




Original Article

## Synthesis, Characterization, and Antibacterial Activity of Some New Oxazepine Derivatives

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### ABSTRACT

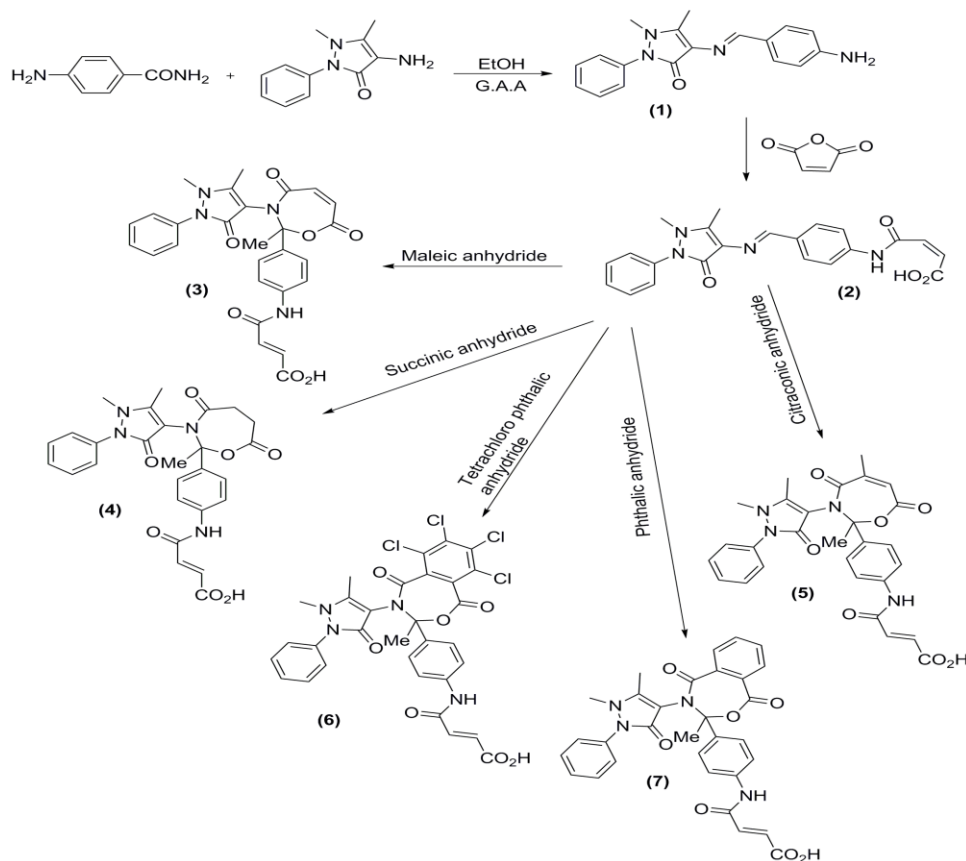
In this work, new 1,3-oxazepine derivatives were synthesized from a Schiff base. The latter was prepared by reacting 4-amino antipyrine with 4-amino acetophenone, then the Schiff base, which has an amine group, reacted with maleic anhydride to produce the corresponding amic acid. The prepared amic acid compound has an azomethine group utilized in synthesizing new derivatives of 1,3-oxazepine through reacting the amic acid with different cyclic anhydrides (succinic anhydride, maleic anhydride, phthalic anhydride, tetrachlorophthalic anhydride, and citraconic anhydride). Different techniques have been used to confirm the structures of synthesized compounds in terms of physical properties and spectroscopic measurements, where proton nuclear magnetic resonance <sup>1</sup>H-NMR and Fourier Transform Infrared FT-IR spectroscopies have been used to confirm the synthesized compounds. In addition, the antibacterial activity of oxazepinederivatives was examined against two types of bacteria, gram-negative and gram-positive.

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## GRAPHICAL ABSTRACT



## Introduction

Oxazepine is an organic molecule with a seven-membered, unsaturated, and non-homologous ring that contains two heteroatoms [1]; oxygen and nitrogen. Several isomers can be attributed to oxazepine based on the locations of the nitrogen and oxygen atoms in its structure. 1,3-oxazepine, for example, is an isomer of oxazepane with the oxygen atom at the first position and the nitrogen atom at third the position [2, 3].

The synthesized oxazepine derivatives have been subjected to many studies for decades. These compounds are very useful in medicine since they have diverse biological functions [4-7]. Nitrogen heterocyclic compounds are particularly important since they represent a large class of natural and synthetic compounds, many of which have beneficial biological properties.

The ability to synthesize heterocyclic compounds might lead to the creation of new drugs. In 1965, an oxazepine derivative was approved for the treatment of treating psychoneuroses characterized by anxiety and tension [8-11].

Oxazepine molecules can be synthesized using a variety of ways. On the other hand, the reaction of imine groups with cyclic anhydrides, is a convenient and efficient technique for generating oxazepinerings [12-16]. In this work, the new derivatives compounds of oxazepine were synthesized with antipyrine moiety by the reaction of new prepared molecules, which possess an imine group with five different cyclic anhydrides.

## Materials and Methods

All the chemicals were acquired from Sigma and CDH suppliers, which were used without further purification. However, the Gallen Kamp capillary melting point apparatus was used to determine prepared compounds' the melting points which were not corrected. Moreover, Shimadzu FT-IR-8400 of Fourier Transform Infrared spectrophotometer was utilized to record the FTIR spectra, whereas Bruker 400 MHz of nuclear magnetic resonance was used to record  $^1\text{H-NMR}$  spectra of the prepared compounds.

### Synthesis of Schiff base (1)

Schiff base was synthesized from the reaction of 4-amino antipyrine and *p*-amino acetophenone, in which 0.01 mol of 4-amino acetophenone was placed in a round bottom flask after dissolving it in an absolute ethanol solvent (25 mL) and followed by adding three drops of glacial acetic acid, the solution was heated with stirring after adding 0.01 mol of 4-amino antipyrine dissolved in ethanol in batches with stirring, and the mixture refluxed for two hours. The formed precipitate was filtered and washed with cold ethanol [17].

### Synthesis of amic acid (2)

Amic acid was synthesized by the reaction of (0.001 moles) amino Schiff base (1) and (0.001 moles) maleic anhydride dissolved in acetone and stirring the mixture for 1.5 hours; the formed solid product was filtered and washed with acetone. Then recrystallization by dissolving in bicarbonate solution then precipitating with hydrochloric acid. After that, the filtered formed solid was washed with deionized water and dried [7].

### Synthesis of 1,3-oxazepine (3-7)

Derivatives of oxazepine were synthesized by reacting the prepared Schiff base (2) with different cyclic anhydrides, namely, maleic anhydride, succinic anhydride, phthalic anhydride, tetrachlorophthalic anhydride, and citraconic anhydride). (0.01 mole) from each compound were dissolved in 30 mL of tetrahydrofuran THF and refluxed for 14-16 hrs. After that, the solvent was evaporated under a

vacuum, and the precipitate was collected and recrystallized from chloroform [12]. The structures of the synthesized compounds of oxazepine derivatives were illustrated in Scheme 1, whereas the physical properties of the synthesized compounds were listed in Table 1.

### Antibacterial measurements

The antibacterial activity was assessed using the Mueller-Hinton agar well diffusion technique, with working zones in millimeters (mm) filled with 100  $\mu$ L of test samples and incubated at 37  $^{\circ}$ C for one day. The diameter of the inhibitory zones was measured using a ruler after incubation. The inhibition regions were obvious and surrounded the injection sites of the samples with no bacterial growth.

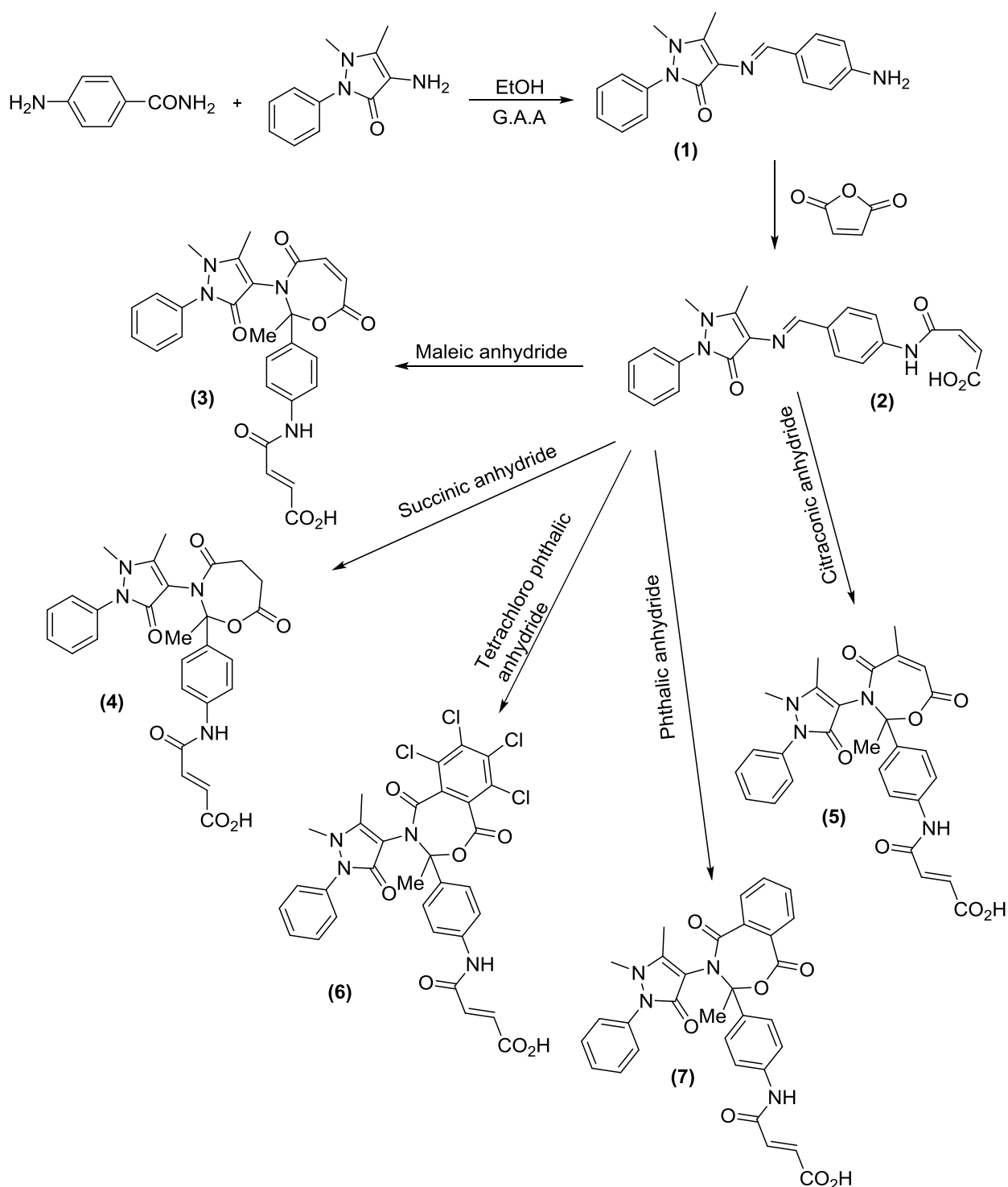
## Results and Discussion

### Infrared spectroscopic analysis (FT-IR)

The absorption values of the major groups contained in the produced compounds were revealed by studying the infrared spectra of the compounds, where the imine group appeared clearly in compound (1) at 1587  $\text{cm}^{-1}$ , and the stretching frequencies at 1653  $\text{cm}^{-1}$  are due to C=O groups of antipyrine ring, and the stretching vibrations of amine group appear at 3336 and 3217  $\text{cm}^{-1}$  [18]. The reaction of compound (1) with maleic anhydride leads to the appearance of new frequencies in the chart at 2500-3203  $\text{cm}^{-1}$ , 1715  $\text{cm}^{-1}$ , and 1678  $\text{cm}^{-1}$  due to O-H carboxylic, C=O amide and C=O carboxylic group, respectively, in addition to the frequencies at 1654  $\text{cm}^{-1}$  due to C=O of antipyrine ring.

**Table 1:** The physical properties of prepared compounds

No.	Color	Melting point	Yield (%)
1	Dark red	Gummy	92
2	Yellow	126-128 $^{\circ}$ C	90
3	Pale brown	120-122 $^{\circ}$ C	88
4	Yellow	Gummy	83
5	Brown	65-67 $^{\circ}$ C	80
6	Pale yellow	152-155 $^{\circ}$ C	87
7	Brown	91-93 $^{\circ}$ C	85



**Scheme 1:** Synthesis processes of oxazepine derivatives

For compounds (3-7), the stretching band of the imine group disappeared, and new (lactam/lactone) groups of oxazepine appeared at 1788-1699  $\text{cm}^{-1}$ , beside other bands at 1678-1650 and 1718-1670  $\text{cm}^{-1}$  due to C=O of amide and carboxylic acid group, respectively [19]. The main absorption FT-IR bands of the main functional groups of the prepared compounds were listed in Table 2.

#### Nuclear magnetic resonance $^1\text{H-NMR}$ spectroscopic analysis

The DMSO- $d_6$  solvent was used to dissolve the prepared compounds to record the  $^1\text{H-NMR}$  spectra. Table 3 contains the result of  $^1\text{H-NMR}$  chemical shifting in ppm for some compounds and polymers prepared.

**Table 2:** Infrared spectroscopic absorption bands for the prepared compounds

Comp. No.	$\nu(\text{N-H})$ $\nu(\text{O-H})$	$\nu(\text{C-H})$	$\nu(\text{C=O})$ Lactone Lactam	$\nu(\text{C=O})$ antipyrene	$\nu(\text{C=O})$ Amide	$\nu(\text{C=O})$ Carbox.	$\nu(\text{C=N})$
1	3336 3215	3074 2960	-	1653	-	-	1593
2	3271 3203	3063 2879	-	1654	1678	1714	1587
3	3414 3263	3065 2985	1778 1718	1629	1655	1670	-
4	3137 3110	3014 2987	1730 1699	1635	1655	1683	-
5	3348 3244	3055 2997	1788 1720	1635	1650	1680	-
6	3210 3183	3070 2974	1786 1720	1635	1672	1683	-
7	3271 3201	3059 2991	1788 1718	1633	1678	1718	-

**Table 3:**  $^1\text{H-NMR}$  chemical shifting in (ppm) for the prepared compounds

Comp. No.	$^1\text{H-NMR}$ chemical shifting in ppm
3	(s, 2.17, $\text{CH}_3$ ), (s, 6.01, CH) of oxazepine ring, (s, 2.53, $\text{CH}_3$ ), and (s, 3.03, $\text{CH}_3$ ) for five-member antipyrene ring, (d, 6.32, CH), (d, 6.47, CH) of vinylic proton, (m, 6.96–7.95, CH) for aromatic rings, (s, 10.7, NH) of amide and (s, 12.8, OH) of carboxylic group.
4	(s, 2.175, $\text{CH}_3$ ), (m, 2.61, $\text{CH}_2$ ), of oxazepine ring, (s, 2.5, $\text{CH}_3$ ), and (s, 3.07, $\text{CH}_3$ ) for five-member antipyrene ring, (d, 6.33, CH), (d, 6.48, CH) of vinylic protons ring, (m, 7.21–7.96, CH) of aromatic rings, (s, 10.64, NH) of amide and (s, 12.38, OH) of carboxylic group [19].
5	(s, 1.75, $\text{CH}_3$ ), (s, 2.18, $\text{CH}_3$ ), (s, 2.61, CH), of oxazepine ring, (s, 2.51, $\text{CH}_3$ ), and (s, 3.06, $\text{CH}_3$ ) for five-member antipyrene ring, (d, 6.32, CH), (d, 6.48, CH) of vinylic protons ring, (m, 7.31–7.96, CH) of aromatic rings, (s, 10.65, NH) of amide and (s, 13.11, OH) of carboxylic group.
6	(s, 2.19, $\text{CH}_3$ ), of oxazepine ring, (s, 2.53, $\text{CH}_3$ ), and (s, 2.73, $\text{CH}_3$ ) for five-member antipyrene ring, (d, 6.19, CH), (d, 6.62, CH) of vinylic protons ring, (m, 7.21–8.14, CH) of aromatic rings, (s, 10.55, NH) of amide and (s, 12.91, OH) of carboxylic group [20].
7	(s, 2.18, $\text{CH}_3$ ), of oxazepine ring, (s, 2.51, $\text{CH}_3$ ), and (s, 2.64, $\text{CH}_3$ ) for five-member antipyrene ring, (d, 6.23, CH), (d, 6.52, CH) of vinylic protons ring, (m, 7.1–8.13, CH) of aromatic rings, (s, 10.65, NH) of amide and (s, 13.25, OH) of carboxylic group

### Solubility of synthesized compounds

The prepared compounds (3-7) have good solubility in different organic solvents, as they dissolved in (ethanol, methanol, THF, DMSO and DMF); however, they were undissolved in (water, benzene, ether, and acetone).

### Antibacterial activity of synthesized compounds

One of the wide spectra of applications that oxazepine compounds possess is the noticeable antibacterial activity. The antibacterial activity of synthesized oxazepane was tested by studying these activities against two types of bacteria:

gram-negative (*Escherichia coli*) and gram-positive (*Staphylococcus aureus*), utilizing the well diffusion approach, which includes tracking the level of inhibition of these compounds by

using the lowest inhibitor concentration. From the results in Table 4, the compounds (7) exhibited the best activity against gram-positive and gram-negative bacteria.

**Table 4:** Antibacterial activities for the prepared compounds (3-7)

Comp. No.	Inhibition zone (mm)	
	<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>
3	20	15
4	15	15
5	17	15
6	18	12
7	24	20

## Conclusion

New derivatives of 1,3-oxazepine compounds were successfully synthesized by many steps, including preparing a Schiff base from 4-aminoantipyrine and 4-amino acetophenone, which was used later to prepare the amic acid that possesses the imine group, which is necessary for synthesizing the targeted new compounds. The amic acid reacted with five different cyclic anhydrides to produce 1,3-oxazepine derivatives. The prepared compounds have been characterized using spectroscopic techniques such as FTIR and <sup>1</sup>HNMR, whereas the physical properties have been determined for all the prepared compounds. While the prepared compounds have exhibited noticeable antibacterial activities, compound (7) showed the highest activity, which indicates promising biological applications.

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## Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

## Conflict of Interest

There are no conflicts of interest in this study.

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