وزارة التعليم العالي و البحث العلمي
جامعة ديالى
كلية التربية للعلوم الصرفة-قسم الكيمياء

تحضير بعض المشتقات الجديدة للسلفاميثوكسازول و دراسة فعاليتها المضادة للبكتريا

رسالة قدمتها الى

مجلس كلية التربية للعلوم الصرفة / جامعة ديالى

و هي جزء من متطلبات نيل درجة الماجستير في علوم الكيمياء

أعداد الطالب

مروان هشام انور

بكالوريوس علوم كيمياء-كلية العلوم-الجامعة المستنصرية

2015-2014

أشراف

أ. م. د زياد طارق ابراهيم

1444 هجري **2022 ميلادي**

Chapter One

Introduction

Chapter one

Introduction

1.1 Heterocyclic Compounds

Carbon participates with different atoms such as oxygen, sulfur, and nitrogen to form various cyclic molecules classified in a large and special branch of chemistry called the chemistry of heterocyclic compounds. These compounds consist of various forms of rings, including ternary, quaternary, pentagonal, hexagonal, monocyclic, bicyclic, and others,[1] a few basic rings of heterocyclic compounds are listed below (Figure 1,1):

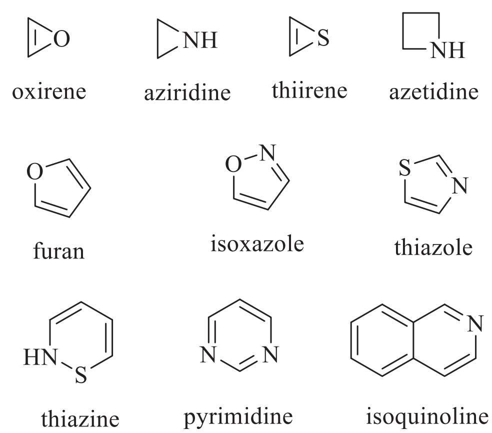
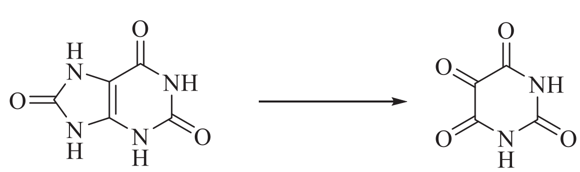


Figure 1,1: Structural formula of some heterocyclic rings

Where the percentage of the number of registered organic compounds in the Comprehensive Medicinal Chemistry (CMC) database that contain heterocyclic compounds is more than 67%.[2] Heterocyclic compounds were known very early, as the isolation of the first heterocyclic alloxan **2** by oxidation of uric acid **1** was recorded by Brugnatelli in 1818s,[3] (Equation 1,1).



1 **2**

Equation 1,1: Alloxan synthesis reaction

Chapter one

Introduction

Since the beginning of the emergence of plant and animal extracts and their isolation by chemists, pharmacists, and physicians, medicinal chemistry arose, which studied extracts from the chemical and biological sides, showing the chemical aspect by classifying them from heterogeneous cyclic compounds mostly. As for the biological aspect, the important therapeutic properties of these extracts have been proven, it is also due to the fact that possess the heterogeneous ring that gives these characteristics.[4]

Heterocycles are present in a wide variety of drugs, most vitamins, many natural products, biomolecules, and biologically active compounds, including antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal agents.[5,6] Also, they have been frequently found as a key structural unit in synthetic pharmaceuticals and agrochemicals. Some of these compounds exhibit significant solvatochromic, photochromic, and chemiluminescence properties. Most of the heterocycles possess important applications in materials science such as dyestuff, fluorescent sensors, brightening agents, information storage, plastics, and analytical reagents. In addition, they have applications in supramolecular and polymer chemistry, especially in conjugated polymers. Moreover, they act as organic conductors, semiconductors, molecular wires, photovoltaic cells, organic light-emitting diodes (OLEDs), light-harvesting systems, optical data carriers, chemically controllable switches, and liquid crystalline compounds. Heterocycles are also of considerable interest because of their synthetic utility as synthetic intermediates, protecting groups, chiral auxiliaries, organocatalysts, and metal ligands in asymmetric catalysts in organic synthesis. Therefore, substantial attention has been paid to developing efficient new methods to synthesize heterocycles.[6]

1.2 Sulfa Drugs

Sulfa drugs or sulfonamides are synthetic medicinal chemical compounds and are one of the most important types of antibacterial drugs while used today for the treatment of bacterial infections and those caused other microorganisms[7] and have many biological activities, including diuretic, hypoglycemic and antithyroid activity[8], Alzheimer's disease **3**.[9] Recently, several new sulfonamide derivatives have been synthesized, which have significant antitumor activity, and this has been demonstrated both in *vivo* and in *vitro*.[10–12] (E7010) **4**, (ER-34410) **5** and (E7070, Indisulam) **6** are examples of sulfonamide derivatives that have been given advanced clinical trials as antitumors (Figure 1,2).[13]

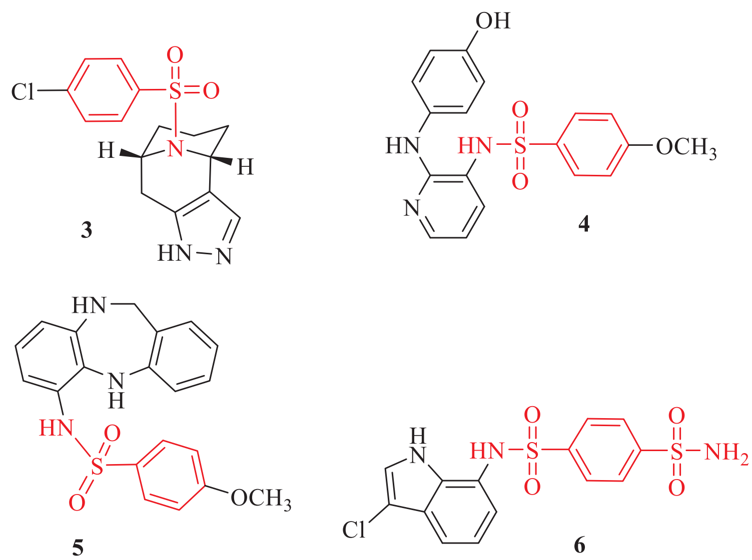
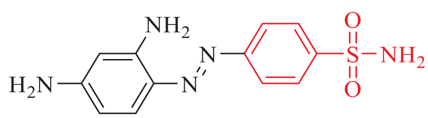


Figure 1,2: Examples of sulfonamide derivatives as antitumors

Indeed, the sulfonamides constitute an important class of drugs, with many types of pharmacological agents possessing antibacterial, anticarbonic anhydrase, anti-obesity, diuretic, hypoglycemic, antithyroid, antitumor, and anti-neuropathic pain activities, among others.[14]

1.2.1 The History of Sulfa Drugs

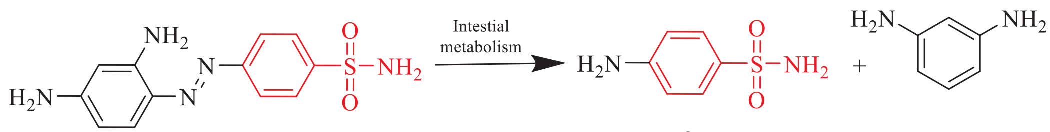
The best example of antibacterial agents acting as antimetabolites is sulfonamides. Sulfonamide was a major source of bacterial therapy before the discovery of penicillin in 1941s.[15] The compound shown in figure 1.3 is considered the first antibiotic chemical compound that contains an azo group and a sulfonamide group called Prontosil **7**. It was introduced for clinical use in the early 1930s.[16]



7

Figure 1,3: Structural formula of Prontosil

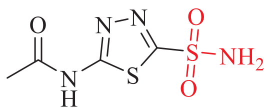
In 1932s, a patent was registered for the compound prontosil, as well as for many compounds containing the azo and sulfonamide groups SO_2NH,[17] which studied their effectiveness against *streptococci*. Domagk tested their activities on mice infected with *streptococci*, and it gave a positive result for the test. In 1933s, Forrest and co-workers applied the activity of prontosil to an infant at the age of ten months who received a dramatic treatment for *staphylococcal septicemia*.[18,19] Buttle and co-workers presented the results of their study on the compound prontosil and its active receptor sulfanilamide, and the results were positive for both *puerperal sepsis* and *meningococcal* infections.[20] These medical reports led to the birth of a new field in the chemotherapy of bacteria and were the outcome of the Domagk Nobel Prize in medicine for his discovery of the compound prontosil and its therapeutic applications.[21–23] Domagk noticed that the prontosil compound is degraded inside the cell to give sulfanilamide **8**, and the latter is the actual antibiotic, not the prontosil.[23,24] (Equation 1,2)



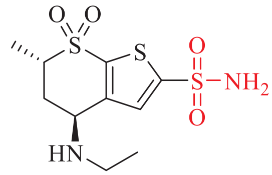
7 **8**

Equation 1,2: Intestinal metabolism of Prontosil

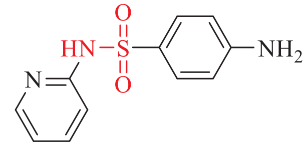
After these important discoveries in the medical field, the sulfonamide compound was developed into many derivatives, reaching 5,000 derivatives,[25] and among this huge number, more than 150 derivatives were used that differ from each other in the heterogeneous ring compensated for sulfonamide in human and veterinary medicine as bactericidal drugs.[26] The common chemical motifs present in the aromatic/heterocyclic/sugar/amino acid sulfonamides endowed with such properties are thus associated with a multitude of biological activities.[27] Figure 1.4 shows the chemical structures of some examples of sulfonamides.[28–33]



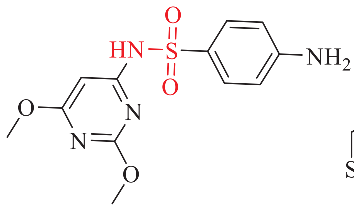
Acetazolamide **9**



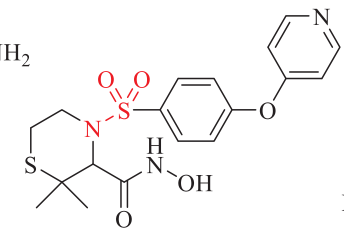
Dorzolamide **10**



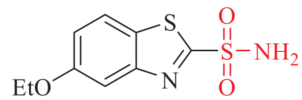
Sulfapyridine **11**



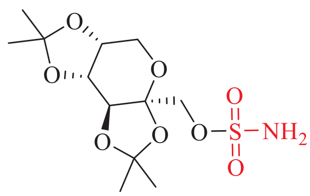
Sulfadimethoxine **12**



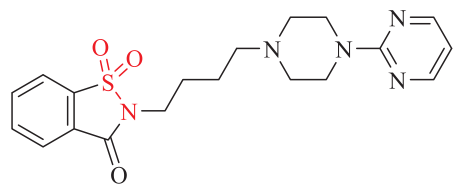
AG 3340 **13**



Ethoxzolamide **14**



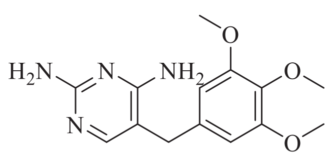
Topiramate **15**



Ipsapirone **16**

Figure 1.4: Examples of sulfonamides

At the present time, among all the many and varied sulfonamides derivatives, the most common and widely used antibiotic to treat bacterial infections in humans is sulfomethoxazole, which is mainly used combined with trimethoprim **17** under trade name, Septrin.[34,35]



17

Figure 1.5 Structural formula of trimethoprim

1.2.2 Action of Sulfonamides

p-aminobenzoic acid (PABA) is a vital component in the biosynthesis of tetrahydrofuric acid, where PABA is key bacterial DNA biosynthesis, here the action of most sulfonamides appears, which prevents the formation of the PABA complex by acting as an anti-acid metabolism.[36] Thus, PABA is unable to synthesize tetrahydrofolic acid and this leads to decreases concentration of thymidine and uridine nucleic acids which are important in cell DNA synthesis, and as a result cell growth and differentiation is disturbed, making it easier for the immune system to kill a bacterial.[37] The effect of sulfonamides on the bacteria entering human beings differs from what is mentioned above because folic acid gets to the person through metabolism, as it is considered important for him because its deficiency causes megaloblastic anemia, diabetes, neural tube defects in developing fetuses, cancer, and cardiovascular diseases, and Alzheimer's disease.[38] When using sulfonamides treatment for humans, it uses the compound trimethoprim, Where the process of killing bacteria takes place in two stages, the first is represented by the binding of sulfomethoxazole **20** with the enzyme dihydropteroate synthase (DHPS) responsible for the synthesis of dihydropteroic acid **22** and thus prevents the action of the enzyme, and therefore in the event of acid formation, the role of trimethprim **17** comes in inhibiting the enzyme dihydrofolate reductase (DHFR) from its work in the synthesis of acid (Figure 1,6). Folic acid **23** is not created inside the cell, which prevents the formation of nucleic acids responsible for building the cell wall, and thus the bacteria die.[39–41]

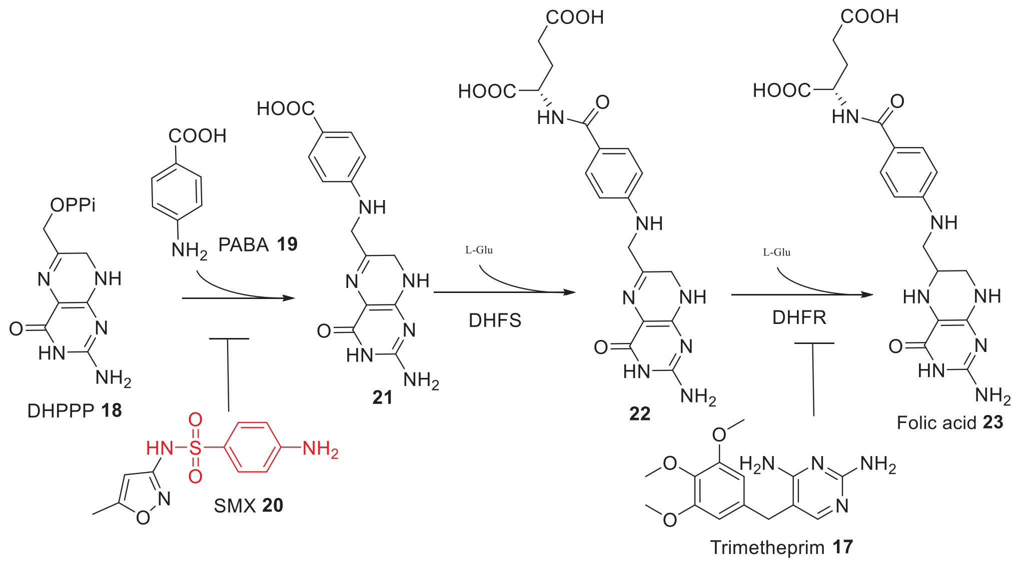
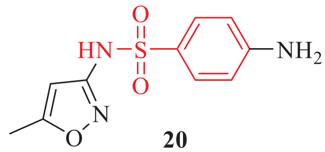


Figure 1,6: Later stages of the folate biosynthetic pathway and related antibacterial drugs that target the pathway

1.3 Sulfamethoxazole

Sulfamethoxazole (SMX) **20** is one of the most important sulfonamide compounds that was chosen to represent this large group due to its wide uses and many discoveries in the aquatic environment,[26] and the reason is because SMX **20** is given to livestock and birds through feed and water provided to animals,[42] and the rate of decomposition or metabolism of the drug within the animal body It does not exceed 50%, so the animal gets rid of it through urine and manure into the aquatic environment.[43] SMX **20** is a chemical compound shown in the figure 1,7 that belongs to the sulfonamide family, since it contains a sulfonamide group represented by a benzene ring attached to an amine group corresponding to the Sulfanilamide scaffold,[44] which is the group that causes the biological activity of this group of drugs.



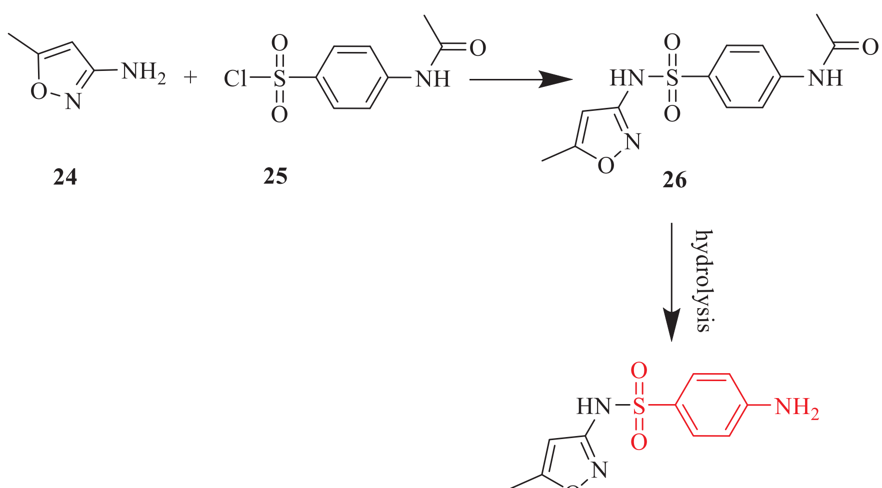
20

Figure 1,7: Structural formula of SMX

The biological uses of SMX began in the early 1960s in a large scale for the treatment of humans and animals,[42] and it is considered primarily an antibiotic against bacteria, including bacteria *Staphylococcus aureus*,[45] *Haemophilus influenza*, *Escherichia colli*. [46]

1.3.1 Synthesis of SMX

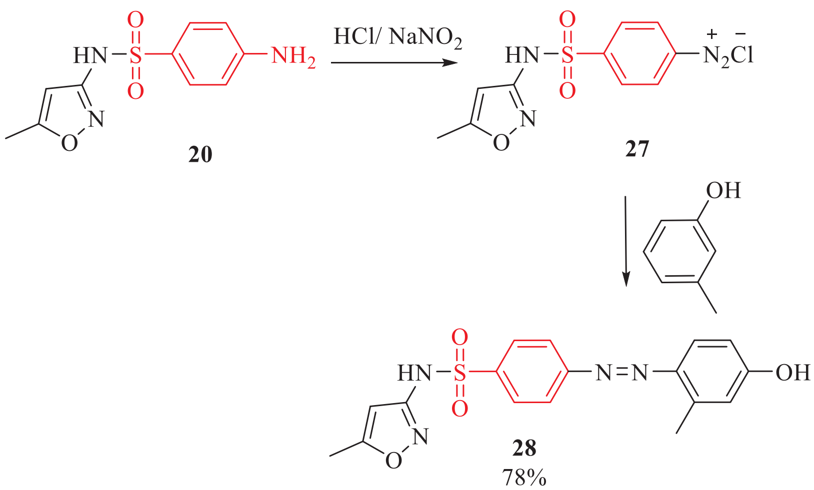
SMX **18** was prepared by the reaction 5-methyl-3-aminoisoxazole **24** reacted with *N*-acetyl-*p*-amino-benzene sulfonylchloride **25** see scheme 1,1. The acetyl group is then cleaved to give SMX **20:**[47]



Scheme 1,1: Synthesis of SMX

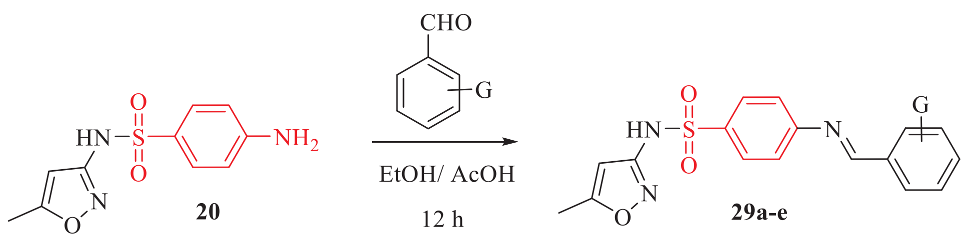
1.3.2 A brief review on recent synthesis of SMX derivatives

The derivative of SMX **28** was prepared by AL-Hammoshi and co-workers in 2011, and these derivative gave good biological activity against *Staphylococcus aureus* bacteria only,[48] (scheme 1,2).



Scheme 1,2: Synthesis of SMX derivatives by AL-Hammoshi and co-workers

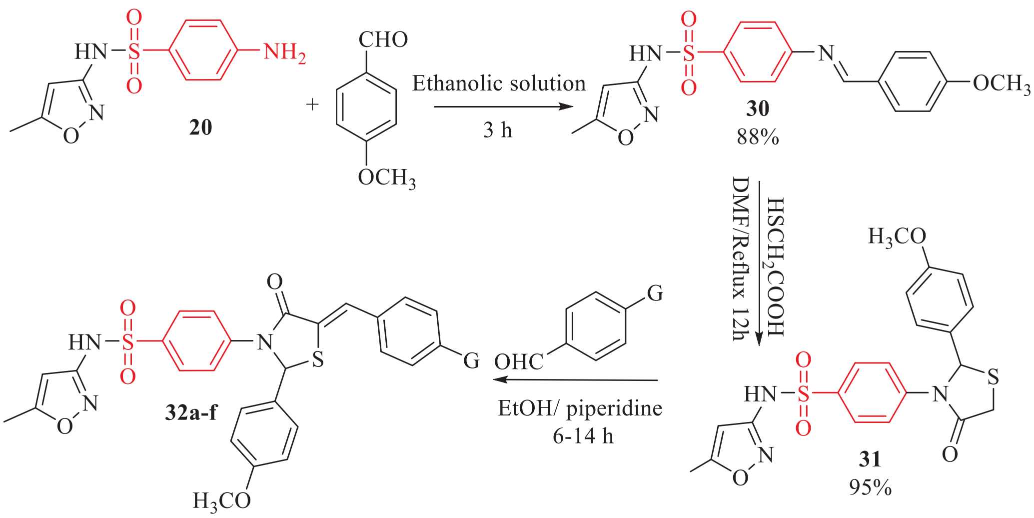
In 2014, Youssef and co-workers synthesized several derivatives of SMX by reacting with several benzaldehydes,[49] (equation 1,3).



G = H , *p*-Br , *m*-NO_2 , *p*-$N(CH_3)_2$, *o*-OH

Equation 1,3: Synthesis of SMX derivatives by Youssef and co-workers

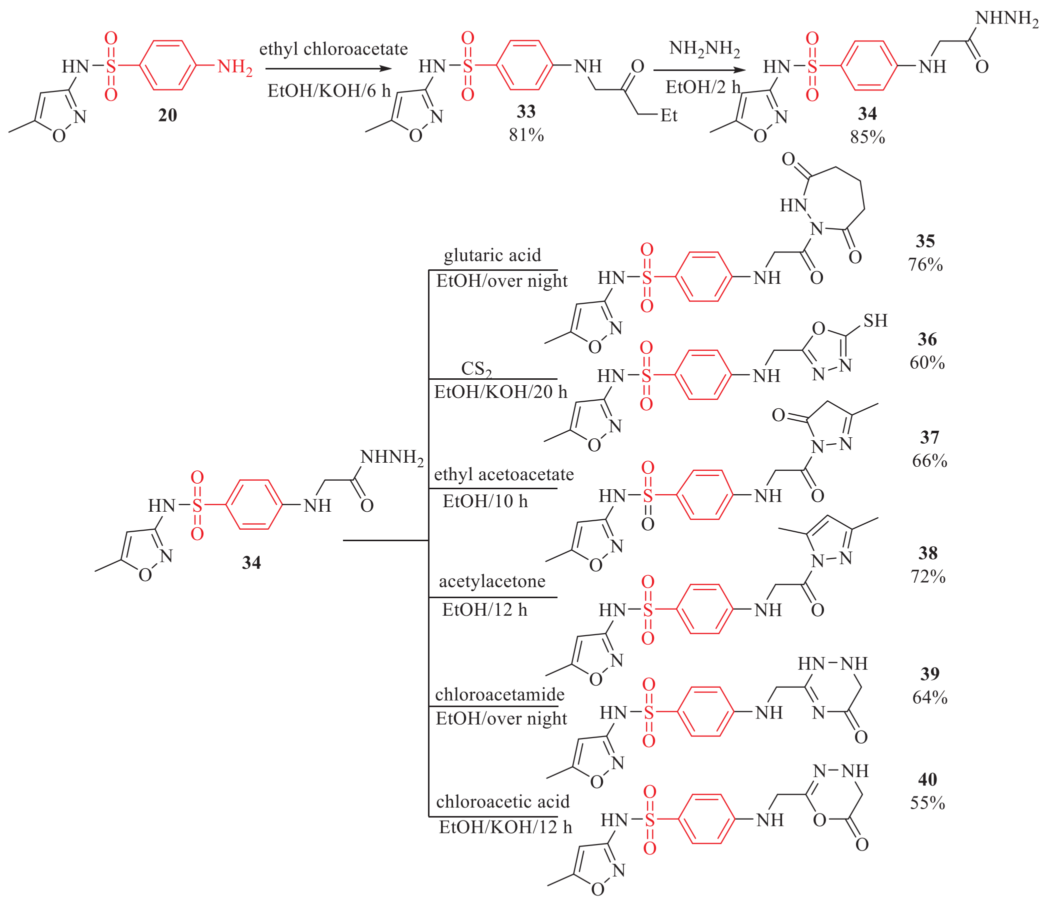
In 2015, SMX derivatives were synthesized *via* an oxothiazolidine ring-forming reaction using a mercaptoacetic acid complex (Scheme 1,3) by Mahdi and co-workers,[50] the final compounds gave good and remarkable biological activity against three types of bacteria (*Escherichia colli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*).



G = H(**a**-67%) , OH(**b**-62%) , OCH_3(**c**-73%) , NO_2(**d**-74%) , Cl(**e**-75%) , $N(CH_3)_2$(**f**-74%)

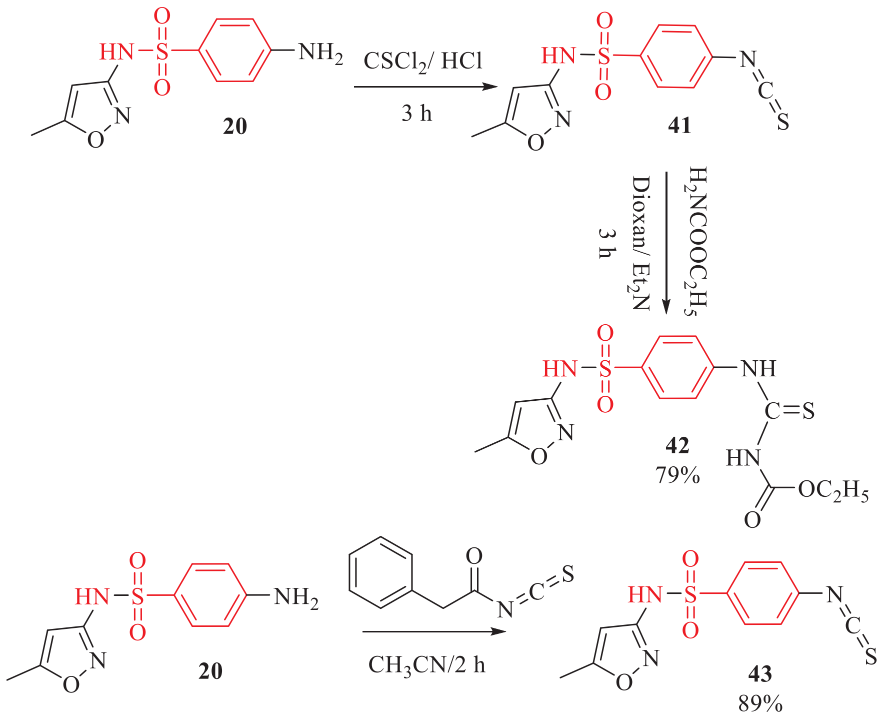
Scheme 1,3: Synthesis of SMX derivatives by Mahdi and co-workers

Synthesis a series of SMX derivatives by researcher Khan, in the year 2017, connected to a heterogeneous ring such as 1,2-diazepane **35**, 1,3,4-oxadiazole **36**, two pyrazoles **37-38**, 1,2,4-triazine **39**, and 1,3,4-oxadiazine **40,** (Scheme 1,4).[51] The derivatives were studied in terms of biological activity against bacteria and fungi using four types of pathogenic bacteria with two types of yeast-like fungi and its activity was perfect against microbes compared to the main drug.



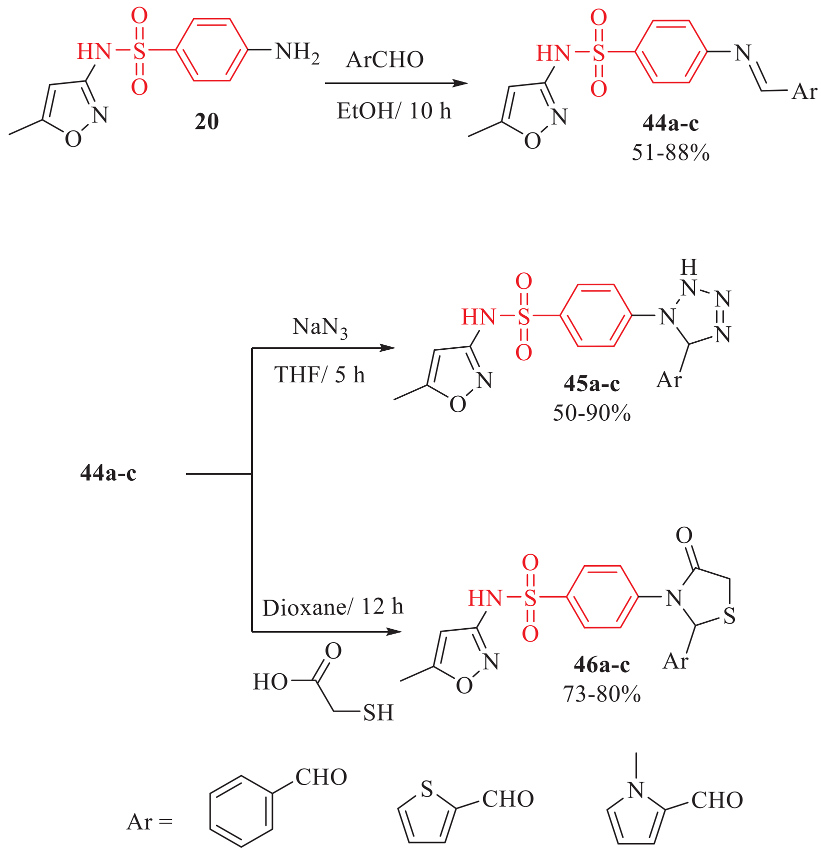
Scheme 1,4: Synthesis of SMX derivatives by researcher Khan

El-Gaby and co-workers in 2018 synthesized some of novel SMX derivatives bearing carbamate/ acyl-thiourea scaffolds (Scheme 1,5). The in *vitro* antimicrobial activities of the synthesized compounds were evaluated for four G^{+} bacteria. *Staphylococcus aureus, Methicillin-Resistant Staphylococcus aureus* (MRSA), *Bacillus subtillis*, *Streptococcus pyogenes*, and three G^{-} organisms *viz*. *Escherichia coli, Proteus vulgaris, Erwiniacarotovora*, as well as one fungi. *Candida Albicans* by agar well diffusion method. Compound **42** exhibited appreciable broad spectrum against both G^{+} and G^{-} bacteria.[52]



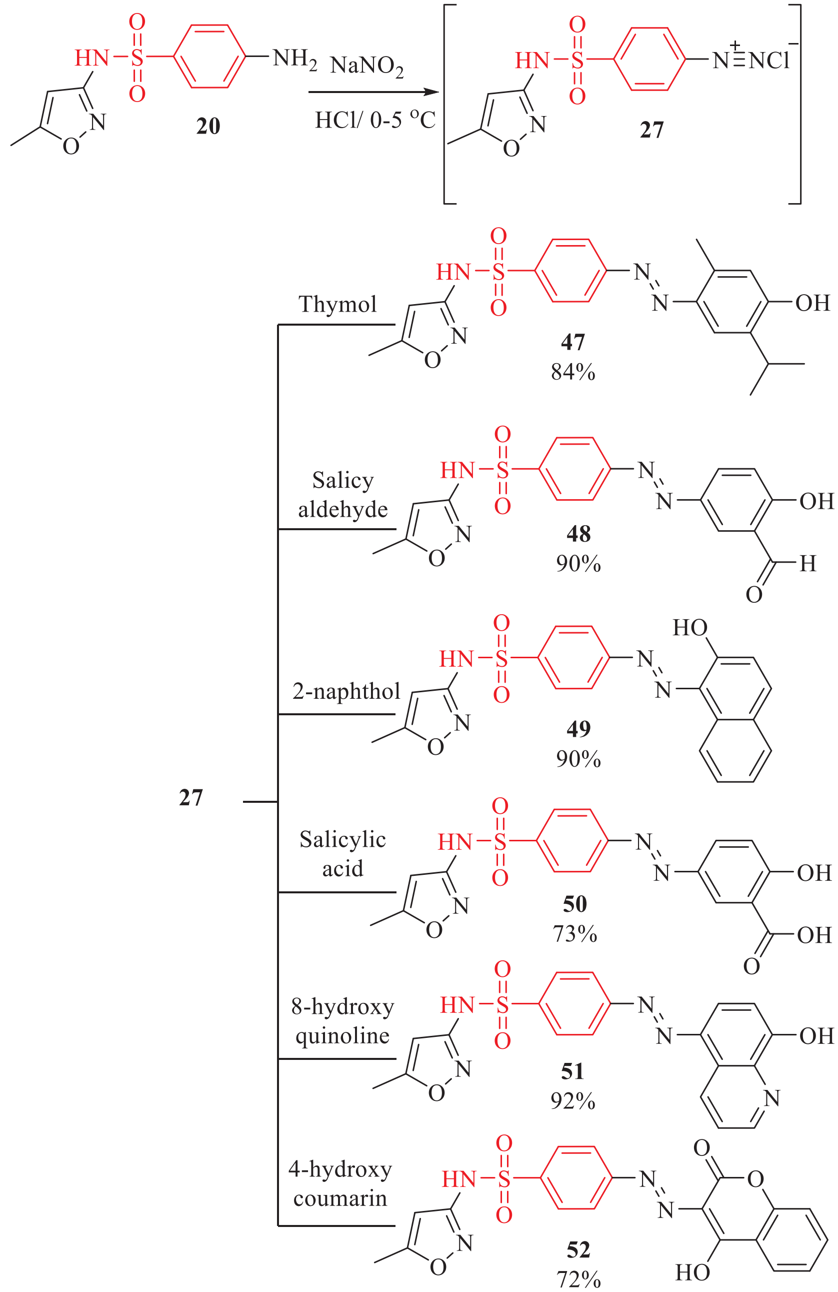
Scheme 1,5: Synthesis of SMX derivatives by El-Gaby and co-workers

Synthesis of tetrazol **45a-c** and thiazolidine **46a-c** rings on SMX (Scheme 1,6) by majeed in 2018 and studying their biological activities against two types of bacteria, G^+ and G^- including *Streptococcus Pyogenic* and *Escherichia Coli,* which gave high biological effect against the mentioned bacteria.[53]



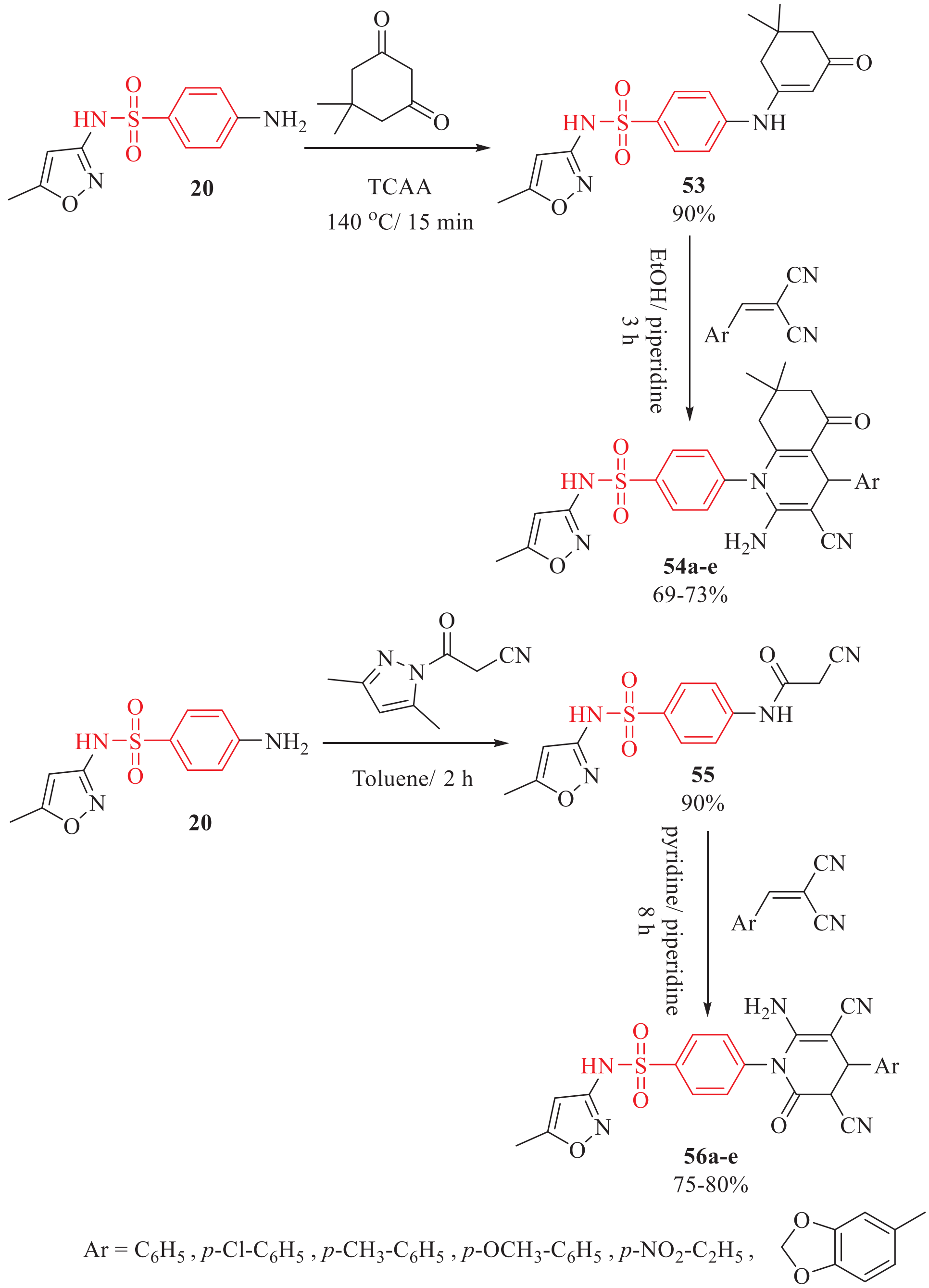
Scheme 1,6: Synthesis of SMX derivatives by majeed

A series of SMX derivatives **47-52** were designed and synthesized coupling a mixture of diazotized with six different phenolic and enolic compounds (Scheme 1,7), by Sahoo and co-workers in 2019 and its biological activities were measured and studied as it showed antibacterial activity against resistance of *Staphylococcus aureus* and *Candida albicans* and description *Cryptococcus neoformans* at a concentration of 31.25 μg/ml.[54]



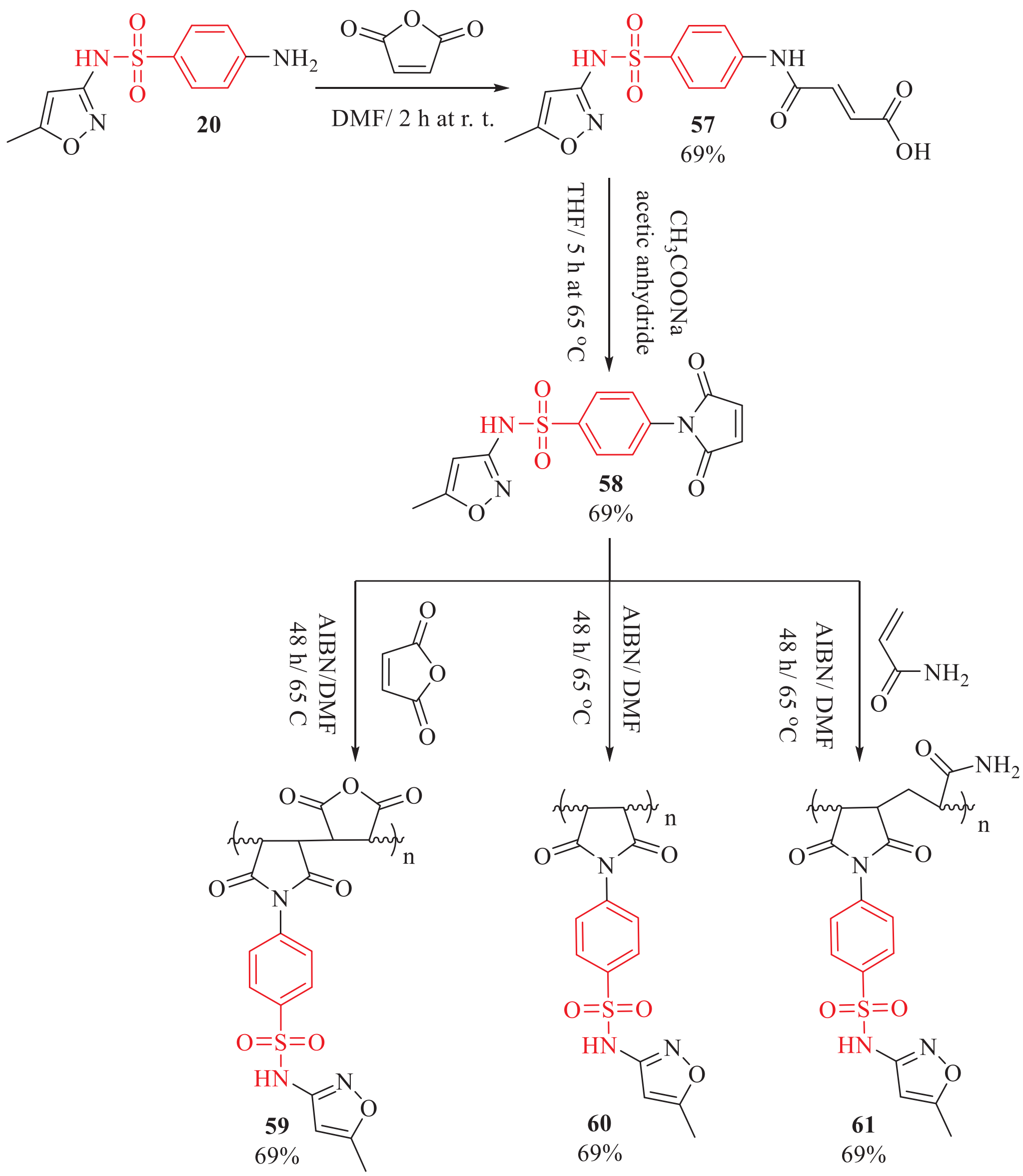
Scheme 1,7: Synthesis of SMX derivatives by Sahoo and co-workers

Synthesis of a novel hexahydroquinoline and 6-amino-2-oxopyridine-3,5-dicarbonitrile involving SMX *via* [3+3] avoidance by M. Abdelmoniem and co-workers in 2019 as illustrated in (Scheme 1,8).[55]



Scheme 1,8: Synthesis of SMX derivatives by Abdelmoniem and co-workers

In 2020, using the free radicals polymerization, Radhia synthesized maleimide polymers from SMX (Scheme 1,9), it was confirmed by spectroscopic analyzes, and it gave thermal stability in 260, 270, and 300 °C.[56]



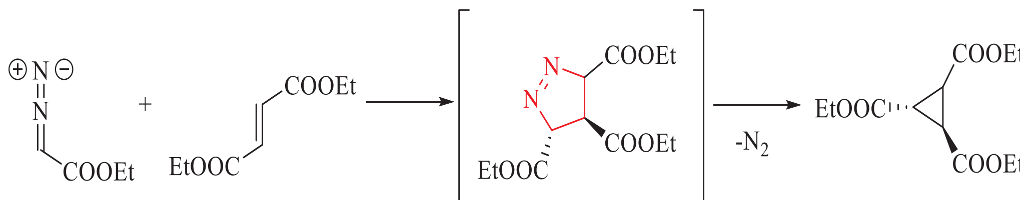
Scheme 1,9: Synthesis of SMX derivatives by Radhia

1.4 Cycloaddition Reactions

Cycloaddition reactions are one of the well known reactions in synthetic organic chemistry that involve the interaction of π-electron systems using two or more molecules.[57] The molecules involved in these reactions take the general formula X+Y, which indicates the number of π-electrons present in both reactants.[58]

Cycloaddition reactions are thermal addition reactions, photonic addition reactions, or binary removal[59] processes that are very useful because they are used to build different structures of new carbon bonds and heterocyclic rings.[60]

In 1888, Huisgen synthesized the first type [2+3] cycloaddition reaction by the react of carboethoxydiazomethane **62** and diethyl fumarate **63** to give 3,4,5-tricarboethoxypyrazoline **64**, which spontaneously converts to 1,2,3-tricarboethoxycyclopropane **65** after removing the nitrogen molecule from it, (Scheme 1,10).[61]



Scheme 1,10: Huisgen synthesized the first type [2+3] cycloaddition reaction

Huisgen explained that the reaction mechanism is the interaction of materials known as 1,3-dipoles inter alia, nitrones, azomethine ylides, carbonyl ylides, nitrile oxides, azides, diazomethane analogs, ozone, many more with each other (Table 1,1),[62] where a simultaneous circular shift of six π-electrons occurs, (Figure 1,8).[63]

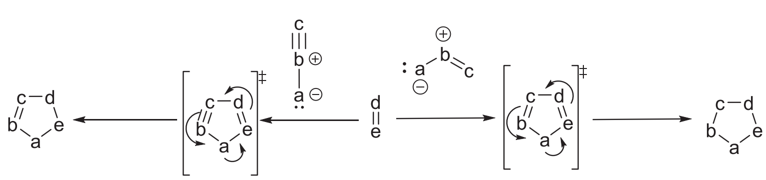


Figure 1,8: Concerted mechanism of 32CA proposed by Huisgen

Name	Structure
Diazoalkane	$\overset{-}{N}=N-\overset{+}{C}R_2 \longleftrightarrow \overset{-}{N}=\overset{+}{N}=CR_2$
Azide	$\overset{-}{N}=N-\overset{+}{N}R_2 \longleftrightarrow \overset{-}{N}=\overset{+}{N}=NR_2$
Azomethine ylide	$R_2\overset{+}{C}-\underset{R}{N}-\overset{-}{C}R_2 \longleftrightarrow R_2C=\underset{R}{\overset{+}{N}}-\overset{-}{C}R_2$
Azomethine imine	$R_2\overset{+}{C}-\underset{R}{N}-\overset{-}{N}R \longleftrightarrow R_2C=\underset{R}{\overset{+}{N}}-\overset{-}{N}R$
Nitrone	$R_2\overset{-}{C}-\underset{R}{\overset{+}{N}}=O \longleftrightarrow R_2C=\underset{R}{\overset{+}{N}}-\overset{-}{O}$
Azimine	$R\overset{+}{N}-\underset{R}{N}-\overset{-}{N}R \longleftrightarrow RN=\underset{R}{\overset{+}{N}}-\overset{-}{N}R$
Nitroso imine	$R\overset{+}{N}-O-\overset{-}{N}R \longleftrightarrow RN=\overset{+}{O}-\overset{-}{N}R$
Carbonyl ylide	$R_2\overset{+}{C}-O-\overset{-}{C}R_2 \longleftrightarrow R_2C=\overset{+}{O}-\overset{-}{C}R_2$
Ozone	$\overset{+}{O}-O-\overset{-}{O} \longleftrightarrow O=\overset{+}{O}-\overset{-}{O}$

Table 1,1: 1,3-Dipolar compounds

1.4.1 1,3-Dipolar Cycloaddition [2+3→5] reactions

It is considered one of the primitive reactions in the chemistry approach of the cycloaddition, which is called the 1,3-dipolar reactions, and also known as the reactions of Huisgen,[64] where Huisgen and co-workers presented many lectures and research in the 1960^{s}, the year that Huisgen began to make applications of this type of reaction to prepare the heterogeneous five-membered ring containing a nitrogen atom since this ring has pharmacological importance and important biological activities.[65] Such reactions are similar to the Diels-Alder reactions, in which coordinated successive additions occur between two molecules.[66] The first is referred to as [a-b-c], called the 1,3-dipole part, and the second is referred to as d-e, an unsaturated reactant called a dipolarophile and contain either double or triple bond between two carbon atoms (Figure 1,9):

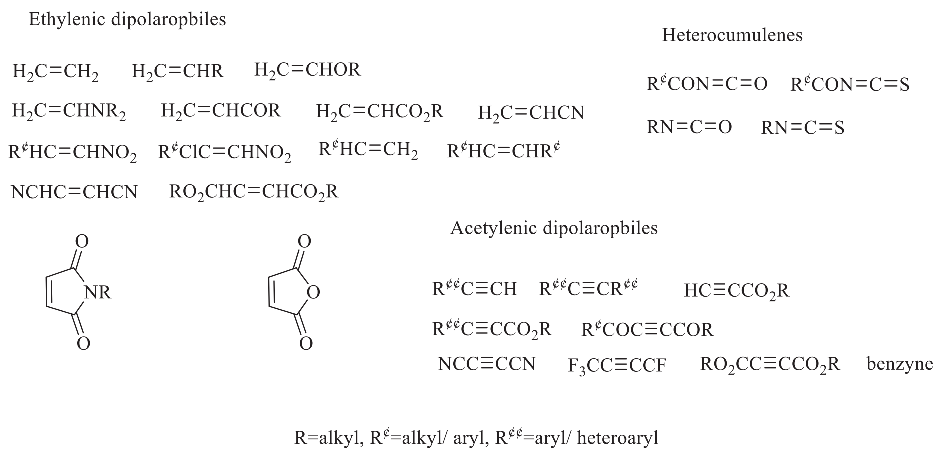


Figure 1,9: lists some commonly used dipolarophiles

Where a contains only six electrons in the outer shell and c contains at least one unshared pair of electrons to eventually give a heterogeneous five-membered ring (Figure 1,10).[62]

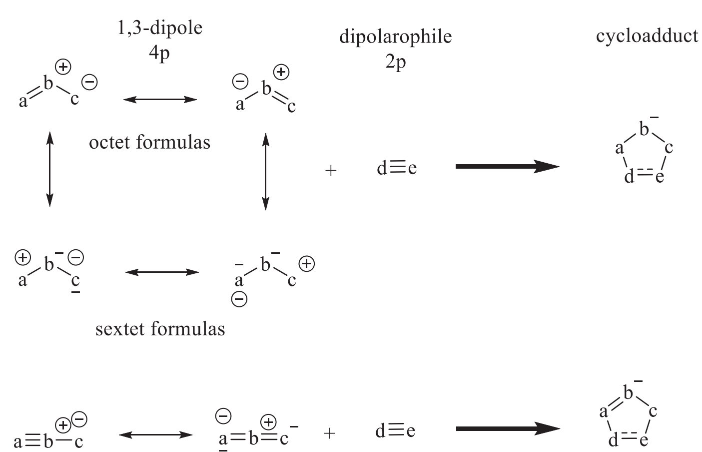


Figure 1,10: 32CA of 1,3-dipoles "abc" to dipolarophiles "de" to give five-membered heterocycles (only lone pairs relevant for the 4p system are drawn)

The transition state is shown in figure 1,11 the 1,3-dipolar reaction resulted from the interaction of two different systems, one has 2π-electrons, is called a dipolarophile, and the other with a 4π-electron is called a 1,3-dipole. The explanation is shown by the boundary orbital theory which shows the differences between the two interacting substances.[67]

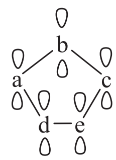
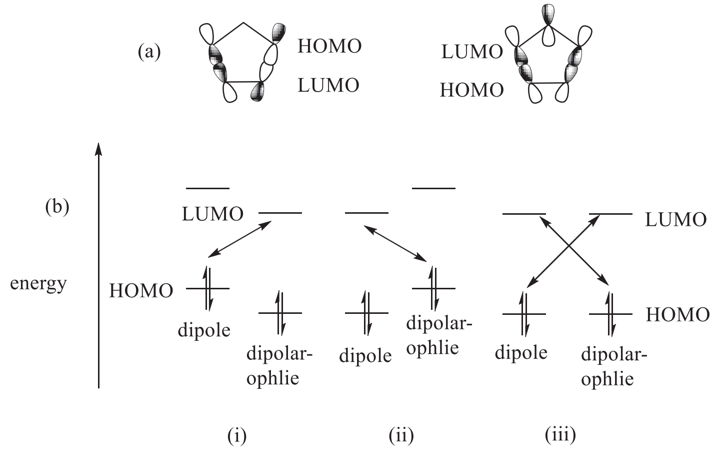


Figure 1,11: The transition state of the 1,3-dipolar reaction

The transition State occurs when the interaction conditions have met the requirement of the presence of a π-orbital field for one of the reactants and the last empty π^*-orbital field for the second substance, as well as the presence of a compatible overlap in energy and direction for each of the overlapping orbitals. And as a result, an overlap between the occupied high-energy π-orbital (HOMO) with the orbitals Low-energy unoccupied (LUMO), and this results in a relative difference in energy for the so-called boundary orbits,[68] (Figure 1,12). 1,3-dipolar reactions prefer that one of the components of its reactants has nucleophilic groups and the other electrophilic groups dipolarophiles, giving easy and preferred interactions, 1,3-dipolar whenever it contains electrophilic groups, it has a lower energy LUMO level, and conversely, for the species that contain nucleophilic groups, it has a high energy HOMO value, and for this see that 1,3-dipolar reactions prevail in the following types.[69]



(a) Frontier orbital combinations in 1,3-dipolar addition
(b) Types of interactions
(i) HOMO (dipole)-LUMO (dipolarophile) dominant
(ii) LUMO (dipole)-HOMO (dipolarophile) dominant
(iii) Neither dominant

Figure 1,12: The relative energies of frontier orbitals

1.4.1.1 Imidazolidin Ring

An aliphatic heterocyclic organic compounds (saturated imidazoles) consist of a five-membered ring consisting two nitrogen atoms in two different positions called imidazolidine also known as tetrahydroimidazoles.[70] It has several derivatives, including imidazolidinone (imidazolidine-2,4-diones) if the ring contains a carbonyl group (C=O) and thioxo imidazolidinone (imidazolidine-2,4-thione) if it has a thion group (C=S), (Figure 1,13).[71]

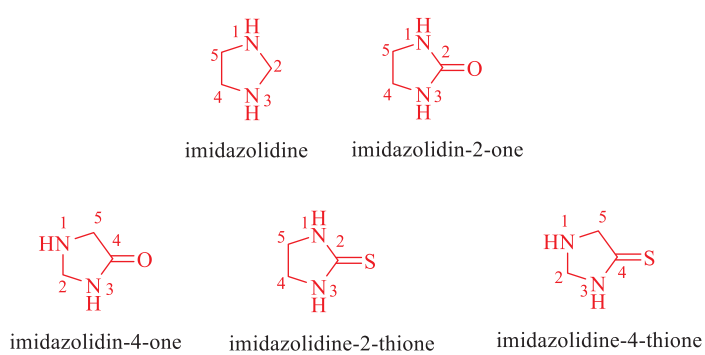
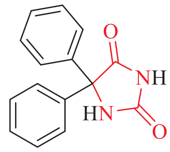
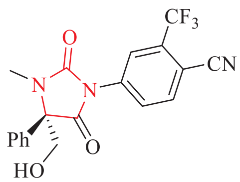


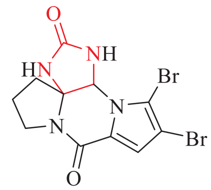
Figure 1,13: The five-membered ring of imidazolidine and nitrogen sites

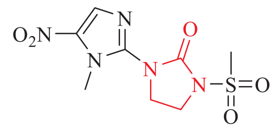
1.4.1.2 Biological and Pharmacological Uses of Imidazolidin

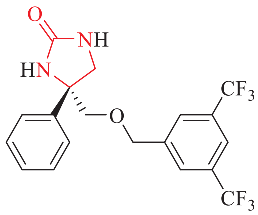
The imidazolidine derivatives possess assorted pharmacological properties.[72] Imidazolidine-2,4-diones (or hydantoins) are well-known compounds since their discovery, over a century ago.[73] Antimicrobial activity of some of these compounds has been investigated against cocci and bacilli,[74] antiulcer,[75] antiarrhythmics,[76] antidiabetic,[77] methicillin-resistant,[78] antifungal,[79] antineuralgic,[80] antiepileptic,[81] treatment of schistosomiasis infections,[82] anti-inflammatory,[83] antimetastatic, antidepressant and antipsychotic.[84] The molecules in figure 1,14 show the importance of the five-membered ring currently being studied, pharmacological and biological, as in molecule phenytoin **66,**[85] which is used as a nerve pain inhibitor, compound GLPO4929 **67**,[86] which is used as a human androgen receptor agonist, dibromophakellstatin **68,**[87] anti-tumor, setranidazole **69,**[88] anti-pain agent, potent NK1 **70,**[89] antagonist, DW2282 **71,**[90] anticancer, pimozide **72,**[91] antipsychotic drug, azlocillin **73,**[92] a derivative of penicillin that is used as an antibacterial and biotin **74,**[93] or vitamin B7 is found in almost all foods.

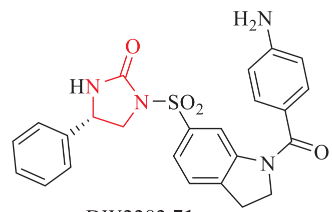

Phenytoin **66**

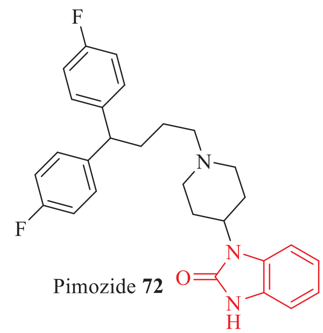

GLPG04924 **67**

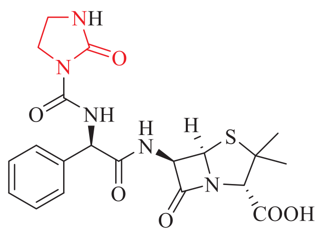

Dibromophakellstatin **68**


Setranidazole **69**


Potent NK1 **70**


DW2282 **71**


Pimozide **72**


Azlocillin **73**

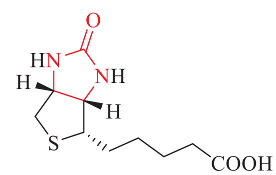
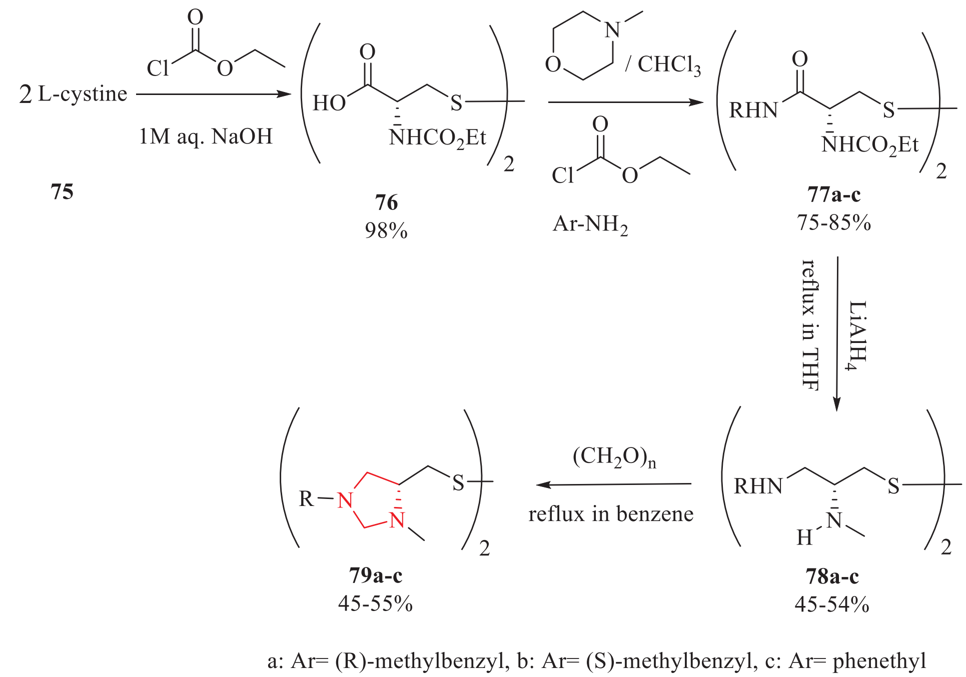

Bioti **74**

Figure 1,14: Some biologically active drugs with imidazolidine skeleton

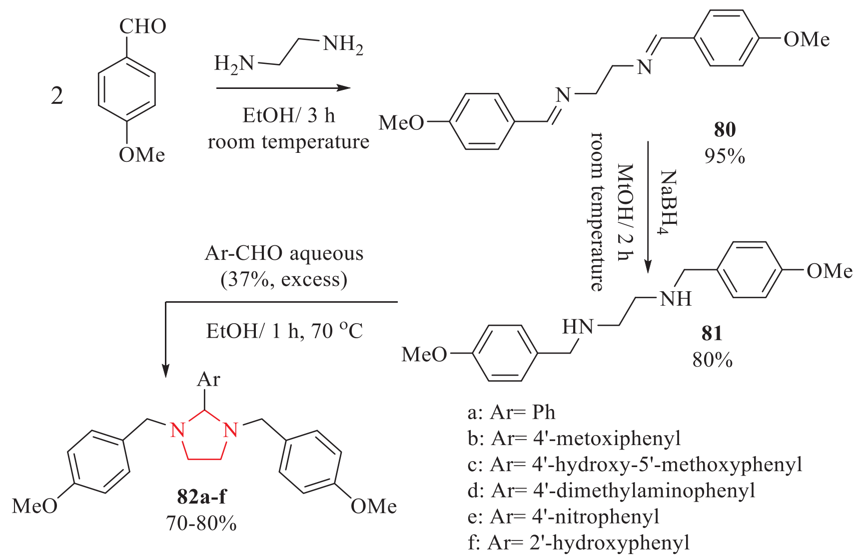
1.4.1.3 Synthesis of Imidazolidines

Braga and co-workers in 2002 managed to synthesize an imidazolidine ring disulfides derivative (Scheme 1,11), where these derivatives act as catalysts for some reactions.[94]



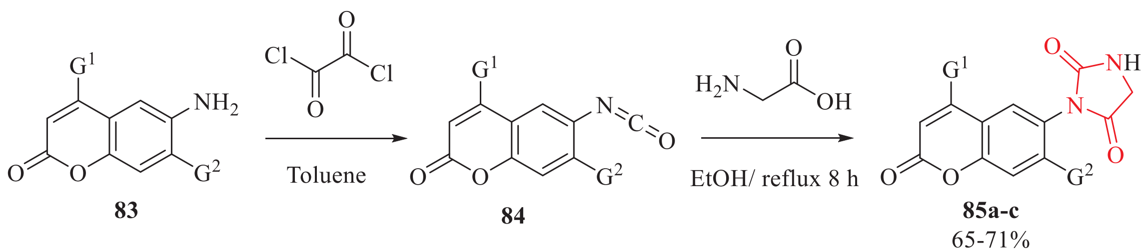
Scheme 1,11: synthesize of imidazolidine by Braga and co-workers

Carvalho and co-workers in 2010 prepared *N*,*N*-disubstituted ethylenediamine and imidazolidine derivatives, (Scheme 1,12) and their in *vitro* biological activities.[95]



Scheme 1,12: synthesize of imidazolidine ring by Carvalho and co-workers

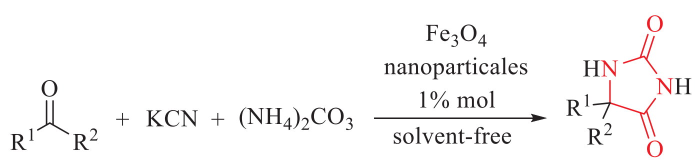
In 2011, Mulwad and co-workers synthesized novel imidazolidine derivatives by reacting 6-aminocoumarin with oxalyl chloride to give the coumarinyl-6-isocynate which on treatment with glycine in the presence of toluene as a solvent gave three the product of imidazolidine derivatives shown scheme 1,13 and then screening their biological activity against three strains of bacteria using disk diffusion method.[96]



84a-85a G^1= H G^2= CH_3
84b-85b G^1= CH_3 G^2= CH_3
84c-85c G^1= H G^2= H

Scheme 1,13: synthesize of imidazolidine ring by Mulwad and co-workers

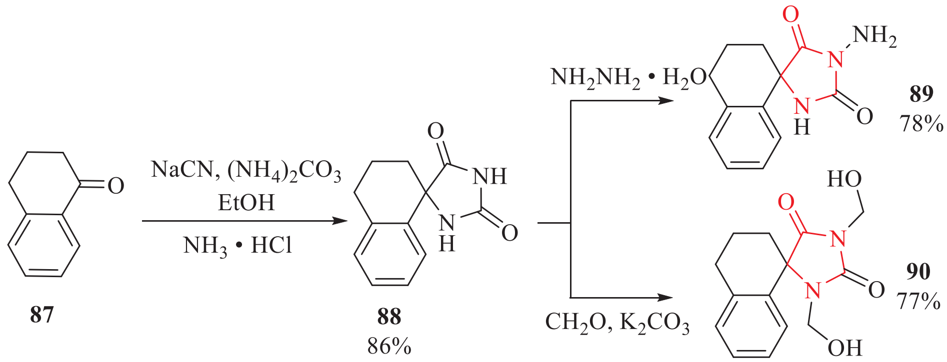
The researcher, Javad Safari,[97] developed a method for the synthesis of imidazolidine derivatives using magnetic Fe_3O_4 nanoparticles in solvent-free conditions (equation 1,4). This method has multiple advantages such as reusing the catalyst again, obtaining a high yield, short time to complete the reaction. In addition the magnetic Fe_3O_4 can be separated from the mixture easily using an external magnet.



86a-o
81-99%

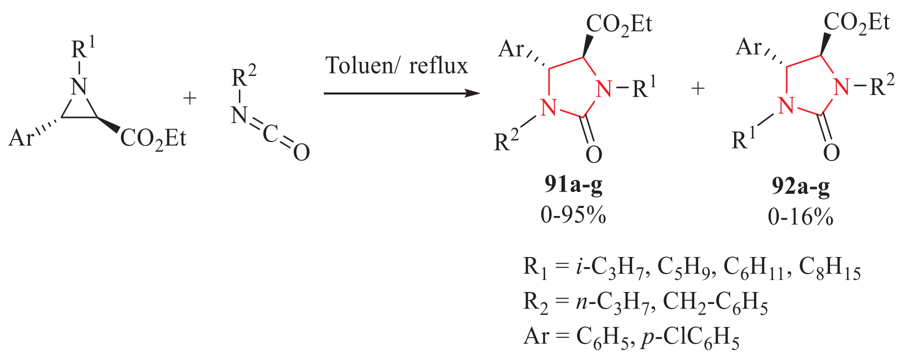
Equation 1,4: synthesize of imidazolidine ring by Javad Safari

Marinov and co-workers in 2014 synthesized two imidazolidine compounds, 2,5- dione derivatives **89** and **90** from the imidazolidine compound **88,** (Scheme 1,14).[98]



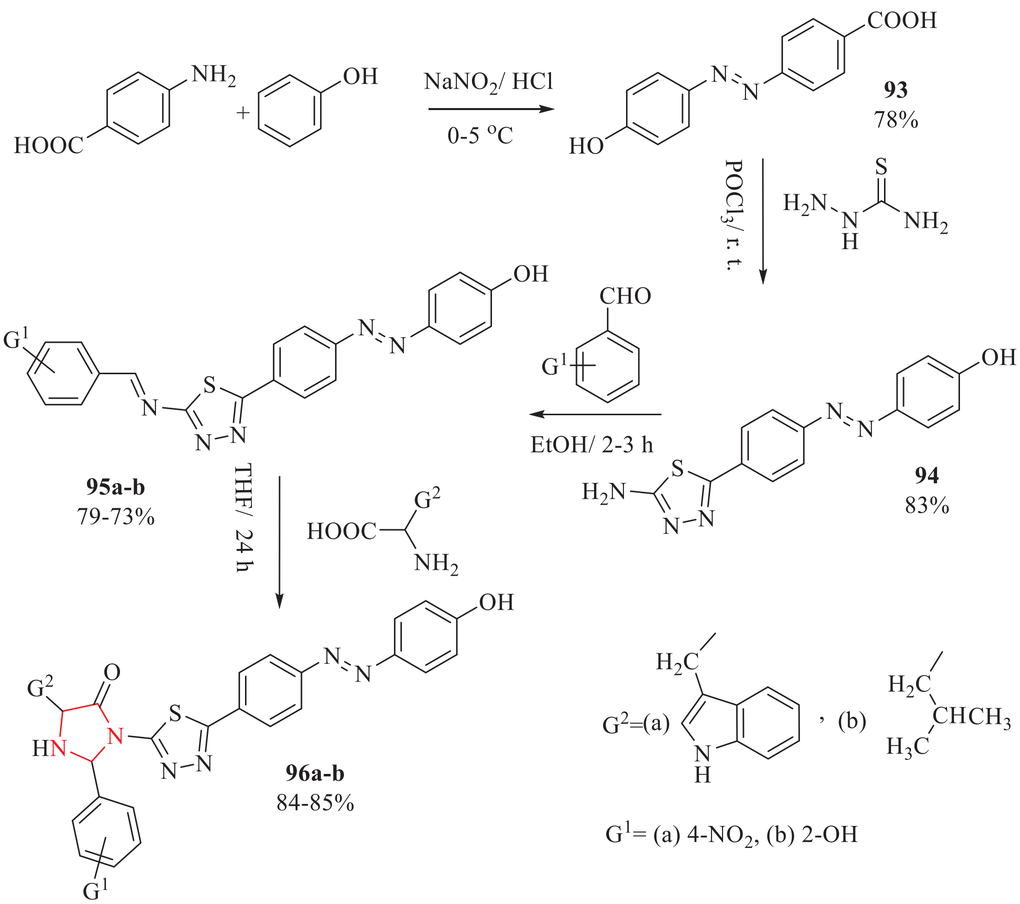
Scheme 1,14: synthesize of imidazolidine ring by Marinov and co-workers

Tabarki, used aziridine-2-carboxylates as starting materials in the reaction synthesis of imidazolidine-2-ones derivatives (Equation 1,5).[99]



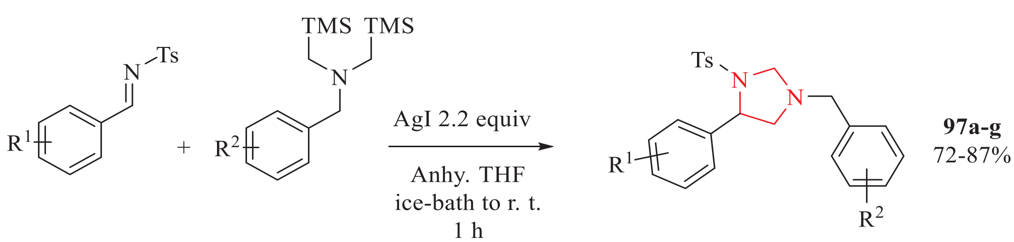
Equation 1,5: synthesize of imidazolidine ring by Tabarki

In 2015, Mohammed and co-workers prepared some derivatives of imidazolidine-2-ones *via* cycloaddition reactions of the imine two types of amino acids to form a five-membered ring, (Scheme 1,15).[100]



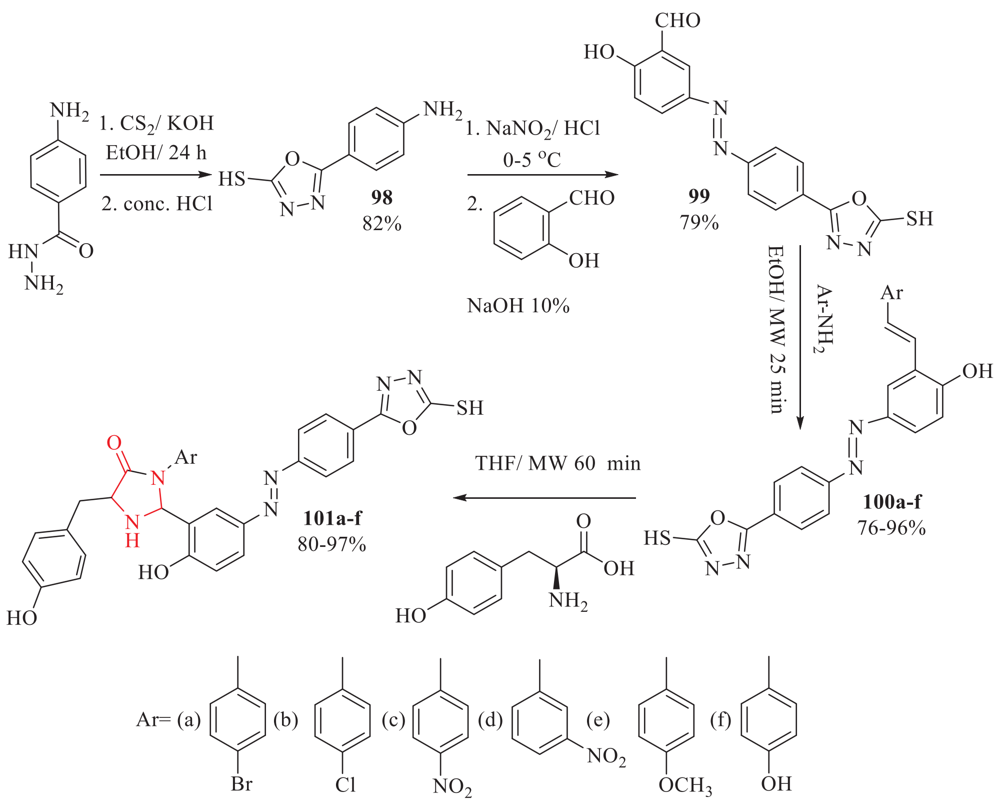
Scheme 1,15: synthesize of imidazolidine ring by Mohammed and co-workers

In 2017, Laha and co-workers developed reaction between non-stabilized azomethine ylides with *N*-sulfonyl imines to give imidazolidene sulfonated derivatives (Equation 1,6), and the research found that the mechanical reactants prefer 1,3-dipolar cycloaddition rather than Michael addition.[101]



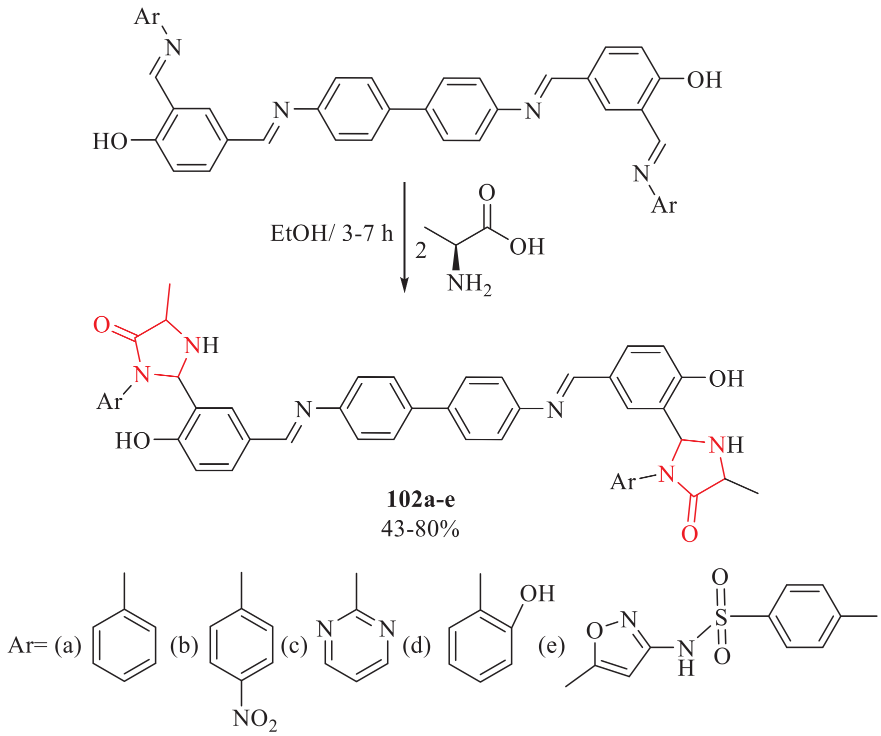
Equation 1,6: synthesize of imidazolidine ring by Laha and co-workers

Using microwave radiation technology, imidazolidine-2-ones derivatives were prepared by reacting compounds containing an imine group with tyrosine (Scheme 1,16) by Abood and co-workers. Their biological activities on *Staphylococcus aurous* and *Escherichia coli* bacteria, gave good activity.[102]



Scheme 1,16: synthesize of imidazolidine ring by Abood and co-workers

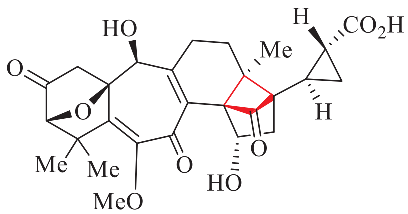
Several imidazolidine derivatives were synthesized as shown in equation 1,7 by Dalaf and co-workers, derivatives containing an imine group with aniline gave compounds **102a-e**. Testing the biologically activity against different types of bacteria, such as *Escherichia coli*, *Klebsiella Staphylococcus aurous*,and *Staphylococcus epideridis*.[103]



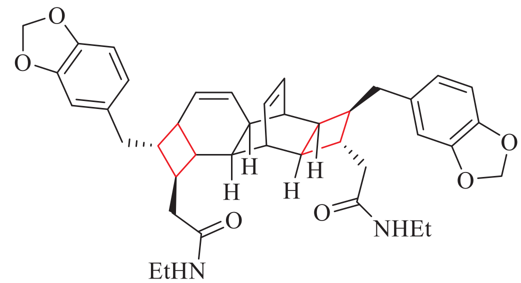
Equation 1,7: synthesize of imidazolidine ring by Dalaf and co-workers

1.4.2 Cycloaddition [2+2→4] Reactions

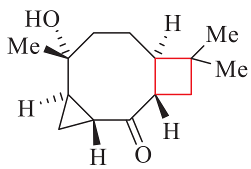
To synthesize the heterocyclic tetracyclic ring, cycloaddition reactions are used, through which the ring can be formed.[104] And this ring is important in terms of being the basic structure of organic chemistry compounds where there is a carbocyclic consisting of four carbon atoms such as cyclobutanes and cyclobutenes in many complex natural products, (Figure 1,15).[105]



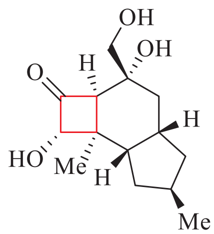
Solanoeclepin A **103**



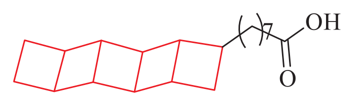
Kingianin A **104**



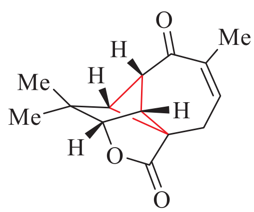
Rumphellolide F **105**



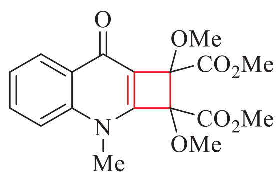
Tsugicoline M **106**



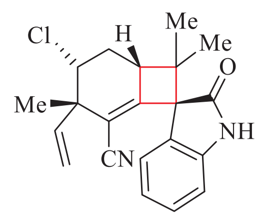
Pentacycloanammoxic acid**107**



(+)-Aquatolide **108**



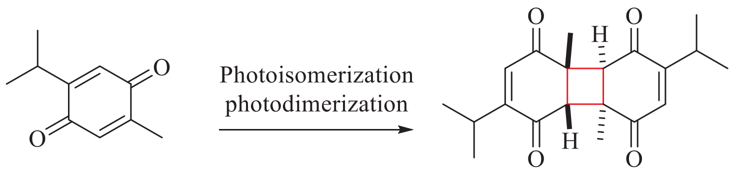
Cyclomegistine **109**



Weiwitindolinone **110**

Figure 1,15: Some biologically active drugs with four-membered ring skeleton

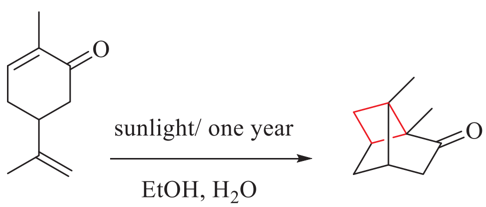
One of the most common and quick ways to synthesize butane rings is the [2+2] photocycloaddition using two unsaturated reactants.[106] Among the substances that enter this kind of reaction are olefins which are effective against sunlight and ultraviolet rays, and the first photochemical compound found in the *Nigella Sativa* plant is thymoquinone **111**,[107] Which consists of unsaturated double bonds that have undergone photoreactions to form cyclobutane **112,**[108] as discovered by Liebermann in 1877, (Equation 1,8).[109]



111 112

Equation 1,8: Fotoisomerization of thymoquinone

The first [2+2] photocycloaddition reaction was reported by Prof. Giacomo Ciamicin and Dr. Paolo Silber in 1908 when they observed the formation of carvone camphor **114** on exposure of carvone **113** to sunlight for one year, (Equation 1,9).[110]



113 114 6%

Equation 1,9: The first [2+2] photocycloaddition reaction

Other common methods for cyclobutane synthesis include cyclization of acyclic precursors, thermal ketene [2+2] cycloaddition, Lewis-acid promoted formal cycloaddition, ring expansions, and ring contractions, (Figure 1,16).[111]

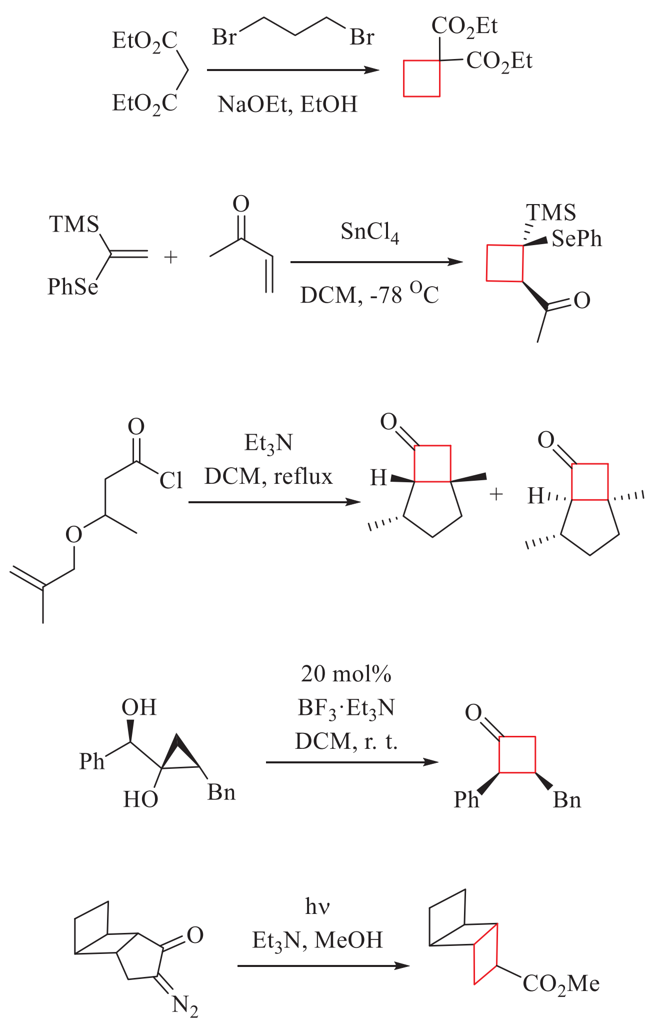
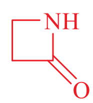


Figure 1,16: Common methods for cyclobutane synthesis

1.4.2.1 *β*-lactam Ring

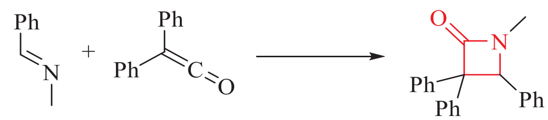
β-Lactam, commonly known as 2-Azetidinones, *β*-lactam ring is a four-membered cyclic amide. It is named as such, because the nitrogen atom is attached to the *β*-carbon relative to the carbonyl group, the above is illustrated in figure 1,17 below.[112]



β-lactam
β-propiolactam
2-Azacyclobutanone
2-Azeyidinone
Azetidin-2-one

Figure 1,17: General structure of the β-lactam ring

The first synthetic β-lactam **117** was reported by Staudinger in 1907 *via* the reaction of the compound **115** with diphenylketene **116** in a [2+2] cycloaddition, (Equation 1,10).[113]



Equation 1,10: The first synthetic β-lactam

The history of the β-lactam ring, arguably one of the most acclaimed heterocycles studied over the last century, tells a tale rich in curiosity, serendipity, and gravity spanning the fields of chemistry, biology, and medicine. Its fame is attributed to the enormous influence of β-lactam antibiotics on global health since Sir Alexander Fleming's discovery of penicillin and its ability to annihilate pathogenic bacteria in 1928[114] and Dorothy Crowfoot-Hodgkin's confirmation of its structure by X-ray crystallography in 1945.[115] The β-lactam ring exist in many antibiotics, as it is considered the main part of the effectiveness of these antibiotics. Hence, it gained its importance in the synthesis of organic chemicals and clinical and biological treatments.[116] The β-lactam ring is included in many of the most common antibiotics, amounting to half of the global antibiotics. Penicillin, cephalosporins, their derivatives, and others. (Figure 1,18) shows some them.[117]

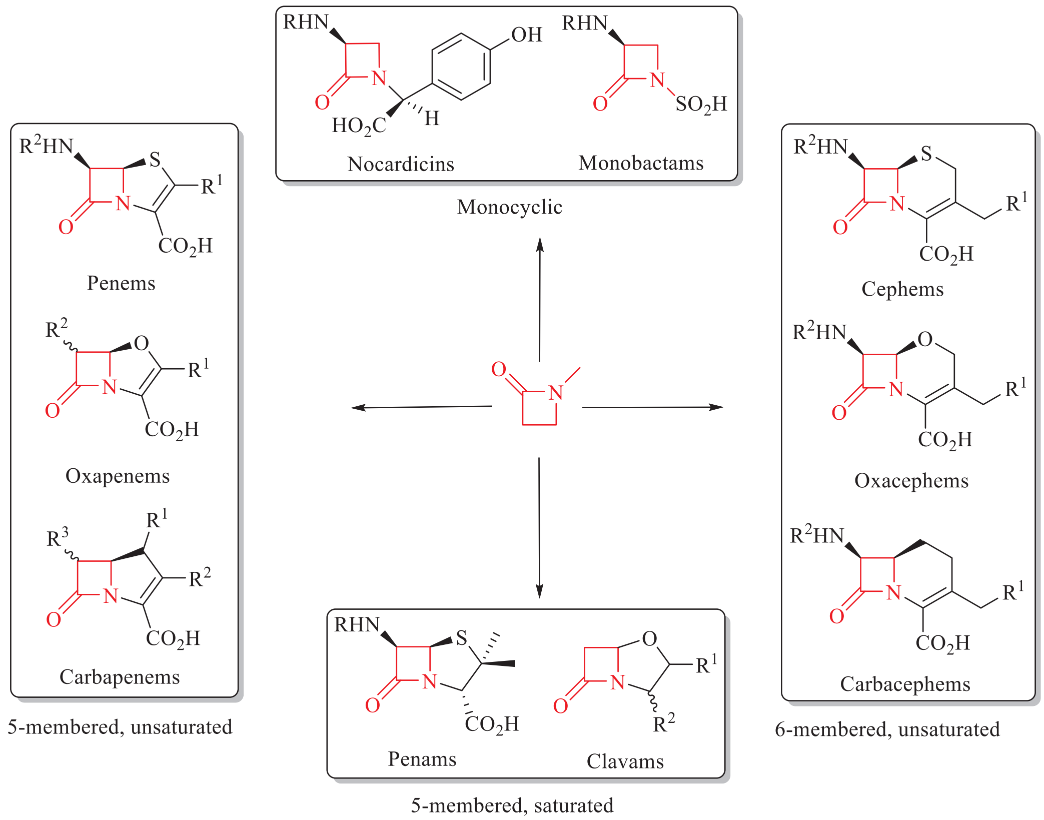


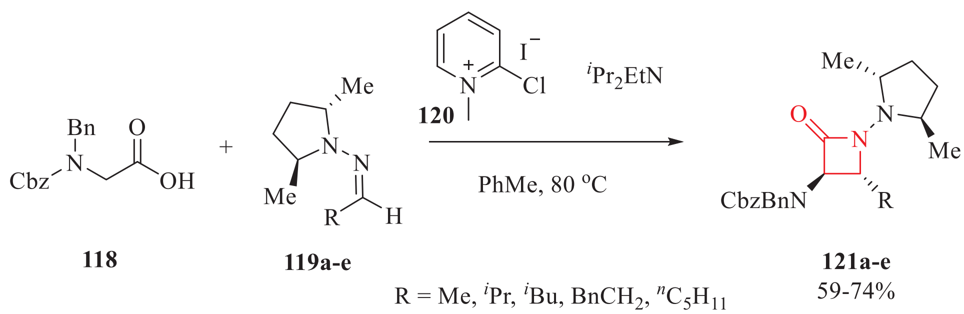
Figure 1,18: General structures of the derivatives of theβ-lactam ring

β-Lactam have also other pharmaceutical uses such as anti-inflammatory, antifungal, anti-hepatitis, analgesic properties, antihyperglycemic, LHRH antagonists, cholesterol absorption, inhibitors, and anticancer agents.[118] In addition, the ring has received significant attention from medical and synthetic chemists because of its importance in organic synthesis as a versatile synthetic intermediate and chiral synthons.[119] All of these biological, clinical, and medical activities of these drugs have either been reduced or disappeared in recent years due to the resistance shown by bacteria and viruses towards the mechanism of the drug to eliminate them. Therefore, it has become necessary to develop these drugs by forming functional groups on them to increase their ancient activities against diseases.[120]

1.4.2.2 Synthesis of *β*-Lactam Ring

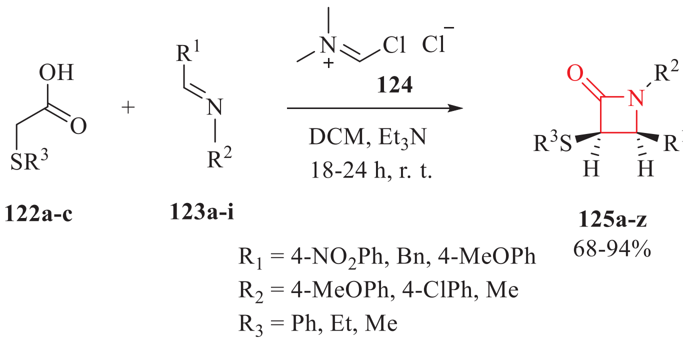
1.4.2.2.1 Staudinger's Keten-Imine Reaction

The Staudinger's cycloaddition reaction is the most fundamental and versatile method for the synthesis of 2-azetidinones (Scheme 1.26)[121], The experiment was conducted by Lopez and co-workers in 2008 using organic acid (*N*-benzyl-*N*-(benzyloxycarbonyl)glycine) **118** as ketene compound with imine derivatives (aliphatic hydrazones) **119a-e** in the presence of catalysts such as Mukaiyamas's reagent **120**, where a *β*-lactam ring was formed for different derivatives **121a-e** and with different yield (59-74%), (Equation 1,11).[122]



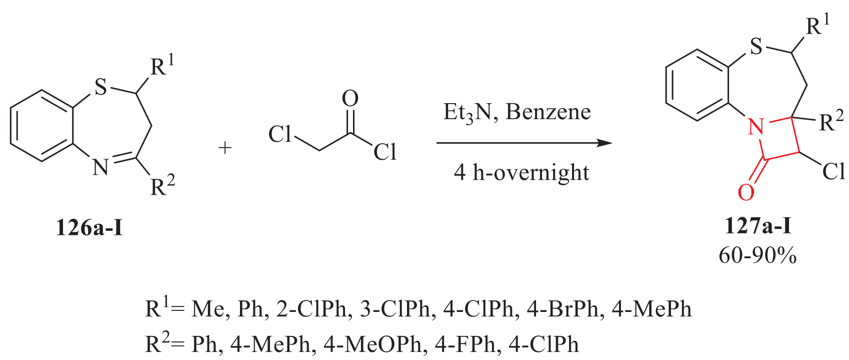
Equation 1,11: synthesize of *β*-lactam ring by Lopez and co-workers

Zarei in 2011, [123] used the Staudinger reaction for mercaptoacetic acids **122a-c** with Schiff base **123a-i** in the presence of the Vilsmeier reagent **124** at room temperature leading to the formation of 3-thiolated-2-azetidinones **125a-z** in good to excellent yields constitutes an excellent example of application of a sulfur-substituted ketene precursor in the Staudinger reaction, (Equation 1,12).



Equation 1,12: synthesize of β-lactam by Zarei

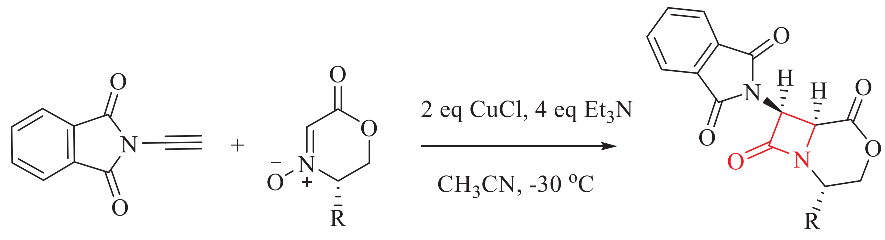
Fused β-lactam has been reported to be obtained from benzothiazepine-β-lactam by Staudinger cycloaddition of 2,3-dihydro-1,5-benzothiazepines **126a-l** and chloroacetyl chloride in the presence of Et_3N as a catalyst, (Equation 1,13):[124]



Equation 1,13: synthesize of β-lactam ring by Zarei

1.4.2.2.2 Kinugasa Reaction

In 1972, Kinugasa and Hashimoto reported the formation of β-lactam by a reaction of copper (I) phenylacetylide and nitrones with pyridine as both base and solvent.[125] Chmielewski and co-workers have reported on the Kinugasa reaction of phthalimido acetylene **128** with cyclic nitrones **129**, resulting in bicyclic β-lactam with moderate selectivity, (Equation 1,14).[126]



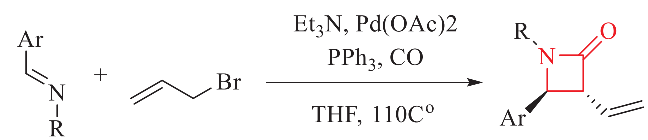
128 129 130a-b
48-66%

R= Ph, CH_2OBn

Equation 1,14: synthesize of β-lactam ring by Chmielewski and co-workers

1.4.2.2.3 Torii's Cyclocarbonylation

The Schiff base compound react under CO pressure with allyl bromide by [2+2] cycloaddition in the presence of Et_2N, $Pd(OAc)_2$ and PPh_3.[127] The synthesis of compound **132** was Pd-catalyzed [2+2] carbonylative cycloaddition between allyl bromide and imine compound (Equation 1,15).[128]



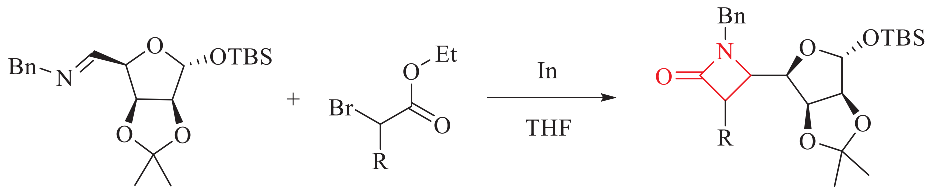
131a-k 132a-k
75-95%

Ar= Ph, 2,4-dimethylthiazole, 2-methylbenzothiazole
4-MePy, 2-MePy, 3-MePy
R= ^{t}Bu, ^{n}Bu, ^{i}Pr, Et

Equation 1,15: synthesize of β-lactam ring by Torii's Cyclocarbonylation

1.4.2.2.4 Reformatsky Reaction

One of the important reaction that form the carbon-carbone bond is the reaction of the alpha-halo ester compound with an aldehyde or a ketone, in the presence of zinc metal, to produces a β-hydroxy ester.[129] The strategy of this reaction can be used to form β-lactams by replacing the aldehyde and ketones with azomethine compounds[130] in the presence of the same metal or by replacing it with rhodium,[131] trimethylsilyl[132] or diethyl zinc.[133] For example, the reaction of carbohydrate imine **133** with 2-alkyl/phenyl-2-bromoesters **134a-c** in the presence of Indium to synthesis of 2-azetidinones **135a-c**, (Equation 1,16):[134]



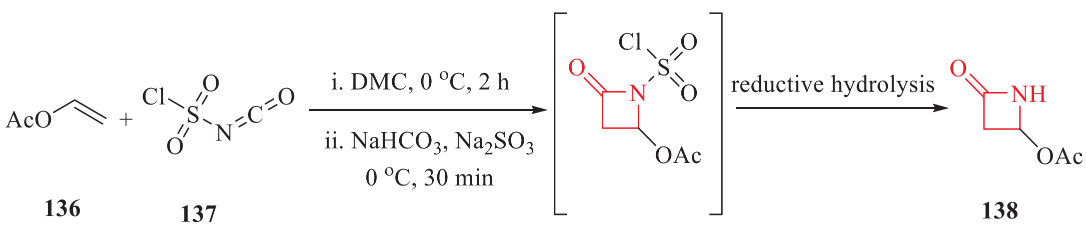
133 **134a-c** **135a-c** 39-61%

R= Ph, Me, ^{n}Pr

Equation 1,16: synthesize of β-lactam ring by Reformatsky reaction

1.4.2.2.5 Alkene-Isocyanate Cycloadditions

A reaction between isocyanate derivatives with electron-deficient alkenes or alenes leads to form a hetrotetracyclic ring.[135] This method is useful for building antibiotic compounds that contains a β-lactam ring.[136] (Scheme 1,17).[137]



136 **137** **138** 35%

Scheme 1,17: synthesize of β-lactam ring by Alkene-Isocyanate cycloadditions

1.4.2.3 Mode of Action β-Lactam and Mechanisms of Resistance

The mechanism of action of the antibiotic towards bacteria is the inhibition of the enzyme transpeptidases responsible for linking the peptides with each other to form peptidoglycan, where the inhibition of such enzyme leads to the absence of binding and thus disruption of the bacteria cell walls,[138] (Figure 1,19).

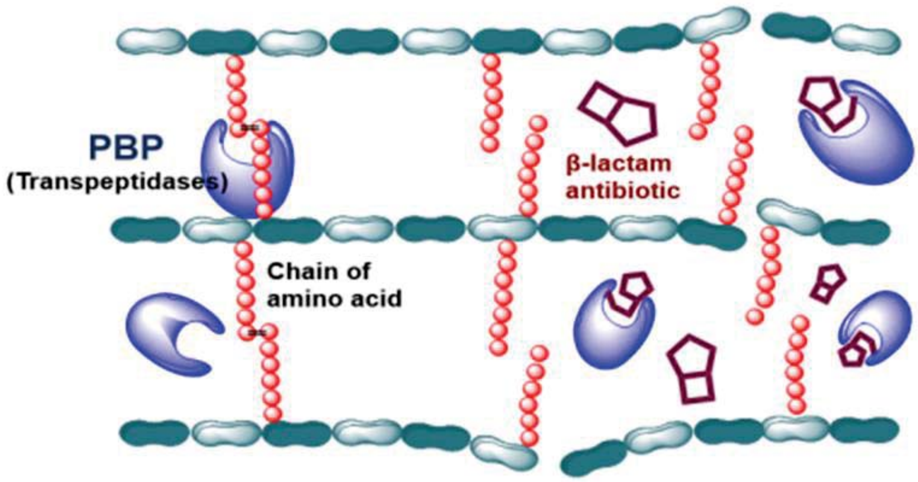


Figure 1,19: A simplified diagram of the mechanism of action of β-lactams

Since the discovery of penicillin and the accompanying medical revolution in the field of antibiotics for the treatment of infectious diseases,[139] and, after six years of the introduction penicillin into the therapeutic field, it was noticed that great resistance to its effectiveness start appeared. For example, the rate of resistance of *staphylococcus aureus* increased from 10% to 60% in British Hospitals has reached 90% at the global level.[140] Bacterial resistance to β-lactams is a threat and a global health concern to our weapon of antibiotics. The resistance shown by bacteria against β-lactam drugs is a threat and a global health concern to our weapon of antibiotics against bacterial infections.[141] The resistance of bacteria appeared in the form of their synthesis of an enzyme that attacks the β-lactam ring, opening it, canceling its effectiveness and preventing the attack of bacteria. The enzyme is β-lactamase enzyme.[142]The enzyme formed by the bacteria enzymatically degrades the amide bond of the β-lactam ring, and this decomposition loses its effectiveness and the antibody becomes inactive against the penicillin-binding proteins (PEPs) enzyme responsible for building the bacteria wall.[143]From this standpoint, successive attempts began to develop antibiotics to overcome the resistance shown by bacteria against antibiotics.

1.4.3 Cycloaddition Reactions [2+5→7]

This type of cycloaddition reaction takes place to synthesize the heterogeneous seven-membered ring[144] containing atoms such as oxygen, sulfur and nitrogen, and what is relevant to our study is the seven-membered ring that contains nitrogen and oxygen as two heterogeneous atoms in the seven-membered ring, which is called oxazepine,[145] there are three different types of oxazepine, (Figure 1,20).[146]

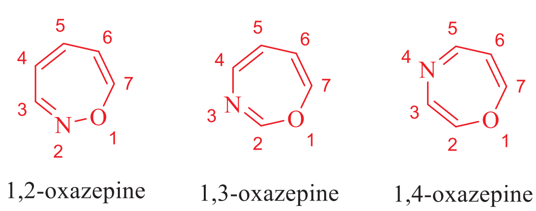
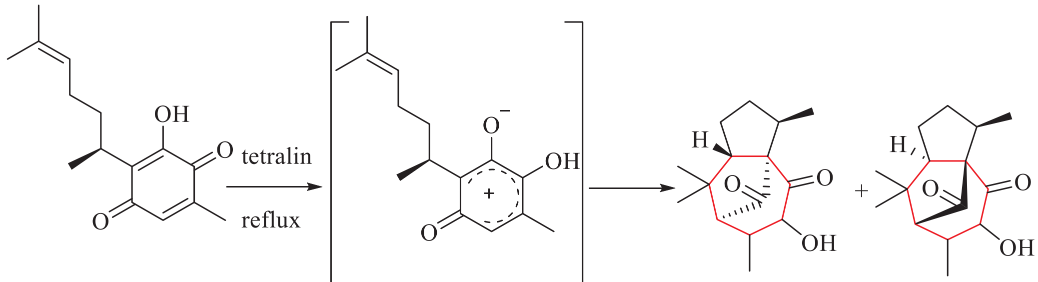


Figure 1,20: Structures of oxazepin rings depending on the positions of the oxygen and nitrogen atoms

The first reaction reported for the synthesis of the seven-membered ring was in 1885, by which perezone **139** to pipitzol **140** by Anschutz and Leather using the [2+5] cycloaddition mechanism, which was not explained at that time,[147] (Scheme 1,18).



a-pipitazol b-pipitazol

139 140

Scheme 1,18: The first reaction for the synthesis of the seven-membered ring

Later, this type of reaction has been given great attention, as great progress has been made, especially in the field of manufacturing natural compounds, where seven types of reactions have been identified through which the seven-membered rings are obtained, and these are shown in the figure 1,21.[148]

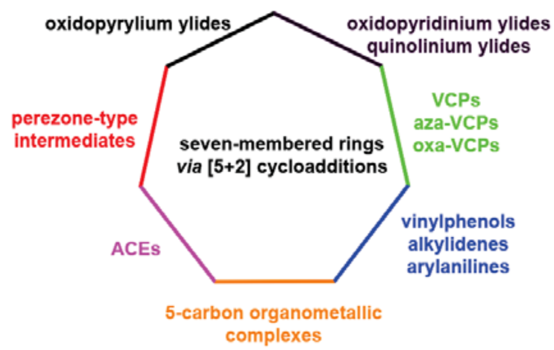
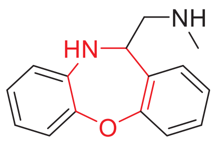
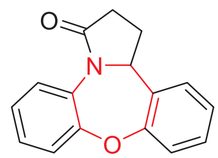


Figure 1,21: Main types of intermediates involved in [2+5] cycloadditions

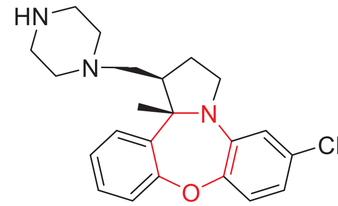
The seven-membered ring is involved in many life compounds, including pharmaceutical,[149] natural[144] and biological ones,[150] and it has considerable biological importance, it is used as an antagonistic, anti-cancer, anti-bacterial, anti-fungal, and many more, which brought a lot of attention of biological research groups,[151] (Figure 1,22).



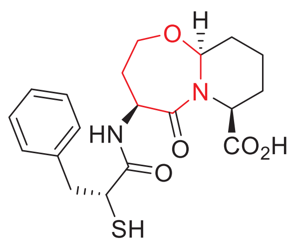
H1 receptor antagonist **141**



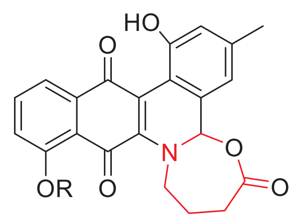
Sintamil **142**



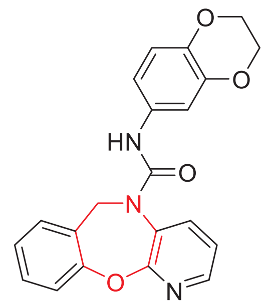
5-HT 2B antagonist **143**



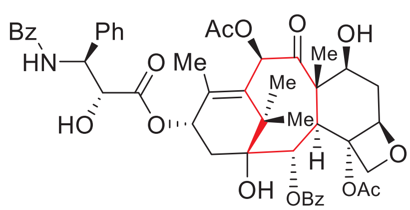
ACE and NEP inhibitor **144**



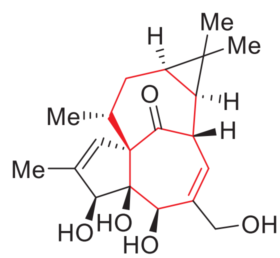
Jadomycin Hep **145**



SHMT2 inhibitor **146**



Taxol **147**



Ingenol **148**

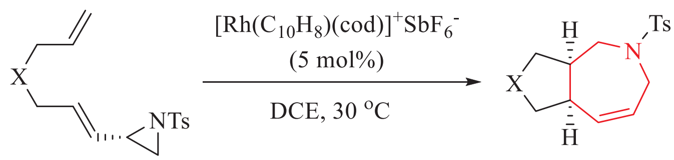
Figure 1,22: Examples of biologically active compounds bearing the 1,3-oxazepine and 1,4-oxazepine core structure

1.4.3.1 Synthesis of Seven-Membered Ring

This type of interaction has several routes to synthesize the seven-membered ring, which is of great importance, especially in natural products, the following is a model only for the many types of interactions, and to read the scientific paper, which is a review of many interactions to make up the seven-membered ring.[152]

1.4.3.1.1 Hetro [2+5] Cycloadditions of Vinylaziridines

Recently chemists have developed this type of reaction,[153] which forms the heterocyclic ring containing nitrogen atom for the importance of this ring in natural products.[154] Rhodium, Wender in 2002[155] as well as the methods of Zhang developed for a heterogeneous group of rings Heterogeneous catalysis of rhodium also by reacting vinylaziridine with alkyne.[156] In 2015, Zhang and co-works published a paper on the first catalytic reaction with rhodium-catalyzed, which yields a heterogeneous seven-membered ring through the [2+5] cycloaddition mechanism between vinylaziridines and alkene, (Equation 1,17).[157]



149

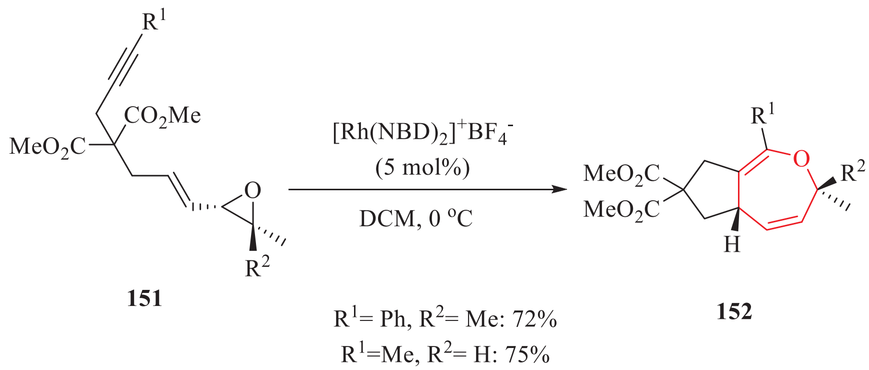
150
84-96%

X= NTs, NNs, O, $C(CO_2Me)_2$

Equation 1,17: synthesize of seven-membered ring by Zhang and co-workers

1.4.3.1.2 Hetero [2+5] Cycoladditions of Vinyloxiridines

The triple bond in vinyloxiranee reacts in the presence of a rhodium catalyst (5 mol%), Feng and Zhang reported the first reaction to produce the seven-membered ring containing the heterooxygen atom in 2017, as in equation 1,18, to form 2,5-dihydrooxepine **152**.[158]



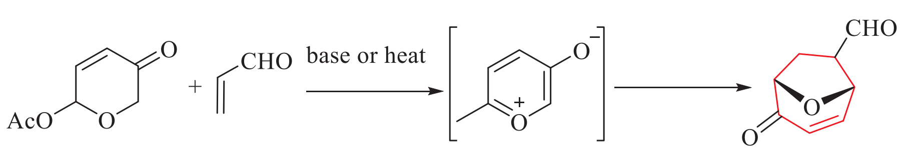
151

152

Equation 1,18: synthesize of seven-membered ring by Feng

1.4.3.1.3 Intermolecular [2+5] Cycloadditions

Using oxidopyrylium ions to synthesize the seven-bridge rings through thermal [2+5] cycloadditions, whereby using heat or using a base such as Et_3N,[159] acetooxyridine or its derivatives gives the 3-oxidopyrylium ion, these reactions were first reported by Hendrickson and Farina in 1980 with the reaction of acetoxyptranone **153** with acrolein **154** as shown in scheme 1,19.[160] Since then, many different alkenes with different groups have been used in this type of reaction by many researchers. Moreover, many of the products of these reactions have been used as main materials for the synthesis of many natural products.[161]

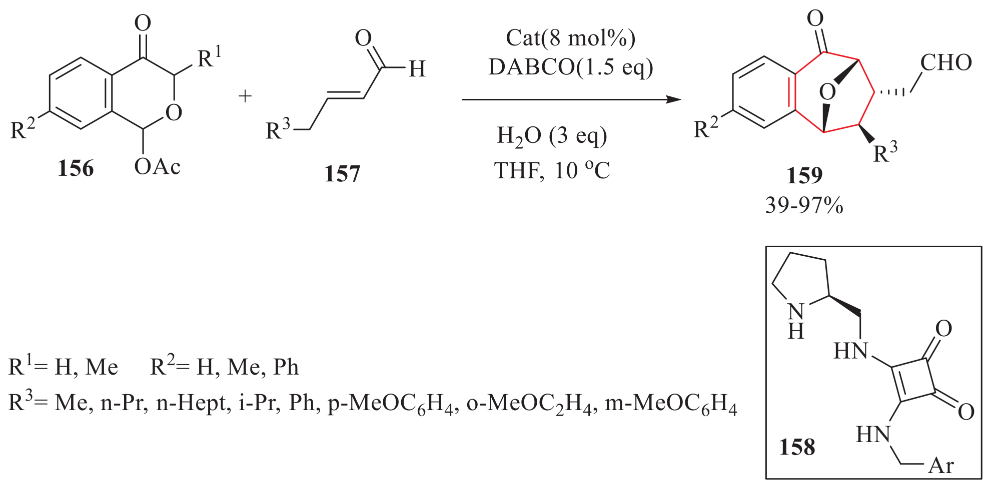


153 **154** **155** 69%

Scheme 1,19: synthesize of seven-bridge rings through thermal [2+5] cycloadditions

In 2011, Jacobsen and co-workers reported in a paper this type of reaction using a bifunctional primary amine organocatalyst, by reacting 1-acetoxyisochroman-4-ones **156** with a range of *α*,*β*-unsaturated aldehydes

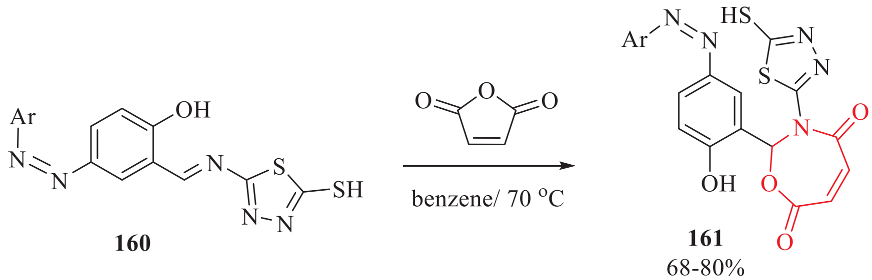
157 promoted by proline-derived squaramide bifunctional **158** to afforded 8-oxzbicyclo[3.2.1]octane derivatives **159,** (Equation 1,19).[162]



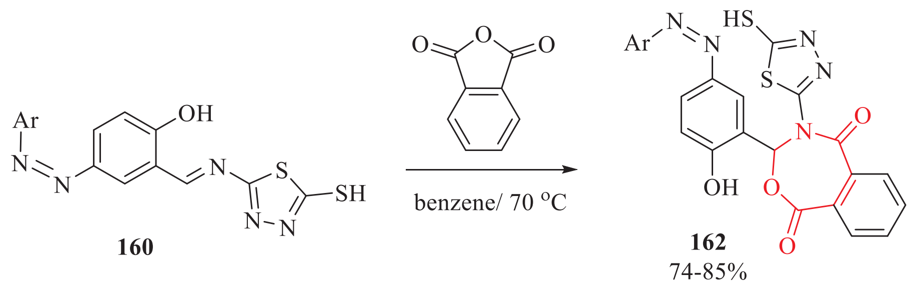
Equation 1,19: synthesize of seven-bridge rings by Jacobsen and co-workers

1.4.3.1.4 Miscellaneous [2+5] Cycloadditions

In 2015, Abood and co-workers reported the synthesis of novel 1,3-oxazepine moiety on the basis of [2+5] cycloadditions of the corresponding azoimies **160** with malic and phthalic anhydrides, as shown in equation 1,20, the reactions occurred through simple thermolysis at 70 °C in benzene.[163]



Ar= p-ClC_6H_4, p-$O_2NC_6H_4$, p-$MeOC_6H_4$, 2,4-$Cl_2C_6H_3$, 2,4-$Me_3C_6H_3$, 3-pyridyl



Ar= p-ClC_6H_4, p-$O_2NC_6H_4$, p-$MeOC_6H_4$

Equation 1,20: synthesize of 1,3-oxazepin ring by Abood and co-workers

1.5 Aim of the Study

The aim of the study is to synthesis a new derivatives of drug SMX by conducting several reactions such as diazotization, azo-coupling, schiff base, and cycloaddition to obtain: imidazolidine, β-lactame, and 1,3-oxazepine rings in order to develop the antibacterial activity of the drug.

Chapter Two

Experimental