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Novel 2-aryl-3-[5–(((5-(3-nitrophenyl)–1,3,4-oxadiazole–2-yl)thio) methyl)–1,3,4–thiadiazole–2-yl]–2,3– dihydroquinazolines-4-(1*H*)-one containing heterocyclic moiety.

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Abstract

A series of oxadiazole derivatives of 5-(3-nitrophenyl)-1,3,4-oxadiazole-2-thiol [3] were synthesized in various steps . Organic acid 3-nitrobenzoic acid was successfully converted into ester [1] , and consequently into its acid hydrazide [2] in the presence of hydrazine hydrate and absolute ethanol as a solvent. Further, 3-nitrobenzoic acid hydrazide [2] yielded 5-(3-nitrophenyl)-1,3,4-oxadiazole-2-thiol [3], when treated with carbon disulfide (CS_2) in alcoholic potassium hydroxide solution, and the reaction of [3] with chloroacetic acid in basic media in (addition- elimination) reaction to give 2-(thio substituted)-1,3,4-oxadiazole-derivative [4] , which stirred with thiosemicarbazide and phosphoryl chloride ($POCl_3$) in cyclization reaction to yield oxadiazole ring bearing thidiazole ring [5]. Schiff's bases [6 $_{a-e}$] were obtained by condensation reaction of compound [5] with various aromatic aldehydes in absolute ethanol and some drops of glacial acetic acid. Finally, Schiff's bases were suffered cyclization reaction with 2-aminobenzoic acid in absolute ethanol to give compounds [7 $_{a-e}$] , which expected have biological significance.

The spectral methods of the prepared compounds were characterized by FT.IR, ^{1}H-NMR (for compound 9 $_b$) , besides melting points were recorded , and the purity was checked through T.L.C. technique . Some of these compounds were tested against bacteria, *Bacillus* (G +), *E.Coli* (G-), and *Klebsiella* (G -).

Keywords: Heterocyclic compounds; 1,3, 4-Oxadiazole; 1, 3, 4-Thiadiazole; Dihydroquinazolines-4(1*H*)-one; Biological activity.

INTRODUCTION

A heterocyclic compound is one which possess a cyclic structures with at least one hetero atom in the ring. Nitrogen,oxygen, and sulphur are the most common hetero atoms. Heterocyclic compounds are very widely distributed in nature and essential to the life in various ways [(1,2)]. Nitrogen heterocycles have special importance because they constitute main class of natural and non-natural products, most of which exhibit useful biological activity [(3)] . Quinolines show a vast sort of biological activities, they occupy a position of worthy in the modern medicinal chemistry., One of the most important compounds of quinoline is quinoline-4-ones because they are considered one of the largest antimicrobial groups used worldwide [(4)]., In addition to their antimicrobial activity the quinoline-4-ones are have many other biological and pharmacological activities, and they can to be as anxiolytic, anti-ischemic, antitumor, antiviral agents, and etc. [(5-7)]

Aim of the work

The aim of this work is to prepare and characterize series of some new heterocyclic derivatives starting from 3-nitrobenzoic acid which it were expected to have a biological and pharmaceutical activity.

EXPERIMENTAL

Instruments

1- All melting points are uncorrected in degree centigrade and determined on ***Gallen kamp*** electric melting point apparatus.
2- FT.IR spectra were recorded on a ***SHIMADZU*** FT.IR 8300 spectrophotometer in the range (4000 - 400) cm^{-1}, and using KBr discs.
3- ^{1}H-NMR spectrum was recorded on fourier transformation bruker spectrometer ,operating at (400MHz) with (DMSO-d_6) , measurement was made at Department of Chemistry, Kashan University - Iran.
4- The reactions progress was monitored by thin-layer chromatography (TLC) using 4- Fertigfollen precoated sheets type Polygram Silg, the detection was followed by coloring with iodine.
5- The biological activity was performed in the central service laboratory , College of Education for Pure Science / Ibn-Al-Haitham , Baghdad University.

Synthesis of: ethyl 3-nitrobenzoate (1) [(8,9)] .

In a separatory funnel containing (0.01 mol , 1 mL) thionyl chloride was gradually added to (0.01 mol , 1.67 gm) of 3-nitrobenzoic acid , The mixture was stirred until the vigorous evolution of gas has nearly ceased , then refluxed for 2 hours ., The reaction was monitored by TLC , after the reaction was complete, cooled to room temperature. The yellow product was liquid with good yield, B.p. = 273-276 ^{0}C, (lit. 275-278 ^{0} C).

This yellow product was added to it (0.01 mol , 25 mL) of absolute ethanol ; The mixture was refluxed at 70 – 80 ^{0}C for 6-7 hours with stirring. The obtained off white crystals was washed by solution of Na_2CO_3 then with distilled water. The product was ester. Re-crystallized from ethanol. M.p = 40-42 ^{0}C , (lit. 41- 43 ^{0}C).

Synthesis of: 3-nitrobenzohydrazide [2] [(10)] .

A mixture of compound (1) (0.01mol, 1.95 gm) and excess of 80 % hydrazine hydrate (0.01mol) in absolute ethanol (25 mL) was refluxed for 10-12 hours with stirring., The mixture was cooled and filtered, then recrystallized from ethanol. Physical properties shown in table (1).

Synthesis of: 5-(3-nitrophenyl)-1,3,4- oxadiazole - 2-thiol [3] [(11)] .

Solution of benzohydrazide (2) (0.01mol) was added to absolute ethanol which is contain potassium hydroxide (0.01mol) and carbondisulphide (CS_2) (0.01mol)., the

mixture was stirred for 1 hour, then refluxed for 7-8 hours , the solvent was removed , cold and softened with water and acidified by hydrochloric acid, filtered and recrystallized from ethanol.
Physical properties shown in table (1).

Synthesis of: 2-[(5-(3-nitrophenyl)-1,3,4- oxadiazole-2-yl)thio]acetic acid [4] [(12)] .
To compound (3) (0.0015 mol, 0.33 gm) dissolved in (25 mL) distilled water was added Chloroacetic acid (0.0015 mol, 0.14 gm) with stirring. The reaction mixture was stirred for 2- 3 hours until the crystals was separated, filtered and recrystallized from ethanol.
Physical properties shown in table (1).

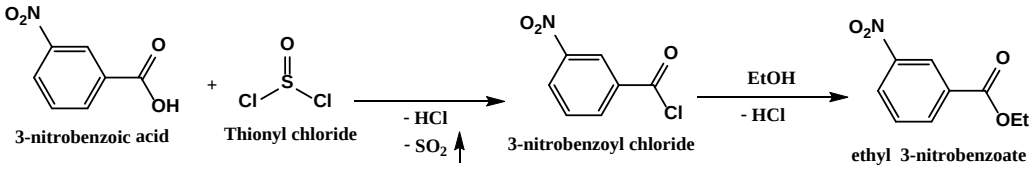
Synthesis of: 5-[((5-(3-nitrophenyl)-1,3,4-oxadiazole-2-yl)thio)methyl)-1,3,4-thiadiazole-2- amine [5] [(13)] .
A mixture of compound (4) (0.0015 mol , 0.5 gm) , thiosemicarbazide (0.0015 mol , 0.14 gm) and phosphoryl trichloride (0.0015 mol , 0.2 mL) was stirred under reflux for 9-10 hours., then (20 mL) of cold distilled water was added to the reaction with stirring , after the addition was complete the mixture was refluxed with continuous reflux for 1 hour. The reaction was monitored by TLC. After the reaction was complete, cooled to room temperature, filtered. The filtration product was naturalized with sodium hydroxide, the brown crystals was formed in good yield , collected, filtered , washed with water , dried , re-crystallization from ethanol. Physical properties shown in table (1).

Synthesis of: Schiff, s bases [6 a- e] [(14,15)] .
A mixture of equimolar quantities (0.001mol, 0.33 gm) of aromatic amine (5) and aromatic benzaldehydes + 2 drops of glacial acetic acid in (25 mL) of absolute ethanol was stirred for 20 min. The reaction mixture was refluxed for 9-10 hours with stirring. The mixture was cooled and kept for 24 hours. The crystals found was filtered, dried and recrystallized from ethanol to give colored products of Schiff's bases. Physical properties shown in table (1).

Synthesis of: 2-aryl-3-[5-(((5-(3-nitrophenyl)-1,3,4-oxadiazole-2-yl)thio)methyl)-1,3,4-thiadiazole-2-yl]-2,3-dihydroquinoline-4(1*H*)-one. [7 $_{a-e}$] [(16)] .
A mixture of Schiff's bases (6 $_{a-e}$) (0.001 mol) , 2-aminobenzoic acid (0.001 mol , 0.13 gm) in (25 mL) absolute ethanol was stirred under reflux for 10-12 hours. The reaction mixture was concentrated and cooled. The solid was filtered, washed with water and recrystallized from ethanol. Physical properties shown in table (1).

RESULTS AND DISCUSSION

The heterocyclic compound chemistry is a great domain of benefit of study both in theory as well as in practical importance.
Ethyl 3-nitrobenzoate [1] was synthesized from the reaction of 3-nitrobenzoic acid with thionyl chloride to form 3-nitrobenzoyl chloride in nucleophilic substitution reaction [(8,17)] , which was then reacted with absolute ethyl alcohol [(9)].



Scheme -1

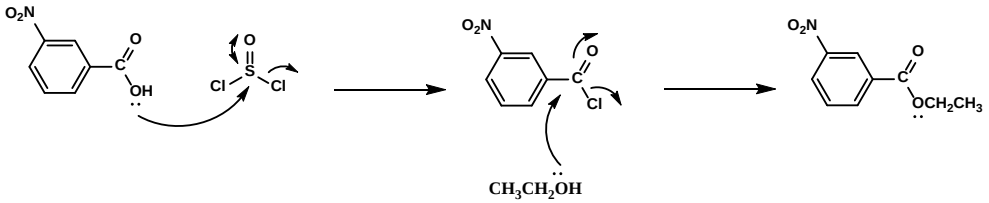
Table-1: Formulas, Molecular weights, and Physical properties of synthesized compounds.

Comp. no.	Formula	M.wt. gm / mol	M.P.^{0} C	Color	Yield %
1	$C_9H_9O_4N$	195	41-43	Off white	94
2	$C_7H_7O_4N_3$	197	139-141	Off white- light yellow	96
3	$C_8H_5O_3N_3S$	223	125-127	Light yellow	60
4	$C_{10}H_7O_5N_3S$	281	260-262	Off white	92
5	$C_{11}H_8O_3N_6S_2$	336	130-132	brown	71
6a	$C_{18}H_{11}O_5N_7S_2$	469	96-98	Light brown	87
6 b	$C_{18}H_{11}O_3N_6S_2Cl$	458.5	187-189	Yellow-green	91
6 c	$C_{18}H_{11}O_3N_6S_2Br$	503	116-118	Dark brown	82
6 d	$C_{18}H_{12}O_4N_6S_2$	440	106-108	Dark brown	90
6 e	$C_{20}H_{17}O_3N_7S_2$	467	94-96	Reddish brown	88
7 a	$C_{25}H_{16}O_6N_8S_2$	588	139-141	brown	74
7 b	$C_{25}H_{16}O_4N_7S_2Cl$	577.5	170-172	Light green	69
7 c	$C_{25}H_{16}O_4N_7S_2Br$	622	113-115	Dark brown	61
7 d	$C_{25}H_{17}O_5N_7S_2$	559	177-179	Dark yellow	71
7 e	$C_{27}H_{22}O_4N_8S_2$	586	140-142	Reddish brown	77

Table-2: FT-IR spectral data of synthesized compounds.

Comp. No.	ν C-H arom.	ν C-H ali.	ν NH_2 , NH	ν C=O	ν C=N endo	ν C= C arom.	ν others
1	3014.74 , 3093.82	2868.15 , 2958.8	-----	ν C=O ester 1714.72	-----	1614.42 , 1473.62	ν NO_2 1525.69 asym. , 1348.24 sym. ν C-O 1265.30
2	3072.6 , 3097.68	-----	3373.20 asym. , 3262 sym.	ν C=O amid 1668.43	-----	1618.28 , 1490	ν NO_2 1517.98 asym. , 1332.81 sym.
3	3095.75	-----	-----	-----	1707	1618 , 1481	ν NO_2 1533 asym. , 1350 sym. ν S-H 2549 ν C-O 1286
4	3091	2925 , 2960	-----	-----	1707	1620 , 1481	ν NO_2 1533 asym. 1354 sym. ν C=O 1774 ν O-H 3438
5	3095.75	2883 , 2962.66	3316.2 asym. , 3286.70 sym.	----	1630 , 1650	1618.28 , 1456.26	ν NO_2 1506.14 asym. , 1344.38 sym, ν C-O 1265.30 ν C-S 798.53

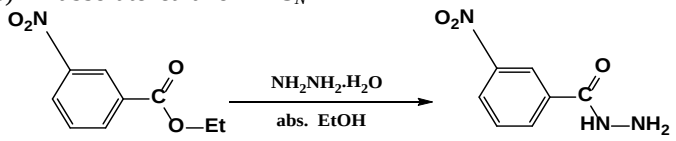
The proposed reaction mechanism is shown in the following scheme:



Scheme -2

The FT.IR spectrum of compound [1], showed disappearance of stretching band of (OH) and appearance of stretching band of (C=O ester) group at (1714.72) cm^{-1} , [18] , (table- 2)

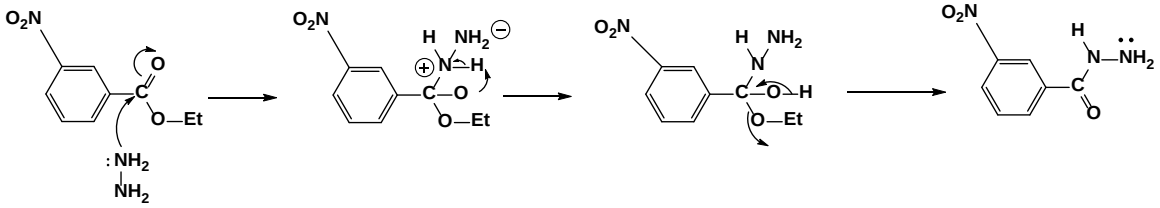
Compounds [2] was synthesized from reaction of ester [1] with hydrazine hydrate (80%) in absolute ethanol in S_N2 mechanism, and has proven by appearance of stretching vibration bands at (3373.20 $_{asym.}$, and 3262 $_{sym.}$) cm^{-1} refers to the terminal amino group, and by shifting of the intense stretching vibration band from (1668.43) cm^{-1} for (C=O) of amidic group. [18] , (table-2)



[1] **[2]**

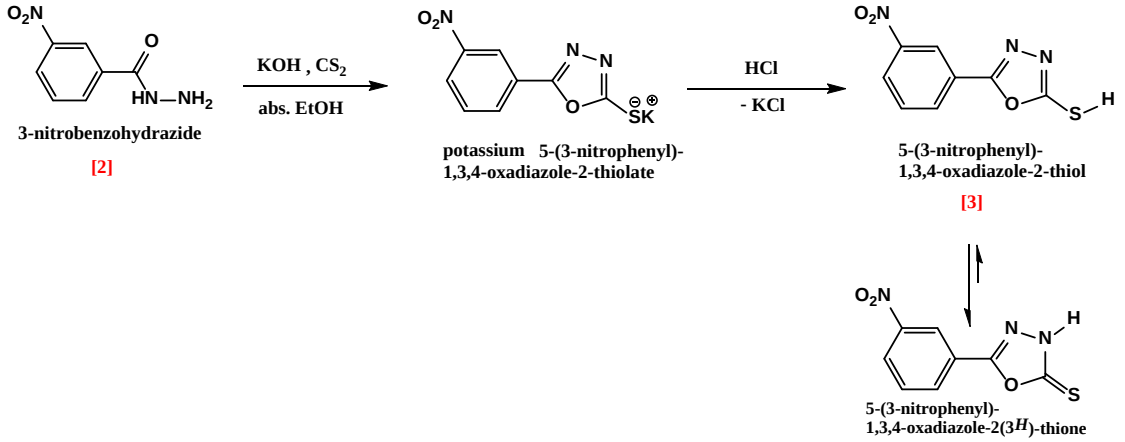
Scheme –3

The proposed reaction mechanism is shown in the following scheme:



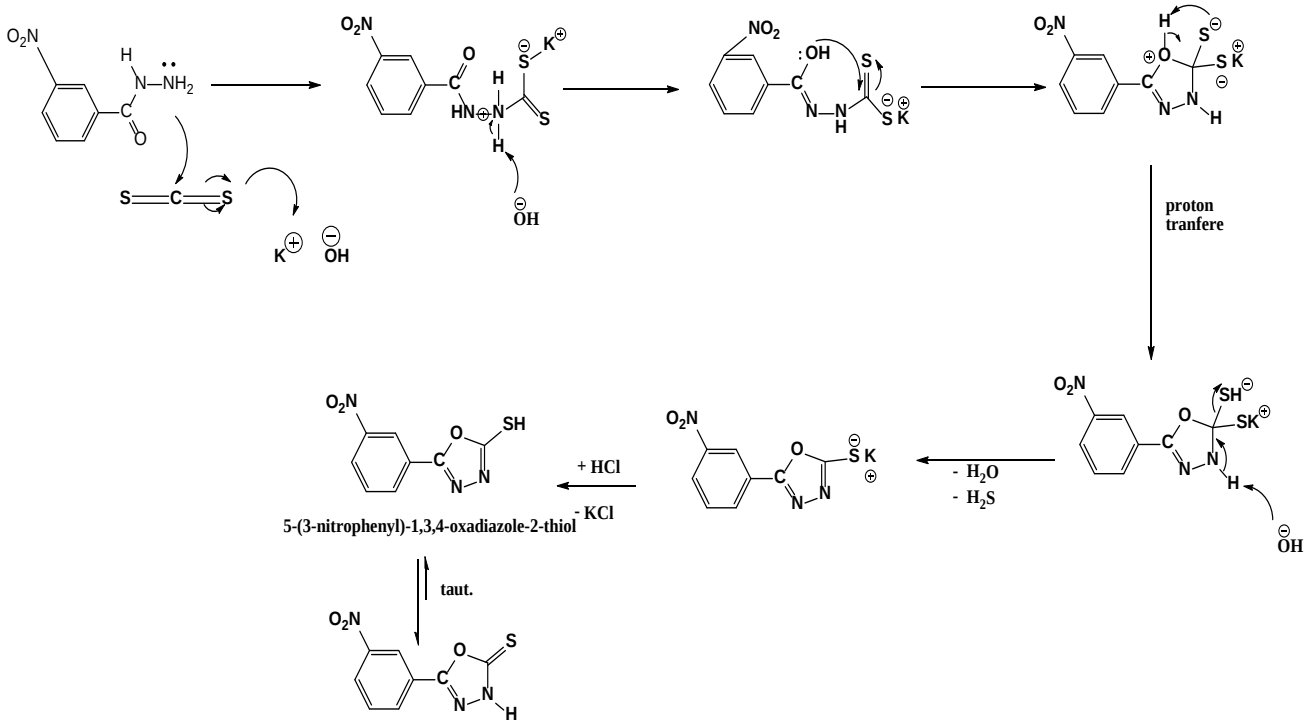
Scheme –4

Aromatic acid hydrazide derivative [2] was reacted with carbon disulphidee (CS_2) in presence of potassium hydroxide in absolute ethanol then acidified with concentrated hydrochloric acid to give 1,3,4-oxadiazole derivative [3] which tautomerized to the stable structure (thione form).[19]



Scheme -5

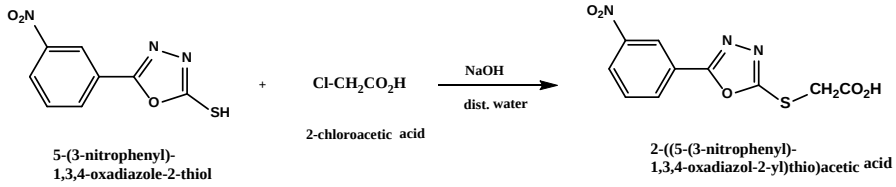
The proposed reaction mechanism is shown in the following scheme:



Scheme -6

The FT-IR spectrum of compound [3] showed disappearance of two stretching bands at (3373.2) cm^{-1} and (3262) cm^{-1} which refer to (NH_2) group , and appearance of strong band at (1707) cm^{-1} refer to endo (C=N) stretching, and strong band in the range (1286) cm^{-1} assigned for (C– O –C) cyclic grouping ; In addition to two another characteristic bands at (3174) cm^{-1} , and (2549) cm^{-1} refer to (N-H form) and (S-H) stretching vibration, respectively., This indicates a thione-thiol equilibrium[18], (table-2)

The 1,3,4-oxadiazole provides number of reactions including nucleophillic substitution, electrophilic substitution, photochemical , and thermal. 1,3,4-oxadiazole-2-thiol [3] undergo nucleophilic substitution reaction similarly as occurring at an aliphatic sp^2 carbon atom, to get corresponding hydrazine derivative [4].[20]



5-(3-nitrophenyl)-1,3,4-oxadiazole-2-thiol

[3]

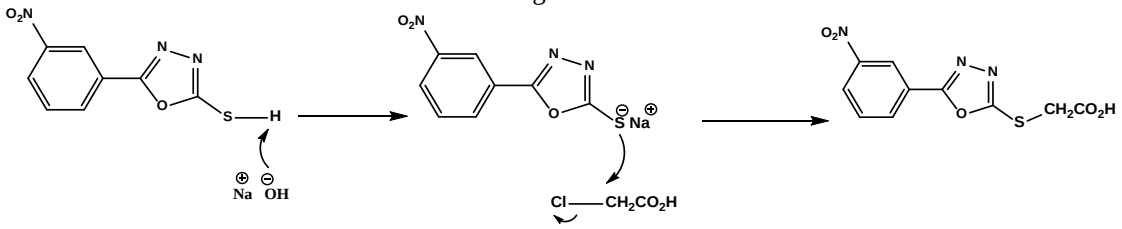
2-chloroacetic acid

2-((5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl)thio)acetic acid

[4]

Scheme -7

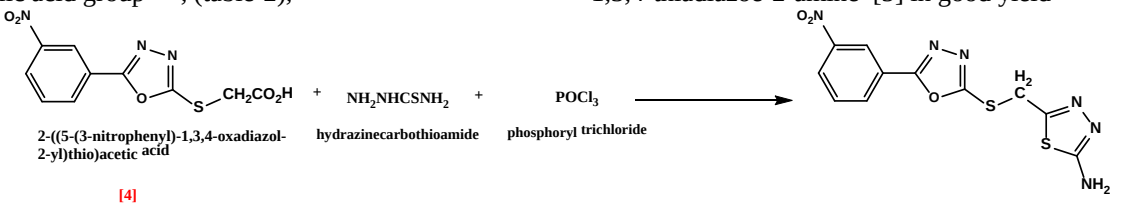
The proposed reaction mechanism is shown in the following scheme:



Scheme -8

The FT-IR spectrum of compound [4] showed appearance of stretching band at (3438) cm^{-1} refer to (OH) of carboxylic acid group [18], (table-2),

Compound [4] was reacted with thiosemicarbazide and phosphoryl trichloride in cyclization reaction to give : 1,3,4-thiadiazoe-2-amine [5] in good yield.[21]



2-((5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl)thio)acetic acid

[4]

hydrazinecarbothioamide

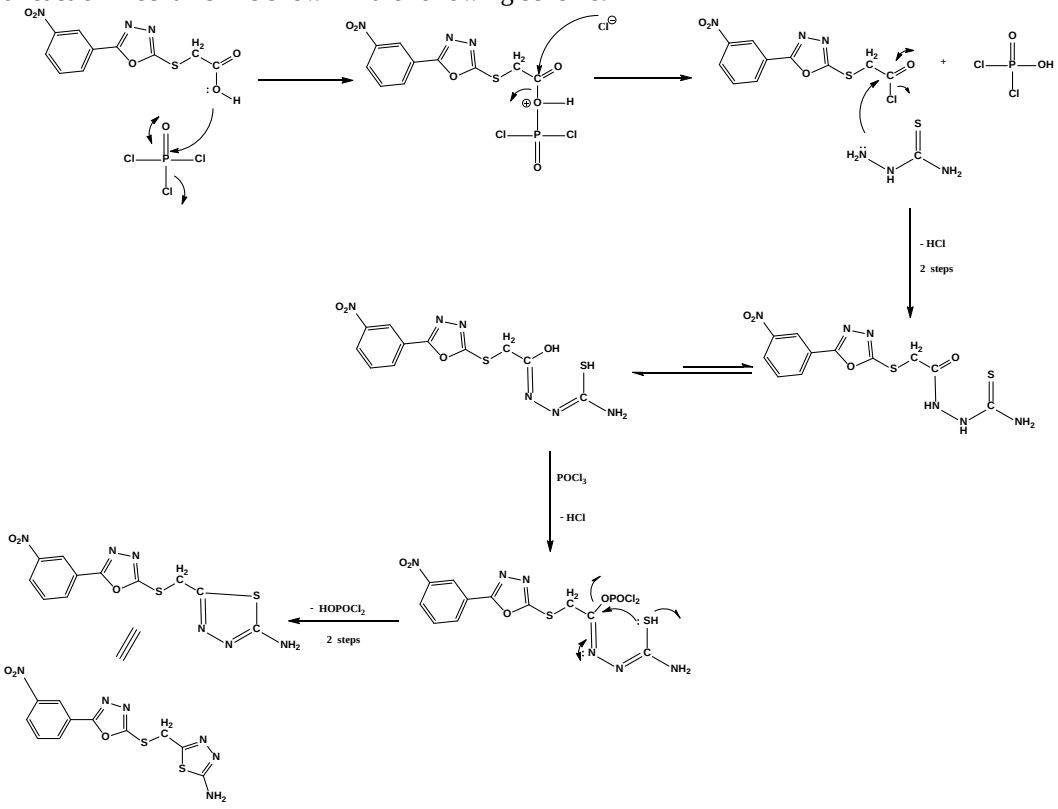
phosphoryl trichloride

5-[((5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl)thio]methyl)-1,3,4-thiadiazole-2-amine

[5]

Scheme -9

The proposed reaction mechanism is shown in the following scheme:



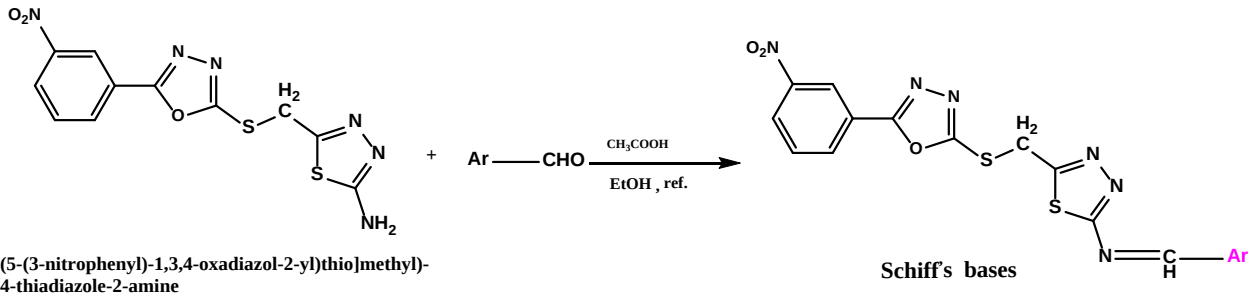
Scheme -10

Compound [5] is a ring of 1,3,4 – oxadiazole bearing thiadiazole ring which expected have an importance in the field of drugs.

Reaction of [5] with varied aromatic aldehydes under slight acidic conditions to give the substituted aromatic Schiff's bases[22,23] , [6 $_{a-e}$], (table-3), which were thereafter cyclized with 2-aminobenzoic acid in absolute ethyl alcohol to yield quinazoline-4(1*H*)-one derivatives[24], [7 a-e].

Schiff's base formation mechanism include nucleophilic addition to the carbonyl group and elimination of a water molecule [25]. Schiff's bases are distinguished by the imine group (-N=CH-) which is important compound due to great flexibility and diverse structural aspects [18]. The FT-IR spectra of Schiff's bases [6 a-e], indicate a disappearance of (N-H) stretching band of the primary amine at region (3316.2 $_{asym.}$ and 3286.7 $_{sym.}$) cm^{-1} , and appearance of stretching band at (1664.57 - 1614) cm^{-1} refer to the formation of imino group (HC=N) [18], (table-3)

For a long time imines have been used successfully in the synthesis of nitrogen containing heterocyclic which expected to have biological importance [26]. 2,3-Dihydroquinazoline ring derivatives [7 $_{a-e}$], were synthesized by refluxing equimolar amounts from the imines [6 $_{a-e}$] with 2-aminobenzoic acid in absolute ethyl alcohol. Cyclization occur where functional group in 2-aminobenzoic acid attack as a nucleophile the carbon of (C=N) bond [27,28].



5-[((5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl)thio]methyl)-1,3,4-thiadiazole-2-amine

[5]

Schiff's bases

[6 a - e]

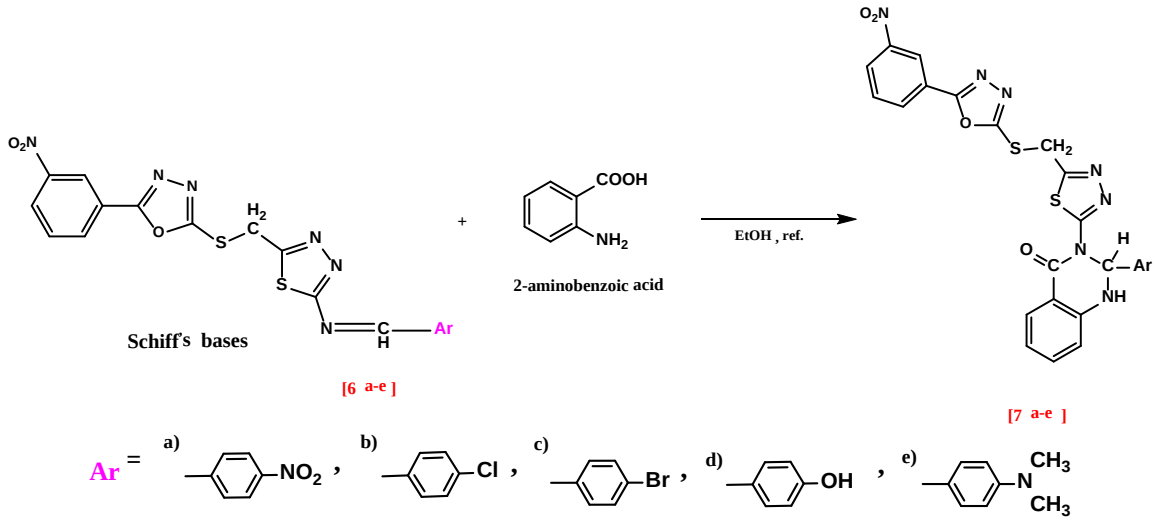
Ar = a) NO_2 , b) Cl , c) Br ,

d) OH , e) $N(CH_3)_2$

Scheme -11

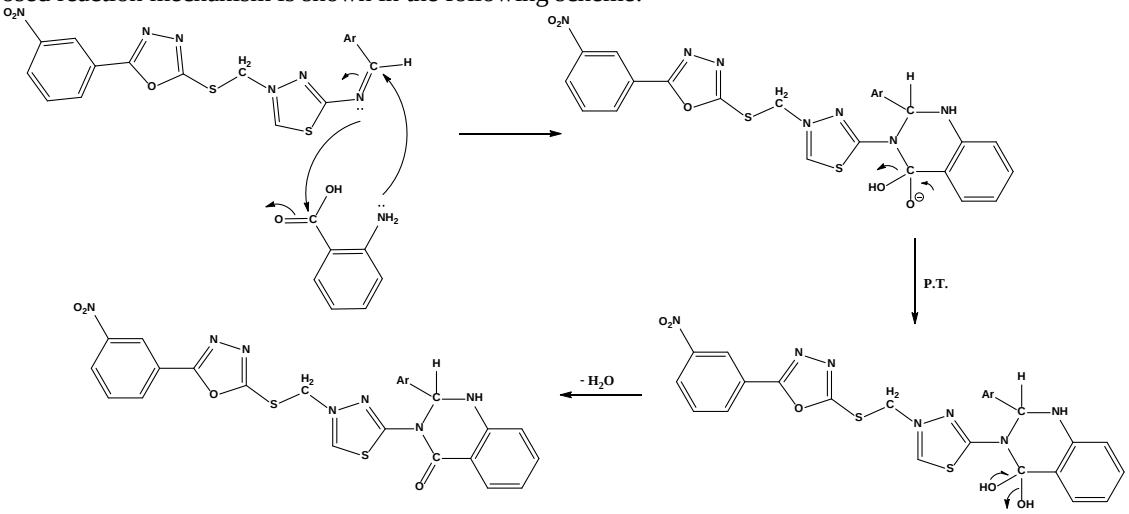
Table-3 : FT-IR spectral data of Schiff's bases.

Comp. No.	Ar	ν C-H arom.	ν C-H ali.	ν C=N exo	ν C=N endo	ν = C - H	ν others
6 a	NO_2	3086.11	2852.72 , 2926.01	1699.29	1616.35	3115	ν C-NO_2 1527.62 (Asym.) ,1350.17 (Sym.)
6 b	Cl	3149.76	2854.65 , 2927.94	1724.36	1614.42	3278	ν C-NO_2 1527.62 (Asym.) , 1350.17 (Sym.) ν C-Cl 736.81
6 c	Br	3024	2925 , 2970	1739	1645	3323	ν C-NO_2 1525.69 (Asym.) , 1346.31 (Sym.) ν C-Br 669
6 d	OH	3118.90	2849.8 , 2932.8	1666.50	1645.28	3167.12	ν C-NO_2 1519.91 (Asym.) , 1350.17 (Sym.) ν C-OH 3371.57 ν C-O 1155.36
6 e	OCH_3, OH	3089.96	2933.3 , 2966.5	1691.57	1664.57	3255.84	ν C-NO_2 155.34 (Asym.) , 1373.32 (Sym.) ν C-OH 3404 ν C-O
6 f	$N(CH_3)_2$	3088.03	2796.78 , 2908.65	1730.15	1656.85	3230	ν C-NO_2 155.34 (Asym.) , 1373.32 (Sym.) ν C-N 1230.58



Scheme -12

The proposed reaction mechanism is shown in the following scheme:



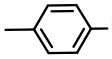
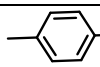
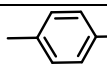
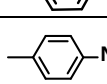
Scheme -13

Quinazolene-4(1*H*)-ones [7_{a-e}] were characterized by FT-IR, ^{1}H-NMR spectrum for compound [9_b], besides the TLC and physical properties (Table- 1).

The FT-IR spectrum of compounds [7_{a-e}], showed the appearance of stretching band of carbonyl group at υ (1712-1670) cm^{-1} due to Guinazoline ring and this was the most characteristic evidence for the success of cyclization step., also showed disappearance of (C=N) stretching band of at υ (1739 – 1666.5) cm^{-1} imine , and appearance stretching band at υ (1287-1230) cm^{-1} due to (C-N) bond in quinazoline ring [18], (table-4)

The ^{1}H-NMR spectrum of compound [9_b] shows the special chemical shifts (δ ppm) at: (3.34 , s, 2H, CH_2), (4.12 , s, 1H, CH), (5.30 , s, 1H, NH quinazoline ring), and (6.472–8.498 , m, 12H, H-aromatic rings) as a multiple overlapping peaks[18]

Table-4: FT-IR spectral data of quinazoline-4-ones.

Comp. No.	Ar	υ N-H	υ C-H arom.	υ C-H ali.	υ C=O	υ C=N endo	υ others
7 a		3332.99	3167.12 , 3082.25	2958.80, 2866.22	1712.79	1608.63	υ C-NO_2 1527.62 (Asym.) ,1350.17 (Sym.)
7 b		3329.14	3282.84 , 3151.69	2900 , 2800	1670.35	1616.35	υ C-NO_2 1527.62 (Asym.) , 1350.17 (Sym.) υ C-Cl 740.67
7 c		3334.92	3074.53	2900 , 2830	1693.5	1664.57	υ C-NO_2 1525.69 (Asym.) , 1346.31 (Sym.) υ C-Br 669
7 d		3300	3086.11	2945 , 2893.22	1678.07	1581	υ C-NO_2 1519.91 (Asym.) , 1350.17 (Sym.) υ C-OH 3406.29
7 e		3414	3093.82	2904.80, 2840, 2808.36	1678.07	1589.34	υ C-NO_2 155.34 (Asym.) , 1373.32 (Sym.) υ C-N 1126.43

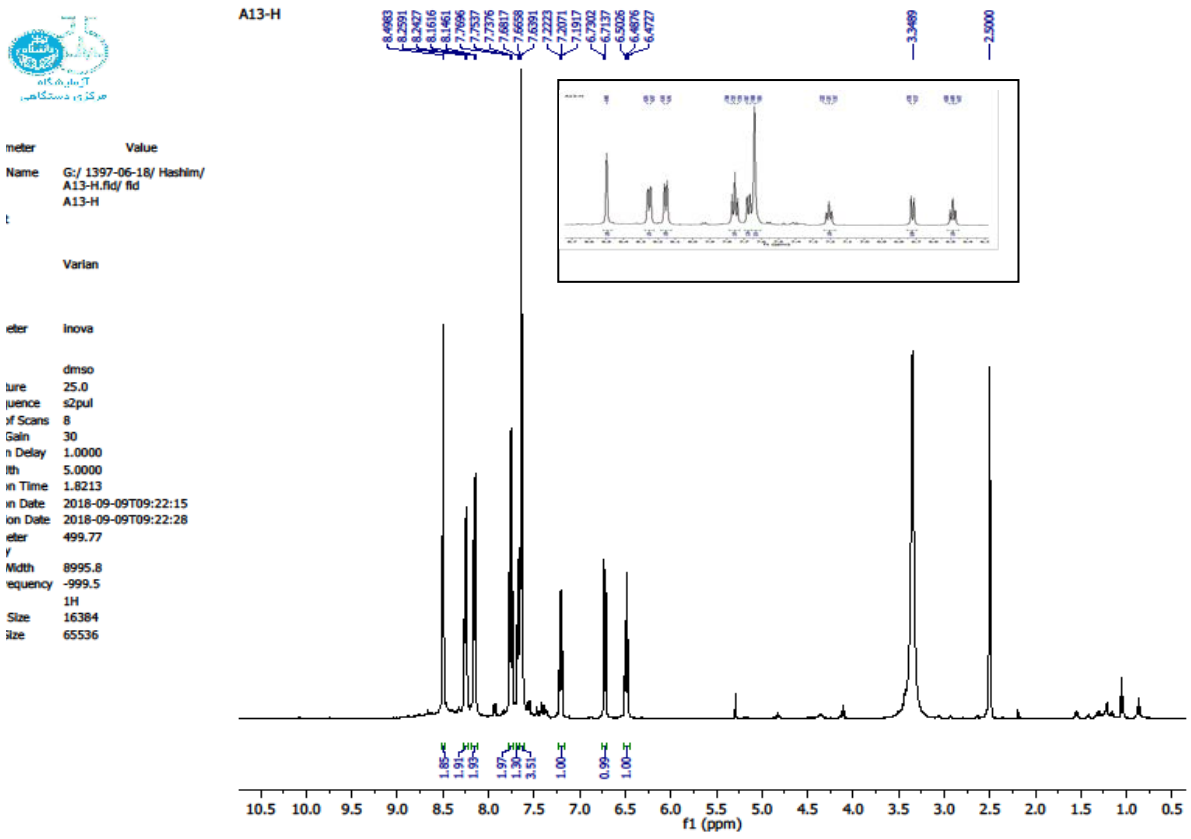


Figure No. (1) : ^{1}H-NMR spectrum of compound (7b).

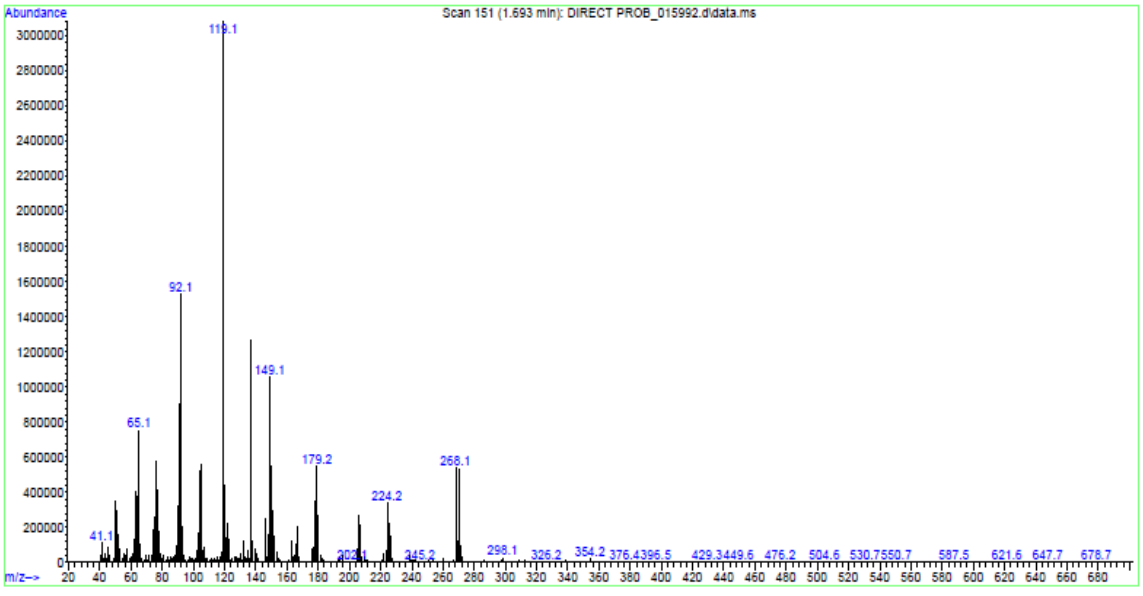


Figure No. (2): The mass spectrum of compound (7a)

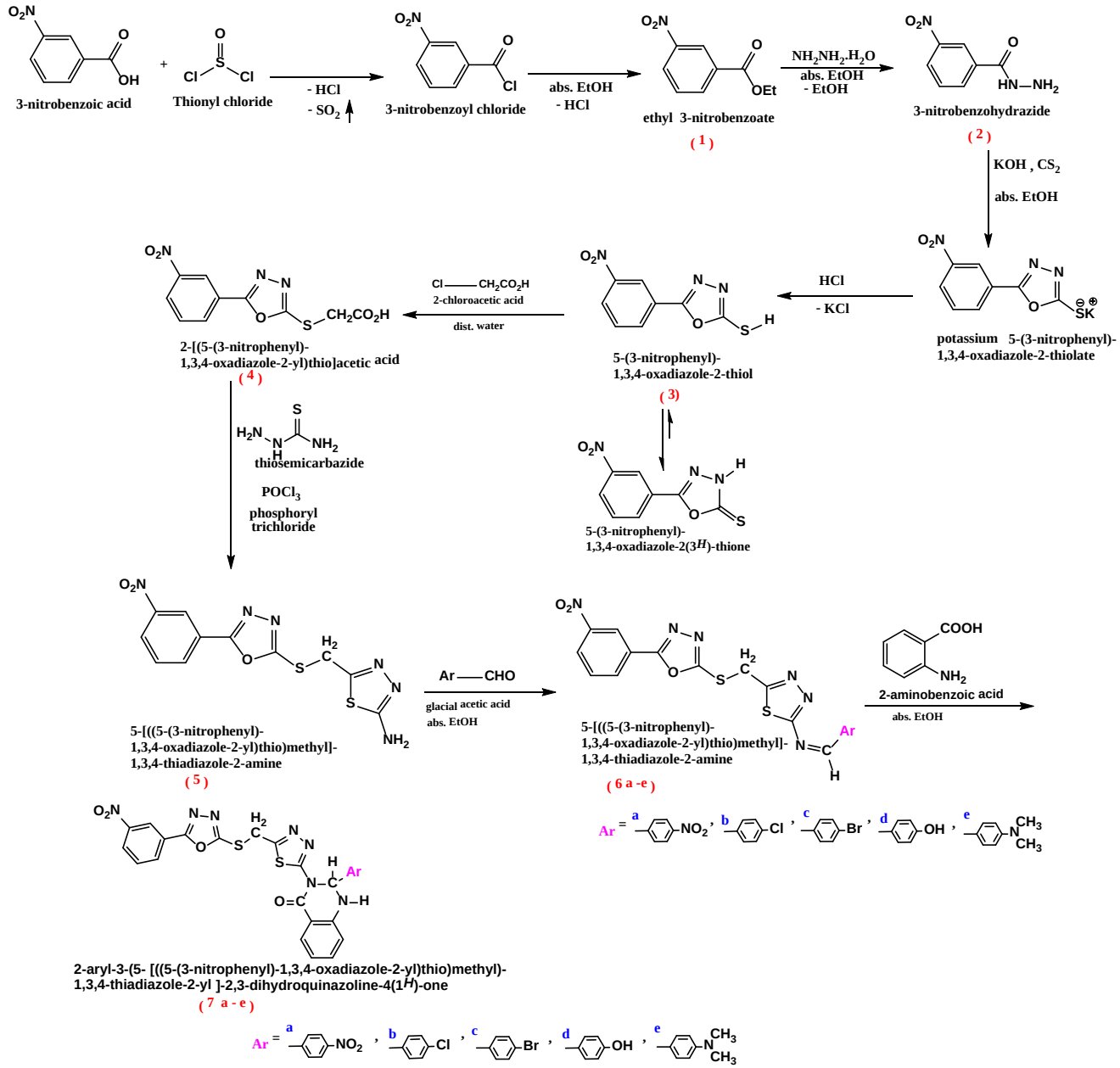


Table -5: Antibacterial actions for some of the synthesized compounds.

Comp. no.	Klebsiella (G-)	E. Coli (G-)	Bacillus (G+)
7 a	++ (15)	++ (16)	++ (16)
7 b	++ (15)	++ (12)	++ (14)
7 c	++ (15)	++ (16)	++ (16)
7 d	-	-	++ (17)

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

Biological screening: Antibacterial activity test

The antibacterial activity test was performed by disc diffusion method for compounds (7a , 7b , 7c , and 7d) which were assayed for their antimicrobial activity in vitro against two strains of Gram negative (G-) bacteria : ***Klebsiella*** and ***Escherichia coli*** (***E. Coli***.) , and Gram positive (G+) bacteria : ***Bacillus subtilis***.

The prepared agar and petri dishes were sterilized by autoclaving for 15min. at 121 ºC. The agar plates were surface inoculated uniformly from the broth culture of the tested microorganisms. In the solidified medium suitably

spaced apart holes were made all 6mm in diameter. These holes were filled with 0.1 ml of the prepared compounds (10 mg of the compound dissolved in 1ml of DMSO solvent.[29]

The control used in the disk was DMSO . The same solvent was used for antibiotics Cephalexine (Keflex) for curing Salmonella ., Cephalexine for Escherichia coli , Klebsiella and Bacillus subtilis were used for comparison.

These plates were incubated at 37 ºC for 24hr for bacteria. The inhibition zones caused by the various compounds were examined.

The results of the preliminary screening tests are :

For ***Bacillus subtilis*** (G+), compound (7d) showed highest activity, while compounds (7a,7b, and 7c) showed less activity on this bacteria.

For ***Klebsiella*** and ***E.coli*** (G-), compound (7a and 7c) have moderately active on ***E.Coli*** bacteria ., While compound 7b showed less activity ., While on ***Klebsiella bacteria*** compounds (7a, 7b , and 7c) showed the same activity on this bacteria. compound (7d) have no effect on both ***Klebsiella*** and ***E. Coli*** bacteria . (table-5).

CONCLUSION

In in this article, we review the recently literature data of synthesis and biological activity of 1,3,4 – oxadiazole bearing thiadiazol ring which synthetically important scaffold and also possesses a wide range of promising biological activities. Some 1,3,4-thiadiazole derivatives have better activity than standard drugs and could become a new drug for the market in future.

Future Aspect

Future investigation could give some interesting results on substitution at various position of 1,3,4- oxadiazole and 1,3,4-thiadiazole rings.

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