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Synthesis of derivatives of flavonoids

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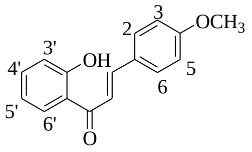
GRAPHICAL ABSTRACT



2'-hydroxy-4-methoxychlcone

ABSTRACT

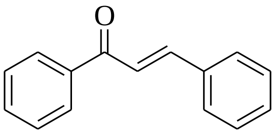
Chalcone is a subgroup of flavonoids that can be found abundantly in edible plants. Chalcones are becoming an interesting target class of compounds which are widely investigated due to their various biological activities. The aim of this study is to synthesize chalcone. Two derivatives of 4-hydroxybenzaldehyde were synthesized through methylation reaction using methyl iodide to obtain brown liquid of 4-methoxybenzaldehyde (36.6%) and prenylation reaction using 1-bromo-2-methyl-but-2-ene to yield 4-*0*-prenylbenzaldehyde (27.65%). The derivative of 3,4-dihdroxybenzaldehyde was synthesized by methylenation reaction with diiodomethane to furnish colourless oil of 3,4-methylenedioxybenzaldehyde (23.1%). 4-methoxybenzaldehyde was subjected to 2-hydroxyacetophenone in the presence of potassium hydroxide as a catalyst to afford 2'-hydroxy-4-methoxychalcone *via* Claisen-Schmidt reaction. All synthesized compounds were purified and characterized using spectroscopic methods, i.e. Fourier Transform-IR (FTIR) and proton Nuclear Magnetic Resonance (1H-NMR). The chromatographic purification followed by structural elucidation of the targeted chalcone will be carried out.

*Keywords: Chalcone, methlation reaction, 4-hydroxybenzaldehyde, 4-methoxybenzaldehyde, prenylation reaction, 4-O-*prenylbenzaldehyde, *methylenation reaction, 3,4-methylenedioxybenzaldehyde, Claisen-Schmidt reaction.*

1. INTRODUCTION

Flavonoids belong to a versatile group of plant secondary metabolites with variable phenolic structures. Polyphenolic compounds commonly occurred in fresh plant cells as derivatives forms such as methyl ethers and glycosides [1]. Flavonoids are typically yellow to orange colored. It can be found in fruits, vegetables, grains, bark, roots, stems, flowers, tea as well as in wine. It is known to be synthesized by plants in response to microbial infection [2]. Flavonoid is a broad collection of C_6-C_3-C_6 carbon framework or known as phenylbenzopyran functionality. Hydroxyl functional group in flavonoids mediates the antioxidant effects by scavenging free radicals and chelating metal ions [3]. Flavonoids have the ability to reduce human protection enzyme system and against infectious bacterial and viral disease and degenerative disease as a method for encapsulating nanomaterials with good spatial organisation and stability to overcome these issues.

Chalcones, dihydrochalcones and aurones are example of flavonoids groups that composed of pigments which turns the yellow colour to oranges in some *Coreopsis* and Asteraceae *taxa* species [4]. Chalcones and aurones are the example of other natural products that also contain C_6-C_3-C_6 backbone. These compounds were categorized as minor flavonoids [5]. Chalcone **(1)** or known as prop-2-en-1-one is an open chain compound with two aromatic rings linked by three carbon α,β-unsaturated carbonyl system. This compound is also known as benzalaacetophenone or benzylidene acetophenone. Chalcone is coloured compounds because of the presence of chromophore –CO-CH=CH- which depends in the presence of other auxochromes. Chalcone derivatives are an aromatic ketone that being a core for a several of biological compounds. The IUPAC name of this compound is 1,3-diphenyl-2-propene-1-one. Chalcones are abundant in edible plants and is a precursor of flavonoids and isoflavanoid [6]. It is well known intermediates for synthesizing various heterocyclic compounds. Chalcone is the parent compound of series of plant pigments. It has relatively low redox potentials and has high probability of undergoing electron transfer reactions [6] because of the delocalisation π-electron system on both benzene rings as it has conjugated double bonds. The reactive side of α,β-unsaturated keto function gives the various antimicrobial activity such as cytotoxic, anticancer chemo preventive [7], mutagenic, antiviral, insecticidal, as well as enzyme inhibitory properties[8].

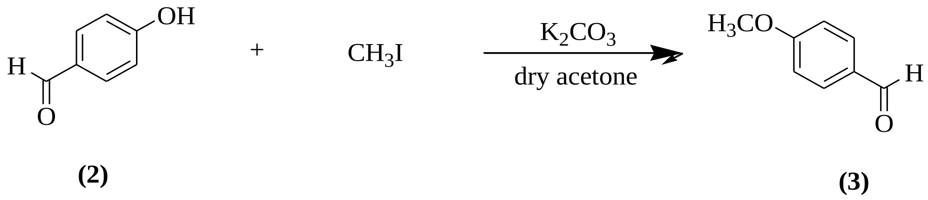


(1)

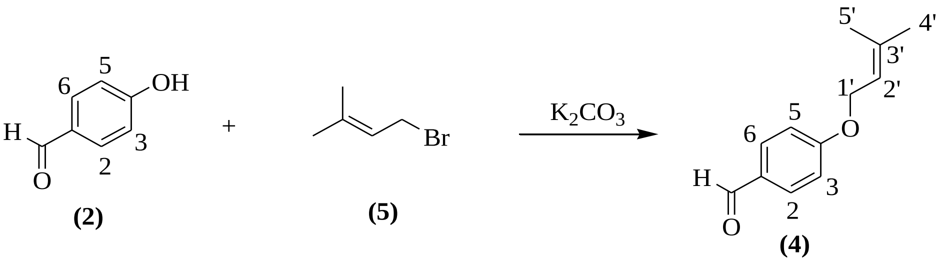
Glychirriza, *Angelica*, *Ruscus* and *Piper* species are examples of chalcones containing plants that have been used as medicine in Asia, Africa and South America. Most of the aromatic rings of natural chalcones are found as hydroxylated. The different position of hydroxyl and alkoxyl groups in the chalcone compounds give different biological activities such as antibacterial, antiulcer, antifungal, antioxidant, vasodilatory [9], antimitotic, antimalarial, antileshmanial, and also inhibition of chemical mediators release, inhibition of leukotriene B4, inhibition of tyrosinase and inhibition of aldose activities [10].

2. EXPERIMENTAL

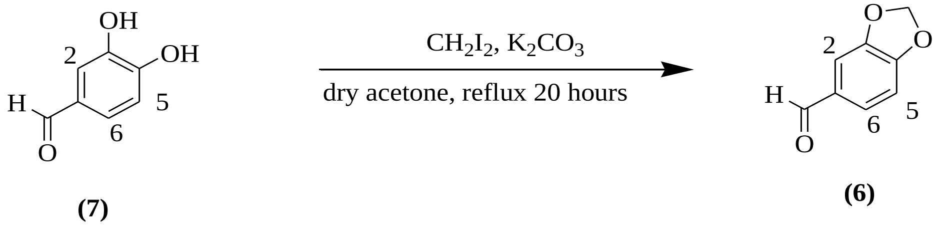
The derivatives of 4-hydroxybenzaldehyde **(2)**; 4-methoxybenzaldehyde **(3)** and 4-*O*-prenylbenzaldehyde **(4)** were synthesized via methylation reaction and prenylation reaction respectively. In methylation reaction, the mixture of 4-hydroxybenzaldehyde **(2)** with CH_3I and anhydrous K_2CO_3 in dry acetone was refluxed meanwhile in prenylation reaction, the reaction mixture of 4-hydroxybenzaldehyde **(2)** with aqueous KOH and 1-bromo-2-methyl-but-2-ene **(5)** was stirred at room temperature. Both of the reaction was monitored by thin layer chromatography (TLC). The methyl compound was purified by column chromatography (n-hexane: diethyl ether, 9:1) and prenyl compound was purified using (n-hexane: ethyl acetate, 4:1). Methylenation reaction was carried out to yield 3,4-methylenedioxybenzaldehyde **(6)** from the reaction mixture of 3,4-dihydroxybenzaldehyde **(7)** with diiodomethane in dry acetone and anhydrous K_2CO_3. 2'-hydroxy-4-methoxychalcone **(8)** was synthesized via Claisen-Schmidt reaction involving the reaction of 2-hydroxyacetophenone **(9)** in ethanol was subjected to 4-methoxybenzaldehyde **(3)**. The reaction mixture was stirred at room temperature and then extracted with CH_2Cl_2. Purification by column chromatography in (n-hexane: diethyl ether; 9:1) as eluents to give the desired product. All compounds were elucidated by Fourier Transform- Infrared spectroscopy (FT-IR) and Nuclear Magnetic Resonance (NMR).



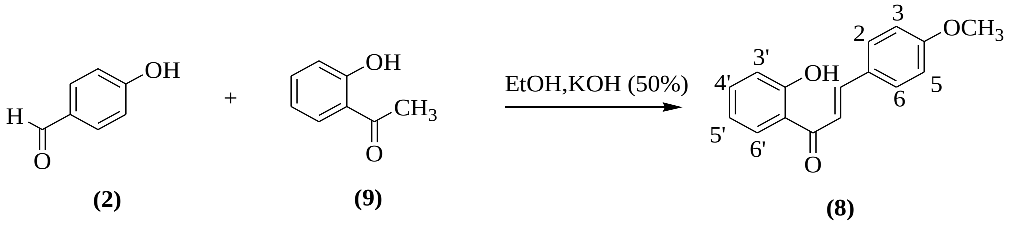
Scheme 1 Synthesis of 4-methoxybenzaldehyde **(3)**



Scheme 2 Synthesis of 4-*O*-prenylbenzaldehyde **(4)**



Scheme 3 Synthesis of 3,4-methylenedioxybenzaldehyde **(6)**



Scheme 4 Synthesis of 2'-hydroxy-4-methoxychalcone **(8)**

3. RESULTS AND DISCUSSION

3.1. Synthesis of 4-methoxybenzaldehyde **(3)**

4-Methoxybenzaldehyde (**3**) successfully synthesized in the form of liquid with 36.6% yield. IR spectrum **(Figure 1)** of 4-methoxybenzaldehyde **(3)** showed two stretching bands at 2840 cm^{-1} and 2741.33 cm^{-1} ascribed for C-H aldehyde. sp^2 C-H and sp^3 C-H band were observed at 3009.85 cm^{-1} and 2937.60 cm^{-1} respectively. Stretching frequencies of conjugated C=O was observed at 1680.10 cm^{-1} while for C=C aromatic was observed at 1596.01 cm^{-1} and 1509.76 cm^{-1}. The stretching frequencies for both functional group are lower due to the conjugation effect between C=O and C=C aromatic. Two strong intensity bands at 1256.47 cm^{-1} and 1158.38 cm^{-1} were attributed to C-O moieties.

The ^{1}H NMR spectrum **(Figure 2)** showed a singlet at δ 3.91 integrated to three protons contributes to a methoxyl group C-4. Table 4.1 showed the ^{1}H NMR assignments of compound **(3).** The presence of the signal showed the successful of methylation reaction. In addition two doublet signals which were observed at δ 7.03 (*J*=8.8 Hz) and 7.86 (*J*=8.8 Hz) were ascribed to H-3/H-5 and H-2/H-6 aromatic protons. A downfield singlet appeared at δ 9.91 was assigned to the aldehyde proton.

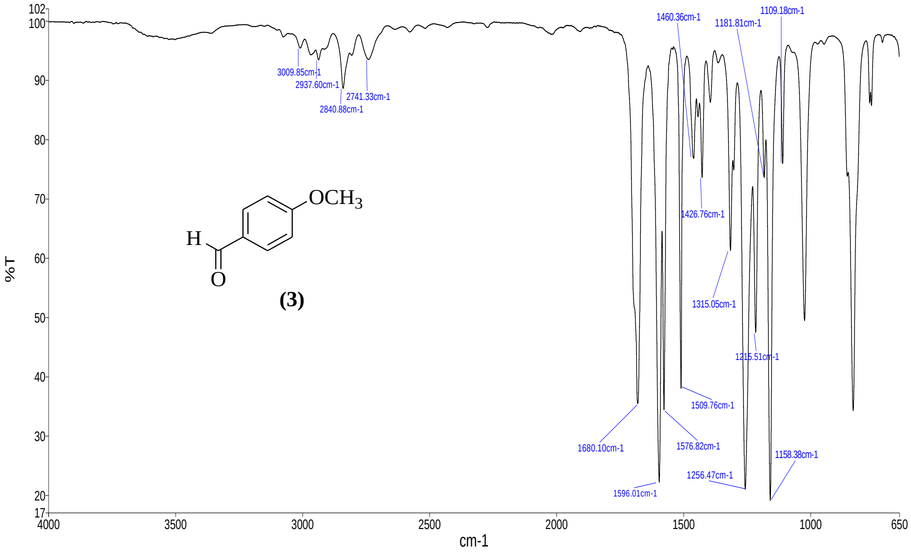


Figure 1 IR spectrum of 4-methoxybenzaldehyde **(3)**

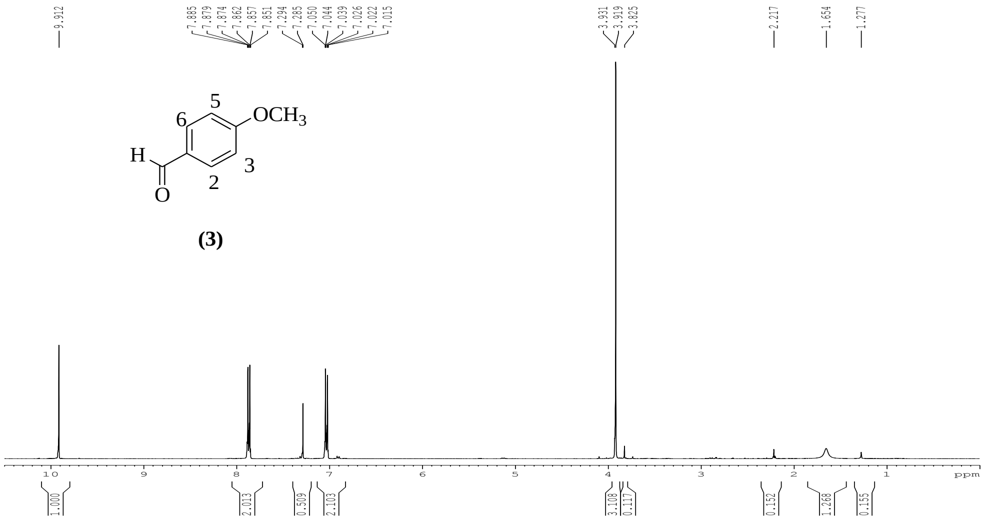


Figure 2 ^{1}H-NMR spectrum of 4-methoxybenzaldehyde **(3)**

3.2. Synthesis of 4-*O*-prenylbenzaldehyde **(4)**

Treatment of 4-hydroxybenzaldehyde **(2)** with prenyl bromide **(5)** and K_2CO_3 for 48 hours at room temperature gave 27.65% of 4-*O*-prenylbenzaldehyde **(4)**. IR spectrum **(Figure 3)** showed the absorption band of sp^2 C-H alkene at 1684.76 cm^{-1}. The absorption band at 1597.94 cm^{-1} indicates for carbonyl group (C=O). C=C aromatic band were observed at 1576 and 1508.56 cm^{-1} respectively. The C-O stretching frequency was observed at 1247.07 cm^{-1}.

^1H NMR spectrum **(Figure 4)** of 4-*O*-prenylbenzaldehyde **(4)** showed signals due to prenyl moiety at δ 1.70 (6H, m, H-4' and H-5'), 4.62 (2H, d, J=6.8 Hz, H-1'), and 5.30 (1H, m, H-2'). The overlapping spectrum at δ 7.8-7.9 indicates the aromatic protons H-2 and H-6. The aldehyde proton gave a singlet at δ 9.91.

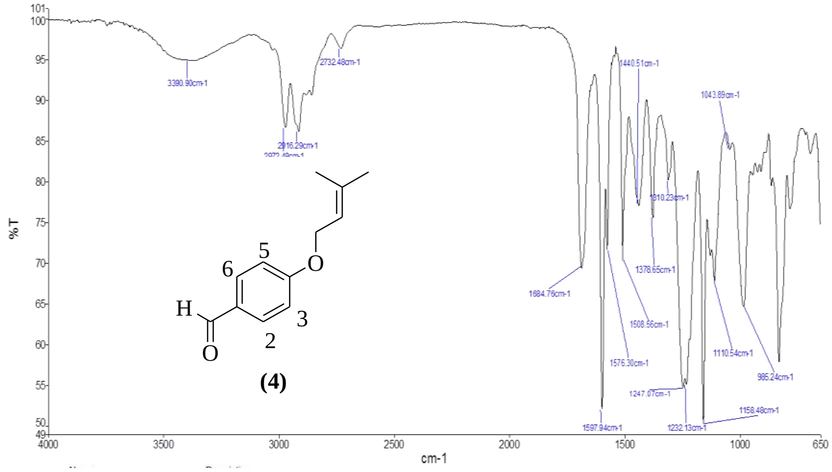


Figure 3 IR spectrum of 4-*O*-prenylbenzaldehyde **(4)**

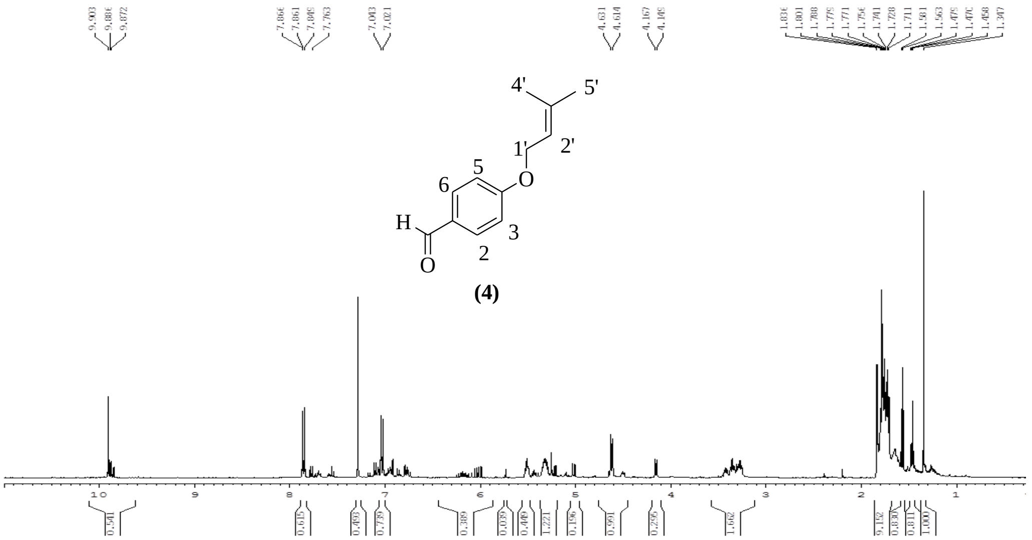


Figure 4 ^1H NMR spectrum of 4-*O*-prenylbenzaldehyde **(4)**

3.3. Synthesis of 3,4-methylenedioxybenzaldehyde **(6)**

The reaction of 3,4-dihydroxybenzaldehyde **(7)** with diiodomethane in the presence of K_2CO_3 in dry acetone afforded colourless oil of 3,4-methylenedioxybenzaldehyde **(6)** in 23.1 % yield. The structure of 3,4-methylenedioxybenzaldehyde **(6)** was elucidated by IR spectrum **(Figure 5)** which showed the absorption band at 1681 cm^{-1} assigned for conjugated carbonyl. The absorption bands for aromatic double bond were observed at 1600 cm^{-1} and 1445 cm^{-1}. The C-O stretching frequency was observed at 1252 cm^{-1}.

The 1H NMR spectrums (**Figure 6**) showed a methylenedioxy signal at δ 5.97 (2H) indicated the methylenation reaction has occurred. Two doublet peaks observed at δ 6.78 with a coupling constant of 8.0 Hz was assigned to H-5. A doublet of doublet signals was attributed to H-6 (J=8.8 Hz) while the one resonated at δ 6.81 was attributed to a meta-coupled H-2 (J=1.6 Hz). Signal associated to aldehyde proton was observed at δ 9.81 in the spectrum. However, the existence of methylenedioxy signal has proven the success of this reaction.

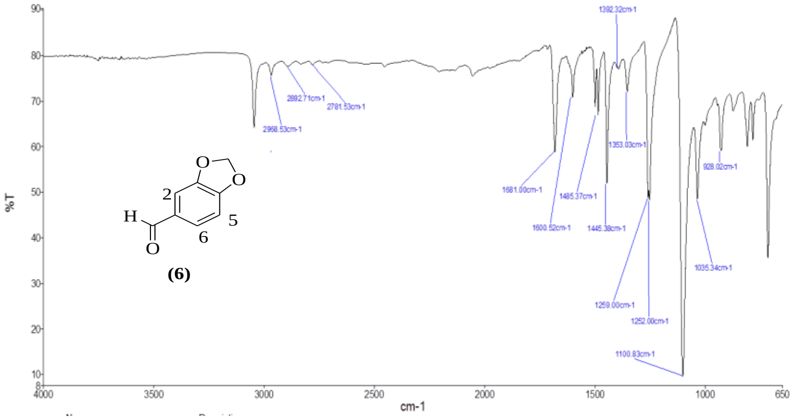


Figure 5 IR spectrum of 3,4-methylenedioxybenzaldehyde **(6)**

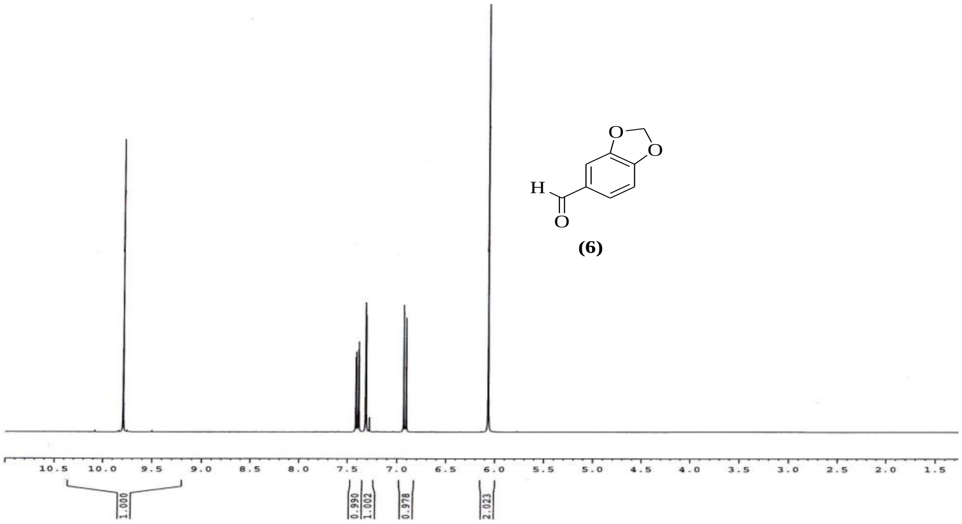


Figure 6: ^{1}H NMR spectrum of 3,4-methylenedioxybenzaldehyde **(6)**

3.4. Synthesis of 2’-hydroxy-4-methoxychalcone **(8)**

The Claisen-Schmidt reaction between 2-hydroxyacetophenone **(9)** and 4-methoxybenzaldehyde **(3)** was carried out in highly basic medium which yield yellow solution of 2’-hydroxy-4-methoxchalcone **(8)** in 16.41%. The IR spectrum (Appendix 7) of compound (13) reveals the C=O band at 1690 cm-1, C=C olefinic at 1603 cm-1, C=C aromatic at 1571 and 1463 cm-1 and C-O at 1254 cm-1. 1H NMR spectrum (Appendix 8) exhibit a downfield signal at δ 9.91 attributed to Ar-OH. Trans-olefinic protons were observed at δ 7.44 and δ 7.86.

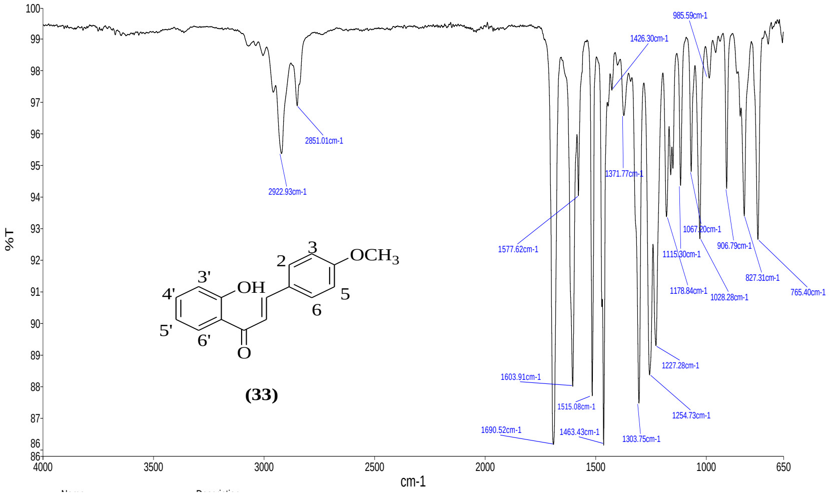


Figure 7 IR spectrum of 2’-hydroxy-4-methoxychalcone **(8)**

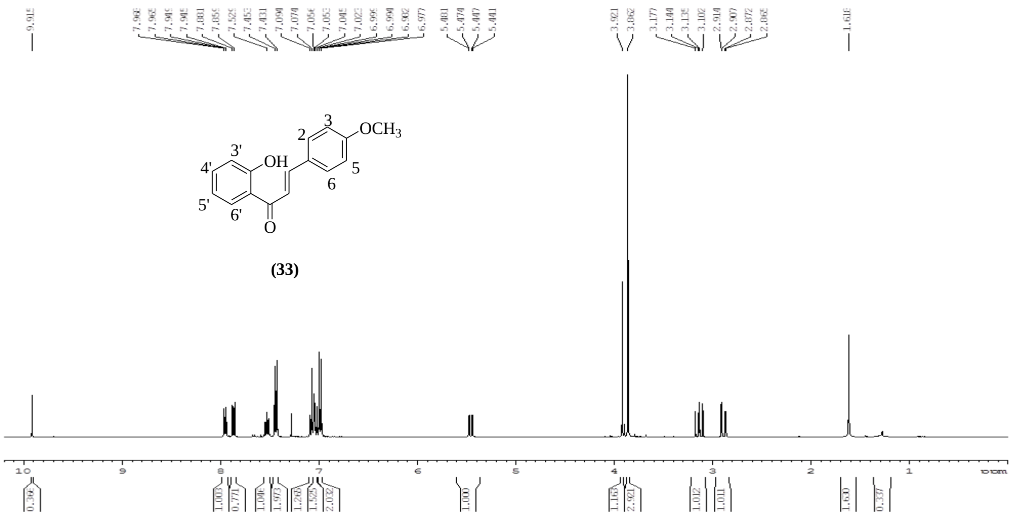


Figure 8 ^{1}H NMR spectrum of 2’-hydroxy-4-methoxychalcone (**8**)

4. CONCLUSION

The objectives of the study were successful achieved. 4-Methoxybenzaldehyde a derivative of 4-hydroxybenzaldehyde was afforded via methylation reaction with methyl iodide. Prenylation reaction with prenyl bromide of 4-hydroxybenzaldehyde produced 4-O-prenylbenzaldehyde while methylenation reaction with diiodomethane furnish 3,4-methlenedioxybenzaldehyde. 2’-hydroxy-4-methoxychalcone was afforded via from the Claisen-Schmidt reaction of 4-methoxybenzaldehyde with 2-hdroxyacetophenone. The reaction was carried out in the presence of potassium hydroxide as a catalyst. All compounds were successfully elucidated by chromatographic and spectroscopic methods.

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