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A review on synthesis and biological screening of oxazepinedione derivatives

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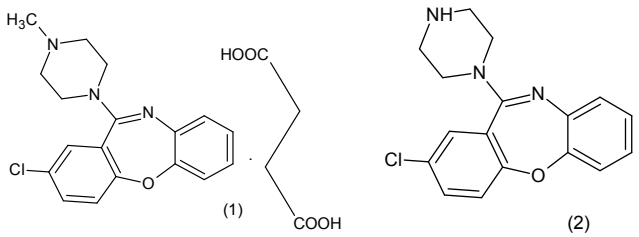
ABSTRACT
At present a number of drugs with various mechanism of action are available for the pharmacotherapy of psychopharmacological disorders. Among them, the most important are dibenzoxazepine and benzodiazepine derivatives. Important drugs contain oxazepine rings are amoxapine and loxapine which are used as typical antipsychotic agents. Oxazepines are seven membered heterocyclic compounds which contribute to various important activities. Nowadays a wide variety of Oxazepinediones derivatives are synthesized and biologically screened for anticancer, antimicrobial and enzymatic activities etc. Oxazepinediones are commonly synthesized by cycloaddition reaction with schiff base and various anhydride (phthalic anhydride/ maleic anhydride/ succinic anhydride) or haloacids.
Keywords: *Oxazepinedione, schiff base, phthalic anhydride, maleic anhydride, succinic anhydride, haloacids.*

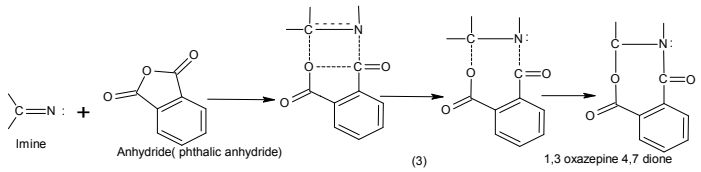
1. INTRODUCTION
Heterocyclic chemistry is the branch of chemistry dealing with the synthesis, properties and applications of heterocyclic compound. Heterocyclic compounds are considered cyclic structures that contain at least two different atoms as members of its ring. Most of the potent and biologically active medicinal agents contain a ring with nitrogen and oxygen as the special atom. Oxazepine is a heterocyclic seven membered compound containing five carbon atoms, one nitrogen atom and one oxygen atom with three double bonds. Oxazepine and their derivatives have various biological and pharmacological activities such as enzyme inhibition, antidepressants, analgesics, and anti-psychoactive drugs. Commonly, the oxazepine derivatives are used as psychopharmacological agents such as dibenzoxazepine.



For example, loxapine succinate (1) is frequently used as typical antipsychotic agent and amoxapine (2) is used as antidepressant and in the management of schizophrenia. In animals amoxapine reduce the uptake of nor epinephrine and serotonin and blocked the response of dopamine receptors (D_1, D_2, D_3, D_4, D_5) to dopamine.

2. CHEMISTRY MECHANISM
One of the novel derivatives of oxazepine are the oxazepinediones. Cycloaddition is the mechanism behind the synthesis of oxazepinedione. Cyclo addition is a type of pericyclic reaction, where pericyclic reaction is often proceed by nearly simultaneous reorganization of bonding electron pairs by the way of cyclic transition states and the reaction progresses in a concerted fashion way. Oxazepinedione is commonly synthesized by the reaction of equimolar quantities of Schiff's bases with acid halides or anhydride (e.g.: phthalic anhydride / maleic anhydride/ succinic anhydride etc.) to give the corresponding macrocyclic seven membered oxazepine derivatives. Schiff base or imines (C=N) are double bonded compounds synthesized by the condensation reaction between an aromatic aldehyde and aromatic amine with the removal of water molecule. Therefore, it is expected that the synthesized Schiff base would react with various anhydrides. It was classified as a 5+2→7, cycloaddition reaction, containing a 5-atoms component of anhydride and 2-atoms component of Schiff base leading to 7-membered cyclic ring, the mechanism involved will be written as follows.

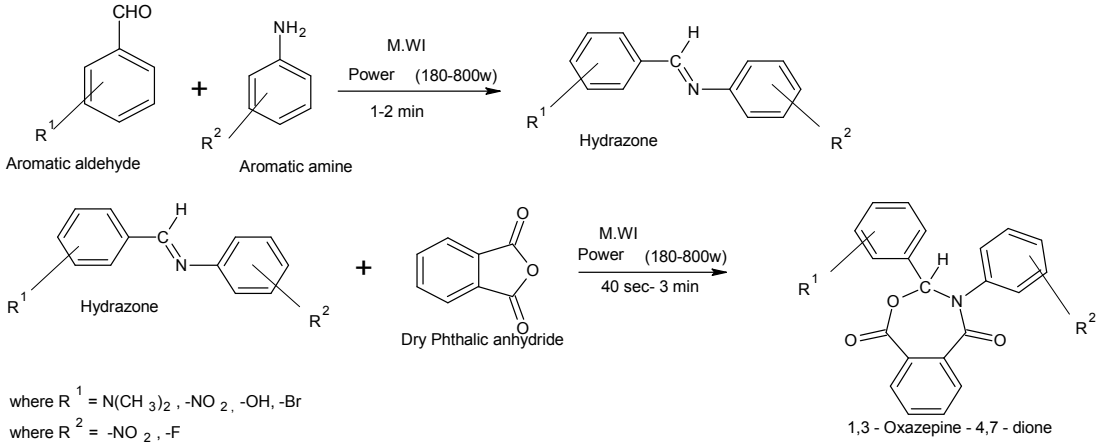
The mechanism (3) involves the addition of one σ-carbonyl to π-bond (N=C) to give 4- membered cyclic and 5-membered cyclic ring of anhydride in the same transition state, which opens into various anhydride (e.g.: phthalic anhydride) to a give a 7-membered cyclic ring 1,3-oxazepine 4,7 dione. Compared to other derivatives of oxazepine much less studies are so far conducted for oxazepinediones. It includes antimicrobial studies, antitumor activity and anticorrosive studies



2.1. Synthesis of various oxazepinedione derivates.
Abed M. Daher Al-Jibory *et al.,* in 2013 carried out a study on the topic "The modern Microwave technique used to synthesis new derivatives of 1, 3 – Oxazepine – 4, 7 - dione compounds" [1].

In this research, they took direct reaction line between the aromatic aldehydes and aromatics amines for a reaction in the Microwave technique to obtain clean and safe chemistry with very short time and high yield and purity,comparative to the thermal method.

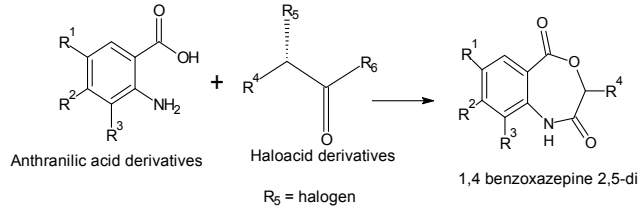
The above compounds allowed to react to produce (hydrazone) or which named (Schiff bases) compounds. The last step is the cyclization step, done by irradiation with Microwave and by reaction between hydrazone compounds and phthalic anhydride to produce (1, 3 Oxazepine) new derivatives as final compounds. The prepared compounds were identified using melting point apparatus and Infrared Spectroscopy; the results are in agreement with the proposed method assigned to the synthesized compounds.



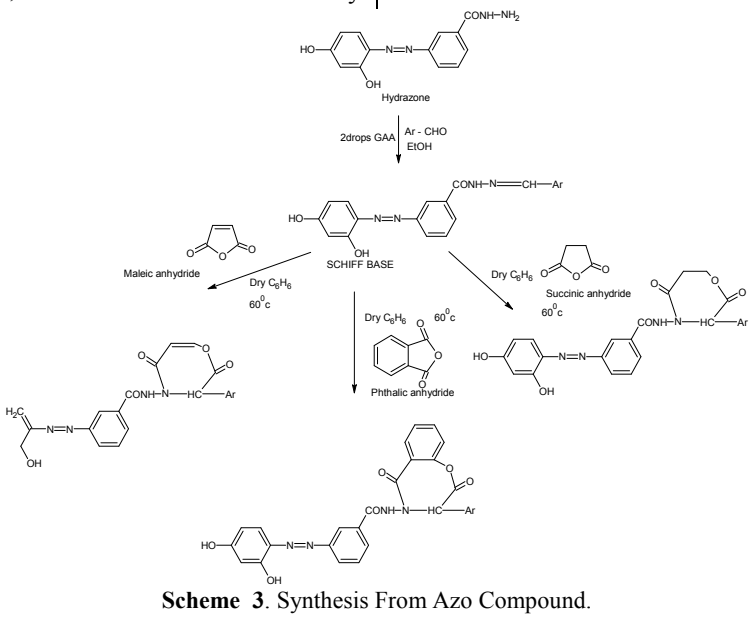
Scheme 1. Synthesis from Hydrazone.

Syeda Laila Rubab *et al., in* 2013 conducted a study on the topic "Asymmetric Synthesis of 4, 1 Benzoxazepine-2, 5-Diones from (2S)-α-Haloacids" [2].

Novel chiral 4, 1-benzoxazepine-2, 5-diones have been unusually synthesized in a single step by exploiting the chiral pool methodology. This strategy involved chiral pool methodology in which chiral substrates are coupled with achiral anthranilic acids to afford chiral 4,1-benzoxazepine-2,5-diones.They planned to synthesize 4, 1-benzoxazepines in two steps, which involve coupling of α-haloacids with various anthranilic acids, followed by intramolecular cyclization to afford corresponding 4,1-benzoxazepine-2,5- diones. For this purpose (−)-(*S*)-2-chloroacids or (−)-(*S*)-2-bromoacidswere prepared in high *ee (enantiomeric excess)* (95%–98%) *via* diazotization of naturally occurring (+)-(*S*)-amino acids [13]. The coupling of α-chloroacidsafforded *N*-acyl anthranilic acid as expected, but the use of α-bromoacids resulted in the formation of seven membered ring compounds, in most cases. Aseel F. Kareem *et al.,* in 2015 also carried out a study on the topic "Synthesis and identification some of 1, 3-oxazepine derivatives containing azo group" [3]. Several series of oxazepine compounds were synthesized from Schiff base as azo and azomethine derivatives by using primary amine as starting material with ethanol in the presence sulfuric acid to give ester. Then esters react with hydrazine hydrate to give hydrazones derivatives. The hydrazones derivative reacts with various benzaldehyde derivatives to give azomethine compound, then the schiff bases reacting with maleic, phathalic and succinic anhydride respectively. The chemical structures of synthesized compound were confirmed on the bases of FT-IR and ^{1}H-NMR.



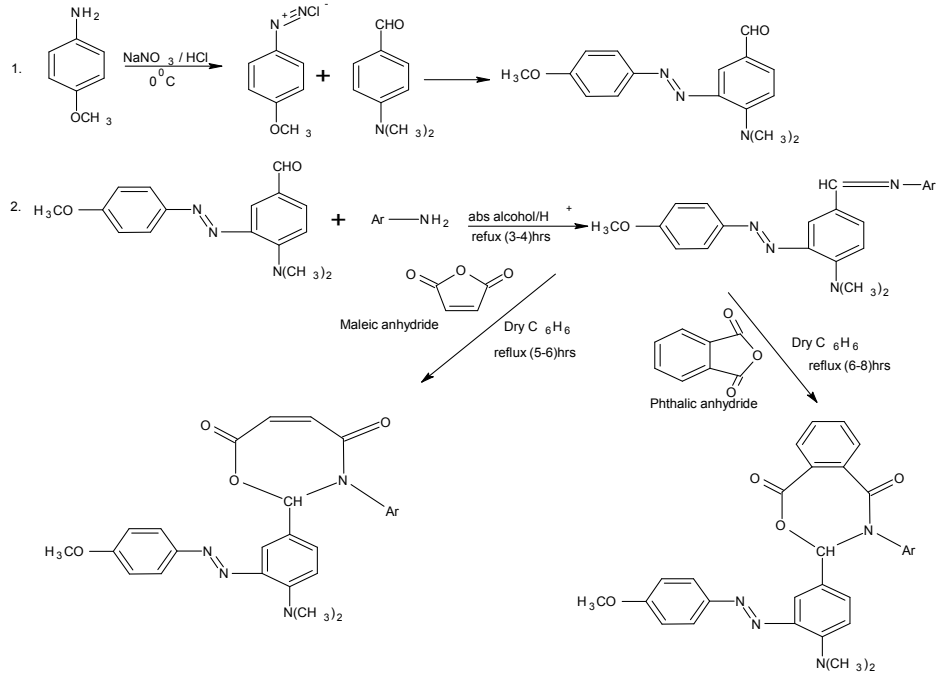
Scheme 2. Synthesis from anthranilic acid.



Scheme 3. Synthesis From Azo Compound.

Zainab Amer Sallal *et al.*, in 2011, conducted a study on the "Synthesis of new 1, 3 oxazepine derivatives containing azo group" [4].

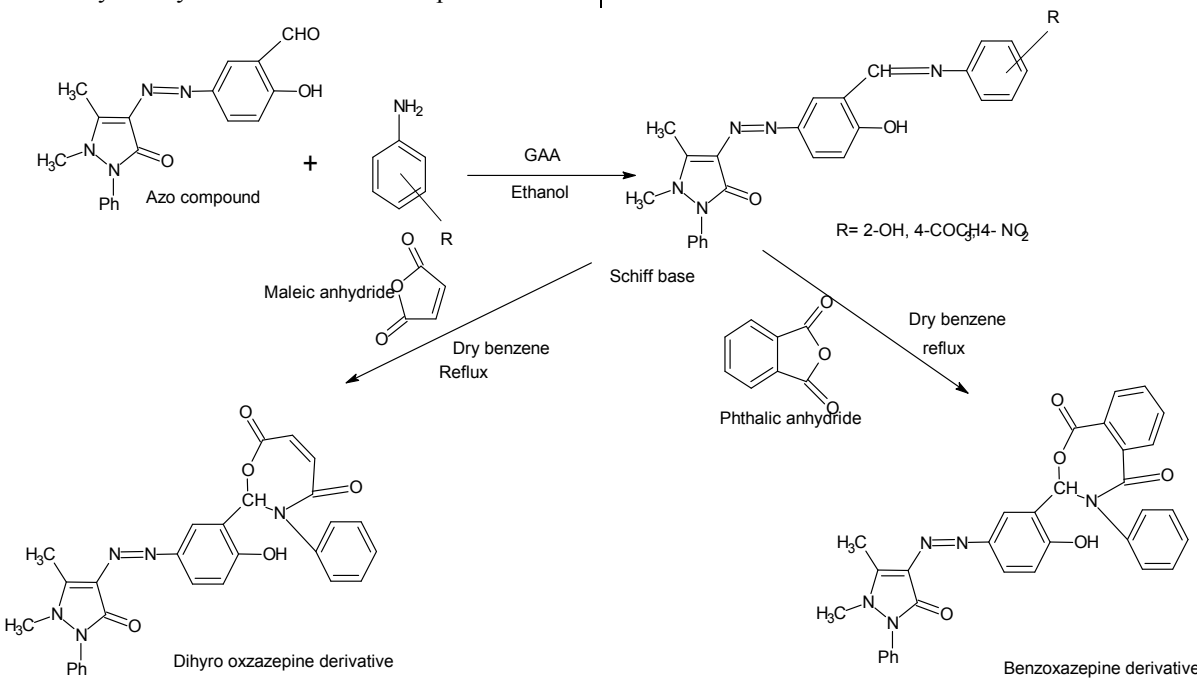
In this work new 1, 3-oxazepine derivatives containing azo group have been prepared. In the first step, 4-methoxyaniline was converted to 4-(dimethylamino)-3-((4-methoxy phenyl) diazenyl) benzaldehyde. In the second step, the aldehyde group of the new azo derivative was condensed with different primary aromatic amines, In the third step, the resulting imine derivatives were reacted with maleic anhydride and phthalic anhydride to give new 1,3-oxazepine-4,7-dione ring derivatives. All these compounds were characterized by melting points and FTIR spectroscopy; some of them were characterized by 1H-NMR spectroscopy and CHNanalysis.



Scheme 4. Synthesis from Methoxy aniline.

Thanaa A. Helal *et al.,* in 2014 worked on the following topic "Synthesis and identification of new 4-amino phenazone derivatives containing azo group" [5].

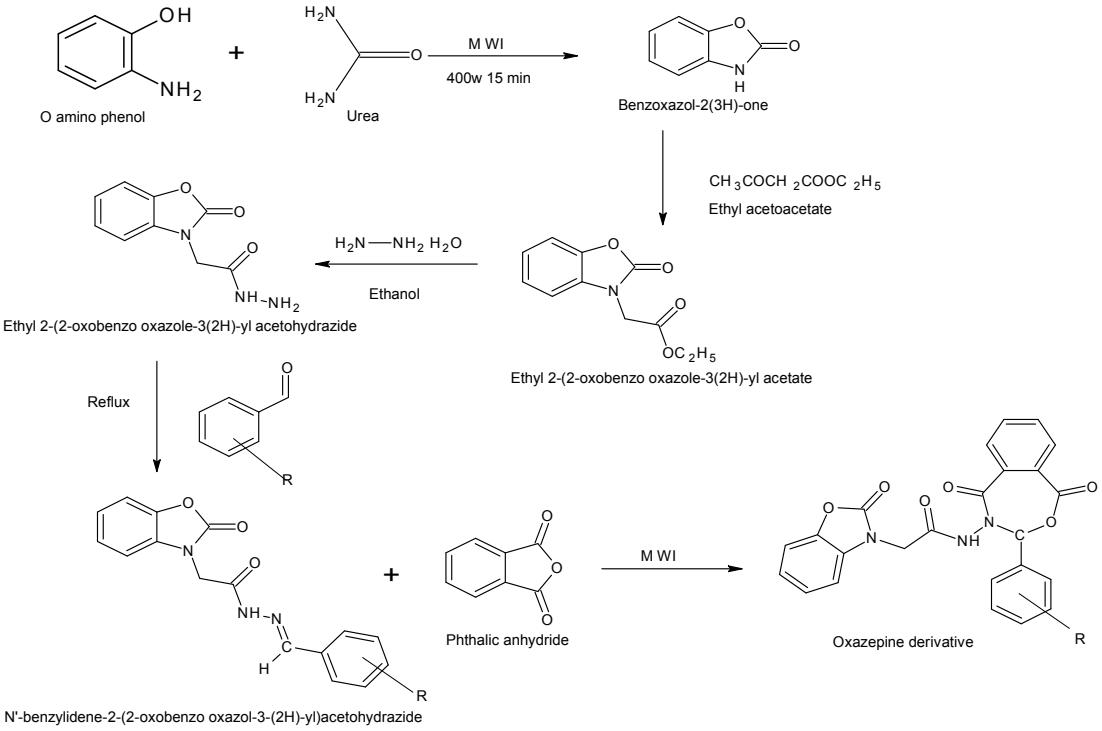
Here, the derivatives were prepared by reacting 4-Amino phenazone with Salicylaldehyde to form an azo compound. In the second step, the azo compound reacts with various amines to give Schiff bases. Then Schiff bases react with maleic and phthalic anhydride. The chemical structures of the synthesized compounds were confirmed on the basis of their spectral data.



Scheme 5. Synthesis from 4-Amino Phenazone.

Purnima Verma *et al.,* in 2015 conducted a study on the topic "Catalyst-free and facile green synthesis of some novel oxazepine derivatives" [6].

This research work involves the synthesis of some new oxazepine derivatives. Benzoxazole 1, 3– oxazepine are prepared by condensation of Schiff base with anhydride to give corresponding cyclo addition products. Benzoxazole-2(3H) - one when treated with ethyl acetoacetate gave the corresponding acetate. Hydrazinolysis with hydrazine hydrate furnished 2-[2-oxobenzoxazole-3(2H)-yl] acetohydrzine. Refluxing of 2-[2-oxobenzoxazole-3(2H)-yl] acetohydrazine with appropriate aldehyde yielded acetohydrazide derivatives and further cyclization of acetohydrazide with Phthalic anhydride afforded [1, 3] oxazepine derivatives. The structures of all the new compounds were confirmed by elemental analysis and spectral data.



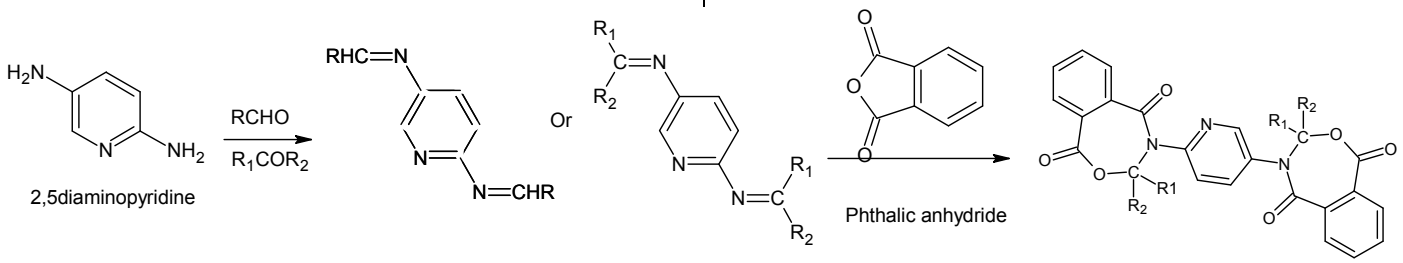
Scheme 6. Synthesis From Benzoxazole-2(3H) - one.

3. BIOLOGICAL ACTIVITIES OF OXAZEPINE DIONE DERIVATIVES

3.1. Antimicrobial activity.

Shatha F.N *et al*., in 2013 conducted a study on "Synthesis of some heterocyclic compound based on 2, 5-disubstituted pyridine" [7].

The work involved preparation, starting from 2, 5–diaminopyridine, with a variety of Schiff base from aldehyde, ketone and heterocycle oxazepine that have been synthesized. All proposed structures were supported by FT-IR, 'H-NMR and elemental analysis. Antimicrobial activity was studied on both gram positive bacteria and gram negative bacteria. Some of the derivatives show a moderate antimicrobial activity on *Staphylococcus aureus* and *Bacillus subtilis.*



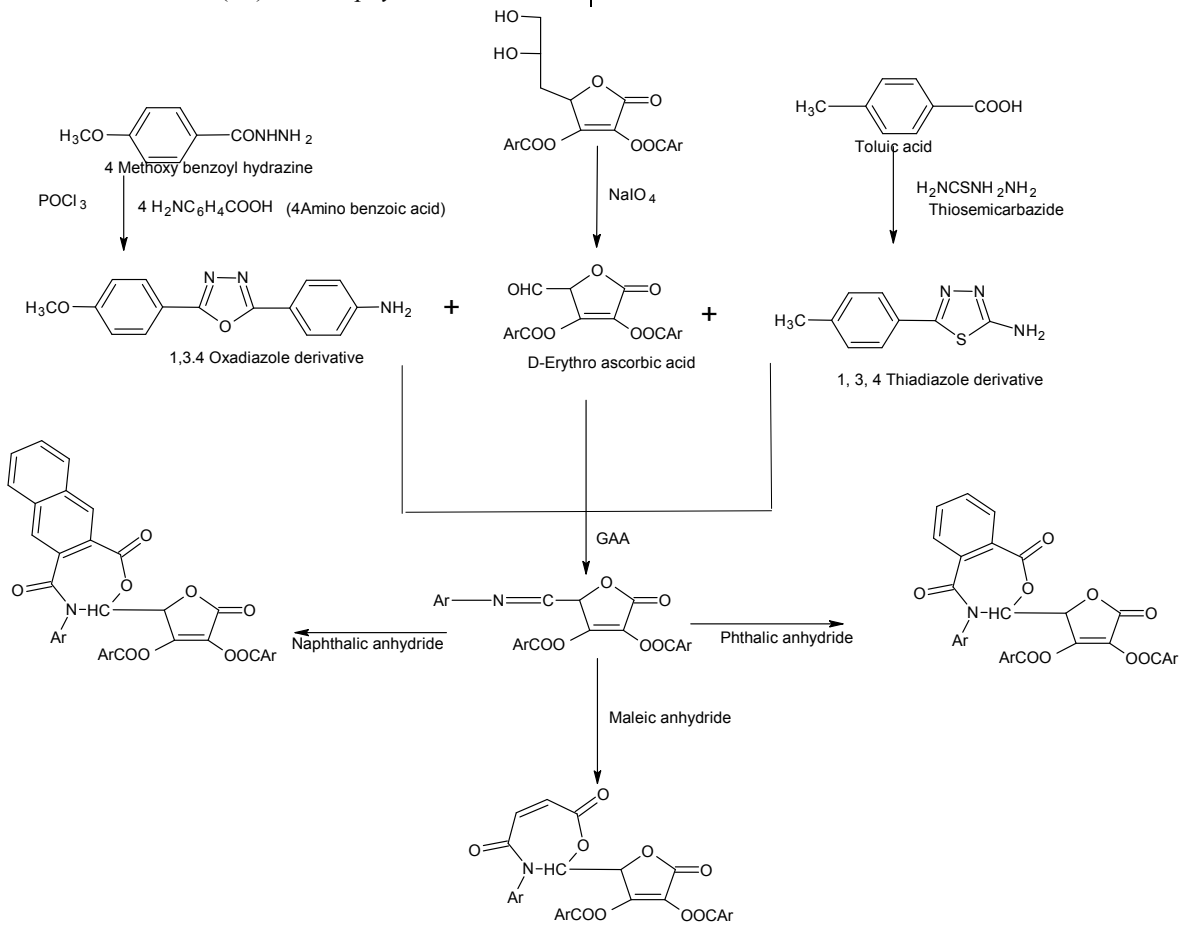
Scheme 7. Synthesis From2, 5- disubstituted pyridine.

A. A. Mukhlus *et al.,* in 2012 carried out a study on the "Synthesis and characterization of new oxazepines derived from D-Erythroascorbic acid" [8].

The new schiff bases derived from D-erythroascorbic acid containing heterocyclic unit were synthesized by condensation of D-erythroascorbic acid with aromatic amine (containing 1, 3, 4-oxadiazole or 1, 3, 4-thiadiazole unit) in dry benzene using glacial acetic acid as a catalyst. D- erythroascorbic acid was synthesized by four steps, while the primary aromatic amine which containing 1,3,4-oxadiazole or 1,3,4-thiadiazole synthesized by the reaction of 4- methoxy benzoyl hydrazine with 4-amino benzoic acid or by the reaction of tuloic acid with thiosemicarbazide, respectively in the presence of $POCl_3$. The new 1, 3-oxazepine derivatives were obtained by addition reaction of Schiff bases with different anhydrides maleic, phthalic, naphthalic anhydride or pyromellitic dianhydride) in presence of dry benzene.

The structure of synthesized compounds have been characterized by their melting points, elemental analysis and by their spectral data; FTIR, UV-Vis, Mass and ^{1}HNMR, ^{13}CNMR spectroscopy. All the synthesized compounds have been screened

for their antibacterial activities. They exhibited good antibacterial activity against *Escherichia coli* (G-) and *Staphylococcus aureus* (G+).



Scheme 8. Synthesis from D-Erythroascorbic acid.

Muhaned J. Mahmoud *et al.,* in 2013 published a study on the subject "Synthesis and characterization of five, seven heterocyclic membered rings" [9].

New compounds containing heterocyclic units have been synthesized. These compounds include 2-amino 5- phenyl-1, 3, 4-thiadiazole as starting material to prepare the Schiff bases. They were synthesized by equimolar amounts of appropriate aldehyde and the amine.

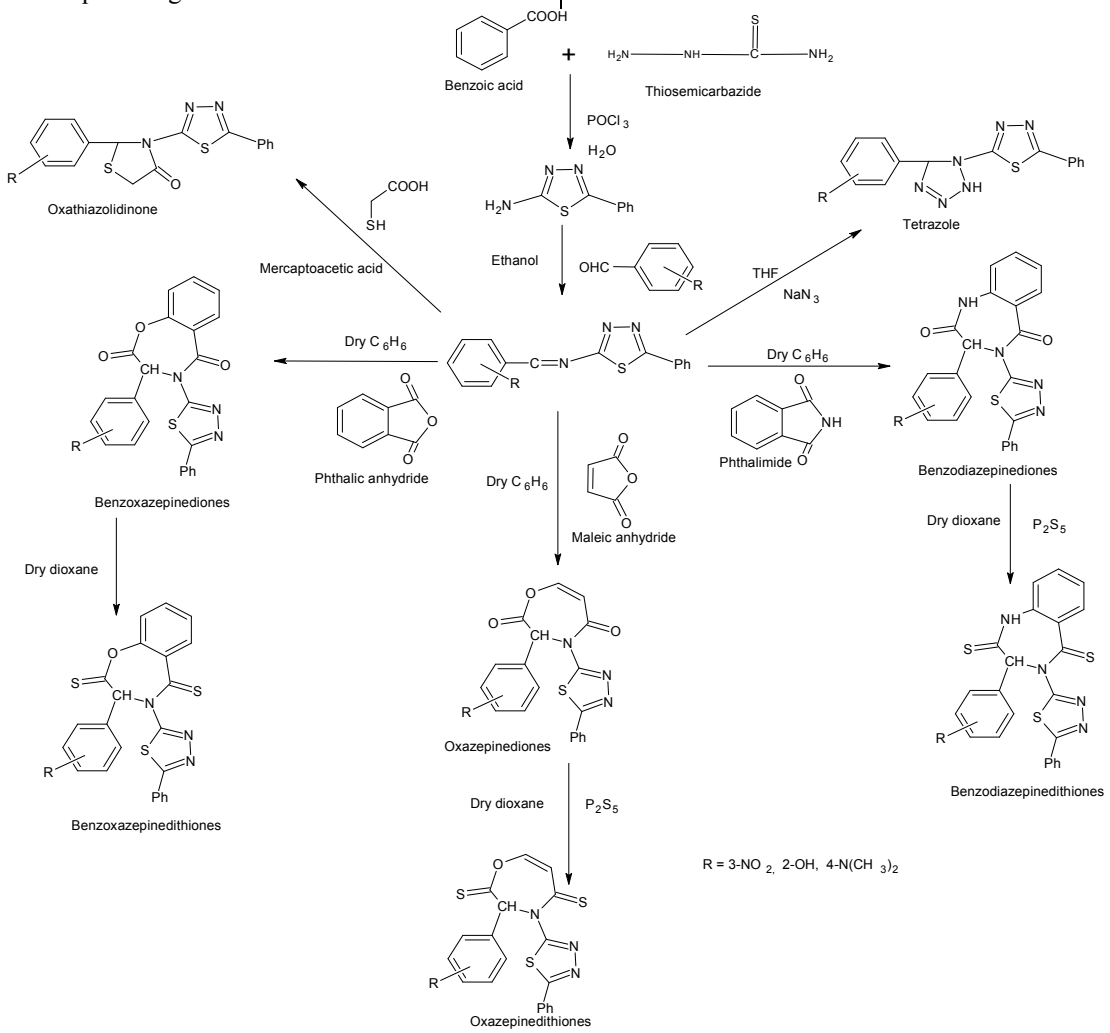
The schiff bases underwent a cycloaddition reaction with compounds like anhydride (maleic anhydride and phthalic anhydride), phthalimide, mercaptoacetic acid and sodium azide in order to obtain oxazepinediones, benzodiazepine 4,7 dione, oxathiazolidinone and tetrazole derivatives, respectively. A mixture of compounds of oxazepine and diazepine derivatives, respectively, was stirred in dry dioxane, in the presence of pentasulfide in order to obtain oxazepine -dithiones, benzodiazepine and dithione, respectively. Microbiological tests were performed for some of the derivatives, according to the disc diffusion method against Gram negative bacteria (*Escherichia coli*) and Gram positive bacteria (*staphylococcus aureus*). The inhibition zones caused by the various compounds were examined. for *Escherichia coli*, oxazepine -dithiones, benzodiazepine -dithione compounds showed moderate effect, while benzodiazepinedione shows no activity against this bacteria, tetrazole oxathiazolidinone showed slight effect on this bacteria. For *Staphylococcus aureus* all compounds have moderate effects, except Schiff base.

3.2. Antitumor activity.

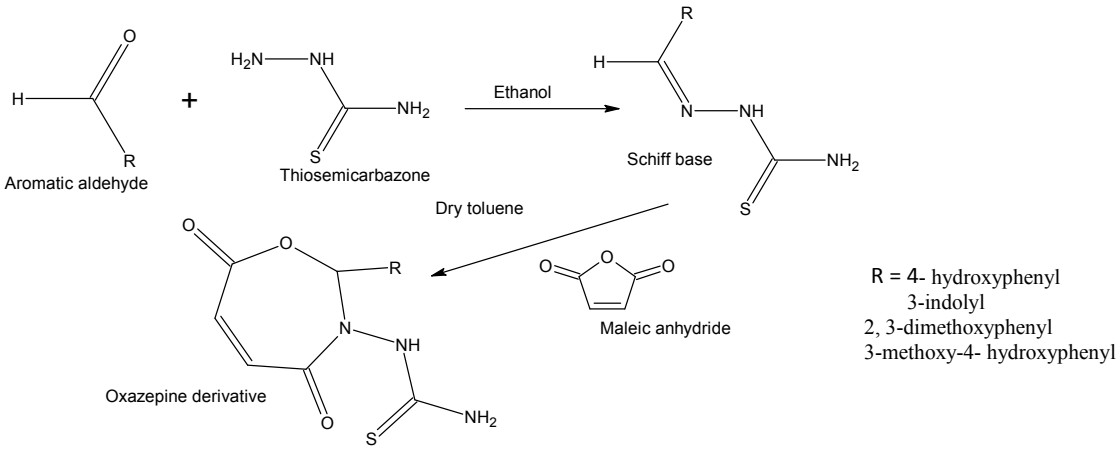
Dhanya Sunil *et al.,* in 2014 carried out a research on the topic "Oxazepine Derivative as an Antitumor Agent and Snail1 Inhibitor against Human Colorectal Adenocarcinoma" [10].

Colorectal cancer is the third most common malignancy in man, with significant morbidity and mortality. The effectiveness of many anticancer drugs is limited by their toxicity to normal rapidly growing cells. Four oxazepines were synthesized by the cycloaddition reaction between Schiff bases and maleic anhydride, which were characterized by CHN analysis and advanced spectral techniques. The cytotoxicity of oxazepines against HCT116 (human colon cancer) cell lines were studied using Sulphorhodamine-B (SRB) assay, and their antimigratory properties using wound healing assay. 1-[2-(2, 3-dihydro-1*H*-indol-3-yl)-4,7-dioxo-4,7-dihydro-1,3-oxazepin-3(2*H*)-yl]thiourea exhibited very low IC50 in SRB assay with good antimigratory activity as observed in wound healing assay. Snail 1, a transcription regulator of E-cadherin induces epithelial to mesenchymal transition, reduces intercellular adhesion and increases cell motility and endows epithelial cancer cells with migration and invasive properties.Snail1 is up regulated in several human cancers and is frequently associated with apoptotic resistance, invasiveness, metastasis and poor prognosis and it can act as a molecular target in cancer treatment. The docking studies

of the above derivatives with the active site of snail1 suggest it to be a potent chemotherapeutic agent in the treatment of colorectal cancer(scheme 10).



Scheme 9. Synthesis from 2-amino 5- phenyl-1, 3, 4-thiadiazole



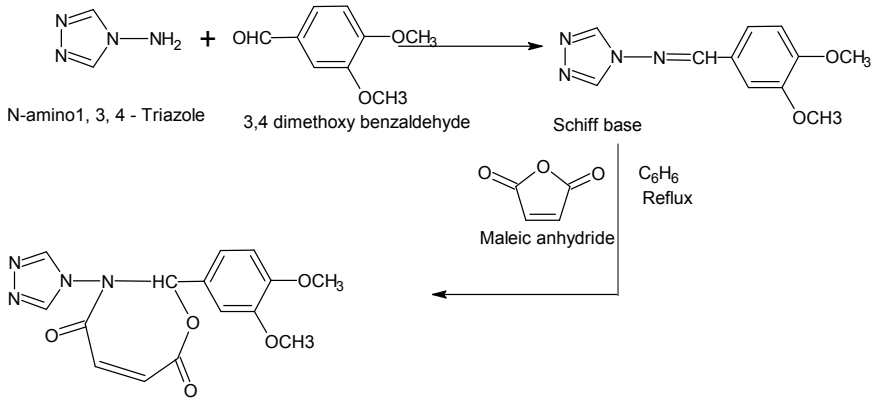
Scheme 10. Synthesis from Thiosemicarbazone.

3.3. Metabolic enzyme inhibition.

Abdul Zaid *et al.,* in 2010 carried out a study on the topic "Synthesis and Inhibition effect of 1,3-Oxazepine derivative on AST and ALT activities *by in Vitro* study" [11].

In order to study the Kinetic of human serum alanine amino transferase (ALT) and aspartate amino transferase (AST),a novel oxazepine derivative prepared in our laboratory was used to study its effect on ALT and AST since both enzymes are involved in the evaluation of hepatic disorder and on the other hand, oxazepine, among other drugs that are eliminated by the liver. The kinetic study confirmed that this oxazepine derivative acts as noncompetitive inhibitor for both ALT (GPT) and AST (GOT).The V max was found to be 113.5 U/mL and 85.18 U/mL for the non – inhibited and inhibited ALT, respectively, with Km value of 2.5 ×10 mol/L. As for AST, the Vmax was found to be 207 U/mL for the non-inhibited enzyme and 164.1 U/mL for the inhibited AST. The Km Value Which is the same for the

uninhibitedALT and the inhibited enzyme was found to be 1.2×10^{-3} mol/L.



Scheme 11. Synthesis from N-amino 1,3,4 Triazole.

4. CONCLUSIONS

Oxazepines are an important class of heterocyclic compounds. Among the different oxazepines, the oxazepinediones are much less studied. So far, pharmacological activities such as anticancer, antimicrobial, antibacterial and enzymatic activities are studied. This review gives an overview on the various oxazepinedione derivatives and their pharmacological activities. The importance of oxazepinediones moiety can be magnified by carrying out further studies on its possible substitution and thus to synthesize better agents that can have strong future commitment.

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