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Microwave Synthesis and Preliminary Antibacterial Activities of New 5-Substituted-2-thiol/thione-1,3,4- Oxadiazoles Containing the Oxazepine and Oxazepane Moieties

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Abstract: ***5-(4-aminophenyl)-2-thiol-1,3,4-oxadiazole 1 was synthesized via the reaction of carbon disulfide with 4-aminobenzoyl hydrazide in presence of potassium hydroxide in absolute ethanol. Compound 1 was converted to the corresponding diazonium salt which was introduced in coupling reaction with alkaline solution of 2-hydroxybenzaldehyde as coupling reagent to give azo-oxadiazole derivative 2 containing aldehyde group. The resulting aldehyde 2 was then introduced in condensation reactions with the primary aromatic amines including (4-bromoaniline, 4-chloroaniline, 2,4-dichloroaniline, 4-nitroaniline, 3-nitroaniline, 4-methoxyaniline, 2-methoxyaniline and 4-hydroxyaniline) using microwave irradiation technique in absolute ethanol to produce eightazoimine derivatives of 1,3,4-oxadiazole 3a-h, respectively. Treatment of the resulting imines 3a-h with both maleic and succinic anhydrides under (2+5) cycloaddition conditions using microwave irradiation in dry benzene afforded sixteen new oxadiazoles4a-h and 5a-h substituted with 1,3-oxazepine and 1,3-oxazepane moieties, respectively. Preliminary in vitro antibacterial activity of the target compounds were investigated usingtwo types of bacteria, Staphylococcusaureus (Gram-positive) and Escherichia coli (Gram-negative). The results indicated that the newly synthesizedoxadiazoles (compounds 4aand 5h)exhibited equipotent activities to gentamycin against Gram-positive bacteria. On the other hand, just one compound (compound 5f) showed better activityagainst Gram-negative bacteriawhen compared with that of the control drug (Gentamycin).***

Keywords:1,3,4-Oxadiazoles;Imines;1,3-Oxazepanes; 1,3 Oxazepines

1. Introduction

Oxadiazolesare five-membered heteroaromatic compounds including two nitrogen atoms and one oxygen atom on the ringand considered very weak base because there is an inductive effect of extra heteroatom[1]. Oxadiazole moiety is derived from furan by replacing two -CH= group with two pyridine typed nitrogen (-N=)[2].1,3,4-Oxadiazoles constitute an important family of heterocyclic compounds as they have attracted significant interest in medicinal chemistry, pesticide chemistry and polymer science[3].Oxadiazoles also possess antitubercular[4],antimalarial[5], antileishmanial[6], antimicrobial[7], anti-inflammatory, analgesic[8], anti-HIV[9], antimycobacterial[10], cathepsin K inhibitors[11]tyrosinase inhibitors[12], monoamine oxidase (MAO) inhibitors[13] and anticancer[14] activities. Most of the marketed antihypertensive agents such as Tiodazosin[15]drug **A** and Nesapidil[16]drug **B** as well as antibiotics such as Furamizole[3]drug **C** ,Raltegravir[17], an antiretroviral drug **D** and Zibotentan[18], an anticancer agent **E**contain oxadiazole nucleus currently used in clinical medicine. One of the common methods for the synthesis of 1,3,4-oxadiazole-2-thione / thiol derivatives reported byYong and Wood[19]from reaction of benzoic hydrazides with carbon disulfide in presence of potassium hydroxide in absolute ethanol. Rashid[20]et al. were synthesized some 1,3,4-oxadiazole derivativesunder microwave irradiation in good yields, and compound **F**showed significant to good anticancer activity.

Heterocyclic seven-membered ring constitutes the core or a key fragment of a number of bioactive compounds including isolated from natural products[21], oxazepines and oxazepanes are a well-known class of seven-membered heterocycles with two heteroatoms(oxygen and nitrogen)[22]. Oxazepine compoundshave medical and biological importance and they have medicinal[23,24]andpharmaceutical applications[25].Some Oxazepine derivatives are considered a medical drugagainst the disease[26] and some of them act as inhibitorsof some enzymes action[27].Fusedoxazepinone derivatives have attracted considerable attention owing to their promising biological activities[28], such as antihistaminic[29], anti-HIV[30],antidepressant[31], and antitumor activities[32].Asendin (Amoxapine) drug is used as antidepressant[33]and active drug for schizophrenia[34].

Thus, in this article, we reported here the synthesis of new5-substituted-2-thiol-1,3,4-oxadiazole derivativesbearing biologically active heterocyclic moieties including, oxazepine, oxazepane, in addition of azo group, which might have some biological activity.

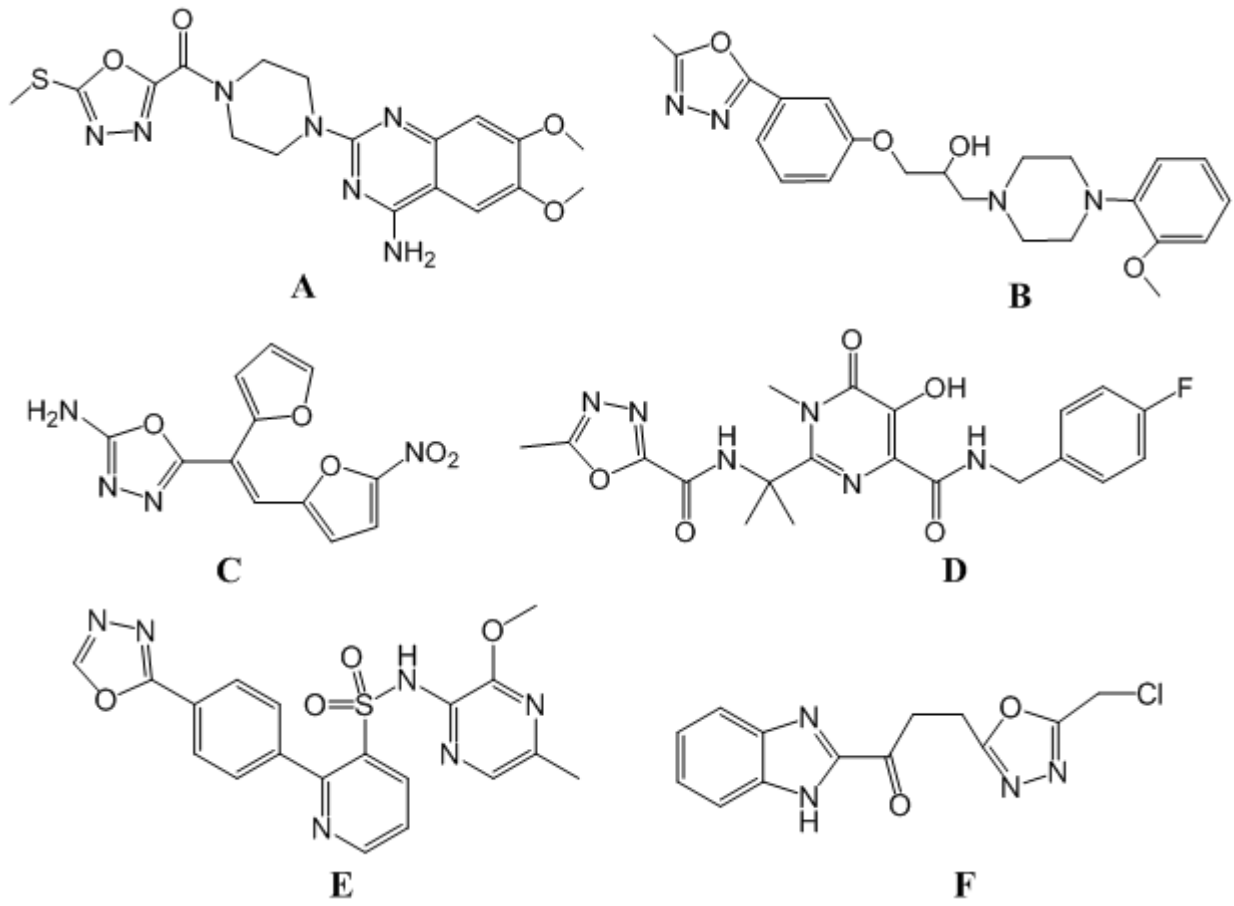


Figure 1: Structures of some bioactive 1,3,4-oxadiazole derivatives

2. Experimental

2.1. General

The chemicals were used as provided from Fluka, sigma aldrich and Merck.Microwave reactions were performed on Domestic microwave oven in crucible. Analytical TLC was performed with silica gel 60 F_{254} plates. The reactions were monitored by TLC and visualized by development of the TLC plates with iodine vapor. Melting points were recorded on an Electro thermal Stuart SMP 30 capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on SHIMADZU FTIR–8400S Infrared Spectrophotometer as potassium bromide discs. ^{1}H NMR spectra was collected on NMR spectrometer 300 MHz, Ascennd^{TM}400 Bruker, Germany at 300 MHz in DMSO–d_6 as solvent and TMS as an internal standard at a Faculty of Science, University of Ferdosi, buali center, Iran.(CHNS) Elemental Analysis was carried out with Perkin Elmer 300A Elemental Analyzer at a Faculty of Science, University of Ferdosi, buali center, Iran.

2.2. Chemical methods

2.2.1. 5-(4-aminophenyl)-2-thiol-1,3,4-oxadiazole (1) was synthesized according toYong and Wood conditions[19] as pale yellow crystals, mp 234-236ºC, yield 76 %; IR (cm^{-1}) : 3448 (νas. NH2), 3352 (νs. NH2), 3086 (νN-H, thione form and νC-H, benzene, vib. coupling), 2947 and 2764 (υN-H, intramolecularly hydrogen bonded, thione form), 2590 (νS-H, thiol form), 1604 (νC=N, oxadiazole and δ NH2, vib. coupling), 1512 (νC=C, benzene) , 1068 (νC=S, thione form), 835 (δo.o.p. C-H, benzene).

2.2.2. (E)-2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)benzaldehyde(2) was synthesized following the method described by Acton[35]as red solid, mp 196-198ºC, yield 78 %;IR (cm^{-1}): 3402br (νO-H),3190(νN-H, thione form), 3095 (νC-H, benzene), 2937 and 2748 (νN-H, intramolecularly hydrogen bonded, thione form), 2885 (νC-H, aldehyde), 2580 (νS-H, thiol form), 1662 (νC=O, aldehyde), 1604 (νC=N, oxadiazole), 1477 (νC=C, benzene), 1411 (νN=N), 1068 (νC=S, thione form), 842 (δo.o.p. C-H, benzene).

2.2.3. General procedurefor thesynthesis ofoxadiazolic-imines 3a-h:
All reactions were carried out on Domestic microwave oven in crucible. Reactions contained the azoaldehyde derivative 2 (0.815 g, 2.5 mmol), equimolar amount (2.5 mmol) of aniline derivatives (4-bromoaniline, 4-chloroaniline, 2,4-dichloroaniline, 4-nitroaniline, 3-nitroaniline, 4-methoxyaniline, 2-methoxyaniline and 4-hydroxyaniline respectively) and absolute ethanol (2 mL). The crucible was introduced to the center of a Domestic microwave oven and then heated to 72 ºC for 20 minutes. TLC (*n*-hexane: EtOAc) showed that the reactions were completed. The products were washed with diethyl ether and then recrystallized from ethanol.

2-((E)-((4-bromophenyl)imino)methyl)-4-((E)-(4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenol(3a): IR (cm^{-1}): 3365 (νO-H), 3063 (νN-H, thione form and νC-H, benzene, vib. coupling), 2928 and 2750 (νN-H, intramolecularly hydrogen bonded, thione form), 1608s (νC=N, oxadiazole and νC=N, imine, vib. coupling), 1487 (νC=C, benzene), 1411 (νN=N), 1068 (νC=S, thione form), 827 (δo.o.p. C-H, benzene).

2-((E)-((4-chlorophenyl)imino)methyl)-4-((E)-(4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenol(3b):IR (cm^{-1}): 3061 (νO-H, νN-H, thione form and νC-H, benzene, vib. coupling), 2924 and 2750 (νN-H, intramolecularly hydrogen bonded, thione form), 2596 (νS-H, thiol form), 1608s (νC=N, oxadiazole and νC=N, imine, vib. coupling), 1494 (νC=C, benzene), 1410 (νN=N), 1066 (νC=S, thione form), 829 (δo.o.p. C-H, benzene).

2-((E)-((2,4-dichlorophenyl)imino)methyl)-4-((E)-(4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenol(3c):IR (cm^{-1}): 3336 (νO-H), 3068 (νN-H, thione form and νC-H, benzene, vib. coupling), 2933 and 2748 (νN-H, intramolecularly hydrogen bonded, thione form), 2590 (νS-H, thiol form), 1610s (νC=N, oxadiazole and νC=N, imine, vib. coupling), 1508 and 1479 (νC=C, benzene), 1411 (νN=N), 1064 (νC=S, thione form), 839 (δo.o.p. C-H, benzene).

4-((E)-(4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)-2-((E)-((4-nitrophenyl)imino)methyl)phenol(3d):IR (cm^{-1}):3333 (νO-H), 3070 (νN-H, thione form and νC-H, benzene, vib. coupling), 2931 and 2760 (νN-H, intramolecularly hydrogen bonded, thione form), 2590 (νS-H, thiol form), 1599s (νC=N, oxadiazole and νC=N, imine, vib. coupling), 1510s (νC=C, benzene and νas. NO2, vib.coupling), 1411 (νN=N), 1338 (νs. NO2), 1066 (νC=S, thione form), 839 (δo.o.p. C-H, benzene).

4-((E)-(4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)-2-((E)-((3-nitrophenyl)imino)methyl)phenol(3e):IR (cm^{-1}):3340 (νO-H), 3080 (νN-H, thione form and νC-H, benzene, vib. coupling), 2931 and 2752 (νN-H, intramolecularly hydrogen bonded, thione form), 2563 (νS-H, thiol form), 1604s (νC=N, oxadiazole and νC=N, imine, vib. coupling), 1525s (νC=C, benzene and νas. NO2, vib.coupling), 1411 (νN=N), 1348 (νs. NO2), 1068 (νC=S, thione form), 840 (δo.o.p. C-H, benzene).

4-((E)-(4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)-2-((E)-((4-methoxyphenyl)imino)methyl)phenol(3f):IR (cm^{-1}):3333 (νO-H), 3057 (νN-H, thione form and νC-H, benzene, vib. coupling), 2906 and 2744 (νN-H, intramolecularly hydrogen bonded, thione form), 2833 (νCH3), 2555 (νS-H, thiol form), 1610s (νC=N, oxadiazole and νC=N, imine, vib. coupling), 1508 (νC=C, benzene), 1411 (νN=N), 1068 (νC=S, thione form), 829 (δo.o.p. C-H, benzene).

4-((E)-(4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)-2-((E)-((2-methoxyphenyl)imino)methyl)phenol(3g):IR (cm^{-1}):3342 (νO-H), 3072 (νN-H, thione form and νC-H, benzene, vib. coupling), 2931 and 2754 (νN-H, intramolecularly hydrogen bonded, thione form), 2592 (νS-H, thiol form), 1604s (νC=N, oxadiazole and νC=N, imine, vib. coupling), 1504 (νC=C, benzene), 1411 (νN=N), 1066 (νC=S, thione form), 839 (δo.o.p. C-H, benzene).

2-((E)-((4-hydroxyphenyl)imino)methyl)-4-((E)-(4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenol (3h):IR (cm^{-1}):3340 and 3279 (νO-H), 3032 (νN-H, thione form and νC-H, benzene, vib. coupling), 2924 and 2754 (νN-H, intramolecularly hydrogen bonded, thione form), 2592 (νS-H, thiol form), 1608s (νC=N, oxadiazole and νC=N, imine, vib. coupling), 1508s (νC=C, benzene), 1411 (νN=N), 1068 (νC=S, thione form), 829 (δo.o.p. C-H, benzene).

2.2.4. General procedurefor thesynthesis ofoxadiazolic-oxazepines4a-h

A mixture of equimolar amounts of azoimine derivatives **3a-h** (1 mmol) and maleic anhydride (0.098 g, 1 mmol) in dry benzene (1 mL) was heated in microwave oven for 30 min at 72 °C. TLC (*n*-hexane: EtOAc) showed that the reactions were completed. The products were washed with diethyl ether and then recrystallized from ethanol.

(E)-3-(4-bromophenyl)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione (4a): IR (cm^{-1}): 3431 (νO-H), 3059 (νN-H, thione form and νC-H, benzene, vib. coupling), 2893 and 2758 (νN-H, intramolecularly hydrogen bonded, thione form), 2563 (νS-H, thiol form), 1708 (νC=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1608 (νC=N, oxadiazole), 1539 and 1491 (νC=C, benzene), 1066 (νC=S, thione form), 827 (δo.o.p. C-H, benzene);^{1}H NMR: δ (ppm) = 6.23 (s, 2H, 2×olefinic =CH, oxazepine), 7.14–8.06 (12H, Ar–H and C–H, oxazepine), 9.14 (s, 1H, N–H, thione form), 10.49 (s, 1H, O–H). The singlet signals around 2.51 ppm and 3.37 ppm attributed to DMSO and absorbed H_2O in DMSO, respectively; Anal.Calcd.for $C_{25}H_{16}N_5O_5SBr$:C, 51.91;H, 2.79;N, 12.11;S, 5.54; Found C, 51.63;H, 2.82; N, 12.43; S, 5.83 .

(E)-3-(4-chlorophenyl)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione (4b): IR (cm^{-1}): 3063 (νO-H, νN-H, thione form and νC-H, benzene, vib. coupling), 2941 and 2764 (νN-H, intramolecularly hydrogen bonded, thione form), 2575 (νS-H, thiol form), 1710 (νC=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1606 (νC=N, oxadiazole), 1489 (νC=C, benzene), 1406 (νN=N), 1068 (νC=S, thione form), 833 (δo.o.p. C-H, benzene); ^{1}H NMR: δ (ppm) = 6.16 (s, 2H, 2×olefinic =CH, oxazepine), 7.26–8.10 (12H, Ar–H and C–H, oxazepine), 9.32 (s, 1H, N–H, thione form), 10.69 (s, 1H, O–H).The singlet signals at 2.51 ppm and 3.33 ppm assigned to DMSO and absorbed H_2O in DMSO, respectively; Anal.Calcd.for $C_{25}H_{16}N_5O_5SCl$:C, 56.24;H, 3.02;N, 13.12;S, 6.01; Found C, 55.91;H, 3.05; N, 13.38; S, 6.37.

(E)-3-(2,4-dichlorophenyl)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione (4c):IR (cm^{-1}): 3070 (νO-H, νN-H, thione form and νC-H, benzene, vib. coupling), 2931 and 2762 (νN-H, intramolecularly hydrogen bonded, thione form), 2592 (νS-H, thiol form), 1705 (νC=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1602 (νC=N, oxadiazole), 1508 and 1481 (νC=C, benzene), 1411 (νN=N), 1066 (νC=S, thione form), 842 (δo.o.p. C-H, benzene); ^{1}H NMR: δ (ppm) = 6.22 (s, 2H, 2×olefinic =CH, oxazepine), 7.17–8.35 (11H, Ar–H and C–H, oxazepine), 9.28 (s, 1H, N–H, thione form), 10.38 (s, 1H, O–H).The singlet signals around 2.51 ppm and 3.33 ppm attributed to DMSO and absorbed H_2O in DMSO, respectively; Anal.Calcd.for $C_{25}H_{15}N_5O_5SCl_2$:C, 52.83;H, 2.66;N, 12.32;S, 5.64; Found C, 52.62;H, 3.01; N, 12.30; S, 5.98 .

(E)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-3-(4-nitrophenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione (4d): IR (cm^{-1}): 3288 (νO-H), 3207 (νN-H, thione form), 3084 (νC-H, benzene), 2947 and 2762 (νN-H, intramolecularly hydrogen bonded, thione form), 2561 (νS-H, thiol form), 1707 (νC=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1600 (νC=N, oxadiazole), 1560 (νC=C, benzene), 1508 (vas. NO2), 1411 (νN=N), 1338 (νs. NO2), 1068 (νC=S, thione form), 850 (δo.o.p. C-H, benzene); ^{1}H NMR: δ (ppm) = 6.24 (s, 2H, 2×olefinic =CH, oxazepine), 7.37–8.26 (12H, Ar–H and C–H, oxazepine), 9.29 (s, 1H, N–H, thione form), 10.68 (s, 1H, O–H).The singlet signals at 2.51 ppm and 3.37 ppm attributed to DMSO and absorbed H_2O in DMSO, respectively; Anal.Calcd.for $C_{25}H_{16}N_6O_7S$:C, 55.15;H, 2.96;N, 15.43;S, 5.89; Found C, 54.92;H, 3.08; N, 15.81; S, 6.13 .

(E)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-3-(3-nitrophenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione (4e): IR (cm^{-1}): 3277 (νO-H), 3198 (νN-H, thione form), 3091(νC-H, benzene), 2982 and 2879 (νN-H, intramolecularly hydrogen bonded, thione form), 2576 (νS-H, thiol form), 1712 (νC=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1599 (νC=N, oxadiazole), 1531 (νas. NO2), 1483 (ν C=C, benzene), 1410 (ν N=N), 1350 (νs. NO2), 1068 (ν C=S, thione form), 846 (δ o.o.p. C-H, benzene); ^{1}H NMR: δ (ppm) = 6.26 (s, 2H, 2×olefinic =CH, oxazepine), 7.37–8.17 (12H, Ar–H and C–H, oxazepine), 8.67 (s, 1H, N–H, thione form), 10.78 (s, 1H, O–H).The singlet signals around 2.51 ppm and 3.37 ppm assigned to DMSO and absorbed H_2O in DMSO, respectively;Anal.Calcd.for $C_{25}H_{16}N_6O_7S$:C, 55.15;H, 2.96;N, 15.43;S, 5.89; Found C, 54.86;H, 3.23; N, 15.06; S, 5.99 .

(E)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-3-(4-methoxyphenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione (4f): IR (cm^{-1}): 3255 (νO-H), 3200 (νN-H, thione form), 3064 (νC-H, benzene), 2972 and 2766 (νN-H, intramolecularly hydrogen bonded, thione form), 2839 (νCH3), 2573 (νS-H, thiol form), 1708 (νC=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1606 (νC=N, oxadiazole), 1537 and 1508 (νC=C, benzene), 1408 (νN=N), 1068 (νC=S, thione form), 831 (δo.o.p. C-H, benzene);^{1}H NMR: δ (ppm) = 3.73 (s, 3H, O-CH_3), 6.14 (s, 2H, 2×olefinic =CH, oxazepine), 6.91–8.06 (12H, Ar–H and C–H, oxazepine), 9.15 (s, 1H, N–H, thione form), 10.43 (s, 1H, O–H).The singlet signal at 2.51 ppm due to DMSO solvent; Anal.Calcd.for $C_{26}H_{19}N_5O_6S$:C, 58.97;H, 3.62;N, 13.23;S, 6.06; Found C, 58.69;H, 3.59; N, 12.91; S, 5.70 .

(E)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-3-(2-methoxyphenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione (4g):IR(cm^{-1}): 3059 (νO-H, νN-H, thione form and νC-H, benzene, vib. coupling), 2935 and 2758 (νN-H, intramolecularly hydrogen bonded, thione form), 2848 (νCH3), 2569 (νS-H, thiol form), 1708 (νC=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1608 (νC=N, oxadiazole), 1510 and 1467 (νC=C, benzene), 1392 (νN=N), 1066 (νC=S, thione form), 846 (δo.o.p. C-H, benzene);^{1}H NMR: δ(ppm) = 3.91 (s, 3H, O-CH_3), 6.17 (s, 2H, 2×olefinic =CH, oxazepine), 7.06–8.08 (12H, Ar–H and C–H, oxazepine), 9.22 (s, 1H, N–H, thione form), 10.38 (s, 1H, O–H).The singlet signal at 2.51 ppm due to DMSO solvent; Anal.Calcd.for $C_{26}H_{19}N_5O_6S$:C, 58.97;H, 3.62;N, 13.23;S, 6.06; Found C, 58.64;H, 3.59; N, 13.33; S, 6.38.

(E)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-3-(4-hydroxyphenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione (4h): IR (cm^{-1}): 3163 (νO-H), 3066 (νN-H, thione form and νC-H, benzene, vib. coupling), 2974 and 2764 (νN-H, intramolecularly hydrogen bonded, thione form), 2586 (νS-H, thiol form), 1705 (νC=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1606 (νC=N, oxadiazole), 1510 (νC=C, benzene), 1410 (νN=N), 1068 (νC=S, thione form), 837 (δo.o.p. C-H, benzene); ^{1}H NMR: δ (ppm) = 6.13 (s, 2H, 2×olefinic =CH, oxazepine), 7.06–8.07 (12H, Ar–H and C–H, oxazepine), 9.38 (s, 1H, N–H, thione form), 10.40 (s, 2H, 2×O–H).The singlet signals around 2.51 ppm and 3.37 ppm attributed to DMSO and absorbed H_2O in DMSO, respectively; Anal.Calcd.for $C_{25}H_{17}N_5O_6S$:C, 58.25;H, 3.32;N, 13.59;S, 6.22; Found C, 57.98;H, 3.65; N, 13.30; S, 6.54 .

2.2.5. General procedure for thesynthesis ofoxadiazolic-oxazepanes5a-h:

A mixture of equimolar amounts of azoimine derivatives **3a-h** (1 mmol) and succinic anhydride (0.1 g, 1 mmol) in dry benzene (1 mL) was heated in microwave oven for 60 min at 72 °C. TLC (*n*- hexane: EtOAc) showed that the reactions were completed. The products were washed with diethyl etherand then recrystallized from ethanol.

(E)-3-(4-bromophenyl)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-1,3-oxazepane-4,7-dione (5a): IR (cm^{-1}): 3064 (νO-H, νN-H, thione form and νC-H, benzene, vib. coupling), 2933 and 2760 (νN-H, intramolecularly hydrogen bonded, thione form), 2656 and 2548 (νS-H, thiol form), 1695 (νC=O, O=C-O and O=C-N, oxazepane, vib. coupling), 1606 (νC=N, oxadiazole), 1512 (νC=C, benzene), 1415 (νN=N), 1068 (νC=S, thione form), 837 (δo.o.p. C-H, benzene);^{1}H NMR: δ (ppm) = 2.43 (s, 4H, 2×CH_2, oxazepane), 7.12–7.84 (12H, Ar–H and C–H, oxazepane), 9.32 (s, 1H, N–H, thione form), 10.34 (s, 1H, O–H).The singlet signals around 2.51 ppm and 3.30 ppm assigned to DMSO and absorbed H_2O in

DMSO, respectively; Anal. Calcd.for $C_{25}H_{18}N_5O_5SBr$: C, 51.73; H, 3.13; N, 12.07; S, 5.52 Found C, 51.66; H, 3.44; N, 12.42; S, 5.87 .

(E)-3-(4-chlorophenyl)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-1,3-oxazepane-4,7-dione (5b): IR (cm^{-1}): 3066 (νO-H, νN-H, thione form and νC-H, benzene, vib. coupling), 2941 and 2756 (νN-H, intramolecularly hydrogen bonded, thione form), 2596 (νS-H, thiol form), 1703 (νC=O, O=C-O and O=C-N, oxazepane, vib. coupling), 1604 (νC=N, oxadiazole), 1504 (νC=C, benzene), 1413 (νN=N), 1068 (νC=S, thione form), 835 (δo.o.p. C-H, benzene); ^{1}H NMR: δ (ppm) = 2.43 (s, 4H, 2×CH_2, oxazepane), 7.17–7.90 (12H, Ar–H and C–H, oxazepane), 9.31 (s, 1H, N–H, thione form), 10.38 (s, 1H, O–H).The singlet signals around 2.51 ppm and 3.30 ppm attributed to DMSO and absorbed H_2O in DMSO, respectively; Anal. Calcd.for $C_{25}H_{18}N_5O_5SCl$: C, 56.03; H, 3.39; N, 13.07; S, 5.98 Found C, 55.88; H, 3.32; N, 13.35; S, 6.22 .

(E)-3-(2,4-dichlorophenyl)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-1,3-oxazepane-4,7-dione (5c):IR (cm^{-1})**:**3078 (νO-H, νN-H, thione form and νC-H, benzene, vib. coupling), 2941 and 2756 (νN-H, intramolecularly hydrogen bonded, thione form), 2582 (νS-H, thiol form), 1708 (νC=O, O=C-O and O=C-N, oxazepane, vib. coupling), 1606 (νC=N, oxadiazole), 1506 (νC=C, benzene), 1411 (νN=N), 1066 (νC=S,thione form), 839 (δo.o.p. C-H, benzene); ^{1}H NMR: δ (ppm) = 2.43 (s, 4H, 2×CH_2, oxazepane), 7.05–8.24 (11H, Ar–H and C–H, oxazepane), 9.35 (s, 1H, N–H, thione form), 10.39 (s, 1H, O–H).The singlet signals around 2.51 ppm and 3.34 ppm due to DMSO and absorbed H_2O in DMSO, respectively; Anal. Calcd.for $C_{25}H_{17}N_5O_5SCl_2$: C, 52.64; H, 3.00; N, 12.28; S, 5.62 Found C, 52.31; H, 2.96; N, 12.59; S, 5.91 .

(E)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-3-(4-nitrophenyl)-1,3-oxazepane-4,7-dione (5d): IR (cm^{-1}): 3084 (νO-H, νN-H, thione form and νC-H, benzene, vib. coupling), 2935 and 2758 (νN-H, intramolecularly hydrogen bonded, thione form), 2576 (νS-H, thiol form), 1701 (νC=O, O=C-O and O=C-N, oxazepane, vib. coupling), 1600 (νC=N, oxadiazole), 1506s (νC=C, benzene and υas. NO2, vib.coupling), 1413 (νN=N), 1342 (νs. NO2), 1068 (νC=S, thione form), 840 (δo.o.p. C-H, benzene); ^{1}H NMR: δ (ppm) = 2.43 (s, 4H, 2×CH_2, oxazepane), 7.37–8.23 (12H, Ar–H and C–H, oxazepane), 9.29 (s, 1H, N–H, thione form), 10.38 (s, 1H, O–H). The singlet signals around 2.51 ppm and 3.37 ppm attributed to DMSO and absorbed H_2O in DMSO, respectively; Anal. Calcd.for $C_{25}H_{18}N_6O_7S$: C, 54.94; H, 3.32; N, 15.38; S, 5.87 Found C, 54.84; H, 3.32; N, 15.57; S, 6.15 .

(E)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-3-(3-nitrophenyl)-1,3-oxazepane-4,7-dione (5e): IR (cm^{-1}): 3080 (νO-H, νN-H, thione form and νC-H, benzene, vib. coupling), 2928 and 2760 (νN-H, intramolecularly hydrogen bonded, thione form), 2584 (νS-H, thiol form), 1703 (νC=O, O=C-O and O=C-N, oxazepane, vib. coupling), 1602 (νC=N, oxadiazole), 1510s (νC=C, benzene and νas. NO2, vib.coupling), 1413 (νN=N), 1348 (νs. NO2), 1068 (νC=S, thione form), 840 (δo.o.p. C-H, benzene); ^{1}H NMR: δ (ppm) = 2.43 (s, 4H, 2×CH_2, oxazepane), 7.18–8.07 (12H, Ar–H and C–H, oxazepane), 9.30 (s, 1H, N–H, thione form), 10.37 (s, 1H, O–H).The singlet signals around 2.51 ppm and 3.32 ppm assigned to DMSO and absorbed H_2O in DMSO, respectively; Anal. Calcd.for $C_{25}H_{18}N_6O_7S$: C, 54.94; H, 3.32; N, 15.38; S, 5.87 Found C, 54.76; H, 3.15; N, 15.65; S, 6.11 .

(E)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-3-(4-methoxyphenyl)-1,3-oxazepane-4,7-dione (5f): IR (cm^{-1}): 3053 (νO-H, νN-H, thione form and νC-H, benzene, vib. coupling), 2931 and 2746 (νN-H, intramolecularly hydrogen bonded, thione form), 2652 and 2548 (νS-H, thiol form), 1693 (νC=O, O=C-O, oxazepane), 1643 (νC=O, O=C-N, oxazepane), 1606 (νC=N, oxadiazole), 1508 (νC=C, benzene), 1417 (νN=N), 1068 (νC=S, thione form), 833 (δo.o.p. C-H, benzene);^{1}H NMR: δ (ppm) = 2.43 (s, 4H, 2×CH_2, oxazepane),3.70 (s, 3H, O-CH_3), 6.85–7.83 (12H, Ar–H and C–H, oxazepane), 9.37 (s, 1H, N–H, thione form), 10.35 (s, 1H, O–H).The singlet signal at 2.51 ppm due to DMSO solvent; Anal.Calcd.for $C_{26}H_{21}N_5O_6S$: C, 58.75; H, 3.98; N, 13.18; S, 6.03 Found C, 58.47; H, 3.93; N, 13.43; S, 6.23 .

(E)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-3-(2-methoxyphenyl)-1,3-oxazepane-4,7-dione (5g):IR(cm^{-1}): 3064 (νO-H, νN-H, thione form and νC-H, benzene, vib. coupling), 2933 and 2756 (νN-H, intramolecularly hydrogen bonded, thione form), 2656 and 2553 (νS-H, thiol form), 1695 (νC=O, O=C-O and O=C-N, oxazepane, vib. coupling), 1606 (νC=N, oxadiazole), 1506 (νC=C, benzene), 1415 (νN=N), 1068 (νC=S, thione form), 842 (δo.o.p. C-H, benzene);^{1}H NMR: δ (ppm) = 2.43 (s, 4H, 2×CH_2, oxazepane),3.79 (s, 3H, O-CH_3), 6.88–8.10 (12H, Ar–H and C–H, oxazepane), 9.34 (s, 1H, N–H, thione form), 10.37 (s, 1H, O–H).The singlet signals around 2.51ppm and 3.35ppm attributed to DMSO and absorbed H_2O in DMSO, respectively; Anal. Calcd.for $C_{26}H_{21}N_5O_6S$: C, 58.75; H, 3.98; N, 13.18; S, 6.03 Found C, 58.55; H, 3.93; N, 13.38; S, 6.21 .

(E)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-3-(4-hydroxyphenyl)-1,3-oxazepane-4,7-dione (5h): IR (cm^{-1}): 3063 (νO-H, νN-H, thione form and νC-H, benzene, vib. coupling), 2935 and 2758 (νN-H, intramolecularly hydrogen bonded, thione form), 2659 and 2549 (νS-H, thiol form), 1693 (νC=O, O=C-O and O=C-N, oxazepane, vib. coupling), 1608 (νC=N, oxadiazole), 1510 (νC=C, benzene), 1417 (νN=N), 1070 (νC=S, thione form), 835 (δo.o.p. C-H, benzene); ^{1}H NMR: δ (ppm) = 2.43 (s, 4H, 2×CH_2, oxazepane),6.65–8.04 (12H, Ar–H and C–H, oxazepane), 9.35 (s, 1H, N–H, thione form), 9.70 (s, 2H, 2×O–H). The singlet signals around 2.51ppm and 3.36ppm assigned to DMSO and absorbed H_2O in DMSO, respectively; Anal. Calcd.for $C_{25}H_{19}N_5O_6S$: C, 58.02; H, 3.70; N, 13.53; S, 6.20 Found C, 57.79; H, 3.89; N, 13.24; S, 6.43 .

2.2 Preliminary antibacterial assay

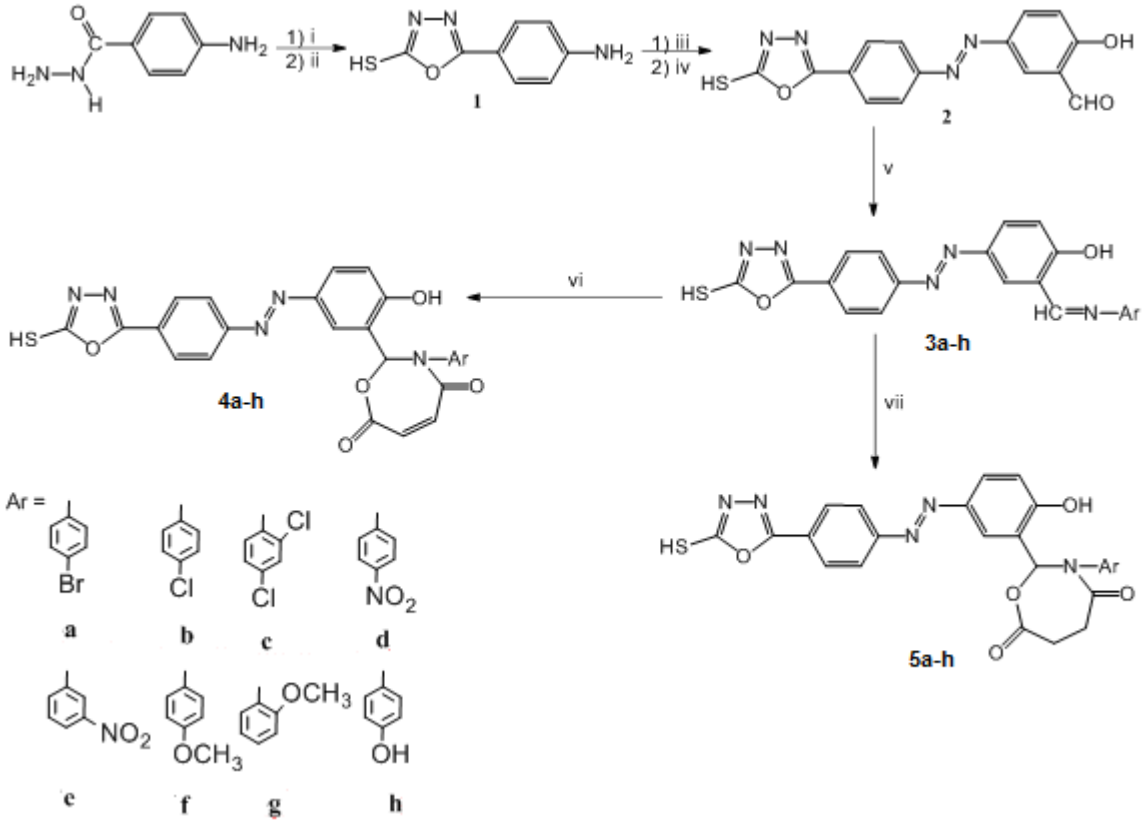
The antibacterial activities of the newly synthesized oxadiazoles**4a-h** and **5a-h**were determined by the agar diffusion method[36] using representative Gram (+) and Gram (–) bacteria on tryptic soya agar media. The test microorganisms to evaluate the potential antibacterial activity of the newly synthesized oxadiazoles were*Staphylococcusaureus* (Gram-positive) and *Escherichia coli* (Gram-negative). The oxadiazoles were dissolved in dimethylsulfoxide to prepare the test solutions of 5 mg/ML concentration. Gentamycin was used as a reference and the activities were presented as zones of inhibition for each compound (Table-2).

3. Results and Discussion

3.1 Chemistry

4-aminobenzoic hydrazide was converted to5-(4-aminophenyl)-2-thiol-1,3,4-oxadiazole **1** by treating it with carbon disulfide in presence of potassium hydroxide as catalyst in absolute ethanol[19]. Diazotization of amino group in compound **1** using sodium nitrite and hydrochloric acid generated the corresponding diazonium salt which was directly introduced in coupling reaction with 2-hydroxybenzaldehyde dissolved in sodium hydroxide solution to give azo-oxadiazole derivative**2**containing aldehyde group[35].Aldehyde group ofazo-oxadiazole derivative **2** was condensed with the primary aromatic amines including (4-bromoaniline, 4-chloroaniline, 2,4-dichloroaniline, 4-nitroaniline, 3-nitroaniline, 4-methoxyaniline, 2-methoxyaniline and 4-hydroxyaniline) using microwave irradiation in absolute ethanol to produce eight azoimine derivatives of 1,3,4-oxadiazole **3a-h** respectively, as the platforms for this work (**Scheme-I** and**II**). A concerted reactions involving the (2+5) cycloadditions of imine group of the oxadiazolic-imines **3a-h**withmaleic and succinic anhydrides, as five-membered components, in dry benzene using microwave irradiation gave the seven-membered 1,3-oxazepine and 1,3-oxazepane derivatives of 1,3,4-oxadiazole**4a-h**and **5a-h** respectivelyin good yields (Table-1).

The chemical structures of the target compounds synthesized were deduced from IR, ^{1}H NMR spectral measurements and (CHNS) elemental analysis and were in good agreement with the proposed structures.



Scheme-I: Synthesis of 1,3,4-oxadiazoles, Reagents and conditions (i) CS_2, KOH, EtOH, 70 ^oC, 24 h; (ii) Conc. HCl; (iii) $NaNO_2$,HCl, 0-5 ^oC; (iv) 2-hydroxybenzaldehyde, NaOH 10% , 5^oC; (v) Ar-NH_2,EtOH, MW (300W), 72^oC, 20 min; (vi) maleic anhydride, dry benzene, MW (300W), 72^oC, 30 min; (vii) succinicanhydride, dry benzene, MW (300W), 72^oC, 60 min.

Scheme-II: Proposed mechanism for the addition of cyclic anhydrides to imine.

The IR and ^{1}H NMR spectra of the desired compounds (**4a-h**) and (**5a-h**) were described in details in the Experimental section. The IR spectrum of oxadiazole derivative **1**showed the disappearance of the sharp doublet band forhydrazide group (-NHNH$_2$) at (3307,3236)cm^{-1} and the strong band at 1627cm^{-1} due to (C=O)str., additionallythe appearance ofthe following characteristic bands: the doublet band at 3448cm^{-1} and 3352cm^{-1} assigned to (-NH$_2$)str. that substituted in benzene ring, the strong band at 1604cm^{-1} attributed to theoxadiazolic (C=N)str. and (-NH$_2$)bend. due to the vibration coupling interaction. The weak and strong bands at 2590cm^{-1} and 1068cm^{-1} belong to (S-H)str. and (C=S)str. in thioenol and thioketone forms, respectively. The IR spectrum of azo-oxadiazole derivative **2**indicated theabsence ofa doublet band at3448cm^{-1} and 3352cm^{-1} for (-NH$_2$)str. and appearance ofthe following characteristic bands: the weak band at 1411cm^{-1} attributed to azo group (N=N)str., the broad band at 3402cm^{-1}assigned to (O-H)str., the sharp and strong band at 1662cm^{-1} belong toaldehydic (C=O)str.,theoxadiazolic(C=N)str. appeared as weak band at 1604 cm^{-1} due to disappearance of the bendingvibration of (-NH$_2$) group. IR spectra of the oxadiazolic-imines **3a-h** showeddisappearing the sharp and strong band at 1662 cm^{-1} for aldehydic (C=O)str., also disappearing the sharp doublet band for (-NH$_2$)str. in the starting amines at the general range (3400-3250) cm^{-1} and appearing a sharp and strong band at the range (1599-1610) cm^{-1} assigned to the iminic and oxadiazolic (C=N)str. due to the vibration coupling interaction. The IR spectra of the oxadiazolic-oxazepines and oxazepanes**4a-h** and **5a-h**showed the appearance of strong band at the range 1693-1712cm^{-1} attributed to the stretching vibrations of carbonyl groups (O=C-N and O=C-O) of the oxazepine and oxazepane rings. Also the appearance of a strong band at the range 1599-1608cm^{-1} assigned to oxadiazolic (C=N)str.

The structures of oxazepine compounds**4a-h**wereproven by their^{1}H NMR spectra (300 MHz, DMSO-d$_6$) whichshowedthe phenolic (O-H) proton as a singlet at**δ**10.49, 10.69, 10.38, 10.68, 10.78, 10.43, 10.38 and 10.40 ppm, respectively.The (N-H) proton for thione form as a singlet at 9.14, 9.32, 9.28, 9,29, 8.67, 9.15, 9.22 and 9.38 ppm, respectively.Moreover, the olefinic (=CH) protons of the oxazepine ring appeared as singlet at 6.23, 6.16, 6.22, 6.24, 6.26, 6.14, 6.17 and 6.13 ppm.The signals of aromatic protons(Ar–H) and (C–H) proton of oxazepine ring appeared at**δ** 6.91-8.35 ppm. The methoxy protons (O–CH$_3$) in compounds **4f** and **4g** appeared as a singlet at**δ** 3.73ppm and 3.91ppm, respectively. Thestructures of the prepared oxazepane compounds **5a-h,**wereconfirmed by their^{1}H NMR spectra which appeared singlet signal at **δ** 10.34, 10.38, 10.39, 10.38, 10.37, 10.35, 10.37 and 9.70ppm, respectively belong to the phenolic (O-H) proton. The (N-H) proton forthione form as singlet at 9.32, 9.31, 9.35, 9.29, 9.30, 9.37, 9.34 and 9.35 ppm, respectively. The signals of aromatic protons (Ar–H) and (C–H) proton of oxazepane ring appeared at**δ** 6.65-8.24 ppm. The methoxy protons (O–CH$_3$) in compounds **5f** and **5g** appeared as a singlet at**δ** 3.70ppm and 3.79ppm, respectively. Thesinglet signal at δ2.43 ppmassigned to methylene group protons (–CH$_2$–)of the oxazepane ring.

Moreover, the (CHNS) elemental analysis results were within ± 0.4% of the theoretical values and in good agreement with the proposedchemical structures for compounds **4a-h**and **5a-h** and given in the experimental section.

3.1. Antibacterial activities

The antibacterial activities of the newly synthesized oxadiazoles**4a-h** and **5a-h** were evaluated by the agar diffusion method[36]using representative standard strains of Gram (+) and Gram (–) bacteria on tryptic soya agar media, as listed in Table-2. Dimethylsulfoxide was used as solvent for the test compounds.

Oxadiazole compounds **4a** and**5h** were found to be equipotent to gentamycin against Gram-positive bacteria, while compound **5f** showed greater activity than the control drug against Gram-negative bacteria.

Table 1: Physical Properties of the synthesized compounds

Product	Physical state	R$_f$(developer	Mp (^{o}C)	Yield (%)
3a	Orange solid	0.75 (*n*-hexane/ EtOAc, 1:3)	202-204	78
3b	Yellow solid	0.78 (*n*-hexane/ EtOAc, 1:3)	179-181	82
3c	Dark orange solid	0.70 (*n*-hexane/ EtOAc, 1:3)	170-172	75
3d	Yellow solid	0.72 (*n*-hexane/ EtOAc, 1:3)	150-152	79
3e	Orangesolid	0.76 (*n*-hexane/ EOAc, 1:3)	214-216	81
3f	Dark brown solid	0.71 (*n*-hexane/ EtOAc, 1:3)	152-154	86
3g	Brown solid	0.73 (*n*-hexane/ EtOAc, 1:3)	166-168	89
3h	Dark brown solid	0.69 (*n*-hexane/ EtOAc, 1: 3)	149-151	89
4a	Dark Orange solid	0.62 (*n*-hexane/ EtOAc, 1: 1)	220-222	89
4b	Dark orange solid	0.64 (*n*-hexane/ EtOAc, 1: 1)	210-212	86
4c	Dark orange solid	0.63 (*n*-hexane/ EtOAc, 1: 1)	212-214	83

4d	Dark orange solid	0.65 (*n*-hexane/ EtOAc, 1: 1)	184-186	89
4e	Orange solid	0.60 (*n*-hexane/ EtOAc, 1: 1)	180-182	82
4f	Dark brownsolid	0.61 (*n*-hexane/ EtOAc, 1: 1)	153-155	80
4g	Brown solid	0.58 (*n*-hexane/ EtOAc, 1: 1)	180-182	81
4h	Dark brownsolid	0.67 (*n*-hexane/ EtOAc, 1: 1)	146-148	80
5a	Yellowsolid	0.68 (*n*-hexane/ EtOAc, 1: 1)	115-117	74
5b	Yellowsolid	0.70 (*n*-hexane/ EtOAc, 1: 1)	151-153	73
5c	Dark orangesolid	0.71 (*n*-hexane/ EtOAc, 1: 1)	165-167	70
5d	Orange solid	0.65 (*n*-hexane/ EtOAc, 1: 1)	132-134	74
5e	Dark orangesolid	0.66 (*n*-hexane/ EtOAc, 1: 1)	140-142	77
5f	Orange solid	0.69 (*n*-hexane/ EtOAc, 1: 1)	145-147	76
5g	Dark orangesolid	0.74 (*n*-hexane/ EtOAc, 1: 1)	125-127	78
5h	Dark brown solid	0.72 (*n*-hexane/ EtOAc, 1: 1)	105-107	79

Table 2: The Antibacterial Activity of Compounds **4a-h** ,**5a-h and** Gentamycinas control Drug

Product	*Staphylococcus aureus* (Gram-positive)	*Escherichia coli* (Gram-negative)
4a	22	0
4b	17	0
4c	14	0
4d	16	14
4e	14	0
4f	16	10
4g	17	0
4h	21	0
5a	10	0
5b	11	0
5c	0	0
5d	19	0
5e	12	0
5f	0	21
5g	10	0
5h	22	0
DMSO	0	0
Gentamycin	22	17

4. Conclusions

The microwave irradiation is efficient technique including short reaction time and high yield. Rates of cycloaddition reactions for formation of oxadiazolic-oxazepines**4a-h** are relatively higher than that of oxadiazolic-oxazepanes**5a-h**.All synthesized oxadiazoles have relatively high solubility in water. The synthesized oxadiazoles appeared higher biological action against Gram-positive bacteria than that of Gram-negative bacteria. The synthesized oxadiazoles (**4a** and **5h**) showed equipotent activities to gentamycin against Gram-positive bacteria. Also, compound **5f** appeared higher activity against Gram-negative bacteria than that of control drug.

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