Synthesis Identification & Biological Study of New Derivatives of 1,3,4-Thiadiazol, 1,3,4-Triazol and 1,3,4-Oxadiazol.

Kasim Mohammed Hello

Dep. of Chemistry, Collage of Sciences, Al-Muthanna University

(NJC)

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Abstract

In this present work a novel derivatives of 1,3,4-Triazol, 1,3,4-Thiadiazol and 1,3,4-Oxadiazol were prepared via aromatic Schiff's bases. The new prepared compounds identified by their m.ps, I.R, UV-Visible and H.N.M.R spectra.

The activity of 1,3,4-Triazol(7) , 1,3,4-Thiadiazol(8) and 1,3,4-oxadiazol(9) were tested against *E.coli, Staphyllococus aureus, Klebsilla spp, Streptococcus pyogen, Listeria Moncytogen, Sallmonela typhi., Pseudoms aerugenosa* and *Brucella.*

الخلاصة

في هذه الدراسة حضرت مشتقات جديدة للحلقات الخماسية غير المتجانسة4,3,1- ثاياديـازول، 4,3,1- ترايزول و4,3,1 – اوكساديازول المعوضة من خلال قواعد شف الأروماتية وقد شخصت المركبـات المحـضرة بقياس نقاط الانصهار وأطياف الاشعه فوق البنفسجية- المرئية وأطياف الأشعة تحت الحمراء وكذالك أطياف الرنين النووي المغناطيسي لذرة الهيدروجين. كما تم دراسة الفعالية البيولوجية للمركبات المحضرة تجاه ثمان عتر مختلفـة من البكتريا وقد أظهرت المركبات المحضرة فعالية بيولوجية تجاه معظم أنواع البكتريا المدروسة.

Introduction

Heterocyclic compounds are highly attractive compounds in the research and development of materials for organic chemistry. Several methods have been reported in the literature for the synthesis of 1,3,4-thiadiazole, 1,3,4-triazole and 1,3,4-oxadiazle[1-3]. Thiadiazole oxadiazole and triazole derivatives are an important groups of heterocyclic compounds [2-3]due to which their chemistry and uses have been highlighted in numerous reports [3-4]. They have been used in a wide variety of biological applications [4] such as anti-bacterial [5], fungicidal [6], anti inflammatory [7], herbicidal [8], antiviral (against Dengue and Junin virus) [9] and treatment of breast cancer [10].

The choice of heterocyclic ring substituents was based on literature reports where the increase of biological activity in several compounds was related to the presence of asymmetric centers [11] and/or halogens in their structure [12].

In view of the above-mentioned findings, the purpose of the present work was to design, synthesize and investigate the in vitro antibacterial activities of some novel 1,3,4-thiadiazole, 1,3,4-triazole and 1,3,4-oxadiazole derivatives.

Experimental

Melting points were determined by Stuart melting point apparatus and uncorrected; IR spectra were recorded on a Shimadzu FT-IR 8400S spectrophotometer using KBr discs, UV-Visible. spectra were recorded on Shimadzu UV-Visible Recorder Spectrophotometer 1665PC. in the 190 - 1000 nm range, using 10^{-3} M solution of compounds in DMF as a solvent for the compounds(7, 8, 9) and the others by ethanol. The ^{1}HNMR spectra were recorded on a Bruker 400 MHz in Baath university collage of science in Syria, $CDCl_3$ was used as solvent and TMS as internal reference.

1-Synthesis of Schiff Base (1) :-

A mixture of 0.01 mole (0.93 ml) of aromatic amine (aniline), 0.01 mole (1.1ml) of aromatic aldehyde (benzaldehyde) , 10 ml ethanol and one drop of glacial acetic acid, was refluxed for 30 min. then left to cool in a bath of ice-water, whereby yellowish white crystals separated out . The crystals were filtered, washed with 2% HCl, then with water and recrystallized from ethanol absolute [13].

2-Synthesis of N-α-chlorobenzyl-N-phenylglycine (2):-

To 0.011 mole (1.9gm) of Schiff base in 10 ml of dry benzene was added 0.011 mole (1.03gm) of chloroacetic acid and the reaction mixture was refluxed for 1hr. The solvent was evaporated and the remaining green crystals was separated and recrystallized from ethanol- water (1:1) [14].

3-Synthesis of N-α- chlorobenzyl-N-phenylglycinoylchloride (3):-

A mixture of compound (2) 0.009 mole (2.48gm) and excess from thionyl chloride and 3 drops of DMF was refluxed gently for 2hr. After cooling, the excess of thionyl chloride was removed under vacuum and recrystallized from trihydrofurane (THF).

4-Synthesis of N-α-chlorobenzy-N-phenylglycinoylthiosimicarbazone (4)

To a stirring mixture of compound (3) 0.007 mole (2.02gm) in pyridine, a 0.007 mole (0.63gm) of thisimicarbazide and two drops of DMF was added, after that the mixture was stirring for 24 hrs. The a few drops of water was added. The crystals was filtered and recrystallized from ethanol absolute.

5- Synthesis of 2-(N-α-chlorobenzyl-N-phenyl)N-methyl-5-thiao-1,3,4-traiazol (7) :-

A compound (4) 0.0048 mole (1.7gm) was refluxed with NaOH solution (20 ml,4%) for 3 hrs., cooled, poured into excess of water, stirred and the crystals was filtered and the recrystallization has been done by THF.

6- Synthesis of 2-(N-α-chlorobenzyl-N-phenyl)-N-methyl-5-amino-1,3,4-thiadiazol(8) :-

A compound (4) 0.0048 mole was dissolved in cold concentrated H_2SO_4 and the continuer were kept at room temperature for 24 hrs. with stirred. After that a few drops of water was added and the crystals was filtered and recrystallized from THF.

7- Synthesis of N-α-chlorobenzyl-N-phenyl-N-acetinoyl hydrazide(5):-

To a stirring mixture of compound (3) 0.005 mole (1.5gm) in pyridine, a mixture of hydrazine hydrate (99%) 0.005 mole (0.2ml) and pyridine 10 ml was added drop wise. After that, the mixture was refluxed for 1hr. After cooling, a few drops of water was added and the crystals

was filtered and recrystallized from ethanol absolute.

9- Synthesis of 2-(N-α-chlorobenzyl-N-phenyl)-N-methyl-5-thiaol-1,3,4-oxadiazol (9) :-

A mixture of compound (5) 0.0049 mole (1.3gm), KOH 0.0049 mole (0.27gm) was dissolved in ethanol. Then CS_2 0.0049 mole (0.3ml) was added drop wise. After addition, the reaction mixture was refluxed with stirred for 3 hrs. after cooling, the obtained solid was filtered off, dried and used as such further reaction. This solid was dissolved in ice cold water, after that, a few drops of concentrated HCl was added. The crystals was filtered and recrystallized from THF.

Biological Test:

1) Bacteria strain :

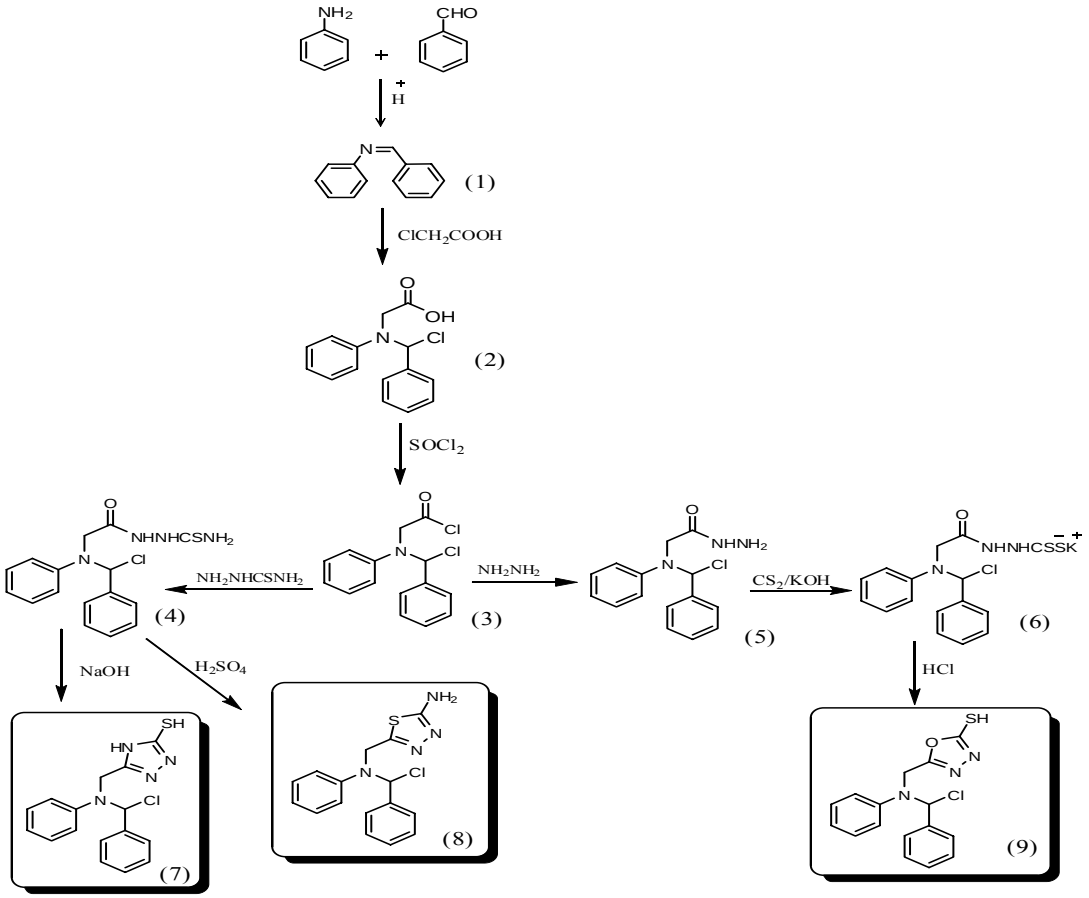
All of bacteria strain were obtained from biology department, collage of sciences Al-muthanna University . The bacteria cultured in nutrient Moller-Hanten agar at 37 C^o, (0.5 ml) of each bacteria was spread over surface of Moller- Hanten agar [15].

2) Antibacterial activity :

Disc of filter paper (6mm) were sterilized at 140 C^o for 1 hr. and impregnated with (1ml) of a concentration (10, 1, 0.1, 0.01) mg\ml of solution of each compounds and then dried, dry Dimethylsulphoxide (DMSO) was used as a solvent for all compounds and blank disc, of DMSO were used as a control. The inoculated plate were incubated at 37 C^o for 24 hrs., and the inhibition zones were measured in all experiments, the mean of each triplicate was measured [16-19]. All data listed in table (3).

Results and Discussion

The synthetic strategies adopted to obtain the target compounds are depicted in Scheme 1 .



Scheme (1) summarizes all reactions in this work.

In this paper primary aromatic amine (aniline) reacted with aromatic aldehyde (benzaldehyde) to give Schiff base (1), the reaction is usually catalyzed by a drop of glacial acetic acid [16]. The reaction is followed by appearance of C=N at 1630 cm^{-1} in their FT-IR spectra. We found that schiff base reacted with α-chloroacetic acid to give N-α-chlorobenzyl-N-phenylglycine (2). The reaction is followed by disappearance of C=N at 1630 cm^{-1} and appearance of O-H at 3500 - 3250 cm^{-1} and appearance of C-Cl at 750 cm^{-1} in their FT-IR spectra. The ^{1}HNMR of compound (2) showed : δ(ppm) 4.3 (s, 2H, $-CH_2$) , 6.7(s, 1H, -CHCl) ,7-8.5 (m,10 H, Aromatics), 9.8 (s,1H, -OH) see fig.(1). The peaks at 0.9-2.0 ppm could be impurity in the compounds. Table (1) show all physical data, the major FT-IR absorption of compound (2) is given in Table(2).

The N-α-chlorobenzyl-N-phenylglycinoyl chloride (3) is prepared by the reaction of (2) with thionyl chloride. The reaction is followed by disappearance of O-H at 3500 – 3250 cm^{-1} and appearance of C=O at 1750 cm^{-1} in their FT-IR spectra.

It is found that the thiosimicarbazide reacted with compound (3) to give N-α-chlorobenzyl-N-

phenylglycinoylthiosimicarbzone (4) as a thiosimicarbzone derivatives (4). The reaction is followed by appearance of NH_2 at 3430 - 3400 cm^{-1} and appearance of NH at 3300 cm^{-1} and appearance of C=S at 1210 cm^{-1}in their FT-IR spectra .

The cyclization of thiosemicarbazone derivative(4) with NaOH give, 3,4-Traiazol derivative(7). The FT-IR spectra of compound (7) showed appearance of SH at 2650 cm^{-1} and appearance of C=N at 1620 cm^{-1}. The ^{1}HNMR of 1,3,4-Traiazol derivatives (7) showed:- δ(ppm) 6.5(s,1H,CHCl), 4.4(s, 2H, -CH_2), 1.9(s, 1H,NH), 7-8 (m,10 H, Aromatics), 12(s,1H,SH). See fig.(2). When we compare the ^{1}H.N.M.R spectrum of compound (7) with the spectrum of compound (2) we found that the signal for OH proton was missing and the signal for NH,SH proton was present see fig.(1,2) simply we can concluded the successful reaction has been done .

The cyclization of thiosemicarbazone derivative(4) with H_2SO_4 give 1,3,4-thiadiazol derivative (8). The FT-IR spectra of compound (8) showed appearance of NH_2 stretching at 3400 - 3380 cm^{-1} and appearance of C=N at 1630 cm^{-1}.

It is found that the compounds (3) reacted with hydrazine hydrate to give N-α-chlorobenzyl-N-phenyl-N-acetinoyl hydrazide (5). The FT-IR spectra of compound (5) showed appearance of NH_2 stretching at 3500 - 3460 cm^{-1} and appearance of NH at 3300 cm^{-1} .

The xanthat salt (6) is prepared by the reacted of (5) with CS_2 in KOH. The FT-IR spectra of compounds (6) showed appearance of C=S at 1200 cm^{-1} and disappearance of NH_2 at 3600 cm^{-1}, dissolved of compound (6) in water make us a good sign that we are on the correct way in the synthesis. The cyclization of compound (6) with HCl give 2-(N-α-chlorobenzyl-N-phenyl)-N-methyl-5-thiaol-1,3,4-oxadiazol (9), the FT-IR showed appearance of SH at 2400 cm^{-1} and appearance of C=N at 1640 cm^{-1} and disappearance of C=S at 1200 cm^{-1}.

All bacteria showed higher sensitivity against compound (7),(8) and (9) except *E.coli* and *Ps.aerugenosa* showed resistance against (7) and (8). *Klebsilla spp.* and *Staph aureus* showed resistance against compound (8) and (9). *Listeria Moncytogen* showed resistance against compound (8). The anti bacteria activity diameter of inhibition zone is shown in table (3).

Table (1) physical properties for the compounds 1-9.

Comp. No.	m.p C^o	Yield %	λ_{Max} nm
1	50	80	217, 360
2	120-122	70	218, 350, 430
3	90-92	75.32	269,309,601,779
4	162-170	70.53	310,598,789
5	140	60	229, 339, 660,766
6	220-224	90.82	367, 530, 726, 790
7	258-260	69.43	334,385,443,780
8	70-75	53.13	249,312,598,780
9	190	65	307, 563, 665, 766

Table (2) FT-IR absorption bands for functional groups in KBr disc.

Comp. No.	Characteristic absorption bands υ cm^{-1}							
	NH_2	NH	OH	C=O	SH	C=N	C=S	C-Cl
1	-	-	-	-	-	1630	-	-
2	-	-	3500-3250	1700	-	-	-	750-700
3	-	-	-	1750	-	-	-	750-700
4	3430-3400	3300	-	1700	-	-	1210	750-700
5	3500-3460	3300	-	1700	-	-	-	700
6	-	3320	-	1700	-	-	1200	700
7	-	3300	-	-	2650	1630	-	600
8	3400-3380	-	-	-	-	1620	-	590
9	-	-	-	-	2400	1640	-	710

Table (3) Antimicrobial activity and diameter of inhibition zone(mm) of compound (7,8 and 9).

Type of Bacteria	Comp. No. 7	Comp. No. 8	Comp. No. 9
	10/1/0.1/0.01 mg/ml	10/1/0.1/0.01 mg/ml	10/1/0.1/0.01 mg/ml
E.Coli	-/-/-/-	-/-/-/-	7.1/6.7/6.5/6.4
Staph aureus	15/6/-/-	25/21/15/10	7.9/-/-/-
Klebsilla spp	-/-/-/-	30/25/16/7	-/-/-/-
Listeria Moncytogen	-/-/-/-	22/18/15/5	7.3/7/-/-
Streptococcus pyogen	22/15/-/-	15/5/-/-	6.5/6.4/-/-
Sallmonela	9.8/7/6.7/-	7.7/7.4/6.8/6.5	7.1/6.7/6.6/-
Ps. aerugenosa	-/-/-/-	-/-/-/-	7.8/7.4/6.7/6.5
Brucella	8.2/7.8/7.3/6.3	7.3/7.1/6.3/6	8.1/6.4/-/-

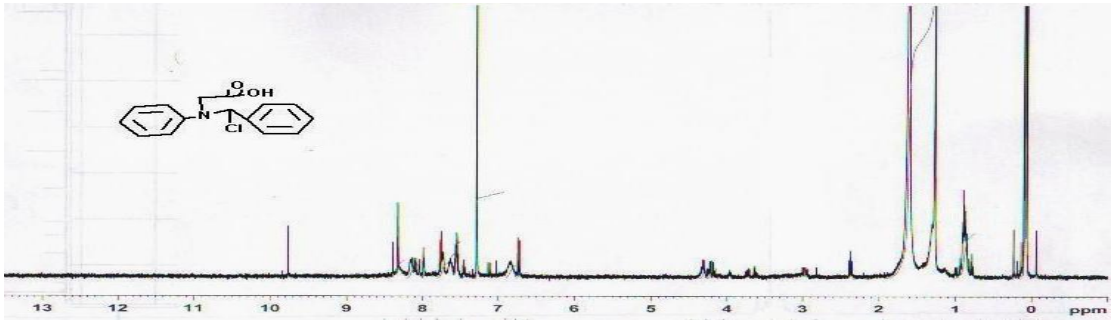


Fig (1) The HNMR of N-α- chlorobenzyl-N-phenylglycine(2)

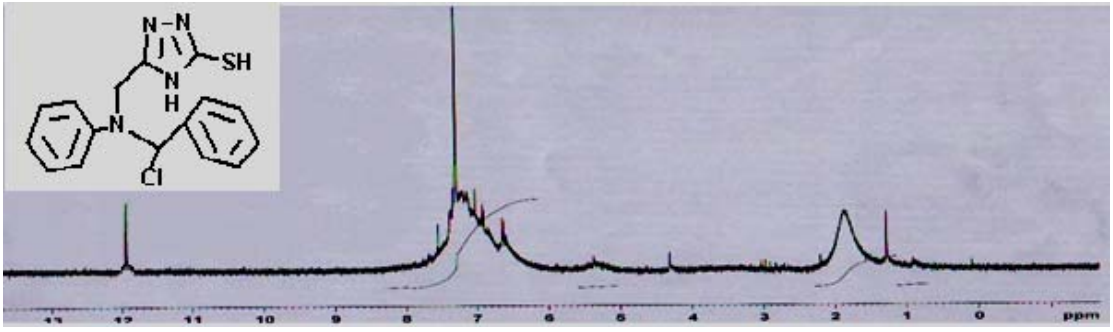


Fig (2) The HNMR of 2-(N-α- chlorobenzyl-N-phenyl) N-methyl-5-thiaol-1,3,4-traiazol. (7) :-

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