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RESEARCH ARTICLE

Synthesis and Biological Activities of Some New Derivatives Based on 2-amino-5-mercapto-1, 3, 4-Thiadiazole Containing Imide, β-Lactam Rings

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Abstract

New series of 2-amino-5-mercapto-1,3,4-thiadiazole derivatives compounds are synthesized [S_1-S_4], then converted to Schiff's base [S_5-S_{10}] which is reacted with chloro acetyl chloride due to the existence of β-Lactam compound[S_{11}-S_{16}]. The prepared derivatives are identified by infrared spectra studies, ^{1}HNMR, and physical properties. The antibacterial strains have been investigated: an activity has been shown against Gram (+ve) bacterial (stapylococus and Gram (- ve) bacteria (Esherichiacoli).

Key words: *1, 3, 4-Thiadiazole, Schiff bases, Heterocyclic rings, Biological activity.*

Introduction

The heterocyclic compounds have attracted the attention of researches over the times. Hetrocyclic compound have wide application in pharmaceutical and chemical fields. There are many researches concerning heterocyclic compounds such as (thiazole, triazole, oxazole, tetrazole) and so on [1-4]. Thiadiazole is one of heterocyclic compounds that consist of five members containing two nitrogen atoms and one sulpher atom as hetro atoms. There are several isomers of thiadiazole as shown in Figure (1) [5].

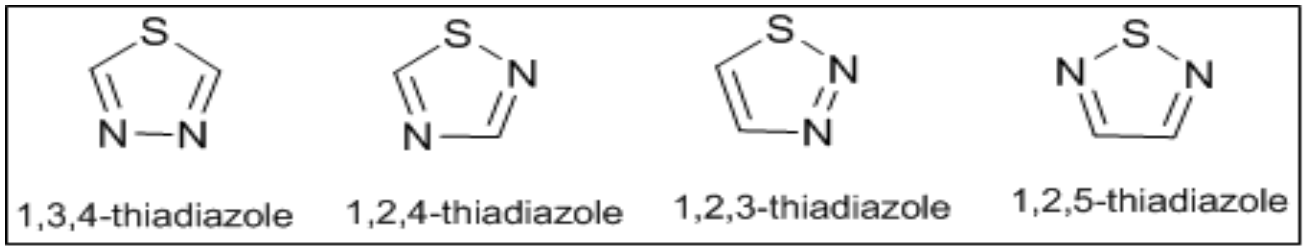


Figure 1: Structure of Thiadiazole Isomers

In the middle of these four forms of thiadiazole, 1, 3, 4- thiadiazole is famous. 1,3,4-Thiadiazole was first defined in 1882 by Fischer and further advanced by Busch and his coworkers [6].Works study exposed that many thiadiazoles have resulted in many possible medications and are known to display a broad range of pharmacological properties [7]. The specific pharmacological activities including antitumor [8] antiviral, antibacterial, amoebicidal, anti-inflammatory, antipyretic, anticancer, antischistosomal [9] herbicide, insecticide, pesticidal and hypoglycemic [5].Triazole contains unsaturated rings, that contain three nitrogen atoms [10].Triazole compounds are different in the biological effectiveness whether their rings present alone or in case of fusing with other rings and they have biological activities [11] like anti-inflammatory [12] and have affected the growth in plants [13].Cyclic imides considered as N-diacyl derivatives of ammonia or amine with the general structure in Figure (2) [14].

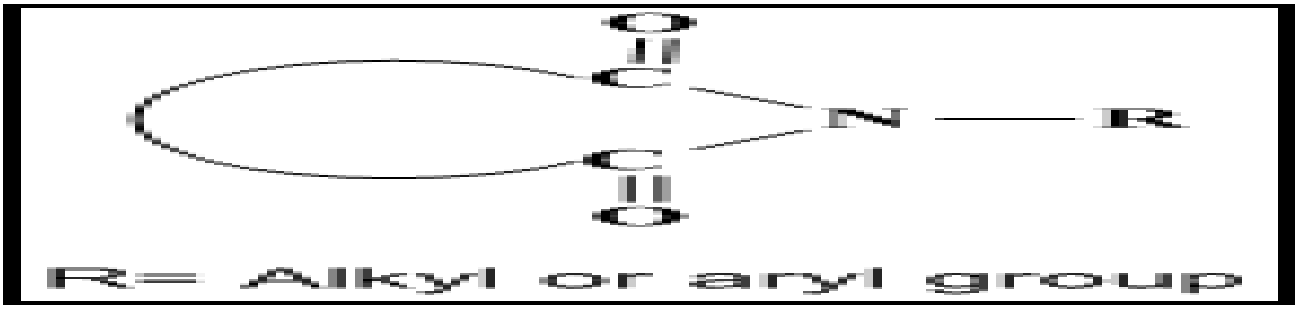


Figure 2:

Most cyclic imides which are used as plastic modifiers to improve heat resistant, antioxidant, and anti foul ant [15]. Schiff's bases were first stated by Hugo Schiff in 1864 [16]. They are an important discussion of organic compounds due to wide spectrum of biological activities such as anti-malarial [17], antifungal [18], antibacterial [19], anti-tubercular [20], antiviral [21], and proliferative [22]. The common structural feature of these compounds is the azomethine group with the general formula where R and R^1 are alkyl, aryl, cycloalkyl, or heterocyclic groups [23] Figure (3).

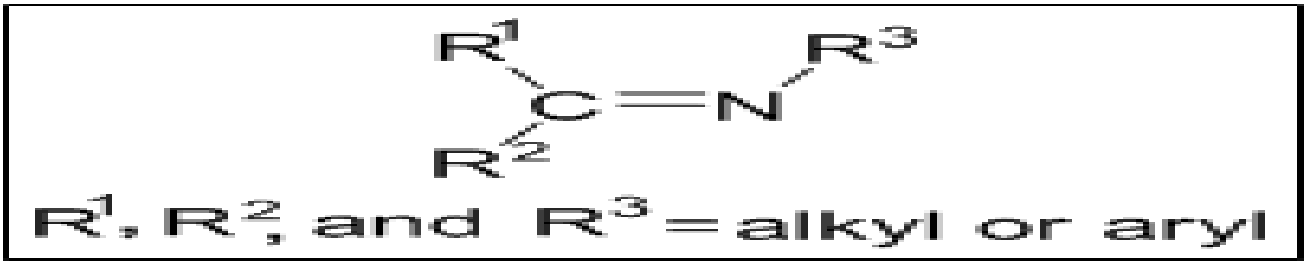


Figure 3:

ß-lactam represents heterocyclic amide ring, consisting of three carbon atoms and one nitrogen atom [24].ß-Lactams are an intensively studied family of heterocycles primarily because of their biological activity. For example, ß-Lactam antibiotics such as penicillins and cephalosporins have occupied a central role in the fight against pathogenic bacteria [24]. Beta lactam antibiotics are considered among the most important drugs for the history of mankind, and, due to their ease of delivery, potent activity, relatively low toxicity and low costs, they still remain among the most frequently used classes of antimicrobial drugs [25].

Material and Methods

All chemicals were supplied from diverse corporations such as Thomas baker, Merck, BDH, GCC and Scharlau and used without further purification. Melting points were determined on an electro thermal melting point apparatus (Stuart Germany), and they were uncorrected. End of purity and reaction of all compounds were checked on aluminum coated T.L.C plates 60 F245 (E. Merck) by using appropriate solvent as the mobile phase and imagined under iodine vapor. Resolves of infrared spectra were done and recorded as a KBr disks in the range of (400 - 4000 cm^{-1}) using FTIR Shimadzu (Japan).The proton ^{1}H-NMR spectra were tested for the synthesized compounds using Bruker DMX-500 spectrophotometer (500 MHZ, solvent DMSO-d_6).

Preparation of Compound (2,5-Dimercapto-1,3,4-Thiadiazole) [S_1] [26]

Thiosemicarbazide (0.05 mol, 4.56 gm) has been dissolved in (15) ml of absolute ethanol then (0.005 mol, 2.84 gm) of anhydrous sodium carbonate added (after drying for 30 minute in 40 °C) with continues stirring, (12 ml) of CS_2 added and the mixture refluxed in sand bath at temperature (50)°C for (1) hrs then increase the temperature to (120-130) °C for (7) hrs, After the completion of the reaction (checked by T.L.C), the mixture cooled at room temperature, the precipitate filtered and washed by hot distilled water, then (drop by drop) of concentrated HCl added to the filtered until precipitate shown, the precipitate washed by cold dist. water to remove acid presence.

To indicate the presence of the acid, used a solution of $AgNO_3$ (0.01N), the clarity of the filtered mean that the acid has been removed. The precipitate purified by purification from distilled water then dried.

The physical properties of compound [S_1] are shown in Table (1)

Preparation of Compound [1,2,4] triazolo [3,4-*b*][1,3,4] thiadiazole- 3, 6-diamine [S_2] [27]

Compound [S_1] (0.015 mol, 2g) reaction with thiosemicarbazide (0.015 mol ,1.36 g) in round bottom flask ,the mixture was dissolved in (10) ml of absolute ethanol then was refluxed for (5) hrs. After the completion of reaction (checked by T.L.C), the mixture was filtered and purified by re-crystallization from distilled water then dried .The physical properties of the prepared compound [S_2] are given in Table (1).

Preparation of Imide Compounds [S_3, S_4] [28]

Compound [S_2] (0.006 mol,1g) has been dissolved in (10) ml of dry benzene then add different anhydride {succinic anhydride and itaconic anhydride} with (3) drops glacial acetic acid. The mixture was refluxed with stirred for (5) hrs. After the completion of reaction (checked by T.L.C), the mixture was filtered and purified by recrystallization from distilled water then dried. The physical properties of the prepared compound [S_2] are given in table (1).

Synthesis of Schiff bases Compound [S_5-S_{10}] [29]

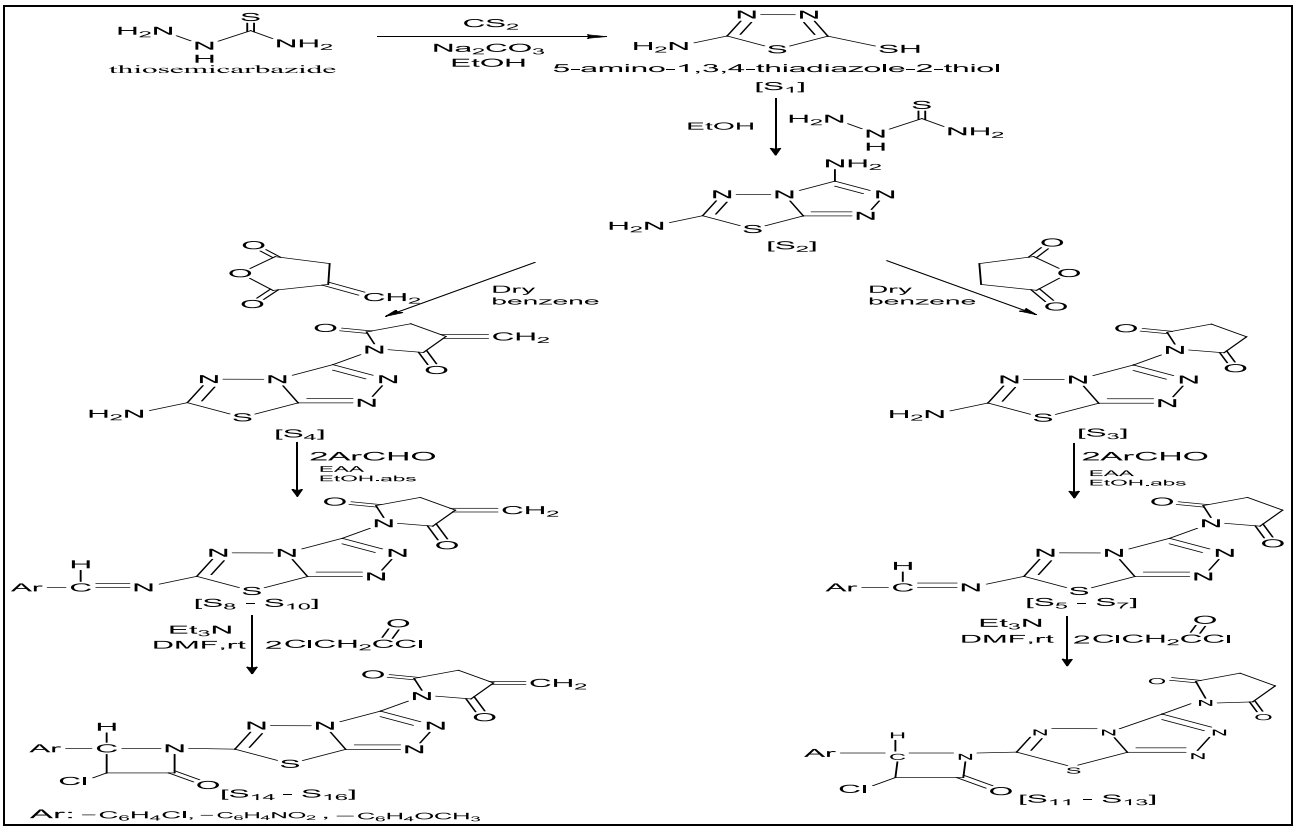
Compounds [S_3, S_4] (0.004 mol) with different aldehydes {p-chlorobenzaldehyde, p-nitro benzaldehyde, p-methoxy benzaldehyde} (0.004mol) respectively in (10 ml) from absolute ethanol and drops of glacial acetic acid are added, the mixture is reflexed for (8-9) hrs. After the completion of reaction (checked by T.L.C), the mixture was filtered and purified by recrystallization from ethanol. The physical properties to those compounds are given in Table (1).

Synthesis of *β*-Lactam Derivatives (S_{11}-S_{16}) [30]

A mixture of a Schiff bases [S_5-S_{10}] (0.003 mol) respectively, triethyl amine (0.5 ml) was dissolved dimethylformamide (10 ml). To this mixture, a solution of chloro acetyl chloride (0.5 ml) was added drop wise with vigorous stirring at room temperature for (6) hrs. After the reaction mixture was kept at room temperature for two days and then poured into crushed ice water. The solid precipitate was filtered off, washed with water and purified from ethanol/H_2O (1:1) .The physical properties of this compound are listed in table (1).

Results and Discussion

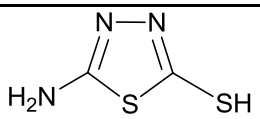
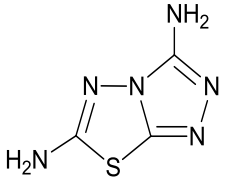
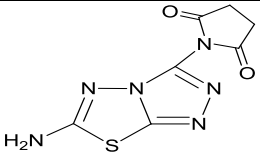
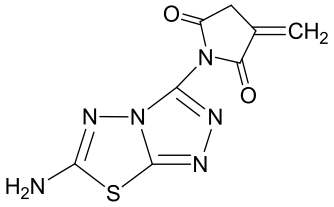
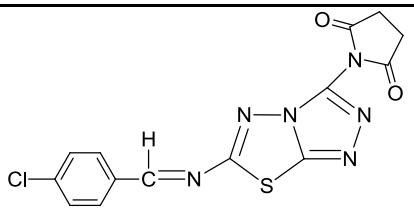
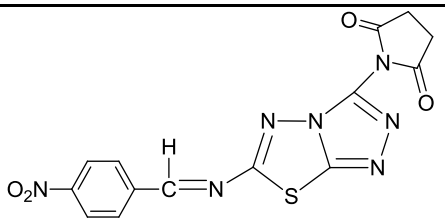
The general reaction is briefed in Scheme (1)

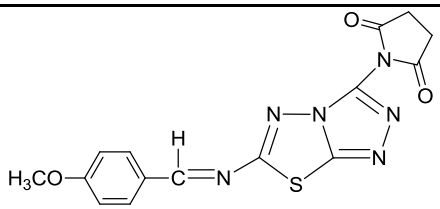
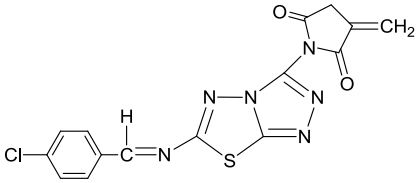
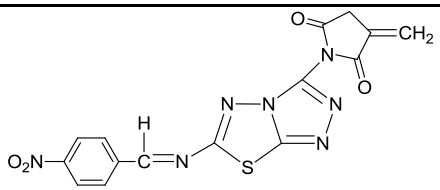
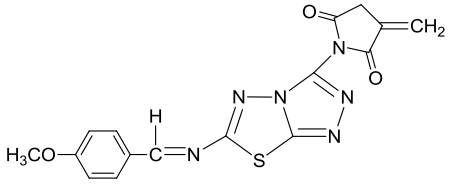
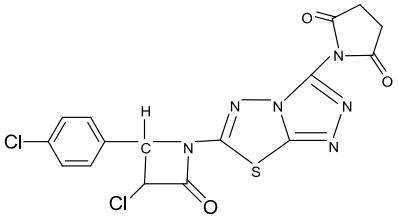
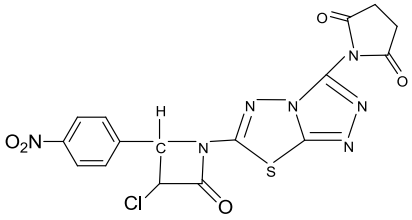
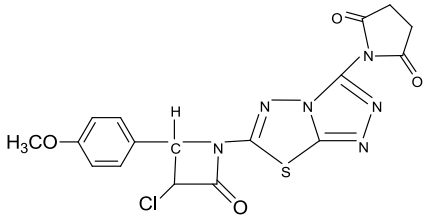


Scheme 1: Path way for Synthesis [S_1-S_{16}] compounds

The Compound [S_2] is prepared from the reaction compound [S_1] with thiosemicarbazide in the presence of absolute ethanol as a solvent. Physical properties to compound [S_2] are listed in table (1). FT-IR spectrum of compound is shown [S_1- S_{16}] in Table (2). The compound [S_2] showed absorption band at (3196, 3126) is due to υ (NH_2) symmetric and asymmetric.The compound [S_3] showed absorption band at (3385, 3167) is due to υ (NH_2) symmetric and asymmetric and (1670) due to (C=O). The compound [S_4] showed absorption band at (3277, 3163) due to υ (NH_2) symmetric and asymmetric and (1652) due to (C=O).The Compound [S_5] appearance absorption band at (3024-3095) due to υ (C-H) aromatic. Other absorptions Schiff base compounds are found in the Table (2). In ^{1}H-NMR spectrum, compound [S_5] appears at (8.2,s,1H, HC=N), (6.7-7.8,m,4H,Ar-H), (3.6-3.9,t,4H,2CH_2), and (2.5,s,H_2O in DMSO. Compound [S_{16}] appearance (6.5-7.5,m,4H,ArH),(6.3,s, 1H, HC-N), (4.5,s, 2H,=CH_2),(4,s, 3H,CO-CH_3), (2.8,s, 2H, CH_2), and (2.5,s, H_2O in DMSO).

Table 1: Physical Properties of Synthesized Compounds [S1-S16]

Comp. No	Structure of compounds	Color Yield %	M.p C°	Recryst. Solvent
S_1	 5-amino-1,3,4-thiadiazole-2-thiol	Light-yellow 90%	230-232	distilled water
S_2	 [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3,6-diamine	White 70%	216-218	distilled water
S_3	 1-(6-amino-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl) pyrrolidine-2,5-dione	White 68%	200-202	distilled water
S_4	 1-(6-amino-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl) -3-methylenepyrrolidine-2,5-dione	Yellow 60%	210-212	distilled water
S_5	 1-(6-((4-chlorobenzylidene)amino)-[1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazol-3-yl)pyrrolidine-2,5-dione	Yellow 55%	Oily	Ethanol
S_6	 1-(6-((4-nitrobenzylidene)amino)-[1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazol-3-yl)pyrrolidine-2,5-dione	White 58%	Oily	Ethanol

S_7	 1-(6-((4-methoxybenzylidene)amino)-[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)pyrrolidine-2,5-dione	**Brown 60%**	**Oily**	**Ethanol**
S_8	 1-(6-((4-chlorobenzylidene)amino)-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazol-3-yl)-3-methylenepyrrolidine-2,5-dione	**Brown 62%**	**Oily**	**Ethanol**
S_9	 1-(6-((4-chlorobenzylidene)amino)-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazol-3-yl)-3-methylenepyrrolidine-2,5-dione	**Yellow 68%**	**Oily**	**Ethanol**
S_{10}	 1-(6-((4-chlorobenzylidene)amino)-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazol-3-yl)-3-methylenepyrrolidine-2,5-dione	**Yellow 55%**	**Oily**	**Ethanol**
S_{11}	 1-(6-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)-[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-1*H*-pyrrole-2,5-dione	**Yellow 60%**	**208-210**	**Ethanol/H_2O (1:1)**
S_{12}	 1-(6-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)-[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-1*H*-pyrrole-2,5-dione	**Orange 58%**	**220-222**	**Ethanol/H_2O (1:1)**
S_{13}	 1-(6-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)-[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-1*H*-pyrrole-2,5-dione	**Light yellow 55%**	**225-227**	**Ethanol/H_2O (1:1)**

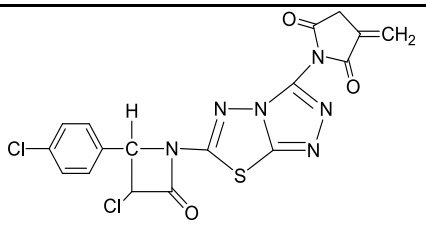
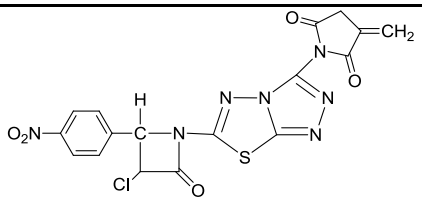
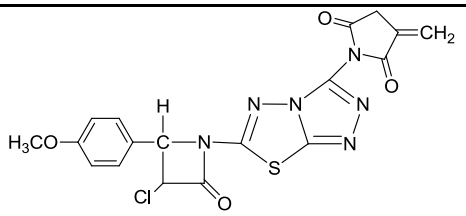
S_{14}	 1-(6-(2,3-dichloro-4-oxoazetidin-1-yl)-[1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazol-3-yl)-3-methylenepyrrolidine-2,5-dione	**Yellow 55%**	**222-224**	**Ethanol/H_2O (1:1)**
S_{15}	 1-(6-(3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)-[1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazol-3-yl)-3-methylenepyrrolidine-2,5-dione	**Brown 58%**	**220-222**	**Ethanol/H_2O (1:1)**
S_{16}	 1-(6-(3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)-[1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazol-3-yl)-3-methylenepyrrolidine-2,5-dione	**Brown 58%**	**235-233**	**Ethanol/H_2O (1:1)**

Table 2: Spectral Data of Compounds [S_2-S_{16}]

Comp. No	υ(NH_2)	υ(C-H) aromatic	υ(C-H) aliphatic	υ(C=O)	υ(C=N)	υ(N-N)	υ(C-N)	υ(C-S-C)	υ(C=S)	Other
S_2	3263, 3196	3078	--------	--------	1608	1591	1338	738	1282	--------
S_3	3385, 3167	--------	2850 2787	1670	1606	1541	1325	738	1246	--------
S_4	3277, 3163	--------	2924 2866	1654	1610	1551	1338	769	1230	--------
S_5	--------	3024	2958 2864	1650	1600	1523	1367	744	1228	C-Cl 1034
S_6	--------	3070 3022	2949 2893	1654	1610	1597	1361	750	1242	C-Cl 1026
S_7	--------	3086	2939 2846	1631	1616	1595	1330	750	1236	NO_2 1524, 1370
S_8	--------	3097	2929 2873	1647	1610	1554	1375	771	1265	NO_2 1568, 1388
S_9	--------	3061 3030	2949 2895	1654	1610	1558	1336	742	1234	--------
S_{10}	--------	3078	2941 2872	1661	1610	1502	1354	769	1255	--------
S_{11}	--------	3084	2974 2870	1650	1610	1577	1319	761	1242	C-Cl 1041
S_{12}	--------	3067	2910 2823	1650	1610	1548	1336	727	1232	C-Cl 1040
S_{13}	--------	3074	2934 2872	1666	1635	1500	1377	769	1234	NO_2 1512, 1332
S_{14}	--------	3051	2951 2872	1645	1635	1523	1373	788	1240	NO_2 1509. 1323
S_{15}	--------	3050	2900 2850	1650	1606	1550	1370	738	1250	--------
S_{16}	--------	3095	2900 2800	1650	1616	1550	1359	750	1250	--------

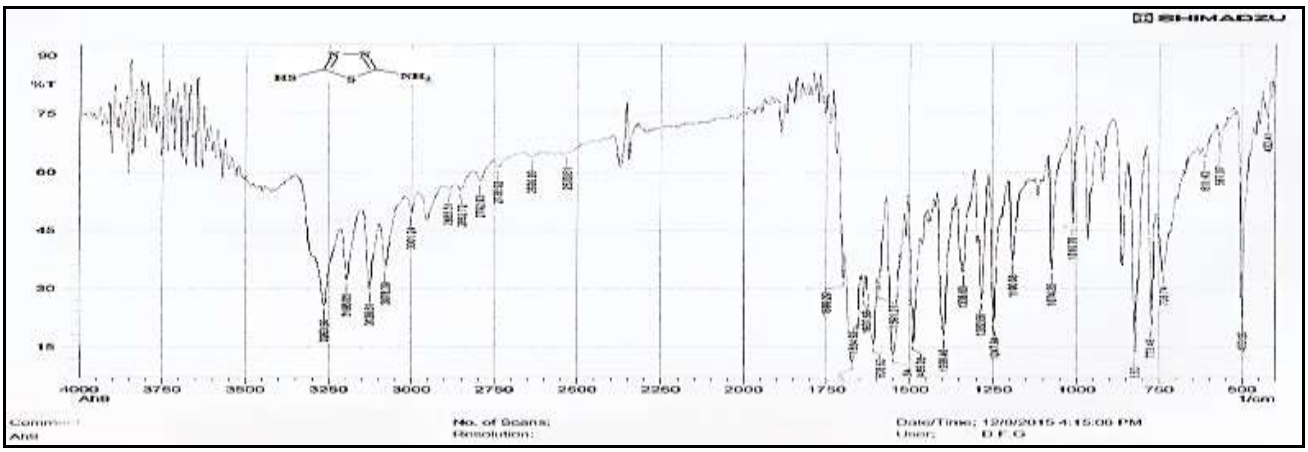


Figure 1: FT-IR spectrum for compound [S_1]

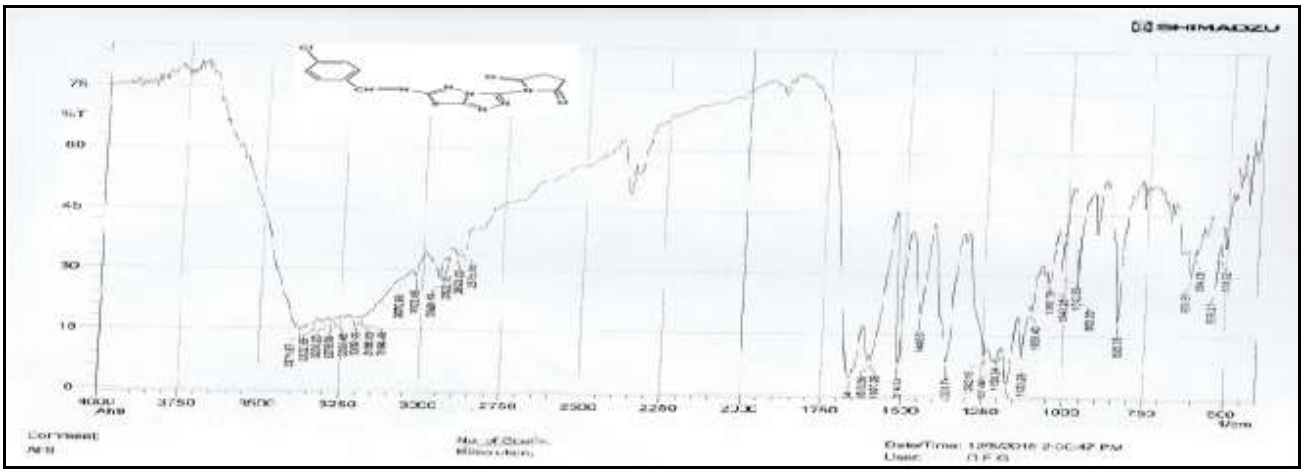


Figure 2: FT-IR spectrum for compound [S_5]

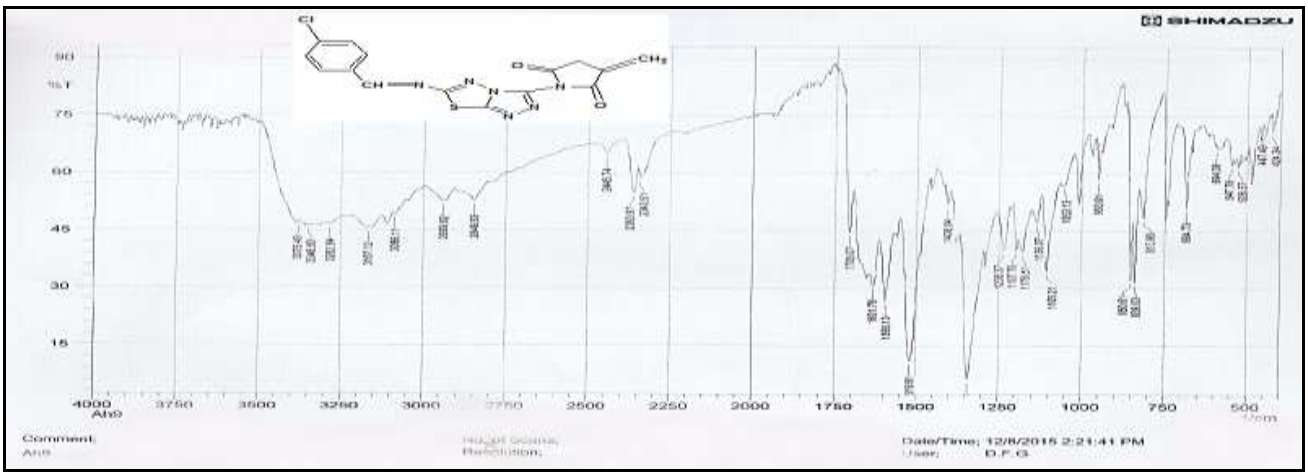


Figure 3: FT-IR spectrum for compound [S_8]

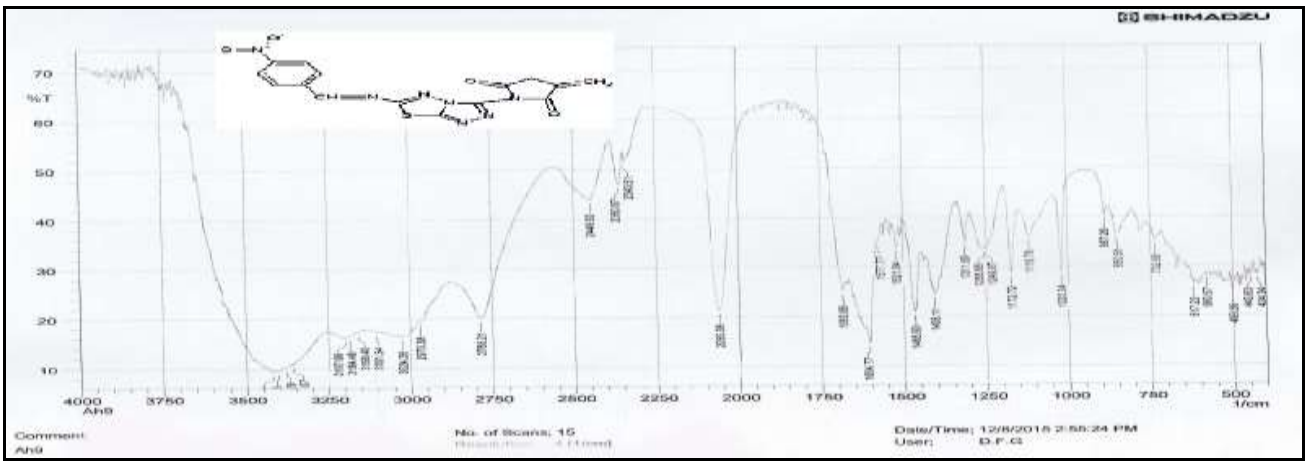


Figure 4: FT-IR spectrum for compound [S_9]

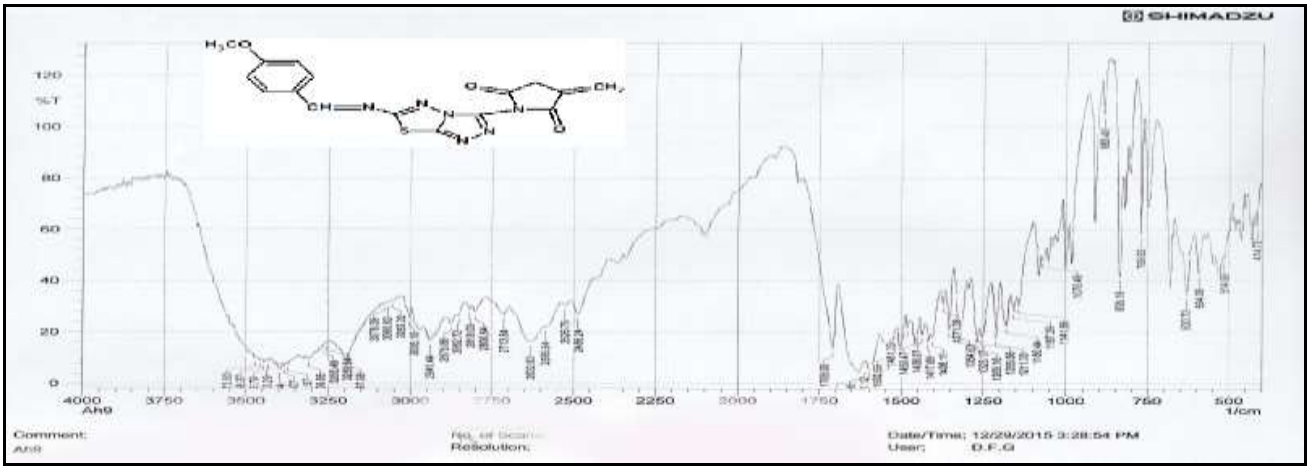


Figure 5: FT-IR spectrum for compound [S_{10}]

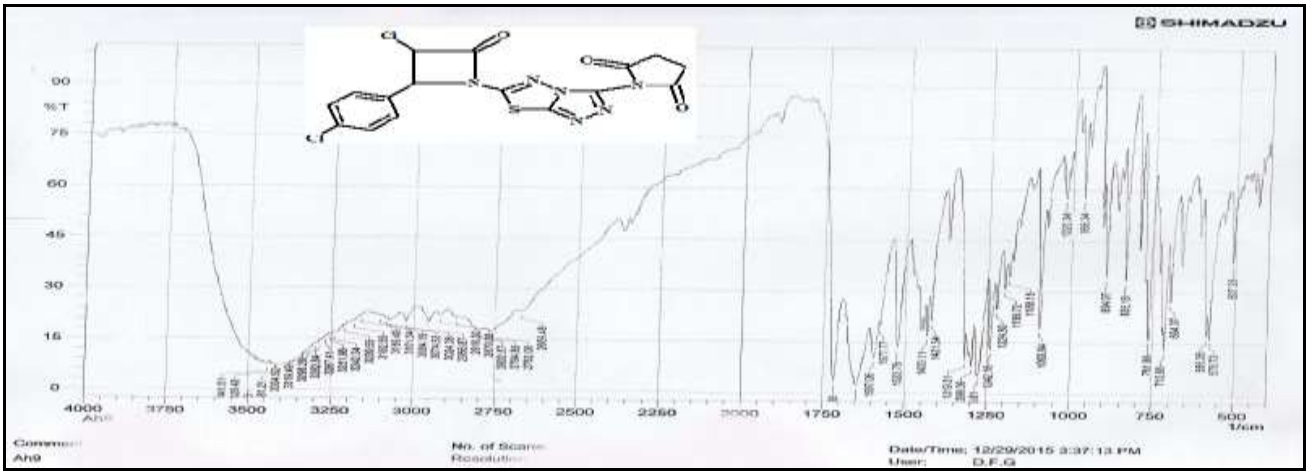


Figure 6: FT-IR spectrum for compound [S_{14}]

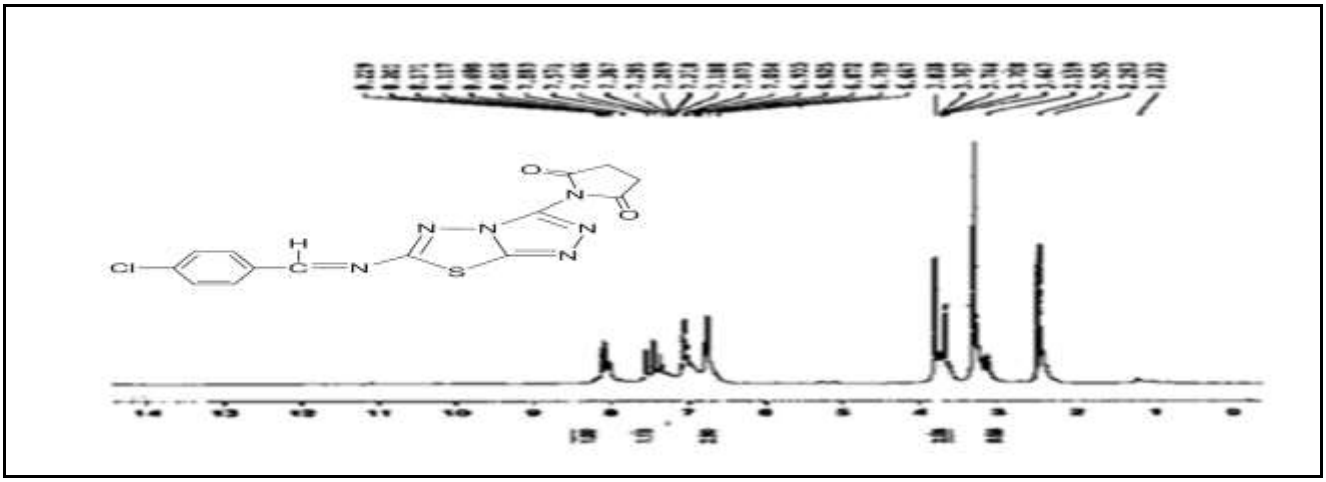


Figure 7: The ^{1}H-NMR of compound [S_5]

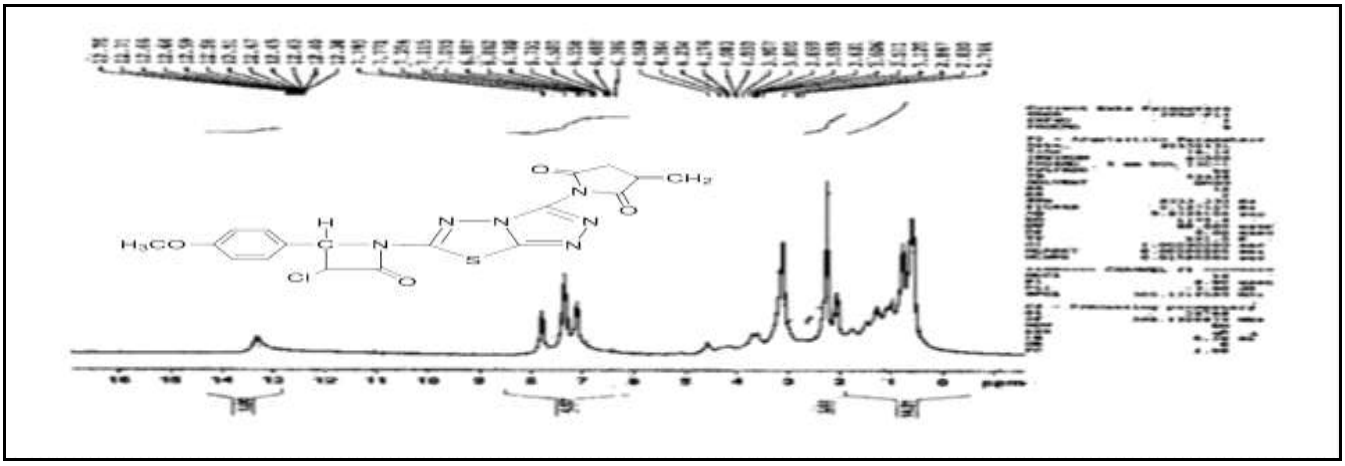


Figure 8: The ^{1}H-NMR of compound [S_{16}]

Biological Part

This study has used two types of bacteria which are [Esherichia coli and Staphylococcus] and one type of fungi which is Candida albicans. The selection of these types of bacteria and fungi is because of their importance in the medical field as cause for many different diseases. The method used in the inhibitory effect of chemical compound account on these types has been (Ager Diffusion Method).

Table 3: Biological Bacteria

Compound No 1000 ppm	Inhibition zone (MM.)		
S_2	Gram positive	Gram Negative	Fungi
	Staphylococcus aureus	E-coli	Caudidaalbicas
	20	15	12
S_3	22	18	15
S_8	25	20	15
S_{14}	25	22	15

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