Synthesis of a New Series of Ethyl Indolepropionates and Study of Their Biological Activity of Some Prepared Compounds

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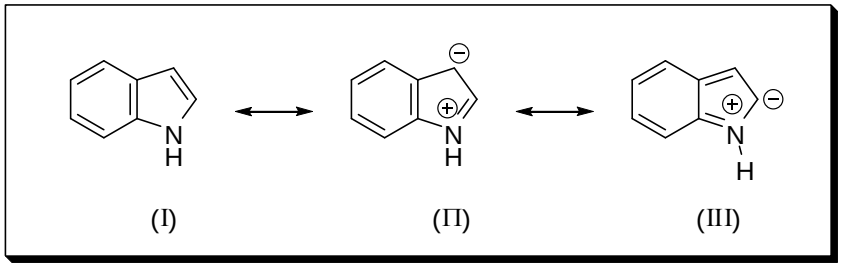
الخلاصة
يتضمن البحث تحضير مشتقات جديدة للاثيل اندول بروبيونات من خلال التحلل الايثانولي لمشتقات الاندول حامض الملدرم المقابلة باستخدام النحاس كعامل مساعد حضرت أولا باستخدام تكاثف يونيميتسو. شخصت المركبات المحضرة باستخدام تقنيات الأشعة تحت الحمراء، الرنين النووي المغناطيسي، تحليل العناصر و قياس درجة الانصهار. وكذلك تضمن البحث دراسة التائثير البايولجي للمركبات المحضرة على نوع واحد من البكتريا*pseudomonas aerogenosa* باستخدام طريقة الحفر بالا كار ووجد إن لهذه المركبات فعالية متفاوتة القوة في تثبيط فعالية البكتريا المدروسة.

Abstract
Ethyl indolepropionate derivatives were prepared by the decarboxylative ethanolysis of indole meldrum's acid derivatives in presence of copper powder, indole meldrum's acid derivatives were prepared earlier via Yonemitsu condensation. Their structures were identified on the basis of elemental analysis, IR, NMR and melting point. Also some of the prepared compounds have been tested for their antibacterial activity against *pseudomonas aerogenosa* (Gram positive) bacteria by using of agar well diffusion method. Finally we found that the compounds show different activity of inhibition of growth of the bacteria.

Introduction

Indole is classified as a π-excessive aromatic compound, which is isoelectronic with naphthalene.[1]



(I) (Π) (III)

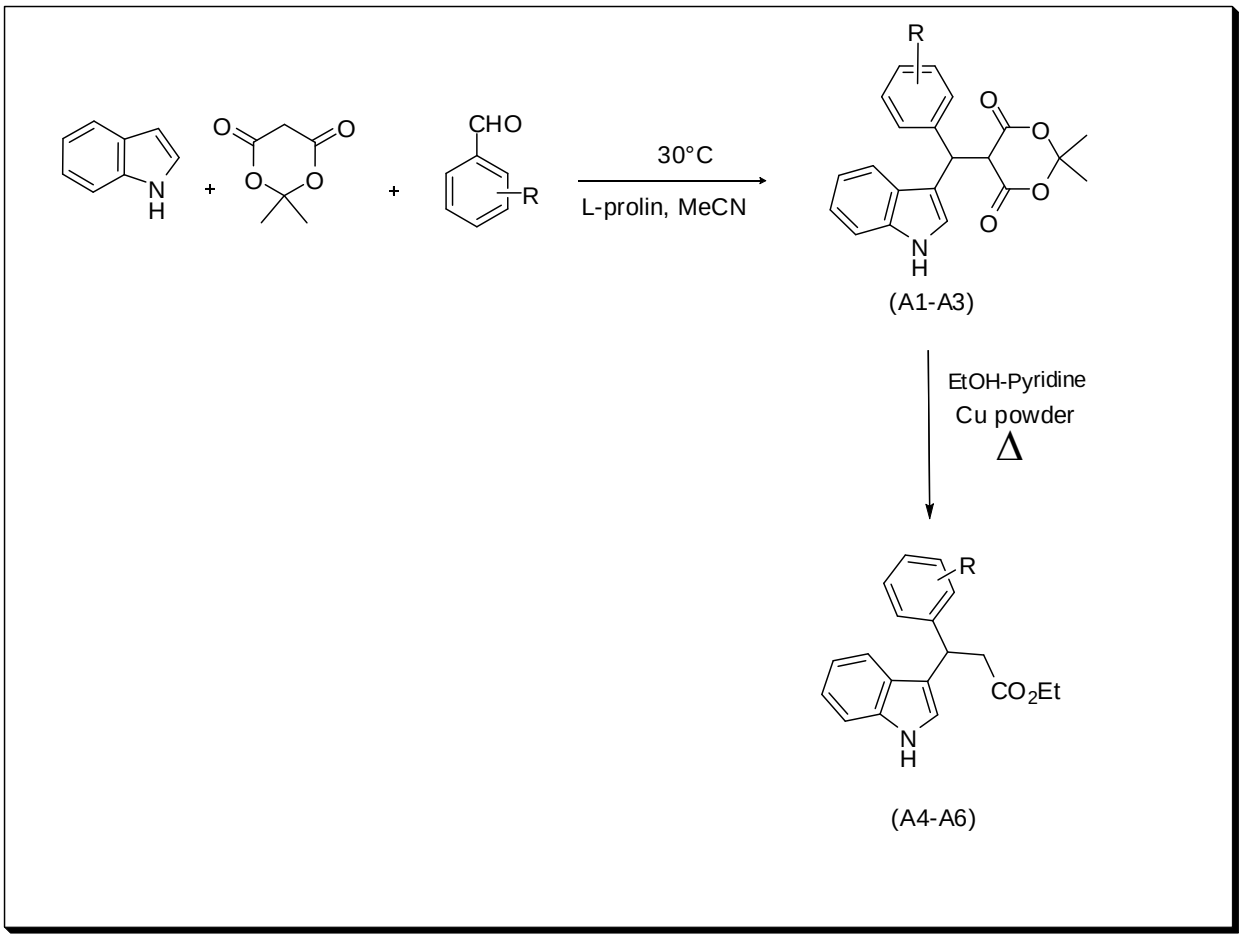
Scheme (1): stability of the resultant anion

Experimental studies have shown that indoles have a protective effect against estrogen-related cancer such as breast cancers [2], colon and other types of cancer.[3,4] They block the estrogen receptors, thus inhibiting the growth of tumors in the mammary gland and in other locations. Among the indole derivatives, indole-3-carbinol takes an important role because of being an important antitumor agent. It has achived notoriety as a therapeutic phytochemical.In animal models, indole-3-carbinol prevents the development of malignancies, including cervical cancer[5], breast cancer [6], prostate cancer [2], endometrial cancer [7] and skin cancer.[8] It is a

strong antioxidant and stimulators of detoxifying enzymes, protecting the structure of DNA.The other indole derivatives which have found use as drugs are indomethacine, one of the first anti-inflammatory agent[9]; sumatriptan, which is used in the treatment of migraine headaches; pindolol , one of the important beta blockers ; and auxin (indole-3-acetic acid), acts as plant growth hormone.

Ethyl indolepropionates are required as starting material for the synthesis of antitumor ellipticine analogs.[10] However, there is no practical method for obtaining of indolepropionic acid and their esters. Indolepropionic acid itself can be synthesized from indole and acrylic acid, but substituted acrylic acids such as crotonic acid not react with indole.

In this work, we synthesized new ethyl indolepropionates by using Yonemitsu method[10] which involves firstly condensation between three components, indole meldrum's acid and aldehydes then decarboxylative ethanolysis of the products to give the corresponding ethyl indolepropanioates as illustrated below in scheme (2).



Scheme 2: Synthesis of ethyl indolepropionates

Experimental

- Electro thermal melting point apparatus was used to measure the melting point of prepared compounds
- Infrared spectra were recorded as KBr discs using Fourier Transform Infrared spectrophotometer FTIR-8400s SHIMADZU, Kufa University (Iraq)
- ^{1}H-NMR spectra were recorded by Brukur ,Ultra Shield 300 MHz, Switzerland with TMS as internal standard in DMSO-d^{6}, Al-albayt University(Jordan)
- TLC was used for monitoring of reaction progress by preparing of 1 % indole solution in ethanol and using of n-hexane - ethyl acetate (3/1 v/v) as developer, molecular Iodine was used for detection.
- Elemental analysis was recorded using elemental analyzer EA ERUO 3000, Milano, Italy, Central Lab. University of Kufa.
- The biological test has been done in College of Science, Department of Biology, University of Kufa.

Preparation methods

preparation of 5-((1H-Indol-3-yl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione. (A1-A3)

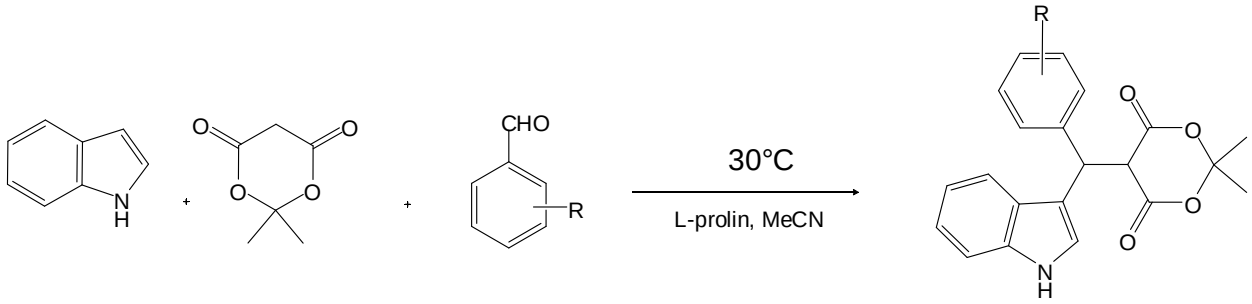
General procedure: To a solution of indole (1.17g , 0.01 mol) in CH_3CN (10 ml),were added Meldrum's acid (1.44g , 0.01 mol),appropriate aldehyde (0.01 mol) and L-proline (0.06g ,0.5 mmol) ,and the reaction mixture was stirred at rt (25-30)ºC.[11] Then reaction progress was monitored by TLC .Evaporating of the solvent gave the crude products, which crystallized from ethanol. As colored powder.

preparation of Ethyl indolepropionates. (A4-A6)

General procedure: A mixture of appropriate derivative (A1-A3) (1equiv) and copper (0.2 equiv) was dissolved in a 10:1 pyridine/ethanol (0.1 M) solution.[12]The mixture was heated under reflux to 100 °C for 3 hours. Removal of the Cu powder and evaporating of the solvent by evaporator gave the crude products which recrystalized from ethyl acetate - n-hexane. As colored powder.

Result and Discussion

In this work we are to treated Meldrum's acid with various aromatic aldehyde ,indole is shown on scheme (3).



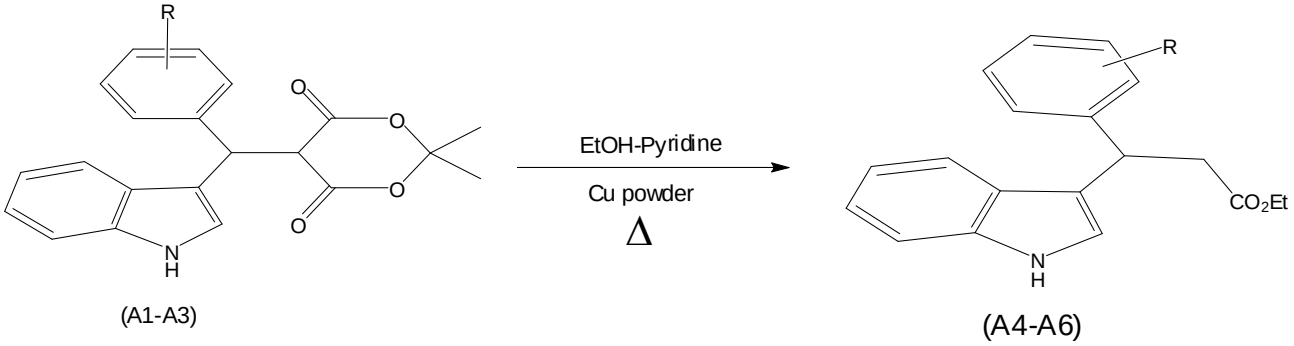
Scheme 3:

Compound A1: 5-((2-bromophenyl)(1H-Indole-3-yl)Methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione.

Compound A2: 5-((1H-Indole-3-yl)(4methoxyphenyl)Methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione.

Compound A3: 5-((3-hydroxyphenyl)(1H-Indole-3-yl)Methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione.

The decarboxylative ethanolysis of the products(A1-A3) to give the corresponding ethyl indolepropanioates as illustrated below in scheme (4).



Scheme 4:

Compound A4: Ethyl 3-(2-bromophenyl)-3-(1*H*-indol-3-yl)propanoate.

Compound A5: Ethyl 3-(1*H*-indol-3-yl)-3-(4-methoxyphenyl)propanoate.

Compound A6: Ethyl 3-(3-hydroxyphenyl)-3-(1*H*-indol-3-yl)propanoate.

The physical properties of the prepared derivatives and its yield are shown on table(1)

Table 1: Physical properties of prepared compounds

Comp. No.	M.P.(°C)	Yield%	Color
A1	80 -82	80	Pink
A2	77 – 79	79	Red
A3	94 - 96	83	Red
A4	66 – 68	77	Black
A5	65 -68	68	Black
A6	102 – 104	60	Brown

Table (2) show the identification of the prepared derivative using an IR, H-NMR spectroscopic method. Which was coincided with the structure . Also CHN analysis were done for these derivatives.

Table (2) Identification of the prepared compounds.

product	IR (KBr) cm^{-1}	^{1}H NMR	Anal.	
A1	ν NH 3409 ν CH 2993,2939 ν C=O 1777-1750, ν C=C 1618,1591,	δ 1.23(s,3H), δ 1.5(s,3H)[12], δ 2.73(d,1H), δ 6.55(d,1H), δ 7.02-7.36 (m) δ 8.92(s,1H)	Calc.% $C_{21}H_{18}BrNO_4$ C,58.89; H,4.24; N,3.27.	Found % C,60.01; H,5.48; N,3.33.
A2	ν NH 3404 ν CH 2999,2940 ν C=O 1774-1747 ν C=C 1610,1591			
A3	ν NH 3415 ν CH 3056,2999 ν C=O 1770-1728 ν C=C 1600,1589			
A4	ν NH 3411 ν CH 2979,2925 ν C=O 1722,1618 ν C=C 1606	δ 2.38(t,3H), δ 3.68(d,2H), δ 3.83(t,1H), δ 4.31(q,2H), δ 6.34-7.81 (m) δ 8.42(s,1H)		

A5	ν NH 3417 ν CH 2954,2925, ν C=O 1731,1608, ν C=C 1560			
A6	ν NH 3406 ν CH 3055,2979, ν C=O 2930,1716, ν C=C 1600,1591,			

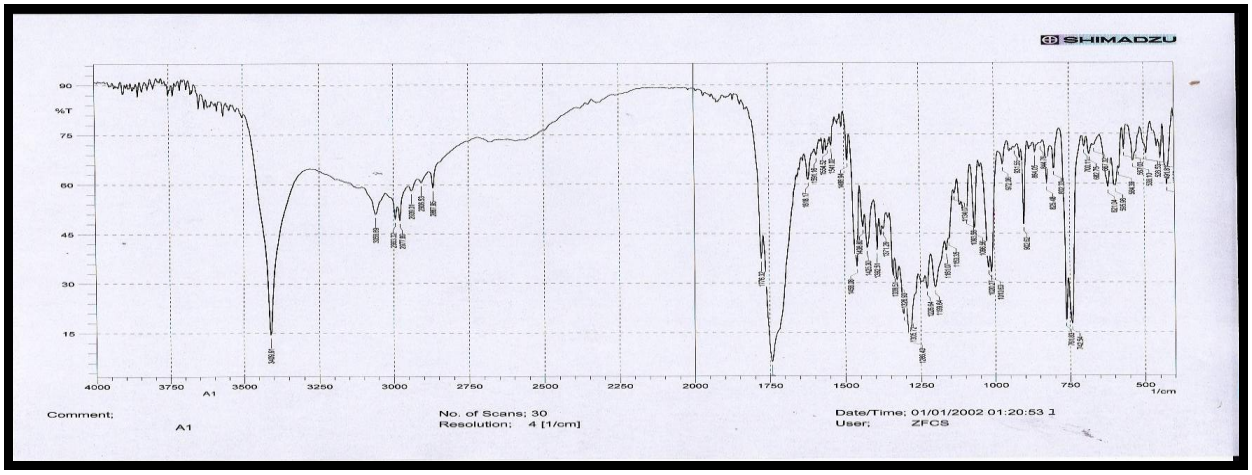


Figure (1) IR spectrum of compound A1.

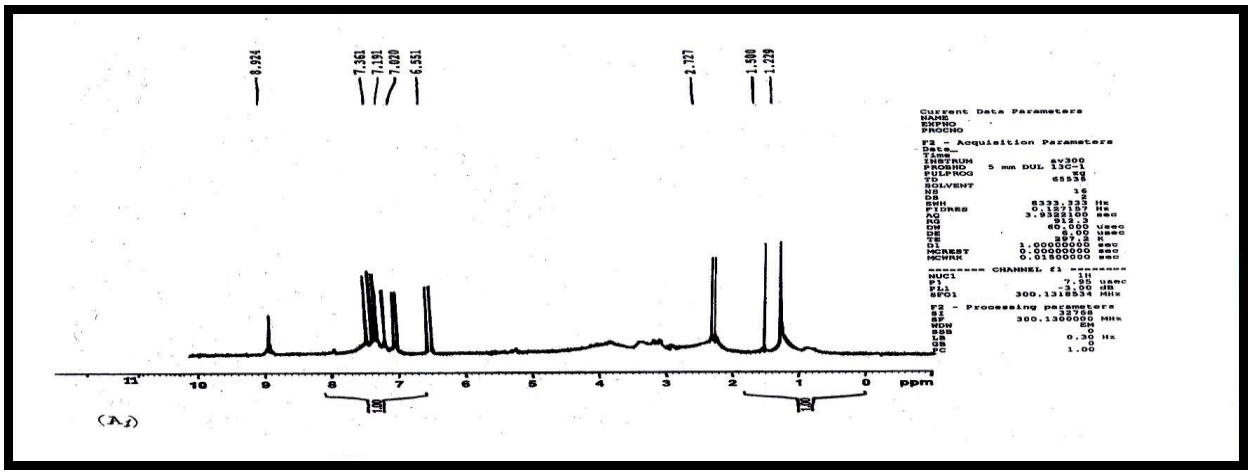


Figure 2: ^{1}HNMR spectrum of compound A1.

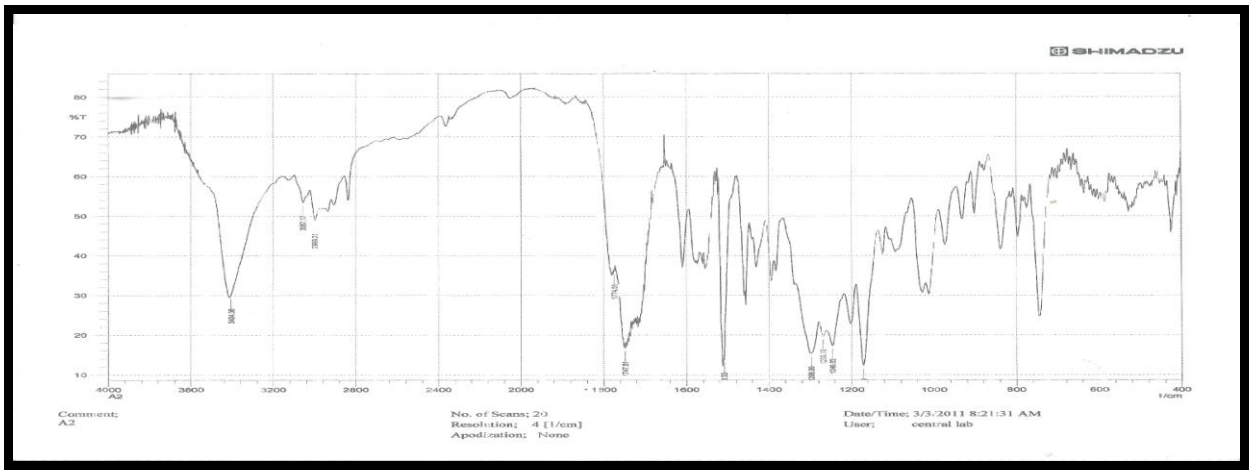


Figure 3: IR spectrum of compound A2.

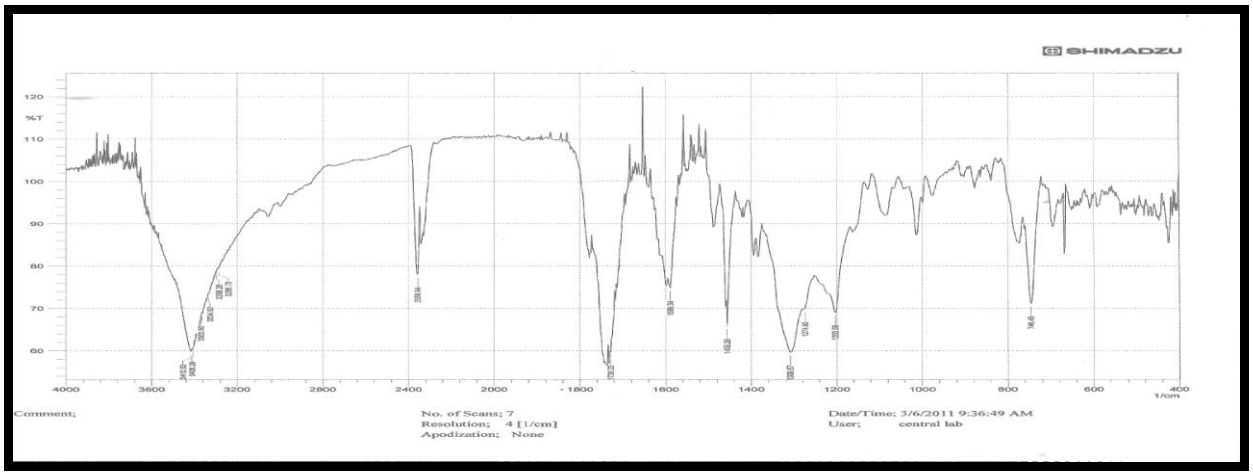


Figure 4: IR spectrum of compound A3.

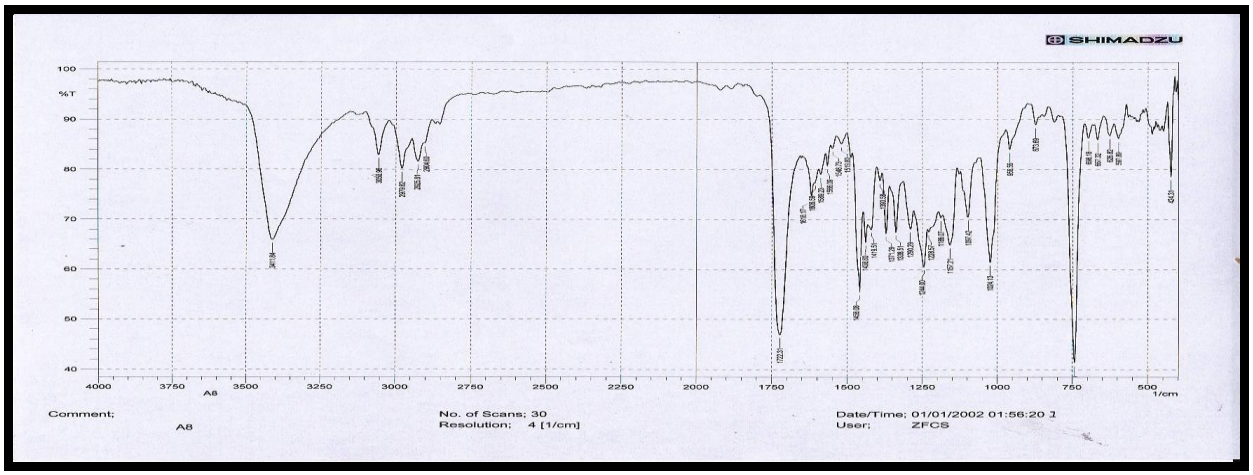


Figure 5: IR spectrum of compound A4.

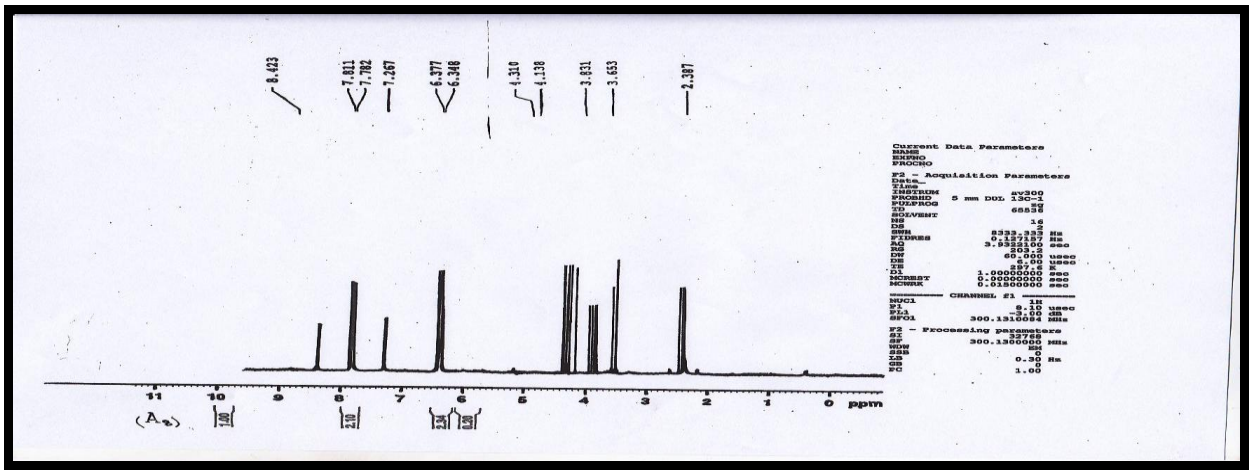


Figure 6: ^{1}HNMR spectrum of compound A4.

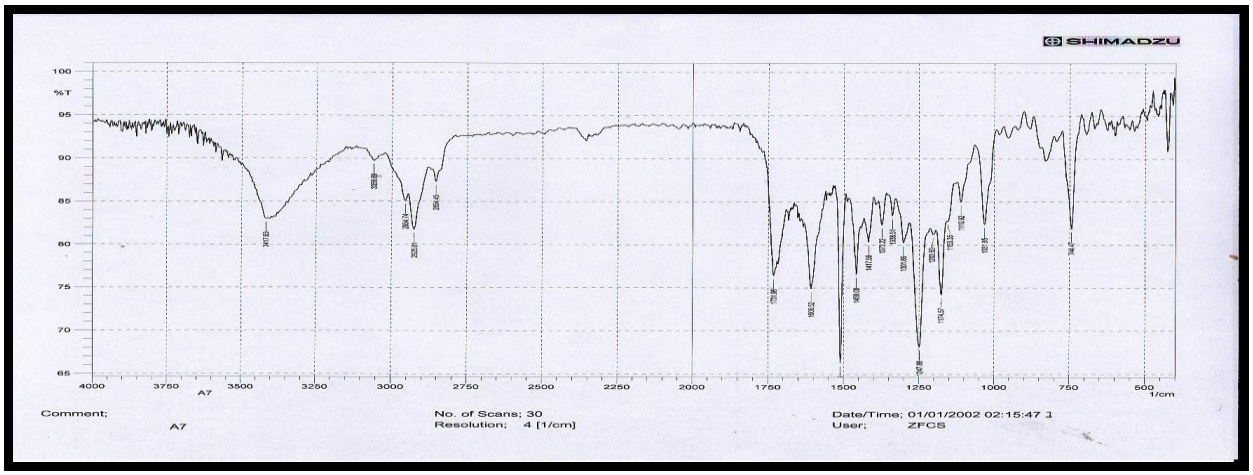


Figure 7: IR spectrum of compound A5.

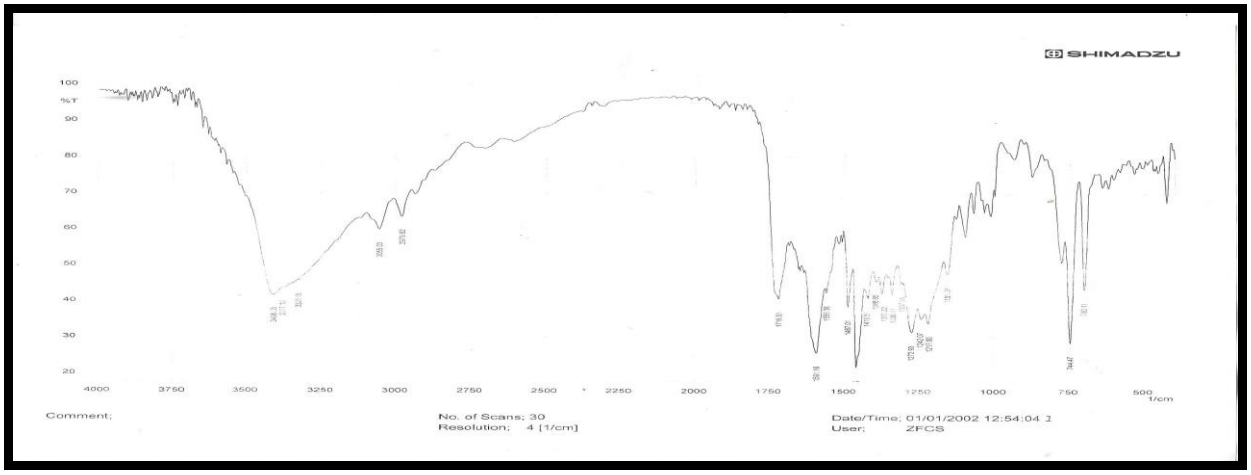


Figure 8: IR spectrum of compound A6.

Treatment of indole with meldrum's acid and benzaldehyde derivatives, following the procedure of farlow et al., gave indolyl derivatives A1-A3 in 79-80% yield. In this case, we found that, the benzaldehyde derivatives with electron withdrawing groups gave the highest yield and the shortest reaction time, in case of, electron donating groups, the in contrast. The indolyl derivatives A1-A3 were treated with mixture of ethanol-pyridine (1-10 v/v) in presence of small amount of Cu powder gave the corresponding ethyl indolepropionate derivatives A4-A5 in 60-77% yield. Antimicrobial studies was performed by preparing five concentration, of each prepared compound and the indole in DMSO (5,10, 20,30 and 40 mg/ml) were tested for antibacterial activity against *pseudomonas aeruginosa* (Gram positive) by well diffusion method in Mueller-Hinton agar medium. Then and after 24 h of incubation, the inhibition zones were measured, we found that these prepared compounds have different biological activities but all compounds less activity than the starting material which show high biological activity against this type of bacteria. The results of biological activity were measured in (mm) and tabulated below in table (3).

Table 3: Inhibition Zone of Some Compounds in mm

Conc. / Comp.	5 mg/ml	10mg/ml	20mg/ml	30mg/ml	40mg/ml	Control (DMSO)
Indole	23	34	37	40	42	R
A1	R	R	10	12	14	R
A2	R	R	R	R	4	R

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