พฤกษเคมีและฤทธิ์ทางชีวภาพของ *Knema glauca* และ *Knema furfuracea*

นายนพดล รังแก้ว

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
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PHYTOCHEMICAL AND BIOACTIVITIES OF *KNEMA GLAUCA* AND *KNEMA FURFURACEA*

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นพดล รังแก้ว: พฤกษเคมีและฤทธิ์ทางชีวภาพของ *Knema glauca* และ *Knema furfuracea.* (PHYTOCHEMICAL AND BIOACTIVITIES OF *KNEMA GLAUCA* AND *KNEMA FURFURACEA*) อ. ที่ปรึกษาวิทยานิพนธ์หลัก : รศ.ดร.รุทธ์ สุทธิศรี, 284 หน้า.

การศึกษาองค์ประกอบทางเคมีจากลำต้น, ใบและผลของ *Knema glauca* (วงศ์ Myristicaceae) สามารถแยกสารใหม่ในกลุ่ม linear diterpene 1 ชนิด คือ glaucaic acid, สารในกลุ่ม phenylacylresorcinol 1 ชนิด คือ 2,6-dihydroxyphenyl-tetradecan-1-one, สารในกลุ่ม acylresorcinol 1 ชนิด คือ malabaricone A, สารในกลุ่ม phenylacylphloroglucinol 1 ชนิด คือ1-(2,4,6-trihydroxy-phenyl)-9-phenylnonan-1-one, สารในกลุ่ม acylphloroglucinol 1 ชนิด คือ 1-(2,4,6-trihydroxy-phenyl)-undecan-1-one, สารในกลุ่ม flavan-acylphloroglucinol 1 ชนิด คือ myristinin A, สารในกลุ่ม flavan-phenylacylphloroglucinol 1 ชนิด คือ myristinin D, สารในกลุ่ม furofuran lignan 2 ชนิด คือ asarinin และ sesamin และสารในกลุ่ม flavan 1 ชนิด คือ (±)-7,4´-dihydroxy-3´-methoxyflavan สำหรับการศึกษาองค์ประกอบทางเคมีจากลำต้นและใบของ *Knema furfuracea* ซึ่งเป็นพืชอีกชนิดหนึ่งในวงศ์ Myristicaceae สามารถแยกสารชนิดใหม่ในกลุ่ม lignan ได้ 1 ชนิดคือ furfuracin รวมทั้งสารกลุ่มนี้ที่เคยมีรายงานมาแล้ว 2 ชนิด คือ (+)-*trans*-1,2-dihydrodehydroguaiaretic acid และ fragransin A_2, สารในกลุ่ม acylbenzoic acid 2 ชนิด คือ สารผสม 1:1 ระหว่าง gingkoic acid และ anarcardic acid, สารในกลุ่ม phenylacylbenzoic acid 2 ชนิด คือ สารผสม 1:2ระหว่าง 2-hydroxy-6-(12-phenyldodecyl) benzoic acid และ 2-hydroxy-6-(12-phenyldodecen-8´*Z*-yl) benzoic acid นอกจากนั้นยังพบสารในกลุ่ม isoflavone 1 ชนิด คือ biochanin A พิสูจน์โครงสร้างทางเคมีของสารทั้งหมดที่สกัดได้โดยอาศัยเทคนิคทางวิเคราะห์เชิงสเปคตรัมของ UV, IR, MS และ NMR ร่วมกับการเปรียบเทียบข้อมูลของสารที่เคยมีรายงานมาแล้ว

สาร 1-(2,4,6-trihydroxy-phenyl)-undecan-1-one มีความเป็นพิษระดับปานกลางต่อ NCI-H187 cell line ด้วยค่า IC_{50} 5.60 ไมโครกรัมต่อมิลลิลิตร ในขณะที่สาร 2,6-dihydroxyphenyl-tetradecan-1-one มีความเป็นพิษระดับปานกลางต่อ KB cell line ด้วยค่า IC_{50} 9.15 ไมโครกรัมต่อมิลลิลิตร สาร 1-(2,4,6-trihydroxy-phenyl)-9-phenylnonan-1-one แสดงความเป็นพิษระดับปานกลางต่อ BC cell line ด้วยค่า IC_{50} 8.23 ไมโครกรัมต่อมิลลิลิตร สาร malabaricone, 1-(2,4,6-trihydroxy-phenyl)-undecan-1-one และ1-(2,4,6-trihydroxy-phenyl)-9-phenylnonan-1-one แสดงฤทธิ์ต้านเชื้อวัณโรค ไวรัสเริม และสามารถยับยั้งการสร้าง advanced glycation end-products ได้ นอกจากนั้น สาร malabaricone A ยังแสดงฤทธิ์ในการต้านเชื้อมาลาเรียได้ดีกว่า dihydroartemisinin ที่ใช้เป็นสารมาตรฐานด้วยค่า IC_{50} เท่ากับ 2.78 นาโนโมลาร์

สาขาวิชา เภสัชเคมีและผลิตภัณฑ์ธรรมชาติ...ลายมือชื่อนิสิต...นพดล รังแก้ว.....

ปีการศึกษา 2551..... ลายมือชื่อ อ. ที่ปรึกษาวิทยานิพนธ์หลัก...รุทธ์ สุทธิศรี.....

#4576956133: MAJOR PHARMACEUTICAL CHEMISTRY AND NATURAL PRODUCTS

KEYWORDS: *KNEMA GLAUCA* / *KNEMA FURFURACEA* / MYRISTICACEAE / LINEAR DITERPENE / ARYLNAPHTHALENE LIGNANS

NOPPADON RANGKAEW: PHYTOCHEMICAL AND BIOACTIVITIES OF *KNEMA GLAUCA* AND *KNEMA FURFURACEA*. ADVISOR: ASSOC.PROF. RUTT SUTTISRI, Ph.D., 284 pp.

Chemical investigation of the stems, leaves and fruits of *Knema glauca* (family Myristicaceae) led to the isolation of a new linear diterpene named glaucaic acid, a phenylacylresorcinol, 2,6-dihydroxyphenyl-tetradecan-1-one. In addition to an acylresorcinol, malabaricone A, a phenylacylphloroglucinol, 1-(2,4,6-trihydroxyphenyl)-9-phenylnonan-1-one, an acylphloroglucinol, 1-(2,4,6-trihydroxyphenyl)-undecan-1-one, a flavan-acylphloroglucinol, myristinin A, a flavan-phenylacylphloroglucinol, myristinin D, two furofuran lignans, asarinin and sesamin, and a flavan, (±)-7,4′-dihydroxy-3′-methoxyflavan. From the stems and leaves of *Knema furfuracea*, another myristicaceous plant, a new arylnaphthalene lignan named furfuracin, together with two known lignans, (+)-*trans*-1,2-dihydrodehydroguaiaretic acid and fragransin A_2, two acylbenzoic acids as a 1:1 mixture of gingkoic acid and anarcardic acid, two phenylacylbenzoic acids as a 1:2 mixture of 2-hydroxy-6-(12-phenyldodecyl)benzoic acid and 2-hydroxy-6-(12-phenyldodecen-8′*Z*-yl)benzoic acid, and an isoflavone, biochanin A, were isolated. The chemical structures of these compounds were determined by spectroscopic analyses, including UV, IR, MS and NMR, and comparison with previously reported data.

1-(2,4,6-Trihydroxy-phenyl)-undecan-1-one was moderately cytotoxic against NCI-H187 cell line with an IC_{50} value of 5.60 µg/ml, whereas 2,6-dihydroxyphenyl-tetradecan-1-one was moderately cytotoxic against KB cell line with an IC_{50} value of 9.15 µg/ml. 1-(2,4,6-Trihydroxy-phenyl)-9-phenylnonan-1-one exhibited moderate cytotoxicity against BC cell line with an IC_{50} value of 8.23 µg/ml. Malabaricone A, 1-(2,4,6-trihydroxy-phenyl)-undecan-1-one and 1-(2,4,6-trihydroxy-phenyl)-9-phenylnonan-1-one were active against *Mycobacterium tuberculosis*, herpes simplex virus type 1 and were able to inhibit the formation of Advanced Glycation End-Products. Moreover, malabaricone A was able to display higher anti-malarial activity than the standard compound, dihydroartemisinin, with an IC_{50} value of 2.78 nM.

Field of Study: Pharmaceutical Chemistry and Natural Products...Student's Signature: Noppadon Rangkaew

.....Advisor's Signature: Rutt Suttisri

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LIST OF SCHEMES

LIST OF ABBREVIATIONS

$[\alpha]^{25}_{D}$	=	Specific rotation at 25° and sodium D line (589 nm)
acetone-d_6	=	Deuterated acetone
AGEs	=	Advanced glycation endproduct
br s	=	Broad singlet (for NMR spectra)
BSA	=	Bovine serum albumin
c	=	Concentration
°C	=	Degree Celsius
calcd	=	Calculated
$CDCl_3$	=	Deuterated chloroform
CFU	=	Colony forming unit
$CHCl_3$	=	Chloroform
CH_2Cl_2	=	Dichloromethane
cm	=	Centimeter
cm^{-1}	=	reciprocal centimeter (unit of wave number)
^{13}C NMR	=	Carbon-13 Nuclear Magnetic Resonance
Con A	=	Concanavalin A
2D NMR	=	Two dimentional Nuclear Magnetic Resonance
d	=	doublet (for NMR spectra)
dd	=	doublet of doublets (for NMR spectra)
ddd	=	doublet of doublet of doublet (for NMR spectra)
dt	=	doublet of triplets (for NMR spectra)
DEPT	=	Distortionless Enhancement by Polarization Transfer
DMSO-d_6	=	Deuterated dimethyl sulfoxide
δ	=	Chemical shift
ε	=	Molar absorptivity
ED_{50}	=	Median effective dose
EI MS	=	Electron Impact Mass Spectrometry
ESI MS	=	Electrospray Ionization Mass Spectrometry
ESI TOF MS	=	Electrospray Ionization Time of Flight Mass Spectrometry
EtOAc	=	Ethyl acetate
EtOH	=	Ethanol

em.	=	Emission
ex.	=	Excitation
FT-IR	=	Fourier Transform Infrared Spectrum
g	=	Gram
h	=	Hour
^{1}H NMR	=	Protron Nuclear Magnetic Resonance
^{1}H-^{1}H COSY	=	Homonuclear (Protron-Protron) Correlation Spectroscopy
HMBC	=	^{1}H-detected Hetronuclear Multiple Bond Coherence
HMQC	=	^{1}H-detected Hetronuclear Multiple Quantum Coherence
HPLC	=	High Performance Liquid Chromatography
HR	=	High Resolution
HSQC	=	Heteronuclear Single Quantum Correlation
Hz	=	Hertz
IC_{50}	=	Median Inhibitory Concentration
IR	=	Infrared Spectrum
J	=	Coupling constant
KBr	=	Potassium bromide
Kg	=	Kilogram
L	=	Liter
λ_{max}	=	Wavelength at maximal absorption
M	=	Meter
µg	=	Microgram
µg/ml	=	Microgram per milliter
µl	=	Microliter
µM	=	Micromolar
[M]+	=	Molecular ion
m	=	Multiplet (for NMR spectra)
MeOH	=	Methanol
mg	=	Milligram
MHz	=	Megahertz
MIC	=	Minimum inhibitory concentration
min	=	Minute
ml	=	Milliliter
mM	=	Millimolar

mm	=	Millimeter
mp	=	Melting point
MS	=	Mass Spectrometry
MW	=	Molecular Weight
m/z	=	Mass to charge ratio
ν_{max}	=	Wave number at maximal absorption
Nm	=	Nanometer
NMR	=	Nuclear Magnetic Resonance
NOESY	=	Nuclear Overhauser Enhancement Spectroscopy
OD	=	Optical density
PBS	=	Phosphate Buffer Saline
ppm	=	Part-per-million
p	=	Pentet (for NMR spectra)
s	=	Singlet (for NMR spectra)
rpm	=	Round per minute
TFA	=	Trifluoroacetic acid
TLC	=	Thin Layer Chromatography
UV	=	Ultraviolet

CHAPTER I

INTRODUCTION

Myristicaceae is a homogenous family which belongs within the order Magnoliales. Several members of this plant family are famous for their traditional and medicinal uses in Southeast Asian countries. The seed (nutmeg) and aril (mace) of *Myristica fragrans* are one of the most popular spices with various medicinal uses. They are known as carminative and stomachic. In China, the powdered nut is a remedy for stomach cramps, heart diseases and chronic rheumatism. In Indo-China, the powdered seed is used to cure dysentery, anorexia and colic. It is also used in tonics to treat malaria, rheumatism and given post partum to cure sciatica. Oil from the seeds and aril is rubbed on the temples to relieve headache (Perry, 1980). However, using nutmeg in too large doses can be toxic, causing convulsions in the patient. The aromatic bark and leaves of another member of this plant family, *Horsfieldia glabra*, have been used in Indonesia to treat intestinal disorders. Its bark is also a treatment for sores and pimples.

Extracts from several myristicaceous plants have been shown to be biologically active. Hexane extract of nutmeg seeds displayed both acute and chronic effects on the electrophysiology of toad heart. Acute treatment with the extract resulted in a dose-related sinus tachycardia, faster atrioventricular conduction speed and an increased amplitude of ventricular action potential. Chronic treatment resulted in sinus bradycardia and decreased amplitude and increased duration of ventricular action potential (Saleh *et al.*, 1989). It was also reported as having anxiogenic activity in mice (Sonavane *et al.*, 2002). Ethanolic extract of nutmeg showed antidiarrheal, hypnotic, analgesic, anti-hypertensive (Grover *et al.*, 2002) and aphrodisiac activities in male mice (Tajuddin, Latif and Dasmi, 2003), whereas its chloroform extract was demonstrated to be anti-inflammatory by inhibiting the carrageenan-induced rat paw oedema. The extract also possessed analgesic activity and offered protection against thrombosis induced by ADP/adrenaline mixture in mice (Olajide *et al.*, 1999). Extract from the aril (mace) of this plant was chemopreventive against DMBA-induced papillomagenesis on the skin of male Swiss albino mice. The skin papilloma incidence was reduced by 50% when the animal received diet treatment with 1%

mace during the periinitiational phase of tumorigenesis (Jannu, Hussain and Rao, 1991). Myristicin, isolated from the methanol extract of mace, showed anti-inflammatory activity on acetic acid-induced vascular permeability in mice at the dose of 0.17 mg/kg (Ozaki *et al.*, 1989).

Other examples of bioactive extracts from plants of this family are as follows. The methanol extract of the leaves of *Iryanthera lancifolia* exhibited antibacterial activity (Rojas *et al.*, 2003), while similar extract of the stem bark of *I. laevis* was shown to possess significant antimalarial activity against *Plasmodium berghei* by reducing the parasitaemia in swiss male mice down 59% when given at 100 mg/kg (Munoz *et al*., 2000). The methanol extract of the leaves of *Otoba novogranatensis*, a Colombian plant, was active against chloroquine-resistant *Plasmodium falciparum* with an IC_{50} value of 26 µg/ml. In addition, the dichloromethane and methanol extracts of the fruits of this plant was active against amastigotes of *Leishmania panamensis* at ED_{50} values of 6.5 and 10.6 µg/ml, respectively (Weniger *et al*., 2001). Both the ethanolic extract of the stem bark of *Pyncnanthus angolensis*, a plant used in traditional medicine of islanders in the Gulf of Guinea (Madureira *et al*., 2002), and the volatile oil from the leaves of *Virola surinamensis*, used by Waiapi Amazon Indians to treat malaria (Lopes *et al*., 1999), were active *in vitro* against the chloroquine-resistant *P. falciparum*.

From the above data, it is evident that members of the family Myristicaceae possess several interesting biological activities. However, studies have been done on only a limited number of its genera. One of these is the genus *Knema* which consists of approximately 95 species, seventeen of which can be found in Thailand. Some *Knema* species are used medicinally, for example, in Indo-China the oily seeds of *Knema globularia* (เลือดแรด) are made into ointment and soap to treat skin diseases, especially scabies. In Indonesia, decoction of the bark of *K. glaucescens* (เลือดนวลน้อย) is used as a treatment for abdominal illnessses. Only a number of phytochemical and biological studies have been done on plants of this genus, and, therefore, two *Knema* species were selected for the current study. The first one is *Knema furfuracea* Warb. (Thai name: เลือดควายใบใหญ่). Previous investigations of this plant have revealed two antibacterial acylphloroglucinols (knerachelins A and B) from its leaves (Zahir *et al*., 1993), whereas its stems yielded two lignans [dehydroguaiaretic acid and (+)-*trans*-

1,2-dihydrodehydroguaiaretic acid], an isocoumarin [8-hydroxy-3-(l0-phenyl-dodecyl)-isocoumarin], an acylphenol [3-(l2-phenyldodecyl)-phenol] and a phenyl-alkylbenzoic acid [2-hydroxy-6-(10´-phenyldecyl) benzoic acid] (Pinto *et al*., 1990). Preliminary bioactivity screenings of this plant revealed that the EtOAc extracts of its leaves and stem and the hexane extract of its stem were active against *Mycobacterium tuberculosis* at MIC values of 100, 25 and 50 µg/ml, respectively. The hexane, EtOAc and methanol extracts of its leaves and stem exhibited antiviral activity against herpes simplex virus type 1 (HSV-1) at IC_{50} values of 23.4, 5.1, 1.9, 2.4, 1.2 and 35.3 µg/ml, respectively. In addition, the EtOAc extracts of the leaves and stem were weakly (IC_{50} = 16.4 µg/ml) and moderately active (IC_{50} = 8.7 µg/ml), respectively, against oral human epidermoid carcinoma (KB) cell line.

The second *Knema* species chosen for this study is *Knema glauca* var. *glauca* Petermann. The plant has not been previously investigated. Preliminary assay results on its extracts showed that the EtOAc extract of its fruits was cytotoxic against human small cell lung cancer (NCI-H187) cell line with an IC_{50} value of 0.9 µg/ml. The hexane and methanol extracts of its leaves exhibited antimycobacterial activity at the same MIC value of 100 µg/ml, while the latter extract also showed anti-HSV-1 activity with an IC_{50} value of 100 µg/ml.

These two *Knema* plants were therefore selected for further investigation of their bioactive chemical constituents, and the purposes of this research are as follows:

1. Isolation and purification of compounds from *Knema glauca* and *Knema furfuracea.*
2. Determination of chemical structures of the isolated compounds.
3. Evaluation of biological activities of the isolated compounds.

CHAPTER II

HISTORICAL

1. The family Myristicaceae

Myristicaceae is a homogenous family which belongs within the order Magnoliales. The family comprises of about 20 genera and 500 species. The members of this plant family are dioecious or monoecious trees growing 3-40 m high. The bark usually exudes a red sap on cutting. Their leaves are simple, having no stipule. Their small flowers are usually in racemose umbels, with 2-5 lobed perianths that are sometimes splitted to the base. The stamens are united in a column. Each flower contains single, superior ovary with 2 stigmas and 1 ovule. The fruits are globose to oblong in shape, turning to yellow or red colour when ripe and splitted open by a circumferential suture into 2 lobes. The single, large seed is covered by red or orange-red waxy aril, both of which are aromatic.

In Thailand, there are about 5 genera and 30 species of this plant family. The names of these genera and approximate number of species are (de Wilde, 2002):- *Endocomia* (2), *Gymnacranthera* (2), *Horsfieldia* (8), *Knema* (17) and *Myristica* (8). Some examples of myristicaceous plants in Thailand are *Endocomia canarioides* (กรวยป่า), *Gymnacranthera farquhariana* var. *farquhariana* (กาบพร้าว), *Horsfieldia brachiata* (จันทน์ผา), *Knema austrosiamensis* (หันช้าง) and *Myristica fragrans* (จันทน์เทศ, nutmeg) (de Wilde, 2002).

2. The genus *Knema*

The genus *Knema* comprises about 95 species in tropical South-East Asia to Western New Guinea. Seventeen *Knema* species can be found in Thailand, mostly in the Peninsular region. Members of this plant genus are dioecious trees growing 3-30 m high. Their bark is smooth, fissured or flanking. Their leaf blades are up to 65 cm long; the texture is membranous to coriaceous. Their flowers have varied, persistent tomentum, but some are glabrescent. The inside of the flower is glabrous, having reddish, pinkish or greenish-creamy colour. The fruits are sessile to 20 mm stalked; the pericarp is thick, hard-fleshy or woody,

with various tomentum, sometimes soon glabrescent; the aril is lacinate at apex only (de Wilde, 2002).

3. *Knema glauca* var. *glauca* and *K. furfuracea*

Knema glauca var. *glauca* Petermann. (**Figure 1**) can be found growing in the south of Thailand. The plant is a tree of 5–30 m in height, with striate lower bark. Its leaf blades are membranous or chartaceous, elliptic to lanceolate in shape, 6–20 (-25) by 2–5.5 (-11) cm, greenish or brown above on drying. The lower leaf surface is grayish, at first with scattered stellate hair. The leaf veins are 12–22 pairs, raised or flat on the upper leaf surface. The pedicels of male flowers are 4-10 mm long; the flowers have persistent bracteole, reddish inside. The number of anthers are 8-10 and their diameter is 1.5–2 mm. The staminal column is 0.5–1 mm long. The pedicel of female flower is 1–6 mm long. The fruits are subglobose, ovoid or ellipsoid in shape, 1.8–3 by 1.4–1.8 cm, at first with short (not more 0.1 mm) scale-like hair. The fruit stalk is 3–7 mm long.

The second plant, *Knema furfuracea* Warb. (**Figure 2**), is a tree of 8-25 m. in height with brown to blackish bark. Its leaf blade is coriaceous, oblong to lanceolate (10 -25 cm long) in shape, with cordate base. On drying, the upper surface of the leaf turns to greenish to brown colour. The pedicel of male flower is 3–15 mm long. The bracteole of the flower is minute and red inside. The number of anthers is 3. The pedicel of female flower is 1.5–2 mm long; the perianth bud is ellipsoid or obovoid. The fruit is obovoid or subglobose, with hair (1–2 mm long) and stalk of 2–5 mm in length (de Wilde, 2002).

Both *Knema* species belong to the family Myristicaceae, of which a number of characteristic chemical constituents, including alkyl- and acylphenols, lignans and flavonoids, are found. A review of the chemical constituents of *Knema* plants, along with reviews of linear diterpenes and arylnaphthalene lignans found in higher plants, are presented below.

A

B

Figure 1. *Knema glauca* var. *glauca* Petermann.

A) Leaves, B) Fruits

A

B

Figure 2. *Knema furfuracea* Warb.

A) Leaves, B) Fruits

4. Linear Diterpenes in Higher Plants

In the plant kingdom, linear diterpenes can be found in both higher and lower plants. Several marine brown algae were reported to contain this type of diterpenoids. In the higher plants, linear diterpenes are chiefly distributed in the family Compositae. For examples, they were found in the aerial parts of *Bejaranoa semistriata* (Bohlmann *et al.*, 1981), *Baccharis thymifolia* (Saad, Pestchanker and Giordano, 1987), several *Conyza* species (Bohlmann and Wegner, 1982; Zdero *et al.*, 1990; Galal *et al*., 1998), *Helogyne apaloidea* (Zdero, Bohlmann and Dillon, 1988), *Mikania sessilifolia* (Bohlmann *et al*., 1981), *Nardophyllum lanatum* (Zdero, Bohlmann and Niemeyer, 1990), *Olearia axillaris* (Warning *et al*., 1988), *Pteronia eenii* (Zdero, Jakupovic and Bohlmann, 1990), a number of *Viguiera* species (Guerreiro, 1986; Zdero *et al.*, 1988), and *Wyethia helenioides* (Tamayo-Castillo *et al.*, 1989). This type of compounds was also isolated from members of some major plant families such as Labiatae, Euphorbiaceae, Solanaceae and Umbelliferae.

There have been a few reports on the biological activities of these terpenoids. The most well-known linear diterpene which has been commercially developed as a pharmaceutical product is plaunotol [**1.144**], which was extracted from a Thai medicinal plant, plau-noi (*Croton sublyratus*, family Euphorbiaceae). The compound is used as a cytoprotective antiulcer agent for gastritis and gastric ulcer in Japan (Kobayashi *et al*., 1982). Plaunotol has anti-ulcer activity both in experimental ulcer and in clinical trials. It has a strong bactericidal effect against *Helicobacter pylori*, which is associated with gastritis, duodenal ulcer, gastric ulcer and epidemic form of gastric carcinoma (Koga *et al*., 1996). Moreover, the compound showed gastroprotective action by inducing COX-2 expression and increasing PEG2 production in serum-starved RGM1 cells via activation of the NF-κB and CRE sites of *Cox-2* gene promoters (Fu *et al*., 2005) and inhibited indomethacin-induced gastric mucosal injury by inhibiting neutrophil activaton (Murakami *et al*., 1999). Another linear diterpene, centipedic acid [**1.39**], isolated from *Egletes viscosa* (Compositae), also showed gastroprotective activity by significantly reducing the mucosal lesions induced by 96% ethanol (Guedes *et al*., 2002; 2008) and indomethacin. Moreover, the compound was shown to possess anti-inflammatory and hepatoprotective activities (Lima *et al*., 1996). Thymifodioic acid [**1.151**], isolated from the aerial parts of *Baccharis thymifolia*,

showed insect growth regulatory effect against *Tenebrio molitor* larvae (Hikawczuk *et al*., 2008).

Distribution of linear diterpenes in higher plants is shown in **Table 1**, and their chemical structures are shown in **Figure 3**.

Table 1. Distribution of linear diterpenes in higher plants.

Compounds	Source	Family	Part	References
Acanthoaustralide [**1.1**]	*Acanthospermum australe*	Compositae	aerial parts	Bohlmann *et al*., 1981a
	Melampodium longipilum		aerial parts	Quijano and Fischert, 1984
Acetoxy ligantrol [**1.2**]	*Liatris elegans*	Compositae	n.i.	Herz and Sharma, 1975
9-Acetoxy-1,6,10-phyta-triene-3,5,14,15-tetrol [**1.3**]	*Geigeria burkei*	Compositae	n.i.	Bohlmann, Zdero and Ahmed, 1982b
19-Acetoxy-12, 20-dihydroxygeranylnerol [**1.4**]	*Lasiolaena morii*	Compositae	root	Bohlmann *et al*., 1982a
18-Acetoxy-12,19-di-hydroxy geranylnerol [**1.5**]	*Blainvillea latifolia*	Compositae	aerial parts	Singh *et al*., 1988
19-Acetoxy-15-hydroxy-12-oxo-13*E*,14*E*-dehydro-10,11,14,15-tetrahydro-geranylnerol [**1.6**]	*Siegesbeckia orientalis*	Compositae	aerial parts	Zdero *et al*., 1991
18-Acetoxy-16,20-di-hydroxygeranylnerol [**1.7**]	*Mikania periplocifolia*	Compositae	aerial parts	Gutierrez *et al*., 1985

Table 1. (continued)

Compounds	Source	Family	Part	References
18-acetoxy-17,18,19-trihydroxy-6,7,10,11-tetra-hydrogeranylgeraniol-20,1-lactone [**1.8**]	*Nardophyllum lanatum*	Compositae Labiatae	n.i. aerial parts	Jakupovic *et al.*, 1986a
18-Acetoxy-17-hydroxy-geranylgeraniol [**1.9**]	*Chiliotrichium rosmarinifolium*			
19-Acetoxy-18-hydroxy-geranylnerol [**1.10**]	*Ageratina ligustrina*	Compositae	aerial parts	Tamayo-Castillo *et al.*, 1988
1-Acetoxy-18-hydroxy-geranylgeraniol-19-oic acid [**1.11**]	*Microglossa pyrrhopappa*	Compositae	aerial parts	Zdero, Bohlmann and Mungai, 1990c
19-Acetoxy-20-hydroxy-geranylnerol [**1.12**]	*Ageratina tritis*	Compositae	n.i.	Bohlmann, *et al.*, 1985a
19-Acetoxy-20-hydroxy-geranylnerol-17-acid [**1.13**]	*Helogyne apaloidea*	Compositae	aerial parts	Zdero, Bohlmann and Dillon, 1988a
9-Acetoxy-5-hydroxy-geranyllinalol [**1.14**]	*Geigeria burkei*	Compositae	n.i.	Bohlmann *et al.*, 1982b
13-Acetoxy-5-hydroxy-geranyllinalol [**1.15**]				
1-Acetoxy-6,7-epoxy-19-hydroxy-12-oxo-smallan-tha-2*Z*,13*E*-diene [**1.16**]	*Smallanthus glabratus*	Compositae	aerial parts	Bohlmann *et al.*, 1985b

Table 1. (continued)

Compounds	Source	Family	Part	References
1-Acetoxy-6,7-epoxy-19-hydroxy-12-oxo-smallan-tha-2*Z*,14(21)-diene [**1.17**]	*Smallanthus glabratus*	Compositae	aerial parts	Bohlmann *et al*., 1985b
1-Acetoxyacanthoaustra-lide [**1.18**]	*Acanthospermum australe*	Compositae	aerial parts	Bohlmann, *et al*., 1981a
17-Acetoxyacanthoaustra-lide [**1.19**]	*Blainvillea latifolia*	Compositae	aerial parts	Singh *et al*., 1988
13-Acetoxygeranyllinalol [**1.20**]	*Geigeria burkei*	Compositae	aerial parts	Bohlmann *et al*., 1982b
20-Acetoxygeranylnerol [**1.21**]	*Stevia lemmonia*	Compositae	n.i.	Bohlmann and Zdero, 1985c
17-Acetoxygutiesobriolide [**1.22**]	*Gutierrezia solbrigii*	Compositae	n.i.	Jakupovic *et al*., 1985a
17-Acetoxyichthyouleolide [**1.23**]	*Ichthyothere ule*	Compositae	n.i.	Bohlmann *et al*., 1982c
17-Acetoxyisogutie-solbriolide [**1.24**]	*Gutierrezia solbrigii*	Compositae	n.i.	Jakupovic *et al*., 1985a
17-Acetoxythymifodioic acid [**1.25**]	*Baccharis thymifolia*	Compositae	aerial parts	Saad, Pestchanker, and Giordano, 1987

Table 1. (continued)

Compounds	Source	Family	Part	References
Axinyssene [**1.26**]	*Otostegia integrifolia*	Labiatae	leaves	Tesso and König, 2004
Capsianoside A [**1.27**]	*Capsicum annuum*	Solanaceae	fruits	Izumitani, Yahara and Nohara, 1990
Capsianoside I [**1.28**]				Marino *et al*., 2006
Capsianoside II [**1.29**]				
Capsianoside III [**1.30**]				
Capsianoside IX [**1.31**]				
Capsianoside L [**1.32**]				
Capsianoside V [**1.33**]				
Capsianoside VIII [**1.34**]				
Capsianoside X [**1.35**]				
Capsianoside XIII [**1.36**]				
Capsianoside XV [**1.37**]				
Capsianoside XVI [**1.38**]				
Centipedic [**1.39**]	*Baccharis pingraea*	Compositae	aerial parts	Wächter, Montenegro and Timmer-mann, 1999
	Centipeda orbicularis	Compositae	n.i.	Bohlmann and Mahanta, 1979
	Egletes viscosa	Compositae	n.i.	Guedes *et al*., 2008

Table 1. (continued)

Compounds	Source	Family	Part	References
Centipedic [**1.39**]	*Egletes viscosa*	Compositae	flower buds	Guedes *et al.*, 2002 Lima *et al.*, 1996
Clibadic acid [**1.40**]	*Clibadium pittierii*	Compositae	aerial parts	Tamayo-Castillo *et al.*, 1988
Conypododiol [**1.41**]	*Conyza podocephala*	Compositae	aerial part	Bohlmann and Wegner, 1982d
Conyzaleucolide A [**1.42**]	*C. hypoleuca*	Compositae	aerial parts	Zdero, Bohlmann and Mungai, 1991b
13,14-Dehydro-14,15-dihydro-5,15-dihydroxy-12-oxogeranylgeraniol [**1.43**]	*Ophryosporus floribundus*	Compositae	aerial parts	Zdero, Bohlmann and Niemeyer, 1990a
18,19-Diacetoxy-16,20-dihydroxygeranylnerol [**1.44**]	*Mikania periplocifolia*	Compositae	aerial parts	Gutierrez *et al.*, 1985
18,19-Diacetoxy-17,18,19-trihydroxy-6,7,10,11-tetra-hydrogeranylgeraniol-20,1-lactone [**1.45**]	*Nardophyllum lanatum*	Compositae	n.i.	Jakupovic *et al.*, 1986a

Table 1. (continued)

Compounds	Source	Family	Part	References
5,9-Diacetoxygeranyl-linalol [**1.46**]	*Geigeria* sp.	Compositae	n.i.	Bohlman *et al*., 1982b
16,18-Didroxynerylgeran-1,20-olide [**1.47**]	*Pteronia eenii*	Compositae	aerial parts	Zdero, Jakupovic and Bohlmann, 1990b
17,18-Didroxynerylgeran-1,20-olide[**1.48**]				
10,11-Dihydro-12,19-dioxogeranylnerol [**1.49**]	*Milleria quinqueflora*	Compositae	aerial parts	Jakupovic, Castro and Bohlmann, 1987
14,15-Dihydro-14,15-dihydroxygeranyllinalol [**1.50**]	*Geigeria* sp.	Compositae	n.i.	Bohlmann *et al*., 1982
10, 11-Dihydro-19-hydroxy-12-oxogeranyl-geraniol [**1.51**]	*Lasiolaena santosii*	Compositae	aerial parts	Bohlmann *et al*., 1981b
6,7-Dihydrogeranylgera-niol-18,19-dioic acid [**1.52**]	*Microglossa pyrrhopappa*	Compositae	aerial parts	Zdero, Bohlmann and Mungai, 1990c
Dihydromicroglossic acid [**1.53**]	*M. zeylanica*	Compositae	aerial parts	Gunatilaka *et al*., 1987
6,7-Dihydrothymifodioic acid [**1.54**]	*Olearia lepidophylla*	Compositae	aerial parts	Warning *et al*.,1988
	O. muelleri			
	O. subspicata			

Table 1. (continued)

Compounds	Source	Family	Part	References
3,15-Dihydroxy-1,6,13-phytatrien-12-one [**1.55**]	*Helichrysum oreophilum*	Compositae	aerial parts	Jakupovic *et al*., 1986b
1,15-Dihydroxy-12-oxo-2,6,13-phytatrien-19-al [**1.56**]	*Milleria quinqueflora*	Compositae	aerial parts	Jakupovic, Castro and Bohlmann, 1987
1,19-Dihydroxy-12-oxo-smallantha-2*Z*,6*Z*,10*E*, 13*E*-tetraene [**1.57**]	*Smallanthus glabratus*	Compositae	aerial parts	Bohlmann *et al*., 1985b
1,19-Dihydroxy-12-oxo-smallantha-2*Z*,6*Z*,10*E*,14 (21)-tetraene [**1.58**]				
9-(15,16-Dihydroxy-15-methylene)-*p*-cymene [**1.59**]	*Tanacetum annuum*	Compositae	flower	Barrero *et al*., 1992
(10*E*)-3,12-Dihydroxy-3,7,11,15-tetramethyl-1,10,14-hexadecatrien-5,13-diene [**1.60**]	*Croton salutaris*	Euphorbiaceae	twig	Itokawa *et al*., 1991
1,19-Dihydroxy-6,7-epoxy-12-oxo-smallantha-2*Z*,10*E*,13*E*-triene [**1.61**]	*Smallanthus glabratus*	Compositae	aerial parts	Bohlmann *et al*., 1985b

Table 1. (continued)

Compounds	Source	Family	Part	References
1,19-Dihydroxy-6,7-epoxy-12-oxo-smallantha-2*Z*,10*E*,14(21)-triene [**1.62**]	*Smallanthus glabratus*	Compositae	aerial parts	Bohlmann *et al*., 1985b
12,18-Dihydroxygeranyl-geraniol [**1.63**]	*Lasiolaena santosii*	Compositae	aerial parts	Bohlmann *et al*., 1981b
5,13-Dihydroxygeranyl-geraniol [**1.64**]	*Ophryosporus floribundus*	Compositae	aerial parts	Zdero, Bohlmann and Niemeyer, 1990a
12, 19-Dihydroxygeranyl-geraniol [**1.65**]	*Lasiolaena santosii*	Compositae	aerial parts	Bohlmann *et al*., 1981b
5,13-Dihydroxygeranyl-linalol [**1.66**]	*Geigeria* sp.	Compositae	n.i.	Bohlmann *et al*., 1982b
17,20-Dihydroxygeranyl-nerol [**1.67**]	*Chiliotrichium rosmarinifolium*	Labiatae	aerial parts	Jakupovic *et al*., 1986c
18,19-Dihydroxyneryl-geraniol [**1.68**]	*Vittadinia gracilis*	Compositae	aerial parts	Zdero *et al*., 1988b
Dimerobrasiolide [**1.69**]	*Dimerostemma brasilianum*	Compositae	roots	Bohlmann *et al*., 1982e

Table 1. (continued)

Compounds	Source	Family	Part	References
Dimeroperatic acid [**1.70**]	*D. asperatum*	Compositae	n.i.	Bohlmann *et al*., 1981c
Dimeroperatic acid methyl ester [**1.71**]				
Dimethyl (2*E*,6*Z*)-2-[(3′*Z*,7′*E*)-9′-hydroxy-4′,8′-dimethylnona-3′,7′-dienyl]-6-methylocta-2,6-diene-dioic acid [**1.72**]	*Eremophila exilifolia*	Myoporaceae	leaves, branches	Ghisalberti, Jefferies and Proudfoot, 1981
3, 13-Di-O-*β*-*D*-glucopyra-nosyl geranyllinalol [**1.73**]	*Geigeria* sp.	Compositae	n.i.	Bohlmann *et al*., 1982b
Divaricatic acid [**1.74**]	*Pteronia divaricata*	Compositae	aerial parts	Zdero, Jakupovic and Bohlmann, 1990b
Epivittadinal [**1.75**]	*Vittadinia gracillus*	Compositae	aerial parts	Zdero *et al*., 1988b
6,7-Epoxy-19-hydroxy-12-oxo-6,7-dihydrogeranyl-nerol [**1.76**]	*Smallanthus glabratus*	Compositae	aerial parts	Bohlmann *et al*., 1985b
6,7-Epoxy-2,10,14-phyta-pentraene-1,8,12,19-diol [**1.77**]	*Balsamorhiza sagittata*	Compositae	aerial parts	Bohlmann *et al*., 1985c

Table 1. (continued)

Compounds	Source	Family	Part	References
11,15-Epoxy-3(20)-phytene-1,2-diol [**1.78**]	*Anisopappus pinnatifidus*	Compositae	aerial parts	Zdero and Bohlmann, 1989
14,15-Epoxy-3-hydroxy-1,6,10-phytatrien-13-one [**1.79**]	*Geigeria burkei*	Compositae	aerial parts	Bohlmann *et al*., 1982b
13-O-[*β-L*-Fucopyranosyl (1→6)-*β-D*-glucopyrano-syl] geranyllinalol [**1.80**]	*Viguiera gilliesii*	Compositae	aerial parts	Guerreiro, 1986
Furodivaricatic acid [**1.81**]	*Pteronia divaricata*	Compositae	aerial parts	Zdero, Jakupovic and Bohlmann, 1990
Furosolidagonone [**1.82**]	*Solidago drummondii*	Compositae	n.i.	Bohlmann *et al*., 1985d
(2*E*,6*E*)-9-(3-Furyl-6-methyl-2-(4-methylpent-3-enyl)-nona-2,6-dienoic acid [**1.83**]	*Dimerostemma brasilianum*	Compositae	roots	Bohlmann *et al*., 1982e
Geranylgeraniol-18,19-dioic acid [**1.84**]	*Microglossa pyrrhopappa*	Compositae	aerial parts	Zdero, Bohlmann and Mungai, 1990c

Table 1. (continued)

Compounds	Source	Family	Part	References
(2*Z*,6*Z*,10*E*)-Geranylgeraniol-19-oic acid [**1.85**]	*Picea abies*	Pinaceae	n.i.	Kimland and Norin, 1967
(2*E*,6*Z*,10*Z*)-Geranylgeraniol-19-oic acid [**1.86**]	*Conyza pyrifolia*	Compositae	aerial parts	Zdero *et al.*, 1990d
(2*Z*,6*Z*,10*E*)-Geranylgeraniol-19-oic methyl ester [**1.87**]	*Mikania congesta*	Compositae	aerial parts	Herz and Kulanthaivel, 1985
(2*E*,6*Z*,10*Z*)-Geranylgeraniol-19-oic methyl ester [**1.88**]	*Conyza pyrifolia*	Compositae	aerial parts	Zdero *et al.*, 1990d
Geranyllinalol-19,9-olide [**1.89**]	*Baccharis pteronioides*	Compositae	n.i.	Jakupovic *et al.*, 1990
(3R,6*E*,10*E*)-Geranyllinalool [**1.90**]	*Picea abies*	Pinaceae	n.i.	Kimland and Norin, 1967
(3S,6*E*,10*E*)-Geranyllinalool [**1.91**]				
Hanliuine I [**1.92**]	*Salix matsudan*	Berberidaceae	leaves	Zheng *et al.*, 2000
Hanliuine III [**1.93**]			leaves	Wang *et al.*, 2002
Helogynic acid [**1.94**]	*Helogyne apaloidea*	Compositae	aerial parts	Zdero, Bohlmann and Dillon, 1988a
10-Hydrogeranylgeraniol-20,1-lactone [**1.95**]	*Baccharis ochracea*	Compositae	aerial parts	Schenkel *et al.*, 1997

Table 1. (continued)

Compounds	Source	Family	Part	References
18-Hydroxy-19-oxogera-nylgeranial [**1.96**]	*Viguiera sylvatica*	Compositae	aerial parts	Tamayo-Castillo *et al*., 1989
(2*E*,6*E*,10*Z*)-1-Hydroxy-2,6,10,14-phytapentraen-18-al [**1.97**]	*Croton kerrii*	Euphorbiaceae	leaves	Sato, Ogiso and Kuwano, 1980
(2*E*,6*E*, 10*E*)-1-Hydroxy-2,6,10,14-phytapentraen-18-al [**1.98**]				
(2*Z*,6*E*,10*Z*,14*Z*)-16-Hydroxy-2,6,10,14-phyta-tetraene-1,19-dioic acid [**1.99**]	*Eremophila glutinosa*	Myoporaceae	n.i.	Ghisalberti, Jefferies and Proudfoot, 1981
(2*Z*,6*E*,10*Z*,14*E*)-16-Hydroxy-2,6,10,14-phyta-tetraene-1,19-dioic acid [**1.100**]				
17-Hydroxyacanthoaustra-lide [**1.101**]	*Melampodium longipilum*	Compositae	aerial parts	Quijano and Fischert, 1984
20-Hydroxygeranyl geraniol-9,18-olide [**1.102**]	*Diplostephium meyenii*	Compositae	aerial parts	Bittner, Schuster and Jakupovic, 1991
16-Hydroxygeranylgera-niol [**1.103**]	*Mikania goyazensis*	Compositae	n.i.	Kramp and Bohlmann, 1986

Table 1. (continued)

Compounds	Source	Family	Part	References
18-Hydroxygeranylgera-niol-19-oic acid [**1.104**]	*Microglossa pyrrhopappa*	Compositae	aerial parts	Zdero, Bohlmann and Mungai,1990c
5-Hydroxygeranyllinalool [**1.105**]	*Geigeria* sp.	Compositae	n.i.	Bohlmann *et al*., 1982b
13-Hydroxygeranyllinalol [**1.106**]	*Geigeria burkei*		aerial parts	
5-Hydroxygeranyllinalool [**1.107**]	*Nicotiana sylvestris*	Solanaceae	n.i.	Wallin *et al*., 1980
20-Hydroxygeranylnerol [**1.108**]	*Kingianthus paradoxus*	Compositae	n.i.	Bohlmann *et al*., 1981c
17-Hydroxygutiesobriolide [**1.109**]	*Gutierrezia solbrigii*	Compositae	n.i.	Jakupovic *et al*., 1985a
(10*E*)-17-Hydroxygutiesol-briolide [**1.110**]				
17-Hydroxyisogutiesolbri-olide [**1.111**]				
4-Hydroxyisophytol [**1.112**]	*Lemma minor*	Lemnaceae	n.i.	Previtera and Monaco, 1984
Ichthyouleolide [**1.113**]	*Ichthyothere ulei*	Compositae	roots	Bohlmann *et al*., 1982c

Table 1. (continued)

Compounds	Source	Family	Part	References
Incanic acid [**1.114**]	*Baccharis thymifolia*	Compositae	aerial parts	Saad, Pestchanker and Giordano, 1987
	Conyza incana	Compositae	aerial parts	Galal *et al*., 1998
Isoacanthoaustralide [**1.115**]	*Acanthospermum australe*	Compositae	aerial parts	Bohlmann *et al*., 1981a
Koanoadmantic acid [**1.116**]	*Koanophyllon admantium*	Compositae	roots	Bohlmann *et al*., 1981d
Ligantrol [**1.117**]	*Liatris elegans*	Compositae	n.i.	Herz and Sharma, 1975
Lingulatusin [**1.118**]	*Aster ligulatus*	Compositae	whole plant	Shao *et al*., 1998
Microglossic acid [**1.119**]	*Microglossa zeylanica*	Compositae	aerial parts	Gunatilaka *et al.*, 1987
Mikanifuran [**1.120**]	*Mikania sessilifolia*	Compositae	aerial parts	Bohlmann *et al.*, 1981f
Neophytadiene [**1.121**]	*Nicotiana tabacum*	Solanaceae	leaves	Rowland, 1957
Oleaxillaric acid [**1.122**]	*Olearia axillaris*	Compositae	aerial part	Warning *et al*., 1988
Oleaxillaric methyl ester [**1.123**]				
Oxepanes tomentol [**1.124**]	*Montanoa tomentosa*	Compositae	leaves	Quijano *et al*., 1985a

Table 1. (continued)

Compounds	Source	Family	Part	References
12-Oxo-10,11-dihydro-geranyllinalool [**1.125**]	*Helichrysum oreophilum*	Compositae	n.i.	Bohlmann *et al*., 1980
18-Oxo-19-hydroxyneryl-geraniol [**1.126**]	*Vittadinia gracilis*	Compositae	n.i.	Zdero *et al*., 1988b
18-Oxo-2,6,10,14-phyta-tetraen-1,16-dioic acid [**1.127**]	*Eremophila glutinosa*	Myoporaceae	n.i.	Ghisalberti, Jefferies and Proudfoot, 1981
(2*S*,3*S*)-18-Oxo-6,10,14-phytatriene-1,16-dioic acid [**1.128**]				
13-Oxogeranyllinalol [**1.129**]	*Geigeria burkei*	Compositae	aerial parts	Bohlmann *et al*., 1982b
12-Oxogeranyllinalool [**1.130**]	*Helichrysum krebsianum*	Compositae	n.i.	Bohlmann *et al*., 1980
Peucelinendiol [**1.131**]	*Peucedanum oreoselinum*	Umbelliferae	roots	Lemmich, 1979
2,6-Phytadiene-1,16,17,18-tetrol [**1.132**]	*Pteronia incana*	Compositae	aerial parts	Zdero, Jakupovic and Bohlmann, 1990b
Phytal [**1.133**]	*Tetragonia tetragonoide*	Aizoaceae	leaves	Aoki *et al*., 1982

Table 1. (continued)

Compounds	Source	Family	Part	References
1,6,10,13-Phytatetraen-3,15-diol [**1.134**]	*Geigeria burkei*	Compositae	aerial parts	Bohlmann *et al*., 1982b
1,6,10,13,15-Phytapenta-en-3-ol [**1.135**]				
1,6,10,14-Phytapentraen-3,9-diol [**1.136**]				
2,6,10,14-Phytatetraen-1,16,18-dioic acid [**1.137**]	*Eremophila glutinosa*	Myoporaceae	n.i.	Ghisalberti, Jefferies and Proudfoot, 1981
2,6,10,14-Phytatetraene-1,16,18,20-tetrol [**1.138**]	*Viguiera sylvatica*	Compositae	aerial parts	Tamayo-Castillo *et al*., 1989
2,6,10,14-Phytatetraene-1,18,19,20-tetrol [**1.139**]	*V. gilliesii*	Compositae	aerial parts	Guerreiro, 1986
1,6,10-Phytatriene-3,5,14, 15-tetrol [**1.140**]	*Geigeria burkei*	Compositae	n.i.	Bohlmann *et al*., 1982b
3(20)-Phytene-1,2-diace-toxy [**1.141**]	*Senecio gallicus*	Compositae	aerial parts	Urones *et al*., 1987
3(20)-Phytene-1,2-diol [**1.142**]				
Phytofuran [**1.143**]	*Nicotiana tabacum*	Solanaceae	leaves	Wahlberg *et al*., 1977

Table 1. (continued)

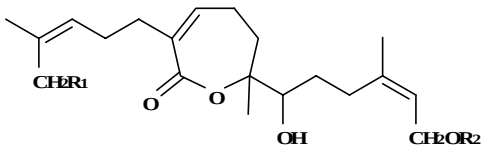
Compounds	Source	Family	Part	References
Plaunotol [**1.144**]	*Croton sublyratus, C. columnaris*	Euphorbiaceae	leaves	Ogiso *et al*., 1978
Saurufuran A [**1.145**]	*Saururus chinensis*	Saururaceae	roots	Hwang *et al*., 2002
Saurufuran B [**1.146**]	*Olearia axillaris*	Compositae	aerial parts	Warning *et al*., 1988
3,7,11,15-Tetramethyl-hexadeca-2,6,10,14-tetraen-7-[(acetyloxy)-methyl]-12-oxo-1,19-diol [**1.147**]	*Carpesium triste*	Compositae	seeds	Gao, Lin and Jia, 2007
(2*E*,6*Z*,11*S*,12*R*)-3,7,11,15-Tetramethylhexadeca-2,6,14- triene-7-[(acetyl-oxy) methyl]-1,12-diol-1-acetate [**1.148**]				
(2*E*,6*E*,11*S*,12*R*)-3,7,11,15-Tetramethylhexadeca-2,6,14-triene-1,12-diol [**1.149**]				
(2*E*,6*E*,11*S*,12*R*)-3,7,11,15-Tetramethylhexadeca-2,6,14-triene-7-[(acetyl-oxy)methyl]-1,12-diol [**1.150**]				

Table 1. (continued)

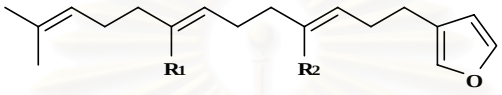
Compounds	Source	Family	Part	References
Thymifodioic acid [**1.151**]	*Baccharis thymifolia*	Compositae	aerial parts	Saad, Pestchanker and Giordano, 1987
Tomentanol [**1.152**]	*Montanoa tomentosa*	Compositae	leaves	Oshima, Cordell and Fong, 1986
Tomexanthin [**1.153**]			aerial parts	Seaman, Malcolm and Fischer, 1984
Tomexanthol [**1.154**]			leaves	Quijano *et al.*, 1985a
1,6,7-Trihydroxy-17-acetoxymelcantholide [**1.156**]	*Malampodium leucanthum*	Compositae	aerial parts	Quijano *et al.*, 1985b
16,17,18-Trihydroxy-2,6,10,14-phytatetraen-1,20-olide [**1.157**]	*Pteronia eenii*	Compositae	aerial parts	Zdero, Jakupovic and Bohlmann, 1990b
16,18,20-Trihydroxy-6-oxo-7,19-dehydro-6,7-dihydrogeranylnerol [**1.158**]	*Viguiera sylvatica*	Compositae	aerial parts	Tamayo-Castillo *et al.*, 1989

Table 1. (continued)

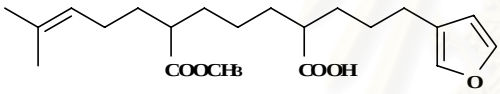
Compounds	Source	Family	Part	References
16,18,19-Trihydroxygera-nylnerol [**1.159**]	*Helianthopsis bishopii*	Compositae	aerial parts	Bohlmann *et al.*, 1985e
8,12,19-Trihydroxygera-nylnerol [**1.160**]	*Balsamorhiza sagittata*	Compositae	aerial parts	Bohlmann *et al.*, 1985f
8,12,19-Trihydroxygera-nylnerol-6,7-epoxide [**1.161**]				
1,10,17-Trihydroxymel-fusanolide [**1.162**]	*Melampodium diffusum*	Compositae	n.i.	Quijano and Fischert, 1984
Tuxpanolide [**1.163**]	*Perymenium hintonii*	Compositae	aerial parts	Maldonado *et al.*, 1998
Viguieric acid [**1.164**]	*Viguiera deltoidea*	Compositae	leaves	Gao and Mabry, 1985
Vittadinal [**1.165**]	*Vittadinia gracillus*	Compositae	aerial parts	Zdero *et al.*, 1988b
Vittadinol [**1.166**]				
Wyethic acid [**1.167**]	*Wyethia helenioides*	Compositae	aerial parts	Bohlmann *et al.*,1981e
Zoapatanol [**1.168**]	*Montanoa tomentosa*	Compositae	leaves	Kanojia *et al.* 1982
Zoapatol A [**1.169**]			aerial parts	Quijano *et al.*, 1991



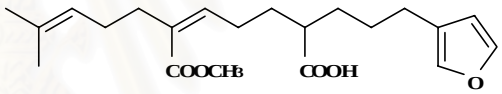
	R_1	R_2
Acanthoaustralide [**1.1**]	H	H
1-Acetoxyacanthoaustralide [**1.18**]	H	$COCH_3$
17-Acetoxyacanthoaustralide [**1.19**]	$OCOCH_3$	H
17-Hydroxyacanthoaustralide [**1.101**]	OH	H



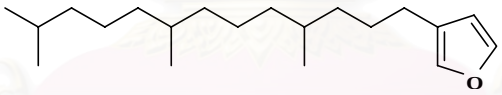
	R_1	R_2
Centipedic [**1.39**]	COOH	CH_3
Conypododiol [**1.41**]	CH_2OH	CH_2OH



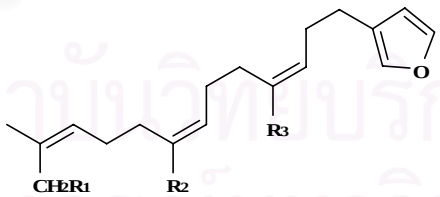
Dihydromicroglossic acid [**1.53**]



Microglossic acid [**1.119**]

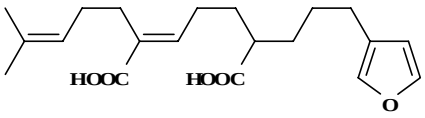


Phytofuran [**1.143**]

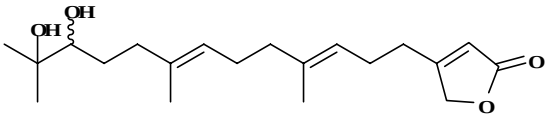


	R_1	R_2	R_3
17-Acetoxythymifodioic acid [**1.25**]	$OCOCH_3$	COOH	COOH
Incanic acid [**1.114**]	H	CH_2OH	CH_2OH
Thymifodioic acid [**1.151**]	H	COOH	COOH

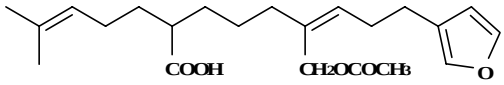
Figure 3. Chemical structure of linear diterpenes in higher plants



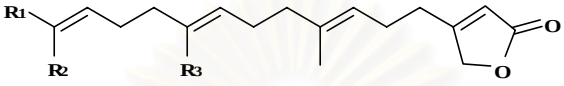
6,7-Dihydrothymifodioic acid [**1.54**]



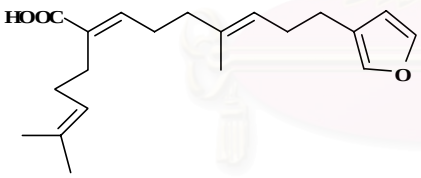
Dimerobrasiolide [**1.69**]



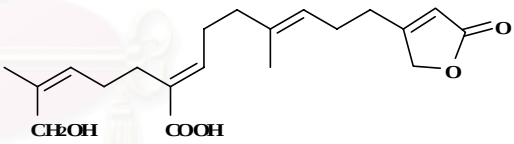
Furodivaricatic acid [**1.81**]



	R_1	**R_2**	**R_3**
17-Acetoxygutiesobriolide [**1.22**]	H	CH_2OCOCH_3	COOH
16,18-Didroxynerylgeran-1,20-olide [**1.47**]	CH_2OH	CH_3	CH_2OH
17,18-Didroxynerylgeran-1,20-olide [**1.48**]	H	CH_2OH	CH_2OH
Dimeroperatic acid [**1.70**]	H	COOH	CH_3
Dimeroperatic acid methyl ester [**1.71**]	H	$COOCH_3$	CH_3
17-Hydroxygutiesobriolide [**1.109**]	H	CH_2OH	COOH
16,17,18-Trihydroxy-2,6,10,14-phytatetraen-1,20-olide [**1.157**]	CH_2OH	CH_2OH	CH_2OH

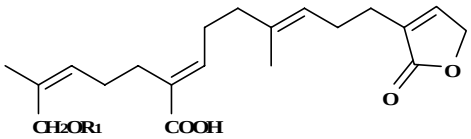


(2*E*, 6*E*)-9-(3-Furyl)-6-methyl-2-(4-methylpent-3-enyl)-nona-2,6-dienoic acid [**1.83**]



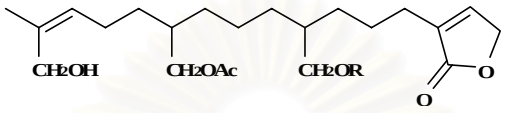
(10*E*)-17-Hydroxygutiesobriolide [**1.110**]

Figure 3. (continued)



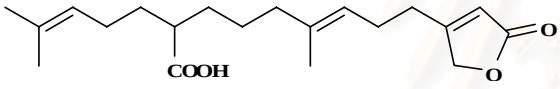
17-Acetoxyisogutiesolbriolide [**1.24**]: R = $COCH_3$

17-Hydroxyisogutiesolbriolide [**1.111**]: R = H

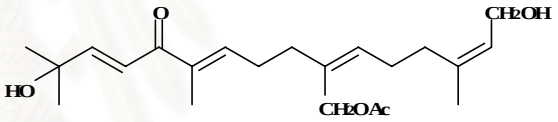


18-Acetoxy-17,18,19-trihydroxy-6,7,10,11-tetrahydrogeranylgeraniol-20,1-lactone [**1.8**]: R = H

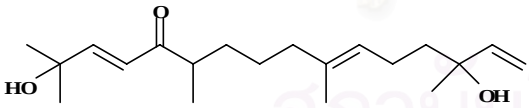
18,19-Diacetoxy 17,18,19-trihydroxy-6,7,10,11-tetrahydrogeranylgeraniol-20,1-lactone [**1.45**]: R = $COCH_3$



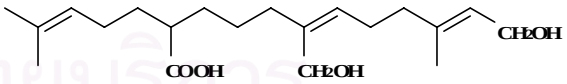
10-Hydrogeranylgeraniol-20,1-lactone [**1.5**]



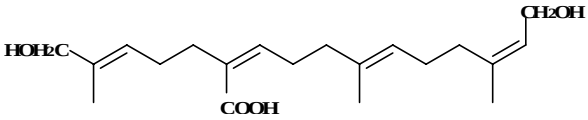
19-Acetoxy-15-hydroxy-12-oxo-13,14*E*-dehydro-10,11,14,15-tetrahydro-geranylnerol [**1.6**]



3,15-Dihydroxy-1,6,13-phytatrien-12-one [**1.55**]

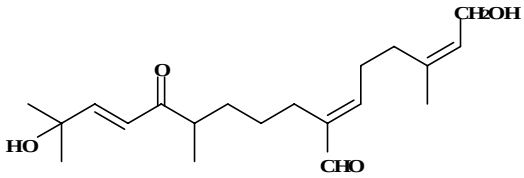


Divaricatic acid [**1.74**]

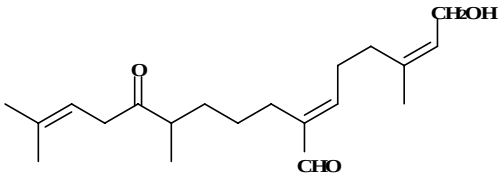


Wyethic acid [**1.172**]

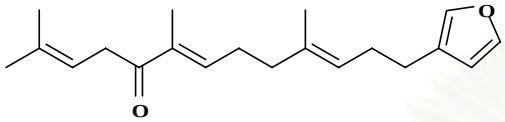
Figure 3. (continued)



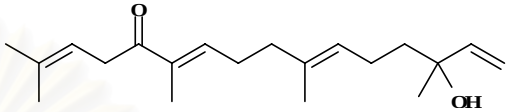
1,15-Dihydroxy-12-oxo-2,6,13-phytatrien-19-al [**1.56**]



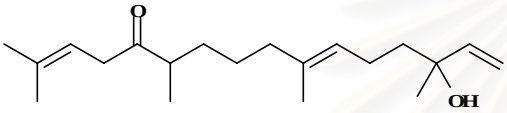
10,11-Dihydro-12,19-dioxogeranylnerol [**1.49**]



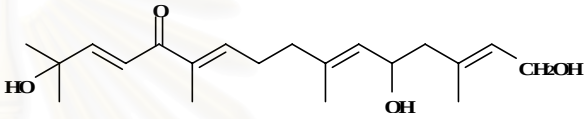
Furosolidagonone [**1.82**]



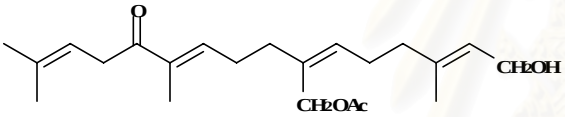
12-Oxogeranyllinalool [**1.130**]



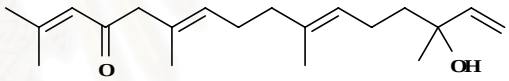
12-Oxo-10,11-dihydrogeranyllinalool [**1.125**]



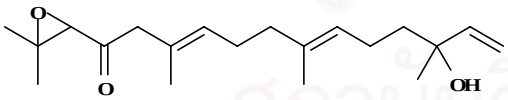
13,14-Dehydro-14,15-dihydro-5,15-dihydroxy-12-oxogeranylgeraniol [**1.43**]



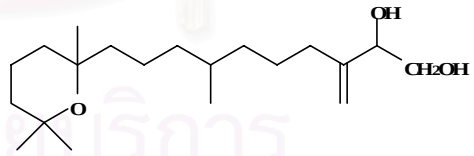
3,7,11,15-Tetramethylhexadeca-2,6,10,14-tetraen-7-[(acetyloxy)-methyl]-12-oxo-1,19-diol [**1.147**]



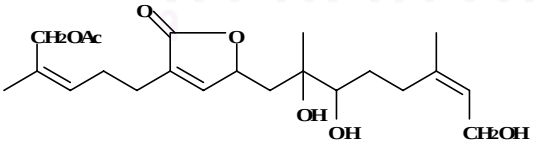
13-Oxogeranyllinalol [**1.129**]



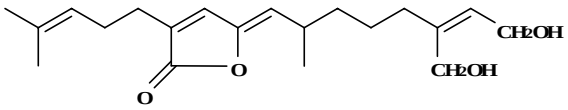
14,15-Epoxy-3-hydroxy-1,6,10-phytatrien-13-one [**1.79**]



11,15-Epoxy-3(20)-phytene-1,2-diol [**1.78**]

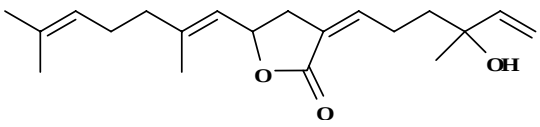


1,6,7-Trihydroxy-17-acetoxymelcantholide [**1.156**]

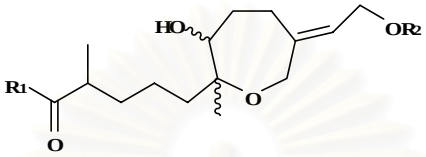


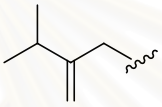
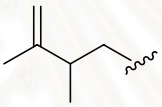
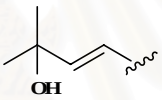
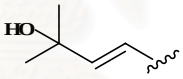
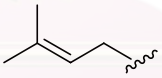
20-Hydroxygeranyl geraniol-9,18-olide [**1.102**]

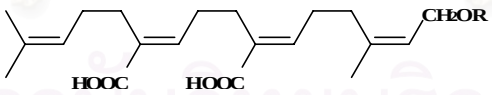
Figure 3. (continued)



Geranyllinalol-19,9-olide [**1.89**]

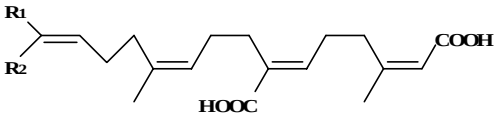


	R_1	R_2
Oxepane tomentol [**1.146**]		H
Tomentanol [**1.152**]		H
Tomexanthin [**1.153**]		Ac
Tomexanthol [**1.154**]		H
Zoapatanol [**1.168**]		H

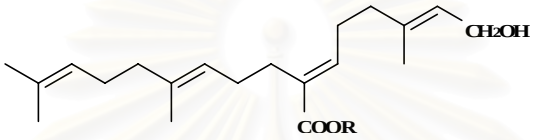


	R
Oleaxillaric acid [**1.122**]	H
Oleaxillaric methyl ester [**1.123**]	$COCH_3$

Figure 3. (continued)

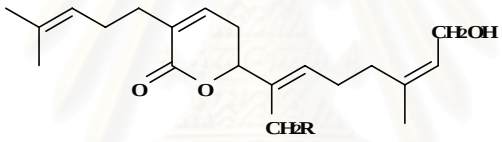


	R_1	R_2
(2*Z*,6*E*,10*Z*,14*Z*)-16-Hydroxy-2,6,10,14-phytatetraene-1,19-dioic acid [**1.99**]	CH_2OH	CH_3
(2*Z*,6*E*,10*Z*,14*E*)-16-Hydroxy-2,6,10,14-phytatetraene-1,19-dioic acid [**1.100**]	CH_3	CH_2OH



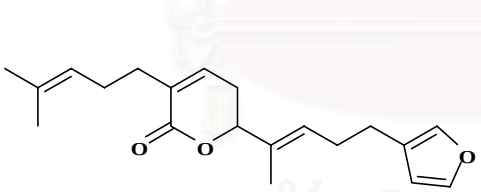
(2*E*,6*Z*,10*Z*)-Geranylgeraniol-19-oic acid [**1.86**]: R = H

(2*E*,6*Z*,10*Z*)-Geranylgeraniol-19-oic methyl ester [**1.88**]: R = CH_3

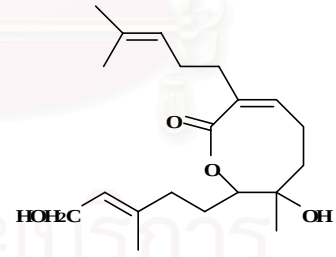


17-Acetoxyichthyouleolide [**1.23**]: R = $OCOCH_3$

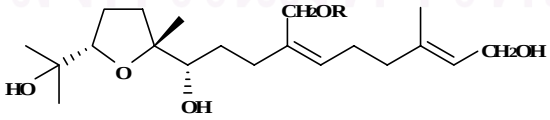
Ichthyouleolide [**1.113**]: R = H



Conyzaleucolide A [**1.42**]



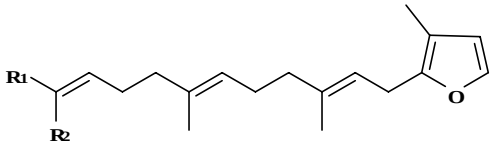
Isoacanthoaustralide [**1.115**]



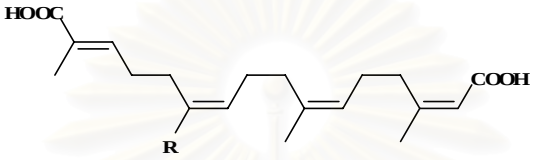
Acetoxy ligantrol [**1.2**]: R = $COCH_3$

Ligantrol [**1.117**]: R = H

Figure 3. (continued)

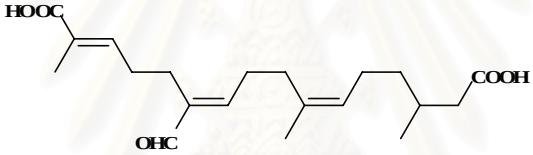


	R_1	R_2
Mikanifuran [**1.120**]	CH_3	CH_3
Saurufuran A [**1.145**]	CH_3	COOH
Saurufuran B [**1.146**]	COOH	CH_3

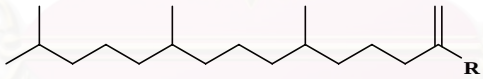


18-Oxo-2,6,10,14-phytatetraen-1,16-dioic acid [**1.127**]: R = CHO

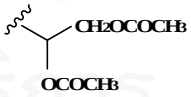
2,6,10,14-Phytatetraen-1,16,18-dioic acid [**1.137**]: R = COOH

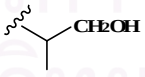


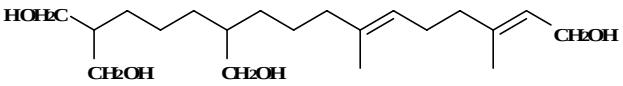
(2S,3S)-18-Oxo-6,10,14-phytatriene-1,16- dioic acid [**1.130**]



Neophytadiene [**1.121**]: R = 

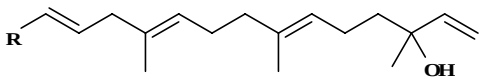
3(20)-Phytene-1,2-diacetoxy [**1.141**]: R = 

3(20)-Phytene-1,2-diol [**1.142**]: R = 



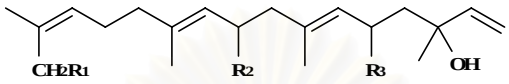
2,6-Phytadiene-1,16,17,18-tetrol [**1.132**]

Figure 3. (continued)

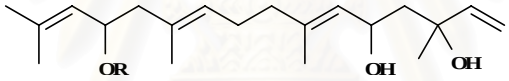


1,6,10,13-Phytatetraen-3,15-diol [**1.134**]: R = 

1,6,10,13,15-Phytapentaen-3-ol [**1.135**]: R = 

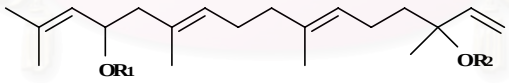


	R_1	R_2	R_3
9-Acetoxy-5-hydroxygeranyllinalol [**1.14**]	H	$OCOCH_3$	OH
5,9-Diacetoxygeranyllinalol [**1.46**]	H	$OCOCH_3$	$OCOCH_3$
5-Hydroxygeranyllinalool [**1.105**]	H	H	OH
20-Hydroxygeranyllinalool [**1.107**]	OH	H	H
1,6,10,14- Phytatetraen-3,9-diol [**1.136**]	H	OH	H



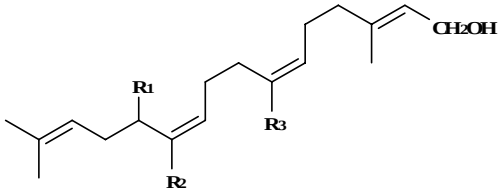
13-Acetoxy-5-hydroxygeranyllinalol [**1.15**]: R = $COCH_3$

5,13-Dihydroxygeranyllinalol [**1.66**]: R = H

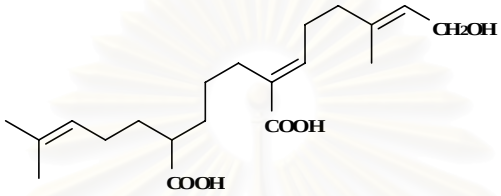


	R_1	R_2
13-Acetoxygeranyllinalol [**1.20**]	$COCH_3$	H
3, 13-Di-O- *β-D*-glucopyranosyl geranyllinalol [**1.73**]	Glc	Glc
13-O[*β-L*-Fucopyranosyl(1→ 6)-*β-D*-glucopyranosyl] geranyllinalol [**1.80**]	Fuc-Glc	H
13-Hydroxygeranyllinalol [**1.106**]	H	H

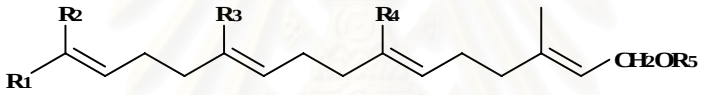
Figure 3. (continued)



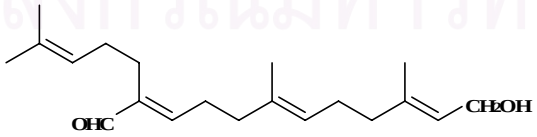
	R_1	R_2	R_3
12,18-Dihydroxygeranylgeraniol [**1.63**]	OH	CH_2OH	CH_3
Geranylgeraniol-18,19-dioic acid [**1.84**]	H	COOH	COOH



6,7-Dihydrogeranylgeraniol-18,19-dioic acid [**1.52**]

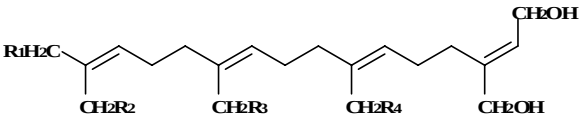


	R_1	R_2	R_3	R_4	R_5
18-Acetoxy-17-hydroxygeranylgeraniol [**1.9**]	CH_3	CH_2OH	CH_2OCOCH_3	CH_3	H
(*2E*,*6E*, *10Z*) 1-Hydroxy-2,6,10,14- phytapentraen-18-al [**1.97**]	CH_3	CH_3	CHO	CH_3	H
16- Hydroxygeranylgeraniol [**1.103**]	CH_2OH	CH_3	CH_3	CH_3	H
Koanoadmantic acid [**1.116**]	COOH	CH_3	CH_3	CH_3	$COCH_3$
Plaunotol [**1.144**]	CH_3	CH_3	CH_3	CH_2OH	H

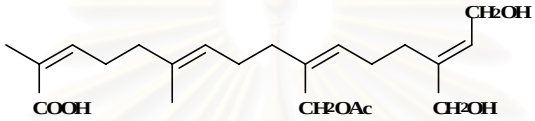


(2*E*,6*E*,10*E*)-1-Hydroxy-2,6,10,14- phytapentraen-18-al [**1.98**]

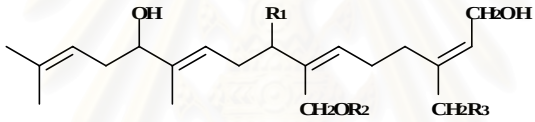
Figure 3. (continued)



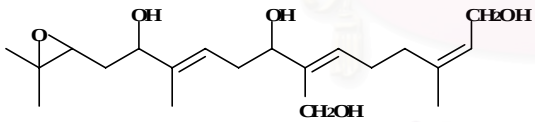
	R_1	R_2	R_3	R_4
19-Acetoxy-18- hydroxygeranylnerol [**1.10**]	H	H	OH	$OCOCH_3$
17,20-Dihydroxygeranylnerol [**1.67**]	H	OH	H	H
20-Hydroxygeranylnerol [**1.108**]	H	H	H	H
2,6,10,14- Phytatetraene-1,16,18,20-tetrol [**1.138**]	OH	H	OH	H
2,6,10,14- Phytatetraene-1,18,19,20-tetrol [**1.139**]	H	H	OH	OH



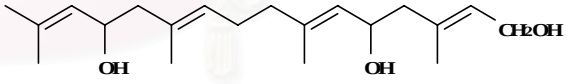
19-Acetoxy-20-hydroxygeranylnerol-17-acid [**1.13**]



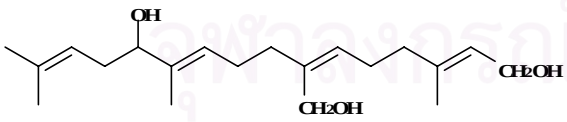
	R_1	R_2	R_3
19-Acetoxy-12,20-dihydroxygeranylnerol [**1.4**]	H	$COCH_3$	OH
8,12,19-Trihydroxygeranylnerol [**1.160**]	OH	H	H



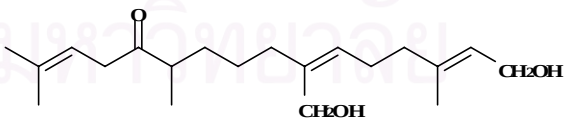
6,7-Epoxy-2,10,14-phytapentraene-1,8,12, 19-diol [**1.77**]



5,13-Dihydroxygeranylgeraniol [**1.64**]

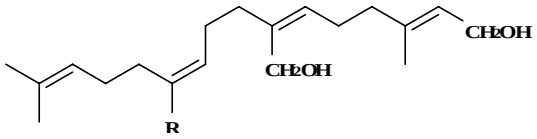


12,19-Dihydroxygeranylgeraniol [**1.65**]



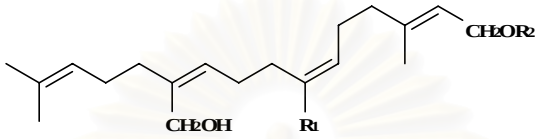
10,11-Dihydro-19-hydroxy-12-oxogeranylgeraniol [**1.51**]

Figure 3. (continued)

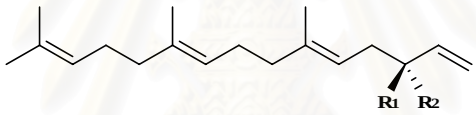


18,19-Dihydroxynerylgeraniol [**1.68**]: R = CH_2OH

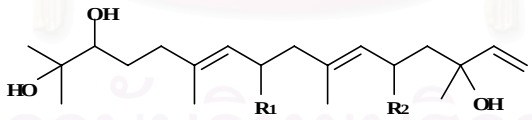
18-Oxo-19-hydroxynerylgeraniol [**1.126**]: R = CHO



	R_1	R_2
1-Acetoxy-18-hydroxygeranylgeraniol-19-oic acid [**1.11**]	COOH	$COCH_3$
18-Hydroxy-19-oxogeranylgeranial [**1.96**]	CHO	H
18-Hydroxygeranylgeraniol-19-oic acid [**1.104**]	COOH	H

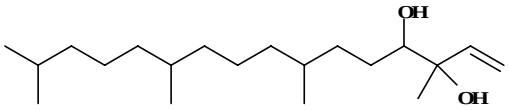


	R_1	R_2
(3*R*,6*E*,10*E*)- Geranyllinalool [**1.90**]	CH_3	OH
(3*S*,6*E*,10*E*)- Geranyllinalool [**1.91**]	OH	CH_3

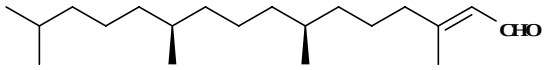


	R_1	R_2
9-Acetoxy-1,6,10-Phytatriene-3,5,14,15-tetrol [**1.3**]	$OCOCH_3$	H
14,15-Dihydro-14,15-dihydroxygeranyllinalol [**1.50**]	H	H
1,6,10-Phytatriene-3,5,14,15-tetrol [**1.140**]	H	OH

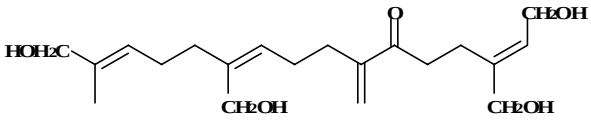
Figure 3. (continued)



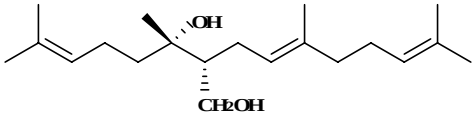
4-Hydroxyisophytol [**1.112**]



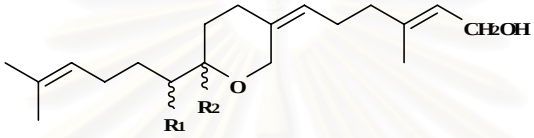
Phytal [**1.133**]



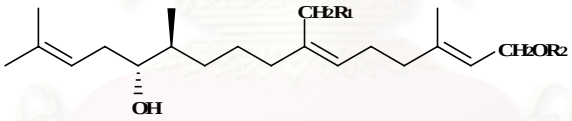
16,18,20-Trihydroxy-6-oxo-7,19-dehydro-6,7-dihydrogeranylnerol [**1.158**]



Peucelinendiol [**1.131**]

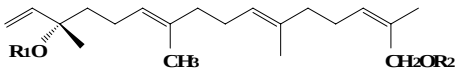


	R_1	R_2
Epivittadinal [**1.75**]	α-H	β-CH_3
Vittadinol [**1.166**]	β-CH_2OH	α-H
Vittadinal [**1.169**]	β-CH_3	α-H

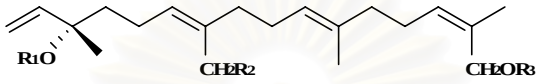


	R_1	R_2
(2*E*,6*Z*,11*S*,12*R*)-3,7,11,15-Tetramethylhexadeca-2,6,14-triene-7-[(acetyloxy)methyl]-1,12-diol-1-acetate [**1.148**]	$OCOCH_3$	$COCH_3$
(2*E*,6*E*,11*S*,12*R*)-3,7,11,15-Tetramethylhexadeca-2,6,14-triene-1,12-diol [**1.149**]	H	H
(2*E*,6*E*,11*S*,12*R*)-3,7,11,15-Tetramethylhexadeca-2,6,14-triene-7-[(acetyloxy)methyl]-1,12-diol [**1.150**]	$OCOCH_3$	H

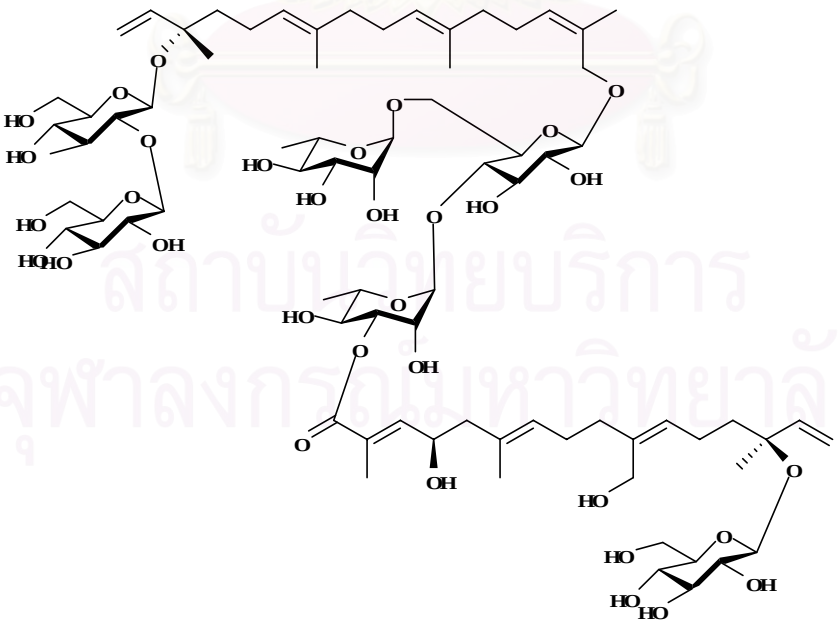
Figure 3. (continued)



	R_1	R_2
Capsianoside II [**1.29**]	Glc-Glc	Glc-Rha, Rha
Capsianoside III [**1.30**]	Glc-Glc	Glc-Rha, Glc
Capsianoside IX [**1.31**]	Glc-Glc, Glc	Glc-Rha, Rha

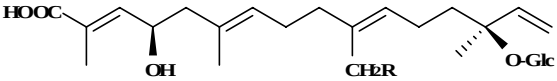


	R_1	R_2	R_3
Capsianoside VIII [**1.34**]	Glc, Glc	H	Glc-Rha, Glc
Capsianoside X [**1.35**]	Glc-Glc, Glc	H	Glc-Rha, Glc
Capsianoside XIII [**1.36**]	Glc, Glc	H	Glc-Rha, Rha
Capsianoside XV [**1.37**]	Glc, Glc	OH	Glc-Rha, Rha
Capsianoside XVI [**1.38**]	Glc-Glc, Glc	H	Glc-Rha, Glc—Rha



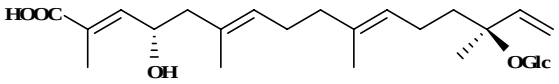
Capsianoside L [**1.32**]

Figure 3. (continued)

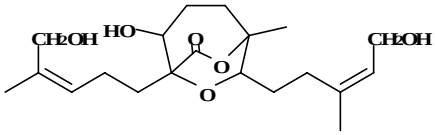


Capsianoside I [**1.28**]: R = H

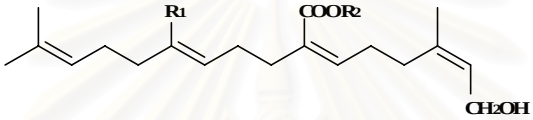
Capsianoside V [**1.33**]: R = OH



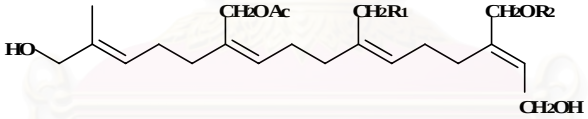
Capsianoside A [**1.27**]



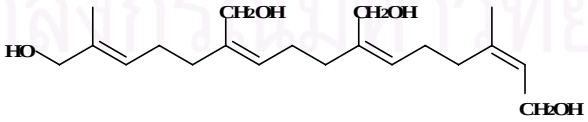
1,10,17-Trihydroxymelfusanolide [**1.162**]



	R_1	**R_2**
(2*Z*,6*Z*,10*E*)-Geranylgeraniol-19-oic acid [**1.85**]	CH_3	H
(2*Z*,6*Z*,10*E*)-Geranylgeraniol-19-oic methyl ester [**1.87**]	CH_3	CH_3
Viguieric acid [**1.164**]	CHO	H

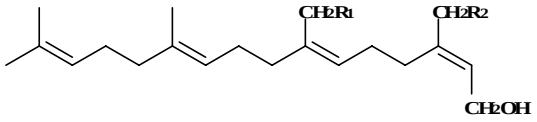


	R_1	**R_2**
18-Acetoxy-16,20-dihydroxygeranylnerol [**1.7**]	H	H
18,19-Diacetoxy-16,20-dihydroxygeranylnerol [**1.44**]	OAc	H
18,19,20-Triacetoxy-16-hydroxygeranylnerol [**1.155**]	OAc	Ac

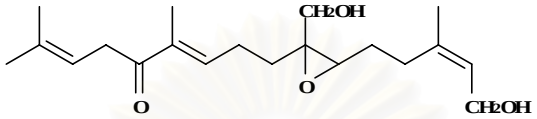


16,18,19-Trihydroxygeranylnerol [**1.159**]

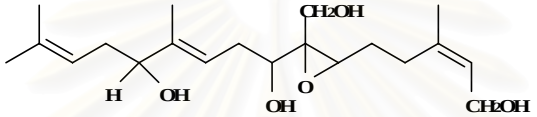
Figure 3. (continued)



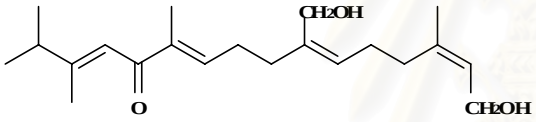
	R_1	R_2
19-Acetoxy-20-hydroxygeranylnerol [**1.12**]	Ac	OH
20-Acetoxygeranylnerol [**1.21**]	H	Ac



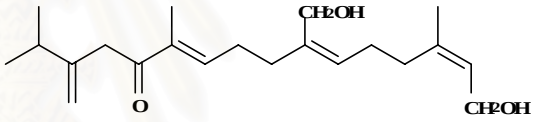
6,7-Epoxy-19-hydroxy-12-oxo-6,7-dihydrogeranylnerol [**1.76**]



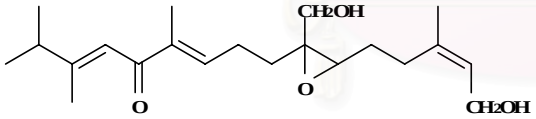
8,12,19-Trihydroxygeranylnerol-6,7-epoxide [**1.161**]



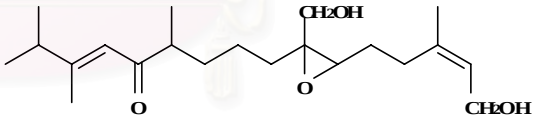
1,19-Dihydroxy-12-oxo-smallantha-2*Z*,6*Z*,10*E*,13*E*-tetraene [**1.57**]



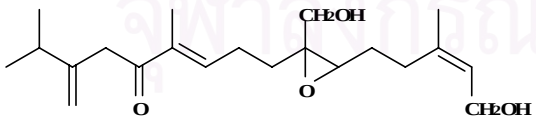
1,19-Dihydroxy-12-oxo-smallantha-2*Z*,6*Z*,10*E*,14(21)-tetraene [**1.58**]



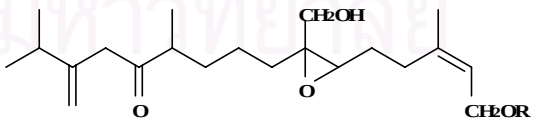
1,19-Dihydroxy-6,7-epoxy-12-oxo-smallantha-2*Z*,10*E*,13*E*-triene [**1.61**]



1-Acetoxy-6,7-epoxy-19-hydroxy-12-oxo-smallantha-2*Z*,13*E*-diene [**1.16**]

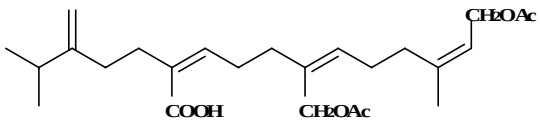


1,19-Dihydroxy-6,7-epoxy-12-oxo-smallantha-2*Z*,10*E*,14(21)-triene [**1.62**]

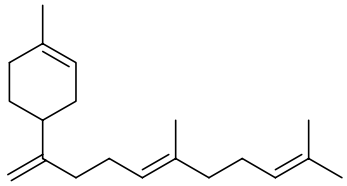


1-Acetoxy-6,7-epoxy-19-hydroxy-12-oxo-smallantha-2Z,14(21)-diene [**1.17**]

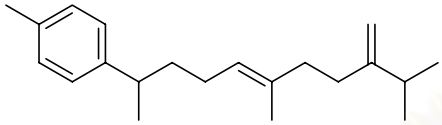
Figure 3. (continued)



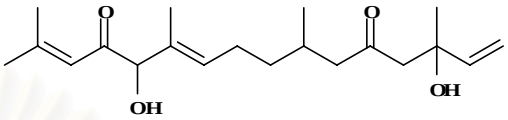
Clibadic acid [**1.40**]



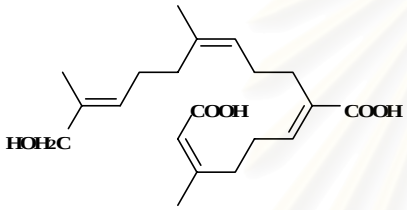
Axinyssene [**1.26**]



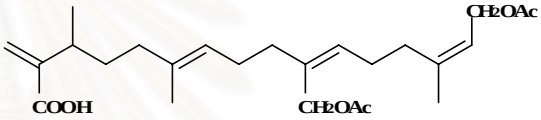
9-(15,16-Dihydro-15-methylene)-*p*-cymene [**1.59**]



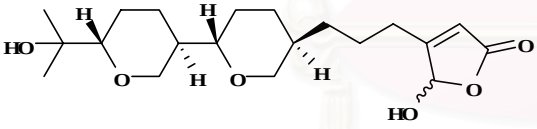
(10*E*)-3,12-Dihydroxy-3,7,11,15-tetramethyl-1,10,14-hexadecatrien-5,13-dione [**1.60**]



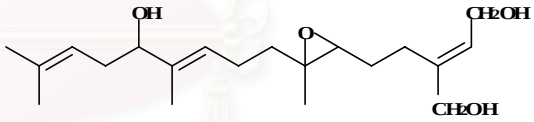
Dimethyl (2*E*,6*Z*)-2-[(3′*Z*,7′*E*)-9′-hydroxy-4′,8′-dimethylnona-3′,7′-dienyl]-6-methylocta-2,6-diene-dioic acid [**1.72**]



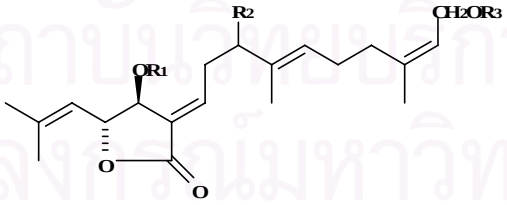
Helogynic acid [**1.94**]



Lingulatusin [**1.118**]



Zoapatol A [**1.169**]



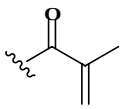
	R_1	**R_2**	**R_3**
Hanliuine I [**1.92**]	Ac	OAc	COC_6H_5
Hanliuine III [**1.89**]	Ac	H	
Tuxpanolide [**1.163**]	H	OH	H

Figure 3. (continued)

5. Arylnaphthalene Lignans in Higher Plants

The arylnaphthalene lignans is a subgroup of lignans that can be found in several plant families; some of these lignans have been reported as being cytotoxic. Examples of these cytotoxic arylnaphthalene lignans are justicidin B [**2.34**], which was isolated from several sources including *Linum* cell culture (Vasilev and Ionkova 2005), *Phyllanthus piscatorum* (Gertsch *et al*., 2003) and *Justicia pectoralis* (Joseph *et al*., 1988); dehydropodophyllotoxin [15] from *Hyptis verticillata* (Novelo *et al*., 1993); cleistanthin A [**2.8**] from *Phyllanthus taxodiifolius* (Tuchinda *et al*., 2006); cleistanthin B [**2.9**] (Prabhakaran *et al*., 1996); phyllanthusmins A-C [**2.55-2.57**] from *Phyllanthus oligospermus* (Wu and Wu 2006); and tuberculatin [**2.66**] from *Justicia patentiflora* (Susplugas *et al*., 2005). Justicidin B also possessed antifungal activity against the pathogenic fungi *Aspergillus fumigatus*, *A. flavus* and *Candida albicans*, antiprotozoal activity against *Trypanosoma brucei rhodesiense* (IC_{50} = 0.2 mcg/mL) and *T. cruzi* (IC_{50} = 2.6 mcg/mL), and piscicidal property against zebra fish (Gertsch *et al*., 2003). Furthermore, this compound displayed anti-inflammatory effect on the production of nitric oxide and the cytokines tumor necrosis factor-α and interleukin-12 from murine peritoneal macrophages (Rao, Fang and Tzeng, 2006). Helioxanthin [**2.27**] from the root of *Acanthopanax chiisanensis* was able to inhibit the production of prostaglandin E (Ban *et al*., 2002). Some arylnaphthalene lignans were reported to induce apoptosis, for example, cleistanthin A from *Cleistanthus collinus* induced apoptosis in Chinese hamster ovary cells, cervical carcinoma (SiHa) cells and in a p53-deficient cell line K562 (Pradheepkumar, Panneerselvam and Shanmugam, 2000), whereas cleistanthin B from the same plant induced apoptosis of cervical carcinoma (SiHa) cells (Kumar, Pande and Shanmugam, 1998).

The distribution of arylnaphthalene lignans in higher plants is presented in **Table 2**, and their structures are shown in **Figure 4.**

Table 2. Distribution of arylnaphthalene lignans in higher plants.

Compounds	Sources	Family	Part	References
4″-O-Acetylmananthoside B [**2.1**]	*Justicia patentiflora*	Acanthaceae	leaves	Susplugas *et al.*, 2005
4″-O-Acetylpatenetiflorin B [**2.2**]				
Azizin [**2.3**]	*Haplophyllum buxbaumii*	Rutaceae	n.i.	Al-Abed *et al*., 1998
Cannabisin B [**2.4**]	*Cannabis sativa*	Cannabidaceae	fruits	Sakakibara, *et al*., 1992
Cannabisin C [**2.5**]				
Cannabisin D [**2.6**]				
Chinensin [**2.7**]	*Polygala chinensis*	Polygalaceae	whole plants	Ghosal , Chauhan and Srivastava, 1974
Cleistanthin A [**2.8**]	*Cleistanthus collinus*	Euphorbiaceae	heartwood	Pinho and Kijjoa, 2007
Cleistanthin B [**2.9**]	*C. patulus*			Sastry *et al*., 1987.
Cleistanthin C [**2.10**]				Pinho and Kijjoa 2007
Cleistanthin D [**2.11**]				
Cyclogalgravin [**2.12**]	*Araucaria angustifolia*	Araucariaceae	knots	Fonseca, Nielsen and Rúveda, 1979
Daurinol glycoside [**2.13**]	*Haplophyllum buxbaumii*	Rutaceae	whole plants	Al-Abed *et al*., 1990
Dehydroguaiaretic acid [**2.14**]	*Guastiacum officinale*		heartwood	King and Wilson, 1964

Table 2. (continued)

Compounds	Sources	Family	Part	References
Dehydropodo-phyllotoxin [**2.15**]	*Podophyllum hexandrum*	Podophyllaceae	leaves	Rahman *et al*., 1995
	Hyptis verticillata	Labiatae	aerial parts	Kuhnt, Rimpler and Heinrich, 1994
1,2-Dihydro-6,8-dimethoxy-7-hydroxy-1-(3,4-dihydroxyphenyl)-N^1-N^2-bis-[2-(4-hydroxyphenyl) ethyl]-2,3-naphthalene dicarboxamide [**2.16**]	*Porcelia macrocarpa*	Annonaceae	branches	Chaves and Roque, 1997
1,2-Dihydro-6,8-dimethoxy-7-hydroxy-1-(3,5-dimethoxy-4-hydroxyphenyl)-N^1,N^2-bis-[2-(4-hydroxyphenyl)ethyl]-2,3-naphthalene dicarboxamide [**2.17**]				
7,8-Dihydroisojusticidin [**2.18**]	*Linum perenne*	Linaceae	aerial part	Schmidt *et al.*, 2007

Table 2. (continued)

Compounds	Sources	Family	Part	References
7,8-Dihydroretrohelioxanthin [**2.19**]	*Linum perenne*	Linaceae	aerial part	Schmidt *et al.*, 2007
7,8-Dihydrotaiwanin [**2.20**]				
3,4-Dimethoxy-3′, 4′-methylenedioxy-9′-oxo- $\Delta^{7,8,7',8'}$-6, 7′, 8, 8′-neolignan [**2.21**]	*Virola sebifera*	Myristicaceae	fruits	Lopes, Yoshida and Gottlieb, 1984
3,4-Dimethoxy-3′,4′-methylenedioxy-9′-oxo-$\Delta^{7,8,7',8'}$-6,7′,8,8′-neolignan [**2.22**]				
7-O-(Dimethylallyl) isodaurinol [**2.23**]	*Haplophyllum myrtifolium*	Rutaceae	aerial parts	Saglum, Gozler and Gozler, 2003
Diphyllin [**2.24**]	*Phyllanthus oligospermus*	Euphorbiaceae	stems and roots	Wu and Wu, 2006
Haplomyrtin [**2.25**]				
(-)-Haplomyrtoside [**2.26**]	*Haplophyllum cappadocicum*	Rutaceae	whole plants	Gözler *et al*., 1996
Helioxanthin [**2.27**]	*Heliopsis scabra*	Compositae	n.i.	Burden, Crombie and Whiting, 1969

Table 2. (continued)

Compounds	Sources	Family	Part	References
9′-Hydroxy-3,4-dimethoxy-3′, 4′-methylenedioxy-9′-oxo-$\Delta^{7,8,7',8'}$-6,7′,8,8′-neolignan [**2.28**]	*Virola sebifera*	Myristicaceae	fruits	Lopes, Yoshida and Gottlieb, 1984
Hydroxy-4-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde [**2.29**]	*Vitex negundo*	Verbenaceae	seeds	Chawla *et al*., 1992
Isodaurinol [**2.30**]	*Haplophyllum cappadocicum*	Rutaceae	n.i.	Gozler *et al*. 1992
Isojusticidin [**2.31**]	*Linum leonii*	Linaceae	cell culture	Vasilev *et al*., 2006
Justalakonin [**2.32**]	*Justicia purpurea*	Acanthaceae	whole plants	Kavitha *et al*., 2003
Justicidin A [**2.33**]	*Phyllanthus oligospermus*	Euphorbiaceae	stems and roots	Wu and Wu, 2006
Justicidin B [**2.34**]	*Linum leonii*	Linaceae	cell culture	Vasilev *et al*., 2006
	Justicia procumbens var. *leucantha*	Acanthaceae	n.i.	Okigawa , Maeda and Kawano, 1970
Justicidin P [**2.35**]	*J.extensa*	Acanthaceae	leaves	Wang and Ripka 1983

Table 2. (continued)

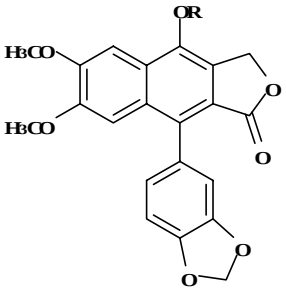
Compounds	Sources	Family	Part	References
Justicinol [**2.36**]	*J. flava*	Acanthaceae	leaves	Olaniyi A. A. and Powell J. W. 1980.
Kolelreuterin I [**2.37**]	*Koelreuteri a henryi*	Sapindaceae	leaves, twig	Song *et al*., 1994
Lignan J1 [**2.38**]	*Justicia hyssopifolia*	Acanthaceae	leaves	Trujillo *et al*., 1990.
Lignan J2 [**2.39**]				
Linoxepin [**2.40**]	*Linum perenne*	Linaceae	aerial part	Schmidt *et al.*, 2007
Magnoliadiol [**2.41**]	*Magnolia fargesii*	Magnoliaceae	Flower buds	Miyazawa, Kasahara and Kameoka, 1996
Magnoshinin [**2.42**]	*M. salicifolia*	Magnoliaceae	buds	Kikuchi *et al.*, 1983
Orosunol [**2.43**]	*Justicia flava*	Acanthaceae	roots	Olaniyi and Powell, 1980
Otobane [**2.44**]	*Virola cuspidata*	Myristicaceae	n.i.	Blair *et al.*, 1969
Patentiflorin A [**2.45**]	*Justicia patentiflora*	Acanthaceae	leaves, stem	Susplugas *et al.*, 2005
Patentiflorin B [**2.46**]				
Phyllamyricins A [**2.47**]	*Phyllanthus myrtifolius*	Euphorbiaceae	n.i.	Lin, Lee and Liu, 1995
Phyllamyricins B [**2.48**]				

Table 2. (continued)

Compounds	Sources	Family	Part	References
Phyllamyricins C [**2.49**]	*Phyllanthus myrtifolius*	Euphorbiaceae	n.i.	Lin , Lee and Liu 1995.
Phyllamyricins D [**2.50**]				Lee *et al*., 1996
Phyllamyricins E [**2.51**]				
Phyllamyricoside A [**2.52**]				
Phyllamyricoside B [**2.53**]				
Phyllamyricoside C [**2.54**]				
Phyllanthusmins A [**2.55**]	*P. oligospermus*	Euphorbiaceae	Stems, roots	Wu and Wu, 2006
Phyllanthusmins B [**2.56**]				
Phyllanthusmins C [**2.57**]				
Plicatinaphthalene [**2.58**]	*Thuja plicata*	Cupressaceae	Heart-wood	MacLean and MacDonald, 1969
Plicatinaphthol [**2.59**]				
Retrohelioxanthin [**2.60**]	*Linum leonii*	Linaceae	aerial part	Schmidt *et al.*, 2007.
Tawanin C [**2.61**]	*Cleistanthus patulus*	Euphorbiaceae	heartwood	Sastry and Rao 1983.

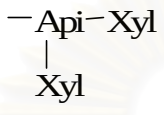
Table 2. (continued)

Compounds	Sources	Family	Part	References
Tawanin H [**2.62**]	*Taiwania cryptomerioides*	Taxodiaceae	heartwood	Chang *et al*. 2000
1,2,3,4-Tetradehydropodophyllotoxin [**2.63**]	*Hernandia ovigera*	Hernandiaceae	Seed	Yamaguchi *et al.*,1982.
Thomasic acid [**2.64**]	*Ulmus thomasii*	Ulmaceae	heartwoods	Seikel, Hostettler and Johnson, 1968
Thomasidoic acid [**2.65**]				Hostettler and Seikel, 1969
Tuberculatin [**2.66**]	*Haplophyllum tuberculatum*	Rutaceae	n.i.	Sheriha and Amer 1984



4″-O-Acetylmananthoside B [**2.1**]: R = 7-O-Ara-3,4-Acetyl-Glc

4″-O-Acetylpatenetiflorin B [**2.2**]: R = 4″-O-Acetyl-Fuc

Azizin [**2.3**] : R = 

Cleistanthin A [**2.8**]: R = 3,4-di-O-methyl Xyl-Glc

Cleistanthin B [**2.9**]: R = 4-O-methyl Xyl

Cleistanthin C [**2.10**]: R = Glc-2,3-di-O-methyl Xyl

Cleistanthin D [**2.11**]: R = 2,3,5-tri-O-methyl Xyl

Justicidin A [**2.33]**: R = CH_3

Justicidin B [**2.34**]: R = H

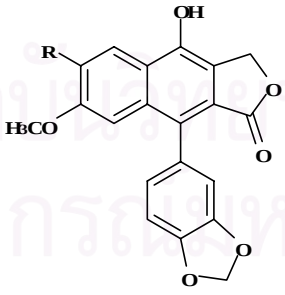
Patentiflorin A [**2.45**]: R = Deoxy-Glc

Patentiflorin B [**2.46**]: R = Fuc

Phyllanthusmins B [**2.56**]: R = 4″-O-Acetyl-Xyl

Phyllanthusmins C [**2.57**]: R = Xyl

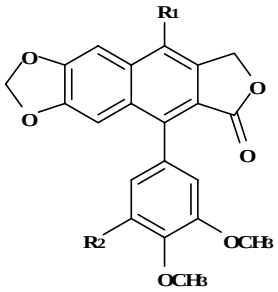
Tuberculatin [**2.66**]: R = Api



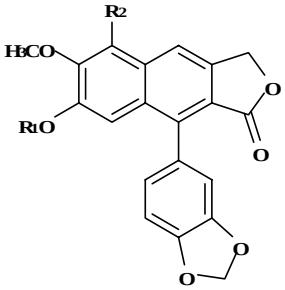
Diphyllin [**2.24**]: R = OCH_3

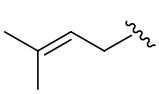
Haplomyrtin [**2.25**]: R = H

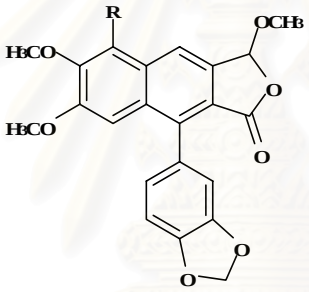
Figure 4. Chemical structures of arylnaphthalene lignans in higher plants.



	R_1	R_2
Chinensin [**2.7**]	H	H
Dehydropodophyllotoxin [**2.15**]	OH	OCH3
Tetradehydropodophyllotoxin [**2.63**]	H	OCH3

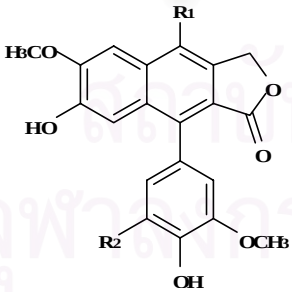


	R_1	R_2
7-O-(3, 3-Dimethylallyl) isodaurinol [**2.23**]		H
Isodaurinol [**2.30**]	H	H
Phyllamyricin C [**2.49**]	CH_3	OCH_3



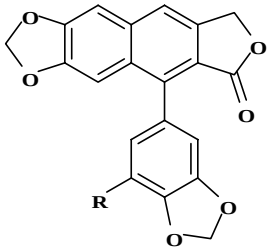
Phyllamyricin D [**2.50**] : R = OCH_3

Phyllamyricin E [**2.51**] : R = H



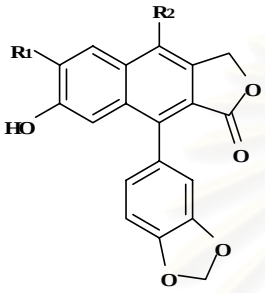
	R_1	R_2
Plicatinaphthalene [**2.58**]	H	OH
Plicatinaphthol [**2.59**]	OH	H

Figure 4. (continued)

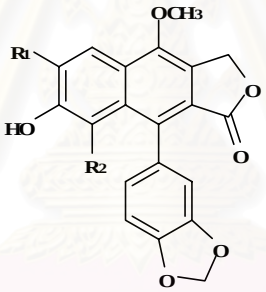


Kolelreuterin 1[**2.37**]: R = OCH_3

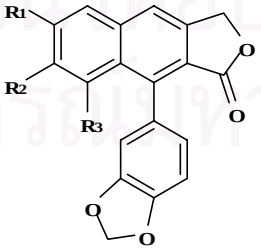
Tawanin C [**2.61**]: R = H



	R_1	R_2
Daurinol glycoside [**2.13**]	OGlc	H
(-)-Haplomyrtoside [**2.26**]	OCH_3	Api

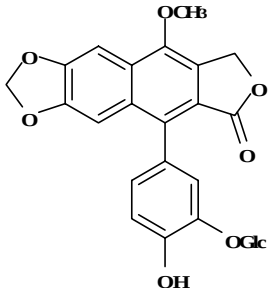


	R_1	R_2
Orosunol [**2.43**]	H	OH
Phyllanthusmin A [**2.55**]	OCH_3	H

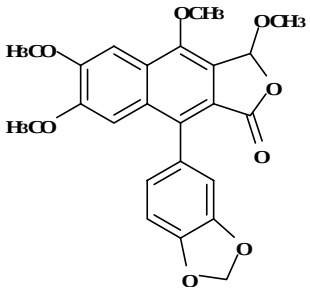


	R_1	R_2	R_3
Isojusticidin [**2.31**]	H	OCH_3	OCH_3
Retrohelioxanthin [**2.60**]	OCH_3	-OCH_2O-	

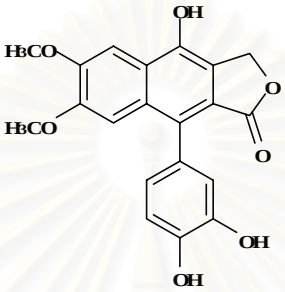
Figure 4. (continued)



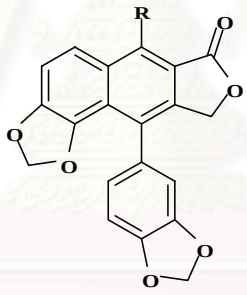
Justalakonin [**2.32**]



Justicidin P [**2.35**]

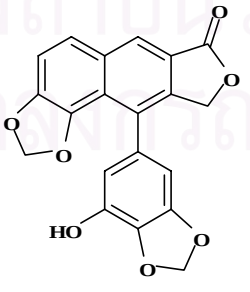


Tawanin H [**2.62**]

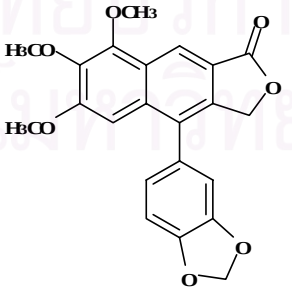


Helioxanthin [**2.27**]: R = H

Lignan J1 [**2.38**]: R = OCH_3

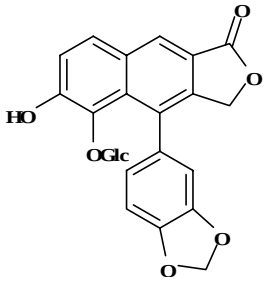


Justicinol [**2.36**]

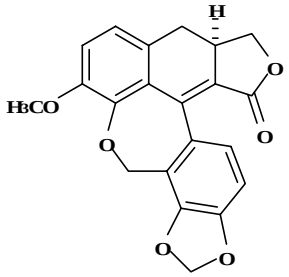


Phyllamyricin A [**2.47**]

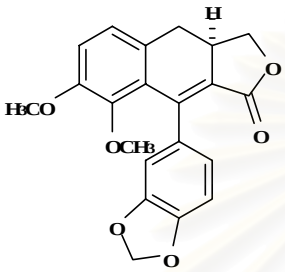
Figure 4. (continued)



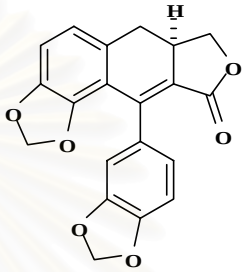
Lignan J2 [**2.39**]



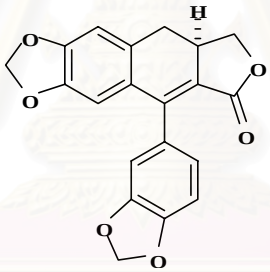
Linoxepin [**2.40**]



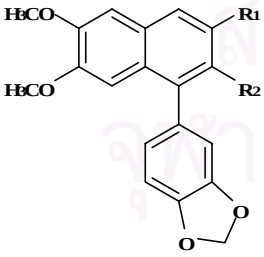
7, 8-Dihydroisojusticidin [**2.18**]



7, 8-Dihydroretrohelioxanthin [**2.19**]

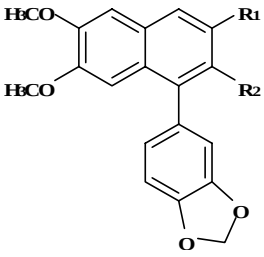


7, 8-Dihydrotaiwanin [**2.20**]

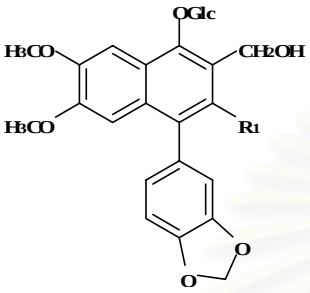


	R_1	R_2
3,4-Dimethoxy-3′,4′-methylenedioxy-9′-oxo-$\Delta^{7,8,7',8'}$-6,7′,8,8′-neolignan [**2.22**]	CH_3	CHO
3,4-Dimethoxy-3′,4′-methylenedioxy-9′-oxo-$\Delta^{7,8,7',8'}$-6,7′,8,8′-neolignan [**2.21**]	CH_3	CH_3

Figure 4. (continued)

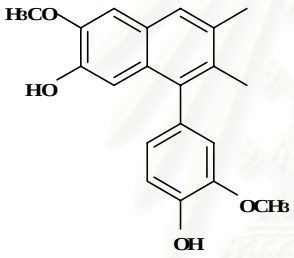


	R_1	R_2
9′-Hydroxy-3,4-dimethoxy-3′,4′-methylenedioxy-9′-oxo-$\Delta^{7,8,7',8'}$-6,7′,8,8′-neolignan [**2.28**]	CH_3	COOH
Phyllamyricins B [**2.48**]	CH_2OCH_3	CHO

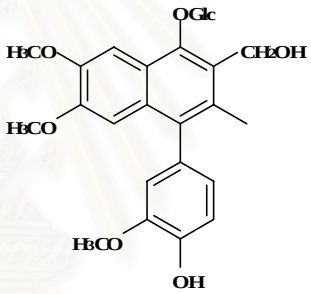


Phyllamyricoside A [**2.52**]: R = CH_3

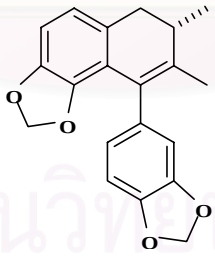
Phyllamyricoside B [**2.53**]: R = CH_2OH



Dehydroguaiaretic acid [**2.14**]

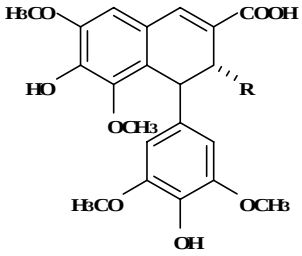


Phyllamyricoside C [**2.54**]



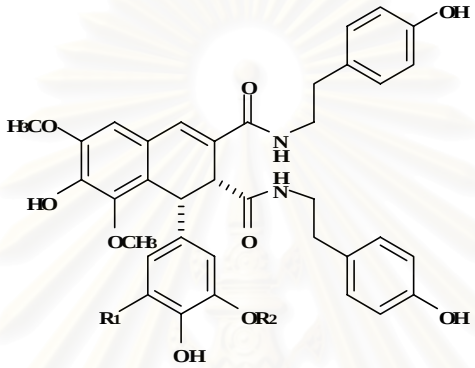
Otobane [**2.44**]

Figure 4. (continued)



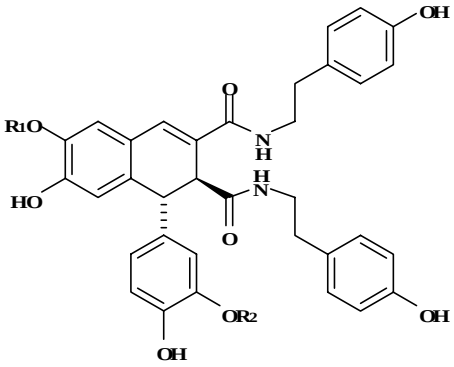
Thomasic acid [**2.64**]: R = CH_2OH

Thomasidioc acid [**2.65**]**:** R = COOH

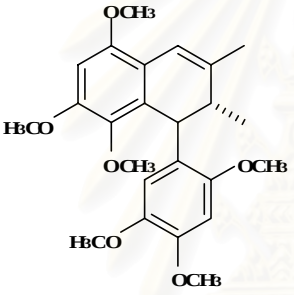


	R_1	R_2
1,2-Dihydro-6,8-dimethoxy-7-hydroxy-1-(3,4-dihydroxyphenyl)-N^1-N^2-bis-[2-(4-hydroxyphenyl)ethyl]-2,3-naphthalene dicarboxamide [**2.16**]	H	H
1,2-Dihydro-6,8-dimethoxy-7-hydroxy-1-(3,5-dimethoxy-4-hydroxyphenyl)-N^1,N^2-bis-[2-(4-hydroxyphenyl)ethyl]-2,3-naphthalene dicarboxamide [**2.17**]	OCH_3	CH_3

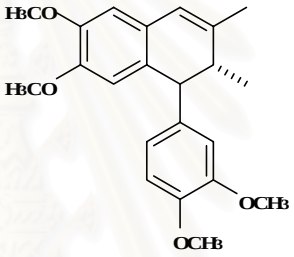
Figure 4. (continued)



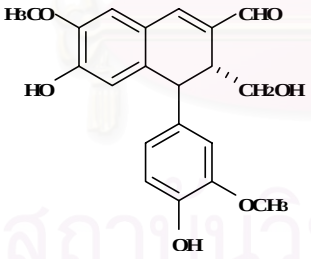
	R_1	R_2
Cannabisin B [**2.4**]	H	H
Cannabisin C [**2.5**]	CH_3	H
Cannabisin D [**2.6**]	CH_3	CH_3



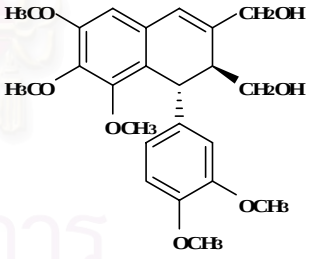
Magnoshinin [**2.42**]



Cyclogalgravin [**2.12**]



6-Hydroxy-4-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde [**2.29**]



(+)-Magnoliadiol [**2.41**]

Figure 4. (continued)

6. Chemical Constituents of Plants in the Genus *Knema*

Currently, researches on the chemical constituents of *Knema* plants have been performed on 8 members of this genus: *K. attenuata*, *K. austrosiamensis*, *K. elegans*, *K. furfuracea*, *K. glomerata*, *K. hookeriana*, *K. laurina* and *K. tunuinervia* ssp. *setosa*. Biosynthetically, these compounds are produced from only 2 pathways, that is, the acetate-malonate and shikimate pathways or their combination. These secondary metabolites are phenylpropanoids, acylphenols, phenylacylphenols, acetophenones, alkyl-, acyl-, phenylalkyl- and phenylacylresorcinols, acyl- and phenylacylphloroglucinols, flavan-acyphloroglucinols, alkyl- and phenylalkylbenzoic acids, stilbenes, lignans and isocoumarins.

Some phenylalkylphenols exhibited significant toxicity toward three human tumor cell lines (Zeng *et al*., 1994). Myristinins A [**3.36**] and D [**3.37**], the flavan-acylphloroglucinols from the trunkwood of *K. elegans*, potently inhibited the enzyme DNA polymerase *β* (Deng *et al.*, 2005). Isolated from the leaves of *K. furfuracea*, knerachelin A [**3.38**], which is a phenylacylphloroglucinol, and knerachelin B [**3.40**], a phenylacylresorcinol, showed antibacterial activity against *Staphylococcus aureus* (strain 209P) with MIC of 8 and 4 μg/ml, respectively (Zahir *et al*., 1993).

Chemical constituents of plants in the genus *Knema* are shown in **Table3**, and their structures are displayed in **Figure 5**.

Table 3. Chemical constituents of plants in the genus *Knema*

Compound	Sources	Part	References
Phenylpropanoid			
1-(4-Hydroxy-2-methoxyphenyl)-3-(3-hydroxy-4-methoxyphenyl)-propane [**3.1**]	*K. austrosiamensis*	wood	Gonzaléz *et al*., 1993
Alkylphenols			
3-Undecylphenol [**3.2**]	*K. hookeriana*	n.i.	Alen *et al*., 2000
3-(8-Pentadecenyl) phenol [**3.3**]	*K. elegans* *K. tunuinervia*	stem bark	Pinto and Kijjoa, 1990
	K. laurina		Gonzalez *et al*., 1996
Phenylalkylphenols			
3-(12-Phenyldodec-8-enyl) phenol [**3.4**]	*K. elegans* *K. tunuinervia*	stem bark	Pinto and Kijjoa, 1990
Kneglomeratanol [**3.5**]	*K. glomerata*	stem	Zeng *et al*., 1994
3-(12´-Phenyldodecyl) phenol [**3.6**]	*K. furfuracea*	stem bark	Pinto and Kijjoa,1990
			Pinto *et al*., 1990
3-(10´-Phenyldecyl) phenol [**3.7**]	*K. glomerata*	stem	Zeng, *et al*., 1994
Acetophenone			
2,4-Dihydroxy-6-(10´-phenyldecyl) acetophenone [**3.8**]	*K. elegans*, *K. tunuinervia* ssp. *setosa*	stem bark	Pinto and Kijjoa,1990
Kneglomeratanones A [**3.9**]	*K. glomerata*	stems	Zeng *et al*., 1994
Kneglomeratanones B [**3.10**]			

Table 3. (continued)

Compound	Sources	Part	References
Alkylresorcinols			
5-Tridecyl resorcinol [**3.11**]	*K. elegans*	seeds	Spencer *et al*., 1980
5-Pentadecyl resorcinol [**3.12**]	*K. glomerata*	stem	Zeng *et al*., 1994
5-(8*Z*-Pentadecenyl) resorcinol [**3.13**]	*K. elegans*	seed	Spencer *et al*., 1980
Phenylalkylresorcinols			
5-(10´-Phenyldodecyl) resorcinol [**3.14**]	*K. elegans*	seed	Spencer *et al*., 1980
	K. glomerata	stems	Zeng *et al*., 1994
5-(12´-Phenylundecyl) resorcinol [**3.15**]	*K. elegans*	seed	Spencer *et al*., 1980
	K. glomerata	stems	Zeng *et al*., 1994
5-(12´-Phenyl-8*Z*-tridecyl) resorcinol [**3.16**]	*K. elegans*	seed	Spencer *et al*., 1980
	K. laurina	Stem bark	Gonzalez *et al*., 1996
Phenylalkylbenzoic acids			
2-Hydroxy-6-(12´-phenyldodecyl) benzoic acid [**3.17**]	*K. glomerata*		Zeng *et al*., 1994
	K. elegans *K. furfuracea* *K. tunuinervia*	stem bark	Pinto and Kijjoa, 1990
2-Hydroxy-6-(10´-phenyldecyl) benzoic acid [**3.18**]	*K. laurina*		Gonzalez *et al*., 1996

Table 3. (continued)

Compound	Sources	Part	References
Phenylalkylbenzoic acids (continued)			
2-Hydroxy-6-(12′-phenyl-8*Z*-dodecyl) benzoic acid [**3.19**]	*K. elegans*	seed	Spencer *et al*., 1980
2-Hydroxy-6-(8*Z*-pentadecenyl) benzoic acid [**3.20**]	*K. laurina*	Stem bark	Gonzalez *et al*., 1996
2-Hydroxy-6-(10*Z*-pentadecenyl) benzoic acid [**3.21**]	*K. elegans*	seed	Spencer *et al*., 1980
2-Hydroxy-6-(8*Z*-heptadecenyl) benzoic acid [**3.22**]			
2-Hydroxy-6-(12*Z*-pentadecenyl) benzoic acid [**3.23**]			
Alkylbenzoic acids			
2-Hydroxy-6-undecenyl benzoic acid [**3.24**]	*K. elegans*	seed	Spencer *et al*., 1980
2-Hydroxy-6-tridecenyl benzoic acid [**3.25**]			
2-Hydroxy-6-pentadecenyl benzoic acid [**3.26**]			
Stilbenes			
3,5-Dihydroxy-4′-methoxy-*trans*-stilbenes [**3.27**]	*K. austrosiamensis*	wood	Gonzaléz *et al*., 1993
3-Hydroxy-5,4′-dimethoxy-*trans*-stlbene [**3.28**]			
Lignans			
Dehydroguaiaretic acid [**3.29**]	*K. furfuracea*	stem bark	Pinto and Kijjoa,1990
(+)-*trans*-1,2-Dihydrodehydroguaiaretic acid [**3.30**]			Pinto *et al*., 1990

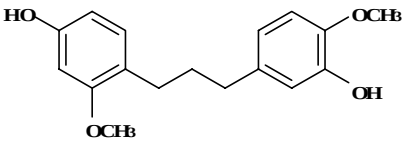
Table 3. (continued)

Compound	Sources	Part	References
Lignans (continued)			
Attenuol [**3.31**]	*K. attenuata*	bark	Joshi *et al*., 1977
(+)-Episesamin [**3.32**]	*K. austrosiamensis*	wood	Gonzaléz *et al*., 1993
(+)-Xanthoxylol [**3.33**]			
Isocoumarins			
8-Hydroxy-(12-phenyldodecyl) isocoumarin [**3.34**]	*K. furfuracea*	stem bark	Pinto and Kijjoa, 1990
8-Hydroxy-6-methoxy-3-pentyl isocoumarin [**3.35**]			Pinto *et al*., 1990
Flavan-Acyphloroglucinols			
(+)-Myristinin A [**3.36**]	*K. elegans*	trunk wood	Deng *et al*., 2005
(+)-Myristinin D [**3.37**]			
Phenylacylphloroglucinols			
Knerachelin A [**3.38**]	*K. furfuracea*	leaves	Zahir *et al*., 1993
1-(2,4,6-Trihydroxyphenyl)-9-phenylnonan-1-one [**3.39**]	*K. austrosiamensis*	wood	Gonzaléz *et al*., 1993
Phenylacylresorcinols			
Knerachelin B [**3.40**]	*K. furfuracea*	leaves	Zahir *et al*., 1993
1-(2,6-Dihydroxyphenyl)-9-phenylnonan-1-one [**3.41**]	*K. austrosiamensis*	wood	Gonzaléz *et al*., 1993
Acylphloroglucinol			
1-(2,4,6-Trihydroxyphenyl) decan-1-one [**3.42**]	*K. austrosiamensis*	wood	Gonzaléz *et al*., 1993
1-(2,4,6-Trihydroxyphenyl) tetradecan-1-one [**3.43**]			

Table 3. (continued)

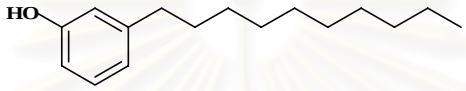
Acylphloroglucinol (continued)			
1-(2,4,6-Trihydroxyphenyl) dodecan-1-one [**3.44**]	*K. austrosiamensis*	wood	Gonzaléz *et al.*, 1993
(*Z*)-1-(2,4,6-Trihydroxyphenyl) tetradec-5-en-1-one [**3.45**]			
Acylresorcinols			
1-(2,6-Dihydroxyphenyl) decan-1-one [**3.46**]	*K. austrosiamensis*	wood	Gonzaléz *et al.*, 1993
1-(2,6-Dihydroxyphenyl) tetradecan-1-one [**3.47**]			
1-(2,6-Dihydroxyphenyl) dodecan-1-one [**3.48**]			
(*Z*)-1-(2,6-Dihydroxyphenyl) tetradec-5-en-1-one [**3.49**]			
Flavan			
(+)-7,4′-Dihydroxy-3′-methoxyflavan [**3.50**]	*K. austrosiamensis*	wood	Gonzaléz *et al.*, 1993

Phenylpropanoid

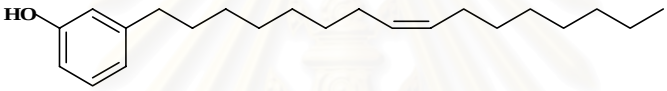


1-(4-Hydroxy-2-methoxyphenyl)-3-(3-hydroxy-4-methoxyphenyl)-propane [**3.1**]

Alkylphenols

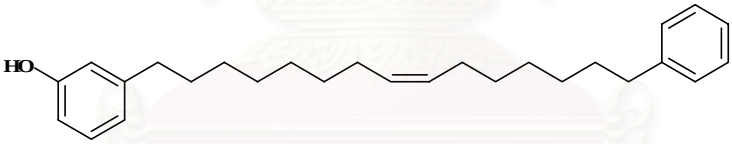


3-Undecylphenol [**3.2**]

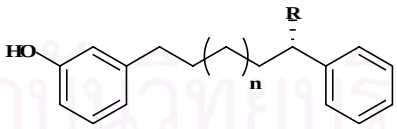


3-(8*Z*-Pentadecenyl)-phenol [**3.3**]

Phenylacylphenols



3-(12-Phenyldodec-8*Z*-enyl)-phenol [**3.4**]



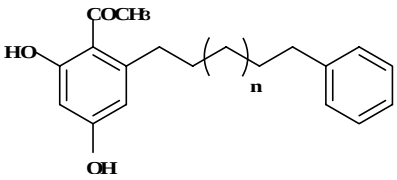
Kneglomeratanol [**3.5**]: n= 6, R= OH

3-(12´-Phenyldodecyl) phenol [**3.6**]: n = 8, R = H

3-(10´-Phenyldecyl) phenol [**3.7**]: n = 6, R = H

Figure 5. Chemical structure of constituents of plants in the genus *Knema*

Acetophenones

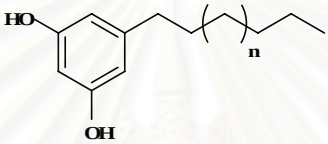


2,4-Dihydroxy-6-(10′-phenyldodecyl) acetophenone [**3.8**]: n = 6

Kneglomeratanones A [**3.9**]: n = 4

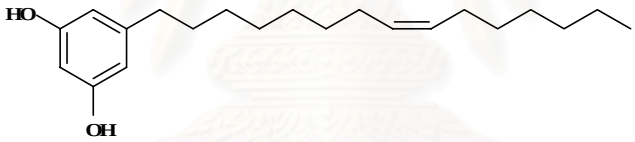
Kneglomeratanones B [**3.10**]: n = 8

Alkylresorcinols



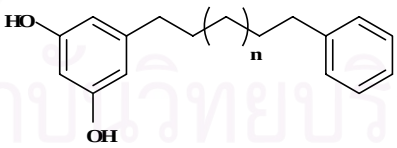
5-Tridecyl resorcinol [**3.11**]: n = 8

5-Pentadecyl resorcinol [**3.12**]: n = 10



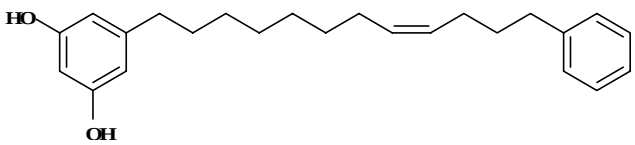
5-(8*Z*-Pentadecenyl) resorcinol [**3.13**]

Phenylalkylresorcinols



5-(10′-Phenyldodecyl) resorcinol [**3.14**]: n =6

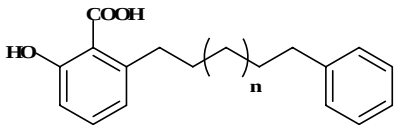
5-(12′-Phenylundecyl) resorcinol [**3.15**]**:** n = 8



5-(12′-Phenyl-8*Z*-tridecyl) resorcinol [**3.16**]

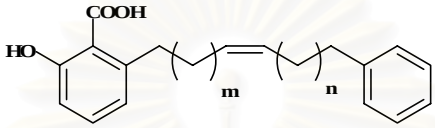
Figure 5. (continued)

Phenylalkylbenzoic acids



2-Hydroxy-6-(12′-phenyldodecyl) benzoic acid [**3.17**]: n = 8

2-Hydroxy-6-(10′-phenyldecyl) benzoic acid [**3.18**]: n = 6



2-Hydroxy-6-(12′-phenyl-8*Z*-dodecyl) benzoic acid [**3.19**]: m = 6, n = 2

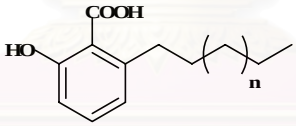
2-Hydroxy-6-(8*Z*-pentadecenyl) benzoic acid [**3.20**]: m = 6, n = 4

2-Hydroxy-6-(10*Z*-pentadecenyl) benzoic acid [**3.21**]: m = 8, n = 2

2-Hydroxy-6-(8*Z*-heptadecenyl) benzoic acid [**3.22**]: m = 6, n = 4

2-Hydroxy-6-(12*Z*-pentadecenyl) benzoic acid [**3.23**]: m = 10, n = 2

Alkylbenzoic acids

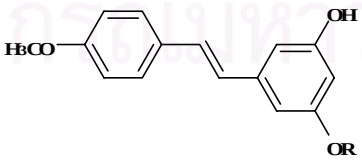


2-Hydroxy-6-undecenyl benzoic acid [**3.24**]: n = 7

2-Hydroxy-6-tridecenyl benzoic acid [**3.25**]: n = 9

2-Hydroxy-6-pentadecenyl benzoic acid [**3.26**]: n = 11

Stilbenes

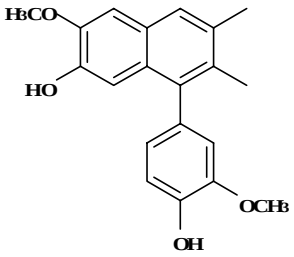


3,5-Dihydroxy-4′-methoxy-*trans*-stilbenes [**3.27**]: R = H

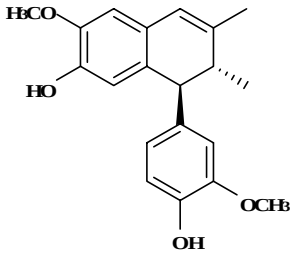
3-Hydroxy-5,4′-dimethoxy-*trans*-stlbene [**3.28**]: R = CH_3

Figure 5. (continued)

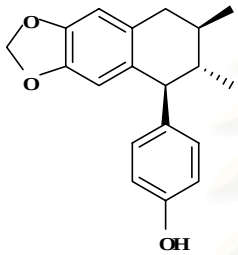
Lignans



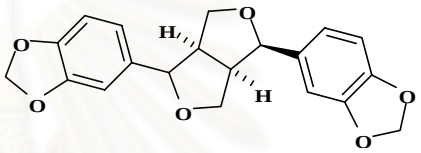
Dehydroguaiaretic acid [**3.29**]



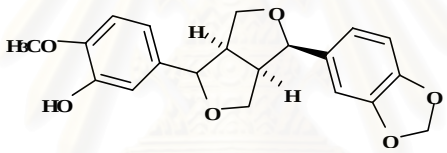
(+)-*trans*-1,2-Didydrodehydroguaiaretic acid [**3.30**]



Attenuol [**3.31**]

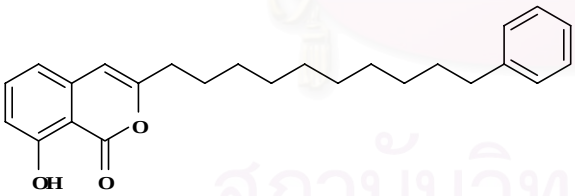


(+)-Episesamin [**3.32**]

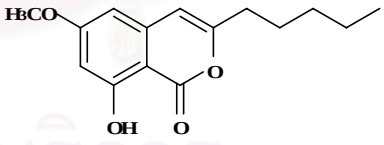


(+)-Xanthoxylol [**3.33**]

Isocoumarins



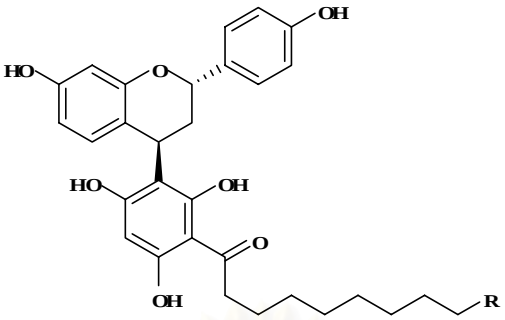
8-Hydroxy-(12-phenyldodecyl) isocoumarin [**3.34**]



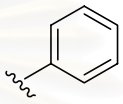
8-Hydroxy-6-methoxy-3-pentyl isocoumarin [**3.35**]

Figure 5. (continued)

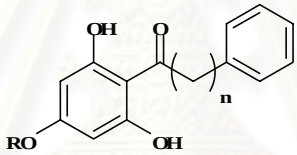
Flavan-acylphloroglucinols



(+)-Myristinins A [**3.36**] :R = $CH_2CH_2CH_3$

(+)-Myristinins D [**3.37**] :R = 

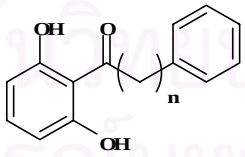
Phenylacylphloroglucinols



Knerachelin A [**3.38**]: n= 4, R = CH_3

1-(2,4,6-Trihydroxyphenyl)-9-phenylnonan-1-one [**3.39**]: n = 8, R = H

Phenylacylresorcinols

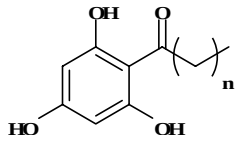


Knerachelin B [**3.40**]: n = 4

1-(2,6-Dihydroxyphenyl)-9-phenylnonan-1-one [**3.41**]: n = 8

Figure 5. (continued)

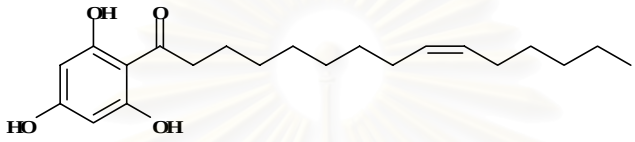
Acylphloroglucinols



1-(2,4,6-Trihydroxyphenyl) decan-1-one [**3.42**]: n = 8

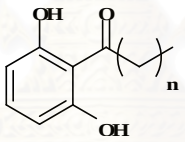
1-(2,4,6-Trihydroxyphenyl) tetradecan-1-one [**3.43**]: n = 12

1-(2,4,6-Trihydroxyphenyl) dodecan-1-one [**3.44**]: n = 10



(*Z*)-1-(2,4,6-Trihydroxyphenyl tetradec-5-en-1-one[**3.45**]

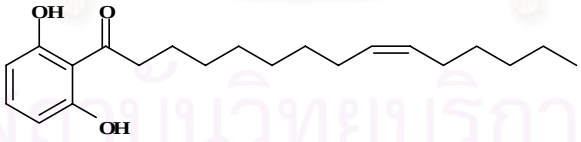
Acylresorcinols



1-(2,6-Dihydroxyphenyl) decan-1-one [**3.46**]: n = 8

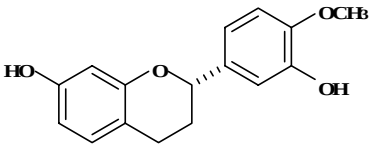
1-(2,6-Dihydroxyphenyl) tetradecan-1-one [**3.47**]: n = 12

1-(2,6-Dihydroxyphenyl) dodecan-1-one [**3.48**]: n = 10



(*Z*)-1-(2,6-Dihydroxyphenyl tetradec-5-en-1-one [**3.49**]

Flavan



(+)-7,4′-Dihydroxy-3′-methoxyflavan [**3.50**]

Figure 5. (continued)

CHAPTER III

EXPERIMENTAL

1. Source of Plant Materials

The fruits, leaves and stems of *Knema glauca* var. *glauca* and the leaves and stems of *K. furfuracea* were collected in Nakhon Sri Thammarat, Thailand, in March, 2004. Voucher specimens of both species were deposited at the Forest Herbarium, Bangkok, and at the herbarium of the Department of Pharmacognosy and Pharmaceutical Botany, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand.

2. General Techniques

2.1 Solvents

Throughout this work, all organic solvents were of commercial grade and were redistilled prior to use.

2.2 Analytical Thin-Layer Chromatography (TLC)

Technique	:	One dimension, ascending
Adsorbent	:	Silica gel 60 F_{254} (E. Merck) pre-coated plates
Layer thickness	:	0.2 mm
Distance	:	5.0 cm
Temperature	:	Laboratory temperature (25-30 $^{\circ}$C)
Detection	:	1. Ultraviolet light (254 and 365 nm) 2. 10% Sulfuric acid and heating at 105 $^{\circ}$C for 10 min

2.3 Column Chromatography

2.3.1 Conventional Column Chromatography

Gel filter	:	Silica gel 60 (No. 9385) particle size 0.040-0.063 nm (E. Merck)
Packing method	:	Wet packing: The absorbent was mixed with the eluent into slurry, then poured into a column and allowed to settle.
Sample loading	:	The sample was dissolved in a small amount of the eluent, and then applied gently on top of the column.

Detection : Fractions were examined by TLC technique in the same manner as described in section 2.2.

2.3.2 Gel Filtration Chromatography

Gel filter : Sephadex LH-20 (Pharmacia Biotech AB)

Packing method : Gel filter was suspended in the eluent and left standing to swell for 24 hours prior to use. It was then poured into the column and allowed to set tightly.

Sample loading : The sample was dissolved in a small amount of eluent and then applied gently on top of the column.

Detection : Fraction were examined by TLC technique in the same manner as described in section 2.2

2.3.3 High Pressure Liquid Chromatography (HPLC)

Column

(Semi-preparative) : Cosmosil 5C18-AR II (20 × 250 mm)

(Analytical) : Cosmosil C18 AR II (4.6 × 150 mm)

Mobile phase : MeOH-H_2O gradient

Pump : Waters 600

Detector : 996 photodiode-array

Temperature : 25 °C

2.4 Spectroscopy

2.4.1 Ultraviolet (UV) Spectra

UV spectra were obtained either on a Shimadzu UV-160A spectrophotometer (Pharmaceutical Research Instrument Center, Faculty of Pharmaceutical Sciences, Chulalongkorn University) or a Hitachi U-3010 spectrophotometer (Kobe Pharmaceutical University).

2.4.2 Infrared (IR) Spectra

IR spectra (KBr disc and film) were recorded on a Perkin Elmer FT-IR 1760X spectrometer (Scientific and Technological Research Equipment Center, Chulalongkorn University).

2.4.3 Mass Spectra

Electrospray Ionization Time of Flight (ESI-TOF) mass spectra were obtained on a Micromass LCT mass spectrometer (National Center for Genetic Engineering and Biotechnology, BIOTEC, Thailand) and the electron-impact (EI), high

resolution electron impact (HR-EI), secondary ion (SI) (with glycerol for a matrix) and high resolution secondary ion (HR-SI) mass spectra were recorded on a Hitachi M-4100 instrument (Kobe Pharmaceutical University, Kobe, Japan).

2.4.4 Proton and Carbon-13 Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR) Spectra

^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were measured on a Bruker DPX-300 FT-NMR spectrometer (Pharmaceutical Research Instrument Center, Faculty of Pharmaceutical Sciences, Chulalongkorn University).

^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were measured on a JEOL JMN-A500, a Varian unity INOVA (both at the Scientific and Technological Research Equipment Center, Chulalongkorn University), a Varian nVXR-500 (Kobe Pharmaceutical University, Kobe, Japan) or a Bruker-AV 500 MHz spectrometer (National Center for Genetic Engineering and Biotechnology, BIOTEC, Thailand).

2.4.5 Fluorescence Spectrophotometer

Fluorescence spectra were measured on a Hitachi F-2000 Fluorescence Spectrophotometer (Kobe Pharmaceutical University, Kobe, Japan).

2.5 Physical properties

2.5.1 Melting points

Melting points were obtained on a Fisher-John melting point apparatus (Department of Pharmaceutical Botany, Faculty of Pharmaceutical Sciences, Chulalongkorn University).

2.5.2 Optical Rotations

Optical rotations were measured on a Perkin-Elmer 314 polarimeter using a sodium lamp operating at 589 nm (Pharmaceutical Research Instrument Center, Faculty of Pharmaceutical Sciences, Chulalongkorn University).

3. Extraction and Isolation

3.1 Extraction and Isolation of Compounds from *Knema glauca* var. *glauca*

3.1.1 Extraction of the fruits of *K. glauca* var. *glauca*

The ground, dried fruits of *K. glauca* var. *glauca* (350 g) were successively macerated with hexane (5 × 3L), EtOAc (5 × 3L) and MeOH (5 × 3L). Removal of the organic solvents from the filtrate yielded the hexane (65.7 g, 18.8% based on dried

weight of the fruits), EtOAc (67.8 g, 19.4% yield) and MeOH extracts (14.4 g, 4.1% yield), respectively.

3.1.2 Isolation of Compounds from the First Batch of the EtOAc Extract of *K. glauca* var. *glauca* Fruits

A batch of the EtOAc extract (30 g) was subjected to silica gel column chromatography. The extract was redissolved in a small amount of EtOAc, triturated with silica gel, dried at room temperature, then applied to the top of a silica gel column (400 g, 9.5 × 10 cm). The eluent was a gradient mixture of hexane-acetone (4:1 to 1:1). Eighty–three fractions were collected and combined according to their TLC profiles into nine fractions (A1-A9) as shown in **Table 4.**

Table 4. Combined fractions from the first batch of the EtOAc extract of *K. glauca* var. *glauca* fruits

Fraction Code	Weight (g)
A1	0.99
A2	0.31
A3	0.24
A4	0.19
A5	6.16
A6	2.18
A7	7.81
A8	2.40
A9	9.72

3.1.2.1 Isolation of Compound KG-F1 (2,6-Dihydroxyphenyl-tetradecan-1-one)

Fraction A1 (0.99 g) was further chromatographed on a silica gel column (30 g, 2 × 20 cm) eluted with a gradient of hexane-CH_2Cl_2 (2:3 to 1:4). The eluates (41 fractions) were examined by TLC, then combined to yield 5 fractions (A11-A15). Fraction A12 (212.9 mg) was further fractionated on another silica gel column (10 g, 2 × 10 cm), eluted with hexane–acetone (10:1), into 18 fractions. These were combined, after TLC, into 4

major fractions (A121-A124). Compound KG-F1 (3.3 mg, 0.0009 % yield of dry friuts weight) precipitated as yellow amorphous solid from fraction A123.

3.1.2.2 Isolation of Compounds KG-F2 (Asarinin) and KG-F3 (Sesamin)

The components of fraction A4 (0.19 g) was separated according to their size, on a Sephadex LH-20 column with CH_2Cl_2-MeOH (1:1) as the eluent, into 6 fractions (A41-A46). Fraction A45 (32.6 mg) was further fractionated on another Sephadex LH-20 column, using EtOAc as the eluent, into two major fractions (A451-A452).

Fraction A451 (20.0 mg) was subjected to silica gel column chromatography (400 g, 9.5 × 10 cm), employing CH_2Cl_2 as the mobile phase, to give 4 combined fractions (A4511-A4514). Evaporation of fraction A4512 to dryness gave compound KG-F2 as colorless needles (14.3 mg, 0.0041% yield). Similarly, solvent evaporation of fraction A4513 yielded compound KG-F3 as colorless needles (9.9 mg, 0.0028% yield).

3.1.2.3 Isolation of Compound KG-F4 (Glaucaic acid)

Fraction A6 (2.18 g) was separated on a silica gel column (60g, 3 × 15 cm), eluting with hexane-acetone (7:3), to give 50 fractions (10 ml each). These fractions were pooled, after TLC monitoring, into 7 fractions (A61-A67). Fraction A63 (0.86 g) was further separated on a Sephadex LH-20 column, washed down with CH_2Cl_2-MeOH (1:1), into 4 fractions (A631-A634). Gel filtration of fraction A632 (0.66 g) on a Sephadex LH-20 column with CH_2Cl_2-MeOH (30:1) as the mobile phase afforded compound KG-F4 (130.2 mg, 0.0372% yield).

3.1.2.4 Isolation of Compound KG-F5 (Myristinin F)

Fraction A7 (7.81 g) was subjected to silica gel column chromatography (250 g, 6 × 15 cm), eluting with a hexane-acetone gradient (7:3 to 6:4), to give 94 fractions which were then combined according to TLC pattern into six major fractions (A71-A76). Fraction A75 (6.26 g) was gel filtrated on a Sephadex LH-20 column with CH_2Cl_2-MeOH (1:1) as the mobile phase to give four major fractions (A751-A754). Separation of fraction A753 (4.43 g) on a silica gel column, eluted with a gradient mixture of CH_2Cl_2-MeOH (50:1 to 5:1), yielded seven fractions (A7531-A7537).

Fraction A7536 (3.56 g), which displayed a yellow spot on TLC, was purified on a silica gel column (107 g, 2.5 × 20 cm) using CH_2Cl_2-acetone (8:2) as the mobile phase. The fraction was further separated into 3 subfractions and compound KG-F5 was

obtained as yellow amorphous solid (24.0 mg, 0.0068 % yield), upon evaporation of the second subfraction.

3.1.3 Isolation of Compounds from the Second Batch of EtOAc Extract of *K. glauca* var. *glauca* Fruits

Another batch of the EtOAc extract of *K. glauca* var. *glauca* fruits (24.2 g) was separated on a silica gel column (400 g, 9.5 × 10 cm) eluted with a gradient of hexane-acetone (4:1 to 1:1) into 126 fractions, then the column was washed down with MeOH. These fractions were combined on the basis of their TLC profiles into ten major fractions (B01-B10, **Table 5**)

Table 5. Combined fractions from the second batch of EtOAc extract of *K. glauca* var. *glauca* fruits

Fraction Code	Weight (g)	Fraction Code	Weight (g)
B01	0.58	B06	0.71
B02	0.71	B07	4.30
B03	0.89	B08	1.33
B04	2.78	B09	4.06
B05	0.93	B10	5.19

3.1.3.1 Isolaton of Compound KG-F6 (Malabaricone A)

Fraction B02 (0.71 g), which displayed a prominent, dark orange spot on TLC, was subjected to silica gel column chromatography (80 g, 2.5 × 20 cm) eluted with a gradient mixture of $CHCl_3$-acetone (1:0 to 19:1). The eluates were collected, monitored by TLC and combined into five fractions (B021-B025). Fraction B022 (0.24 g) was further separated on another silica gel column (20 g, 2 × 15 cm), using a gradient mixture of cyclohexane-CH_2Cl_2 (0:1 to 1:0) as the mobile phase, to afford 92 fractions (5 ml each). These were later combined into 4 fractions (B0221-B0224) based on their TLC pattern. Fraction B0221 (42.9 mg) was subjected to reversed–phase preparative HPLC (Cosmosil C18-ARII, 20 × 250 nm, flow rate 1 ml/min, detected at 360 nm) with a gradient mixture of water-methanol (3:7 to 1:9) as the mobile phase. All collected fractions were examined by TLC and pooled into six fractions (B02211-B02216).

Removal of organic solvent from fraction B02215 yielded compound KG-F6 (20.0 mg, 0.0057% yield) as amorphous solid.

3.1.3.2 Isolation of Compounds KG-F7 [Dodecanoylphloroglucinol] and KG-F8 [1-(2,4,6-Trihydroxyphenyl)-9-phenylnonan-1-one]

Fraction B04, when developed with hexane-acetone (3:2), displayed two major yellow spots and one brown spot on TLC. The fraction (2.78 g) was chromatographed on a silica gel column (40 g, 2.5 × 6 cm), eluted with hexane-acetone (3:2), to give 50 fractions which were later combined into fractions B041-B045. Fraction B043, which showed two yellow spots with closely similar Rf values on TLC, was separated using a reverse-phase HPLC column (analytical column: Cosmosil C18 ARII, 4.6 × 15 nm, flow rate 1 ml/ min) with a gradient mixture of water-methanol (2:8 to 1:9) as the mobile phase. The eluates were combined based on their HPLC chromatograms into 4 fractions (B0431-B0434). Removal of the solvent yielded compound KG-F7 (42.5 mg, 0.0120% yield) and compound KG-F8 (114.2 mg, 0.0320% yield) as amorphous solid from the fractions B0432 and B0433, respectively.

3.1.4 Extraction of the Leaves of *K. glauca* var. *glauca*

The dried, powdered leaves of *Knema glauca* var. *glauca* (570 g) were extracted with hexane (5 × 3L), EtOAc (5 × 3L), and MeOH (5 × 3L), successively. Each extract was evaporated to dryness to give a hexane extract (9.2 g, 1.6 % yield), an EtOAc extract (55.5 g, 9.73% yield) and a MeOH extract (23.7 g, 4.16% yield).

3.1.5 Isolation of Compound from the EtOAc extract of *K. glauca* var. *glauca* Leaves

A portion of the EtOAc extract (16.0 g) was fractionated by silica gel column (380 g, 10 × 10 cm) using a gradient mixture of hexane-acetone (4:1 to 1:1) as the mobile phase. Each collected fraction was 100 ml; one hundread and two fractions were collected. After TLC examination, fractions with similar pattern were combined to yield eight major fractions (C1-C8, **Table 6**).

Table 6. Combined fractions from the EtOAc extract of *K. glauca* var. *glauca* leaves

Fraction code	Weight (g)
C1	0.57
C2	0.78
C3	2.28
C4	1.57
C5	1.63
C6	2.79
C7	1.00
C8	5.28

3.1.5.1 Isolation of Compound KG-L1 (Myristinin C)

Fraction C5 (1.5 g) was purified on a silica gel column (40 g, 2 × 15 cm) eluted with $CHCl_3$-acetone (7:3) to give 60 fractions, which were then combined into 5 fractions (C51-C55). Fraction C54 (0.34 g) was further chromatographed on a Sephadex LH-20 column, washed down with CH_2Cl_2-MeOH (1:1). Thirty-five fractions, 5 ml each, were collected and combined according to their TLC behavior into 6 fractions (C541-C546). Purification of fraction C545 (0.26 g) on another Sephadex LH-20 column, eluted with MeOH, yielded 23 fractions which were then combined to give fractions C5451-C5454. Compound KG-L1 was obtained as yellow amorphous solid (10.3 mg, 0.0018% yield) from fraction C5451.

3.1.6 Extraction of the Stems of *K. glauca* var. *glauca*

The dried, ground stems of *K. glauca* var. *glauca* (700 g) were macerated with hexane (5 × 3L), EtOAc (5 × 3L) and MeOH (5 × 3L), successively, and filtered. Each filtrate was pooled and evaporated under reduced pressure at temperature not exceeding 40^{o}C to give the hexane extract (5.08 g, 0.72 % yield), EtOAc extract (16.64 g, 2.37% yield) and MeOH extract (28.12 g, 4.01% yield).

3.1.7 Isolation of Compound from the EtOAc extract of *K. glauca* var. *glauca* Stems

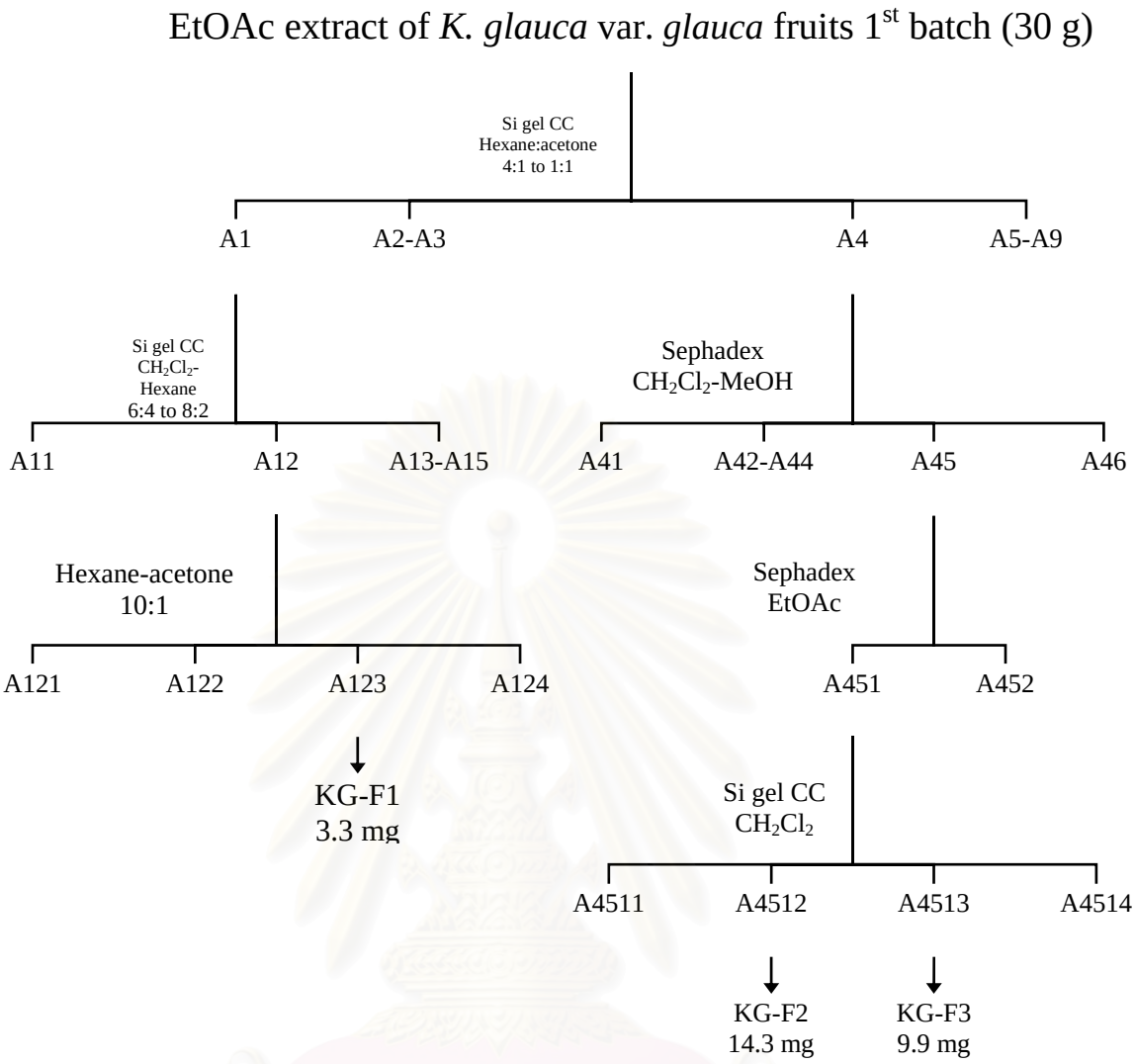
A portion of the EtOAc extract of *K. glauca* var. *glauca* stems (11.0 g) was chromatographed on a silica gel column (200 g, 10 × 8 cm) eluted stepwise with a gradient mixture of hexane-EtOAc (4:1 to 0:1). Two hundred and sixty-eight fractions (30 ml each) were collected and examined by TLC. Fractions with similar chromatographic pattern were combined to yield twenty-one pooled fractions (BEA – BEU, **Table 7**).

Table 7. Combined fractions from the EtOAc extract of *K. glauca* var. *glauca* stems

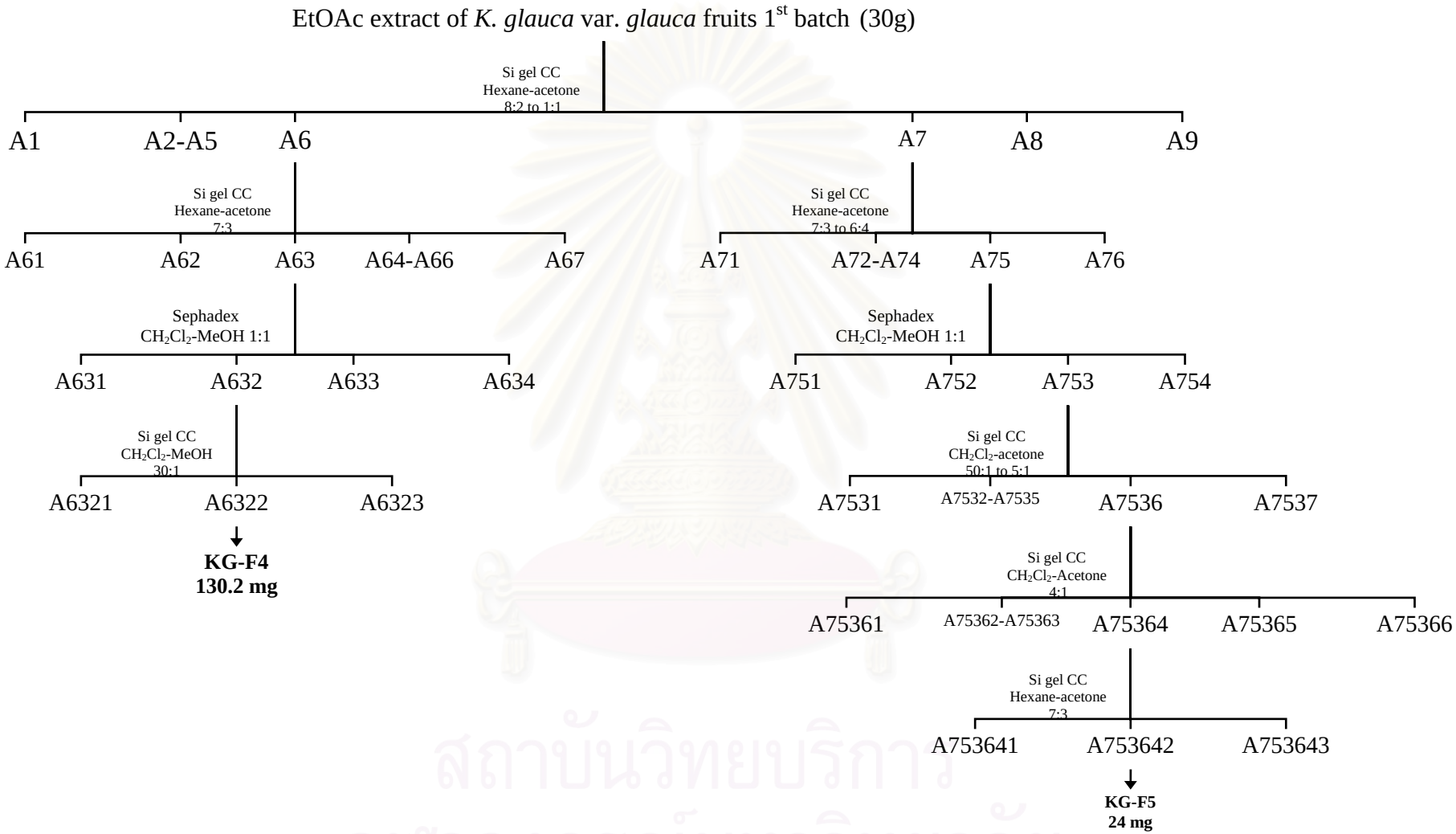
Fraction Code	Weight (g)
D1	2.17
D2	2.76
D3	1.55
D4	0.64
D5	0.58
D6	0.86
D7	0.64
D8	2.04

3.1.7.1 Isolation of Compound KG-S1 ((±)-7,4´-Dihydroxy-3´-methoxy-flavan)

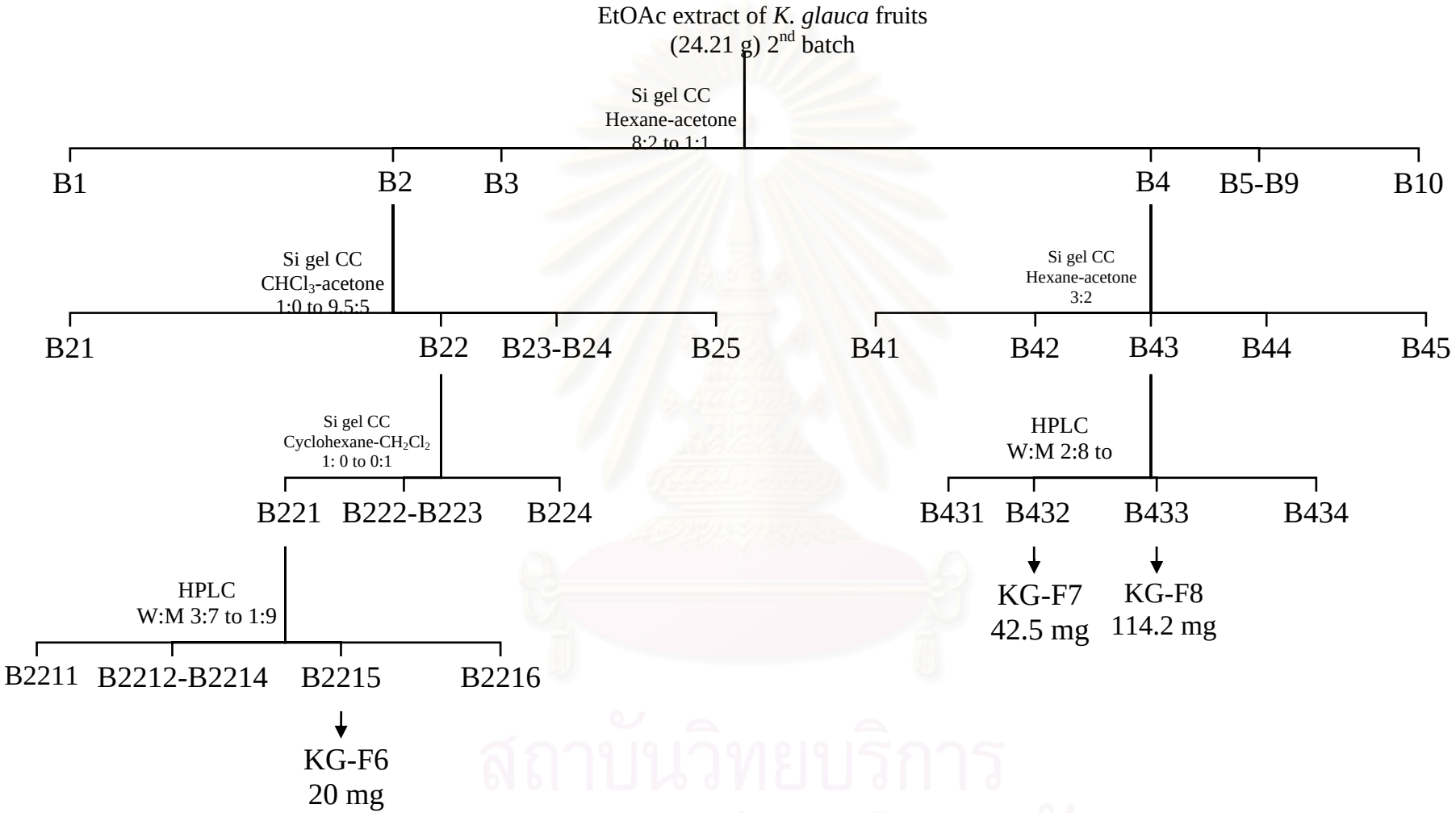
Separation of fraction D3 (1.55 g) on a silica gel column (20 g, 2 × 15 cm) eluted with hexane-acetone (3:1) yielded 54 collected fractions, which were examined by TLC and combined into 4 major fractions (D31-D34). Gel filtration chromatography of fraction D33 (0.34 g) on a Sephadex LH-20 column washed down with MeOH gave 3 combined fractions (D331-D333). Purification of fraction D332 (0.11 g) on a silica gel column (20 gm, 2 × 15 cm) using hexane-acetone (13:7) as the eluting solvent afforded compound KG-S1 as brown amorphous solid (50.0 mg, 0.014 % yield).



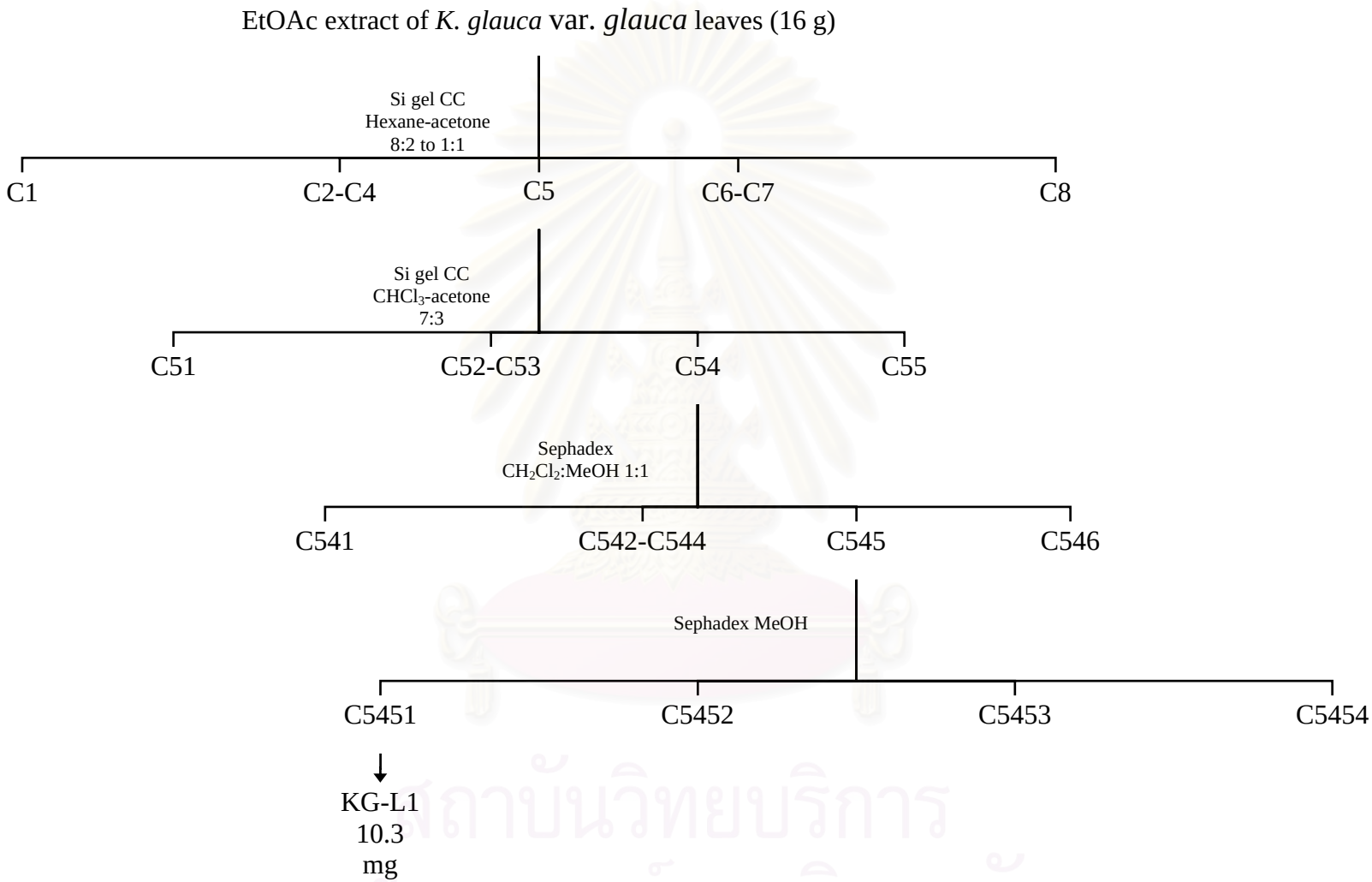
Scheme 1. Extraction and isolation of compounds from the EtOAc extract of *K. galuca* var. *glauca* fruits (1st batch).



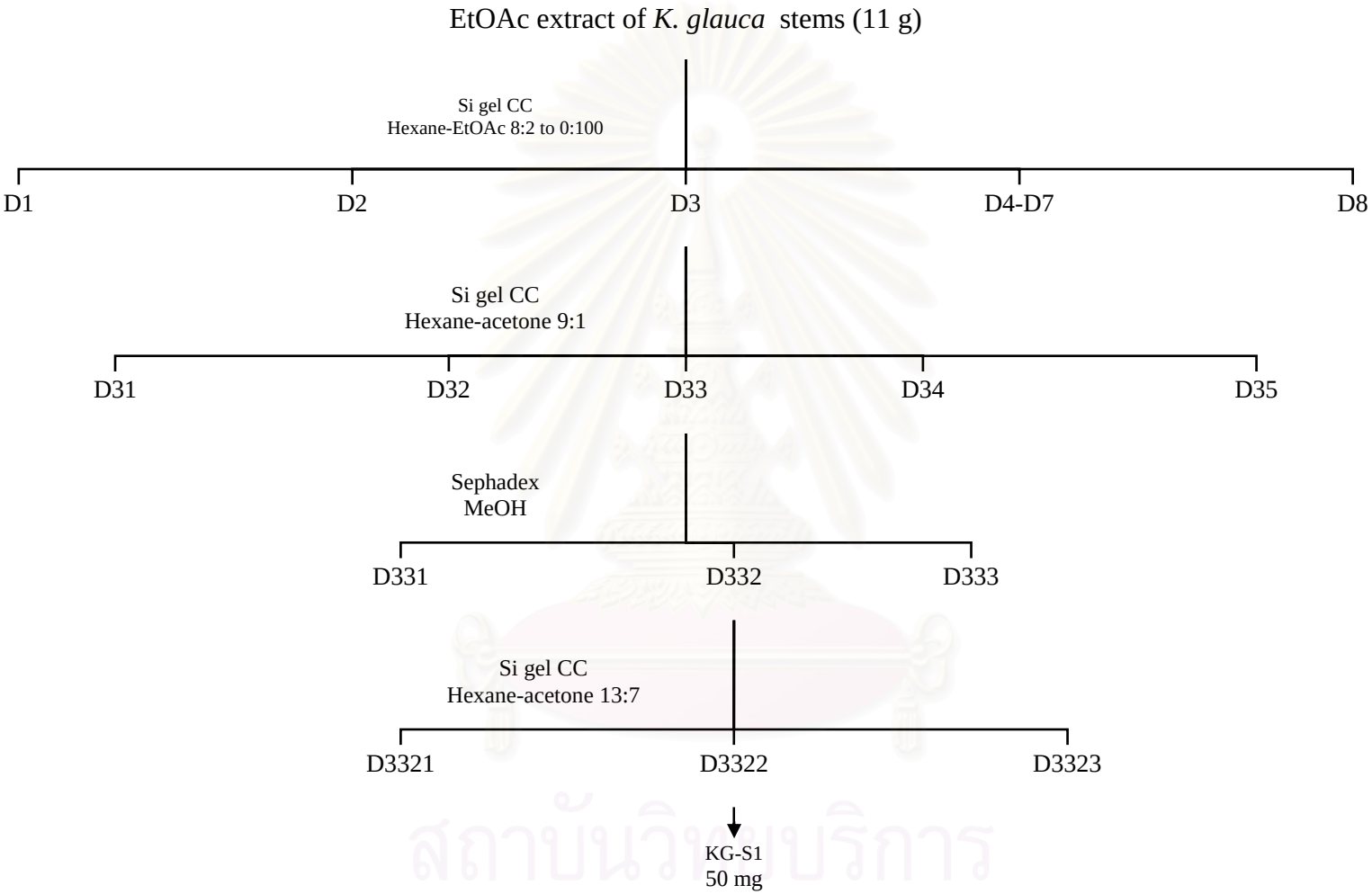
Scheme 1. (continued).



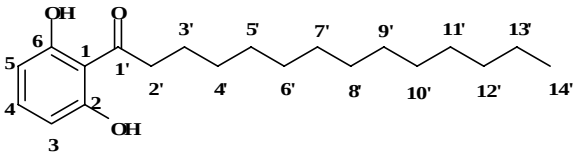
Scheme 2. Extraction and isolation of compounds from the EtOAc extract of *K. galuca* var. *glauca* fruit (2nd batch).



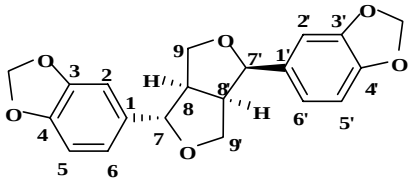
Scheme 3. Extraction and isolation of compound from the EtOAc extract of *K. glauca* var. *glauca* leaves.



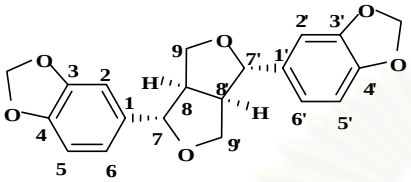
Scheme 4. Extraction and isolation of compound from the EtOAc extract of *K. glauca* var. *glauca* stems.



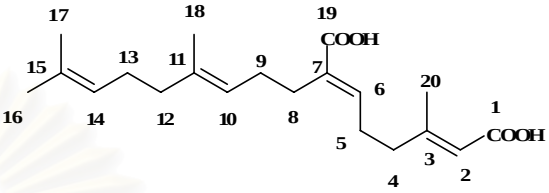
KG-F1



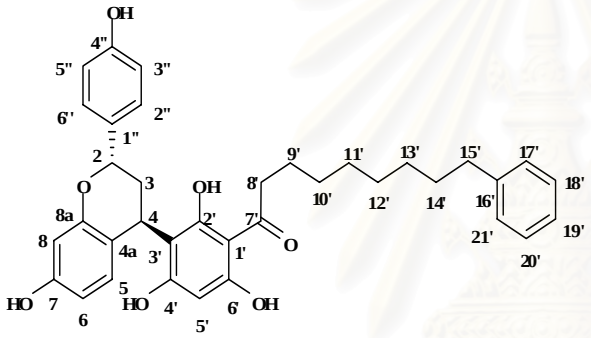
KG-F2



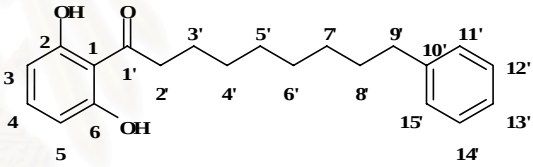
KG-F3



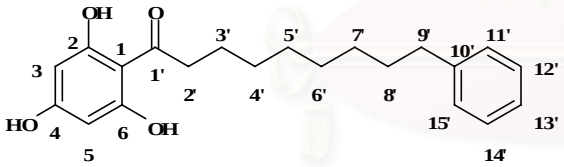
KG-F4



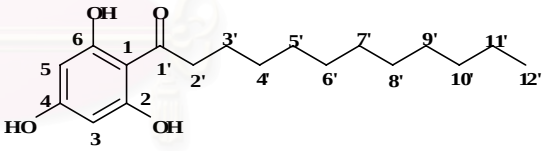
KG-F5



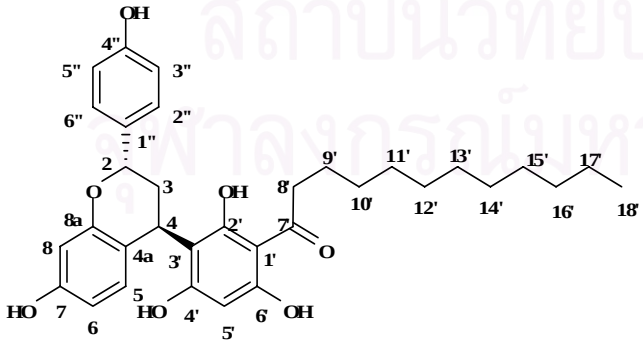
KG-F6



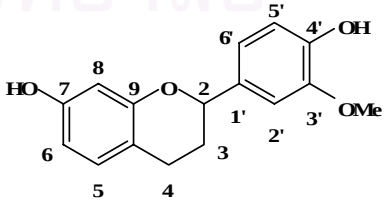
KG-F7



KG-F8



KG-L1



KG-S1

Figure 6. Structures of compounds isolated from *Knema glauca* var. *glauca*

3.2 Extraction and Isolation of Compounds from *Knema furfuracea*

3.2.1 Extraction of the Stems of *K. furfuracea*

The dried stems of *K. furfuracea* (700 g) were ground and macerated with hexane (5 × 3L), EtOAc (5 × 3L) and MeOH (5 × 3L), respectively. Each extract was evaporated under reduced pressure to afford the hexane (5.67 g, 0.80% yield of dry stem weight), EtOAc (4.44 g, 0.63% yield) and MeOH extracts (5.93 g, 0.84% yield of dry stem weihgt), respectively.

3.2.2 Isolation of Compounds from the Hexane Extract of *K. furfuracea* Stems

A portion of the hexane extract (4.0 g) was chromatographed on a silica gel column (200 g, 20 × 8 cm) eluting stepwise with a gradient mixture of hexane-acetone (49:1 to 4:1). Two hundred and twenty-five 50-ml fractions were collected and combined according to their TLC pattern into 9 fractions (E1-E9, **Table 8**).

Table 8. Combined fractions from the hexane extract of *K. furfuracea* stems

Fraction code	Weight (g)
E1	0.11
E2	0.34
E3	0.30
E4	0.40
E5	0.30
E6	0.50
E7	0.55
E8	0.95
E9	0.54

3.2.2.1 Isolation of Compounds KF-S1 [(+)-*trans*-1,2-Dihydrodehydro-guaiaretic acid] and KF-S2 (Fragransin A_2)

Fraction E8 (0.95 g) was subjected to silica gel column chromatography (80 g, 2.5 × 20 cm), using hexane-CH_2Cl_2 (1:24) as the eluent, to yield 6 combined fractions (E81-E86). Fraction E82 was repeatedly chromatographed on a Sephadex LH-20 column,

eluted with MeOH, to yield compound KF-S1 as white amorphous solid (7.9 mg, 0.0011% yield of dry stem weight).

Fraction E86 (0.19 g), which exhibited a major purple spot on TLC, was further separated on a silica gel column, eluted with CH_2Cl_2-acetone (9:1), into 2 fractions (E861-E862). Removal of organic solvent from the second fraction gave compound KF-S2 (15.3 mg, 0.0022% yield).

3.2.3 Isolation of Compounds from the EtOAc Extract of *K. furfuracea* Stems

The EtOAc extract (4.0 g) was subjected to silica gel column chromatography (100 g, 2.5 × 15 cm). Gradient elution with hexane-acetone (24:1 to 2:3) was performed and 167 fractions (50 ml per fraction) were collected. Fractions with similar TLC pattern were combined to yield 10 fractions (F01-F10, **Table 9**).

Table 9. Combined fractions from the EtOAc extract of *K. furfuracea* stems

Fraction code	Weight (g)	Fraction code	Weight (g)
F01	0.33	F06	0.29
F02	0.31	F07	0.41
F03	0.26	F08	0.67
F04	0.25	F09	0.34
F05	0.49	F10	0.65

3.2.3.1 Isolation of Compounds KF-S3 (Biochanin A) and KF-S4 (Mixture of Anarcardic acid and Ginkgolic acid)

Fraction F05 (0.49 g) was subjected to silica gel column chromatography (40 g, 2.5 ×10 cm) eluted with CH_2Cl_2. Thirty-six fractions were collected and combined based on their TLC behavior into 5 main fractions (F051-F055). Fraction F055 was then separated on another silica gel column, eluted with a gradient mixture of hexane-acetone (4:1 to 3:2), into 6 fractions (F0551-F0556). Compound KF-S3 precipitated as amorphous solid (6.0 mg, 0.0086% yield) fraction F0553. Gel filtration chromatography of fraction F0554 on a Sephadex LH-20 column with MeOH as the eluent afforded compound KF-S4 as colorless needles (38.7 mg, 0.0096% yield of dry stem weight).

3.2.3.2 Isolation of compound KF-S5 (Mixture of 2-Hydroxy-6-(12-phenyldodecyl) benzoic acid and 2-Hydroxy-6-(12-phenyldodecen-8′*Z*-yl) benzoic acid)

Silica gel column chromatography (40 g, 2.5 × 10 cm) of fraction F07 (0.41 g) using a gradient mixture of CH_2Cl_2–acetone (40:1 to 10:1) as the mobile phase gave 45 fractions, which were later combined after TLC monitoring into 4 main fractions (F071-F074). Chromatographic separation of fraction F072 (0.11 g) on another silica gel column (20 g, 2 × 15 cm), eluted with CH_2Cl_2-acetone (10:1), yielded compound KF-S5 as amorphous solid (11.5 mg, 0.0016% yield).

3.2.4 Extraction of the Leaves of *K. furfuracea*

The dried, powdered leaves of *K. furfuracea* (1.4 kg) were macerated with hexane (5 × 3L), EtOAc (5 × 3L) and MeOH (5 × 3L), respectively. Each solvent extract was pooled and evaporated under reduced pressure to afford the hexane extract (19.82 g, 1.41% yield), EtOAc extract (14.6 g, 1.04% yield) and MeOH extract (44.46 g, 3.17% yield), respectively.

3.2.5 Isolation of Compounds from the Hexane Extract of *K. furfuracea* Leaves.

The hexane extract (10 g) was separated by a silica gel column (silica gel no. 7734, 350 g). The elutes were collected 138 ml per fraction. Elution was performed in a polarity gradient manner with mixture of hexane and acetone (9:1 to 6:4). One hundred-thirty eight fractions were collected. Fraction with similar TLC pattern was combined to yield 13 fractions (G01-G013, **table 10**).

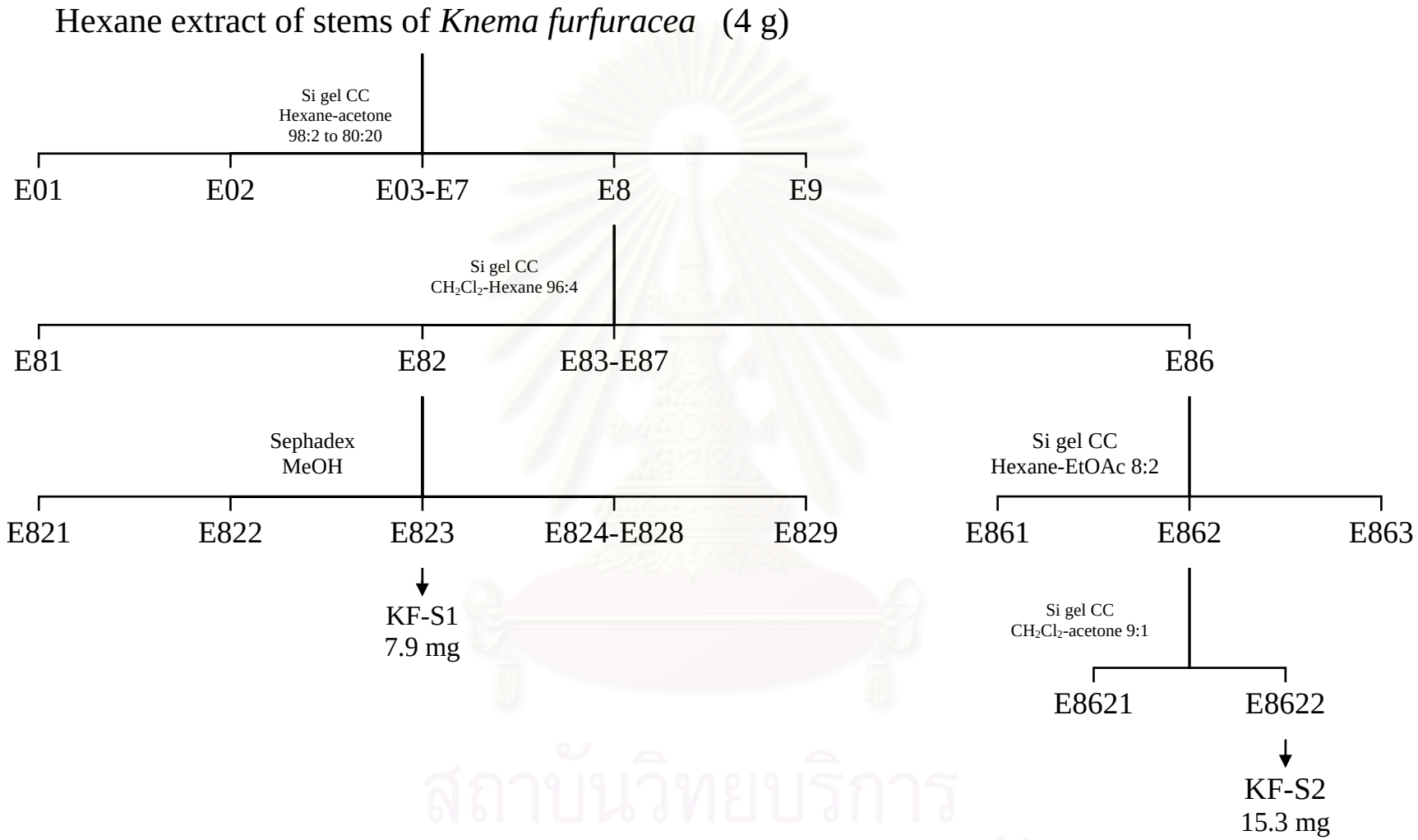
Table 10. Combined fractions from the hexane extract of *K. furfuracea* leaves.

Fraction code	Weight (g)	Fraction code	Weight (g)
G01	4.8338	G08	0.4123
G02	0.2436	G09	1.0508
G03	0.3282	G10	0.8475
G04	0.4207	G11	0.2528
G05	0.1099	G12	0.3649
G06	0.1698	G13	0.2674
G07	0.6983		

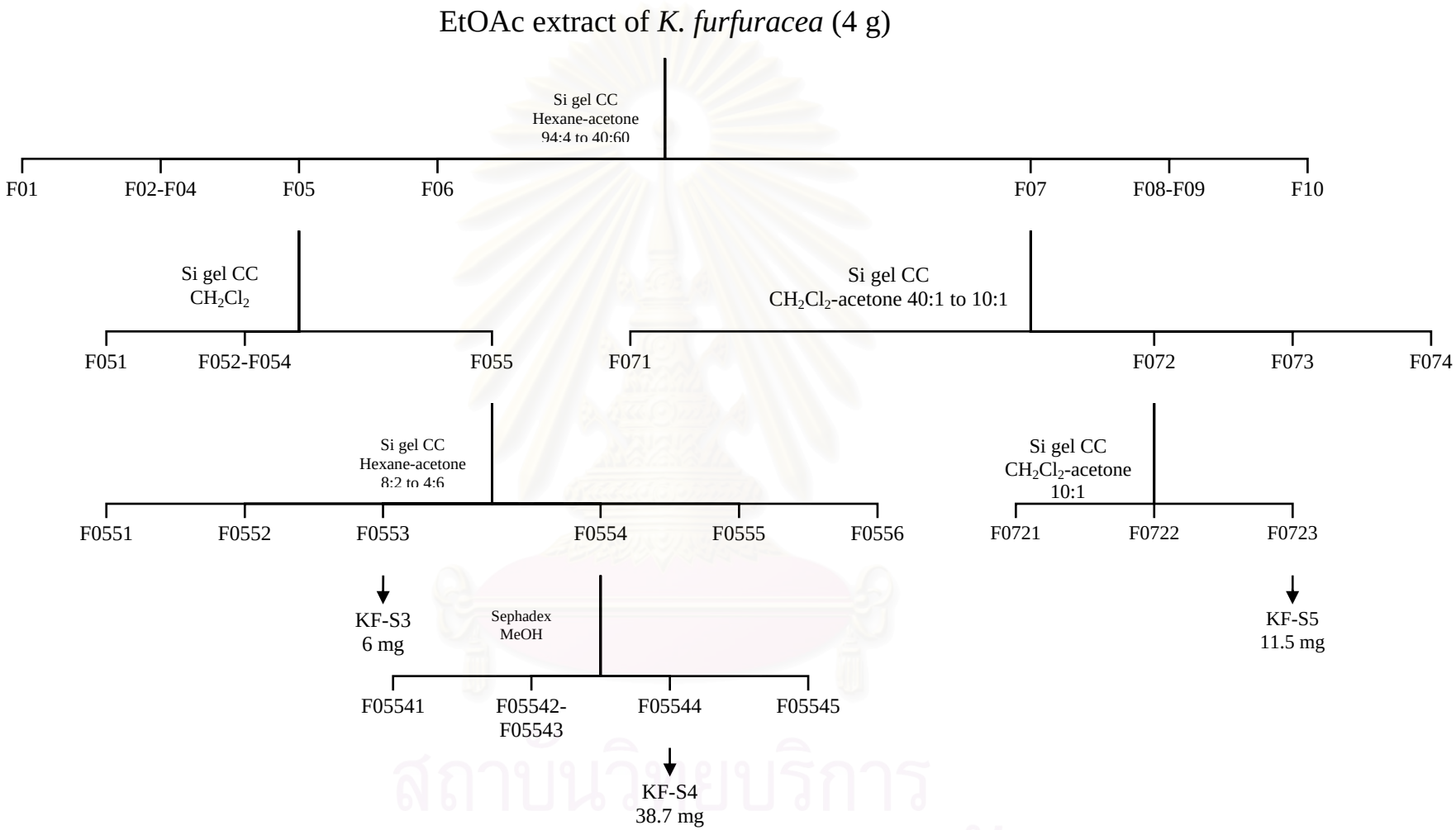
3.2.5.1 Isolation of Compound KF-L1 (Furfuracin).

Fraction G12 (0.3649 g) was subjected to column chromatography using silica gel (no. 7734) as adsorbent. Mixtures of hexane and acetone gradient (8:2 to 6:4) were used as mobile phase. Purification of fraction G122 0.1388 g by silica gel column chromatography using 30% acetone in hexane as eluents. Fifteen fractions was collected and combined with similar TLC pattern give five fractions (G1221 – G1225).

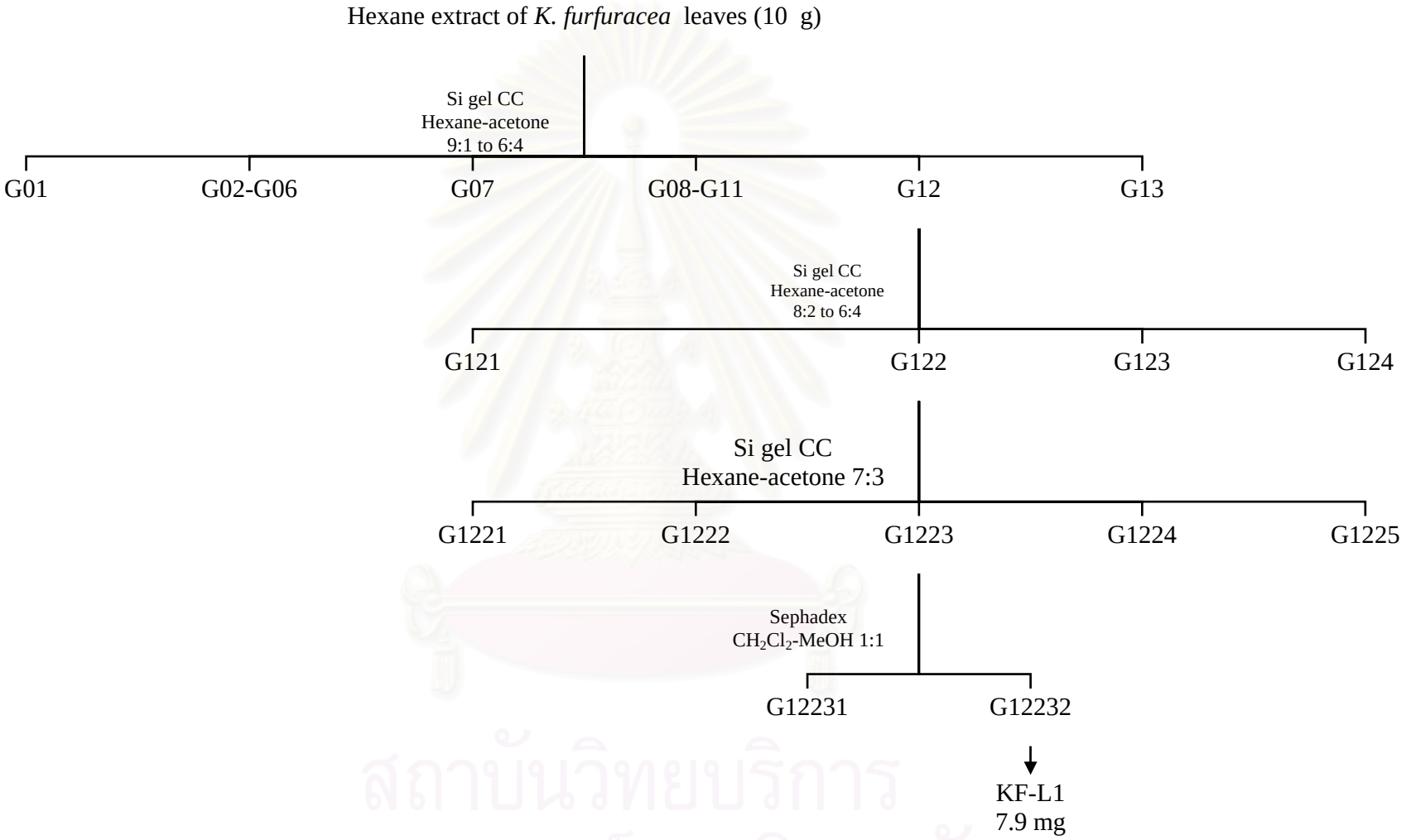
Fractionation of fraction G1223 (0.0293 g) by using a Sephadex LH-20 column eluted with a mixture of CH_2Cl_2-MeOH (1:1) pool seven fractons. Combined the fraction with similar TLC behavior yielded two fractions (G12231 – G12232). Fraction G12232 was gave purple spot on TLC when sprayed with 10% sulfuric acid in EtOH and heat and after organic solvent was removed yielded colorless amorphous crystal, KG-L1, 0.0079 g (0.000564 % yield based on dried weight of the stems).



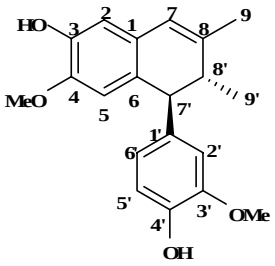
Scheme 5. Extraction and isolation of compounds from the Hexane extract of *K. furfuracea* stems.



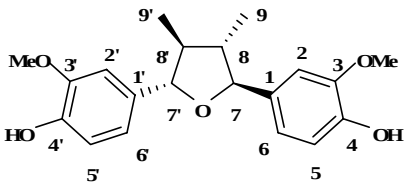
Scheme 6. Extraction and isolation of compounds from the EtOAc extract of *K. furfuracea* stems.



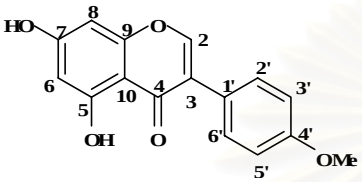
Scheme 7. Extraction and isolation of compound from the hexane extract of *K. furfuracea* leaves.



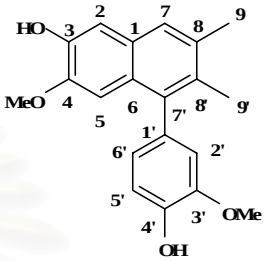
KF-S1



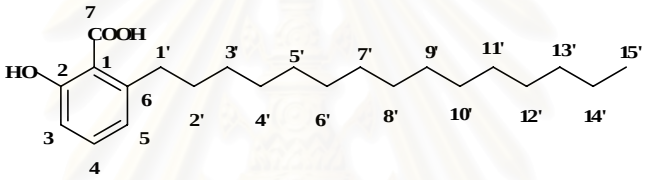
KF-S2



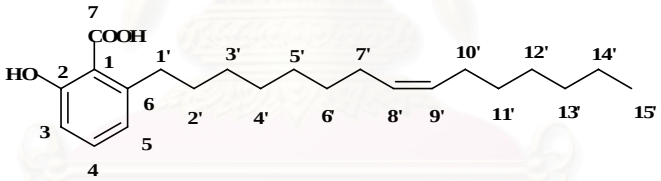
KF-S3



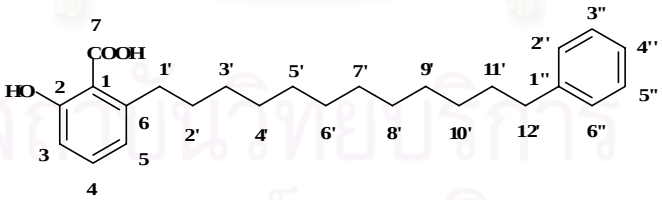
KF-L1



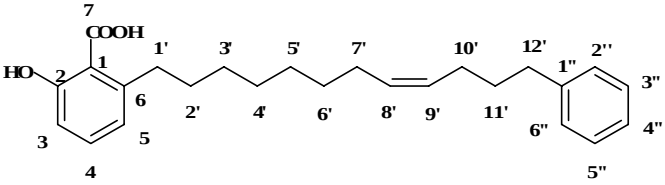
KF-S4 (first component)



KF-S4 (second component)



KF-S5 (major component)



KF-S5 (minor component)

Figure 7. Structure of compounds isolated from *K. furfuracea*.

4. Physical and Spectral Data of Isolated Compound

4.1 Compound KG-F1 (2,6-Dihydroxyphenyl-tetradecan-1-one)

Compound KG-F1 was obtained as yellow amorphous powder, dissolved in CH_2Cl_2 (0.0033 g, 0.000942 % yield of dry plant weight)

ESI-TOF-MS : *m/z* (% rel. int.): 321 $[M+H]^+$ (18), 320 $[M]^+$ (21), 318 (37), 305 (6), 304 (100), 302 (8); see **Figure 10.**

UV : λ_{max} nm (log ε), MeOH ; 206 (4.2), 224 (4.2), 270 (4.2); see **Figure 8.**

IR : ν_{max} cm^{-1}, KBr ; 3625 (OH), 2917, 2852, 1636, 1603, 1455, 1250, 1035, 964, 793, 716; see **Figure 9.**

^1H NMR : δ ppm, 500 MHz, in $CDCl_3$; **Table 11** and **Figure 11.**

^{13}C NMR : δ ppm, 125 MHz, in $CDCl_3$; **Table 11** and **Figure 12.**

4.2 Compound KG-F2 (Asarinin)

Compound KG-F2 was obtained as colorless needle, dissolved in CH_2Cl_2 (0.0143 g (0.00408 % yield of dry plants weight)

ESI-TOF-MS : *m/z* (% rel. int.): 377 $[M+H]^+$ (0.2), 304 (19), 282 (100) ; see **Figure 19.**

mp : 108-109°C

$[\alpha]^{25}_D$: +123° (*c* = 0.10, CH_2Cl_2).

UV : λ_{max} nm (log ε), MeOH; 237 (3.8), 287 (3.7); see **Figure 17.**

IR : ν_{max} cm^{-1}, KBr; 3433, 2868, 1505, 1490, 1442, 1257, 1076, 1036, 930; see **Figure 18.**

^1H NMR : δ ppm, 500 MHz, in $CDCl_3$; **Table 12** and **Figure 20.**

^{13}C NMR : δ ppm, 125 MHz, in $CDCl_3$; **Table 12** and **Figure 21.**

4.3 Compound KG-F3 (Sesamin)

Compound KG-F3 was obtained as colorless needle, dissolved in CH_2Cl_2 (0.0099 g, 0.0028 % of dry plant weight)

ESI-TOF-MS : *m/z* (% rel. int.) 377 $[M+H]^+$ (100), 304 (48), 201 (26); see **Figure 28.**

mp : 118-120 °C

$[\alpha]^{25}_D$: - 0.6574 (*c* 1.0, CH_2Cl_2)

UV : λ_{max} nm (log ε), MeOH ; 237 (3.9), 287 (3.9); see **Figure 26.**

IR : ν_{max} cm^{-1}, KBr ; 3434, 2851, 1500, 1444, 1366, 1250, 1058, 1036, 927; see **Figure 27.**

^{1}H NMR : δ ppm, 500 MHz, in $CDCl_3$; **Table 13** and **Figure 29.**

^{13}C NMR : δ ppm, 125 MHz, in $CDCl_3$; **Table 13** and **Figure 30.**

4.4 Compound KG-F4 (Glaucaic acid)

Compound KG-F4 was obtained as pale yellow oil, dissolved in CH_2Cl_2 (130.2 mg, 0.0372 % % based on dried weight of fruits)

HR-ESI-MS : *m/z*; 357.2048 $[M+Na]^+$ (calcd. for $C_{20}H_{30}O_4Na$: 357.2042); see **Figure 32.**

IR : ν_{max} cm^{-1}, KBr; 3300-2500 (OH), 2966, 2929, 2860, 1689, 1673, 1417, 1245, 1161, 949, 866; see **Figure 31**.

^{1}H NMR : δ ppm, 500 MHz, in $CDCl_3$; **Table 14** and **Figures 33a-33b.**

^{13}C NMR : δ ppm, 125 MHz, in $CDCl_3$; **Table 14** and **Figure 34.**

4.5 Compound KG-F5 (Myristinin D)

Compound KG-F5 was obtained as brown amorphous solid, dissolved in acetone (24.0 mg, 0.0068 % based on dried weight of fruits)

ESI-TOF-MS : *m/z* (% rel. int.): 606 $[M+H+Na]^+$ (15), 605 $[M+Na]^+$ (100); see **Figure 42.**

$[\alpha]^{25}_{D}$: +84° (*c* = 0.12, MeOH)

UV : λ_{max} nm (log ε), MeOH ; 228 (4.7), 290 (4.4) ; see **Figure 40.**

IR : ν_{max} cm^{-1}, KBr ; 3391 (OH), 2926, 2853, 1617 (C=O), 1518, 1453, 1226, 1154, 1088, 833 ; see **Figure 41**.

^{1}H NMR : δ ppm, 500 MHz, in acetone-d_6; **Table 15** and **Figures 43a-43c.**

^{13}C NMR : δ ppm, 125 MHz, in acetone-d_6; **Table 15** and **Figures 44a-44b.**

4.6 Compound KG-F6 (Malabaricone A)

Compound KG-F6 was obtained as yellow amorphoue solid, dissolved in acetone (0.02 g, 0.00571% yield of dry plant weight)

EI-MS : *m/z* (% rel. int.): 326 $[M]^+$ (20), 308 (9), 165 (30), 137 (100), 91 (29), 43 (19), 28 (52) ; see **Figure 52.**

UV : λ_{max} nm (log ε), MeOH; 209 (5.5), 242 (4.7), 269 (5.3), 346 (4.7); see **Figure 50.**

IR : ν_{max} cm^{-1}, KBr ; 3254 (OH), 2925, 2850, 1635 (C=O), 1600, 1471, 1246, 1038, 966, 876; see **Figure 51.**

^{1}H NMR : δ ppm, 500 MHz, in acetone-d_6; **Table 16** and **Figure 53**.

^{13}C NMR : δ ppm, 125 MHz, in acetone-d_6; **Table 16** and **Figure 54**.

4.7 Compound KG-F7 (Dodecanoylphloroglucinol)

Compound KG-F7 was obtained as white amorphous solid, dissolved in acetone (0.0425 g, 0.012 % yield of dry plant weight).

EI-MS : *m/z* (% rel. int.): 308 $[M]^+$ (8), 271 (17), 229 (30), 211 (68), 181 (25), 168 (37), 153 (100), 134 (34), 98 (46) ; see **Figure 62.**

UV : λ_{max} nm (log ε), MeOH; 209 (4.2), 217 (4.2), 227 (4.2), 286 (4.3); see **Figure 60**.

IR : ν_{max} cm^{-1}, KBr ; 3400, 3250, 2912, 2849, 1650, 1618, 1537, 1472, 1242, 1213, 1086, 924, 810; see **Figure 61.**

^{1}H NMR : δ ppm, 500 MHz, in acetone-d_6; **Table 17** and **Figures 63a-63c**.

^{13}C NMR : δ ppm, 125 MHz, in acetone-d_6; **Table 17** and **Figure 64.**

4.8 Compound KG-F8 (1-(2,4,6-Trihydroxy-phenyl)-9-phenylnonan-1-one)

Compound KG-F8 was obtained as yellow amorphous solid, dissolved in acetone (114.2 mg, 0.032 % yield of dry plant weight)

EI-MS : *m/z* (% rel. int.): 342 $[M]^+$ (9), 324 (6), 299 (12), 256 (28), 234 (17), 183 (36), 168 (29), 153 (86), 91 (100); see **Figure 71.**

UV : λ_{max} nm (log ε), MeOH; 209 (4.3), 228 (4.2), 286 (4.3); see **Figure 69.**

IR : ν_{max} cm^{-1}, KBr ; 3253 (OH), 2926, 2853, 1635, 1600, 1570, 1524, 1464, 1391, 1242, 1198, 1074, 812, 698.; see **Figure 70.**

^{1}H NMR : δ ppm, 500 MHz, in acetone-d_6; **Table 18** and **Figure 72.**

^{13}C NMR : δ ppm, 125 MHz, in acetone-d_6; **Table 18** and **Figure 73.**

4.9 Compound KG-L1 (Myristinin A)

Compound KG-L1 was obtained as brown amorphous solid, dissolved in acetone (0.0103 g, 0.0018 % yield of dry plant weight)

ESI-TOF-MS : *m/z* (% rel. int.); 571 $[M+Na]^+$ (100), 548 $[M]^+$ (1), 304 (10); see **Figure 81**.

$[\alpha]^{25}_{D}$: +40° (*c* = 0.12, MeOH)

UV : λ_{max} nm (log ε), MeOH ; 228 (4.7), 289 (4.4); see **Figure 79.**

IR : ν_{max} cm^{-1}, KBr ; 3392 (OH), 2924, 2853, 1618 (C=O), 1518, 1455, 1261, 1153, 1088, 1024, 831; see **Figure 80.**

^{1}H NMR : δ ppm, 500 MHz, in acetone-d_6; **Table 19** and **Figures 82a-82b.**

^{13}C NMR : δ ppm, 125 MHz, in acetone-d_6; **Table 19** and **Figure 83.**

4.10 Compound KG-S1 ((±)-7,4´-Dihydroxy-3´-methoxyflavan)

Compound was obtained as amorphous powder, dissolved in CH_2Cl_2 (0.05g, 0.014 % yield of dry stems weight).

ESI-TOF-MS : *m/z*; 295 $[M+Na]^+$; see **Figure 91.**

mp : 148-150°C

$[\alpha]^{25}_{D}$: 0^o (*c* 0.1, MeOH)

UV : λ_{max} nm (log ε), MeOH ; 253 (3.8), 283 (3.1); see **Figure 89.**

IR : ν_{max} cm^{-1}, KBr ; 3429 (OH), 1622, 1611, 1594, 1523, 1510, 1276, 1152, 1106, 1034, 996; see **Figure 90.**

^{1}H NMR : δ ppm, 500 MHz, in acetone-d_6; **Table 20** and **Figure 92.**

^{13}C NMR : δ ppm, 125 MHz, in acetone-d_6; **Table 20** and **Figure 93.**

4.11 Compound KF-S1((+)-*trans*-1,2-Dihydrodehydroguaiaretic acid)

Compound was obtained as amorphous powder, dissolved in CH_2Cl_2 (0.05g, 0.014 % yield of dry plant weight)

ESIMS : *m/z*; 349.1400 $[M+Na]^+$ (calcd. for $C_{20}H_{22}O_4$+Na : 349.1416); see **Figure 100.**

mp : 148-150 °C

$[\alpha]^{25}_{D}$: -0.7619

UV : λ_{max} nm (log ε), MeOH; 207 (4.70), 220 (4.60), 228 (4.63), 260 (4.01), 282 (4.20); see **Figure 98.**

IR : ν_{max} cm^{-1}, KBr ; 3497 (OH), 1508, 1266, 1030, 871, 770; see **Figure 99.**

^{1}H NMR : δ ppm, 500 MHz, in acetone-d_6; **Table 21** and **Figure 101.**

^{13}C NMR : δ ppm, 125 MHz, in acetone-d_6; **Table 21** and **Figure 102.**

4.12 Compound KF-S2 (Fragransin A_2)

Compound KF-S2 was obtained as colorless needles, dissolved in (0.0153 g, 0.00218 % based on dried weight of the stems)

HR-ESI-TOF-MS: *m/z*; $[M+Na]^+$ at *m/z* 367.1523 (calcd. For $C_{20}H_{23}O_5Na$: 367.1521); see **Figure 109.**

mp : 195-196 ^oC

$[\alpha]^{25}_D$: -1.6448

UV : λ_{max} nm (log ε), MeOH; 234(4.23), 253(3.16), 281(3.81);see **Figure 107.**

IR : ν_{max} cm^{-1}, KBr; 3365(OH), 2950, 2892, 1611, 1500, 1449, 1437, 1275, 1270, 1250, 1002, 810; see **Figure 108.**

^1H NMR : δ ppm, 500 MHz, in acetone-d_6; **Table 22** and **Figure 110.**

^{13}C NMR : δ ppm, 125 MHz, in acetone-d_6; **Table 22** and **Figure 111.**

4.13 Compound KF-S3 (Biochanin A)

Compound KF-S3 was obtained as a yellow powder, dissolved in acetone (6.0 mg, 0.00857 % yield based on dried weight of the stems)

HR-ESI-MS : *m/z*; 285.0760 [M+H]+ (calcd. For $C_{16}H_{12}O_5$+H: 258.0763); see **Figure 119.**

UV : λ_{max} nm (log ε), MeOH; 209 (7.75), 230 (7.44), 261 (7.90); see **Figure 117.**

IR : ν_{max} cm^{-1}, KBr; 3380 (OH), 1651, 1622, 1567,1143,1023; see **Figure 118.**

^1H NMR : δ ppm, 500 MHz, in acetone-d_6; **Table 23** and **Figure 120.**

^{13}C NMR : δ ppm, 125 MHz, in acetone-d_6; **Table 23** and **Figure 121.**

4.14 Component KF-S4 (Mixture of Anarcardic acid and Ginkgolic acid)

Component KF-S4 was obtained as colorless amorphous solid, dissolved in acetone (0.0672 g, 0.0096 % yield based on dried weight of the stems)

ESI-TOF-MS : *m/z*; $[M+Na]^+$ 346 and and 348; see **Figure 128.**

UV : λ_{max} nm (log ε), MeOH ; 307 (3.63), 242 (3.89), 209 (4.55); see **Figure 126.**

IR : ν_{max} cm^{-1}, KBr; 3428(OH), 2920, 1652, 1607, 1577, 1449, 1220, 1169, 1126; see **Figure 127.**

^1H NMR : δ ppm, 500 MHz, in acetone-d_6; **Tables 24-25** and **Figure 129.**

^{13}C NMR : δ ppm, 125 MHz, in acetone-d_6; **Tables 24-25** and **Figures 130a-130b.**

4.15 Component KF-S5 (Mixture of 2-Hydroxy-6-(12-phenyldodecyl) benzoic acid and 2-Hydroxy-6-(12-phenyldodecen-8´*Z*-yl) benzoic acid)

Component KF-S5 was obtained as colorless amorphous solid, dissolved in acetone (0.0115 g, 0.00164 % yield based on dried weight of the stems)

ESI-TOF-MS : *m/z*; $[M + Na]^+$ 403 and 405; see **Figure 137.**

UV : λ_{max} nm (log ε), MeOH; 301 (3.58), 208 (4.66); see **Figure 135.**

IR : ν_{max} cm^{-1}, KBr; 3428 (OH), 2921, 2850, 1650, 1604, 1572, 1496, 1469, 1447, 1312, 1248, 1217, 1207; see **Figure 136.**

^{1}H NMR : δ ppm, 500 MHz, in acetone-d_6; **Tables 26-27** and **Figures 138a-138b.**

^{13}C NMR : δ ppm, 125 MHz, in acetone-d_6; **Tables 26-27** and **Figures 139a-139b.**

4.16 Compound KF-L1 (Furfuracin)

Compound KF-L1 was obtained as colorless amorphous crystals, dissolved in CH_2Cl_2 (7.9 mg, 0.000564 % based on dried weight of dry weight leaves).

HR-ESI-TOF-MS: *m/z*; 325.1443 $[M]^+$; see **Figure 145.**

mp : 205-207 °C

UV : λ_{max} nm (log ε), MeOH ; 236 (4.97), 287 (4.18), 324 (3.65); see **Figure 143.**

IR : ν_{max} cm^{-1}, KBr ;3420, 1506, 1260, 1025; see **Figure 144.**

^{1}H NMR : δ ppm, 500 MHz, in acetone-d_6; **Table 28** and **Figure 146a-146b.**

^{13}C NMR : δ ppm, 125 MHz, in acetone-d_6; **Table 28** and **Figure 147.**

5. Evaluation of Biological Activities

5.1 Determination of Antimycobacterial Activity

Antimycobacterial activity was assessed against *Mycobacterium tuberculosis* H_{37}Ra using the Microplate Alamar Blue assay (MABA) (Collins and Franzblau, 1997). The mycobacteria were grown in 100 ml of 7H9GC broth containing 0.005 % Tween 80. Cultures were incubated in 500-ml plastic flask on a rotary shaker at 200 rpm and 37°C until they reached an optical density of 0.4-0.5 at 550 nm. Bacteria were washed and suspended in 20 ml of phosphate-buffered saline and passed through a filter. The filtrates were aliquoted and stored at -80°C.

The susceptibility testing was performed in 96-well microplates. Samples were initially diluted with either dimethyl sulfoxide or distilled deionized water, then diluted by Middlebrook 7H9 media containing 0.2% v/v glycerol and 1.0 gm/L 7H9GC broth, and subsequent two-fold dilutions were performed in 0.1 ml of 7H9GC broth in microplates. Frozen inocula were diluted 1:100 in 7H9GC broth and adding of 0.1 ml to the well resulted in final bacterial titers of about 5×10^4 CFU/ml. Wells containing sample only were used to determine whether the tested samples themselves can reduce the dye or not. Additional control wells consisted of bacteria only (B) and medium only (M). Plates were incubated at 37°C. Starting at day 6 of incubation, 20 µl of Alamar Blue solution and 12.5 µl of 20% Tween 80 were added to one B well and one M well, and plates were re-incubated at 37°C. The B wells were observed for a color change from blue to pink, at which time reagents were added to all remaining wells. Plates were then incubated at 37°C, and results were recorded at 24 h post-reagent addition. Visual MIC values were defined as the lowest concentration of sample that prevented a color change. Rifampicin, isoniacid and kanamycin sulfate were used as the reference compounds.

5.2 Determination of Antimalarial Activity

Plasmodium falciparum (K1, multi-drug resistant strain) was cultivated *in vitro* using the method of Trager and Jensen (1976) in RPMI 1640 medium containing 20 mM HEPES (N-2-hydroxyethylpiperazine-N′-2-ethanesulfuric acid), 32 mM $NaHCO_3$ and 10% heat-inactivated human serum with 3% erythrocytes and incubated at 37°C in an incubator with 3% CO_2. Cultures were diluted with fresh medium and erythrocytes every day according to cell growth. Quantitative assessment of antimalarial activity *in vitro* was determined by microculture radioisotope technique (Desjardin *et al.*, 1979). Briefly, a mixture of 200 µl of 1.5% erythrocytes with 1% parasitemia at the early ring stage was pre-exposed to 25 µl of the medium containing a test sample dissolved in 1% DMSO (0.1% final concentration) for 24 h at the incubation condition described above. Subsequently, 25 µl of [^{3}H]-hypoxanthine (Amersham, USA) in culture medium (0.5 µCi) were added to each well and plates were incubated for an additional 24 h. Level of labeled hypoxantine incorporated indicating parasite growth was determined using the Top Count microplate scintillation counter (Packard, USA). The IC_{50} value represents the concentration which indicates 50% reduction of parasite growth. The standard sample was dihydroartemisinin (DHA).

5.3 Determination of Cytotoxic Activity

5.3.1 Human Small Cell Lung Carcinoma (NCI-H187)

Cytotoxicity to NCI-H187 cells (human small cell lung carcinoma, ATCC CRL-5804) was determined by MTT assay (Plumb *et al.*, 1989). Briefly, cells were diluted to 10^5 cells/ml. Test compounds were diluted in distilled water and added together with cells to microplates in a total volume of 200 µl. Plates were incubated at 37°C, 5% CO_2 for 3 days. Then, 50 µl of 2 mg/ml MTT solution (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) were added to each well of the plate. Plates were wrapped with aluminium foil and incubated for 4 h. After incubation period, the microplates were spinned at 200 ×g for 5 min. MTT was then removed from the wells and the formazan crystals were dissolved in 200 µl of DMSO and 25 µl of Sorensen's glycine buffer. Absorbance was read in microplate reader at the wavelength of 510 nm, with ellipticine as the reference substance. The activity was expressed as 50% inhibitory concentration (IC_{50}), which inhibited cell growth by 50% compared with untreated cells.

5.3.2 Human Epidermoid Carcinoma (KB) and Breast Cancer (BC).

Cytotoxicity to KB (human epidermoid carcinoma of cavity, ATCC CCL-17) and BC or MCF-7 (breast cancer) cell lines were determined by a colorimetric assay that measured cell growth from cellular protein content (Skehan *et al.*, 1990). Ellipticine and doxorubicin were used as positive control, whereas DMSO was used as negative control. Briefly, cells at a logarithmic growth phase were harvested and diluted to 10^5 cells/ml with fresh medium and gently mixed. Extracts or test compounds were diluted in distilled water and put into microplates together with cells in a total volume of 200 µl. Plates were incubated at 37°C, 5% CO_2 for 3 days. After incubation period, cells were fixed by 5% trichloroacetic acid. The plates were incubated at 4°C for 30 min, washed with tap water and air-dried at room temperature. The plates were stained with 0.05% sulforhodamine B (SRB) for 30 min, then SRB was removed with 1% acetic acid. Plates were air-dried before bound dye was solubilized with 10 mM Tris-base for 5 min on shaker. Absorbance was read in microplate reader at the wavelength of 510 nm. The compound was considered strongly active, moderately active, weakly active or inactive if its IC_{50} value was less than 5 µg/ml, between 5-10 µg/ml, between 10-20 µg/ml or more than 20 µg/ml, respectively.

5.3.3 Vero Cells

Compounds were tested for their cytotoxic effect against Vero cells (African green monkey kidney fibroblast) in 96-well plates. Vero cell suspension (190 µl) containing 1×10^5 cells/ml and 10 µl of tested compound solution were added to each well in triplicate. Ellipticine and 10% DMSO were used as positive and negative control, respectively. The cells were incubated at 37°C in 5 % CO_2 for 3 days. After incubation, the cytotoxicity was determined as above. If % cell viability was more than 50%, the IC_{50} value was reported as > 50 µg/ml, and if % cell viability was less than 50%, the IC_{50} value was reported from two-fold serial dilution.

5.4 Determination of Anti-Herpes Simplex Activity

Anti-herpes simplex virus type-1 (HSV-1) activity of pure compounds was tested against HSV-1 strain ATCC VR260, using colorimetric microplate assay as previously mentioned. Growth of the host cells (Vero cell line ATCC CCL-81) infected with virus and treated with the extract was compared with control cells infected with virus only. Acyclovir and DMSO were used as positive and negative control, respectively. The extracts were tested at non-cytotoxic concentrations (inhibition of cell growth of less than 25%). Extracts which produced more than 50% inhibition were considered active, while those which gave 35-50% and 25-35% inhibition were considered moderately active and weakly active, respectively. Extracts that inhibited virus more than 50% were further tested to determine the IC_{50} value.

5.5 Determination of Advance Glycation End-products (AGEs) Formation Inhibition Activity

Assay of this inhibitory activity employs the measurement of fluorescent material based on AGEs in order to detect the inhibitory effect of test samples on the Maillard reaction (Matsuura *et al*., 2002). The plant extract or pure compound was dissolved in DMSO. The reaction mixtures, containing 400 µg of bovine serum albumin (BSA), 200 mM glucose and 10 µl of test sample solution or DMSO in a total volume of 500 µl of 50 mM phosphate buffer (pH 7.4) were incubated at 60°C for 30 h. The blank sample was kept at 4°C until measurement. After cooling, aliquots of 250 µl were transferred to 1.5-ml plastic tubes, then, 25 µl of trichloroacetic acid (TCA) was added to each tube and stirred. The supernatant was removed after centrifugation (15,000 rpm) at 4°C for 4 min and the AGEs-BSA precipitate was dissolved with 1 ml of alkaline phosphate buffer

saline (PBS). These solutions were monitored by using spectrofluorescence intensity (ex. 360 nm, em. 460 nm) based on AGEs. The % inhibition was calculated as:

[1-(ΔA sample/min) - (ΔA blank/min)/(ΔA control/min - ΔA blank/min)] × 100

whereas -(ΔA sample/min) represents a decrease of absorbance for 1 min with a test sample, ΔA blank/min with DMSO and water instead of the sample and substrate, respectively, and ΔA control/min with DMSO in place of the sample.

CHAPTER IV

RESULTS AND DISCUSSION

The dried and milled fruits, leaves and stems of *Knema glauca* var. *glauca* were separately extracted with organic solvents to give the hexane, EtOAc and MeOH extracts of these plant parts. Chromatographic techniques were used to isolate and purify eight compounds (KG-F1, KG-F2, KG-F3, KG-F4, KG-F5, KG-F6, KG-F7 and KG-F8) from the EtOAc extract of the fruits. Similar extract of its leaves was extensively chromatographed to yield compound KG-L1. Finally, separation of the EtOAc extract of the stems furnished compound KG-S1.

The dried leaves and stems of *Knema furfuracea* were ground and separately macerated with hexane, EtOAc and MeOH, respectively, to give each solvent extract. Two compounds (KF-S1 and KF-S2) were isolated from the hexane extract of its stems; whereas, one compound (KF-S3) and two 2-component mixtures (KF-S4 and KF-S5) were obtained from the EtOAc extract. The hexane extract of its leaves yielded compoundKF-L1.

1. Structure Determination of Compounds Isolated from *Knema glauca* var. *glauca*

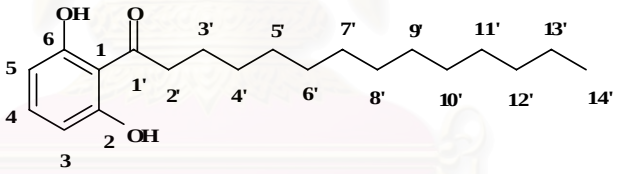
1.1 Identification of Compound KG-F1 [1-(2,6-Dihydroxyphenyl)-tetradecan-1-one]

Compound KG-F1, obtained as yellow amorphous solid, the ESI-TOF mass spectrum (**Figure 10**) and ^{13}C NMR data (**Figure 12**) suggested its molecular formula as $C_{20}H_{32}O_3$. Its IR spectrum (**Figure 9**) exhibited absorption bands of conjugated carbonyl at 1636 cm^{-1} and chelated hydroxyl at 3625 cm^{-1}.

The ^1H NMR spectrum (**Figure 11**) exhibited resonances of a 1,2,3-trisubstituted benzene ring at δ 7.20 (1H, *t*, *J* = 8.3 Hz, H-4) and 6.36 (2H, *d*, *J* = 8.3 Hz, H-3 and H-5). The presence of a long-chain hydrocarbon within the molecule was evident from a couple of resonances of an aliphatic chain at δ 1.30 (20H, *m*, H-3′ to H-12′) and 1.68 (2H, *m*, H-13′), a triplet of methylene protons next to a carbonyl group at δ 3.10 (2H, *t*, *J* = 8.0 Hz, H-2′) and a terminal methyl protons at δ 0.86 (3H, *t*, *J* = 8.0 Hz, H-14′).

The ^{13}C NMR displayed one keto-carbonyl signal at δ 207.8 (C-1′), two methine signals at δ 108.5 (C-3/C-5) and 135.5 (C-4), and two quaternary signals at δ 100.1 (C-1) and 161.1 (C-2/C-6), supporting the presence of a phenyl ketone unit. The remaining carbon signals include a set of methylene signals at δ 24.4 (C-3′), 22.7 (C-13′), 29.3-29.6 (C-4′ to C-11′), 31.9 (C-12′) and 44.8 (C-2′), and methyl signal at δ 14.1 (C-14′), indicating the unbranched nature of the acyl chain.

Based on the above spectral evidence and by comparison of its NMR data with those previously published (Kumar, Herath and Karunaratne, 1988), compound KG-F1 was identified as an acylresorcinol derivative, 1-(2,6-dihydroxyphenyl)-tetradecan-1-one. This acyl resorcinol has been isolated from several plants of the family Myristicaceae, mostly in the genus *Myristica*, including *Myristica malabarica* (Patro *et al.*, 2005), *M. ceylanica* (Herath, 1997; Herath and Padmasiri, 1999), *M. dactyloides* (Cooray *et al.*, 1987; Kumar *et al.*, 1988; Herath and Priyadarshani, 1996) and *M. castaneifolia* (Ali, Read and Sotheeswaran**,** 1993). It was also found in two *Knema* species i.e. *Knema laurina* (Gonzalez *et al.*, 1996) and *K. austrosiamensis* (Gonzalez *et al.*, 1993; 1996).



1-(2,6-Dihydroxyphenyl) tetradecan-1-one

Table 11. Comparison of the ^{1}H (300 MHZ) and ^{13}C (125 MHz) NMR spectral data of 1-(2,6-dihydroxyphenyl)-tetradecan-1-one and compound KG-F1 (in acetone-d_6)

Position	KG-F1		1-(2,6-Dihydroxyphenyl)-tetradecan-1-one*	
	^{13}C	^{1}H	^{13}C	^{1}H
1	100.1	-	110.8	-
2	161.1	-	162.8	-
3	108.5	6.36 (1H, *d*, *J* = 8.3 Hz)	108.0	6.32 (1H, *d*, *J* = 8.0 Hz)
4	135.5	7.20 (1H, *t*, *J* = 8.3 Hz)	136.4	7.18 (1H, *t*, *J* = 8.0 Hz)
5	108.5	6.36 (1H, *d*, *J* = 8.3 Hz)	108.0	6.32 (1H, *d*, *J* = 8.0 Hz)
6	161.1	-	162.8	-
1′	207.8	-	209.5	-
2′	44.8	3.10 (2H, *t*, *J* = 8.0 Hz)	45.4	3.12 (2H, *t*, *J* = 7.0 Hz)
3′	22.4	1.68 (2H, *m*)		
4′				
5′				
6′				
7′	29.3–29.6	1.30 (18H, *m*)		1.33 (20H, *m*)
8′				
9′				
10′				
11′				
12′	31.9			
13′	22.7	2.25 (2H, *m*)		1.60 (2H, *m*)
14′	14.1	0.86 (3H, *t*, *J* = 8.0 Hz)	14.3	0.89 (3H, *t*, *J* = 7.0 Hz)
2-OH, 6-OH	-	9.42 (2H, *br s*)	-	9.40 (2H, *s*)

*Kumar *et al.*, 1988

1.2 Identification of Compound KG-F2 [Asarinin]

Compound KG-F2 was obtained as colorless amorphous solid having the molecular formula $C_{20}H_{18}O_6$, according to its $[M + Na]^+$ peak at *m/z* 377 in the ESI-TOF mass spectrum (**Figure 19**) and carbon NMR data (**Figure 21**). Its UV absorption maxima at 237 and 287 nm (**Figure 17**) indicate the presence of aromatic ring(s) within the molecule of a furofuran-type lignan (Venkataraman and Gopalakrishman, 2002).

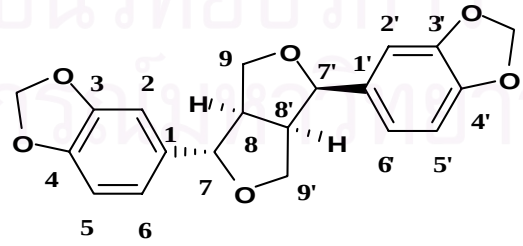
The ^{1}H NMR spectrum (**Figure 20**) exhibited two different proton systems of the bicyclic lignan skeleton i.e. the aliphatic bicyclic and two aromatic rings. Each group displayed COSY correlations (**Figures 22a-22b**) within its own system. The first system consists of a methine proton appearing at δ 2.79 (1H, *qd*, *J* = 7.3, 0.8 Hz, H-8′), which coupled to an oxymethine doublet at δ 4.32 (1H, *d*, *J* = 7.3 Hz, H-7′) and one asymmetrical methylene signal at δ 3.75 (1H, *d*, *J* = 9.5 Hz, H-9′α). The H-8′ signal also coupled to another methine resonance at δ 3.25 (1H, *m*, H-8), which, in turn, coupled to the H-9α methylene proton resonating at δ 3.22 (1H, *m*, H-9α) and an oxymethine signal at δ 4.76 (1H, *d*, *J* = 5.5 Hz, H-7). The second system includes the signals of two symmetrical 1,3,4-tri-substituted benzene rings resonating at δ 6.71 (1H, *d*, *J* = 8.0 Hz, H-5), 6.74 (1H, *d*, *J* = 8.0 Hz, H-5′), 6.74 (1H, *dd*, *J* = 8.0, 1.8 Hz, H-6), 6.75 (1H, *dd*, *J* = 8.0, 1.8 Hz, H-6′) and 6.80 (2H, *d*, *J* = 1.8 Hz, H-2 and H-2′). Two methylenedioxy signals could also be observed at δ 5.96 (3,4-OCH_2O-) and 5.95 (3′,4′-OCH_2O-). These are indicative of a lignan having 2,6-diaryl-3,7-dioxabicyclo-[3,3,0]-octane structure.

The ^{13}C NMR spectrum exhibited signals representing two methylenedioxy carbons at δ 101.0 (3,4-OCH_2O- and 3′,4′-OCH_2O-). The furofuran unit gave two oxymethylene signals at δ 69.6 (C-9) and 70.9 (C-9′), two oxymethine signals at δ 82.0 (C-7) and 87.6 (C-7′), and two methylene signals at δ 50.1 (C-8) and 54.6 (C-8′). The rest of the carbon signals, including those of methine carbons at δ 106.3 (C-2), 106.5 (C-2′), 108.1 (C-5 and C-5′), 118.6 (C-6) and 119.5 (C-6′), and quaternary carbons at 132.2 (C-1), 135.1 (C-1′), 146.5 (C-3), 147.2 (C-4), 147.6 (C-3′) and 147.9 (C-4′), belong to the two aromatic rings of the lignan molecule. Although both aryl portions of this lignan molecule are the same piperonyl group, their orientation is opposite, as evidenced from the difference in the coupling constant between H-7/H-8 and H-7′/H-8′ of the furofuran ring. H-7/H-8 orientation is *trans*,

according to their observed coupling constant of about 5.5 Hz, whereas a larger coupling constant of about 7.3 Hz for H-7′/H-8′ suggested a *cis* orientation. Based on these spectroscopic data and comparison with reported values (Gunatilaka *et al*., 1982), compound KG-F2 was identified as the furofuran lignan known as asarinin.

Asarinin has previously been reported as a constituent of a number of plants within the family Myristicaceae. For example, it was found in the fruit and seeds of *Virola surinamensis* (Cavalcante, Yoshida and Gottlieb, 1985; Ester, Sobral and Massayoshi, 1997), the seeds of *Horsfieldia irya* (Wimalasena and Karunawansha, 1994) and *H. iryaghedhi* (Kitagawa *et al*., 1972; Gunatilaka *et al*., 1982), and the aril and seeds of *H. glabra* (Gonzalez *et al*., 1988; Pinto *et al*., 1988).

The lignan has also been isolated from the bark, leaves and root of several *Zanthoxylum* species of the family Rutaceae (Vaquette *et al*., 1973; Stermitz, Caolo and Swinehart, 1980; Ren *et al*., 1984; Adesina, 1986; 1987; Adesina, Olatunji and Akinwusi, 1986; Chen *et al*., 1988; Liang *et al*., 1988; Lu, Jin and Xing, 1988; Cuca *et al*., 1998; Narendra, Bikram and Ram, 1999; Ju *et al*., 2000; Arrieta *et al*., 2001), and from the root of *Stauranthus perforatus* (Anaya *et al*., 2005) of the same family. It was also found in a number of *Piper* species (family Piperaceae) including *P. longum* (Virinder *et al*., 1998), *P. sarmentosum* (Rukachaisirikul *et al*., 2004) and *P. sumatranum* var. *andamanica* (Malhotra *et al*., 1990). The lignan has been reported to possess amoebicidal and giardicidal activities (Arrieta *et al*., 2001) and was cytotoxic to HL-60 (human leukemia) cells (Ju *et al*., 2000). It also displayed an effect on the acute heart transplantation rejection and the expression of adhesion molecule (Zhang *et al*., 2006).



Asarinin

Table 12. Comparison of the ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectral data of compound KG-F2 and asarinin (in $CDCl_3$)

Position	KG-F2		Asarinin*	
	^{1}H	^{13}C	^{1}H	^{13}C
1	-	132.2	-	132.3
2	6.80 (1H, *d*, *J* = 1.8 Hz)	106.3	6.75-6.80 (1H, *m*)	106.3
3	-	146.5	-	146.5
4	-	147.2	-	147.6
5	6.71 (1H, *d*, *J* = 8.0 Hz)	108.1	6.75-6.80 (2H, *m*)	108.1
6	6.74 (1H, *dd*, *J* = 8.0, 1.8 Hz)	118.6		118.7
7	4.76 (1H, *d*, *J* = 5.5 Hz)	82.0	4.80 (1H, *d*)	82.0
8	3.25 (1H, *m*)	50.1	3.35 (1H, *m*)	50.1
9α	3.22 (1H, *m*)	69.6	4.03 (2H, *m*)	69.6
9*β*	3.76 (1H, *d*, *J* = 9.5 Hz)			
1′	-	135.1	-	135.3
2′	6.80 (1H, *d*, *J* = 1.8 Hz)	106.5	6.75-6.80 (1H,*m*)	106.5
3′	-	147.6	-	147.2
4′	-	147.9	-	147.9
5′	6.74 (1H, *d*, *J* = 8.0 Hz)	108.1	6.75-6.80 (2H, *m*)	108.1
6′	6.75 (1H, *dd*, *J* = 8.0, 1.8 Hz)	119.5		119.5
7′	4.32 (1H, *d*, *J* = 7.3 Hz)	87.6	4.40 (1H, *m*)	87.6
8′	2.79 (1H, *qd*, *J* = 7.3, 0.8 Hz)	54.6	2.85 (1H, *m*)	54.6
9′*α*	3.75 (1H, *d*, *J* = 9.5 Hz)	70.9	3.35 (1H, *m*)	70.9
9′*β*	4.02 (1H, *dd*, *J* = 9.5, 0.8 Hz)		3.85 (1H, *m*)	
3,4-OCH_2O-	5.96 (2H, *s*)	101.0	5.90 (2H, *s*)	101.0
3′,4′-OCH_2O-	5.95 (2H, *s*)	101.0	5.90 (2H, *s*)	101.0

*Gunatilaka *et al.*, 1982

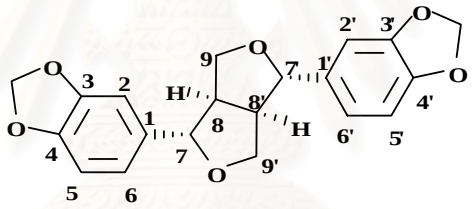
1.3 Identification of Compound KG-F3 [Sesamin]

From the $[M + Na]^+$ peak at *m/z* 377 in the ESI-TOF mass spectrum of compound KG-F3 (**Figure 28**) and its ^{13}C NMR data (**Figure**), its molecular formula was determined as $C_{20}H_{18}O_6$. Similar to compound KG-F2, its UV absorption maxima at 237 and 287 nm (**Figure 26**) correspond to the furofuran-type of lignan structure (Venkataraman and Gopalakrishman, 2002). However, the presence of only ten carbon signals in its ^{13}C NMR spectrum suggested that its molecular structure consisted of two symmetrical portions. These ten signals could be classified into those of two methylenedioxy carbons at δ 101.1 (O-CH_2-O), two methylene carbons at δ 71.7 (C-9/C-9′), two methine carbons at δ 54.3 (C-8/C-8′), two oxymethine carbons at δ 85.8 (C-7/C-7′), twelve aromatic carbons including six methine carbons at δ 106.5 (C-5/C-5′), 108.2 (C-2/C-2′) and 119.3 (C-6/C-6′), and six quaternary carbons at δ 135.0 (C-1/C-1′), 147.1 (C-3/C-3′) and 148.0 (C-4/C-4′). These data help in deducing compound KG-F3 as a lignan with methylenedioxy substitutions in the benzene rings.

The ^1H NMR spectrum of this compound (**Figure 29**) exhibited two oxymethylene signals at δ 3.80 (2H, *dd*, *J* = 9.0, 4.0 Hz, H-9*α*/H-9′*α*) and 4.16 (2H, *dd*, *J* = 9.0, 7.0 Hz, H-9*β*/H-9′*β*), a methine signal at δ 2.98 (2H, *m*, H-8/H-8′) and an oxymethine signal at δ 4.64 (2H, *d*, *J* = 4.5 Hz, H-7/H-7′). These signals represent the bicyclic substructure at the center of the furofuran lignan molecule. The two symmetrical 1,3,4-tri-substituted aromatic rings of the lignan gave proton signals at δ 6.70 (2H, *d*, *J* = 8.0 Hz, H-5/H-5′), 6.73 (2H, *dd*, *J* = 8.0, 1.5 Hz, H-6/H-6′) and 6.77 (2H, *d*, *J* = 1.5 Hz, H-2/H-2′). Finally, a singlet which integrated for 4 protons at δ 5.88 represented the methylenedioxy substitutions on both benzene rings. The observed coupling constant of both H-7/H-8 and H-7′/H-8′ (4.5 Hz) suggested that each pair of vicinal protons was *trans*-oriented. These spectroscopic evidences helped identify compound KG-F3 as the lignan sesamin (Fukuda *et al*., 1986; Venkataraman and Gopalakrishnan, 2002).

Similar to asarinin, sesamin has also been isolated from several *Zanthoxylum* species of the Rutaceae, for example, from the leaves and stem bark of *Z. riedelianum* (Lima *et al*., 2007) and *Z. davyi* (Tarus *et al*., 2006). Other sources of this lignan are the leaves of *Esenbeckia alata*, family Rutaceae (Cuca *et al*., 2007); *Cinnamomum kotoense* (Chen, 2006) and the stem of *C. camphora*, family

Lauraceae (Hsieh *et al*., 2006); the seeds of *Piper cubeba*, family Piperaceae (Bodiwala *et al*., 2007); the seeds of *Sesamum indicum*, family Pedaliaceae (Moazzami, Haese and Kamal-Eldin, 2007). The lignan showed anti-tumor activity by down-regulating cyclin D1 protein expression in human breast cancer cell line (MCF-7) (Yokota *et al*., 2007). It also inhibited vascular endothelial cell growth and angiogenic activity of lung adenocarcinoma cells; its anti-angiogenic activity upon the growth of human umbilical vein endothelial cells was without causing significant cytotoxicity (Tsai et al., 2006). Sesamin had an effect on nitric oxide content in vital organs of renal hypertensive rats (Guo *et al*., 2006; Li, Yang and Zhu, 2007). It displayed neuroprotective effect *in vivo* against cerebral ischemia in gerbil brain (Cheng *et al*., 2006), and offered protection and prevention of stroke from nervous degeneration (Hou *et al*., 2007). Moreover, the lignan showed antibacterial activity against *Escherichia coli* (Zhou *et al*., 2006).



Sesamin

Table 13. Comparison of the ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectral data of compound KG-F3 and sesamin (in $CDCl_3$).

Position	KG-F3		Sesamin	
	^{1}H	^{13}C	$^{1}H^{*}$	$^{13}C^{**}$
1, 1′	-	135.0	-	134.9
2, 2′	6.77 (2H, *d*, *J* = 1.5 Hz)	108.2	6.83 (2H, *m*)	108.0
3, 3′	-	147.1	-	146.9
4, 4′	-	148.0	-	147.7
5, 5′	6.70 (2H, *d*, *J* = 8.0 Hz)	106.5	6.83 (2H, *m*)	106.3
6, 6′	6.73 (2H, *dd*, *J* = 8.0, 1.5 Hz)	119.3	6.83 (2H, *m*)	119.1
7, 7′	4.64 (2H, *d*, *J* = 4.5 Hz)	85.8	4.75 (*d*, *J* = 4.0 Hz)	85.6
8, 8′	2.98 (2H, *m*)	54.3	2.88 (2H, *m*)	54.2
9*α*, 9′*α*	3.80 (2H, *dd*, *J* = 9.0, 4.0 Hz)	71.7	3.74 (2H, *dd*, *J* = 8.5, 4.0 Hz)	71.6
9*β*, 9′*β*	4.16 (2H, *dd*, *J* = 9.0, 7.0 Hz)		4.10 (2H, *dd*, *J* = 8.5, 6.0 Hz)	
O-CH_2-O	5.88 (4H, *s*)	101.1	5.92 (4H, *s*)	100.9

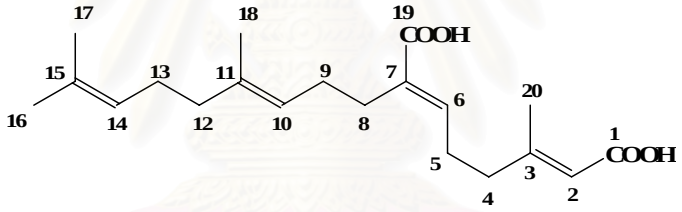
* Fukuda *et al*., 1986

** Venkataraman and Gopalakrishman, 2002

1.4 Structure Elucidation of Compound KG-F4 [Glaucaic acid]

Compound KG-F4 was isolated as pale yellow oil from the EtOAc extract of *K. glauca* var. *glauca* fruits. Its molecular formula was determined as $C_{20}H_{30}O_4$ from its $[M+Na]^+$ ion peak at *m/z* 357.2048 (calculated from $C_{20}H_{30}O_4Na$) (**Figure 32**) in the high resolution mass spectrum. The IR spectrum (**Figure 31**) displayed broad O-H stretching absorption of carboxylic acid functions at 3300-2500 cm^{-1}, which corresponded to two carbonyl signals at δ 172.3 and 173.5 in its ^{13}C-NMR spectrum (**Figure 34**). The ^{1}H-NMR spectrum (**Figures 33a-33b**) exhibited olefinic signals of four tri-substituted double bonds at δ 5.06 (1H, *br t*, *J* = 7.0 Hz, H-14), 5.11 (1H, *br t*, *J* = 7.5 Hz, H-10), 5.67 (1H, *br s*, H-2) and 6.84 (1H, *t*, *J* = 7.0 Hz, H-6), and four methyl resonances at δ 1.57 (H-17), 1.60 (H-18), 1.65 (H-16) and 2.15 (H-20). These spectral data and the molecular formula suggested the presence of an acyclic diterpene with two carboxyl functions. The proton chemical shift of the olefinic H-6 (δ 6.84) clearly indicated that it was β to a carbonyl group (Ghisalberti *et al.*, 1981; Warning *et al.*, 1988) and, therefore, a carboxyl group could be located

at position 19. This was confirmed by the HMBC correlations (**Figures 38a-38b**) between this proton signal and those of C-7 (δ 131.4), C-8 (δ 27.6) and C-19 (δ 173.5) (**Table 14**). The chemical shift value of this proton was also consistent with an *E*-configuration of the C-6/7 double bond (Galal *et al.*, 1998; Abdel-Sattar, 2001). Another carboxyl group was assigned the position 1 according to the HMBC correlations between the broad H-2 singlet at δ 5.67 and this carbonyl carbon (δ 172.3), C-3 (δ 162.7), C-4 (δ 41.0) and C-20 signals (δ 19.1). The *E*-configuration assigned to the C-2/3 double bond was based on the chemical shift of the vinylic methyl H-20 at δ 2.15 (Ghisalberti *et al.*, 1981). Finally, the configuration of C-10/11 double bond was also deduced as *E* by comparison of the NMR data with related compounds (Coates *et al.*, 1978; Zdero *et al.*, 1990). Therefore, the structure of KG-F4 was established as 3,11,15-trimethyl-2*E*,6*E*,10*E*,14-hexadecatetraen-1,19-dioic acid, and named glaucaic acid. This compound is a rare example of diterpenes in Myristicaceae and the first acyclic diterpenoid to be found in this plant family.



Glaucaic acid

Table 14. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectral data of compound glaucaic acid (in $CDCl_3$)

Position	^{1}H	^{13}C	HMBC
1	-	172.3	
2	5.67 (1H, *br s*)	115.3	1, 3, 4, 20
3	-	162.7	
4	2.18 (2H, *m*)	41.0	2, 5, 20
5	2.18 (2H, *m*)	25.8	4
6	6.84 (1H, *t*, *J* = 7.0 Hz)	145.0	7, 8, 19
7	-	131.4	
8	2.09 (2H, *t*, *J* = 7.0 Hz)	27.6	6, 7, 9, 10
9	2.28 (2H, *t*, *J* = 7.0 Hz)	26.7	7, 8, 10

Table 14. (continued)

Position	^{1}H	^{13}C	HMBC
10	5.11 (1H, *br t, J = 7.5 Hz*)	123.8	8, 9, 12, 18
11	-	135.0	
12	2.09 (1H, *m*)	38.3	10, 11, 13, 14, 18
13	2.28 (2H, *t, J* = 7.0 Hz)	27.2	11, 12, 14
14	5.06 (1H, *br t, J = 7.0 Hz*)	123.6	12, 13, 16, 17
15	-	132.3	
16	1.65 (3H, *br s*)	25.7	14, 15, 17
17	1.57 (3H, *br s*)	17.6	14, 15, 16
18	1.60 (3H, *br s*)	16.0	10, 11, 12
19	-	173.5	
20	2.15 (3H, *d, J = 1.0* Hz)	19.1	2, 3, 4

1.5 Identification of Compound KG-F5 [Myristinin D]

The molecular formula of compound KG-F5, a brown amorphous solid, was determined as $C_{36}H_{38}O_7$ from its $[M + Na]^+$ ion peak at *m/z* 605 in the ESI-TOF mass spectrum (**Figure 42**). IR absorption bands of the compound (**Figure 41**) at 3391 and 1617 cm^{-1} revealed the presence of hydroxyl and carbonyl functions, respectively.

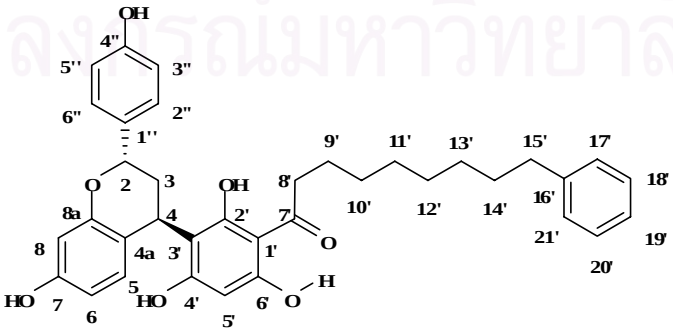
The ^{13}C NMR spectrum (**Figures 44a-44b**) and DEPT experiment (**Figure 45**) revealed 36 carbon signals; twenty-four of which belong to 4 aromatic rings within the molecule. The remaining carbon resonances were those of one keto-carbonyl at δ 206.0 (C-7′), two methine carbons at δ 74.9 (C-2) and 29.5 (C-4), and nine methylene carbons at δ 44.2 (C-8′), 35.6 (C-15′), 34.3 (C-3), 31.4 (C-14′), 29.1 (C-11′ and C-12′), 29.0 (C-10′ and C-13′) and 25.4 (C-9′).

Its ^{1}H NMR spectrum (**Figures 43a-43c**) displayed signals of a flavan unit with hydroxyl substitutions at the C-7 position of ring A and at the *para*-position of ring B similar to those of compound KG-L1. The ^{1}H-^{1}H COSY spectrum (**Figures 47a-47b**) displayed the correlations between the signals at δ 2.19 (H-3*ax*)/2.21 (H-3*eq*) to both H-2 (δ 4.86) and H-4 (δ 4.55) signals, confirming the connectivity of C-

2/C-3 and C-3/C-4 of the flavan unit. Another connection between C-4 of this unit and C-3′ of the acylphloroglucinol unit was supported by the HMBC correlations (**Figures 48a-48d**) observed between the signals of H-4 (δ 4.55) and C-3′ signal (δ 102.7). However, the dodecanoyl unit of compound KG-L1 was replaced by signals of methylene protons at δ 0.96 (2H, *m*, H-11′), 1.06 (2H, *m*, H-12′), 1.20 (4H, *m*, H-10′ and H-13′), 1.46 (2H, *quintet*, *J* = 7.6 Hz, H-9′), 1.54 (2H, *quintet*, *J* = 7.5 Hz, H-14′), 2.55 (2H, *t*, *J* = 7.5 Hz, H-15′) and 2.82 (2H, *m*, H-8′) and of a mono-substituted aromatic ring at δ 7.11 (1H, *t*, *J* = 7.4 Hz, H-19′), 7.16 (2H, *br d*, *J* = 7.4 Hz, H-17′/H-21′) and 7.22 (2H, *br d*, *J* = 7.4 Hz, H-18′/H-20′). These data indicated the acyl unit of compound KG-F5 to be a 9-phenylnona-1-one chain. HMBC cross-peaks of H-15′ signal (δ 2.55) with the carbon signals at δ 142.8 (C-16′) and 128.3 (C-17′/C-21′), and of H-14′ signal (δ 1.54) with C-16′ signal (δ 142.8) confirmed the position of a benzene ring at the end of the acyl chain. A hydroxyl group which resonated as the most downfield, hydrogen-bonded singlet at δ 14.04 was assigned the C-6′ position according to HMBC correlations observed between this signal and the carbon signals of both C-1′ (δ 104.3) and C-5′ (95.4).

The orientation between H-2 and H-4 was deduced as *trans* according to the Chem3D® modelling with MM2 energy minimization and analysis of H-2/H-3 and H-3/H-4 coupling constants.

Based upon these data and comparison with literature (Sawadjoon *et al*., 2002), compound KG-F5 was identified as myristinin D. This compound was originally isolated from the fruits of *Myristica cinnamomea* and was demonstrated to preferentially inhibit the enzyme COX-2 with an IC_{50} value of 1.4 μg/mL (Sawadjoon *et al*., 2002).



Myristinin D

Table 15. The ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectral data of compound KG-F5 (in acetone-d_6)

Position	^{1}H	^{13}C	HMBC
2	4.86 (1H, *dd*, *J* = 11.4, 1.7 Hz)	74.9	4a
3*eq*	2.19 (1H, *br d*, *J* = 11.4, 1.7 Hz)	34.3	4, 4a, 3′
3*ax*	2.21 (1H, *td*, *J* = 11.4, 4.5 Hz)		
4	4.55 (1H, *d*, *J* = 4.5 Hz)	29.5	4a, 3′
4a	-	122.9	
5	6.50 (1H, *d*, *J* = 8.2 Hz)	129.5	4, 7, 8a
6	6.20 (1H, *dd*, *J* = 8.2, 2.1 Hz)	105.6	
7	-	156.7	
8	6.41 (1H, *d*, *J* = 2.1 Hz)	102.8	6, 7, 4a, 8a
8a	-	155.2	
1′	-	104.3	
2′	-	159.2	
3′	-	102.7	
4′	-	162.9	
5′	6.02 (1H, *s*)	95.4	1′, 3′, 4′, 6′
6′	-	165.6	
7′	-	206.0	
8′	2.82 (2H, *m*)	44.2	7′, 9′
9′	1.46 (2H, *quintet*, *J* = 7.6 Hz)	25.4	
10′	1.20 (2H, *m*)	29.0	7′
11′	0.96 (2H, *m*)	29.1	
12′	1.06 (2H, *m*)	29.1	
13′	1.26 (2H, *m*)	29.0	
14′	1.54 (2H, *quintet*, *J* = 7.5 Hz)	31.4	15′, 16′
15′	2.55 (2H, *t*, *J* = 7.5 Hz)	35.6	16′, 17′
16′	-	142.8	
17′	7.16 (1H, *br d*, *J* = 7.4 Hz)	128.3	
18′	7.22 (1H, *t*, *J* = 7.4 Hz)	128.1	

Table 15. (continued)

Position	^{1}H	^{13}C	HMBC
19′	7.11 (1H, *t*, *J* = 7.4 Hz)	125.5	17′, 18′, 20′, 21′
20′	7.22 (1H, *t*, *J* = 7.4 Hz)	128.1	
21′	7.16 (1H, *br d*, *J* = 7.4 Hz)	128.3	
1″	-	131.3	
2″	7.19 (1H, *br d*, *J* = 8.4 Hz)	128.1	3″, 4″
3″	6.81 (1H, *br d*, *J* = 8.4 Hz)	115.2	1″, 4″
4″	-	157.7	
5″	6.81 (1H, *br d*, *J* = 8.4 Hz)	115.2	1″, 4″
6″	7.19 (1H, *br d*, *J* = 8.4 Hz)	128.2	4″, 5″
7-OH	-	-	
2′-OH	-	-	
4′-OH	9.32 (1H, *br s*)	-	
6′-OH	14.04 (1H, *br s*)	-	1′, 5′
4″-OH	-	-	

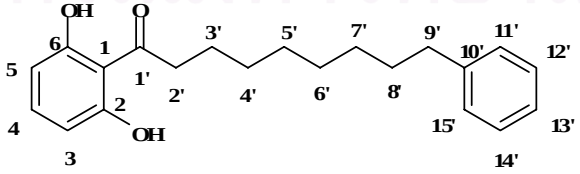
1.6 Identification of Compound KG-F6 [Malabaricone A]

Compound KG-F6 was obtained as yellow amorphous solid, exhibiting a UV absorption maximum of benzoyl group at 346 nm (**Figure 50**). Its IR spectrum (**Figure 51**) showed absorption bands of conjugated carbonyl group at 1635 cm^{-1} and phenolic hydroxyl group at 3254 cm^{-1}. The EI mass spectrum (**Figure 52**) displayed its molecular ion peak at *m/z* 326. This data and the number of carbon resonances in its ^{13}C NMR spectrum (**Figure 54**) suggested the molecular formula of KG-F6 as $C_{21}H_{26}O_3$.

The ^{13}C NMR spectrum of compound KG-F6 displayed twenty-one carbon signals, corresponding to one keto-carbonyl carbon at δ 208.8, four quaternary carbons at δ 110.0, 143.6, 163.1 (2C), eight methine carbons at δ 108.4 (2C), 126.4, 129.1 (2C), 129.2 (2C) and 136.8, and eight methylene carbons at δ 25.2, 30.0 (2C), 30.2 (2C), 32.3, 36.5 and 45.3. The mass and carbon NMR spectral data supported the presence of two aromatic rings as parts of the molecular structure of this compound.

The ^{1}H NMR spectrum (**Figure 53**) displayed the resonance of two symmetrical, hydrogen-bonded hydroxyl protons at δ 11.40. Methylene protons next to the keto-carbonyl resonated at δ_H 3.16 (2H, t, *J* = 7.5 Hz, H-2′) (δ_C 45.3), while one benzylic methylene group gave a triplet at δ_H 2.61 (2H, *t*, *J* = 7.5 Hz, H-9′) (δ_C 36.5). The presence of a 2,6-dihydroxy-substituted aromatic moiety could be deduced from the downfield peaks at δ 6.42 (2H, *d*, *J* = 8.0 Hz, H-3 and H-5) and δ 7.25 (1H, *t*, *J* = 8 Hz, H-4). Another set of proton signals at δ 7.15 (1H, *tt*, *J* = 7.5, 1.3 Hz, H-13′), 7.20 (2H, *br d*, *J* = 7.5 Hz, H-11′ and H-15′) and 7.26 (2H, *t*, *J* = 7.5 Hz, H-12′ and H-14′) indicated that the second aromatic ring was mono-substituted. The two benzene rings should therefore be linked by an acyl chain, as shown by the HMBC correlations (**Figure 58**) of the methylene signal at δ 2.61 (H-9′) with the benzyl carbon signals of C-10′ (δ 143.6) and C-11′/C-15′ (δ 129.2), and the correlations of both methylene signals at 3.16 (H-2′) and 1.70 (H-3′) with the keto-carbonyl carbon (C-1′). The presence of a base peak at *m/z* 137 in the mass spectrum was therefore due to α-cleavage of the carbonyl group and the mass fragment at *m/z* 91 was due to the benzylic cleavage.

Therefore, these spectroscopic data demonstrated that compound KG-F6 was identical to malabaricone A (Pham *et al*., 2000), which is an acyl resorcinol derivative isolated from a number of plants within the family Myristicaceae, e.g. *Myristica malabarica* (Bauri *et al*., 2006), from the fruits of *M. gigantean* (Pham *et al*., 2002) and *M. maingayi* (Pham *et al*., 2000) and the nutmeg of *M. cagayanesis* (Kuo, Lin and Wu, 1989). The compound has been showned to be an antipromastigote (Sen *et al*., 2007) and an antioxidant (Patro *et al*., 2005).



Malabaricone A

Table 16. Comparison of the ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectral data of malabaricone A and compound KG-F6 (in acetone-d_6)

Position	KG-F6			Malabaricone A *	
	^{1}H	^{13}C	HMBC	^{1}H	^{13}C
1	-	110.0		-	110.0
2	-	163.1		-	161.3
3	6.42 (1H, *d*, *J* = 8.0 Hz)	108.4	1, 2	6.40 (1H, *d*, *J* = 8.3 Hz)	108.2
4	7.25 (1H, *t*, *J* = 8.0 Hz)	136.8	2, 6	7.26 (1H, *m*)	135.9
5	6.42 (1H, *d*, *J* = 8.0 Hz)	108.4	1, 6	6.40 (1H, *d*, *J* = 8.3 Hz)	108.2
6	-	163.1		-	161.3
1′	-	208.8		-	208.5
2′	3.16 (2H, *t*, *J* = 7.5 Hz)	45.3		3.15 (2H, *t*, *J* = 7.5 Hz)	44.7
3′	1.70 (2H, *quintet*, *J* = 7.5 Hz)	25.2	2′	1.71 (2H, *p*, *J* = 7.5 Hz)	24.4
4′	1.35 (8H, *m*)	30.0		1.33 (8H, *br s*)	29.3
5′		30.1			29.3
6′		30.2			29.3
7′		30.2			29.1
8′	1.62 (2H, *q*, *J* = 7.5 Hz)	32.3		1.61 (2H, *p*, *J* = 7.5 Hz)	31.4
9′	2.61 (2H, *t*, *J* = 7.5 Hz)	36.5	8′, 10′, 11′, 15′	2.6 (2H, *t*, *J* = 7.5 Hz)	35.9
10′	-	143.6		-	142.9
11′	7.20 (1H, *br d*, *J* = 7.5 Hz)	129.2	10′	7.17 (1H, *m*)	128.3
12′	7.26 (1H, *t*, *J* = 7.5 Hz)	129.1	10′	7.26 (1H, *m*)	128.1
13′	7.15 (1H, *tt*, *J* = 7.5, 1.3 Hz)	126.4	11′, 12′	7.17 (1H, *m*)	125.5
14′	7.26 (1H, *t*, *J* = 7.5 Hz)	129.1		7.26 (1H, *m*)	128.1
15′	7.20 (1H, *br d*, *J* = 7.5 Hz)	129.2		7.17 (1H, *m*)	128.3
2-OH, 6-OH	11.40 (2H, *s*)	-		-	-

* Pham *et al*., 2000

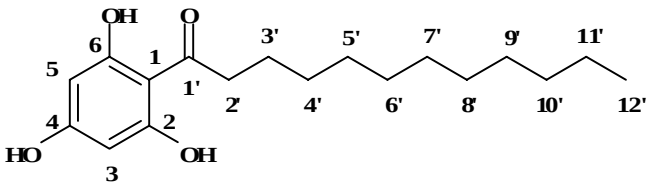
1.7 Identification of Compound KG-F7 [Dodecanoylphloroglucinol]

Compound KG-F7 was obtained as yellow amorphous solid. Its UV absorption maxima (**Figure 60**) at 227 and 286 nm suggested the presence of a 2,4,6-trihydroxyphenylketone chromophore (Kitagawa *et al.*, 1972) and supported by IR absorption peaks at 3400, 3250 (hydroxyl), 1650 (conjugated carbonyl) and 1618 cm^{-1} (phenyl). A molecular ion peak at *m/z* 308 in its EI mass spectrum (**Figure 62**) and the carbon NMR data (**Figure 64**) suggested the molecular formula $C_{18}H_{28}O_4$ for this compound. The mass fragment ions at *m/z* 153 (base peak) and 181 represented the α- and γ-cleavage of the 2,4,6-trihydroxyphenylketone moiety, respectively.

The ^{1}H NMR spectrum (**Figures 63a-63c**) showed a singlet signal of two symmetrical, hydrogen-bonded hydroxyl groups at δ 11.70 (2-OH/6-OH) and another hydroxyl proton singlet at δ 9.57 (4-OH). A two-proton singlet representing a 1,2,4,6-tetrasubstituted benzene ring resonated at δ 5.93 (2H, *s*, H-3/H-5), whereas an extended aliphatic chain gave a set of signals at δ 3.07 (2H, *t*, *J* = 7.3 Hz, H-2′), 1.67 (2H, *quintet*, *J* = 7.3 Hz, H-3′), 1.32 (16H, *m*, H-4′ to H-11′) and 0.88 (3H, *t*, *J* = 7.0 Hz, H-12′).

The ^{13}C NMR spectrum showed signals corresponding to one keto-carbonyl carbon at the most downfield chemical shift of δ 206.6 (C-1′), and the most upfield signal of one methyl carbon at δ 14.4 (C-12′). The tetra-substituted aromatic ring was represented by a methine carbon signal at δ 95.8 (C-3/C-5), a quaternary carbon signal at δ 105.2 (C-1), and two hydroxy-substituted aromatic carbon signals at δ 165.4 (C-2/C-6) and 165.1 (C-4). The rests were signals of the eleven-carbon alkane chain.

From these spectral data, the chemical structure of compound KG-F7 was identified as dodecanoylphloroglucinol, which has previously been found in the wood of *Knema austrosiamensis* (Gonzalez *et al*., 1993), and also in another member of the family Myristicaceae i.e. in the bark and seeds of *Horsfieldia iryaghedi* (Kitagawa *et al*., 1972; Tillekeratne *et al*., 1982).



Dodecanoylphloroglucinol

Table 17. Comparison of ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectral data of dodecanoylphloroglucinol and compound KG-F7 (in acetone-d_6)

Position	KG-F7		Dodecanoylphloroglucinol*
	^{1}H	^{13}C	^{1}H
1	-	105.2	-
2	-	165.4	-
3	5.93 (1H, *s*)	95.8	5.86 (1H, *br s*)
4	-	165.1	-
5	5.93 (1H, *s*)	95.8	5.86 (1H, *br s*)
6	-	165.4	-
1′	-	206.6	-
2′	3.07 (2H, *t*, *J* = 7.3 Hz)	44.5	3.01 (2H, *t*, *J* = 6.5 Hz)
3′	1.67 (2H, *quintet*, *J* = 7.3 Hz)	25.6	1.66 (2H, *m*)
4′	1.32 (16H, *m*)	30.0	1.23 (16H, *m*)
5′		30.0	
6′		30.2	
7′		30.3	
8′		30.3	
9′		30.3	
10′		32.6	
11′		23.3	
12′	0.88 (3H, *t*, *J* = 7.0 Hz)	14.4	0.86 (3H, *t*, *J* = 6.5 Hz)
2-OH, 6-OH	11.70 (2H, *br s*)	-	11.50 (2H, *br s*)
4-OH	9.57 (1H, *br s*)	-	8.65 (1H, *br s*)

*Gonzalez *et al*., 1993

1.8 Identification of Compound KG-F8 [1-(2,4,6-Trihydroxyphenyl)-9-phenyl-nonan-1-one]

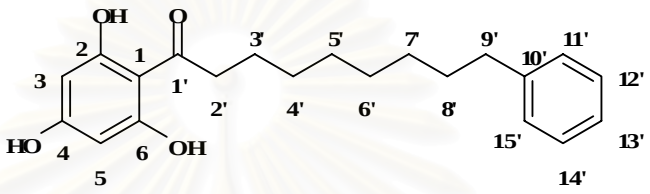
Compound KG-F8 was obtained as yellow amorphous solid. Its UV absorption maxima (**Figure 69**) at 228 and 286 nm suggested that the compound carry a 2,4,6-trihydroxyphenyl ketone chromophore (Kitagawa *et al*., 1972), whereas its IR peaks at 3253 cm^{-1} indicated hydroxyl moiety and at 1635 (C=O), 1600 and 1570 cm^{-1} (**Figure 70**) suggested the presence of a benzoyl moiety within the structure. The similarities between both the UV and IR spectra of compounds KG-F8 and KG-F6 suggest that they belong to the same group of compounds. The EI mass spectrum (**Figure 71**) showed molecular ion peak of compound KG-F8 at *m/z* 342, which is 16 mass units higher than that of compound KG-F6, indicating an additional hydroxyl group. Other important mass fragments were observed at *m/z* 153 and 91 due to the formation of a trihydroxybenzoyl and a benzylic group, respectively.

Preliminary examination of the proton NMR data (**Figure 72**) confirmed that compound KG-F8 is closely similar to KG-F6. The presence of two sets of aromatic signals is again observed. However, while the signals of a mono-substituted benzene ring could be observed at δ 7.15 (1H, *tt*, *J* = 7.5, 1.3 Hz, H-13′), 7.20 (2H, *br d*, H-11′ and H-15′) and 7.26 (2H, *br t*, *J* = 7.0 Hz, H-12′ and H-14′), there was only one signal due to the other aromatic ring at δ 5.93 (2H, *s*, H-3 and H-5), suggesting a 1,2,4,6-tetrasubstituted benzene moiety. The methylene signals of the connecting acyl chain appeared in the aliphatic region at δ 1.35 (8H, *m*, H-4′ to H-7′), 1.62 (2H, *quintet*, *J* = 7.5 Hz, H-8′), 1.67 (2H, *quintet*, *J* = 7.5 Hz, H-3′), 2.61 (2H, *t*, *J* = 7.5 Hz, H-9′) and 3.06 (2H, *t*, *J* = 7.5 Hz, H-2′). Finally, in addition to the signal of two symmetrical, hydrogen-bonded hydroxyl groups at δ 11.72 (2H, *s*, 2-OH and 6-OH), another hydroxyl proton resonated at a more upfield chemical shift of δ 9.16 (1H, *s*, 4-OH). This signal displayed HMBC correlations (**Figure 77**) with those of C-4 (δ 165.4) and C-2/C-6 (δ 95.8), confirming its location at position C-4.

The ^{13}C NMR spectral data (**Figure 73**) of compound KG-F8 were also similar to those of KG-F6, except for a signal of an additional quaternary carbon attached to a heteroatom at δ 165.4 (C-4) in place of an aromatic methine carbon signal at δ 136.8 in the previous compound. HMQC (**Figure 76**) and HMBC spectra were employed in the total assignments of these carbon signals. HMBC spectra

confirmed the connection of mono-substituted aromatic ring to the acyl chain by the correlations between the signal of H-9′ (δ 2.61) to those of C-10′ (δ 143.6) and C-11′/C-15′ (δ 129.2).

Based on these spectral data and comparison with literature values (Gonzalez *et al*., 1993), compound KG-F8 was identified as an acyl phloroglucinol derivative, 1-(2,4,6-trihydroxyphenyl)-9-phenylnonan-1-one, originally isolated from the wood of *Knema austrosiamensis*, another plant of the same genus (Gonzalez *et al*., 1993).



1-(2,4,6-Trihydroxyphenyl)-9-phenylnonan-1-one

Table 18. Comparison of ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectral data of 1-(2,4,6-trihydroxyphenyl)-9-phenylnonan-1-one and compound KG-F8 (in acetone-d_6)

Position	KG-F8			1-(2,4,6-Trihydroxyphenyl)-9-phenylnonan-1-one*
	^{1}H	^{13}C	HMBC	^{1}H
1	-	105.1		-
2	-	165.1		-
3	5.93 (1H, *s*)	95.8	1, 2, 4	5.91 (1H, *br s*)
4	-	165.4		-
5	5.93 (1H, *s*)	95.8	1, 4, 6	5.91 (1H, *br s*)
6	-	165.1		-
1′	-	206.2		-
2′	3.06 (2H, *t*, *J* = 7.5 Hz)	44.4	1′	3.01 (2H, *t*, *J* = 7.5 Hz)
3′	1.67 (2H, *quintet*, *J* = 7.5 Hz)	25.5	2′	1.30, 1.23 (6H, *br s*)
4′	1.35 (4H, *m*)	30.0		
5′		30.1		

Table 18. (continued)

Position	KG-F8			1-(2,4,6-Trihydroxyphenyl)-9-phenylnonan-1-one*
	^{1}H	^{13}C	HMBC	^{1}H
6′	1.35 (4H, *m*)	30.2		1.30, 1.23 (4H, *br s*)
7′		30.2		
8′	1.62 (2H, *quintet*, *J* = 7.5 Hz)	32.4		
9′	2.61 (2H, *t*, *J* = 7.5 Hz)	36.5	8′, 10′, 11′, 15′	2.57 (2H, *t*, *J* = 7.0 Hz)
10′	-	143.6		-
11′	7.19 (1H, *br d*, *J* = 7.0 Hz)	129.2		7.14-7.32 (5H, *m*)
12′	7.26 (1H, *br t*, *J* = 7.0 Hz)	129.1		
13′	7.15 (1H, *tt*, *J* = 7.0, 1.0 Hz)	126.4		
14′	7.26 (1H, *br t*, *J* = 7.0 Hz)	129.1		
15′	7.19 (1H, *br d*, *J* = 7.0 Hz)	129.2		
2-OH, 6-OH	11.72 (2H, *s*)	-		
4-OH	9.16 (1H, *s*)	-	3, 5	

* Gonzalez *et al*., 1993

1.9 Identification of Compound KG-L1 [Myristinin A]

Compound KG-L1 was obtained as brown amorphous solid which developed a yellow color upon spraying with 10% sulfuric acid in ethanol, followed by heating. The IR spectrum (**Figure 80**) showed hydroxyl absorption band at 3392 cm^{-1} and conjugated keto-carbonyl band at 1618 cm^{-1}. Its molecular formula of $C_{33}H_{40}O_7$ was confirmed by a molecular ion peak at *m/z* 548 and an $[M + Na]^+$ peak at *m/z* 571 in the ESI-TOF mass spectrum (**Figure 81**) together with its ^{13}C NMR spectral data (**Figure 83**).

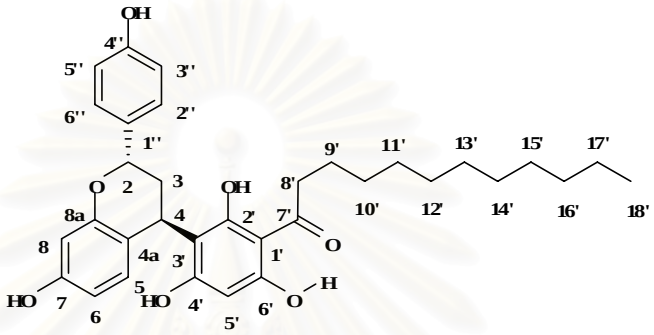
The ^{13}C NMR spectrum and DEPT experiment (**Figure 84**) showed eighteen aromatic carbon signals, suggesting that compound KG-L1 comprised of three substituted benzene rings in its structure. A keto-carbonyl signal was observed at δ 206.2 (C-7′). Other signals were those of a terminal methyl carbon at δ 14.3 (C-18′), two methine carbons at δ 75.7 (C-2) and 30.4 (C-4), and twelve methylene carbon signals.

The ^{1}H NMR spectrum (**Figures 82a-82b**) revealed the presence of a flavan moiety from the *ortho*-coupled signals of a *para*-substituted aromatic ring at δ 6.72 (2H, *d*, *J* = 8.8 Hz, H-3″/H-5″) and 7.13 (2H, *d*, *J* = 8.8 Hz, H-2″/H-6″), assignable to the B- ring protons of the flavan unit, as well as the signals of the A-ring protons at δ 6.11 (1H, *dd*, *J* = 8.0, 2.3 Hz, H-6), 6.32 (1H, *d*, *J* = 2.3 Hz, H-8) and 6.45 (1H, *d*, *J* = 8.0 Hz, H-5). In addition, the oxymethine proton resonance at δ 4.79 (1H, *dd*, *J* = 11.5, 2.5 Hz, H-2), coupling to a pair of methylene proton peaks at δ 2.13 (1H, *t*, *J* = 2.5 Hz, H-3*ax*) and 2.15 (1H, *dd*, *J* = 11.5, 5.0 Hz, H-3*eq*) which, in turn, coupled with another methine proton resonance at δ 4.49 (1H, *dd*, *J* = 5.0, 2.0 Hz, H-4), completed the third, middle ring (ring C) of the tri-substituted flavan unit. This moiety was therefore substituted at positions 4, 7 and 4″.

The C-4 position was substituted by a dodecanoylphloroglucinol unit, represented by an aromatic proton singlet at δ 5.88 (H-5′), a methyl triplet at δ 0.75 (3H, *t*, *J* = 7.0 Hz, H-18′) and a set of aliphatic methylene signals at δ 2.73 (2H, *m*, H-8′), 1.38 (2H, *quintet*, *J* = 7.5 Hz, H-9′), 1.15 (8H, *m*, H-10′, H-11′, H-16′ and H-17′) and 0.99 (6H, *m*, H-13′ to H-15′). A 4″-hydroxyl substitution of the B-ring of flavan unit was confirmed by HMBC experiment (**Figures 87a-87c**) showing the correlation of the 4″-OH signal at δ 8.47 to those of C-3″/C-5″ (δ 116.0) and C-4″ (δ 158.4). Another hydroxyl substitution at C-7 of the A-ring was also confirmed by HMBC correlations of this hydroxyl proton signal at δ 8.04 to those of C-6 (δ 106.6), C-7 (δ 157.6) and C-8 (δ 103.6).

The Chem3D® modeling with MM2 energy minimization and analysis of the coupling constants between H-2/H-3 and H-4/H-3 were used to deduce the orientation between H-2 and H-4 as *trans*. From the above spectral information and comparison with previous data, compound KG-L1 was identified as a flavan-acylphloroglucinol derivative named myristinin A (Sawadjoon *et al*., 2002). This flavan-acylphloro-glucinol has previously been isolated from *Myristica cinnamomea*

and reported as exhibiting antifungal activity against *Candida albican*s, cytotoxicity against Vero cells and inhibitory activity against the enzyme COX-2 with IC_{50} values of 8.8, 17.7 and 16.9 µg/ml, respectively (Sawadjoon *et al*., 2002). The compound was later isolated from *Knema elegans* and shown to be an inhibitor of DNA polymerase *β*, as well as causing DNA damage (Deng *et al*., 2005; Maloney *et al*., 2005).



Myristinin A

Table 19. The ^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectral data of compound KG-L1 (in acetone-d_6)

Position	^{1}H	^{13}C	HMBC
2	4.79 (1H, *dd*, *J* = 11.5, 2.5 Hz)	75.7	3, 4, 1″, 2″, 6″
3*eq*	2.13 (1H, *t*, *J* = 2.5 Hz)	35.1	2, 4, 4a, 3′, 1″
3*ax*	2.15 (1H, *td*, *J* = 11.5, 5.0 Hz)		
4	4.49 (2H, *dd*, *J* = 5.0, 2.0 Hz)	30.4	2, 3, 4a, 5, 8a, 2′, 3′, 4′
4a	-	123.7	
5	6.45 (1H, *d*, *J* = 8.0 Hz)	130.5	4, 7, 8a
6	6.11 (1H, *dd*, *J* = 8.0, 2.3 Hz)	106.6	4a, 7, 8
7	-	157.6	
8	6.32 (1H, *d*, *J* = 2.3 Hz)	103.6	4a, 6, 7, 8a
8a	-	155.9	
1′	-	105.4	
2′	-	160.1	
3′	-	103.4	

Table 19. (continued)

Position	^{1}H	^{13}C	HMBC
4′	-	163.3	
5′	5.88 (1H, *s*)	96.3	1′, 3′, 6′
6′	-	166.6	
7′	-	206.2	
8′	2.73 (2H, *m*)	45.2	7′, 9′, 10′
9′	1.38 (2H, *quintet*, *J* = 7.5 Hz)	26.2	7′, 8′, 11′
10′	1.15 (4H, *m*)	30.0	
11′		30.0	
12′	0.90 (2H, *m*)	30.2	
13′	0.99 (6H, *m*)	30.3	
14′		30.3	
15′		30.3	
16′	1.15 (4H, *m*)	32.6	
17′		23.3	
18′	0.75 (3H, *t*, *J* = 7.0 Hz)	14.3	16′
1″	-	132.4	
2″	7.13 (1H, *d*, *J* = 8.8 Hz)	129.0	2, 3″, 6″
3″	6.72 (1H, *d*, *J* = 8.8 Hz)	116.0	1″, 5″
4″	-	158.4	
5″	6.72 (1H, *d*, *J* = 8.8 Hz)	116.0	1″, 3″
6″	7.13 (1H, *d*, *J* = 8.8 Hz)	129.0	2″, 5″
7-OH	8.04 (1H, *s*)	-	6, 7, 8
2′-OH	8.41 (1H, *s*)	-	
4′-OH	9.39 (1H, *s*)	-	4′, 5′
6′-OH	13.85 (1H, *s*)	-	1′, 5′, 6′
4″-OH	8.47 (1H, *s*)	-	4″, 3″, 5″

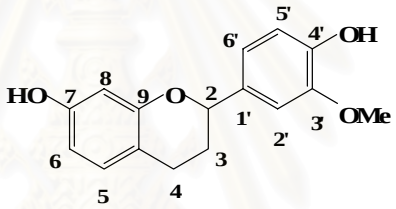
1.10 Identification of Compound KG-S1 [(±)-7,4′-Dihydroxy-3′-methoxy-flavan]

Compound KG-S1 was obtained as brown amorphous powder. Its $[M + Na]^+$ peak in the ESI-TOF mass spectrum (**Figure 91**) at *m/z* 295 together with ^{13}C NMR spectrum (**Figure 93**) suggested a molecular formula of $C_{16}H_{16}O_4$. Its UV absorption maxima at 253 and 283 nm (**Figure 89**) suggested the flavan structure (Martinez and Cuca, 1987), whereas its IR spectrum (**Figure 90**) showed OH stretching band at 3429 cm^{-1}.

The ^{13}C NMR spectrum of compound KG-S1 displayed 16 carbon resonances, supporting its molecular formula. The carbon signals could be classified by DEPT experiment as those of one methoxy carbon at δ 55.4 (3′-OCH_3), two methylene carbons at δ 24.3 (C-3) and 30.1 (C-4), one aliphatic oxymethine carbon at δ 77.6 (C-2), six aromatic methine carbons at δ 103.1 (C-8), 108.0 (C-6), 109.8 (C-2′), 114.7 (C-5′), 118.9 (C-6′) and 129.9 (C-5), and six aromatic quaternary carbons at δ 112.8 (C-10), 133.6 (C-1′), 146.2 (C-4′), 147.4 (C-3′), 156.0 (C-9) and 156.7 (C-7).

In the ^1H NMR spectrum (**Figure 92**), characteristic resonances for a flavan molecule with 7,3′,4′-trisubstitution were evident from the signals of a 1,3,4-trisubstituted aromatic ring B at δ 6.83 (1H, *d*, *J* = 8 Hz, H-5′), 6.89 (1H, *dd*, *J* = 8.0, 1.8 Hz, H-6′) and 7.04 (1H, *d*, *J* = 1.8 Hz, H-2′), while the proton signals of ring A were observed at δ 6.31 (1H, *d*, *J* = 2.4 Hz, H-8), 6.37 (1H, *dd*, *J* = 8.2, 2.4 Hz, H-6) and 6.87 (1H, *d*, *J* = 8.2 Hz, H-5). Two hydroxyl signals at δ 7.72 (4′-OH) and 8.32 (7-OH) and one methoxyl signal at δ 3.84 (3H, *s*, 3′-OCH_3) could also be observed. A double doublet of an oxymethine proton appearing at δ 4.92 (*J* = 10.3, 2.1 Hz, H-2) was coupled to two proton multiplets at δ 2.65 (1H, *ddd*, *J* = 15.9, 5.0, 3.0 Hz, H-3eq) and 2.85 (1H, *ddd*, *J* = 15.9, 11.7, 5.9 Hz, H-3ax). Another multiplet at δ 1.98 (1H, *m*, H-4*ax*) and 2.11 (1H, *m*, H-4*eq*) is attributed to a benzylic methylene. HMBC experiment (**Figure 96**) helped in confirming the substitution pattern on the B ring of the flavonoid, of which the 4′-OH signal at δ 7.72 showed correlation to C-4′ signal at δ 146.2, while the 3′-OCH_3 signal at δ 3.84 showed cross-peak with C-3′ signal at δ 147.4. A hydroxyl group was therefore deduced as locating on C-4′ and a methoxy group on C-3′, based on HMBC evidences and biogenetic consideration. The substitution of another hydroxyl group on the C-7 position of ring A was

deduced from the HMBC correlation of hydroxyl proton signal at δ 8.32 to C-7 signal (δ 156.7). According to its $[\alpha]_D$ value of 0^o, compound KG-S1 is a racemic mixture. The compound was thus identified as the known flavan (±)-7,4′-dihydroxy-3′-methoxyflavan (Filho, Diaz and Gottlier, 1980; Gonzalez *et al.*, 1993). Within the family Myristicaceae, this flavan has previously been reported as a constituent of the trunk wood of *Iryanthera elliptica* (Filho *et al*. 1980) and *I. grandis* (Diaz *et al*., 1986), and the wood of *Knema austrosiamensis* (Gonzalez *et al*., 1993.). The flavonoid was also found in the wood of *Terminalia argentea* (Garcez *et al*., 2003) and *T. fagifolia* (Garcez *et al*., 2006) of the family Combretaceae. It has been shown to exhibit cytotoxic activity against two human cancer cell lines: Hep2 larynx carcinoma and H2a2 lung mucoepidermoid carcinoma (Garcez *et al*., 2006). The compound also inhibited tube-like formation of human umbilical venous endothelial cells (Nam *et al*., 2004).



(±)-7,4′-Dihydroxy-3′-methoxyflavan

Table 20. Comparison of the ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectral data of compound KG-S1 and (±)-7,4′-dihydroxy-3′-methoxyflavan (in acetone-d_6)

Position	KG-S1		(±)-7,4′-Dihydroxy-3′-methoxyflavan	
	^{1}H	^{13}C	^{1}H*	^{13}C**
2	4.92 (1H, *dd*, *J* = 11.0, 2.5 Hz)	77.6	4.95 (1H, *dd*, *J* = 8.5, 3.5 Hz)	77.8
3*ax*	2.85 (1H, *ddd*, *J* = 15.9, 11.0, 5.5 Hz)	24.3	1.9-2.3 (2H, *m*)	24.6
3*eq*	2.65 (1H, *ddd*, *J* = 15.9, 5.5, 2.5 Hz)			
4*ax*	1.98 (1H, *m*)	30.1	2.6-2.9 (2H, *m*)	30.1
4*eq*	2.11 (1H, *m*)			
5	6.87 (1H, *d*, *J* = 8.2 Hz)	129.9	6.98 (1H, *d*, *J* = 8.0 Hz)	-
6	6.37 (1H, *dd*, *J* = 8.2, 2.4 Hz)	108.0	6.42 (1H, *dd*, *J* = 8.0, 3.0 Hz)	107.9
7	-	156.7	-	154.8
8	6.31 (1H, *d*, *J* = 2.4 Hz)	103.1	6.29 (1H, *d*, *J* = 3.0 Hz)	103.5
9	-	156.0	-	155.9
10	-	112.8	-	114.2
1′	-	133.6	-	133.6
2′	7.04 (1H, *d*, *J* = 1.8 Hz)	109.8	6.93 (1H, *br s*)	107.9
3′	-	147.4	-	146.6
4′	-	146.2	-	145.4
5′	6.83 (1H, *d*, *J* = 8.0 Hz)	114.7	6.93 (1H, *br s*)	108.7
6′	6.89 (1H, *dd*, *J* = 8.0, 1.8 Hz)	118.9	6.93 (1H, *br s*)	119.2
3′-OMe	3.84 (3H, *s*)	55.4	3.92 (3H, *s*)	56.0
4′-OH	7.72 (1H, *s*)	-	5.62 (1H, *s*)	-
7-OH	8.32 (1H, *s*)	-	4.85 (1H, *s*)	-

*Filho, Diaz and Gottlier, 1980

**Gonzalez *et al.*, 1993

2. Structure Determination of Compounds Isolated from *Knema furfuracea*

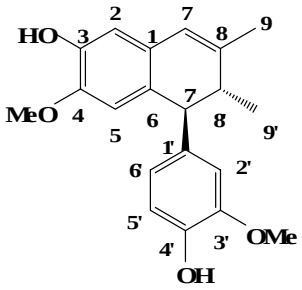
2.1 Identification of Compound KF-S1 [(+)-*trans*-1,2-Dihydrodehydro-guaiaretic acid]

Compound KF-S1 was obtained as colorless amorphous crystals. Its ESI-TOF mass spectrum (**Figure 100**) showed an $[M + Na]^+$ peak at *m/z* 349.1416, corresponding to a molecular formula of $C_{20}H_{22}O_4$. Its IR spectrum (**Figure 99**) revealed hydroxyl absorption band at 3497 cm^{-1}.

The ^{13}C NMR spectrum (**Figure 102**) exhibited 20 carbon peaks classifiable into those of two methyl carbons at δ 18.5 (C-9′) and 22.0 (C-9), two methoxy carbons at δ 55.5 (3-OMe) and 55.7 (3′-OMe), eight methine carbons at δ 41.1 (C-8′), 49.5 (C-7′), 111.7 (C-2′), 112.8 (C-2), 113.5 (C-5), 115.0 (C-5′), 119.4 (C-6′) and 121.0 (C-7), and eight quaternary carbons at δ 126.0 (C-6), 126.6 (C-1), 136.8 (C-4), 137.9 (C-8), 144.6 (C-1′), 144.8 (C-4′), 146.2 (C-3) and 147.1 (C-3′) by DEPT experiment (**Figure 103**).

The ^1H NMR spectrum (**Figure 101**) exhibited signals of a 1,3,4-trisubstituted benzene ring at δ 6.33 (1H, *dd*, *J* = 8.1, 2.0 Hz, H-6′), 6.55 (1H, *d*, *J* = 8.1 Hz, H-5′) and 6.88 (1H, *d*, *J* = 2.0 Hz, H-2′), two aromatic singlets at δ 6.50 (H-2) and 6.59 (H-5), one olefinic proton at δ 6.03 (1H, *d*, *J* = 1.22 Hz, H-7), two methyl signals resonating at δ 0.97 (3H, *d*, *J* = 7.02 Hz, H-9′) and 1.73 (3H, *d*, *J* = 1.22 Hz, H-9) and two upfield methine protons at δ 2.29 (1H, *dq*, *J* = 6.7, 2.5 Hz, H-8′) and 3.60 (1H, *d*, *J* = 2.5 Hz, H-7′).

According to the molecular formula, the calculated degree of unsaturation for this compound was 10, which corresponds to two aromatic rings, one double bond and one cyclic structure. A possible structure for compound KF-S1 was thus a 1,2-dihydronaphthalene lignan skeleton. The observed HMBC correlations from the signal of H-7′ at δ 3.60 to both C-5 (δ 113.5) and C-8 (δ 137.8) (**Figures 106a-106d**) confirmed the connectivity of the 1,3,4-trisubstituted benzene ring to the 1,2-dihydronaphthalene moiety. The *trans* configuration between H-7′ and the pseudoaxial H-8′ was assigned based on their coupling constant (2.5 Hz) and comparison with previous report (Pinto *et al*., 1990). Compound KF-S1 was therefore identified as (+)-*trans*-1,2-dihydro-dehydroguaiaretic acid, an aryl dihydronaphthalene lignan.



(+)-*trans*-1,2-Dihydrodehydroguaiaretic acid

Table 21. Comparison of the ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectral data of (+)-*trans*-1,2-dihydro-dehydroguaiaretic acid and compound KF-S1 (in DMSO-d_6)

Position	KF-S1			(+)-*trans*-1,2-Dihydro-dehydroguaiaretic acid*	
	^{1}H	^{13}C	HMBC	^{1}H	^{13}C
1	-	126.6		-	127.7
2	6.50 (1H, *s*)	112.8		6.66 (1H, *s*)	112.1
3	-	146.2		-	144.1
4	-	136.8		-	136.8
5	6.59 (1H, *s*)	113.5		6.52 (1H, *s*)	113.5
6	-	126.0		-	126.9
7	6.03 (1H, *d*, *J* = 1.2 Hz)	121.0	2, 6, 9, 8′	6.10 (1H, *s*)	121.1
8	-	137.9		-	137.8
9	1.73 (3H, *d*, *J* = 1.2 Hz)	22.0	7, 8, 8′	1.77 (3H, *d*, *J* = 1.3 Hz)	22.15
1′	-	144.6		-	138.8
2′	6.68 (1H, *d*, *J* = 2.0 Hz)	111.7		6.55 (1H, *d*, *J* = 1.0 Hz)	110.1
3′	-	147.1		-	146.2
4′	-	144.8		-	145.1
5′	6.55 (1H, *d*, *J* = 8.1 Hz)	115.0		6.55 (1H, *d*, *J* = 8.0 Hz)	113.9
6′	6.33 (1H, *dd*, *J* = 8.1, 2.0 Hz)	119.4		6.76 (1H, *dd*, *J* = 8.0, 1.0 Hz)	120.3

Table 21. (continued)

Position	KF-S1			(+)-*trans*-1,2-Dihydro-dehydroguaiaretic acid*	
	^{1}H	^{13}C	HMBC	^{1}H	^{13}C
7′	3.60 (1H, *d*, *J* = 2.5 Hz)	49.5	5, 8	3.65 (1H, *d*, *J* = 3.2 Hz)	42.1
8′	2.29 (1H, *dq*, *J* = 6.7, 2.5 Hz)	41.1	6, 8, 9′	2.35 (1H, *dq*, *J* = 7.0, 3.2 Hz)	51.0
9′	0.97 (3H, *d*, *J* = 7.0 Hz)	18.5	8, 7′, 8′	1.07 (3H, *d*, *J* = 7.0 Hz)	18.72
3′-OMe	3.65 (3H, *s*)	55.7		3.78 (3H, *s*)	56.0
3-OMe	3.65 (3H, *s*)	55.5		3.76 (3H, *s*)	55.8
4′-OH	8.68 (1H, *s*)	-		5.51 (1H, *s*)	-
4-OH	8.68 (1H, *s*)	-		5.53 (1H, *s*)	-

*Pinto *et al*., 1990.

2.2 Identification of Compound KF-S2 [Fragransin A_2]

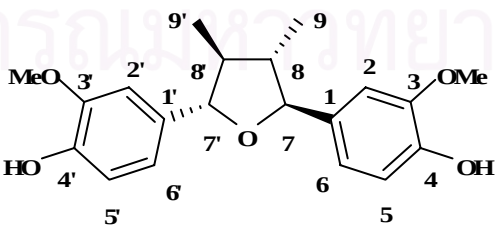
The UV absorption maxima of the colourless compound KF-S2 at 234, 253, 281 nm (**Figure 107**) and the IR bands at 1611 and 1250 cm^{-1} (**Figure 108**) indicated the presence of aromatic ring in the molecule, while the IR band at 3365 cm^{-1} indicated the hydroxyl group. Its molecular formula was determined as $C_{20}H_{24}O_5$ from its $[M + Na]^+$ ion peak at *m/z* 367.1523 (calculated mass: 367.1521 for $C_{20}H_{24}O_5Na$) in the high resolution mass spectrum (**Figure 109**). However, its ^{13}C NMR spectrum (**Figure 111**) showed only ten signals, suggesting that the compound was consisted of two symmetrical portions. These carbon signals could be classified into those of two methoxy carbons at δ 55.5 (3-OCH_3/3′-OCH_3), two methyl carbons at δ 13.2 (C-9/C-9′), two methine carbons at δ 51.1 (C-8/C-8′), two oxymethine carbons at δ 88.1 (C-7/C-7′), twelve aromatic carbons including six methine carbons at δ 109.7 (C-2/C-2′), 114.5 (C-5/C-5′) and 119.1 (C-6/C-6′), and six quaternary carbons at δ 134.6 (C-1/C-1′), 146.0 (C-4/C-4′) and 147.4 (C-3/C-3). These spectral data indicated compound KF-S2 to be a lignan with methoxy and hydroxyl substitutions in the benzene ring.

The ^{1}H NMR spectrum (**Figure 110**) exhibited one methyl doublet at δ 1.00 (*J* = 6.0 Hz, H-9/H-9′) coupling to a methine resonance at δ 1.75 (*m*, H-8/H-8′), which, in turn, to be coupled to an oxymethine signal at δ 4.60 (*d*, *J* = 9.0 Hz, H-7/H-7′), as shown in the ^{1}H-^{1}H COSY spectrum (**Figure 113**). Three aromatic proton signals were observed at δ 7.05 (*d*, *J* = 2.0 Hz, H-2/H-2′), 6.85 (*dd*, *J* = 8.0, 2.0 Hz, H-6/H-6′) and 6.80 (*d*, *J* = 8.0 Hz, H-5/H-5′). Their coupling constants indicated the 1,3,4-trisubstituted pattern on the benzene ring. A methoxy singlet at δ 3.85 (3-OCH_3/3′-OCH_3) and a hydroxyl singlet at δ 7.50 (4-OH/4′-OH) were also observed.

HMBC correlations (**Figures 115a-115b**) from the H-7 signal at δ 4.60 to both C-2 (δ 109.7) and C-6 signals (δ 119.1), as well as from the signal of H-2 (δ 7.05) to C-7 signal (δ 88.1), established the connectivity of the lignan molecule between the C-1 position of the aromatic ring and the C-7 position of the three-carbon subunit. HMBC cross-peaks between H-8 signal at δ 1.75 and C-8′ (δ 50.9), and vice versa, indicated the connectivity of both sides of the lignan molecule through these positions.

The NOESY correlation (**Figure 116**) between the methoxy and H-2 signals confirmed their proximity on the same side of the aromatic ring. Therefore, the methoxy and hydroxyl groups could be assigned at the C-3/C-3′ and C-4/C-4′ positions of the aromatic portions of the lignan molecule, respectively.

Compound KF-S2 was thus identified as fragransin A_2, an epoxy lignan previously isolated from the aril of nutmeg (*Myristica fragrans*) (Hattori *et al*., 1987).



Fragransin A_2

Table 22. Comparison of the ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectral data of fragransin A_2 and compound KF-S2 (in $CDCl_3$)

Position	KF-S2			Fragransin A_2*	
	^{1}H	^{13}C	HMBC	^{1}H	^{13}C
1	-	134.6		-	134.2
2	7.05 (1H, *d*, *J* = 2.0 Hz)	109.7	3, 7	6.84-6.95 (1H, *m*)	109.2
3	-	147.4		-	146.5
4	-	146.0		-	145.0
5	6.80 (1H, *d*, *J* = 8.0 Hz)	114.5	1, 4	6.84-6.95 (1H, *m*)	114.1
6	6.85 (1H, *dd*, *J* = 8.0, 2.0 Hz)	119.1	3, 7	6.84-6.95 (1H, *m*)	119.3
7	4.60 (1H, *d*, *J* = 9.0 Hz)	88.1	2, 6, 9	4.63 (1H, *d*, *J* = 9.2 Hz)	87.3
8	1.75 (1H, *m*)	51.1	9, 8′	1.78 (1H, *m*)	44.3
9	1.00 (3H, *d*, *J* = 6.0 Hz)	13.2	1, 7, 8	1.04 (3H, *d*, *J* = 6.0 Hz)	12.9
1′	-	134.6		-	134.2
2′	7.05 (1H, *d*, *J* = 2.0 Hz)	109.7	3′, 7′	6.84-6.95 (1H, *m*)	109.2
3′	-	147.4		-	146.5
4′	-	146.0		-	145.0
5′	6.80 (1H, *d*, *J* = 8.0 Hz)	114.5	1′, 4′	6.84-6.95 (1H, *m*)	114.1
6′	6.85 (1H, *dd*, *J* = 8.0, 2.0 Hz)	119.1	3′, 7′	6.84-6.95 (1H, *m*)	119.3
7′	4.60 (1H, *d*, *J* = 9.0 Hz)	88.1	2′, 6′, 9′	4.63 (1H, *d*, *J* = 9.2 Hz)	87.3
8′	1.75 (1H, *m*)	51.1	8, 9′	1.78 (1H, *m*)	44.3
9′	1.00 (3H, *d*, *J* = 6.0 Hz)	13.2	1′, 7′, 8′	1.04 (3H, *d*, *J* = 6.0 Hz)	12.9
3-OCH_3	3.85 (3H, *s*)	55.4		3.92 (3H, *s*)	55.9
4-OH		-		5.57 (1H, *s*)	-
3′-OCH_3	3.85 (3H, *s*)	55.4		3.92 (3H, *s*)	55.9
4′-OH		-		5.57 (1H, *s*)	-

*Hattori *et al*., 1987

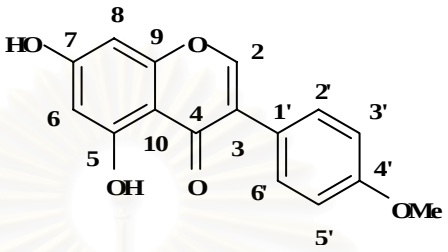
2.3 Identification of Compound KF-S3 [Biochanin A]

Compound KF-S3, which was isolated as yellow amorphous powder, displayed its $[M+H]^+$ peak in the high resolution ESI-TOF mass spectrum (**Figure 119**) at *m/z* 285.0760. Its molecular formula was therefore determined as $C_{16}H_{12}O_5$ (calculated mass: 285.0763). The colour of the compound and the number of carbon atom were suggestive of a flavonoid molecule. IR absorption bands in its IR spectrum (**Figure 118**) at 3388 (hydroxyl), 1651 (conjugated C=O), 1622 (conjugated C=C) and 1567 (C=C aromatic) cm^{-1}, and its UV absorption maxima at 261 nm (**Figure 117**) indicated compound KF-S3 to be an isoflavone containing a chelated hydroxyl group (Markham, 1982). The most downfield proton singlet of a hydrogen-bonded hydroxyl moiety at δ 12.93 (5-OH) in its ^{1}H NMR spectrum (**Figure 120**), and another singlet at δ 8.18 (H-2) which corresponded to the carbon signal at δ 154.5 (C-2) in the ^{13}C NMR spectrum (**Figure 121**), confirmed the presence of the isoflavone nucleus (Dagne and Bekele, 1990).

The ^{1}H NMR spectrum also exhibited another hydroxyl singlet at δ 9.93 (7-OH), a methoxy singlet at δ 3.82, and two *meta*-coupled doublets at δ 6.28 and 6.40 (each 1H, *d*, *J* = 2.0 Hz), assignable to H-6 and H-8 of ring A, respectively. HMBC correlation (**Figures 124a-124b**) between the signals of 5-OH and C-6 (δ 99.8) could be observed. The presence of an AA′BB′ spin system at δ 7.53 (2H, *d*, *J* = 8.5 Hz, H-2′/H-6′) and 6.98 (2H, *d*, *J* = 8.5 Hz, H-3′/H-5′) indicated a simple *para*-substituted B ring. The signal of H-2′/H-6′ exhibited HMBC correlation with C-3 resonance at δ 131.1. The methoxy group could be located at C-4′, according to its NOESY interaction with H-3′/H-5′ (**Figures 125a-125b**). HMBC correlation was also observed between C-4′ signal (δ 160.6) and H-2′/H-6′ signal, confirming the substitution of the methoxy group at the C-4′ position. Compound KF-S3 was thus identified as the isoflavonoid biochanin A (Talukdar *et al.*, 2000).

This isoflavone has previously been isolated from a number of plants belonging to the family Myristicaceae, including from the wood of *Myristica malabarica* (Talukdar *et al.*, 2000), *Virola caducifolia* (Braz *et al*., 1976), and the roots of *V. surinamensis* (Lopes, Kato and Yoshida. 1999). It was also found in the root bark and wood of several *Dalbergia* species (Leguminosae) (Letcher and Shirley 1976; Parthasarathy, Seshadri and Varma 1976; Cook *et al*., 1978; Reddy *et al*., 2008), the stem bark of *Erythrina sacleuxii* of the same plant family (Abiy *et al*.,

1998), and the roots of *Gynerium sagittatum* (Gramineae) (Benavides *et al*., 2007). Biochanin A was active against the growth and differentiation of myeloid leukemia WEHI-3B (JCS) cells (Fung *et al*., 1997) and mammary carcinoma cell line MCF-7 (Hsu *et al*., 1999). The compound, isolated from *Andira inermis* (Leguminosae), was shown to be antiplasmodial (Kraft *et al*., 2000).



Biochanin A

Table 23. Comparison of the ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR data of biochanin A and compound KF-S3 (in acetone-d_6)

Position	KF-S3		Biochanin A*
	^{1}H	^{13}C	^{1}H
2	8.18 (1H, *s*)	154.5	8.20 (1H, *s*)
3	-	131.1	-
4	-	181.5	-
5	-	163.8	-
6	6.28 (1H, *d*, *J* = 2.0 Hz)	99.8	6.32 (1H, *d*, *J* = 2.5 Hz)
7	-	165.1	-
8	6.40 (1H, *d*, *J* = 2.0 Hz)	94.5	6.44 (1H, *d*, *J* = 2.5 Hz)
9	-	159.0	-
10	-	106.0	-
1′	-	124.1	-
2′	7.53 (1H, *d*, *J* = 9.0 Hz)	131.1	7.40 (1H, *d*, *J* = 8.0 Hz)
3′	6.98 (1H, *d*, *J* = 8.5 Hz)	114.5	6.84 (1H, *d*, *J* = 8.0 Hz)
4′	-	160.5	-

Table 23. (continued)

Position	KF-S3		Biochanin A*
	^{1}H	^{13}C	^{1}H
5′	6.98 (1H, *d*, *J* = 8.5 Hz)	114.5	6.84 (1H, *d*, *J* = 8.0 Hz)
6′	7.53 (1H, *d*, *J* = 9.0 Hz)	131.1	7.40 (1H, *d*, *J* = 8.0 Hz)
4′-OMe	3.82 (3H, *s*)	55.5	3.84 (3H, *s*)
5-OH	12.93 (1H, *s*)	-	13.12 (1H, *s*)
7-OH	9.93 (1H, *s*)	-	9.80 (1H, *s*)

*Talukdar *et al*., 2000

2.4 Identification of Compound KF-S4 [Mixture of Anarcardic acid and Ginkgolic acid]

Compound KF-S4 gave UV absorption maxima at 307, 242 and 209 nm (**Figure 126**) which is typical of 6-alkylsalicylic acid (van Beek and Wintermans, 2001). IR absorption bands at 3428 and 1650 cm^{-1} (**Figure 127**) suggested hydroxyl and chelated carboxylic moieties within the structure. Its ESI-TOF mass spectrum exhibited two molecular ion peaks at *m/z* 346 and 348 (**Figure 128**), suggesting that KF-S4 was indeed a mixture of two highly similar components having the molecular formulas $C_{22}H_{34}O_3$ and $C_{22}H_{36}O_3$, respectively.

The ^{1}H NMR spectra of both components (**Figure 129**) showed typical signals of saturated aliphatic chain as a broad methylene singlet at δ 1.25 (H-3′ to H-14′), a triplet of the terminal methyl protons at δ 0.80 (*J* = 7.0 Hz, H-15′), and another triplet (*J* = 8.0 Hz) of the methylene protons next to a quaternary aromatic carbon at δ 2.92. In addition, proton resonances of a 1,2,3-trisubstituted aromatic ring were detected at δ 6.69 (1H, *d*, *J* = 7.4 Hz, H-5), 6.72 (1H, *d*, *J* = 8.0 Hz, H-3) and 7.20 (1H, *t*, *J* = 8.0 Hz, H-4). A set of lower intensity signals were also observed, suggesting that the second component contains unsaturation in its side-chain. These second proton peaks included an olefinic triplet of a *cis*-double bond at δ 5.25 (2H, *t*, *J* = 5.4 Hz, H-8′ and H-9′) and signals of adjacent methylene protons at δ 1.95 (4H, *q*, *J* = 6.4 Hz, H-7′ and H-10′). Analysis of the NMR integration indicated the ratio of the first and second components of KF-S4 to be 1:1.

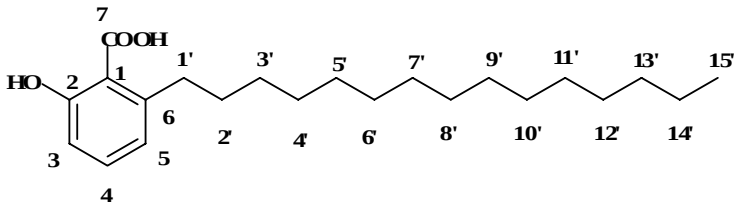
The ^{13}C NMR data (**Figures 130a-130b**) and DEPT experiment, as well as HMQC correlations (**Figure 132**), helped to differentiate the carbon resonances into those of one carboxylic carbon at δ173.1 (C-7), six aromatic carbons at δ 111.8 (C-1), 115.2 (C-3), 122.1 (C-5), 133.9 (C-4), 146.8 (C-6) and 163.1 (C-2), and methylene carbons at δ 29.4-32.1 (C-2′ to C-14′). The second component also exhibited additional signals of two olefinic carbons at δ 129.7 (C-8′ and C-9′) and two methylene carbons adjacent to the double bond at δ 27.1 (C-7′ and C-10′). The HMBC data (**Figures 133a-133c**) showed the correlation peaks from proton signal at δ 2.92 (H-1′) to carbon signals at δ 111.8 (C-1), 122.1 (C-5) and 146.8 (C-6), confirming the alkyl substitution on the benzene ring. These data suggested that both components of KF-S4 were 6-alkyl-2-hydroxybenzoic acid derivatives. Mass spectral and carbon NMR data indicated that the alkyl chain contains 15 carbon atoms. The first component possessing the saturated alkyl chain is anacardic acid, whereas the minor component with one *cis*-double bond at C-8′/C-9′ is ginkgoic acid.

From these data and comparison with literature values (Spencer, Tjarks and Kleiman, 1980; Gonzalez *et al.*, 1996), KF-S4 was identified as a 1:1 mixture of anarcardic acid and ginkgolic acid.

Anarcardic acid is an alkylbenzoic acid which has been reported as a constituent of cashew nut shell (*Anarcardium occidentale*, family Anacardiaceae) (Trevisan *et al*., 2006). It was also found in plants of the genus *Knema* including the stem bark of *K. furfuracea* and *K. tenuinervia* (Pinto and Kijao, 1990). The compound was demonstrated to inhibit the enzymes lipoxygenase (Ha and Kubo, 2005) and DNA polymerase-β (Hecht, 2003). It also displayed antibacterial activity against methicillin-resistant *Staphylococcus aureus* (Kubo, Nihei and Tsujimoto, 2003), *Propionibacterium acnes*, *Streptococcus mutans*, and *Brevibacterium ammoniagenes* (Kubo *et al*., 1993).

From plants in the genus *Knema*, ginkgolic acid has been isolated from the stem bark of *K. austrosiamensis* and *K. laurina* (Gonzalez *et al.*, 1996). The co-occurrence of ginkgolic acid and anarcardic acid in the same plant has previously been reported from the study of the bark of *Ozoroa insignis* (Anacardiaceae). The compound mixture displayed *in vitro* cytotoxic activity against human hepatocellular

carcinoma, mammary adenocarcinoma and primary bladder carcinoma cell lines (Rea *et al*., 2003).



Anarcardic acid

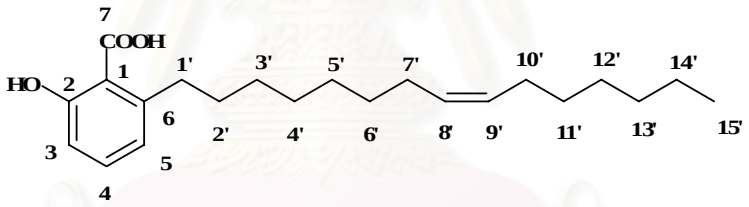
Table 24. Comparison of ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR data of anarcardic acid and the first component of KF-S4 (in acetone-d_6)

Position	KF-S4			Anarcardic acid*	
	^{1}H	^{13}C	HMBC	^{1}H	^{13}C
1	-	111.8		-	110.5
2	-	163.1		-	163.6
3	6.72 (1H, *d*, *J* = 8.0 Hz)	115.2		6.85 (1H, *d*, *J* = 8.4 Hz)	115.8
4	7.20 (1H, *t*, *J* = 8.0 Hz)	133.9	2, 6	7.34 (1H, *t*, *J* = 8.4, 7.6 Hz)	135.3
5	6.69 (1H, *d*, *J* = 7.4 Hz)	122.1	1, 3, 6	6.76 (1H, *d*, *J* = 7.6 Hz)	122.7
6	-	146.8		-	147.8
7	-	175.4		-	175.8
1´	2.92 (2H, *t*, *J* = 7.9 Hz)	36.2	1, 5, 6	2.95 (2H, *t*, *J* = 8.0 Hz)	36.5
2´	1.55 (2H, *m*)	29.4-32.1		1.62 (2H, *m*)	30.2
3´	1.25 (8H, *m*)			1.24 (8H, *m*)	22.7-32.1
4´					
5´					
6´					

Table 24. (continued)

Position	KF-S4			Anarcardic acid*	
	^{1}H	^{13}C	HMBC	^{1}H	^{13}C
7′	1.25 (16H, *m*)	29.4-32.1		1.24 (16H, *m*)	22.7-32.1
8′					
9′					
10′					
11′					
12′					
13′					
14′		22.5			22.7
15′	0.80 (3H, *t*, *J* = 7.0 Hz)	14.1	14′	0.87 (3H, *t*, *J* = 6.4 Hz)	14.1

* van Beek and Wintermans, 2001



Ginkgolic acid

Table 25. Comparison of ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR data of ginkgolic acid and the second component of KF-S4 (in acetone-d_6)

Position	KF-S4		Ginkgolic acid*	
	^{1}H	^{13}C	^{1}H	^{13}C
1	-	111.8	-	110.5
2	-	163.1	-	163.6
3	6.72 (1H, *d*, *J* = 8.0 Hz)	115.2	6.87 (1H, *d*, *J* = 8.4 Hz)	115.8
4	7.20 (1H, *t*, *J* = 8.0 Hz)	133.9	7.34 (1H, *dd*, *J* = 8.4, 7.6 Hz)	135.3
5	6.69 (1H, *d*, *J* = 8.0 Hz)	122.1	6.75 (1H, *d*, *J* = 7.6 Hz)	122.7

Table 25. (continued)

Position	KF-S4		Ginkgolic acid*	
	^{1}H	^{13}C	^{1}H	^{13}C
6	-	146.8	-	147.8
1′	2.92 (2H, *t*, *J* = 7.9 Hz)	36.2	2.98 (2H, *t*, *J* = 7.5 Hz)	36.5
2′	1.55 (2H, *m*)	32.1	1.60 (2H, *m*)	30.2
3′	1.25 (8H, *br s*)	28.8-29.6	1.27 (8H, *m*)	29.0-30.9
4′				
5′				
6′				
7′	1.95 (2H, *quintet*, *J* = 6.4 Hz)	27.1	2.01 (2H, *m*)	27.2
8′	5.25 (2H, *t*, *J* = 5.4 Hz)	129.7	5.35 (2H, *dd*, *J* = 9.0, 5.0 Hz)	129.8
9′				
10′	1.95 (2H, *quintet*, *J* = 6.4 Hz)	27.1	2.01 (2H, *m*)	27.2
11′	1.25 (8H, *br s*)	29.7	1.27 (8H, *m*)	29.7
12′		29.8		29.8
13′		31.8		31.8
14′		22.5		22.7
15′	0.80 (3H, *t*, *J* = 7.0 Hz)	13.8	0.87 (3H, *t*, *J* = 6.4 Hz)	14.1
2-OH	-	-	11.09 (1H, *s*)	-
1-COOH	-	173.1	-	175.8

* Gonzalez *et al*., 1996

2.5 Identification of Compound KF-S5 [Mixture of 2-Hydroxy-6-(12-phenyldodecyl) benzoic acid and 2-Hydroxy-6-(12-phenyldodecen-8′*Z*-yl) benzoic acid]

Compound KF-S5 exhibited UV absorption maxima at 301 and 208 nm (**Figure 135**) and IR absorption bands at 3428 (OH), 1650 (chelated carboxylic), 1604 (C=O) cm^{-1} (**Figure 136**). These UV and IR spectra were similar to those of KF-S4, suggesting that they belong to the same group of compounds. Its ESI-TOF mass spectrum (**Figure 137**) exhibited two quasi-molecular ion peaks ($[M + Na]^+$) of two components at *m/z* 403 and 405, corresponding to the molecular formulas $C_{25}H_{34}O_3$ and $C_{25}H_{32}O_3$, respectively. Calculated degrees of unsaturation of both components (9 and 10, respectively) indicated two aromatic rings within each molecular structure. The difference of 2 mass units suggested the presence of an additional double bond in the compound with lower molecular weight.

The ^1H (**Figure 138a-138b**) and ^{13}C NMR data of KF-S5 (**Figures 139a-139b**) were also similar to those of KF-S4, except more aromatic but less aliphatic proton signals were observed. The ^{13}C NMR spectrum (**Figures 140a-140b**) displayed one carboxylic carbon resonance at δ 175.7 (C-7), eight aromatic methine and four aromatic quaternary carbon peaks. The rest were signals of methylene and olefinic protons of the aliphatic chains. Each component of the mixture should therefore be a phenylalkylbenzoic acid derivative, possessing a molecular structure consisting of two aromatic rings connected through an aliphatic chain.

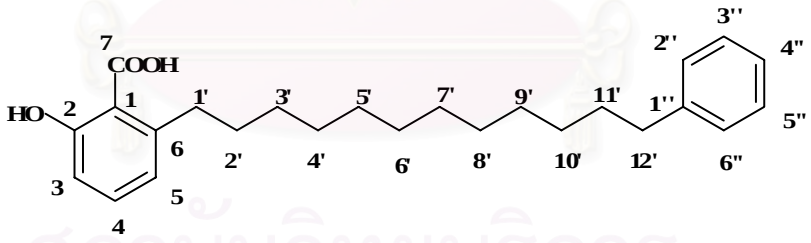
The ^1H NMR spectrum displayed two sets of aromatic proton signals. The first set represented the identical 1,2,3-trisubstituted phenolic rings of both components which resonated at δ 6.82 (2H, *d*, *J* = 7.8 Hz, H-5), 6.92 (2H, *d*, *J* = 7.8 Hz, H-3) and 7.41 (2H, *t*, *J* = 7.8 Hz, H-4). This is the 6-alkyl-2-hydroxybenzoic acid moiety of the structure. The second set, observed at δ 7.22–7.32 (10H, m, H-2″ to H-6″), included complex aromatic signals of unsubstituted aromatic rings at the other end of the aliphatic chains. The major component displayed a triplet signal of methylene protons adjacent to an aromatic ring at δ 3.02 (2H, *t*, *J* = 7.5 Hz, H-1′), which showed COSY correlation to another methylene signal at δ 1.66 (2H, *m*, H-2′). At the other end of the alkyl chain, the H-12′ methylene protons at δ 2.65 displayed long-range HMBC correlations (**Figures 142a-142f**) to δ 143.0 (C-1″), confirming the location of the phenyl group at this end of a 12-carbon chain. The

major component of the mixture KF-S5 was therefore identified as 2-hydroxy-6-(12-phenyldodecyl) benzoic acid (Pinto *et al*., 1990).

In addition to the signals of both aromatic moieties, the ^{1}H and ^{13}C NMR spectra also revealed additional resonances of the minor component. Olefinic protons in the alkyl chain resonated at δ 5.40 (2H, *t*, *J* = 5.4 Hz, H-8′ and H-9′), while their methylene neighbors gave signals at δ 2.05 (4H, *m*, H-7′ and H-10′). These signals corresponded to the carbon resonances at δ 26.8 (C-7′), 27.3 (C-10′), 129.3 (C-8′) and 130.5 (C-9′) in the carbon spectrum. The configuration of the double bond was assigned as *cis* according to its small coupling constant of 5.4 Hz. This minor component of KF-S5 was finally identified as 2-hydroxy-6-(12-phenyldodecen-8′*Z*-yl) benzoic acid (Spencer, Tjarks and Kleiman, 1980).

2-Hydroxy-6-(12-phenyldodecyl) benzoic acid has been isolated from various *Knema* species, including from the stem bark of *K. furfuracea* (Pinto *et al*., 1990), *K. glomerata* (Zeng *et al*., 1994), *K. austrosiamensis* and *K. laurina* (Gonzalez *et al*., 1996).

The co-occurrence of 2-hydroxy-6-(12-phenyldodecyl) benzoic acid and 2-hydroxy-6-(12-phenyldodecen-8′*Z*-yl) benzoic acid in the seed oil of *Knema glauca* has been reported previously (Spencer *et al*., 1980).



2-Hydroxy-6-(12-phenyldodecyl)-benzoic acid

(KF-S5 major component)

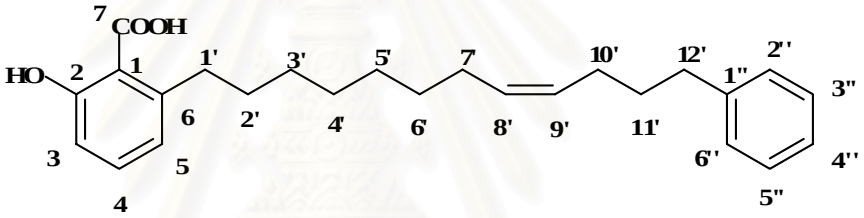
Table 26. Comparison of the ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectral data of 2-hydroxy-6-(12-phenyldodecyl) benzoic acid and the major component of KF-S5 (in acetone-d_6)

Position	KF-S5			2-Hydroxy-6-(12-phenyldodecyl) benzoic acid*	
	^{1}H	^{13}C	HMBC	^{1}H	^{13}C
1	-	110.6		-	110.5
2	-	163.6		-	163.6
3	6.92 (1H, *d*, *J* = 7.8 Hz)	115.9	1, 2, 5	6.87 (1H, *dd*, *J* = 8.0, 1.0 Hz)	115.9
4	7.41 (1H, *t*, *J* = 7.8 Hz)	135.4	2, 6	7.35 (1H, *t*, *J* = 8.0 Hz)	135.4
5	6.82 (1H, *d*, *J* = 7.8 Hz)	122.8	1, 3, 4, 6, 1′	6.77 (1H, *dd*, *J* = 8.0, 1.0 Hz)	122.7
6	-	147.8		-	147.8
7	-	175.7		-	175.6
1′	3.02 (2H, *t*, *J* = 7.5 Hz)	36.5	1, 6	2.97 (2H, *t*, *J* = 7.0 Hz)	36.4
2′	1.66 (2H, *m*)	32.1		1.26-1.59 (20H, *m*)	32.0
3′	1.35 (18H, *m*)	29.7			29.6
4′		29.5-29.7			
5′					
6′					
7′					
8′					
9′					
10′					
11′		31.6			31.5
12′	2.65 (2H, *m*)	36.0	1″, 2″, 6″	2.59 (2H, *t*, *J* = 7.0 Hz)	36.0

Table 26. (continued)

Position	KF-S5			2-Hydroxy-6-(12-phenyldodecyl) benzoic acid*	
	^{1}H	^{13}C	HMBC	^{1}H	^{13}C
1″	-	143.0		-	142.9
2″	7.22 – 7.32 (5H, *m*)	128.2	12′, 4″	7.16 - 7.25 (5H, *m*)	128.2
3″		128.4			128.4
4″		125.5			125.5
5″		128.4			128.4
6″		128.2	12′, 4″		128.2

*Pinto *et al*., 1990



2-Hydroxy-6-(12-phenyldodecen-8′*Z*-yl) benzoic acid

(KG-F5 minor component)

Table 27. The ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectral data of the minor component of KF-S5 (in acetone-d_6)

Position	KF-S5		
	^{1}H	^{13}C	HMBC
1	-	110.6	
2	-	163.6	
3	6.92 (1H, *d*, *J* = 7.8 Hz)	115.9	1, 2, 5
4	7.41 (1H, *t*, *J* = 7.8 Hz)	135.4	2, 6
5	6.82 (1H, *d*, *J* = 7.8 Hz)	122.8	1, 3, 4, 6, 1′
6	-	147.8	

Table 27. (continued)

Position	KF-S5		
	^{1}H	^{13}C	HMBC
7	-	175.7	
1′	3.02 (2H, *t*, *J* = 7.5 Hz)	35.5	1, 6
2′	1.65 (2H, *m*)	32.0	
3′	1.35 (8H, *m*)	29.5-29.7	
4′			
5′			
6′			
7′	2.05 (2H, *m*)	26.8	8′
8′	5.40 (1H, *t*, *J* = 5.4 Hz)	130.5	7′
9′		129.3	10′
10′	2.05 (2H, *m*)	26.8	9′
11′	1.65 (2H, *m*)	31.5	
12′	2.65 (2H, *m*)	36.0	1″, 2″, 6″
1″	-	142.6	
2″	7.22 – 7.32 (5H, *m*)	128.4	12′, 4″
3″		128.3	
4″		125.6	
5″		128.3	
6″		128.4	

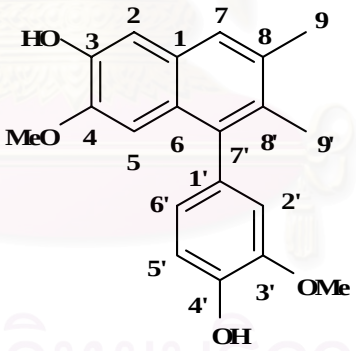
2.6 Structure Elucidation of Compound KF-L1 [Furfuracin]

Compound KF-L1 was obtained as colorless amorphous crystals which exhibited an $[M + H]^+$ ion peak at *m/z* 325.1443 in its high resolution ESI-TOF mass spectrum (**Figure 145**), corresponding to the molecular formula $C_{20}H_{20}O_4$ (calculated mass: 325.1440). Its UV absorption maxima at 236, 287 and 324 nm (**Figure 143**) were indicative of a naphthalene chromophore (Kawazoe, Yutani and Takaishi, 1999). According to its calculated degree of unsaturation, which was eleven, the structure of this compound could be composed of one naphthalene ring and one aromatic ring. The compound also exhibited IR absorption band of hydroxyl moiety at 3481 cm^{-1} (**Figure 144**).

The ^{13}C NMR spectrum (**Figure 147**) and DEPT experiment displayed 20 carbon signals which could be classified into 2 methyl carbon signals at δ 17.5 (C-9′) and 21.0 (C-9), 2 methoxy carbon signals at δ 55.7 (4-OCH_3) and 56.0 (3′-OCH_3), 6 methine (sp^2) carbon signals at δ 106.0 (C-5), 109.7 (C-2), 114.3 (C-2′), 115.8 (C-5′), 123.4 (C-6′) and 126.0 (C-7), and 10 quaternary carbon signals at δ 128.2 (C-1), 129.2 (C-6), 131.3 (C-8′), 133.0 (C-1′), 133.8 (C-8), 138.2 (C-7′), 146.3 (C-4′), 147.0 (C-3), 148.4 (C-3′) and 148.5 (C-4).

Its ^1H NMR spectrum (**Figures 146a-146b**) showed signals of six aromatic protons, two methoxy protons, two methyl protons and two hydroxyl protons. All C-H correlations were revealed by analysis of a HMQC spectrum (**Figure 150**). Three aromatic proton signals at δ 6.66 (1H, *dd*, *J* = 8.0, 2.0 Hz, H-6′), 6.78 (1H, *d*, *J* = 2.0 Hz, H-2′) and 7.00 (1H, *d*, *J* = 8.0 Hz, H-5′) represented a 1,2,4-trisubstituted aromatic ring. The other three aromatic signals at δ 6.70 (1H, *s*, H-5), 7.10 (1H, *s*, H-2) and 7.43 (1H, *s*, H-7) could then be assigned to protons on the naphthalene ring. The HMBC correlation from the signal of H-2′ at δ 6.78 to that of C-7′ (δ 138.2) (**Figures 151a-151b**) established the connectivity of an aryl unit, through C-1′ of the aromatic ring, to the C-7′ position on the naphthalene unit. A methyl singlet which resonated at δ 2.07 (H-9′) displayed long-rang HMBC correlations to C-7′ (δ 138.2) and C-8′ signals (δ 131.3), while another methyl resonance at δ 2.40 (H-9) displayed correlations with the signals of C-7 (δ 126.0), C-8 (δ 133.8) and C-8′ (δ 131.3). These cross-peaks confirmed the positions of both methyl groups at the C-9′ and C-9 positions on the naphthalene moiety, respectively, and the structure of compound KF-L2 could therefore be deduced as an arylnaphthalene lignan.

The methoxy signal at δ 3.84 (3′-OCH_3) gave HMBC correlation with C-3′ signal (δ 148.4) and a NOESY cross-peak (**Figures 152a-152b**) with the signal of H-2′ (δ 6.78), confirming its C-3′ position on the aryl ring. A hydroxyl group could be assigned to the adjacent C-4′ position based on the HMBC cross-peaks between a hydroxyl singlet at δ 7.71 (4′-OH) to both carbon signals of C-3′ and C-4′ (δ 146.3). Another methoxy signal at δ 3.65 (4-OCH_3) showed HMBC cross-peak with the signal of C-4 (δ 148.5), establishing its substitution at this carbon. In addition, it also displayed NOESY cross-peak with H-5 signal (δ 6.70). Its neighboring hydroxyl group (3-OH), which resonated at δ 7.82, showed HMBC correlations with carbon signals at δ 109.7 (C-2), 147.0 (C-3) and 148.5 (C-4). From these data and comparison with those of dehydroguaiaretic acid, an arylnaphthalene lignan previously isolated from the bark of this plant (Pinto *et al*., 1990), compound KF-L1 was found to be different from the known compound in that the substituents at the positions C-3 and C-4 were reversed. Therefore, the structure of KF-L1 was elucidated as 8,8′-dimethyl-3-hydroxy-4-methoxy-7′-(4′-hydroxy-3′-methoxy-phenyl)-naphthalene, and trivially named furfuracin.



Furfuracin

Table 28. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR assignments of furfuracin (in $CDCl_3$)

Position	^{1}H	^{13}C	HMBC
1	-	128.2	
2	7.10 (1H, *s*)	109.7	1, 3, 4
3	-	147.0	
4	-	148.5	
5	6.70 (1H, *s*)	106.0	3, 4, 6, 7′
6	-	129.2	
7	7.43 (1H, *s*)	126.0	1, 2, 6, 8′
8	-	133.8	
9	2.40 (3H, *s*)	21.0	7, 8, 8′
1′	-	133.0	
2′	6.78 (1H, *d*, *J* = 2.0 Hz)	114.3	1′, 3′, 7′
3′	-	148.4	
4′	-	146.3	
5′	7.00 (1H, *d*, *J* = 8.0 Hz)	115.8	3′, 4′
6′	6.66 (1H, *dd*, *J* = 8.0, 2.0 Hz)	123.4	1′, 4′
7′	-	138.2	
8′	-	131.3	
9′	2.07 (3H, *s*)	17.5	7′, 8′
3′-OCH_3	3.84 (3H, *s*)	56.3	3′
4-OCH_3	3.65 (3H, *s*)	55.7	4
4′-OH	7.71 (1H, *s*)	-	3′, 4′
3-OH	7.82 (1H, *s*)	-	2, 3, 4

3. Bioactivity Evaluation of Compounds Isolated from *Knema glauca* var. *glauca* and *Knema furfuracea*

3.1 Bioactive Compounds from *Knema glauca* var. *glauca*

The EtOAc extract of *K. glauca* fruits showed cytotoxic activity against human small cell lung cancer (NCI-H187) cell line at an IC_{50} value of 0.89 µg/ml. The hexane and methanol extracts of its leaves exhibited antimycobacterial activity at a MIC value of 100 µg/ml. The methanol extract of the leaves also showed anti-herpes simplex virus activity with an IC_{50} value of 100 µg/ml.

Chromatographic separation of the EtOAc extract of the fruits gave glaucaic acid, which is a new linear diterpene acid, six acylphenols including myristinins A and D, malabaricone A, 1-(2,4,6-trihydroxyphenyl)-9-phenylnonan-1-one, 1-(2,6-dihydroxyphenyl)-tetradecan-1-one and dodecanoylphloroglucinol, two furofuran lignans, sesamin and asarinin, and the flavan (±)-7,4′-dihydroxy-3′-methoxyflavan. All of these compounds, except myristinins A and D, were evaluated for their biological activities and the results are summarized in **Tables 29** and **30**.

3.1.1 Cytotoxic Activity

1-(2,6-Dihydroxyphenyl)-tetradecan-1-one was the most active isolated compound against oral human epidermoid carcinoma (KB) cell line**.** It was moderately active against the cancer cell line, with an IC_{50} value of 9.15 µg/ml, while dodecanoylphloroglucinol and (±)-7,4′-dihydroxy-3′-methoxyflavan were weakly active and asarinin was inactive (IC_{50} values of 13.20, 16.24 and 33.95 µg/ml, respectively). Both 1-(2,6-dihydroxyphenyl)-tetradecan-1-one (IC_{50} = 9.85 µg/ml) and 1-(2,4,6-trihydroxy-phenyl)-9-phenylnonan-1-one (IC_{50} = 5.60 µg/ml) were moderately cytotoxic to human small cell lung cancer (NCI-H187) cell line, whereas malabaricone A (IC_{50} = 18.05 µg/ml) and (±)-7,4′-dihydroxy-3′-methoxyflavan (IC_{50} = 25.30 µg/ml) were weakly active and inactive against the cell line, respectively. These results confirmed the preliminary screening data on the EtOAc extract of the fruits (IC_{50} = 0.89 µg/ml), although its higher activity indicated that there might be other active constituents in the extract which have not been isolated in this study.

3.1.2 Antimalarial Activity

Although 5 isolated compounds from *K. glauca* were tested for this activity, only one constituent, the acylresorcinol derivative malabaricone A, was found to be

active with an IC_{50} value of 2.78 nM, compared with dihydroartemisinin which has IC_{50} value of 4.10 nM.

Comparison between the antimalarial activity of malabaricone A and 1-(2,4,6-trihydroxyphenyl)-9-phenylnonan-1-one suggested that the 4-OH substitution led to the loss of this activity since malabaricone A, which was active, has no hydroxyl group at this position.

3.1.3 Antimycobacterial Activity

Three out of five tested compounds, including 1-(2,4,6-trihydroxyphenyl)-9-phenylnonan-1-one, dodecanoylphloroglucinol and malabaricone A, were active against the tuberculosis pathogen *Mycobacterium tuberculosis* with MIC values of 100.0, 50.0 and 25.0 µg/ml, respectively. The presence or absence of the 4-OH substitution appears to have similar effect on this activity as well as the antimalarial activity.

3.1.4 Anti HSV-1 Activity

Although initial screening test had demonstrated the methanol extract of *K. glauca* leaves to be somewhat active, the compound which was most active against the herpes simplex virus type 1 (IC_{50} = 3.05 µg/ml) was the acylphloroglucinol derivative dodecanoylphloroglucinol, isolated from its fruits. Two other acylphenols, malabaricone A and 1-(2,4,6-trihydroxyphenyl)-9-phenylnonan-1-one, were weakly and moderately active, respectively. It should therefore be noted that the presence of a phenyl group at the end of the acyl chain appeared to reduce this activity, and the absence of the 4-OH substitution on the phenolic ring further reduced the antiviral activity.

3.1.5 Anti-AGEs Formation Activity

Three acylphenols i.e. 1-(2,4,6-trihydroxyphenyl)-9-phenylnonan-1-one, dodecanoylphloroglucinol and malabaricone A were tested for their activity against advanced glycation end-products formation. All three compounds were active with IC_{50} values of 83.9, 45.5 and 25.7 µM, respectively. The presence or absence of the phenyl moiety at the end of the acyl chain and the 4-OH substitution appeared to have the opposite effect on this activity, when compared to their anti HSV-1 ability.

Table 29. Cytotoxicity of isolated compounds from *Knema glauca* var. *glauca*

Compound	Cytotoxicity IC_{50} (µg/ml)				
	NCI-H187	BC	KB	MCF-7	Vero cell
1-(2,6-Dihydroxyphenyl)-tetradecan-1-one (KG-F1)	9.85	ND	9.15	25.20	ND
Asarinin (KG-F2)	Inactive	ND	33.95	Inactive	ND
Sesamin (KG-F3)	Inactive	ND	ND	Inactive	ND
Glaucaic acid (KG-F4)	Inactive	ND	Inactive	Inactive	>50
Malabaricone A (KG-F6)	18.10	Inactive	Inactive	ND	7.53
Dodecanoylphloroglucinol (KG-F7)	5.60	9.04	13.20	ND	11.68
1-(2,4,6-Trihydroxy-phenyl)-9-phenylnonan-1-one (KG-F8)	Inactive	8.23	Inactive	ND	18.70
(±)-7,4´-Dihydroxy-3´-methoxyflavan (KG-S1)	24.30	ND	16.20	Inactive	>50
Ellipticine	0.44	-	0.37	-	0.65
Doxorubicin	0.04	0.82	0.05	0.82	-

Table 30. Anti-HSV-1, anti TB and antimalarial activities of isolated compounds from *Knema glauca* var. *glauca*

Compound	Anti HSV-1 IC_{50} (µg/ml)	Anti TB MIC (µg/ml)	Antimalarial IC_{50} (nM)	Anti-AGE (µM)
Glaucaic acid (KG-F4)	Inactive	Inactive	Inactive	ND
Malabaricone A (KG-F6)	Weakly active	25.00	2.78	25.70
Dodecanoylphlorocinol (KG-F7)	3.05	50.00	Inactive	45.50
1-(2,4,6-Trihydroxy-phenyl)-9-phenylnonan-1-one (KG-F8)	Moderately active	100.00	Inactive	83.90

Table 30. (continued)

Compound	Anti HSV-1 IC_{50} (µg/ml)	Anti TB MIC (µg/ml)	Antimalarial IC_{50} (nM)	Anti-AGE (µM)
(±)-7,4´-Dihydroxy-3´-methoxy-flavan (KG-S1)	Inactive	Inactive	Inactive	ND
Rifampicin	-	0.02	-	-
Kanamycin	-	1.25	-	-
Isoniazid	-	0.05	-	-
Acyclovir	1.84	-	-	-
Dihydroartemisinin	-	-	4.10	-
Quercetin	-	-	-	11.51

3.2 Bioactive Compounds from *Knema furfuracea*

The EtOAc extracts of *K. furfuracea* leaves and stems and the hexane extract of its stems displayed antimycobacterial activity against *Mycobacterium tuberculosis* at MIC values of 100, 25 and 50 µg/ml, respectively. The hexane extracts of the leaves and stems, the EtOAc extracts of the leaves and stems and the methanol extracts of the leaves and stems exhibited antiviral activity against herpes simplex virus type 1 (HSV-1) at IC_{50} values of 23.4, 5.1, 1.9, 2.4, 1.2 and 35.3 µg/ml, respectively. The EtOAc extracts of the leaves and stems were weakly (IC_{50} = 16.39 µg/ml) and moderately cytotoxic (IC_{50} = 8.69 µg/ml), respectively, against oral human epidermoid carcinoma (KB) cell line.

3.2.1 Cytotoxic activity

The lignans (+)-*trans*-1,2-dihydrodehydroguaiaretic acid and fragransin A_2 isolated from the stems and the new lignan furfuracin from the leaves were weakly cytotoxic against KB cell line with IC_{50} values of 17.75, 16.26 and 21.5 µg/ml, respectively. Although none of the crude extracts was active against NCI-H187 cell line in the preliminary test, three isolated constituents of *K. furfuracea*, including (+)-*trans*-1,2-dihydrodehydroguaiaretic acid and furfuracin from the leaves and biochanin A from the stem, were weakly active with IC_{50} values of 23.2, 19.09 and

32.36 µg/ml, respectively. None of the tested compounds was active against MCF-7 cell line. The isolated lignans and isoflavan were tested for their cytotoxicity against Vero cells (representing normal cell line). The most cytotoxic compound to Vero cells was biochanin A (IC_{50} = 8.66 µg/ml). (+)-*trans*-1,2-Dihydrodehydroguaiaretic acid and furfuracin were only weakly cytotoxic to normal cells, with IC_{50} values of 34.6 and 30.6 µg/ml, respectively.

3.2.2 Antimalarial activity

All crude extracts, as well as the compounds isolated from *K. furfuracea*, were inactive against the microbe *Plasmodium falciparum*.

3.2.3 Antituberculosis activity

In this study, no antituberculosis activity was detected from compounds tested although the EtOAc extract of the leaves and stems and the hexane extract of the stems were shown to be active, suggesting that the active compound(s) have not been isolated.

3.2.4 Anti HSV-1 activity

Contrary to the results obtained with the crude extracts, none of the isolated compounds was shown to possess antiviral activity against herpes simplex virus type 1. The plant might be used for its antiviral activity in the form of its crude extracts, especially the methanol extract of its leaves.

Table 31. Bioactivities of isolated compounds from *Knema furfuracea*

Compound	Cytotoxicity IC_{50} (µg/ml)				Anti HSV-1 IC_{50} (µg/ml)	Anti TB MIC (µg/ml)	Anti-malarial IC_{50} (nM)
	NCI-H187	KB	MCF-7	Vero cell			
(+)-*trans*-1,2-Dihydrodehydroguaiaretic acid (KF-S1)	23.20	17.80	Inactive	34.60	Inactive	Inactive	Inactive
Fragransin A_2 (KF-S2)	Inactive	16.26	Inactive	>50	Inactive	Inactive	Inactive

Table 31. (continued)

Compound	Cytotoxicity IC_{50} (µg/ml)				Anti HSV-1 IC_{50} (µg/ml)	Anti TB MIC (µg/ml)	Anti-malarial IC_{50} (nM)
	NCI-H187	KB	MCF-7	Vero cell			
Biochanin A (KF-S3)	19.09	ND	ND	8.66	Inactive	Inactive	ND
Furfuracin (KF-L1)	32.40	21.50	Inactive	30.60	Inactive	Inactive	Inactive
Rifampicin	-	-	-	-	-	0.02	-
Kanamycin	-	-	-	-	-	1.25	-
Isoniazid	-	-	-	-	-	0.05	-
Ellipticine	0.44	0.37	-	0.65	-	-	-
Doxorubicin	0.04	0.05	0.82	-	-	-	-
Acyclovir	-	-	-	-	1.84	-	-
Dihydro-artemisinin	-	-	-	-	-	-	4.10

CHAPTER V

CONCLUSION

Phytochemical investigation of two *Knema* species of the family Myristicaceae yielded eighteen compounds: ten compounds were isolated from the fruits, leaves and stems of *Knema glauca* and eight compounds from the leaves and stems of *K. furfuracea*. Ten constituents of *K. glauca* isolated in this study include glaucaic acid, a new diterpene acid found in the EtOAc extract of its fruits, which is the first linear diterpenoid from this plant family. Other chemical constituents of the fruits of this plant are myristinin D, which is a flavan-phenylacylphloroglucinol; a phenylacylresorcinol, malabaricone A; an acylresorcinol, 1-(2,6-dihydroxyphenyl)-tetradecan-1-one; a phenylacylphloroglucinol, 1-(2,4,6-trihydroxyphenyl)-9-phenyl-nonan-1-one; an acylphloroglucinol, dodecanoylphloroglucinol**;** and two furofuran lignans, sesamin and asarinin. Myristinin A, which is a flavan-acylphloroglucinol, was isolated from the EtOAc extract of its leaves, whereas the flavan (±)-7,4′-dihydroxy-3′-methoxyflavan was obtained from the EtOAc extract of its stems.

Similar study on the constituents of the leaves and stems of *K. furfuracea* afforded a new arylnaphthalene lignan named furfuracin from the hexane extract of its stems, together with two other lignans: (±)-*trans*-1,2-dihydrodehydroguaiaretic acid and fragransin A_2, a 2:1 mixture of 2-hydroxy-6-(12-phenyldodecyl)-benzoic acid and 2-hydroxy-6-(12-phenyldodecen-8′*Z*-yl) benzoic acid, and a 1:1 mixture of anacardic acid and gingkolic acid.

Malabaricone A, sesamin, fragransin A_2 and biochanin A were reported herein for the first time from *Knema* species, whereas the isolation of (+)-*trans*-1,2-dihydrodehydroguaiaretic acid and anarcardic acid from *K. furfuracea* supported the result from previous investigation of this plant.

These chemical constituents from both plants were assayed for a number of biological activities including cytotoxicity to cancer cell lines, anti-mycobacterial, antimalarial, anti-herpes simplex virus type 1 and anti-AGEs formation. Among the isolated compounds, the most cytotoxic against human small cell lung cancer (NCI-H187) cell line was dodecanoylphloroglucinol (IC_{50} = 5.6 μg/ml), while furfuracin, biochanin A, (+)-*trans*-1,2-dihydrodehydroguaiaretic acid, (±)-7,4′-dihydroxy-3′-methoxyflavan, 2,6-dihydroxyphenyl-tetradecan-1-one and malabaricone A were less

active, with IC_{50} values in the range of 9.85-32.36 µg/ml. Both phloroglucinol derivatives, dodecanoylphloroglucinol and 1-(2,4,6-trihydroxyphenyl)-9-phenyl-nonan-1-one, were active against breast cancer (BC) cell line with IC_{50} values of 9.04 and 8.23 µg/ml, respectively. Five constituents were moderately or weakly active against human oral carcinoma (KB) cell line, with 2,6-dihydroxyphenyltetradecan-1-one as the most active compound (IC_{50} = 9.15 µg/ml). Other less active compounds against this cell line were dodecanoylphloroglucinol (IC_{50} = 13.20 µg/ml), (±)-7,4´-dihydroxy-3´-methoxyflavan (IC_{50} = 16.24 µg/ml), fragransin A_2 (IC_{50} = 16.26 µg/ml) and (+)-*trans*-1,2-dihydrodehydroguaiaretic acid (IC_{50} = 17.75 µg/ml).

Malabaricone A was the only compound that showed antimalarial activity (IC_{50} = 2.78 nM) and was even more active than the positive control, dihydroartemisinin (IC_{50} = 4.10 nM). The phenylacylresorcinol was weakly active against herpes simplex virus type 1, while 1-(2,4,6-trihydroxyphenyl)-9-phenylnonan-1-one was moderately active and dodecanoylphloroglucinol was the most active constituent, with an IC_{50} value of 3.05 µg/ml. All three compounds were active against *Mycobacterium tuberculosis* with MIC values of 25.0, 100.0 and 50.0 µg/ml, respectively.

The results of this research demonstrate the therapeutic values of *Knema* species native to Thailand and a number of their chemical constituents, especially malabaricone A and dodecanoylphloroglucinol, should be further developed as antimalarial and antiviral agents, respectively.

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APPENDIX

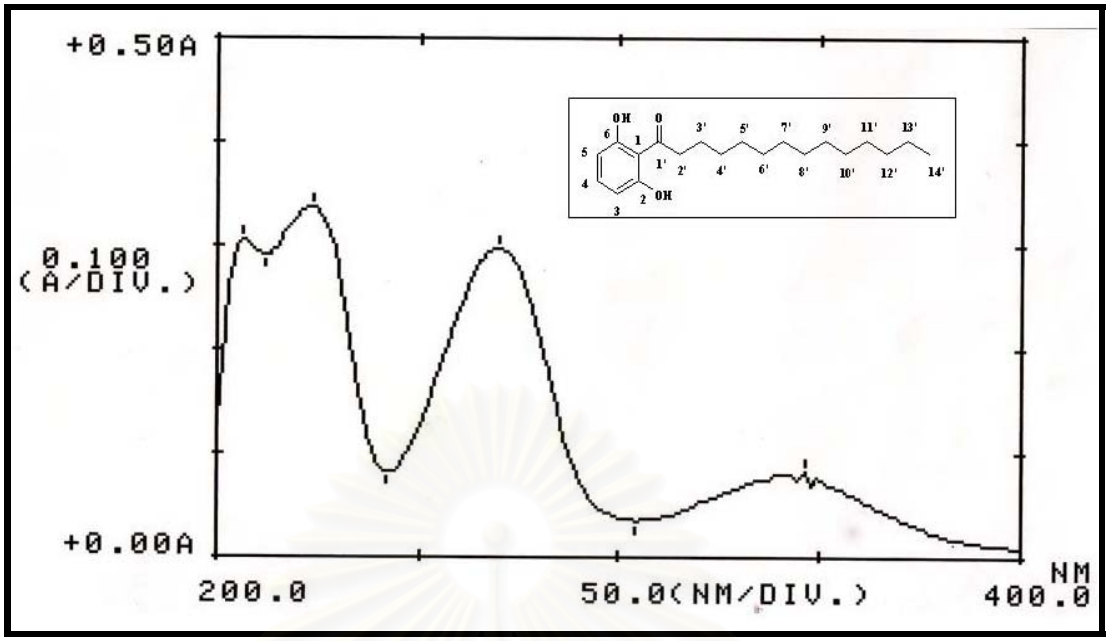

Figure 8. UV Spectrum of compound KG-F1 (in MeOH)

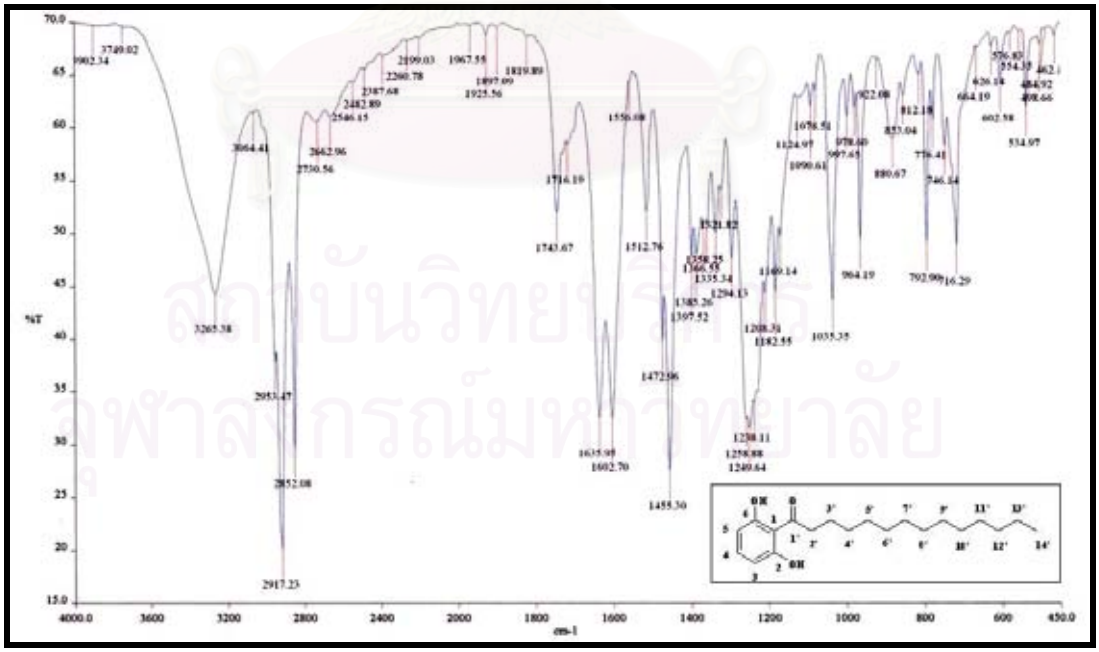

Figure 9. IR Spectrum of compound KG-F1 (KBr disc)

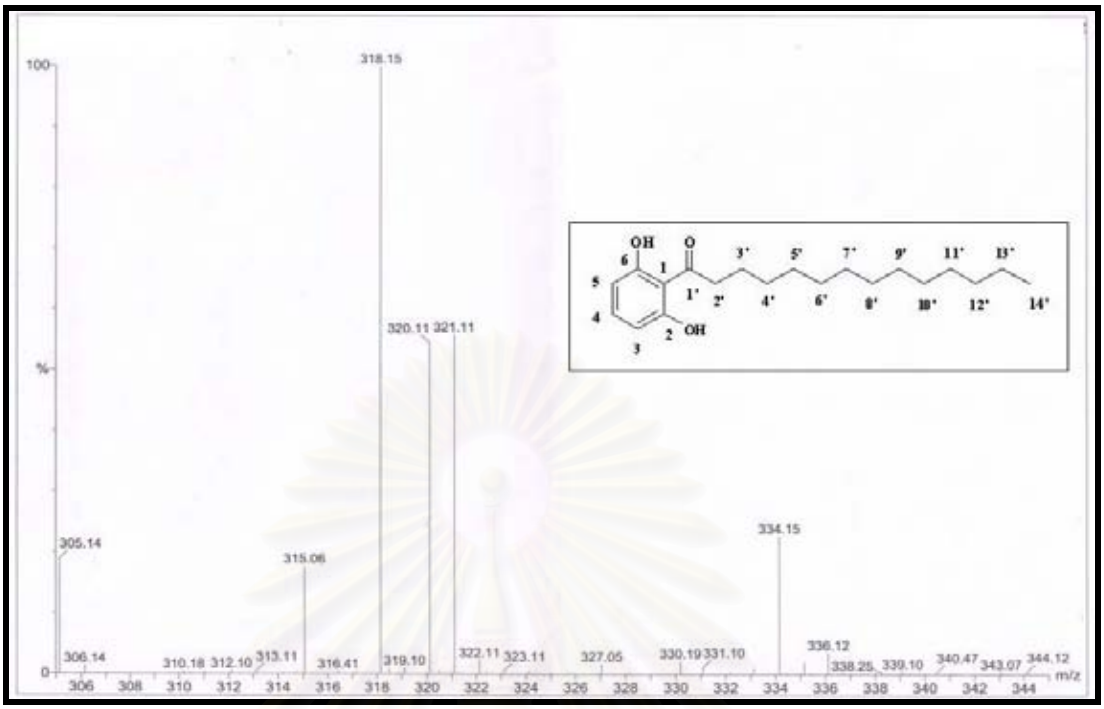

Figure 10. ESI-TOF Mass spectrum of compound KG-F1

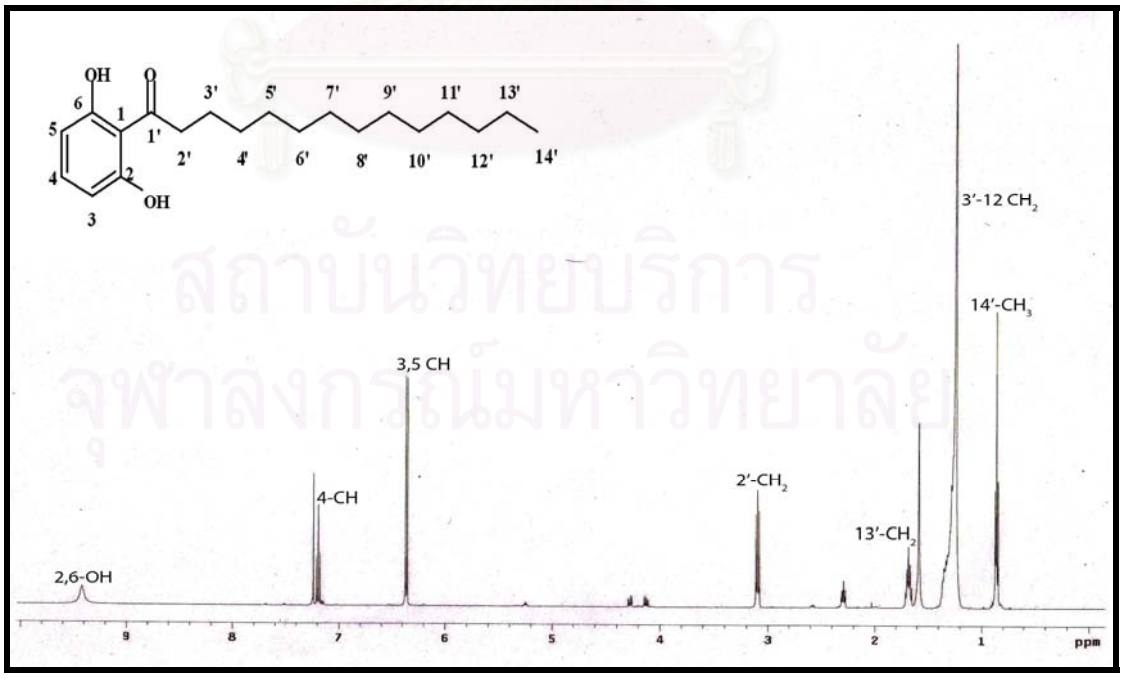

Figure 11. ^{1}H NMR (500 MHz) Spectrum of compound KG-F1 (in acetone-d_6)

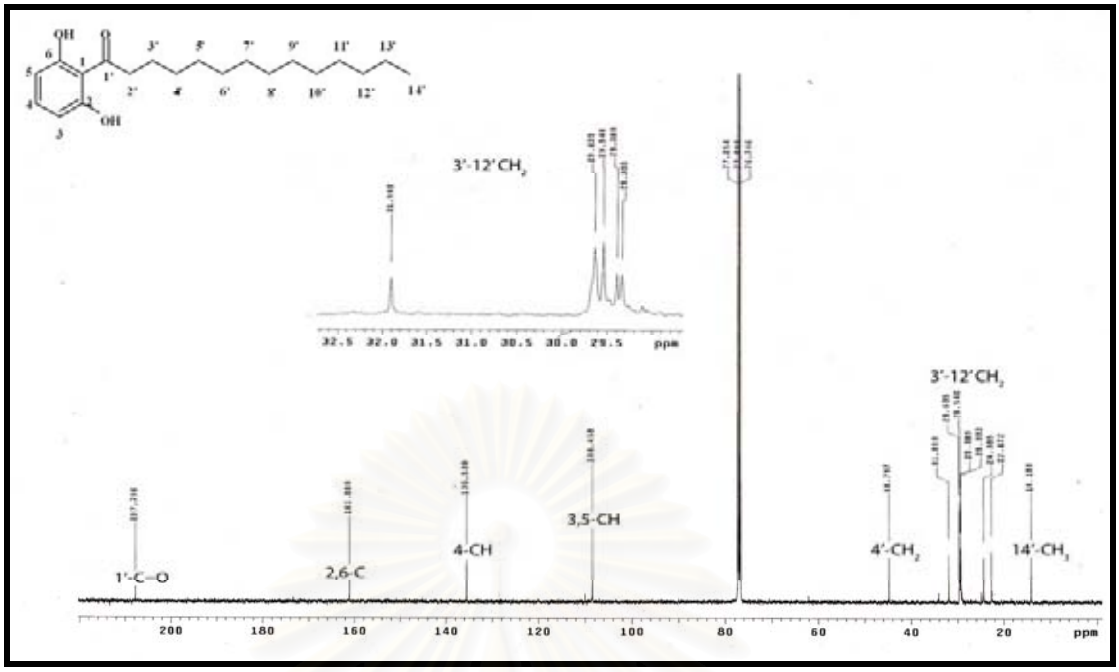

Figure 12. ^{13}C NMR (125 MHz) Spectrum of compound KG-F1 (in acetone-d_6)

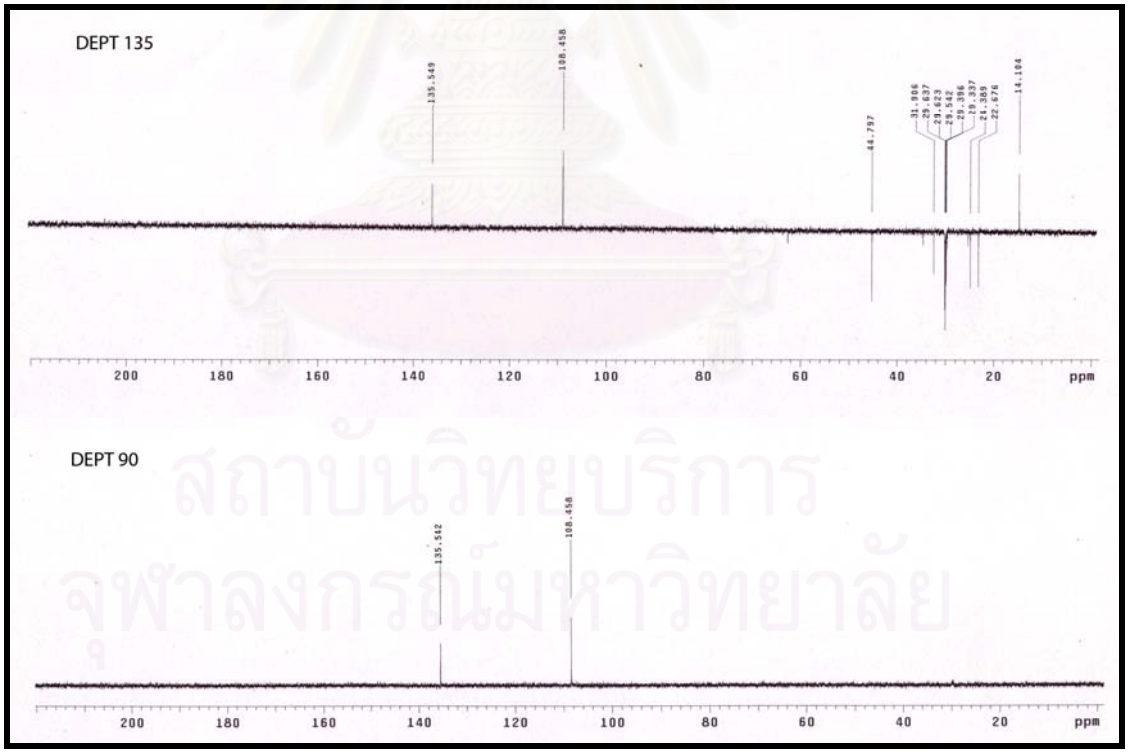

Figure 13. DEPT 90 and DEPT 135 of compound KG-F1

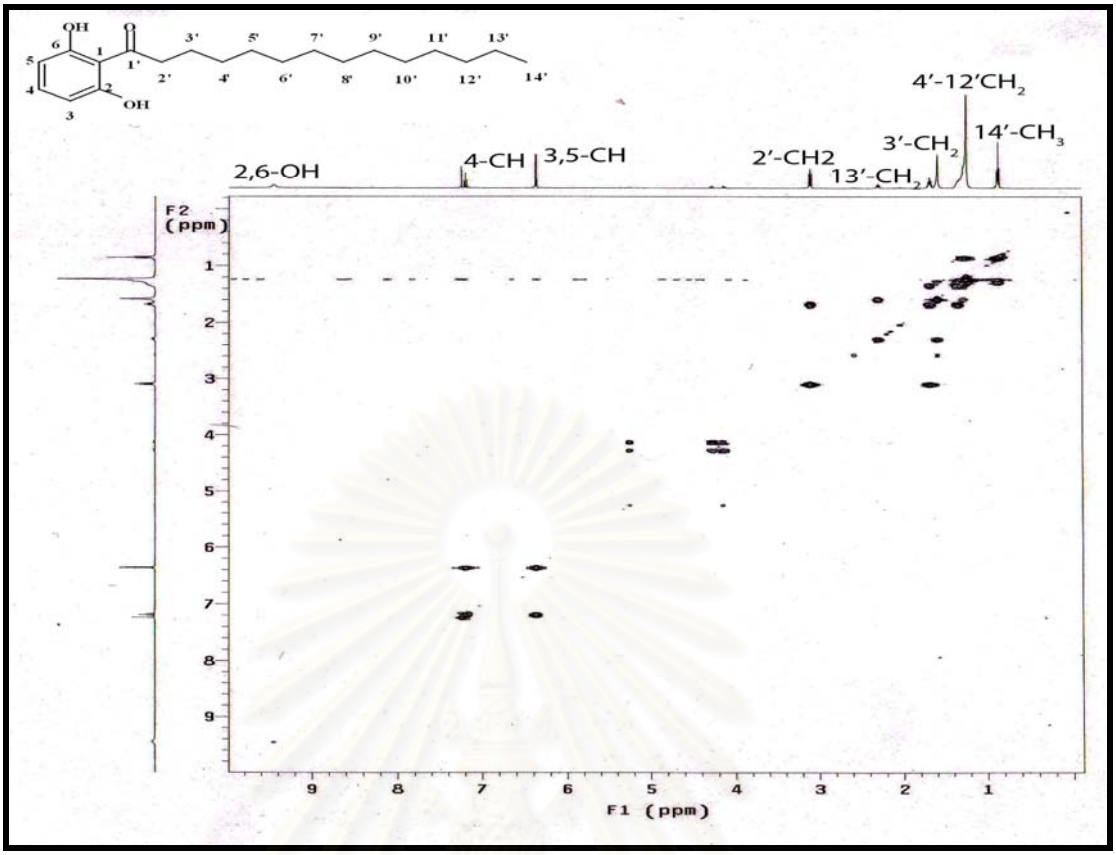

Figure 14. ^{1}H-^{1}H COSY Spectrum of compound KG-F1 (in acetone-d_6)

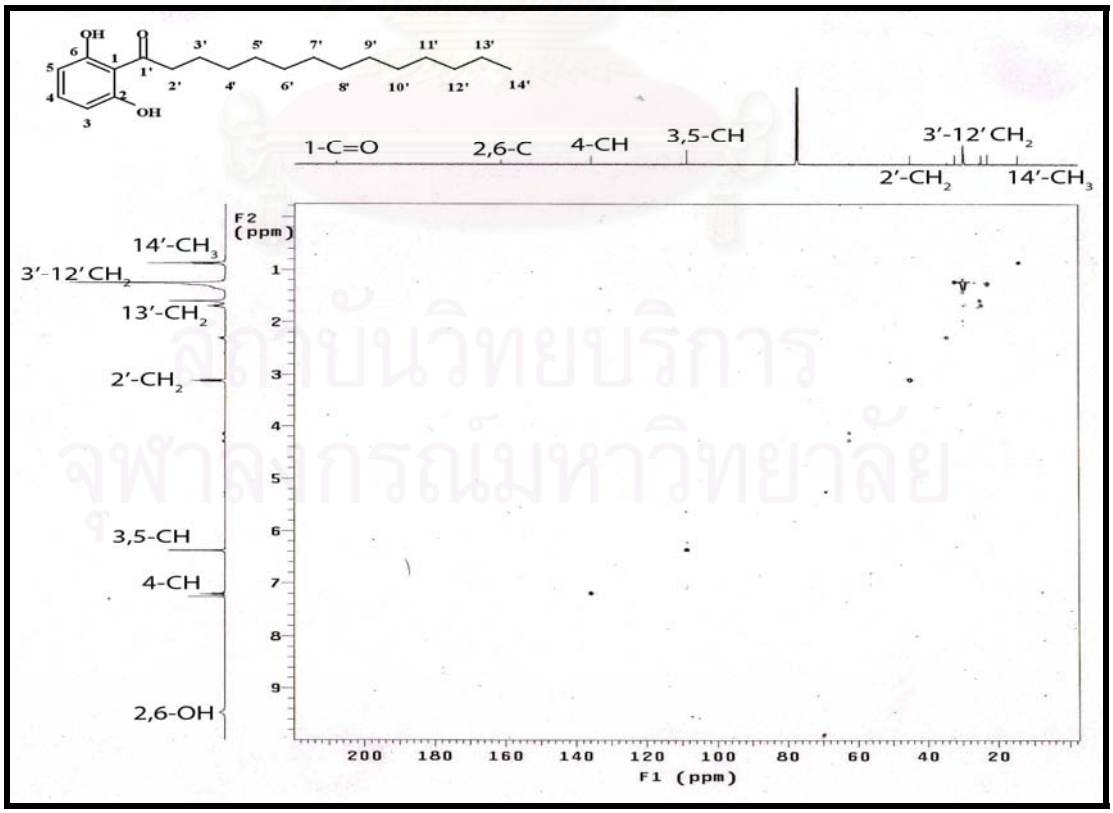

Figure 15a. HMQC Spectrum of compound KG-F1

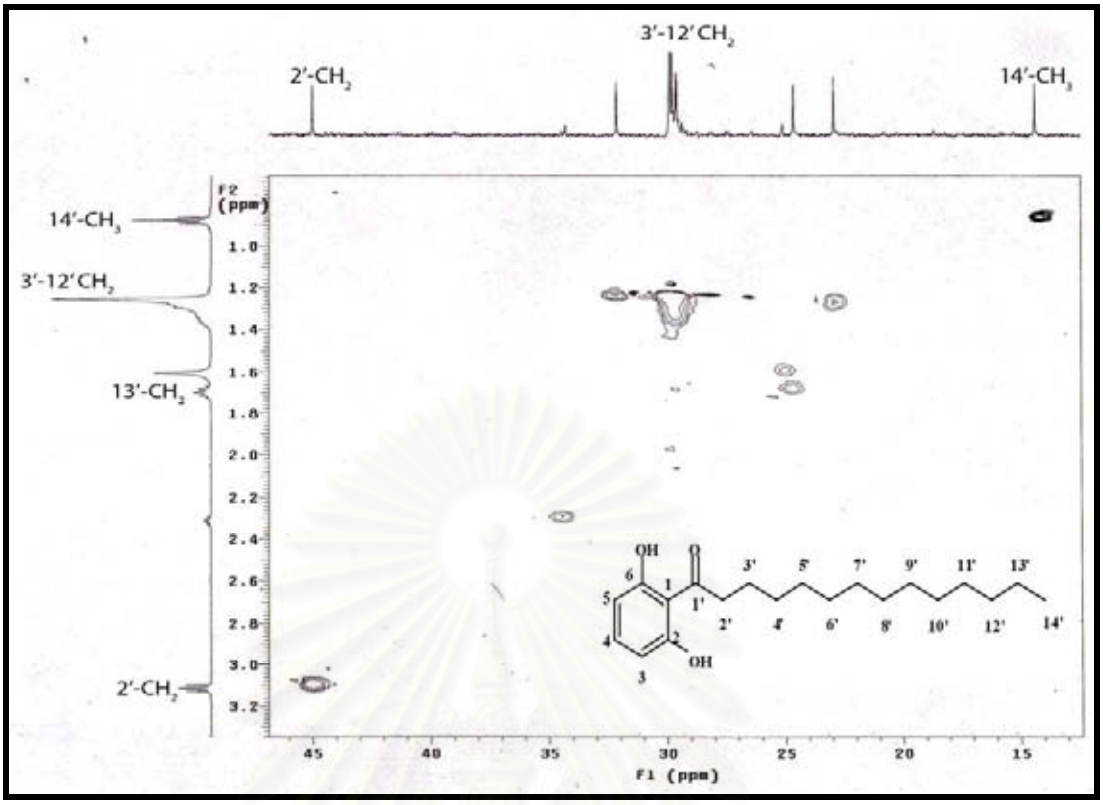

Figure 15b . HMQC Spectrum of compound KG-F1
(expansion between δ_H 0.8-3.2 ppm, δ_C 15.0-45 ppm)

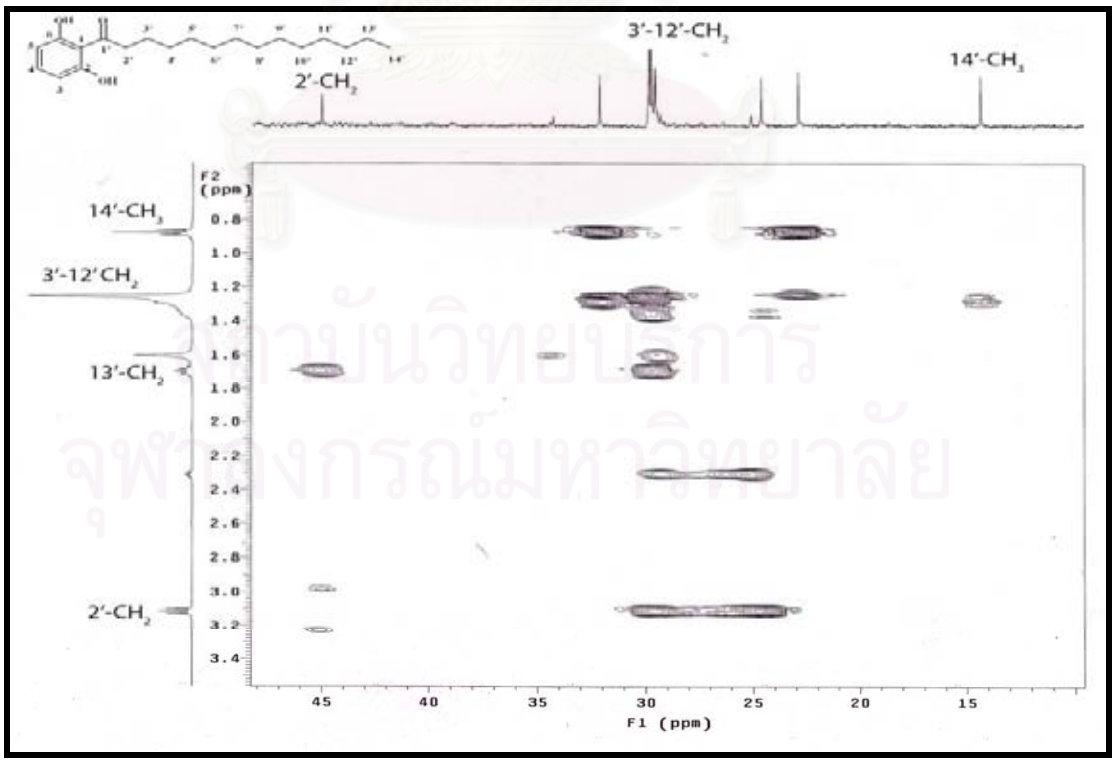

Figure 16a. HMBC Spectrum of compound KG-F1
(expansion between δ_H 0.8-3.4 ppm, δ_C 15.0-45.0 ppm)

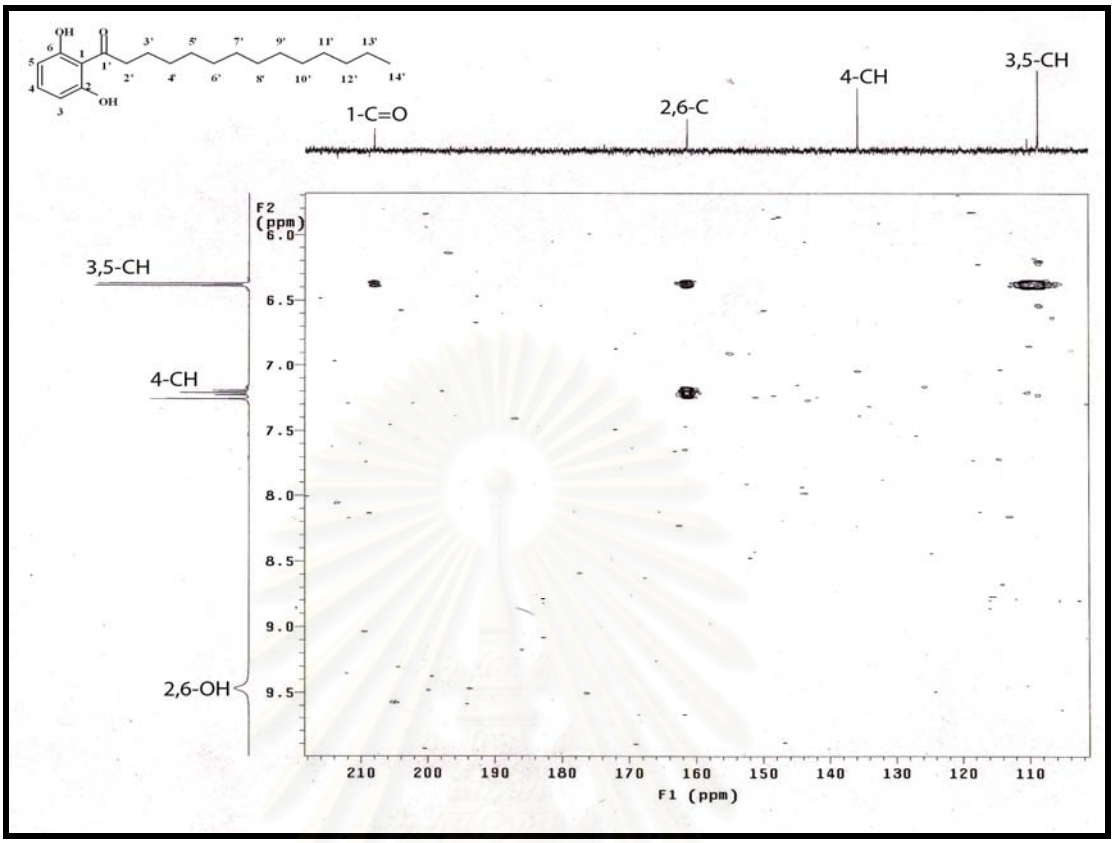

Figure 16b. HMBC Spectrum of compound KG-F1
(expansion between δ_H 6.0-9.5 ppm, δ_C 110.0-210.0 ppm)

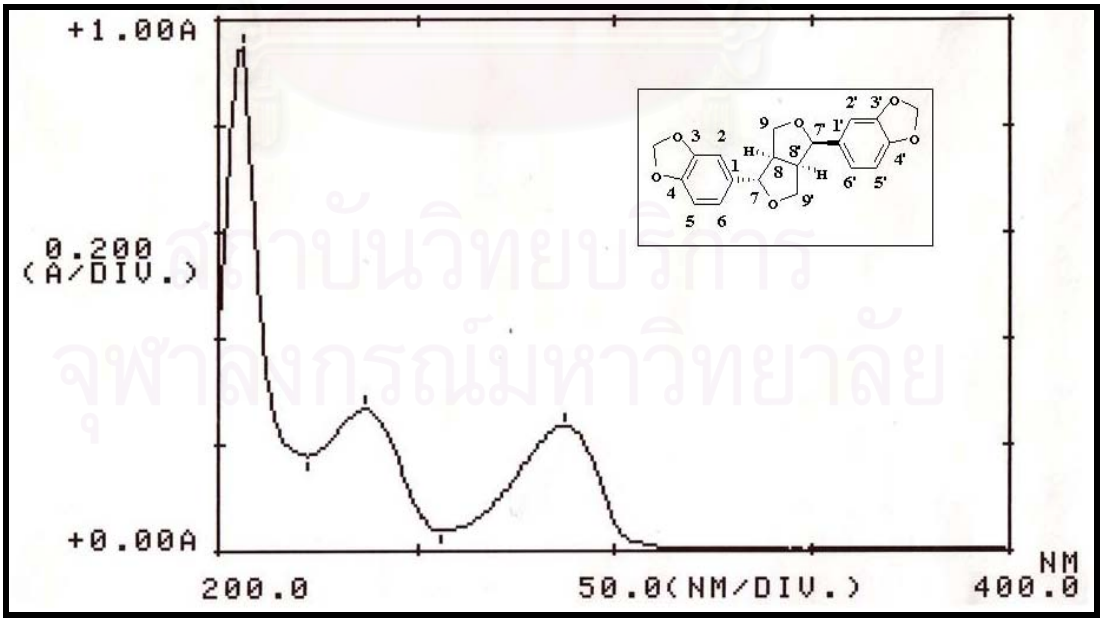

Figure 17. UV Spectrum of compound KG-F2 (in MeOH)

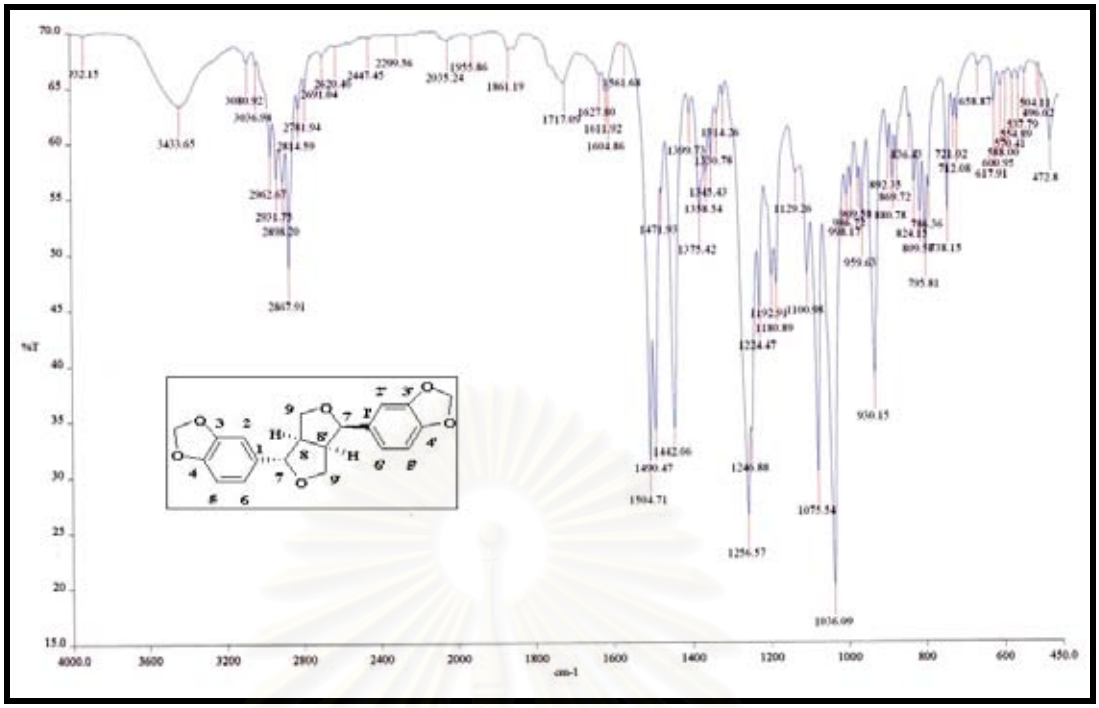

Figure 18. IR Spectrum of compound KG-F2 (KBr disc)

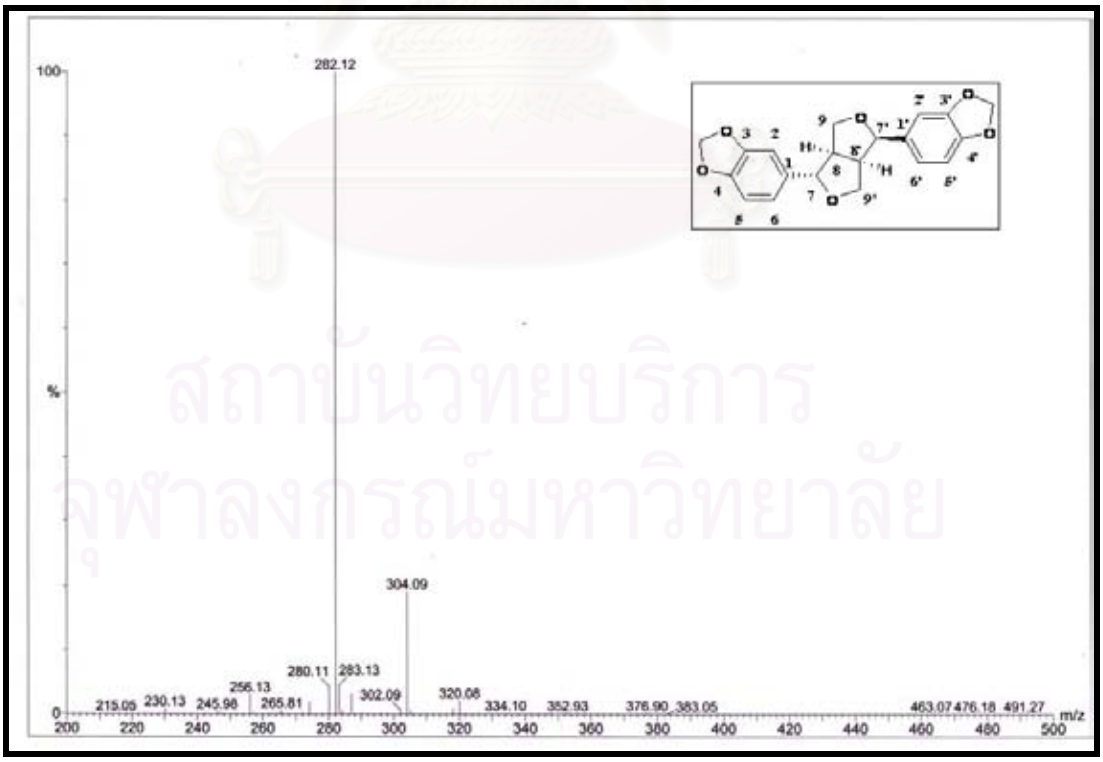

Figure 19. ESI-TOF Mass spectrum of compound KG-F2

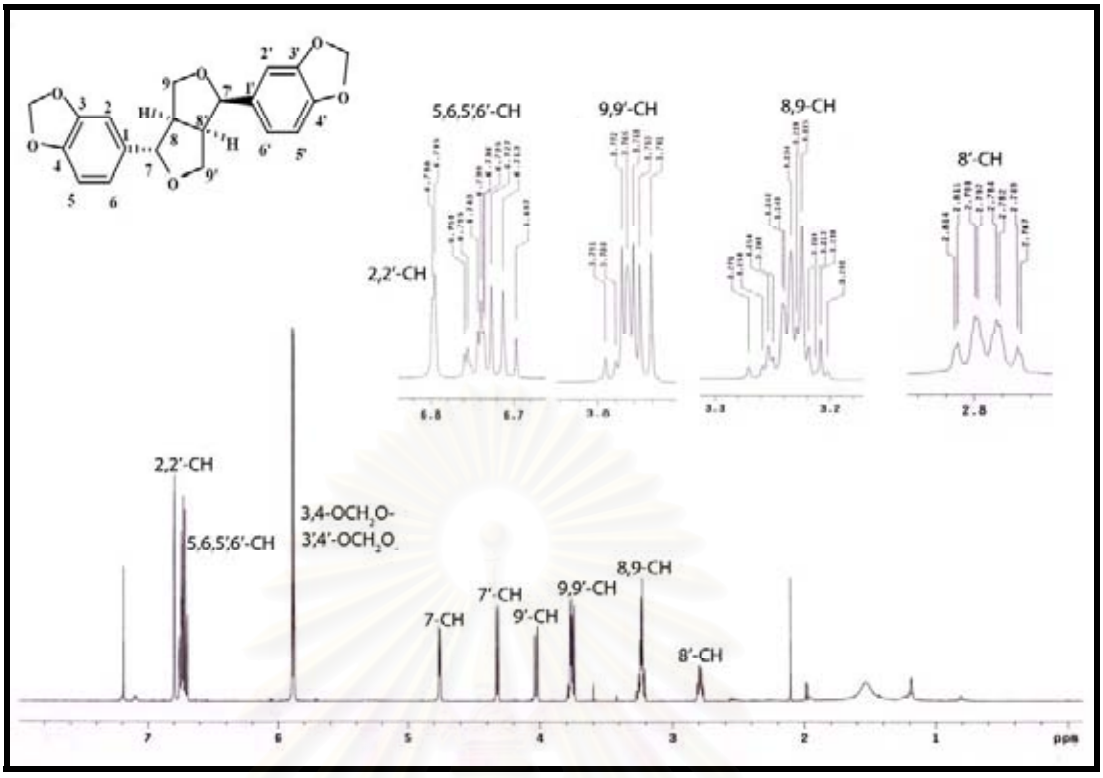

Figure 20. ^{1}H NMR (500 MHz) Spectrum of compound KG-F2 (in $CDCl_3$)

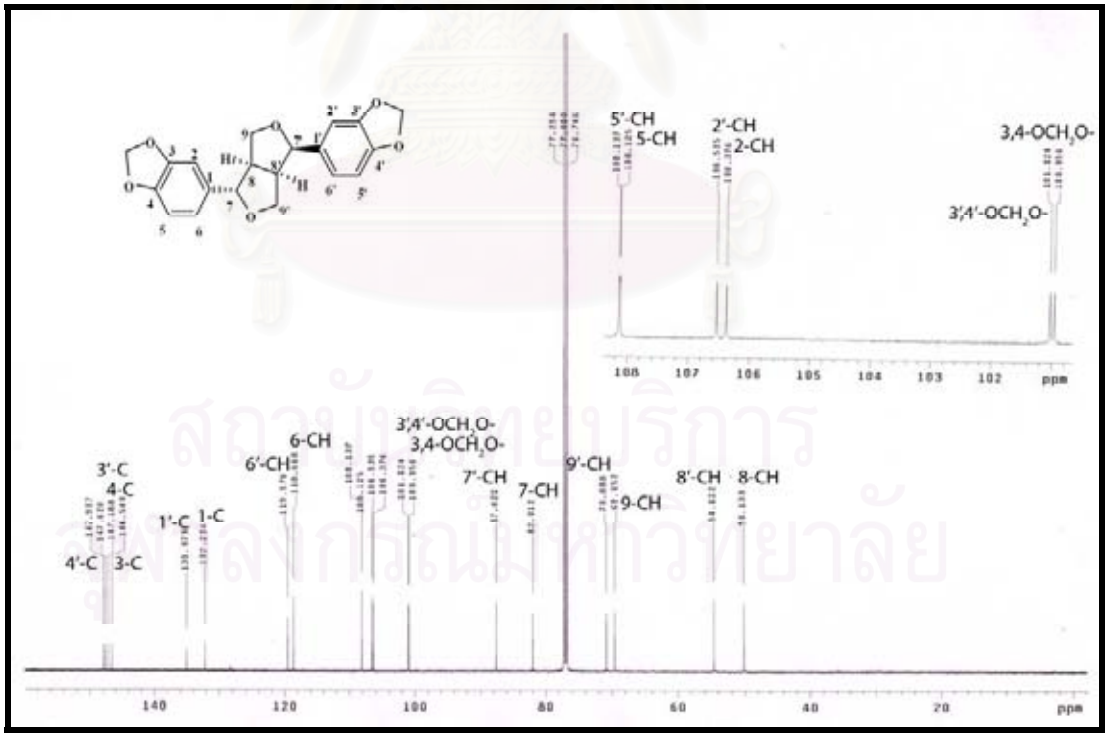

Figure 21. ^{13}C NMR (125 MHz) Spectrum of compound KG-F2 (in $CDCl_3$)

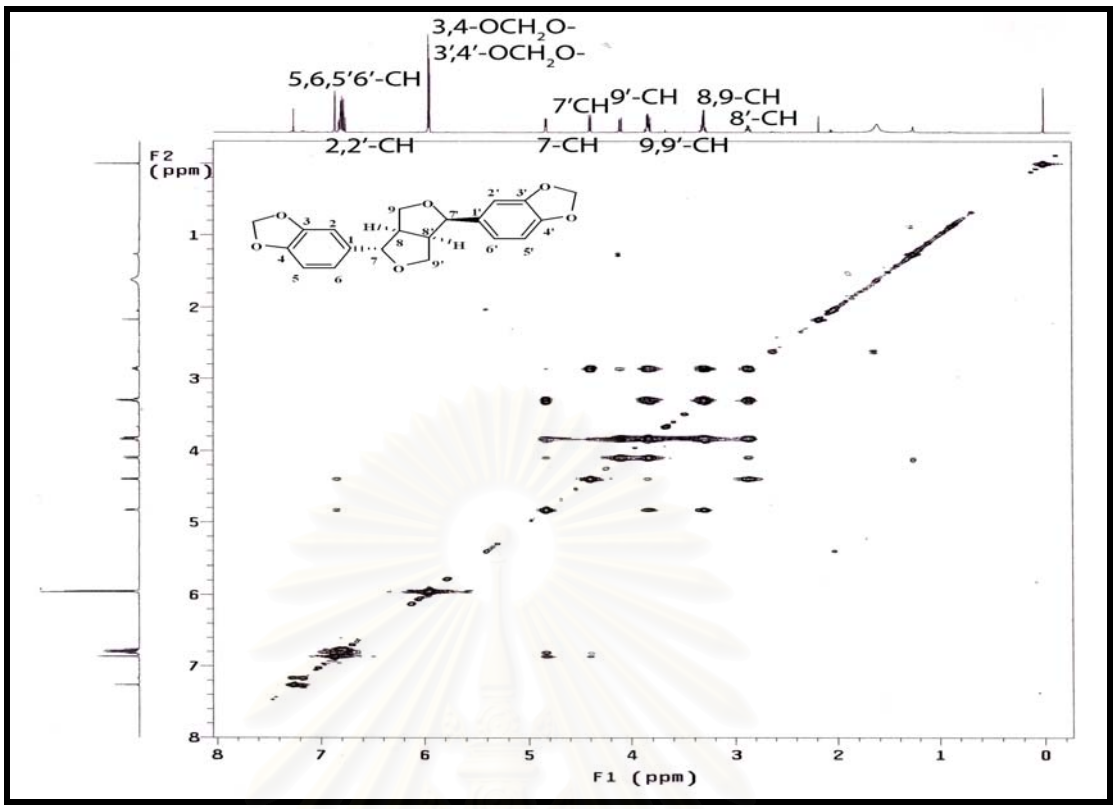

Figure 22a. ^{1}H-^{1}H COSY Spectrum of compound KG-F2 (in $CDCl_3$)

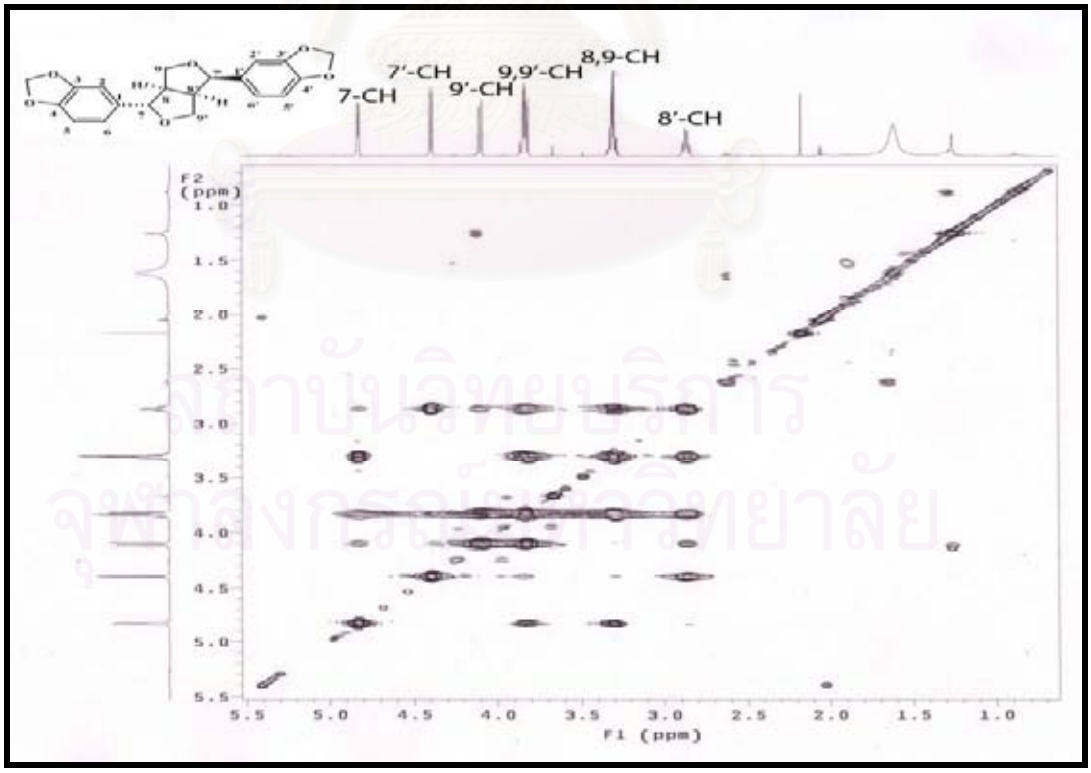

Figure 22b. ^{1}H-^{1}H COSY Spectrum of compound KG-F2 (in $CDCl_3$)
(expansion between δ_H 1.0-5.5 ppm)

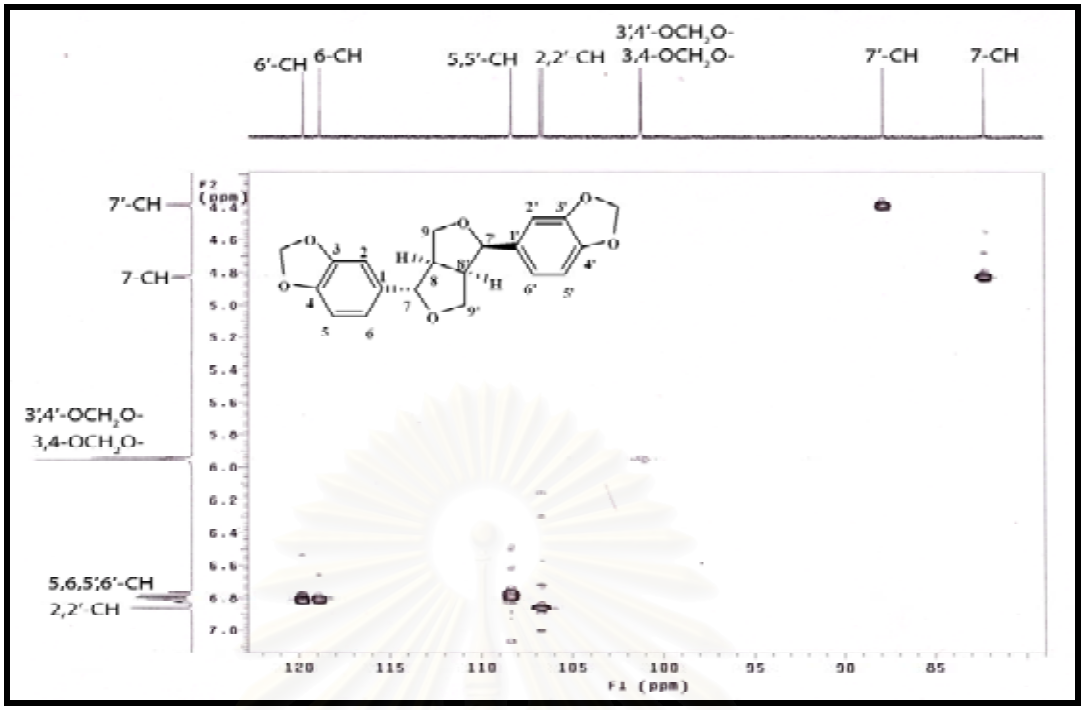

Figure 23a. HMQC Spectrum of compound KG-F2
(expansion between δ_H 4.4-7.0 ppm, δ_C 85.0-120.0 ppm)

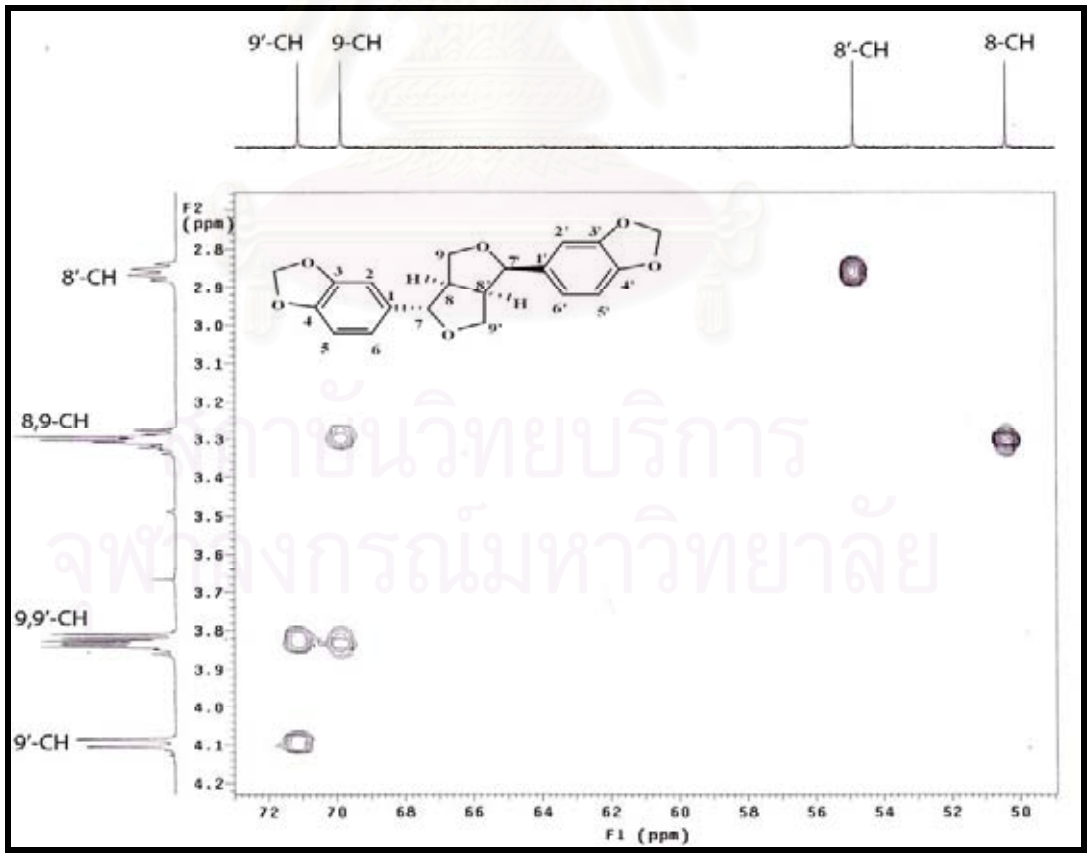

Figure 23b. HMQC Spectrum of compound KG-F2
(expansion between δ_H 2.8-4.2 ppm, δ_C 50.0-72.0 ppm)

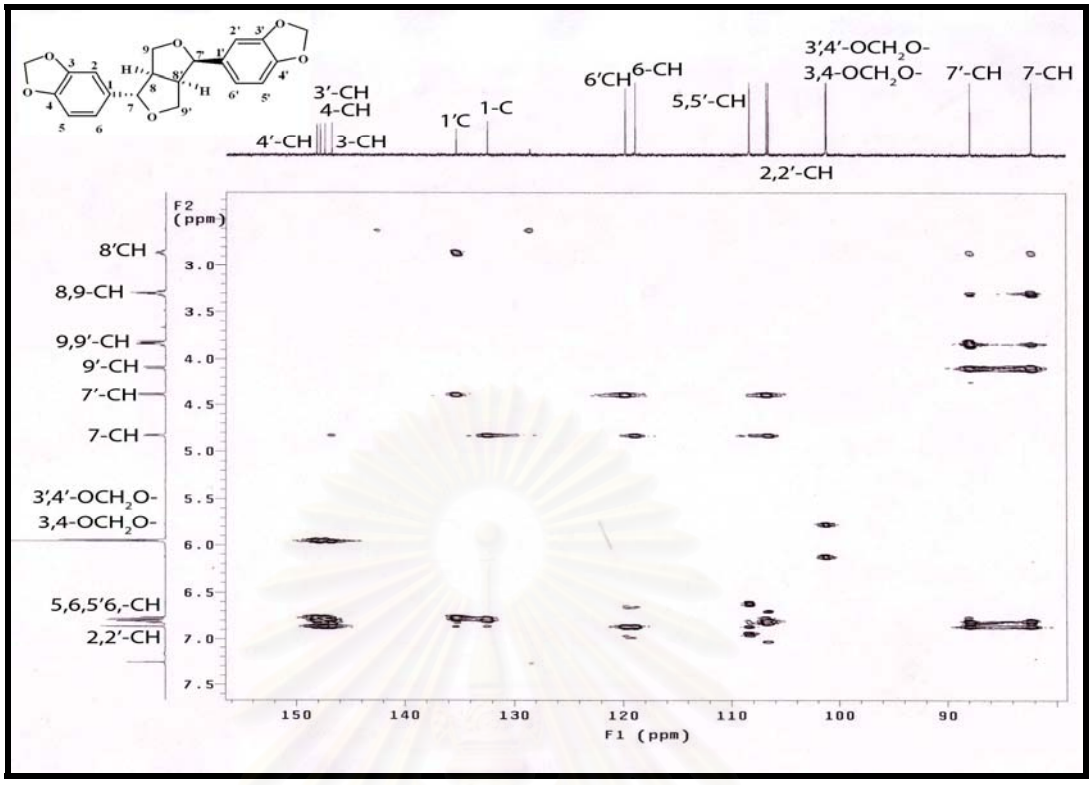

Figure 24a. HMBC Spectrum of compound KG-F2
(expansion between δ_H 3.0-7.5 ppm, δ_C 90.0-150.0 ppm)

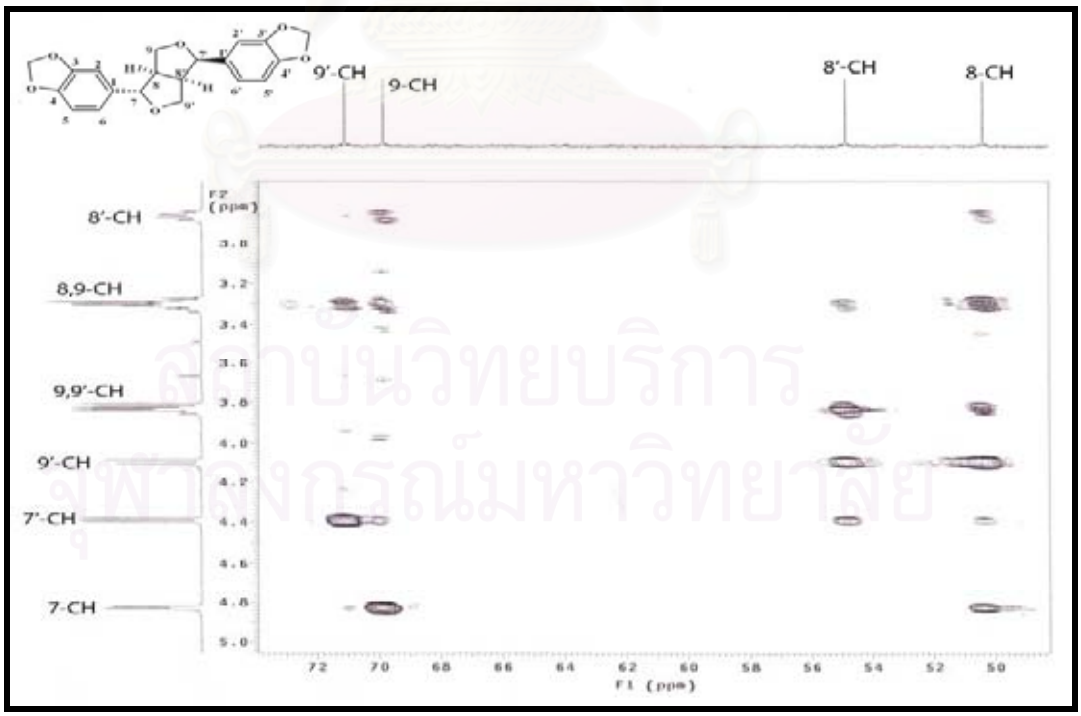

Figure 24b. HMBC Spectrum of compound KG-F2
(expansion between δ_H 3.0-5.0 ppm, δ_C 50.0-72.0 ppm)

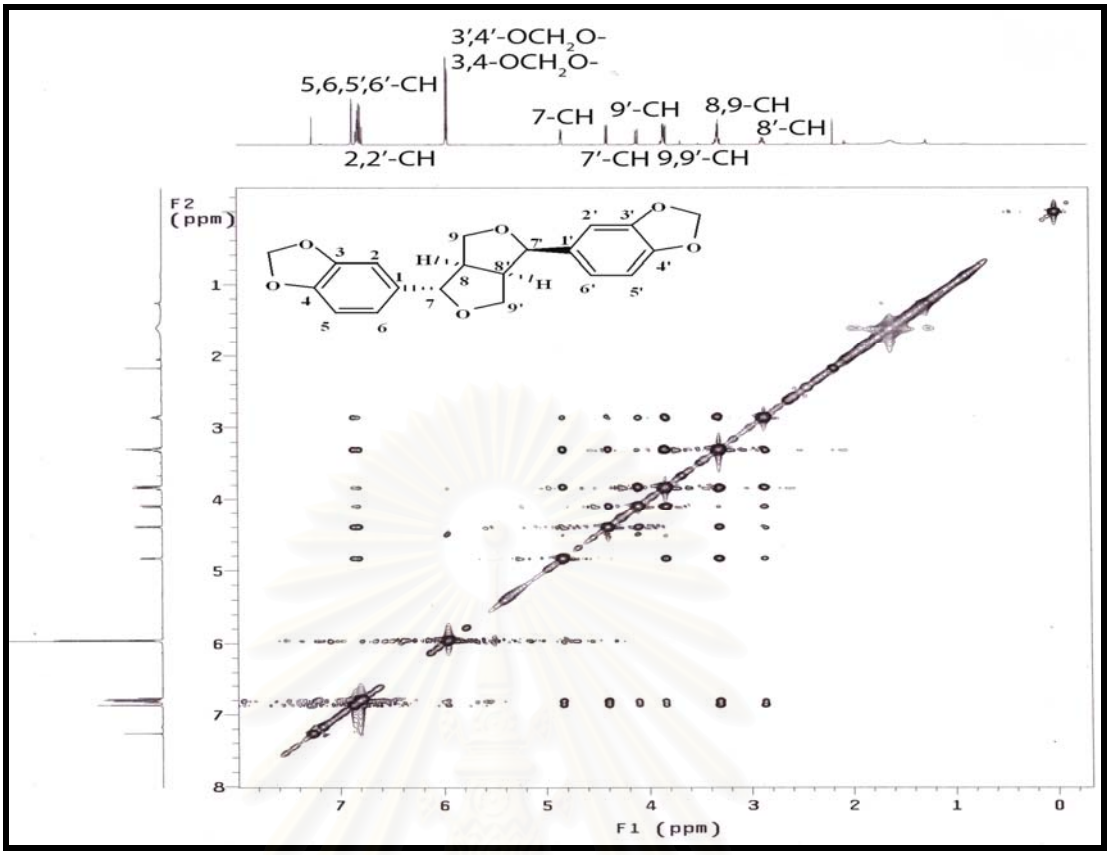

Figure 25a. NOESY Spectrum of compound KG-F2

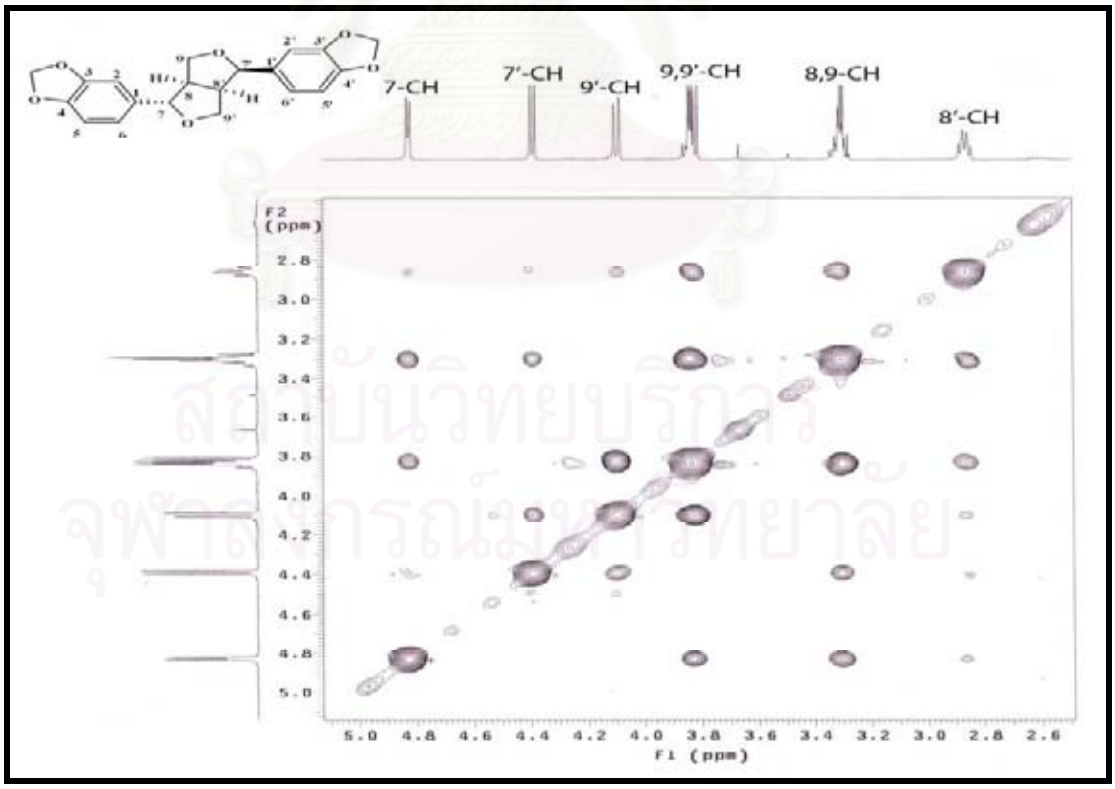

Figure 25b. NOESY Spectrum of compound KG-F2

(expansion between δ_H 2.6-5.0 ppm)

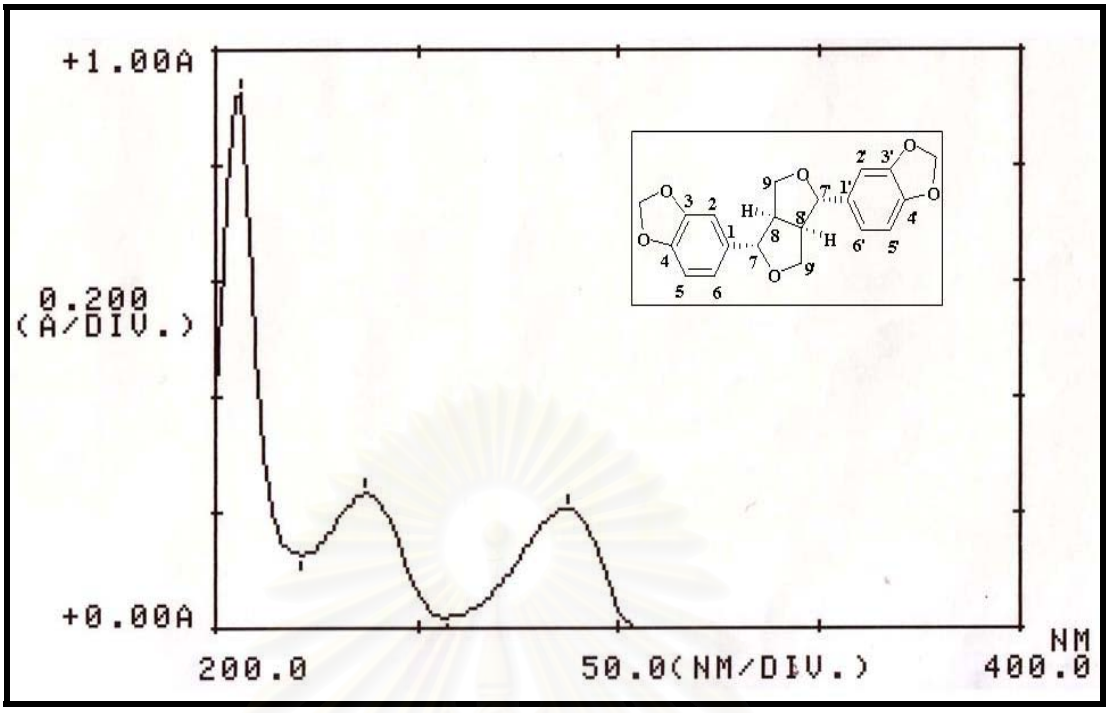

Figure 26. UV Spectrum of compound KG-F3 (in MeOH)

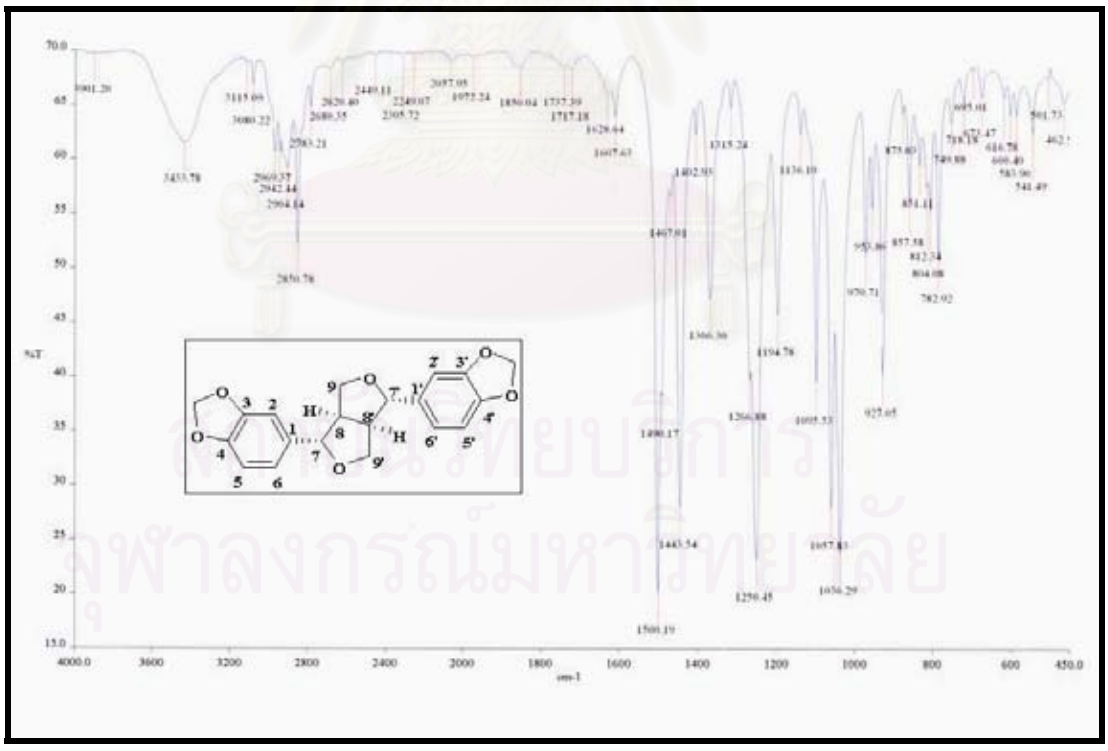

Figure 27. IR Spectrum of compound KG-F3 (KBr disc)

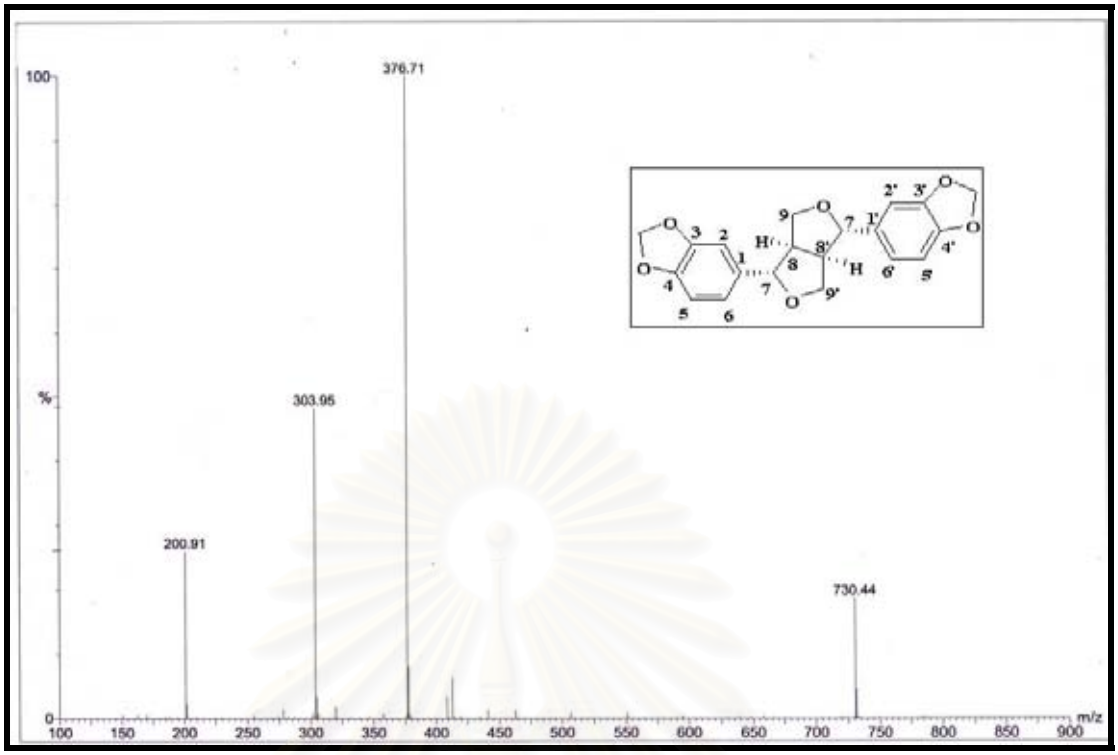

Figure 28. ESI-TOF Mass spectrum of compound KG-F3

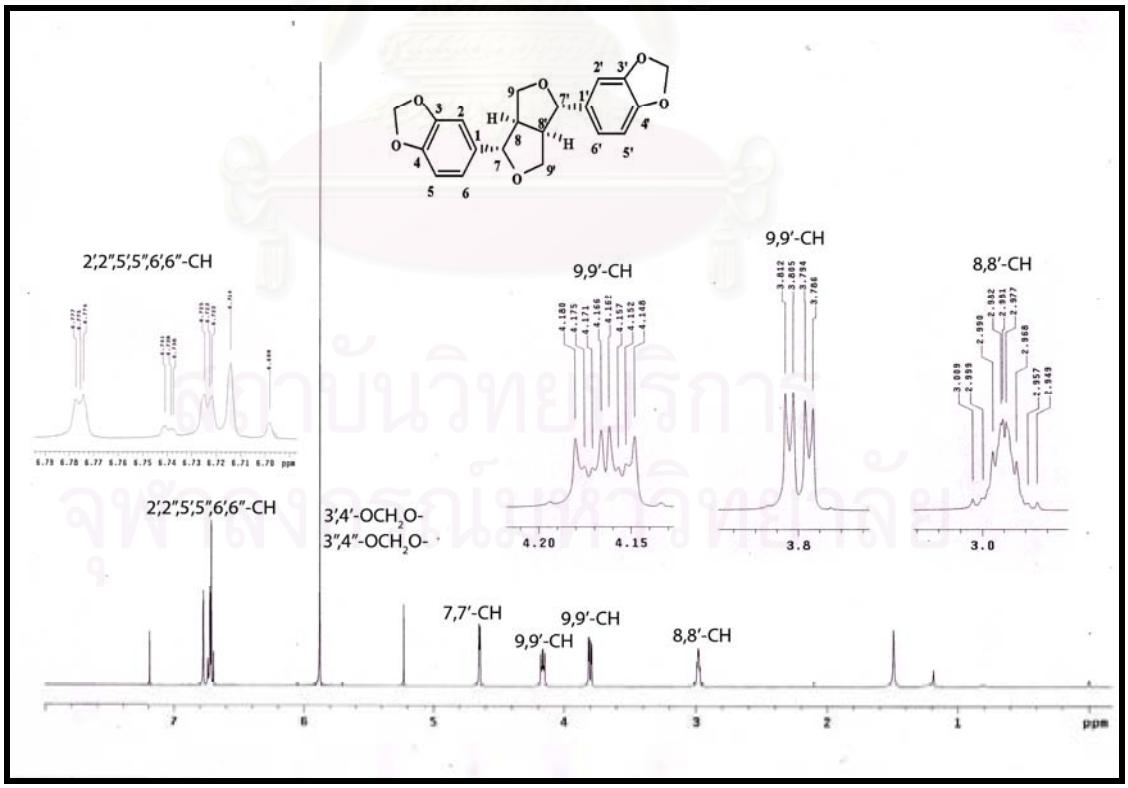

Figure 29. ^{1}H NMR (500 MHz) Spectrum of compound KG-F3 (in $CDCl_3$)

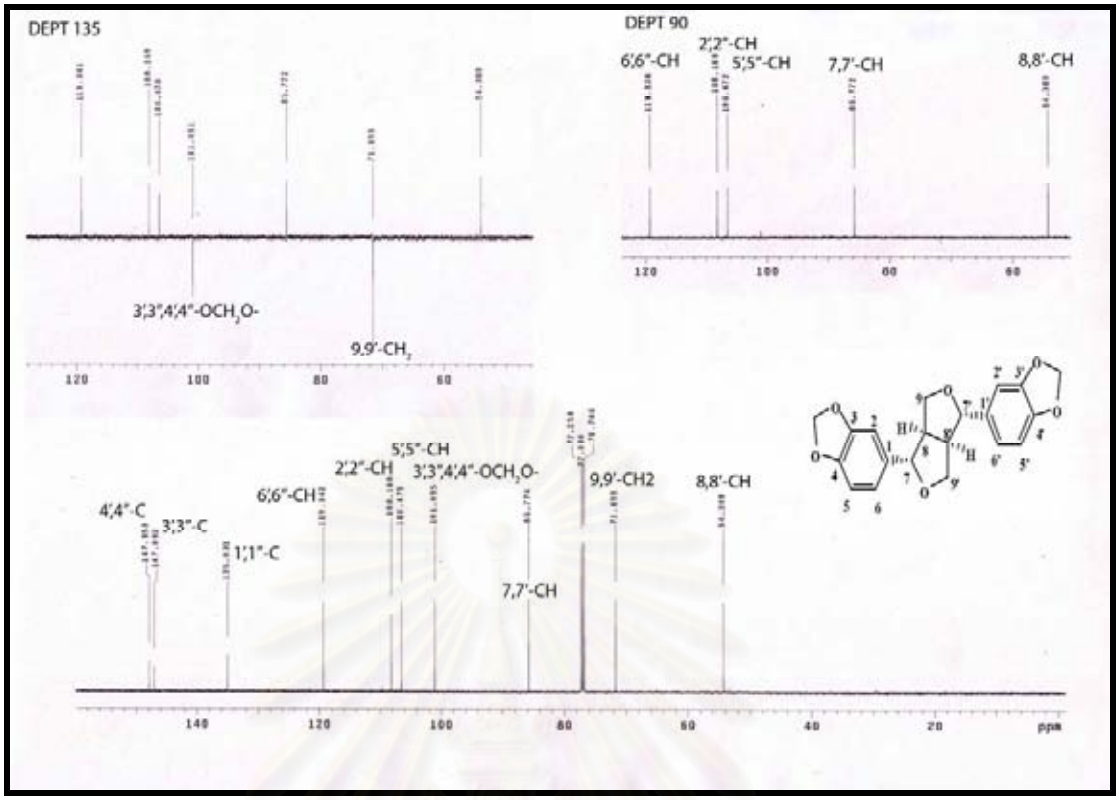

Figure 30. DEPT 135, DEPT 90 and ^{13}C NMR (125 MHz) Spectrum of compound KG-F3 (in $CDCl_3$)

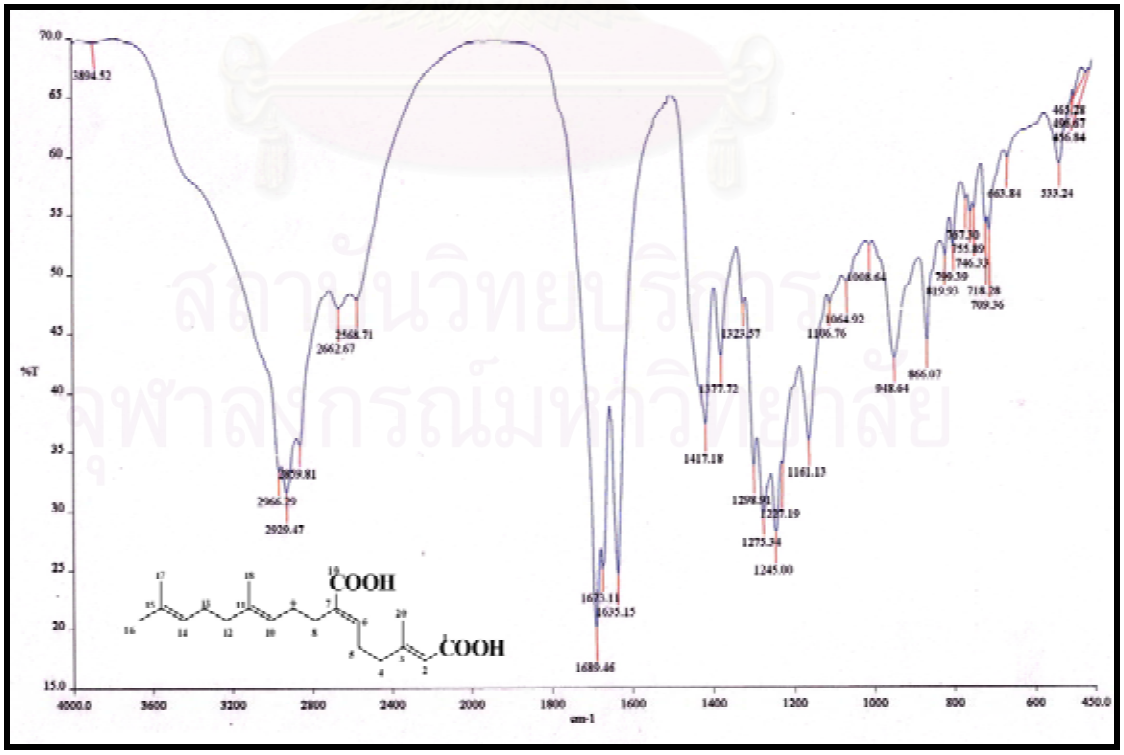

Figure 31. IR Spectrum of compound KG-F4 (KBr disc)

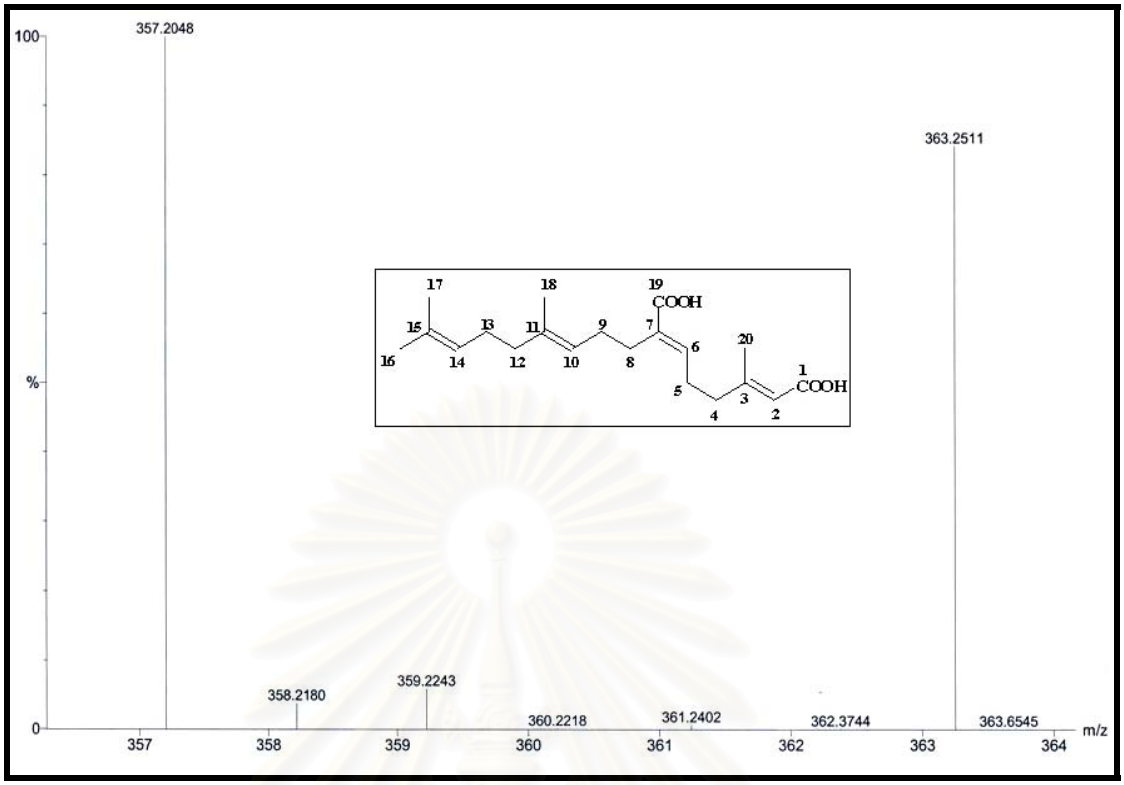

Figure 32. HR-ESI-TOF Mass spectrum of compound KG-F4

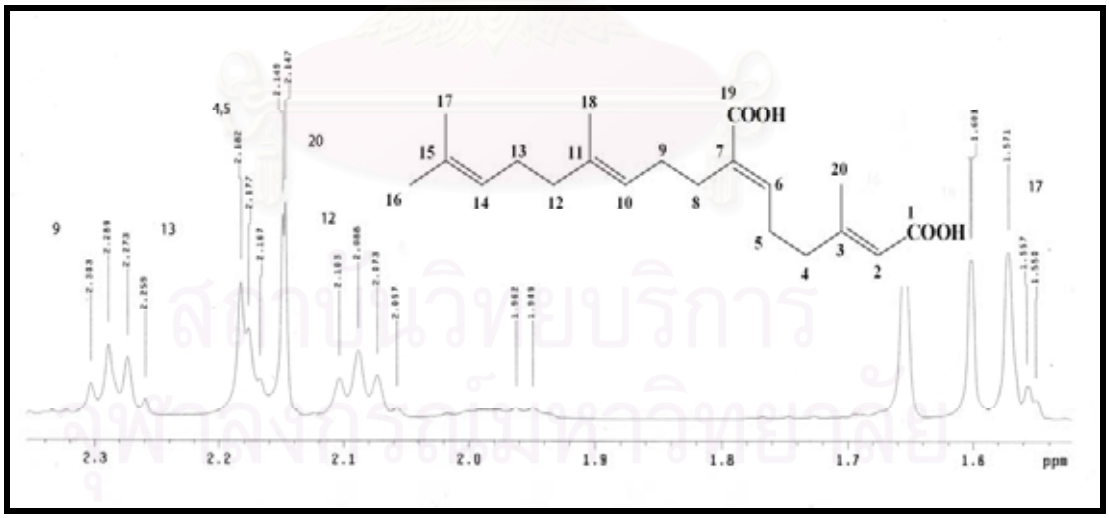

Figure 33a. ^{1}H NMR (500 MHz) Spectrum of compound KG-F4 (in $CDCl_3$) (expansion between δ1.6-2.3 ppm)

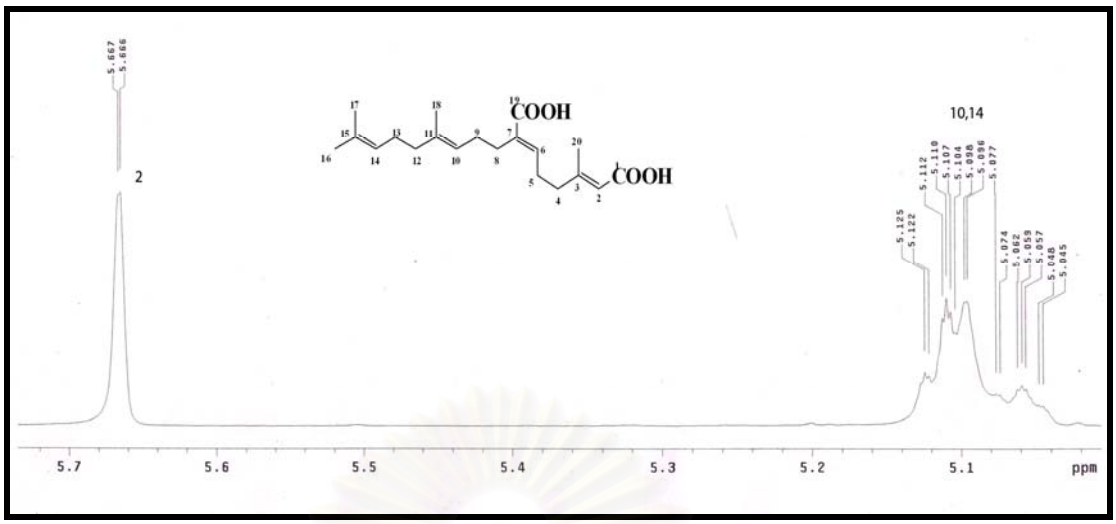

Figure 33b. ^{1}H NMR (500 MHz) Spectrum of compound KG-F4 (in $CDCl_3$) (expansion between δ5.0-5.7 ppm)

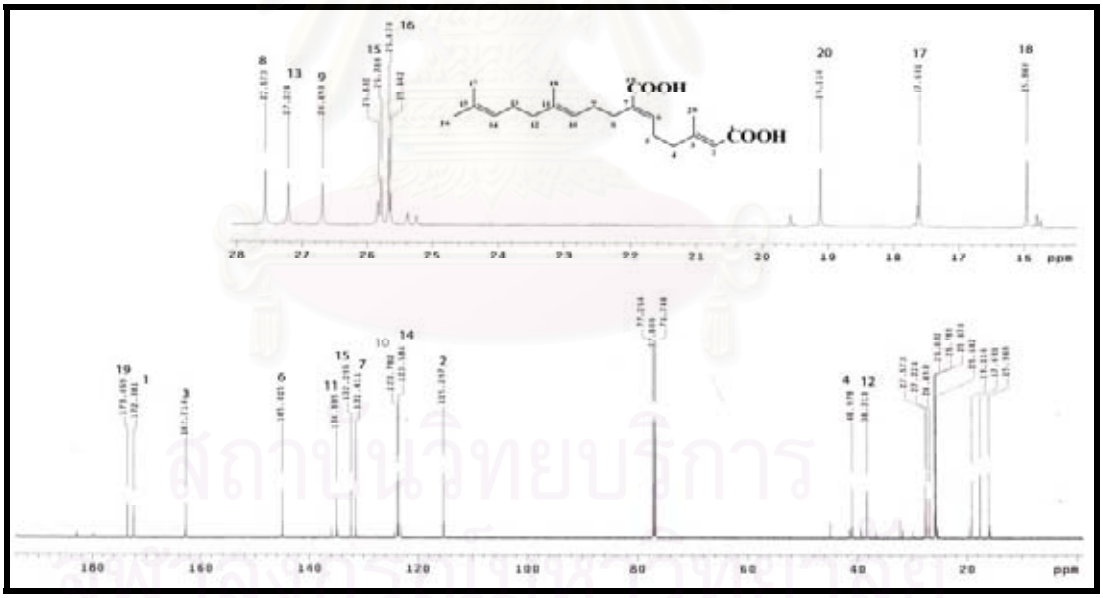

Figure 34. ^{13}C NMR (125 MHz) Spectrum of compound KG-F4 (in $CDCl_3$)

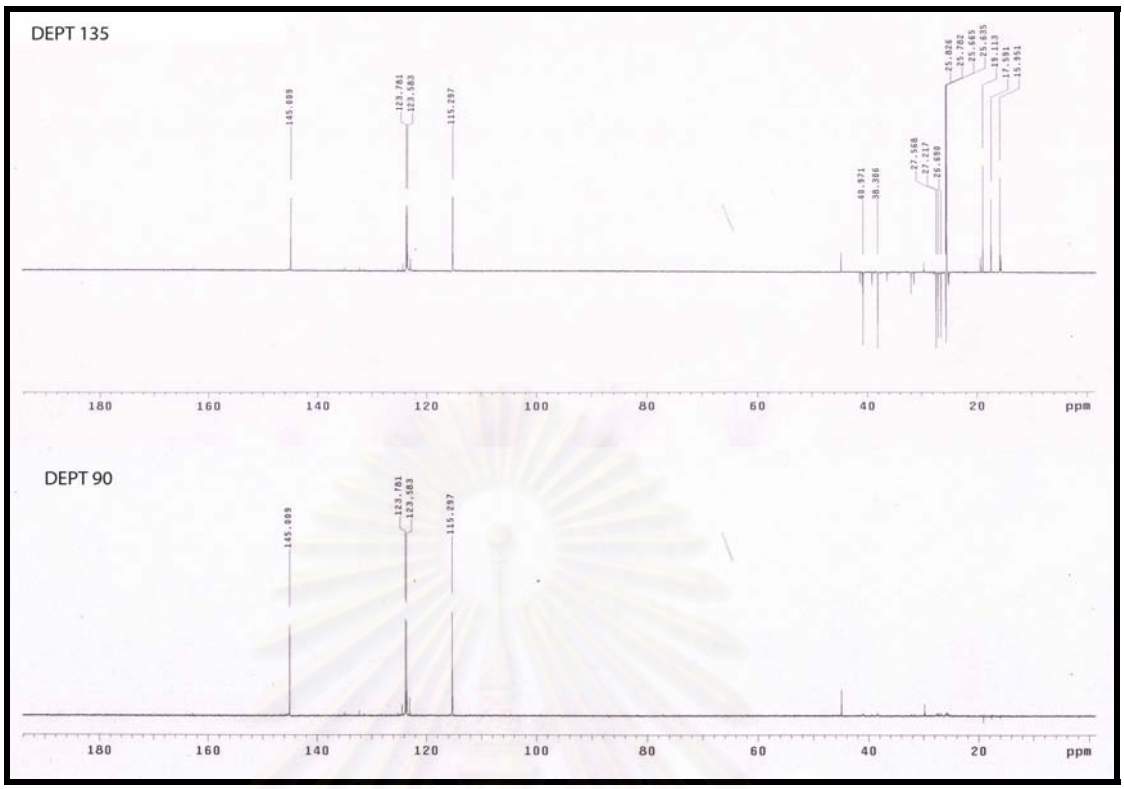

Figure 35. DEPT 90 and DEPT 135 spectrum of compound KG-F4 (in $CDCl_3$)

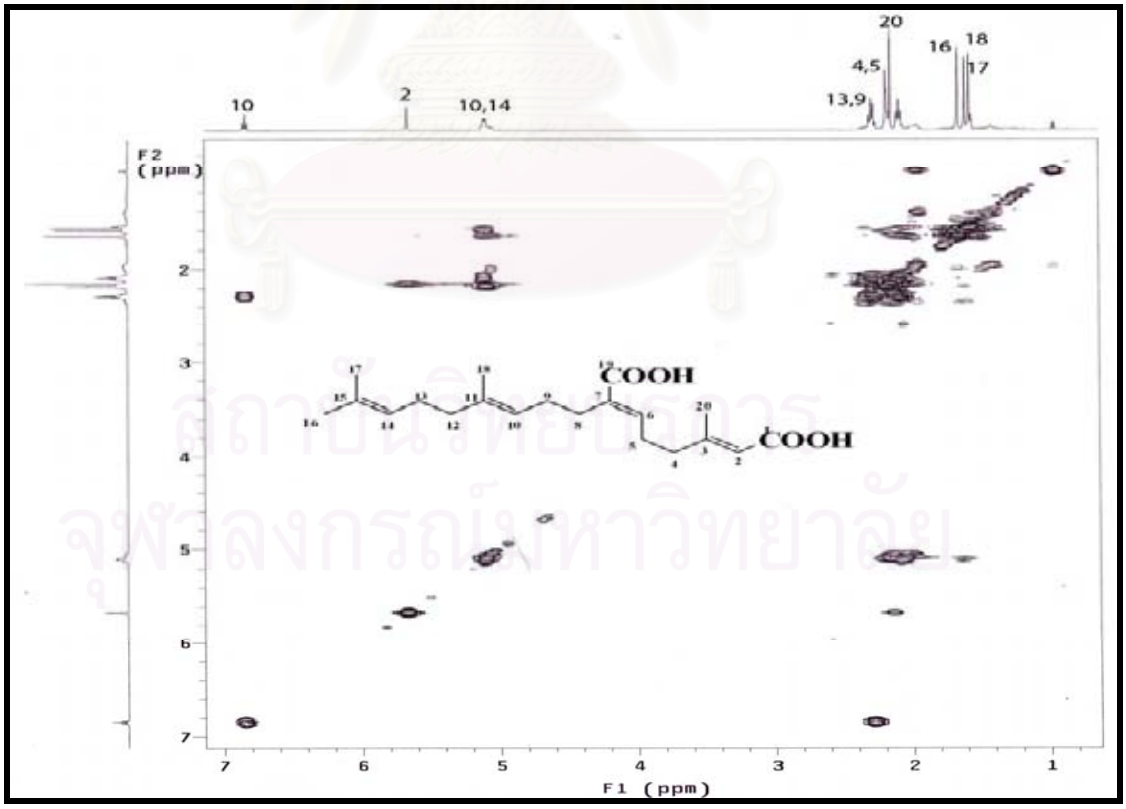

Figure 36a. ^{1}H-^{1}H COSY Spectrum of compound KG-F4 (in $CDCl_3$)

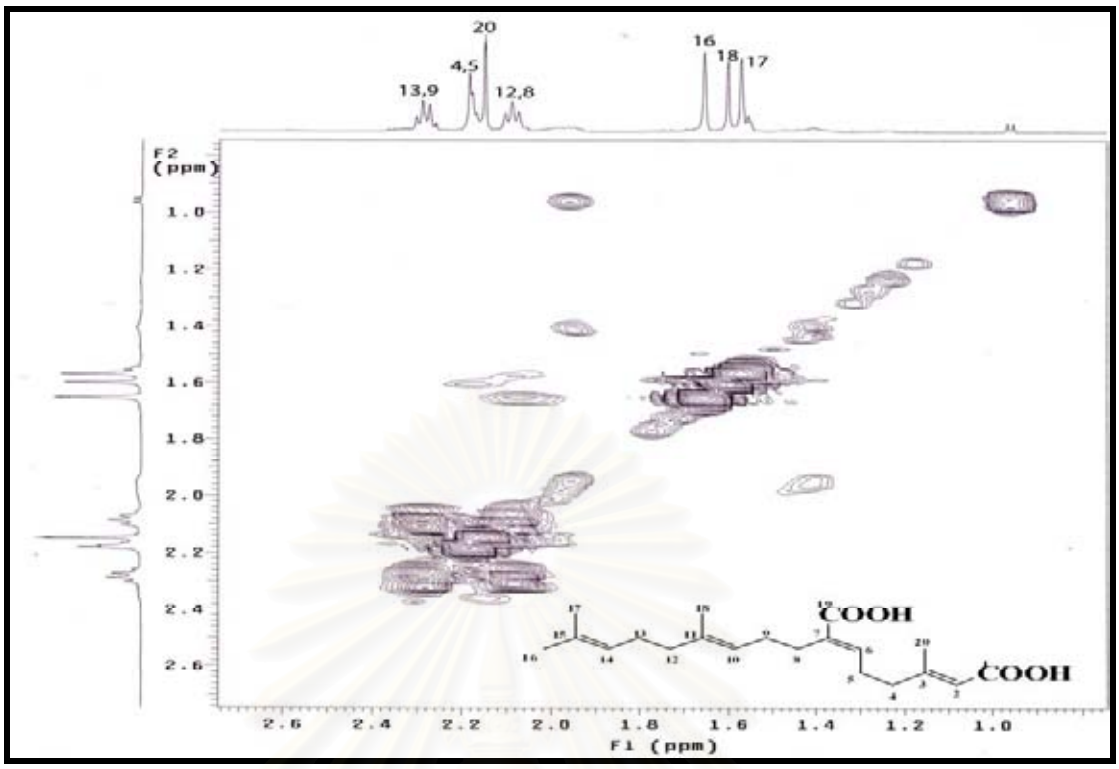

Figure 36b. ^{1}H-^{1}H COSY Spectrum of compound KG-F4 (in $CDCl_3$)
(expansion between δ 1.0-2.6 ppm)

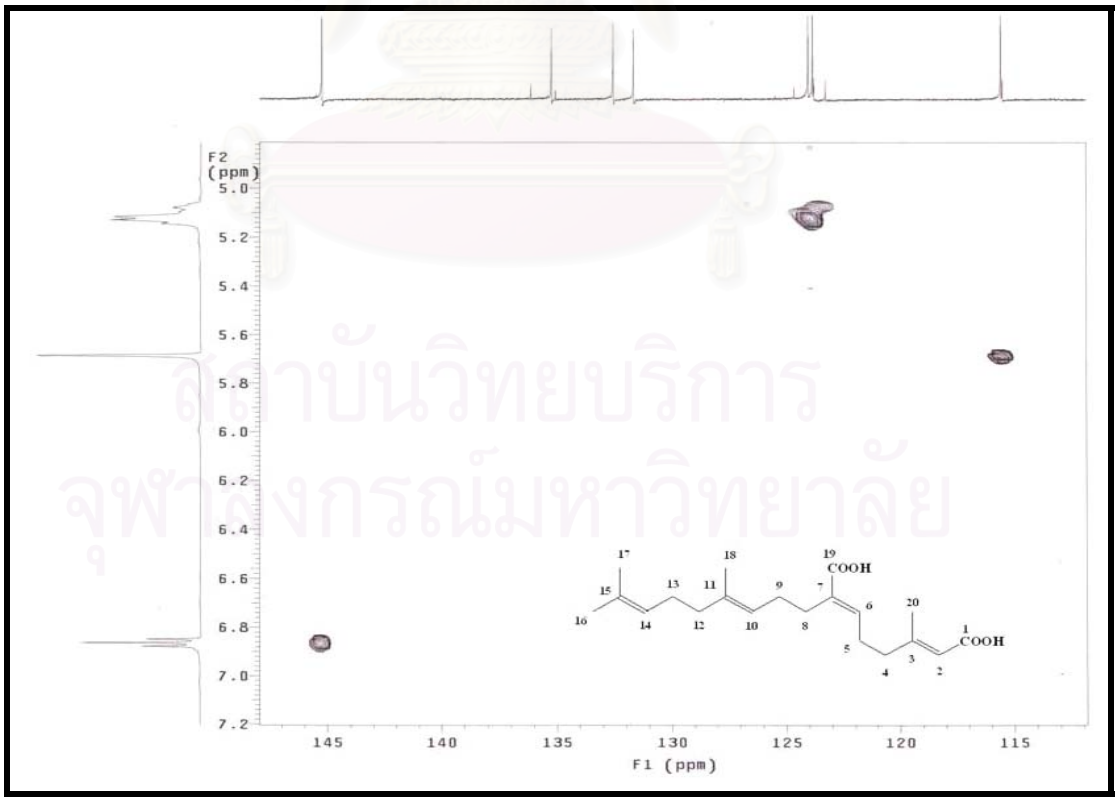

Figure 37a. HMQC Spectrum of compound KG-F4
(expansion between δ_H 5.0-7.2 ppm, δ_C 115.0-145.0 ppm)

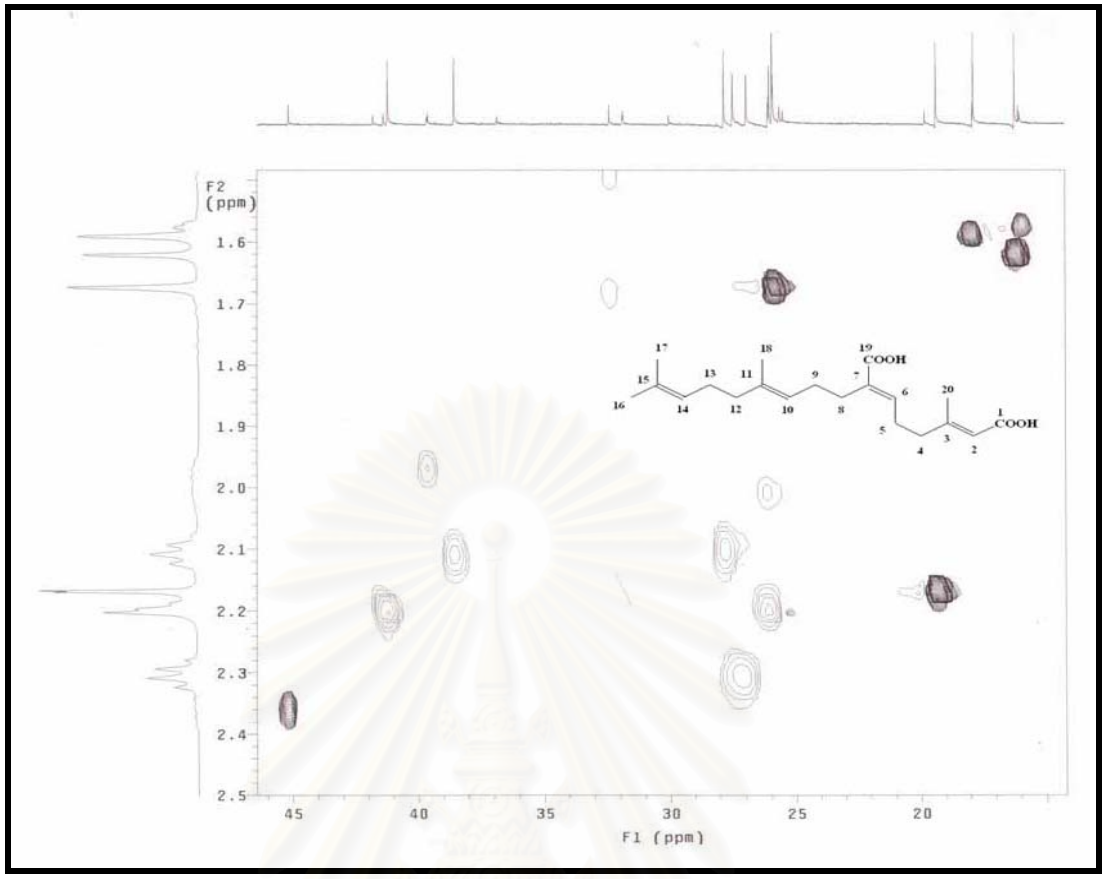

Figure 37b. HMQC Spectrum of compound KG-F4

(expansion between δ_H 1.6-2.5 ppm, δ_C 20.0-45.0 ppm)

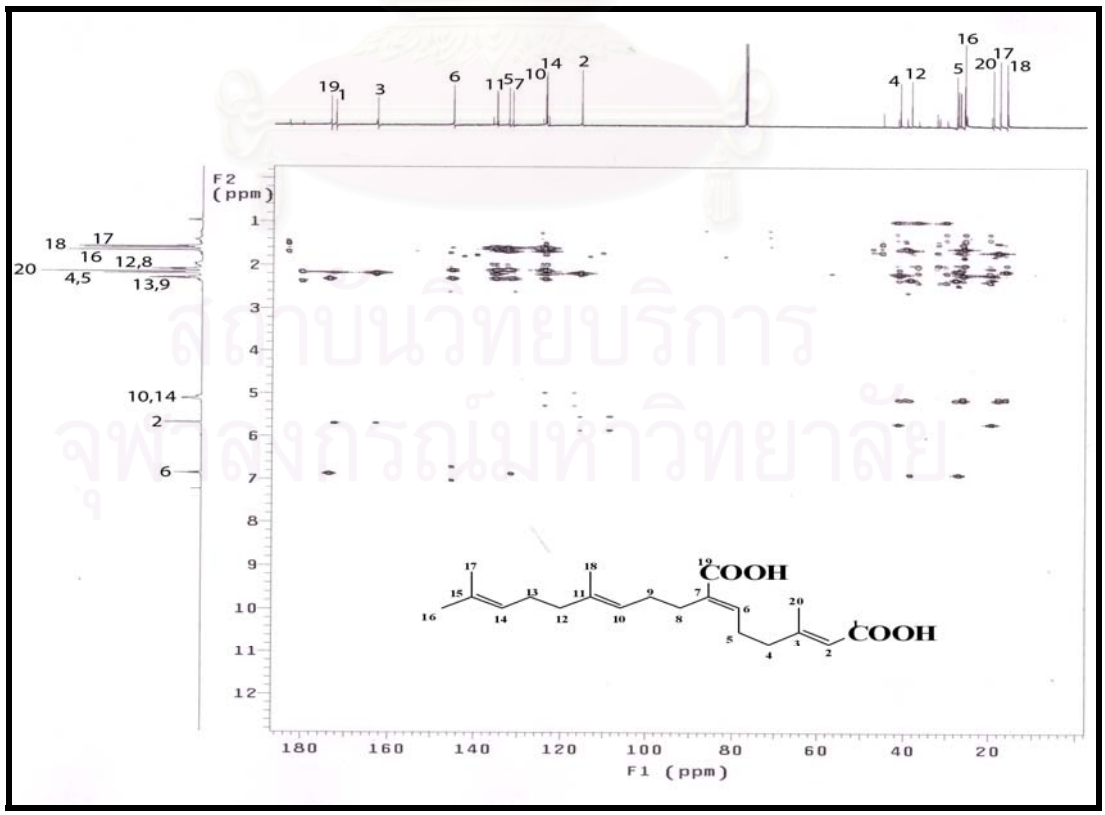

Figure 38a. HMBC Spectrum of compound KG-F4

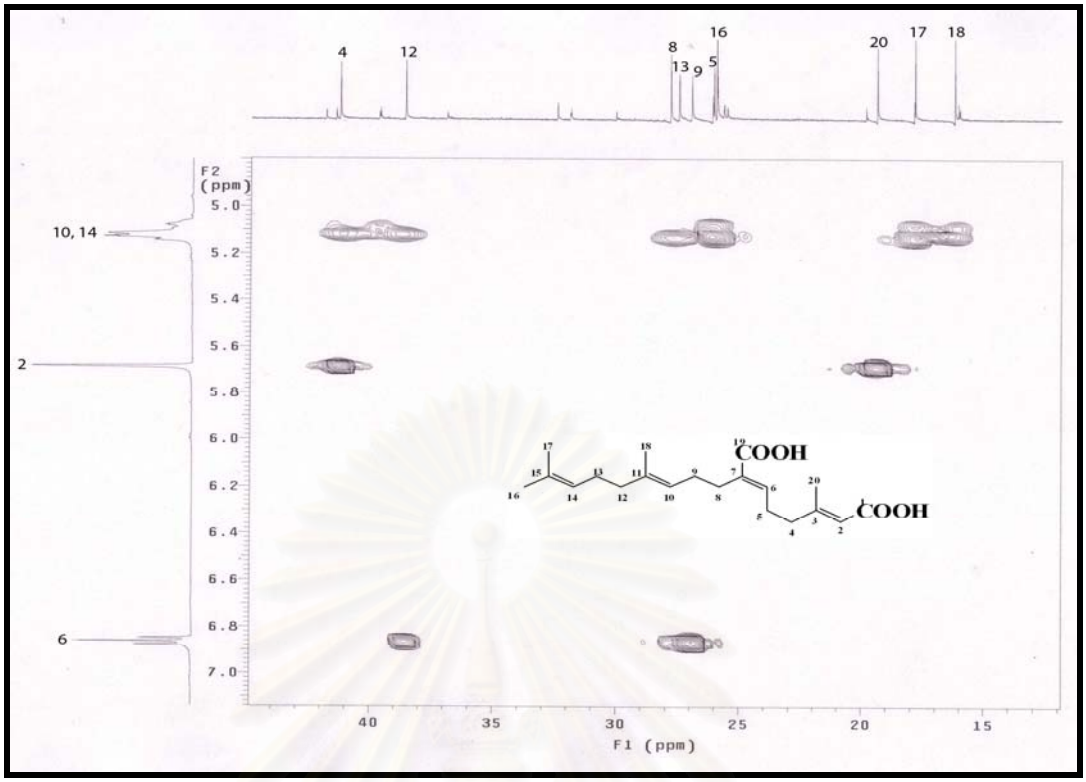

Figure 38b. HMBC Spectrum of compound KG-F4
(expansion between δ_H 5.0-7.0 ppm, δ_C 15.0-45.0 ppm)

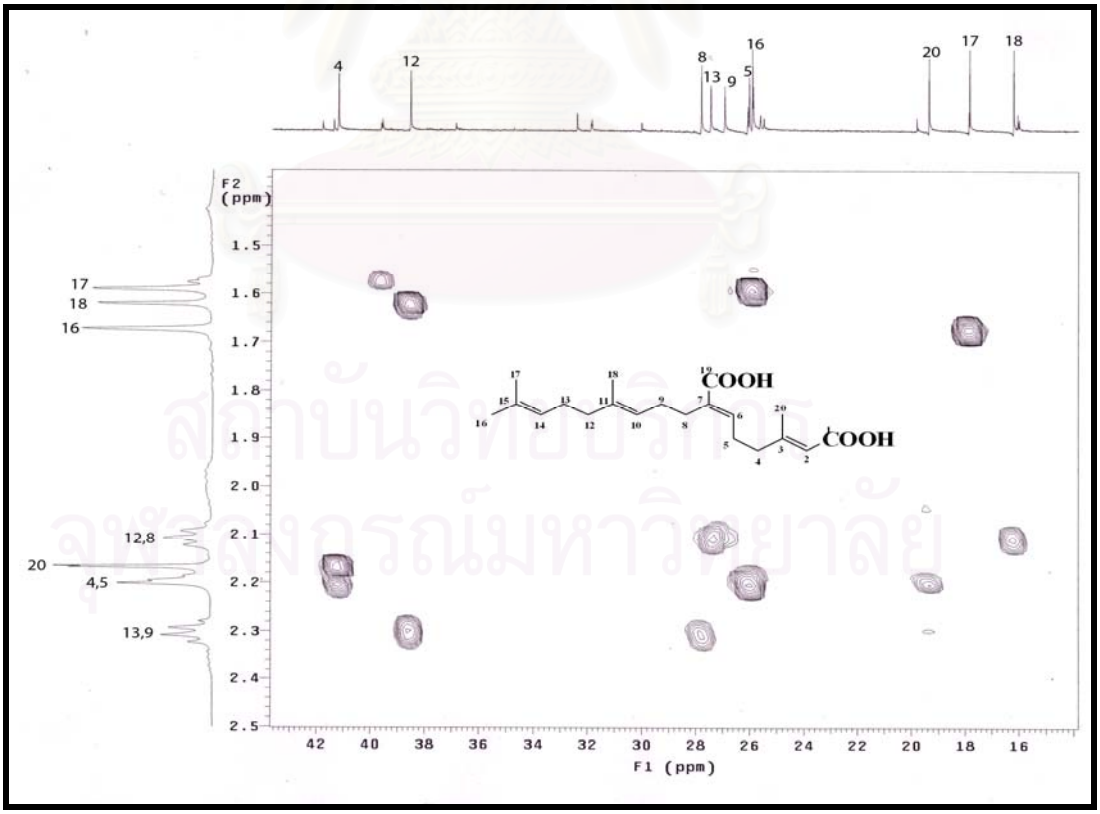

Figure 38c. HMBC Spectrum of compound KG-F4
(expansion between δ_H 1.5 -2.5 ppm, δ_C 16.0-42.0 ppm)

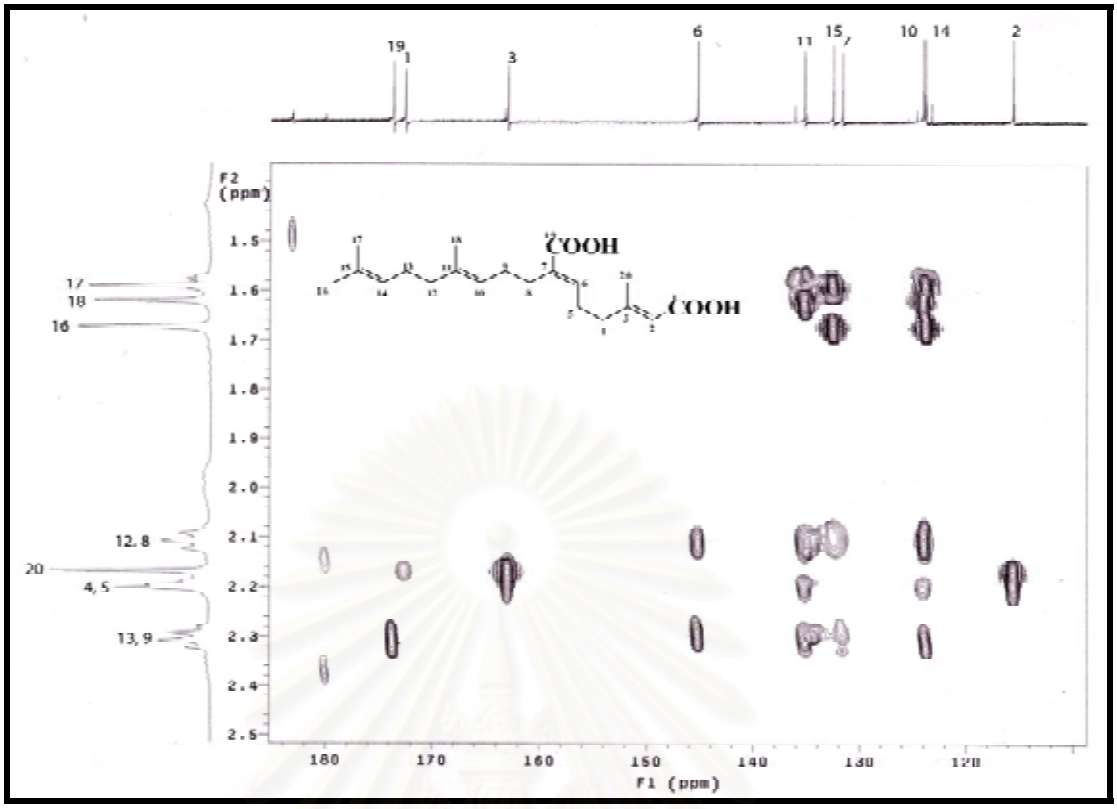

Figure 38d. HMBC Spectrum of compound KG-F4
(expansion between δ_H 1.5 -2.5 ppm, δ_C 120.0-180.0 ppm)

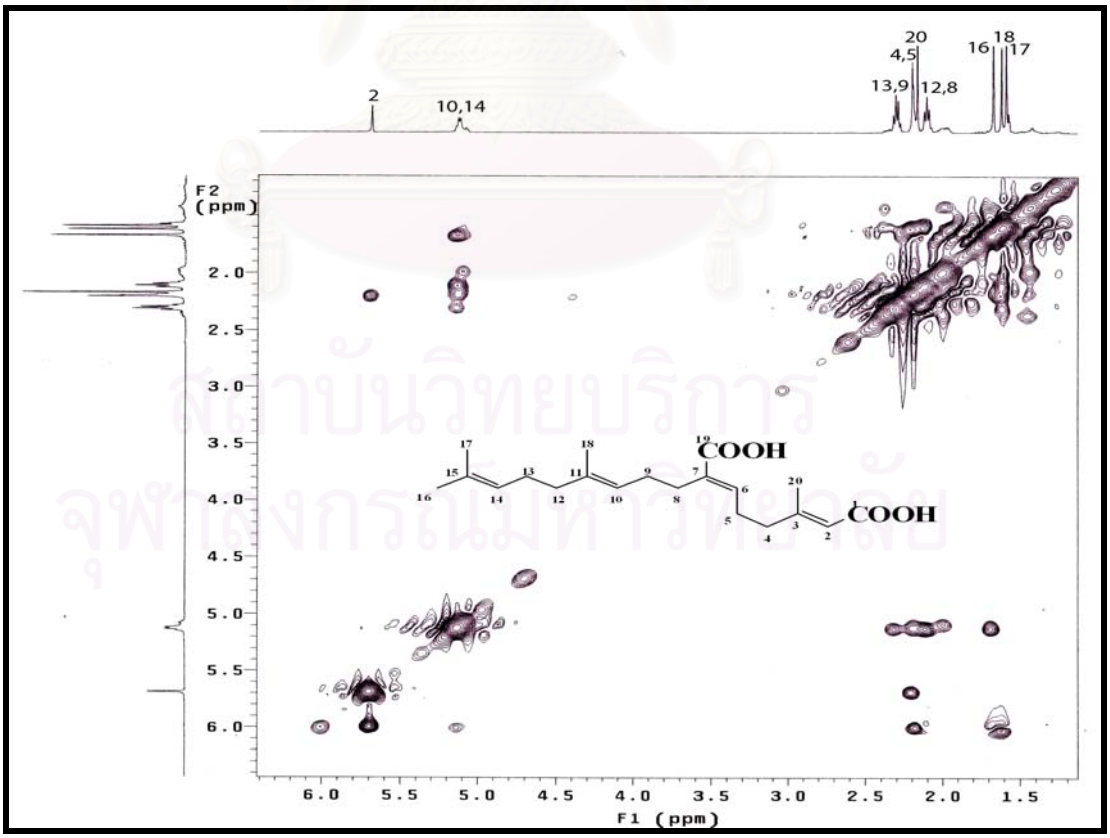

Figure 39. NOESY Spectrum of compound KG-F4

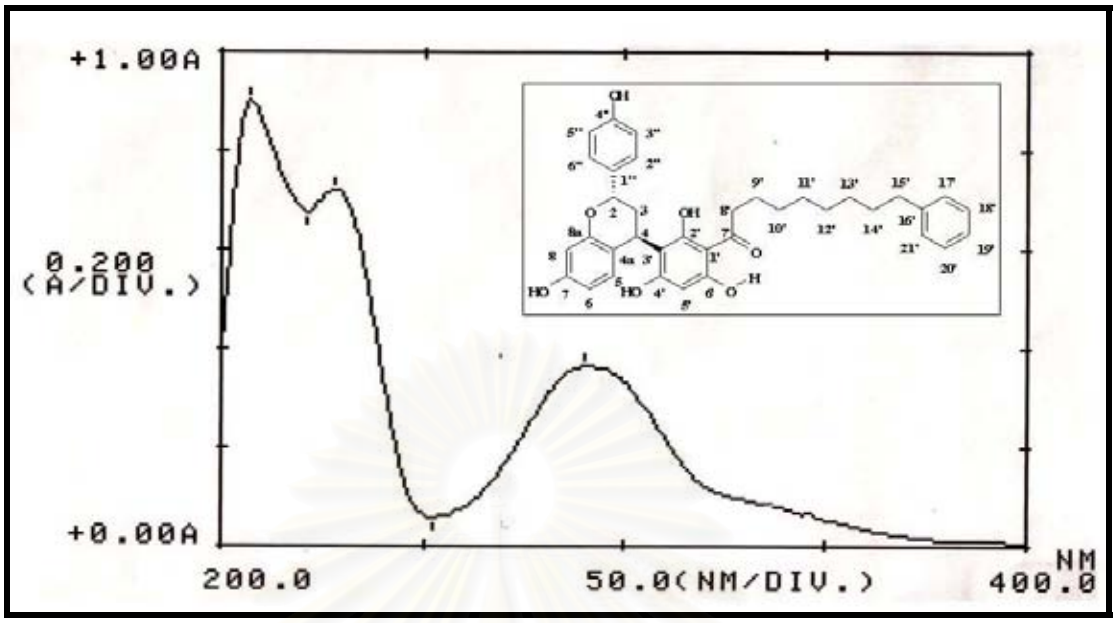

Figure 40. UV Spectrum of compound KG-F5 (in MeOH)

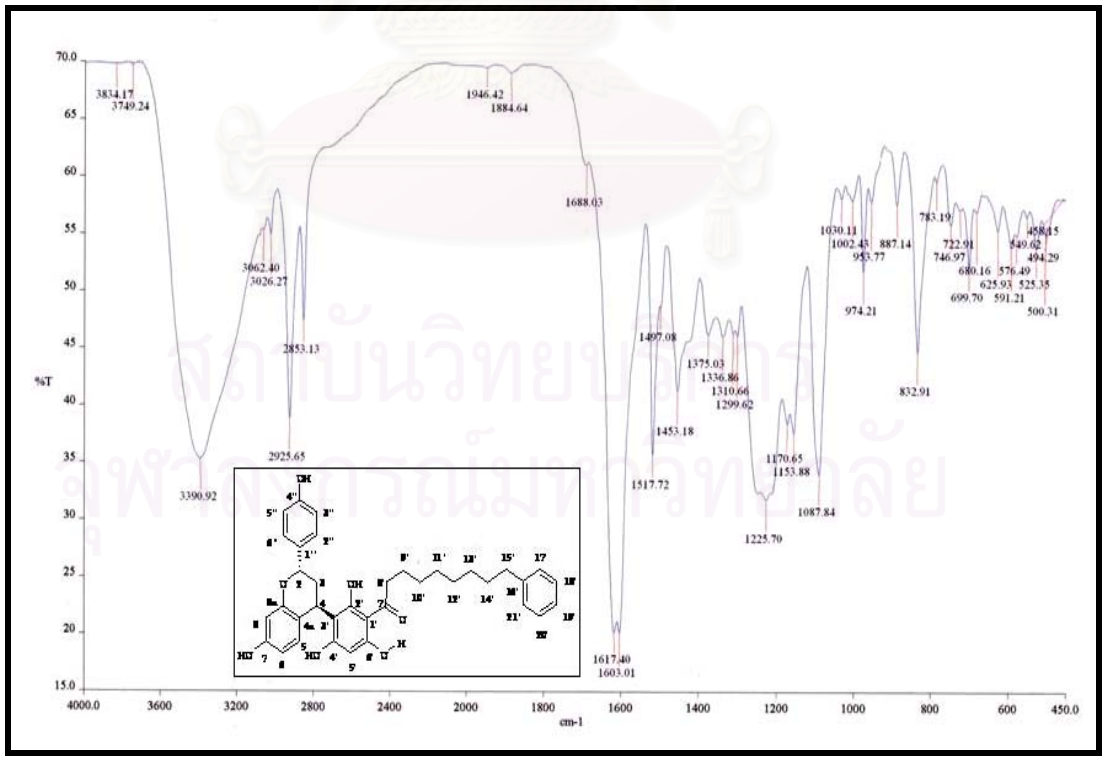

Figure 41. IR Spectrum of compound KG-F5 (KBr disc)

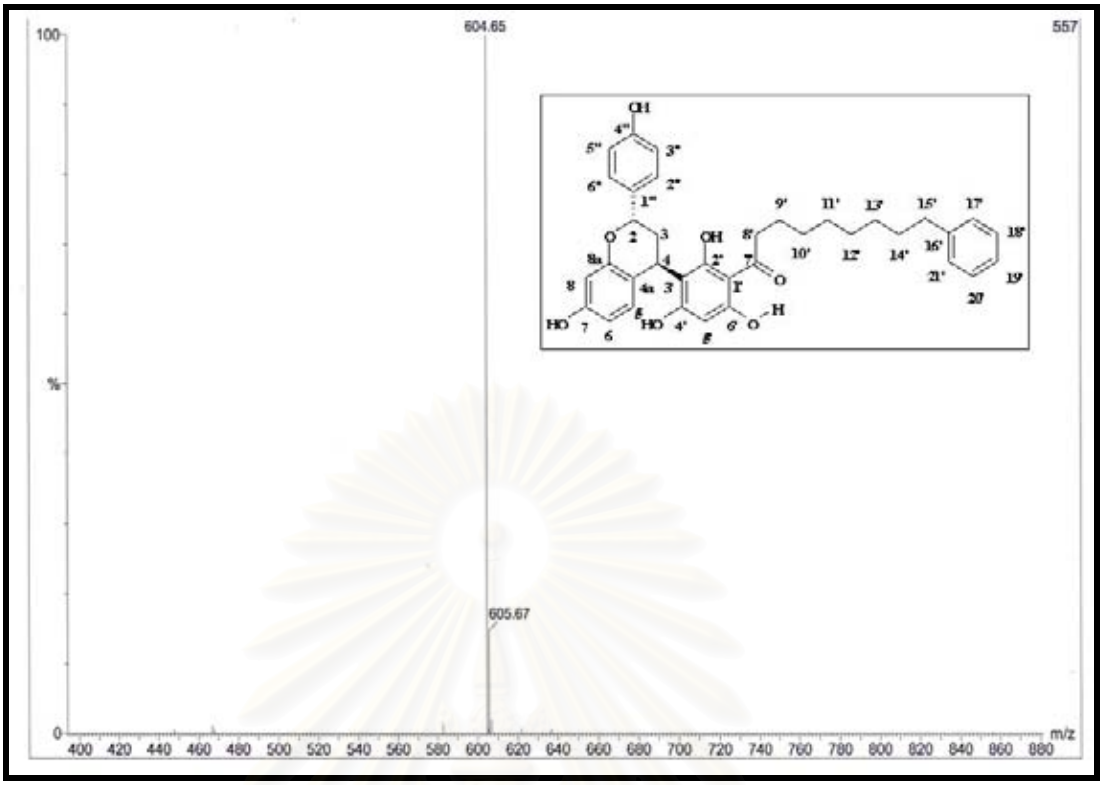

Figure 42. ESI-TOF Mass spectrum of compound KG-F5

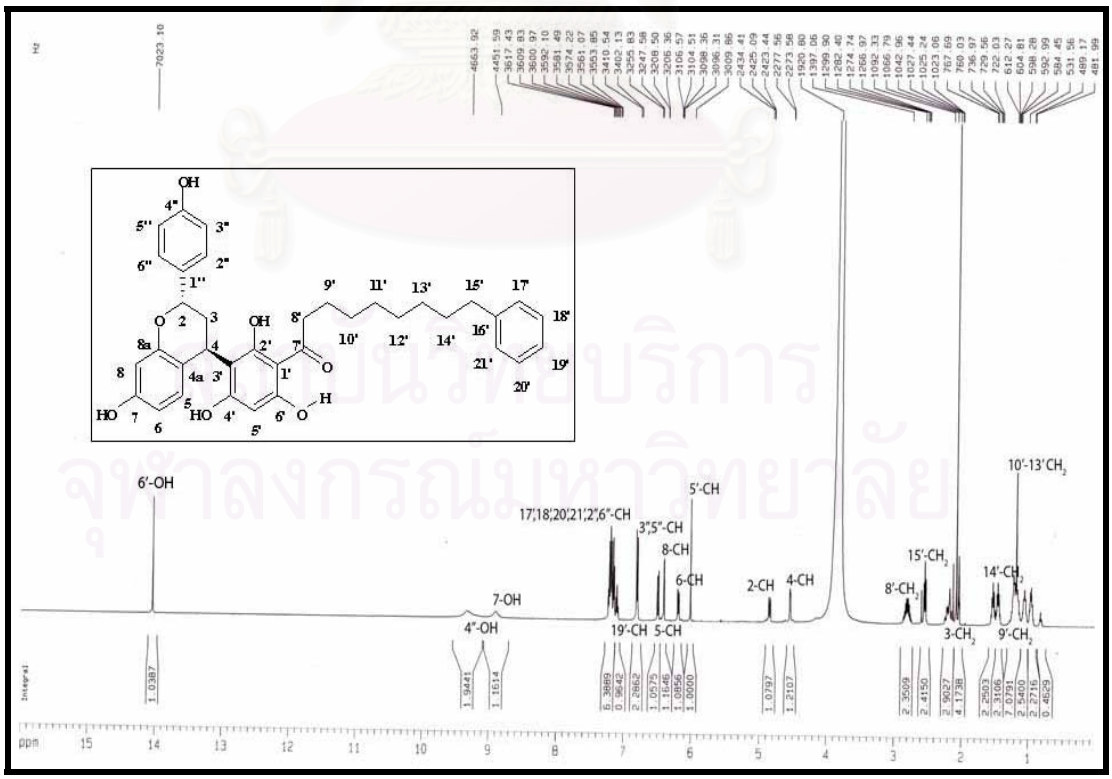

Figure 43a. ^{1}H NMR (500 MHz) Spectrum of compound KG-F5 (in acetone-d_6)

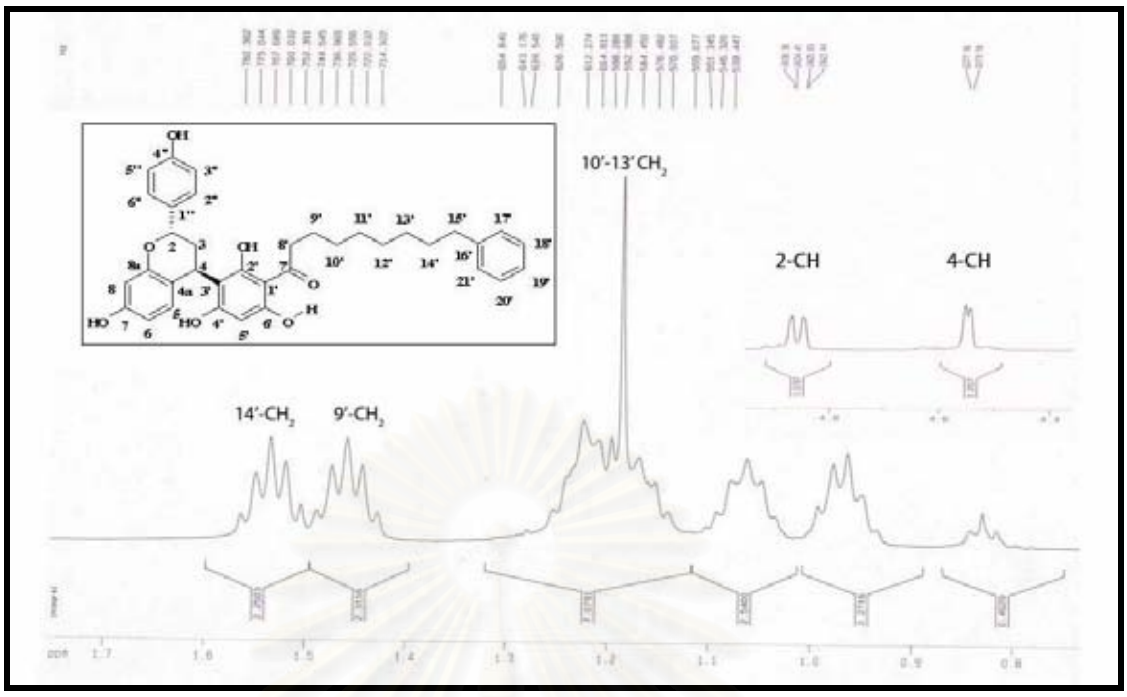

Figure 43b. ^{1}H NMR (500 MHz) Spectrum of compound KG-F5 (in acetone-d_6) (expansion between δ 0.8-4.6 ppm)

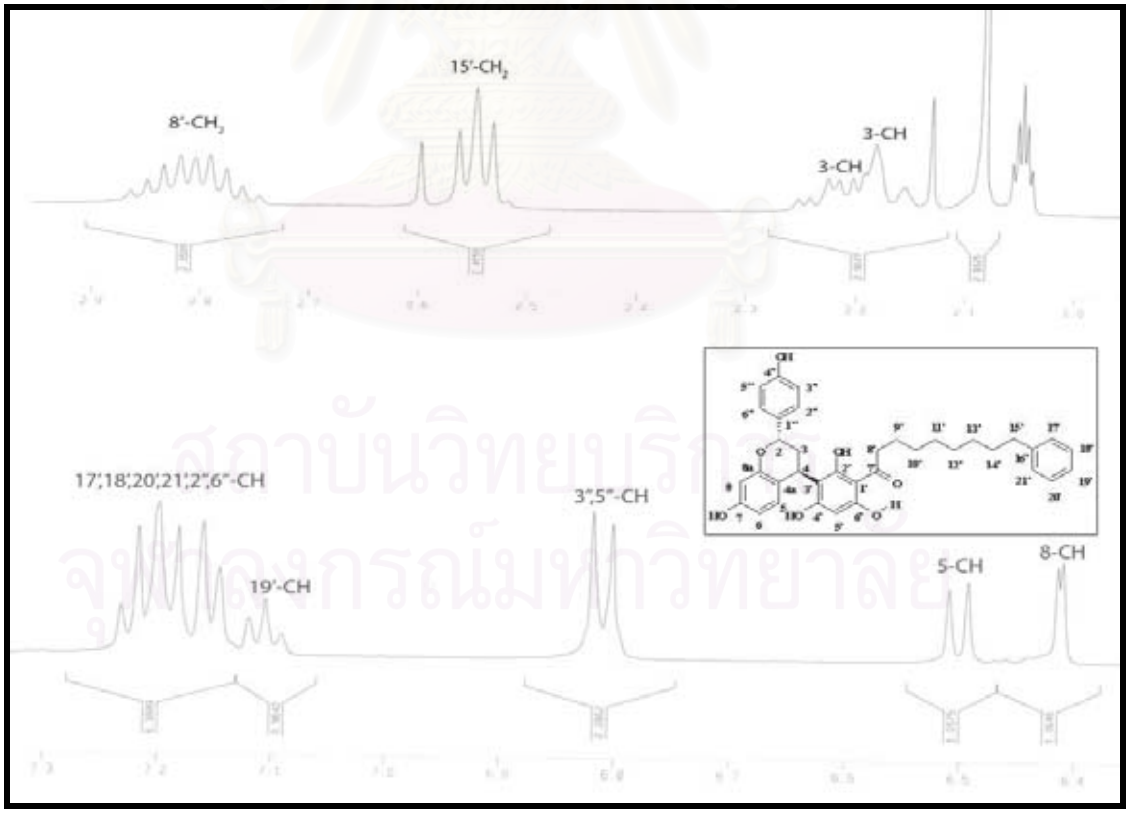

Figure 43c. ^{1}H NMR (500 MHz) Spectrum of compound KG-F5 (in acetone-d_6) (expansion between at δ 2.0-2.9 ppm and δ 6.4-7.3 ppm)

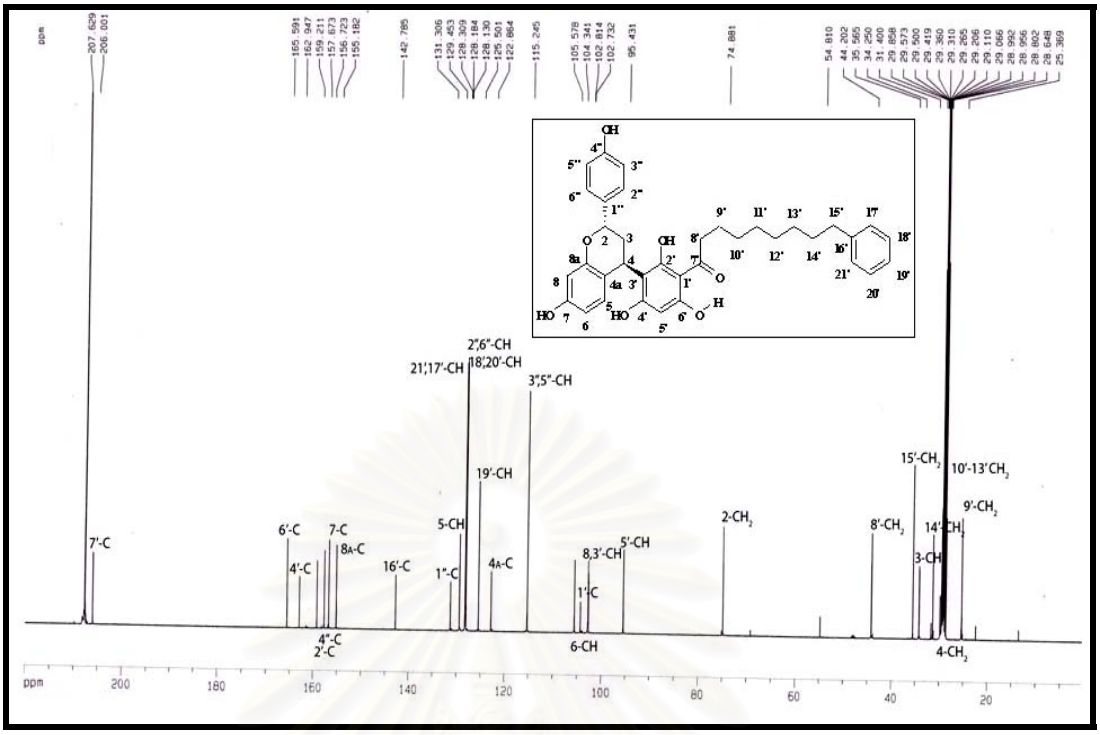

Figure 44a. ^{13}C NMR (125 MHz) Spectrum of compound KG-F5 (in acetone-d_6)

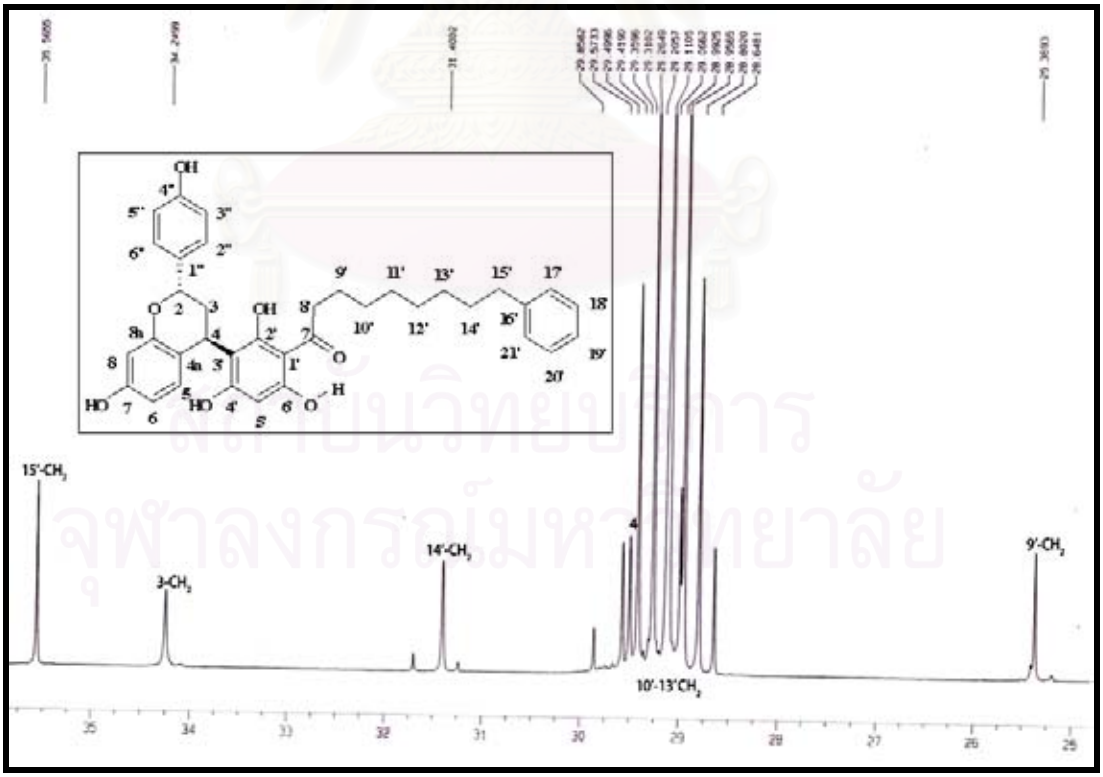

Figure 44b. ^{13}C NMR (125 MHz) Spectrum of compound KG-F5 (in Acetone-*d6*)
(expansion between δ 25.0-36.0 ppm)

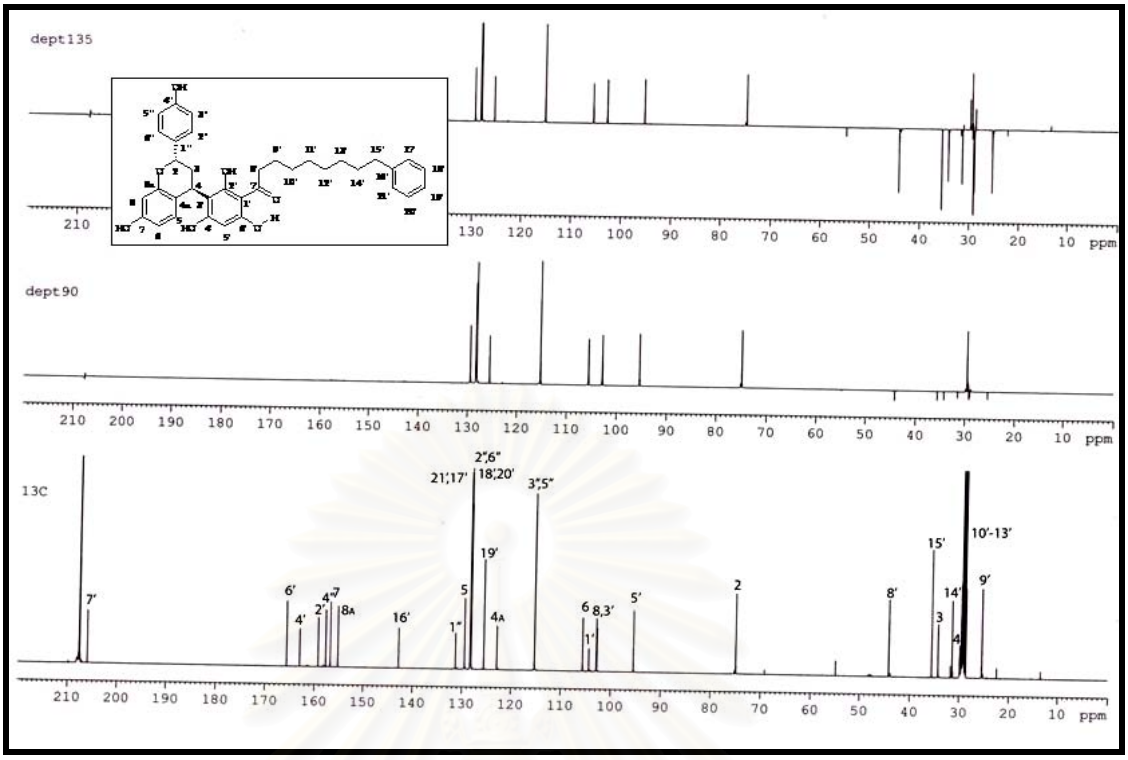

Figure 45. DEPT135, DEPT 90 and ^{13}C NMR Spectrum of compound KG-F5 (in acetone-d_6)

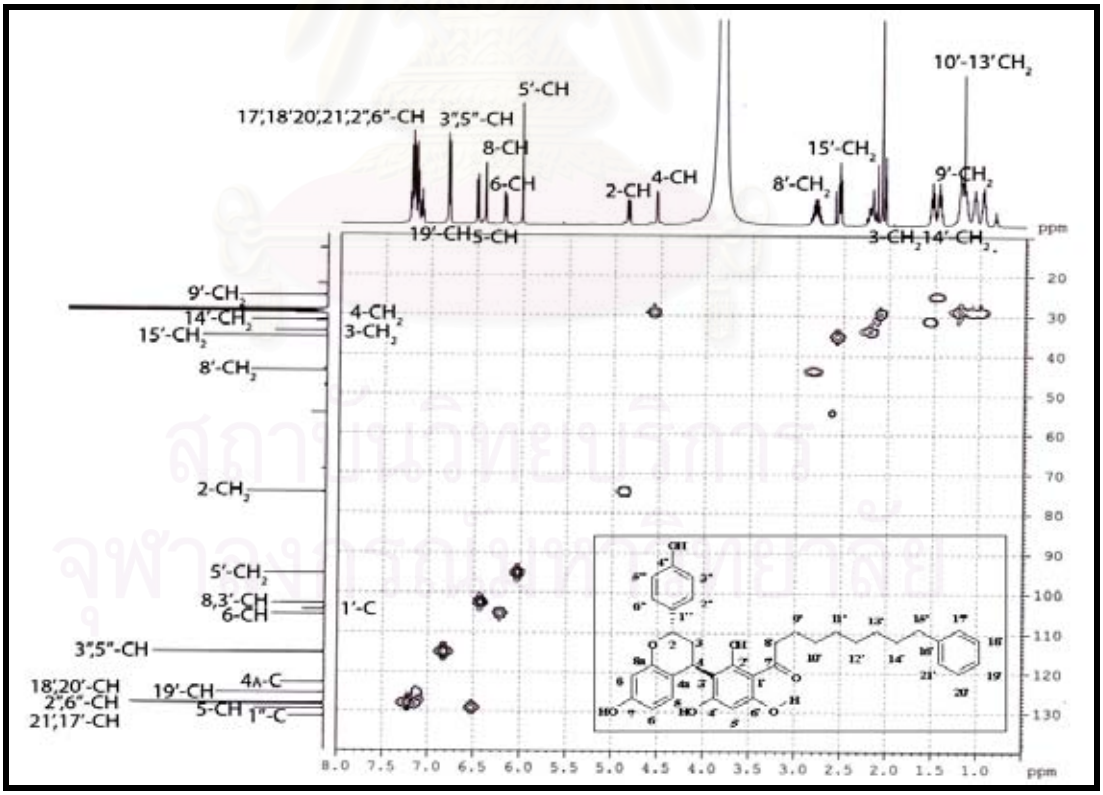

Figure 46. HMQC Spectrum of compound KG-F5 (expansion between δ_H 1.0-8.0 ppm, δ_C 20.0-130.0 ppm)

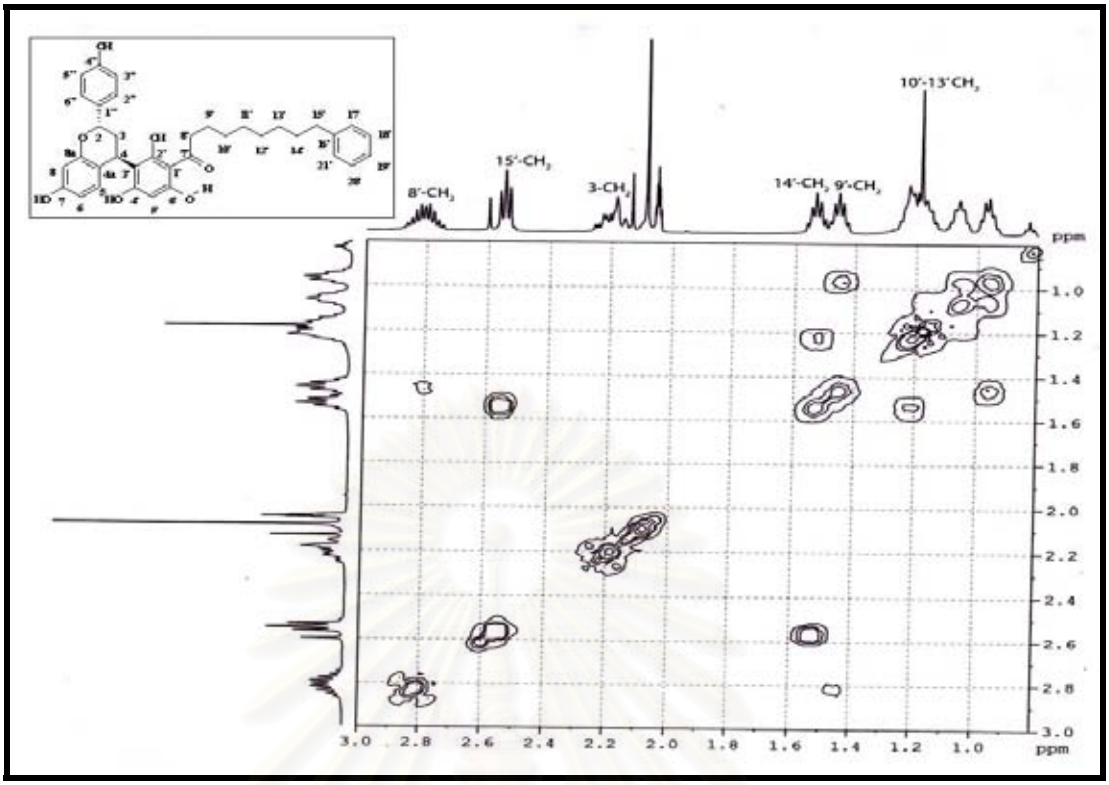

Figure 47a. ^{1}H-^{1}H COSY Spectrum of compound KG-F5 (in acetone-d_6)
(expansion between δ1.0-3.0 ppm)

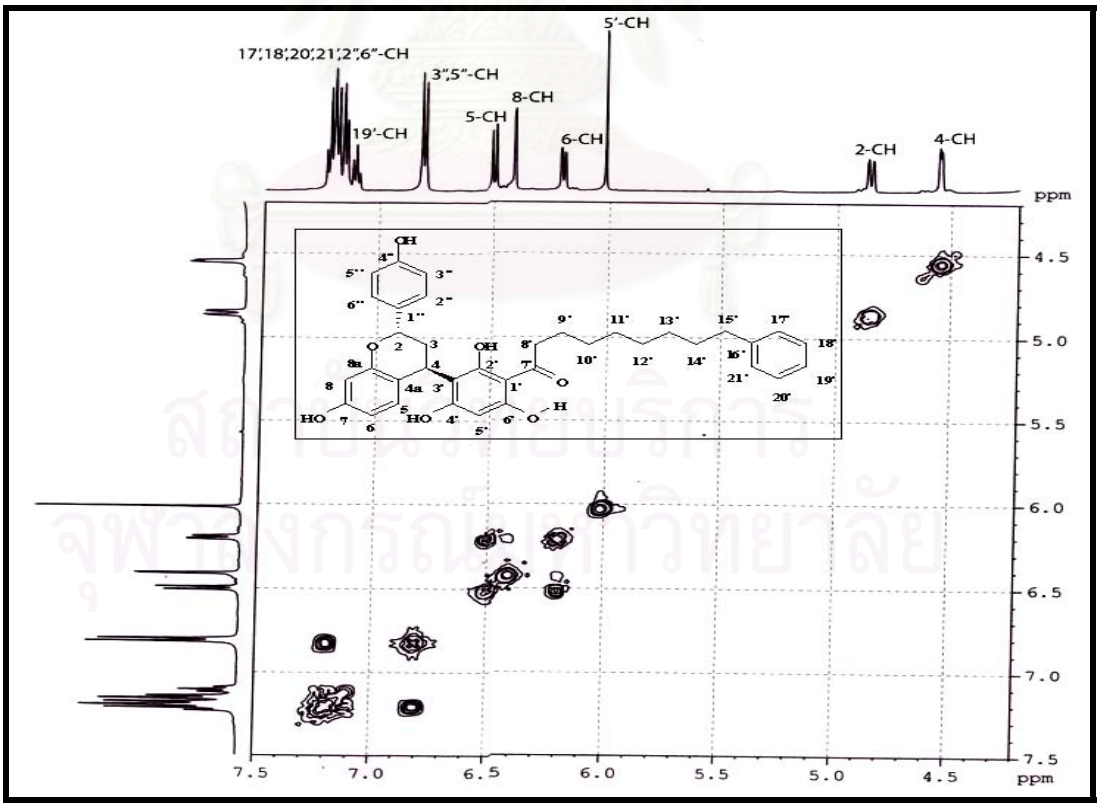

Figure 47b. ^{1}H-^{1}H COSY Spectrum of compound KG-F5 (in acetone-d_6)
(expansion between δ 4.5-7.5 ppm)

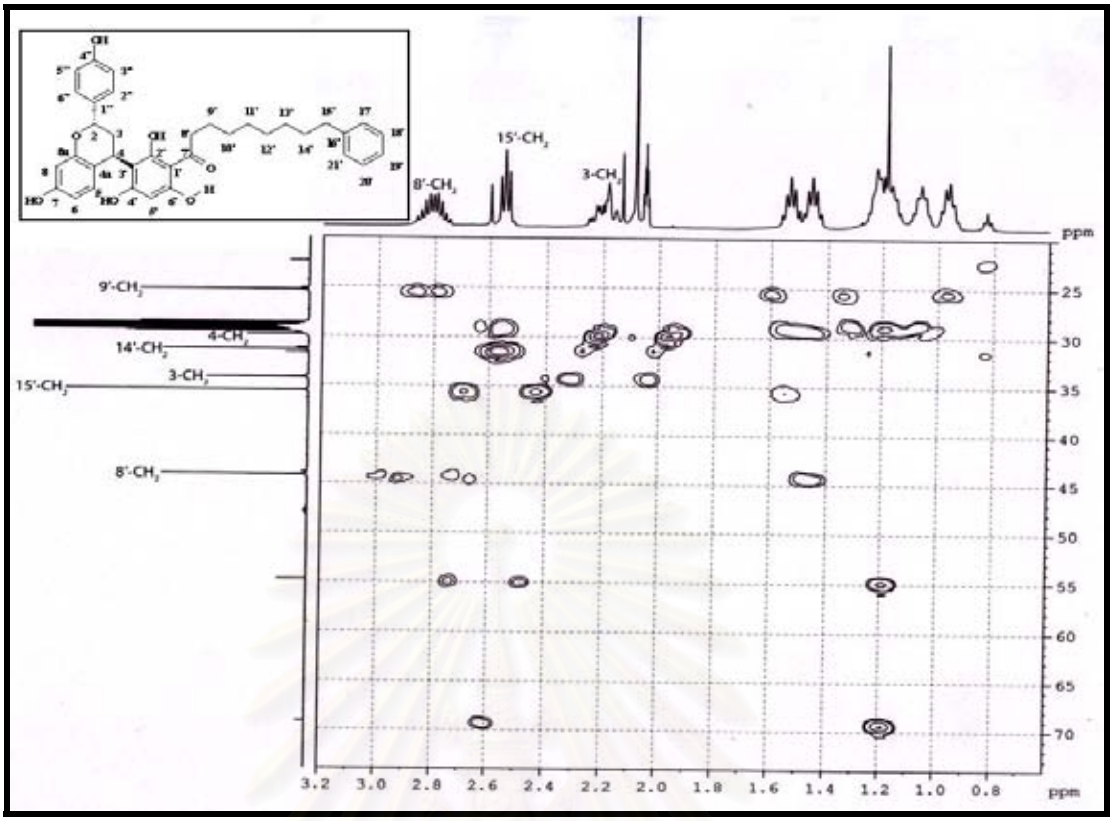

Figure 48a. HMBC Spectrum of compound KG-F5

(expansion between δ_H 0.8-3.2 ppm, δ_C 25.0-75.0 ppm)

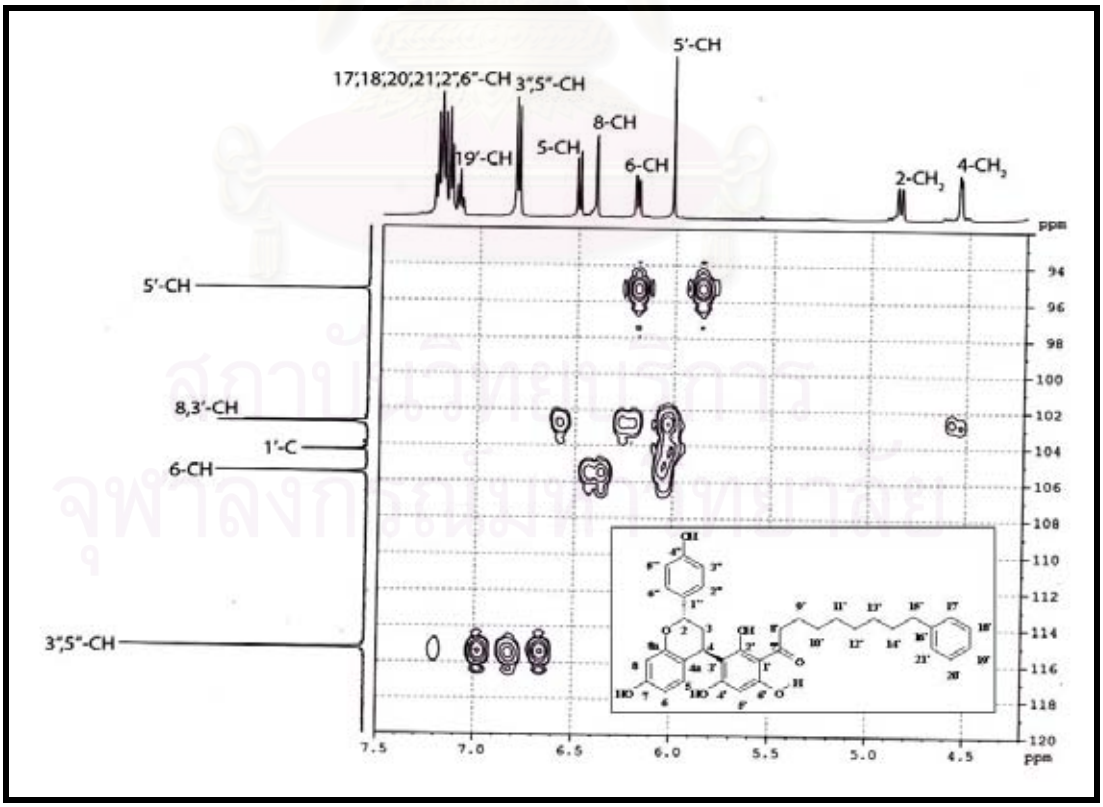

Figure 48b. HMBC Spectrum of compound KG-F5

(expansion between δ_H 4.5-7.5 ppm, δ_C 94.0-120.0 ppm)

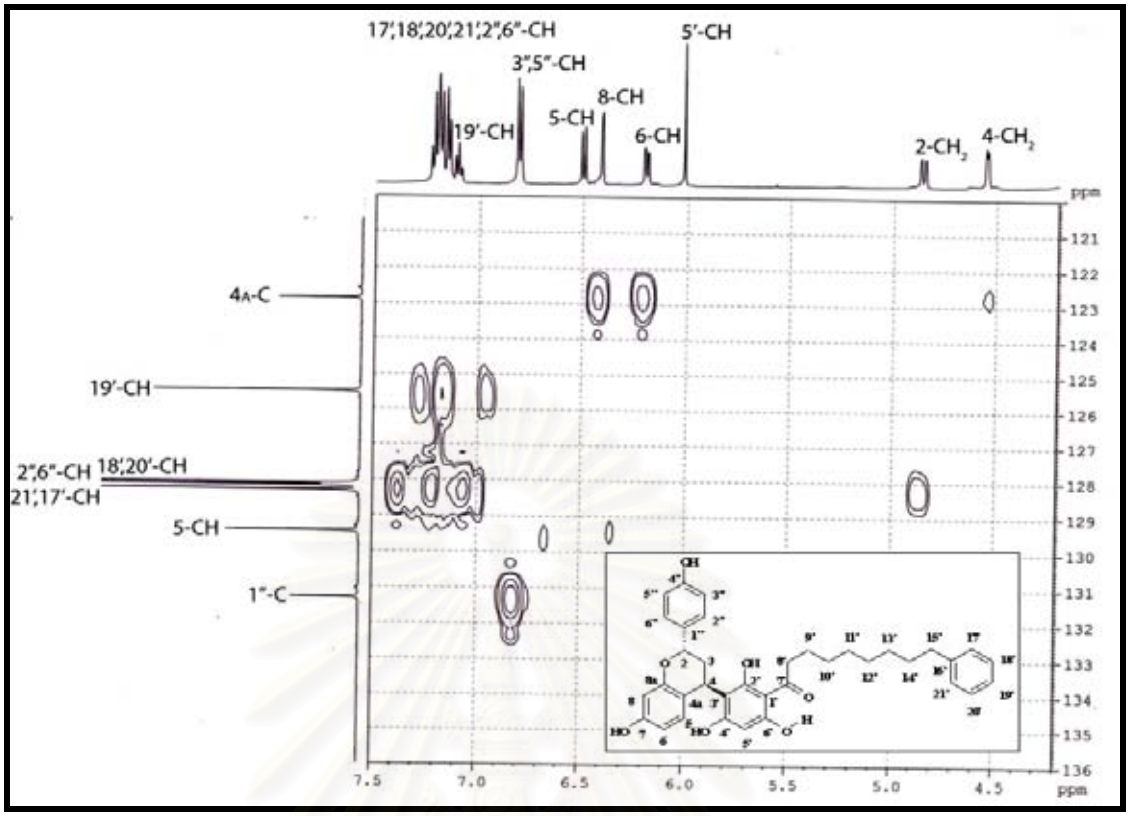

Figure 48c. HMBC Spectrum of compound KG-F5

(expansion between δ_H 4.5-7.5 ppm, δ_C 121.0-136.0 ppm)

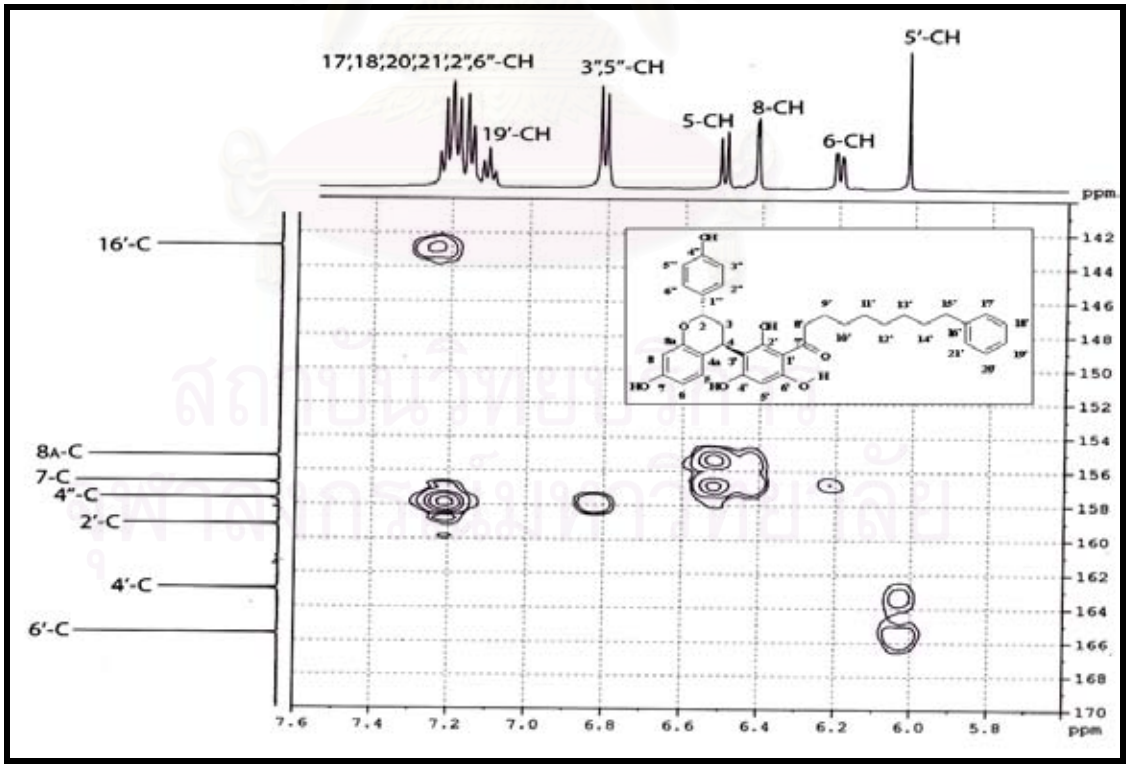

Figure 48d. HMBC Spectrum of compound KG-F5

(expansion between δ_H 5.8-7.6 ppm, δ_C 142.0-170.0 ppm)

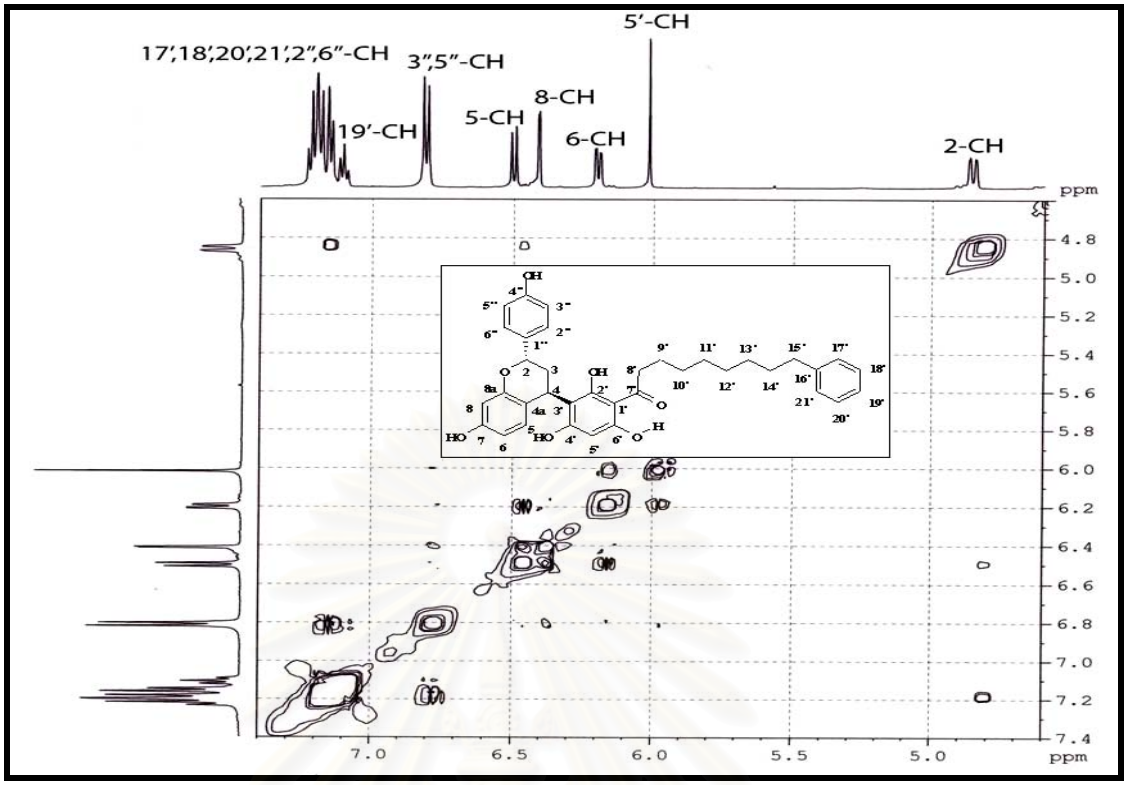

Figure 49a. NOESY Spectrum of compound KG-F5

(expansion between δ 4.8- 7.0 ppm)

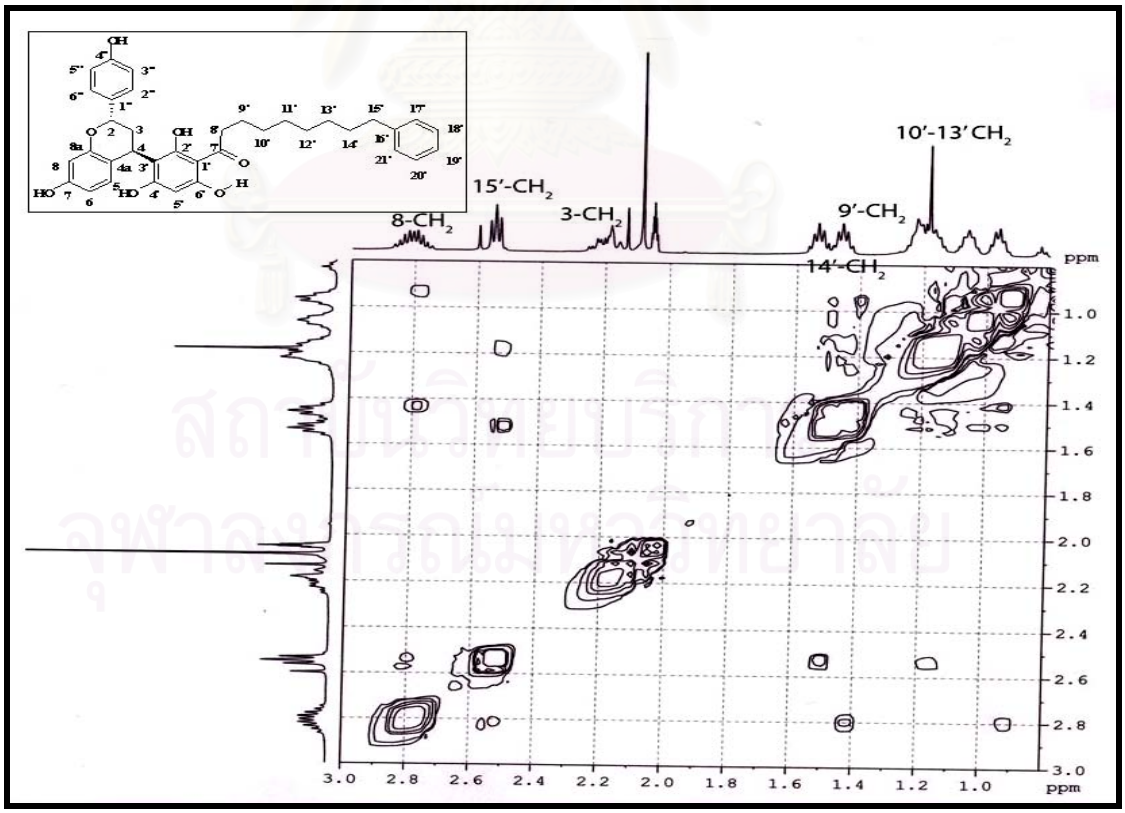

Figure 49b. NOESY Spectrum of compound KG-F5

(expansion between δ 1.0- 3.0 ppm)

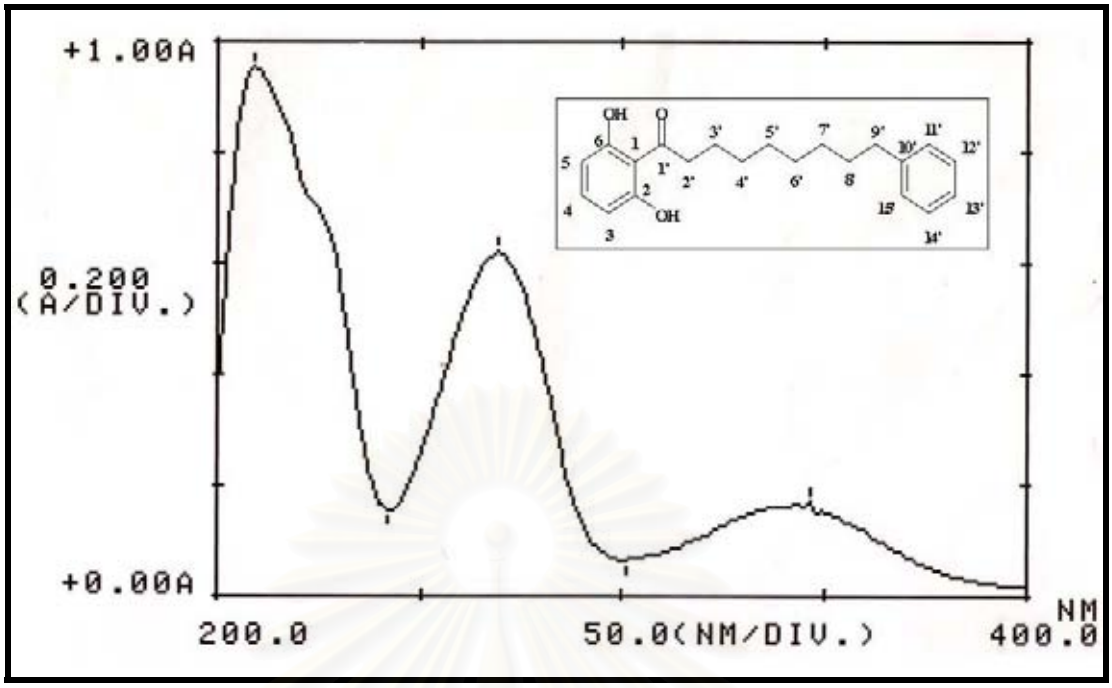

Figure 50. UV Spectrum of compound KG-F6 (in MeOH)

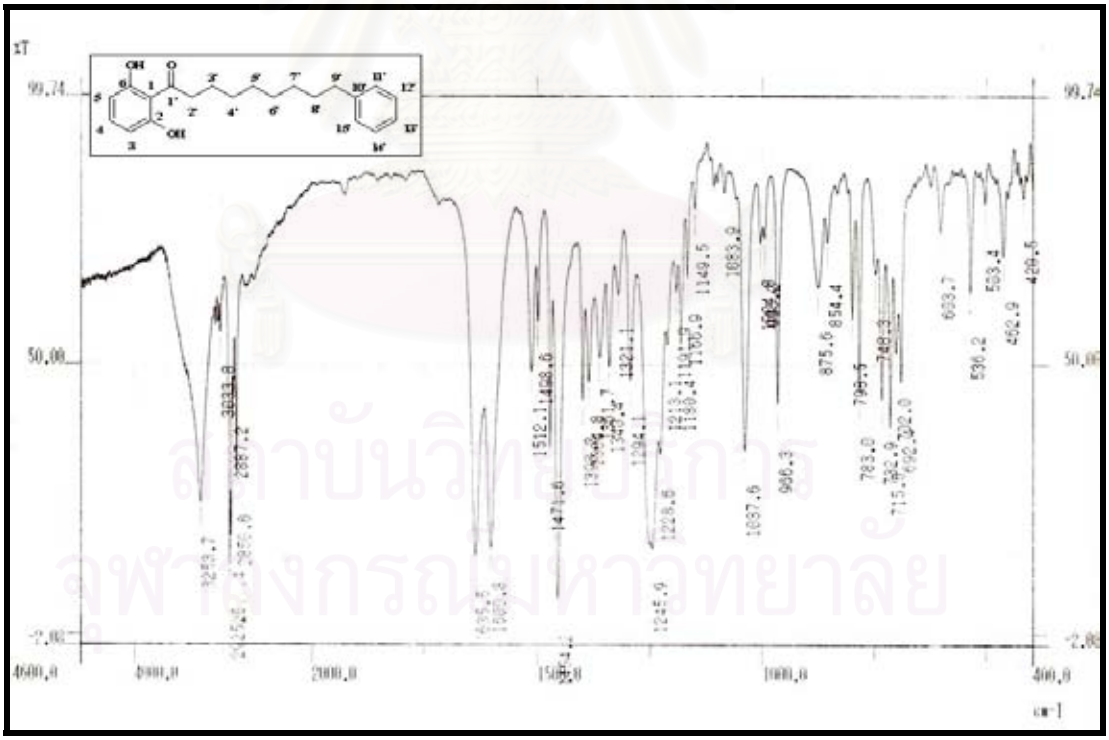

Figure 51. IR Spectrum of compound KG-F6 (KBr disc)

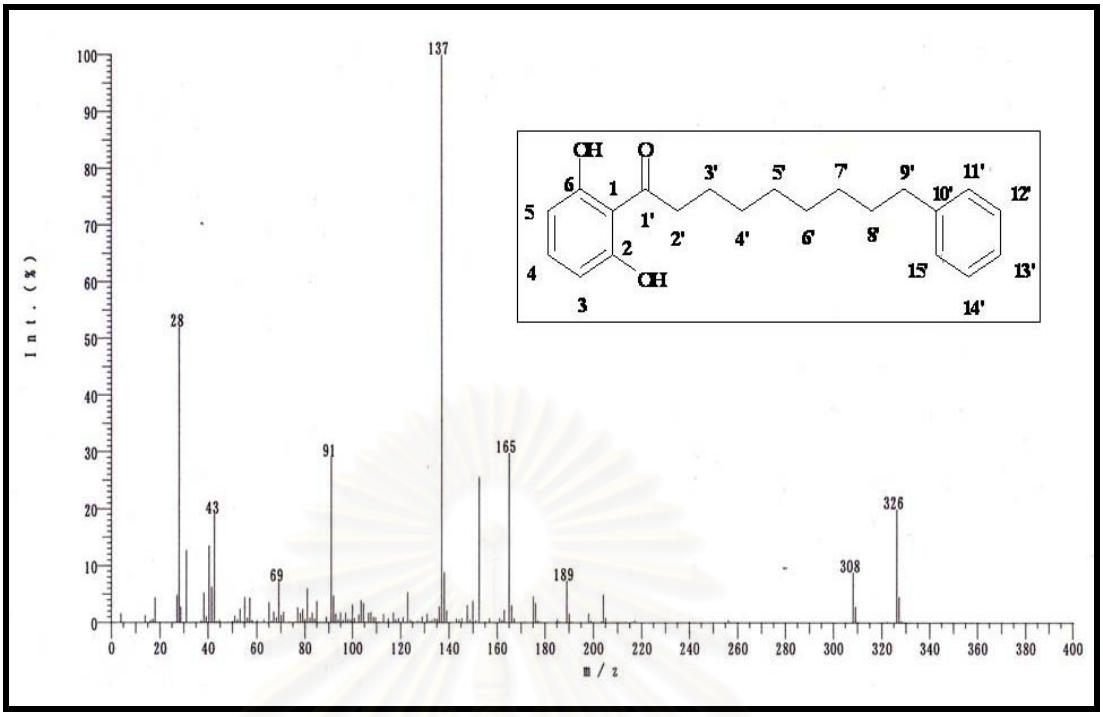

Figure 52. EI Mass spectrum of compound KG-F6

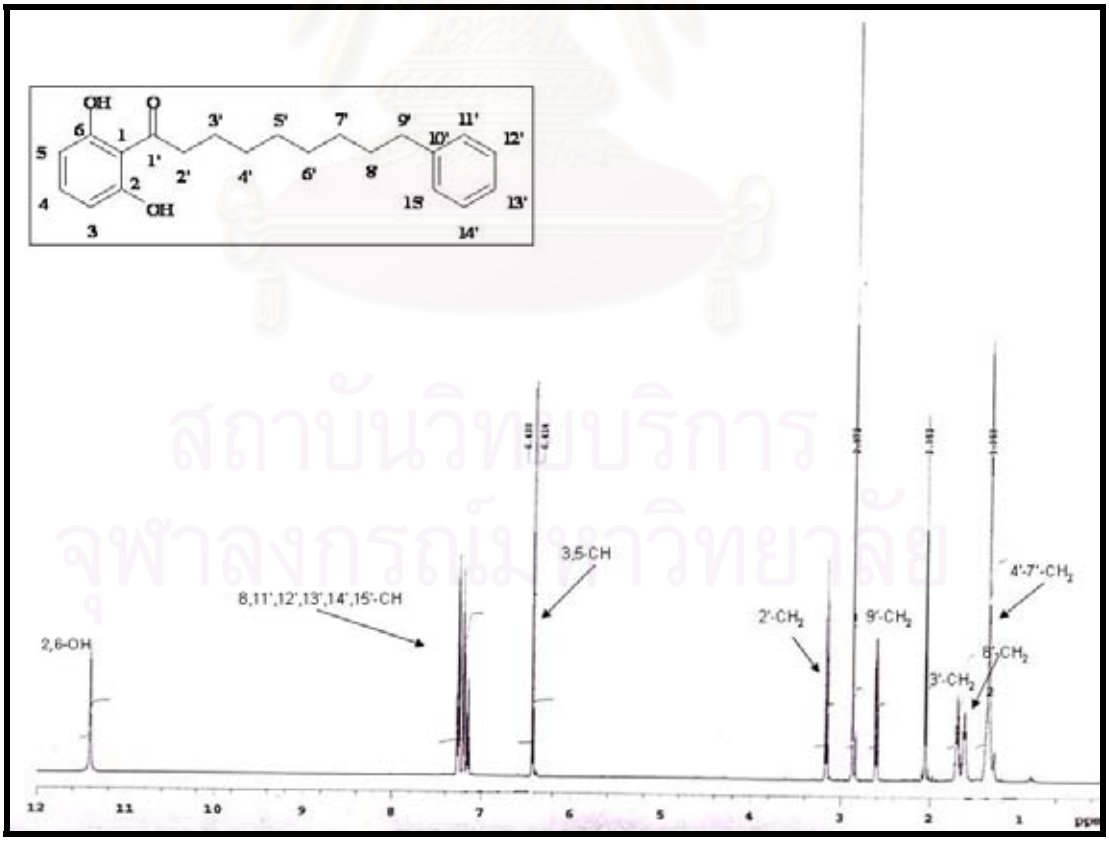

Figure 53. ^{1}H NMR (500 MHz) Spectrum of compound KG-F6 (in acetone-d_6)

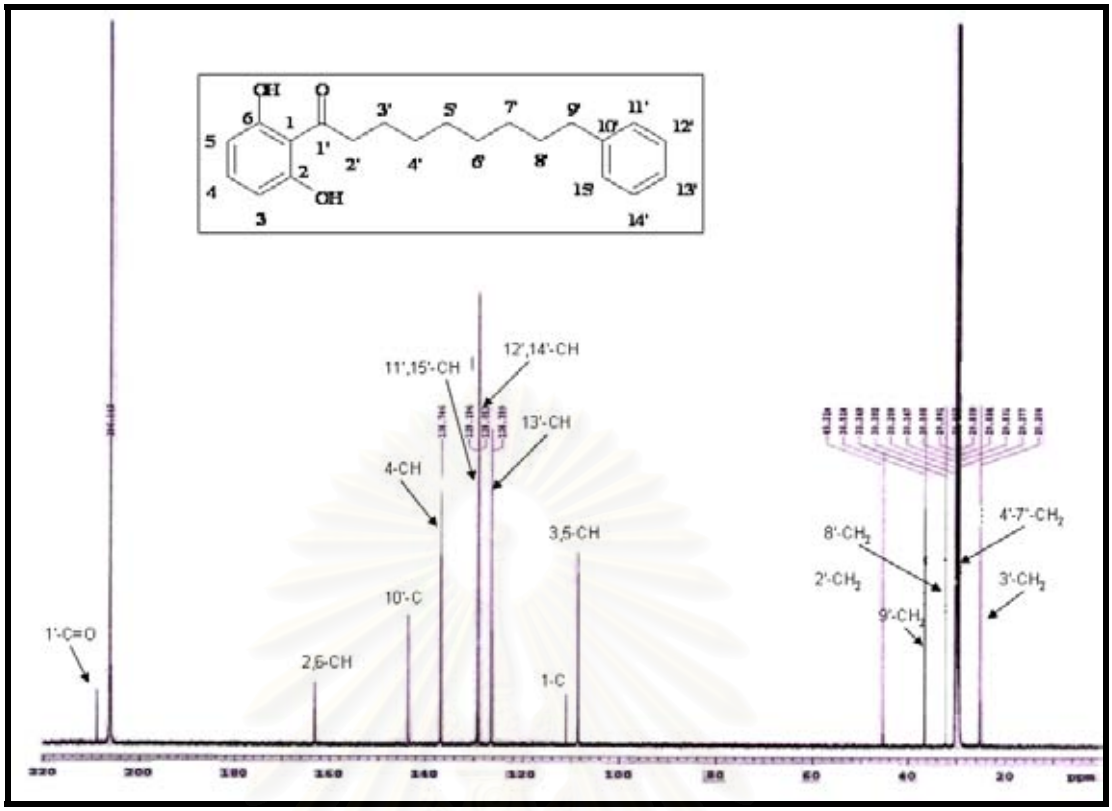

Figure 54. ^{13}C NMR (125 MHz) Spectrum of compound KG-F6 (in acetone-d_6)

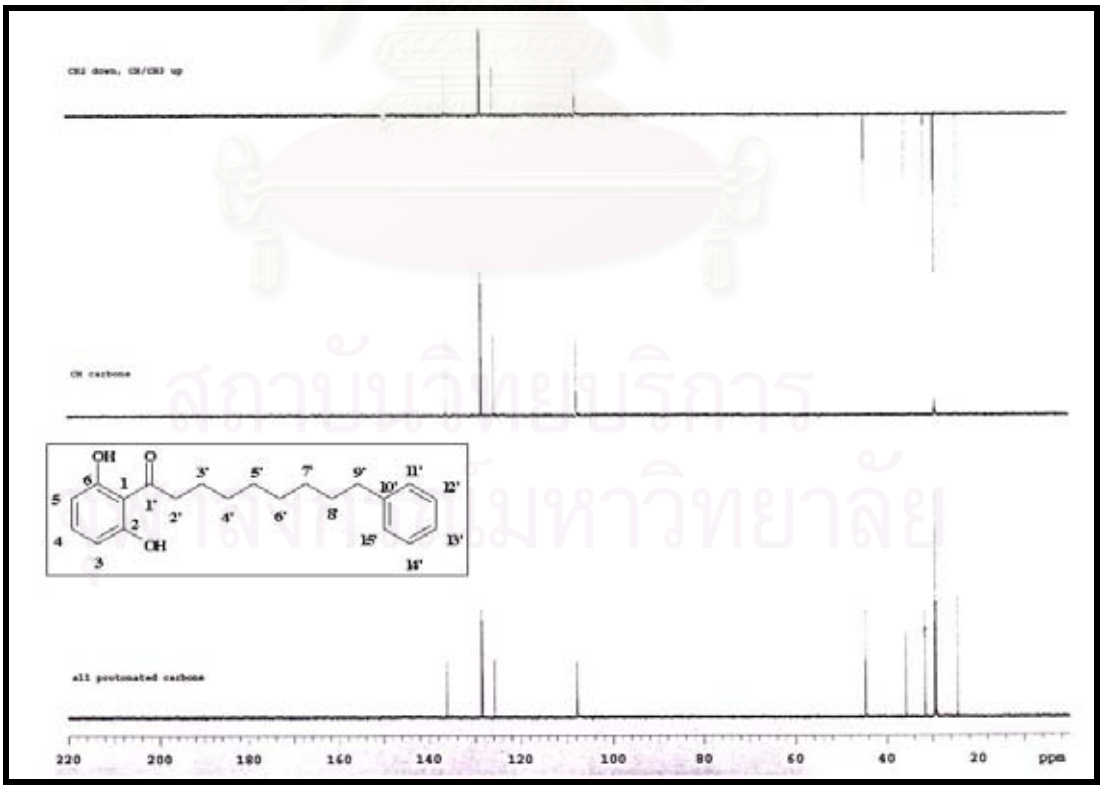

Figure 55. DEPT 135, DEPT 90 and ^{13}C NMR Spectrum of compound KG-F6 (in acetone-d_6)

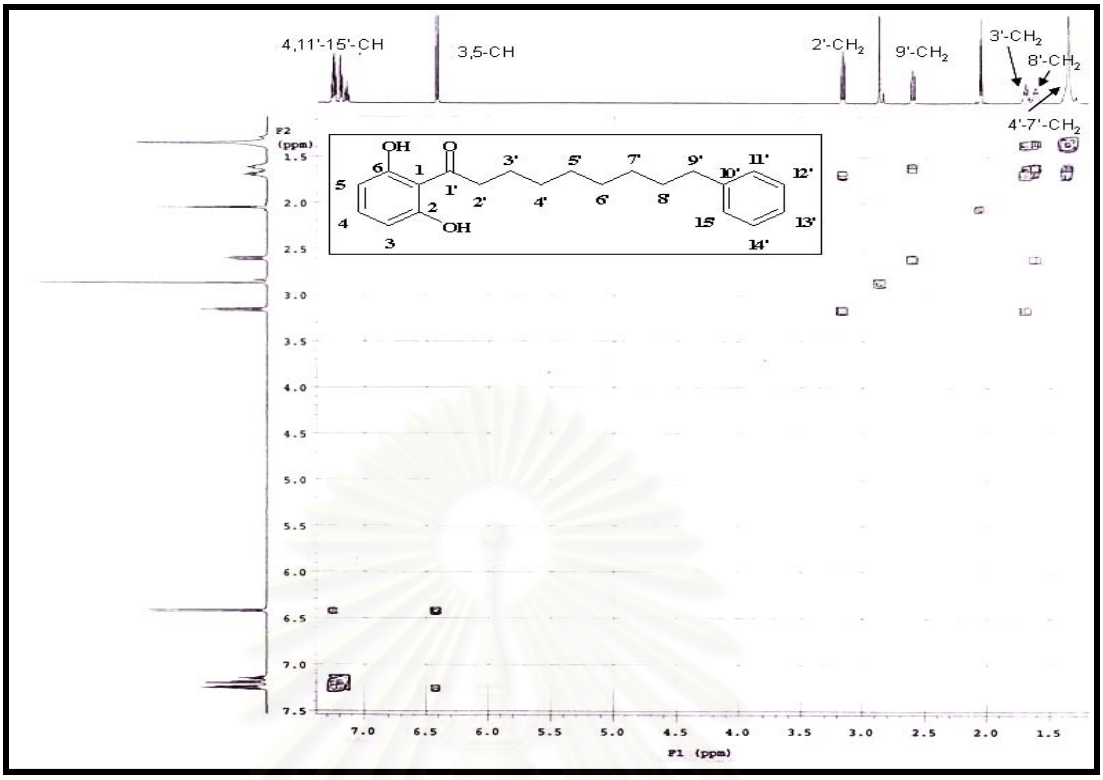

Figure 56. ^{1}H-^{1}H COSY Spectrum of compound KG-F6 (in acetone-d_6)

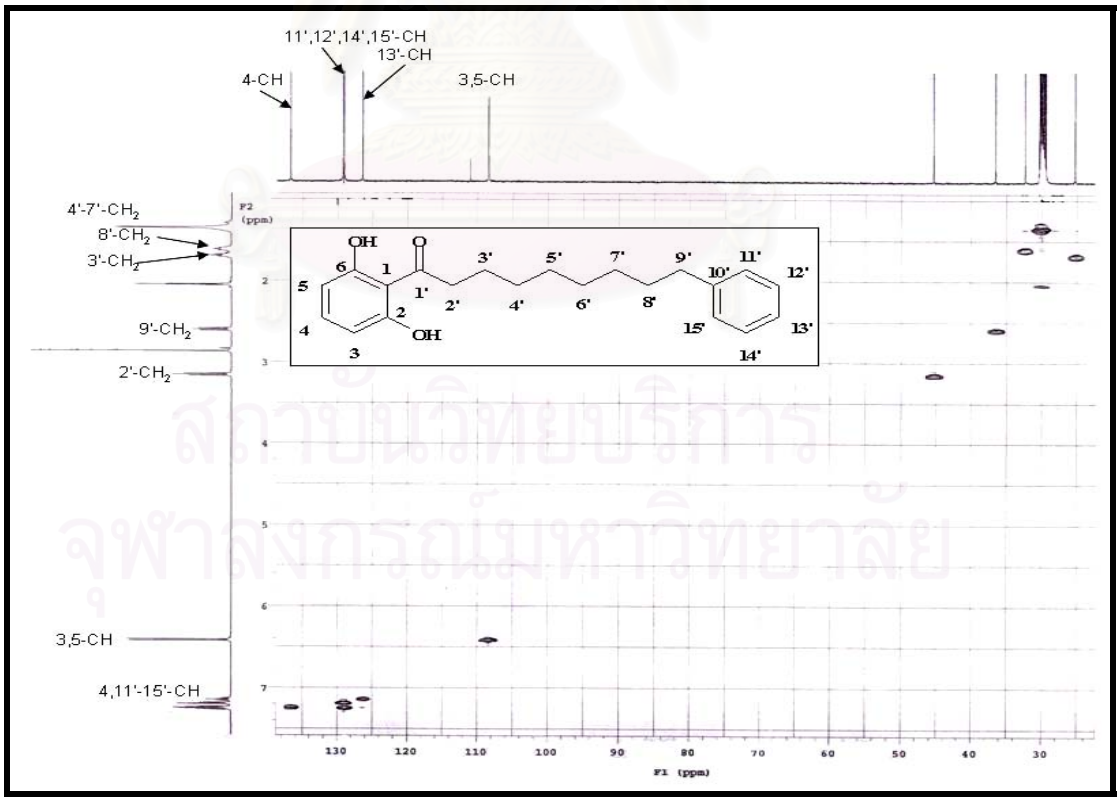

Figure 57. HMQC Spectrum of compound KG-F6

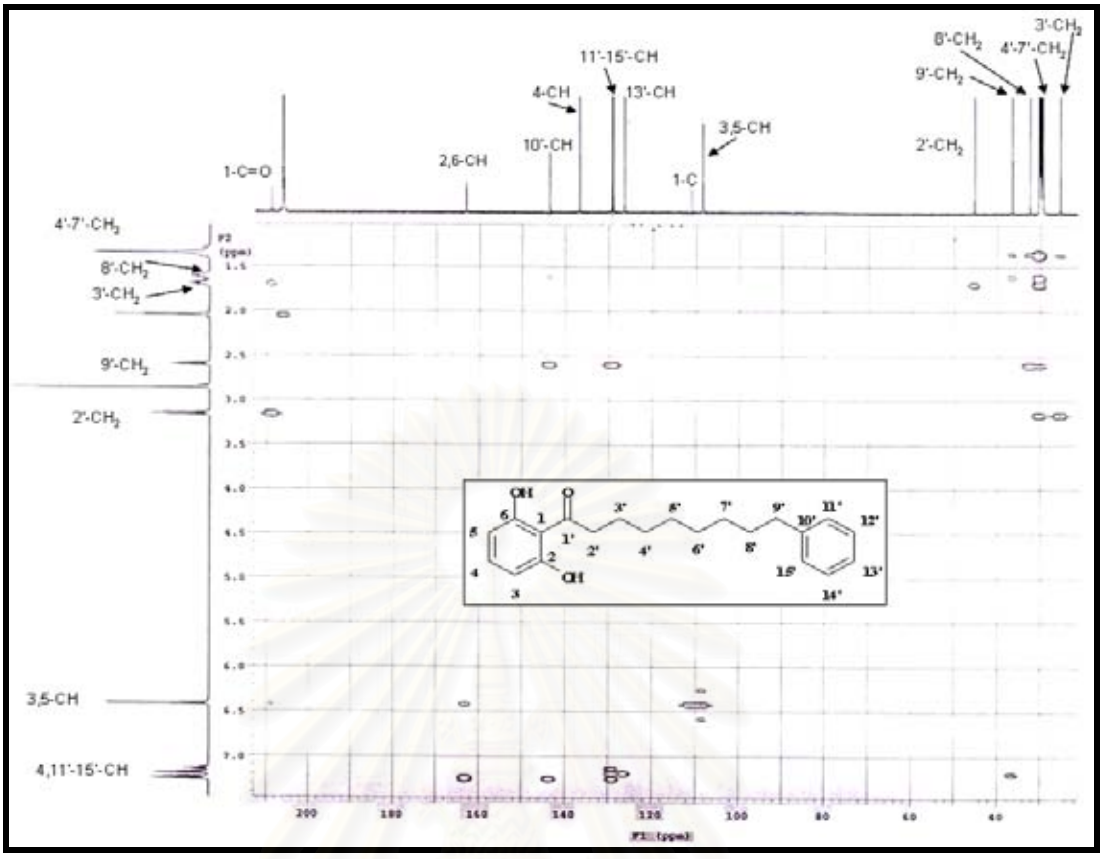

Figure 58. HMBC Spectrum of compound KG-F6

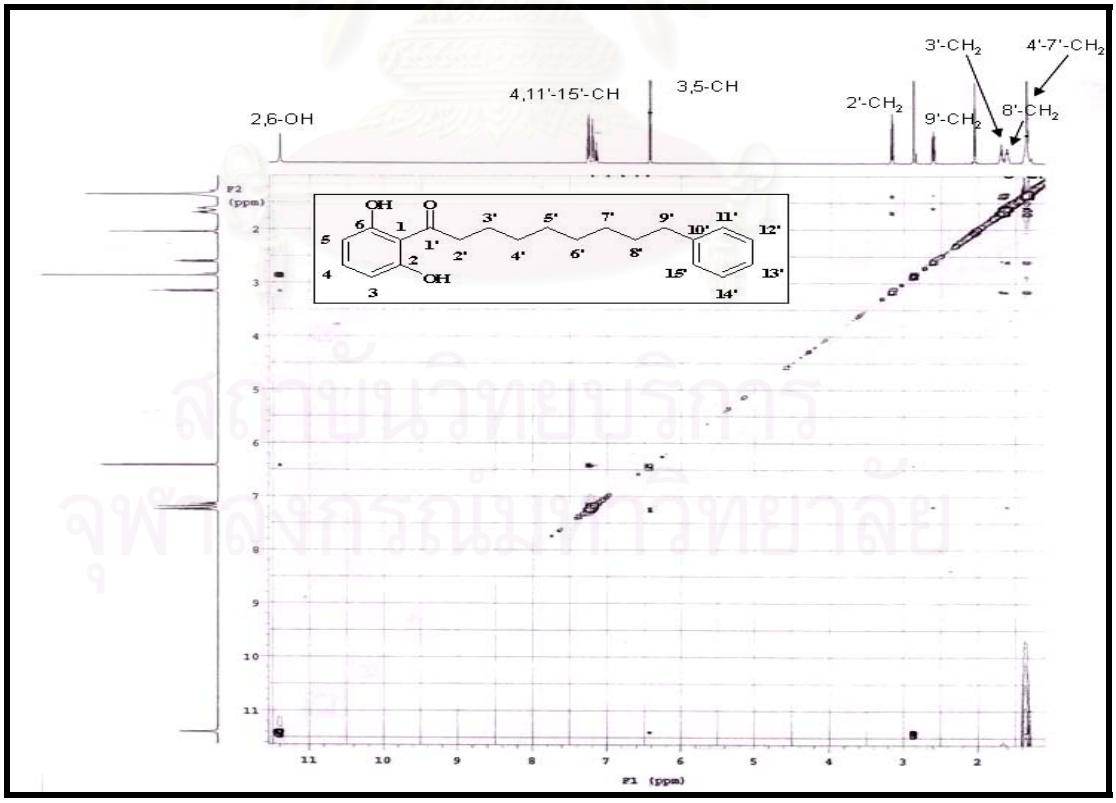

Figure 59a. NOESY Spectrum of compound KG-F6

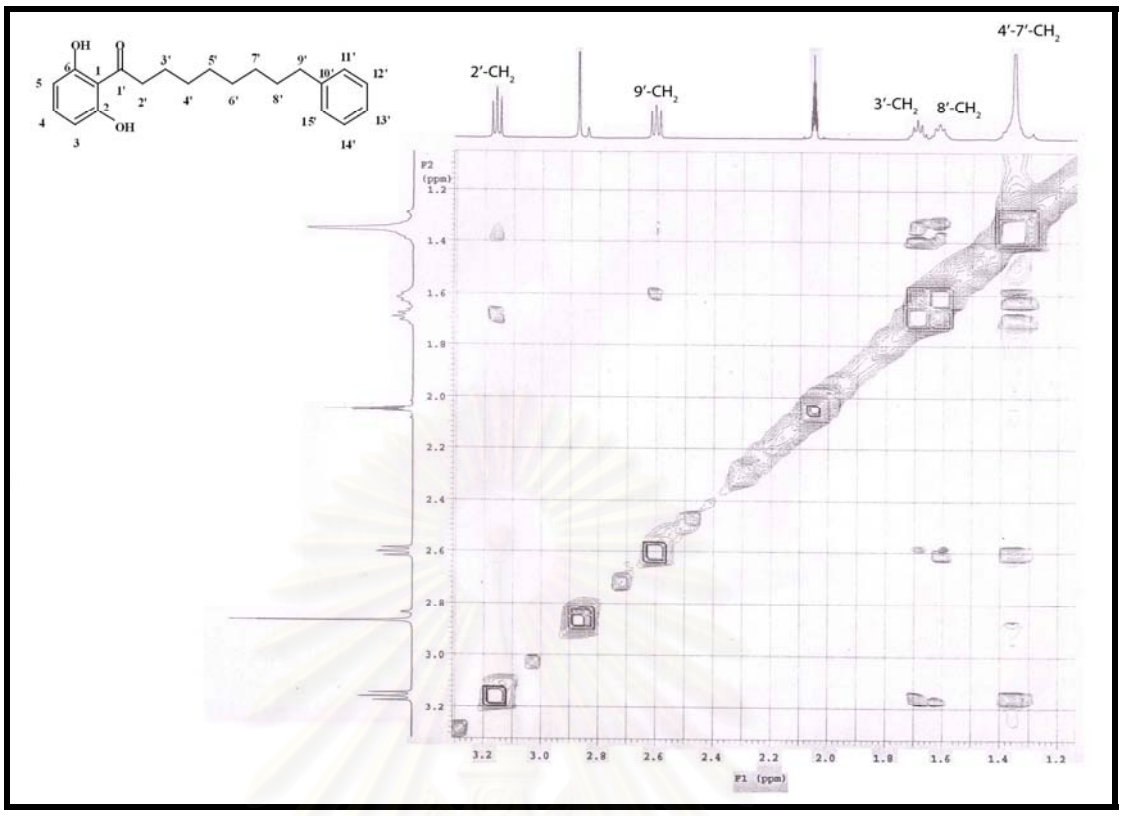

Figure 59b. NOESY Spectrum of compound KG-F6
(expansion between δ_H 1.2-3.2 ppm)

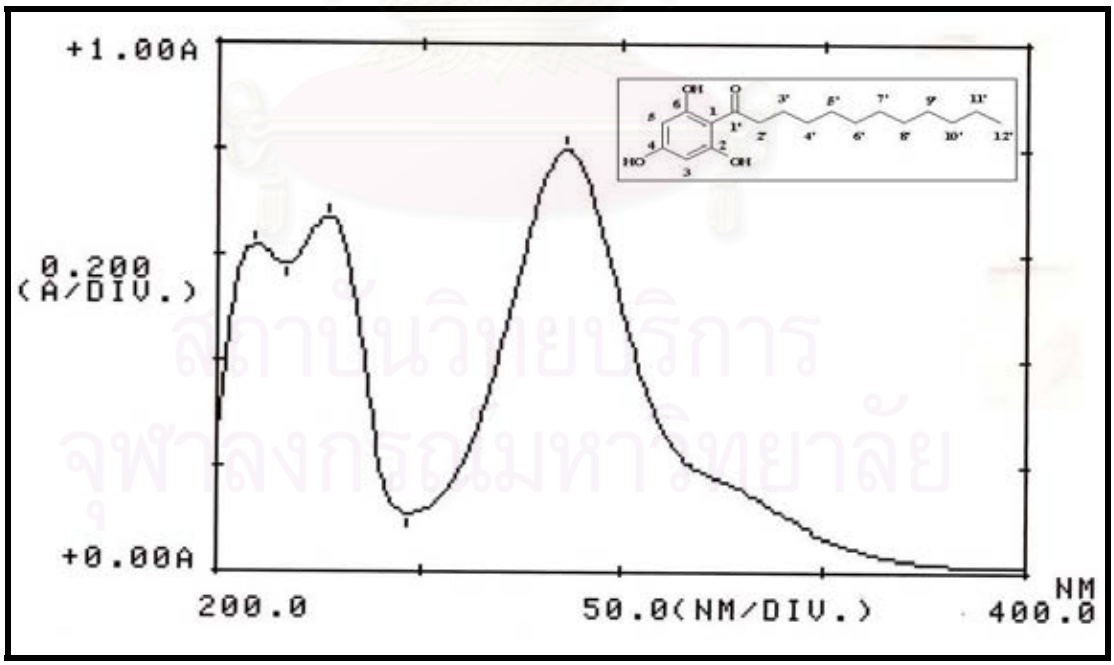

Figure 60. UV Spectrum of compound KG-F7 (in MeOH)

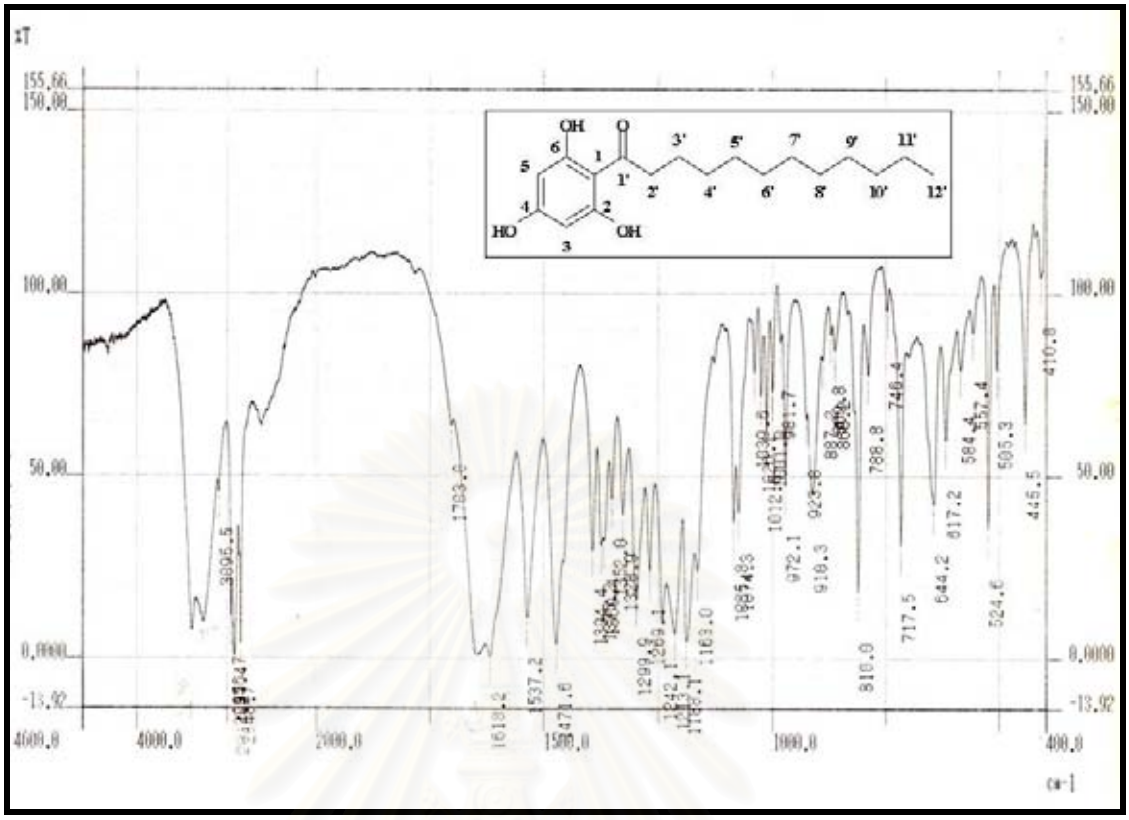

Figure 61. IR Spectrum of compound KG-F7 (KBr disc)

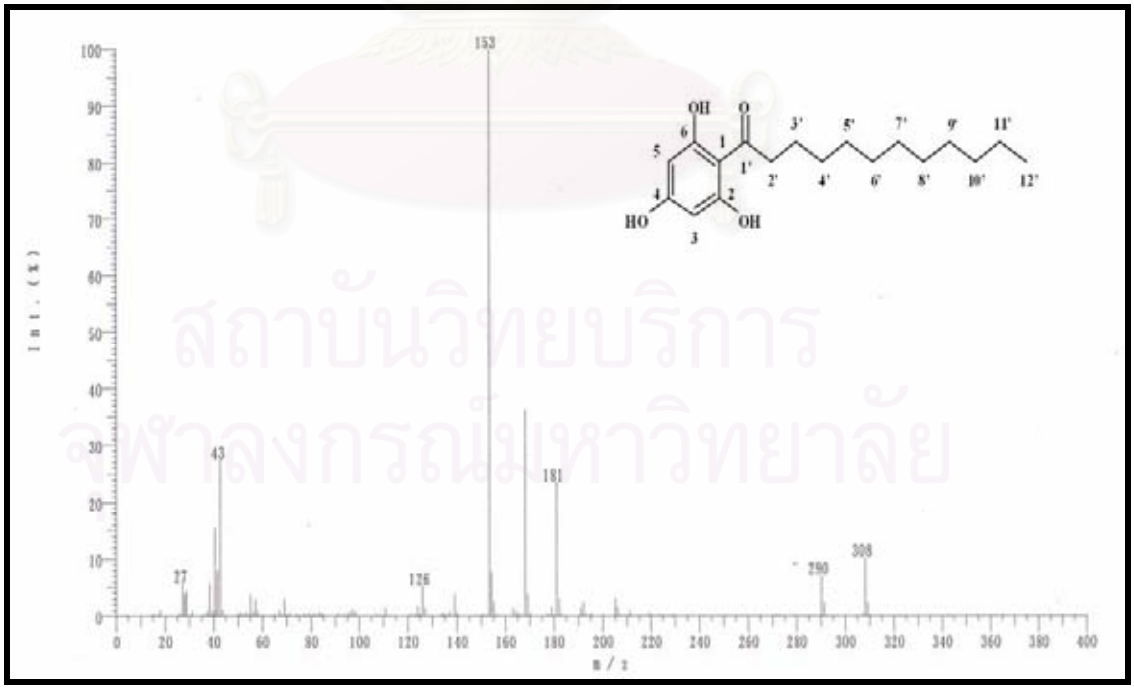

Figure 62. EI Mass spectrum of compound KG-F7

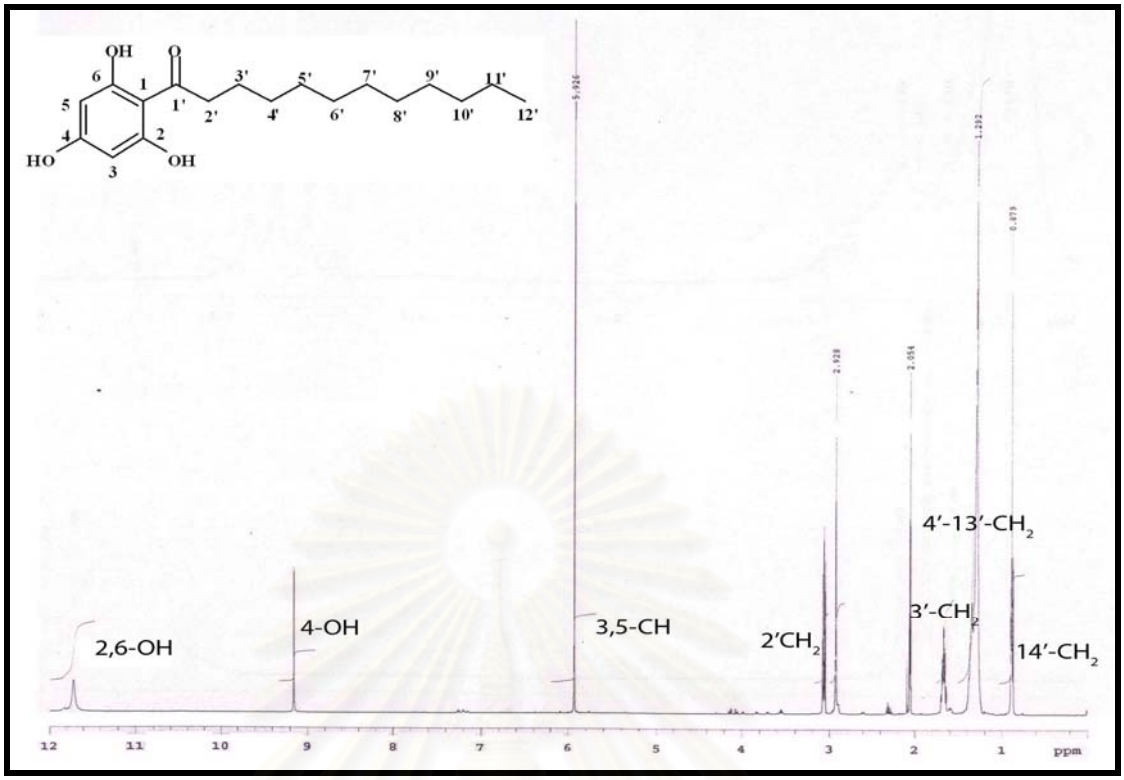

Figure 63a. ^{1}H NMR (500 MHz) Spectrum of compound KG-F7 (in acetone-d_6)

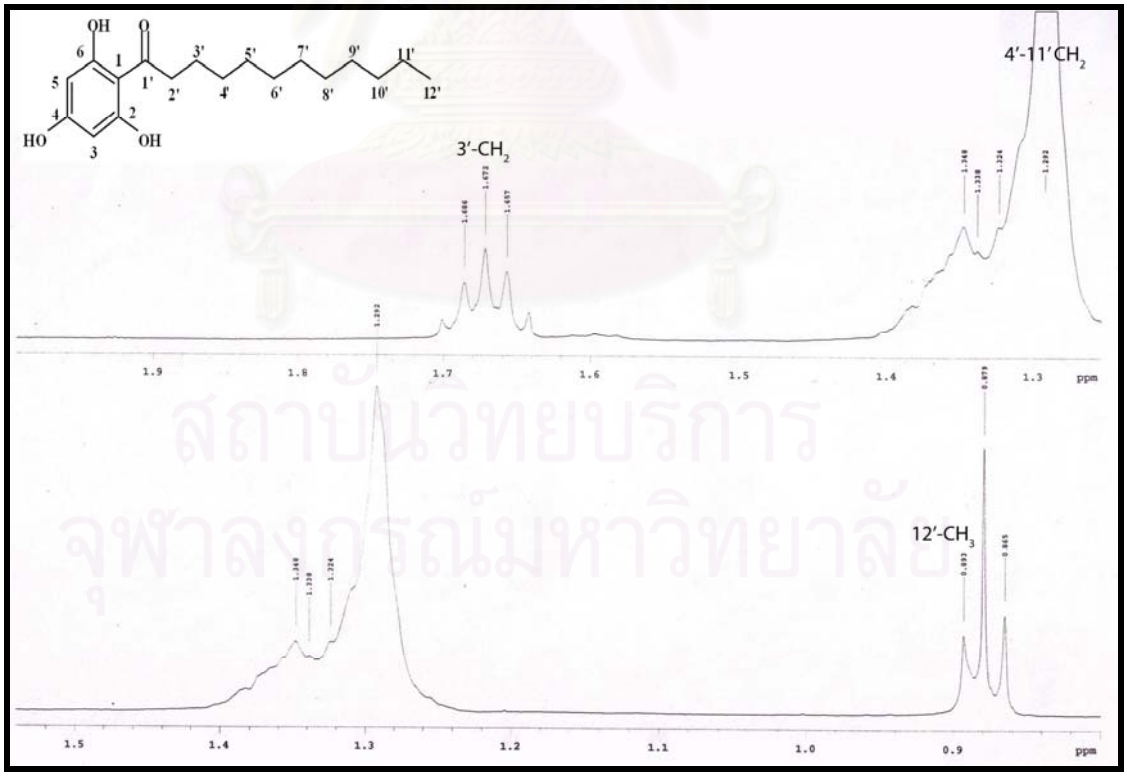

Figure 63b. ^{1}H NMR (500 MHz) Spectrum of compound KG-F7 (in acetone-d_6) (expansion between δ_H 0.9-1.9 ppm)

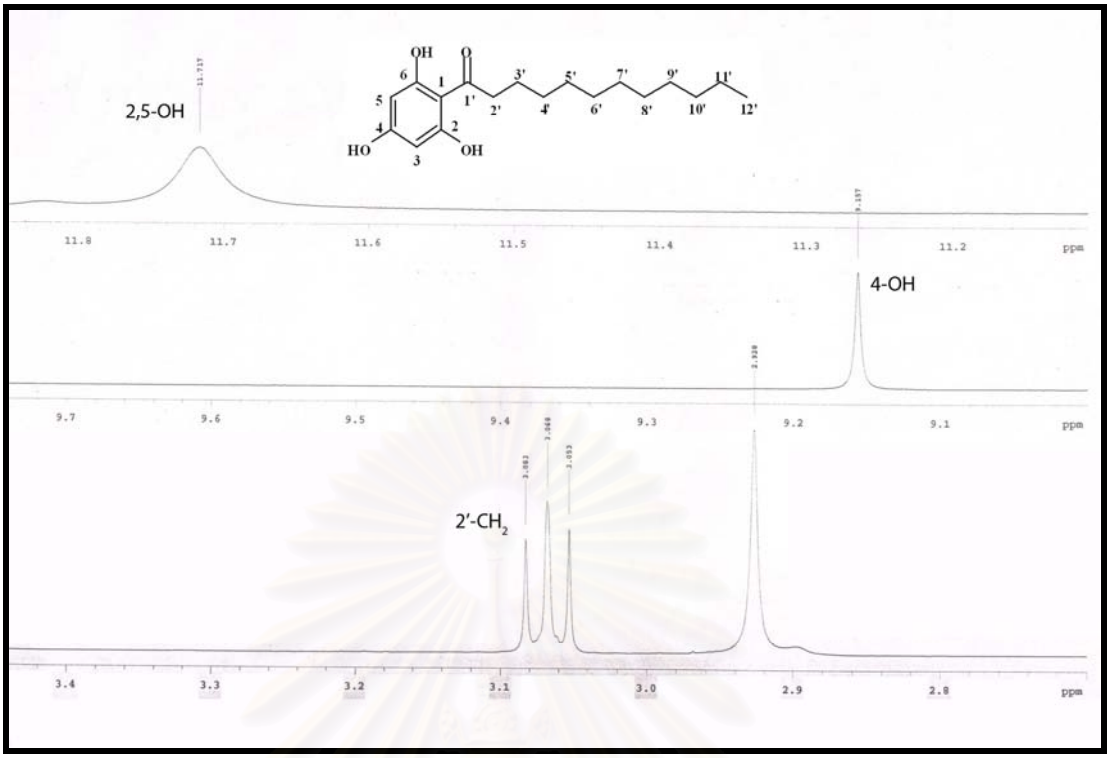

Figure 63c. ^{1}H NMR (500 MHz) Spectrum of compound KG-F7 (in acetone-d_6) (expansion between δ_H 9.1-11.9 ppm)

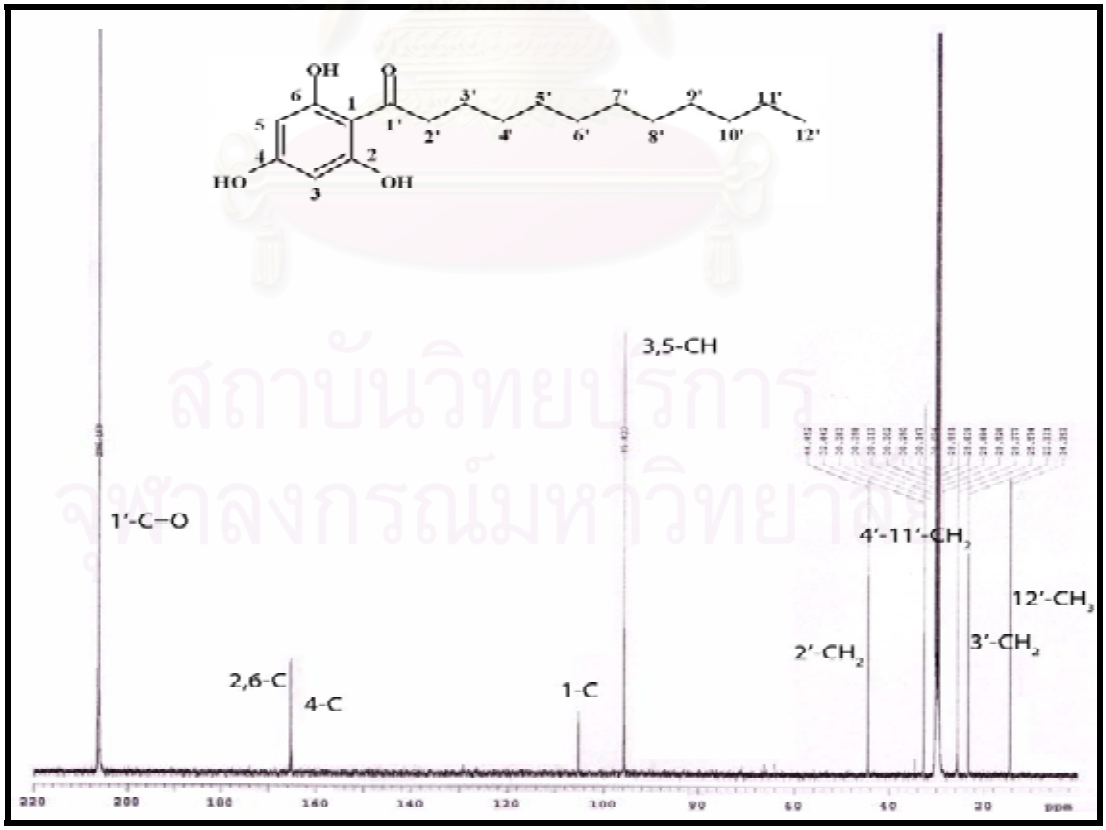

Figure 64. ^{13}C NMR (125 MHz) Spectrum of compound KG-F7 (in acetone-d_6)

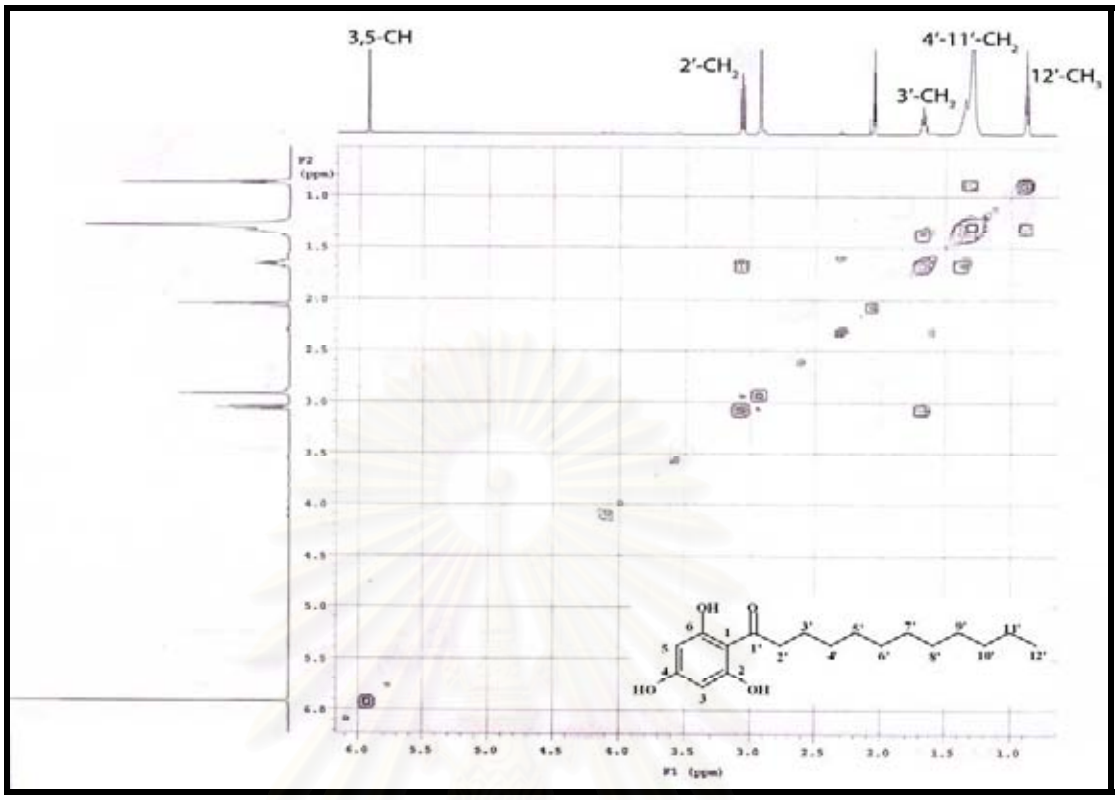

Figure 65a. ^{1}H-^{1}H COSY Spectrum of compound KG-F7 (in acetone-d_6)

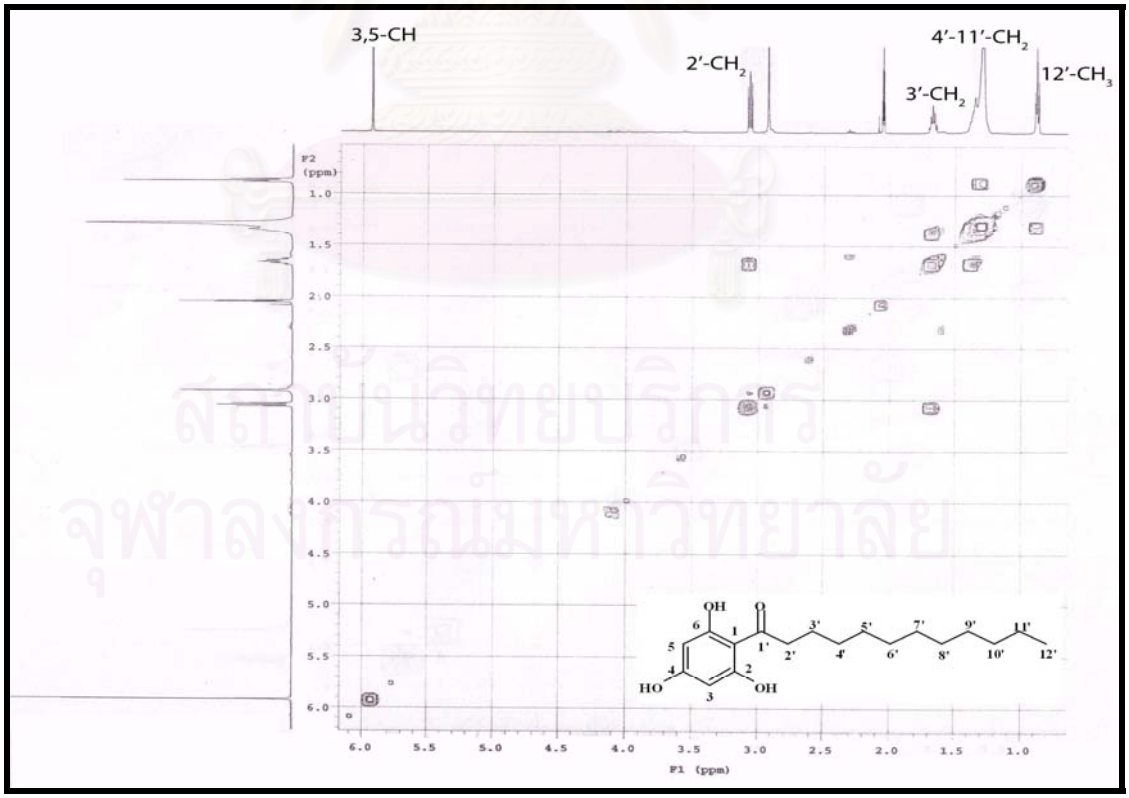

Figure 65b. ^{1}H-^{1}H COSY Spectrum of compound KG-F7 (in acetone-d_6)
(expansion between δ_H 1.0-6.0 ppm)

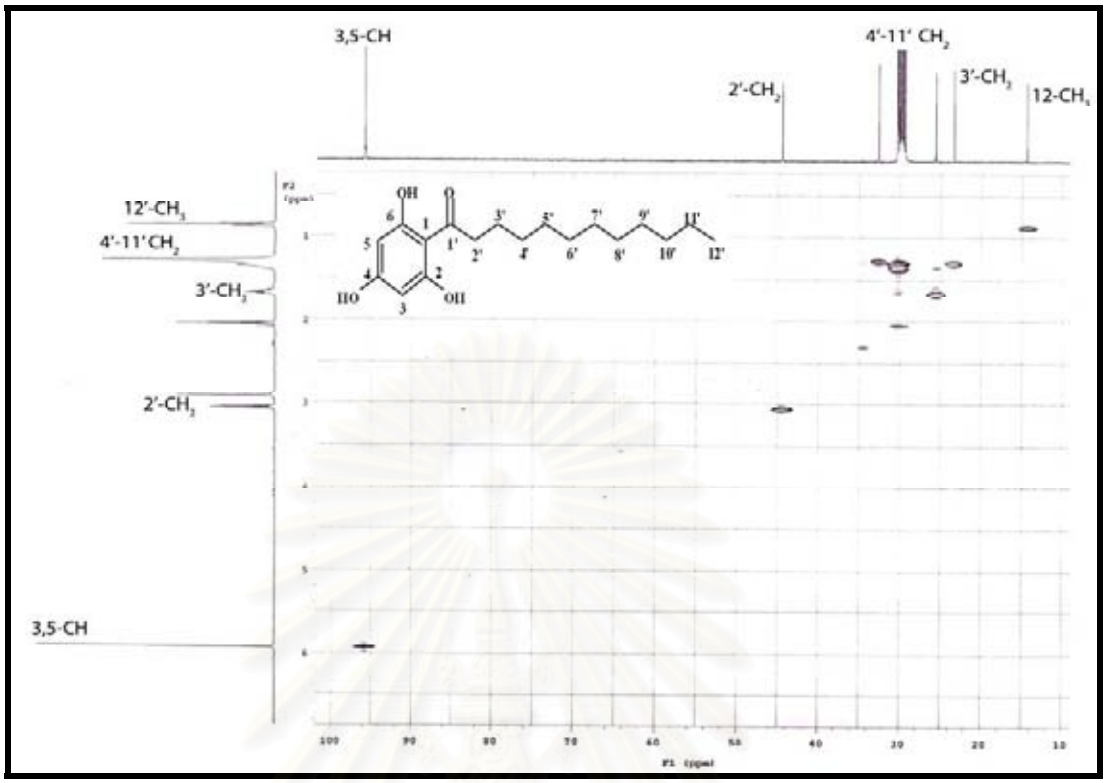

Figure 66. HMQC Spectrum of compound KG-F7

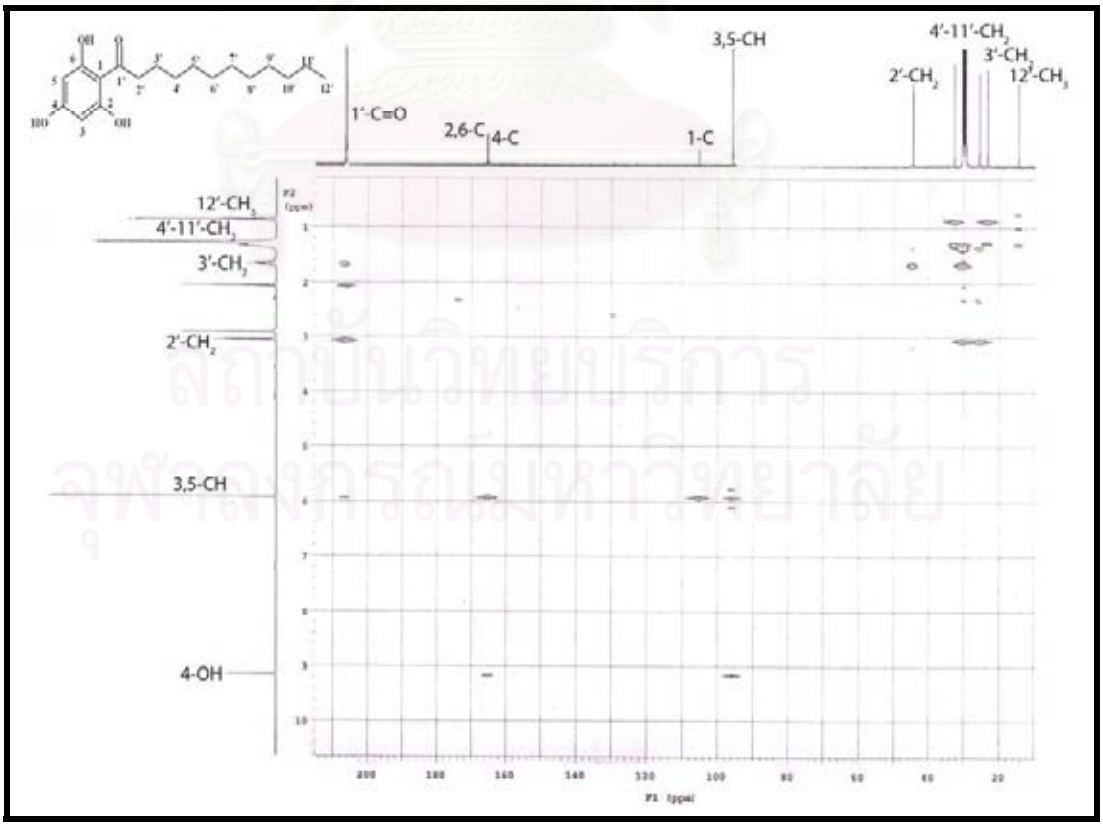

Figure 67. HMBC Spectrum of compound KG-F7

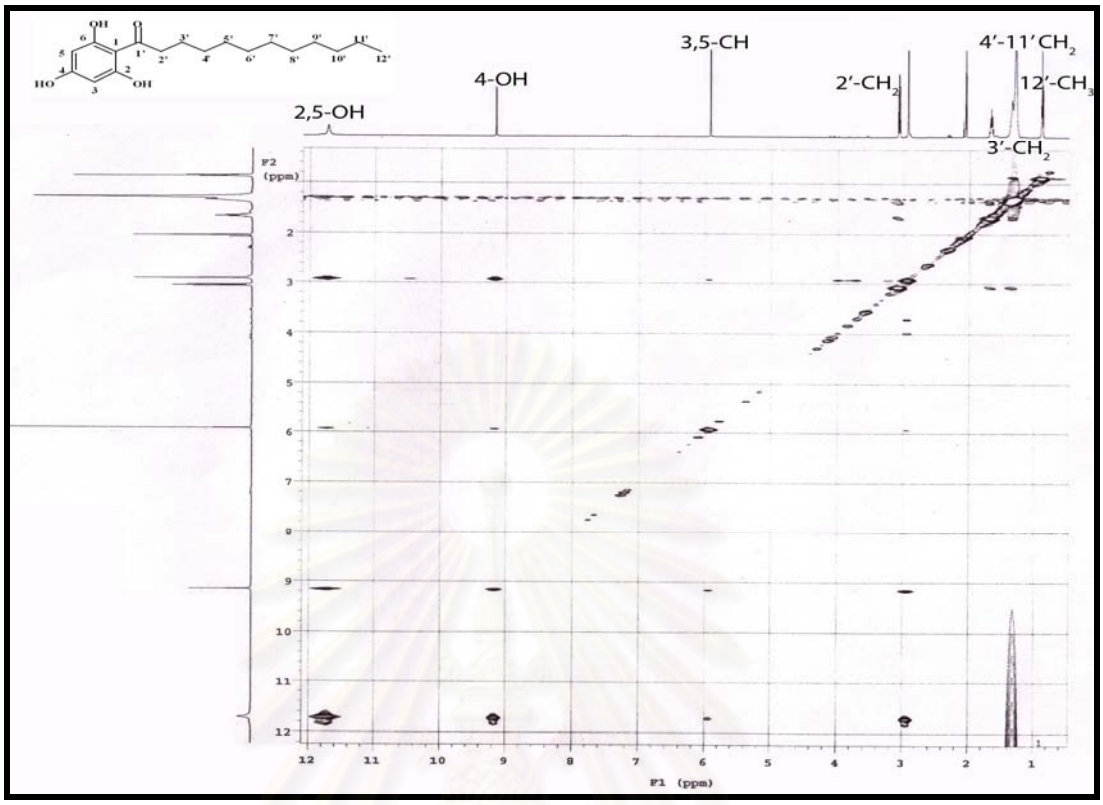

Figure 68. NOESY Spectrum of compound KG-F7

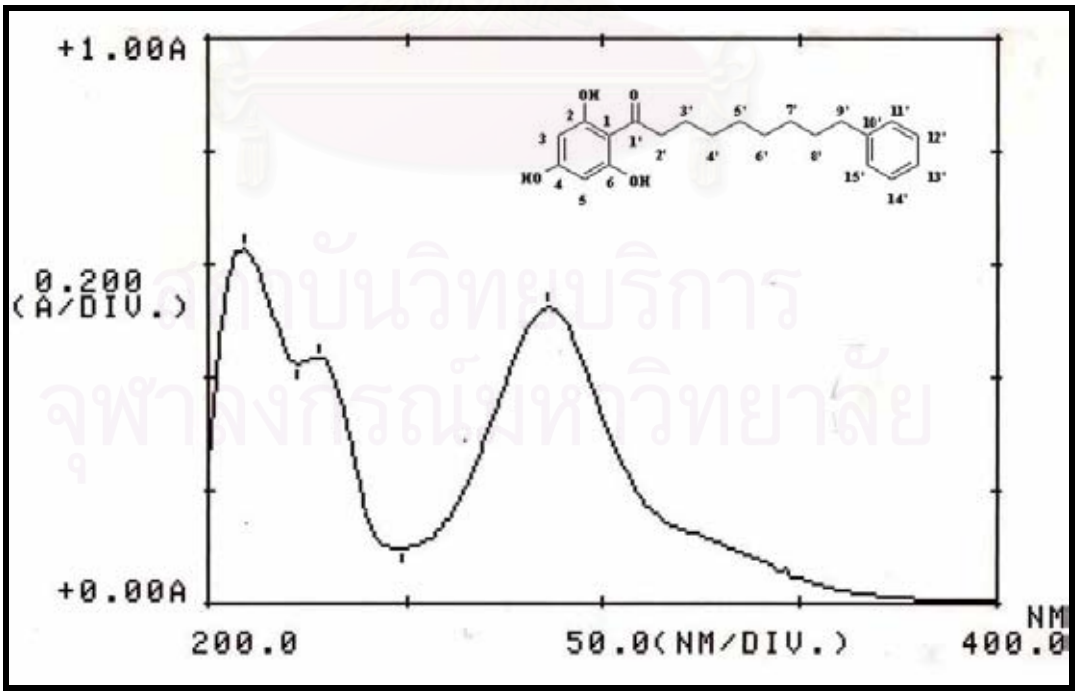

Figure 69. UV Spectrum of compound KG-F8 (in MeOH)

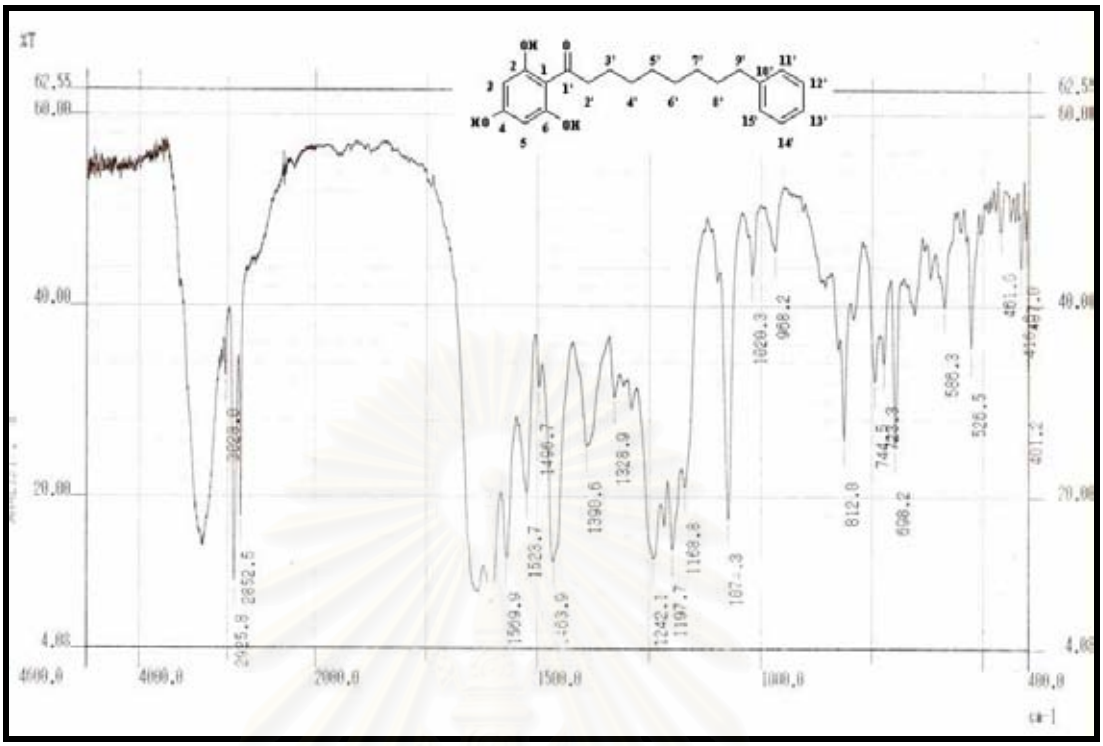

Figure 70. IR Spectrum of compound KG-F8 (KBr disc)

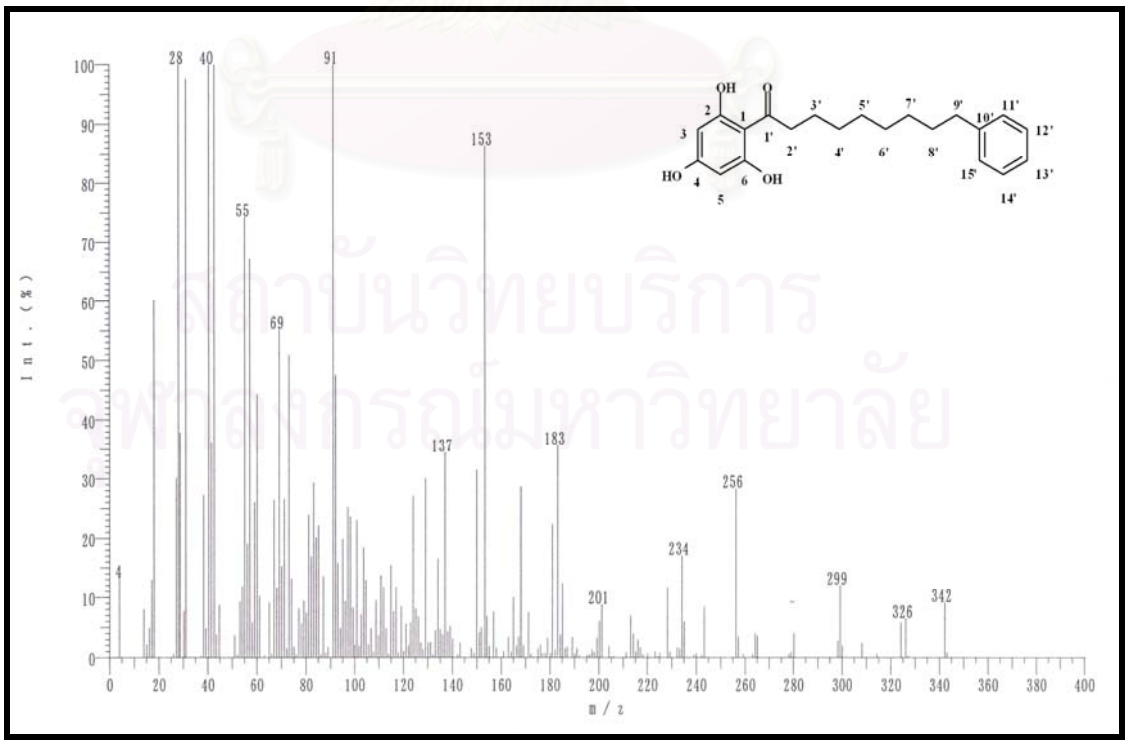

Figure 71. EI Mass spectrum of compound KG-F8

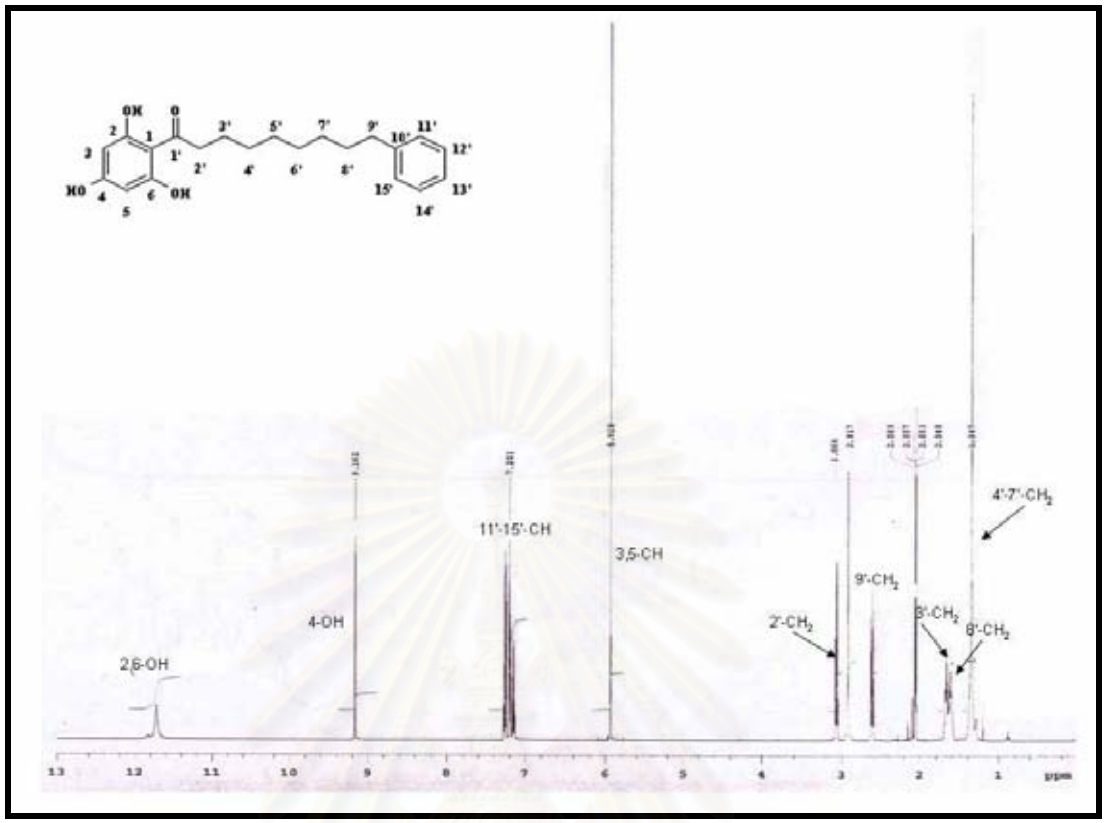

Figure 72. ^{1}H NMR (500 MHz) Spectrum of compound KG-F8 (in acetone-d_6)

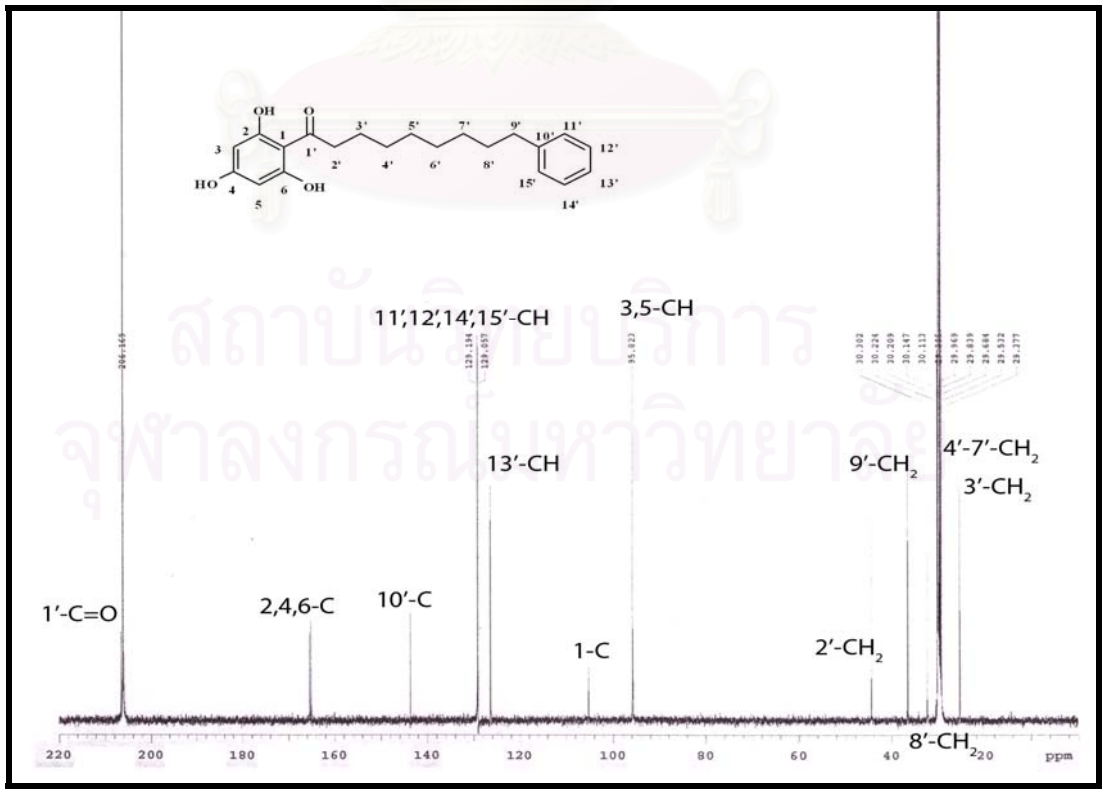

Figure 73. ^{13}C NMR (125 MHz) Spectrum of compound KG-F8 (in acetone-d_6)

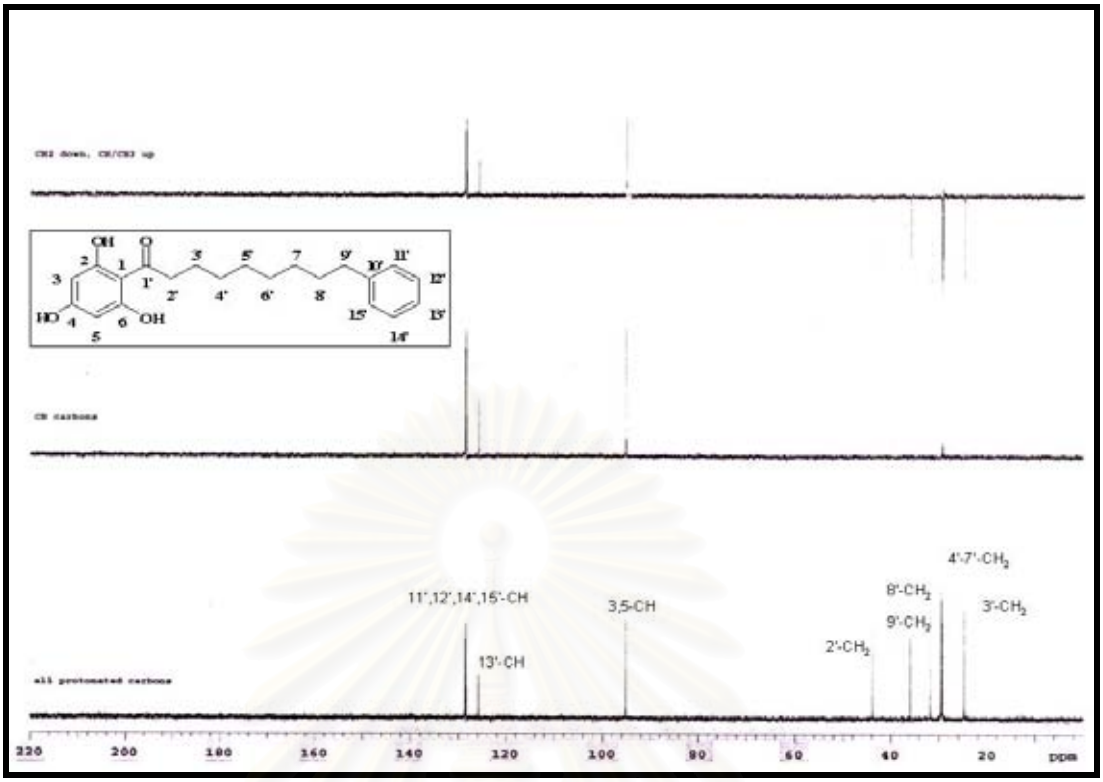

Figure 74. DEPT135, DEPT 90 and ^{13}C NMR Spectrum of compound KG-F8 (in acetone-d_6)

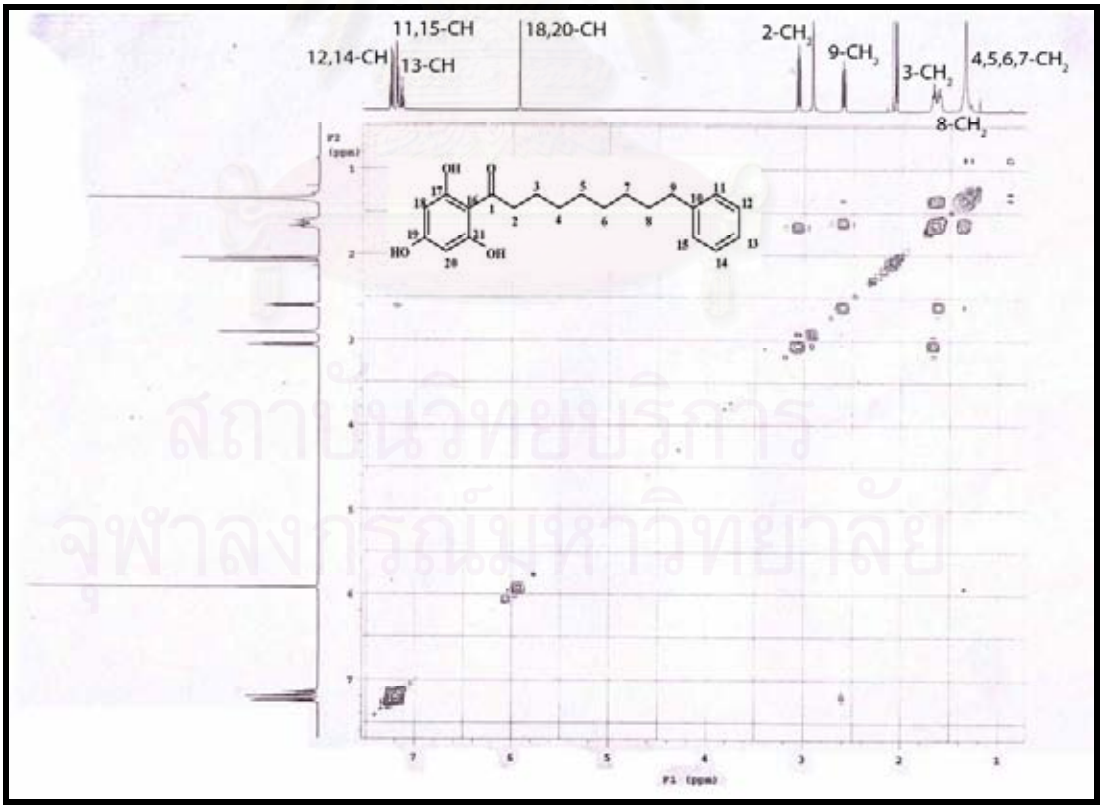

Figure 75a. ^{1}H-^{1}H COSY Spectrum of compound KG-F8 (in acetone-d_6)

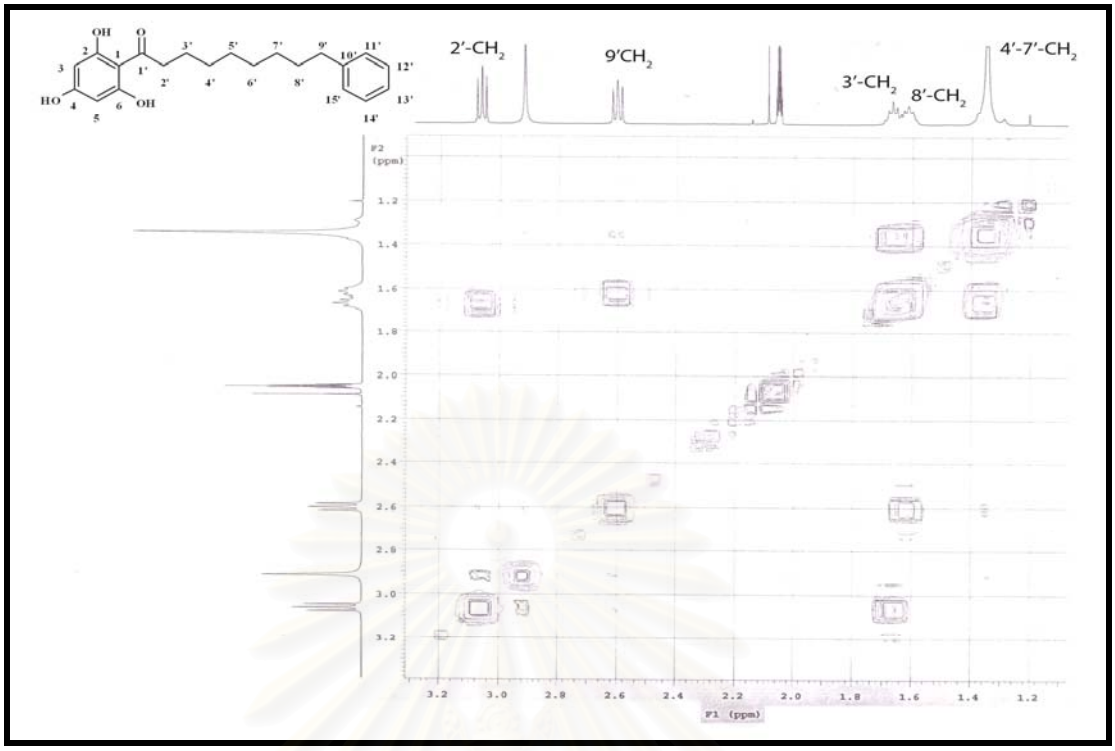

Figure 75b. ^{1}H-^{1}H COSY Spectrum of compound KG-F8 (in acetone-d_6) (expansion between δ_H1.2 to 3.2 ppm)

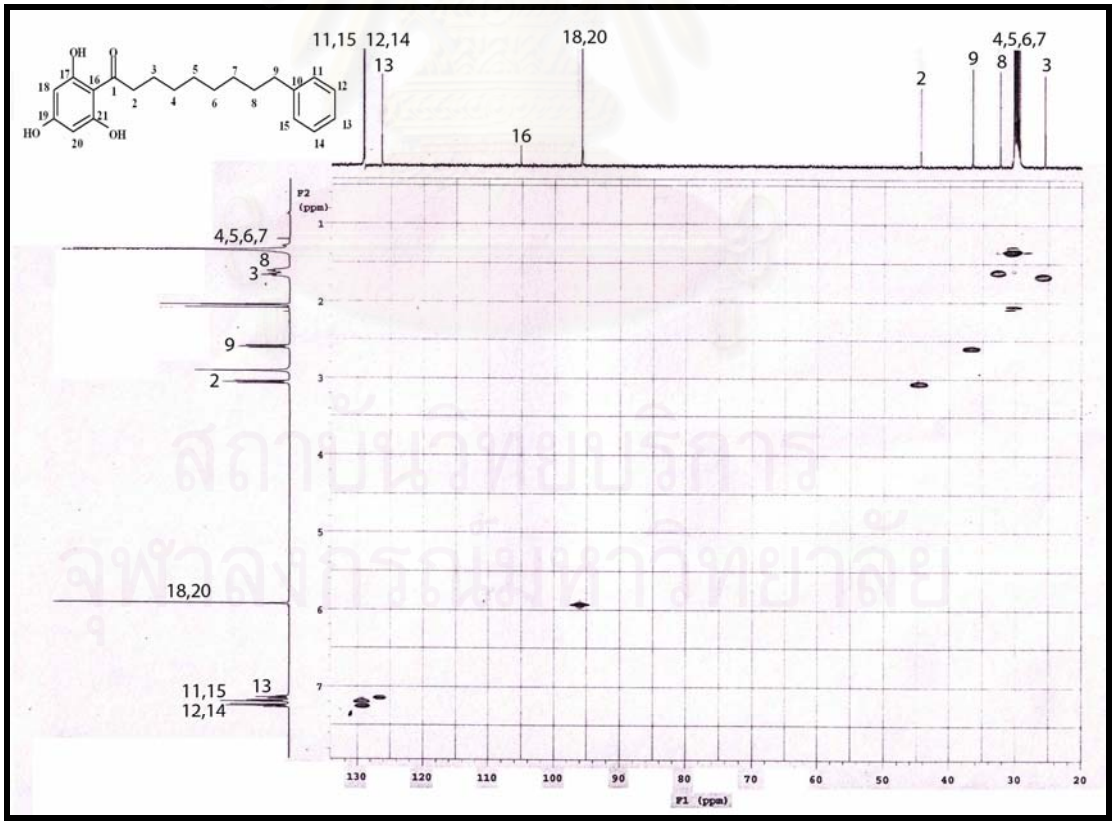

Figure 76. HMQC Spectrum of compound KG-F8

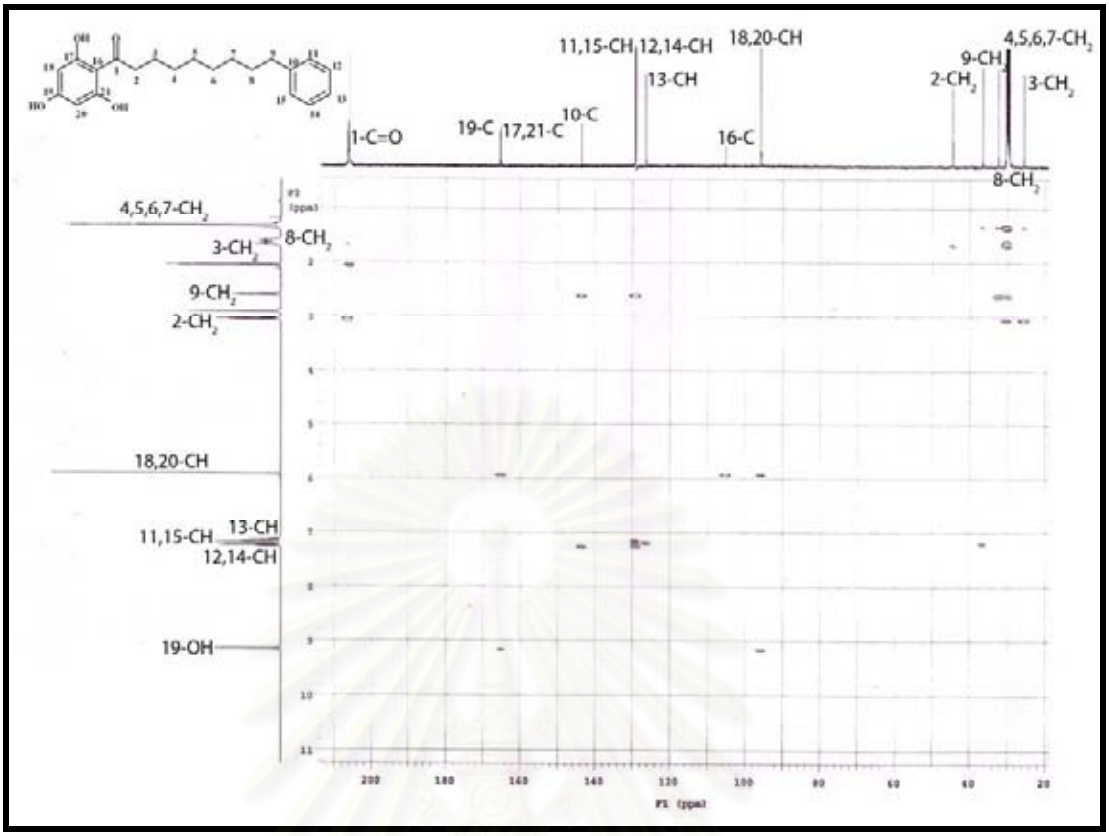

Figure 77. HMBC Spectrum of compound KG-F8

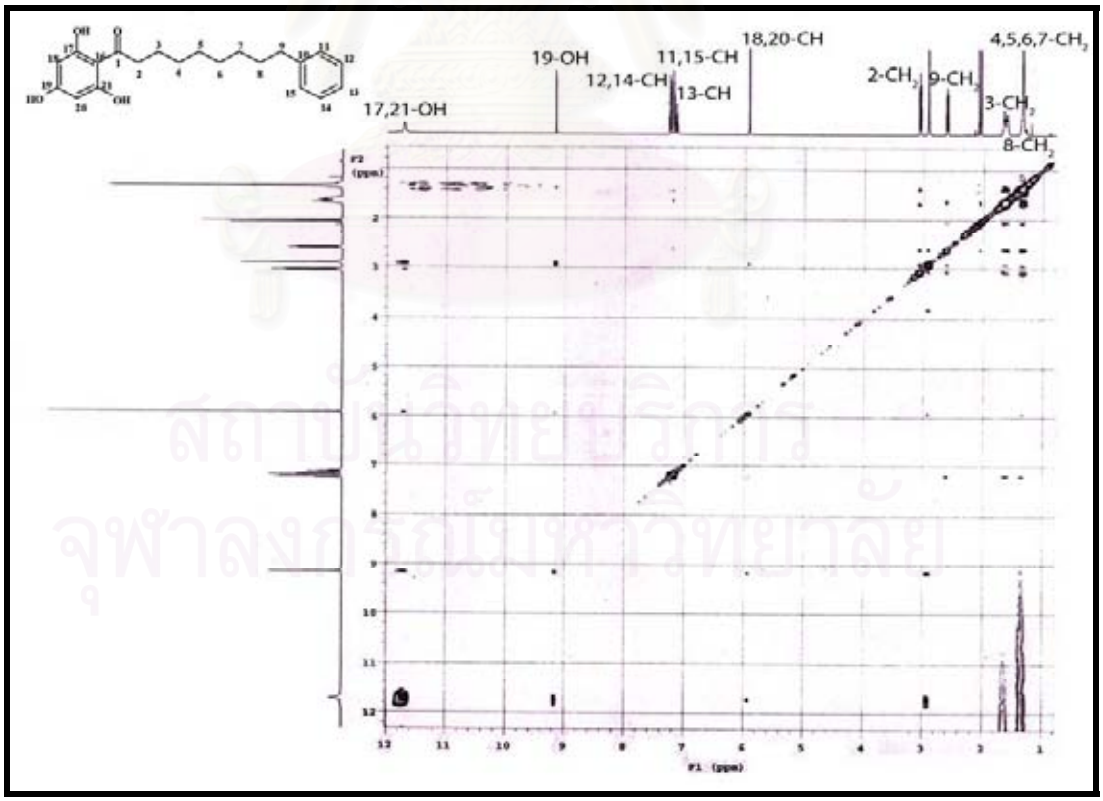

Figure 78a. NOESY Spectrum of compound KG-F8

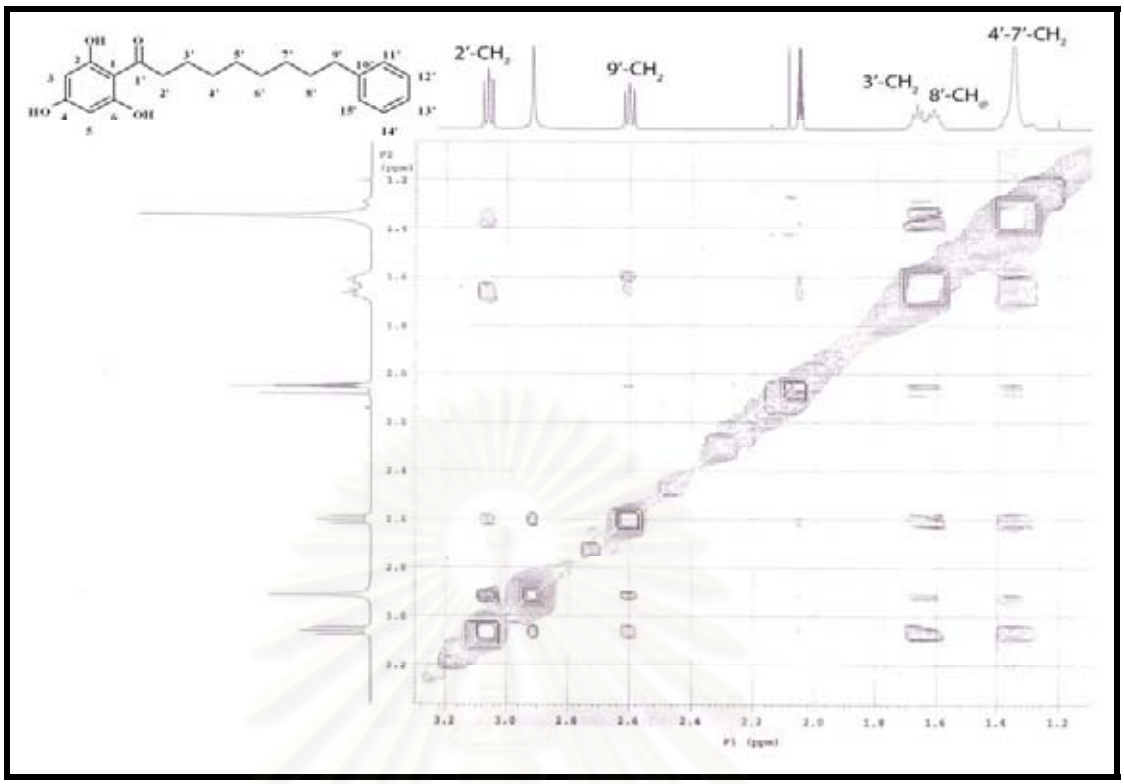

Figure 78b. NOESY Spectrum of compound KG-F8
(expansion between δ_H 1.2 to 3.2 ppm)

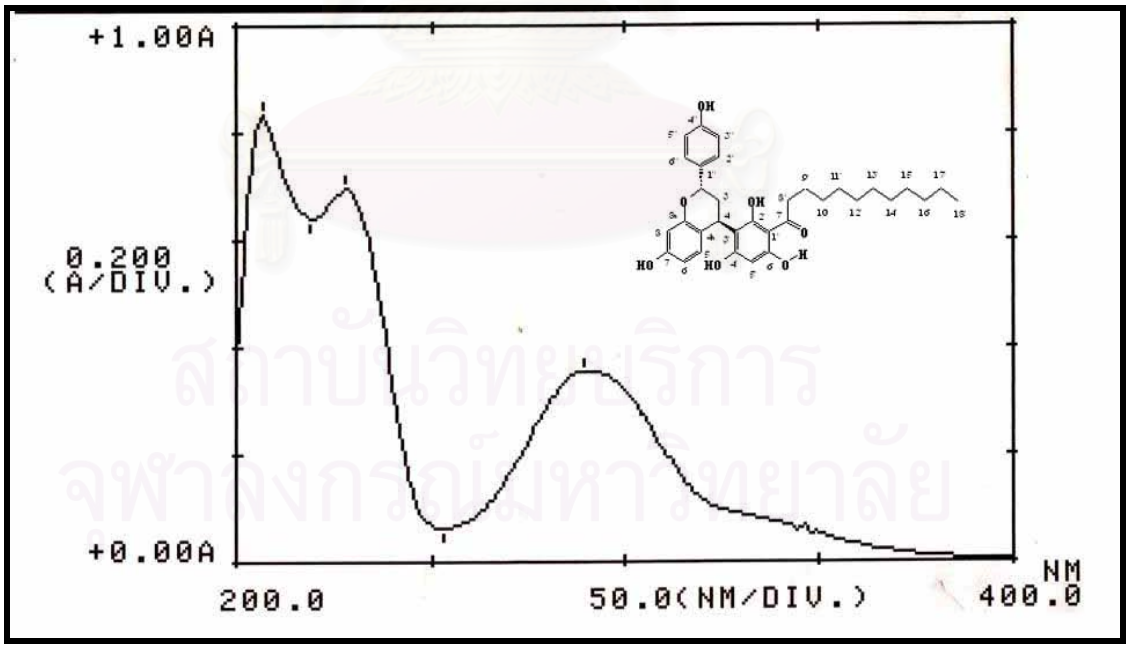

Figure 79. UV Spectrum of compound KG-L1 (in MeOH)

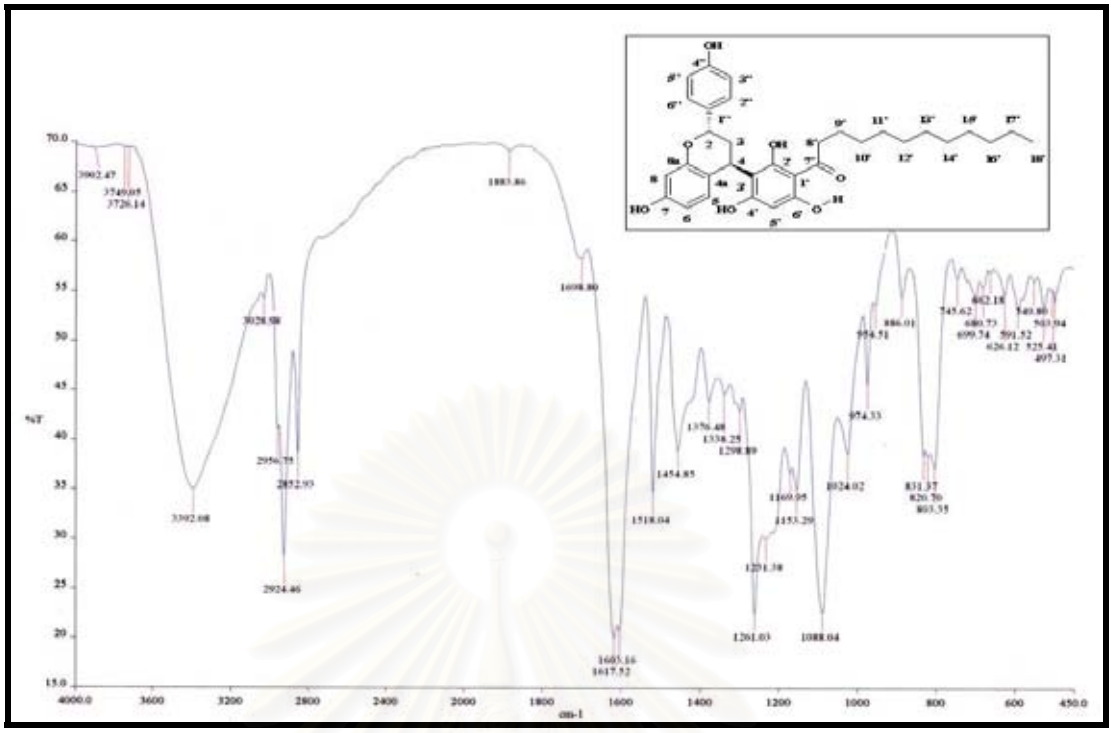

Figure 80. IR Spectrum of compound KG- L1 (KBr disc)

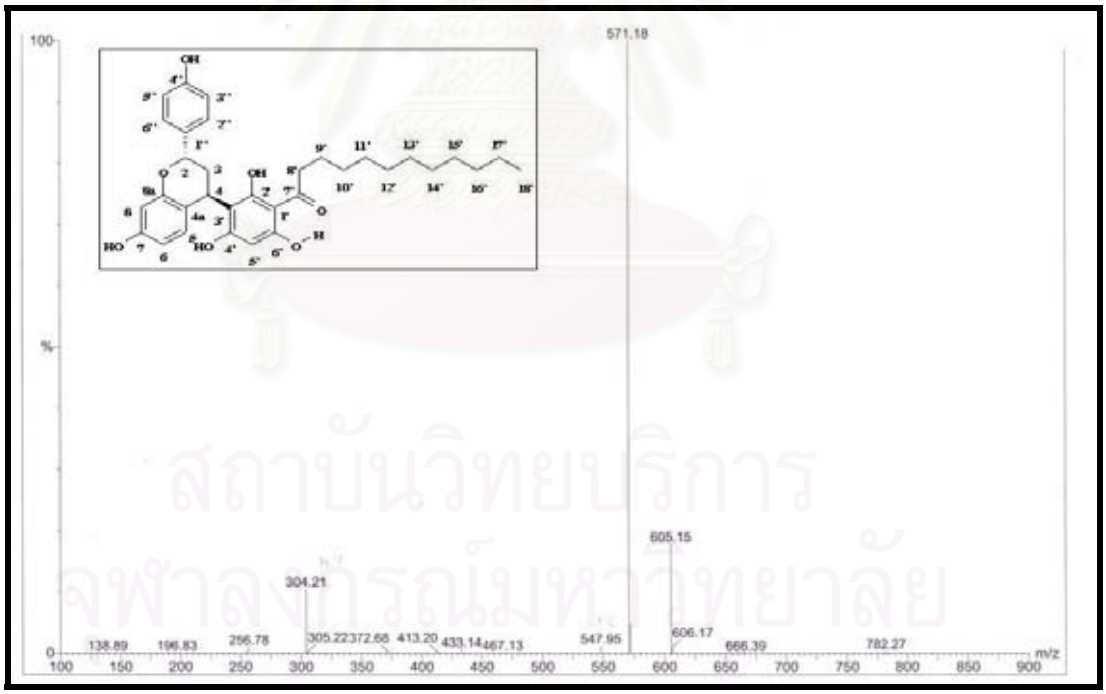

Figure 81. ESI-TOF Mass spectrum of compound KG- L1

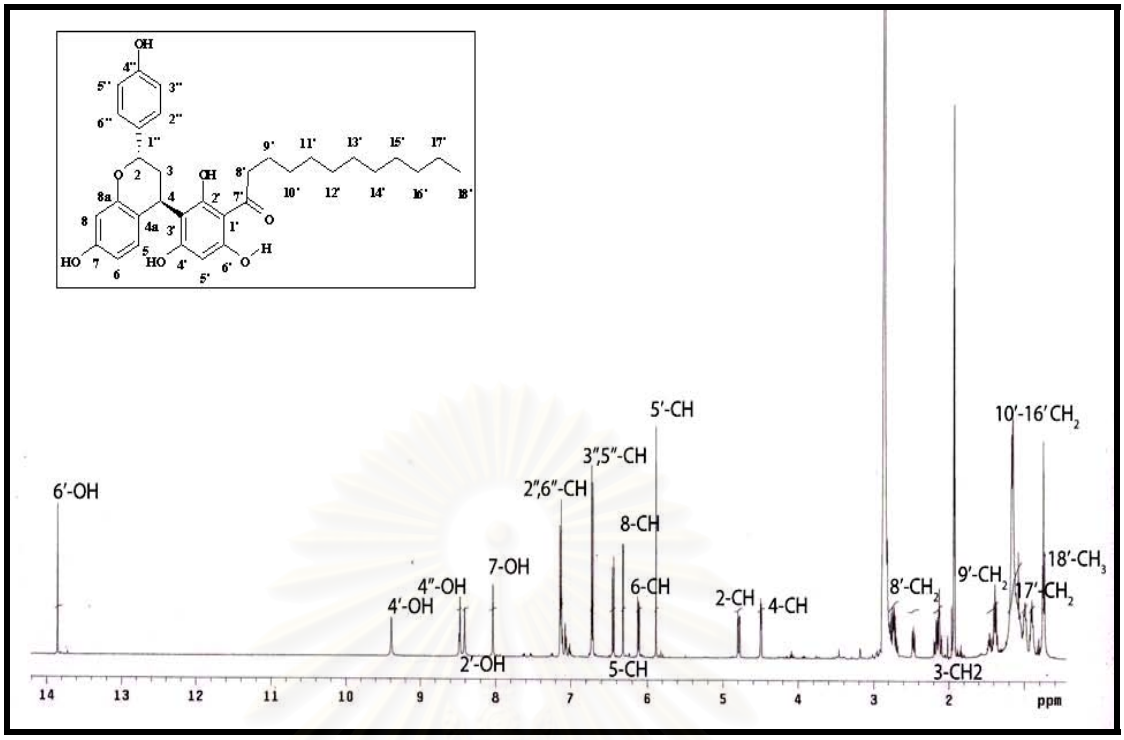

Figure 82a. ^{1}H NMR (500 MHz) Spectrum of compound KG- L1 (in acetone-d_6)

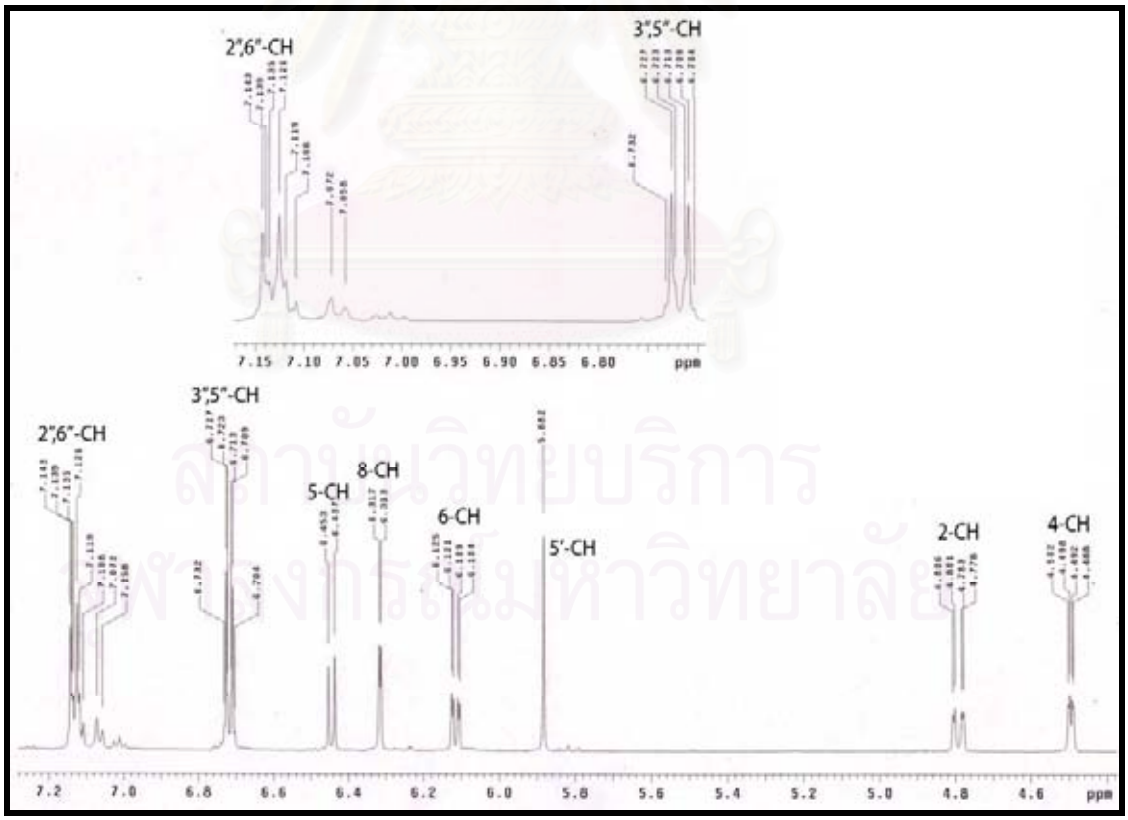

Figure 82b. ^{1}H NMR (500 MHz) Spectrum of compound KG- L1 (in acetone-d_6) (expansion between δ_H 4.6 to 7.2 ppm)

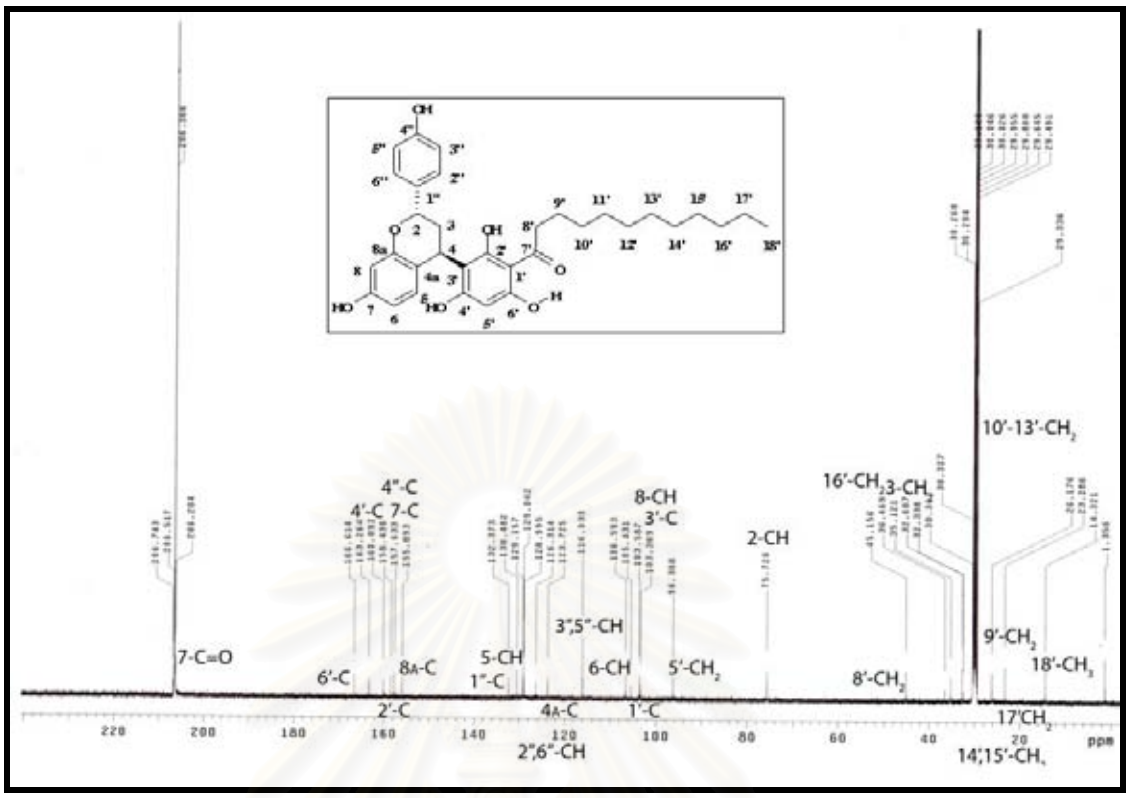

Figure 83. ^{13}C NMR (125 MHz) Spectrum of compound KG- L1 (in acetone-d_6)

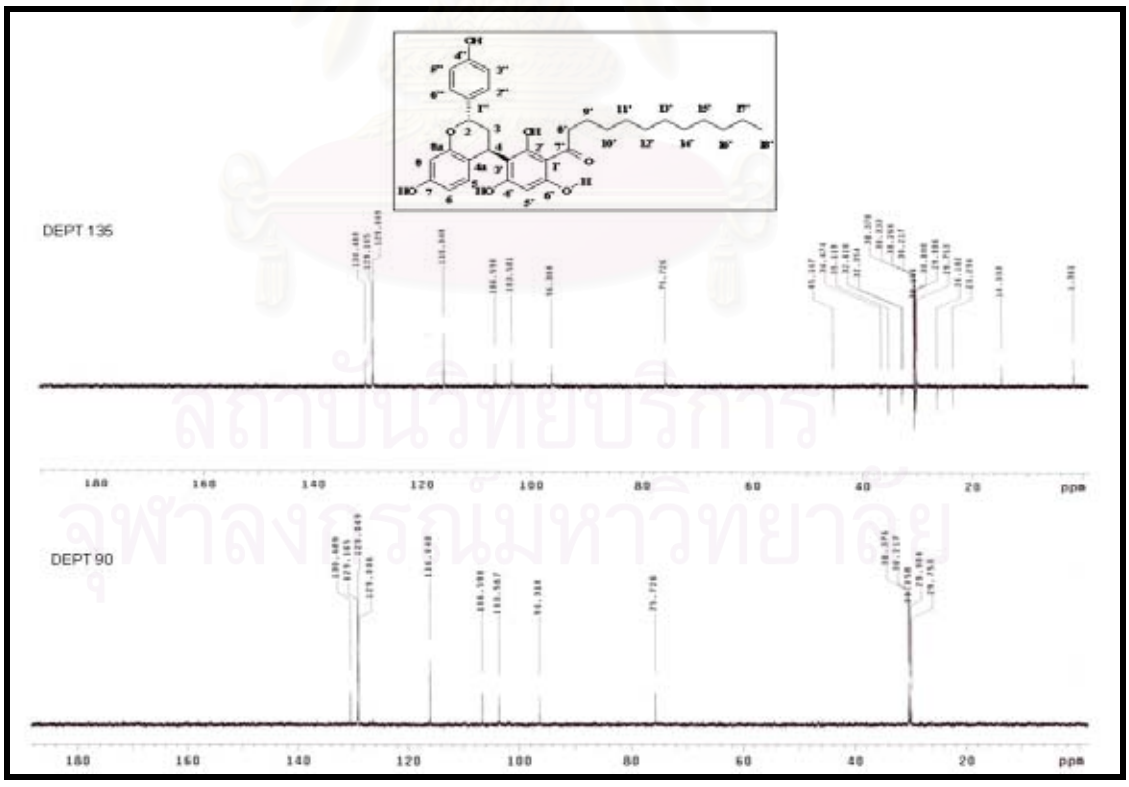

Figure 84. DEPT135 and DEPT 90 NMR Spectrum of compound KG- L1 (in acetone-d_6)

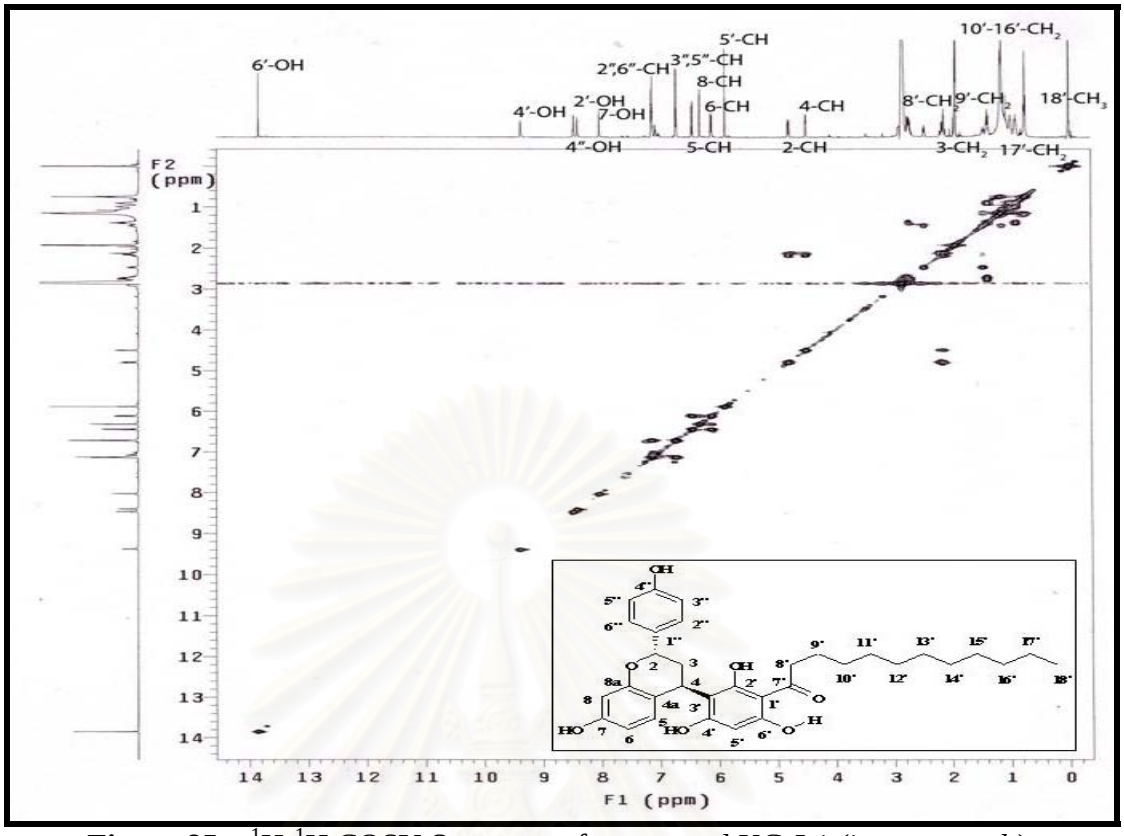

Figure 85a. ^{1}H-^{1}H COSY Spectrum of compound KG-L1 (in acetone-d_6)

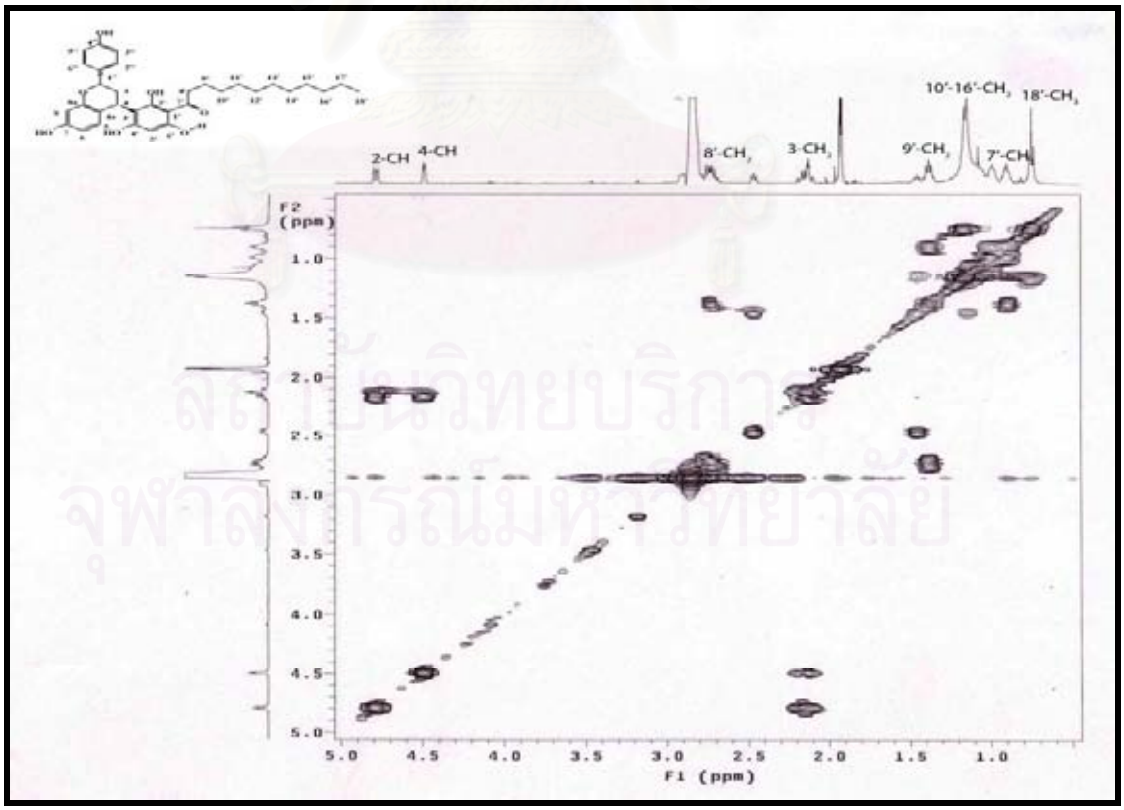

Figure 85b. ^{1}H-^{1}H COSY Spectrum of compound KG-L1 (in acetone-d_6)
(expansion between δ_H 1.0-5.0 ppm)

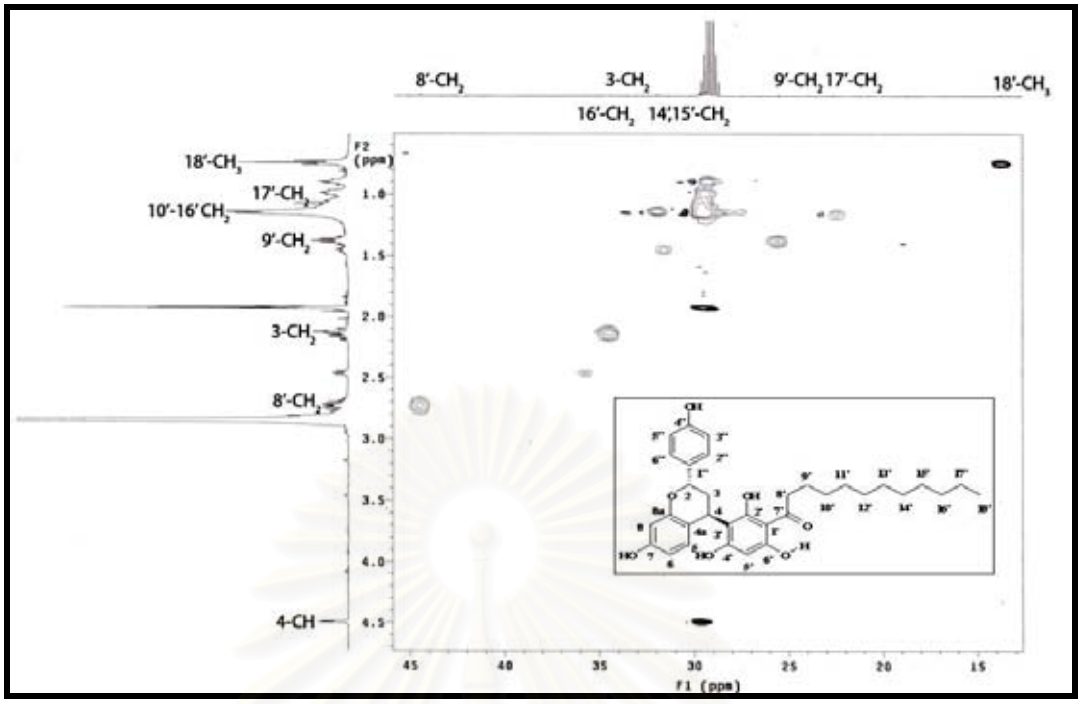

Figure 86a. HMQC Spectrum of compound KG- L1

(expansion between δ_H 0.5-4.5 ppm, δ_C 15.0-45.0 ppm)

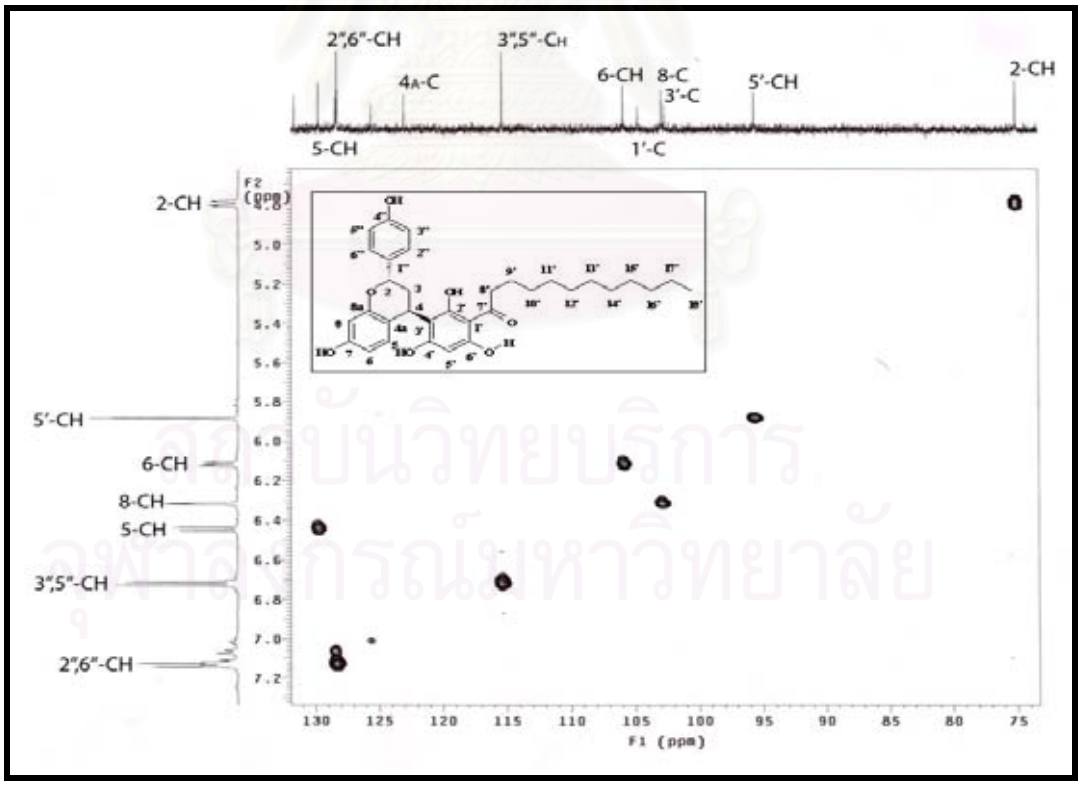

Figure 86b. HMQC Spectrum of compound KG- L1

(expansion between δ_H 4.5-7.2 ppm, δ_C 75.0-130.0 ppm)

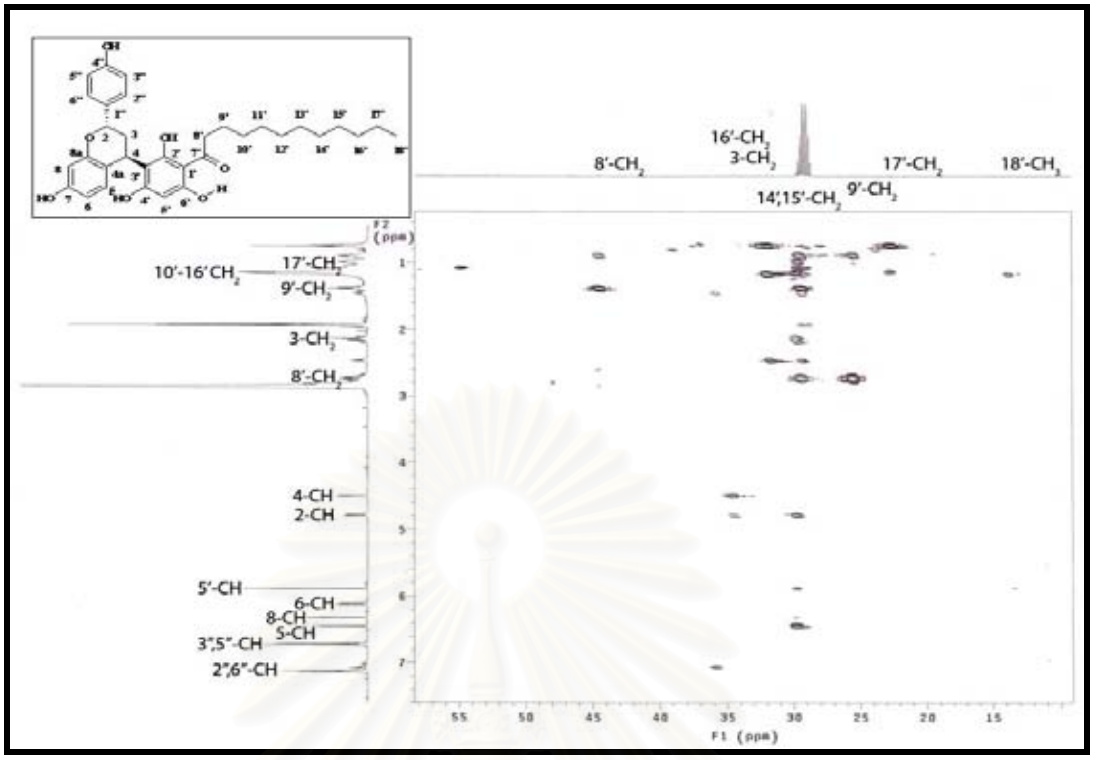

Figure 87a. HMBC Spectrum of compound KG- L1

(expansion between δ_H 0.5-7.5 ppm, δ_C 15.0-60.0 ppm)

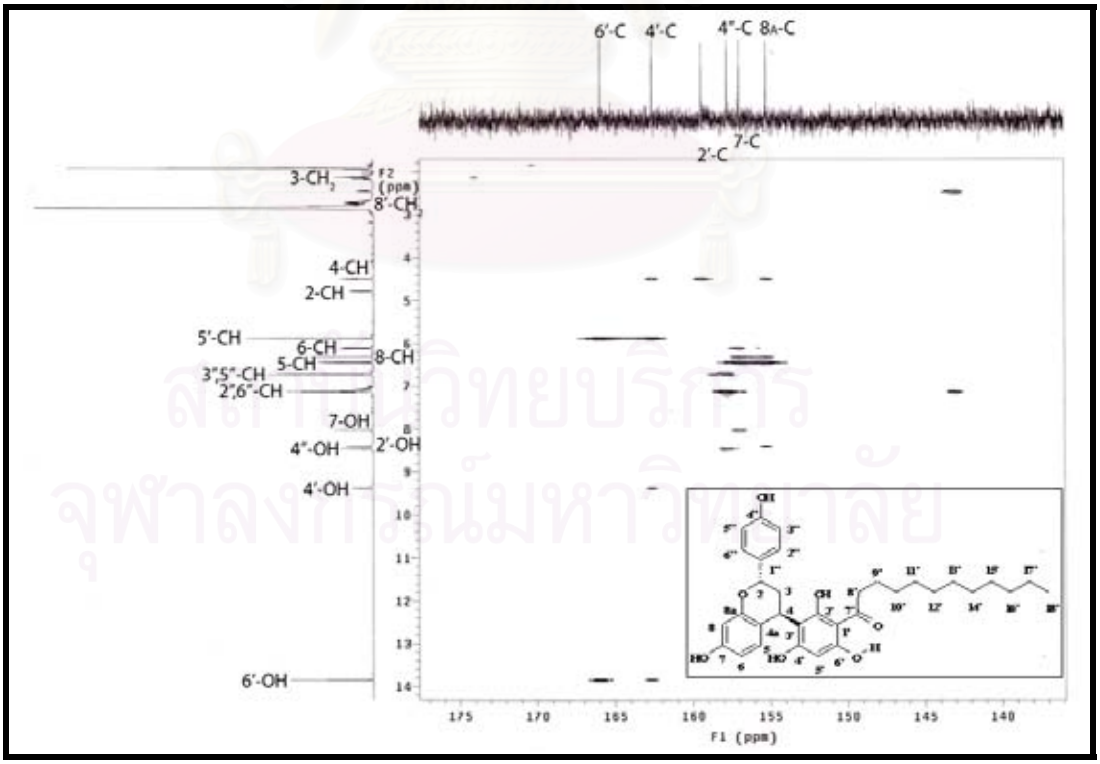

Figure 87b. HMBC Spectrum of compound KG- L1

(expansion between δ_H 0.5-14.0 ppm, δ_C 140.0-175.0 ppm)

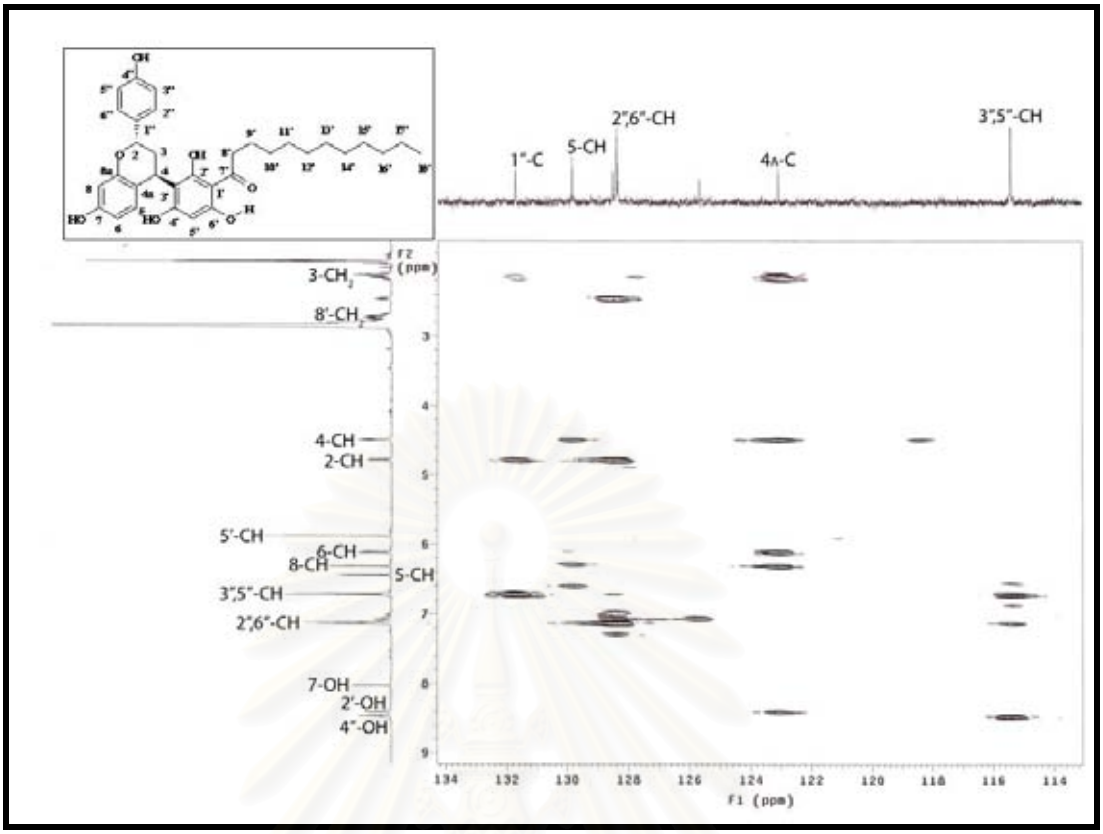

Figure 87c. HMBC Spectrum of compound KG- L1

(expansion between δ_H 2.0-9.0 ppm, δ_C 114.0-134.0 ppm)

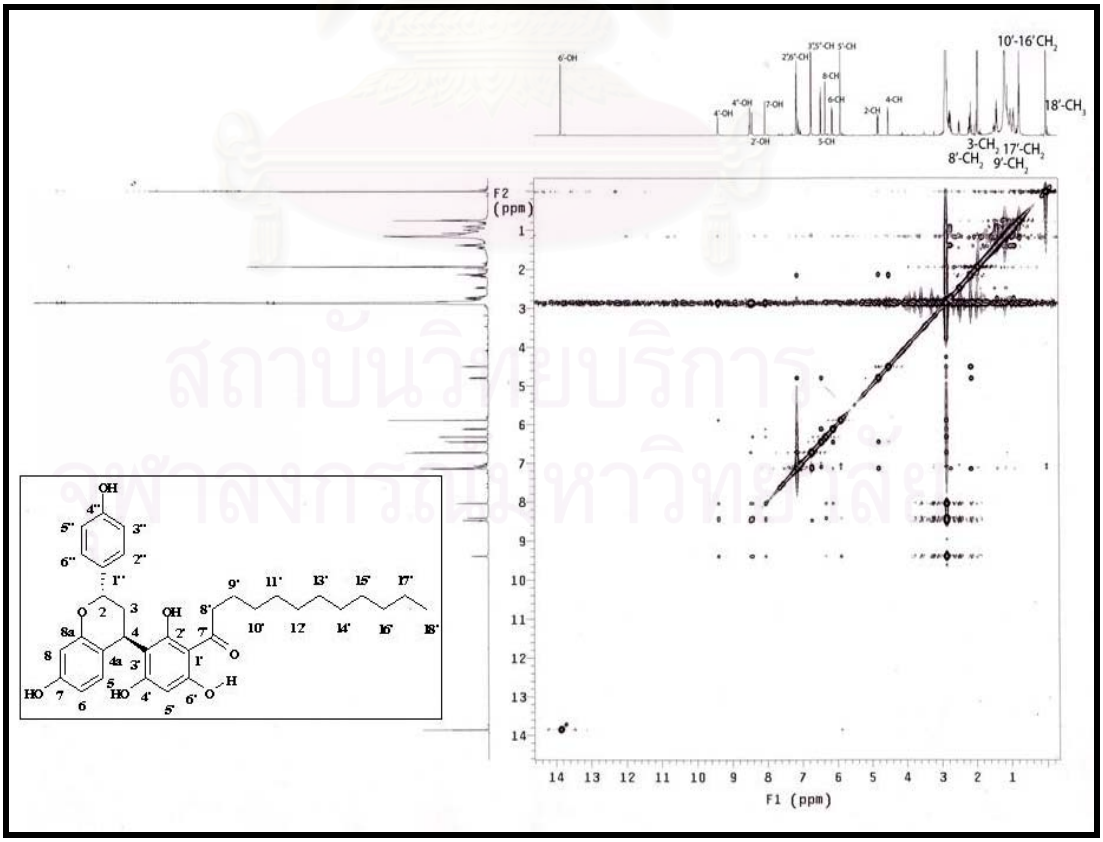

Figure 88a. NOESY Spectrum of compound KG- L1

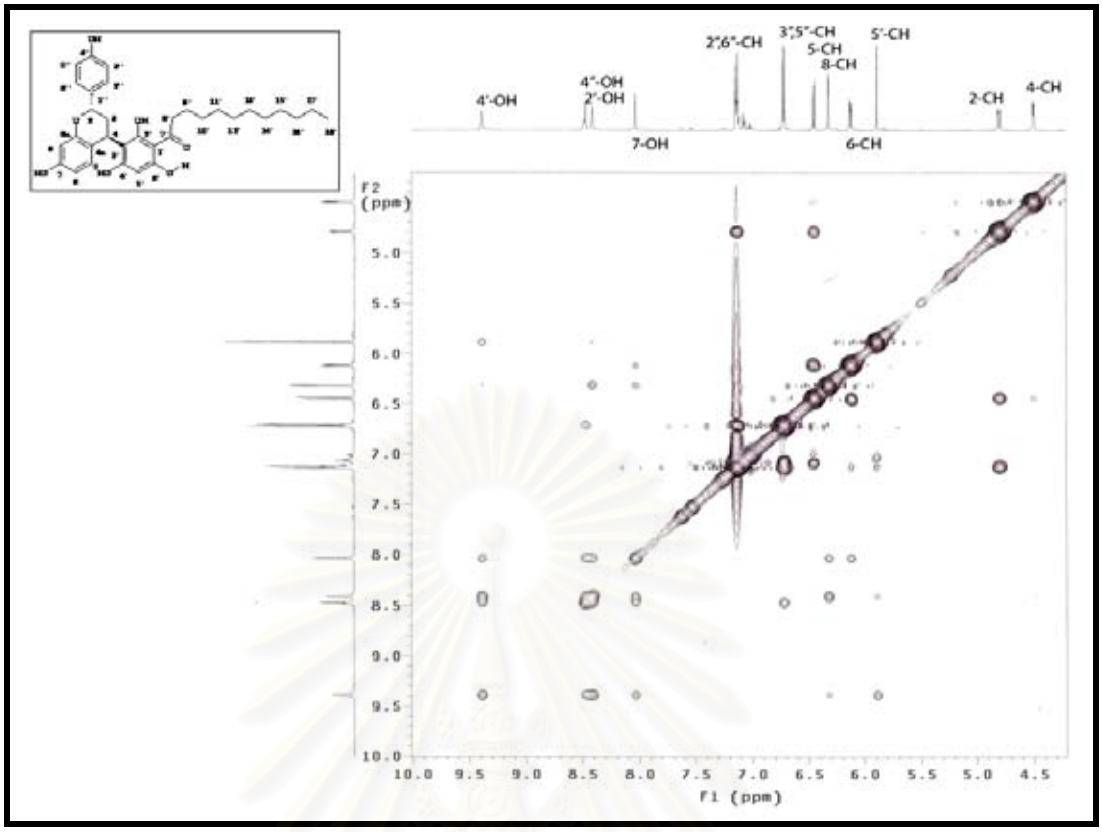

Figure 88b. NOESY Spectrum of compound KG- L1
(expansion between δ_H 4.5-10.0 ppm)

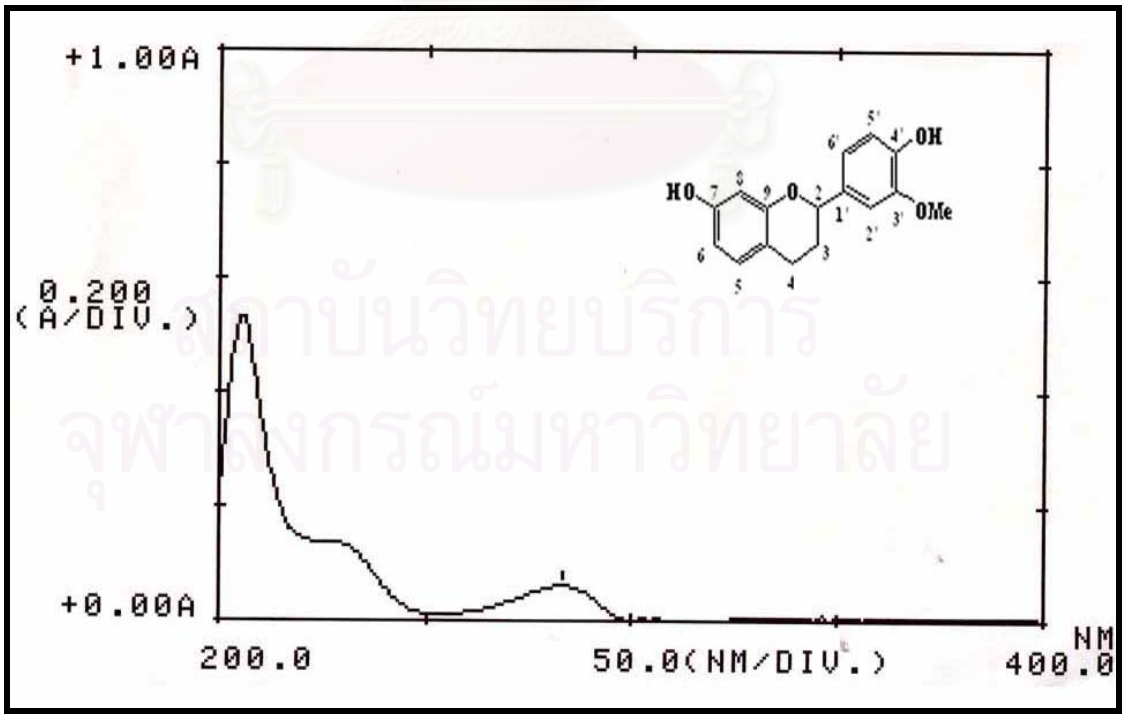

Figure 89. UV Spectrum of compound KG-S1 (in MeOH)

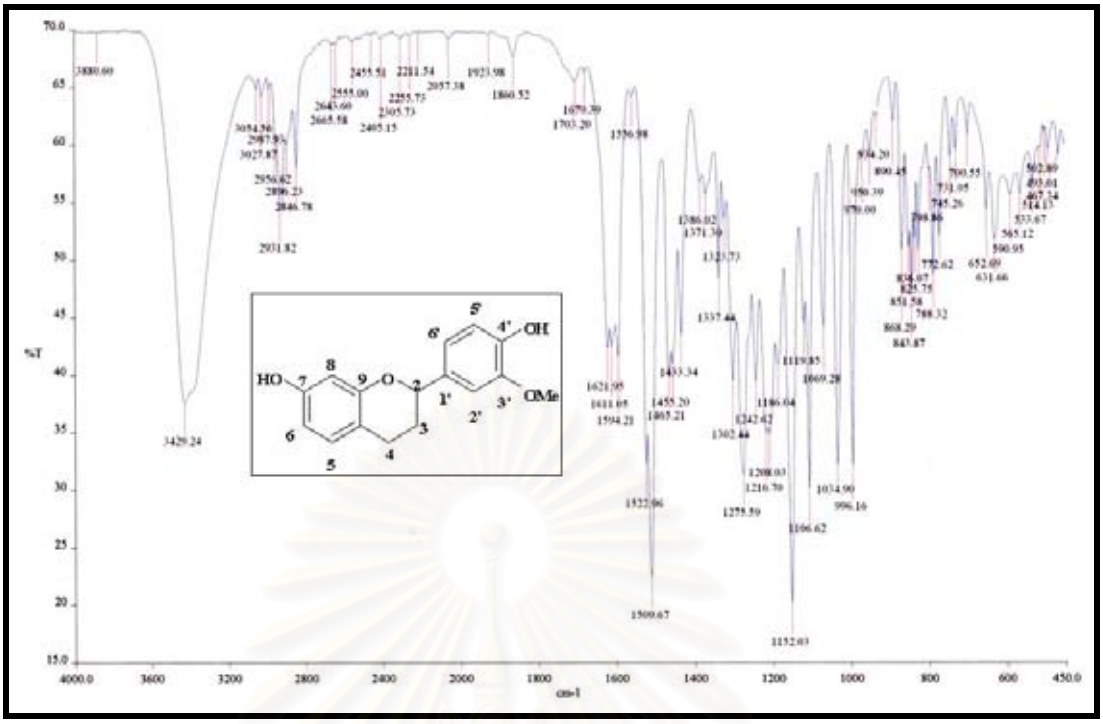

Figure 90. IR Spectrum of compound KG- S1 (KBr disc)

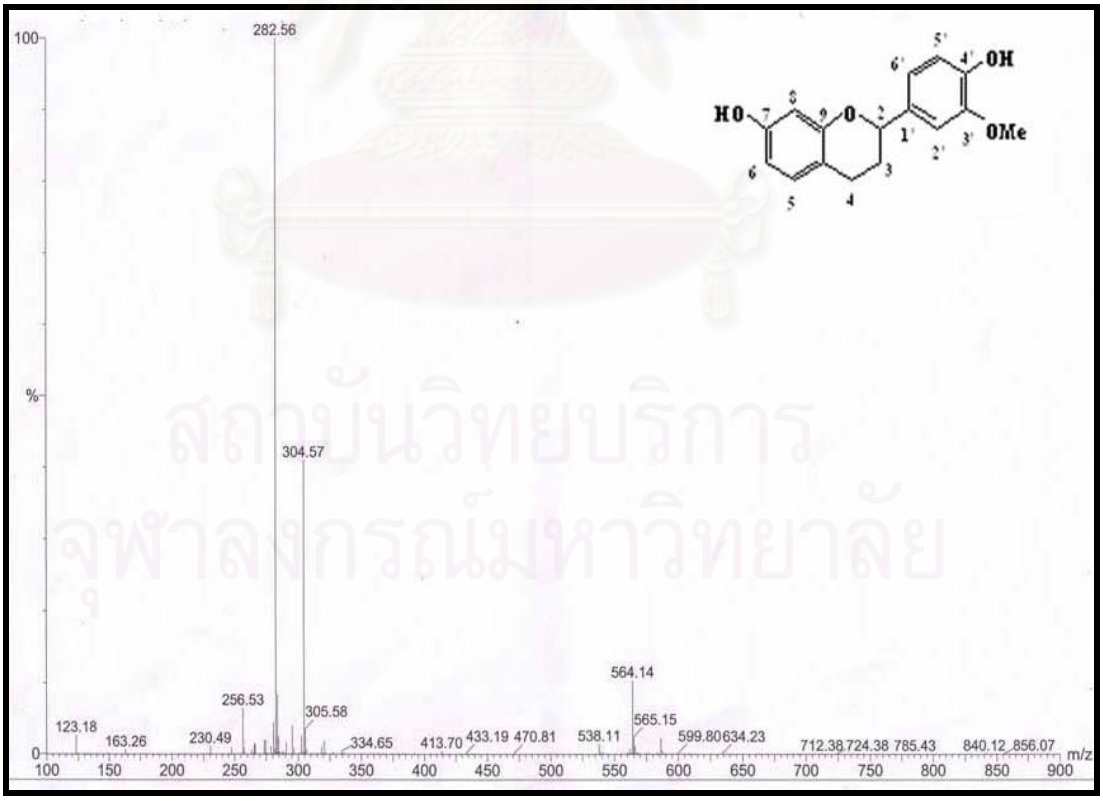

Figure 91. ESI-TOF Mass spectrum of compound KG- S1

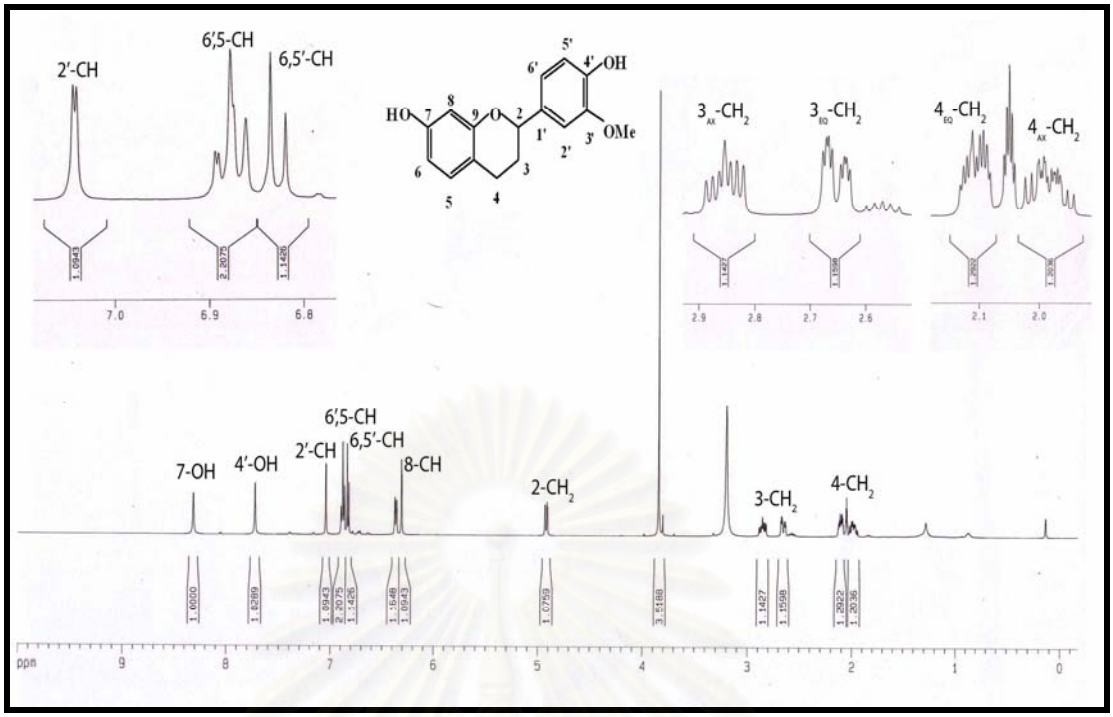

Figure 92. ^{1}H NMR (500 MHz) Spectrum of compound KG- S1 (in acetone-d_6)

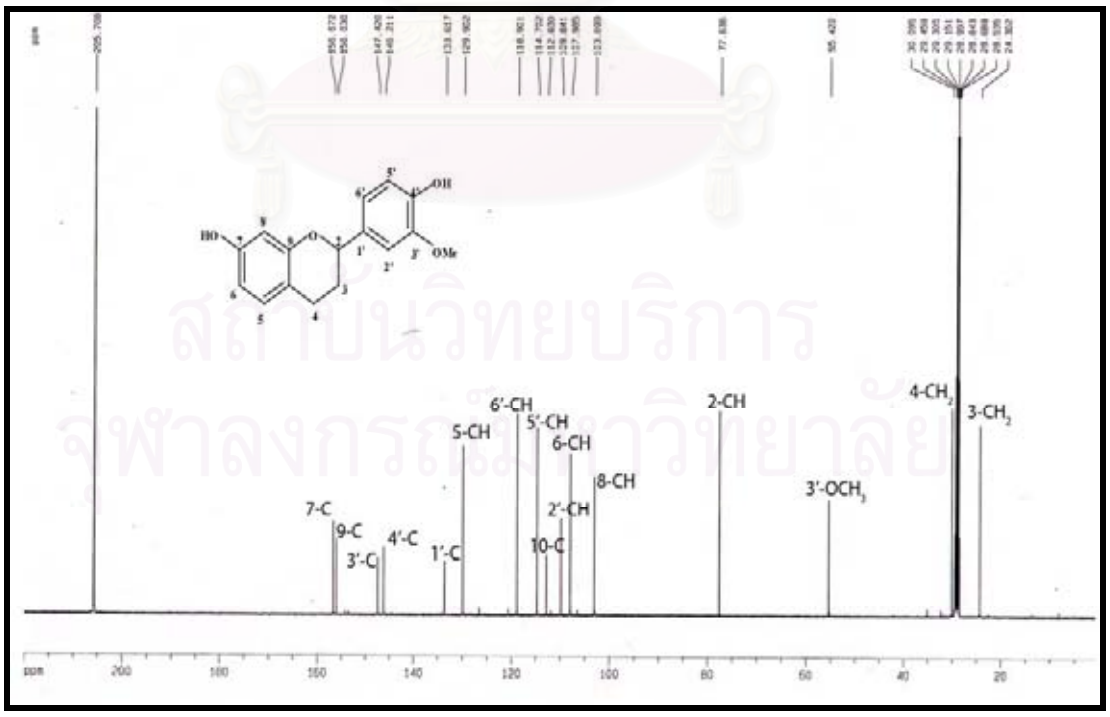

Figure 93. ^{13}C NMR (125 MHz) Spectrum of compound KG- S1 (in acetone-d_6)

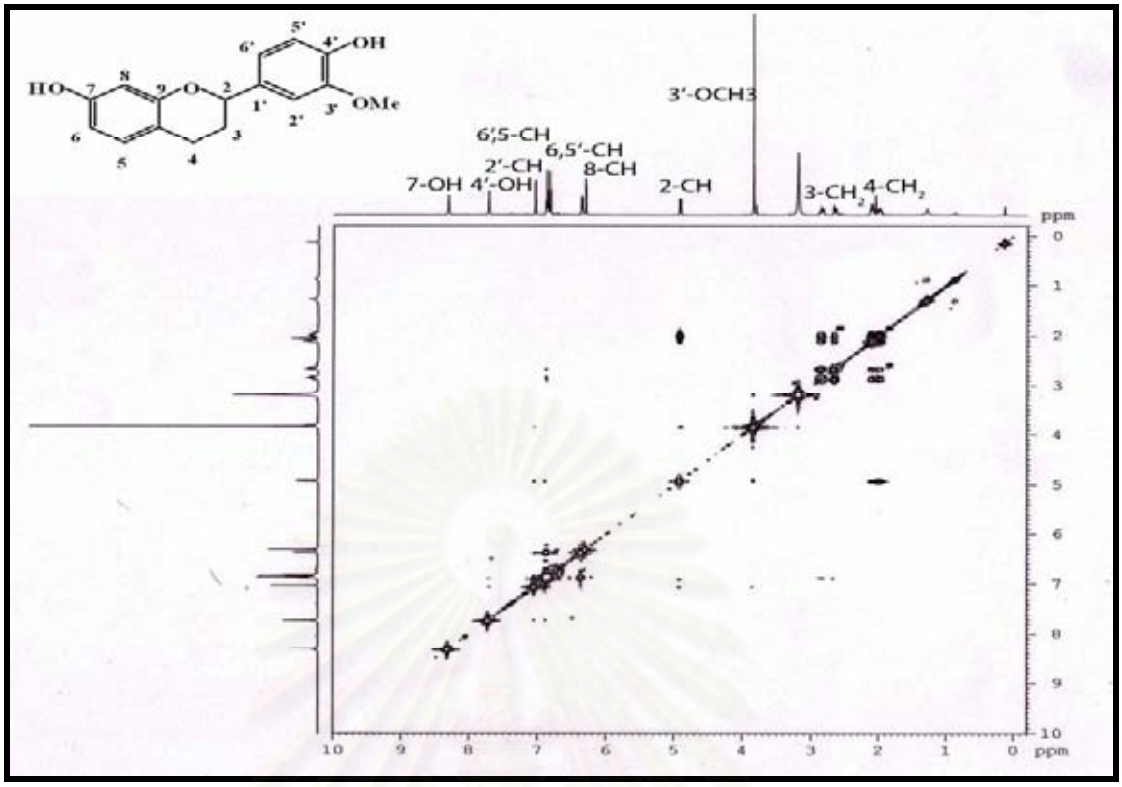

Figure 94a. ^{1}H-^{1}H COSY Spectrum of compound KG- S1 (in acetone-*d_6*)

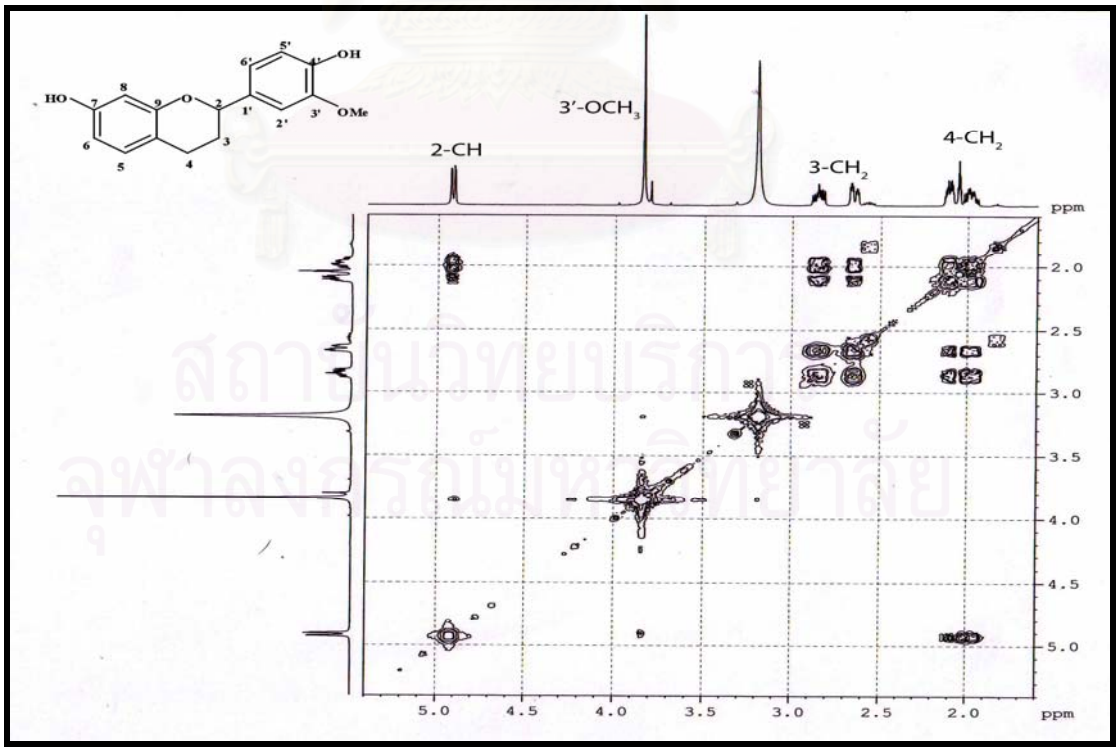

Figure 94b. ^{1}H-^{1}H COSY Spectrum of compound KG- S1 (in acetone-*d6*)
(expansion between δ_H 2.0-5.0 ppm)

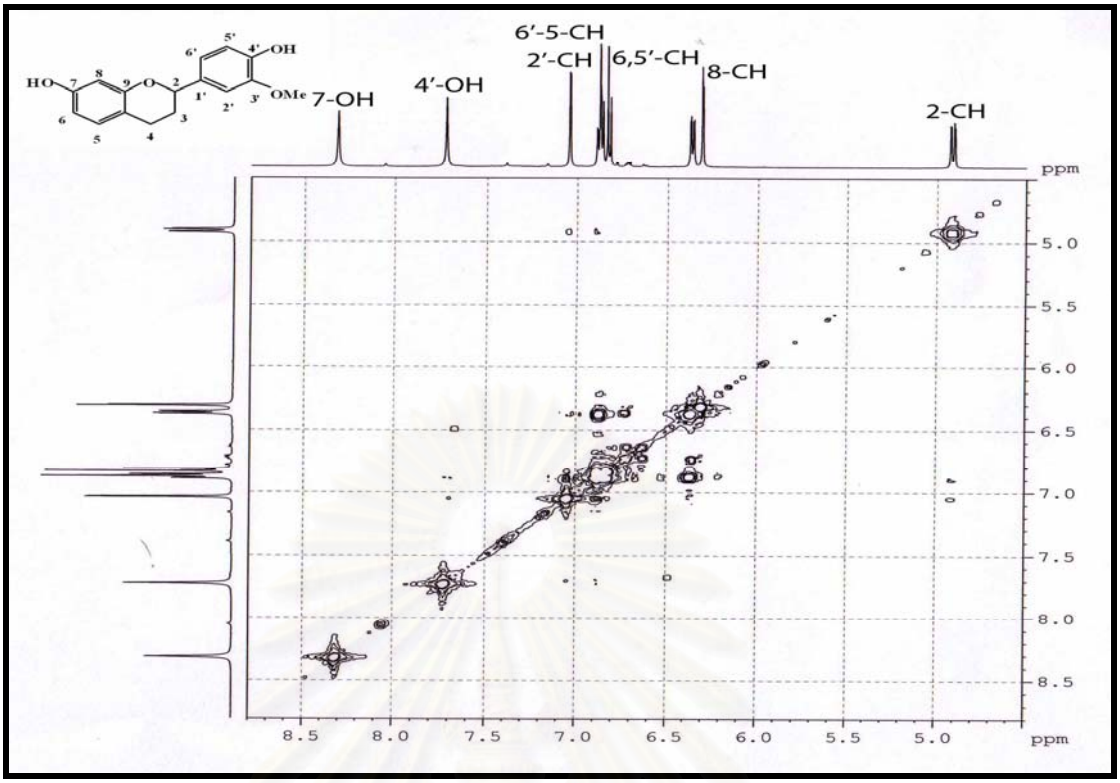

Figure 94c. ^{1}H-^{1}H COSY Spectrum of compound KG- S1 (in acetone-d_6) (expansion between δ_H 5.0-8.5 ppm)

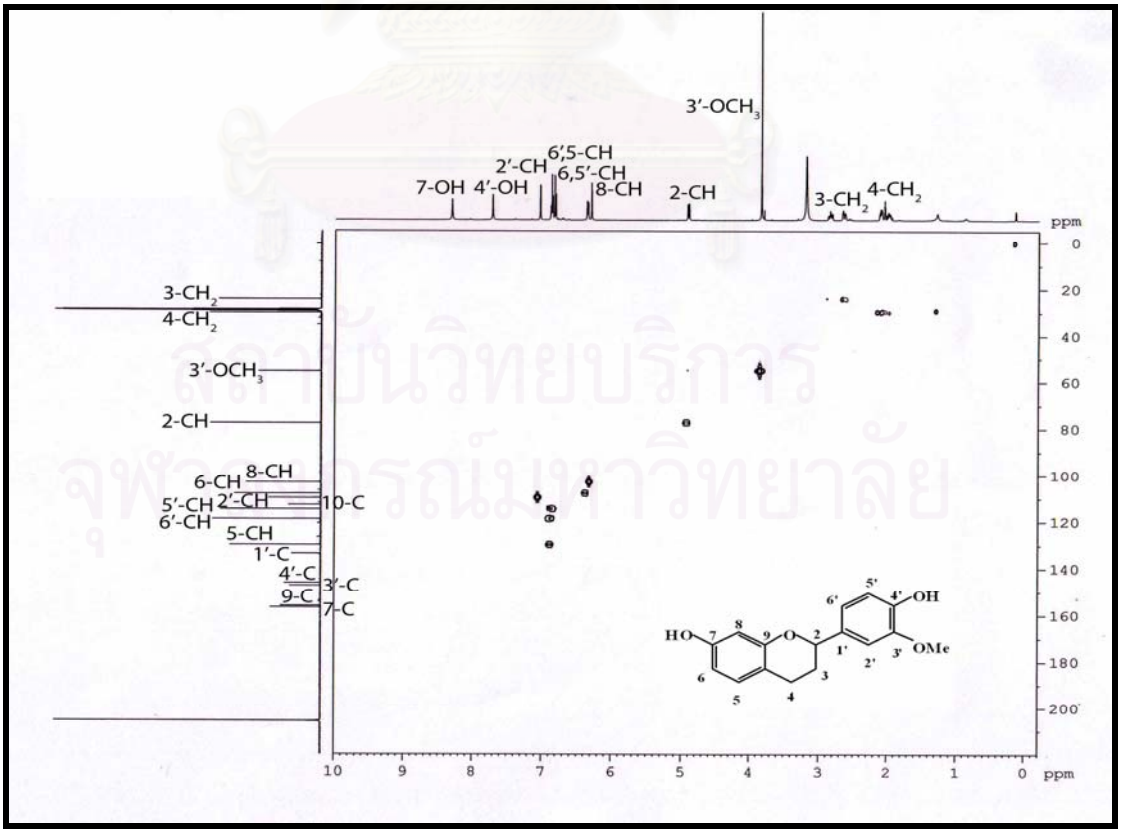

Figure 95. HMQC Spectrum of compound KG- S1

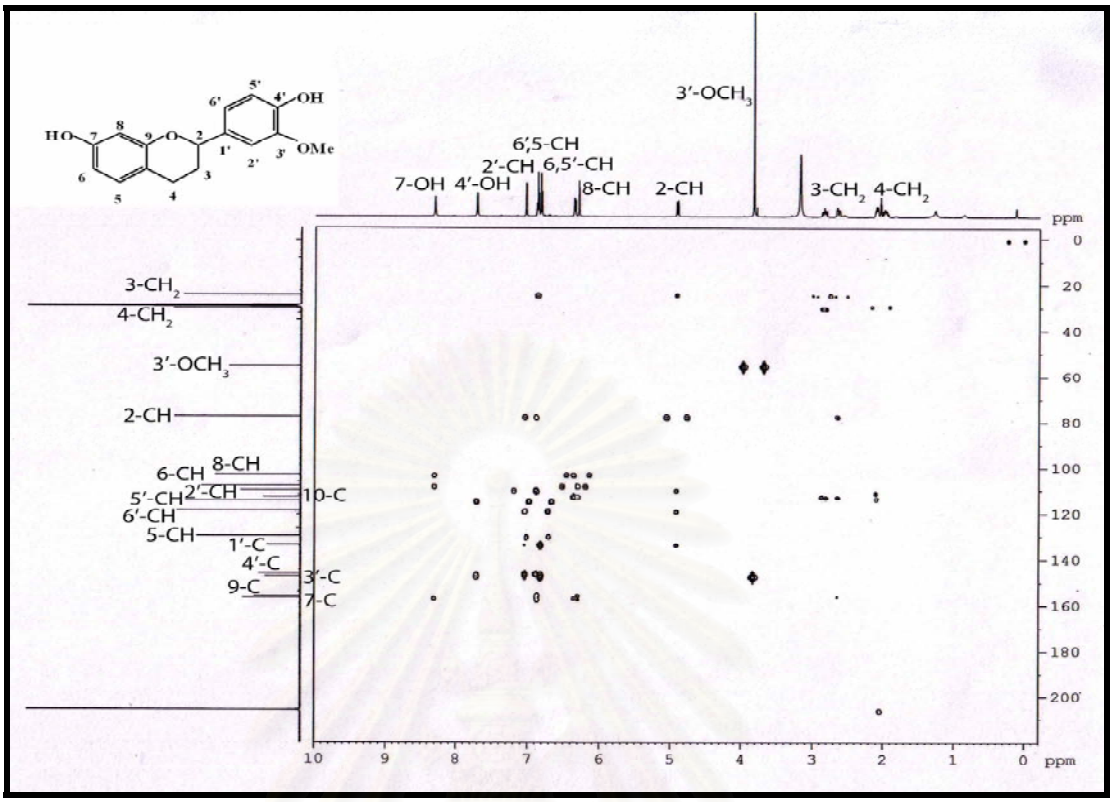

Figure 96. HMBC Spectrum of compound KG- S1

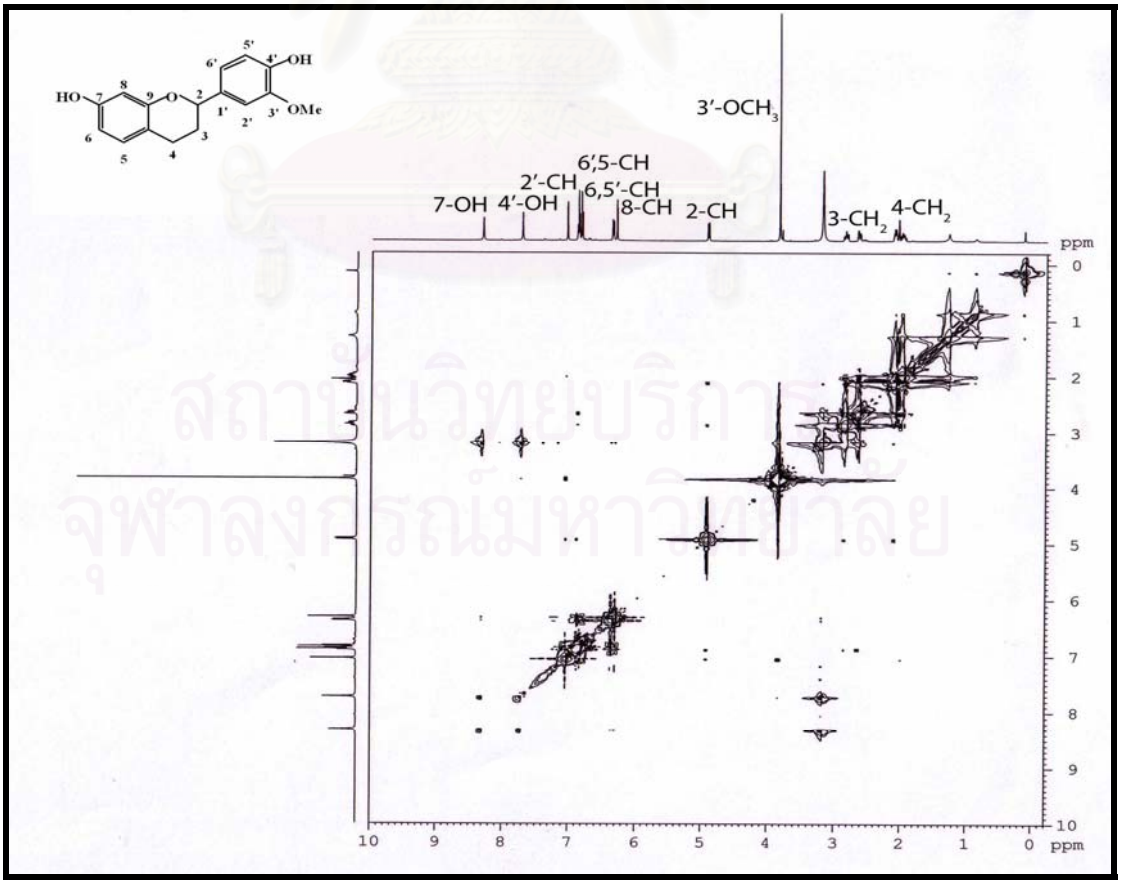

Figure 97. NOESY Spectrum of compound KG- S1

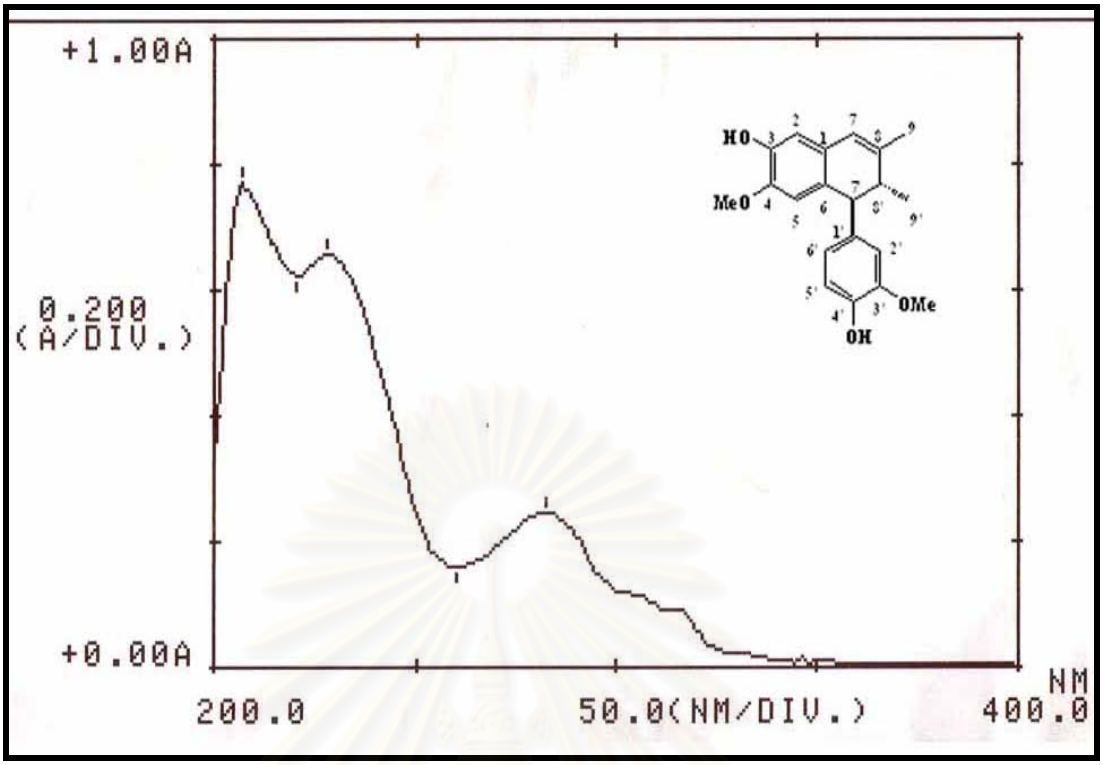

Figure 98. UV Spectrum of compound KF-S1 (in MeOH)

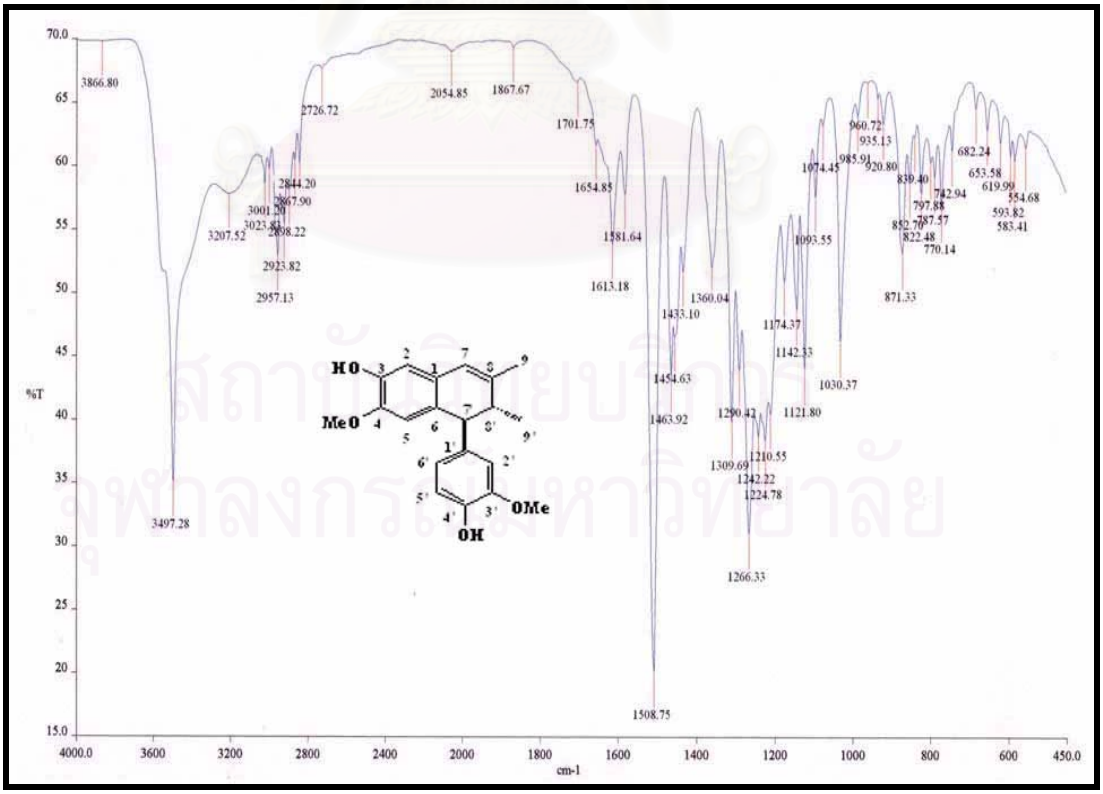

Figure 99. IR Spectrum of compound KF-S1 (KBr disc)

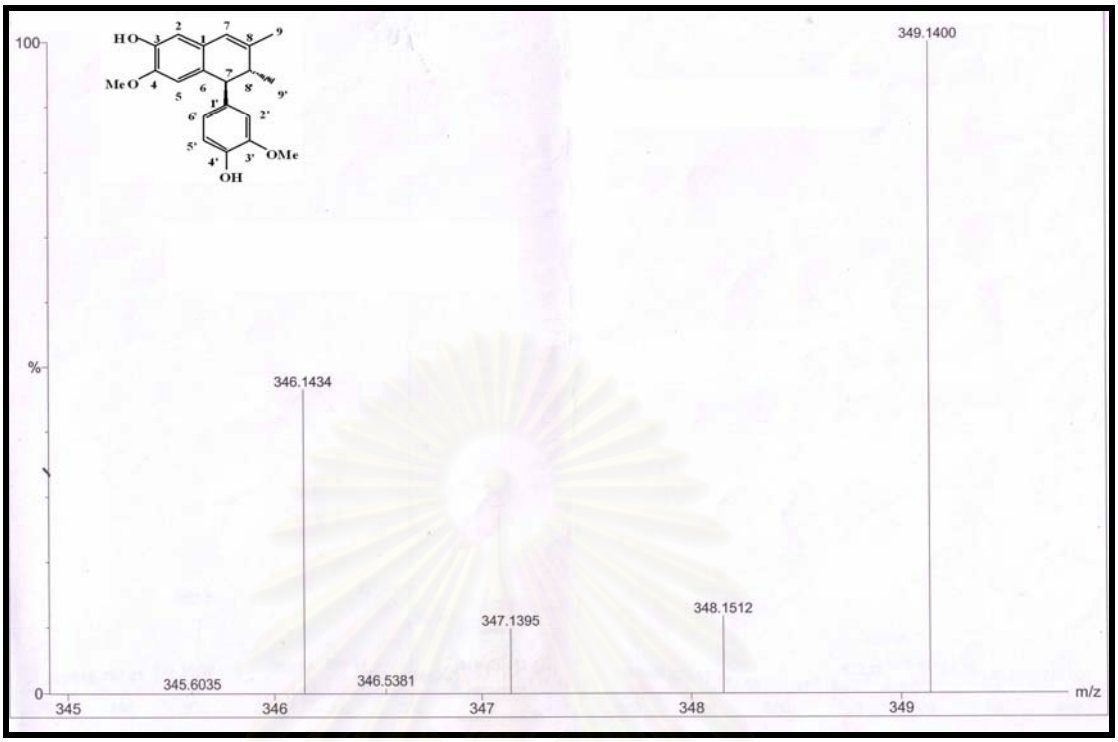

Figure 100. ESI Mass spectrum of compound KF-S1

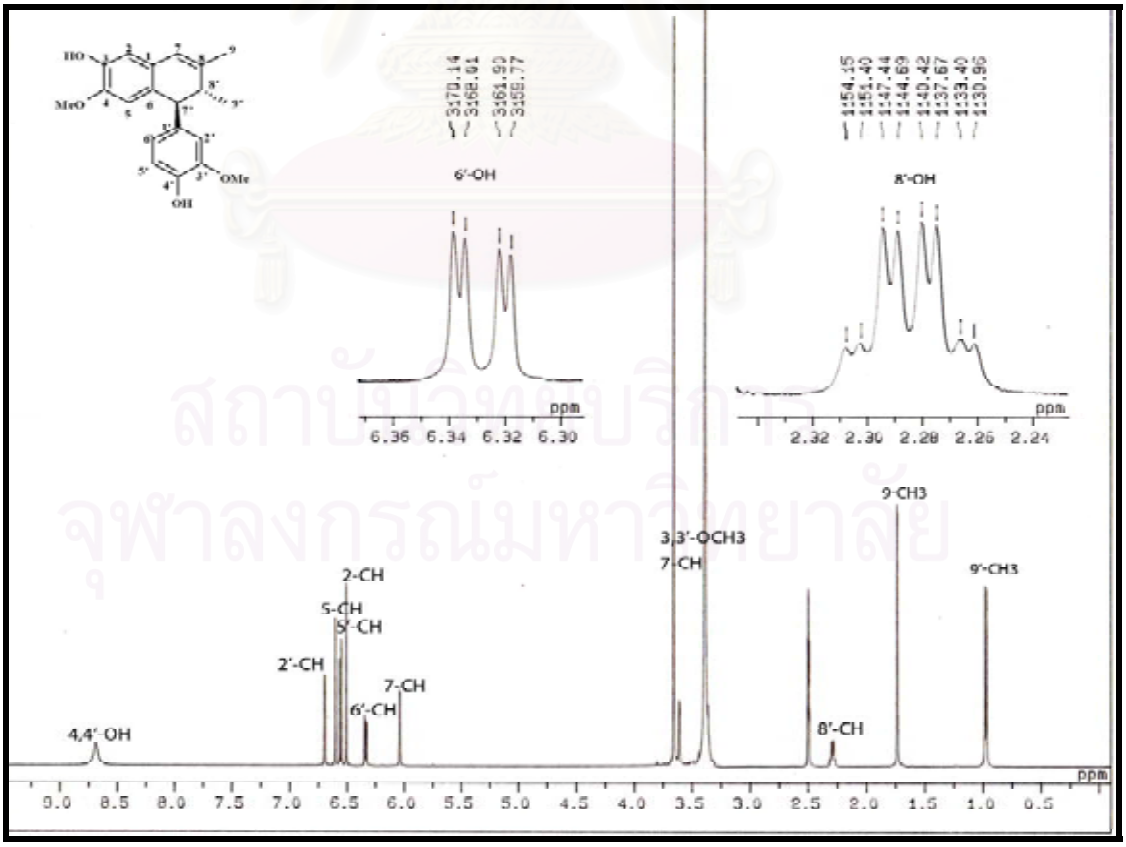

Figure 101. ^{1}H NMR (500 MHz) Spectrum of compound KF-S1 (in acetone-d_6)

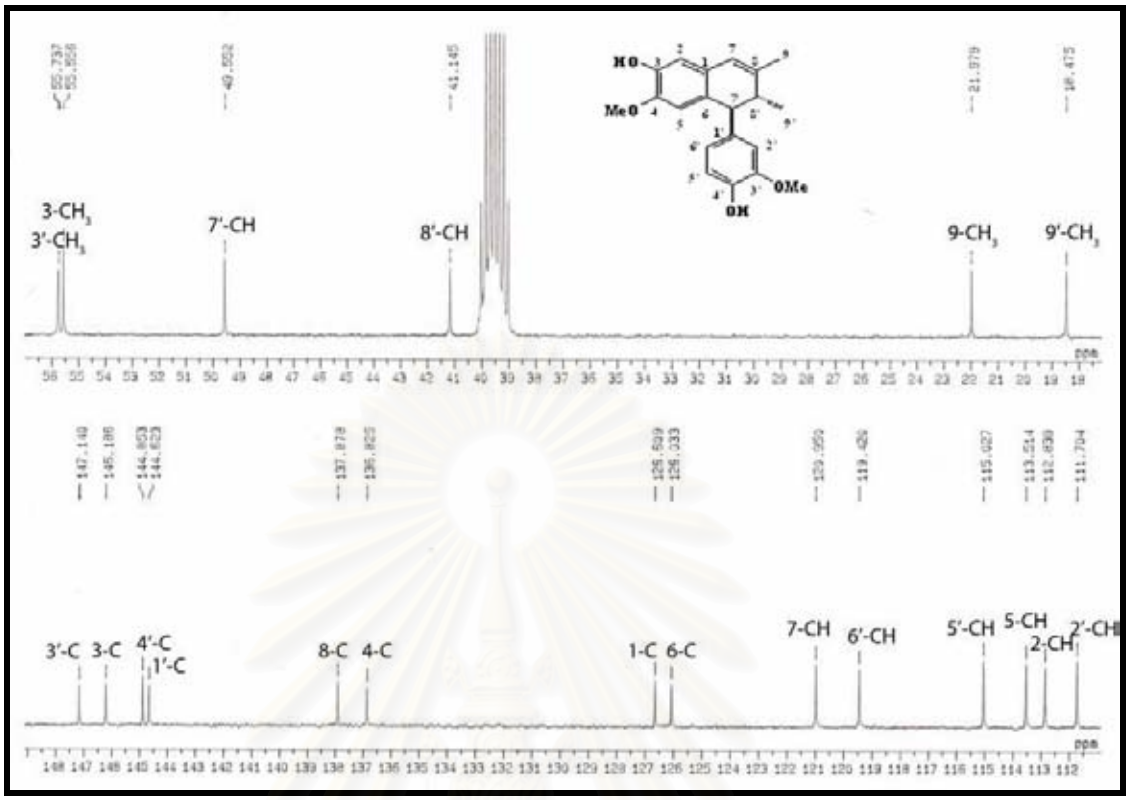

Figure 102. ^{13}C NMR (125 MHz) Spectrum of compound KF-S1 (in acetone-d_6)

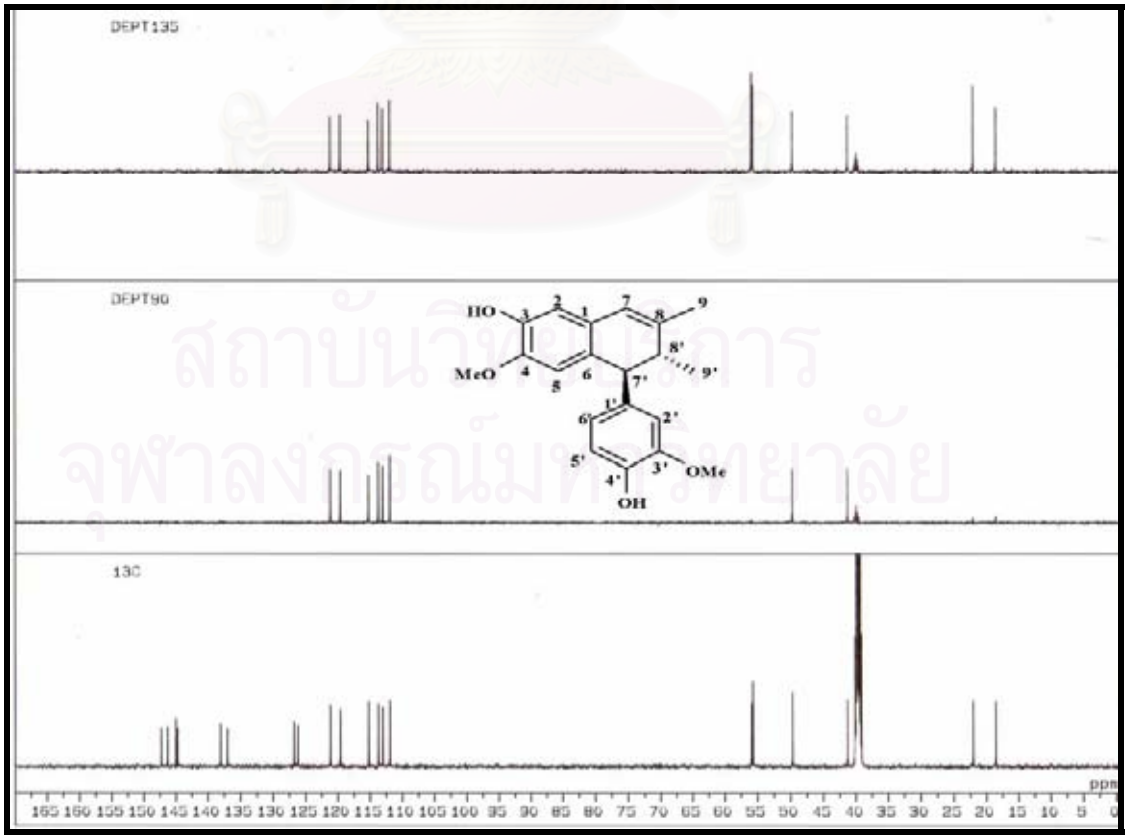

Figure 103. DEPT 135, DEPT 90 and ^{13}C NMR Spectrum of compound KF-S1

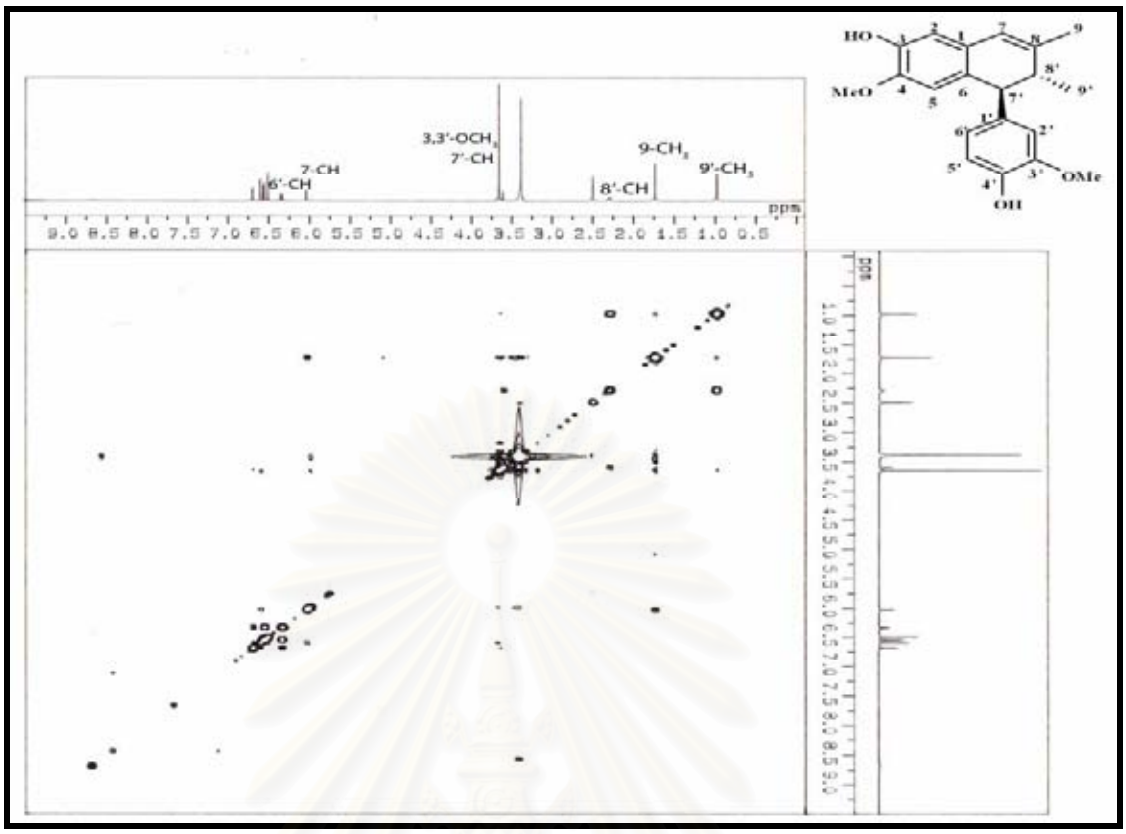

Figure 104a. ^{1}H-^{1}H COSY Spectrum of compound KF-S1 (in acetone-d_6)

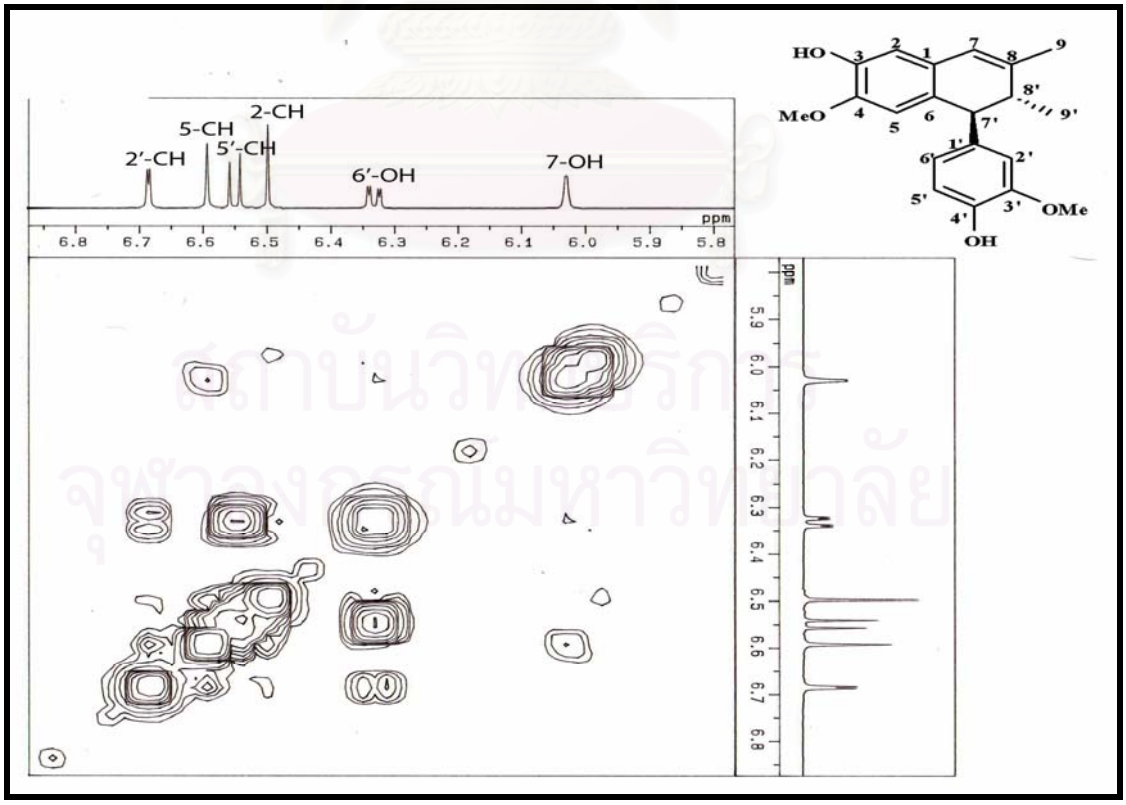

Figure 104b. ^{1}H-^{1}H COSY Spectrum of compound KF-S1

(expansion between δ_H 5.8-6.8 ppm)

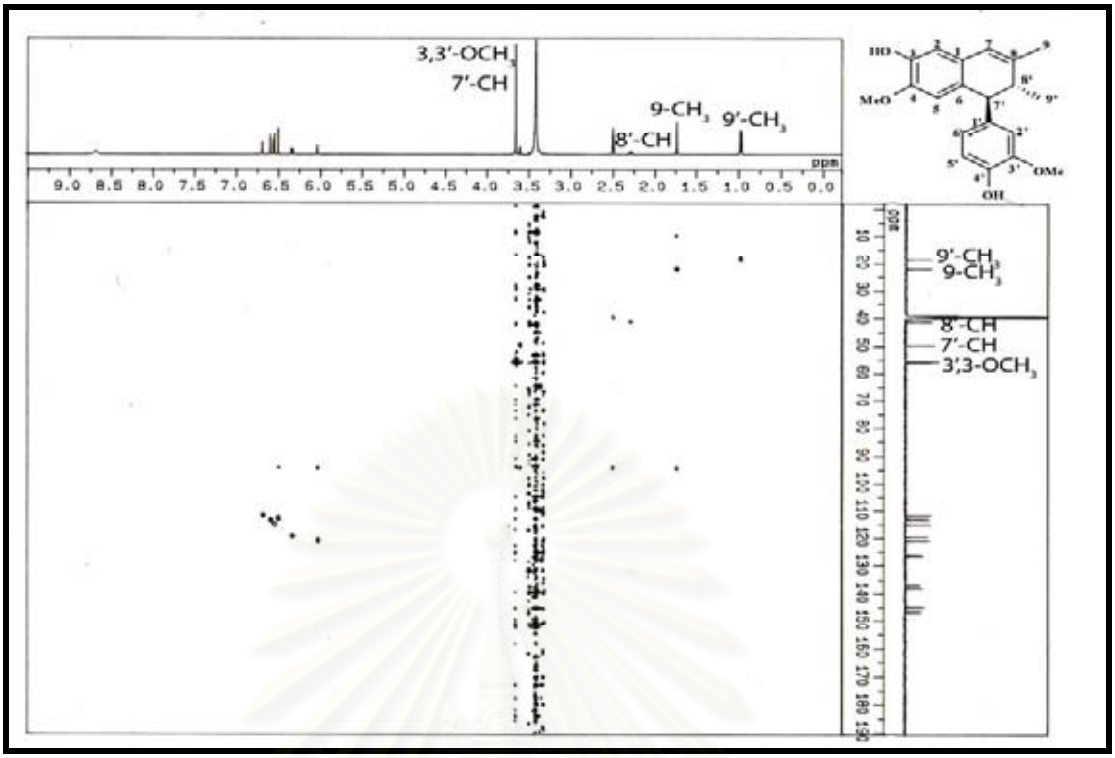

Figure 105a. HMQC Spectrum of compound KF-S1

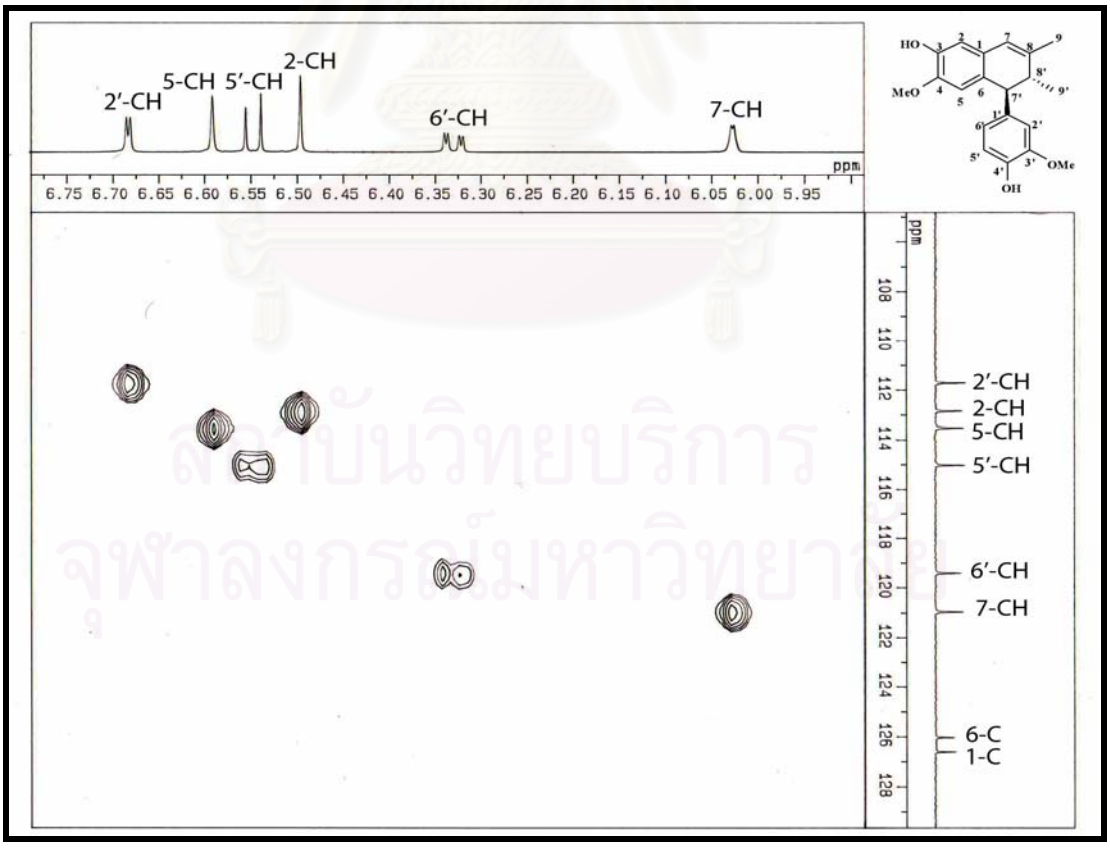

Figure 105b. HMQC Spectrum of compound KF-S1

(expansion between δ_H 5.95-6.75 ppm, δ_C 108.0-128.0 ppm)

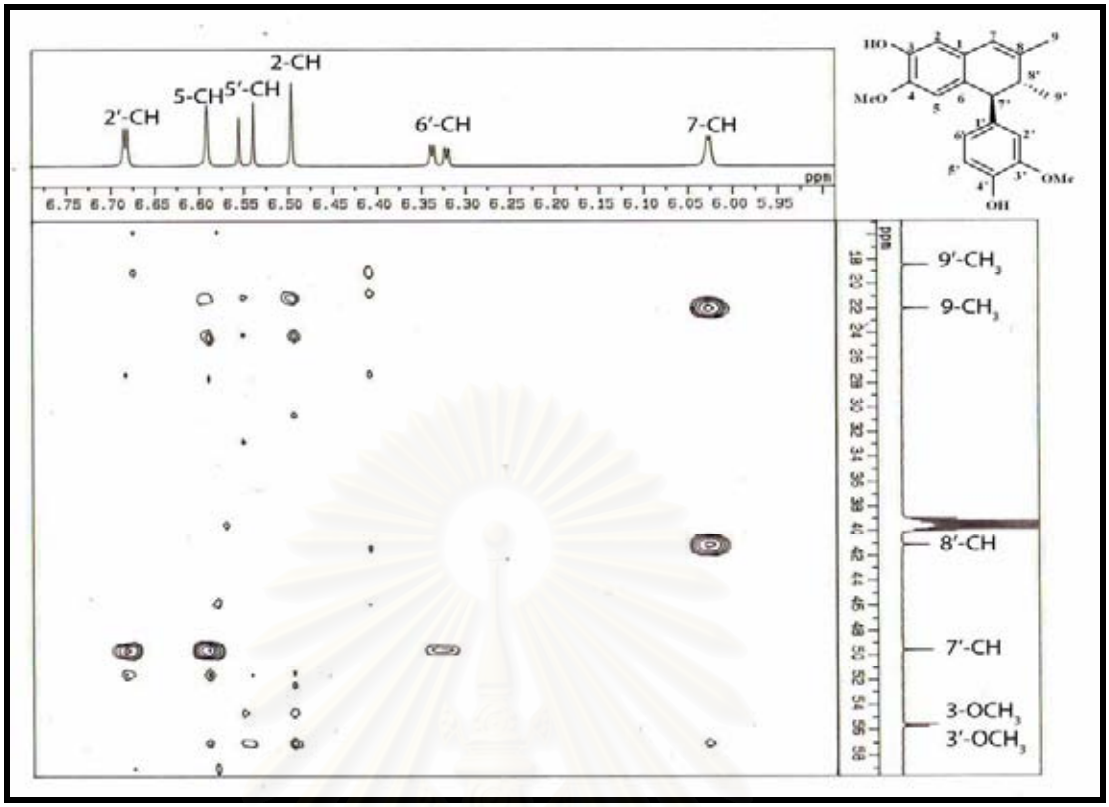

Figure 106a. HMBC Spectrum of compound KF-S1
(expansion between δ_H 5.95-6.75 ppm, δ_C 18.0-58.0 ppm)

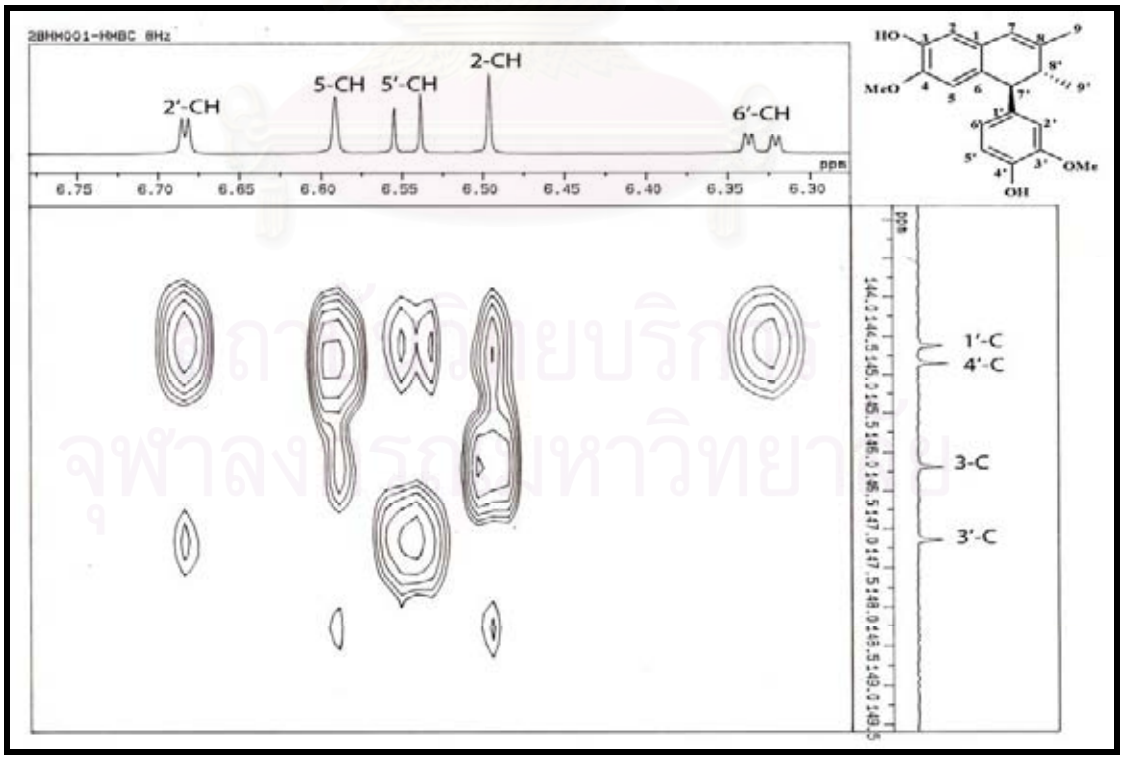

Figure 106b. HMBC Spectrum of compound KF-S1
(expansion between δ_H 6.39-6.75 ppm, δ_C 144.0-149.5 ppm)

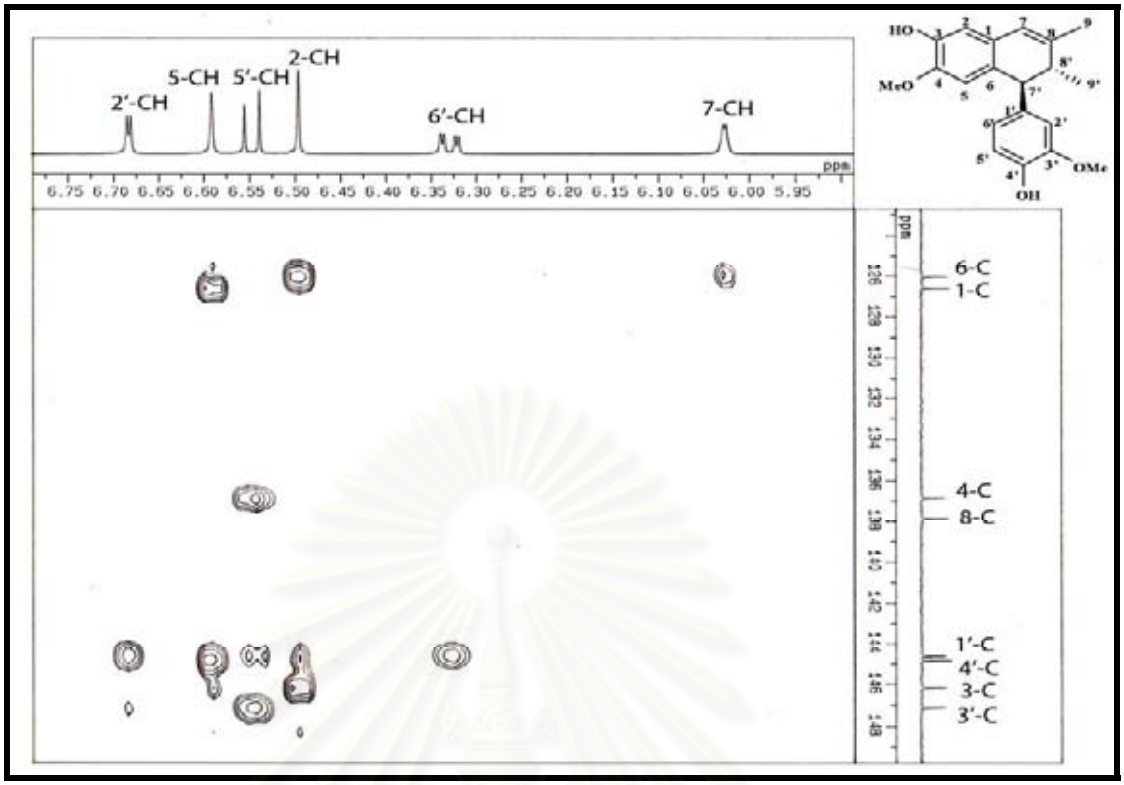

Figure 106c. HMBC Spectrum of compound KF-S1

(expansion between δ_H 5.95-6.75 ppm, δ_C 126.0-148.0 ppm)

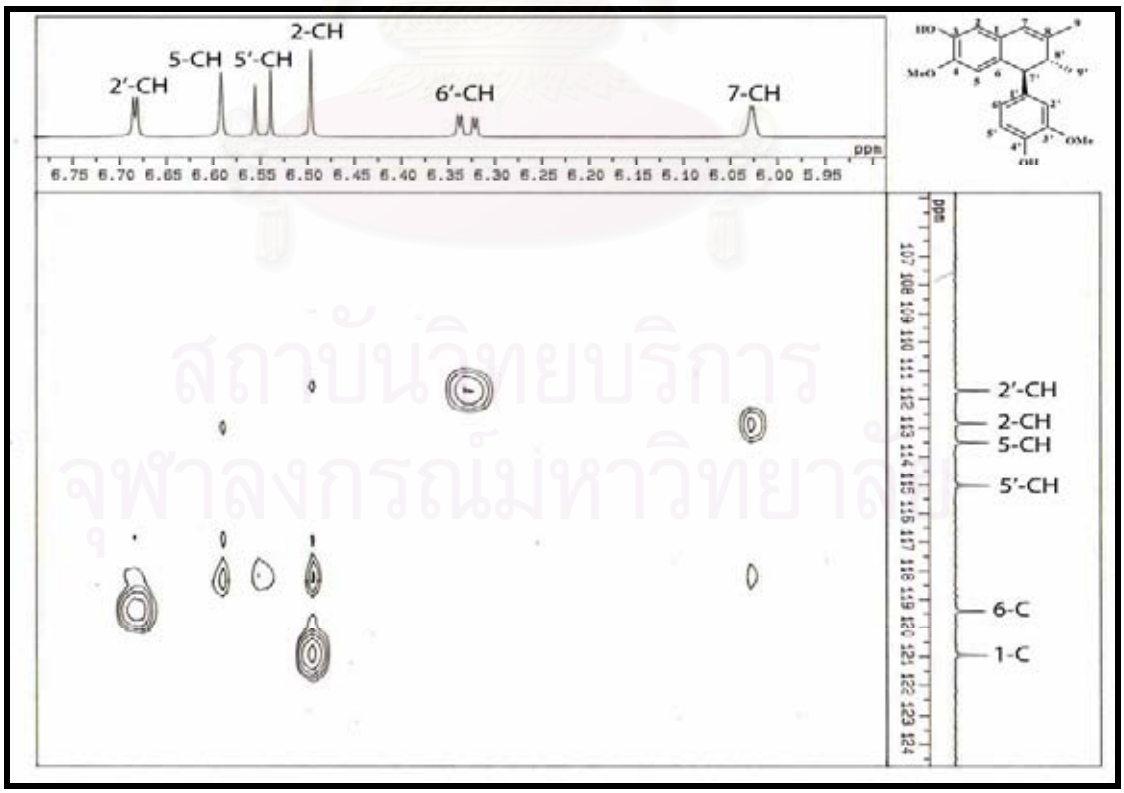

Figure 106d. HMBC Spectrum of compound KF-S1

(expansion between δ_H 5.95-6.75 ppm, δ_C 107.0-124.0 ppm)

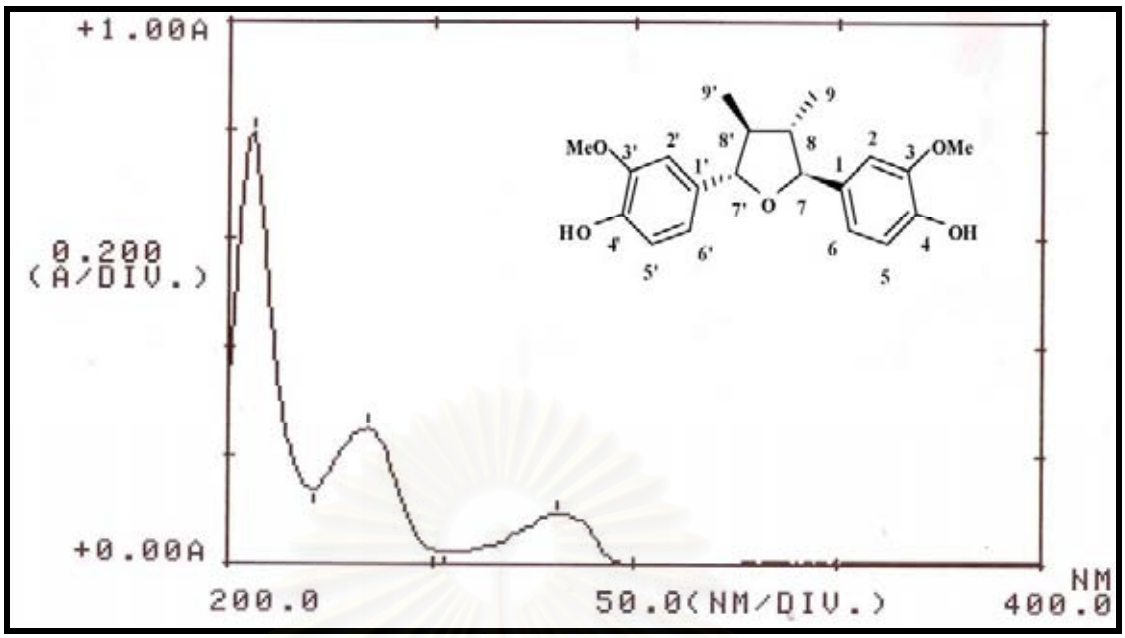

Figure 107. UV Spectrum of compound KF-S2 (in MeOH)

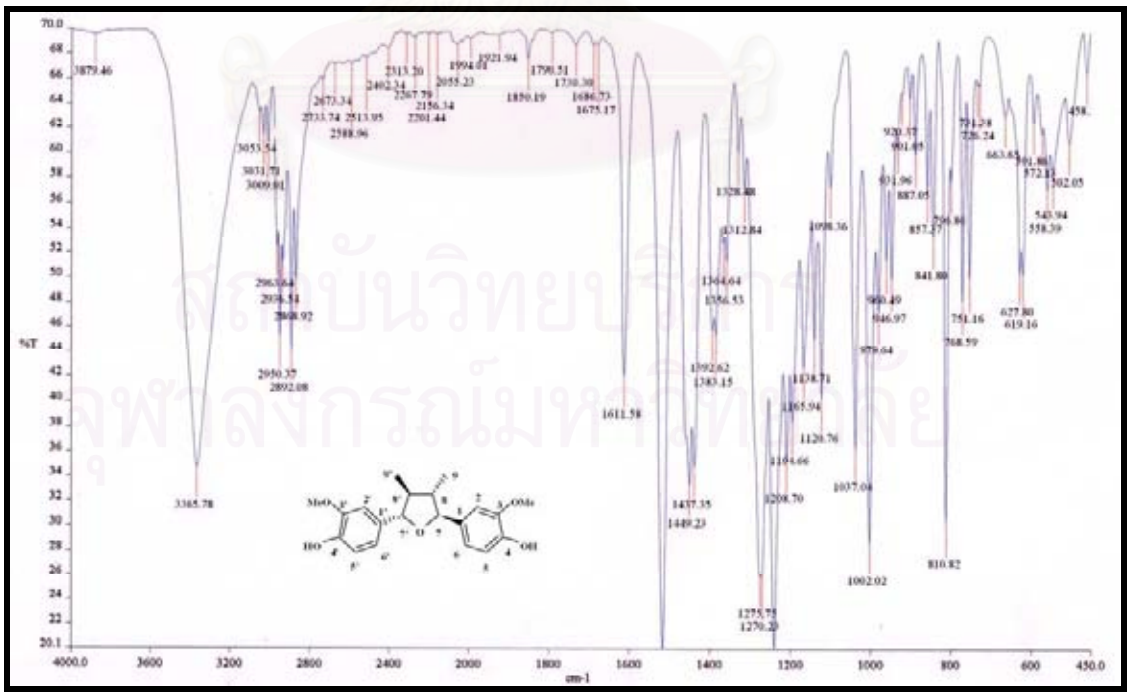

Figure 108. IR Spectrum of compound KF-S2 (KBr disc)

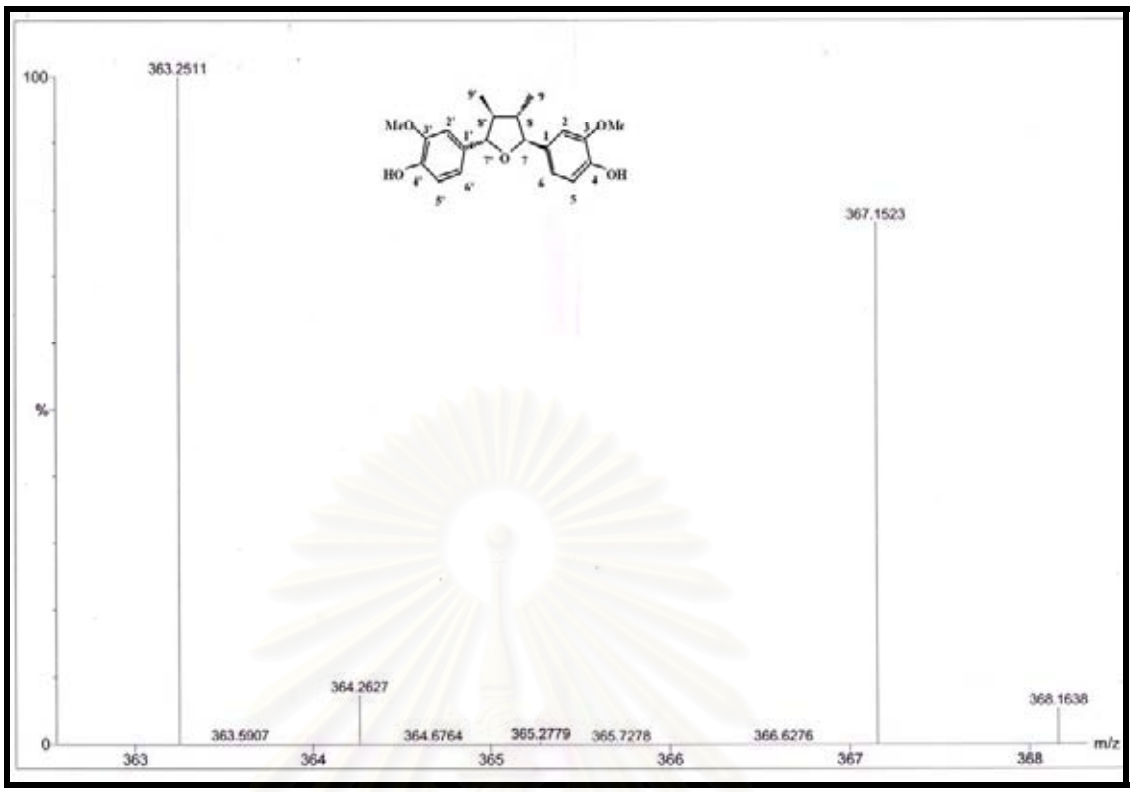

Figure 109. HR-ESI –TOF Mass spectrum of compound KF-S2

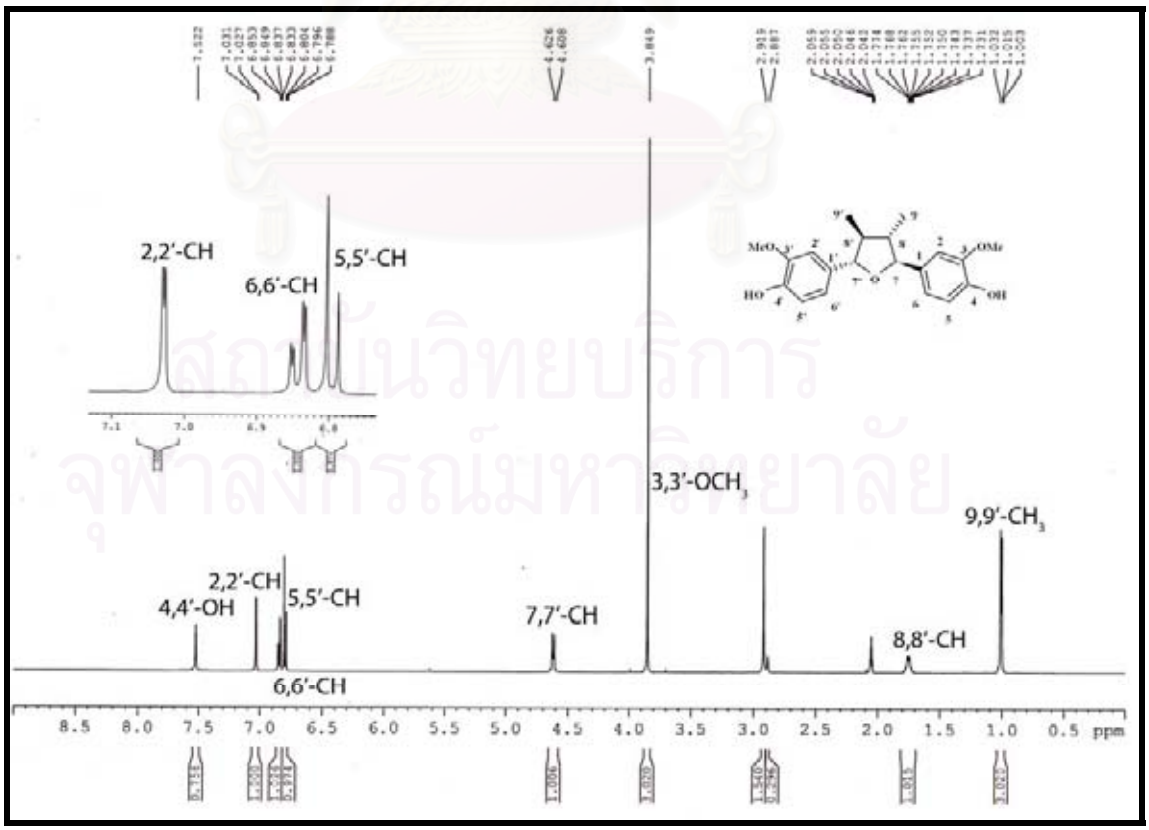

Figure 110. ^{1}H NMR (500 MHz) Spectrum of compound KF-S2 (in acetone-d_6)

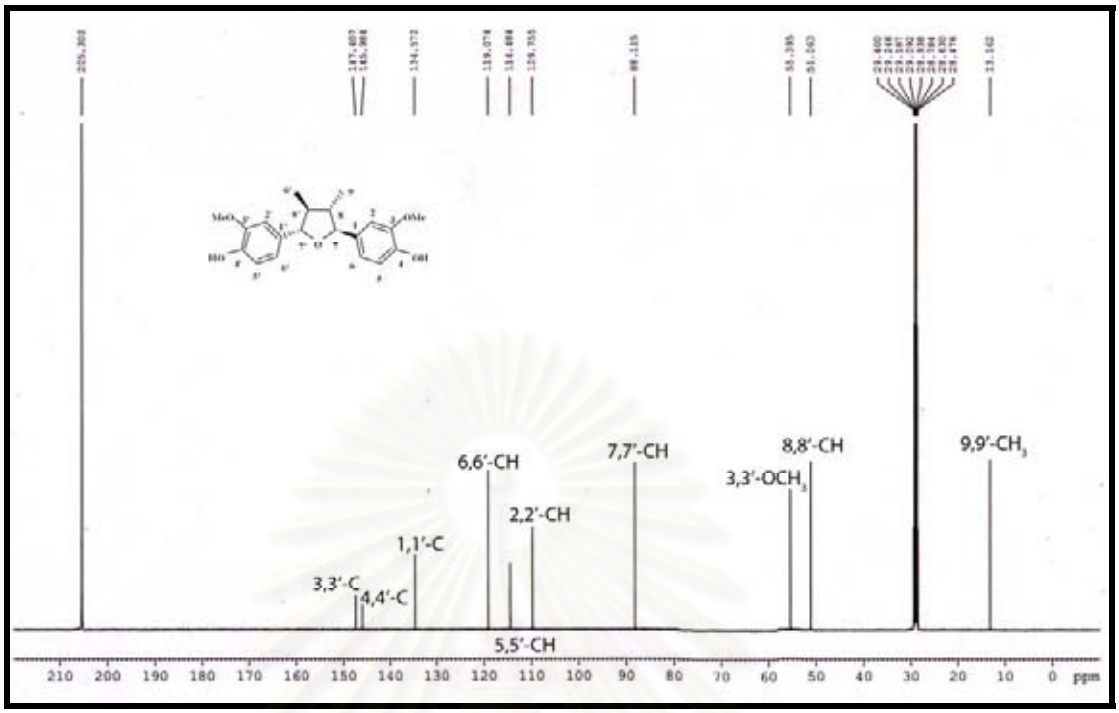

Figure 111. ^{13}C NMR (125 MHz) Spectrum of compound KF-S2 (in acetone-d_6)

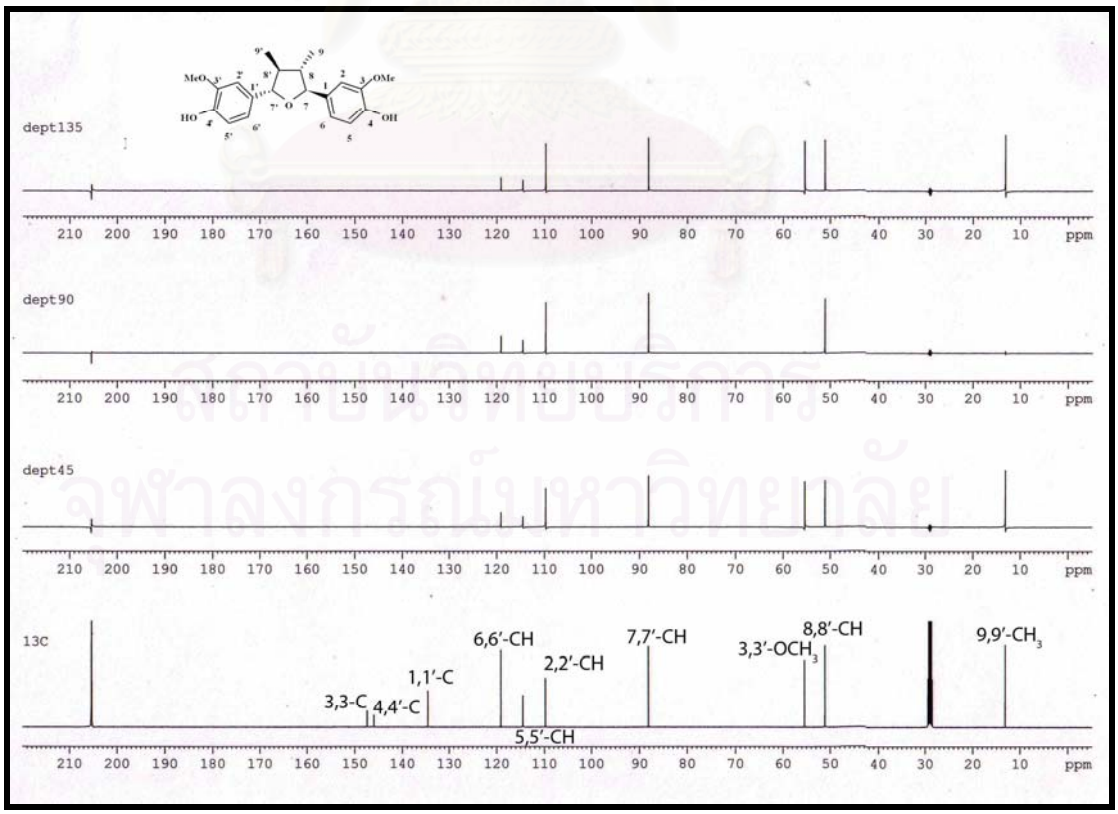

Figure 112. DEPT 135, DEPT 90 and ^{13}C NMR Spectrum of compound KF-S2 (in acetone-d_6)

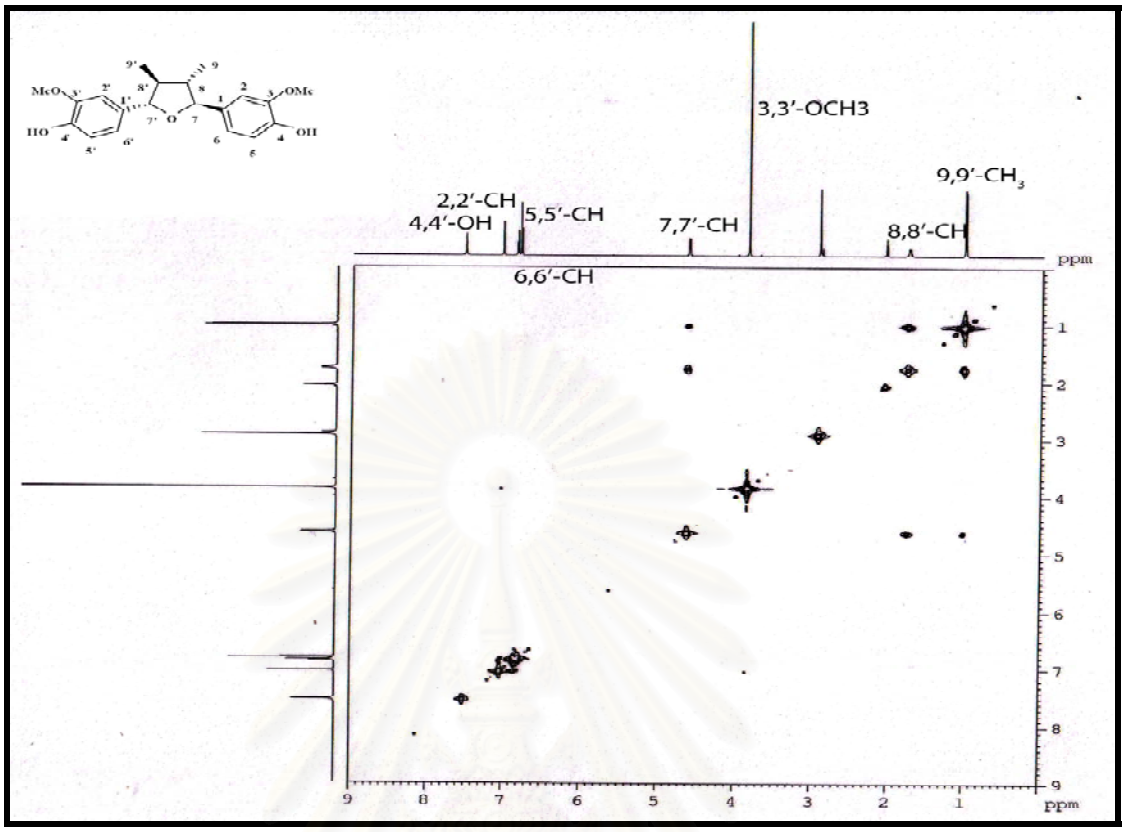

Figure 113. ^{1}H-^{1}H COSY Spectrum of compound KF-S2 (in acetone-d_6)

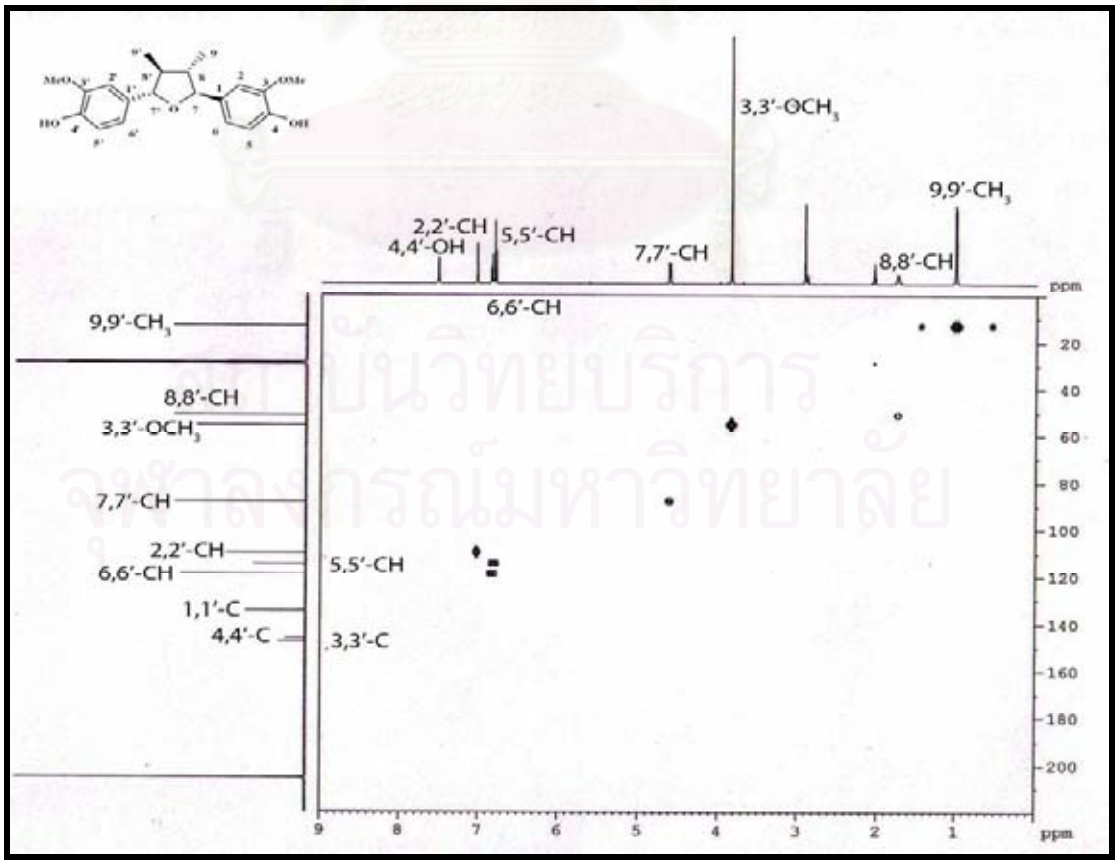

Figure 114. HMQC Spectrum of compound KF-S2

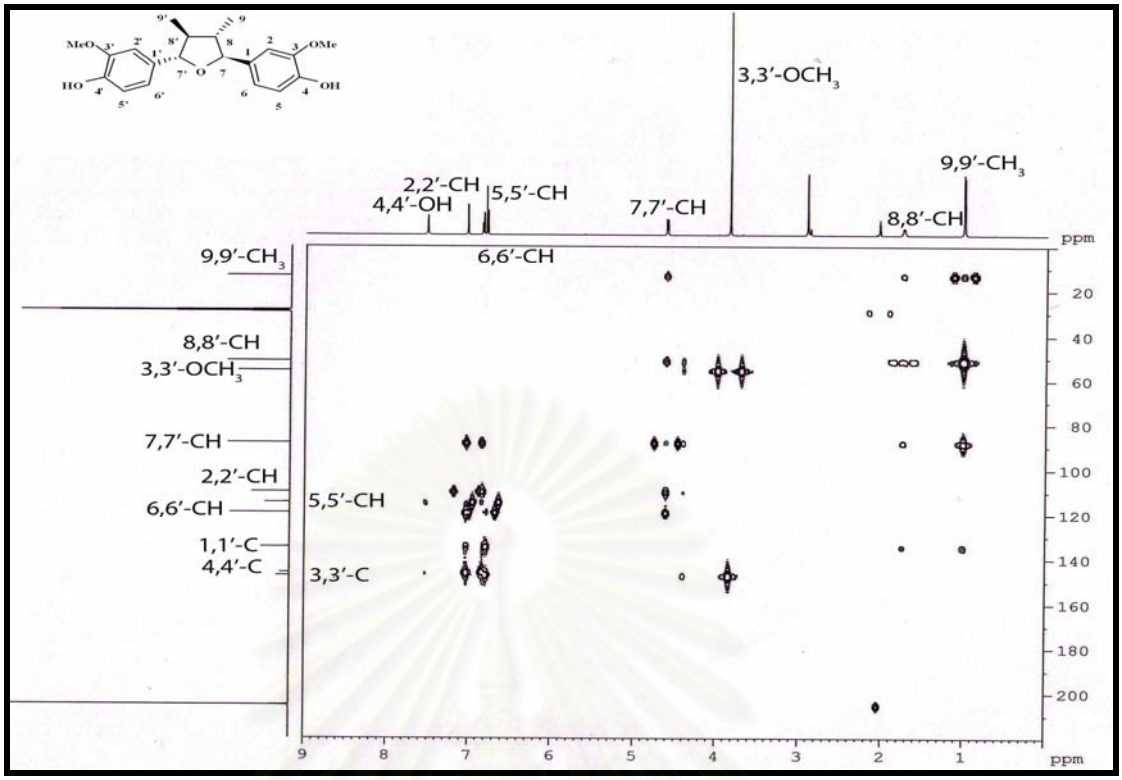

Figure 115a. HMBC Spectrum of compound KF-S2

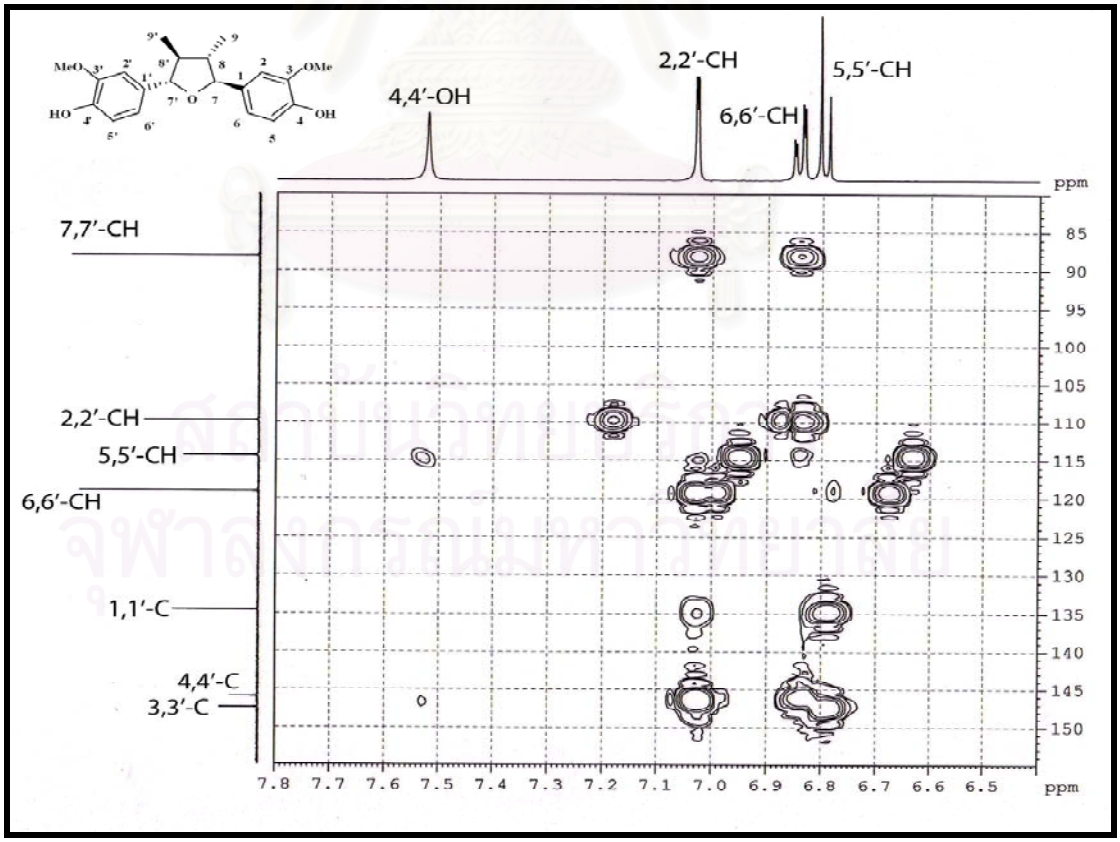

Figure 115b. HMBC Spectrum of compound KF-S2

(expansion between δ_H 6.5-7.8 ppm, δ_C 85.0-150.0 ppm)

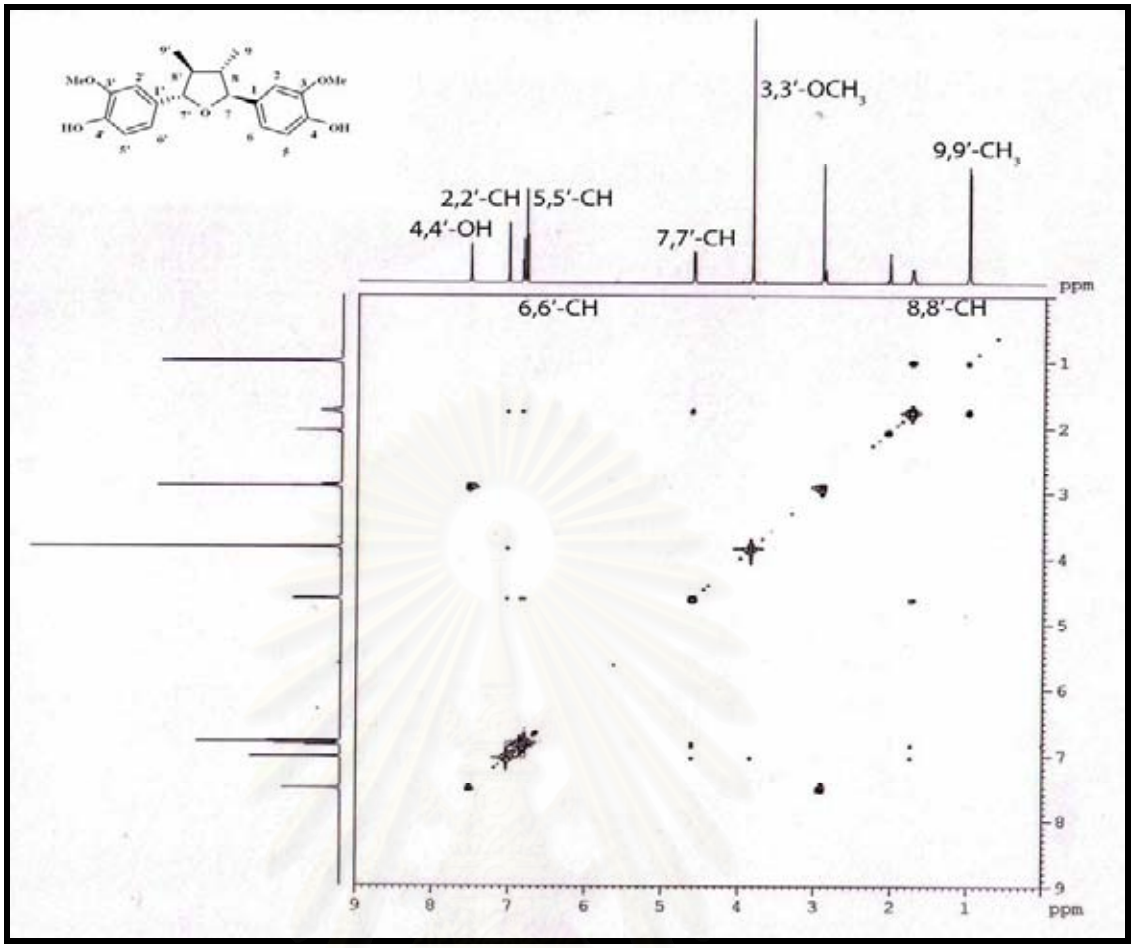

Figure 116. NOESY Spectrum of compound KF-S2

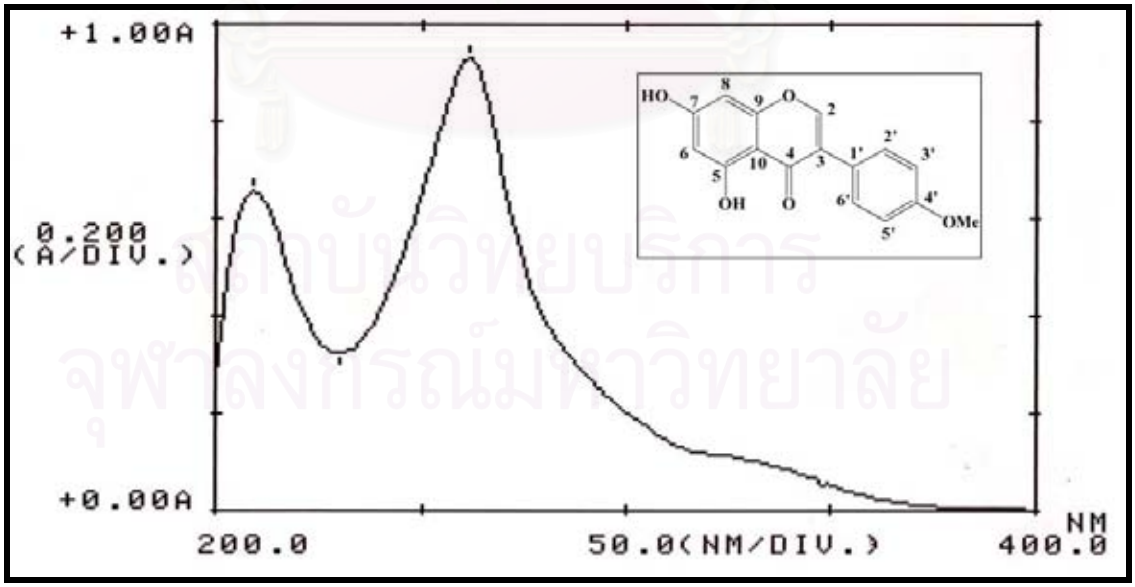

Figure 117. UV Spectrum of compound KF-S3 (in MeOH)

Figure 118. IR Spectrum of compound KF-S3 (KBr disc)

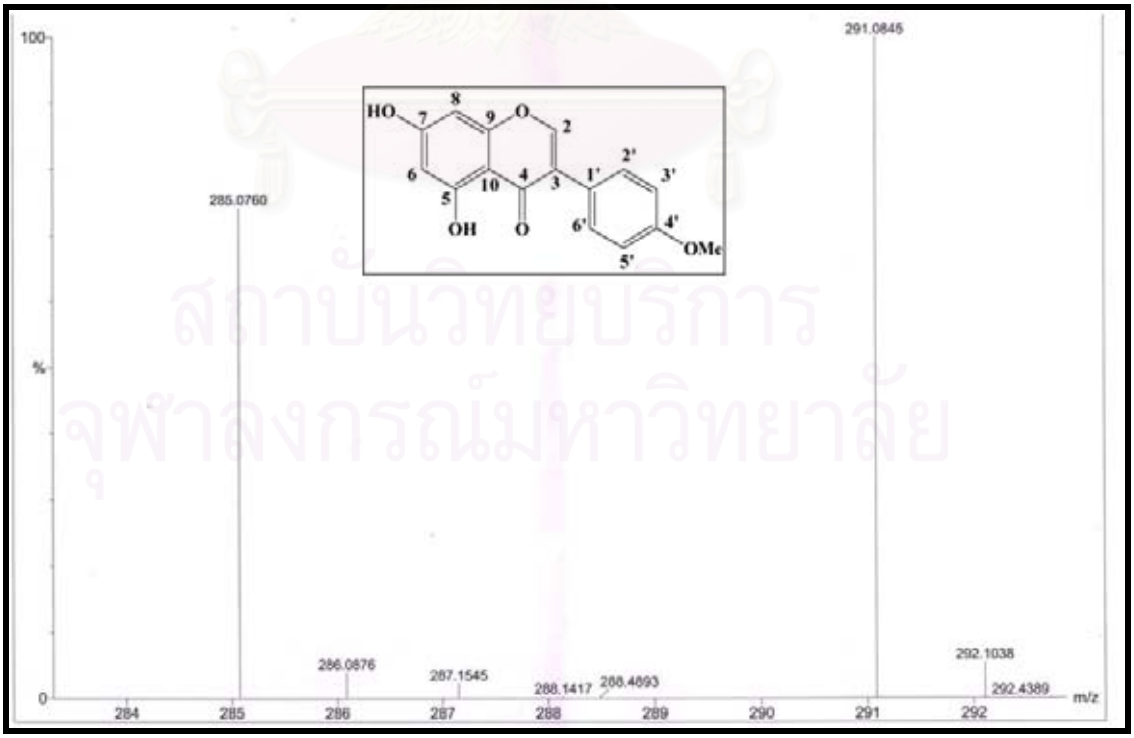

Figure 119. HR-ESI-TOF Mass spectrum of compound KF-S3

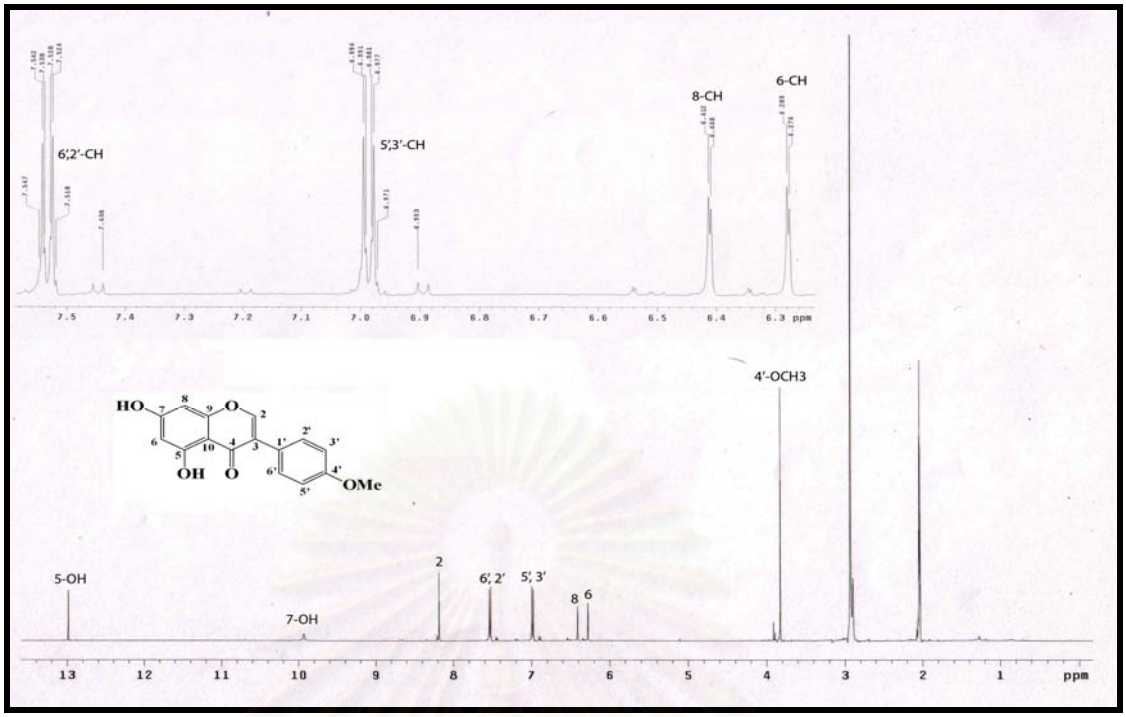

Figure 120. ^{1}H NMR (500 MHz) Spectrum of compound KF-S3 (in acetone-d_6)

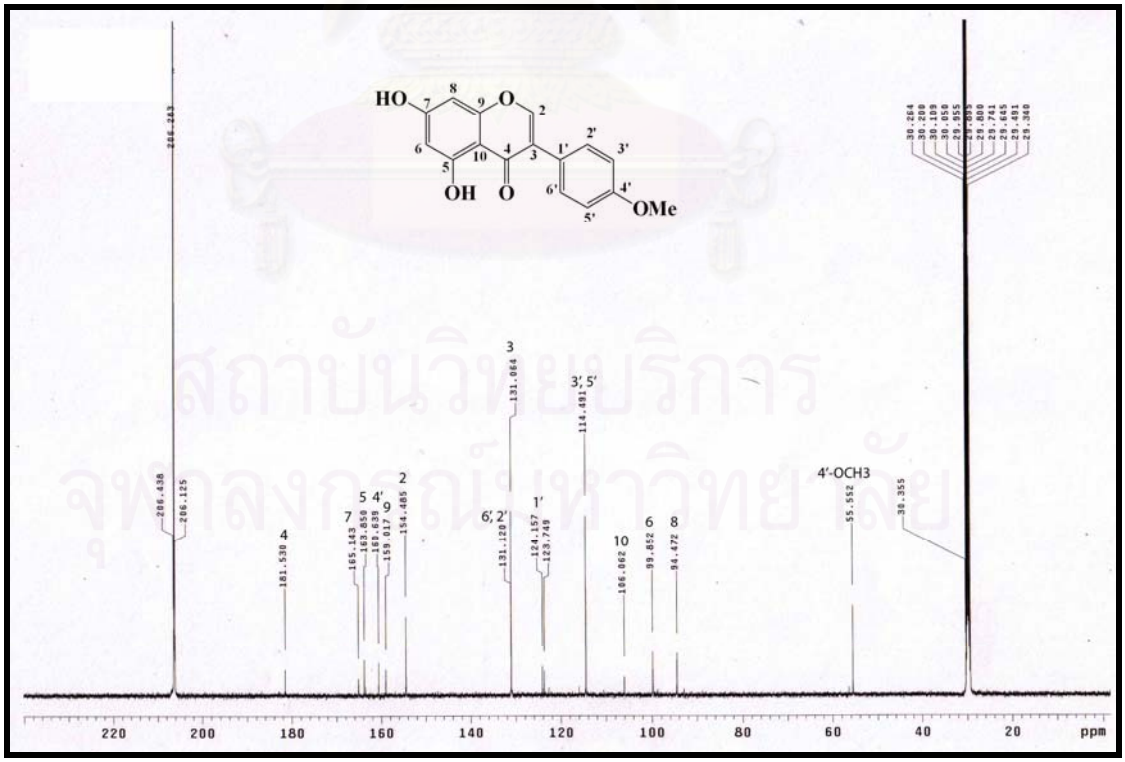

Figure 121. ^{13}C NMR (125 MHz) Spectrum of compound KF-S3 (in acetone-d_6)

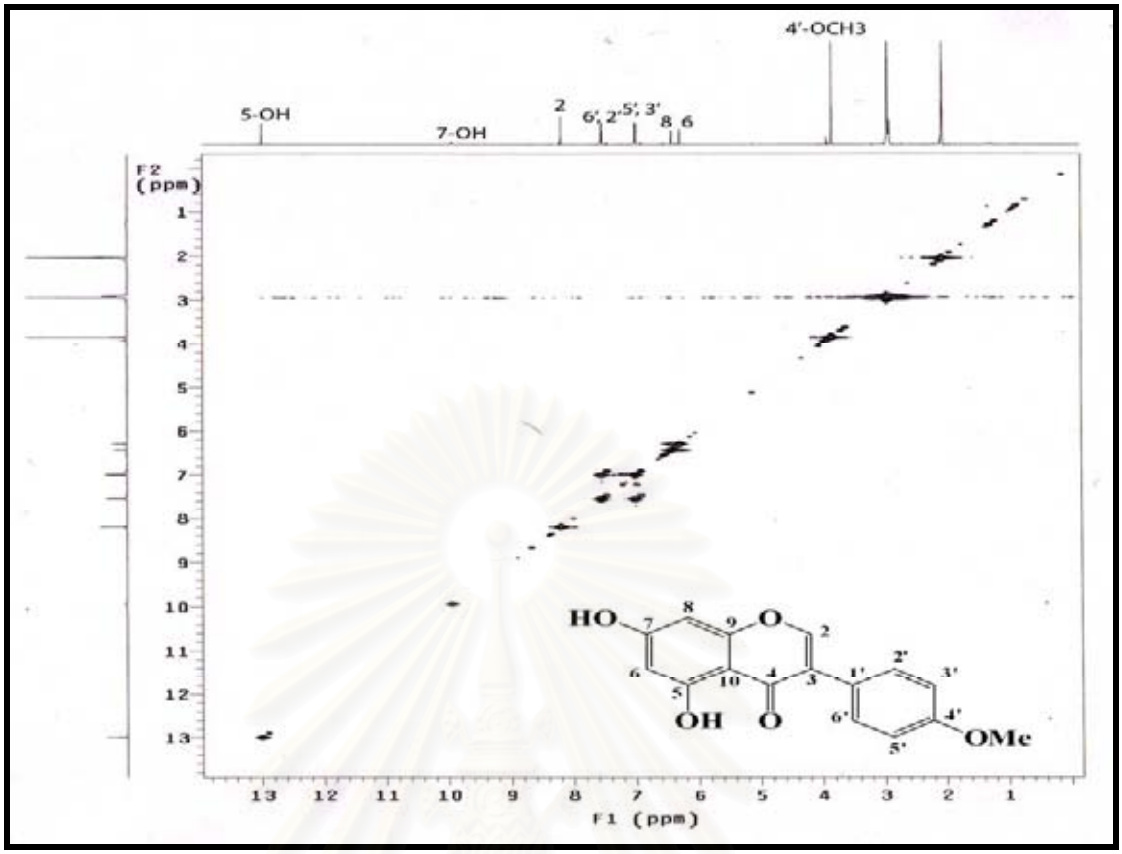

Figure 122a. ^{1}H-^{1}H COSY Spectrum of compound KF-S3 (in acetone-d_6)

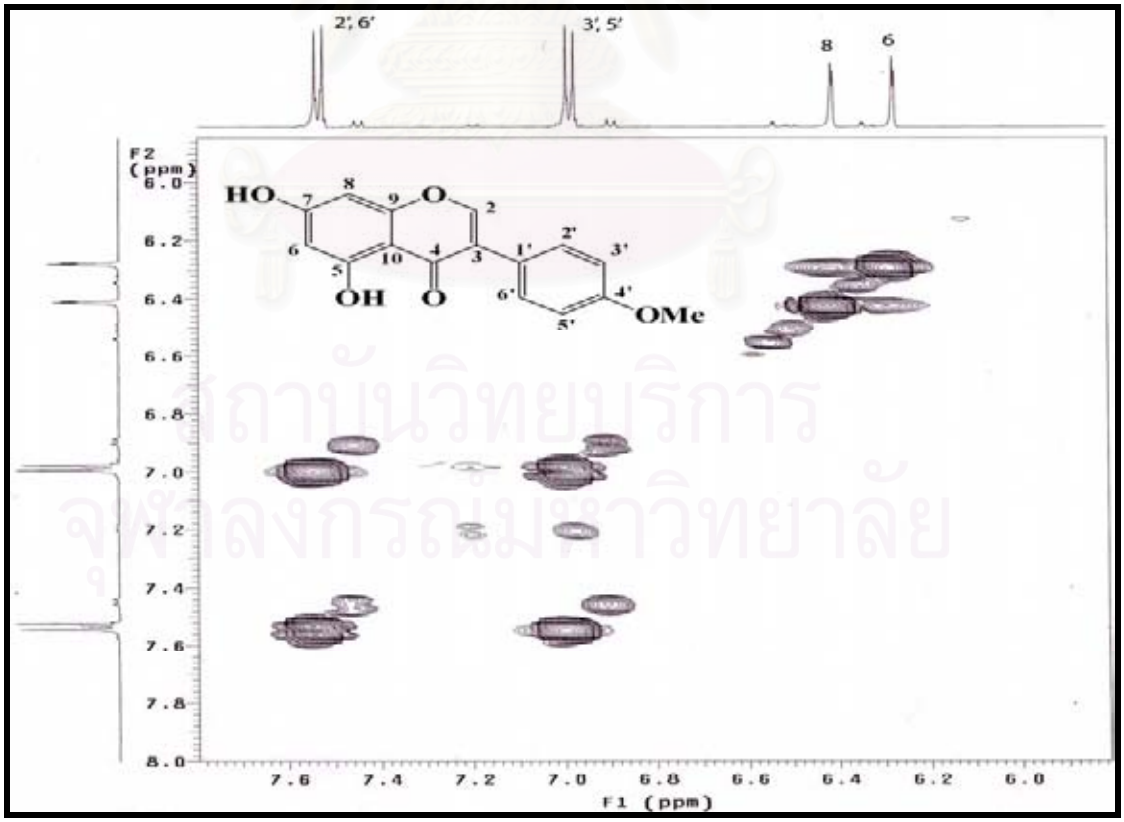

Figure 122b. ^{1}H-^{1}H COSY Spectrum of compound KF-S3

(expansion between δ_H 6.0-7.6 ppm)

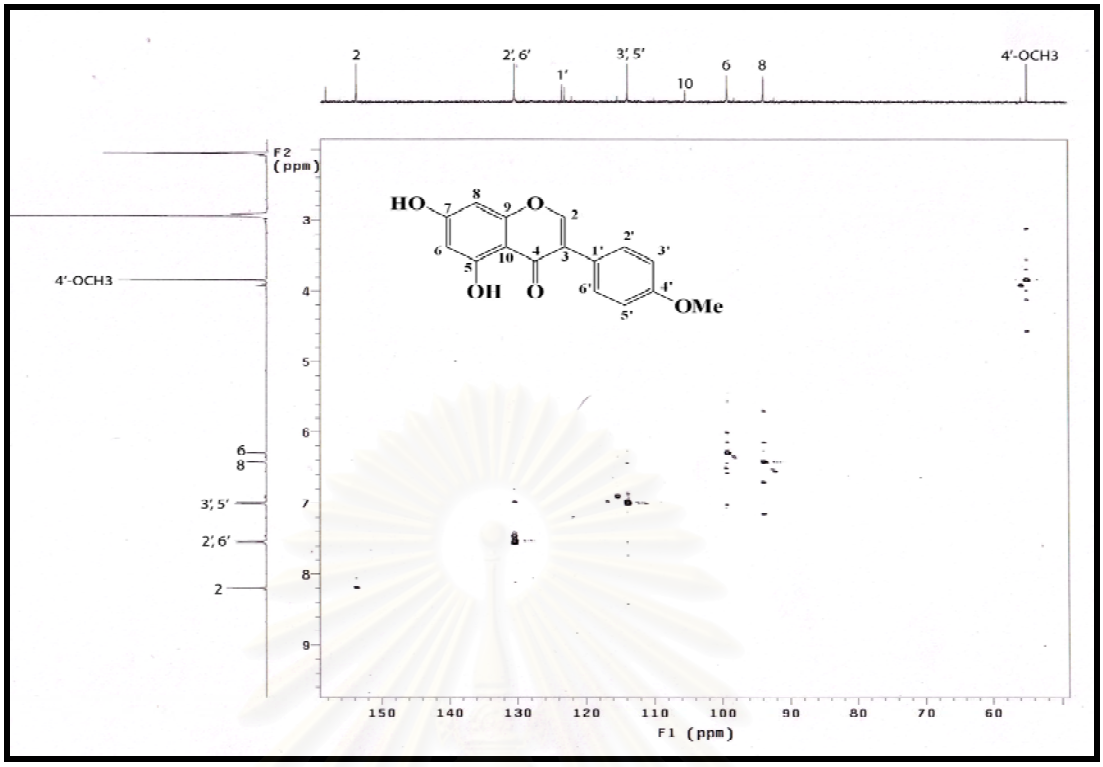

Figure 123. HMQC Spectrum of compound KF-S3

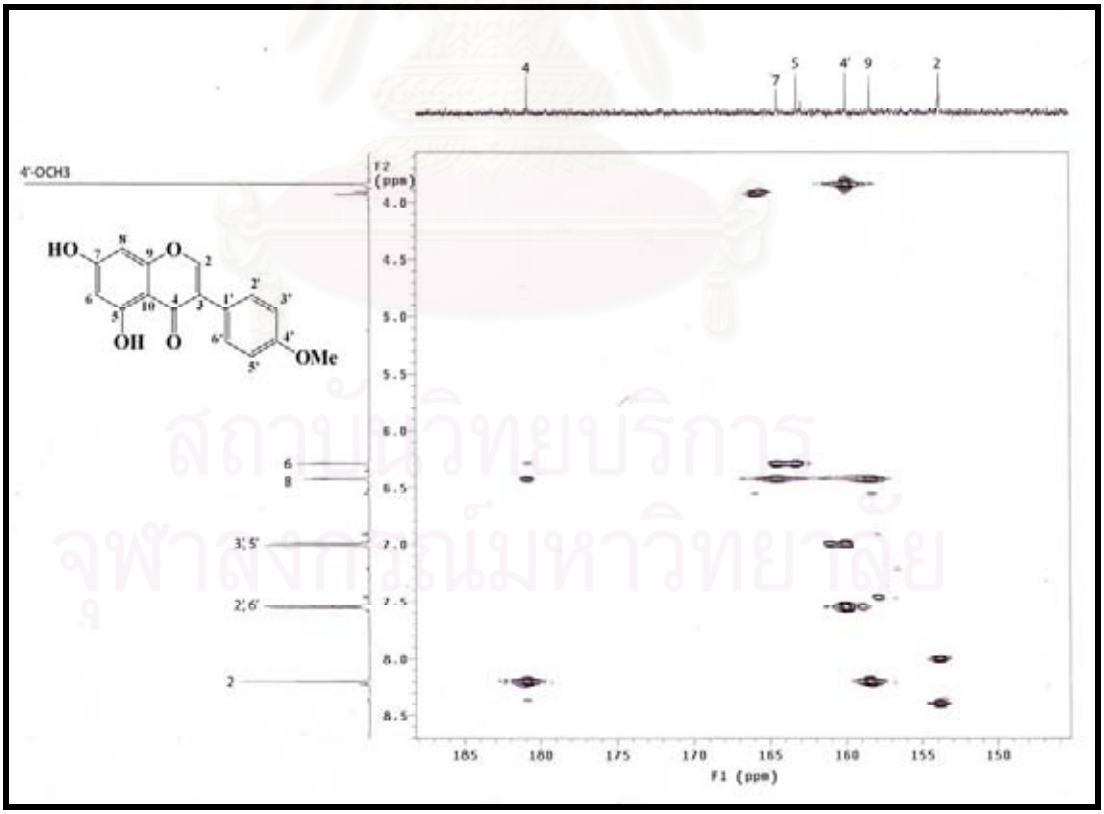

Figure 124a. HMBC Spectrum of compound KF-S3

(expansion between δ_H 4.0-8.5 ppm, δ_C 150.0-185.0 ppm)

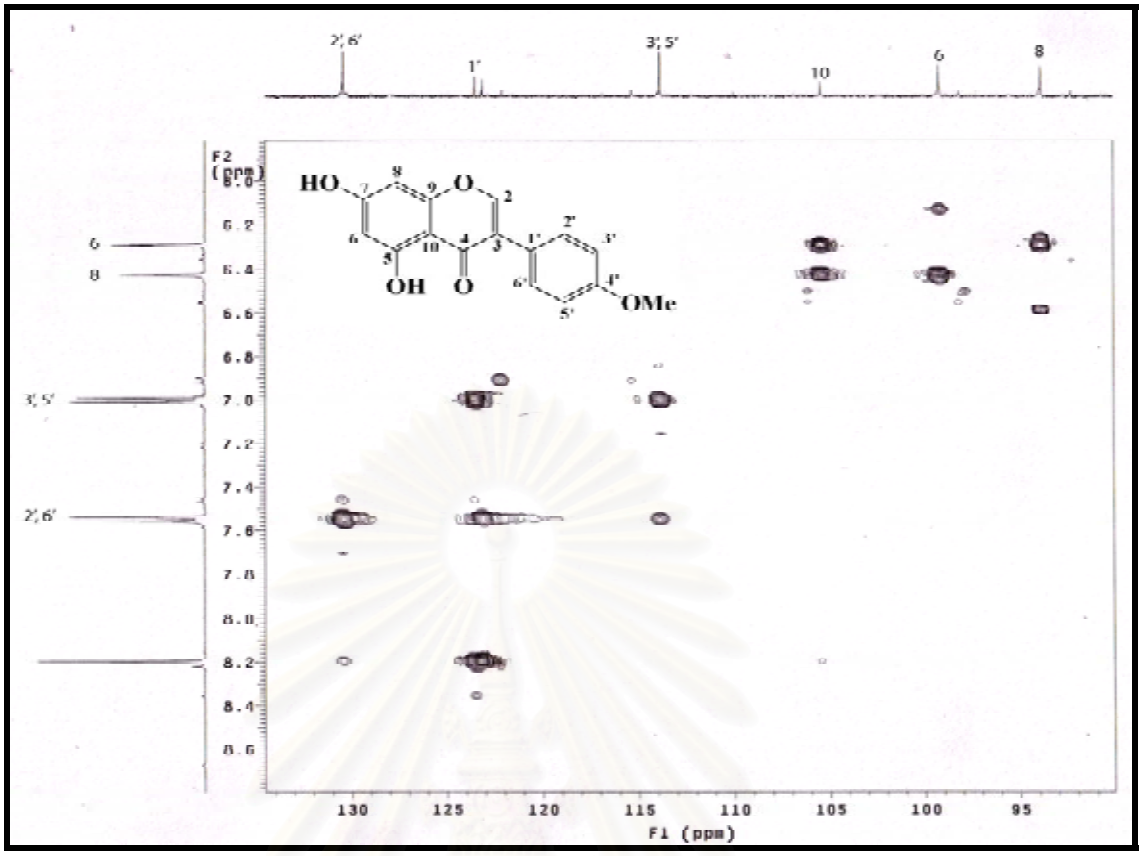

Figure 124b. HMBC Spectrum of compound KF-S3
(expansion between δ_H 6.2-8.5 ppm, δ_C 95.0-130.0 ppm)

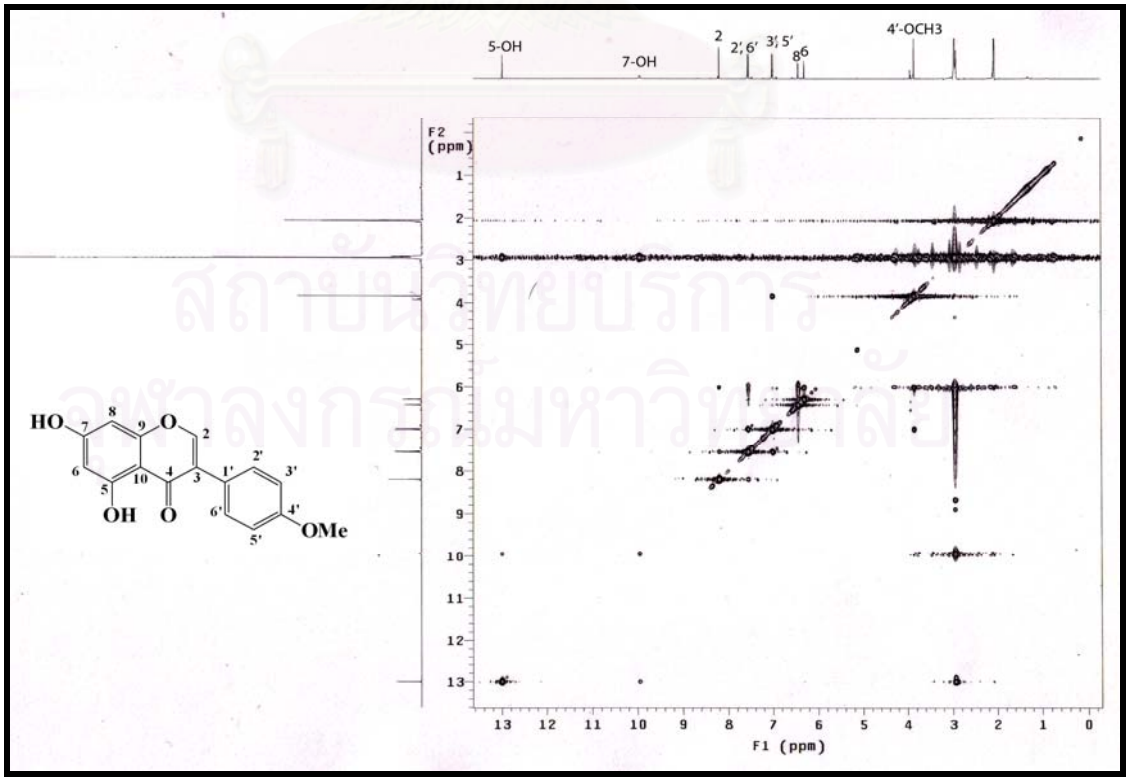

Figure 125a. NOESY Spectrum of compound KF-S3

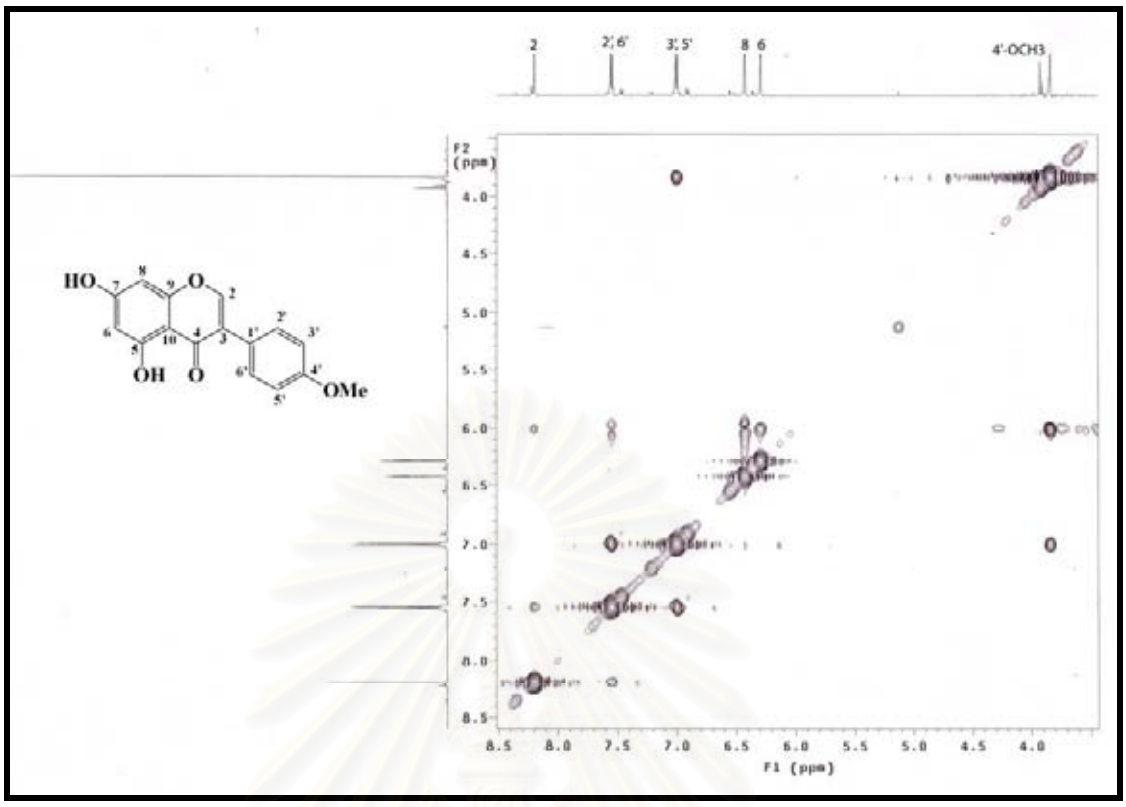

Figure 125b. NOESY Spectrum of compound KF-S3
(expansion between δ_H 4.0-8.5 ppm)

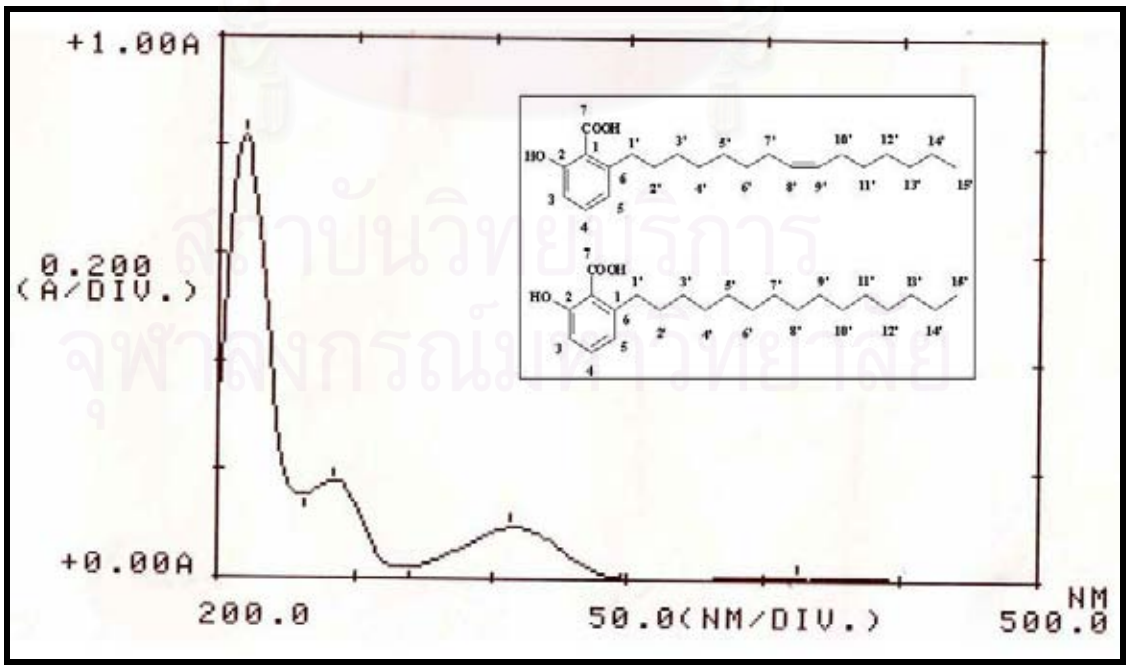

Figure 126. UV Spectrum of compound KF-S4 (in MeOH)

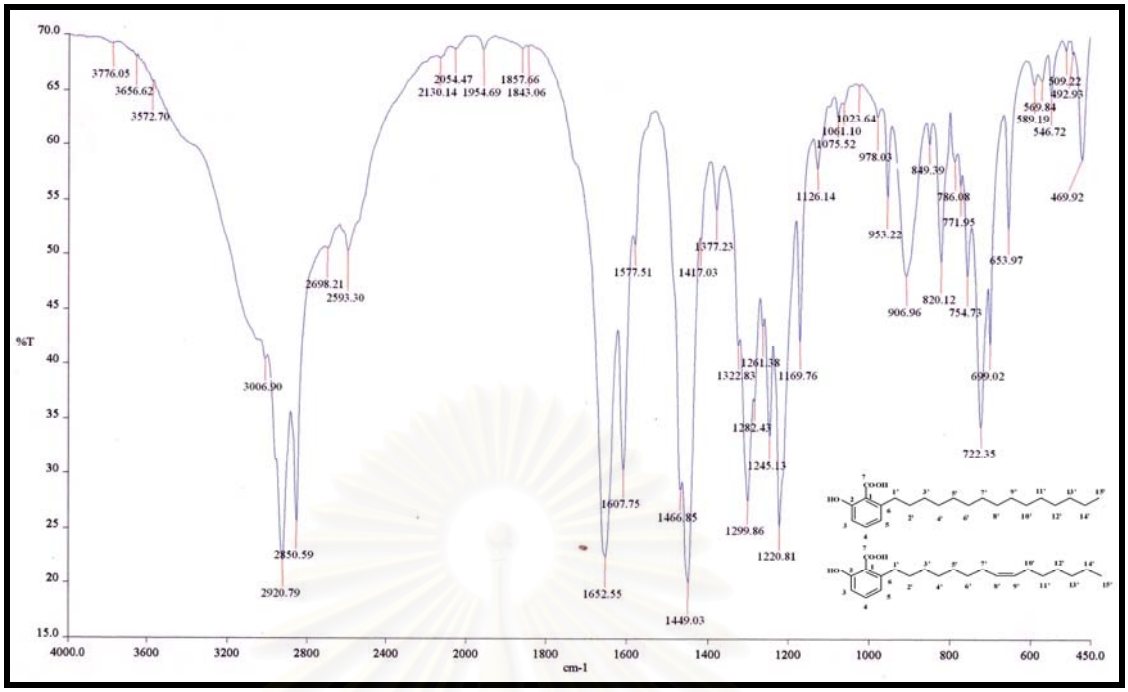

Figure 127. IR Spectrum of compound KF-S4 (KBr disc)

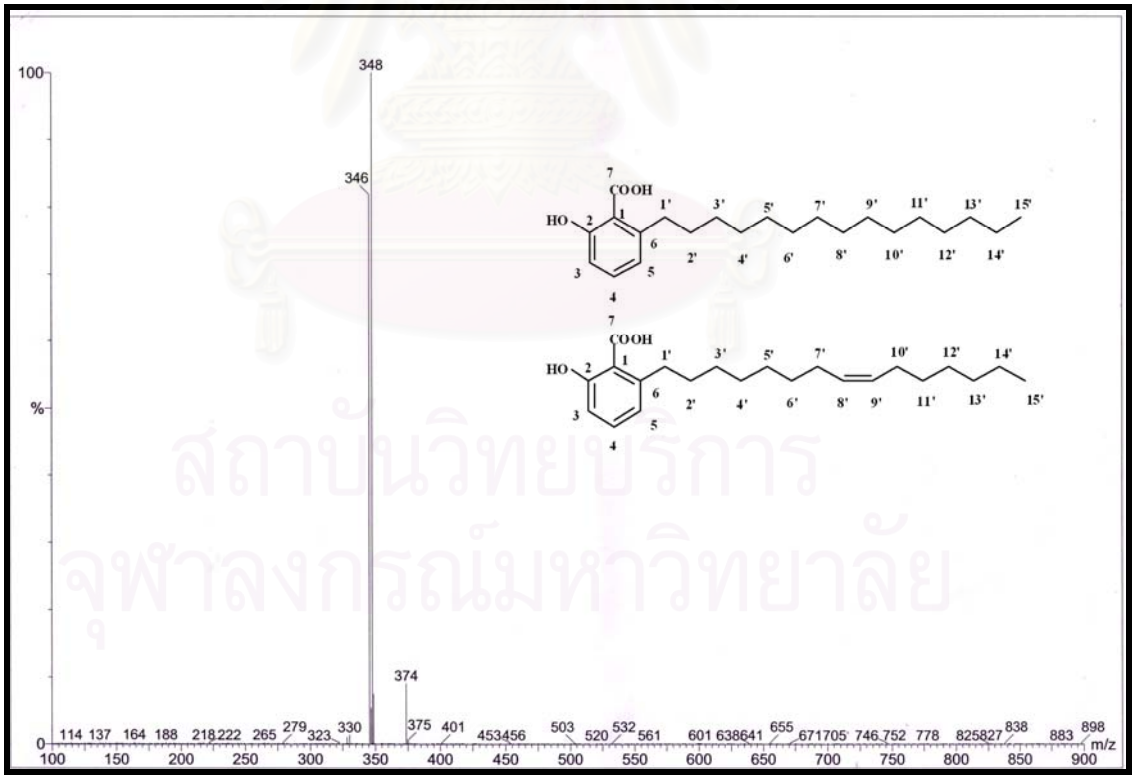

Figure 128. ESI-TOF Mass spectrum of compound KF-S4

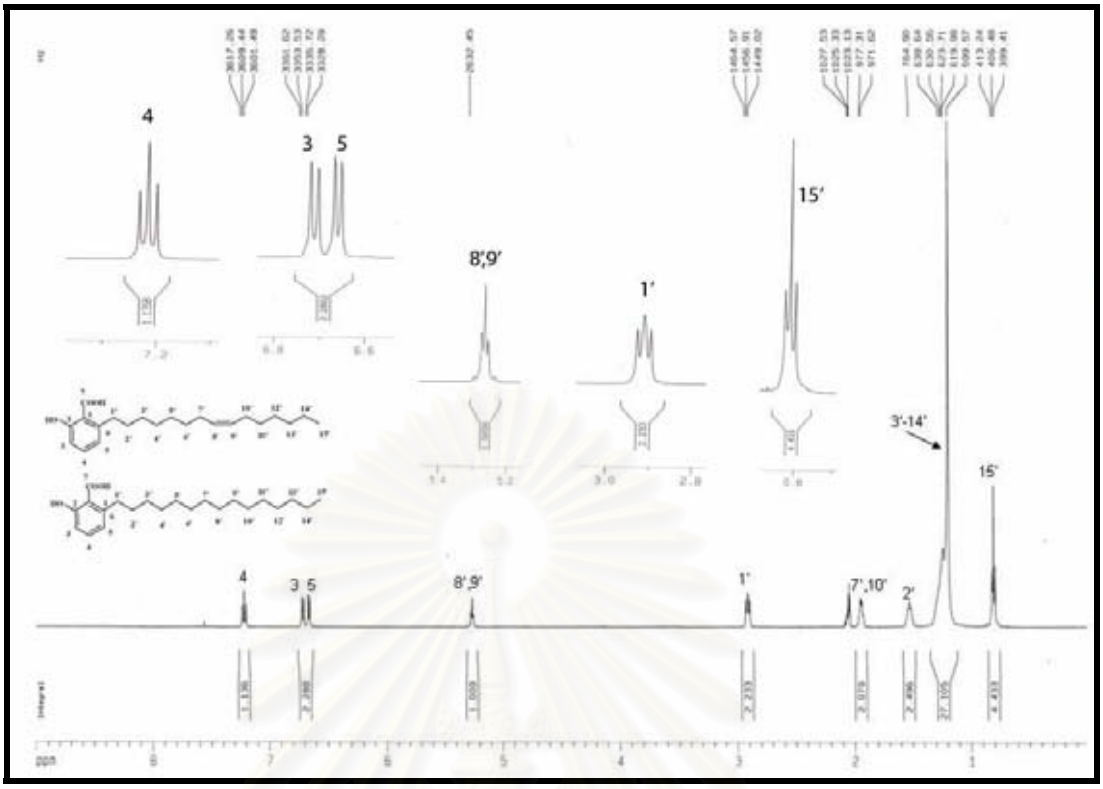

Figure 129. ^{1}H NMR (500 MHz) Spectrum of compound KF-S4 (in acetone-d_6)

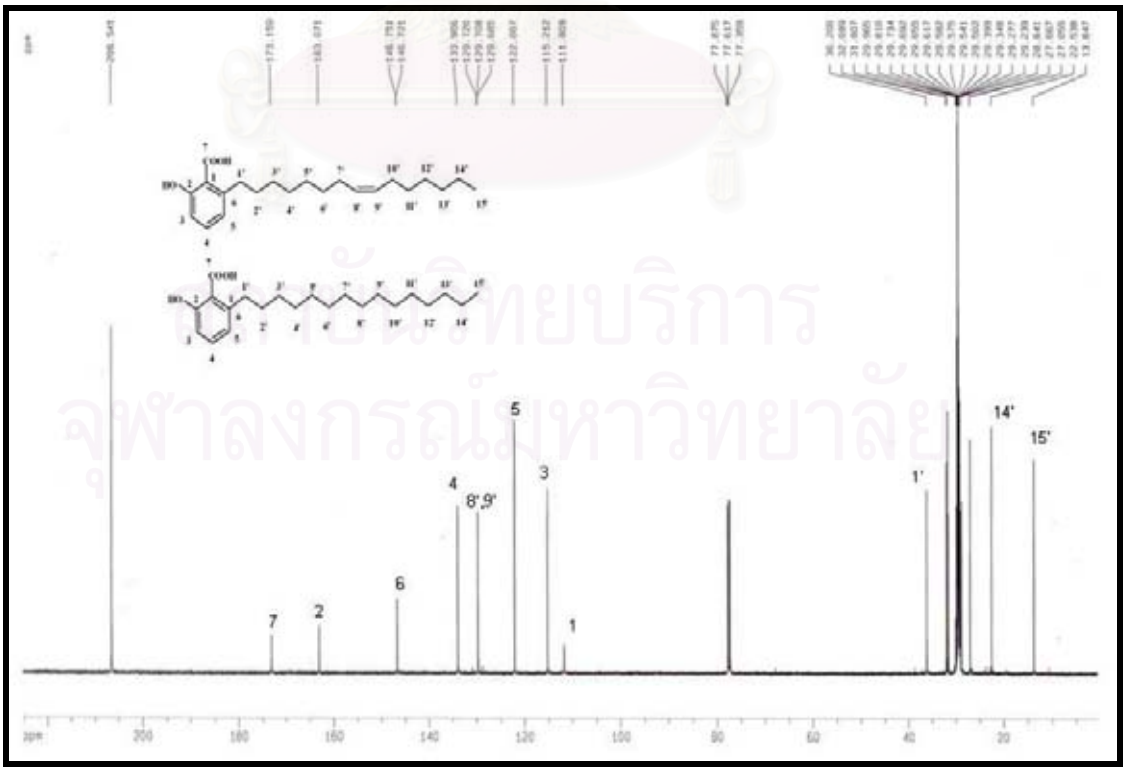

Figure 130a. ^{13}C NMR (125 MHz) Spectrum of compound KF-S4 (in acetone-d_6)

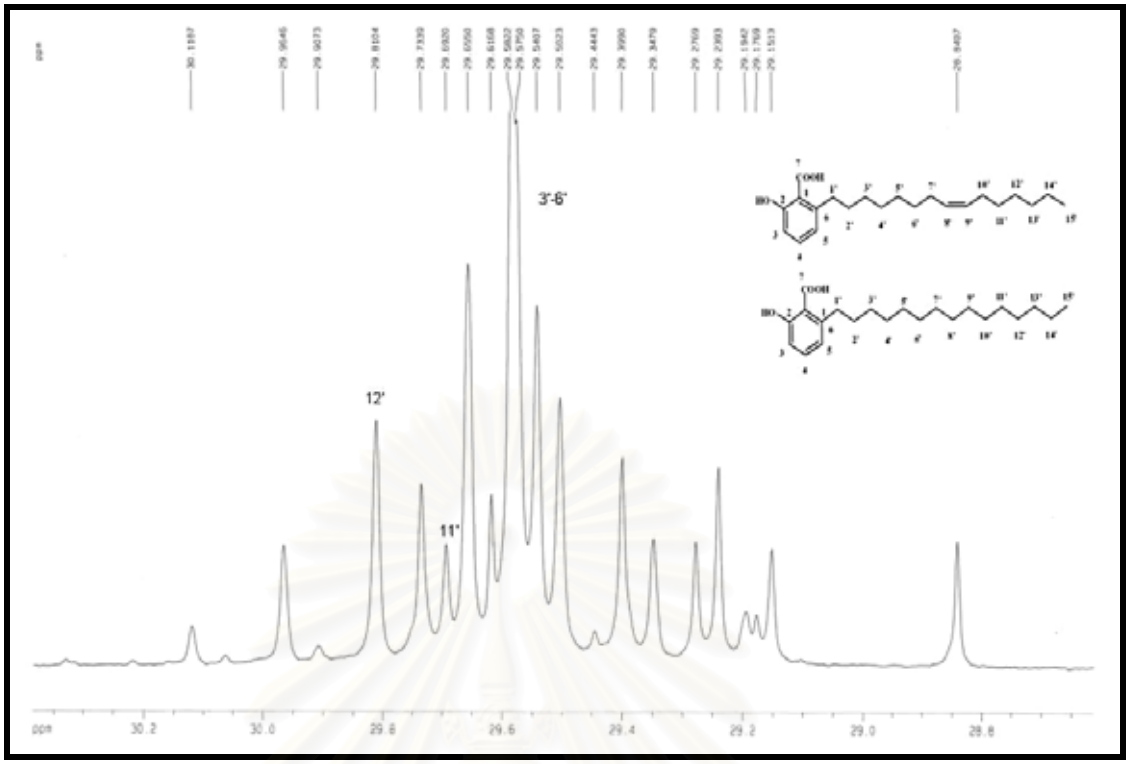

Figure 130b. ^{13}C NMR (125 MHz) Spectrum of compound KF-S4 (expansion between δ_H 29.8-30.2 ppm)

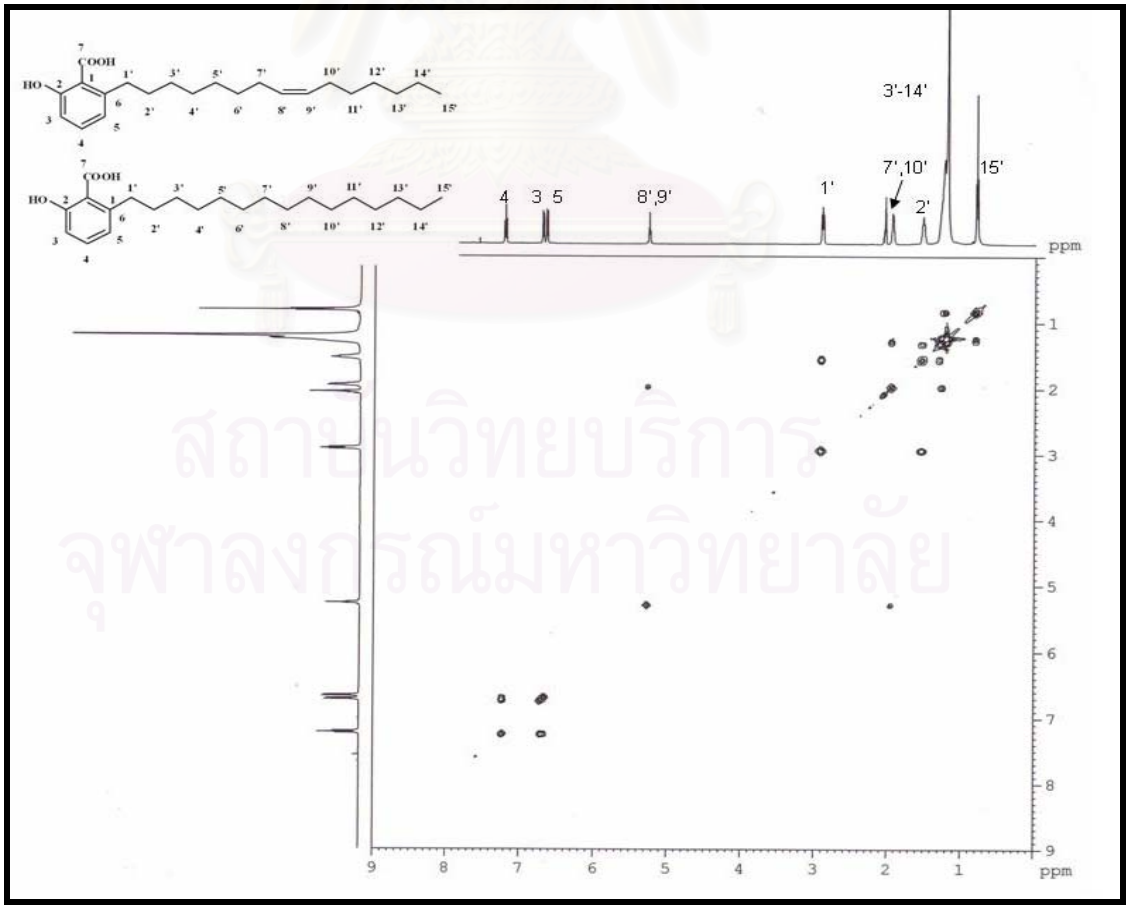

Figure 131. ^{1}H-^{1}H COSY Spectrum of compound KF-S4 (in acetone-d_6)

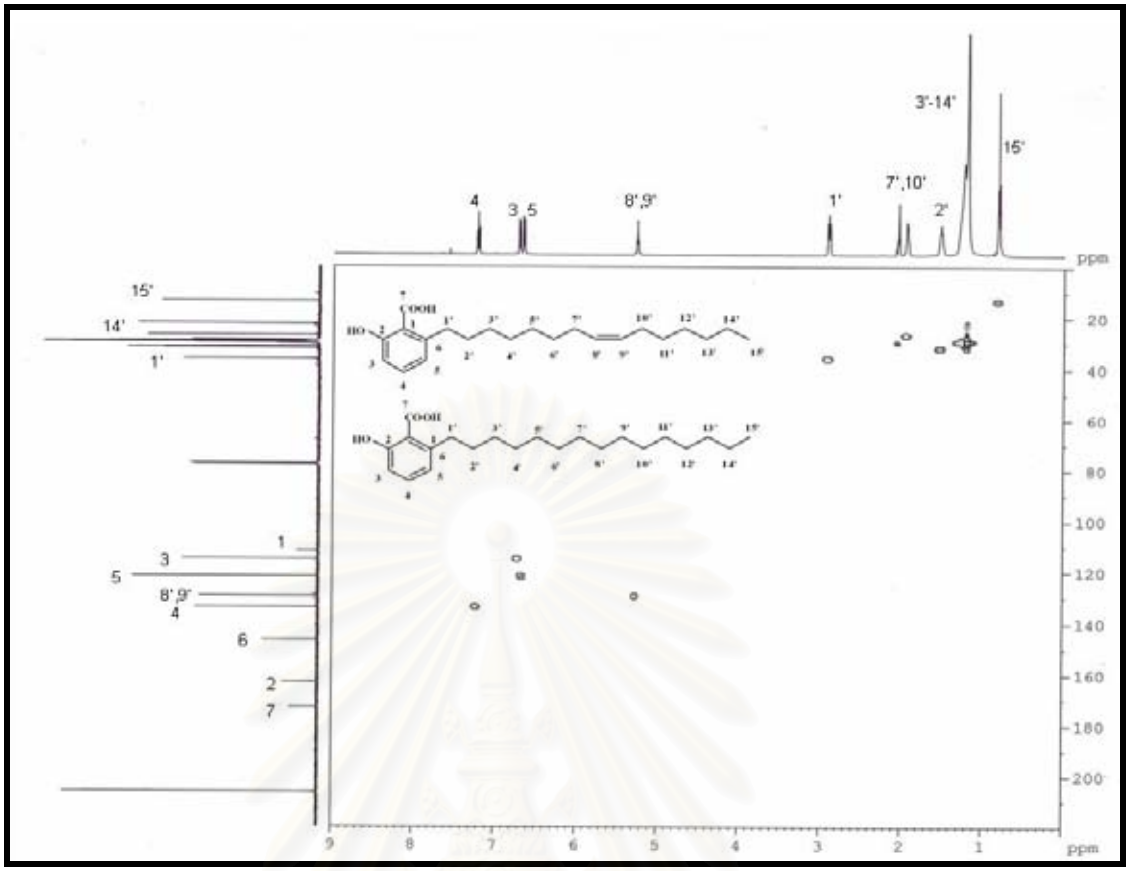

Figure 132. HMQC Spectrum of compound KF-S4

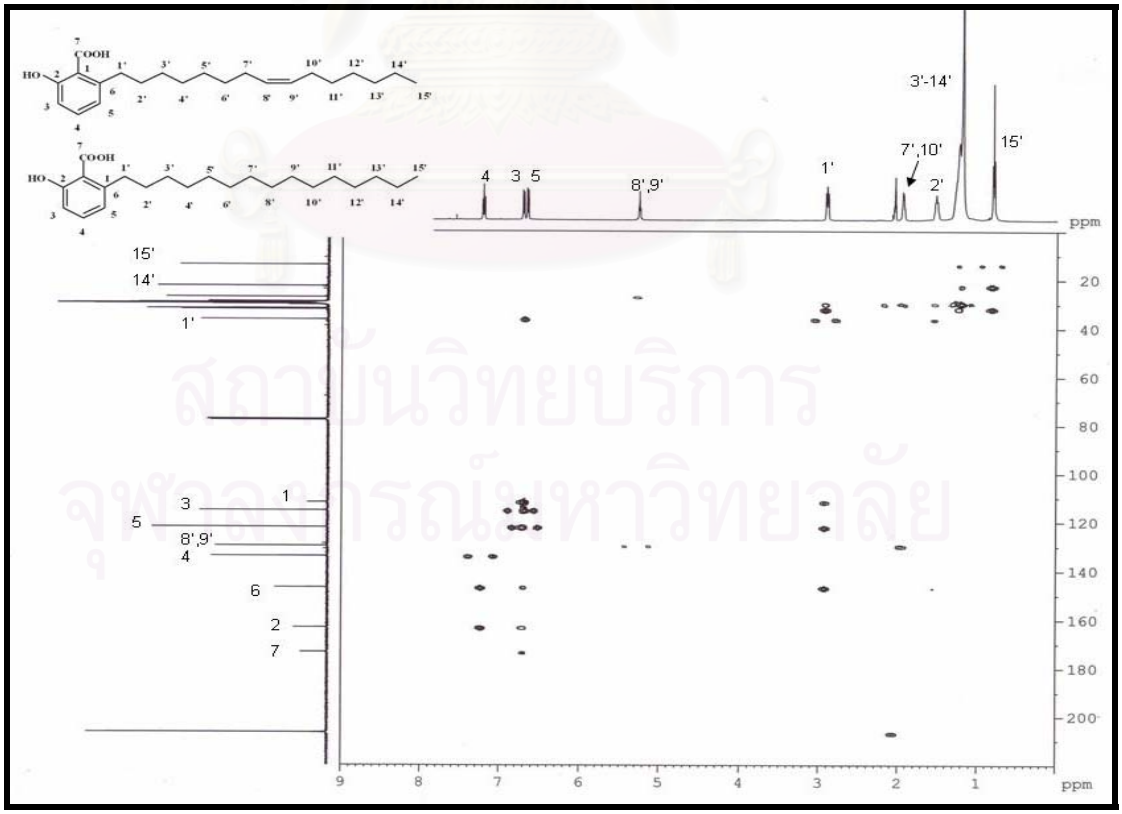

Figure 133a. HMBC Spectrum of compound KF-S4

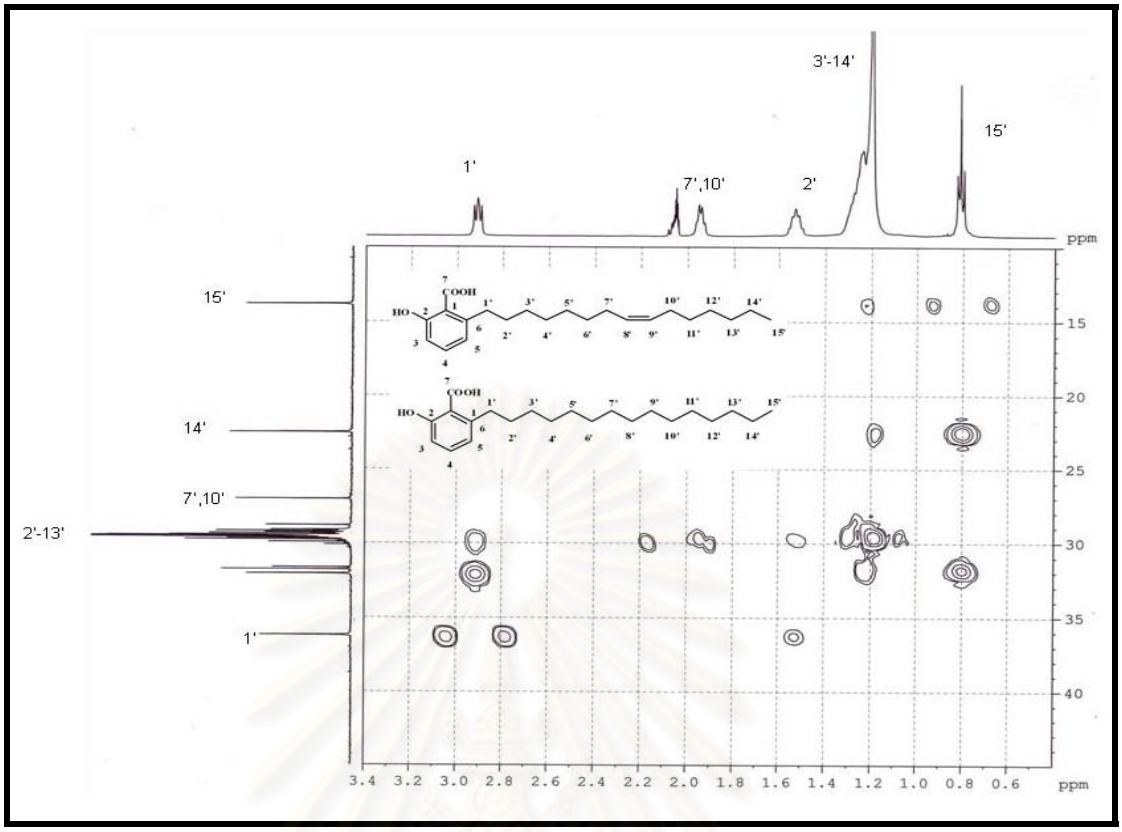

Figure 133b. HMBC Spectrum of compound KF-S4
(expansion between δ_H 0.6-3.2 ppm, δ_C 15.0-45.0 ppm)

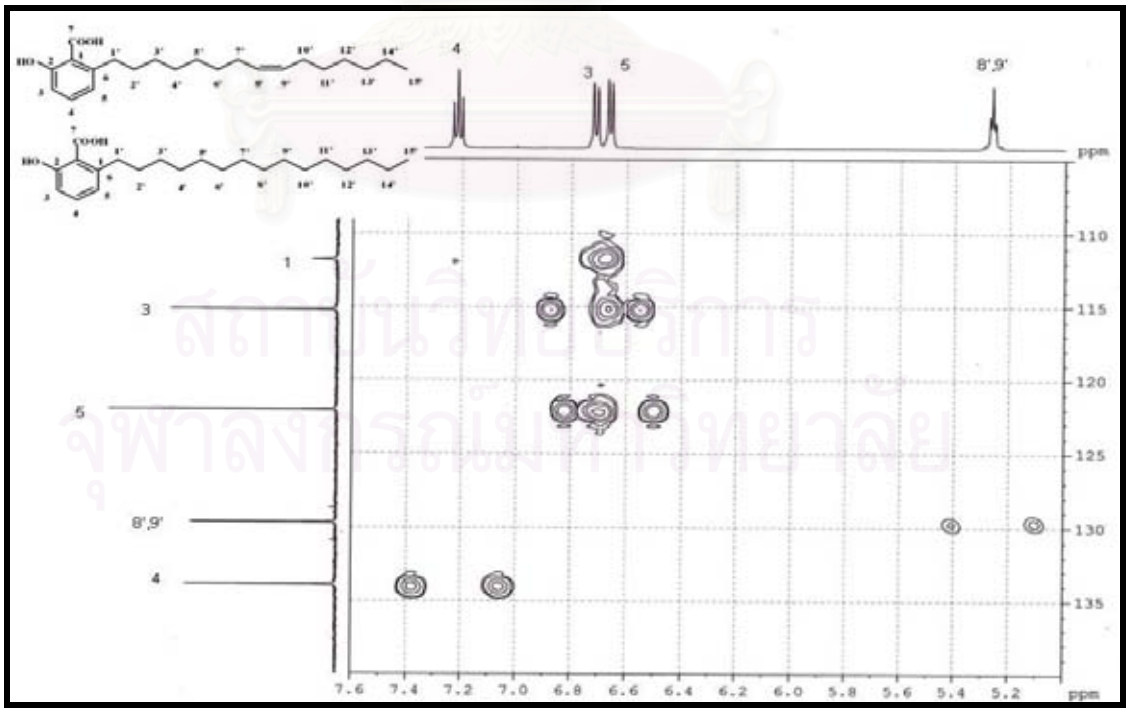

Figure 133c. HMBC Spectrum of compound KF-S4
(expansion between δ_H 5.2-7.6 ppm, δ_C 110.0-135.0 ppm)

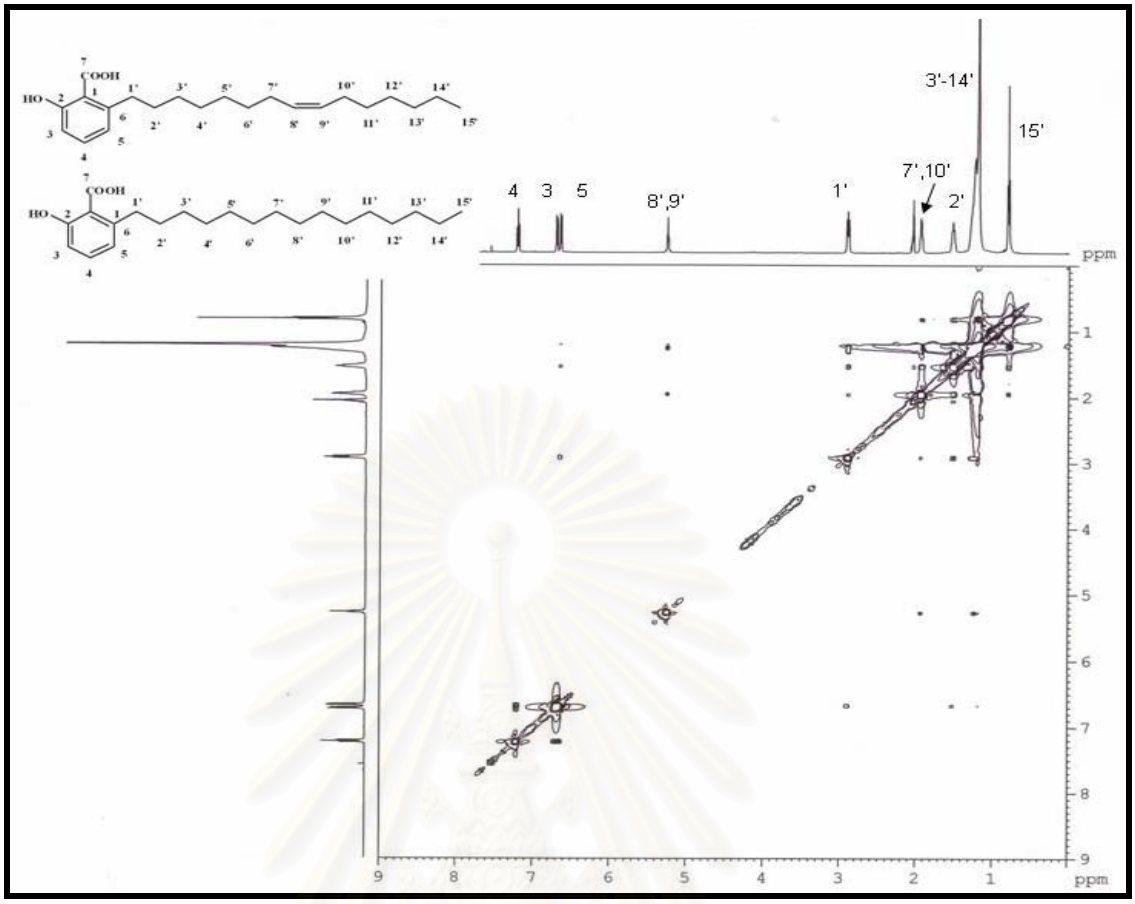

Figure 134. NOESY Spectrum of compound KF-S4

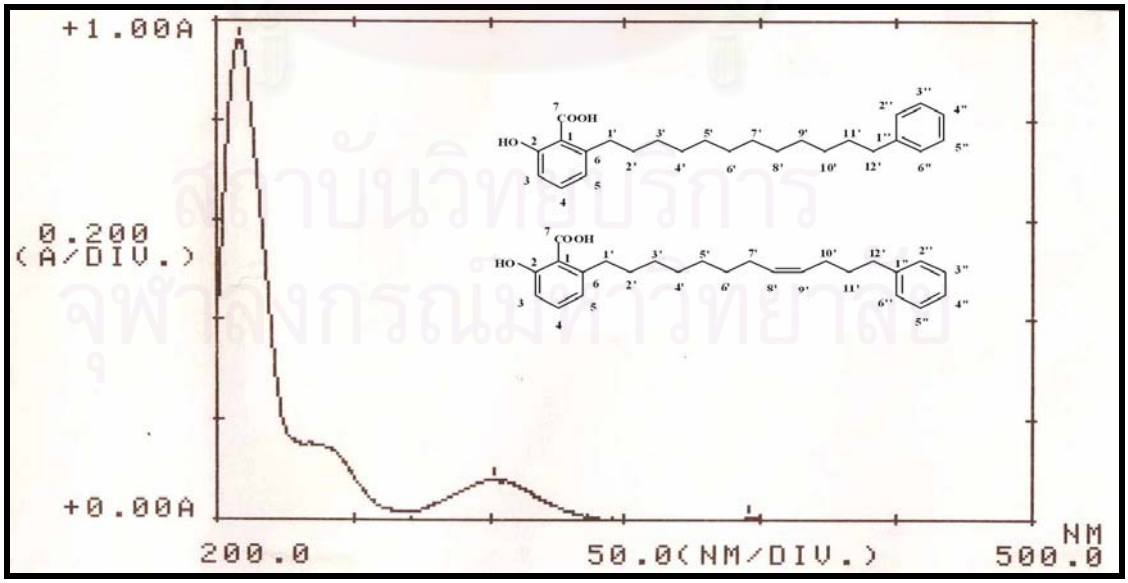

Figure 135. UV Spectrum of compound KF-S5 (in MeOH)

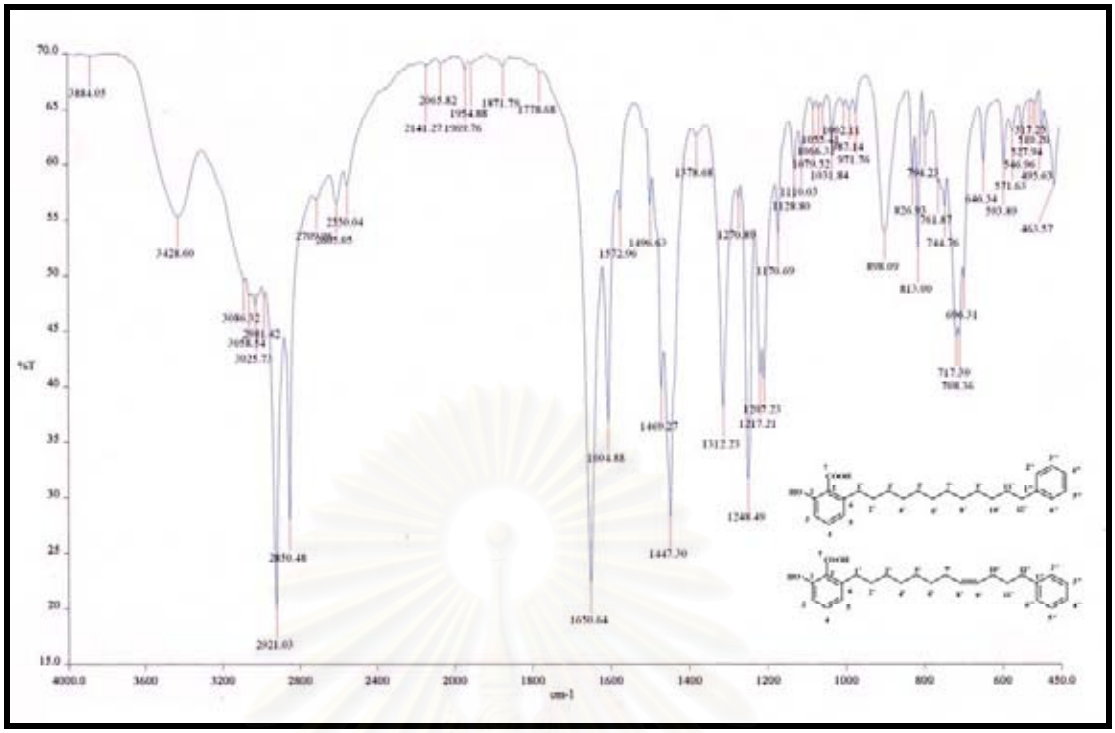

Figure 136. IR Spectrum of compound KF-S5 (KBr disc)

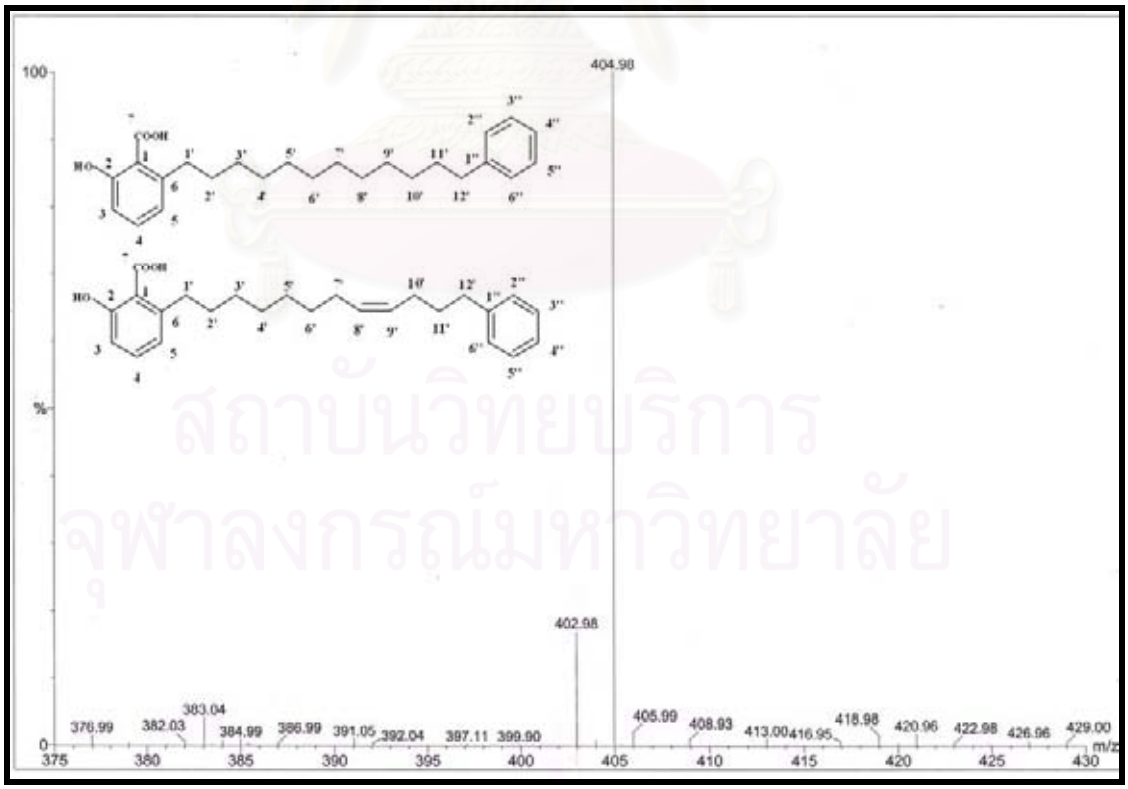

Figure 137. ESI-TOF Mass spectrum of compound KF-S5

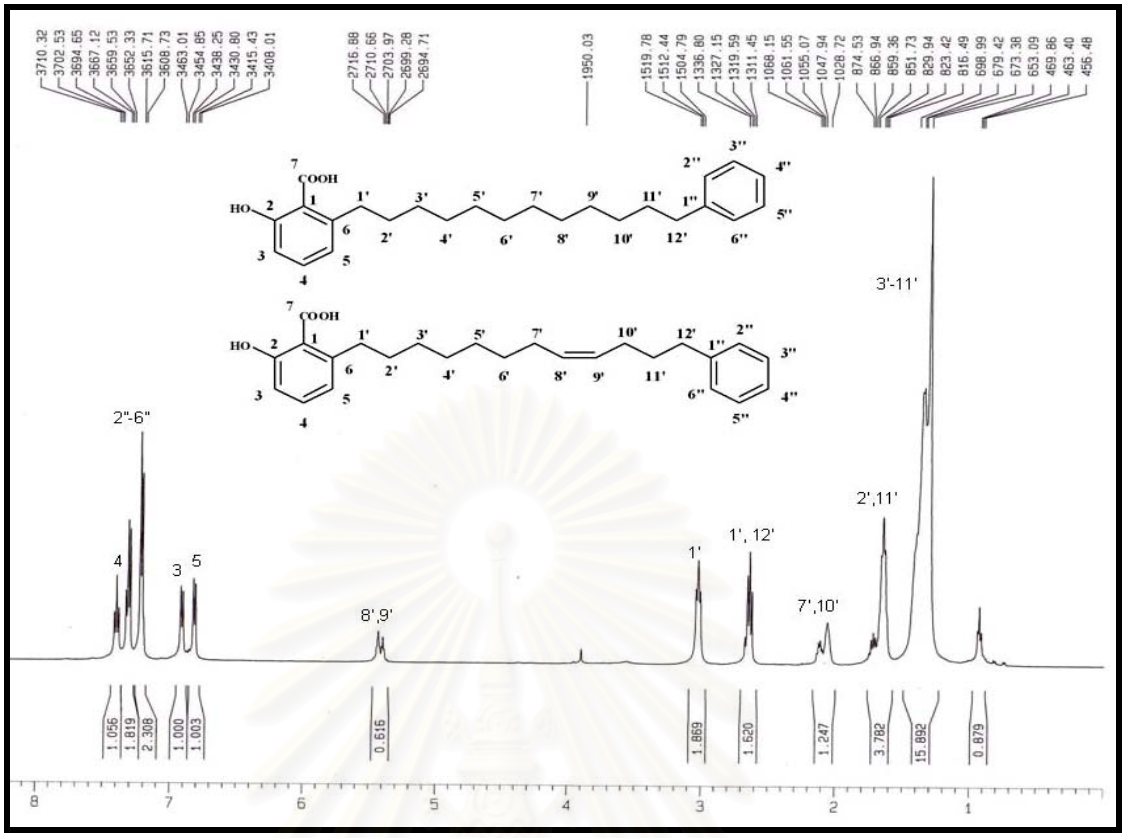

Figure 138a. ^{1}H NMR (500 MHz) Spectrum of compound KF-S5 (in acetone-d_6)

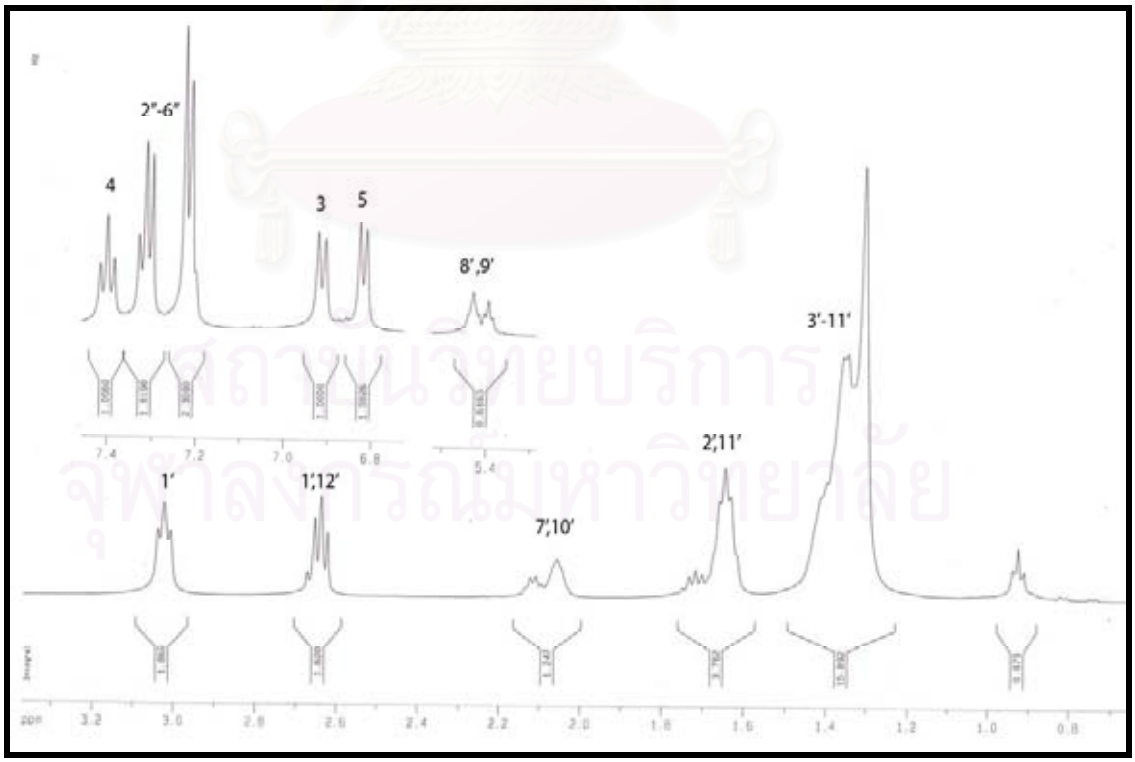

Figure 138b. ^{1}H NMR (500 MHz) Spectrum of compound KF-S5 (in acetone-d_6) (expansion between δ_H 0.8-3.2 ppm and δ_H 5.5- 7.4 ppm)

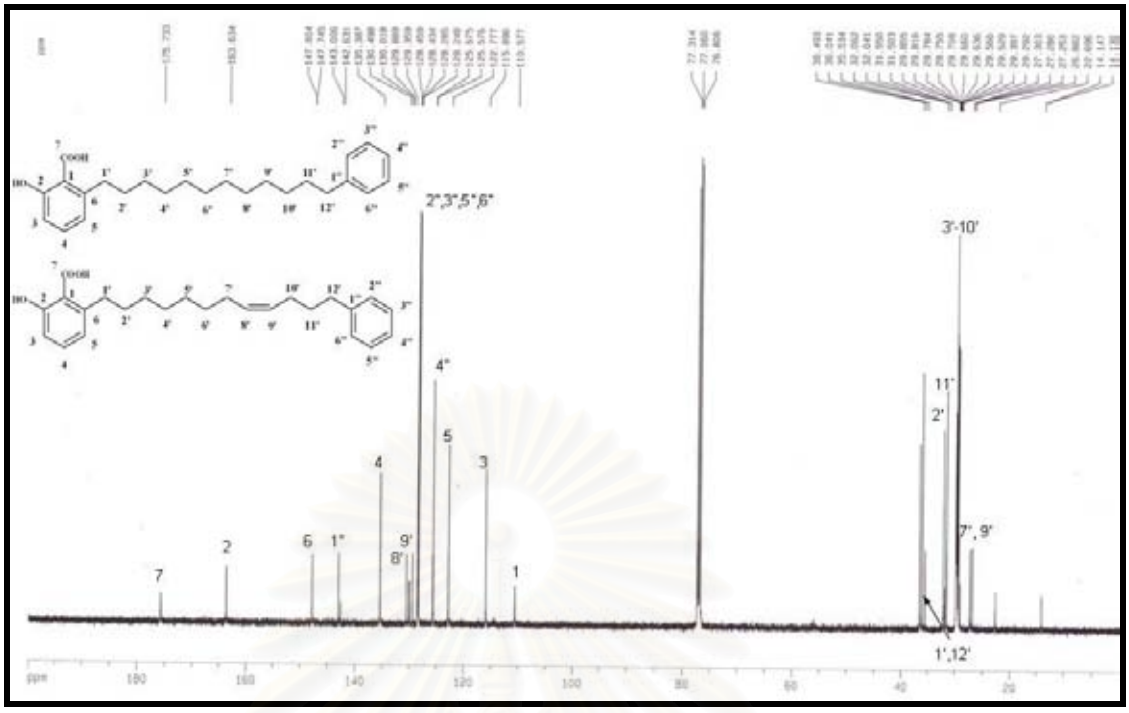

Figure 139a. ^{13}C NMR (125 MHz) Spectrum of compound KF-S5 (in acetone-d_6)

Figure 139b. ^{13}C NMR (125 MHz) Spectrum of compound KF-S5
(expansion between δ_H 29.0-37.0 ppm)

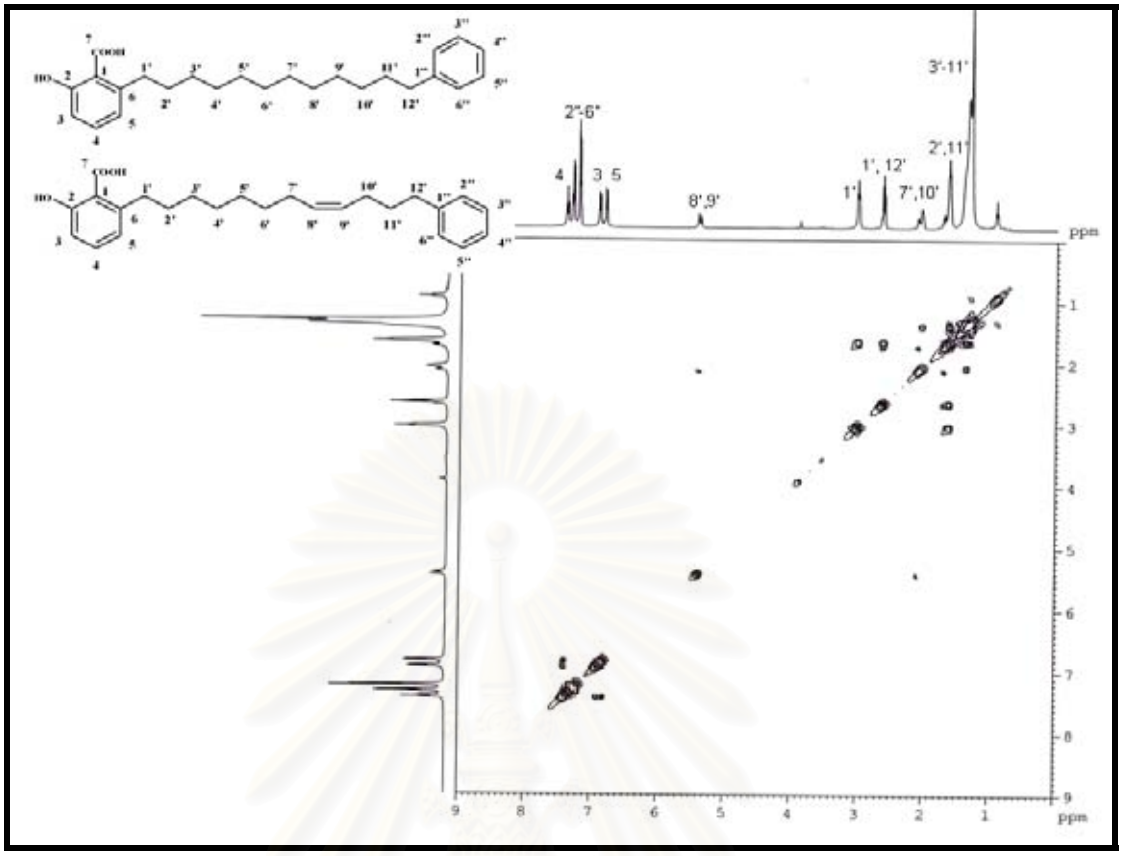

Figure 140. ^{1}H-^{1}H COSY Spectrum of compoundKF-S5 (in acetone-d_6)

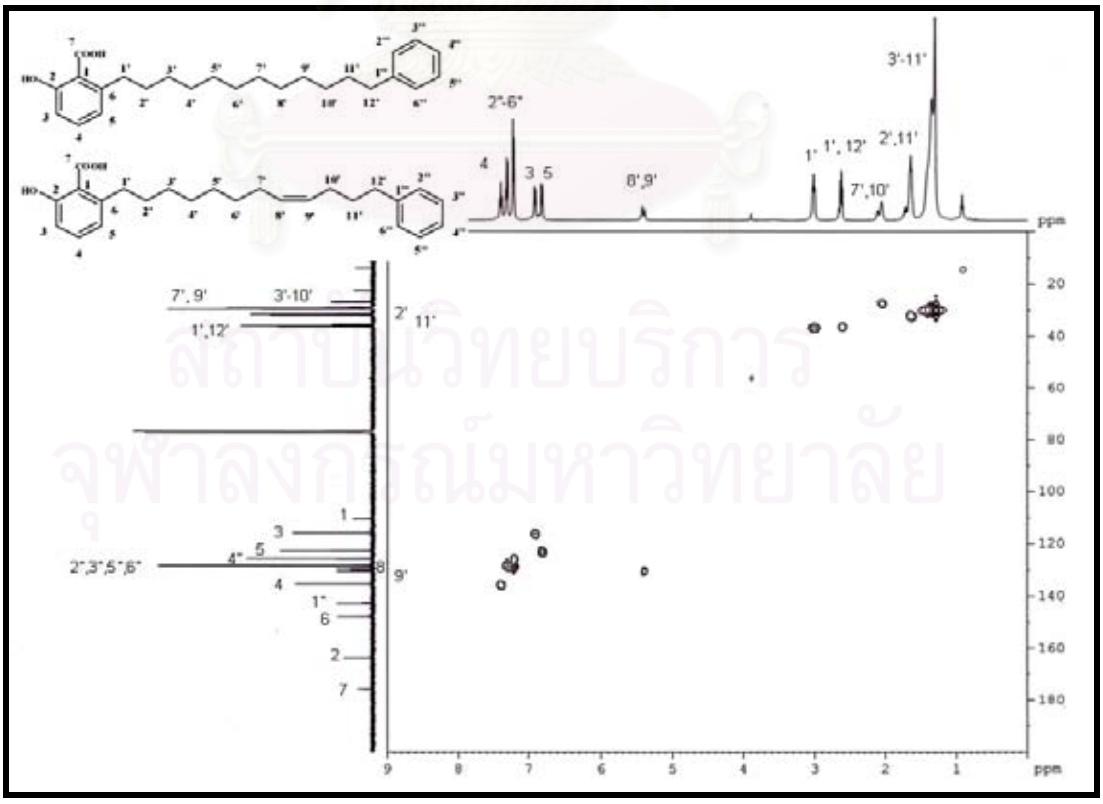

Figure 141a. HMQC Spectrum of compound KF-S5

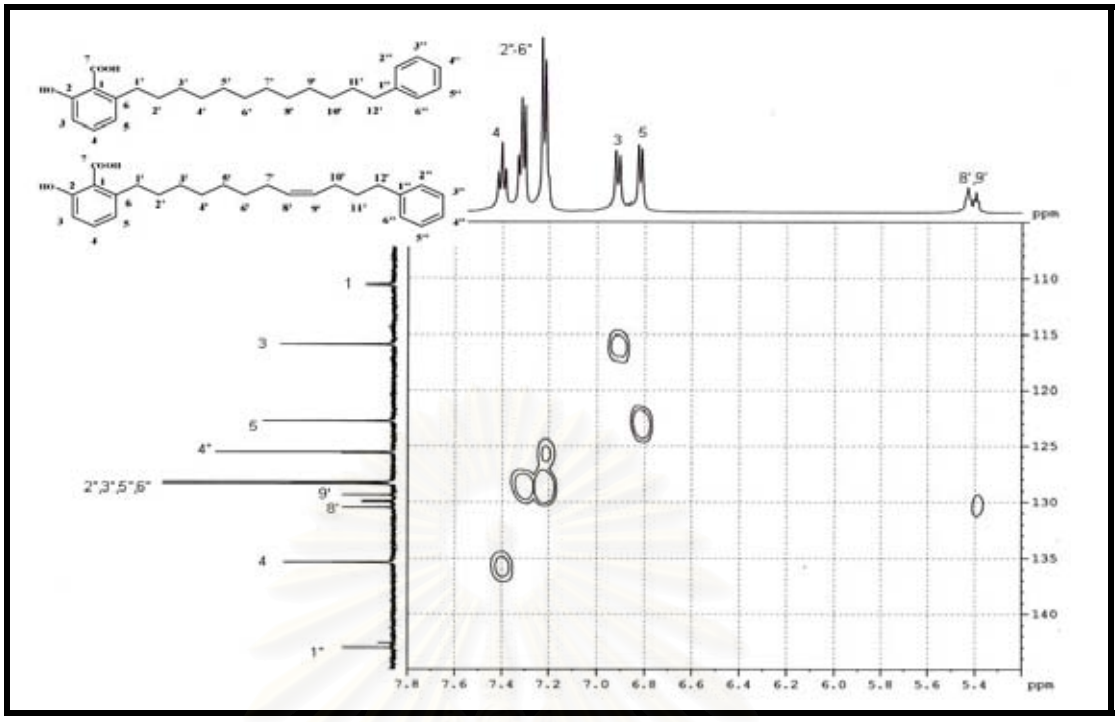

Figure 141b. HMQC Spectrum of compound KF-S5
(expansion between δ_H 5.4-7.8 ppm, δ_C 110.0-145.0 ppm)

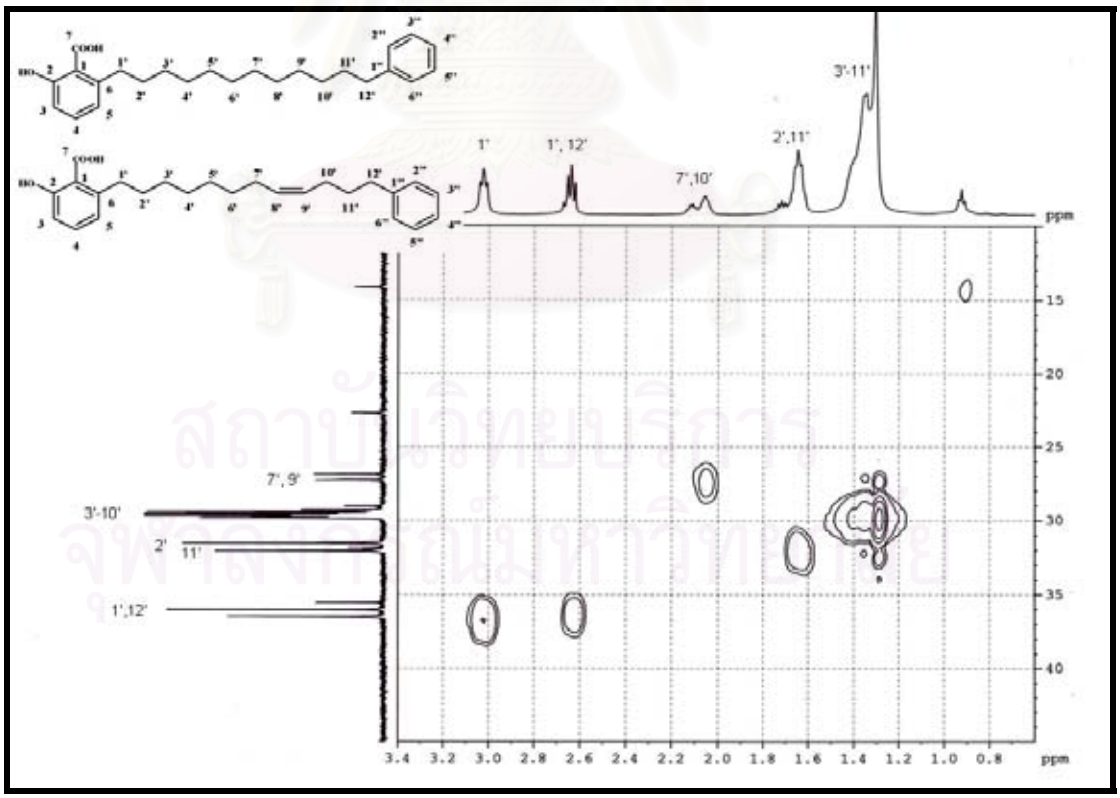

Figure 141c. HMQC Spectrum of compound KF-S5
(expansion between δ_H 0.8-3.4 ppm, δ_C 10.0-45.0 ppm)

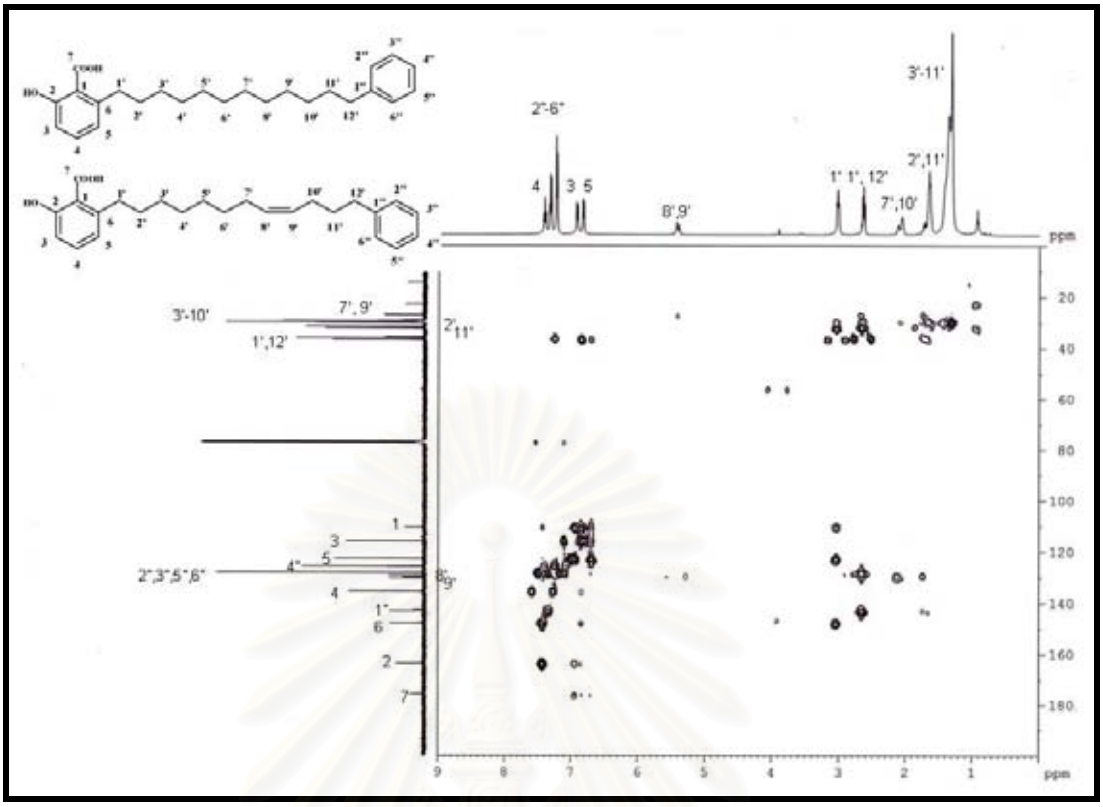

Figure 142a. HMBC Spectrum of compound KF-S5

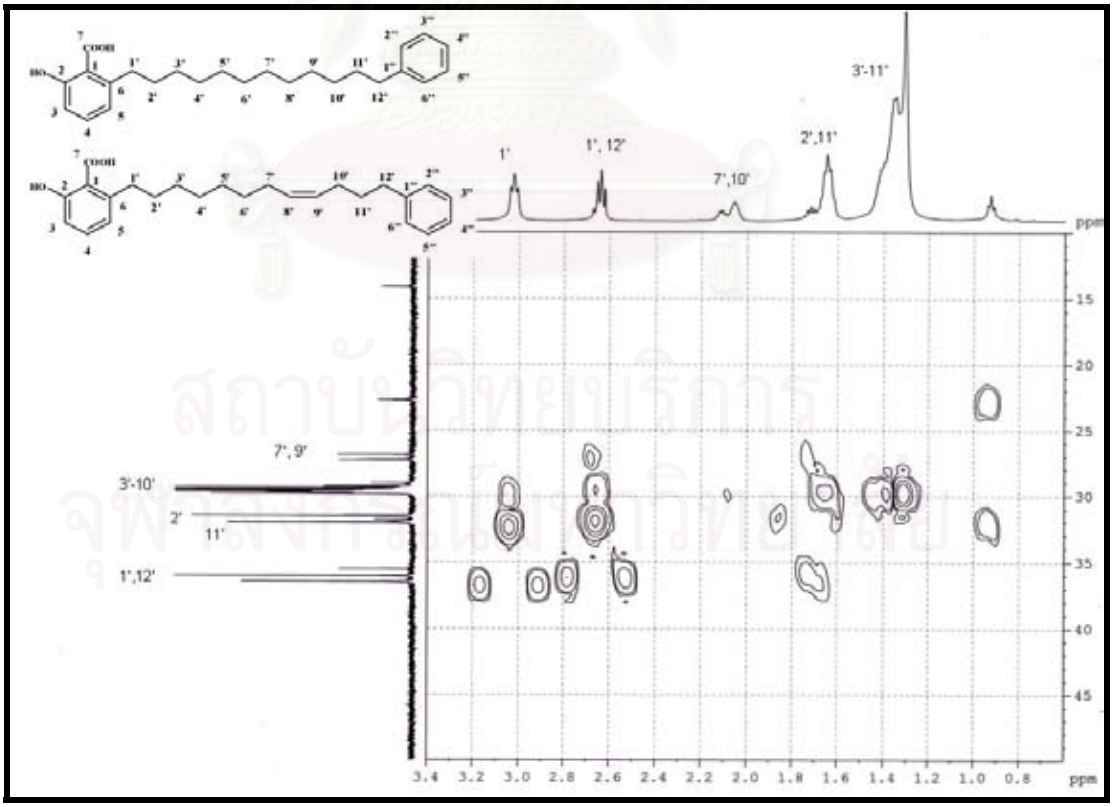

Figure 142b. HMBC Spectrum of compound KF-S5

(expansion between δ_H 0.8-3.4 ppm, δ_C 15.0-45.0 ppm)

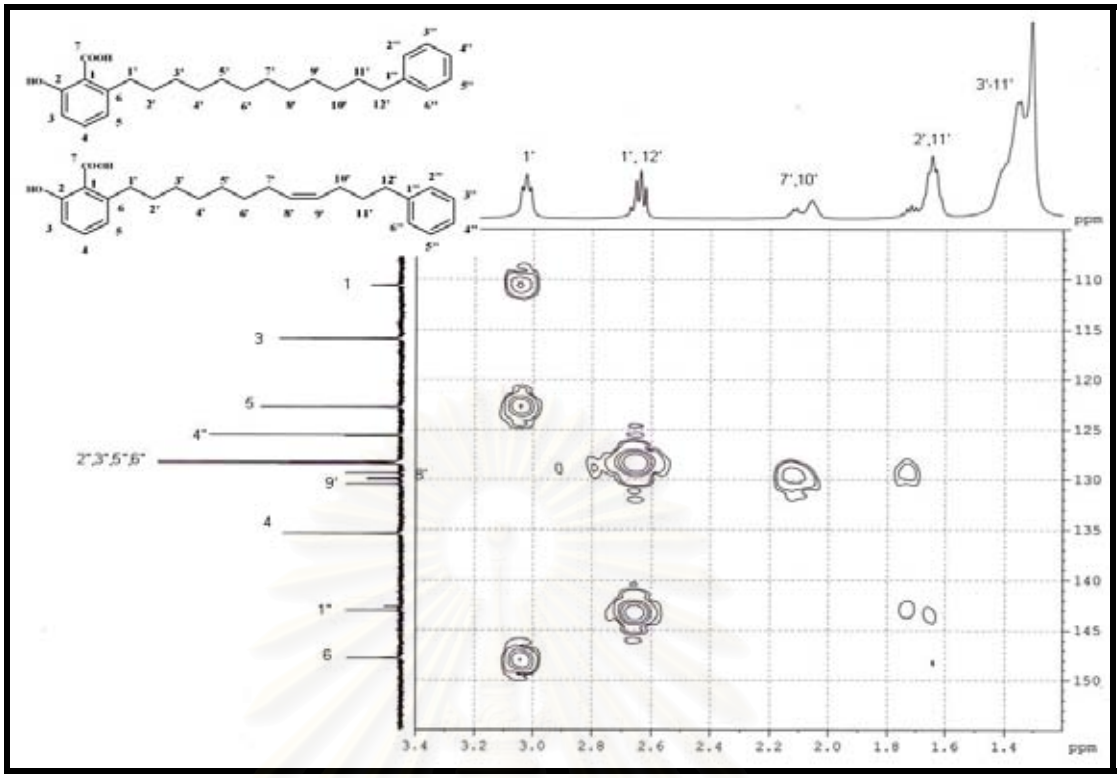

Figure 142c. HMBC Spectrum of compound KF-S5
(expansion between δ_H 1.4-3.4 ppm, δ_C 110.0-150.0 ppm)

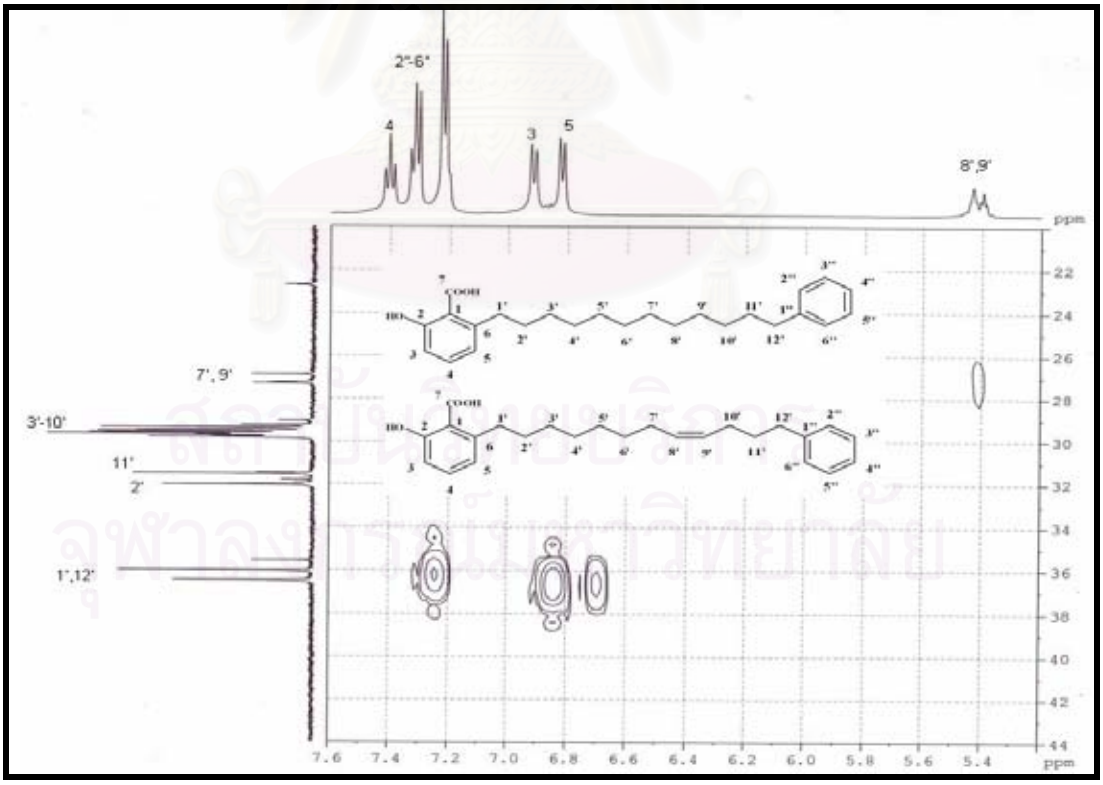

Figure 142d. HMBC Spectrum of compound KF-S5
(expansion between δ_H 5.4-7.6 ppm, δ_C 22.0-42.0 ppm)

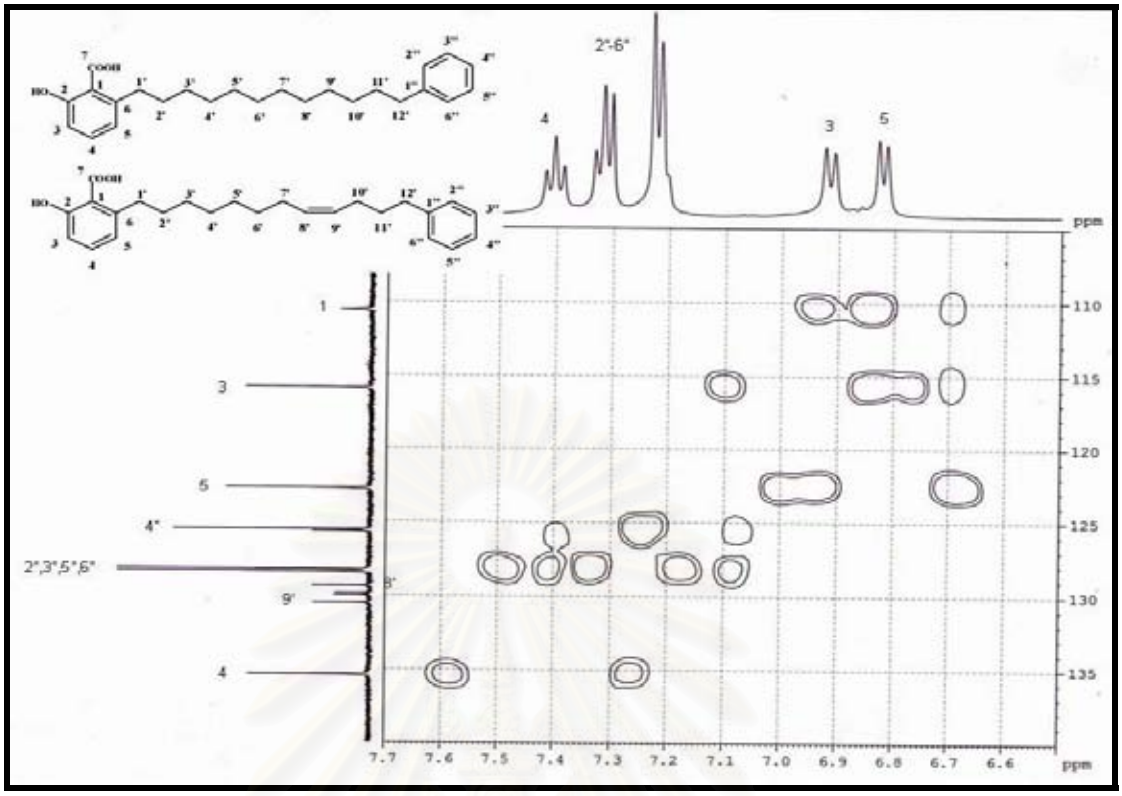

Figure 142e. HMBC Spectrum of compound KF-S5
(expansion between δ_H 6.6-7.7 ppm, δ_C 110.0-135.0 ppm)

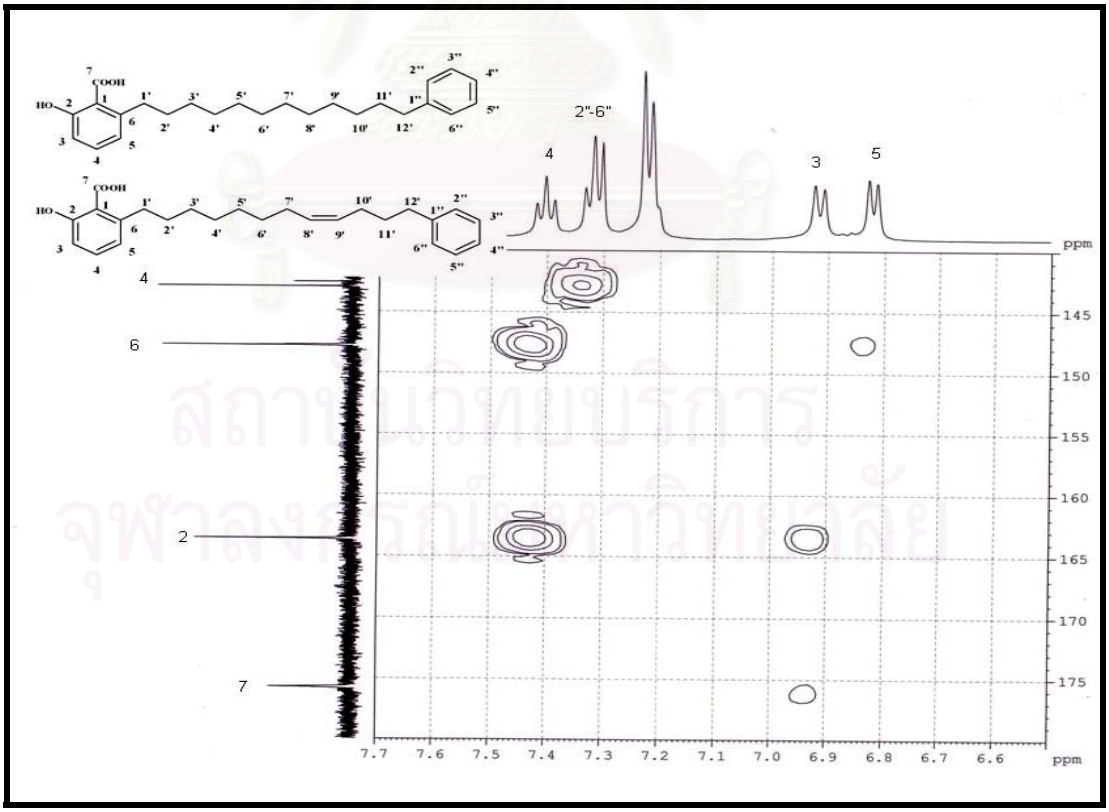

Figure 142f. HMBC Spectrum of compound KF-S5
(expansion between δ_H 6.6-7.7 ppm, δ_C 145.0-175.0 ppm)

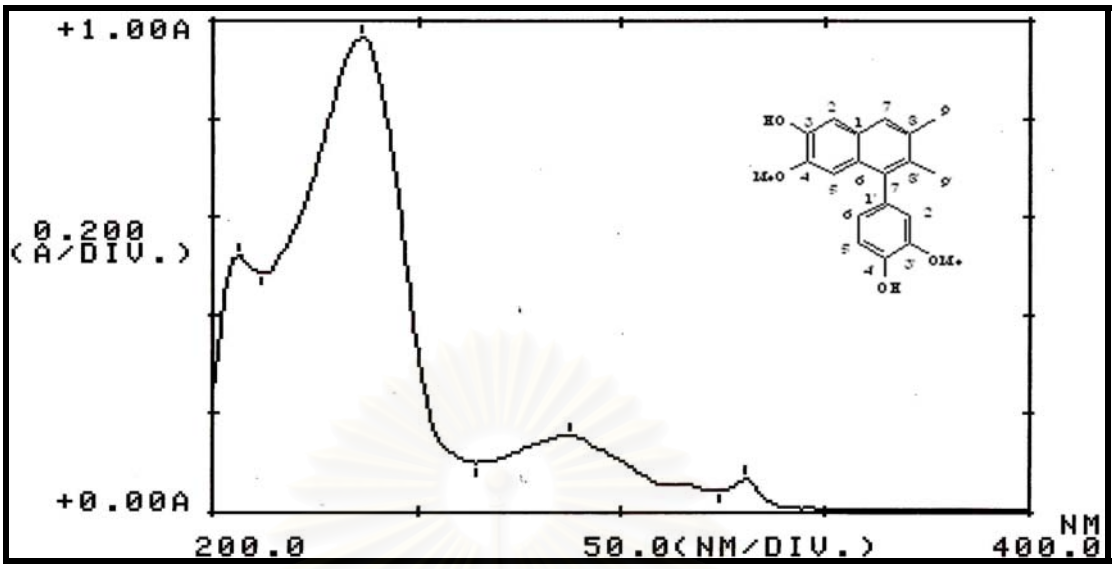

Figure 143. UV Spectrum of compound KF-L1 (in MeOH)

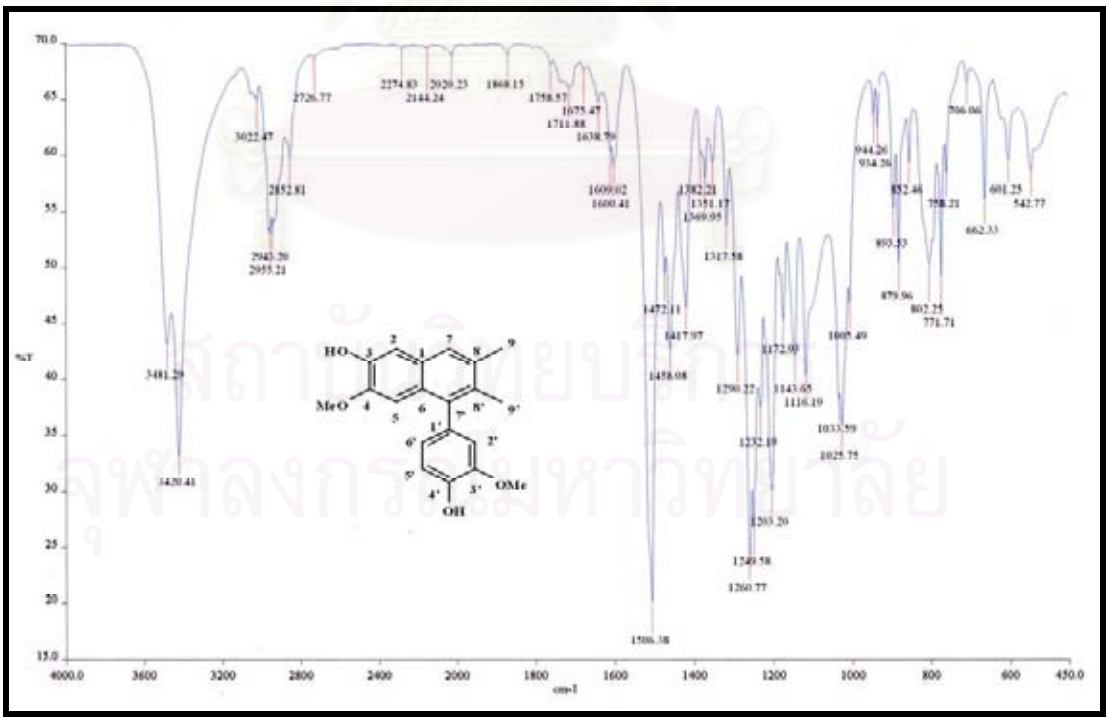

Figure 144. IR Spectrum of compound KF-L1 (KBr disc)

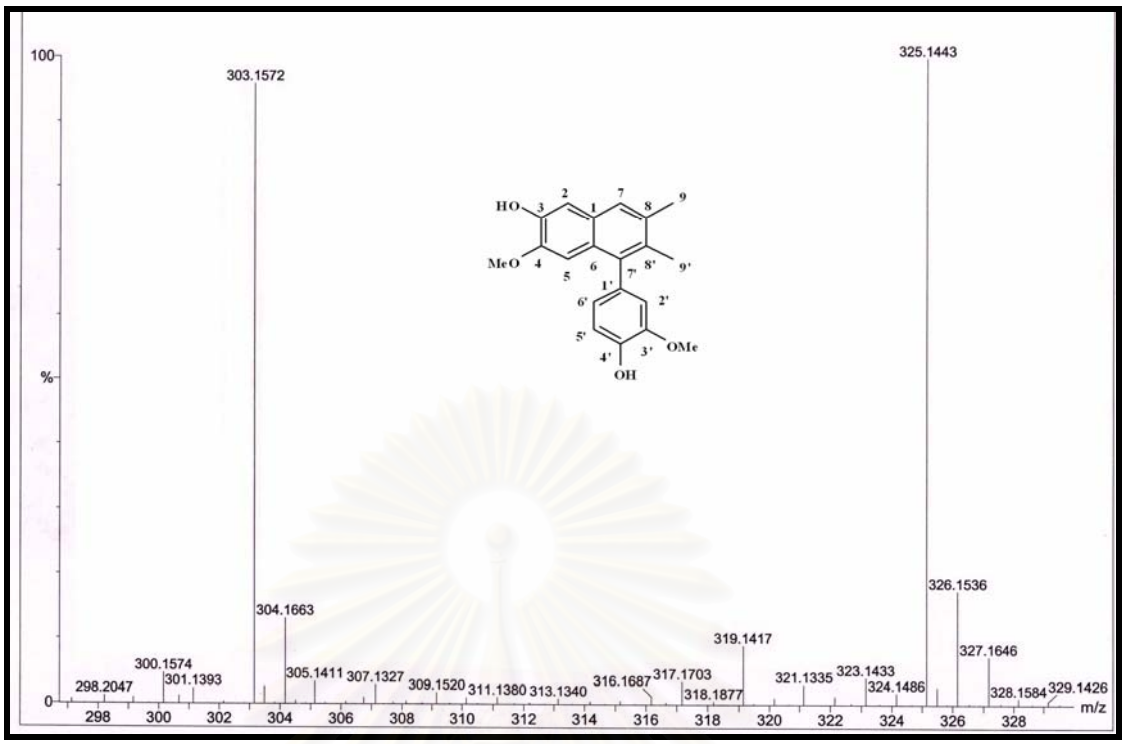

Figure 145. HR-ESI-TOF Mass spectrum of compound KF-L1

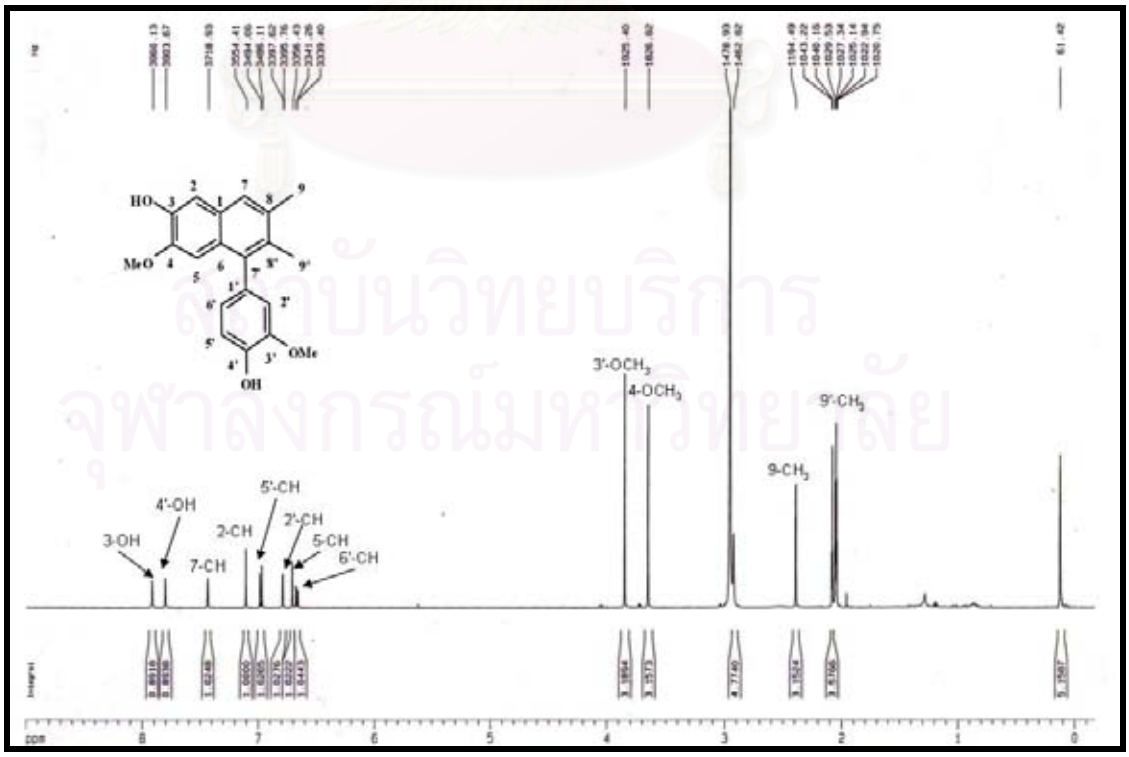

Figure 146a. ^{1}H NMR (500 MHz) Spectrum of compound KF-L1 (in acetone-d_6)

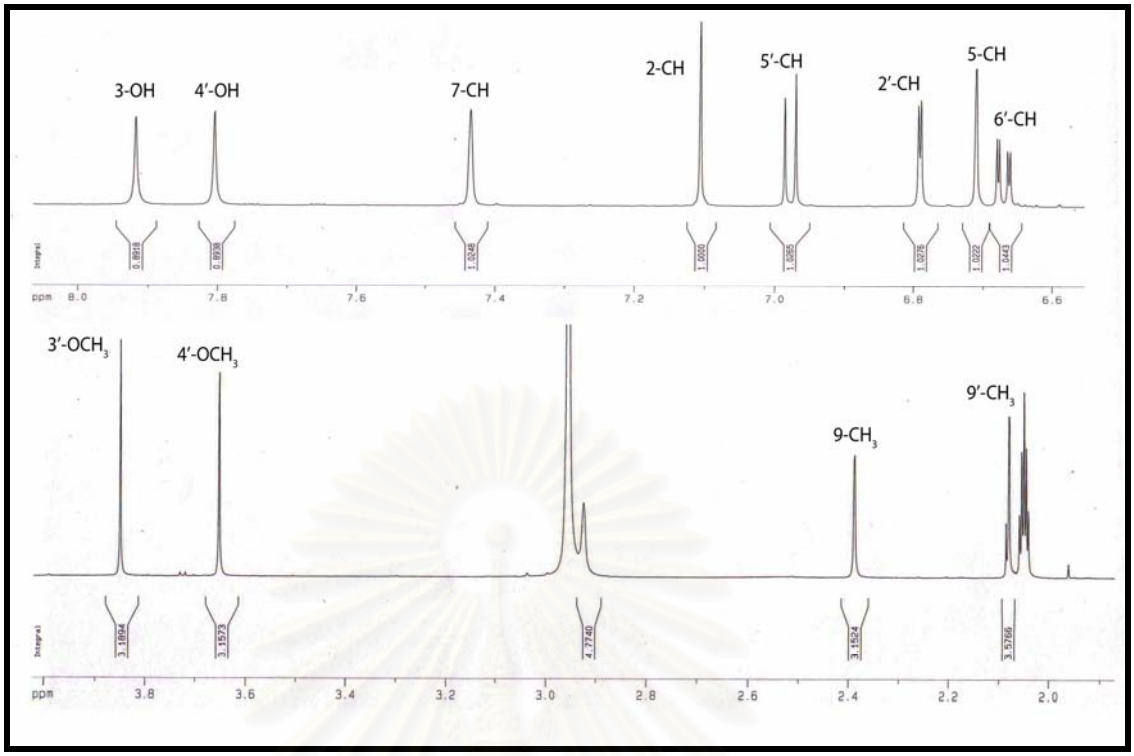

Figure 146b. ^{1}H NMR (500 MHz) Spectrum of compound KF-L1 (in acetone-d_6) (expansion between δ_H 2.0-4.0 ppm and δ_H 6.6-8.0 ppm)

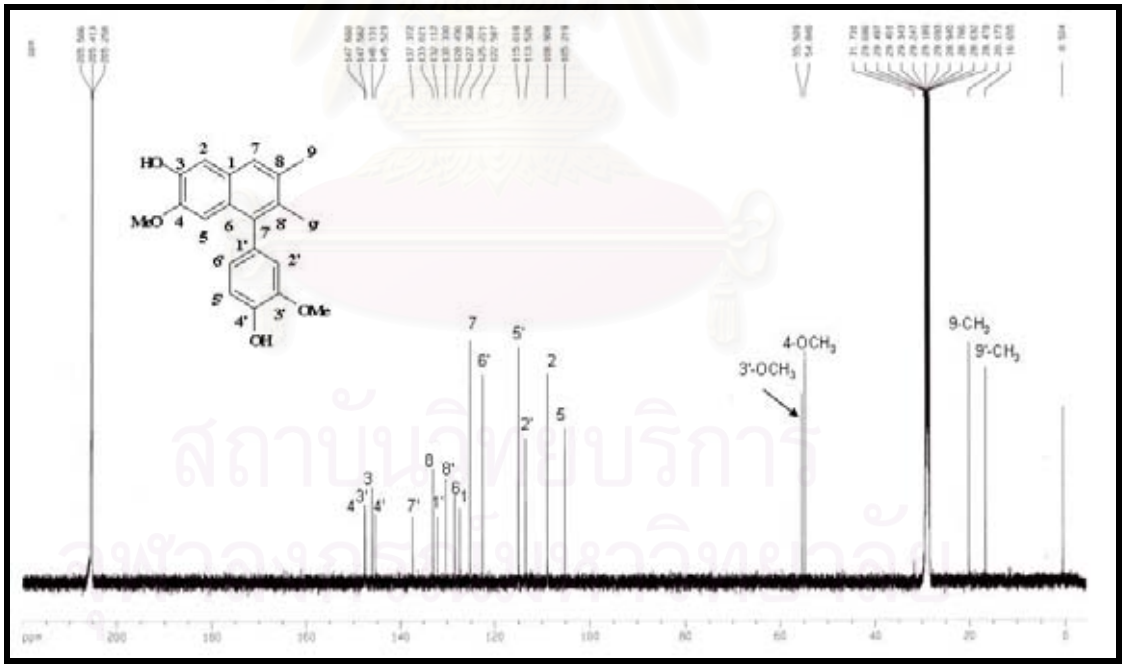

Figure 147. ^{13}C NMR (125 MHz) Spectrum of compound KF-L1 (in acetone-d_6)

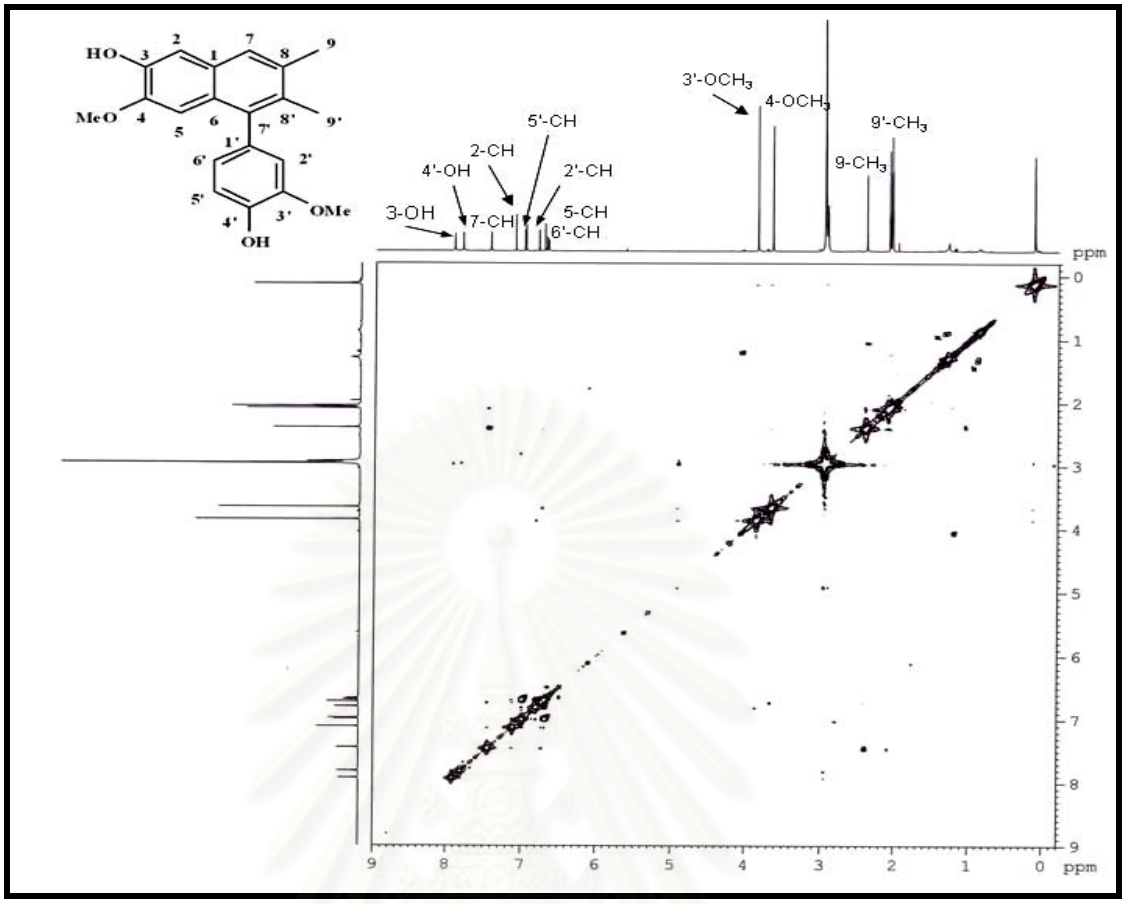

Figure 148. ^{1}H-^{1}H COSY Spectrum of compound KF-L1 (in acetone-d_6)

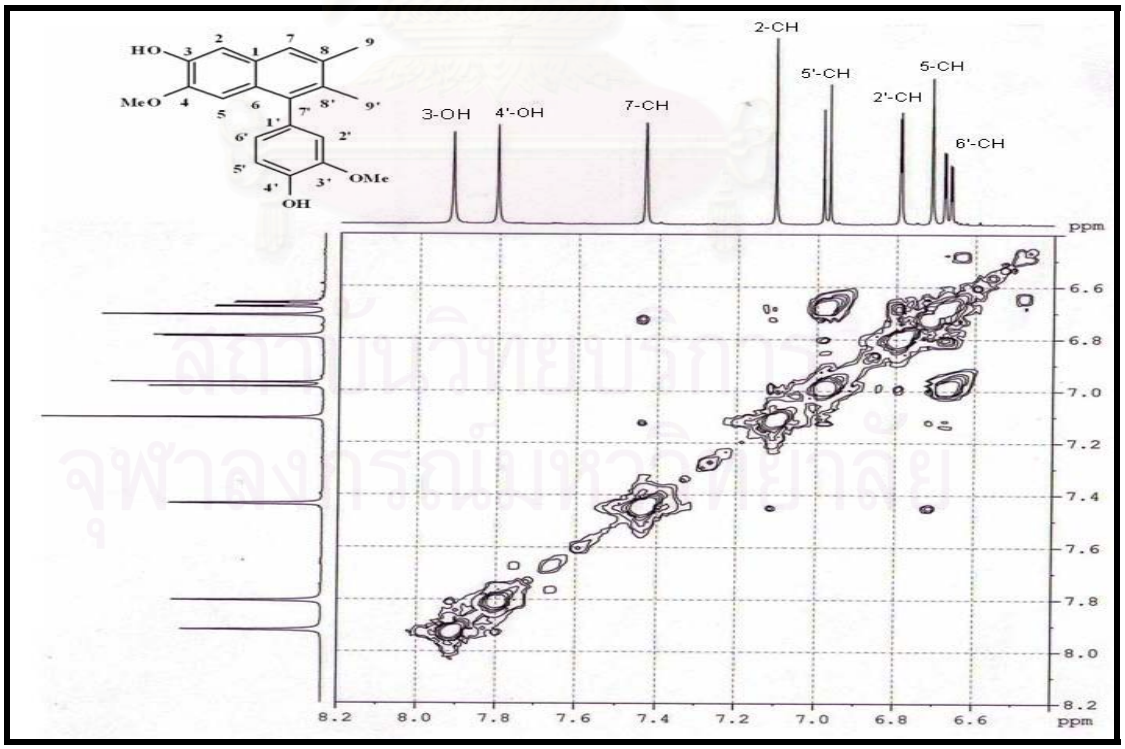

Figure 149. ^{1}H-^{1}H COSY Spectrum of compound KF-L1
(expansion at δ_H 6.6-8.2 ppm)

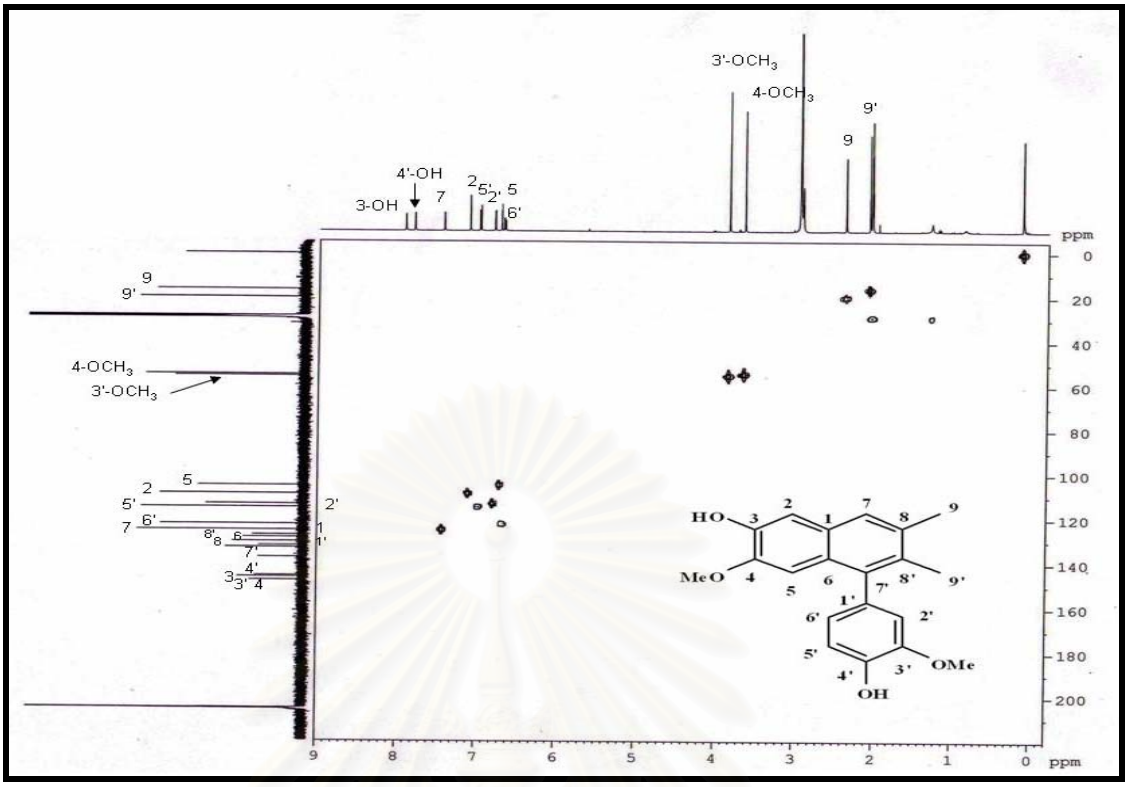

Figure 150. HMQC Spectrum of compound KF-L1

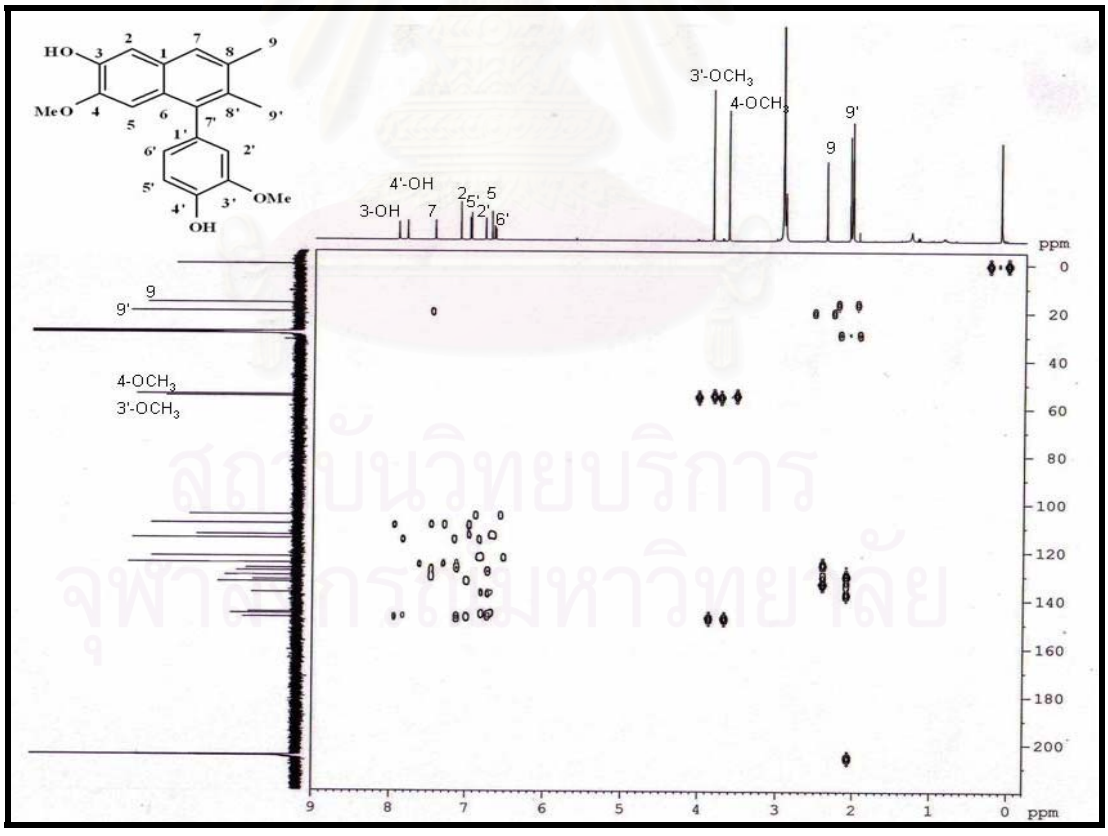

Figure 151a. HMBC Spectrum of compound KF-L1

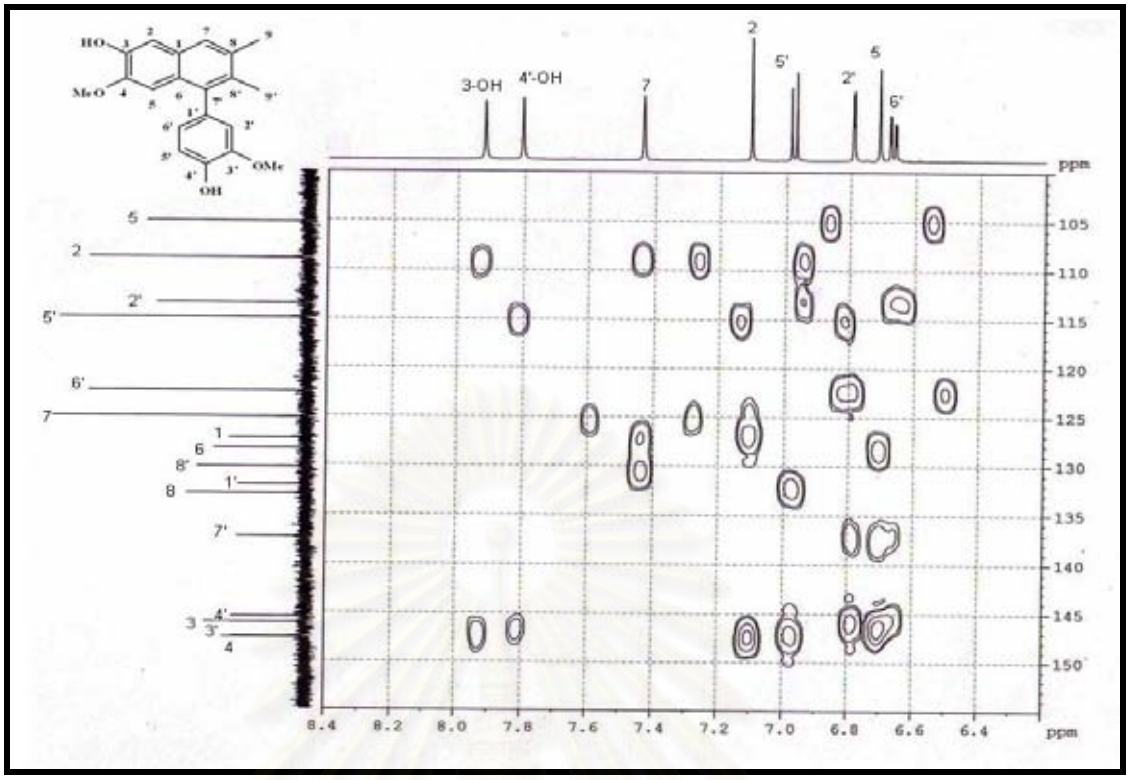

Figure 151b. HMBC Spectrum of compound KF-L1

(expansion between δ_H 6.4-8.4 ppm, δ_C 105.0-150.0 ppm)

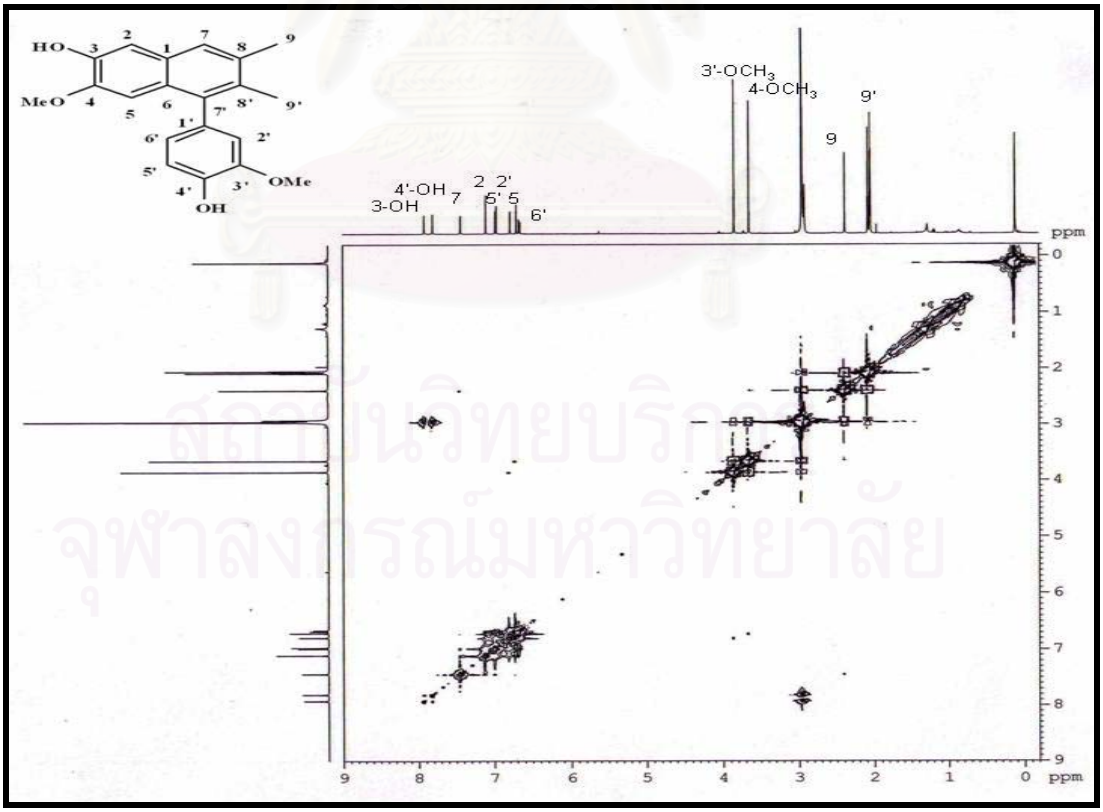

Figure 152a. NOESY Spectrum of compound KF-L1

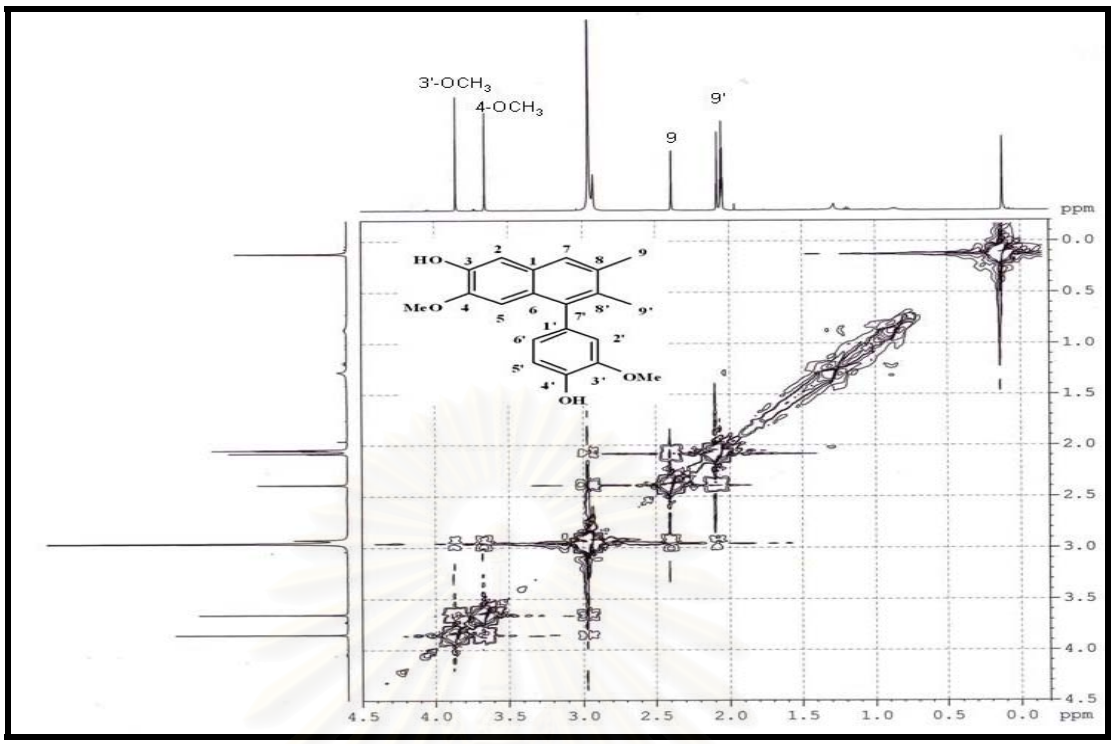

Figure 152b. NOESY Spectrum of compound KF-L1
(expansion between δ_H δ 0.0-4.5 ppm)

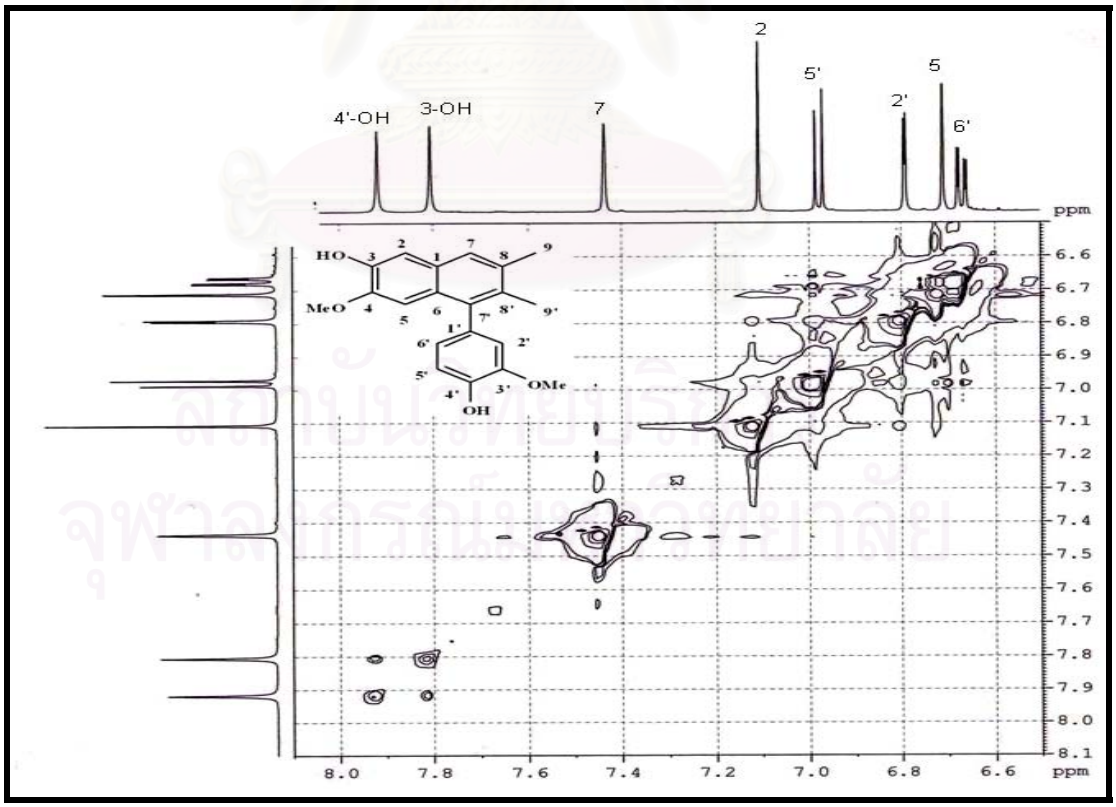

Figure 152c. NOESY Spectrum of compound KF-L1
(expansion between δ_H 6.6-8.1 ppm)

VITA

Mr. Noppadon Rangkaew was born on December 8, 1979 in Chiang Mai, Thailand. He received his Bachelor's degree of science (second class honor degree) in Biotechnology from the Faculty of Sciences, King Mongkut's Institute of Technology Lardkrabang in 2001. He was granted a Royal Golden Jubilee Ph.D. Scholarship from Thailand Research Fund (TRF) in the year 2004.

Publications.

1. Rangkaew, N., Moriyasu, M., Kawanishi, K. and Suttisri, R. A new acyclic diterpene acid and bioactive compounds from *Knema glauca*. Archives of Pharmacal Research, Submitted for publication.
2. Noppadon Rangkaew, Rutt Suttisri, Masataka Moriyasu, Kazuko Kawanishi. A new arylnaphthalene lignan from *Knema furfuracea*. Fitoterapia. Sumitted.

Poster presentations.

1. Rangkaew, N., Moriyasu, M., Kawanishi, K., and Suttisri, R. Chemical constituents of *Knema glauca* and *Knema fufuracea***.** RGJ-Ph.D. Congress IX. April 4-6, 2008. Jomtien Palm Beach Resort, Pattaya, Thailand.
2. Noppadon Rangkaew, Rutt Suttisri, Masataka Moriyasu, and Kazuko Kawanishi. A new acyclic diterpene acid from *Knema glauca* and a new lignan from *Knema furfuracea*.The 8th NRCT-JSPS joint seminar. December 3-4, 2008. Faculty of Pharmaceutical Sciences Chulalongkorn University, Bangkok, Thailand.