Synthesis and Biological evalution of some substituted 2-dibenzyl amino 1,3,4-oxadiazoles , thiadiazoles and 1,2,4-triazoles

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الخلاصة

تم في هذا البحث تحضير بعض معوضات 2 ثنائي بنزيل 1،3،4 – اوكسادايازول , ثايادايازول و1،2،4– ترايازول المشتقة من ثنائي بنزيل امين. تم مفاعلة ثنائي بنزيل الامين مع حامض كلورو الخليك لتعطي N , N – ثنائي بنزيل كلايسين (1) والذي حول الى مثيل / ايثيل استر (2, 3) . تم معاملة الاسترات مع الهيدرازين المائي في الايثانول ليعطي الهيدرازيد (4) والذي تفاعل مع ثايوسيانات الامونيوم ليعطي ثايوسيماكاربازيد (5). اعطت معاملة الثايوسيماكاربازيد مع حامض الكبريتيك المركز والهيدرازين المائي و 4 % هيدروكسيد الصوديوم ومع ايوديد البوتاسيوم واليود معوضات 1،3،4 – ثايادايازول (6) و1،2،4 – ترايازول (7) , 1،2،4 – ترايازول 3– ثايول (8) و5– امينو– 1،3،4 – اوكسادايازول (9) على التوالي.

تم معاملة الحامض (1) مع حامض الفوسفوريك المتعدد والهيدرازين المائي ليعطي1،3،4 – اوكسادايازول 5،2 – ثنائي التعويض (10), ومن ثم سلفنته ليعطي 1،3،4 – ثايادايازول ثنائي التعويض (11) بينما اعطت مفاعلة ا لهيدرازيد مع كلوريدات الحوامض ثنائي الكيتون (12 – 14)والتي تم حولقتها الى معوضات الاوكسادايازول(15 –17) والثايادايزول(18 – 20) بواسطة تفاعلها مع خماسي اوكسيد الفسفور وخماسي كبريتيد الفسفور على التوالي.

ABSTRACT

In this paper the synthesis of some substituted 2-dibenzyl 1,3,4-oxadiazole, thiadiazole and 1,2,4-triazoles derived from dibenzyl amine is reported scheme-1.

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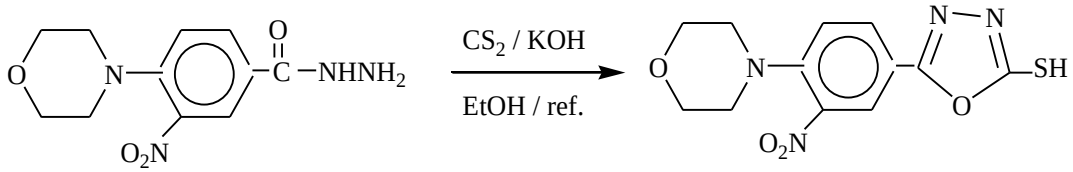
Dibenzyl amine was treated with chloroacetic acid to give N,N –dibenzyl glycine (1) which was converted to its methyl/ ethyl esters (2,3) .The esters were treated with hydrazine hydrate in ethanol to give hydrazide (4)which was reacted with ammounium thiocyanate to give thiosemicarbazide(5).Treatment of thiosemicarbazid(5)with concentrated sulfuric acid , hydrazine hydrate, 4% sodium hydroxide and with potassium iodide / iodine to gave substituted 1,3,4-thiadiazole (6) 1,2,4-triazole (7) 1,2,4-triazole -3-thiol (8) and 5-amino1,3,4-oxadiazole (9) respectively.

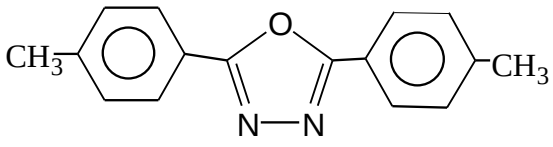
The acid (1) was treated with polyphosphoric acid and hydrazine hydrate to give 2,5- disubstituted oxadiazole (10), sulfonation of (10) gave disubstituted 1,3,4- thiadiazole (11). Hydrazides (4) was treated with acid chlorides to give thediketones (12-14) which cyclized to substituted oxadiazoles (15-17) and thiadiazoles (18-20) by their reaction with phosphorus pentoxideand phosphorus pentasulfide respectively.Some of the synthesized compounds were tested against various types of bacteria. The structures of the synthesized compounds were confirmed by physical and spectral methods.

INTRODUCTION

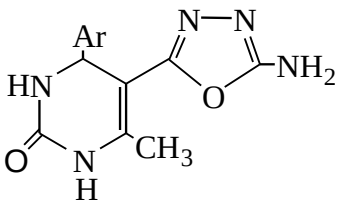
Five membered rings heterocyclic compounds as 1,3,4 – oxadiazole, thiadiazole and 1,2,4 – triazole and their derivatives are will known as biologically active and used in various ways. 1,3,4 – oxadiazole derivatives were synthesized from the reaction of acid hydrazide, 4 – mortholeno – 3 – nitro phenyl hydrazide with carbon disulfide and potassium hydroxide in ethanol by refluxing the reaction mixture for 16 hr[(1)] .



Acid hydrazide was treated with cyanogen bromide[(2)]to give 1,3,4-oxadiazole. Phosphorus oxychloride was used for the synthesis of disubstituted 1,3,4 – oxadiazole as compound (1) from acid hydrazid and carboxylic acid [(3,4)] substituted 1,3,4 – oxadiazole (2) was synthesized using microwave technique[(5)].

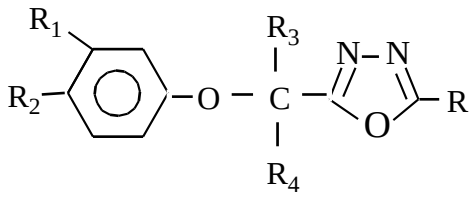


(1)



(2)

1,3,4 – oxadiazoles (3,4) were showed biological activities on revous system and as anti – inflammatery agent. [6,7]



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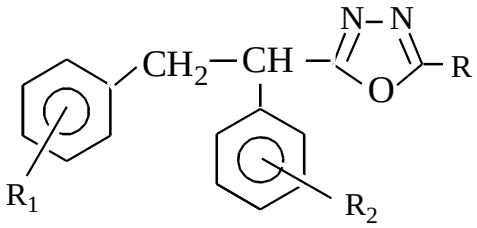
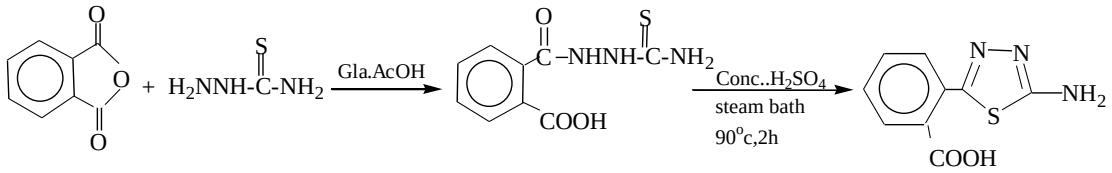
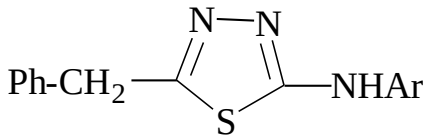


(4)

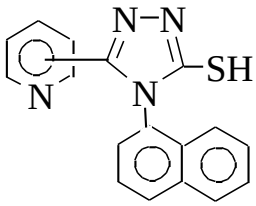
1,3,4 – Thiadiazole were synthesized from phthalic anhydride with thiocemicarbazide in presence of glacial acetic acid then cyclization of the product to thiadiazole with concentrated sulfuric acid [8]



or from cyclization of substituted thiosemicarbazide with methyl sulfonic acid[9] as (5). 1,3,4-Thiadiazoles shows various biological activities [10,11] as antibacterial.[12]1,2,4-Triazole 3-thiol derivatives as(6) were synthesized from substituted thiosemicarbazide by their reaction with sodium hydroxide[13].



(5)



(6)

5-substituted -4- amino 1,2,4- triazole-3-thiol was obtained from potassium thiocarbazite by its treatment with hydrazine hydrate [14,15] whereas 4-amino -3,5-diphenyl 1,2,4-triazole was synthesized by heating benzoic acid hydrazide at 200°C[16]. Some substituted 1, 2, 4 - triazoles shows various biological activities as anticancer[17].

EXPERIMENTAL

All chemicals were purchased from Flucka and BDH Chemical Ltd.The melting points were measued on an Electrothermal 9300 Engineering LTD and are uncorrecterd .IR spectra were recorded on Infrared Spectrophotometer Model Tensor 27 ,Bruker Co.,Germany,

using KBr discs . UV spectra were recorded on Shimadzu Double-Beam Spectrophotometer UV-210 A using ethanol as a solvent.

N,N – dibenzyl glycine (1)[18]

Chloroacetic acid (1.5g, 0.015 mole) was dissolved in water to this solution dibenzyl amine (3g, 0.015 mole) and sodium hydroxide(0.6g/2ml H_2O) were added. The mixture was refluxed for 1.5 hr. (the oily drops material disappears and give clear solution). The mixture then cooled to room temperature and neutralized with 5% hydrochloric acid, the precipitate was filtered to give white powder, m.p. 181-183^oC,yield79%

Methyl/Ethyl N,N – dibenzyl glycinate (2,3)[19]

A mixture of N,N – dibenzyl amine (0.02 mole, 4g), methyl bromoacetate (0.02 mole, 3g) and sodium bicarbonate (3g) in absolute ethanol (30 ml) was refluxed for 5 hr. the solvent was evaporated and the residual poured on crushed ice with stirring, the precipitated was filtered off, dried as white yellowish powder(2), m.p. (40-42^oC), yield 82% and yellow powder(3) m.p.(50-52 ^oC) , yield 86%

N,N–dibenzyl glycine hydrazide (4)[20]

Ester (2 or 3) (0.015 mole) and hydrazine hydrate (4 ml, 0.07 mole) in absolute ethanol (40 ml) were refluxed for 5 hr. the solvent was evaporated under reduced pressure to give white – yellowish crystals (m.p. 112 – 114^oC) yield, ester (2) 83%, ester (3) 94%.

1 – (dibenzyl amino acetyl) thiosemicarbazide (5)[2]

A mixture of hydrazide (4)(3g, 0.0116 mole), ammonium thiocyanate (2.7g, 0.034 mole) and concentrated hydrochloric and in absolute ethanol (50ml) was refluxed for 22 hr. the solvent was evaporated under reduced pressure, precipitate was filtered off and recrystallized from ethanol, m.p. 236^oC, yield: 74% .

2 – (dibenzyl amino methyl)– 5 – amino – 1,3,4 – thiadiazole (6)[21]**.**

A mixture of substituted thiosemicarbazide (5) (2g, 0.006 mole) and concentrated sulfuric acid (12 ml) was stirred at room temperature for 1hr. then heated on water path at 90^oC for 2 hr. with stirring. The mixture was poured on crushed ice and neutralized with concentrated ammonium hydroxide with cooling, the precipitate was filtered off, washed with cold water dried and recrystallized from ethanol, green powder m.p. 151 – 153^oC, yield 17%.

3,4 – diamino – 5 – (dibenzyl amino methyl) – 1,2,4 – triazole (7)[22]**.**

A mixture of thiosemicarbazide (5) (1.6g, 0.005 mole) and hydrazine hydrate (5 ml, 0.1 mole) was refluxed for 2 h. the mixture was cooled, and the precipitated filtered off, washed with water, dried, gave white powder, m.p. 208 – 210^oC, yield 22%.

5 – (dibenzyl amino methyl) – 1,2,4 – triazole – 3 –thiol (8)[21]

Thiosemicarbazide (5), (2g, 0.006 mole)in sodium hydroxide solution (4%, 24ml) was refluxed for 3hr. the mixture was acidified with dilute

hydrochloric acid with cooling PH = 6, the precipitated was filtered off, and recrystallized from ethanol – water to give white powder m.p. > 300°C yield 88% .

2 – (dibenzyl amino methyl) – 5 – amino – 1,3,4 –oxadiazole (9)[23].

To thiosemicarbazide (5)(2.5g, 0.0074 mole) in ethanol (15 ml), 4N sodium hydroxide solution then 5% I2/KI was added slowly with stirring (the color of iodine is appears). The product was extracted with ether (2×20ml), the ether layer dried with magnesium sulfate, evaporated to give yellow oil, yield, 65%.

2,5 – Bis (dibenzyl amino methyl) – 1,3,4 – oxadiazole (10)[24]

Carboxylic acid (1)(7,4g, 0.026 mole) and hydrazine hydrate (0.65ml, 0.013 mole) were added to polyphosphoric acid (27g) respectively. The mixture was heated at 150°C for 15hr with stirring, cooled,then powered on crushed ice, neutralized with 5% sodium bicarbonate solution, pale brown precipitate formed, filtered, dried and recrystallized from ethanol. m.p. : 121 – 123°C, yield, 57%.

2,5 – Bis (dibenzyl amino methyl) – 1,3,4 – thiadiazole (11)[25].

A mixture of oxadiazole (10)(1,2 g,0.0025 mole) and thiourea (0.76g, 0.01 mole) in xylene (30 ml) was refluxed for 30 hr. the solvent was evaporated under reduced pressure to give solid precipitate, filtered off and recrystallized from ether – pt. ether (40-60°C), m.p. 160 – 162, yield 88%

1,2 – Diacyl hydrazine (12 – 14)[26].

Hydrazide (4) ((3g, 0.011 mole) was dissolved in dry tetrahydrofuran (50ml), acid chloride (0.11 mole) was added slowly with stirring and cooling, the mixture was refluxed for 12 h, cool to room temperature and poured on to crushed ice and the mixture neutralized with 15% sodium bicarbonate, the product filtered off, dried and recrystallized from ethanol.

2 – (dibenzyl amino methyl) – 5 – substituted – 1,3,4 – oxadiazole (15 – 17)[27].

A mixture of diacyl hydrazine(12-14) (0.0064 mole) and phosphorus pentaxide (0.17g, 0.0012 mole) in xylene (25ml) was refluxed for 12 h, the solvent was evaporated under reduced pressure and the product recrystallized from ethanol.

2 – (dibenzyl amino methyl) – 5 – substituted – 1,3,4 – thiadiazole (18-20)[28].

A mixture of diacyl hydrazine (12 – 14)(0.0064 mole) and phosphoric pentasulfide (0.26g, 0.0012 mole) in xylene (25ml) was refluxed for 12h. the solvent was evaporated under reduced pressure and the product was recrystallized from ethanol – water .

Table(1) :Physical data of compounds(12-20)

Comp.No.	R	m.p^{0}C	Molecular formula	Yield %	Color
12	CH_3	72-74	$C_{18}H_{21}N_3O_2$	56	Palebrown
13	Ph	205-207	$C_{23}H_{23}N_3O_2$	66	White
14	4-NO_2-C_6H_4	124-126	$C_{23}H_{22}N_4O_4$	74	Pale yellow
15	CH_3	Oily	$C_{18}H_{19}N_3O$	29	yellow
16	Ph	212-214	$C_{23}H_{21}N_3O$	36	Yellowish white
17	4-$NO_2C_6H_4$	132-134	$C_{23}H_{20}N_4O_3$	62	Yellow
18	CH_3	Oily	$C_{18}H_{19}N_3S$	21	Yellow
19	Ph	117-119	$C_{23}H_{21}N_3S$	20	Yellowish brown
20	4-$NO_2C_6H_4$	72-74	$C_{23}H_{20}N_4O_2S$	90	Pale brown

RESULTS AND DISCUSSION

Substituted 2 –dibenzyl amino methyl 1,3,4– oxadiazoles, thiadiazoles and 1,2,4–triazoles were synthesized from dibenzylamine Scheme-1. Dibenzyl amine was treated with chloroacetic acid to give N,N – dibenzyl glycine (1) which show absorption at 1710 cm^{-1} for (C= O, acid), the acid (1) was converted to methyl/ethyl esters (3,4), the IR spectra show absorption for carbonyl group of the esters at 1728, 1747 cm^{-1}. the esters (3,4) were treated with hydrazide hydrate in ethanol to give hydrazine (4) the (C=O) group in (4) shows absorption at 1665 cm^{-1}. the hydrazide (4) was treated with ammonium thiocyanate to give thiosemicarbazide (5), the IR of compound (5) shows absorption at 1665 cm^{-1} for (C=O) and 3379 (N-H). the thiosemicarbazide (5) was treated with concentrated sulfuric acid to give 1,3,4 – thiadiazole derivatives (6), while its reaction with hydrazine hydrate, 4% sodium hydroxide and with potassium iodide/iodine gave 3,4 – diamino – 5 – N,N – dibenzyl amino methyl 1,2,4 – triazole (7), 1,2,4 – triazole – 3 – thiol (8) and 5 – amino 1,3,4 – oxadiazole (9) respectively. The IR spectra of compounds (6 – 9) shows absorption at 1620 – 1652 cm^{-1} (C=N) 3311 – 3424 cm^{-1} (N – H), compound (8) show absorption at 1201(C=S). compound (10) was synthesized from (1) with polyphosphoric acid and hydrazine hydrate, sulfonation of (10) gave disubstituted 1,3,4 – thiadiazole (11). Hydrazide (4) was treated with some acid chlorides to give diketones (12 – 14), the IR spectra shows absorption at 1654 – 1671 cm^{-1} for (C=O), the diketones (12 – 14) then cyclized to substituted oxadiazoles (15 – 17) and thiadiazoles (18 – 20) by their reaction with phosphorus peutoxide and with phosphorus peutasulfide respectively. The IR spectra show absorption at 1635 – 1670 cm^{-1} Scheme - 2. The UV and IR spectra listed at table (2).

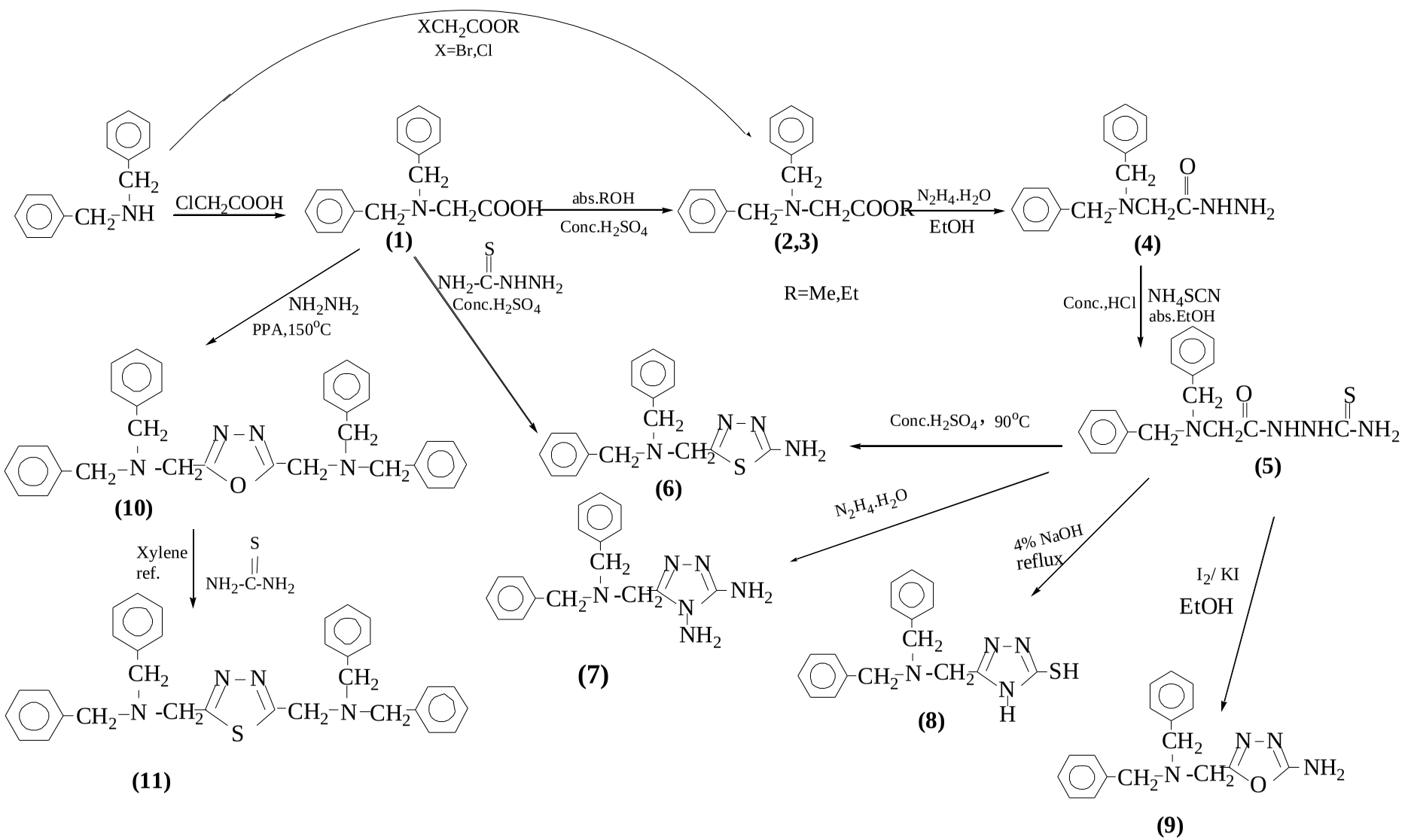
Some of the synthesized compounds were tested against various types of bacteria and showed certain activities. Table (3)

Table(2): IR and UV data of the synthesized compounds .

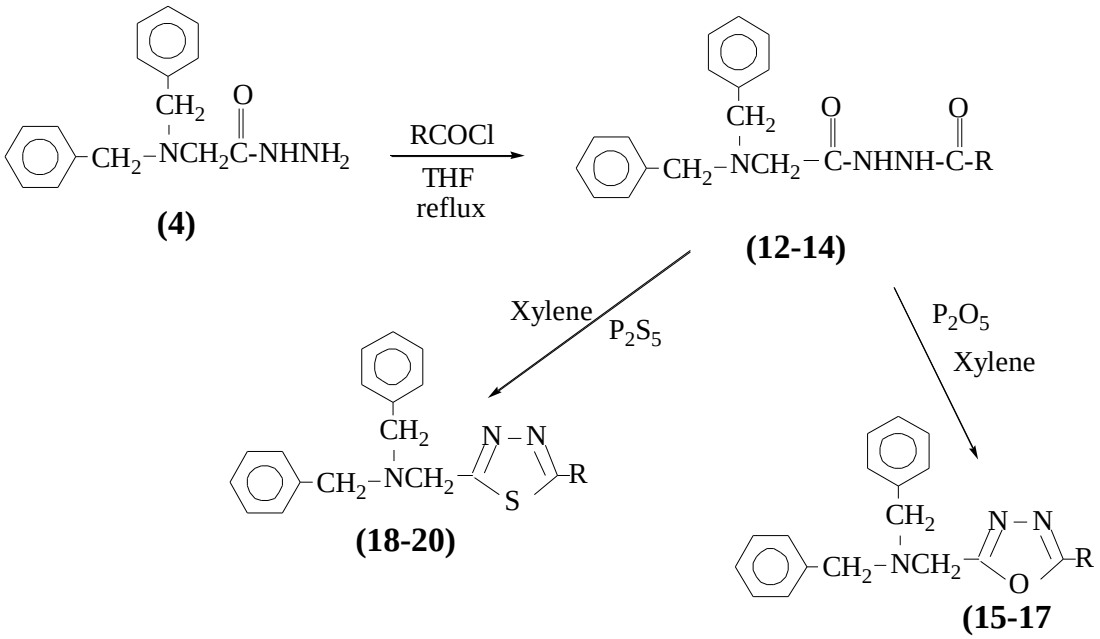
Comp. No.	UV (EtOH) λ_{max}(nm)	IR υ cm^{-1}, (KBr)			
		C=O	N-H	C=N	Others
1		1710	-		OH:3450 Ar-C-H:3086
2	235,271	1728	-		Ar-C-H:3030
3	266,317	1747	-		Ar-C-H:3027
4	242,308	1665	3348		Ar-C-H:3058
5	238,280	1665	3379	-	
6	295,336	-	3313	1620	C-S:1029
7	301,266	-	3423	1624	Ar-C-H:3025
8	284,360	-	3424	1640	C=S:1201
9	293	-	3311	1652,1616	C-OC:1204 Ar-C-H:3062
10	239,265	-	-	1624	ArC-H 3028 C-O-C1294,1110
11	228,288	-	-	1625	C-S-C:1084 ArC-H:3100
12	236,265	1654	3323	-	ArC-H:3026
13	238,302	1668	3424	-	ArC-H :3080
14	283,323	1671	3375	-	NO_2:1346 Sy. 1529asy. ArC-H:3062
15	237,295	-	-	1635	C-O- C:1115,1182 ArC-H:3094
16	243,280	-	-	1667	C-O- C:1108,1287 ArC-H:3052
17	235,248	-	-	1604	C-O-C:1108,125 ArC-H:3029 NO_2:1346,1493
18	238,277	-	-	1637	ArC-H:3061 C-S-C:1120
19	248,304	-	-	1640	ArC-H:3027 C-S-C:1028
20	241,311	-	-	1670	ArC-H:3060 C-S-C :1159 NO2:1345Sy. 1521asy.

Table(3): The antibacterial activity of the tested compounds

Comp.No.		Staphylococcus aureus				Bacillus subtilis				Moraxella catarrhalis				Haemophilus influenza				Klebsiella pneumonia			
		Conc. (mg / ml)																			
		10	1	0.1	0.01	10	1	0.1	0.01	10	1	0.1	0.01	10	1	0.1	0.01	10	1	0.1	0.01
1		7	4	2	--	6	4	--	--	8	5	3	--	9	5	2	--	8	5	2	--
3		5	3	--	--	7	4	2	--	5	3	--	--	6	3	--	--	8	4	2	--
4		8	4	2	--	8	5	3	--	10	6	3	--	10	7	4	--	6	3	--	--
5		9	5	3	--	8	5	2	--	8	5	2	--	8	4	2	--	10	7	5	--
6		6	3	--	--	7	5	3	--	6	4	--	--	8	5	2	--	7	4	2	--
Ceftriaxone 30mg/disk	Control	19				16				20				22				21			
Norfloxacin 10mg/disk	Control	18				16				24				19				27			


XCH2COOR
X=Br,Cl
ClCH2COOH
abs.ROH
Conc.H2SO4
N2H4.H2O
EtOH
(1)
(2,3)
(4)
R=Me,Et
NH2NH2
PPA,150°C
NH2-C-NHNH2
Conc.H2SO4
Conc.,HCl
NH4SCN
abs.EtOH
Conc.H2SO4, 90°C
N2H4.H2O
4% NaOH
reflux
I2/ KI
EtOH
Xylene
ref.
NH2-C-NH2
(5)
(6)
(7)
(8)
(9)
(10)
(11)

Scheme (1)



R = CH_3 , Ph ,4-$NO_2C_6H_4$

Scheme (2)

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