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

Zeid Hassan Abood¹, Osama Hameed Rasheed², Majid Jari Mohammed³

1, 2Chemistry Department, College of Science, University of Kerbala, Kerbala-Iraq
3Chemistry Department, College of Science, University of Kufa, Najaf-Iraq

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 eightazomine 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 oxadiazoles 4a-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 using two types of bacteria, Staphylococcus aureus (Gram-positive) and Escherichia coli (Gram-negative). The results indicated that the newly synthesized oxadiazoles (compounds 4a and 5h) exhibited equipotent activities to gentamycin against Gram-positive bacteria. On the other hand, just one compound (compound 5f) showed better activity against Gram-negative bacteria when compared with that of the control drug (Gentamycin).

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

1. Introduction

Oxadiazoles are five-membered heteroaromatic compounds including two nitrogen atoms and one oxygen atom on the ring and considered very weak base because of an inductive effect of extra heteroatom. Oxadiazole moiety is derived from furan by replacing two -CH= group with two pyridine typed nitrogen (-N=)1, 2,3,4-Oxadiazoles constitute an important family of heterocyclic compounds as they have attracted significant interest in medicinal chemistry, pesticide chemistry and polymer science. Oxadiazoles also possess antitubercular, antimalarial, antileishmanial, antimicrobial, anti-inflammatory, analgesic, anti-HIV, antimiycobacterial, cathepsin K inhibitors, tyrosinase inhibitors, monoamine oxidase (MAO) inhibitors and anticancer activities. Most of the marketed antihypertensive agents such as Tiodazosin drug A and Nesipadil drug B as well as antibiotics such as Furamizole drug C, Raltegravir, an antiretroviral drug D and Zibotentan, an anticancer drug 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 by Yong and Wood from reaction of benzoic hydrazides with carbon disulfide in presence of potassium hydroxide in absolute ethanol. Rashid et al. were synthesized some 1,3,4-oxadiazole derivatives under 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, oxazepines and oxazepanes are a well-known class of seven-membered heterocycles with two heteroatoms (oxygen and nitrogen). Oxazepine and oxazepane compounds have medical and biological importance and they have medicinal and pharmaceutical applications. Some Oxazepine derivatives are considered a medical drug against the disease and some of them act as inhibitors of some enzymes action. Fusedoxazepinone derivatives have attracted considerable attention owing to their promising biological activities, such as antihistaminic, anti-HIV, antidepressant and antitumor activities. Asendin (Amoxapine) drug is used as antidepressant and active drug for schizophrenia.

Thus, in this article, we reported here the synthesis of new 5-substituted-2-thiol-1,3,4-oxadiazole derivatives bearing biologically active heterocyclic moieties including oxazepine, oxazepane, in addition of azo group, which might have some biological activity.
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 F254 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. 'H NMR spectra was collected on NMR spectrometer 300 MHz, Ascend TM400 Bruker, Germany at 300 MHz in DMSO–d6 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 to Yong and Wood conditions as pale yellow crystals, mp 234-236°C, yield 76 %; IR (cm⁻¹): 3448 (ν= NH₂), 3352 (ν=- NH₂), 3086 (ν=N-H, thione form and ν=C-H, benzene, vib. coupling), 2947 and 2764 (ν=N-H, intramolecularly hydrogen bonded, thione form), 1512 (ν=C=C, benzene), 1477 (ν=N=N), 1411 (ν=C=O, aldehyde), 1068 (ν=C=S, thione form), 842 (δ= o.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 as red solid, mp 196-198°C, yield 78 %; IR (cm⁻¹): 3402br (ν= O-H), 3190 (ν=N-H, thione form), 3095 (ν=C-H, benzene), 2978 and 2748 (ν=N-H, intramolecularly hydrogen bonded, thione form), 2885 (ν=C=O, aldehyde), 1662 (ν=C=O, aldehyde), 1604 (ν=C=N, oxadiazole), 1477 (ν=C=C, benzene), 1411 (ν=N=N), 1068 (ν=C=S, thione form), 842 (δ= o.o.p. C-H, benzene).

2.2.3. General procedure for the synthesis of oxadiazolic-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 °C 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.


2.2.4. General procedure for the synthesis of oxadiazolic oxazepines 4a-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(bromomethyl))-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 (vO-H), 3059 (vN-H, thione form and vC-H, benzene, vib. coupling), 2893 and 2758 (vN-H, intramolecularly hydrogen bonded, thione form), 2563 (vS-H, thiol form), 1708 (vC=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1608s (vC=N, oxadiazole), 1539 and 1491 (vC=C, benzene), 1066 (vC=S, thione form), 827 (δo.o.p. C-H, benzene); 1H NMR: δ (ppm) = 6.23 (2H, 2×olefinic =CH, oxazepine), 7.14–8.06 (12H, Ar–H and C–H, oxazepine), 9.14 (s, 1H, O–H), The singlet signals around 2.51 ppm and 3.37 ppm attributed to DMSO and absorbed H2O in DMSO, respectively; Anal. Calcd. for C25H16N5O5SBr: 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(chloromethyl))-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 (vO-H, vN-H, thione form and vC-H, benzene, vib. coupling), 2941 and 2764 (vN-H, intramolecularly hydrogen bonded, thione form), 2575 (vS-H, thiol form), 1710 (vC=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1606 (vC=S, oxadiazole), 1489 (vC=C, benzene), 1406 (vN=N), 1068 (vC=S, thione form), 833 (δo.o.p. C-H, benzene); 1H NMR: δ (ppm) = 6.16 (2H, 2×olefinic =CH, oxazepine), 7.26–8.10 (12H, Ar–H and C–H, oxazepine), 9.32 (s, 1H, O–H), The singlet signals around 2.51 ppm and 3.33 ppm assigned to DMSO and absorbed H2O in DMSO, respectively; Anal. Calcd. for C25H22N5O4SBr: 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)diazienyl)phenyl)-2,3-dihydro-1,3-oxazine-4,7-dione (4c): IR (cm⁻¹): 3070 (vO-H, νN-H, thione form and νC=H, benzene), 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 2018 (νC=C, benzene), 1411 (νN=N), 1068 (νC=S, thione form), 850 (δo.o.p. C-H, benzene); ¹H NMR: δ (ppm) = 6.24 (s, 2H, 2×olefinic =CH, oxazepine), 7.17–8.33 (11H, Ar–H and C–H), 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 H₂O in DMSO, respectively; Anal.Calcd. for C₃₂H₂₃N₅O₆S:C, 58.25;H, 3.32;N, 13.59;S, 6.41; Found 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)-3-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazienyl)phenyl)-3-(3-nitrophenyl)-2,3-dihydro-1,3-oxazine-4,7-dione (4g): IR (cm⁻¹): 3070 (vO-H), 3027 (νN-H, thione form), 2984 and 2762 (νN-H, intramolecularly hydrogen bonded, thione form), 2561 (vS=H, thiol form), 1707 (vC=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1600 (νC=O, O=C-N, oxadiazole), 1560 (νC=C, benzene), 1508 (νC=S, thione form), 1411 (νN=N), 1338 (νO-H, benzene), 1068 (νC=S, thione form), 850 (δo.o.p. C-H, benzene); ¹H NMR: δ (ppm) = 6.24 (s, 2H, 2×olefinic =CH, oxazepine), 7.37–8.12 (12H, Ar–H and C–H), 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 H₂O in DMSO, respectively; Anal.Calcd. for C₃₂H₂₃N₅O₆S:C, 58.97;H, 3.32;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)diazienyl)phenyl)-3-(3-nitrophenyl)-2,3-dihydro-1,3-oxazine-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 (vS=H, thiol form), 1707 (vC=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1600 (νC=O, oxadiazole), 1560 (νC=C, benzene), 1508 (νC=S, thione form), 1411 (νN=N), 1338 (νO-H, benzene), 1068 (νC=S, thione form), 850 (δo.o.p. C-H, benzene); ¹H NMR: δ (ppm) = 6.24 (s, 2H, 2×olefinic =CH, oxazepine), 7.37–8.12 (12H, Ar–H and C–H), 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 H₂O in DMSO, respectively; Anal.Calcd. for C₂₅H₁₉N₅O₆S: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)-3-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazienyl)phenyl)-3-(2-methoxyphenyl)-2,3-dihydro-1,3-oxazine-4,7-dione (4f): 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), 1608 (νC=O, oxadiazole), 1510 and 1467 (νC=O, benzene), 1392 (νN-H), 1066 (νC=S, thione form), 846 (δo.o.p. C-H, benzene); ¹H NMR: δ (ppm) = 6.13 (s, 2H, 2×olefinic =CH, oxazepine), 7.06–8.08 (12H, Ar–H and C–H), 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 C₂₅H₁₉N₅O₆S:C, 58.97;H, 3.32;N, 13.23;S, 6.06; Found C, 58.64;H, 3.59; N, 13.33; S, 6.38.

2.2.5. General procedure for the synthesis of oxadiazolic-oxazepanes5a-h:

A mixture of equal 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 ether and then recrystallized from ethanol.

(E)-3-(4-bromophenyl)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazienyl)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), 1608 (νC=O, oxadiazole), 1512 (νC=O, benzene), 1415 (νN=O), 1068 (νC=S, thione form), 837 (δo.o.p. C-H, benzene); ¹H NMR: δ (ppm) = 2.43 (s, 4H, 2×CH₃, oxazepane), 7.12–7.84 (12H, Ar–H and C–H), 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 H₂O in DMSO, respectively; Anal.Calcd. for C₂₅H₁₉N₅O₆S: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.

Volume 5 Issue 10, October 2016
www.ijsr.net
Licensed Under Creative Commons Attribution CC BY

Paper ID: ART20162255
DOI: 10.21275/ART20162255
1744
(E)-3-(4-chlorophenyl)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-y)phenyl)diazenyl)phenyl)-1,3-oxazepane-4,7-dione (5f): IR (cm⁻¹): 3064 (νO–H, v-H, νN–O, oxazepane), 3058 (s, 3H, O=CH₂), 2927, 2873 and 2849 (νCH₃, oxazepane), 2651 and 2534 (νSH, thione form), 1695 (νC=O, O=CO, oxazepane), 1643 (νC=O, O=C–N, oxazepane), 1606 (νC=N, oxazaozale), 1506 (νC=N, oxazepane), 1505 (νC=O, O=C–O, oxazepane), 1417 (νC–O, O=CO–N, oxazepane), 1405 (νC=C, benzene), 1342 (s, 3H, O–CH₃), 1265 and 1233 (12H, Ar–H and C–H, oxazepane ), 9.35 (s, 1H, N–H, thione form), 10.35 (s, 1H, O–H).The singlet signals around 2.51 ppm and 3.34 ppm attributed to DMSO and absorbed H₂O in DMSO, respectively; Anal. Calcd. for C₂₆H₂₁N₅O₆S: C, 59.80; H, 3.98; N, 13.43; S, 6.23.

(E)-3-(4-chlorophenyl)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-y)phenyl)diazenyl)phenyl)-1,3-oxazepane-4,7-dione (5g): IR (cm⁻¹): 3064 (νO–H, v-H, νN–O, oxazepane), 3058 (s, 3H, O=CH₂), 2927, 2873 and 2849 (νCH₃, oxazepane), 2651 and 2534 (νSH, thione form), 1695 (νC=O, O=CO, oxazepane), 1643 (νC=O, O=C–N, oxazepane), 1606 (νC=N, oxazaozale), 1506 (νC=N, oxazepane), 1505 (νC=O, O=C–O, oxazepane), 1417 (νC–O, O=CO–N, oxazepane), 1405 (νC=C, benzene), 1342 (s, 3H, O–CH₃), 1265 and 1233 (12H, Ar–H and C–H, oxazepane ), 9.35 (s, 1H, N–H, thione form), 10.35 (s, 1H, O–H).The singlet signals around 2.51 ppm and 3.34 ppm attributed to DMSO and absorbed H₂O in DMSO, respectively; Anal. Calcd. for C₂₆H₂₁N₅O₆S: C, 59.80; H, 3.98; N, 13.43; S, 6.23.

(E)-3-(4-chlorophenyl)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-y)phenyl)diazenyl)phenyl)-1,3-oxazepane-4,7-dione (5h): IR (cm⁻¹): 3064 (νO–H, v-H, νN–O, oxazepane), 3058 (s, 3H, O=CH₂), 2927, 2873 and 2849 (νCH₃, oxazepane), 2651 and 2534 (νSH, thione form), 1695 (νC=O, O=CO, oxazepane), 1643 (νC=O, O=C–N, oxazepane), 1606 (νC=N, oxazaozale), 1506 (νC=N, oxazepane), 1505 (νC=O, O=C–O, oxazepane), 1417 (νC–O, O=CO–N, oxazepane), 1405 (νC=C, benzene), 1342 (s, 3H, O–CH₃), 1265 and 1233 (12H, Ar–H and C–H, oxazepane ), 9.35 (s, 1H, N–H, thione form), 10.35 (s, 1H, O–H).The singlet signals around 2.51 ppm and 3.34 ppm attributed to DMSO and absorbed H₂O in DMSO, respectively; Anal. Calcd. for C₂₆H₂₁N₅O₆S: C, 59.80; H, 3.98; N, 13.43; S, 6.23.

(E)-3-(4-chlorophenyl)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-y)phenyl)diazenyl)phenyl)-1,3-oxazepane-4,7-dione (5i): IR (cm⁻¹): 3064 (νO–H, v-H, νN–O, oxazepane), 3058 (s, 3H, O=CH₂), 2927, 2873 and 2849 (νCH₃, oxazepane), 2651 and 2534 (νSH, thione form), 1695 (νC=O, O=CO, oxazepane), 1643 (νC=O, O=C–N, oxazepane), 1606 (νC=N, oxazaozale), 1506 (νC=N, oxazepane), 1505 (νC=O, O=C–O, oxazepane), 1417 (νC–O, O=CO–N, oxazepane), 1405 (νC=C, benzene), 1342 (s, 3H, O–CH₃), 1265 and 1233 (12H, Ar–H and C–H, oxazepane ), 9.35 (s, 1H, N–H, thione form), 10.35 (s, 1H, O–H).The singlet signals around 2.51 ppm and 3.34 ppm attributed to DMSO and absorbed H₂O in DMSO, respectively; Anal. Calcd. for C₂₆H₂₁N₅O₆S: C, 59.80; H, 3.98; N, 13.43; S, 6.23.
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 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 Staphylococcus aureus (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 to 5-(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. 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 giveazo-oxadiazole derivative containing aldehyde group. 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 respectively in good yields (Table-1).

The chemical structures of the target compounds synthesized were deduced from IR, 1H NMR spectral measurements and (CHNS) elemental analysis and were in good agreement with the proposed structures.
Scheme-II: Proposed mechanism for the addition of cyclic anhydrides to imine.

The IR and ¹H 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 for hydrazide group (-NHNH₂) at (3307,3236)cm⁻¹ and the strong band at 1627cm⁻¹ due to (C=O)str., additionally the appearance of these following characteristic bands: the doublet band at 3448cm⁻¹ and 3352cm⁻¹ assigned to (-NH₂)str. that substituted in benzene ring, the strong band at 1604cm⁻¹ attributed to theoxadiazolic (C=N)str. and (-NH₂)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 thienol and thietekone forms, respectively. The IR spectrum of azo-oxadiazole derivative 2 indicated the absence of ofa doublet band at 3448cm⁻¹ and 3352cm⁻¹ for (-NH₂)str. and appearance of these 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., and (-NH₂)bend. due to the vibration coupling interaction. The weak and strong bands at 1712cm⁻¹ attributed to the stretching vibrations of carbonyl group (C=O)str. in thioenol and thioketone forms, respectively. The IR spectra of the oxadiazolic-imines 3a-h showed disappearance of the sharp and strong band at 1662 cm⁻¹ for aldehydic (C=O)str., also disappearing the sharp doublet band for (-NH₂)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 disappearance 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 sharp band at the range 1599-1610cm⁻¹ assigned to oxadiazolic (C=N)str.

The structures of oxazepane compounds 4a-h were proven by their ¹H NMR spectra (300 MHz, DMSO-d₆) which showed the phenolic (O-H) proton as a singlet at 8.10, 8.14, 8.21, 8.24, 8.26, 8.29, 8.32, 8.34, 8.37, 8.40 ppm, respectively. The (N-H) proton for thione form appeared as a singlet at δ 9.14, 9.19, 9.23, 9.27, 9.30, 9.34, 9.37 and 9.40 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–CH₃) in compounds 4f and 4g appeared as a singlet at δ 3.73ppm and 3.91ppm, respectively. The structures of the prepared oxazepane compounds 5a-h, were confirmed by their ¹H NMR spectra which appeared singlet signal at δ 10.34, 10.38, 10.39, 10.37, 10.35, 10.37 and 9.70ppm, respectively belong to the phenolic (O-H) proton. The (N-H) proton for imine form as singlet at δ 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–CH₃) in compounds 5f and 5g appeared as a singlet at δ 3.70ppm and 3.79ppm, respectively. Thesinglet signal at δ 82.43 ppm assigned to methylene group protons (–CH₂–) of the oxazepane ring. Moreover, the (CHNS) elemental analysis results were within ± 0.4% of the theoretical values and in good agreement with the proposed chemical structures for compounds 4a-h and 5a-h 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 method⁹ 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

<table>
<thead>
<tr>
<th>Product</th>
<th>Physical state</th>
<th>Rf (developed)</th>
<th>Mp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>Orange solid</td>
<td>0.75 (n-hexane/ EtOAc, 1:3)</td>
<td>202-204</td>
<td>78</td>
</tr>
<tr>
<td>3b</td>
<td>Yellow solid</td>
<td>0.78 (n-hexane/ EtOAc, 1:3)</td>
<td>179-181</td>
<td>82</td>
</tr>
<tr>
<td>3c</td>
<td>Dark orange solid</td>
<td>0.70 (n-hexane/ EtOAc, 1:3)</td>
<td>170-172</td>
<td>75</td>
</tr>
<tr>
<td>3d</td>
<td>Yellow solid</td>
<td>0.72 (n-hexane/ EtOAc, 1:3)</td>
<td>150-152</td>
<td>79</td>
</tr>
<tr>
<td>3e</td>
<td>Orange solid</td>
<td>0.76 (n-hexane/ EtOAc, 1:3)</td>
<td>214-216</td>
<td>81</td>
</tr>
<tr>
<td>3f</td>
<td>Dark brown solid</td>
<td>0.71 (n-hexane/ EtOAc, 1:3)</td>
<td>152-154</td>
<td>86</td>
</tr>
<tr>
<td>3g</td>
<td>Brown solid</td>
<td>0.73 (n-hexane/ EtOAc, 1:3)</td>
<td>166-168</td>
<td>89</td>
</tr>
<tr>
<td>3h</td>
<td>Dark brown solid</td>
<td>0.69 (n-hexane/ EtOAc, 1:3)</td>
<td>149-151</td>
<td>89</td>
</tr>
<tr>
<td>4a</td>
<td>Dark Orange solid</td>
<td>0.62 (n-hexane/ EtOAc, 1:1)</td>
<td>220-222</td>
<td>89</td>
</tr>
<tr>
<td>4b</td>
<td>Dark orange solid</td>
<td>0.64 (n-hexane/ EtOAc, 1:1)</td>
<td>210-212</td>
<td>86</td>
</tr>
<tr>
<td>4c</td>
<td>Dark orange solid</td>
<td>0.63 (n-hexane/ EtOAc, 1:1)</td>
<td>212-214</td>
<td>83</td>
</tr>
</tbody>
</table>

Volume 5 Issue 10, October 2016

www.ijsr.net
Licensed Under Creative Commons Attribution CC BY

Paper ID: ART20162255
DOI: 10.21275/ART20162255
1747
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.

5. Acknowledgements

Great thanks for the Faculty of Science, University of Ferdos, buali center, Iran for their significant assistance in 1H NMR and Elemental Analysis measurements of the target compounds.

References


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

<table>
<thead>
<tr>
<th>Product</th>
<th>Staphylococcus aureus (Gram-positive)</th>
<th>Escherichia coli (Gram-negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>4b</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>4c</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>4d</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>4e</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>4f</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>4g</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>4h</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>5a</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>5b</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>5c</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5d</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>5e</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>5f</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>5g</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>5h</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>DMSO</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>22</td>
<td>17</td>
</tr>
</tbody>
</table>


