Synthesis , characterization of some new heterocyclic compounds and evaluating their biological activity

Ibtisam K.Jassim* ,Shaymaa A. Suood* and Fawzi H. Jumaa**

* Department of Chemistry,College of Education –Ibn-Al-Haitham,University of Baghdad.Baghdad.

** Department of Chemistry,College of Education –for girls,University of Tikrit.Tikrit.

(K . J . Pharm . Sci)

(Received May 2011 , Accepted Nov. 2011)

Abstract

This work involves synthesis of some heterocyclic compounds including 2- amino-5-[(3,5-dimethyl phenoxymethylene)-1,3,4-thiadiazole [3]. 2-(substituted benzylidene)-1,3,4-Thiadiazole -5- (3,5-dimethyl phenoxy methylene [4,5]. 2- [*p*-nitro or *p*-dimethyl amino phenyl]-3- (1,3,4-thiadiazole-2-yl-5-{3,5-dimethyl phenoxymethylene}) imidazolidine-4-one [6,7]. 2-[*p*-nitro or *p*-dimethyl amino phenyl]-3- (1,3,4-thiadiazole-2-yl-5-{3,5-dimethyl phenoxymethylene}) thiazolidin-4-one [8,9].

The prepared compounds were characterized by spectral methods FT-IR , ^{1}H-NMR and some physical properties with evaluation of their biological activity.

تحضير وتشخيص بعض المركبات الغير متجانسة الجديدة وتقييم فعاليتها الحيوية

ابتسام خليفة جاسم* شيماءعبد سعود* فوزي حميد جمعة **

* قسم الكيمياء / كلية التربية-ابن الهيثم /جامعة بغداد .

** قسم الكيمياء / كلية التربية للبنات /جامعة تكريت.

الخلاصة

تم في هذا البحث تحضير عدد من المركبات وهي 2-امينو-5-(3,5-ثنائي مثيل فينوكسي مثيلين-1و3و4-ثايلدايزول (3) . 2-بنزليدين معوض,1,3,4-ثايادايزول-5-3,5-ثنائي مثيل فينوكسي مثيل(4,5) . 2-(بارا نايترو او بارا ثنائي مثيل امينو فنيل-3-(1,3, 4 ثايادايزول -2-يل-5-(3,5-ثنائي مثيل فينوكسي مثيلين)اميدازولين -4-اون(6,7) . 2-(بارانايترو او باراثنائي مثيل امينو فنيل)-3-(1,3,4-ثايادايزول)-2-يل -5-(3,5-ثنائي مثيل فينوكسي مثيلين)ثايازوليدين-4-اون (8,9) .

شخصت المركبات المحضرة عن طريق اطياف FT-IR ,H-NMR وبعض الخصائص الفيزيائية كما قيمت الفعالية الحيوية

Introduction

Heterocyclic compounds like 1,3,4-thiadiazoles 1,3,4-triazoles 1,3,4-oxadiazoles constitute a potential class of compounds which posses a broad spectrum of biological activity[1-4] ,involving antimicrobial , anticonvulsant, and antinflamatory [5-7].

2-amino-1,3,4-thiadiazoles have a great role in medical and industrial applications[8]. A great number of variously substituted 1,3,4-thiadiazole derivatives have been synthesized and tested for their fungicidal[9]nematocidal[10]antibacterial[11] and anti-inflamatory activities[12] . Some polymers containing thiadiazole ring have been synthesized and found that these polymers have biological activity also[13]. Schiff bases, result from condensation of primary amines with aldehydes or ketones. Due to great flexibility and diverse structural aspects, a wide range of Schiff bases have been synthesized and their complexation behavior studied[14]. Furthermore Schiff bases are reported to show a variety of interesting biological activities[15].

Imidazole drugs have broadened scope in remedying various dispositions in clinical medicine[16],it was found that interconnecting the imidazoline and phenyl ring, as was achieved in 2,3-dihydroimidazole [1,2-a] benzimidazole or 1,2,3,5-tetrahydro-imidazoline [2,1-b] quinazoline afforded capable of lowering the blood pressure of experimental animals[17].

Thiazolidinones are derivatives of thiazolidines with carbonyl group in the 4-position[18]. Ahmed et.,al.,[19] and Mohaned[20] et.,al.have prepared some new thiazolidinones from the reaction of Schiff bases and thioglycolic acid in benzene and found that these compounds have biological activity against some bacterias. In continuation with our previous researches[21] ,we have synthesized some thiadiazole,Schiff bases ,imidazol and thiazolidinones.

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 ,Univrsity of Baghdad.
3- ^{1}H –NMR spectrum (DMSO) was recorded on BRUKER-av-300 instrument with TMS as an internal standard,University of Al-Albayt,Jordan.

3- Thin layer chromatography (TLC) was carried out, and the plates were developed with iodine vapour.
4- The biological activity was performed by Biotechnology Department, Tikrit University .

Methods

1-Synthesis of ethyl 3,5-dimethyl phenyl acetate [2][(22)].

3,5-dimethyl phenol (0.01mole) was dissolved in absolute ethanol (100ml) with (0.01 mol) of potassium carbonate and heated in a water bath. 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).

3-Synthesis of 2- amino-5-[(3,5-dimethyl phenoxymethylene)-1,3,4-thiadiazole [3][(23)].

A mixture of ethyl 3,5- dimethyl phenylacetate (0.01mole) ,thiosemicarbazide (0.01mole) and (10 ml) phosphorous oxy chloride was refluxed for 5 hrs. The cold reaction mixture was poured on crushed ice and neutralized by adding sodium hydroxide solution. The resulting solid was filtered and re-crystallized from chloroform to give a white crystals of amino thiadiazole [3].

4- Synthesis of 2-(substituted benzylidene)-1,3,4-Thiadiazole -5- (3,5-dimethyl phenoxy methylene (4,5) [(24)].

A mixture of compound [3] (0.01mol) and substituted benzaldehydes (0.01mol) was refluxed in absolute ethanol (15ml) containing few drops of glacial acetic acid for 3hrs. After cooling to room temperature the precipitate was filtered and dried. The products were re-crystallized from ethanol. (Yield 80%).

5-Synthesis of 2- [*p*-nitro or *p*-dimethyl amino phenyl]-3- (1,3,4-thiadiazole-2-yl-5-{3,5-dimethyl phenoxymethylene}) imidazolidine-4-one.(6,7)[(25)]:

A mixture of Schiff's base (0.01mole) and glycine (0.01 mole in 20 ml THF was refluxed for 24 h then it was cooled to room temperature then the precipitate was filtered and re-crystallized from ethanol and THF .

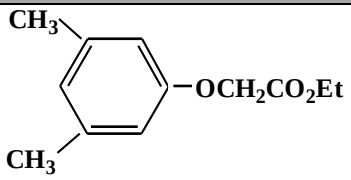
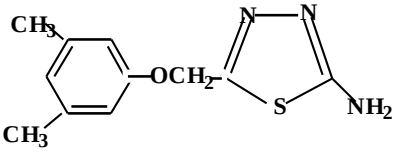
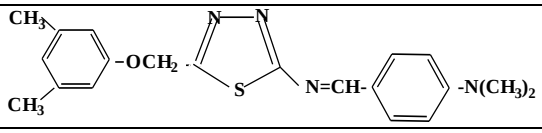
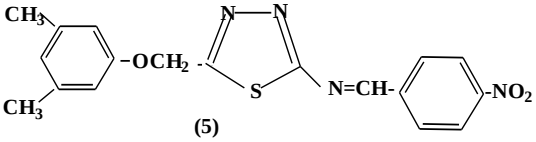
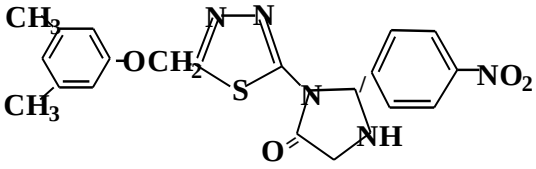
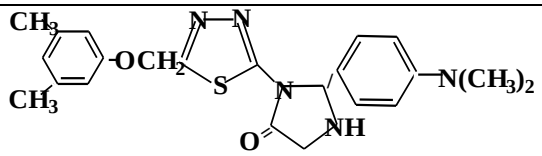
6- Synthesis of 2-[*p*-nitro or *p*-dimethyl amino phenyl]-3- (1,3,4-thiadiazole-2-yl-5-{3,5-dimethyl phenoxymethylene}) thiazolidin-4-one .(8,9)[(26)]:

A (0.01mole) of 2-mercapto acetic acid was added dropwise to (0.01mole)of

Schiff's base in dry benzene , the mixture was refluxed for 24 h., the solvent was evaporated and the precipitate was re-crystallized from ethyl acetate and benzene.

Physical properties of compounds [2-9] are listed in Table (1).

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

Comp.No	The structure	Yield %	M.P ^{0}C	Colour	Recryst. solvent
2		**75**	145	white	EtOH
3		60	154-156	white	EtOH
4		75	163-165	yellow	EtOH
5	 (5)	80	158-160	yellow	EtOH
6		65	117-119	White	EtOH
7		60	168-170	white	EtOH

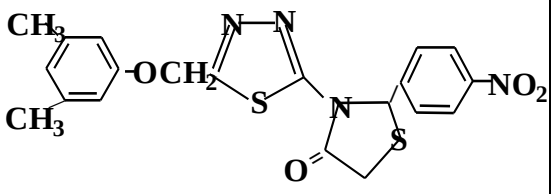
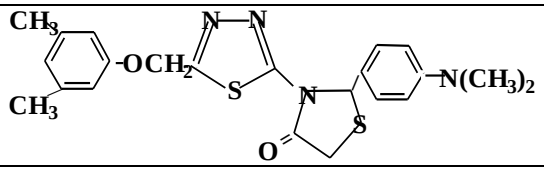
8		67	165-168	Off white	EtOH
9		65	208-210	White	EtOH

Table (2): FT-IR spectral data for the prepared compounds.

Comp. No.	υ(N-H) cm^{-1}	υ(C-H) Aliphatic. cm^{-1}	υ(C=O) cm^{-1}	υ(C=N) cm^{-1}exo	υ(C-H)Ar cm^{-1}	Others
3	**3450**	**2920**	**-**	**1620**	**3090**	-
4	**-**	**2895**	**-**	**1610**	**3105**	**$N(CH_3)_2$** υ(N-Me) 1373
5	**-**	**2900**	**-**	**1620**	**3095**	υ(NO_2) 1350-1415
6	**3320**	**2910**	**1630**	**-**	**3108**	
7	**3310**	**2930**	**1630**	**-**	**3100**	
8	**-**	**2912**	**1635**	**1600**	**3090**	
9	**-**	**2900**	**1620**	**1600**	**3095**	

Results and discussion

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 (2). FT-IR spectrum shows the band at 1720 $cm^{-1}$for υ(C=O) of ester, 2920 $cm^{-1}$for (C-H) aliphatic [27], and disappearance of υ(O-H) absorption band of phenolic group.

The compound [2] was converted to Thiadiazole derivative [3] by the reaction of ester with Thiosemicarazide in $POCl_3$. The FT-IR spectrum of compound [3] showed bands at 3450 cm^{-1}asym. and sym, for NH_2 group and at 1620 for (C=N) group . ^{1}H-NMR spectrum of compound (3) showed the signals at 1.3ppm for DMSO also at δppm 2.25-2.91(S,2H,-CH_2 -); 4.39 (broad,2H,-

NH_2); (6.9-8) (m,3H,Ar-H) fig (1) .Compounds (4) and (5) were prepared from the reaction of (3) and appropriate benzaldehydes in presence of glacial acetic acid. The FT-IR spectrum of compound (4) exhibited the stretching band at 1610 cm^{-1}due to C=N bond besides the disappearance of υ(C=O) band of the aldehyde and disappearance of N(NH_2) band at 3450 cm^{-1}.

Imidazolidine derivatives prepared by the heating of Schiff bases derivatives with glycine (α –amino acetic acid)in THF ,the products were identified by the FT-IR spectra which show the appearance of NH vibration in 3320 $cm^{-1}$and the disappearance of υ (C=N) band in 1610 and 1620 cm^{-1}.

Thiazolidinone derivatives prepared by the reaction of Schiff bases and mercaptoacetic acid in dry benzene ,the products were characterized by FT-IR spectroscopy and the melting points ,TLC were determined . The FT-IR spectrum of compound (8) showed the appearance of the υ(C=N) absorption band in 1600 cm^{-1}.

Microbiological tests:

In this work, the antibacterial test was performed according to the disc diffusion method. Compounds (3-9) were assayed for their antimicrobial activity in *vitro* against Gram-negative bacteria and Gram-positive bacteria (*Escherichia coli , staphylococcus aurous, Sal. typhi,a*nd *Ps. aerugenosa*). Prepared agar and Petri dishes were sterilized by autoclaving for 15min at 121C°. DMSO was used as a solvent. These plates were incubated at 37C° for 24h for both bacteria. The inhibition zones caused by the various compounds were examined. The results of the preliminary screening tests are listed in table (3).

The biological activity test showed that compounds with free (-NH_2) groups having a biological effect on each of *E.Coli* and *Staph.aureus* .

Table (3) :Antimicrobial activity for some prepared compounds .

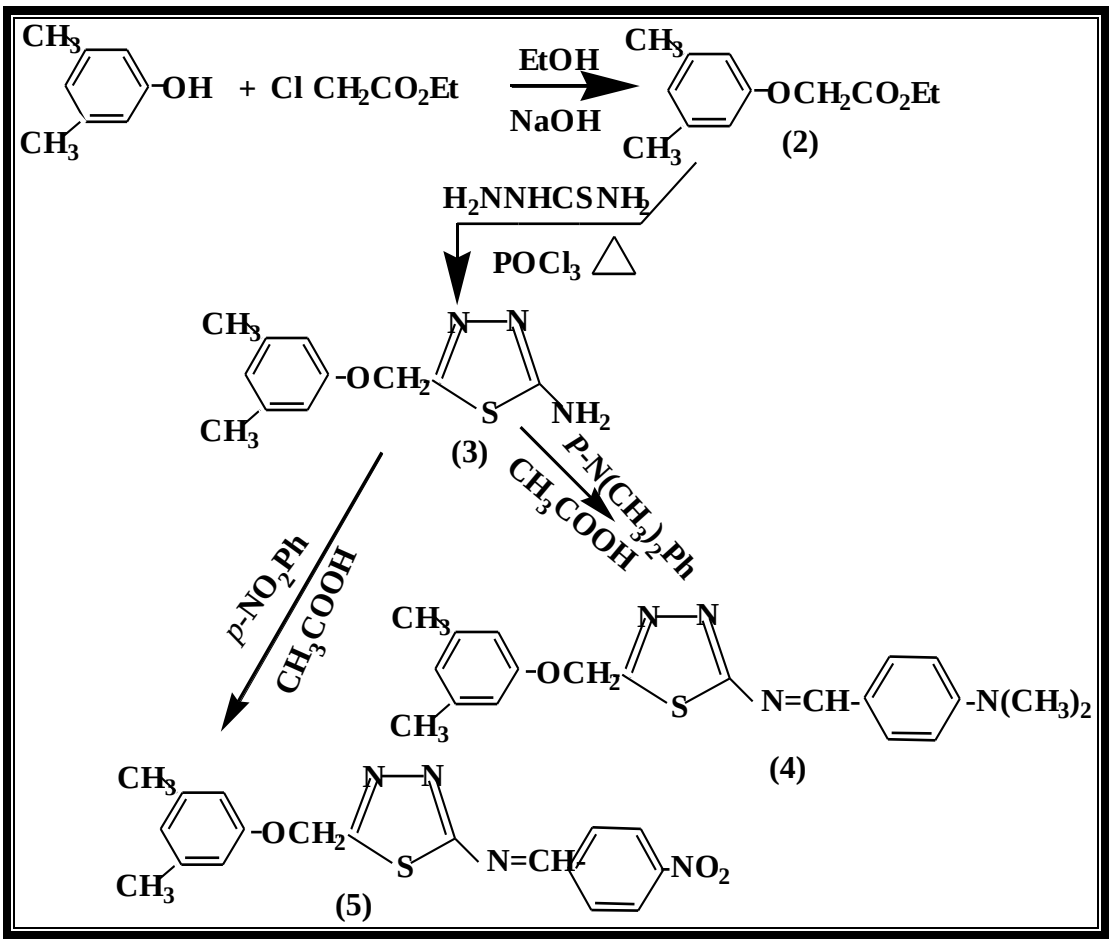
Comp. No.	*Staph. aureus*	*E. coli*	*Sal. typhi*	*Ps. aerugenosa*
3	+	++	++	++
4	-	+	+	-
5	-	+	-	+
6	+	+	+	+
7	-	+	-	-
8	+	++	-	+
9	+	+	-	+

Key the symbols :(-) = No inhibition , (+) = 5-10 mm, (++) = 11-20 m.

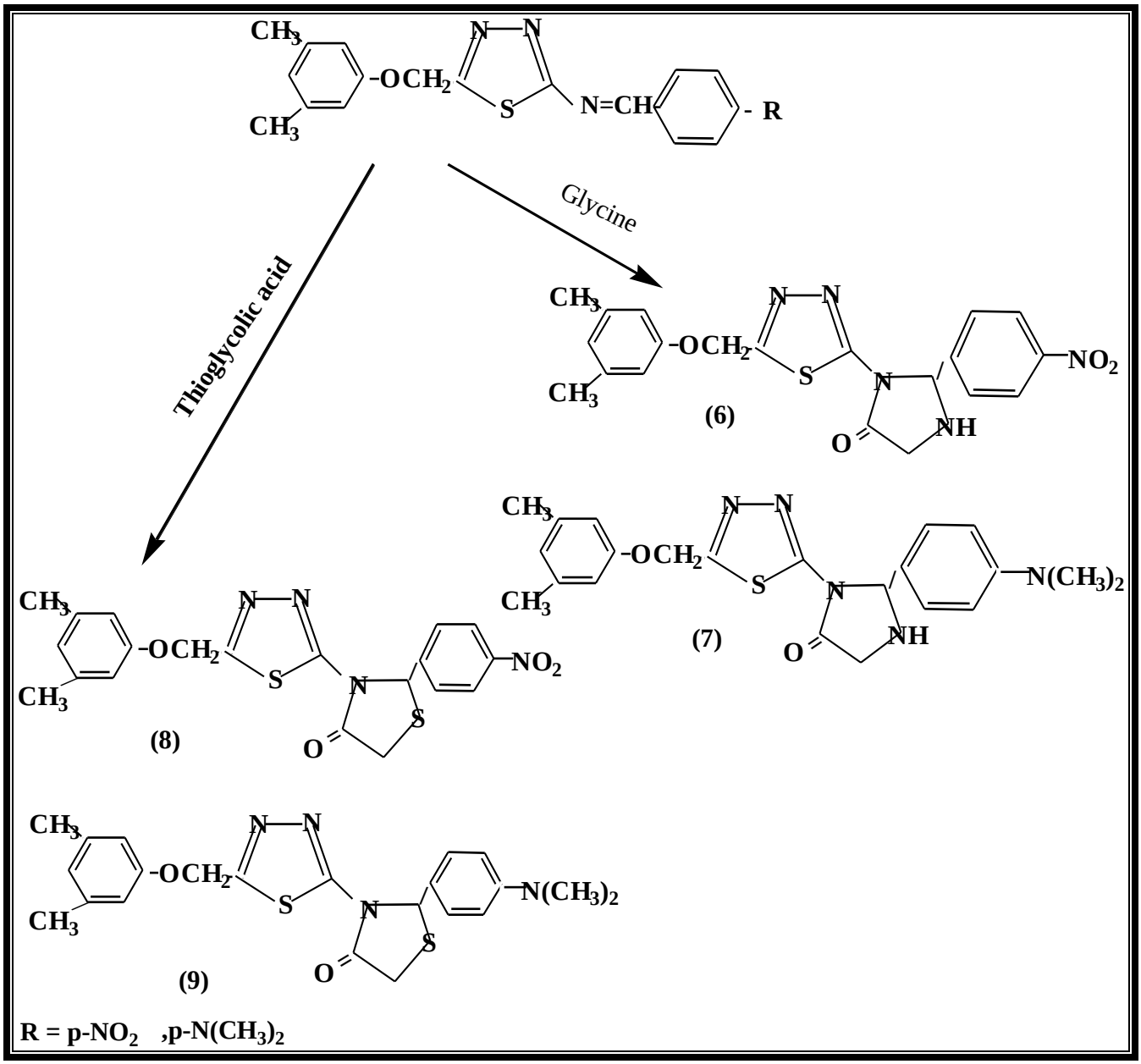
Note:
- = No inhibition = inactive
+ = (5-10) mm = slightly active
++ = (11-20) mm = moderately active

Conclusion

1. Compounds [6] showed slightly activity on *E*scherichia coli, Staph.aureus and *S*al. Typhi.
2. Compounds [3] showed slightly activity on *Staphylococcus aureus*, while on *E*scherichia coli, *Sal. Typhi a*nd *Ps. aerugenosa* ,its moderately active .
3. Compound [8] showed slight activity on these bacteria.



Scheme 1.



Scheme 2 .

References

1-L.Z.Xu,k.Jioo,S.S.Zhang and -1 S.P.Kuang,Bull-Korean chem..Soc.,23,12 (2002).

2-Liang-Zhangxw Shu-sheng Zhang, shu-Yon Nia, Xong-Qi Qin, xuemei Li and Kuii Jiao, Moleules, 9,913 (2004).

3-Khosrow Zamani, Khalil Faghihi,Taraeh Tofighi, Mohammad rezas Hariatzadeh, *Turk. J.Chem.*,28,913 (2004).

4-Mohye Abdel-Fatah and Ibrahimm El-Deen, *Indian J. Chem.*, 35B, 1067 (1996).

5-A.Shafiee, A.Reza and M.Sharifaoleh , *Daru*, 11(2), 15 (2003).

6-P. Coudert, E. Albusson, J.Y. Boir and P. Bastide, *Eur. J. Med. Chem*., 29,471 (1994).

7-Ruaa M. Al-Juburi ,MSc Thesis, University of Al-Nahrain (2006).

8-. H. l. Yalc and k. Losee, *J.* Med. Chem., **9**, 478 (1966).

9. J. Wang and D. Ming, *J.Tetrahedron Asymmetry*, **15**, 119 (2004).

10- T. H. Chan and G. Z. Zhang, Can, *J. Chem.*, **75**, 629 (1997).

11-. A. K. Chosh, P. Mathivanan, Cappiello, *J. Tetrahedron Asymmetry*, **9**, 1 (1998).

12-. H. J. Zhu, B. T. Zhao, W. M. Dai, J. Zhau and X. J. Hao, *J. Tetrahedron Asymmetry*, **9**, 2879 (1998).

13-Ibtisam K.J, Khalida A.O and Gazwan H.,*Tikrit Jof pure Science* Vol. 13 (2)(2008).

14-P.G.More, R.B.Bhalvankar and S.C.Pattar,*J. Ind. Chem. Soc*.,78,7474(1988).

15-F.D.Karia and P.H.Parsania, *Asian J.Chem*., 11,991(1989).

16-C.Kus and N.Altaular, Turk.J.Chem., 27,35 (2003).

17-Z.Kang, C. dykstra and D. Boykin, *Molecules*,9,35(2003).

18-J.A. Mohan, G. S. Anjaneyulu and R. Kiran, *Indian J. Chem*., 27B,128(1988).

19-Ahmed TH.S,PhD Thesis,University of Al-Nahrain (2008).

20-Mohaned A.M,PhD Thesis, University of Baghdad (2010).

21-Ibtisam K.J, Susan H.,Ruaa M.D,JTikrit .Pharmaceutical Science(in press).

22- A. I. Volgel, "Practical Organic Chemistry", **3**, (1945)., E. S. El- Tamaty, M. E. Abdel- Fattah and I. M. El- Deen, Indian *J. Chem. **35 B**, 1067 (1996).*

23- Suaad M.H Al-Majidi and Zainab A.K.Al-Messri,J.Al-Nahrain,Vol.10(1),30 (2007).

24-S.A. Nassar, M.A. El-Hashsash,Egypt J. Chem.,40,239(1997).

25-K.D.Berlin and M.D.Hherd
Proc.Okla.Acad.Sci. 71,29 (1991).
26-A.H.El-masry, H.H.Fahmy and S.H.Ali Abdelwahed,Molecules (5)1429 (2000).
27- Silverstein R.M.,Bassler G.C.and Morrill T.C., Spectrometric Identification of organic compounds 4th ed .,,john ,Wiley and Sons (1980).

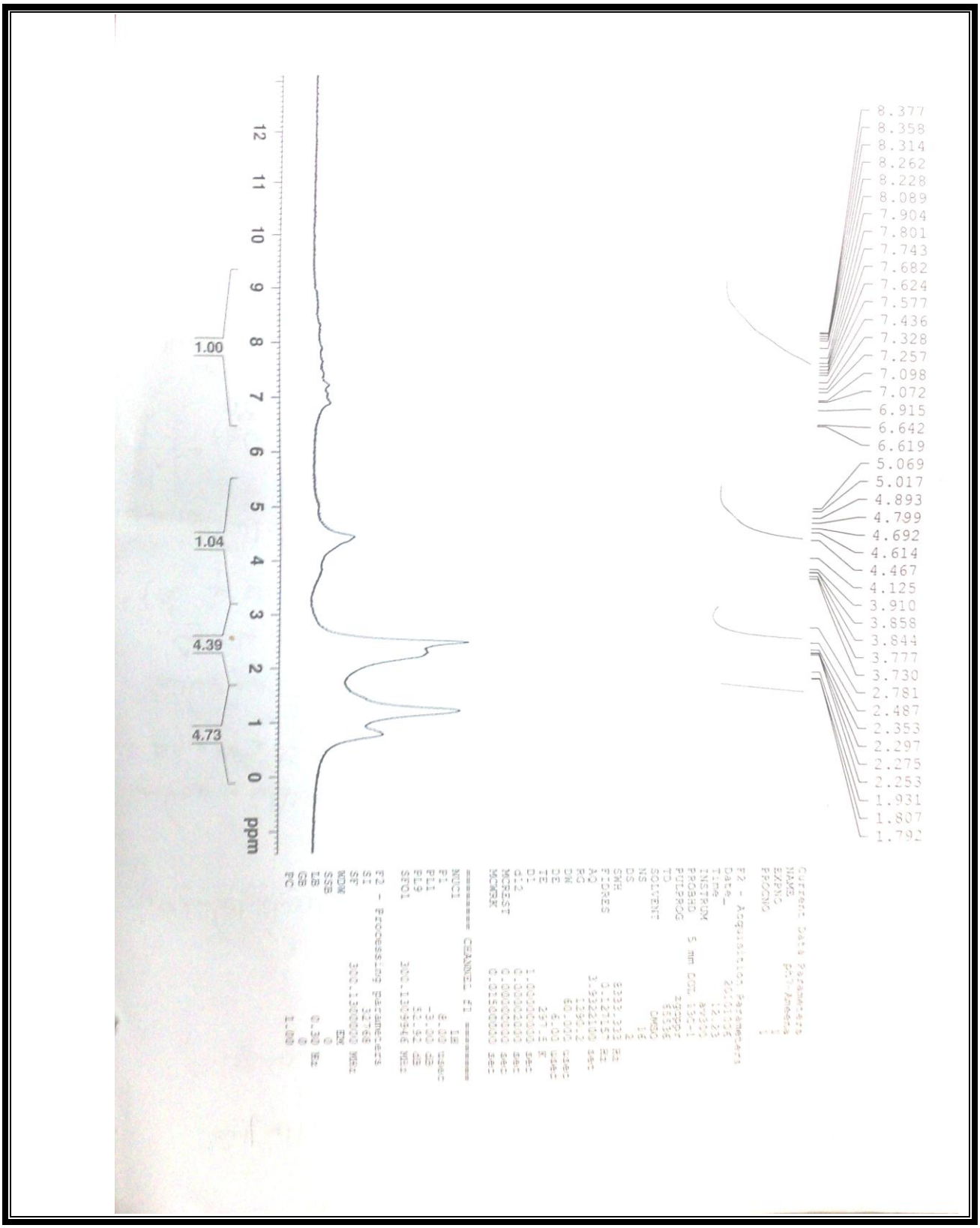


Fig.(1a): H-NMR spectrum of compound 3.

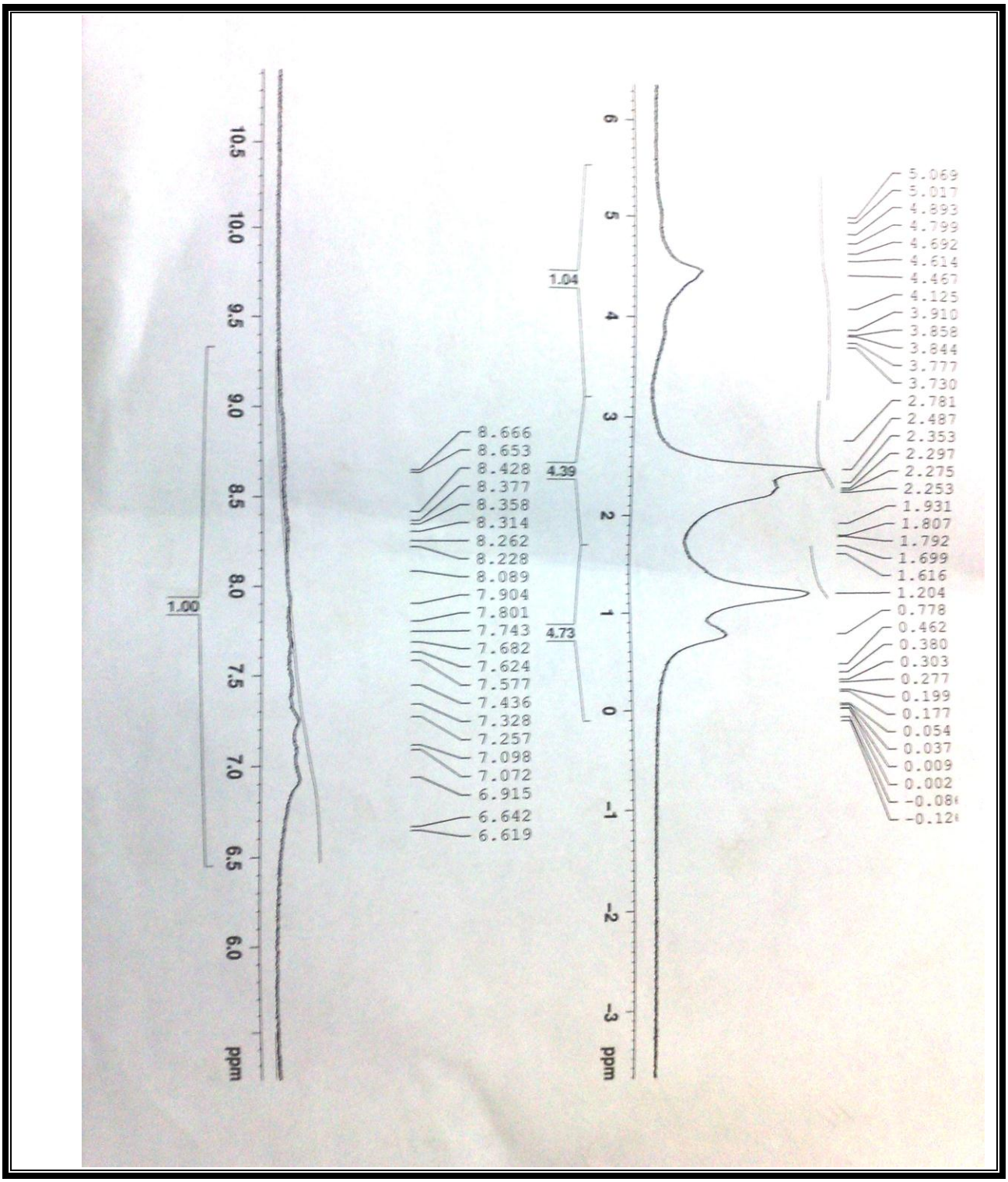


Fig.(1b): H-NMR spectrum of compound 3.