complex technological procedures. In view of this, there is the need to encourage synthetic analogues of these compounds. There have been several synthetic pathways to produce resveratrol and two of them have been outlined in Schemes 2 and 3. Scheme 2 was developed by Polunin et al. [72]. Scheme 3 was developed by Mingfu Wang et al. [73].
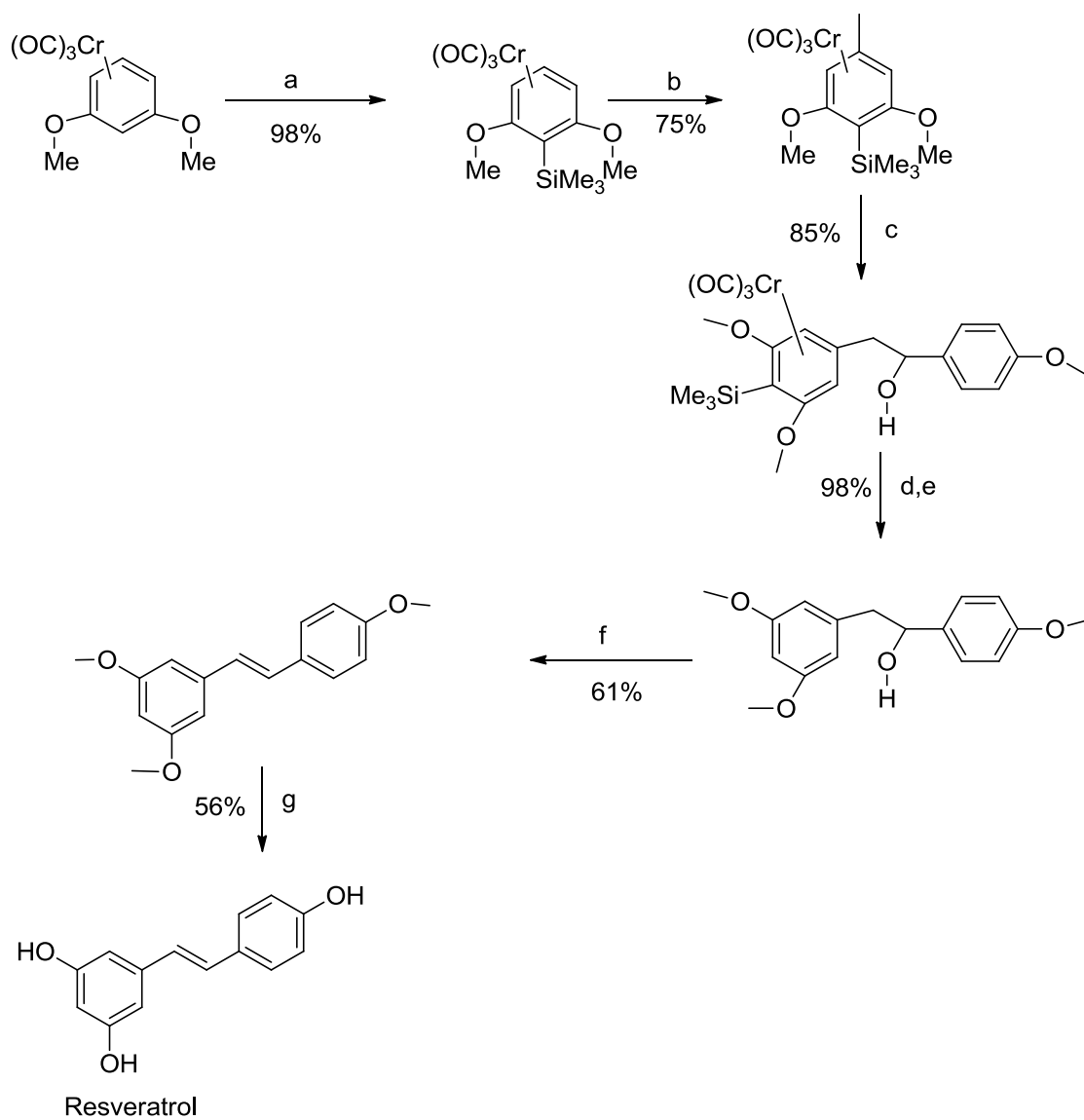
Scheme 2. Chemical synthesis of resveratrol by Polunin et al.

Reagents and Conditions: [72] a. n-BuLi, THF, TMSCl, -78°C ; b. LiTMP, THF, MeI, -50°C ;

c n-BuLi, THF, -40 ^{o}C,

anisaldehyde, -20; d. nBu$_4$NF, H$_2$O, 2 h; e. hv, Et$_2$O, 2 days;

f. TsOH, PhH, 80 ^{o}C,

13 h; g. MeMgI,100°C, 30 min;
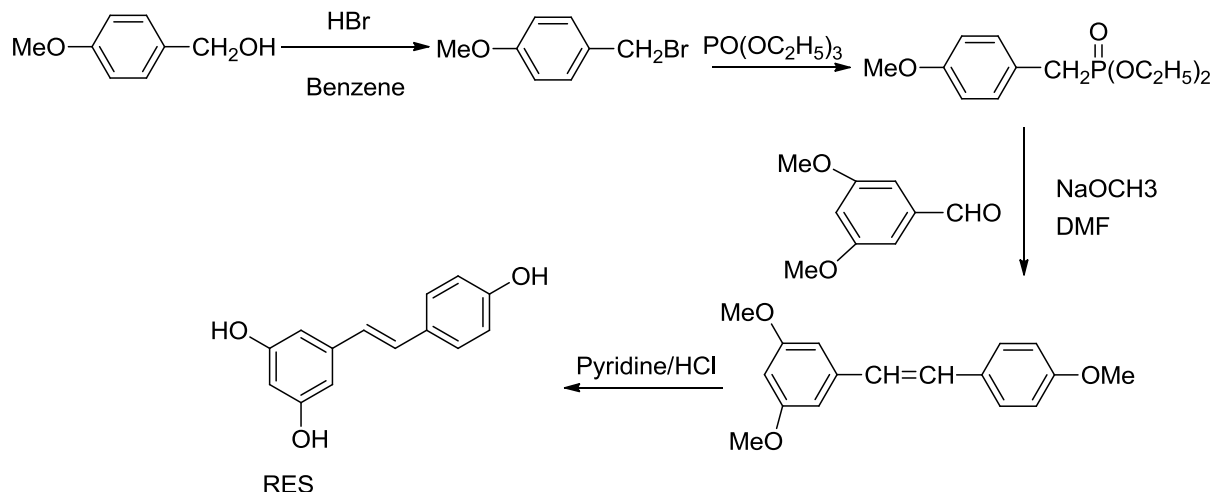
Scheme 3. Chemical synthesis of resveratrol by Mingfu Wang et al.

Purpose of this Research

The fundamental objective of this research is to synthesize a water soluble anti-cancer compound. Low water solubility and low bioavailability of chemotherapeutic agents are some of the big challenges facing synthetic organic chemists and most pharmaceutical industries. Derivatives and analogues of potential chemo preventative compounds are being synthesized and evaluated to ascertain their bioavailability and water solubility. In this research, attempt was made to modify Juglone into water soluble derivative, but we could not reproduce the result and therefore there was the need to change the direction of the research to include modification of resveratrol.

Proposed Synthetic Pathway for Synthesis of Juglone

The synthesis of Juglone **2** was a cupper catalyzed oxidation of dihydroxynaphthalene **1** as outlined in Scheme 4 [74].
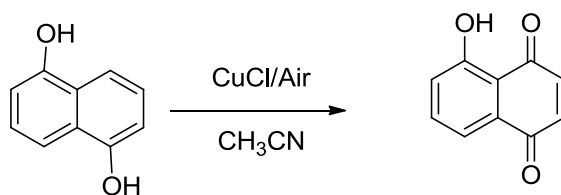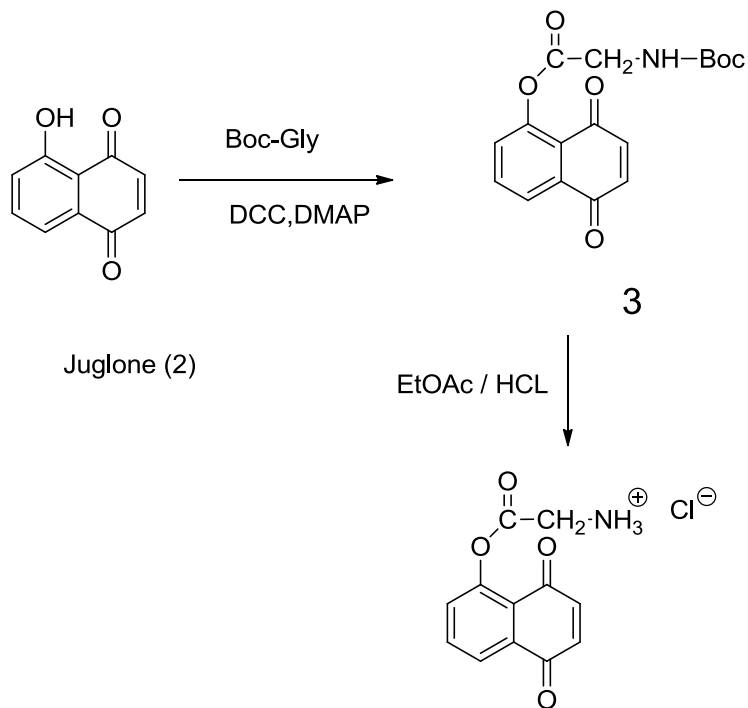

Scheme 4. Synthesis of Juglone

$$Cu^{\oplus} + O_2 \longrightarrow Cu^{2+} + {}^{\cdot}O{-}O^{\cdot}$$
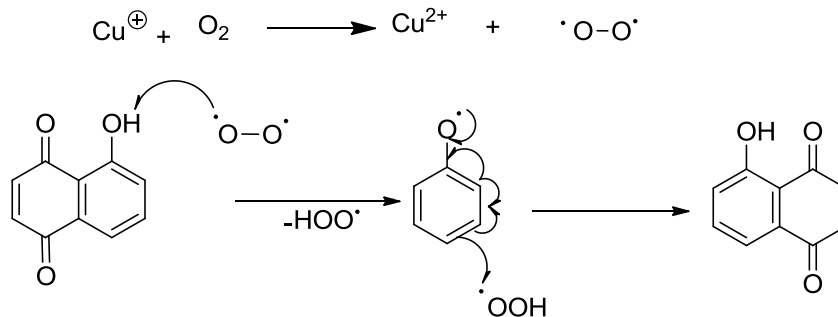
Scheme 5. Mechanism for oxidation of 1, 5-dihydroxynaphthalene

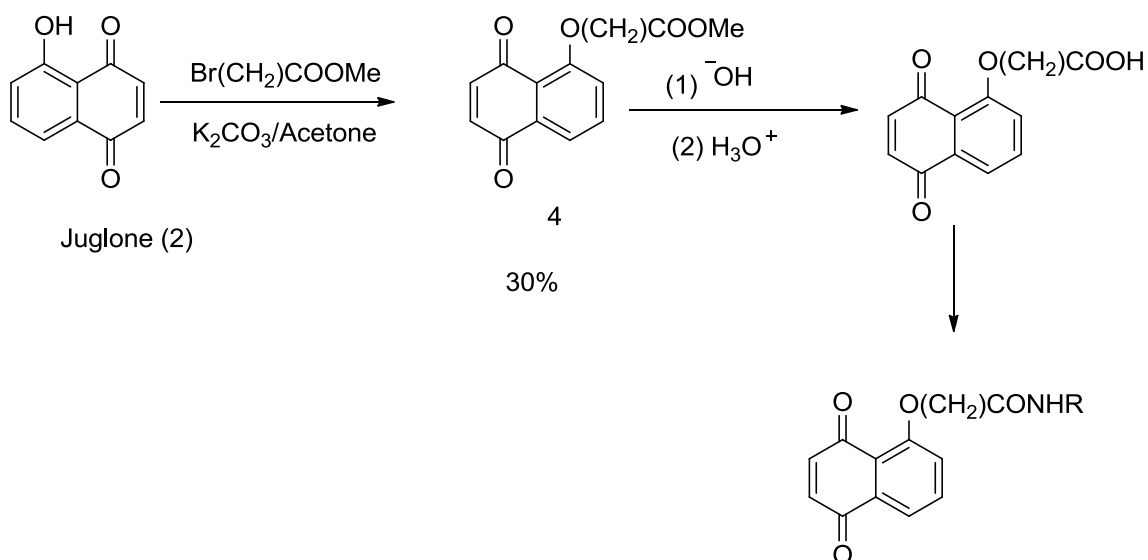Proposed Synthetic Pathway for Modification of Juglone

Two synthetic schemes were employed as part of the efforts to modify Juglone: Scheme 6 and Scheme 8. Scheme 6 involved room temperature esterification of juglone using Boc-protected amino acids in the presence of DicyclohexylCarbodiimide (DCC) and Dimethylaminopyridine (DMAP). The purpose of using DCC and DMAP is to activate the Boc protected amino acid which will ensure S_N2 attack by the alcohol group (Scheme 7). This pathway was not successful and it was therefore abandoned. Scheme 8 is based on Williamson's ether synthesis using bromoester as the alkylating agent. Weak base K_2CO_3 was used to deprotonate the hydroxyl group of the Juglone to form phenoxide which was then alkylated with the bromo ester via S_N2 mechanism (Scheme 9).
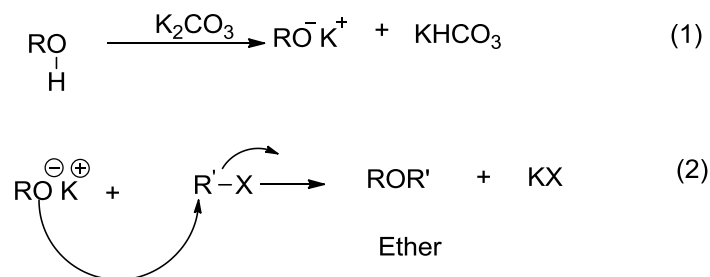
30

Scheme 6. Room temperature esterification of Juglone
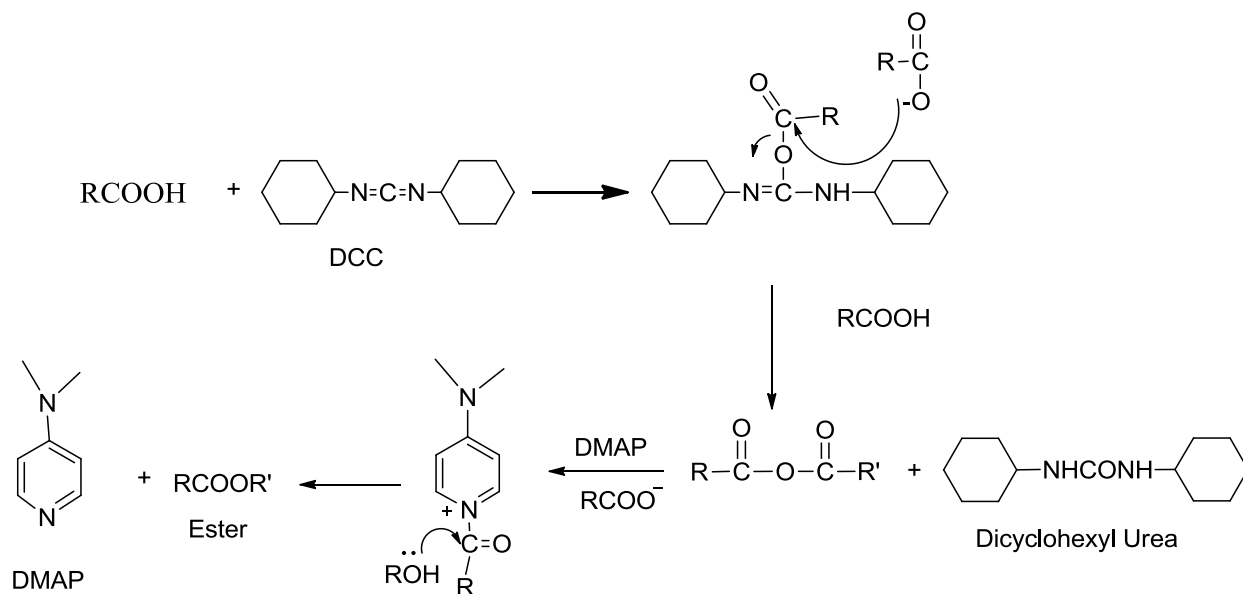
Scheme 7. Mechanism for Room Temperature Esterification of Juglone

Scheme 8. Modification of Juglone by Williamson Etherification

Scheme 9. Mechanism for Williamson Ether Synthesis

Proposed Synthetic Pathway for Modification of Resveratrol

Modification of the trans-Res was performed by selective alkylation of para-OH group using Williamson's ether synthesis approach to obtain the mono alkylated product. (Mechanism is similar to Scheme 9). The phenoxide form from deprotonation of para hydroxyl-group is more stable compared to that of meta-proton abstraction as indicated by resonance structures in Scheme 11 and 12 respectively.
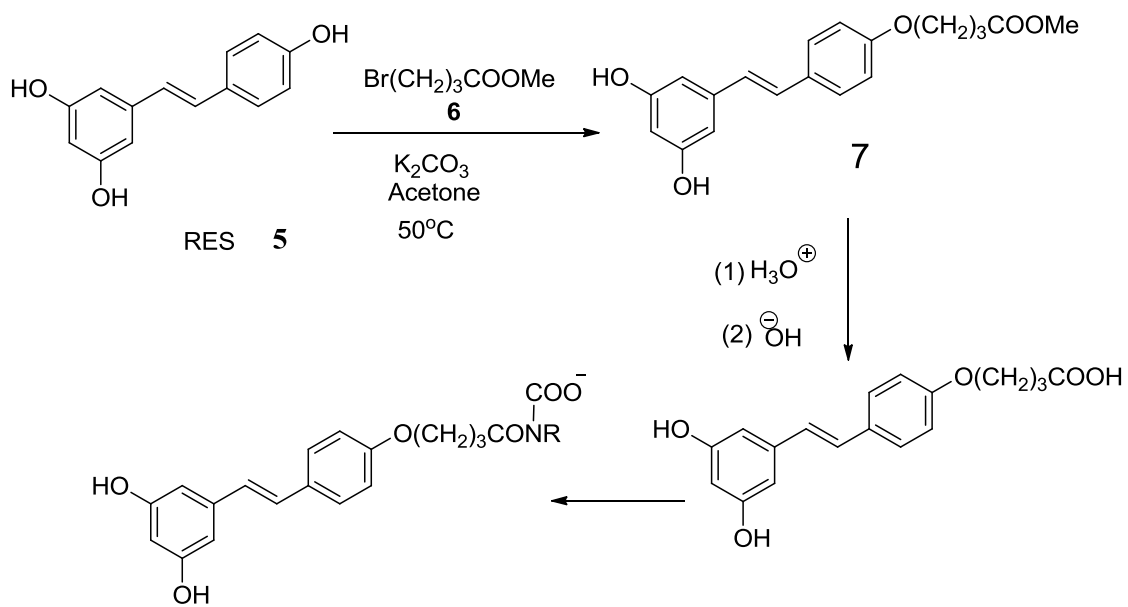
Scheme 10. Modification of resveratrol by Williamson etherification
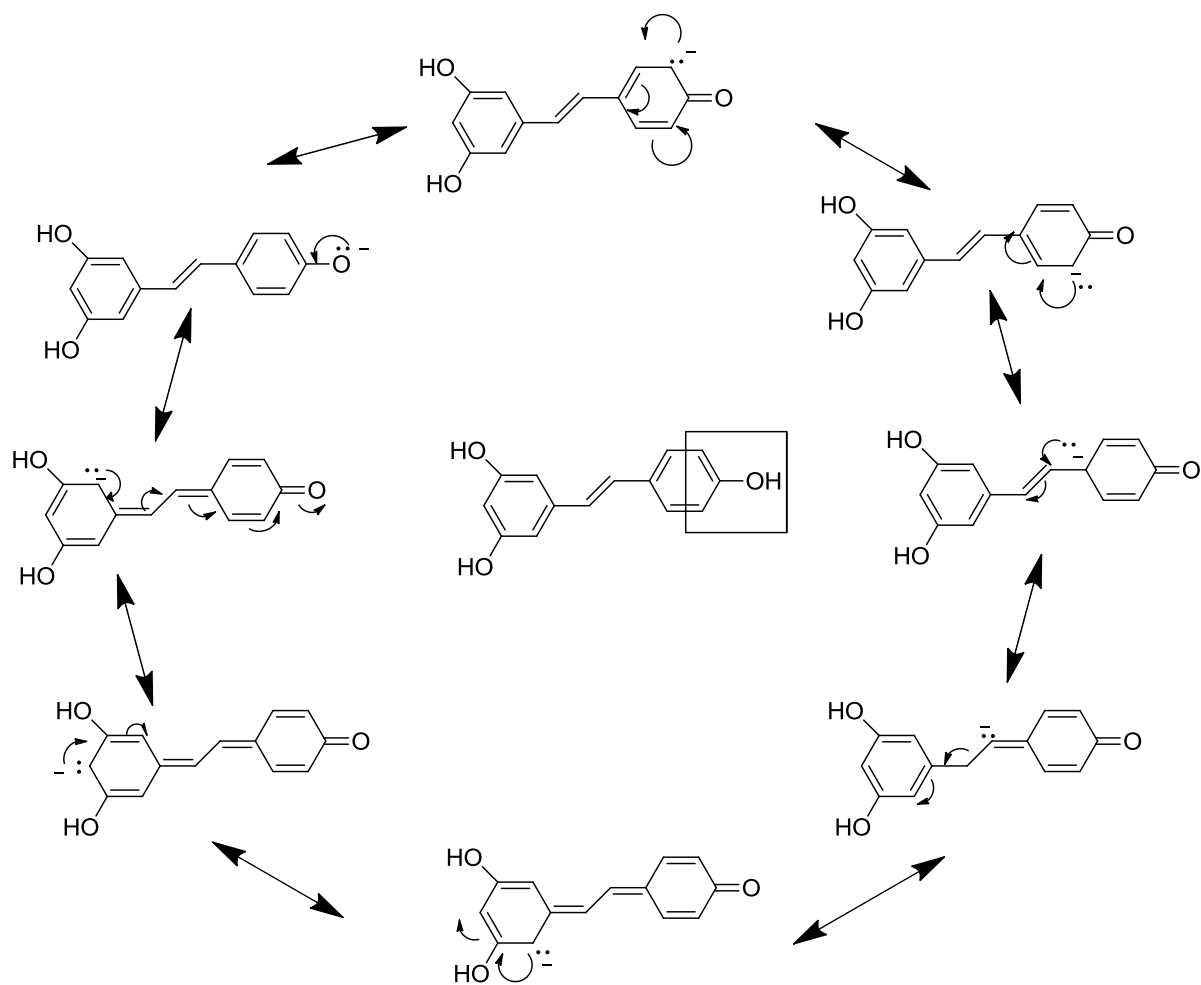
Scheme 11. The resonance structures of resveratrol by para hydrogen abstraction.
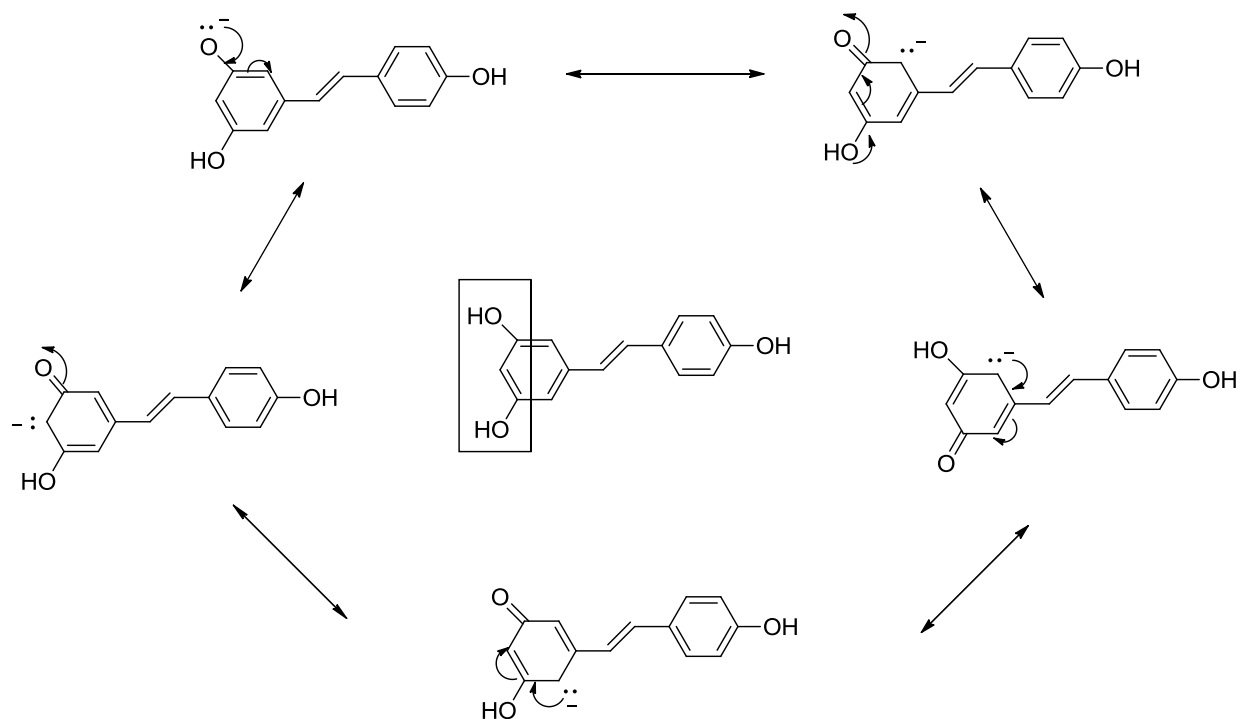
Scheme 12. The resonance structures of resveratrol by meta hydrogen abstraction.

Proposed Synthetic Pathway for Synthesis of Methyl 4-Bromobutyrate

$$Br(CH_2)_3COOMe$$
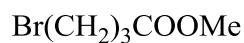
6

Compound **6** was synthesized by employing Fisher esterification reaction between 4-bromobutyric acid and methanol as shown in Scheme 13.
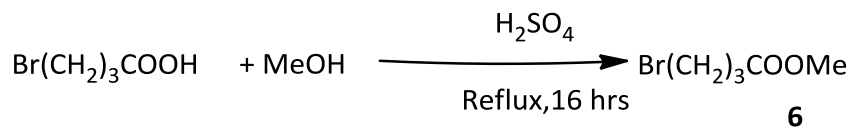
Scheme 13. Synthetic Pathway for 4-Bromomethylbutyrate by Fischer esterification

Scheme 14. Mechanism for Fischer esterification

CHAPTER 2

RESULTS AND DISCUSSION

Synthesis of 5-hydroxy-1, 4 -naphthoquinone (Juglone) **2**

2

Compound **2** was obtained as orange crystals after purification of the crude product using soxhlet extraction method based on the previous reported method [74]. A moderate yield of 30% was obtained that is relatively lower than the reported yield of 33% [74]. The oxidation reaction occurs by free radical mechanism as shown in Scheme 5.
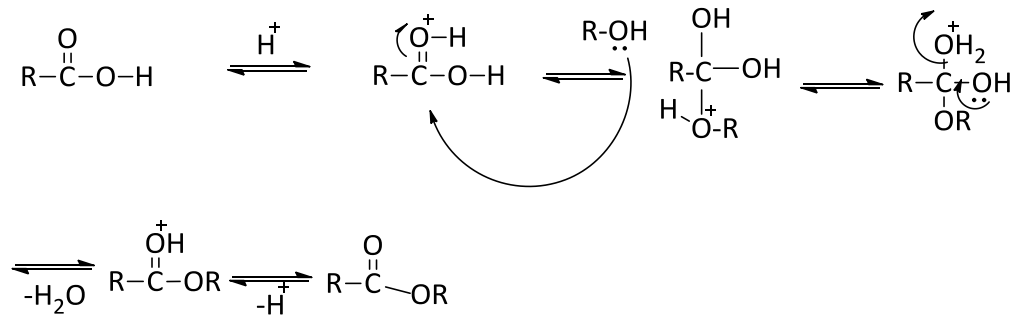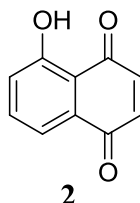
Synthesis of Methyl 5-[(1, 4-naphthenedionyl) oxy]-acetate **4**

4
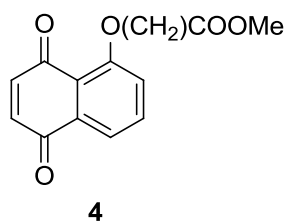
The synthesis of this compound was based on the theory of Williamson's ether synthesis where the base reacts to form the phenoxide. The phenoxide reacted with the bromoester to yield 30% product (Scheme 8). Unfortunately this procedure could not be reproduced. For this reason there was the need to change the direction of our research to include resveratrol.

Synthesis of Methyl 4-Bromobutyrate **6**

$$Br(CH_2)_3COOMe$$
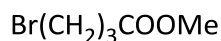
6

In order to synthesize our novel Res derivative, there was the need to synthesize the alkylating agent **6**. A white-yellow liquid was obtained by reaction of the bromobutyric acid with methanol catalyzed by sulfuric acid. The reaction mechanism followed the Fisher esterification

reaction as shown in Scheme 13.

Synthesis of Methyl 4-{-[(1E)-2-(3, 5,-dihydroxyphenyl)-ethenyl] - phenoxy} butyrate **7**
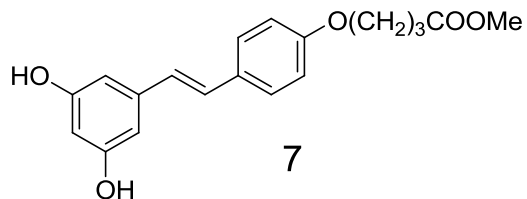
Compound **7** was obtained as white solid crystals with low yield of 10%. The low yield could be attributed to highly competitive side products such as di and tri alkylated products. The regiochemistry of the alkylating step is very crucial for selective product formation. Effort was made to control selectivity of alkylation by varying reaction conditions, and the summary of results is shown in Table1.

Table 1. Summary of Reaction Results

RES (mol ratio)	K$_2$CO$_3$ (mol ratio)	Br(CH$_2$)$_3$COOMe (mol ratio)	Temperature (^{o}C)	Mono (%)	Di (%)	Tri (%)	Recovered (RES) (%)	Reaction Time (Hrs)
1	2	1	≥70	None	None	80	20	12
1	2	1	25	None	None	None	100	12
1	1.5	0.7	60	3	25	30	42	12
1	2	1	50	10	35	20	35	12

Millimole amount of the alkylating agent and reaction temperature were the two main factors controlling selectivity. At high temperatures the selectivity was low and tri alkylated product was mainly the product. It was observed that at room temperature there would be no reaction. The best temperature for the reaction was found to be 50^oC. It was also found that the molar equivalent ratio of 1:2:1 with respect to resveratrol, potassium carbonate, and the bromo ester was suitable for the reaction. It was observed that addition of the bromoester in dropwise was very important for controlled selectivity. It must be noted that in all the cases tri and di alkylated products were separated. Another interesting observation was the fact that the mono alkylated product is present in two forms: mono alkylation occurring at the meta position together with the expected mono alkylated product at para position. This was revealed by ^{H}NMR (Appendix E) after column purification and hence recrystalization method was used to purify the product.

Conclusion

The objective of the research was partly fulfilled due to time constrain by synthesizing a novel intermediate (compound **7**) that could be subjected to further chemical transformation to obtain the amino acid derivatives. The low yield (10%) was attributed to the competitive side reactions and also the need to recrystallize the product to remove the isomer that was present even after column purification. We also made an effort to determine the best condition to reduce side reactions in other to improve the yield. The result obtained could be useful for future experimentation to obtain a better yield.

It must be noted that Juglone was also synthesized based on the initial objective in relatively good yield 30% (reported yield of 33%). It should be noted that one of the factors that was affecting the reaction to obtained compound **4** was hydrogen bonding between the H of hydroxyl group and the carbonyl oxygen group on the Juglone structure **2**. Reaction temperature must be carefully studied to overcome the hydrogen bonding in other to obtain good results.

EXPERIMENTAL

General Methods

Resveratrol and other commercial reagents were used without further purification and were purchased from sigma (St.Louis, MO, USA). All proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on JEOL-NMR Eclipse spectrometer operating at 400 MHz and 100 MHz for proton and carbon nuclei respectively. Spectra were obtained using $CDCl_3$ unless otherwise stated. Chemical shifts were recorded as delta values in parts per million (ppm) relative to TMS. The multiplicity of signals is reported as follows: s, singlet; d, doublet; m, multiplet. Thin layer chromatography (TLC) was performed with silica gel plate using appropriate solvent mixture and visualized under UV Fluorescent indicator. Column chromatography was performed using silica gel and appropriate solvent. Melting points were recorded on Cambridge MEL-TEMP instruments and were not corrected. All weighing were done using Mettler PJ360 Delta Range scale unless otherwise stated.

Experimental Procedures

Synthesis of 5-hydroxy-1, 4-naphthoquinone (Juglone) **2**
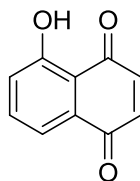
2

A suspension of 1.2 g (0.012 mol) CuCl in acetonitrile (150 mL) was placed in three-necked flask. A strong current of air was bubbled through it. A suspension of 1, 5-dihydroxynaphthalene (3.0 g, 0.019 mol) in acetonitrile (150 mL) was added with vigorous stirring at room temperature in a dark over 30 min, and the resultant mixture stirred for 7 h. The mixture was filtered and washed with acetonitrile and the solvent removed under reduced pressure. Soxhlet extractor was used to purify the crude using n-heptane as solvent to give **2** (0.36 g, 30%) as an orange solid [74]. The reported yield was 33%, M.p 155-159°C; Lit M.p 154-161 °C. [1H]NMR (400 MHz, CDCl₃): δ 6.94 (s, Ar-H) 7.29 (dd, J=6.3, 2.9Hz); 7.64 (m, Ar-H); 11.9 (s, OH); ^{13}CNMR (100 MHZ, CDCl₃) δ 115.05, 119.27, 124.64, 131.83, 136.68, 138.76, 139.69, 161.53, 184.37, 190.40

Synthesis of Methyl 4-Bromobutyrate **6**

$$Br(CH_2)_3COOMe$$
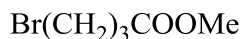
6

To a one-neck round-bottomed flask were added 5 g (0.03 mol) 4-bromobutyric acid**,** twenty-five milliliters of methanol was added followed by 2 drops of sulfuric acid and the mixture was reflux for 16 hrs (60^oC). The mixture was concentrated, washed with 5% $NaHCO_3$, and extracted with diethyl ether. The extract was dried with $MgSO_4$ (anhydrous) and the ether was evaporated to afford 4.7 g (94%) **6.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H, OCH_3); 3.45 (t, 2H, CH_2); 2.49 (t, 2H, CH_2); 2.17 (m, 2H, CH_2).

Synthesis of Methyl 4-{-[(1E)-2-(3, 5,-dihydroxyphenyl)-ethenyl]-phenoxy} butyrate **7**
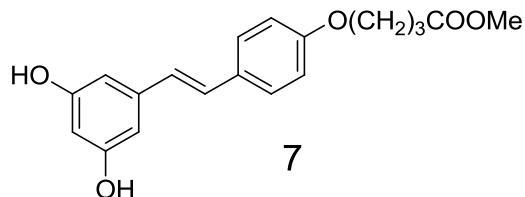
To a one-neck round bottomed flask were added 0.3 g (1.3 mmol) resveratrol, 15 mL acetone, and 0.36 g K_2CO_3 (2.8 mmol). 0.235 g (1.3 mmol) of compound **6** was added in dropwise(50% added initially and stirred for 6 hrs and the remaining half added and stirred for the next 10 hrs) at the temperature of 50^oC. The mixture was decomposed with concentrated ammonium chloride, extracted with ethyl acetate, and dried with anhydrous $MgSO_4$. The solvent was evaporated and the resulting mixture was purified using column chromatography (25-40% of acetone in hexane volume) to give compound **7** (0.03 g, 10%). The compound was recrystallized from ethyl acetate hexane (1:10 volume) to obtain 0.02 g, (6.7%), R_F value 0.65 (Acetone /hexane 40:60 v/v). Mp.148-150^oC. ^{1}HNMR (CD_3COCD_3, 400 MHz, ppm) δ 2.038 (t, 2H, CH_2); δ 2.5 (m, 2H, CH_2); δ 3.6 (s, 3H,CH_3); δ 4.03 (t, 2H, OCH_2); 8.2 (s, 2H, OH); 7.5 (d, 2H, Ar-H), 6.94 (m, 4H, Ar-H); 6.5 (s, 2H, Ar-H); 6.29 (s, 1H, Ar-H); ^{13}C NMR (CD_3COCD_3 ,100 MHz ,ppm) δ 28.6, 50.8, 66.7, 101.95, 104.91, 114.68, 126.7, 127.8, 127.9, 130.23, 139.9, 158.78, 173.00.

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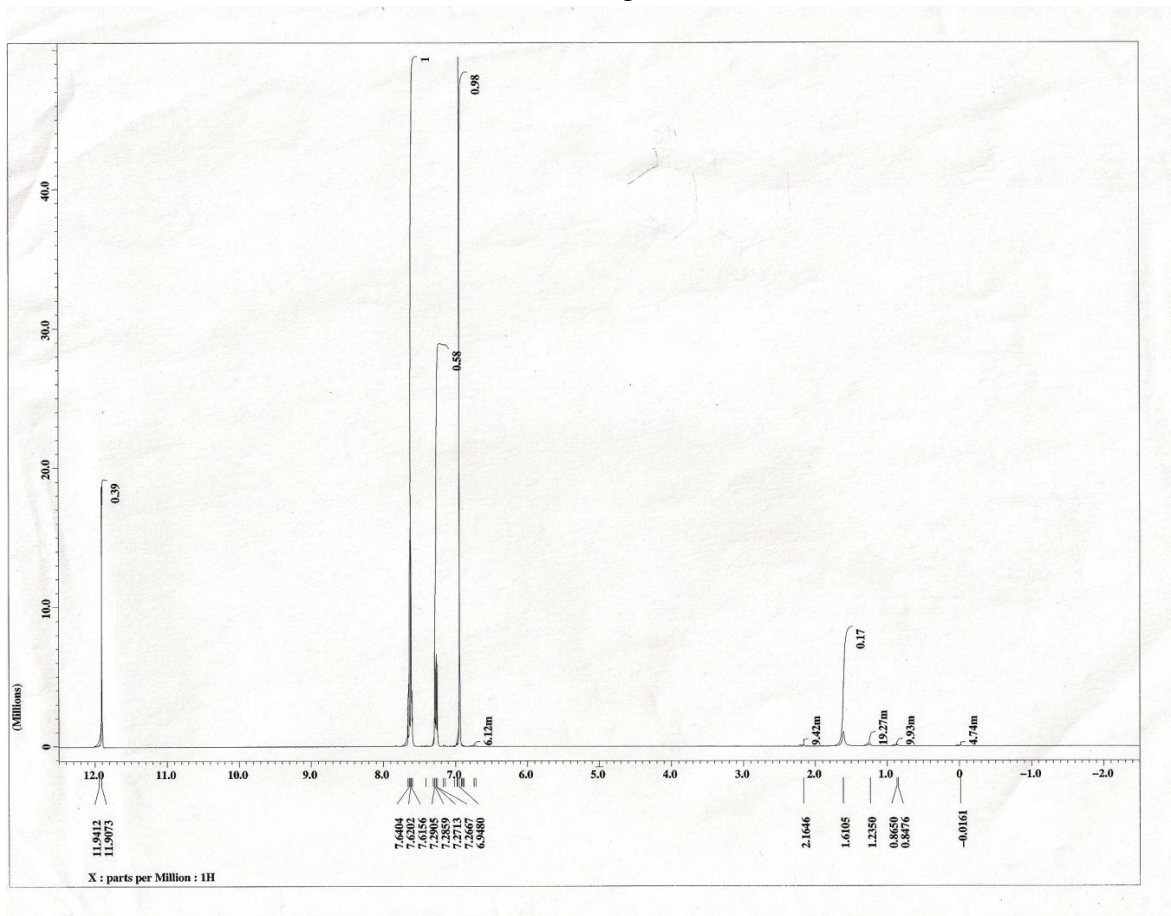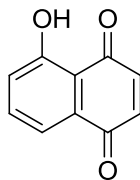
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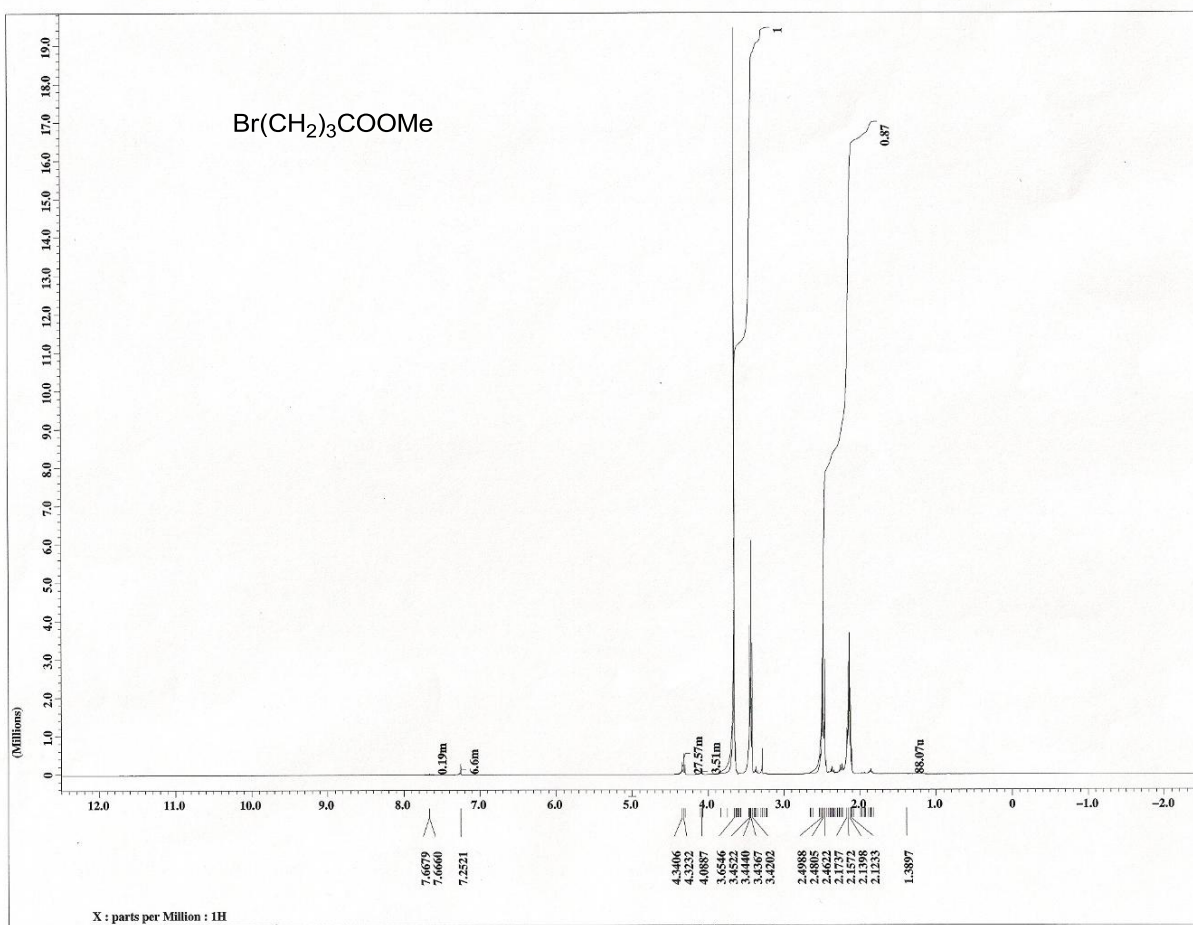
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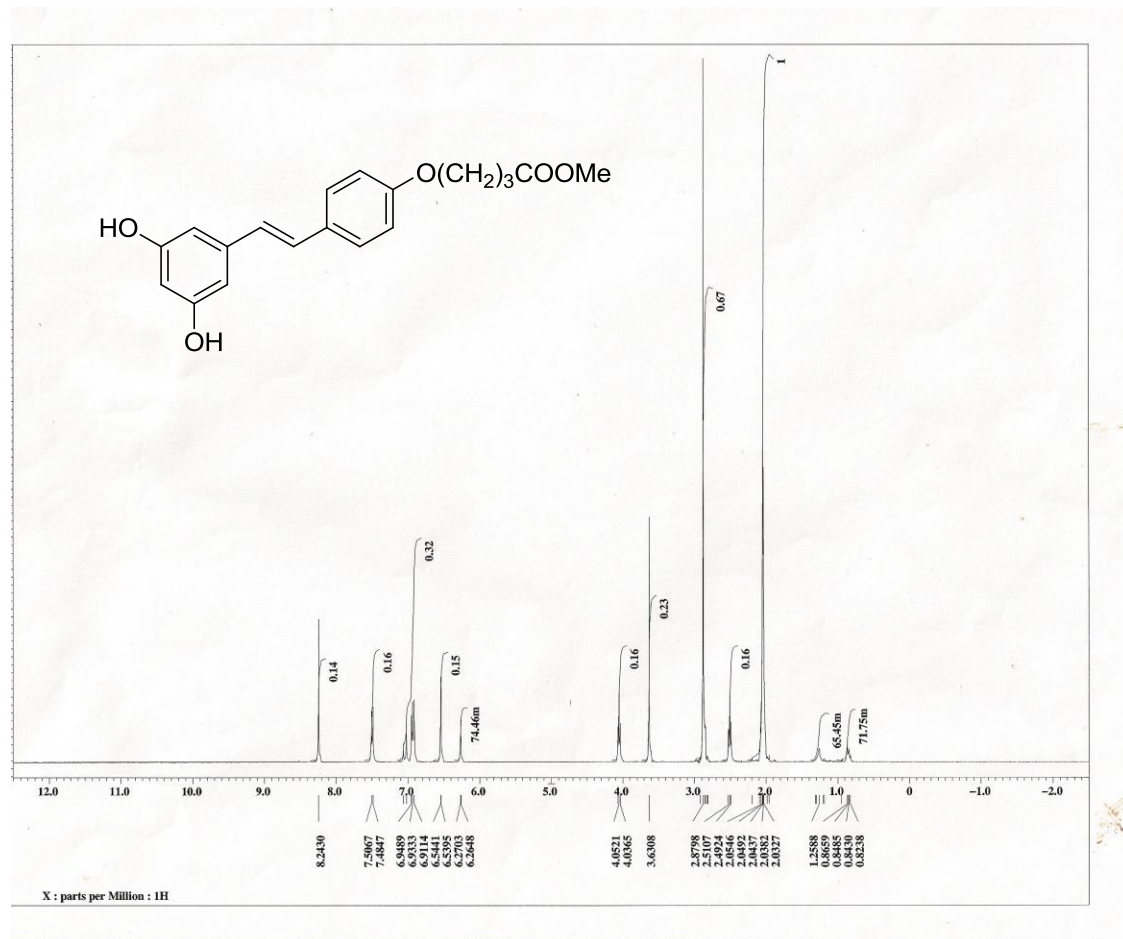74. Tietze, L. F.; Guntner, C.; Gericke, K. M. *Eur. J. Org. Chem.* **2005**, 2459.

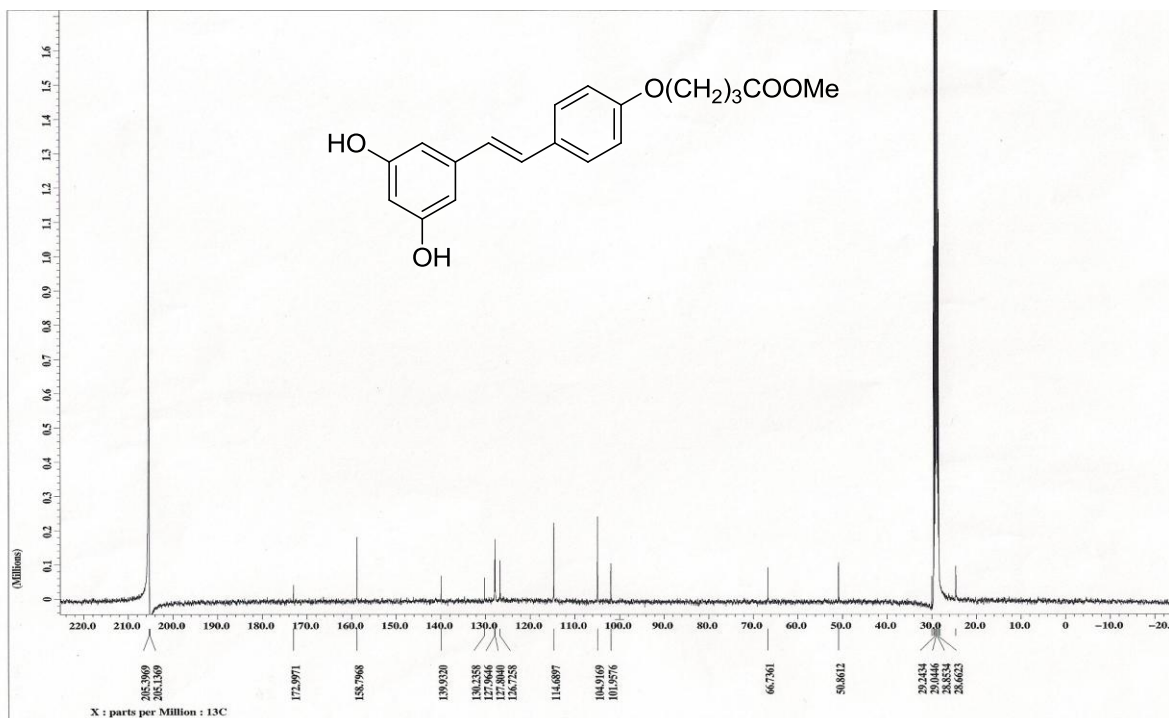APPENDIX A: ^{1}HNMR Spectrum of Compound **2** in CDCl$_3$

Br(CH$_2$)$_3$COOMe

X : parts per Million : 1H

O(CH$_2$)COOMe
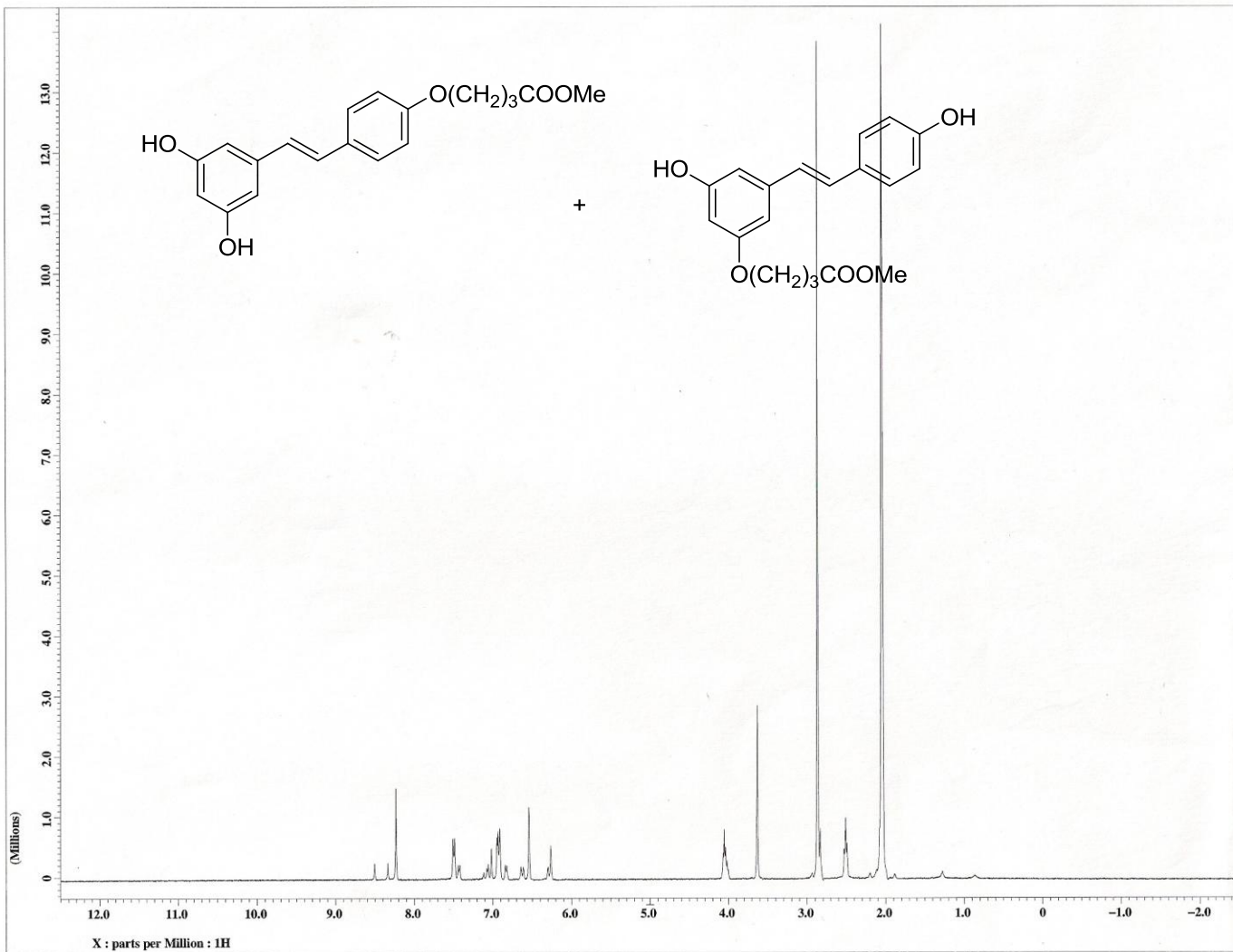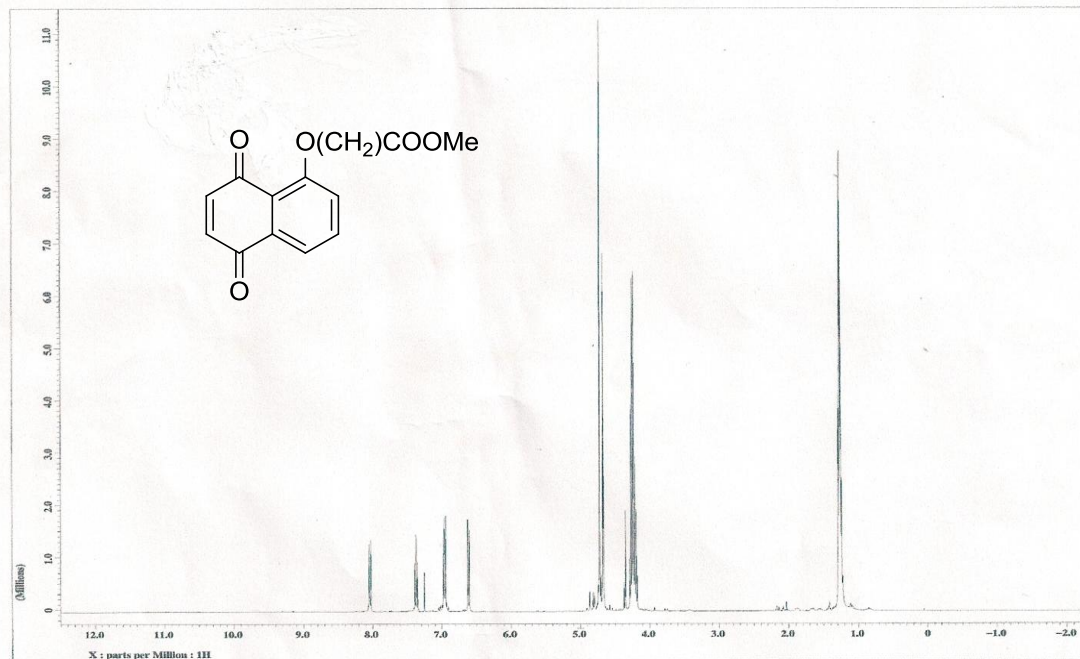
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