ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

Synthesis and Preliminary Antibacterial Effects of New 1, 3, 4-Oxadiazoles

Zeid Hassan Abood, Husham Attallah Suhail*, Zahraa Kadum Chafcheer

Chemistry Department, College of Science, University of Kerbala, Kerbala-Iraq.

***Corresponding Authors: Husham Attallah Suhail**

Abstract

4-aminobenzoyl hydrazide [I] was reacted with carbon disulfide in the existence of potassium hydroxide in ethyl alcohol to give 5-(4-aminophenyl)-2-thiol-1,3,4-oxadiazole [II]. The initiator aldehyde [III] was prepared via coupling reaction of 2-hydroxybenzaldehyde with the corresponding diazonium salt of compound [II]. Aldehyde [III] was condensed with some anilines including (3-bromoaniline, 4-aminophenol, 3-aminophenol, 2-aminophenol, 4-methoxyaniline, 2, 4-dimethylaniline and 4-acetamidoaniline) utilizing microwave irradiation technique in ethyl alcohol to yield seven imines [IV] $_{a\text{-}g}$. Treatment of imines [IV]$_{a\text{-}g}$ with phthalic anhydride in microwave oven gave seven 1,3-benzoxazepine-4,7-diones derivatives of 1,3,4-oxadiazole [V]$_{a\text{-}g}$. The antibacterial activities for the desired compounds were investigated on bacteria, *Staphylococcus aurous* and *Escherichia coli*. The results showed that the synthesized 1, 3, 4-oxadiazoles (compounds [V]$_a$, [V]$_b$, [V]$_c$, [V]$_d$ and [V]$_e$ expressed better activity to gentamycin athwart positive bacteria. On the other hand, the 1,3-oxazepine-4,7-diones [V]$_a$, [V]$_b$, [V]$_c$, [V]$_d$, [V]$_f$ and [V]$_g$ exhibited greater effect against negative bacteria in comparison with that of the control drug (Gentamycin).

Keywords: *1, 3, 4-Oxadiazoles, Benzoxazepines, Imines, Cycloaddition, Antibacterial action.*

Introduction

Development of new biological compounds based on the molecular recognition is significant goal in the medicinal chemistry and attracted considerable interest [1]. Nowadays, scientists focus on the nitrogen containing heterocyclic species because of their wide spectrum of biological activities and pharmacological importance [2, 3] as antibacterial [4], antiviral [5], anti-inflammatory [6], antiallergic [7], analgesic [8], anticancer [9] and antitumor [10].

Compound structure is the main dynamic source to act as a novel biologically active species [11]. Oxadiazole is an aromatic heterocyclic nucleus possessing one oxygen and two nitrogen atoms in a five-membered ring [12]. 1,3,4-Oxdiazole found in four different isomeric structures namely, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole [13]. Among these, 1,3,4-oxadiazole is an important heterocyclic core and becomes significant structural motif for the discovery of new drugs [14] because of its capability to engage in the hydrogen bonding and metabolic profile [15].

1,3,4-Oxadiazoles undergo several reactions like photochemical [16], thermal [17], electrophilic [18] and nucleophilic [19] substitution. Synthesis of 1,3,4-oxadiazole containing compounds and investigation of their chemical and biological properties has accelerated in recent years [20-23]. Heterocyclic seven-membered ring constitutes the core or a key fragment of a number of bioactive compounds involving isolated from natural products [24].

Fused oxazepinone derivatives have attracted considerable attention owing to their promising biological activities [25, 26], such as antihistaminic [27], anti-HIV [28], antidepressant [29], and antitumor activities [30]. Asendin (Amoxapine) drug is used as antidepressant [31] and active drug for schizophrenia [32]. Oxazepine compounds have biological importance and they have medicinal [33, 34] and pharmaceutical

applications [35, 36]. Thus, in this article, we reported here the synthesis of new 1, 3, 4-oxadiazole derivatives bearing the biologically active 1, 3-benzoxazepine-4, 7-dione moiety which probably have some biological activities.

Experimental

General

All chemical were equipped from Fluka and sigma Aldrich. Melting points was measured using an Electro thermal Stuart SMP 30 capillary melting point apparatus, UK. (IR) spectra were recorded on SHIMADZU FTIR–8400S Infrared Spectrophotometer using (KBr) disc. Proton magnetic resonance were collected on INOVA 500 MHz varian, USA NMR spectrometer in DMSO-d_6 as solvent and TMS as an internal standard, at University of Tehran, Iran. (CHNS) Analyses were deduced with Perkin Elmer 300A at University of Tehran, Iran.

Preparation Methods

Preparation of 5-(4-aminophenyl)-2-thiol-1, 3, 4-oxadiazole [II] [37]

4-aminobenzoic hydrazide **[I]** (1.51 g, 10 mmol) was dissolved in absolute ethanol (25 mL) and put on ice bath. To this mixture, carbon disulfide (1 mL) was added drop-wise with stirring, then potassium hydroxide (0.56 g, 10 mmol) was added. The reaction mixture was stirred for 15 min, then refluxed with stirring on a water bath for 24 h in 70 ºC. TLC (n-hexane: EtOAc, 1:1, Rf = 0.64) showed that the reaction was completed. The mixture was then cooled down to room temperature.

The solvent was removed under reduced pressure, the resulting solid was dissolved in distilled water (100 mL) and the solution was acidified carefully with concentrated hydrochloric acid to give pale yellow precipitate that was filtered under reduced pressure, washed well with distilled water and recrystallized from ethanol to give pale yellow crystals, yield (1.4475 g, 75 %), m.p. 234-236 ºC, Lit.[37] 235 °C.

Preparation of (E)-2-hydroxy-5-((4-(5-mercapto-1, 3, 4-oxadiazol-2-yl) phenyl) diazenyl) benzaldehyde [III] [38]

5-(4-aminophenyl)-2-thiol-1, 3, 4-oxadiazole [II] (1.93 g, 10 mmol) was dissolved in a mixture of concentrated hydrochloric acid (3.2 mL) and distilled water (10 mL). The mixture was cooled at (0 °C) in an ice bath, then a solution of sodium nitrite (0.69 g, 10 mmol) dissolved in distilled water (5 mL) was added drop-wise to the mixture with stirring. The temperature of the ice bath was controlled between (0-5 °C) during the addition.

A solution of 2-Hydroxybenzaldehyde (1.22 g, 10 mmol) dissolved in (15 mL) of (10%w/v) sodium hydroxide solution was prepared and cooled to (5 oC) by immersion in an ice bath and stirred vigorously, then the diazonium salt solution was added very slowly to the phenoxide solution, a red precipitate soon separated.

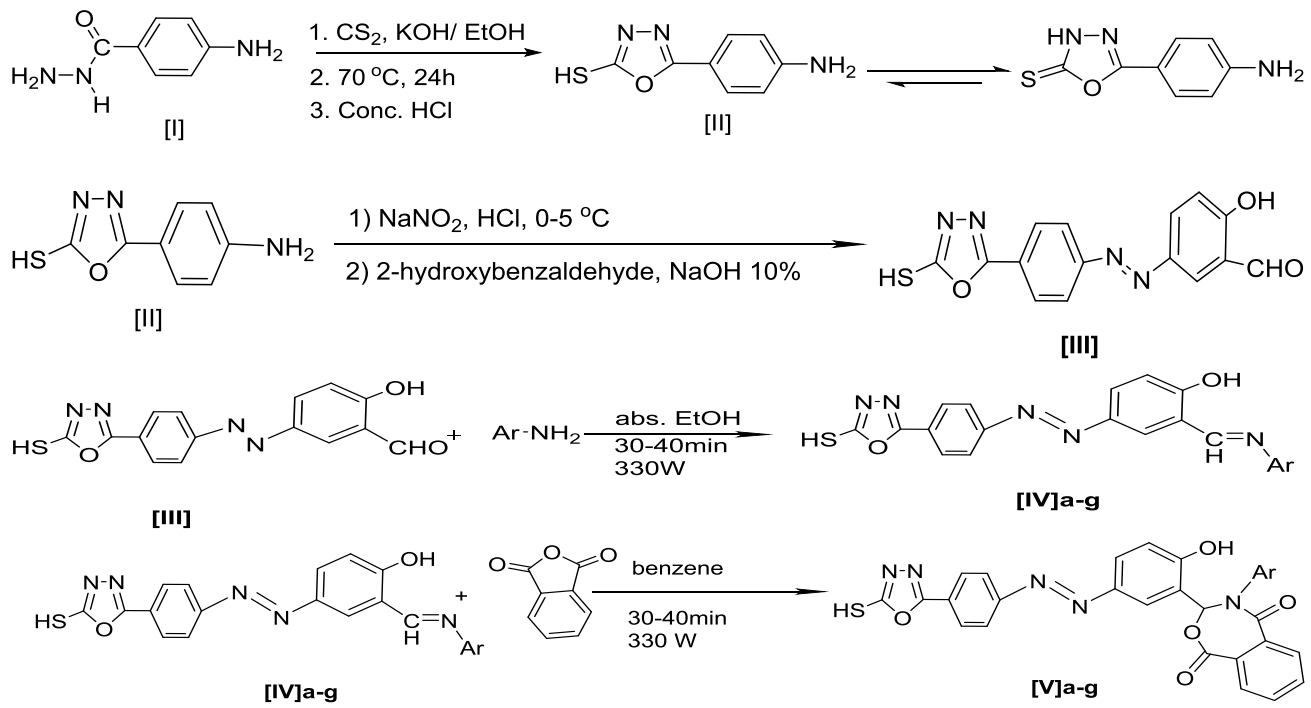
When all the diazonuim salt solution has been added, the mixture was allowed to stand in an ice bath for (30 min.) with occasional stirring, then the solution was filtered and the precipitate was washed well with distilled water, dried upon filter paper then in oven and recrystallized from ethanol, yield (1.956 g, 60 %), m.p. 166-168 ºC, Rf (developer) 0.41(n-hexane: EtOAc, 1: 3).

General Procedure for the Preparation of Imines [IV]$_{a-g}$

The aldehyde derivative **[III]** (0.326 g, 1 mmol), suitable aromatic amines (1 mmol) and absolute ethanol (1 mL) were placed in crucible. The reaction mixture was irradiated in a domestic microwave oven at (330W) for (30-40) min. TLC (*n*-hexane: EtOAc, 1:3) showed end of reactions. Recrystallization of crude yields was carried out using ethanol. Some physical properties and other characteristics of compounds [IV]a-g are given in Table 1.

General procedure for the preparation of 1, 3-benzoxazepine-4, 7-diones [V]$_{a-g}$

Compounds **[IV]$_{a-g}$** (1 mmol), phthalic anhydride (0.148 g, 1 mmol) and benzene (1 mL) were mixed and irradiated in microwave oven at (330W) for (30-40) min. TLC (*n*-hexane: EtOAc, 1:1) showed end of reactions. The crude yield was recrystallized from ethanol. Some physical properties and other characteristics of compounds [V]a-g are listed in Table 1.



Ar = m-BrC_6H_4-, p-OHC_6H_4-, m-OHC_6H_4-, o-OHC_6H_4-, P-$OCH_3C_6H_4$-, 2,4-di-$CH_3C_6H_3$- p-$NHCOCH_3C_6H_4$-

[V]a **[V]b** **[V]c** **[V]d** **[V]e** **[V]f** **[V]g**

Scheme 1: Synthesis of 1,3,4-oxadiazoles, (i) CS_2, KOH, EtOH, 70 °C, 24 h; (ii) Conc. HCl; (iii) $NaNO_2$, HCl, 0-5 °C; (iv) 2-hydroxybenzaldehyde, NaOH 10% , 5°C; (v) Ar-NH_2, EtOH, MW (30W), 25 min; (vi) phthalic anhydride, benzene, MW (550-600W), 60 min

Preliminary Antibacterial Assay

The antibacterial activities of the newly synthesized oxadiazoles $[V]_{a-g}$ were determined by the agar diffusion method [41] using Gram (+) and Gram (-) bacteria on agar media. The test bacteria to evaluate the effect of the target compounds were *Staphylococcus aurous* (Gram-positive) and *Escherichia coli* (Gram-negative). A solution of 10 mg/mL was prepared using (DMSO) as solvent. Gentamycin was used as standard drug to record the diameters assigned for inhibition zones of compounds Table 2.

Results and Discussion

5-(4-aminophenyl)-2-thiol-1,3,4-oxadiazole**[II]**was synthesized via reaction of 4-aminobenzoyl hydrazide **[I]** with carbon disulfide in the presence of potassium hydroxide in absolute ethanol [37]. Reaction of compound **[II]** with (HCl/ $NaNO_2$) generated aryldiazonium chloride which was treated with salicylaldehyde dissolved in (NaOH) solution to yield azoaldehyde [**III**] [38]. Aldehyde [**III**] was treated with some aniline derivatives (3-bromoaniline, 4-aminophenol, 3-aminophenol, 2-aminophenol, 4-methoxyaniline, 2, 4-dimethylaniline and 4-acetamidoaniline) on microwave oven in absolute ethanol to produce seven imines $[IV]_{a-g}$ of 1,3,4-oxadiazole, respectively. Treatment of imines $[IV]_{a-g}$ with phthalic anhydride using microwave irradiation gave 1, 3-benzoxazepin-4, 7-diones derivatives of 1, 3, 4-oxadiazole $[V]_{a-g}$. Structures of target compounds synthesized were confirmed by infrared, ^1H NMR spectra, and (CHNS) analysis and were in good agreement with the suggested structures.

The IR spectrum of oxadiazole derivative [I] showed the absence of the sharp doublet band for hydrazide group (-$NHNH_2$) at (3307, 3236) cm^{-1} and the strong band around 1627 cm^{-1} belong to (C=O)str., additionally the appearance of the following characteristic bands: the doublet band at 3450 cm^{-1} and 3352 cm^{-1} attributed to (-NH_2)str. substituted in benzene ring, the strong band at 1606 cm^{-1} assigned to the oxadiazolic (C=N)str. and (-NH_2)bend. due to the vibration coupling interaction.

The weak and strong bands at 2592 cm^{-1} and 1068 cm^{-1} due to (S-H)str. and (C=S)str. in thioenol and thioketone forms, respectively. The IR spectrum of azo-oxadiazole derivative [II] indicated the disappearance of a doublet band at 3450 cm^{-1} and 3352 cm^{-1} for (-

NH_2)str. and appearance of the following characteristic bands: the weak band at 1417 cm^{-1} assigned to azo group (N=N)str., the broad band at 3074 cm^{-1} due to (O-H)str., the band at 1658 cm^{-1} belong to (C=O)str., the oxadiazolic (C=N)str. appeared at 1599 cm^{-1}. IR spectra of the oxadiazolic-imines $[IV]_{a-g}$ showed disappearing the peak at 1658 cm^{-1} for carbonyl group, also disappearance of peaks of ($-NH_2$) in the starting amines around (3400-3250) cm^{-1}, in addition to appearing a peak around (1591-1608) cm^{-1} recorded to the imine group. Other bands were listed in Table 3.

1,3-benzoxazepin-4,7-diones $[V]_{a-g}$ indicated peak around 1595-1606 cm^{-1} for (C=N) group in oxadiazole ring, also appearance band at 1641-1718 cm^{-1} attributed to stretching of carbonyl groups (O=C-N and O=C-O) of oxazepine. Other bands were listed in Table 3. The structures of benzoxazepine compounds $[V]_{a-g}$ were proven by their ^1H NMR spectra (500 MHz, DMSO-d_6) which showed the (N-H) proton for thione form as a singlet at 12.19, 12.02, 12.18, –, 10.22, –, and 10.22 ppm, respectively [39, 40].The sulfhydryl (S-H) proton as a singlet at **δ** 11.45, 11.45, 11.44, 11.60, 10.11, 11.46 and 10.11 ppm, respectively.

The phenolic (O-H) proton as a singlet at δ 10.93, (10.24, 9.76), 9.74, 9.83, 9.74, 9.90 and 9.74 ppm, respectively. The signals of aromatic protons (Ar–H) and (C–H) proton of oxazepine ring appeared at **δ** 6.70-8.35 ppm. Moreover, the methoxy protons ($O-CH_3$) in compound $[V]_e$ appeared as a singlet at δ 3.75 ppm.

The protons of methyl groups ($2–CH_3$) and ($4-CH_3$) in compound $[IV]_f$ appeared as a singlet at δ 2.06 and 2.33 ppm, respectively. The proton of (N-H) and protons of methyl group (CH_3) of acetamide group ($-NHCOCH_3$) in compound $[V]_g$ appeared as a singlet at δ 4.35 and 3.80 ppm, respectively. Moreover, the (CHNS) elemental analysis results for compounds $[V]_{a-g}$ afforded good agreement with the proposed structures and shown in Table 4.

Antibacterial Activities

Compounds $[V]_a$,$[V]_b$, $[V]_c$, $[V]_d$ and $[V]_e$ showed better activity than control drug against Gram-positive bacteria, while compounds $[V]_a$,$[V]_b$, $[V]_c$, $[V]_d$, $[V]_f$ and $[V]_g$ were found to be greater activity than gentamycin against Gram-negative bacteria.

Table 1: Some physical properties of compounds $[IV]_{a-g}$ and $[V]_{a-g}$

Product	Physical state	Rf (developer)	Mp (°C)	Yields (%)	Time (min)
$[IV]_a$	Brown solid	0.90 (n-hexane/EtOAc. 1:3)	152-154	92	30
$[IV]_b$	Dark brown solid	0.92 (n-hexane/EtOAc. 1:3)	106-108	82	30
$[IV]_c$	Dark brown solid	0.88 (n-hexane/EtOAc. 1:3)	196-198	88	30
$[IV]_d$	Brown solid	0.87 (n-hexane/EtOAc. 1:3)	196-198	96	40
$[IV]_e$	Brown solid	0.90 (n-hexane/EtOAc. 1:3)	138-142	92	30
$[IV]_f$	Dark brown solid	0.84 (n-hexane/EtOAc. 1:3)	145-147	88	30
$[IV]_g$	Dark brown solid	0.93 (n-hexane/EtOAc. 1:3)	150-154	87	30
$[V]_a$	Brown solid	0.90 (n-hexane/EtOAc. 1:1)	162-164	96	30
$[V]_b$	Dark brown solid	0.94 (n-hexane/EtOAc. 1:1)	206-208	90	30
$[V]_c$	Brown solid	0.93 (n-hexane/EtOAc. 1:1)	203-205	82	30
$[V]_d$	Brown solid	0.94 (n-hexane/EtOAc. 1:1)	200-202	83	40
$[V]_e$	Dark brown solid	0.93 (n-hexane/EtOAc. 1:1)	174-176	88	30
$[V]_f$	Dark brown solid	0.86 (n-hexane/EtOAc. 1:1)	154-156	95	30
$[V]_g$	Brown solid	0.88 (n-hexane/EtOAc. 1:1)	191-193	95	30

Table 2: The antibacterial activities of compounds $[V]_{a-g}$ and gentamycin as control drug

Product	*Staphylococcus aurous* (Gram-positive)	*Escherichia coli* (Gram-negative)
$[V]_a$	17	18
$[V]_b$	19	19
$[V]_c$	19	19
$[V]_d$	17	17
$[V]_e$	16	14
$[V]_f$	15	20
$[V]_g$	14	17
DMSO	0	0
Gentamycin	15	15

Table 3: FT-IR data of compounds $[IV]_{a-g}$ and $[V]_{a-g}$ in cm^{-1}

Com. No.	FT-IR bands
$[IV]_a$	3460 and 3344 (vO-H), 3217 (vN-H, thione form), 3057 vC-H, benzene), 1591 (vC=N, imine and vC=N, oxadiazole, vib. coupling), 1533,1508 and 1485 (vC=C, benzene), 1415 (vN=N), 1064 (vC=S, thione form), 840 (δo.o.p.C-H, benzene.
$[IV]_b$	3329 (vO-H and vN-H, thione form, vib. coupling), 3068 (vC-H, benzene), 2603 (vS-H), 1602 (vC=N, imine and vC=N, oxadiazole, vib. coupling), 1510 (vC=C, benzene), 1415 (vN=N), 1070 (vC=S, thione form), 829 (δo.o.p.C-H, benzene.
$[IV]_c$	3209 (vO-H,vN-H, thione form and vC-H, benzene, vib. coupling), 2621 (vS-H), 1606 (vC=N, imine and vC=N, oxadiazole, vib. coupling), 1510 and 1448 (vC=C, benzene), 1419 (vN=N), 1074 (vC=S, thione form), 835 (δo.o.p.C-H, benzene.
$[IV]_d$	3371 (vO-H), 3219 (vN-H, thione form) 3064 (vC-H, benzene), 2576 (vS-H), 1608 (vC=N, imine and vC=N, oxadiazole, vib. coupling), 1570, 1492 and 1465 (vC=C, benzene), 1431 (vN=N), 1091 (vC=S, thione form), 748 (δo.o.p.C-H, benzene.
$[IV]_e$	3342 (vO-H), 3219 (vN-H, thione form), 3047 (vC-H, benzene), 2937 (vasC-H, OCH_3), 2833 (vsC-H, OCH_3), 2596 (vS-H), 1606 (vC=N, imine and vC=N, oxadiazole, vib. coupling), 1546, 1512 and 1465 (vC=C, benzene), 1442 (vN=N), 1109 (vC=S, thione form), 827 (δo.o.p.C-H, benzene.
$[IV]_f$	3344 (vO-H), 3215 (vN-H, thione form) 3032 (vC-H, benzene), 2920 (vasC-H, CH_3), 2860 (vsC-H, CH_3), 1608 (vC=N, imine and vC=N, oxadiazole, vib. coupling), 1543 and 1502 (vC=C, benzene), 1078 (vC=S, thione form), 829 (δo.o.p.C-H, benzene.
$[IV]_g$	3254 (vO-H and vN-H, thione form, vib. coupling), 3051 (vC-H, benzene), 2978 (vC-H, CH_3), 1660 (vC=O, amide), 1608 (vC=N, imine and vC=N, oxadiazole, vib. coupling), 1512 (vC=C, benzene), 1410 (vN=N), 1047 (vC=S, thione form), 835 (δo.o.p.C-H, benzene.
$[V]_a$	3473 (vO-H), 3288 (vN-H, thione form), 3064 (vC-H, benzene), 1714 (vC=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1595 (vC=N, oxadiazole), 1545, 1500 and 1475 (vC=C, benzene), 1421 (vN=N), 1072 (vC=S, thione form), 713 (δo.o.p.C-H, benzene.
$[V]_b$	3416 (vO-H), 3255 (vN-H, thione form), 3068 (vC-H, benzene), 1716 (vC=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1604 (vC=N, oxadiazole), 1512 (vC=C, benzene), 1076 (vC=S, thione form), 717 (δo.o.p.C-H, benzene.
$[V]_c$	3414vO-H), 3288 (vN-H, thione form), 3072 (vC-H, benzene), 1712 (vC=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1606 (vC=N, oxadiazole), 1512 and 1469 (vC=C, benzene), 1425 (vN=N), 1080 (vC=S, thione form), 715 (δo.o.p.C-H, benzene.
$[V]_d$	3360 (vO-H), 3221 (vN-H, thione form), 3064 (vC-H, benzene), 1716 (vC=O, O=C-O, oxazepine), 1641 (vC=O, O=C-N), 1604 (vC=N, oxadiazole), 1572, 1504 and 1460 (vC=C, benzene), 1419 (vN=N), 1076 (vC=S, thione form), 744 (δo.o.p.C-H, benzene.
$[V]_e$	3281 (vO-H), 3209 (vN-H, thione form), 3066 (vC-H, benzene), 2966 (vasC-H, OCH_3), 2841 (vsC-H, OCH_3), 1712 (vC=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1600 (vC=N, oxadiazole), 1550, 1506 and 1464 (vC=C, benzene), 1084 (vC=S, thione form), 831 (δo.o.p.C-H, benzene.
$[V]_f$	3470 vO-H), 3308 (vN-H, thione form), 3059 (vC-H, benzene), 2922 (vasC-H, CH3), 2864 (vsC-H, CH3), 1718 (vC=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1600 (vC=N, oxadiazole), 1543 and 1500 (vC=C, benzene), 1076 (vC=S, thione form), 715 (δo.o.p.C-H, benzene.
$[V]_g$	3468 (vO-H), 3294 (vN-H, thione form), 3064 (vC-H, benzene), 1714 (vC=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1668 (vC=O, amide), 1606 (vC=N, oxadiazole), 1512 (vC=C, benzene), 1408 (vN=N), 1074 (vC=S, thione form), 713 (δo.o.p.C-H, benzene.

Table 4: (CHNS) Elemental analysis of compounds $[V]_{a-g}$

Com. No.	Calculated %				Found %			
	C	**H**	**N**	**S**	**C**	**H**	**N**	**S**
$[V]_a$	55.42	2.89	11.14	5.10	55.07	3.19	10.78	4.70
$[V]_b$	61.59	3.39	12.38	5.67	61.21	3.69	12.73	6.06
$[V]_c$	61.59	3.39	12.38	5.67	61.98	3.68	11.99	5.40
$[V]_d$	61.59	3.39	12.38	5.67	61.88	3.74	11.98	5.26
$[V]_e$	62.17	3.65	12.08	5.53	61.78	4.02	12.49	5.17
$[V]_f$	64.46	4.01	12.12	5.55	64.81	4.42	11.77	5.32
$[V]_g$	61.38	3.66	13.85	5.29	60.98	4.04	13.47	4.90

Conclusions

Preponderance of synthesized 1, 3, 4-Oxadiazoles showed greater effect against positive and negative bacteria than that of control drug. Compounds $[V]_a$,$[V]_b$, $[V]_c$, $[V]_d$ and $[V]_e$ were found to be better effect than gentamycin against positive germ, while compounds $[V]_a$,$[V]_b$, $[V]_c$, $[V]_d$, $[V]_f$ and $[V]_g$ showed greater activity to gentamycin athwart negative germ.

Acknowledgements

The author's great thanks for staff of the central lab. University of Tehran, Iran for recording ^1H NMR and elemental analysis for target compounds.

References

1. Santosh R, Prabhu A, Selvam MK, Krishna PM, Nagaraja GK, Rekha PD (2019) Design, synthesis, and pharmacology of some oxadiazole and hydroxypyrazoline hybrids bearing thiazoyl scaffold: antiproliferative activity, molecular docking and DNA binding studies. Heliyon, 5(2):e01255. doi:10.1016/j.heliyon.2019.e01255
2. Kais R, Adnan S (2019) Synthesis, Identification and Studying Biological Activity of Some Heterocyclic Derivatives from 3, 5-Dinitrosalicylic Acid. J. Phys. Conf. Ser., 1234(1). doi:10.1088/1742-6596/1234/1/012091
3. Al-lami N, Salom KJ (2019) Pharmacological Studies On Some New 3-Cyclic Oxazepine-2- Aryl Imidazo (1, 2-A) Pyridine Derivatives, 11(1):125-130.
4. Tambe MS, Choudhari A, Sarkar D, Sangshetti J, Patil R, Gholap SS (2018) Design, Synthesis and Biological Screening of Novel 1,3,4-Oxadiazoles as Antitubercular Agents. Chemistry Select, 3(47): 13304-13310. doi:10.1002/slct.201802227
5. Wang L, Wu YR, Ren ST, et al (2018) Synthesis and bioactivity of novel C2-glycosyl oxadiazole derivatives as acetylcholinesterase inhibitors. Heterocycl. Commun., 24(6):333-338. doi:10.1515/hc-2018-0166
6. Kumar V, Sharma S, Husain A (2015) Synthesis and in vivo Anti-inflammatory and Analgesic activities of Oxadiazoles clubbed with Benzothiazole nucleus. Int. Curr. Pharm. J., 4(12):457-461. doi:10.3329/icpj.v4i12.25597
7. Khalilullah H, J Ahsan M, Hedaitullah M, Khan S, Ahmed B (2012) 1,3,4-Oxadiazole: A Biologically Active Scaffold. Mini-Reviews Med. Chem., 12(8):789-801. doi:10.2174/138955712801264800
8. Biju C, Ilango K, Prathap M, Rekha K (2012) Design and microwave-assisted synthesis of 1,3,4-oxadiazole derivatives for analgesic and anti-inflammatory activity. J. Young Pharm., 4(1):33-37. doi:10.4103/0975-1483.93576
9. Sumalatha S, Namrata V, Lakshmi M, Sridhar G (2019) Synthesis and Anticancer Activity of Oxadiazole Incorporated Ellipticine Derivatives. Russ. J. Gen. Chem., 89(3):505-510. doi:10.1134/S107036321903023X
10. Pitasse-santos P, Sueth-santiago V, Lima MEF (2018) 1,2,4- and 1,3,4-Oxadiazoles as Scaffolds in the Development of Antiparasitic Agents. Braz. Chem. Soc., 29(3):435-456.
11. Ahmad A, Varshney H, Rauf A, Sherwani A, Owais M (2017) Synthesis and anticancer activity of long chain substituted 1,3,4-oxadiazol-2-thione, 1,2,4-triazol-3-thione and 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine derivatives. Arab J. Chem., 10: S3347-S3357. doi:10.1016/j.arabjc.2014.01.015
12. Zhu G, Yi Z, Zhou J, et al (2018) Bran-New Four-Molecule and Five-Molecule Cascade Reactions for One-Pot Synthesis of Pyrano[3,2- c]chromen-5-ones and Spiro[benzo[b][1,4]diazepine-2,2′-pyrano[3,2- c]chromen]-5′-ones under Catalyst- and Solvent-Free Conditions. ACS Omega., 3(10):13494-13502. doi:10.1021/acsomega.7b02017
13. Sharma S, Sharma PK, Kumar N, Dudhe R (2010) Chemistry and pharmacological potentials of Oxadiazoles: A Review. Der Pharma Chem., 2(4):253-263. http://derpharmachemica.com/vol2-iss4/DPC-2010-2-4-253-263.html.
14. Aljamali NM (2018) Review in Chemical Structures of Drugs. Int. J. Eng. Technol., 7(December):644-654. doi:10.14419/ijet.v7i4.36.24216
15. Wai K, Syahida A, Ul-haq Z, Basyaruddin M, Rahman A, Lajis NH (2010) Bioorganic & Medicinal Chemistry Letters Synthesis and biological activity of oxadiazole and triazolothiadiazole derivatives as tyrosinase inhibitors. Bioorg Med. Chem. Lett., 20(12):3755-3759. doi:10.1016/j.bmcl.2010.04.067
16. Yousif E, Hasan A (2015) Photostabilization of poly(vinyl chloride)-Still on the run. J. Taibah Univ. Sci., 9(4):421-448. doi:10.1016/j.jtusci.2014.09.007
17. Abid OH, Ramadan AK (2018) Preparation and Identification of Novel 1, 3-Oxazepine Derivatives by Cycloaddition Reactions [2+5] of Selected Carboxylic Acid

Anhydrides with Imines Derived from 4-methyl aniline. Al-Mustansiriyah J. Sci., 29(2):93. doi:10.23851/mjs.v29i2.331

18. Wong JYF, Tobin JM, Vilela F, Barker G (2019) Batch Versus Flow Lithiation–Substitution of 1,3,4- Oxadiazoles: Exploitation of Unstable Intermediates Using Flow Chemistry. Chem. A Eur. J., 25(53):12439-12445. doi:10.1002/chem.201902917
19. Orsi DL, Easley BJ, Lick AM, Altman RA (2017) Base Catalysis Enables Access to α,α-Difluoroalkylthioethers. Org Lett., 19(7):1570-1573. doi:10.1021/acs.orglett.7b00386
20. Shamsuzzaman, Siddiqui T, Alam MG, Dar AM (2015) Synthesis, characterization and anticancer studies of new steroidal oxadiazole, pyrrole and pyrazole derivatives. J. Saudi. Chem. Soc., 19(4):387-391. doi:10.1016/j.jscs.2012.04.009
21. Hari B (2018) Design and Synthesis OF Novel 1 , 3 , 4-Oxadiazole AND 1 , 2 , 4-European of Biomedical and Pharmaceutical sciences. Eur. J. Biomed Pharm. Sci., 6(July):576-578.
22. Purushotham N, Poojary B (2018) An Expeditious Synthesis of Chiral 1,2,4-Oxadiazole Peptidomimetics from Heteroaroyl Monopeptides. Chemistry Select, 3(39):10996-10998. doi:10.1002/slct.201801921
23. Rayam P, Polkam N, Kummari B, et al (2019) Synthesis and Biological Evaluation of New Ibuprofen-1,3,4-oxadiazole-1,2,3-triazole Hybrids. J. Heterocycl. Chem., 56(1): 296-305. doi:10.1002/jhet.3409
24. Synthesis, Characterization (2017) Biological Activity Studies of Schiff Bases and Cyclohexane. J. Sci., 58(4):1998-2011.
25. Hussein IA, Narren SF, Hasan IMM, Saleh AM (2018) Synthesis and biological activities of some new derivatives based on bis (4, 4'-diamino phenoxy) ethane containing Oxazpines, Terazole rings. J. Pharm. Sci. Res., 10(10):2461-2469.
26. Muslim RF, Saleh SE (2019) Synthesis, Characterization and Evaluate the Biological Activity of Novel Heterocyclic Derivatives from Azomethine Compounds. Orient J. Chem., 35(4):1360-1367. doi:10.13005/ojc/350416
27. Asif M, Abida (2019) A mini review on biological potential of 1,3,4-oxadiazole derivatives. Int J. Pharm. Chem. Anal., 5(4):179-187. doi:10.18231/2394-2797.2018.0028
28. Garofalo A, Grande F, Brizzi A, Aiello F, Dayam R, Neamati N (2008) Naphthoxazepine inhibitors of HIV-1 integrase: Synthesis and biological evaluation. Chem. Med. Chem., 3(6):986-990. doi:10.1002/cmdc.200800026
29. Ruang DAN, Rsud A, Johannes PWZ (2019) Synthesis and characterization of (4,7- and-1,5-dione) 1,3- oxazepine derivatives and poly hydrazones. J. Univ. Kerbala, 16(September):126-133.
30. Hassan AY, Husseiny EM (2019) Synthesis and Anticancer Evaluation of Some Novel Thiophene, Thieno[3,2- d]pyrimidine, Thieno[3,2- b]pyridine, and Thieno[3,2- e] [1,4]oxazepine Derivatives Containing Benzothiazole Moiety. J. Heterocycl. Chem. doi:10.1002/jhet.3629
31. Choudhary S, Singh A, Yadav J, et al (2019) ض. New J. Chem., 43(2):953-962. doi:10.1039/C8NJ04861D
32. Jain MS, Surana SJ (2017) Synthesis and evaluation of antipsychotic activity of 11-(4′-(N-aryl carboxamido/N-aryl-α-phenyl-acetamido)-piperazinyl)-dibenz[b,f][1,4]-oxazepine derivatives. Arab. J. Chem., 10: S2032-S2039. doi:10.1016/j.arabjc.2013.07.033
33. Azeez H, Qadir K (2017) Synthesis and Spectroscopic Characterization of a New Series of Benzo[E][1,3]Oxazepine Compounds from Schiff Bases. Sci. J. Univ. Zakho., 5(1):101-106. doi:10.25271/2017.5.1.309
34. Shaabani S, Shaabani A, Kucerakova M, Dusek M (2019) A One-Pot Synthesis of Oxazepine-Quinazolinone bis-Heterocyclic Scaffolds via Isocyanide-Based Three-Component Reactions. Front Chem., 7(September). doi:10.3389/fchem.2019.00623
35. T AL-Sa'adi W, F Al-Tai A, H Al-Saeed H, K Mahmood A (2015) Effect of 1,3-Oxazepine Derivative on Alkaline Phosphatase and Lactate Dehydrogenase Activity in Healthy Iraqi Females Serum. J. Fac. Med., 57(3):254-256. doi:10.32007/med.1936/jfacmedbagdad.v57i3.17

36. Sadiq HM (2017) Synthesis and Characterization of Novel 1,3-Oxazepine Derivatives From Aminopyrazine. World J. Pharm Pharm Sci., 6(5):186-198. doi:10.20959/wjpps20175-9081

37. Yong RW, Wood KH (1955) J. Am. Chem. Soc., 77: 400-403.

38. Acton QA (2011) Azo Compounds: Advances in Research and Application, Scholarly Paper Edition, Atlanta.

39. Koparir M, Çetin A, Cansiz A (2005) 5-Furan-2yl[1,3,4]oxadiazole-2-thiol, 5-furan-2yl-4h [1,2,4] triazole-3-thiol and their thiol-thione tautomerism. Molecules, 10(2):475-480. doi:10.3390/10020475

40. Rayam P, Polkam N, Kummari B, et al (2019) Synthesis and Biological Evaluation of New Ibuprofen-1,3,4-oxadiazole-1,2,3-triazole Hybrids. J. Heterocycl. Chem., 56(1):296-305. doi:10.1002/jhet.3409

41. Egorove NS (1985) Antibiotics Scientific Approach", Mir. Publishers, Moscow.

