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Synthesis, Characterization of New 3-Chloro- Azetidine-2-One and 1, 3-Thiazinan-4-One Derivatives from Di Imines

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ABSTRACT

The study Included synthesis of some new Derivatives of (benzylideneamino)-3-chloro-4-phenylazetidin-2-one and 3-(3-chloro- 2-oxo-4-phenylazetidin-1-yl)-2-phenyl-1,3-thiazinan-4-one by tow steps; The first include amino group of the di amino was condensed with different aromatic aldehydes in the presence of absolute ethanol to give new Schiff bases derivatives [1– 3] respectively. The second step , the resulting imines derivatives [1 – 3] were reacted with chloro acetyl chloride in presence of triethylamine in dry benzene by per cyclic reaction to give novel 3-(3-chloro-2-oxo-4-phenylazetidin-1-yl) derivatives (A_1-A_3) and reacted with 3-mercapto propanoic acid with (Schiff-base) in dry benzene to give1,3-thiazinan-4-one derivative's(Z_1- Z_9) The composites prepared were described by melting point .Most of these derivatives were confirmed by "FT-IR, 1HNMR spectra.

Keywords---Schiff's bases, (benzylideneamino)-3-chloro-4- phenylazetidin-2-one, 3-(3-chloro-2-oxo-4-phenylazetidin-1-yl)-2- phenyl-1,3-thiazinan-4-one

Introduction

Azetidine, a four-member heterocyclic ring system with (N) as a heteroatom, is the parent heterocyclic ring of azetidinone. The second position of 2-azetidinone has a carbonyl group, which is one of the most prevalent heterocyclic rings found in many antibiotics [1].Although the ring of azetidinone was known since (1907) but the realization of their chemistry began from (1947) only. These are presently used for chemotherapy of bacterial infections [2-4]. Realization of their chemistry began from (1947) only. These are presently used for chemotherapy of bacterial infections [2-4].] cycloaddition, also known as the Staudinger reaction, is a reaction between imine and ketene that is one of the most important and versatile techniques for the synthesis of structurally diverse 2-azetidinone derivatives[5]. The Staudinger reaction is thermally or photochemically enhanced by utilizing acid chlorides in the presence of (Et3N) triethylamine or a-diazoketones as ketene precursors[6]. Azetidinone is a four-membered cyclic that has been used as a useful building block for the preparation of a variety of chemical compounds by utilizing the strain energy associated with it[7] . Sulfadiazine is a sulfonamide antibiotic that is listed on the WHO's "List of Essential Medicines." It kills bacteria that cause infections by preventing the bacterial cell from producing folic acid, and it's commonly used to treat "urinary tract infections" (UTIs) and burns[8,9]. The four-membered cyclic amide azetidinone, often known as "-lactam," is produced from 3-amino-propanoic acid [10,11]. Azetidine is the parent heterocyclic ring of azetidinone, which is a four-membered heterocyclic ring system with (N) as the heteroatom. The second position of 2-azetidinone has a carbonyl group, which is one of the most prevalent heterocyclic rings found in many antibiotics[10]. Although the ring of azetidinone has been known since 1907, its chemistry has only recently been discovered (1947) Azetidine, a four- member heterocyclic ring system with (N) as a heteroatom, is the parent heterocyclic ring of azetidinone. The second position of 2-azetidinone has a carbonyl group, which is one of the most prevalent heterocyclic rings found in many antibiotics[12]. Although the ring of azetidinone has been known since 1907, the chemistry of the compound was finally discovered in 1947. These are currently being utilized to treat bacterial infections [13-15]. Thiazinanones (six- membered heterocyclic) have not been extensively studied in the past, but they have important biological properties such as immunopotentiating [16], anti- inflammatory [17], antimalarial [18], and antibacterial [19]. The current study additionally looked at how thiazolidinones have been synthesized in recent years [19, 20]. The methods utilized in nonconventional sonochemistry were of great interest to the researchers [21, 22]. The research is the first to look at the thiazinanone ring's chemistry. Thus, using 2-picolylamine, aldehydes, and MercaptoPropanoic acid, the current work produced 15 novel thiazinanones. The goal of this research is to look at the antioxidant properties of thiazolidinones [23] and novel thiazinanones that have been synthesized in the past. N-bromo compounds are antibacterial, antifungal, and anti-HIV chemicals that have a bromine atom linked to nitrogen [22-27]. The antibacterial activity of 2-(4-((1-aryl- 1H-1, 2, 3-triazol-4-yl)methoxy)phenyl)2-(2-oxoazetidin-1-yl) acetamide against different G-positive (Staphylococcus aureus and Bacillus subtilis) acetates was investigated.The 2-(4-((1-aryl-1H-1, 2, 3-triazol-4-yl)methoxy)phenyl)2-(2-oxoazetidin-1-yl) acetamide product was characterized and their antibacterial activities were evaluated against various G-positive (Staphylococcus aureus and Bacillus subtilis) and G-negative (Pseudomonas aeruginosa and Escherichia coli) bacteria, using minimal inhibition concentration.[28].

Steps of the theoretical study to estimate the biological effectiveness

In this study, the structural formulas of the prepared compounds were drawn using ChemDraw Professional 16.0 program. After that, the structural formula was modified and the files were converted to mol format using Chem3D 16.0 program. In the next step, Discovery Studio 4.0 Client converted the files to pdb. The last step, the files of the structural formulas were uploaded to the website www.dockthor.com to complete the process of molecular docking of the compounds after specifying the email to which the results will be sent after the bond strength assessment is completed. After receiving the results, they were included in Table No. (7).

Materials and Methods

Using the electro thermal 9300 melting point LTD, UK, the melting points were recorded and reported in degrees (0c). TLC was carried out on aluminum and glass plates that were coated with a 0.25mm layer of silica gel (Fluka). Iodine vapor was used to detect some of the derivatives. Fourier transform infrared (SHIMADZU, 8400) spectrophotometer, Japan the prang 4000-600cm-1 FT-IR spectra The samples were put through their paces on a KBr disc. The 13c and 1H-NMR spectra were measured in (ppm) units in DMSO-d6 as the solvent (Bruker- Ultra Shield 300 MHz Switzerland).

Synthesis of Schiff-bases [1-9]:

Mixture of diamines (0.01 mol) and the corresponding aldehydes (0.02mol) in ethanol (30ml) was treated with (3-5) drops glacial acetic acid and refluxed for (5h). The reaction of mixture was cooled and filtered. The final compounds were purified by recrystallization from ethanol [**29**].The physical properties for these compounds are listed in table (): In the same way, the rest of Schiff's rules were prepared. (1-3)

Synthesis of Heterocyclic Compounds:-

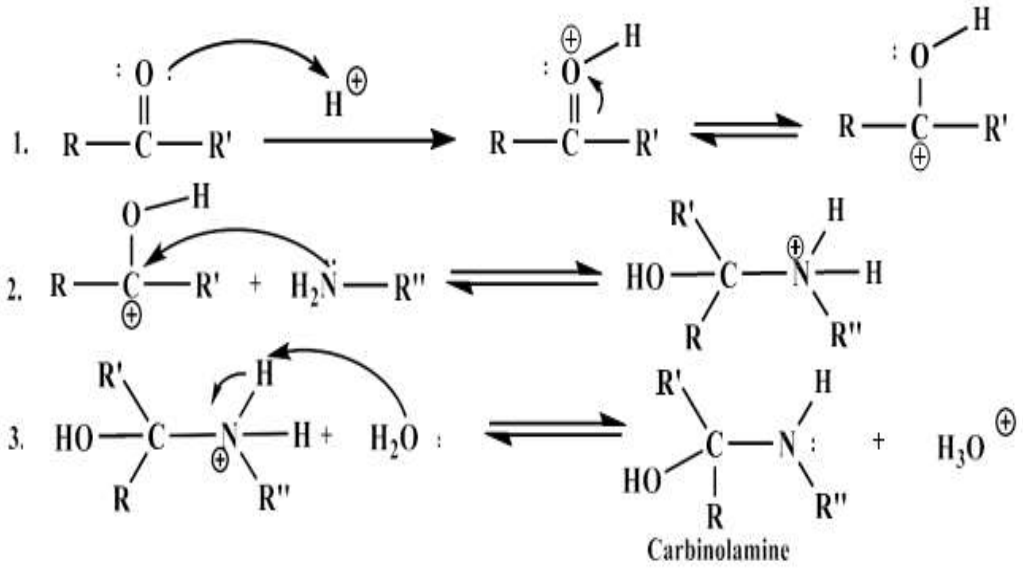
Synthesis of 3-(3-chloro-2-oxo-4-phenylazetidin-1-yl) derivatives (A_1-A_9). A mixture of Schiff bases (0.001mol) with (0.002 mol) of chloroacetyl chloride in dry benzene (30ml) was added drop wise at room temperature. and (3-5) drops of triethyl amine .Content was stirred vigorously for 15 minutes and refluxed for 8hrs. Mixture was cooled at room temperature, filtered, washed with ice-cooled water, dried and recrystallized from ethanol [**30**]. In the same way, the rest of Schiff's rules were prepared. (1-8)Some of the physical properties and yield of compounds are listed in table ():

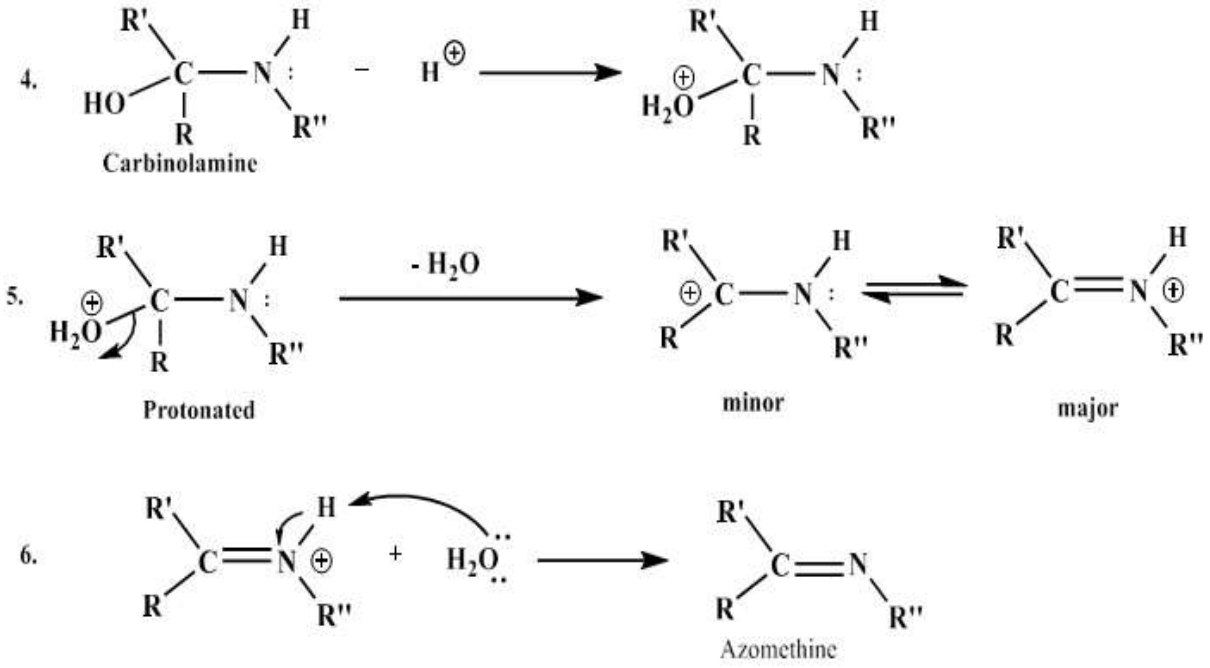
Synthesis of 1, 3-Thiazinane -6-one Derivatives (Z1-Z9)

"(0.01mole) of Schiff bases (A1-A9) with (0.01 mole, 1.085 g) of (3- Mercaptopropanoic acid) in (20 mL)" dry benzene and two drops of ZnCl2 , refluxed for 6 hours, then the solvent was dissolved. After that, 100% ethanol was used to recrystallize the molded precipitate. The rest of Schiff's regulations were prepared in the same way. (A1-A9) Table 1 shows the physical characteristics (3).

Results and Discussion

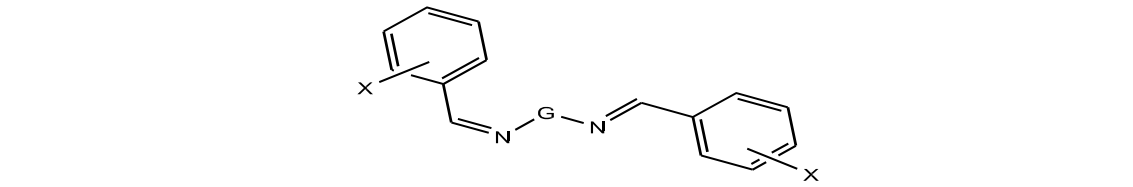
In this work, A number of diamines compounds which on condensation with various selected aromatic aldehydes in the presence of absolute ethanol and few drops of glacial acetic acid formed Schiff bases derivatives [1 -9]. The spectral data respectively. and is illustrated in scheme 1. Of FT.IR of [1

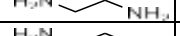
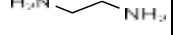
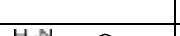
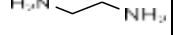
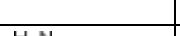
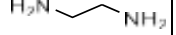
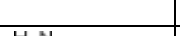
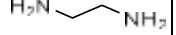




Scheme-(1): Mechanism of Imine formation

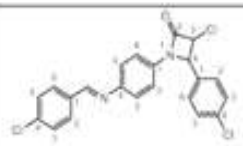
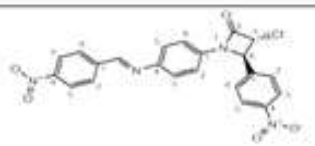
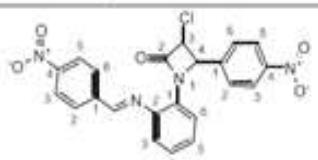
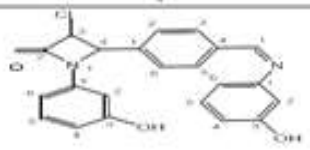
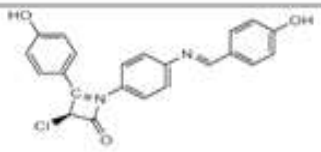
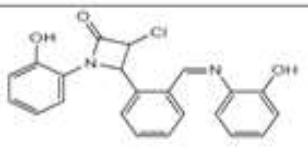
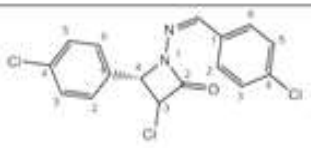
Table (1): values of FT-IR absorption bands for Schiff bases (1-9) measured in cm-

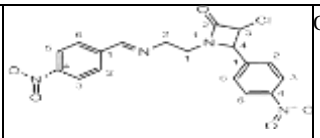


Code	X	G	Molc. Formula	M.Wt	m.p	Yelid %	Colour
6	o-OH		$C_{16}H_{16}N_2O_2$	268.31	621-621	60	Yellow
2	P-NO2		$C_{16}H_{14}N_4O_4$	326.31	184-186	80	Golden
3	P-B r		$C_{16}H_{14}Br_2N_2$	394.11	150-152	78	yellow
4	P-OH		$C_{16}H_{16}N_2O_2$	268,31	218-220	73	white
5	P-Cl		$C_{16}H_{14}Cl_2N_2$	305.20	172-174	70	brown
6	o-OH		$C_{14}H_{12}N_2O_2$	240	204-206	69	white
7	*P*-Cl		$C_{14}H_{10}Cl_2N_2$	277	212-214	70	Yellow
8	*P*-NO_2		$C_{14}H_{10}N_4O_4$	298	273-275	74	Golden

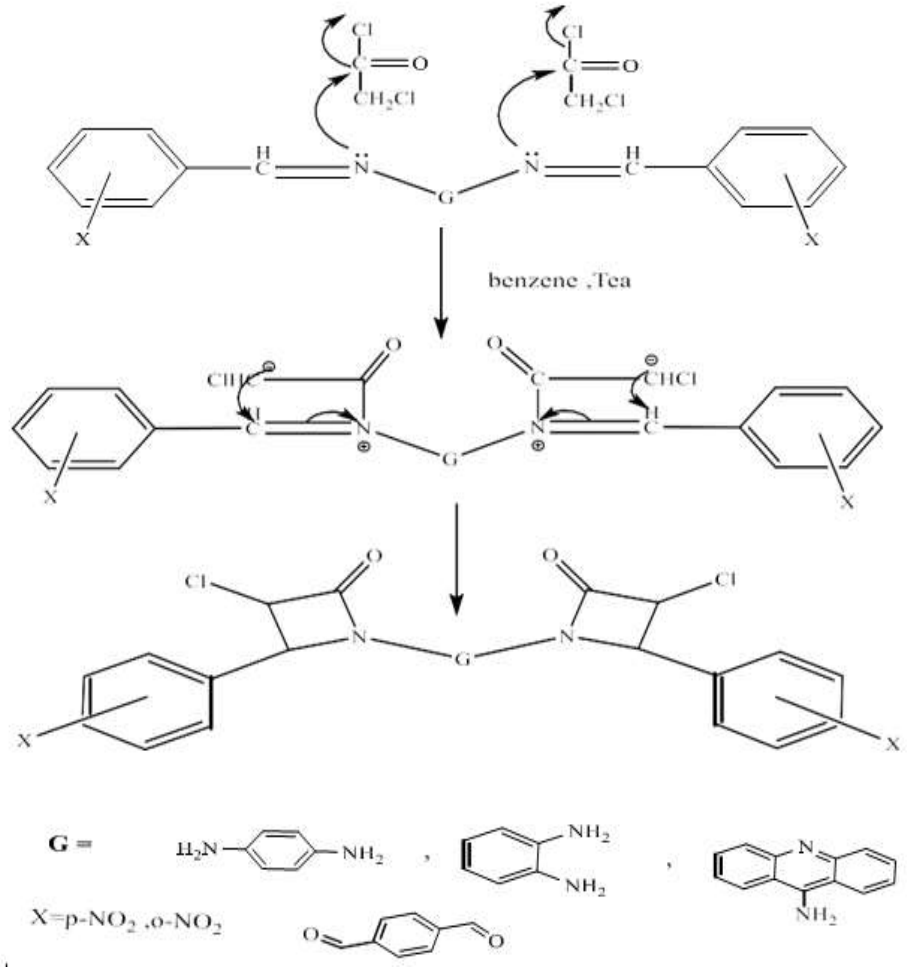
9	*P*-OH	H_2N—NH_2	$C_{14}H_{12}N_2O_2$	240.26	272-274	70	orange
10	*P*-NO_2		$C_{20}H_{14}N_4O_4$	374	206-208	75	Yellow
11	*P*-Cl		$C_{20}H_{14}Cl_2N_2$	352	138-140	74	Orange

Table (2): The chemical formula, molecular weights % yield, melting points, colours, of the azetidine compounds (A_1-A_9)

Comp.No	Nomenclature	Structural formula	Molec. formula	M.p. Co	Color
A_1	(E)-3-chloro-1-(4-((4-chlorobenzylidene)amino)phenyl)-4-(4-chlorophenyl)azetidin-2-one		$C_{22}H_{15}N_2OCl_3$	208-210	Green
A_2	**3**R,4R)-3-chloro-1-(4-(((E)-4-nitrobenzylidene)amino)phenyl)-4-(4-nitrophenyl)azetidin-2-one		$C_{22}H_{15}N_4O_5Cl$	248-246	yellow
A_3	(Z)-1-(acridin-9-yl)-4-(4-((acridin-9-ylimino)methyl)phenyl)-3-chloroazetidin-2-one		$C_{36}H_{23}N_4OCl$	Dec.	yellow
A_4	(E)-3-chloro-1-(2-((4-nitrobenzylidene)amino)phenyl)-4-(4-nitrophenyl)azetidin-2-one		$C_{22}H_{15}N_4O_5Cl$	206-204	orange
A_5	(Z)-3-chloro-1-(3-hydroxyphenyl)-4-(4-(((3-hydroxyphenyl)imino)methyl)phenyl)azetidin-2-one		$C_{22}H_{17}N_2O_3Cl$	211-213	red
A_6	(S,E)-3-chloro-1-(4-((4-hydroxybenzylidene)amino)phenyl)-4-(4-hydroxyphenyl)-114-azet-2(3H)-one		$C_{22}H_{17}N_2O_3Cl$	220-219	yellow
A_7	(Z)-3-chloro-1-(2-hydroxyphenyl)-4-(2-(((2-hydroxyphenyl)imino)methyl)phenyl)azetidin-2-one		$C_{22}H_{17}ClN_2O_3$	162-160	orange
A_8	(**4**S)-3-chloro-1-(((Z)-4-chlorobenzylidene)amino)-4-(4-chlorophenyl)azetidin-2-one		$C_{16}H_{11}N_4O_5Cl$	222-218	yellow

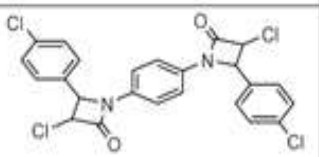
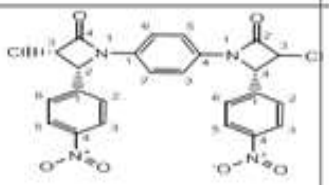
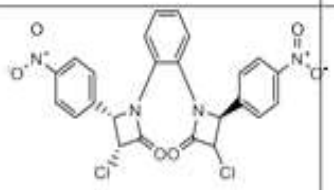
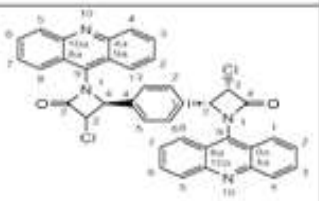
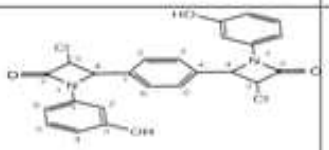
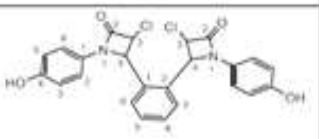
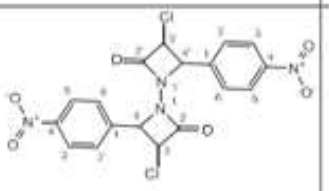
A_9	(E)-3-chloro-1-(2-((4-nitrobenzylidene)amino)ethyl)-4-(4-nitrophenyl)azetidin-2-one		C16H11N2OCl3	292-290	orange

The four-membered β-lactam ring was introduced by the cycloaddition of [1 – 9] and chloroacetyl chloride in the presence of triethylamine catalyst to give (benzylideneamino)-3-chloro-4-phenylazetidin-2-one [A_1 – A_{18}] . Title compounds [A_1 – A_9] shown IR bands at (1695 – 1799) cm-1 confirming the formation of (C=O) β-lactam and appearance of the vibration between (702 – 784) cm-1 was due to the (C-Cl) β-lactam which was further substantiated with the help of 1H-NMR data with the signals at δ (5.09 – 5.16) shown the presence of (N-CH) β-lactam(4.8- 6.50),(5.93-5.95) , and signal was observed for δ ppm for (HC-Cl) β-lactam (6.48- 6.50),(6.08-6.10)



Scheme-2: Mechanism of 3-Chloro-Azetidine-2-One formation

Table (4): Show the nomenclature, melting points, structural and molecular formula for compounds (A_{10}-A_{18}).

Comp.No	Nomenclature	Structural formula	Molec. formula	M.p. Co	Color
A_{10}	-'**1,1(1,4-**phenylene)bis(3-chloro-4-(4-chlorophenyl)azetidin-2-one)		$C_{24}H_{16}N_2O_2Cl_4$	212-210	green
A_{11}	(**4**S)-3-chloro-1-(4-((2R,3S)-3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)phenyl)-4-(4-nitrophenyl)azetidin-2-one		$C_{24}H_{16}N_4O_6Cl_2$	240-238	yellow
A_{12}	(**3**R,4S)-3-chloro-1-(2-((2S)-3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)phenyl)-4-(4-nitrophenyl)azetidin-2-one		$C_{24}H_{16}N_4O_6Cl_2$	222-220	orange
A_{13}	(**4**S)-1-(acridin-9-yl)-4-(4-((2R,3S)-1-(acridin-9-yl)-3-chloro-4-oxoazetidin-2-yl)phenyl)-3-chloroazetidin-2-one		$C_{38}H_{24}N_4O_2Cl_2$	Dec.	yellow
A_{14}	-'**4,4(1,4-**phenylene)bis(3-chloro-1-(3-hydroxyphenyl)azetidin-2-one)		$C_{24}H_{18}N_2O_4Cl2$	250-252	red
A_{15}	-'**4,4(1,1-**phenylene)bis(3-chloro-1-(4-hydroxyphenyl)azetidin-2-one)		$C_{24}H_{18}N_2O_2Cl_2$	226-224	brown
A_{16}	-'**3,3**dichloro-4,4'-bis(4-nitrophenyl)-[1,1'-biazetidine]-2,2'-dione		$C_{18}H_{14}N_2O_6Cl_2$	290-288	yellow

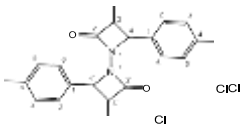
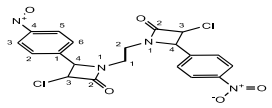
A17	**-'3,3**dichloro-4,4'-bis(4-chlorophenyl)-[1,1'- biazetidine]-2,2'-dione		C18H12N2O2Cl4	210-208	Light green
A18	**-'1,1**(ethane-1,2-diyl)bis(3-chloro-4-(4-nitrophenyl)azetidin-2-one)		C24H16N4O6Cl2	222-220	orange

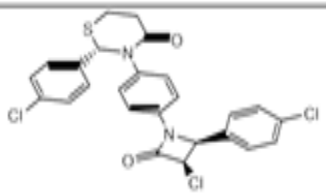
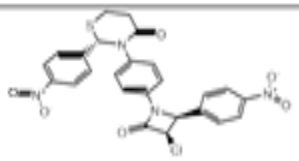
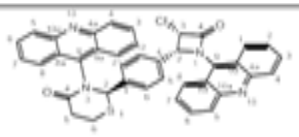
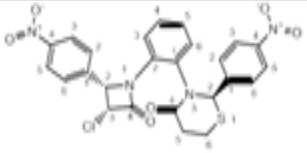
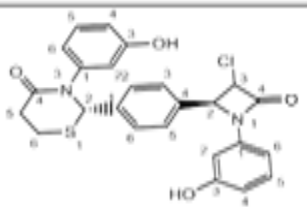
Table (5): Wave numbers in cm-1 of I.R spectrum for prepared compounds: (A_1-A_9)

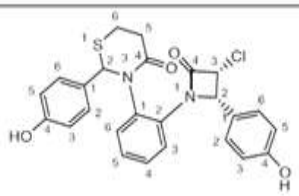
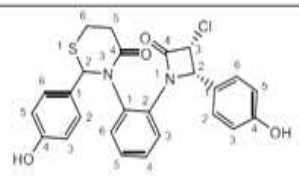
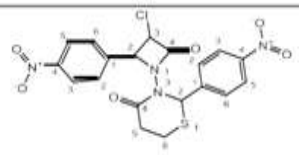
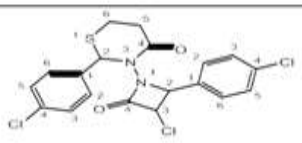
Comp. NO.	ν C-H arom.	ν C-H (-CH_2-) aliphatic		ν C=O lactam	ν C=N	ν C=C ring		ν C-N	ν C-Cl	Others
		Asym.	Sym.							
A_1	3081	2991	—	1668	1612	1582	1485	1270	680	766 C-Cl
A_2	3081	2853	—	1670	1621	1593	1492	1265	648	1415,1339 C- NO_2
A_3	3100	2913	—	1670	1647	1586	1480	1263	679	
A_4	3040	2884	—	1680	1635	1594	1511	1275	684	1446,1340 C- NO_2.
A_5	3000	2950	—	1686	1686	1597	1505	1280	688	3594 O-H
A_6	3030	2922	—	1654	1654	1594	1463	1241	740	3237 O-H
A_7	3068	2985	—	1675	1620	1609	1474	1234	734	3465 O-H
A_8	3052	2986	—	1670	1635	1605	1491	1278	748	1457,1320 C-NO_2
A_9	3046	2997	—	1660	1618	1590	1483	1285	708	780 C-Cl

Comp. No.	ν C-H arom.	ν C-H (-CH_2-) aliphatic		ν C=O lactam	ν C=C ring		ν C-N	ν C-Cl	Others
		Asym.	Sym.						
A10	3102	2939	2848	1635	1597	1514	1205	742	,-NO2 Asy **1114**,**1114**
A11	3053	2987	—	1670	1585	1488	1271	681	740C-Cl
A12	3082	2853	—	1688	1592	1493	1190	683	1414,1338 C-NO_2 Asy.
A13	3063	2933	—	1680	1590	1488	1270	688	1435, 1347C-NO_2 Asy.
A14	3136	2945	—	1648	1588	1480	1265	755	
A15	3165	2988	—	1684	1604	1503	1236	717	3387 O-H
A16	3060	2945	—	1665	1590	1470	1256	735	3457 O-H
A17	3092	2990	—	1680	1601	1478	1245	727	1430,1335 C-NO_2 Asy.
A18	3086	2956	—	1684	1590	1518	1238	718	734C-Cl

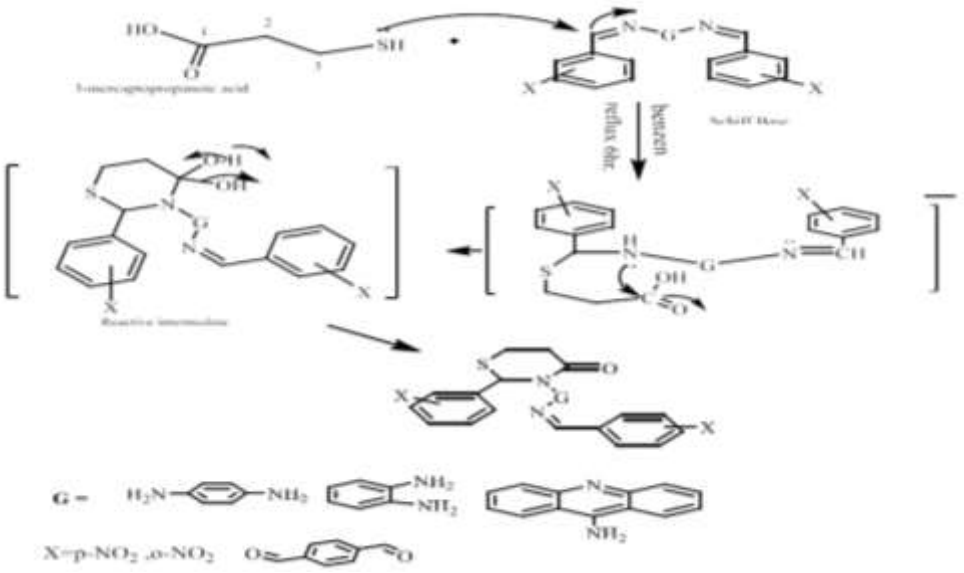
Table (5): Wave numbers in cm-1 of I.R spectrum for prepared compounds: (A_{10}- A_{18})

Table (3): Show the nomenclature, melting points, structural and molecular formula for Compounds (Z_1-Z_9).

Comp.No.	Nomenclature	Structural formula	Mole. formula	M.p.	Color
Z_1	(S)-3-(4-((2S,3R)-3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)phenyl)-2-(4-chlorophenyl)-1,3-thiazinan-4-one		$C_{25}H_{19}N_2O_2Cl_3S$	208-210	yellow
Z_2	(S)-3-(4-((2S,3R)-3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)phenyl)-2-(4-nitrophenyl)-1,3-thiazinan-4-one		$C_{25}H_{19}N_4O_6ClS$	248-246	yellow
Z_3	(R)-3-(acridin-9-yl)-2-(4-((2R,3S)-1-(acridin-9-yl)-3-chloro-4-oxoazetidin-2-yl)phenyl)-1,3-thiazinan-4-one		$C_{39}H_{27}N_4O_2ClS$	Dec.	yellow
Z_4	(R)-3-(2-((2S,3R)-3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)phenyl)-2-(4-nitrophenyl)-1,3-thiazinan-4-one		$C_{25}H_{19}N_4O_6ClS$	206-204	orange
Z_5	(1S)-2-(4-((2S)-3-chloro-1-(3-hydroxyphenyl)-4-oxoazetidin-2-yl)phenyl)-3-(3-hydroxyphenyl)-1,3-		$C_{25}H_{21}N_2O_4Cl\ S$	211-213	red

	thiazinan-4-one				
Z_6	(((**3**R,4S)-3-chloro-1-(2-(((E)-4-hydroxybenzylidene)amino)phenyl)-4-(4-hydroxyphenyl)azetidin-2-one		$C_{25}H_{21}N_2O_4ClS$	220-219	yellow
Z_7	**-3**(**1**-((**1**S,3R)-3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl)phenyl)-2-(4-hydroxyphenyl)-1,3-thiazinan-4-one		$C_{19}H_{15}N_4O_6ClS$	162-160	orange
Z_8	**-3**(**3**-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)-2-(4-nitrophenyl)-1,3-thiazinan-4-one		$C_{19}H_{15}N_2O_2Cl_2S$	222-218	yellow
Z_9	**-3**(**3**-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)-2-(4-chlorophenyl)-1,3-thiazinan-4-one		$C_{21}H_{19}N_4O_6ClS$	292-290	orange

1,3-Thiazinan-6-one compounds [Z_1-Z_9] prepared by reaction of 3- mercaptopropanoic acid compound with [A_1-A_9] by using dry benzene as a solvent and ammonia. FT-IR spectrum showed bands at (3020 –3055) cm-1 for benzene ring, at (1640-1674) cm-1 for(C=O) lactone and lactam compounds, at (1360- 1385) cm-1 for (C-N) and (1587–1592) cm-1 for (C=C) aromatic ring. and appearance of band at (684-692) cm-1to C-S.

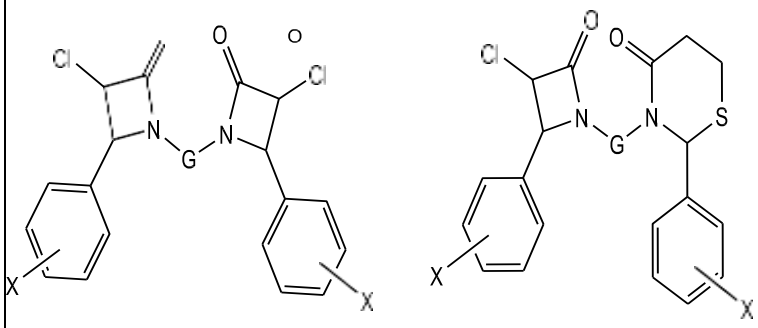


Scheme-2: Mechanism of 1,3-Thiazinan-6-one formation

Table (5): Wave numbers in cm-1 of I.R spectrum for prepared compounds: (Z_1-Z_9)

Comp. N.O	ν C-H arom.	ν C-H (-CH2-) aliphatic		ν C=O lactam	ν C=O lacta m	ν C=C ring		ν C-N	ν C-Cl	ν C-S	Others
		Asym.	Sym.								
Z1	3050	2978	2845	1650	6165	1598	1478	1265	740	682	755 =C-Cl
Z2	3065	2985	2875	1678	6120	1589	1485	1275	729	681	1430 =C-NO2 Asy. 1345 =C-NO2 sy.
Z3	3048	2965	2890	1666	6160	1592	1465	1255	735	692	
Z 4	3044	2968	2838	1648	6122	1587	1495	1248	727	684	1432 =C-NO2 Asy. 1350 =C-NO2 sy
Z 5	3070	2976	2865	1645	6166	1592	1475	1269	718	695	3394 O-H
Z 6	3025	2985	2895	1635	6101	1586	1468	1238	708	682	3347 O-H
Z 7	3035	2980	2845	1670	6165	1601	1488	1285	735	697	3365 O-H
Z 8	3064	2990	2866	1665	6166	1592	1487	1278	740	685	1436 =C-NO2 Asy. 1340 =C-NO2 sy.
Z 9	3075	2946	2878	1652	6162	1589	1478	1257	738	678	743=C-Cl

Table (6): 1H-NMR Data of 3-Chloro-1-(Pyrimidin-2-Yl) Azetidin-2- One and thiazinan-4-One Compounds (A_1, A_3, Z_1, Z_3).



Comp. No.	δ(CH2 Thiazine) ppm 4H,t	δ(HC-Cl) β-lactam ppm 1H,s	δ(CH-Aromatic) ppm nH,m	δ(HC-N) lactam ppm 3H,m	δ (CH-S) Ppm 1H,s
A_1	-	d6.48-6.50	dd8.00-8.76	d.4.8-6.50	-
A_3	-	d6.08-6.10	m6.44-8.02	d5.93-5.95	-
Z_1	1.72-1.74	5.60-5.56	7.26-7.98	4.06-4.07	6.79
Z_3	.48-2.61	5.45-5.47	6.38-7.58	5.30-5.32	6.79

Applied efficacy

It has been found from the results that we obtained from the compounds prepared in the laboratory as in the table ( ), which are expressed in the unit (Kcal/mole), some of them have varying effectiveness,. Lung and chest cancer and with the anti-fungal, as well as with the bacteria E coli, Staphyll l, so it can be considered in the future as good pharmaceutical medical compounds, especially that some of them have carcinogenic activity. it was effective with all except with breast cancer Compound A_2(it gave good efficacy with all except for E coli bacteria and compound A_4 ,A_8,Z_8) gave good efficacy with all, especially with breast cancer, but it did not give with anti-fungal type.

Table (7):- Represents the applied effectiveness of some prepared compounds with the values of some drugs

Code	Breast cancer	Lung cancer	Anti-Fungal	E. coli	Staphyll
A2	-	-72116	-32113	-	-
A4	-112746	-12643	-42064	-	-62637
A8	-11.908	-7.022	-	-8.505	-8.79
A11	-	-	-	-42117	-62144
A12	-	-42311	-	-	-102411
A14		-4271	-	-12414	-12133
A15			-32616	-	-
Z1				-42111	
Z4		-72633		-72163	
Z8	-11211				
Tamoxifen	-112371				
Fulvestrant	-112441				
Raloxifene	-62443				
Toremifene	-112743				
Gefitinib		-42341			
Erlotinib		-4243			
Terbinafine			-42746		
Fluconazole			-12613		
Miconazole			-42166		
Econazole			-62316		
Clotrimazole			-42441		
Cephalexin				-72461	
Trimethoprim				-12661	
Trimethoprim					-62447
Cephalexin					-12371

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