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Synthesis, Characterization, and Antimicrobial Evaluation of Thiadiazole Derivatives Derived from 2-Amino-5-Thio-1,3,4-Thiadiazole

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Abstract

This manuscript introduces a series of novel Schiff base and heterocyclicring compounds, focusing on derivatives of 1,3-oxazepine and thiazo-lidinone.The derivative (2-Hydroxy-N-(5-mercapto-[1,3,4] thiadiazol-2-yl)-2-phenyl-acetamide was created by reacting ethyl mandelate ester[M_1] and 2-amino-5-thio-1,3,4-thiadiazole compound to produce new compound [M_2] and after that, compound [M_2] was reacted with hydrazine hydrate 99% in dry DMF solvent, yielding the compound (N-(5-Hydrazino-[1,3,4]thiadiazol-2-yl)-2-hydroxy-2-phenyl-acetamide [M_3]. In contrast , the Schiff base compound [M_4] were synthesized by reacting compound [M_3] with aromatic heterocyclic aldehyde (furan-2-carbaldehyde) in the presence of glacial acetic acid as a catalyst, and then Schiff base [M_4] was reacted with maleic anhydride in dry benzene as a solvent to produce (1,3-Oxazepine) derivative [M_5]. Additionally, the thiazolidinone derivative [M_6] was synthesized through the reaction of equimolar amounts of (N-[5-(N'-Furan-2-yl-methylene-hydrazino)-[1,3,4]-thiadiazol-2-yl]-2-hydroxy-2-phenyl-acetamide [M_4] with thioacetic acid compound in chloroform as a solvent. The structural formula of all derivatives was confirmed by FT-IR and (^{1}HNMR, ^{13}CNMR) spectroscopy. The synthesized derivatives [M1-M6] were screened for their evaluated for antibacterial activity against *S. aureus*, *S. epidermidis*, *E. coli*, *Klebsiella sp.*, and the fungus Candida albicans. Dimethyl sulfoxide (DMSO) was used as the solvent. Also, the ampicillin compound was used as the standard drug for comparison.

1. Introduction

The most widely used important chemical is 1,3,4-thiadiazole. Thiadaizole condensed heterocyclic compound have unique chemical and biological properties [1]. In the design of drugs. Thiadiazole derivatives and their various biological activities, include anti-cancer [2- 5], anti-inflammatory [6, 7], anti-tuberculosis [8], antibacterial [9], antifungal [10], antivirus [11, 12], anti-leishmania [13, 14] and they are also used to control corrosion [15], as dyes [16], and as catalyst [17].

Schiff bases are an important class of compounds that contain an azomethine group (-C=N) and are synthesized by the condensation of active carbonyl with primary amine [18]. These compounds have attached attention due to a wide range of biological properties such as anthelmintic [19], antimicrobial [20], fungicidal activities [21], pharmaceutical fields and industrial applications [22-26].

In 1965, oxyzepine derivative were developed for the treatment of psychoneurosis characterised by anxiety and tension [27]. Oxazepine molecules are of medical and biological important, including pharmacological effects such as enzyme inhibitors [28], analgesics, and antidepressants [29].

Thiazolidine is a sulfur containing pentacyclic compound that has been widely found in nature in various forms. Thiazolidine ring system has a special important role from the fact that it plays an important role in pharmaceutical chemistry, which had a wide range of biological activity [30, 31].

Thaidiazole ring is well known biologically active compounds with wide spectrum of biological applications, thus the aim of this work is design and synthesis of new compounds which their chemical structures contain beside thaidiazole other biologically active components like oxyzepine and Thiazolidine. The resulted new compounds are expected to possess more biological activities due to the presence of two or more biologically active components in their molecules leading to important applications.

2. Experimental Procedure

2.1. Materials

All chemicals and solvents used in the synthesis compounds were obtained from companies such as Merck, British Drug Houses (BDH), Fulka and Sigma Aldrich.

2.2. Characterization

Melting points of synthesized compounds were determined using the Gallenkamp MFB-600 capillary device Stuart SMP 10, Biocote, uk in the Mustansiriyah University, College of Science. FT-IR spectra were recorded using (Bruker model FTIR-8400S). Infrared spectrophotometer, range [4000-400] in the Mustansiriyah University, College of Science. By using DMSO-d6 as the solvent and tetra-methylsilane (TMS) as internal standard, 400 MHz ^{1}-H, ^{13}CNMR spectra utilized a Bruker BiospinGmb H model ultra-shield in the Al -Albyt University-Jordan.

2.3. Synthesis Methods

2.3.1. Ethyl mandelate [M_1]:

Compound [M1] is prepared by Samuel K. Tulashie et al. [32].

2.3.2. Synthesis of compound (2-Hydroxy-N-(5-mercapto-[1,3,4] thiadiazol-2-yl)-2-phenyl-acetamide) [M_2]:

Ethyl mandelate [M_1] (0.18 g, 0.001 mol) was dissolved in 50 mL of dried fresh distilled THF for the synthesis of compound M_2. 5-amino-2-marcapto-1,3,4-thiadiazole (0.13 g, 0.001 mol) was added to the solution. After 6 hours of stirring and reflux, the mixture was cooled and the precipitated solid was filtered. A after the solvent was removed, the residue was crystallised from ethanol.

2-Hydroxy-N-(5-mercapto-[1,3,4]thiadiazol-2-yl)-2-phenyl-acetamide:
White solids, yield (%72, m.p:226-227°C). FTIR (ATR, cm^{-1}), ν max: 3400 (-OH), 3185 (NH), 3053 (Ar-CH), 2927, 2862 (CH Alph.), 2676 (SH), 1673 (amide C=O), 1606 (C=N), 1582, 1498, 1437 (Ar C=C). ^{1}HNMR (400 MHz, DMSO-d6): 10.9 ppm (s, IH, SH), 9.5ppm (s, 1H, CONH), 8.4- 6.9 ppm (m, 5H, aromatic), 6.8 (s, 1H, CH), 5.2ppm (s, IH, OH). ^{13}CNMR (100 MHz, DMSO-d6): 167 (amide CONH), 157,158 (C thaidazole ring), 129- 109 (C aromatic ring), 89 (C-OH).

2.3.3. Synthesis of compound (N-(5-Hydrazino-[1,3,4]thiadiazol-2-yl)-2-hydroxy-2-phenyl-acetamide [M_3]:

Compound [M_2] (0.26 g, 0.001 mol) was dissolved in (10 mL) dry DMF, followed by (0.1mL, 0.001mol) hydrazine hydrate. After a 10hrs reflux period, the reaction was monitored with ethyl acetate paper to detect H_2S gas release. After completion of the reaction, the solvent was evaporated to give a precipitate and crystallized ethanol [33].

N-(5-Hydrazino-[1,3,4]thiadiazol-2-yl)-2-hydroxy-2-phenyl-acetamide:
Yellow solids, yield (78%, m.p. 168-170 C). FTIR (ATR, cm−1), ν max: 3295(OH), 3201, 3167, 3113 (NH2, NH), 3079 (Ar-CH), 2958, 2853(CH Alph.), 1703 (amide C=O), 1621 (C=N), 1591, 1570, 1521 (Ar C=C). ^{1}HNMR (400 MHz, DMSO-d6): 9.5ppm (s, 1H, CONH), 8.1 – 7.2 ppm (m, 5H, aromatic), 6.7 ppm (s, 1H, CH), 6.5 ppm (s, 1H.NH), 5.3ppm (s, IH, OH), 4.08 ppm (s.2H, NH_2). ^{13}CNMR (100 MHz, DMSO-d6): 166 (amide CONH), 159-157 (C thaidazole ring), 129-112 (C phenyl aromatic), 88 (C-OH).

2.3.4. Synthesis of compound (N-[5-(N'-Furan-2-ylmethylene-hydrazino)-[1,3,4]thiadiazol-2-yl]-2 hydroxy-2-phenyl-acetamide [M_4].
The ethanol solution of (0.26 g, 0.001 mol) of [M_3] compound was added to ethanol solution of (0.09 g, 0.001 mol) of Furan-2-carbaldehyde, the mixture was continuously stirred and refluxed for 8 hrs. The solution was cooled, and the resulting solid product was separated by filtration, washed with diethyl ether, and then dried in a vacuum over anhydrous calcium chloride [34].

N-[5-(N'-Furan-2-ylmethylene-hydrazino)-[1,3 ,4]thiadiazol-2-yl]-2-hydroxy-2-phenyl-acetamide:
Light yellow solids, yield (68%, m.p. 133-136°C). FTIR (ATR, cm^{-1}), ν max: 3286(OH), 3167, 3113 (NH), 3073, 3059, 3012 (Ar-CH), 2958, 2879 (CH Alph.), 1706 (amide C=0), 1641 (C=N), 1591, 1571, 1525 (Ar C=C). ^{1}HNMR (400 MHz, DMSO-d6): 9.6ppm (s, 1H, CONH), 8.6 ppm. (s, 1H, N=CH), 7.7-7.2 ppm (m, 8H, aromatic), 6.8 ppm (s, 1H, CH),6.6 ppm(s, 1H, NH), 5.3ppm (s, IH, OH). ^{13}CNMR (100 MHz, DMSO-d6): 171 (amide CONH), 165 (=CH), 161-130 (C Hetro ring), 126 -112 (C phenyl aromatic), 93 (C-OH).

2.3.5. Synthesis of compound N-[5-(2-Furan-2-yl-4,7-dioxo-4,7-dihydro-[1,3]oxazepin-3-ylamino) [1,3,4]thiadiazol-2-yl]-2-hydroxy-2-phenyl-acetamide) [M_5]:
In a (20mL) solvent (dried benzene), a combination of compound [M_4] (0.34 g, 0.001 mol) and maleic anhydride (0.098g, 0.001 mol) was melted. The mixture was mixed and refluxed for 9 hrs. Thin layer chromatography (TLC) is used to monitor the development of the reaction (hexane: ethyl acetate 5:2). The excess solvent was distilled, and the resulting solid crystals were filtered and recrystallized from dioxin [35].

N-[5-(2-Furan-2-yl-4,7-dioxo-4,7-dihydro-[1,3]oxazepin-3-ylamino)-[1,3,4]thiadiazol-2-yl]-2-hydroxy-2-phenyl-acetamide:
Yellow solids, yield (69%, m.p. 133-136°C). FTIR (ATR, cm^{-1}), ν max: 3248(OH), 3161(NH), 3025 (Ar-CH), 2905, 2839 (CH Alph.), 1749.1691,1656 C=O), 1600 (C=N), 1503, 1484, 1456 (C=C). ^{1}HNMR (400 MHz, DMSO-d6: 11.5 ppm (s, IH, NH), 9.5ppm (s, 1H, CONH), 8.5- 7.6 ppm (m.8H, aromatic), 7.66-6.04 ppm (dd., 2H, CH=), 5.7ppm (s, 1H, CH), 5.5ppm (s, 1H, OH). ^{3}C NMR (100 MHz, DMSO-d6): 180 ppm (C lacton), 177ppm (C lactam), 163 ppm C amide), (148,150) ppm (CH=CH), (161,160,158,125) ppm (C hetero ring), 129 - 128 (C aromatic), (115, 92) ppm (C-O).

2.3.6. Synthesis of compound (N-[5-(2-Furan-2-yl-4-oxo-thiazolidin-3-ylamino)-[1,3,4]thiadiazol-2 yl]2-hydroxy-2-phenyl-acetamide [M_6].
A solution of compound [M_4] (0.26g, 0.001mol,) in 25 mL chloroform was added to the mixture with thioglycolic acid (0.001 mol, 0.35 mL) and refluxed for 10 hrs. Thin layer chromatography (TLC) utilizing the hexane ethyl acetate system (3:1) was used to monitor reaction completion. The solvent was recovered under reduced pressure, and the residue was treated with a 10% $NaHCO_3$ solution to remove the excess mercaptoacetic acid before being washed with water, dried, and recrystallized from ethanol [36].

N-[5-(2-Furan-2-yl-4-oxo-thiazolidin-3-ylamino)-[1,3,4] thiadiazol-2-yl]-2-hydroxy-2-phenyl acetamide:
Brown solids, yield (67%, m.p. 272-274°C). FTIR (ATR, cm^{-1}), ν max: 3255(OH), 3194(NH), 3078, 3085 (Ar-CH), 2952, 2885 (CH Alpha), 1731, 1712 (C=O), 1656 (C=N), 1582, 1526, 1512, 1456 (C=C). ^{1}HNMR (400 MHz, DMSO-d6): 10.01(s, 1H, NH), 9.5 (s, 1H, CONH), 8.5-6.7 (m, 8H, ArH), 6 (s, IH, N-CH), 5.6 (s, 1H, OH), 5.2 (s, 1H, CH), 3.3 (s, 2H, CO-CH2-S). ^{13}C NMR (100 MHz, DMSO-d6): 167 ppm (CO thiazolidin ring), 164ppm (amide CON), (161-130) ppm (C hetro ring), (126 -112) ppm (C aromatic), 94 ppm (C-OH), (57, 35) (CH2, CH thiazolidin ring).

2.4. Biological Activity of Synthesis Compounds

Biological activities In vitro antimicrobial testing effects of thiadiazole derivatives were estimated against four bacterial strains namely *(S. aureus, S. epidermidis, E. coli, Klebsiella sp. and fungi candida albicans).* The antimicrobial activity was determined using the agar well diffusion method [37].

Dimethyl sulfoxide worked as a control and the test was outright at 100mg/mL concentration using (DMSO) as solvent and ampicillin was taken as the standard compound. The fungi and 4 bacteria was sub cultured in agar. The plates were incubated at 37°C and checking after 24 hrs. For bacteria and 48 hrs for fungi. Inhibition zones caused by these compounds were determined and list in table (Table1).

3. Results and Discussion

All reactions of the prepared compounds and structures was displayed in Figure (1). The structures of the compounds was characterized on the basis of thin-layer chromatography (TLC) and spectroscopic data.

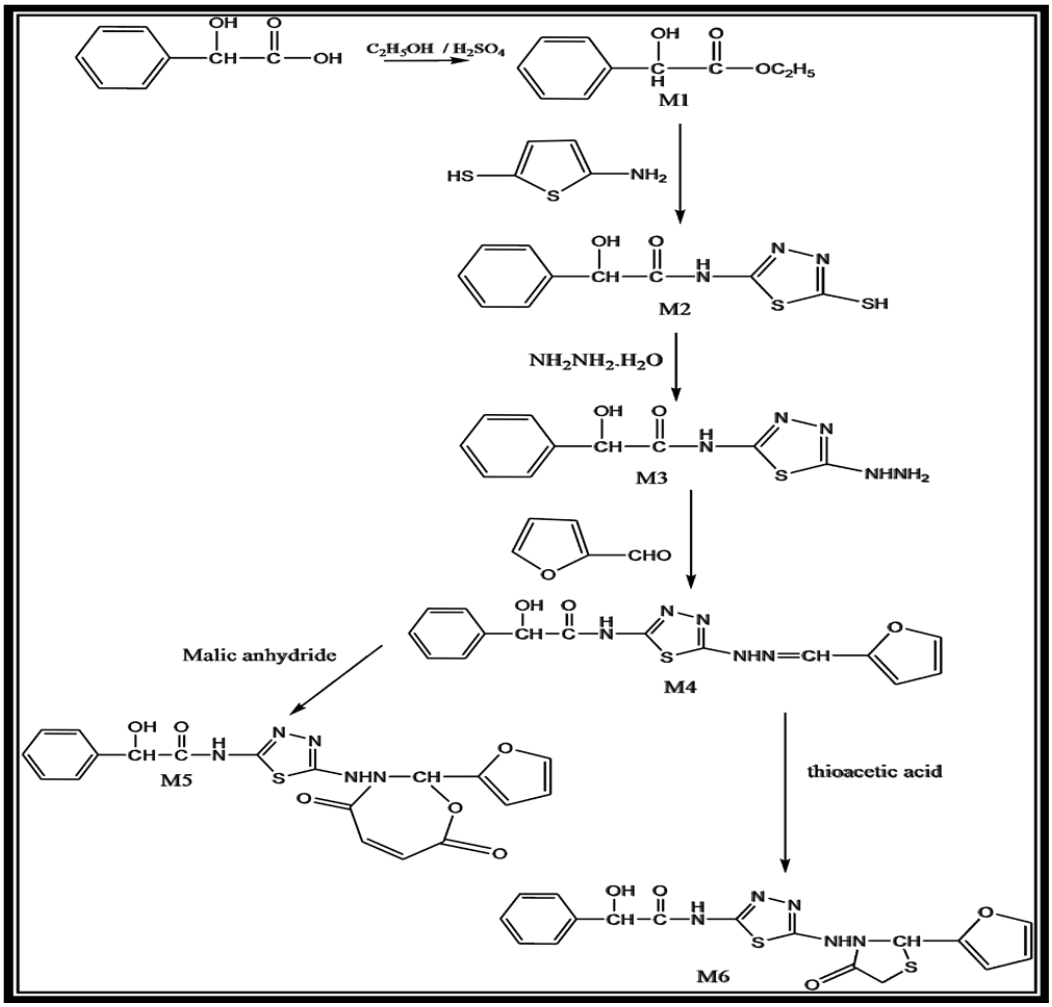

Figure (1): The reaction compounds (M_1-M_6) and structures.

Compound [M_1] is the main intermediate for the compounds synthesized later in this work. It has been prepared by the condensation of the mandelic acid with ethanol in the presence of concentrated sulfuric acid. Compound [M_2] was prepared by the reaction of compound [M_1] and 5-amino-2-marcapto -1,3,4-thiadiazole. FTIR spectrum of compound [M_2] in Figure (2) shows the appearance of clear absorption bands at υ (1673) cm^{-1} and υ (2676) cm^{-1} related to stretching vibration for (C=O amide) and (SH) group respectively [38]. The ^{1}HNMR spectrum in DMSO-d6 as a solvent shows the following data: 10.9 ppm (s, 1H, SH), 9.5ppm (s, IH, CONH), 8.4 – 6.9 ppm (m, 5H, aromatic), 6.8 (s, 1H, CH), 5.2ppm (s, IH, OH). The ^{13}CNMR spectrum in DMSO- d6 as a solvent shows the following data: 167 (amide CONH), (157-158) (C thaidazole ring), (129-109) (C aromatic ring), 89 (C-OH).

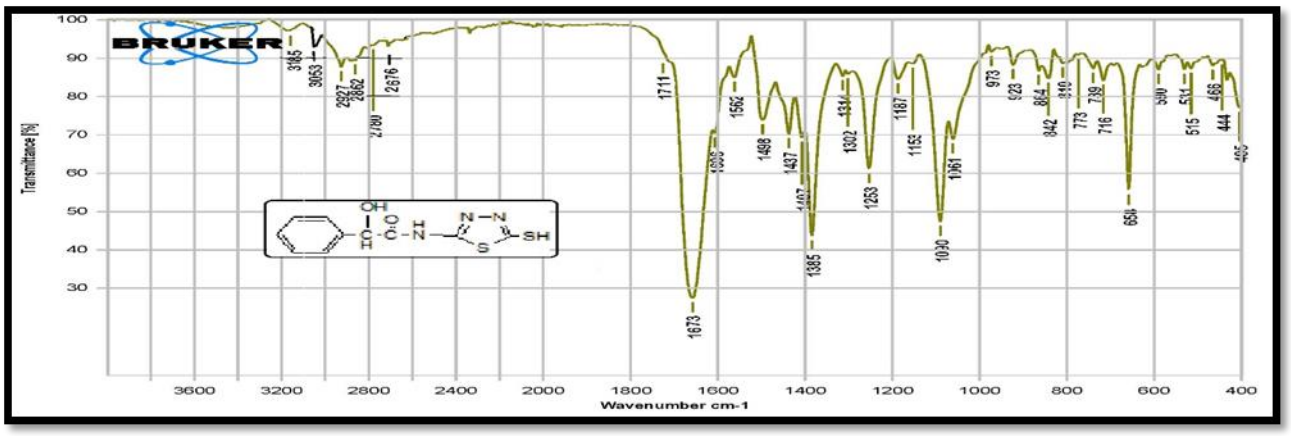

Figure (2): FTIR Spectrum of compound [M_2].

Compound M_3 was synthesized by reaction of compound M_2 with hydrazine hydrate to add NH2-NH- group instead of SH group [39]. FTIR spectrum of compound [M_3] in the Figure (3) shown appearance clear absorption bands at (3201-3113 cm^1) attributed to the asymmetric and symmetric stretching vibration of (NH2, NH) group and disappearance of absorption bands at 2676 (SH) for compound [M_2] this Evidence of the formation of compound M_3, Other absorption band at υ (1703) cm^{-1} related to stretching vibration for (C=O amide) [38]. The ^{1}HNMR spectrum of compound [M_3] showed the chemical shifts at: 9.5ppm (s, 1H, CONH), 8.1 – 7.2 ppm (m, 5H, aromatic), 6.7 ppm (s, 1H, CH), 6.5 ppm (s, 1H, NH), 5.3ppm (s, IH, OH), 4.08 ppm (s.2H, NH_2). ^{13}CNMR Spectrum of compound [M_3] exhibited these signals (DMSO-D6, ppm) 166 (amide CONH), (159-157) (C thaidazole ring), (129-112) (C phenyl aromatic), 88 (C-OH).

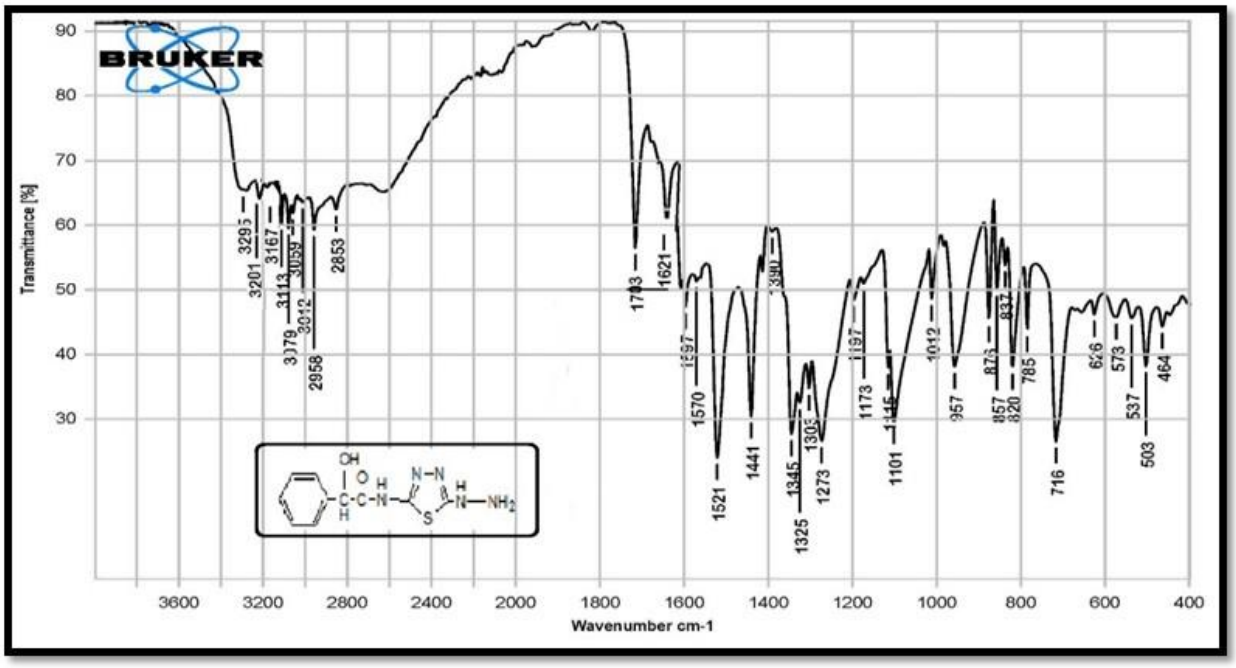

Figure (3): FTIR Spectrum of compound [M_3].

Schiff base [M_4] was synthesized by condensation of one mole of compound [M_3] with one mole of Furan-2-carbaldehyde in the presence of absolute ethanol as solvent. FTIR spectrum of compound [M_4] in the Figure (4) shown disappearance of the stretching vibration bands for (asymmetric and symmetric) for NH_2 group of compound [M_3] at 3167, 3113 cm' and appearance absorption band at 1641 c m^{-1} due to isomethane (C=N) group in compound. ^{I}HNMR spectrum of this base DMSO-d6 as a solvent show the following data signals at 9.6ppm due to proton of (amide CONH), 8.6 ppm for imine proton (N=CH). Multiplet signals at 7.7-7.2 ppm for aromatic

protons and singlet signals at 6.8 ppm, 6.6 ppm and 5.3 ppm due to (CH, NH, OH) respectively. The ^{13}C-NMR spectrum of compound M_4 showed signals at 171ppm for amide carbon, 165 ppm (N=CH), 161-130 ppm for furan carbons, (126 -112) ppm for aromatic carbons, 93ppm (C-OH).

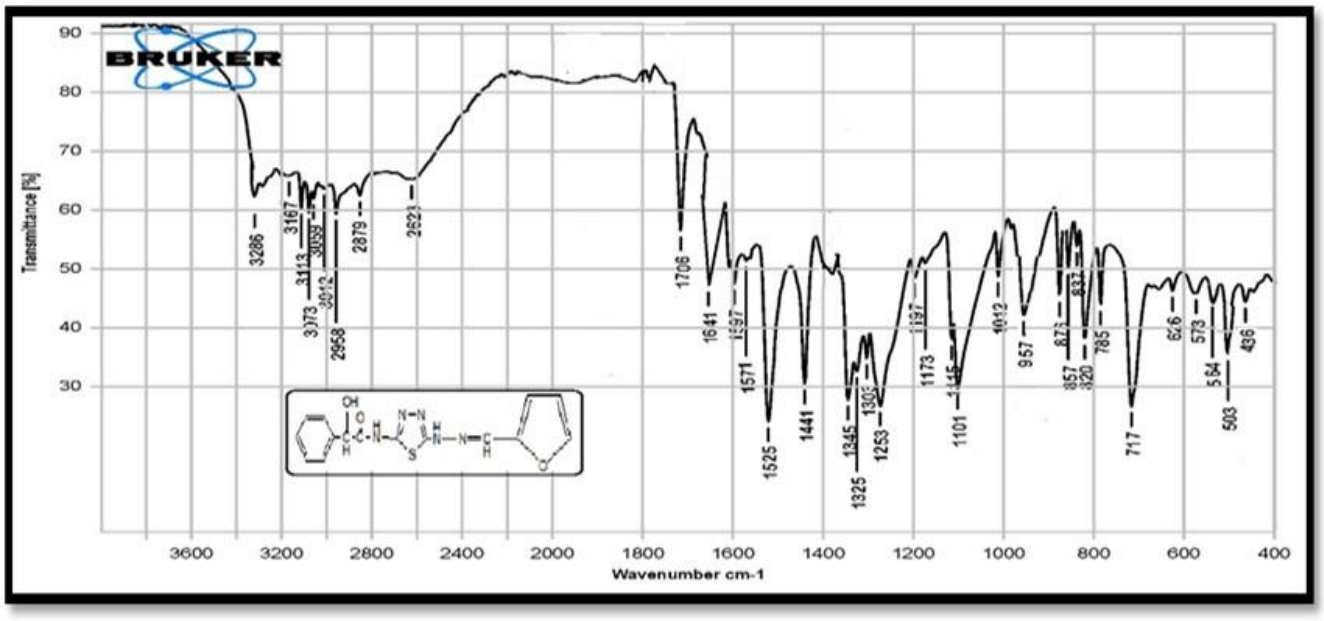

Figure (4): FTIR Spectrum of compound [M_4].

The reaction of a Schiff base [M_4] with maleic anhydride in the presence of dry benzene as a catalyst to produce the compound oxazapine [M_5]. FTIR spectrum of oxazepine compound M_5 in Figure (5) showed the appearance of absorption bands at υ (1749.1691) cm^{-1} due to (C=O lactone and lactam) and υ (1656) cm^{-1} υ (C=O amide group). The ^{1}HNMR spectrum of compound [M_5] shown the following data signals at: 8-11.5 (s, IH, NH), 9.5 (s, 1H, CONH), 8.5 - 7.6 (m, 8H, aromatic), 7.66-6.04 (dd, 2H, CH=), 5.7 (s, 1H, CH) 5.5 (s, 1H, OH). The ^{3}CNMR spectrum of compound M_4 showed signals at (180,177) ppm for (Carbon lactone, lactam respectively), and signals at (148,150) ppm for carbon CH=CH, respectively.

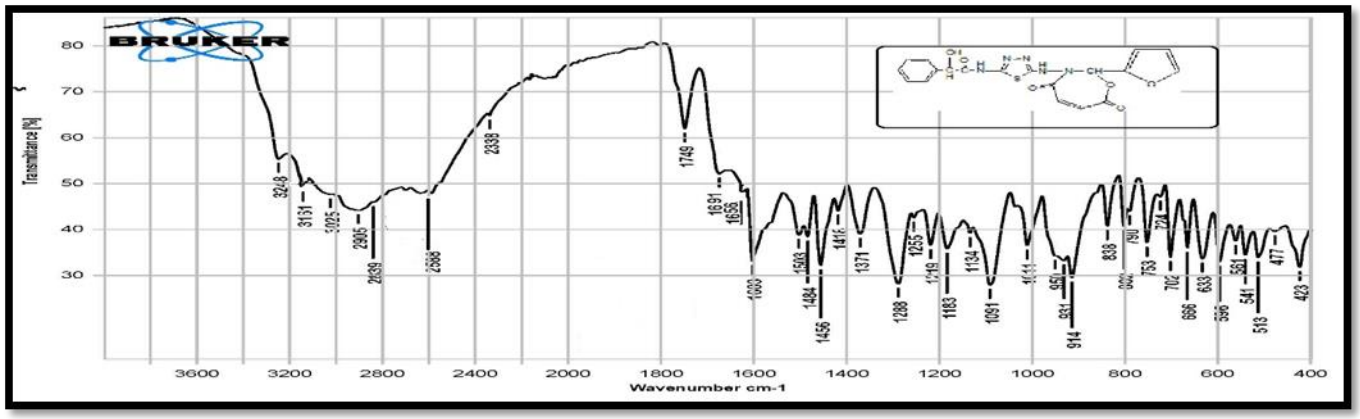

Figure (5): FTIR Spectrum of compound M_5.

Also, the thiazolidnone compound [M_6] was synthesised by reaction of a Schiff base M_4 with thioglycolic acid in chloroform as solvent. FTIR spectrum of compound [M_5] in Figure (6) showed the appearance of absorption bands at υ (1731) cm^{-1} and υ (1751) cm^{-1} due to (C=O, C-S) for of thiozolidinone ring [38]. The ^{1}HNMR spectrum of thiazolidnone M_6 DMSO-d6 as a solvent shows the following data signals at 8=3.3 ppm (s, 2H, CO-CH$_2$-S) and 6

ppm (s, IH, N-CH). The ^{13}CNMR spectrum of compound M_6 showed signals at = (167, 57, 35) ppm for Carbon, (C=O, CH2, CH thiazolidin ring), respectively.

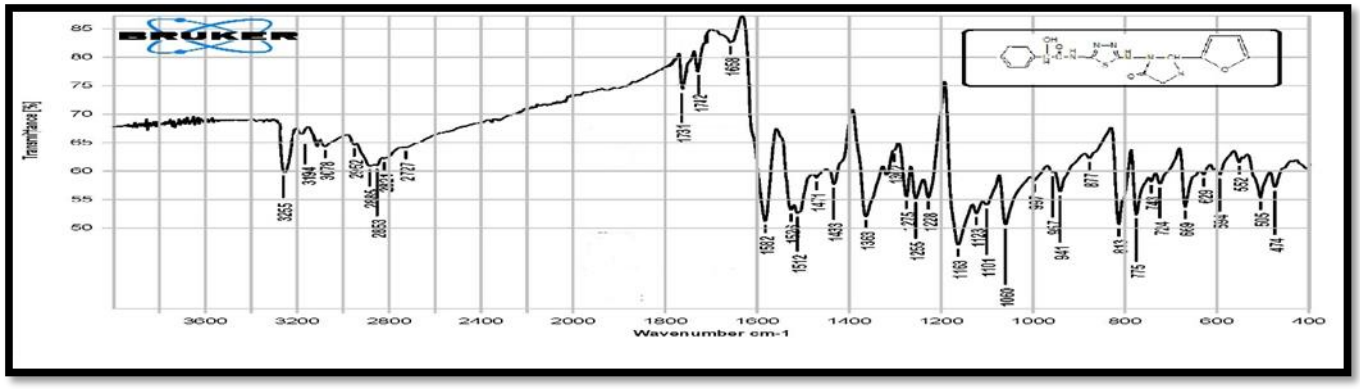

Figure (6): FTIR Spectrum of compound [M_6].

4. Biological Activity

A comparative zone of inhibition (mm) for compounds [M_2-M_6] and standard drugs are reported in Table (1). From which it is clear that the compounds M_5, M_6 have a high degree of anti-bacterial activity and antifungal activity compared to the [M_2-M_4] compound in comparison with standard drugs .Our believe, compounds [M_5] and [M_6] are due to the presence of oxazepin and thiazolidnone rings in that have biological activity as found in the literature, but all compounds [M_2-M_6] showed lower activity than amoxicillin as a standard drug because amoxicillin drug contains active groups, including a beta-lactam ring, which has high effectiveness against bacteria and viruses [40].

Table (1): Antimicrobial evaluation of compounds.

Comp.			inhibition zone (mm) at 100 mg/mL		
	Gram positive			Gram negative	Fungi
	S .aureus	***S. epidermidis***	***Klebsiella sp***	***E.coli***	***candida albicans***
M_2	**2**	**3**	**3**	**2**	**2**
M_3	**2**	**4**	**3**	**4**	**3**
M_4	**4**	**3**	**4**	**3**	**4**
M_5	**7**	**6**	**7**	**8**	**9**
M_6	**9**	**11**	**10**	**10**	**15**
Amoxicillin	**10**	**17**	**19**	**16**	**21**

5. Conclusions

Six new compounds were synthesized and characterized on the basis of analytical (melting point, colour, thin-layer chromatography (TLC) and spectral data such as (FTIR and ^{1}H, ^{13}CNMR spectroscopy). The analysis of these compounds were proven formation of compounds. In addition, some of the prepared compounds showed good antibacterial activity against the antibacterial such as *(S .aureus, S. epidermidis, E.coli, Klebsiella sp. and fungi candida albicans).*

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Conflict of Interest: The authors declare that there are no conflicts of interest associated with this research project. We have no financial or personal relationships that could potentially bias our work or influence the interpretation of the results.

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