ARTICLE TYPE

Synthesis, Characterization and Screening their Antibacterial Activity of some New Oxazepine and Diazepine Compounds Containing 1,3,4-Oxadiazole Ring Derived from L-Ascorbic Acid

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ABSTRACT

The search involve the synthesis of some new 1,3-oxazepine and 1,3-diazepine derivatives were synthesized from Schiff base. The Schiff base (VIII) prepared from reaction of aldehyde (IV) derived from L-ascorbic acid with aromatic amine ([2-(4-nitrophenyl)-5-(4-aminophenyl)-1,3,4-oxadiazole] (VII). Oxazepine compounds (IX-XI) were synthesized from the cyclic condensation of Schiff base (VIII) with (maleic, phthalic and 3-nitrophthalic) anhydride, compounds (IX-XI) that were reacted with p-methoxyaniline to give diazepine derivatives (XII-XIV). The structures of the new synthesized compounds have been confirmed by physical properties and spectroscopy measurements such as FTIR, and some of them by $^1$H-NMR, $^{13}$C-NMR, Mass, and evaluated their antibacterial activity as (Escherichia Coli (G-), Staphylococcus aureus (G+)).

Keywords: 1,3,4-oxadiazole, Schiff base, 1,3-oxazepine, 1,3-diazepine, L-Ascorbic acid.

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Conflict of interest: None

INTRODUCTION

Vitamin C (ascorbic acid), is a water soluble vitamin used in food and cosmetic industry by modification its properties. Vitamin C antioxidant properties because of its ability of quenching or stabilizing free radicals that lead to degenerative diseases, include cardiovascular, cataracts and cancer. The development of simple synthesis route to widely used organic compounds ring, using readily available reagents is one of the main objectives of organic synthesis. Nitrogen heterocyclic are of a special interest because they constitute an important class of natural and non natural products, many of which exhibit useful biological activities, one–pot efficient synthesis of heterocyclic derivatives, may permit the development of novel therapies for the treatment of epilepsy, pain and other neurodegenerative disorder. The 1,3,4-oxadiazole have anti-microbial activity. They exhibited antifungal and antibacterial activity against the fungi viz. A. niger and C. albicans and bacteria viz. B. subtilis and S. aureus. The compounds containing 1,3,4-oxadiazole unit currently used in clinical medicine are: Raltegravir, an antiretroviral drug and Zibotentan, an anticancer agent. 2,5-Disubstituted 1,3,4-oxadiazoles have also attracted great interest due to their applications in organic light emitting diodes, photoluminescence, polymers and material science. Some Schiff bases bearing aryl groups or heterocyclic residues possess excellent biological activities, which has attracted many researchers’ attention in recent year. They have been reported to be used as analgesic, anthelmintic, antitubercular, plant growth regulator, antiviral, antifungal and anticancer. Oxazepine derivative was introduced in 1965 for use in relief of the psychoneuroses characterized by anxiety and tension; oxazepine is non-homologous seven member ring contain two hetero atoms (oxygen and nitrogen). Oxazepine compounds have medical and biological important and they have medicinal and pharmaceutical application. Among the wide chemical derivatives are a heteropolymer which have activity and effectiveness against cancer, they also are effective against fungi and bacteria. It was found that some oxazepine derivatives are considered a medical drug against the disease. Oxazepine and their derivatives have some important biological pharmacological activities such as enzyme inhibitors, analgesic, antidepressant and psychoactive drugs. Amoxapine is a group of drugs called tricyclic antidepressants. It is used to treat symptoms of depression, anxiety and agitation. Diazepines and derivatives have various therapeutic applications. Many members of the diazepine family are widely used as anticonvulsants, antianxiolitics, analgesics, sedatives, antidepressives and hypnotic agents. Benzodiazepine derivatives are used as dyes for acrylic fibers.
**EXPERIMENTAL**

**Materials**
Whole chemicals have been gained by (BDH, Fluka and Sigma-Aldrich).

**Instruments**
Uncorrected melting points were determined by using Hot-Stage, Gallen Kamp melting point apparatus and DigiMelt MSRS. FT-IR spectra were recorded using KBr discs on FTIR-600 FTIR spectrometer, a Shimazu (IR prestige-21) Fourier Transform Infrared spectrophotometer and Shimadzu FTIR-8400S spectrophotometer at Ibn-Sina company. ¹H-NMR spectra were recorded in DMSO-d_6 on Varian (500 MHz), Inova NMR spectrometer, at University of Kashan, Iran and Brucker BioSpin GmbH (400 MHz), at Tehran University, Iran. ¹³C-NMR spectra were recorded in DMSO-d_6 on Brucker BioSpin GmbH, (75 MHZ), at Tehran University, Iran. The chemical shifts were recorded as values in ppm using tetramethylsilane (TMS) as internal standard. The mass spectra were recorded on Agilent mass spectrometer model 5975CVL MSD at the Tehran University, Iran. Some reactions and the purity of the synthesized compounds were monitored by using TLC (silica gel).

**Preparation of 5,6-O-isopropyldiene-L-AA (I)²⁰**
Dry (HCl) was quickly bubble with moving (20 min) inside a (flask 250ml) including (100ml of dry CH_3COCH_3 & 10g of L-AA). After addition (80ml of C_6H_5OH), moving and refrigeration in an (snow aqueous), decanted has been the supernatant. Washed has been the sediment (4 times) with (154 ml of hexane-acetone) mixture (7:4 v/v), refrigeration in an (snow aqueous) and elimination of supernatant next every addition. The final sediment has been dehydrated beneath miniature pressure to yield (I) (93%) as a white solid, m.p. (210-212 ºC), (lit. 210-212 ºC). R_f (0.69) (methanol: benzene, v/v, 1:1).

**Synthesis of 2,3-O-di(p-chlorobenzoyl)-5,6-O-isopropyldiene-L-AA (II)**
(10g, 46mmol) of compound (I) in dry pyridine (50ml) has been cooled, (15ml, 115mmol) of (p-chlorobenzoyl chloride) was added with moving. The subsequent blend was stirred for (2 hrs), subsequently preserved in murky venue at normal temperature to (22 hrs). Pourd has been the mixture inside (ice water) and moving until (20 min), extracted has been the oil layer by (chloroform 2×150 ml), laundered by water, (HCl 5%) (2×100ml), saturated watery NaHCO_3 (100ml) & water. Dehydrated over anhydrous MgSO_4. Evaporated has been Chloroform. The residue recrystallized from absolute ethanol to give (II) (87%) as a brown solid, m.p. (110-112 ºC). R_f (0.78) (benzene: methanol, v/v, 3:2).

**Synthesis of 2,3-O-di(p-chlorobenzoyl)-L-AA (III)**
(10g, 19.45mmol) of compound (II) was dissolved in blend of (CH_3COOH 65%) (30ml) and (10ml) of (abs. CH_3CH_2OH) and moved until (48 hrs) at normal temperature. The TLC appeared that the interaction has been accomplished (benzene: methanol, 3:2) (v/v). Filter the mixture, (40ml) of a benzene was added to the resulting solution and volatilized (reoccur this procedure four times). The residue recrystallized from absolute ethanol to yield (III) (85%) as a deep brown solid, m.p. (150-152 ºC), R_f (0.58) (benzene: methanol, v/v, 3:2).

**Synthesis of pentulosono-γ-lactone-2,3-enedi(p-chlorobenzoate) (IV)**
A solution of compound (III) (10g, 22mmol) in (abs. CH_3CH_2OH) (60ml) was added dropwise to the solution of (NaIO_4) (4.7g, 22mmol) in distilled water (60ml) at (0 ºC) with stirring. (0.5ml) of (HO-CH_3.CH_2-OH) has been added as dropwise after stirring for (15 min). Stirring was went on at normal temperature for (2 h). (40ml) of distilled water has been added to the mixture after has been filtered subsequently the yield was taken away by (ethyl acetate 3×50ml), the extracts dehydrated via (anhydrous MgSO_4), subsequently filtered and the solvent have been removed and recrystallized has been the residue by chloroform to give the compound (IV) (74%) as a yellow solid, m.p. (198-200 ºC). R_f (0.76) (benzene: methanol, v/v, 3:2).

**Preparation of ethyl 4-nitrobenzoate (V)**
Conc. H_2SO_4 (5 drops) was added dropwise to a solution of 4-nitrobenzoic acid (10mmol) in absolute ethanol (10ml). The mixture was refluxed for (5 hours). After completing reaction, the solvent was removed under reduced pressure. The crude product was extracted with ethyl acetate (2×25ml), the organic layer was washed with saturated solution of sodium hydrogen carbonate, then with distilled water and dried under anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was recrystallized from absolute ethanol to afforded compound (V) as a white crystals, (74%), m.p. (55-59 ºC), (lit. 55-59 ºC).

**Preparation of 4-nitrobenzohydrazide (VI)**
A mixture of (10mmol) of ethyl 4-nitrobenzoate (V), (50mmol) of hydrazine hydrate (80%) and absolute ethanol (10ml) was refluxed for (20 hours). After cooling the solvent and excess hydrazine hydrate were removed under reduced pressure, then recrystallized from absolute ethanol to give (VI) as a brown solid, yield (67%), m.p. (210-214 ºC), (lit. 210-214 ºC).

**Synthesis of 2-(4-nitrophenyl)-5-(4-aminophenyl)-1,3,4-oxadiazole (VII)**
To a mixture of (VI) (3.3mmol) and 4-aminobenzoic acid (3.3mmol) was added phosphorus oxychloride (10ml). The reaction mixture was refluxed at (90-100 ºC) for (5 hours). The reaction mixture was cooled to room temperature, the excess of POCl_3 was concentrated through high vacuum, the residue was quenched with ice and the solid separated was filtered, dried and recrystallized from absolute ethanol to afforded (VII) as a yellow solid, yield (67%), m.p. (250-252 ºC).

**Synthesis of Schiff base [4'-4-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]phenyl-imine]-pentulosono-γ-lactone-2,3-enedi(4-chlorobenzoate)] (VIII)**
A mixture of aldehyde (IV) (0.21g, 0.5mmol), amine (VII) (0.14g, 0.5mmol), DMF (10ml) and 3 drops of glacial acetic
acid was refluxed for (48) hours, the solvent was evaporated and the residue recrystallized from absolute ethanol to product the Schiff base (VIII), as a brown solid, yield (62%), m.p. (250 °dec).

**Synthesis of 1,3-oxazepine compounds (IX-XI)**

A mixture of equimolar amounts (0.3mmol) of Schiff base (VIII) with different acid anhydrides such as (maleic, phthalic and 3-nitrophthalic) anhydride (0.3mmol) in (10ml) of DMF was refluxed for (24) hours. The solvent was removed and the resulting colored solid recrystallized from absolute ethanol to obtained 1,3-oxazepines (IX-XI). The nomenclature and physical properties of 1,3-oxazepines are listed in Table (1).

**Synthesis of 1,3-diazepine compounds (XII-XIV)**

A mixture of equimolar amounts (0.3mmol) of 1,3-oxazepines (XII,XIII,XIV) with 4-methoxyaniline (0.3mmol) in 5ml of DMF was refluxed for (48) hours. The solvent was removed and the resulting colored solid recrystallized from absolute ethanol to obtained 1,3-diazepines (XII-XIV). The nomenclature and physical properties of 1,3-diazepines are given in Table (1).

**ANTIBACTERIAL TEST**

The antibacterial activity of the synthesized compounds was performed according to the agar diffusion method.21 The synthesized compounds were tested against *E.coli* and *Staph. aureus*. Each compounds was dissolved in DMSO to give concentration (0.01 M), the DMSO was used as control. The plates were then incubated at 37 °C and examined after 24 hrs. The zones of inhibition formed were measured in millimeter.

**RESULTS AND DISCUSSION**

In the present work, we report the synthesis of new 1,3-oxazepine and 1,3-diazepine compounds derived from L-ascorbic acid, Schemes (1) and (2). To obtain these compounds starting to prepare the acetal (I) from reaction of L-ascorbic acid with dry acetone in presence of HCl gas, following Salomon method [20], then esterification of (OH) groups at positions C-2 and C-3 for compound (I) by used p-chlorobenzoyl chloride in presence of dry pyridine yielded compound (II). The structure of compounds (I) and (II) were identified by FTIR spectroscopy. The FTIR spectrum of the ester (II) showed disappearance of absorption band belong to (O-H) at (3240 cm⁻¹) for compound (I) and occurrence of absorption band at (1685 cm⁻¹) assigned to (C=O) group of ester (II). Afforded to the glycol (III) from compound (II) by using (65%) of acetic acid, the stirring until (48 hrs) at normal temperature. The structure of the glycol (III) was confirmed by FTIR spectrum which was shown appearance of absorption band at (3415 cm⁻¹) due to hydroxyl groups. Oxidation of the glycol (III) by sodium periodate yielded the aldehyde (IV),...
the FTIR spectrum of compound (IV), Figure (1) and Table (2) showed the following band at (1728 cm$^{-1}$) assigned to (C=O) aldehydic. This compound (IV) appeared a positive Tolen’s test by forming a mirror of silver.\textsuperscript{22} The $^1$H-NMR spectrum of compound (IV) in DMSO-d$_6$, Figure (2) showed the following signals: signal at \(\delta(4)\) ppm for one proton of lactone ring (H-4), doublet doublet signals at \(\delta(7.56-7.99)\) ppm for aromatic protons, signal at \(\delta(13.19)\) ppm for one proton of (C-H) aldehydic. The $^{13}$C-NMR spectrum of compound (IV) in DMSO-d$_6$ Figure (3) showed signal at \(\delta(166.92)\) ppm for carbon of (C=O) of the lactone ring and ester, signal at \(\delta(138.26)\) ppm for C-3, signals at \(\delta(129.20-131.60)\) ppm for aromatic carbons and C-2. The signal of C-4 with signals of DMSO-d$_6$, and the signal of aldehydic carbonyl was disappeared due it showed out of the scale.\textsuperscript{23}

Oxadiazole (VII) was synthesized from the reaction of acid hydrazide with 4-aminobenzoic acid in presence of POCl$_3$. While the acid hydrazide (VI) which obtained from ethyl benzoate and hydrazine hydrate. The ethyl benzoate (V) formed by the condensation of benzoic acid and ethanol in presence of sulphuric acid as a catalyst. These compounds (V-VII) were characterized by FTIR spectroscopy and the characteristic absorption bands were listed in Table (2) while compound (VII) characterized by FTIR, $^1$H-NMR and mass spectroscopy, Figure (4) showed the FTIR spectrum.

The $^1$H-NMR spectrurn of compound (VII) (in DMSO-d$_6$ as solvent), Figure (5) showed a singlet signal at \(\delta(11.05)\) ppm for two protons of NH$_2$ group, and a complicated signals between in the region \(\delta(7.74-8.51)\) ppm due to eight of aromatic protons. The mass spectrum of compound (VII), Figure (6) showed exhibited m/z = 282.
Table 2: FTIR spectral data of compounds (I-VIII)

<table>
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<th>Comp. no.</th>
<th>$\nu$ NH$_2$</th>
<th>$\nu$ C-H$_{ar}$</th>
<th>$\nu$ C-H$_{al}$</th>
<th>$\nu$ C=O$_{ar}$</th>
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<td>-</td>
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<td>-</td>
<td>1654</td>
<td>1635</td>
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Figure 2: $^1$H-NMR spectrum of aldehyde (IV)

Figure 3: $^{13}$C-NMR spectrum of aldehyde (IV)
The new Schiff base (VIII) was synthesized by refluxing equimolar of aldehyde (IV) derived from L-ascorbic acid with amine (VII) in DMF as a solvent with some drops of glacial acetic acid (GAA). This Schiff base (VIII) was identified by FTIR, $^1$H-NMR and mass spectroscopy. FTIR absorption spectrum, Figure (7) showed the disappearance of absorption bands due to NH$_2$ and C=O groups of the starting materials together with appearance of new absorption band in the region (1635) cm$^{-1}$ which is assigned to azomethine group. The other FTIR spectral data were listed in Table (2).

$^1$H-NMR spectrum in DMSO-d$_6$ of (VIII), Figure (8) showed a signal at $\delta$(11) ppm for one proton of imine group (CH=N), and a complicated signals between in the region $\delta$(7.57-8.52) ppm that could be attributed to the aromatic protons. One signal at $\delta$(3.47) ppm for proton of lactone ring.
The mass spectrum of Schiff base (VIII), Figure (9) exhibited m/z = 685.

Oxazepine derivatives (IX-XI) were synthesized from cycloaddition reaction of Schiff base (VIII) with different acid anhydrides such as (maleic, phthalic and 3-nitrophthalic) anhydride in DMF as a solvent. The mechanism of the reaction is shown in Scheme (3).

The mechanism involves the addition of one σ-carbonyl to π-bond (N=C) to give 4-membered cyclic and 5-membered cyclic ring of anhydride in the same transition state [T.S.] a, which opens into (maleic, phthalic and 3-nitrophthalic) anhydride to give 7-membered cyclic ring 1,3-oxazepine [C]. The oxazepine compounds (IX-XI) were identified by FTIR and $^1$H-NMR spectroscopy for compound (X). The FTIR spectra indicated bands at (1710-1712) cm$^{-1}$ for lactone and (1662-1664) cm$^{-1}$ for lactam and evanescence of absorption band at (1635) cm$^{-1}$ for (C=N) of Schiff base (VIII), Figures (10), (11), (12) showed the FTIR spectrum for compounds (IX-XI). The other FTIR spectral data for compounds (IX-XI) are listed in Table (3).

The $^1$H-NMR spectrum for compound (X), Figure (13) showed the following signals: signal at δ(4.02) ppm for

![Scheme 3: The mechanism of formation of 1,3-oxazepine](image)

![Figure 9: Mass spectrum of Schiff base (VIII)](image)

![Figure 10: FTIR spectrum of compound (IX)](image)
Table 3: FTIR spectral data of compounds (IX-XIV)

<table>
<thead>
<tr>
<th>Comp. no.</th>
<th>ν C-H_ar</th>
<th>ν C-H_al</th>
<th>ν C=O_lact</th>
<th>ν C=O_lactam</th>
<th>ν C=O_car</th>
<th>ν C=C</th>
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<td>-</td>
<td>1712</td>
<td>1664</td>
<td>1647</td>
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<td>ν C-NO₂: 1517, 1338 ν C-Cl: 1088</td>
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<tr>
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<td>3103</td>
<td>-</td>
<td>1710</td>
<td>1662</td>
<td>1637</td>
<td>1597</td>
<td>ν C-NO₂: 1517, 1340 ν C-Cl: 1070</td>
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<td>XI</td>
<td>3101</td>
<td>2927</td>
<td>1710</td>
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<td>1597</td>
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<td>-</td>
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<td>ν C-NO₂: 1517, 1344 ν C-Cl: 1091</td>
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Figure 11: FTIR spectrum of compound (X)

Figure 12: FTIR spectrum of compound (XI)
one proton of lactone ring, signal at δ(6) ppm for proton of oxazepine ring and multiplet signals at δ(7.13-8.81) ppm for aromatic protons.

Diazepine derivatives (XII-XIV) were obtained from compounds (IX-XI) that were reacted with primary aromatic amines in presence of DMF as a solvent. The structures of the new synthesized compounds (XII-XIV) have been confirmed by FTIR, 1H-NMR of compound (XIII). The FTIR spectrum of compound (XIII), Figures (14), (15) and (16) showed the appearances of new characteristic bands at (1708-1710) cm\(^{-1}\) related to stretching vibration band for lactam group. The other FTIR spectral data for compounds (XII-XIV) are given in Table (3).

Furthermore, 1H-NMR spectrum of compound (XIII), Figure (17) (in DMSO-d\(_6\) as solvent) showed the following signals: singlet signal at δ(3.67) ppm for (3H, methoxy group), signal at δ(3.80) ppm for one proton of lactone ring, signal at δ(5.82) ppm for proton of diazepine ring and multiplet signals at δ(6.50-8.45) ppm for aromatic protons.

**Antibacterial activity**

The results of antibacterial activities of synthesized compounds are represented in Table (4). All the compounds exhibit the moderate or low biological activity against only one of the organisms. All compounds showed good inhibition against of the one types of the bacteria (G+).
Figure 15: FTIR spectrum of compound (XIII)

Figure 16: FTIR spectrum of compound (XIV)

Table 4: Antibacterial activity of the synthesized compounds (IV-XIV)

<table>
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<th>Comp. no.</th>
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<th>Staph. aureus (G+)</th>
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CONCLUSION

New compounds of 1,3-oxazepine were synthesized from reaction of Schiff base with (maleic, phthalic, 3-nitrophthalic) anhydride. 1,3-Diazepine compounds were prepared by treatment of 1,3-oxazepine derivatives with 4-methoxyaniline. All new compounds were characterized by different spectral studies and evaluated their antibacterial activity against two types of bacteria *E. Coli* and *Staph. aureus*.

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