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RESEARCH ARTICLE

Identification of Some New Tetrazole and Thiazolidine Derivatives Synthesized From 4-Chlorobenzoic Acid and Evaluation Their Antibacterial Effect

Maysoon Tariq Tawfiq*, Ibtisam K. Jassim, Fatik, Aoliewe Hadi

Chemistry Department, College of Education for Pure Science / Ibn-Al-Haitham, University of Baghdad, Iraq.

***Corresponding Author: Maysoon Tariq Tawf**

Abstract

The research includes the synthesis of some new derivatives of tetrazole and thiazolidine rings from the reactions of 2- (4-chlorophenyl)-5-hydrazinyl- 1,3,4-oxadiazole [4] with various substituted aromatic aldehydes in absolute ethyl alcohol as a solvent and presence of glacial acetic acid as a catalyst to form Schiff's bases [5-10]. The prepared new Schiff's bases [5 -10] reacted with sodium azide , and mercaptoacetic acid in THF to yield five membered rings (tetrazole ring) [11-15], and (thiazolidine ring) [16-20] in good products. The spectral methods of the prepared compounds were characterized by FT.IR, and 1HNMR for compounds [9,13,14,and 19] , besides melting points were recorded , and the purity was checked through T.L.C. technique. Antibacterial activities for some of the synthesized compounds were examined.

Keywords: *Heterocyclic compounds, 4-Chlorobenzoic acid, Acid hydrazide, Oxadiazole, Schiff's bases, Tetrazole, Thiazolidine, Biological activity.*

Introduction

Thousands of studies dealing with the synthesis of new tetrazole derivatives exhibiting diverse biological activities in both medicinal and pharmaceutical, such as hypotensive, anti-microbial, anti-viral, anti-fungal, anti-allergic, anti-inflammatory, anti-nociceptive, nootropic, anti-tubercular activity , and anti-cancer [1, 3]. Tetrazoles can exist in different tautomeric forms and also as anions and cations [1].

Thiazolidinones are derivatives of thiazolidine, which is a main pharmacophoric group responsible for anti-diabetic activity. It acts by enhancing insulin sensitivity in both muscle and adipose tissue and to a lesser extent by inhibiting hepatic glucose production. These agents have a notable effect on improving insulin resistance, particularly when used in combination with other anti-diabetic drugs, but have no effect on insulin secretion. As a class, the thiazolidinediones have also been shown to alter lipid profiles in patients with type *2* diabetes.

They also have effected a decrease in triglyceride levels, increase in total and Low density lipoprotein LDL cholesterol levels [4].

Aim of the Work

The aim of this work is to prepare and characterize series of some new five membered heterocyclic rings: Tetrazole, Thiazolidine, and their derivatives starting from aromatic acid, which are present in many of the bioactive heterocyclic compounds that are of wide interest because of their diverse biological, pharmaceutical and clinical applications.

Experimental

Instruments

- All chemicals, used were of reagent grade (supplied by either Merck, Fluka or Aldrich) and used as supplied
- All melting points are uncorrected in degree centigrade and determined on Gallen *kamp* electric melting point apparatus.

- FT.IR spectra were recorded (KBr disk) on a Shimadzu FTIR 8300 spectrophotometer in the range (4000 - 400) cm^{-1}.
- ^{1}HNMR spectra were determined on a BRUKER- 400 MHz operating spectrometer with tetramethylsilane (TMS) as an internal standard, and the chemical shifts are in δ ppm using deuterated dimethylsulfoxide (DMSO-d_6) as a solvent, measurements were made at Department of chemistry, kashan university Iran.
- The reactions progress was monitored by thin-layer chromatography (TLC) using Fertigfollen precoated sheets type Polygram Silg, and the plates were developed with iodine vapor.
- The biological activity was performed by central laboratory, college of education for pure science, Baghdad University.

Synthesis of: Ethyl 4-chlorobenzoate [1] [5, 6]

A mixture of 4-chlorobenzoic acid (0.01 mol.) with ethanol (25 mL) and concentrated sulfuric acid (5-6 mL) was refluxed for (6-7 hrs.) with stirring. After that the solvent was distilled under vacuum, the product washed by sodium bicarbonate solution.

Synthesis of: 4-chlorobenzohydrazide [2] [7, 8]

A solution of ethyl 4-chlorobenzoate [1] (0.01 mol) with hydrazine hydrate 90 % (0.01 mol) in absolute ethanol (20 mL) was refluxed for (5-6 hrs). After cooling to room temperature, the light brown solid participate was formed, filtered, washed with water, dried and re-crystallized from ethanol. (m.p = 162-163 ^{0}C, Yield = 83 %).

Synthesis of: 5-(4-chlorophenyl)-1, 3, 4-oxadiazole-2-thiol [3] [9].

A mixture of potassium hydroxide (0.84g, 0.015 mol) in absolute ethyl alcohol (25mL), 4-chlorobenzohydrazide [2] (2.55 g , 0.015 mol), and CS_2 (1.14ml, 0.015 mol) was refluxed with stirring for (10-12 hrs.); Dilute the reaction mixture with (100 mL) of ice-cold water and acidify with hydrochloric acid. Resulting off white crystals was filtered and washed with dry ether. (m.p = 252-253 ^{0}C, Yield = 75 %).

Synthesis of: 5-(4-chlorophenyl)-2-hydrazinyl-1, 3, 4-oxadiazole [4] [10]

A mixture of 1, 3, 4-oxadiazole-2-thiol [3] (2.125g, 0.01mol), hydrazine hydrate (1mL, 0.01mol) and absolute ethanol (20 mL) was refluxed for (6-7 hrs). The resulting light brown solid precipitate was filtered, washed with cold water and re-crystallized from ethanol. (m.p. = 199-201 ^{0}C, Yield 62%).

Synthesis of: Schiff's bases [5-10] [11, 12]

In absolute ethyl alcohol (20 mL) a solution of 2-(4- chlorophenyl)- 5- hydrazenyl- 1,3,4 oxadiazole [4] (0.05 mol), appropriate aromatic aldehydes (0.05 mol), and two drops of glacial acetic acid was stirred for (1 hr).After stirring the mixture was refluxed for (4-5 hrs.) with continuous stirring. The mixture was filtered after cooling and washed with cold ethanol and re-crystallized from ether to give colored crystals.

Synthesis of: 5-(4-chlorophenyl)-*N*-(5-(4-aryl)-2, 5-dihydro-1-*H*-tetrazole-1-yl)-1, 3, 4-oxadiazole-2-amine [11-15] [13, 14]

To a stirring solution of Schiff's base [5-10] (0.01mol) in (10 mL) of tetrahydrofuran, sodium azide (0.01mol) in (10 mL) of tetrahydrofuran was added drop wise. After the addition, the mixture was refluxed for (7-8) hours in water bath at (55- 60)^{0}C, then cooled at room temperature and the precipitate was filtered, washed with cold water, re-crystallized with petroleum spirit (40- 60) ^{0}C., yield (71-77) %.

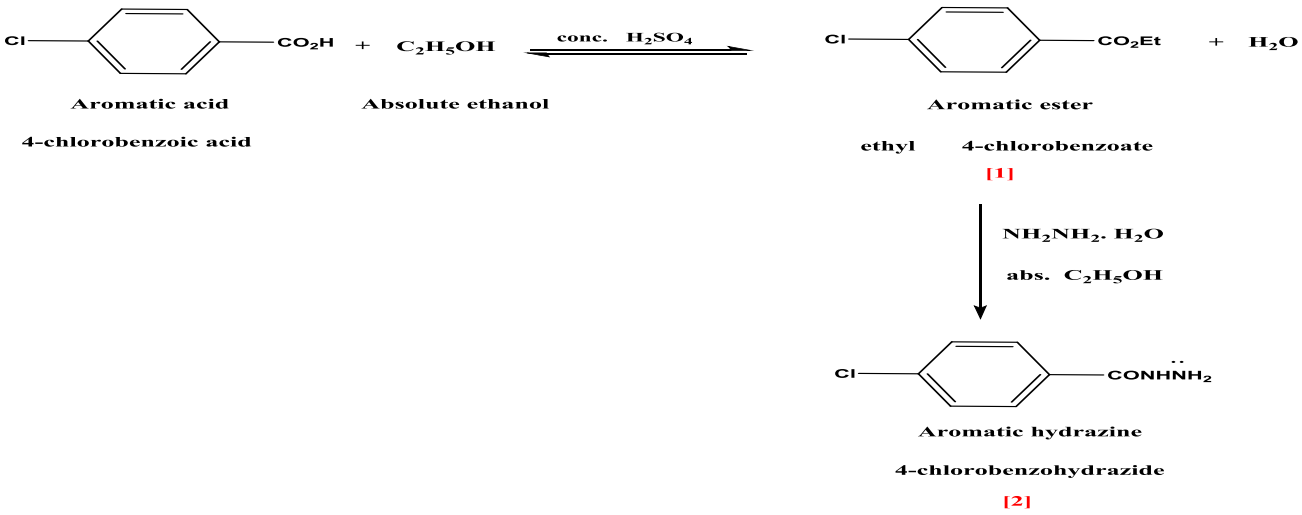
Synthesis of: 3-[(5-(4-chlorophenyl)-1, 3, 4-oxadiazole-2-yl) amino]- 2-(4-aryl) thiazolidine-4-one [16-20] [15, 16]

A mixture of Schiff's base [5-10] (0.01 mol) and 2-mercaptoacetic acid (0.01mol) was stirred with tetrahydrofuran (THF), (15mL). The mixture was refluxed for (6-7) hours in water bath at (60) ^{0}C, then cooled at room temperature and the precipitate was filtered, and re-crystallized with dioxane, yield (65-73) %.

Results and Discussion

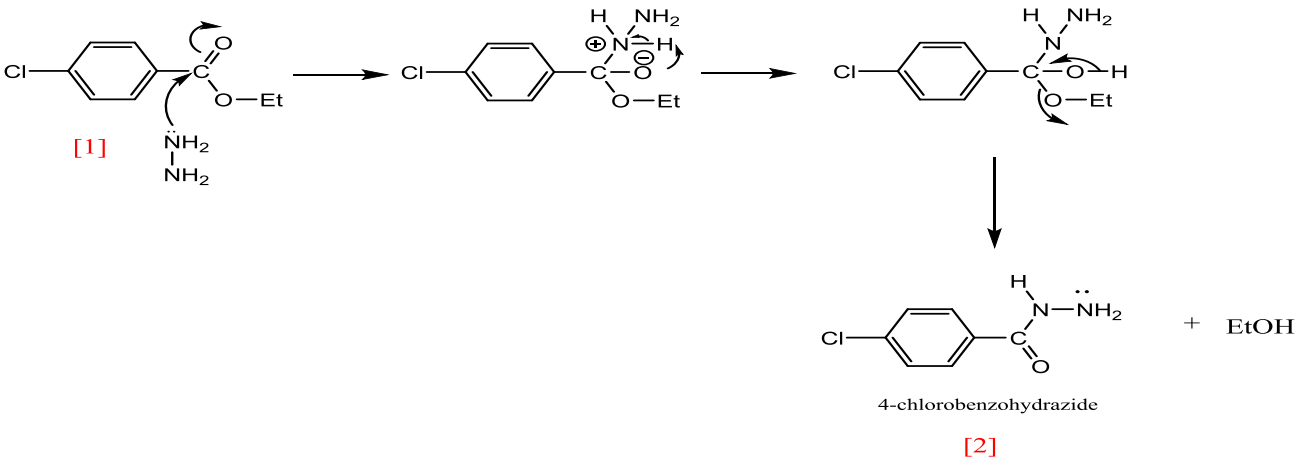
The heterocyclic compounds chemistry has been an interesting field of study for long time., The novel tetrazole derivatives synthesis and examination of their chemical and biological actions has gained more importance in recent decades for biological and pharmaceutical reasons., 1,2,3,4-tetrazole represent an important class of heterocyclic compounds [13]. Ethyl 4-chlorobenzoate [1] was synthesized from 4-

chlorobenzoic acid via Fischer's esterification reaction [17], which was then reacted with hydrazine hydrate in absolute ethanol to give hydrazide derivative [2], (Table-1).



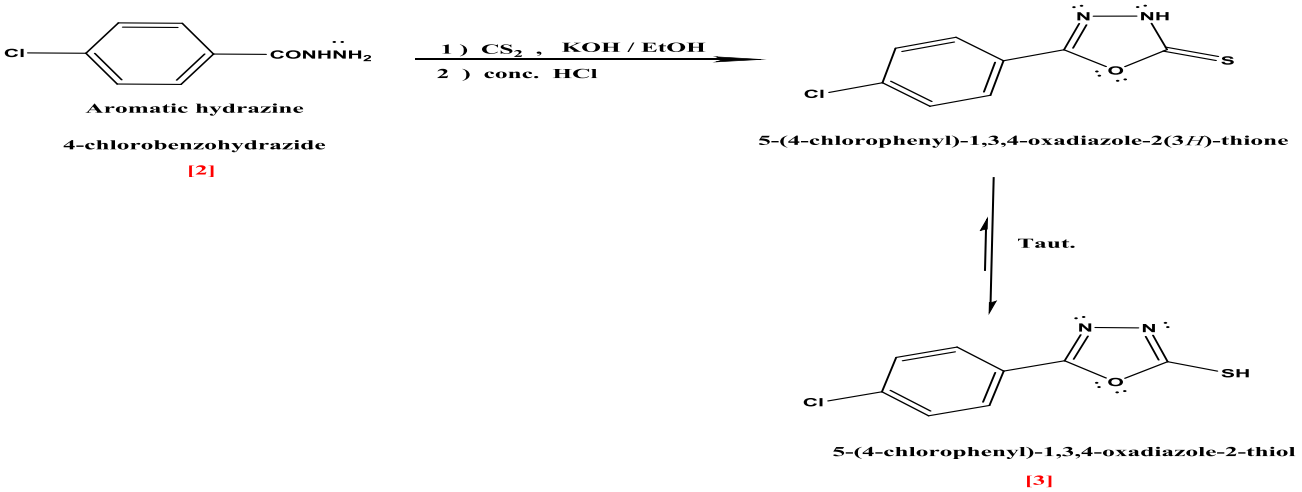
Scheme- 1

The proposed reaction mechanism is shown in the following scheme:



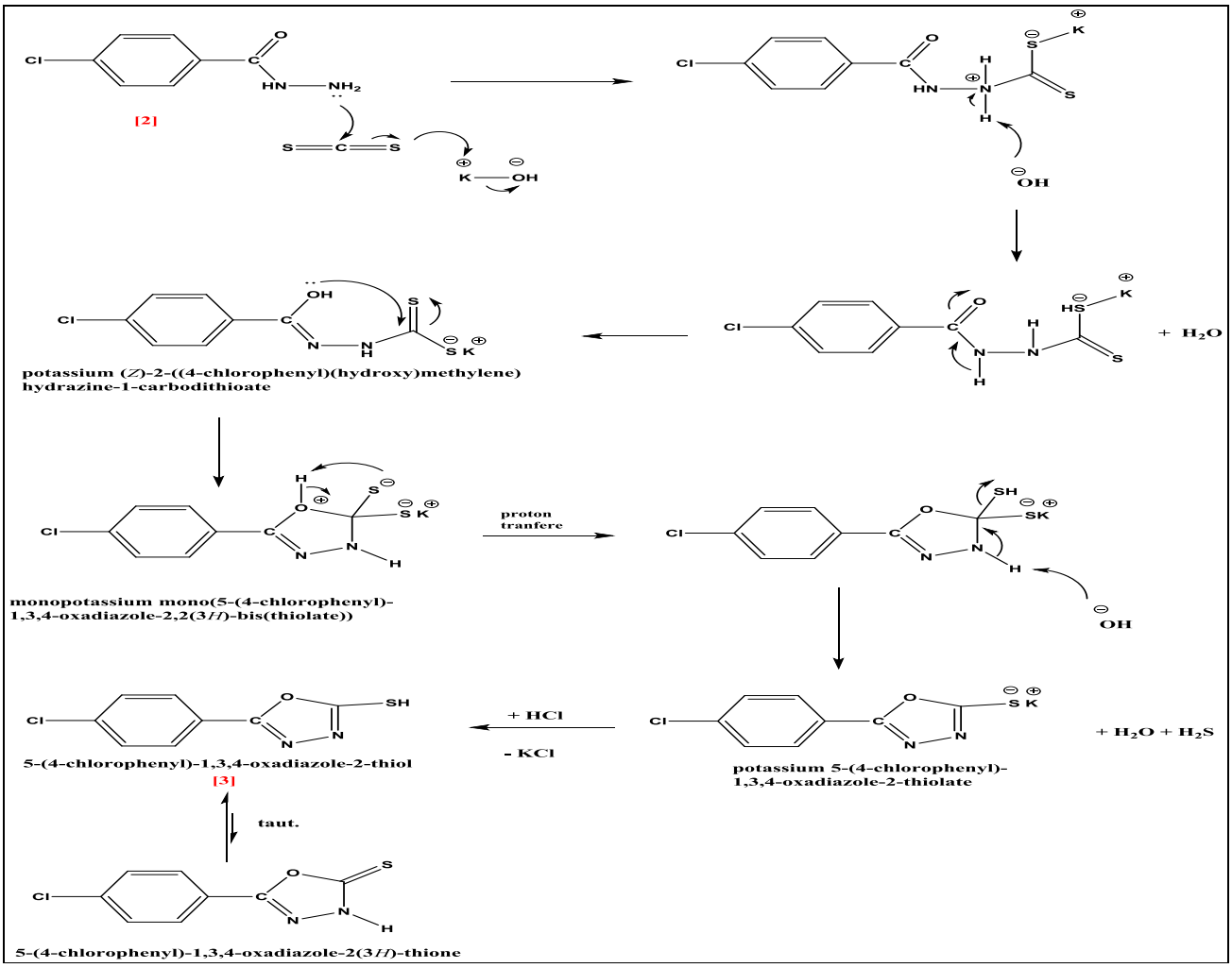
Scheme -2

Compound [2] has proven by appearance of stretching vibration bands at (3425, 3392) cm^{-1} refers to the terminal amino group, and by shifting of the intense stretching vibration band from (1616) cm^{-1} for (C=O) of amidic group. A stretching vibration band is also seen at (3294) cm^{-1} for (N-H) group [18], (Table-2). The substituted aromatic acid hydrazide [2] reacted with carbon disulphidee (CS_2) in presence of potassium hydroxide in absolute ethanol to give 1, 3, 4-oxadiazole derivative [9]: 5-(4-chlorophenyl)-1, 3, 4-oxadiazole-2-thiol [3], (Table-1).



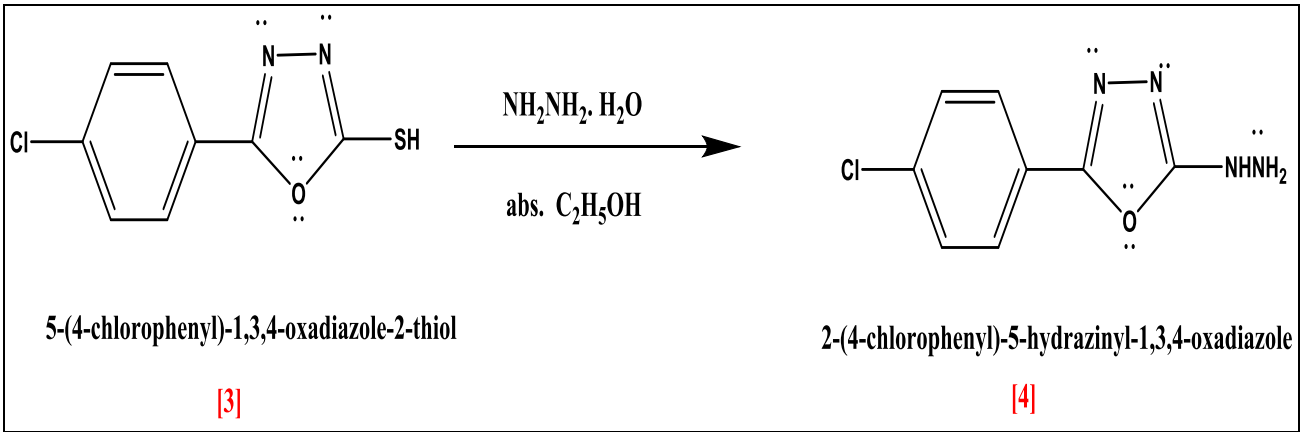
Scheme- 3

The proposed reaction mechanism is shown in the following scheme:



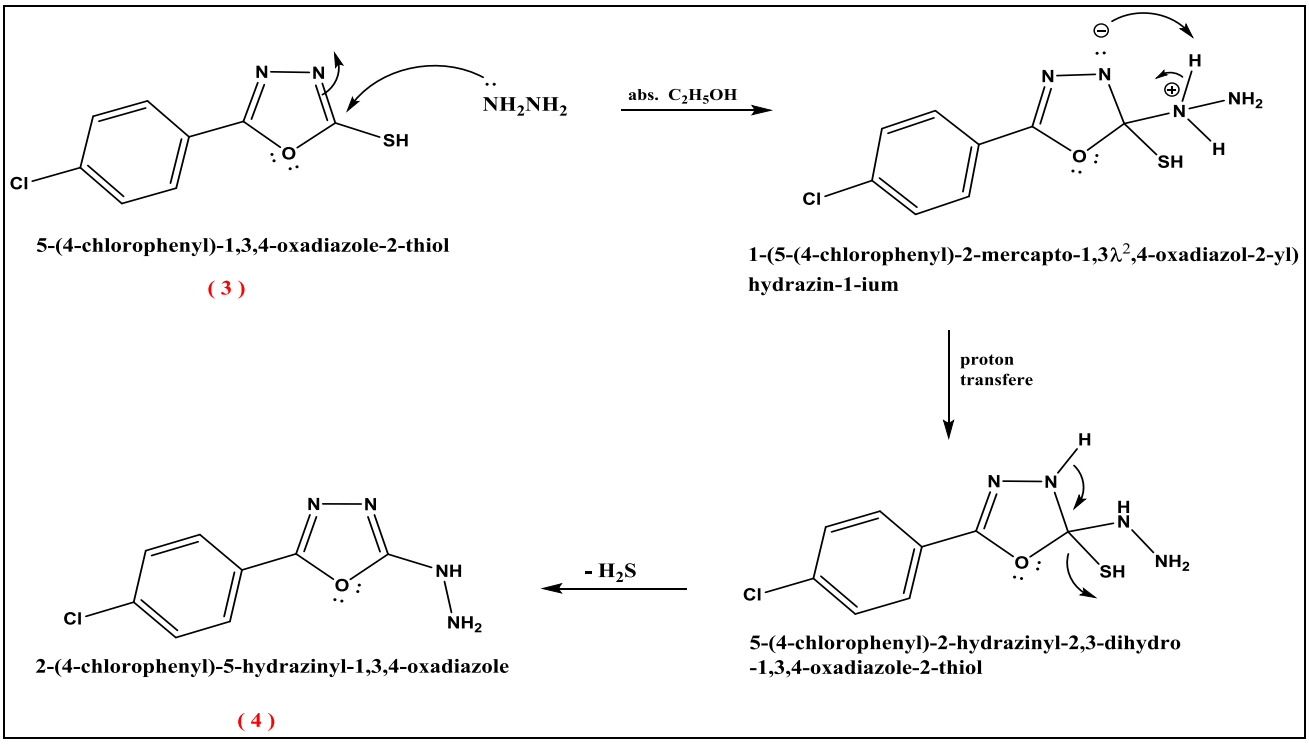
Scheme- 4

The FT-IR spectrum of compound [3] showed disappearance of two stretching bands at (3425) cm^{-1} and (3392) cm^{-1} which refer to (NH_2) group , and appearance of strong band at (1680) cm^{-1} refer to endoo (C=N) stretching, and strong band in the range (1290-1065) cm^{-1} assigned for (C-O-C) cyclic grouping ; In addition to two another characteristic bands at (3174) cm^{-1}, and (2553) cm^{-1} refer to (N-H form) and (S-H) stretching vibration, respectively., This indicates thione-thiol equilibrium [18], (Table-2). The 1, 3, 4-oxadiazole provides number of reactions including electrophillic substitution, nucleophilic substitution, thermal, and photochemical. 1,3,4Oxadiazole-2-thiol [3] undergo nucleophilic substitution reaction with hydrazine hydrate, similarly as occurring at an aliphatic sp^2 carbon atom [10], to get corresponding hydrazine derivative [4] , (Table-1).



Scheme- 5

The proposed reaction mechanism is shown in the following scheme:



Scheme- 6

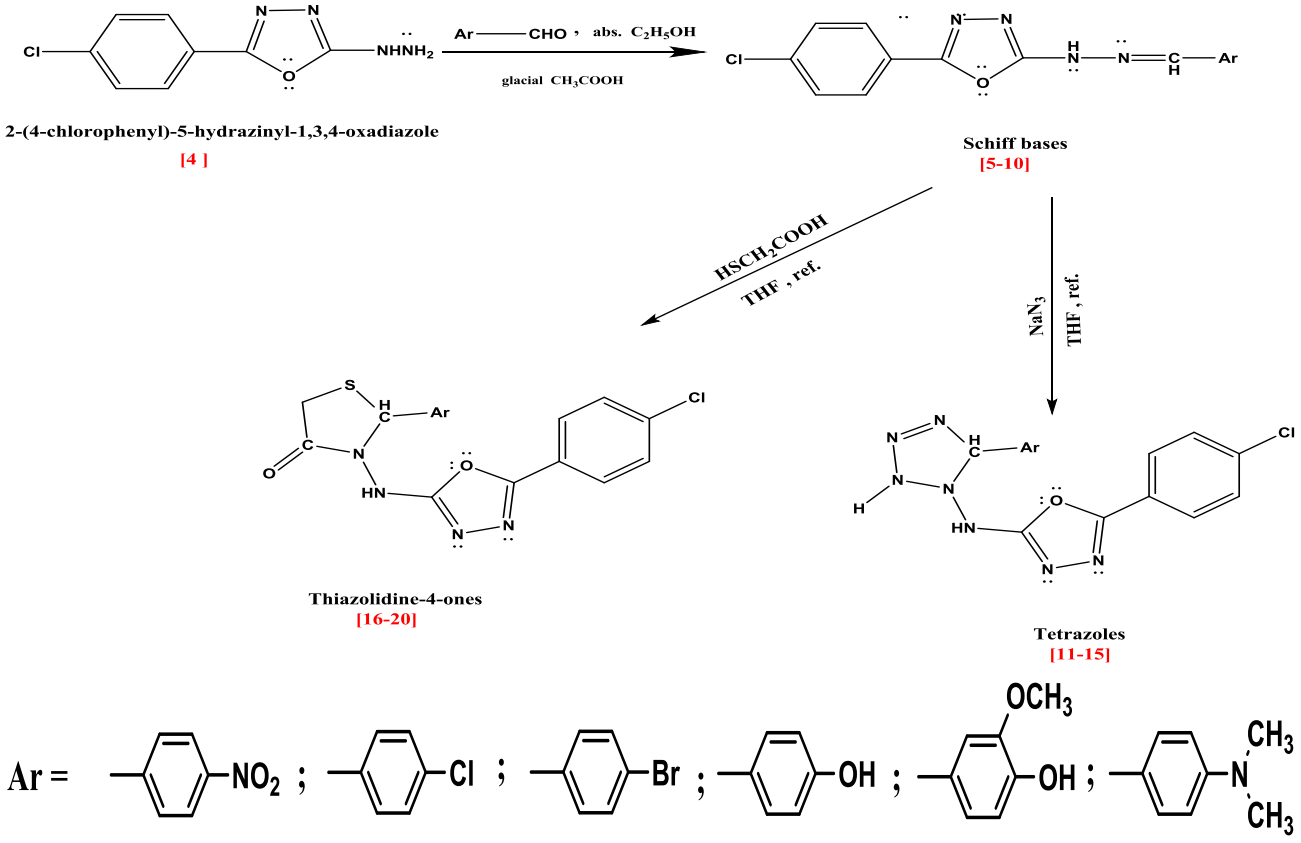
The FT-IR spectrum of compound [4], display disappearance of stretching band at (2553) cm^{-1} due to (S-H) group , and appearance of two stretching bands at (3421) cm^{-1} and (3387) cm^{-1} due to (NH_2) group, and stretching bands at (3296) cm^{-1} due to (NH) group [18], (Table-2). Reaction of substituted aromatic hydrazine [4] with varied aromatic aldehydes under slight acidic conditions to give the substituted aromatic Schiff's bases [5-10], (table-1), which were thereafter cyclized either with sodium azide, or 2-mercaptoacetic acid in THF solvent to yield the final compounds: tetrazole derivatives [14] (11-15), and thiazolidine-4-one derivatives [16] (16-20), (Table-1).

Table 1: Physical properties for synthesized compounds

Comp. no.	M.F.	M. Wt. gm /mol.	M.P. ^{0} C.	Yield %	Color
1	$C_9H_9O_2Cl$	184.5	Oily	85	light yellow
2	$C_7H_7ON_2Cl$	170.5	162-163	83	light yellow
3	$C_8H_5ON_2SCl$	212.5	252-253	75	off white
4	$C_8H_7ON_4Cl$	210.5	199-201	62	light brown
5	$C_{15}H_{10}O_3N_5Cl$	343.5	112-114	71	yellowish green
6	$C_{15}H_{10}ON_4Cl_2$	333	173-175	67	light orange
7	$C_{15}H_{10}ON_4ClBr$	377.5	163-165	61	light brown
8	$C_{15}H_{11}O_2N_4Cl$	314.5	193-195	60	brown
9	$C_{16}H_{13}O_3N_4Cl$	344.5	207-209	57	light brown
10	$C_{17}H_{16}ON_5Cl$	341.5	254-256	74	dark yellow
11	$C_{15}H_{11}O_3N_8Cl$	386.5	177-180	70	yellow
12	$C_{15}H_{11}ON_7Cl_2$	376	175-177	76	brown
13	$C_{15}H_{12}O_2N_7Cl$	357.5	201-204	77	yellow
14	$C_{16}H_{14}O_3N_7Cl$	387.5	229-231	76	light yellow
15	$C_{17}H_{17}ON_8Cl$	384.5	193-195	73	greenish brown
16	$C_{17}H_{12}O_4N_5SCl$	417.5	199-201	64	light yellow
17	$C_{17}H_{12}O_2N_4SCl_2$	407	163-166	59	light brown
18	$C_{17}H_{13}O_3N_4SCl$	388.5	219-221	71	light yellow
19	$C_{18}H_{15}O_4N_4SCl$	418.5	243-245	73	off white
20	$C_{19}H_{18}O_2N_5SCl$	415.5	203-205	75	brown

Table 2: FT-IR spectral data of synthesized compounds

Comp. no.	ν CH aro.	ν CH ali.	ν NH_2 , NH	ν C =O	ν C=N endo	νSH	ν C- Cl
2	3088	---	3425(Asym.), 3392(Sym.), 3294	1616	---	---	829
3	3091	---	---	---	1680	2553	829
4	3082	---	3421(Asym.), 3387(Sym.), 3296	---	1661	---	827



Scheme- 7

Mechanism include nucleophilic addition to the carbonyl group and elimination of a water molecule so, too, reaction of carbonyl compound like an aldehyde or ketone with a reagents having the general structure NH_2–Z (where Z contains an **O** or N atom bonded to the $–NH_2$ group) forms Schiff's base derivative. The outright reaction results in [19]. Schiff's bases are distinguished by the imine group (-N=CH-) which is important compound due to great flexibility and diverse structural aspects. The FT-IR spectra of Schiff's bases [5-10], indicate a disappearance of (N-H) stretching band of the primary amine at region (3421, 3387) cm^{-1}, and appearance of stretching band at (1676-1630) cm^{-1} refer to the formation of imino group (HC=N) [18], (Table-3).

The ^{1}H-NMR spectrum of compound [9] shows the special chemical shifts (δ ppm) at: 2.980 (s, 3H, OCH_3), 3.329 (s, 1H, = CH), 3.353 (s, 1H, NH), 6.762-7.643 (m, 7H, H-aromatic ring), and 8.486 (s, 1H, OH). The Schiff's bases are used to prepare various heterocyclic compounds, which expected to have biological importance, for example, tetrazole and thiazolidinone derivatives in classical or pericyclic reaction. Sodium azides react with Schiff's bases by pericyclic reaction, (Table-1). Pericyclic reactions are important type of concerted reactions; they are distinct as a change in bonding relationship which occurs as a continuous concerted reorganization of electrons.

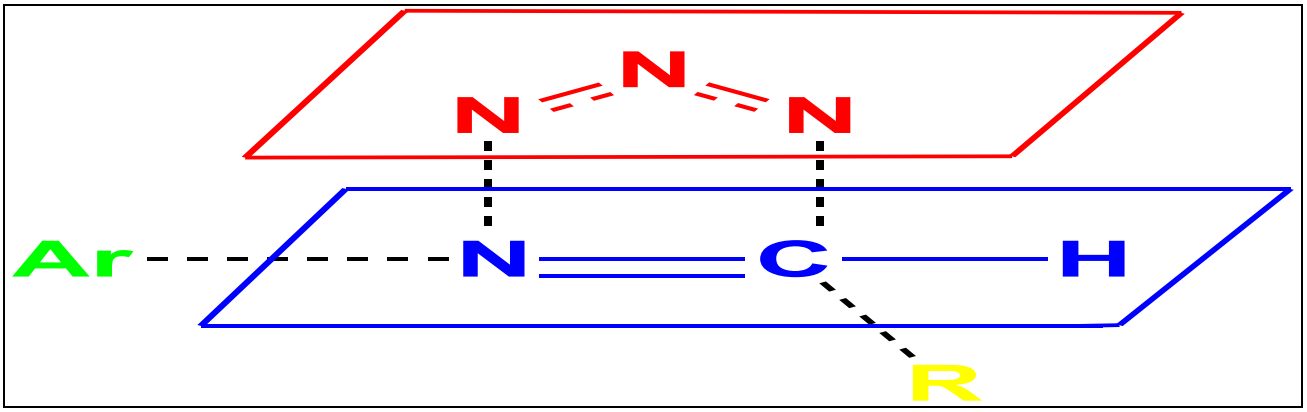
The term "concerted" means that there is a single transition state and thus no intermediate in the process [20]. To preserve continuous smooth electron flow, pericyclic reactions take place through cyclic transition states. Frequently, the cyclic transition states must correspond to an arrangement of the participating orbitals that can maintain a bonding interaction between the reaction components throughout the course of the reaction, and these requirements make pericyclic reactions highly expectable, in terms of such features as relative reactivity, stereo- specificity and regio-selectivity [21].

The mechanism of this reaction classified as [3+2] cycloadditions, it is one of the types of a 1, 3- dipolar cycloadditions [22].

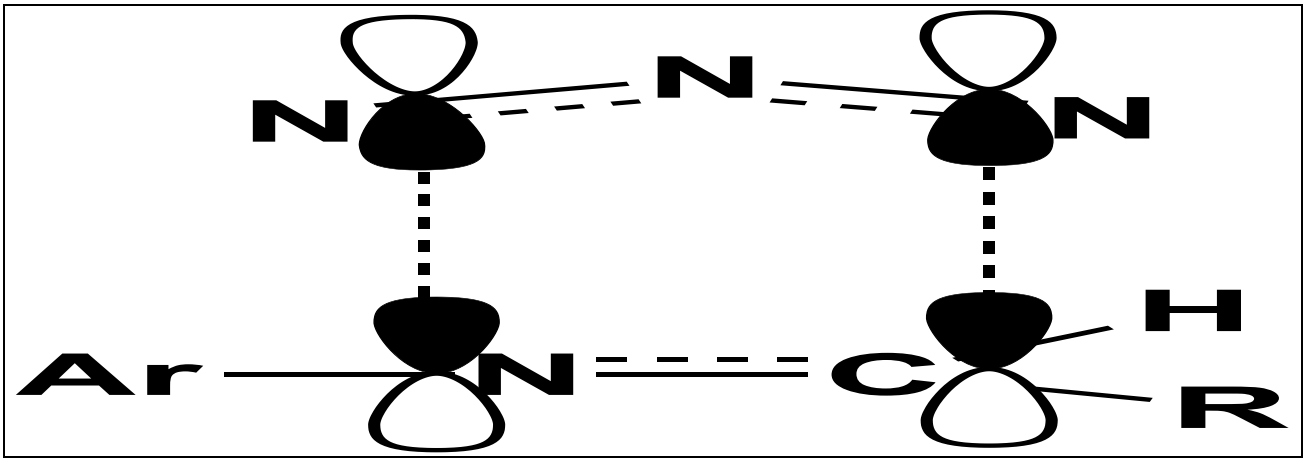
The addition reaction includes addition of unsaturated molecule (dipolarphile) to a molecule type 1,3- dipole which has two charges positive and negative distributed on the 1,3- positions relative to each other. The five member ring results from cycloaddition reaction. The important and prominent type of 1, 3- dipoles are azides which undergo 1, 3- dipolar cycloadditions. They possess great importance of synthetic field and have been studied mechanically in great detail [23]. The mechanism of 1,3- cycloaddition includes T.S. geometry which the azide lies in one plane and in a parallel plan above or below the dipolarphile and its ligands, therefore, orbitals perpendicular to the planes interact to form bonds, as shown in (scheme- 8, and 9) below [24]:

Table 3: FT-IR spectral data of Schiff's bases

Comp. no.	ν C-H aro.	ν C-H azomethine	ν NH	νC =N imine	ν C=N oxadiazole ring	νC-O-C	ν C-Cl	νothers
5	3151, 3086	2931	3312	1676	1627	1267	831	ν NO_2 1527 Asm., 1354 Sym.
6	3143 , 3099	2937	3244	1668	1624	1280	825	ν C-Cl 811
7	3143 , 3097	2938	3245	1676	1622	1278	827	νC-Br 688
8	3136, 3047	2945	3236	1670	1620	1286	827	νC-OH 3411
9	3149, 3022	2935	3245	1630	1618	1278	831	νC-OH 3412 νC-H (ali.) 2898 νC-O 1315
10	3221, 3066	2966	3361	1647	1593	1274	840	ν C-H (ali.) 2885 νC-N 1290



Scheme – 8



Scheme – 9

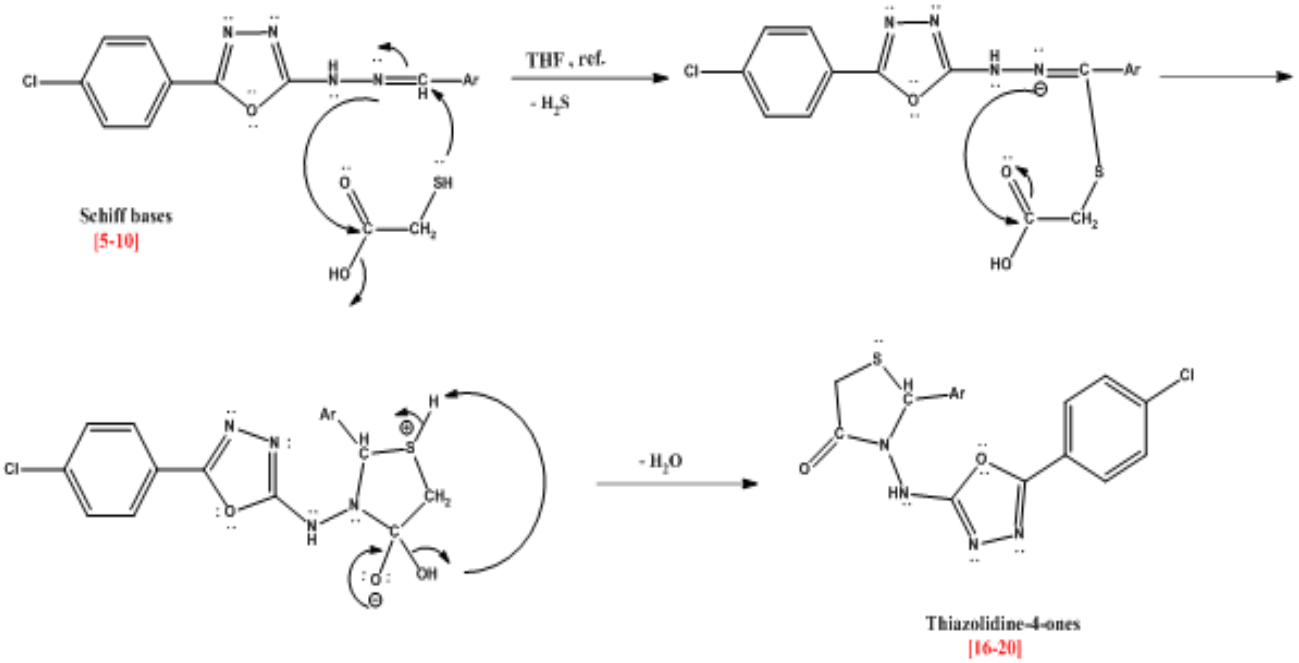
Transition State: The Expected add for orbitals of azide dipole perpendicular to the level of the reactant molecule in cycloaddition reaction

To characterize specific structure of the compounds synthesized were used by spectroscopy of FT.IR. The good evidence for the success of this step of reaction was

disappearance of bands at (1676-1630) cm^{-1} which attributed to (C=N) (imine group) stretching frequency., Also the IR spectra of these compounds devoid of powerful bands at (2120-2160) cm^{-1} attributed stretching frequency of azide group., the bands at (1567- 1512) cm^{-1} were due to the cyclic (N=N) stretching of tetrazole ring., The (N-H) group appears at (3345-3306) cm^{-1} [18], (Table-4). The ^{1}H-NMR spectrum of compound [13] shows the special chemical shifts (δ ppm) at:4.1 (s, 1H, CH), 3.38 (s, 1H, NH) tetrazole ring,7.88 (s, 1H, NH),7.33-7.86 (8H, H-aromatic ring) , and 8.06 (s, 1H, OH)., while the ^{1}H-NMR spectrum of compound [14] shows the special chemical shifts (δ ppm) at:23.175(s,3H,OCH_3) 3.75 (s, 1H, CH), 7.93(s, 1H, NH) tetrazole ring,7-8.004 (s, 1H, NH) ,7.183-8.004 (8H, H-aromatic ring) , and 9.64 (s, 1H, OH). The 2-mercaptoacetic acid react with Schiff's bases via classic reaction, through nucleophilic addition mechanism which include nucleophilic addition of sulfur atom of 2-mercaptoacetic acid to the imine group to form the intermediate which then suffered elimination of a water molecule to give thiazolidine-4-ones [25,26], (Table-1). The proposed reaction mechanism is shown in the following scheme:

Table 4: FT-IR spectral data of tetrazoles

Comp. no.	ν C-H aro.	ν C-H ali.	ν N-H	ν C=N oxadiazole ring	νN=N	νC=C aro.	νothers
11	3078	2947	3345	1570	1523	1442	νC-Cl 848 ν NO_2 1442 , 1346
12	3059	2978	3306	1589	1546	1485	νC-Cl 852
13	3061	2940	3310	1597	1512	1485	νC-Cl 831 ν OH phenolic 3320
14	3048	2943	3332	1693	1550	1431	νC-Cl 779 ν OH phenolic 3365 ν C-O 1284
15	3057	2986,2857	3333	1621	1567	1510	ν C-Cl 823



Scheme - 10

The FT-IR spectra of thiazolidine-4-ones [16-20], showed in the spectrum of FT.IR disappearance of the (C=N) group for imine, and appearance of the carbonyl group (C=O) stretching band at (1759-1695) cm^{-1} due to thiazolidin-4-one ring [18], (Table-5). Compound [19] showed the ^{1}H-NMR spectrums the following characteristic chemical shifts (DMSO-d_6) ppm. Protons of methyl group (OCH_3) appeared at (δ=3.175);Protons of methylene (CH_2) of thiazolidine-4-one ring appeared at (δ=3.759); Proton of methine (CH) of thiazolidine-4-one ring appeared at (δ= 6.46); Proton of (NH) group appeared at(δ= 8.48); Protons of aromatic ring appeared at the range (δ=7.183-8.004) as a multiplate, and the signal at (δ= 9.64) belong to (OH) group.

Table 5: FT-IR spectral data of thiazolidinones

Comp. no.	ν C-H arom.	ν C-H aliph.	ν N-H	ν C=N oxadiazole ring	ν C=O thiazolidinone ring	ν C=C arom.	ν others
16	3082	2956, 2881	3351	1565	1755	1445	νC-Cl 843 ν NO_2 1450 , 1339 ν C-S 723
17	3050	2981, 2881	3320	1593	1710	1487	νC-Cl 848 ν C-S 727
18	3039	2981, 2873	3315	1593	1759	1461	ν C-Cl 865 ν OH phenolic 3325 ν C-S 725
19	3030	2961, 2881	3327	1592	1701	1481	νC-Cl 798 ν OH phenolic 3343 ν C-O 1280 ν C-S 732
20	3051	2979, 2849	3321	1632	1695	1519	ν C-Cl 831 ν C-S 739

Table 6: Antibacterial actions for some of the synthesized compounds

Comp. no.	*Staphylococcus aureus*	*Escherichia coli*
12	-	++
15	-	++
17	-	++
20	-	++

- = No inhibition = inactive
\+ = (5-10) mm = slightly active
++ = (11-20) mm= moderately active

Biological Examination: Anti-bacterial Action Trial

In this labor, the antibacterial trial was accomplished according to disc spread method. The compounds [12, 15, 17, and 20] were examined for their antimicrobial action *in vitro* against two types of Gram negative (G-), and positive bacteria (G+): (*Escherichia Coli*, and Staphylococcus *aureus*). The sterilized agar and petri dishes which prepared were carried out by autoclaving for 15 minutes at 121 ºC.

The surface of the agar plates were uniformly inoculated from the broth culture of the tested microorganisms. In the solidified waist suitably spaced aside gaps were made each 6mm in diameter. These gaps were loaded with (0.1 mL) of the prepared compounds (10mg of the prepared compound dissolved in (1mL) of DMSO solvent. These plates were incubated at 37 °C for 24 hours for bacteria. The inhibition areas of different compounds were examined.

The consequences of the preliminary examining tests are:

For *Staph.* (G+), all the examined compounds [12, 15, 17, and 20] showed on activity on this type of becteria.

For *E. coli* (G-), all compound [12, 15, 17, and 20] showed moderately - highest activity on this bacteria, (Table-6).

Conclusions

In this study tetrazole, and thiazolidine ring derivatives were synthesized using some strategies; the methods used show some feature such as good products, easy procedure, fading cost, and ease of establish. The derivatives have shown significant antimicrobial activity against bacteria such Gram +ve and Gram –ve microorganisms.

Future Expectant Studies

More seeking must be carried out to evaluate more activities of tetrazole for many diseases whose treatment are difficult in the medical sciences. The introduction of the tetrazole ring into a molecule of an organic substrate quite often leads not only to an increase in the effectiveness of new drugs but also to an increase in the prolongation of drug action, and increases in their biological activities.

In patients receiving insulin therapy, the addition of a thiazolidinedione has resulted in significant reductions in daily insulin requirements. The thiazolidinediones are dependent on the presence of insulin for

activity; however, they do not affect insulin secretion. Several economical and social merits have been prospected for these compounds with effects like analgesic, anti-microbial, anti-inflammation, and others.

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