Synthesis and characterization of some substituted heterocyclic compounds and evaluation of biological activity

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Abstract

This work includes preparing of some new derivatives of 1,2,4-Triazoles and oxazoles from the reaction between 3,5-dimethyl phenol and chloroethyl acetate in the presence of potassium carbonate and dry acetone to obtain the ester ethyl 3,5-dimethyl phenoxy acetate , then converted this ester to Thiosemicarbazone and Semicarbazone. Then ,the Triazoles were prepared from the cyclization of these Thiosemcarbazones and Semicarbazones in alkaline media(potassium hydroxide solution) . The prepared compounds were characterized by spectral methods FT-IR ,^{1}H-NMR and measurement of some of its physical properties and evaluation of the biological activity for some of them.

Key words : Triazole ,oxazole ,biological activity.

تحضير وتشخيص بعض المركبات المعوضة غير متجانسة الحلقة وتقييم الفعالية الحيوية

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الخلاصة

يتضمن هذا البحث تحضير بعض المشتقات الجديدة من الترايزول والاوكسازول من التفاعل الحاصل بين 3و5- ثنائي مثيل فينول وكلورو اثيل استيت للحصول على الاستر بوجود كاربونات البوتاسيوم والاسيتون الجاف ومن ثم تحويل هذا الاستر الى مشتقات السيميكاربازون والثايوسيميكاربازون .

حضرت الترايزولات من عملية الغلق الحلقي للسيميكاربازون والثايوسيميكاربازون في الوسط القاعدي بوجود محلول هيدروكسيد البوتاسيوم . شخصت المركبات المحضرة من خلال الطرق الطيفية (طيف الاشعة تحت الحمراء وطيف الرنين المغناطيسي) وقياس بعض خصائصها الفيزياوية وتقييم الفعالية الحيوية للبعض منها .

Introduction

The five member heterocyclic like 1,2,4-Triazole ,1,3,4- oxadiazole and 1,3,4-Thiadiazole constitute a potential class of compounds which possess a broad spectrum of biological activity [1-5],including antimicrobial , sedative ,anticonvulsant and antiinflamatory[6].

Also,certain compounds having 1,2,4-Triazole nucleus[7] have been reported as fungicidal[8],anticonvulsant ,antidepressant [9]and antibacterial activities[10]. The above mention observations encouraged us to prepare the new Triazole compounds with expected antimicrobial potency[11-16].

Experimental section :

1- Melting points are recorded using hot stage Gallen Kamp melting point apparatus and they were uncorrected.

2- Infrared spectra are recorded using Fourier Transform infrared SHIMADZU (8300) (F.T.IR) infrared spectrophotometer, KBr disc .

3- ^{1}H –NMR spectra ($CDCl_3$) were recorded on BRUKER-av-300 instrument with TMS as an internal standard.

4- Thin layer chromatography (TLC) was carried out, and the plates were developed with iodine vapour.

5- The biological activity was performed by Biotechnology Department, Tikrit University .

Methods:

1-Synthesis of ethyl 3,5-dimethyl phenoxy acetate [2].

3,5-dimethyl phenol (0.01mole) was dissolved in absolute ethanol (100ml) and heated in a water bath until the solution became clear. The hot solution was cooled. Ethyl chloro acetate (0.01mole) was added to the mixture. The addition was performed dropwise with stirring for 1 hr.,the stirring and refluxing continued for 4hrs. the reaction mixture was filtered and evaporated to give a white crystals,which was re crystallized from ethanol to give the ester [2]. Physical properties of the products are listed in table (1).

2-Synthesis of 3,5-dimethyl phenoxy acetate semicarbazone [3].

A mixture of ethyl 3,5-dimethyl phenoxy acetate (0.01mol) semicarazide hydrochloride (0.01mol) and sodium a acetate (0.01) in ethanol (25ml) was refluxed for 4hrs .The reaction mixture was filtered and poured on ice water. The precipitate was filtered and re-crystallized from ethanol to give white crystal of the

semicarbazone derivative. Physical properties of the products are listed in table (1).

3-Synthesis of 3,5-dimethyl phenoxyacetate)-1,3,4-triazole-2-ol-[4].

In around bottom flask (0.01mol) of 3,5-dimethyl phenoaceto-semicabazone (from the previous step) was refluxed with 10% aqueous sodium hydroxide solution (25 ml) for (3-4) hrs. The reaction mixture was filtered, cooled, and neutralized by gradual addition of 10% hydrochloric acid, the white formed precipitate was filtered and re-crystallized from ethanol to give a white crystals. Physical properties of the dry product is listed in table [1].

4-Synthesis of 3,5-dimethyl phenoxy aceto thiosemicabazone [6].

A mixture of 3,5-dimethyl phenoxy acetate (0.01mol) and thiosemicabazide (0.01mol) in ethanol (20ml) was refluxed for 3hrs. The reaction mixture was filtered and poured on ice water. The precipitate was filtered and re-crystallized from chloroform to give white crystal of the thiosemicabazone derivative. Physical properties of the products are listed in table (1).

5-Synthesis of 3,5-dimethyl phenoxy acetate)-1,3,4-triazole-2-thiol-[7].

In around bottom flask (0.01mol) of 3,5-dimethyl phenoxy acetate - thiosemicabazone (from the previous step) was refluxed with 10% aqueous sodium hydroxide solution (25 ml) for (3-4) hrs. The reaction mixture was filtered, cooled, and neutralized by gradual addition of 10% hydrochloric acid, the white formed precipitate was filtered and re-crystallized from ethanol to give a white crystals. Physical properties of the dry products are listed in table [1].

6- Synthesis of N-(amido)-3,5-dimethyl phenoxy acetamide [9].

A mixture of ethyl 3,5-dimethyl phenoacetate (0.01mole) in absolute ethanol (20ml), urea (0.01mole) was added. The mixture was refluxed for 5 hrs. After cooling and filtering ,the white precipitate was obtained[17] .

7- Synthesis of N-[4-(*p*-phenyl phenyl] -1,3-oxazol-2-yl] 3.5-dimethyl phenoxy acetamide [10].

To a mixture of compound [9] (0.01mole) in absolute ethanol(15ml) ,*p*- phenylphenacylbromide (0.01mole) was added. The mixture was refluxed for 6hrs., cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered off, washed with water , and petroleum ether B.p (80-100) ^{0}C was used for re crystallization[18] .

8- Synthesis of N-[thioamido)-3,5-dimethyl phenoxy acetamide [11].

Compound [11] was prepared by the same method described for the preparation of [9],white precipitate was obtained .The physical properties are listed in table (1).

9- Synthesis of N-[4-(*p*-phenyl phenacyl)-1,3-thiazole-2-yl]-3,5-dimethyl phenoxyacetamide [12].

Compound [12] was prepared by the same method described for the preparation of [10] ,white precipitate was obtained . The physical properties are listed in table (1).

Results and discussion

Triazoles compounds were prepared from 3,5-dimethyl phenol and Semicarbazide or Thiosemicarbazide with NaOH Scheme 1.

The 3,5-dimethyl phenol was treated with ethyl chloroacetate in presence of potassium carbonate in absolute ethanol to give the ester [2].

The structure of compound [2] was confirmed by physical properties which are listed in table (1). FT-IR spectrum shows the band at 1720 $cm^{-1}$for υ(C=O) of ester, 2920 $cm^{-1}$for υ(C-H) aliphatic, and disappearance of υ(O-H) band.

compound [2] was converted to Semicarbazon or Thiosemicarbazone derivative [3,6] by the reaction of ester with Semicarbazide hydrochloride or Thiosemicarazide in ethanol. The FT-IR spectrum of compound [3] showed bands at 3370-3200 cm^{-1}asym. and sym, for NH_2 group which overlap with band of (NH) group, and at 1730 for (C=O) amide group.

The Semicarbazone derivative [3] was refluxed with 10% NaOH to give compound [4] which toutomerize with compound [5] . The FT-IR spectrum of compound [4],showed absorption at (3189-3175) cm^{-1} for υ(NH),1625 for υ (C=N) and 1695 for υ(C=O), while the ^{1}H-NMR spectra data for compound [5] δppm 4.26(s,2H,-CH_2-); 7-7.6(m, 3H, Ar-H); 13.1(broad, 2H, NH). The absence of –OH proton in the H-NMR spectrum of triazole [5] may be due to the keton –enol structure formation of (C=O) which show band at 1695 cm^{-1} for υ (C=O).

Derivative of Thiosemicarbazone [6] was refluxed with 10% sodium hydroxide solution to give 1,2,4-Triazole [7]. The FT-IR spectrum of compound [7] for example, showed the absorption bands at 1630 $cm^{-1}$for (C=N) ,at 1150cm^{-1} for (C=S), while the ^{1}H-NMR spectrum of compound [7] δppm 4.4(2H,-CH_2-);7-7.7 (m,3H, Ar-H); 12.9 (broad ,2H,NH) the absence of ((-SH) proton in the ^{1}H-NMR spectrum of Triazole [7] may due to thiol-thion structure formation .

The refluxing of ethyl 3,5-dimethyl phenoacetate [2] with urea in absolute ethanol gave compound [9]. The FTIR spectrum showed a split broad band at (3300-3200)cm^{-1}due to the asymmetric

and symmetric bands of (NH_2) and (NH) groups, two other bands at (1650-1639) $cm^{-1}$for the carbonyl and bands group at (3002-1595) cm^{-1}which were due to (C-H) and (C=C) stretching of aromatic system, respectively [19].

The H-NMR spectrum of compound [9] ,showed the significant peaks , δppm 4.1-4.9(2H,-CH_2-);7-7.4 (m,3H, Ar-H); 2.49 (NH_2) , 2.2 for (NH).

The compound [10] was synthesized from the reaction of compound[9] with *p*- phenyl phenacyl bromide under refluxing condition affected on intermolecular cyclization through S_N2 mechanism giving the desired oxazol derivative [10].

The structure of oxazole derivative [10] was confirmed by FTIR spectrum showed a broad band of (N-H) at (3369) cm^{-1} ,carbonyl group shifted to higher frequency (1700) cm^{-1} due to disappearance of possibility of hydrogen bonding. Sharp absorption band at (1585) cm^{-1}due to υ (C=N) group, the aromatic (C=C) at (1566) cm^{-1}, stretching band of (C-O-C) at (1284) cm^{-1}, and at (1495) cm^{-1} for (-NH).

The ^{1}H-NMR spectrum of this compound 1.94 (s.,1H,cyclic), 4.95(2H,-CH_2-);7-8.08(m,4H, Ar-H); and at 2.49 (broad ,1 H,NH) .

The compound [11] was synthesized by the reaction of compound [2] and thiourea. The FTIR spectrum showed a band at (3311-3195) cm^{-1}which was assigned to the asymmetric and symmetric bands of (NH_2) and ((NH) groups, at (1650) cm^{-1} for υ ((C=O), at (1089) $cm^{-1}$for υ (C=S) and bands at (3000-1630) cm^{-1}which were due to υ (C-H) and υ (C=C) stretching of aromatic system, respectively, and at (1467) cm^{-1} for δ (NH).

The ^{1}H-NMR spectrum of this compound[11] , δppm 4.1-4.7(2H,-CH_2-);6.26-8.3 (m,3H, Ar-H); 2.1 and at 2.2 for (NH and NH_2) .

N-[4-(***p***-phenyphenyl)-1,3-thiazol-2-yl]-3,5-dimethyl phenoxyacetamide [12] was synthesized from the reaction of compound [11] and p-phenyl phenacyl bromide.

The FTIR spectrum of compound [12] showed the disappearance of the (C=S) band of compound [11] at 1089) cm^{-1} ,carbonyl group shifted to higher frequency (1701) cm^{-1} due to disappearance of possibility of hydrogen bonding. Sharp absorption band at (1631) cm^{-1} and (3282) cm^{-1} due to υ (C=N) and υ (N-H) cm^{-1}, respectively, the aromatic (C=C) at (1649) cm^{-1} , stretching band of υ (C-

S-C) at (725) cm^{-1} , and band of δ (NH) at (1471) cm^{-1}.

The ^{1}H-NMR spectrum of compound [12] ; δppm 1.93 (s.,1H,cyclic), 1.87(2H,-CH_2-);7-8.7(m,4H, Ar-H); and at 2.48 (broad ,1 H,NH) .

Biological activity: The biological activity of compounds was determined by measuring the diameter of the empty region around the well (Inhibition zone). The results of preliminary screening tests are listed in table (2). The biological activity test showed that compound [3] with free (-NH_2) group having a biological effect more than other compounds.

Conclusions

For *Klebsiella Pneumonia*e (G^-), compounds [3,7,11] showed highest activity, while compounds [9] showed no activity.

1. For *Pseudomonas aeuroginosa* (G^-), some compounds have no effect on this bacteria because this bacteria is highly resistant to a wide range of antibiotic because of the slim poly saccharides in cell wall which blocked antibiotics from bacteria and also there are genetic factor.
2. For *Staphylococcus aureus* (G^+), some compounds have moderate effect on this bacteria.
3. For *Bacillus subtilus* (G^+), all compounds have moderate effect except compounds [3,4] has no effect on these bacteria. For *Klebsiella Pneumonia*e (G^-), compounds [3,7,11] showed highest activity, while compounds [9] showed no activity.
4. For *Pseudomonas aeuroginosa* (G^-), some compounds have no effect on this bacteria because this bacteria is highly resistant to a wide range of antibiotic because of the slim poly saccharides in cell wall which blocked antibiotics from bacteria and also there are genetic factor. For *Bacillus subtilus* (G^+), all compounds have moderate effect except compounds [3,4] has no effect on these bacteria.
5. for *Staphylococcus aureus* (G^+), some comp ounds have moderate effect on this bacteria.

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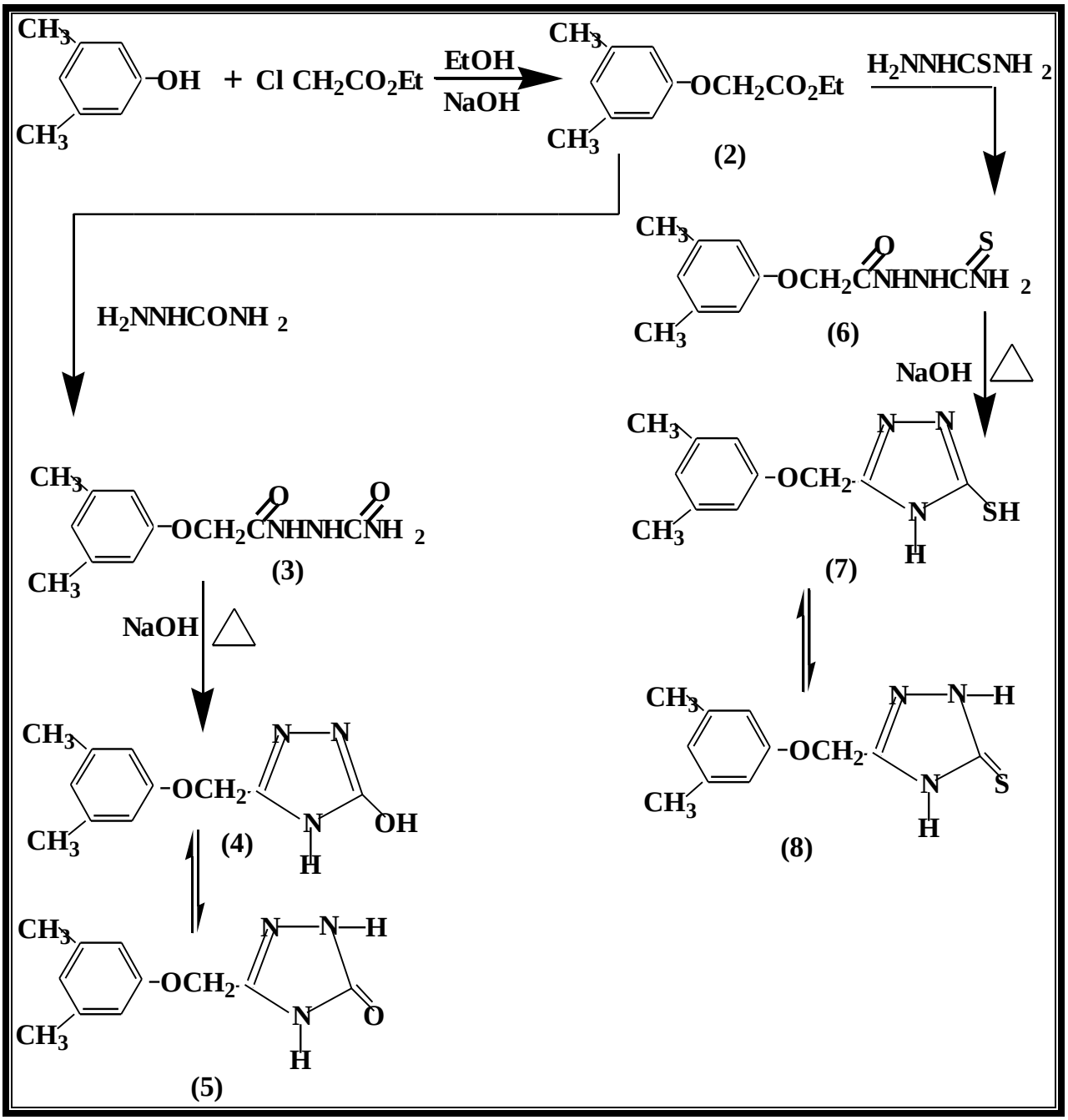
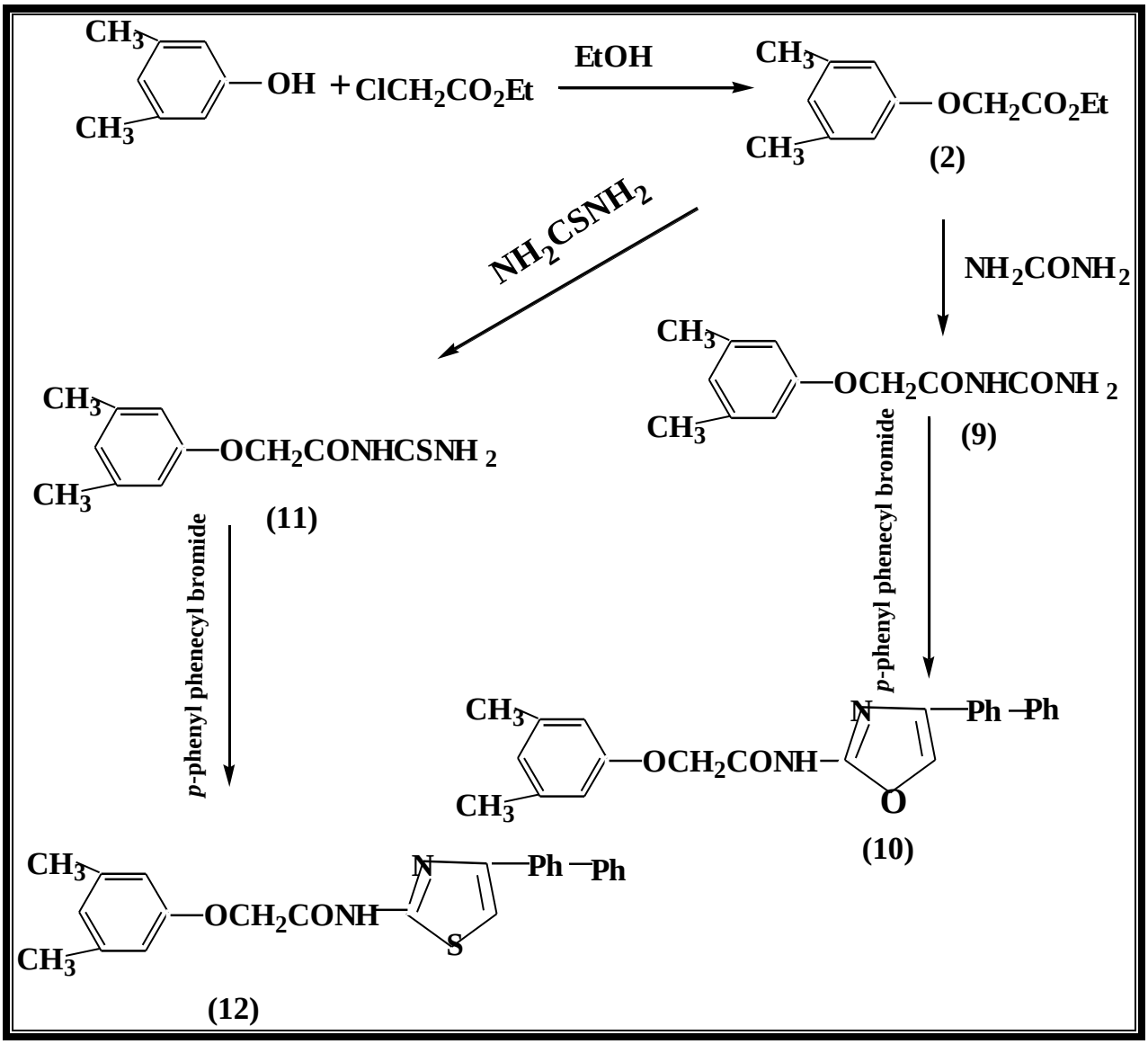
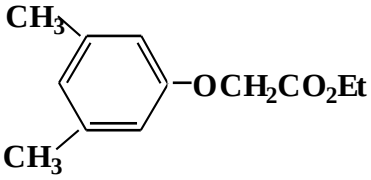
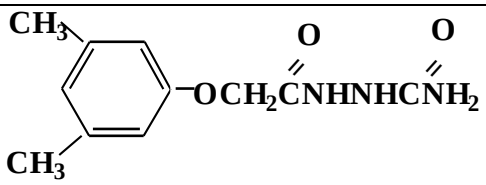
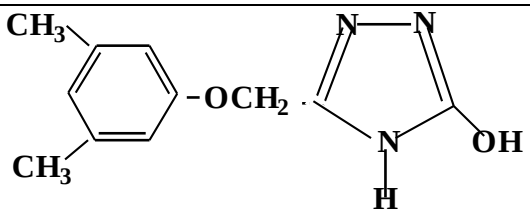
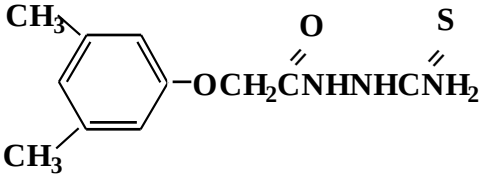
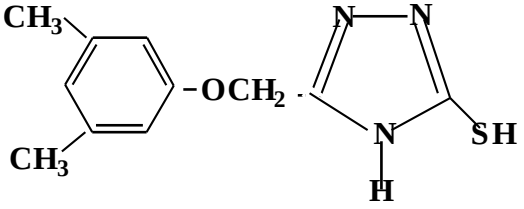
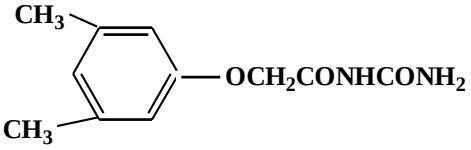
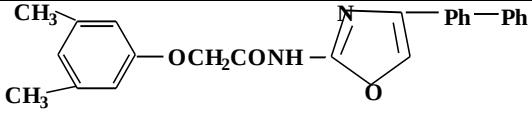


Scheme 1 .


CH3
OH + ClCH2CO2Et
EtOH
OCH2CO2Et
(2)
NH2CSNH2
NH2CONH2
OCH2CONHCONH2
(9)
OCH2CONHCSNH2
(11)
p-phenyl phenecyl bromide
p-phenyl phenecyl bromide
N
Ph
Ph
O
OCH2CONH
(10)
S
(12)

Scheme (2).

Table (1) : Physical properties of the prepared compounds .

Comp.No	The structure	Yield %	M.P ^{0}C	Colour	Recryst. solvent
2		**75**	------	white	EtOH
3		67	>250	Off white	EtOH
4		60	152-154	White	EtOH
6		68	124-126	White	Chloroform
7		70	117-118	White	EtOH
9		60	208-210	White	EtOH
10		80	94-96	Off white	EtOH

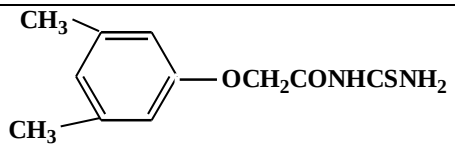
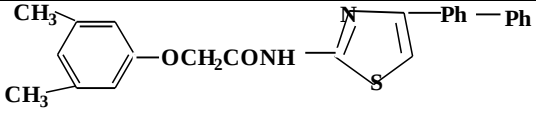
11		80	117-119	White	EtOH
12		75	192-194	Off white	EtOH

Table (2): Antibacterial activities of the synthesized compounds.

Comp. No.	*Klebsiella Pneumoniae*	*Pseudomonas aeuroginosa*	*Staphylococcus aureus*	*Bacillus subtilus*
3	++	++	++	-
4	+	+	-	-
7	++	-	+	++
10	+	++	-	++
9	-	++	+	+
11	++	-	+	+

Note:

- = No inhibition = inactive

\+ = (5-10) mm = slightly active

++ = (11-20) mm = moderately active

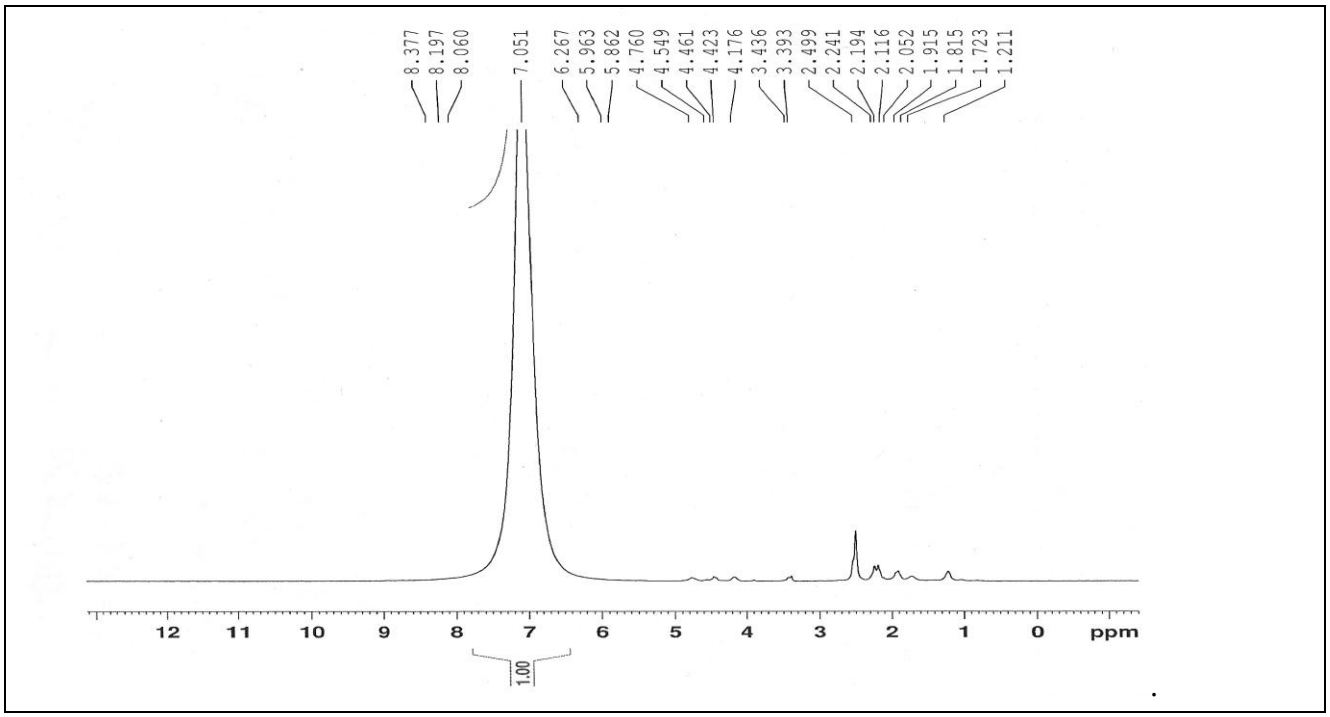


Fig (1) : ^{1}H-NMR spectrum of compound [11].

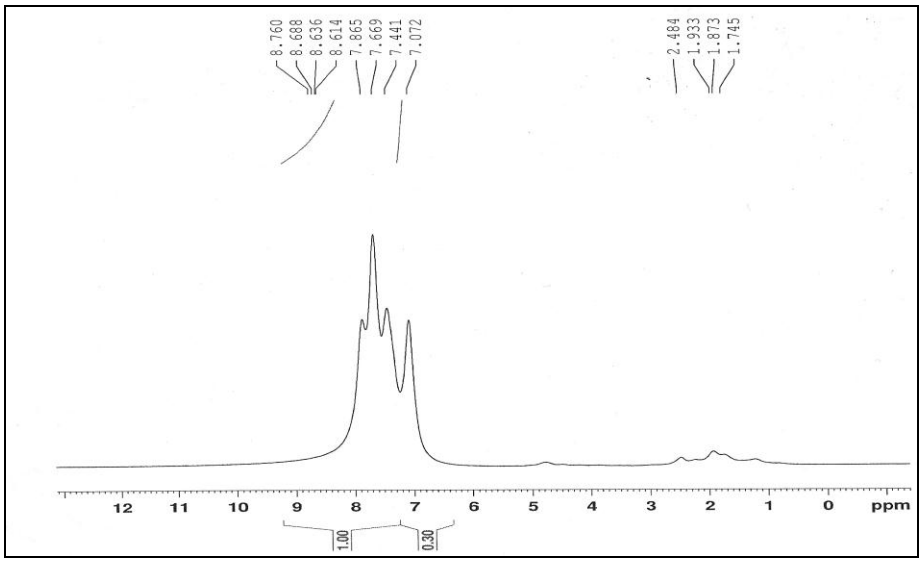


Fig (2) : ^{1}H-NMR spectrum of compound [12].

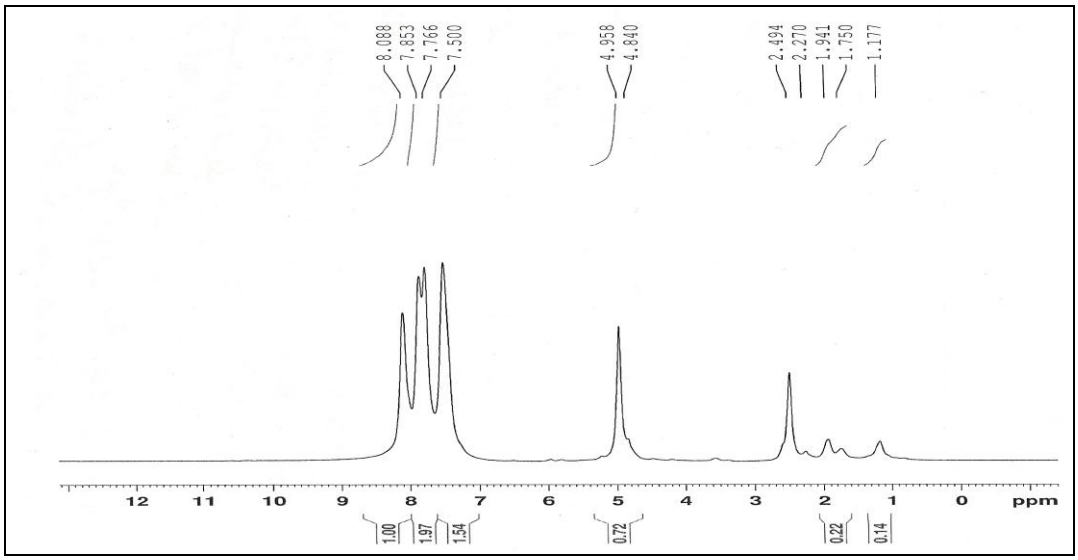


Fig (3) : ^{1}H-NMR spectrum of compound [10].

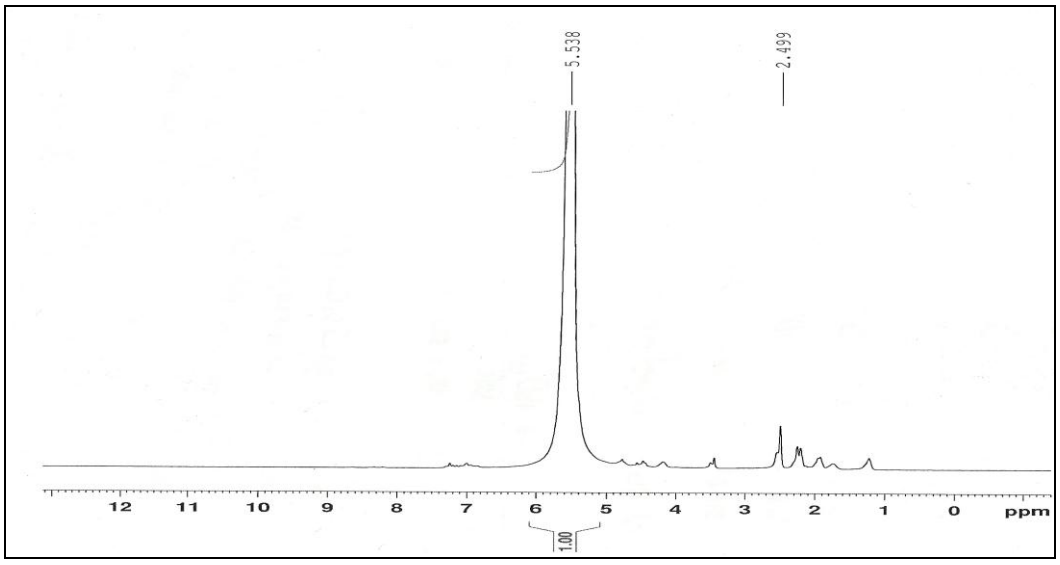


Fig (4) : ^{1}H-NMR spectrum of compound [9].