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Synthesis, Identification, and Antibacterial Effect Assessment of New Thiazolidinones from Some Imines Bearing Substituted Phenyl Sulphonyl Amides

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Synthesis, Identification, and Antibacterial Effect Assessment of New Thiazolidinones from Some Imines Bearing Substituted Phenyl Sulphonyl Amides

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Abstract: A series of new thiazolidinone derivatives (N_{22}-N_{42}) has been prepared from the reaction of some Schiff bases (N_1-N_{21}) containing sulfonylamide group with thioglycholic acid in dry benzene. The whole synthesized chemical materials have been identified through FT – IR spectroscopy. Structures for some of the newly synthesized chemical materials have been proved by proton magnetic rsonance (^{1}H-NMR) using (DMSO-d^6) as a solvent and mass spectroscopy. The biological activity effect of these chemical products has been studied against certain types of bacteria: gram – positive (*Streptococcus pneumonia)* and gram – negative (*Pseudomonas aerugenosa).* Additionally, the anti fungal effect of some chemical products was investigated toward *Aspergillus species* and the resulte were correlated with fungal *Nystatin* as control sample. The results were indicated the highest inhibtion zone diameter value for derivatives (N_{36}, N_{34} and N_{42}). These chemical compounds revealed a promising bioactivity against these microbial agents.

Keywords: Schiff bases, Amino sulfonacetamide, Methylisoxazolyl sulfonamide, Thiazolidinone.

INTRODUCTION

Heterocyclic compounds have been obtained extremely attractive from organic chemist due to their bioactive properties. More than 70% of the medications (or) used today are heterocyclic compounds, and in the preparation of polymers that have many uses in industry [1]. Thiazolidinone compound is one of these powerful materials as it is clinically importance. Thiazolidinones have numerous pharmacological properties, including anti-cancer, anti-diabetic, anti-microbial, antiviral, anti-inflammatory and anticonvulsant properties because of these wide spectrum biological properties. Thiazolidinones are called magic molecules [2]. There are many examples of active thiazolidinones biologically such as antibiofilm [3], hypoglycemic [4], anti diabetic and HIV [5], anti - tuberalosis [6], anticancer [7] and anti-inflammatory activities [8], antioxidant [9] anticonvulsant [10], antihistaminic [11], and anti antimirobial [12]. Recently, some thiazolidinone derivatives have been used as a potent antitrypanosomal agents [13].

It has been documented in the literature, the most common method to prepare thiazolidinone is undergoing a Schiff base compound to a cyclization reaction through the addition of marcapto aetic acid in dry benzene [14]. Some Schiff compounds include imidazoly ring have been convetrted to thiazolidines by the reaction of mercapto acetic acid with the Shiff in ethanol as solvent [15]. Synthesis of thiazolidinones from the addition of mercaptoacetic acid to benzothiazolyl Schiff bases was reported, using dry benzene as solvent [16-18]. The reaction of pyrimidinyl Schiff bases with mercaptoacetic acid has been documented to prepare thiazolidinone, using dry benzene as solvent [19]. Thiazolidinone synthesis has been published through the reaction of benzoxazolyl hydrazine Schiff with mercapto acetic acid in dry benzene as solvent [20]. The addition of mercapto acetic acid to tetrazolyl Schiff bases has been revealed to from thiazolidinones in dioxane as solvent. As a result, a plan has been made to convert some neew Schiff compounds to thiazolidinones. These Schiff bases bearing some pharmaceutical modes 4-aminobenzenesulfon amide, *N*-((4-aminophenyl) sulfonyl) acetamide, 4-amino-*N*-(5-methylisoxazole-3-yl) benzenesulfonamide. This will be academically additional scientific value for the field of organic chemistry. The aim of this research is focused on synthesis of new thiazolidinone-4-one derivatives from Schiff bases attached to pharmaceutical modes. In addition to evaluation their biological activity against two type of bacteria gram–positive (*Streptococcus pneumonia)* and gram–

negative (*Pseudomonas aerugenosa*) and one type of fungi (*Aspergillus species*).

EXPERIMENTAL

Materials and Methods

All the chemicals were used in this research supplied by (BDH, GCC, Merck, Fluke, Alfa, and Aldrich) companies. The high purity of benzene is first dropped, then anhydrous magnesium sulphate ($MgSO_4$) is added to dehydration. The melting point was determined by using electrothermal melting point apparatus model 9300. For the purity of the prepared compounds, we used the TLC techniques. The FT-IR spectra were recorded using the FT-IR 8400s Shimadzu spectrophotometer scale (4000-400) cm^{-1}. H^1-NMR spectra were recorded on Varian operating at 400 MHz instrument using DMSO-d^6 as a solvent, The mass spectra were measured in the laboratories of the College of Applied Sciences - University of Samarra / Iraq using a GCMS-QP2010E device equipped by the Japanese company Shimadzu.

Synthesis of Schiff Bases Derivatives (N_1-N_{21}) [21]

(0.002) Mole of different benzaldehyde and ketone compounds was dissolved in 25 mL of absolute ethanol and (3-4) drops of glacial acetic acid added followed by the addition a solution of (0.002) mole of the pharmaceutical compounds dissolved in absolute ethanol. The mixture was heated at reflux for two houres and the completition time of the reaction was followed by TLC. The reaction mixture was cooled to precipitate and filtrated, dried then recrystallized in absolute ethanol.

Synthesis of 4-Thiazolidinone Derivatives (N22-N42) [22]

(0.001) Mole of prepared Schiff bases [N_1-N_{21}] was dissolved in 10 mL of dry benzene and (0.001) mole of mercapto acetic acid added to it. The reaction mixture was heated under reflux for three hours. and the reaction time was followed by TLC. The mixture was cooled, and the precipitate filtered, dried and recrystallized from absolute ethanol.

Study of Biological Activity

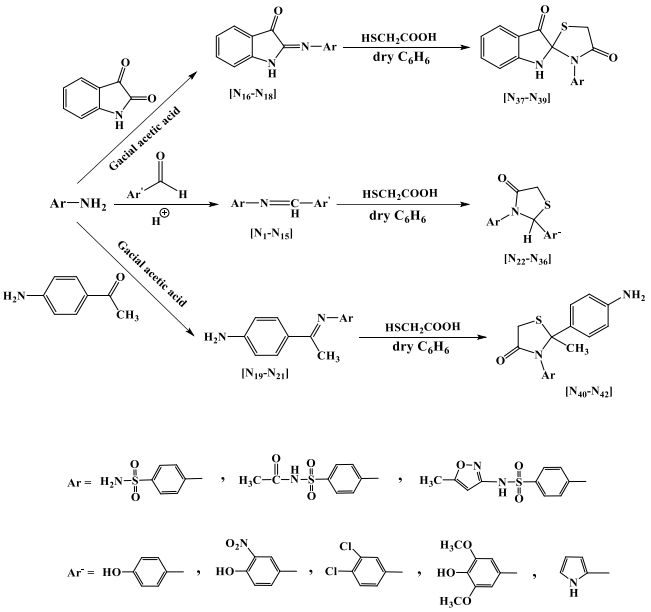
The biological effect of final products wer assessed tword two types of bacteria grams–positive (*Streptococcus pneumonia)* and gram–negative (*Pseudomonas aerugenosa*) and one type of fungi (*Aspergillus species*). The micro-organisms have been isolated and identified at Laboratories for Biology Department/ Science College in Kirkuk University. The chemical concentrations for the tested compounds were prepared using DMSO as solvent for each substance with three concentrations of (5, 10, 15) mg/mL.

Anti Bacterial and Anti fungi Tests Method [23, 24]

For anti bacterial test, the single bacteria have been transferred to a test tube containing 5 mL of nutrition and the broth incubated at 37 °C for 24 hours. The bacterial suspension was prepared and compared with tube number 0.5 of McFarland- standards giving a cell density of (1.5×10^8 cell/mL). A sterile cotton sweep has been dunked into a bacterial suspension and wiped in equally way on the surface of a Muller-Hinton agar plate. After that, the plates have been brooded at 37 °C for 30 minutes. The culture media on the plates have been penetrated (3 wells) by a sterilized cork borer with a diameter of 5 mm. The tested compounds (0.5 mL) were poured into the wells and then incubated at 37 °C for 24 hours. The results of the inhibtion zone diameter were measured using ruler by nanometer. The chemical concentrations for the tested compounds were (5, 10 and 15) mg/mL. For anti fungi test, fungal suspension has been prepared from fresh culture by mixing fungal colonies with 3 ml of sterile distilled water. The inoculum fungi solution was then transferred to the SDA which is supplemented with chloramphenicol using a sterile cotton swab and left to dry. The culture media on the plates were penetrated (3 wells) by a sterilized cork borer with a diameter of 5 mm. The tested compounds (0.5 mL with 5, 10 and 15 mg/mL) have been poured into the wells and then incubated at 25 °C for 7 days. The inhibition zone results have been recorded in mm.

RESULTS AND DISCUSSION

In our work, some new series of thiazolidine derivatives have been synthesized, as shown in Scheme (1). All the new prepared compounds were characterized by FT-IR and some by ^{1}H-NMR and ^{13}C-NMR spectroscopy.



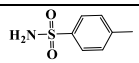
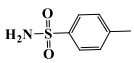
SCHEME 1. Schematic shows all the prepared compounds (N_1-N_{42}).

Characterization of Schiff Base Derivative Compounds (N_1-N_{21})

Schiff bases compounds (N_1-N_{21}) were prepared from the reaction of equimolar of one of the pharmaceutical compounds with various benzaldehyde and ketone compounds in absolute ethanol as a solvent in the presence of (3-4) drops of glacial acetic acid as a catalyst, as shown in Scheme 1.

From the study of FT-IR Spectral absorption, all the spectra of the prepared compounds (N_1-N_{21}) indicated the disappearance of the aldehyde carbonyl group stretch peak (νC=O), and the disappearance of the symmetrical and asymmetrical stretch peak of the amine group. A strong peak has appeared due to the elastic vibration of the azomethene group (νC=N) at (1643-1608) cm^{-1}, and the appearance of absorption peak at the range (3097-3008) cm^{-1} belonging to the elastic stretch (C-H) aromatic. The appearance of two peaks at the range (2995-2915) cm^{-1} and (2933-2812) cm^{-1} is referred to symmetrical and asymmetric stretching (C-H) aliphatic. In addition to the appearance of a strong peak at (1764-1633) cm^{-1} returns to the amide (C=O) group of sulfa drugs, with the appearance of two absorption peaks at the range (1599-1504) cm^{-1} and (1560-1461) cm^{-1} for stretching (C=C) aromatic [25]. Tables (1 and 2) show some physical properties with infrared spectral data of the prepared compounds.

TABLE 1. Some physical properties and IR spectral data of Schiff base derivatives (N_1-N_{15}).

No.	Substituent groups		M. P. °C	IR (KBr) cm^{-1}						Others
	Ar	Ar'		ν (C-H) Arom.	ν (C-H) Aliph.	ν (C=O) Amide	ν (C=N)	ν (C=C) Arom.	ν (SO_2) Asym. Sym.	
N_1			194-196	3068	2925 2856	1625	1579	1510 1467	1380 1170	ν (O-H) 3473
N_2			188-200	3039	2942 2851	1630	1626	1589 1483	1385 1185	ν (O-H) (3343) ν(NO_2), Asym. (1535) Sym. (1367)

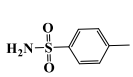
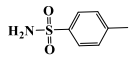
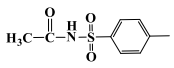
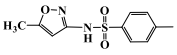
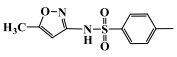
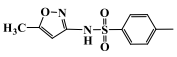
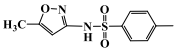
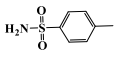
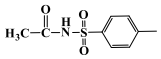
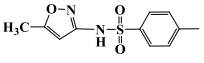
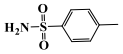
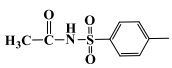
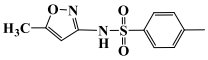
N_4			196-198	3068	2979 2920	1618	1619	1510 1463	1404 1170	ν (O-H) (3452) ν (C-O-C), Asym. (1275) Sym. (1074)
N_5			145-147	3095	2991 2891	1614	1624	1579 1494	1387 1165	ν (N-H) 3349
N_7			225-227	3062	2966 2921	1697	1610	1583 1483	1396 1155	ν (O-H) (3440) ν(NO_2), Asym. (1523) Sym. (1396)
N_{11}			203-205	3022	2915 2886	1764	1641	1599 1480	1383 1172	ν (O-H) 3353
N_{12}			223-225	3089	2995 2832	1642	1619	1593 1481	1377 1168	ν (O-H) (3335) ν(NO_2), Asym. (1537) Sym. (1337)
N_{13}			190-192	3080	2987 2933	1651	1629	1593 1471	1365 1155	ν (C-Cl) 833
N_{15}			205-207	3091	2991 2891	1633	1608	1595 1504	1396 1159	ν (N-H) 3259

TABLE 2. Melting points and IR spectral data of Schiff base derivatives (N_{16}-N_{21}).

No.	Substituent groups	M. P. °C	IR (KBr) cm^{-1}						
	Ar		ν C-H) Arom.	ν (C-H) Aliph.	ν (C=O) Amide	ν (C=N)	ν (C=C) Arom.	ν (SO_2) Asym. Sym.	Others
N_{16}		165-167	3055	2983 2879	1654	1612	1581 1465	1355 1178	ν (N-H) 3353
N_{17}		205-207	3031	2981 2829	1666	1630	1585 1471	1350 1163	ν (N-H) 3260
N_{18}		186-188	3027	2976 2854	1651	1639	1595 1487	1360 1172	ν (N-H) 3270
N_{19}		236-238	3066	2929 2881	1629	1579	1554 1460	1365 1193	ν (N-H) 3299
N_{20}		182-184	3024	2972 2861	1663	1629	1585 1464	1348 1176	ν (N-H) 3350
N_{21}		256-258	3029	2964 2877	1656	1627	1584 1482	1356 1168	ν (N-H) 3360

Characterization of 4-Thiazolidinone Derivatives Compounds (N_{22}-N_{42})

Thiazolidinone compounds (N_{22}-N_{42}) have been prepared from the reaction of Schiff Base derivatives (N_1-N_{21}) with of mercapto acetic acid in dry benzene as a solvent as shown in Scheme 1.The infrared spectra for 4-thiazolidinone (N_{22}-N_{42}) have revealed the disappearance of the medium peak belonging to the (C=N) group and the appearance of a strong peak at the frequency (1680 - 1645) cm^{-1}, corresponded to the elastication of the carbonyl bond (C=O) thiazolidine ring. Additionally, the apperance of other strong peaks at the range (1329-1213) cm^{-1} is attributed to the stretching of the bond (C-N).

The rest of the peaks also maintained their normal ranges on the length of the chain derivatives, as the appearance of absorption peak at range (3098-3016) cm^{-1} belonging to stretching, aromatic (C-H). Moreover, the appearance of two peaks at the range (2987-2871) cm^{-1} and (2893-2816) cm^{-1} for the symmetrical and asymmetrical stretching aliphatic (C-H). Furthermore, two beams have appeared at the range (1610-1510) cm^{-1} and (1562-1431) cm^{-1} due to the vibration of the aromatic (C=C) [23].

Tables (3 and 4) include some physical properties with infrared spectral data of the prepared compounds.

TABLE 3. Melting points and IR spectral data of thiazolidine-4-one derivatives compounds (N_{22}-N_{36}).

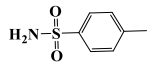
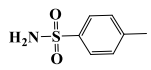
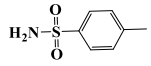
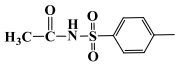
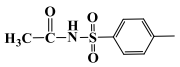
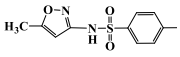
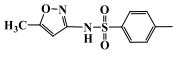
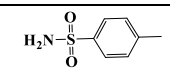
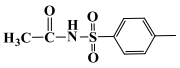
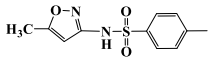
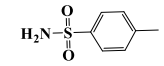
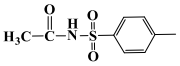
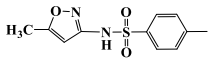
No.	Substituent groups		M. P. °C	IR (KBr) cm^{-1}						
	Ar	Ar -		ν (C-H) Arom.	ν (C-H) Aliph.	ν (C=O) Amide	ν (C=N)	ν (C=C) Arom.	ν (SO_2) Asym. Sym.	Others
N_{22}			221-223	3076	2978 2880	1677	1580	1592 1491	1380 1170	ν (O-H) 3356
N_{23}			165-167	3016	2955 2841	1670	1626	1587 1468	1385 1185	ν (O-H) (3344) ν(NO_2), Asym. (1529) Sym. (1342)
N_{25}			195-197	3068	2979 2920	1618	1619	1510 1463	1404 1170	ν (O-H) (3452) ν(C-O-C), Asym. (1275) Sym. (1074)
N_{27}			180-182	3073	2953 2865	1732	1635	1585 1477	1379 1160	ν (O-H) 3458
N_{31}			119-121	3030	2942 2818	1687	1642	1595 1483	1365 1180	ν (N-H) 3325
N_{32}			251-253	3022	2915 2886	1764	1641	1599 1480	1383 1172	ν (O-H) 3353
N_{35}			240-241	3040	2918 2816	1750	1647	1579 1494	1388 1166	ν (O-H) (3353) ν(C-O-C), Asym. (1270) Sym. (1064)

TABLE 4. Melting points and IR spectral data of thiazolidine-4-one derivatives compounds (N_{37}-N_{42}).

No.	Substituents group	M. P. °C	IR (KBr) cm^{-1}						
	Ar		ν (C-H) Arom.	ν (C-H) Aliph.	ν (C=O) Amide	ν (C=N)	ν (C=C) Arom.	ν (SO_2) Asym. Sym.	Others
N_{37}		178-180	3037	2972 2844	1656	1573	1523 1473	1352 1150	ν (NH_2) 3359,3233
N_{38}		221-223	3053	2945 2879	1685	1630	1589 1466	1350 1163	ν (N-H) 3266
N_{39}		196-198	3024	2963 2840	1676	1639	1539 1489	1362 1155	ν (N-H) 3275
N_{40}		238-240	3067	2981 2869	1666	1579	1598 1458	1365 1193	ν (NH_2) 3352,3277
N_{41}		175-176	3029	2996 2855	1692	1634	1589 1448	1351 1164	ν (N-H) 3348
N_{42}		244-246	3037	2974 2929	1643	1643	1589 1552	1390 1134	ν (N-H) 3328

The mass spectrum of the compound (N_4) ($C_{15}H_{16}N_2O_5S$) has shown the molecular ion (Molecular Ion: 336 (16.2%) and the base peak value appeared at m/z: 167 (100.0%) which is attributed to fractionation $(C_9H_{11}O_3)^+$ as shown in Figure 1. and Scheme 2.

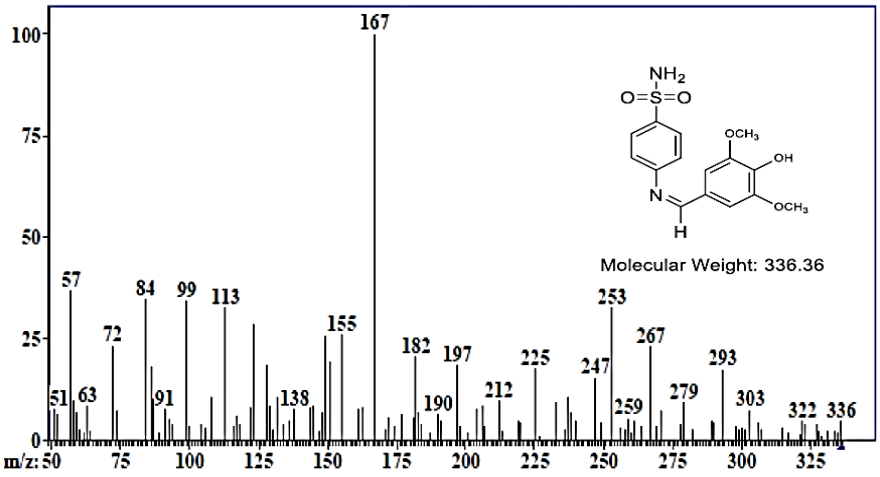
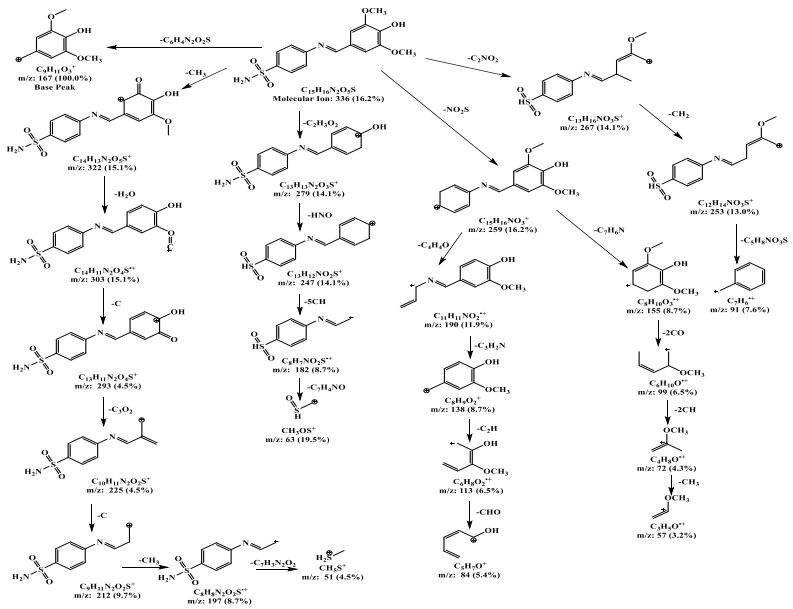


FIGURE 1. Mass spectrum of compound N_4.

The ^{1}H-NMR spectrum of 4-thiazolidinone compound N_{29} has revealed a singlet signal at 3.35 ppm attributed to the HDO protons and a singlet signal was observed at (1.97) ppm attributed to the protons of the CH_3 group labeled (a). A singlet signal appeared at 3.98 ppm corresponded to the protons of the CH_2 group of the thiazolidinone five-membered ring labeled (b). Additionally, a singlet band has appeared at 6.61 ppm represented to the (C-H) proton in the thiazolidinone ring labeled (c) and multiple signals appeared at 7.28-7.87 ppm referred to the protons of the aromatic ring labeled (d) [22] and [26]. Moreover, a single signal appeared at 12.55 ppm contributed with the proton of the (N-H) group labeled (e) as shown in Figure 2.



SCHEME 2. Composite pattern of compound N_4.

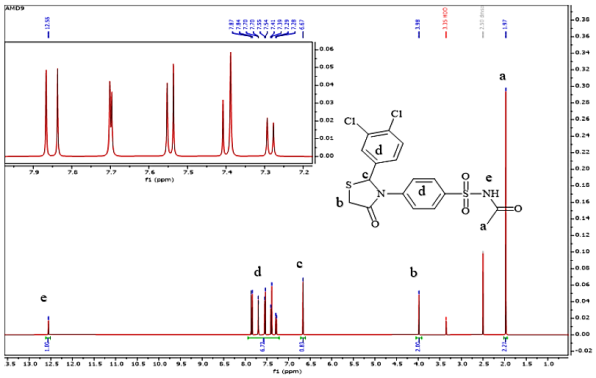


FIGURE 2. ^{1}H-NMR spectrum for compound N_{29}.

Evaluation of the Biological Activity of Some Prepared Compounds

The biological activity has been carried out using newely synthesized compounds (N_{23}, N_{29}, N_{30}, N_{31}, N_{34}, N_{35}, N_{36}, and N_{42}) on two types of bacteria and one type of fungi, where Gram-positive bacteria *(Streptococcus pneumonia)*, Gram-negative bacteria *(Pseudomonas auroginosa)*, and fungs *(Aspergillus spp)*.

The result revealed that all the newly synthesized compounds showed good inhibitory effect in generall toward the tested bacteria and fungi especially at high concentrations compared to the low concentrations. This is related to the high concentration effect. Furthermore, the highest inhibitory effect has been obtained for N_{36}, N_{42} in case of *Streptococcus pneumonia*, N_{34}, N_{36} for *Pseudomonas auroginosa and* N_{23}, N_{36}, N_{42} for *Aspergillus spp* as shown in Tables 5 and 6 and Figures 4-6. These results can be explained by considering the presence of polar groups in the prepared compounds or by comparing the polarity of the prepared compounds with each other or with the standard compounds. The more polarity or the more polar groups the available in compounds will lead to more inhibition

efficiency. However, the lowest inhibitory activity has been recorded for N_{35} in case of *Streptococcus* pneumonia, N_{31} for Pseudomonas auroginosa and N_{35} for Aspergillus spp.

Biological activity effect has relationship the molecular structure and the nature of the substituted groups that are present in the applied materials. The effectiveness of the prepared compounds against bacteria and fungi is attributed to the presence of electron-withdrawing groups such as (Cl, NO_2, the five-membered pyrrole ring) in the prepared compound. Strong electron-withdrawing groups like (NO_2) are more effective than electron-donating groups like (OCH_3) and the five-membered pyrrole ring. Additionally, sulfonamide group inhibits the production of bacteria for folic acid (Vitamin 9).

The mechanism of inhibition can be explained as effect of Gram-positive and Gram-negative bacteria on the distinctive composition of their cell walls. Gram-positive bacteria have a cell wall rich in teichoic acid and a high concentration of peptidoglycan polymer connected by peptide bonds. The thickness of the peptidoglycan layer is (25 nm) in Gram-positive bacteria compared to about (3 nm) in Gram-negative bacteria, allowing for easier penetration of molecules. Gram-negative bacteria contain a lower ratio of peptidoglycan chains with a layer of lipopolysaccharides in addition to phospholipids and lipoproteins, making them highly hydrophobic. The lipopolysaccharide layer in Gram-negative bacteria acts as a protective shield for the bacteria, hindering penetration [27, 28].

TABLE 5. Antibacterial activity values for some of the prepared compounds.

Comp.No.	*Streptococcus pneumonia* (+GVe)			*Pseudomonas aeruginosa* (- GVe)		
	5 (mg/mL)	10 (mg/mL)	15 (mg/mL)	5 (mg/mL)	10 (mg/mL)	15 (mg/mL)
N_{23}	7	10	13	8	11	13
N_{29}	8	9	16	7	9	14
N_{31}	8	11	14	7	10	12
N_{34}	8	9	16	8	11	19
N_{36}	9	13	20	9	11	16
N_{42}	10	15	22	8	12	16
4-minobenzenesulfonamide	4	6	8	5	8	10
N-((4-aminophenyl) sulfonyl) acetamide	3	7	8	6	9	11
4–amino –*N*- (5–methylisoxazole–3-yl) benzenesulfonamide)	5	7	8	8	10	12
Nystatin	6	8	9	7	9	10

Values represent inhibtion zones by cm.

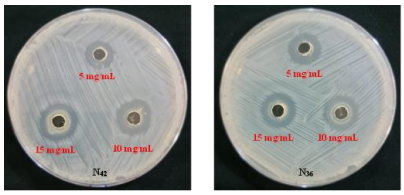


FIGURE 3. Images of biological activity results for (N_{36} and N_{42}) at different concentrations (5, 10 and 15) mg/mL, against *Staphylococcus pneumonia*.

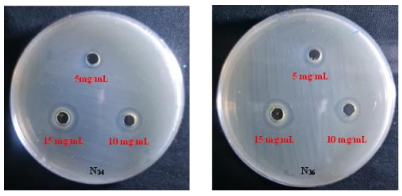


FIGURE 4. Images of biological activity results for (N_{34} and N_{36}) at different concentrations (5, 10 and 15) mg/mL, against *Pseudomonas aeruginosa*.

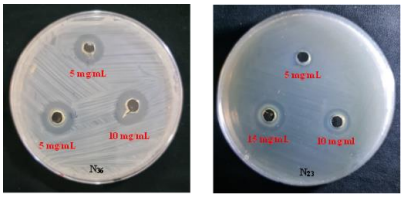


FIGURE 5. Images of biological activity results for (N_{23} and N_{36}) at different concentrations (5, 10 and 15) mg/mL, against *Asspergillus spp*.

TABLE 6.

Comp.No.	*Aspergillus spp*. fungi		
	5 (mg/mL)	10 (mg/mL)	15 (mg/mL)
N_{23}	11	15	20
N_{29}	8	10	12
N_{34}	8	10	12
N_{36}	8	12	18
N_{42}	9	11	15
4-minobenzenesulfonamide	8	10	11
N-((4-aminophenyl) sulfonyl) acetamide	8	11	12
4 – amino – N - (5 – methylisoxazole – 3 - yl) benzenesulfonamide	7	10	11
Nystatin	8	11	12

Antifungal activity values for some of the prepared compounds.

CONCLUSION

Some new thiazolidinone derivatives have been successfully prepared through the cyclization reaction of Schiff bases with mercapto acetic acid, cantaining some active pharmaceutical modes. The all structures for the final series of the chemical products have been confirmed depending on the FTIR and ^{1}H-NMR. In addition to using the mass spectroscopy for some of the newely synthesized thiazolidinone for the products structure verified purposes. Generally, the new prepaered thiazolidinone derivatives h reveal to have good antibacterial and antifungi activity towards the applied bacteria and fungi particularly at high concentrations 15 mg/mL. The results also showed the highest inhibtion zone diameter value for N_{36}, N_{42} against *Streptococcus pneumonia*, N_{34}, N_{36} for *Pseudomonas auroginosa* and N_{23}, $N_{36,}$ N_{42} for *Aspergillus spp.* This is ascribred to the different in the polarity of the new chemical derivatives with each other and standard materials. While the lowest inhibtion zone diameter value has been observed for N_{35} in case of *Streptococcus pneumonia*, N_{31} for *Pseudomonas auroginosa* and N_{35} for *Aspergillus spp*. The results suggest bioactive materials from above to be considered for further investigation.

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