Antibacterial Study of Some Oxazepine Derivatives

Ahmed Ahmed[*], Sarah Mahdi[*], Anwar Hussein[**], Ayad Hamed[***] and Emad Yousif[*]
[*]Department of Chemistry, College of Science, Al-Nahrain University, Baghdad-Iraq.
[**]Central Organization for Standardization and Quality Control, Baghdad-Iraq.
[***]Department of Chemistry, College of Education, Tikrit University, Tikrit-Iraq.

Abstract

Compounds containing 1,3-oxazepine and 1,3,4-oxadiazole (5)-(8) were synthesized by microwave assisted organic synthesis method through the condensation reaction of compounds (1 to 4) with phthalic anhydride respectively. The structure of the synthesized compounds were characterized by spectroscopic methods (^{1}H NMR, FTIR). The synthesized compounds were screened for their antibacterial activity disc diffusion method.

Keywords: 1,3-oxazepine, 1,3,4-oxadiazole, microwave synthesis, antibacterial activity.

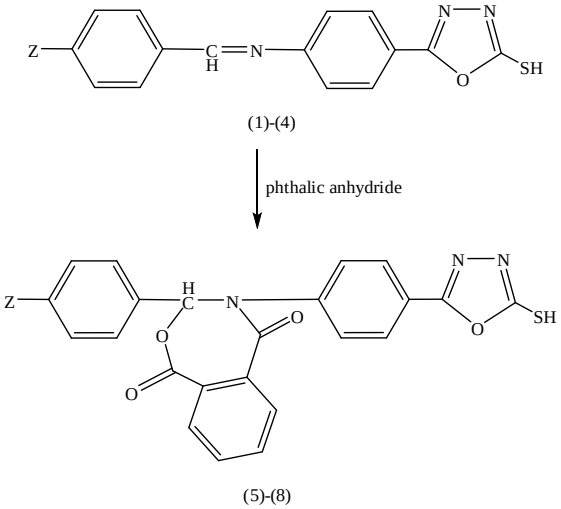
Introduction

Oxazepine derivative was introduced in 1965 for use in relief of the psychoneuroses characterized by anxiety and tension; oxazepam is non-homologous seven member ring contain two hetero atoms (oxygen and nitrogen) [1]. Oxazepine derivatives have medical and biological importance and they have medicinal and pharmaceutical application [2], they also are effective against fungi and bacteria [3]. Oxazepine compounds are considered a medical drug against the disease [4]. Oxazepine are found to be effective against anxiety and associated with schizophrenia [5]. 1,3,4-Oxadiazole is a heterocyclic compound containing an oxygen atom and two nitrogen atoms in a five-membered ring. It is derived from furan by substitution of two methylene groups (=CH) with two pyridine type nitrogens (-N=) [6,7]. There are three known isomers: 1,2,4-oxadiazole, 1,2,3-oxadiazole and 1,2,5-oxadiazole. However, 1,3,4-oxadiazole and 1,2,4-oxadiazole are better known, and more widely studied by researchers because of their many important chemical and biological properties. Among heterocyclic compounds, 1,3,4-oxadiazole has become an important construction motif for the development of new drugs. Compounds containing1,3,4-oxadiazole cores have a broad biological activity spectrum including antibacterial, antifungal, analgesic, anti-inflammatory, antiviral, anticancer, antihypertensive, anticonvulsant, and anti-diabetic properties [8,9].

Experimental

Organic synthesis part

The FTIR spectra were recorded on Perkins-Elmer Fourier-Transform Infrared Spectrophotometer as potassium bromide pelts. H^1 NMR spectra were performed on a Bruker ultra shield (300) MHz, Switzerland spectrometer using D^6-DMSO as solvent and TMS as internal standard. All the chemicals used in this research (solid, liquid) were obtained from Fluka, BDH and Merck companies.



compound No.	Z
(1), (5)	4-OH
(3), (6)	4-N(CH$_3$)$_2$
(4), (7)	4-H
(5), (8)	4-Cl

Fig.(1): The synthesis route for the compounds (5)-(8).

General procedure for the synthesis of the compounds (5)-(8) [10]

3-(4-hydroxyphenyl)-4-(4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)-3,4-dihydro-benzo[*e*][1,3]oxazepine-1,5-dione (5).

3-(4-(dimethylamino)phenyl)-4-(4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)-3,4-di-hydrobenzo[*e*][1,3]oxazepine-1,5-dione (6).

4-(4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)-3-phenyl-3,4-dihydrobenzo[*e*][1,3] oxazepine-1,5-dione (7).

3-(4-chlorophenyl)-4-(4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)-3,4-dihydro-benzo[*e*][1,3]oxazepine-1,5-dione (8).

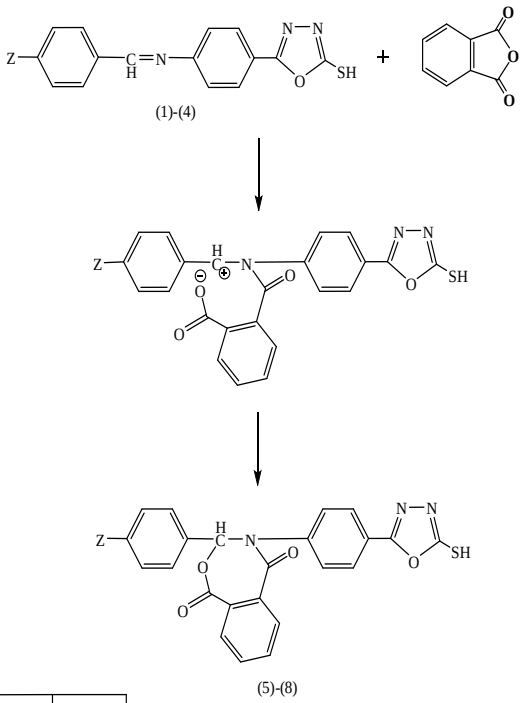
A mixture of (0.001 mole) of compounds (1) and (0.001 mole) of phthalic anhydride were ground with a mortar, mixed, dried and subjected to microwave irradiation for (2-3) minutes, after completion the reaction mixture was cooled to room temperature and the solid obtained was recrystallized twice from absolute ethanol.

Table (1)
Physical properties of the compounds (5)-(8).

Compounds	*Z*	*Yie-ld %*	*Molecular formula*
(5)	-OH	81	$C_{23}H_{16}N_3O_5S$
(6)	$-N(CH_3)_2$	77	$C_{25}H_{21}N_4O_4S$
(7)	-H	91	$C_{23}H_{15}N_3O_4S$
(8)	-Cl	84	$C_{23}H_{15}N_3O_4SCl$

Results and Discussion

The four new compounds of 1,3-oxazepines (5)-(8) were prepared in good yields through the cyclo addition reactions of compounds (1)-(4) with phthalic anhydride under microwave irradiation using a domestic microwave oven, the optimum period of reaction time was found to be (2-3) min.



compound No.	Z
(1), (5)	4-OH
(2), (6)	$4\text{-}N(CH_3)_2$
(3), (7)	4-H
(4), (8)	4-Cl

Fig.(2): The mechanism for the synthesis of oxazepine.

The structures of these four compounds were characterized by spectral data, the FTIR-spectra of these compounds shows the appearance of the absorption bands at (1704-1610) cm^{-1} characteristic to (C=O) of (lactone -lactam), and the disappearing the two absorption bands at (1950-1800) cm^{-1} of the pure phthalic anhydride.

The H^1-NMR spectrum of compounds (5)-(8) showed the following characteristic signals.

Table (2)
The FTIR data of the compounds (5)-(8).

compounds	Z	FTIR spectral data (cm^{-1})					
		C=O str. Lacton, Lactam	C=N	C=C-CO- Str. cyclic	C-O-O Sym., Asym.	C-H Arom.	Others
(5)	-OH	1680, 1665	1587	1610	1060, 1177	3094	3022 (O-H) str.
(6)	$-N(CH_3)_2$	1700, 1637	1593	1613	1169, 1086	3092	2905 (C-H aliph.)
(7)	-H	1690, 1615	1590	1602	1038, 1175	3078	-
(8)	-Cl	1719, 1668	1599	1607	1172, 1099	3089	693 (C-Cl)

Table (3)
The ^1H NMR data of the compounds (5)-(8).

compounds	Proton values (δ, ppm)				
	C-H (aromatic)	O-H	S-H	O-CH-N	Others
(5)	6.68-8.23	9.43	3.00	7.35	-
(6)	6.69-8.23	-	3.00	7.35	$N(CH_3)_2$ 3.06
(7)	7.36-8.23	-	3.00	7.35	-
(8)	7.30-8.23		3.00	7.35	-

Antimicrobial Evaluation

Microorganisms have existed on the earth for more than 3.8 billion years and exhibit the greatest genetic and metabolic diversity. They are an essential component of the biosphere and serve an important role in the maintenance and sustainability of ecosystems. It is believed that they compose about 50% of the living biomass. In order to survive, they have evolved mechanisms that enable them to respond to selective pressure exerted by various environments and competitive challenges. The disease-causing microorganisms have particularly been vulnerable toman's selfishness for survival who has sought to deprive them of their habitat using antimicrobial agents. These microorganisms have responded by developing resistance mechanisms to fight off this offensive. Currently antimicrobial resistance among bacteria, viruses, parasites, and other disease-causing organisms is a serious threat to infectious disease management globally [11].

In order to appreciate the mechanisms of resistance, it is important to understand how antimicrobial agents act. Antimicrobial agents act selectively on vital microbial functions with minimal effects or without affecting host functions. Different antimicrobial agents act in different ways. The understanding of these mechanisms as well as the chemical nature of the antimicrobial agents is crucial in the understanding of the ways how resistance against them develops. However, the mechanism of action of antimicrobial agents can be categorized further based on the structure of the bacteria or the function that is affected by the agents. These include generally the following:

- Inhibition of the cell wall synthesis Inhibition of ribosome function.
- Inhibition of nucleic acid synthesis.
- Inhibition of folate metabolism.
- Inhibition of cell membrane function.

Microorganisms were increasingly becoming resistant to ensure their survival against the arsenal of antimicrobial agents to which they were being bombarded. They achieved this through different means but primarily based on the chemical structure of the antimicrobial agent and the mechanisms

through which the agents acted. The resistance mechanisms therefore depend on which specific pathways are inhibited by the drugs and the alternative ways available for those pathways that the organisms can modify to get a way around in order to survive [12,13].

Resistance can be described in two ways:

I) intrinsic or natural whereby microorganisms naturally do not posses target sites for the drugs and therefore the drug does not affect them or they naturally have low permeability to those agents because of the differences in the chemical nature of the drug and the microbial membrane structures especially for those that require entry into themicrobial cell in order to effect their action or.

II) acquired resistance whereby a naturally susceptible microorganism acquires ways of not being affected by the drug.

Acquired resistance mechanisms can occur through various ways, Fig.(3).

The biological activity of the compounds (5)-(8) against *E.Coli* and *Staph. aurous* was studied.

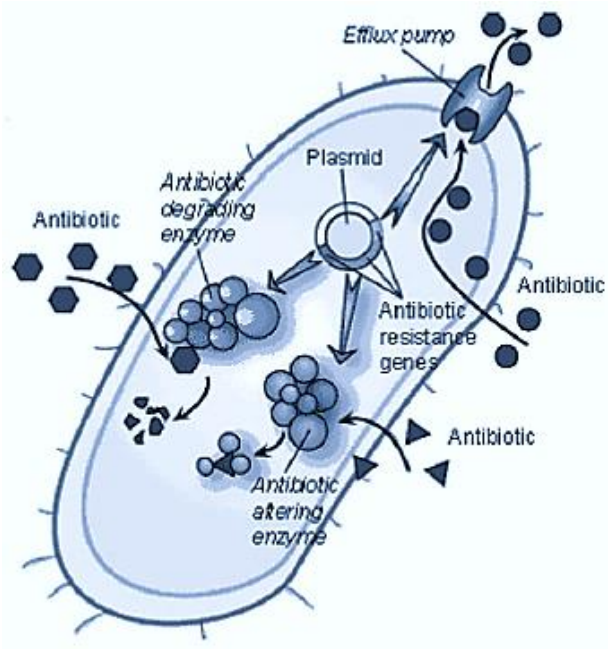


Fig.(3): Illustration of how some antimicrobial agents are rendered ineffective [14].

Table (3)
Antibacterial activities of the compounds (5)-(8).

Compounds	*Escherichia coli*	*Staphococcus aureus*
(5)	+	+
(6)	++	+
(7)	-	±
(8)	±	+

Note: (-): No inhibition, (±) = 6-9 mm, (+) =10-14 mm, (++): 15-22 mm.

Conclusion

Among the synthesized compounds, (5), (6) were found to have a strong antibacterial activity. Compounds (7), (8) were found to have promising antimicrobial activity.

Acknowledgments

We are grateful the support provided by Al-Nahrain University, Central Organization for Standardization and Quality Control and Tikrit University.

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الخلاصة

تم مركبات عضوية تحتوي على ٣،١ – اوكسازبين و ١, ٣, ٤ – اوكساديازول (٥)–(٨) تم تحضيرها بواسطة طريقة التخليق العضوي باستخدام تقنية المايكرويف من خلال تفاعل التكثيف للمركبات (١) و(٢) و(٣) و(٤) مع انهيدريد الفثالك بالتتابع. تم تشخيص تراكيب المركبات المحضرة بواسطة تقنيتي (طيف الاشعة تحت الحمراء و طيف الرنين النووي المغناطيسي للبروتون). تم فحص الفعالية المضادة للجراثيم باستخدام طريقة الانتشار بواسطة الاقراص.

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