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Synthesis of some new heterocyclic compounds derived from β-Lactam derivatives and Their Biological Activity Study

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Abstract

New Imidazol subordinates [12,13] was blended of hipuric acid corrosive subsidiaries [10,11] .The beginning were promptly acquired by response of one of β-Lactam subordinates with sweet-smelling aldehyde them changed over to corrosive chloride [6,7] which response with glycine (2-amino acetic acid) in basic medium . Mixes [12,13] were changed over in to an assortment of subsidiaries like Imidazoles and oxazoles subordinates , The biological activity of the synthesized compounds was also studied. Every new compound were portrayed by FTIR and a portion of their by 1HNMR and UV spectroscopy.

Keywords: β-Lactam, Pyrazole,imidazole, Oxazine, Isoxazole

INTRODUCTION

β-Lactam anti-infection agents have turned out to be chemotherapeutics of in practically identical viability , having abroad range of organic exercises with low host toxicity[(1)] .

The subsequent acknowledgment of the β-Lactam moiety as the key pharma cophoric part of the penam anti-microbials started aflurry of engineered activity[(2)].

1,3-oxazole subordinates gangs abroad range of pharmacological activites, for example, antibacterial [(3-5)], herbicidal[(6)], against inflammatory[(7)], antitumor[(8)] .

The Imidazole ring is available in essential natural building squares, for example, histidine , and the related hormone histamine , numerous medications contain an Imidazole ring, for example, antifungal drugs[(9)] , Synthesis of Imidazole have enthusiasm because of their different organic exercises like antibacterial[(10-12)], anticancer[(13,14)], antifungal[(15)], antimutagenicity[(16)], antitubercular[(17)].

MATERIALS AND METHODS

Instrumental:

Melting points were determined in open capillary tubes on Gallen Kamp melting point apparatus and were uncorrected .The FTIR Spectra were recorded by KBr plate utilizing a Perkin-Elmer 1600 – Series FT-IR spectrometer in AL-Mustansriayh University; results are given cm-1. 1HNMR Spectra were recorded on avariar-Mercury 200MHz spectrometer with utilizing DMSO-d6 as dissolvable in Jordan University.

Experimental:

Synthesis of *7-[4- (N'-Arylidene) amino]-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid* [2, 3]:

Include comparing aromatic aldehyde (0.01mol) to a blended arrangement of compound [1] (0.01mol) in (20ml) ethanol absolute, the blend was refluxed for (7hrs), in the wake of cooling the encourage was separated and recrystallized from appropriate solvent to manage the cost of the coveted mixes. Table (1)

Synthesis of 7-[2-(4-*N'-Aryl*-4-oxo-3-phenylazetidin-1-yl]-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid[4,5]:

Include a blend of (0.01mol) phenyl acetic acid corrosive with (2.02gm) from tri ethylamine in (40ml) chloroform to compound [2,3] , these blend are mixing in ice shower and included drop shrewd at the time a blend from thionyl chloride (5ml) , (20ml) chloroform then the response was mixing for (10hrs) .After than the blend was washed with (30ml,in 1N HCL) and (3X) with water , dried in Na_2SO_4 (5gm) , recrystallized from appropriate solvent to manage the cost of the coveted mixes . Table (1)

Synthesis of *7-[(4- N'-Arylidene) amino]-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carbonyl chloride* [6, 7]:

To a blend of compound [2, 3] (0.01mol), thionyl chloride (15ml) was included, than the blend was refluxed for (8hrs.), after that the overabundance of thionyl chloride was evacuated under decrease strain to get acid chloride. Table (1)

Synthesis *of [({7-[(4- N'-Arylidene) amino]-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-en-2-yl} carbonyl) amino] acetic acid* [8, 9]:

About (0.01mol) of compound [6,7] was added to a mixing arrangement of glycin (0.75gm,0.01mol) and sodium hydroxide (10 ml,10% arrangement), the response was shacked energetically for (1hr.) , a couple of grams of crash ice was included with blending. After that the arrangement was fermented with conc. Hydrochloric acid, the accelerate was gathered and recrystallized from appropriate solvent. Table (1)

Synthesis of *7-[(4- N'-Arylidene) amino]-2-[(4Z)-4-(4- N'-Arylidene)-5-oxo-4, 5-dihydro-1, 3-oxazol-2-yl]-3-methyl-5-thia-1-azabicyclo[4.2.0]oct-2-en-8-one* [10,11]:

About (0.01mol) of compound [8,9] was added to a blend of (5ml) acetic acid and (20ml) acetic anhydride, (0.01mol) aromatic aldehyde . The temperature of response was emerge to (700C) for (10hr), at that point the last blend was poured in to crush ice and mixed for (30min.), the item was gathered and recrystallized from appropriate solvent. Table (1)

Synthesis of *7-[(4- N'-Arylidene)amino]-2-[(4Z)-4-(4- N'-Arylidene)-5-oxo-4,5-dihydro-1H-imidazol-2-yl]-3-methyl-5-thia-1-azabicyclo[4.2.0]oct-2-en-8-one* [12,13]:

To a blend compound [10, 11] (0.01mol) in dry pyridine (5ml) hydrazine hydrate (80%)(0.01mol) was included , the blend was refluxed (2hrs.) .Than the blend was permitted to cool at room temperature , pyridine was expelled under decrease weight the item was recrystallized from appropriate solvent to bear the cost of the coveted mixes. Table (1)

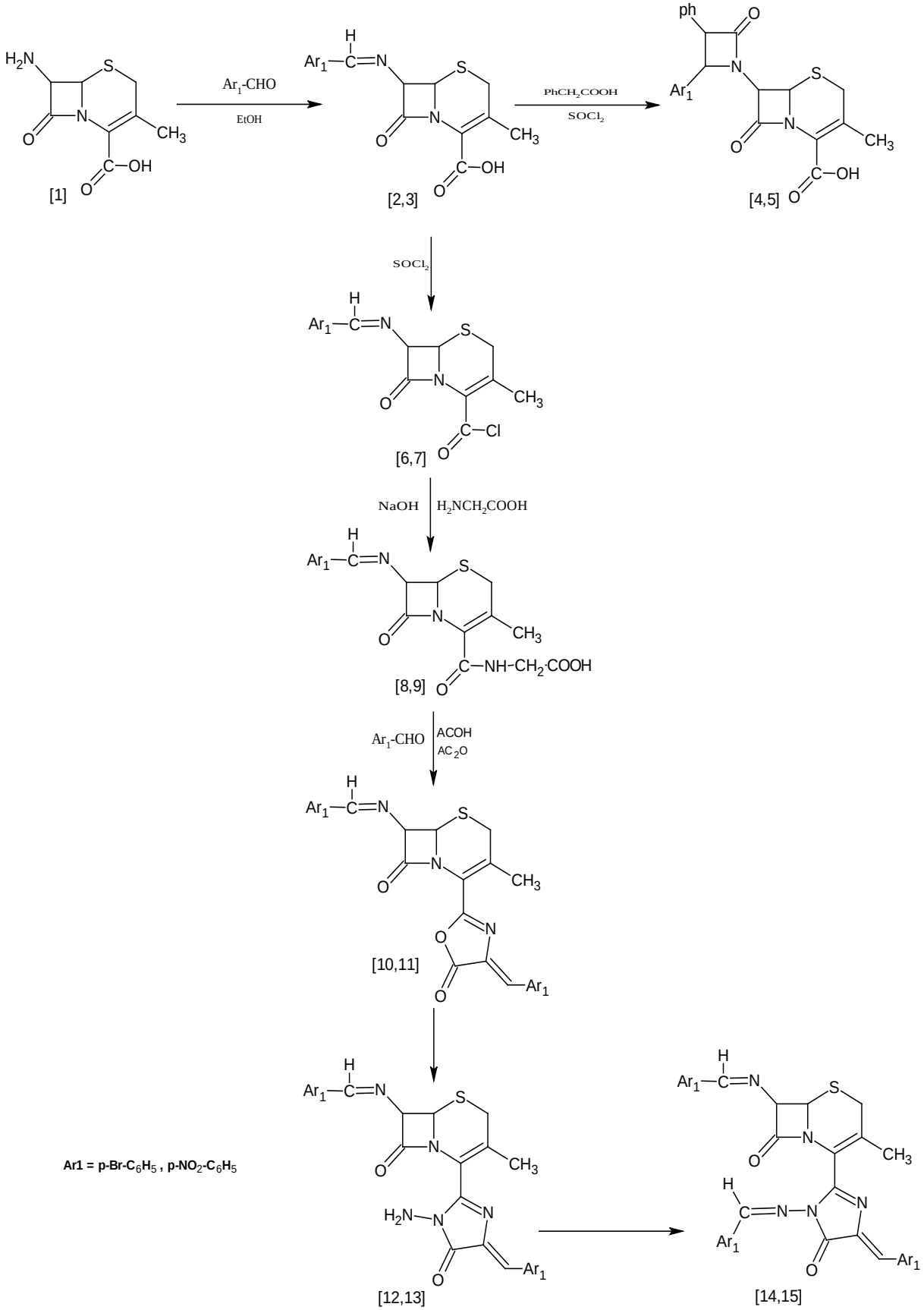
Synthesis of *7-[(4- N'-Arylidene)amino]-2-[(4Z)-4-(4- N'-Arylidene) -1-[(4- N'-Arylidene)amino]-5-oxo-4,5-dihydro-1H-imidazol-2-yl]-3-methyl-5-thia-1-azabicyclo[4.2.0]oct-2-en-8-one* [14,15]:

About (0.01mol) of appropriate aryl aldehyde was added to a blended arrangement of mixes [12,13] (0.01mol) in ethanol outright (20ml) and the blend was refluxed for (3hrs.) . In the wake of cooling the response was filtered and recrystallized from appropriate solvent to bear the cost of the coveted mixes. Table (1)

Antimicrobial assessment:

The recently incorporated heterocyclic mixes, as appeared in Table (3) were tried for their antimicrobial action against the accompanying microorganisms: Escherichiacoli,

klebsiella pneumonia , staphylococcus aureus , Streptococcuslactis , and Candida albicans. The primer screening of the explored mixes was performed utilizing the openings strategy. also, the outcomes are outlined inTable (3).



Scheme 1: Synthesis of new compounds 2-15 from 7-amino-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

RESULTS AND DISCUSSION

Schemes (1) were abridged the amalgamation of various subsidiaries Schiff's base [2,3] was incorporated by treatment of [1] with aromatic aldehyde. The response is trailed by demonstrates vanishing of the NH_2 group and the presence of the new (C=N) band at (1610-1639 Cm-1) and groups at (3419-3245Cm-1) [2] and at (3435-3281Cm-1) [3] for stretching vibration of (OH carboxylic group) and bands. (3028 Cm-1)(CHar.), (2950-2899 Cm-1)(C-H, Asym.&sym.), (1712 Cm-1) for [2] λmax (EtOH) at [2](344 nm) and [3](346 nm) responsible of ($n \rightarrow \pi^*$) progress of (N and O) atoms and [2] at (242 nm) and [3]at (285 nm) due to($\pi \rightarrow \pi$). At the point when the carboxylic group was dealt with thionyl chloride, subordinate [6,7] was gotten in great yield the response happen by tetrahedral component. The IR spectra shown by vanishing band of OH of carboxylic acid at (3419-3245Cm-1) [2] and at (3435-3281Cm-1) [3], and increment band of (C=O) of acid chloride to (1761Cm-1) [6] and (1761Cm-1) ,(1728 Cm-1)(C=O beta-lactam) ,(1660 Cm-1)(C=N) , (1597,1373 Cm-1)(NO_2 Asym. &sym) for [7]. Hipuric acid subordinate [8,9] have been gotten by response of mixes [6,7] with glycine (amino acid) in basic medium, instrument of this response has been demonstrated the solitary combine of electron of amino group has been assaulted carbon of carbonyl group and after that loos HCl. The FTIR spectra of compound show band at (3414-3244 Cm-1) [8] for OH acid, three groups at (1718 Cm-1) (C=O beta-lactam), and at (1612 Cm-1)(C=N) for [8] , and(1712 Cm-1)(C=O beta-lactam), (1523,1348 Cm-1 (NO_2 Asym. &sym) and at (1618 Cm-1)(C=N) for [9] . The U.V spectra of these mixes demonstrated the λmax (EtOH) at (324 nm) [8] and (342 nm) [9], dependable for($n \rightarrow \pi^*$) change of (N and O) atoms and at (223 nm) [8], (276nm) [9] due to ($\pi \rightarrow \pi^*$).The Acetic acid and acetic anhydride has been utilized as cyclizing operator for cyclization of hipuric acid subsidiary [8,9] to create [10,11]. The FTIR spectra of compound [10,11]shows vanishing wide band at (3414-3244Cm-1) [8] and at (3493-3250Cm-1) [9], for extending vibration of (O-H) of carboxylic acid, and increment band of (C=O) to (1782Cm-1)[10]and (1722Cm-1) [11] .λmax (EtOH) at The U.V spectra of these mixes demonstrated the λmax (EtOH) at (344 nm) [10]and (364nm) [11], capable for($n \rightarrow \pi^*$) change of (N and O) atoms and at (245 nm) [10], (238nm) [11] due to ($\pi \rightarrow \pi^*$). Refluxing compound [10,11] with hydrazine hydrate (99%) for 20 hrs offered great yields of compound [12,13]. The IR spectra of mixes [12,13] demonstrates appearance of the two groups (symmetric and asymmetric) at (3465,3315Cm-1) [12] and at (3465,3315 Cm-1) [13] for NH_2 group . The U.V range of mixes [12] and [13] has λmax (EtOH) at (346 nm , 342 nm) individually in charge of ($n \rightarrow \pi^*$) progress of (N and O) molecules and at (248nm, 242 nm) due to ($\pi \rightarrow \pi^*$). Mixes [14,15] have been integrated by the response of compound [12,13] with aryl aldehyde the response continues by end of H_2O particle. The response is trailed by appearance of the new (C=N) band at (1612 and 1610 Cm-1) for [14] and [15]. The ^{1}HNMR range of [15] appears (ppm), (1.23) (s, CH3 group), (4.64)(s, Ph-CH),(5.09)(s, S-CH-N), (2.56) (s, CH2 group), (6.15)($_S$, Ph-CH=C), (7.13) (s,CH, Schiff's base group), (8.06 – 8.24) (m, ArH), (7.35) (s, CH, second Schiff's base group).A number of new bata lactam derivatives [4, 5] product arranged by treatment of mixes [2,3] with phenyl acidic acid. The arrangement of new beta lactam were affirmed byappearance groups of (C=O) at (1708, 1693Cm-1) for [5]. ^{1}HNMR of compound [4] demonstrates the new flags saw at (1.32)(s, CH3 group, (3.86) (s, CH =O new beta lactam) , (3.34) (s, CH – N new beta lactam)), (2.25) (s, CH2 group) , (5.34) (s, S-CH-N), (6.37 – 8.21) (m, ArH), (4.36) (s, Ph-CH-N), (12.78) (S , OH acid), Table (2) .The investigation of organic action of all new prepared compounds were recorded in the Table (3).

Table 1: Physical properties of prepared compounds

Comp. No.	M.P (C°)	State and colour	Recryst-solvent	Yield %
2	256	Solid ,White	Ethanol:H_2O(2:1)	75
3	230	Solid ,White	Ethanol	82
4	288	Solid , Brown	Ethanol	66
5	Decompose	Solid , orange	Ethanol:H_2O(1:1)	56
6	149	Solid ,yellow	Benzene	71
7	173	Solid ,yellow	Ethanol	74
8	277	Solid , orange	Ethanol	65
9	260	Solid , orange	Ethanol	73
10	233	Solid ,yellow	Ethanol	72
11	Decompose	Solid ,orange	Benzene	77
12	155	Solid ,orange	Ethanol:H_2O(1:1)	70
13	130	Solid ,yellow	Ethanol	78
14	172	Solid ,orange	Ethanol	52
15	195	Solid , White	Ethanol	68

Table 2: Chemical FTIR, UV and ^{1}H-NMR spectra of some compounds

Comp. No.	Spectral data	
	IR (ν, cm^{-1})	UV (EtOH)&^{1} H NMR (DMSO-d)
2	(C = N) 1610 $(OH)_{acid}$ 3419-3245 $(C = O)_{lactam}$ 1712 $(C-H)_{ar}$ 3028 $(C-H)_{al}$ 2950-2899	UV (EtOH)(Wavelength(nm)/Abs): 344/0.038, 242/0.408
3	(C = N) 1639 (OH) 3435-3281 $(C = O)_{lactam}$ 1706 (NO_2) 1517-1348 $(C-H)_{ar}$ 3043 $(C-H)_{al}$ 2943-2804	UV (EtOH)(Wavelength(nm)/Abs): 346/0.020, 285/0.316
4	$(C = O)_{lactam}$ 1722 $(C = O)_{lactam}$ 1637 (OH) 3422-3266 $(C-H)_{ar}$ 3047 $(C-H)_{al}$ 2933-2890	UV (EtOH)(Wavelength(nm)/Abs):320/0.523 , 242/0.224,^{1}HNMR (DMSO-d6) (δ) ,6.37-8.21ppm (m, ArH), 4.36ppm ($_S$,Ph-CH-N), 5.34ppm ($_S$,S-CH-N), 3.86ppm ($_S$, CH-N)$_{New\ Lactam}$, 3.34ppm ($_S$,CH=O)$_{Lactam}$, 12.78 ppm (s , OH)$_{acid}$,1.32ppm (s, CH_3), 2.25 ppm (s, CH_2)
5	$(C = O)_{lactam}$ 1720 $(C = O)_{lactam}$ 1637 (OH) 3435-3271 $(C-H)_{ar}$ 3005 $(C-H)_{al}$ 2937-2804 (NO_2) 1579-1327	UV (EtOH)(Wavelength(nm)/Abs):398/0.388 , 290/0.214,^{1}HNMR (DMSO-d6) (δ) , 7.02-8.74ppm (m, ArH), 4.41ppm ($_S$,Ph-CH-N), 5.74ppm ($_S$,S-CH-N), 3.84ppm ($_S$, CH-N)$_{New\ Lactam}$, 3.40ppm ($_S$,CH=O)$_{Lactam}$, 13.11-12.02 ppm (s , OH)$_{acid}$,1.12ppm (s, CH_3), 2.20 ppm (s, CH_2)

Comp. No.	Spectral data	
	IR (v, cm^{-1})	UV (EtOH)&^{1} H NMR (DMSO-d)
6	$(C = O)_{acid}$ 1761 $(C = O)_{lactam}$ 1712 (C=N) 1654 $(C-H)_{ar}$ 3037 $(C-H)_{al}$ 2962-2874	UV (EtOH)(Wavelength(nm)/Abs):315/3.296, 236/0.949
7	$(C = O)_{acid}$ 1761 $(C = O)_{lactam}$ 1728 (C=N) 1660 (NO_2) 1597-1373 $(C-H)_{ar}$ 3066 $(C-H)_{al}$ 2922-2850	UV (EtOH)(Wavelength(nm)/Abs):320/2.643, 227/0.032
8	$(OH)_{acid}$ 3414-3244 $(C = O)_{lactam}$ 1718 (C=N) 1612 (NH) 3281	UV (EtOH)(Wavelength(nm)/Abs):324/0.425 , 223/1.226
9	$(OH)_{acid}$ 3493-3250 $(C = O)_{lactam}$ 1712 (C=N) 1618 (NO_2) 1523-1348	UV (EtOH)(Wavelength(nm)/Abs):342/0.013 , 276/0.016
10	$(C = O)_{lacton}$ 1782 $(C = O)_{lactam}$ 1701 (C=N) 1629	UV (EtOH)(Wavelength(nm)/Abs):344/0.038 , 245/1.216
11	$(C = O)_{lacton}$ 1722 $(C = O)_{lactam}$ 1708 (C=N) 1639 (NO_2) 1523-1348	UV (EtOH)(Wavelength(nm)/Abs):364/0.040 , 238/0.468
12	$((C = O)_{lacton}$ 1703 $(C = O)_{lactam}$ 1681 (C=N) 1649 (NH_2) 3435,3350	UV (EtOH)(Wavelength(nm)/Abs):346/0.020 , 248/0.712
13	$(C = O)_{lacton}$ 1708 $(C = O)_{lactam}$ 1653 (C=N) 1639 (NH_2) 3465,3315 (NO_2) 1530-1348	UV (EtOH)(Wavelength(nm)/Abs):342/0.013 , 242/0.394
14	$(C = O)_{lacton}$ 1720 $(C = O)_{lactam}$ 1660 (C=N) 1612,1577 $(C-H)_{ar}$ 3020 $(C-H)_{al}$ 2983-2828	UV (EtOH)(Wavelength(nm)/Abs):335/0.004 , 241/1.401 ,^{1}HNMR (DMSO-d6) (δ) ,8.87-8.16ppm (m, ArH), 4.21ppm ($_S$,Ph-CH), 5.51ppm ($_S$,S-CH- N), 6.76ppm ($_S$,Ph-CH=C), 7.01ppm ($_S$,CH=N) $_{Shiff\ base}$, 7.22ppm ($_S$,CH=N) $_{second\ Schiff's\ base}$, 1.38 ppm (s, CH_3),2.35 ppm (s, CH_2)
15	$(C = O)_{lacton}$ 1708 $(C = O)_{lactam}$ 1693 (C=N) 1610,1581 $(C-H)_{ar}$ 3022 $(C-H)_{al}$ 2976-2810	UV (EtOH)(Wavelength(nm)/Abs):303/0.723 , 241/1.252,^{1}HNMR (DMSO-d6) (δ) , 8.42-8.06ppm (m, ArH), 4.64ppm ($_S$,Ph-CH), 5.09ppm ($_S$,S-CH- N), 6.15ppm ($_S$,Ph-CH=C), 7.13ppm ($_S$,CH=N) $_{Shiff\ base}$, 7.35ppm ($_S$,CH=N) $_{second\ Schiff's\ base}$,1.23 ppm (s, CH_3), 2.56 ppm (s, CH_2)

Table 3: Biological activities of newly synthesized compounds

Comp. NO.	Zone of Inhibition (mm)									
	Gram-negative				Gram-positive				Fungi	
	E.coli		Klebsiella P.		Steroptococcus SP.		Staphylococcus A.		Candida albicans	
	*1000	*500	1000	500	1000	500	1000	500	1000	500
2	15	0	12	9	0	0	5	7	0	0
3	20	12	19	22	12	22	5	0	0	0
4	15	14	0	0	16	10	12	0	12	0
5	13	12	19	16	12	22	15	13	0	0
6	15	16	5	0	11	14	7	11	7	9
7	12	6	0	0	17	22	10	8	2	0
8	12	9	0	0	9	15	7	3	2	0
9	14	12	19	21	10	12	0	0	0	0
10	10	10	3	0	17	15	13	14	15	14
11	11	12	0	0	8	12	13	9	0	0
12	3	0	5	0	18	10	9	9	3	0
13	12	10	0	0	10	6	9	2	0	0
14	10	11	0	0	10	12	8	10	0	0
15	11	9	6	6	12	4	7	3	5	10
Flagyl	10	0	0	0	10	19	0	0	0	0

E.coli = Escherichia coli , Klebsiella P.= klebsiella pneumonia , Steroptococcus SP.=streptococcus species ,Staphylococcus A.= staphylococcus aureus
The sensitivity of microorganisms to the tested compounds is identified in the following manner: Highly sensitive = Inhibition zone 3–22 mm
Not sensitive = Inhibition zone: 0 mm
*Concentration= 1000,500 ppm

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