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**SYNTHESIS OF THE NEW ETHER DERIVATIVE OF THYMOL BASED ON  
1,4 DI-(CHLORO-METHYL) PHENYL**

*Annotation: In the present work, thymol derivative was synthesized and characterized by spectral studies. the synthesized compound was evaluated for the antibacterial activities against Bacillus subtilis, Staphylococcus aureus,*

*Staphylococcus epidermidis and Escherichia coli using standard well-diffusion method. However, the derivative did not show any antibacterial activity against all the tested strains. The synthesized compound was characterized by IR, <sup>1</sup>H-NMR & <sup>13</sup>C-NMR spectral data.*

**Keywords:** *thymol, a,a-Dichloro-p-xylene, K<sub>2</sub>CO<sub>3</sub>, Antibacterial activity.*

## **СИНТЕЗ НОВОГО ЭФИРНОЙ ПРОИЗВОДНОЙ ТИМОЛА НА ОСНОВЕ 1,4 ДИ-(ХЛОРО-МЕТИЛ) ФЕНИЛА**

**Аннотация:** *В настоящей работе синтезировано и охарактеризовано спектральными исследованиями производное тимола. синтезированное соединение оценивали на антибактериальную активность в отношении Bacillus subtilis, золотистый стафилококк, стафилококк эпидермальный и Эшерихий палочка стандартным хорошо диффузионным методом. Однако производное не проявляло никакой антибактериальной активности в отношении всех тестируемых штаммов. Синтезированное соединение характеризовалось спектральными данными ИК, <sup>1</sup>H-ЯМР и <sup>13</sup>C-ЯМР.*

**Ключевые слова:** *P-нитро салициловым, основания Шиффа, двудерных комплекс, тетраденатными лиганда.*

### 1. Introduction:

Thymol (2-isopropyl-5-methylphenol) (1) is naturally occurring phenolic monoterpene derivative of cymene, which is found in essential oils extracted from plants belonging to the Lamiaceae family [1,c.175]. Since 16th century, thymol-rich essential oils have been evaluated for their benefits in medicinal application [2,c.126/3,c.2231] as well as for their antimicrobial properties[1,c.175/4,c.296]. Thymol (1) itself exhibits a large number of biological activities, such as antibacterial [5,c.375], antileishmanial [6], anti-inflammatory [7,c.895], antitumor [8,c.375] and aedes aegypti larvicidal[9] properties. Thymol also exhibited insecticidal and genotoxic activities on Drosophila melanogaster [10,c.1323]. In continuation of our

interest in searching for potential antibacterial compounds derived from natural products, herein we report the synthesis, characterization and antibacterial evaluation of thymol ethers using well-diffusion method.

## 2. Experimental

### 2.1. Apparatus and chemicals:

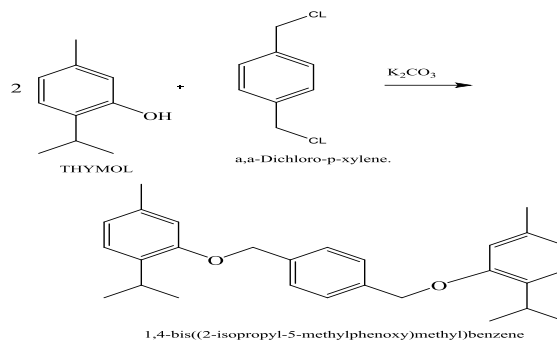
Thymol is commercially available and purchased from Sigma-Aldrich. All of other reagents were obtained from Sigma-Aldrich, Merck or Acros Organics and used without additional purification. All the reactions were performed under nitrogen atmosphere. The reactions were monitored by thin layer chromatography (TLC) using plastic precoated sheets (Silica gel 60 F254, 0.25 mm thick). Plates were visualized under UV 365 nm and UV 254 nm without treatment. Column chromatography was performed on silica gel 60 (230-400 mesh, Merck). NMR data were recorded in CDCl<sub>3</sub> on Bruker FT-400 (400 MHz) (500 MHz) Spectrometer. <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts are given in ppm. Infrared spectra were recorded in KBr disc on Perkin Elmer 100 FT-IR Spectrometer.

### 2.2. Experimental Procedure:

#### 2.2.1. Synthesis of thymol ether:

Thymol ether was synthesized according to the procedure described previously [9]. K<sub>2</sub>CO<sub>3</sub> (0.01 mol) was added to a solution of thymol (0.01 mol) and *o*,*o*-Dichloro-*p*-xylene (0.01 mol) in acetone (10 mL) under an inert atmosphere. The mixture was refluxed upon completion *via* TLC monitoring. After the completion, the reaction crude was diluted with 30 mL of distilled water and then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 30 mL). The organic extract was dried over anhydrous MgSO<sub>4</sub> and concentrated under reduced pressure.

(yield 85%, melting point : (98-100 °C)). The synthesized compound was characterized by IR, <sup>1</sup>H-NMR & <sup>13</sup>C-NMR spectral data.



Scheme 1: Reaction of thymol with a,a-Dichloro-p-xylene.

Table 1. properties of the ether thymol

Compounds	Formulas	Color	Mol.W gr/mol	m.p °C	Yield (%)
thymol ether	C <sub>28</sub> H <sub>36</sub> O <sub>2</sub>	white	402	98-100	85%

### 3.Results and Discussion:

#### 3.1. <sup>1</sup>H-spectroscopic measurements:

The <sup>1</sup>H-NMR spectrum of 1,4 di-(chloro-methyl) phenyl. ( Figure 1 ) and of chemical shifts showed in Table 1.

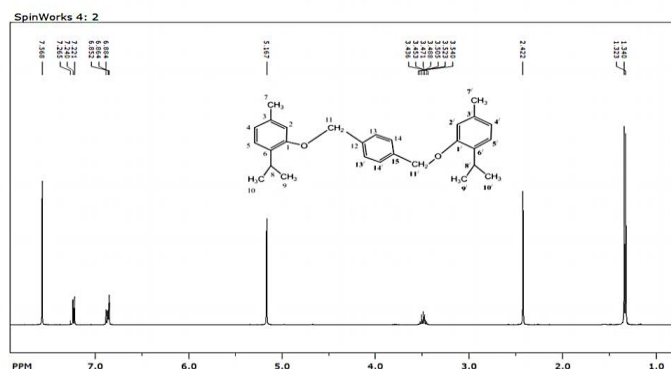


Figure 1: <sup>1</sup>H-NMR spectrum of 1,4 di-(chloro-methyl) phenyl.

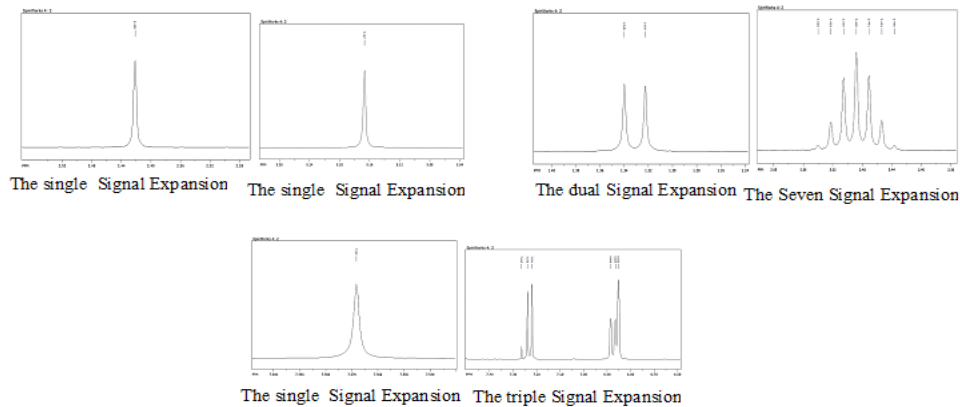


Table 2. The ( $^1\text{H-NMR}$ ) chemical shifts (ppm) of 1,4 di-(chloro-methyl) phenyl.

$^1\text{H-NMR}$ ( $\delta_{\text{H}}$ ppm)	Number of Carbon	
1.32 , 1,34	d ,2H	10,10 <sup>b</sup> ),(9,9 <sup>b</sup> )
2.42	S ,6H	7,7 <sup>b</sup> )
3.48	m ,2H	8,8 <sup>b</sup> )
5.16	S ,4H	(11,11 <sup>b</sup> )
7.56	S ,4H	(13,13 <sup>b</sup> ),(14,14 <sup>b</sup> )
6.85 ,7.27	m ,6H	2,2 <sup>b</sup> ),(4,4 <sup>b</sup> ),(5,5 <sup>b</sup> )

### 3.2. $^{13}\text{C}$ - spectroscopic measurements:

The  $^{13}\text{C}$  NMR spectrum of 1,4 di-(chloro-methyl) phenyl.(Figure 2) showed (12) signals; and of the chemical shifts showed in Table 2.

Figure 2.  $^{13}\text{C}$ -NMR spectrum of spectrum of 1,4 di-(chloro-methyl) phenyl.

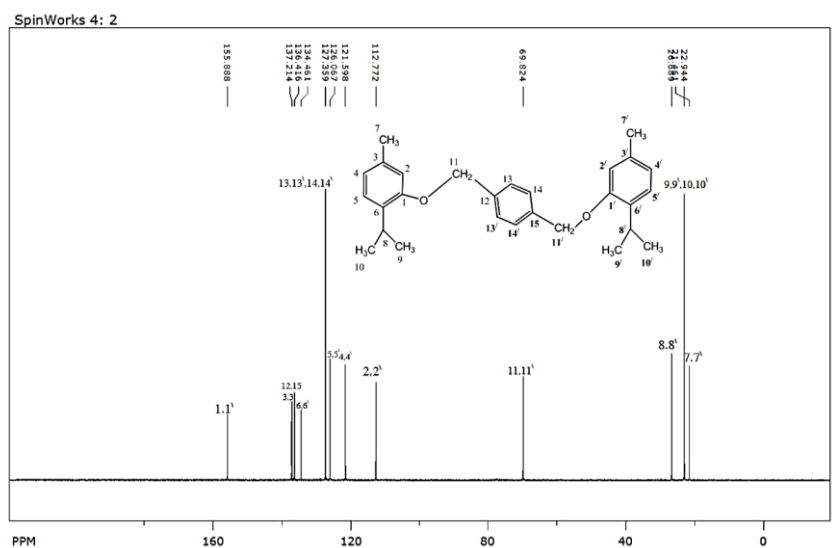


Table 3. The ( $^{13}\text{C}$  -NMR) chemical shifts (ppm) of 1,4 di-(chloro-methyl) phenyl.

$^{13}\text{C}$ -NMR( $\delta_c$ ppm)	Number of Carbon
155.88	(1,1)
112.77	2,2 <sup>\)</sup> (
137.21	3,3 <sup>\)</sup> (
121.59	4,4 <sup>\)</sup> (
126.06	5,5 <sup>\)</sup> (
134.46	(6,6)
21.46	7,7 <sup>\)</sup> (
26.66	(8,8)
22.94	9,9 <sup>\)</sup> ),(10,10 <sup>\)</sup> (
69.82	(11,11 <sup>\)</sup> )
136.41	12,15 <sup>\)</sup> (
127.35	13,13 <sup>\)</sup> ),(14,14 <sup>\)</sup> (

### 3.3. Infrared Spectra:

The infrared spectra for the present compounds taken in the range 400-4000  $\text{cm}^{-1}$  help to indicate regions of absorption vibrations. The main stretching modes are for  $\nu(\text{C-O-C})$ ,  $\nu(\text{C=C})$  and  $\nu(\text{C-H})$ .

The IR data of the spectra of 1,4 di-(chloro-methyl) phenyl is presented in Table 3.

Spectrum of 1,4 di-(chloro-methyl) phenyl shows a sharp band at (1220 $\text{cm}^{-1}$ ) due to  $\nu(\text{C-O-C})$ , 3085 (aromatic C-H), 2963 (aliphatic C-H), 1601 (aromatic C=C), 1453 (aliphatic C=C).

Table 4. Wave number ( $\text{cm}^{-1}$ ) of the functional groups of 1,4 di-(chloro-methyl) phenyl.

Functional Group of chalcone	Wave number [ $\text{cm}^{-1}$ ]
aromatic C-H	3085
aliphatic C-H	2963
aromatic C=C	1601
aliphatic C=C	1453
C-O-C	1220

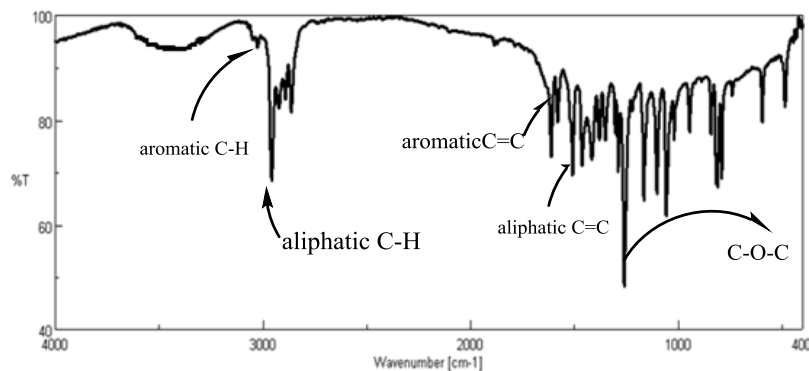


Figure 3: IR spectrum of 1,4 di-(chloro-methyl) phenyl

### 3.4. Germ effectiveness evaluation (microbial effectiveness)

The microbial effectiveness of chemical compounds has been assessed by Leasehold deposition (Matela et al.2004,2013).

Bacterial commentators have been prepared at (0.5)McFarland, equivalent to  $(1.5 \times 10^8)$  microbial unit /ML).

Two types of germs have been used:

Positive gram germs (Staphylococcus aureus). Negative gram germs (Escherichia coli).

Muller hennaton plant was prepared and placed 20 milliliters of liquid plant in petri dishes. 100 Micro liters were taken from the germ commentator and individualized on the entire plate.

Using an 8mm sterile probe, drilling was done within the lease

Was placed 100µL of the chemical compound in several concentrations (1:1-1:2-1:3). Within the ceremony, where it has been extended by chloroform

A sample of the negative witness of chloroform was placed to ensure that the Substance did not affect the germs. [10]

A biohazard ciprofloxacin has been used as a positive witness to the experiment. The improvement in the central moist to prevent the loss of liquid due to evaporation.

Within the incubator, where the optimization at 37°C for 24 hours [11,12].

### Results:

Showed all the extensions chemical compounds effective against germs Gram-positive (Staphylococcus aureus). and Gram-negative (Escherichia coli), it also Showed that chloroform had no effect on the germs.

Was to measure the effectiveness of the witness is positive at 22 mm, or samples of The trade was effectively more than 25 mm, the impact on the positives gram, 21mm. when the negative of a gram, so when you rollover (1:2 and 1:3) , and Extension (1:1). was the event so great as to prevent the growth of germs fully.

Escherichia coli	Escherichia coli	Extension
+	+	positive witness
23	22	Ciprofloxacin(Positive)
No growths	No growths	1:1
21	26	1:2
20	25	1:3

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