



وزارة التعليم العالي والبحث العلمي

جامعة ديالى

كلية العلوم

قسم الكيمياء



## تخليق، تشخيص وتقييم الفعالية البايولوجية لبعض البايرازولات الجديدة المشتقة من اندول - ٢ - يليدين المعوض

رسالة مقدمة الى

مجلس كلية العلوم / جامعة ديالى

وهي جزء من متطلبات نيل درجة الماجستير في علوم الكيمياء

من قبل الطالب

**علي هابيل حسن**

بكالوريوس في علوم الكيمياء ٢٠١٦

كلية العلوم - جامعة ديالى

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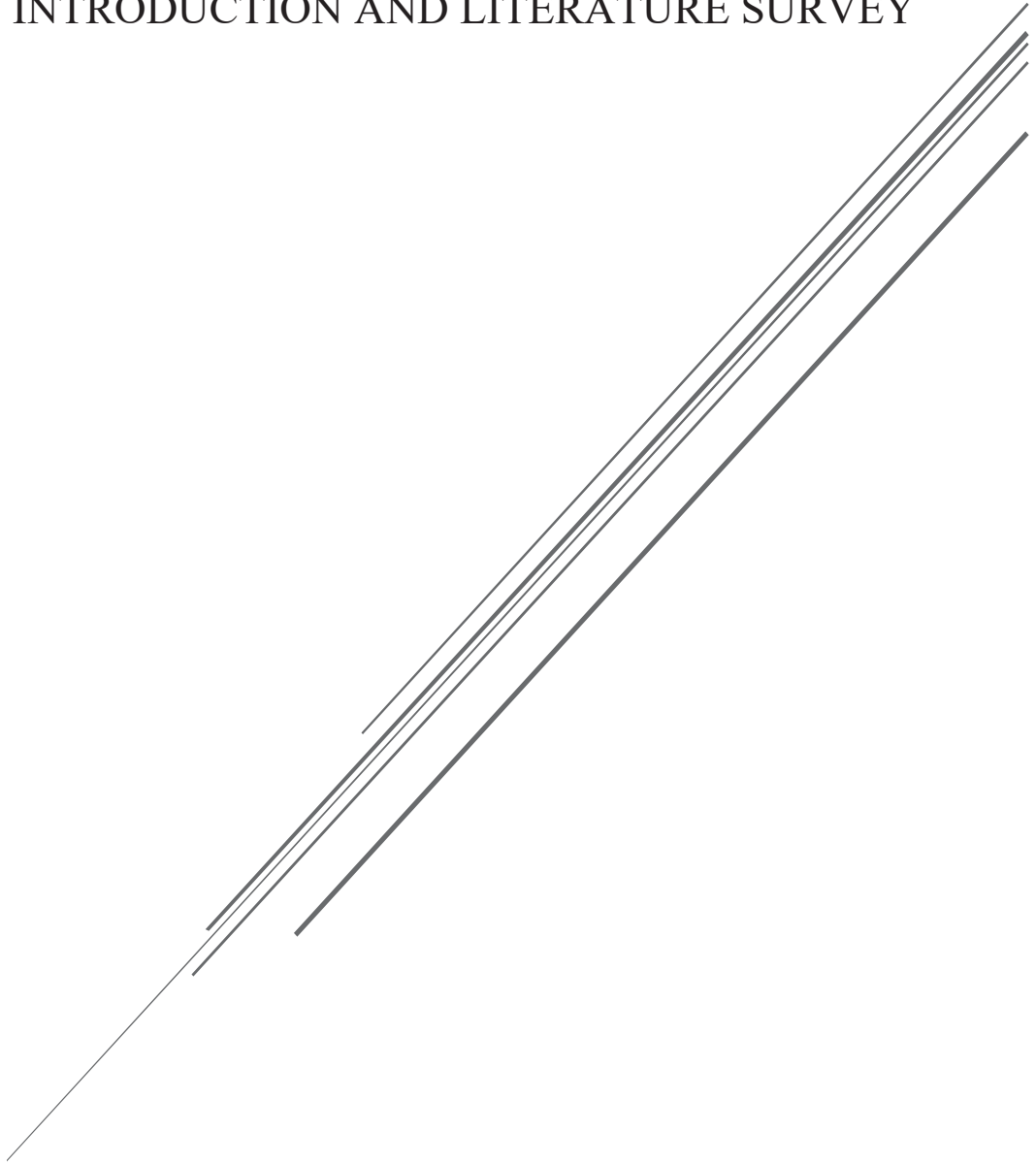
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# CHAPTER ONE

## INTRODUCTION AND LITERATURE SURVEY



## 1. 1. Heterocyclic compounds.

Cyclic compounds in which one or more of the ring atoms are different atom other than carbon are called heterocyclic compounds. Particles that are not carbon is called a heteroatom which is maybe N, O, and S. The heteroatom is a Greek word which means different [1]. Common rings of five-membered heterocyclic compounds containing a single heteroatom are 1*H*-pyrrole, thiophene, and furan. As shown in Figure (1-1)

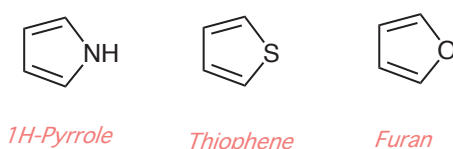


Figure (1-1): The chemical structures of 1*H*-pyrrole, thiophene, and furan.

While five-membered rings containing two heteroatoms (same kind of atoms) are pyrazoline and pyrazole. Figure (1-2)



Figure (1-2): The chemical structures of pyrazoline and pyrazole.

And five-membered rings contain two or three heteroatoms (different kind of atoms) such as oxazole, thiazole, isoxazole, isothiazole, etc. Figure (1-3)[2].

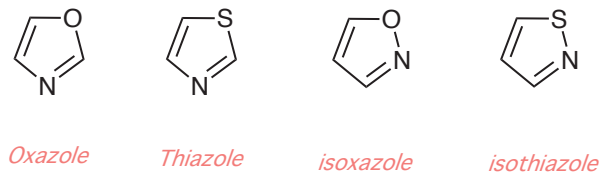


Figure (1-3): The chemical structures of oxazole, thiazole, isoxazole, and isothiazole.

At organic chemistry, heterocyclic compounds have constituted one of the largest areas for research [3]. They have performed a significant role in the evolution of pesticides, medicines and pharmaceutical applications[4-5]. Heterocycles have antiviral, antibiotic, antidepressant, antihypertensive, and anticancer activities. In the Comprehensive Medicinal Chemistry (CMC) database, more than 67% of the compounds listed contain heterocyclic rings. A large number of combinations of carbon, hydrogen, and heteroatoms can be designed, thereby providing compounds with the most diverse physical, chemical, and biological properties [6-7].

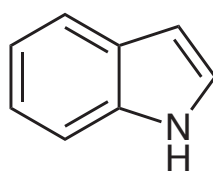
Heterocyclic compounds having nitrogen become attractive to the researchers and their unique structures led to several applications in different fields because of the widespread interest in heterocyclic, the synthesis of these compounds has always been among the most important research areas in synthetic chemistry [8]. In several cases, heterocyclic compounds containing nitrogen are useful building blocks for the development of agrochemicals, pharmaceuticals, functional materials, and dyes. A large number of methods have reported for construction of heterocyclic structures [9]. Because of their efficient, and selective synthetic strategies to access these compounds a diverse array of N-containing six-membered heterocyclic have constructed in higher yields and shorter reaction times as compared to normal conditions [10].

Five and six-membered heterocycles are abundant in nature and great significance to life because of many natural products contains many subunits in their structure such as hormones, vitamins, and antibiotics. Therefore, they have attracted significant attention in the composition of many important biological molecules. A practical method for the synthesis of such compounds is a great interest in synthetic organic chemistry. Among the all

heterocyclic, pyrazoline and pyrazole are a class of compounds with biological activities, such as antitumor, antioxidant, antimicrobial, calcium channel modulators and antipyretic [11].

## 1. 2. Indole.

The name indole is mixing of the word's indigo and oleum. Indole is an aromatic heterocyclic organic compound, and it has a bicyclic structure, consisting of a pyrrole nucleus fused in 2,3 positions with the benzene ring. Indole is non-basic nitrogenous compound. Indole chemistry began to develop with the study of the dye indigo. The word indole is coming from the name India, a blue dye imported from India identified as Indigo. Indigo can be turned to isatin and then to oxindole. Adolf von Baeyer reduced oxindole to indole in 1866 by using zinc dust. And he proposed a formula for indole in 1869 [12]. As shown in figure (1-4)



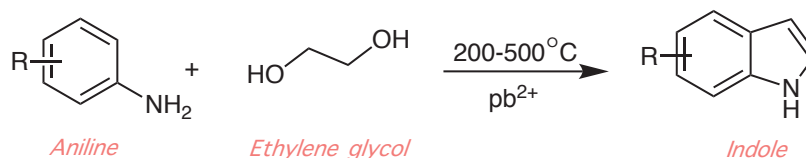
*Indole*

Figure (1-4): Baeyer structure for indole in 1869.

### 1. 2. 1. Review of previous synthesis and approaches to the indole.

The invention of new synthesis route to substituted indole has much attention from synthetic chemistry in the few last past years [13]. Due to its electron-rich character, and immediately reacts with hard and soft electrophiles, and it is not surprising to refer to it as the lord of the rings [14].

The main industrial routes for the synthesis of indole and its substituted derivative started from the reaction of ethylene glycol with aniline in the presence of lead ion as catalyst ( $Pb^{2+}$ ). Equation (1-1)



Equation (1-1): The main industrial routes for the synthesis of indole.

The reactions were conducted between 200 and 500 °C to afford the target compound about a 60% yield. [15].

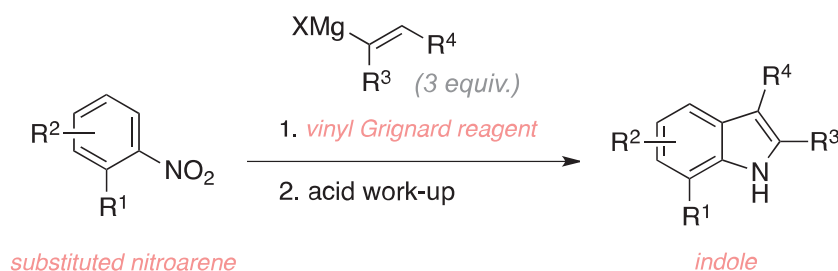
The preparation of indoles rings considered to be one of the most exciting reactions in organic chemistry. The chemistry of indole has been systematically reviewed from time to time [16]. As illustrated in table (1-1)

Table (1-1): Some importance methods for indole synthesis.

NO	Methods	Reactions	References
1	Fischer indole synthesis		[17]
2	Bischler-Mohlau indole synthesis		[18]
3	Gassman indole synthesis		[19]
4	Larock indole synthesis		[20]
5	Baeyer-Emmerling indole synthesis		[21]
6	Leimgruber-Batcho indole synthesis		[22]
7	Bartoli indole synthesis		[23]
8	Fukuyama indole synthesis		[24]
9	Hemetsberger indole synthesis		[25]
10	Madelung indole synthesis		[26]

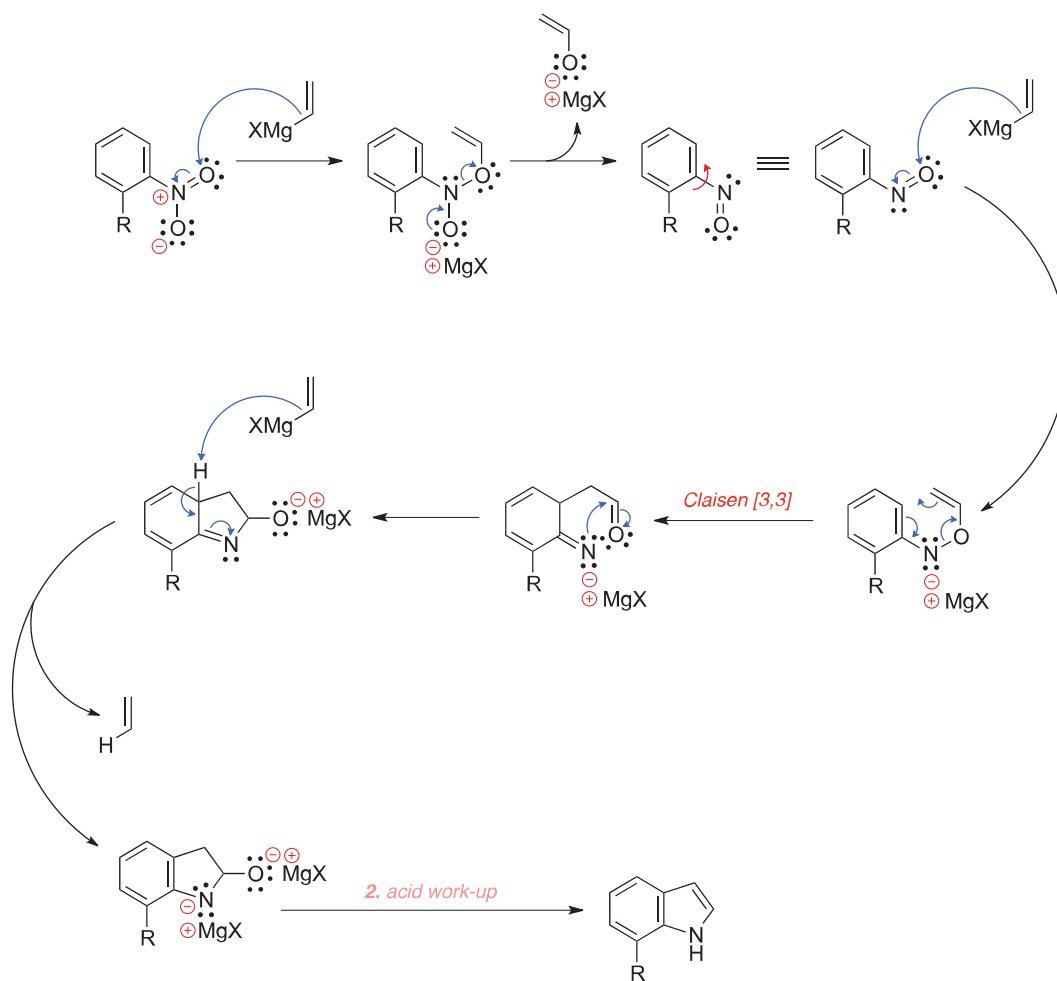
### 1. 2. 2. Bartoli indole synthesis.

The Bartoli indole is an organic reaction where a substituted nitroarene is turned to an indole using an excess of a vinyl Grignard reagent succeeded by an acid workup. The yield of this reaction has affected by the substituents on the nitroarene, and the highest yield observed with ortho substituted reagents and the bulky groups — equation (1-2). The mechanism of Bartoli indole synthesis began with a series of attacks on the nitroarene reagent by the Grignard reagents and followed by a [3,3] sigmatropic rearrangement (Claisen) step which results in an aldehyde intermediate. Then the aldehyde is quickly attacked by the nearby nitrogen intramolecularly, and a subsequent attack by the third equivalent of the Grignard reagent restored aromaticity. A final acid workup step affords the indole product. As illustrated in the scheme (1-1) [27].



Equation (1-2): Bartoli indole synthesis.

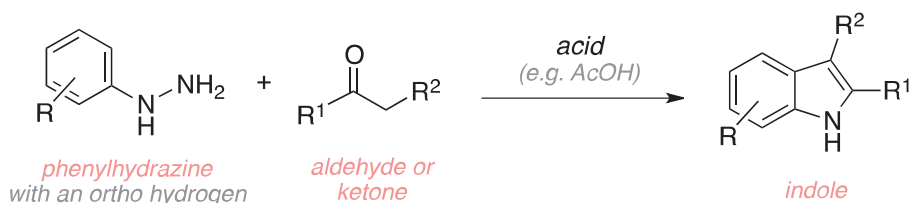




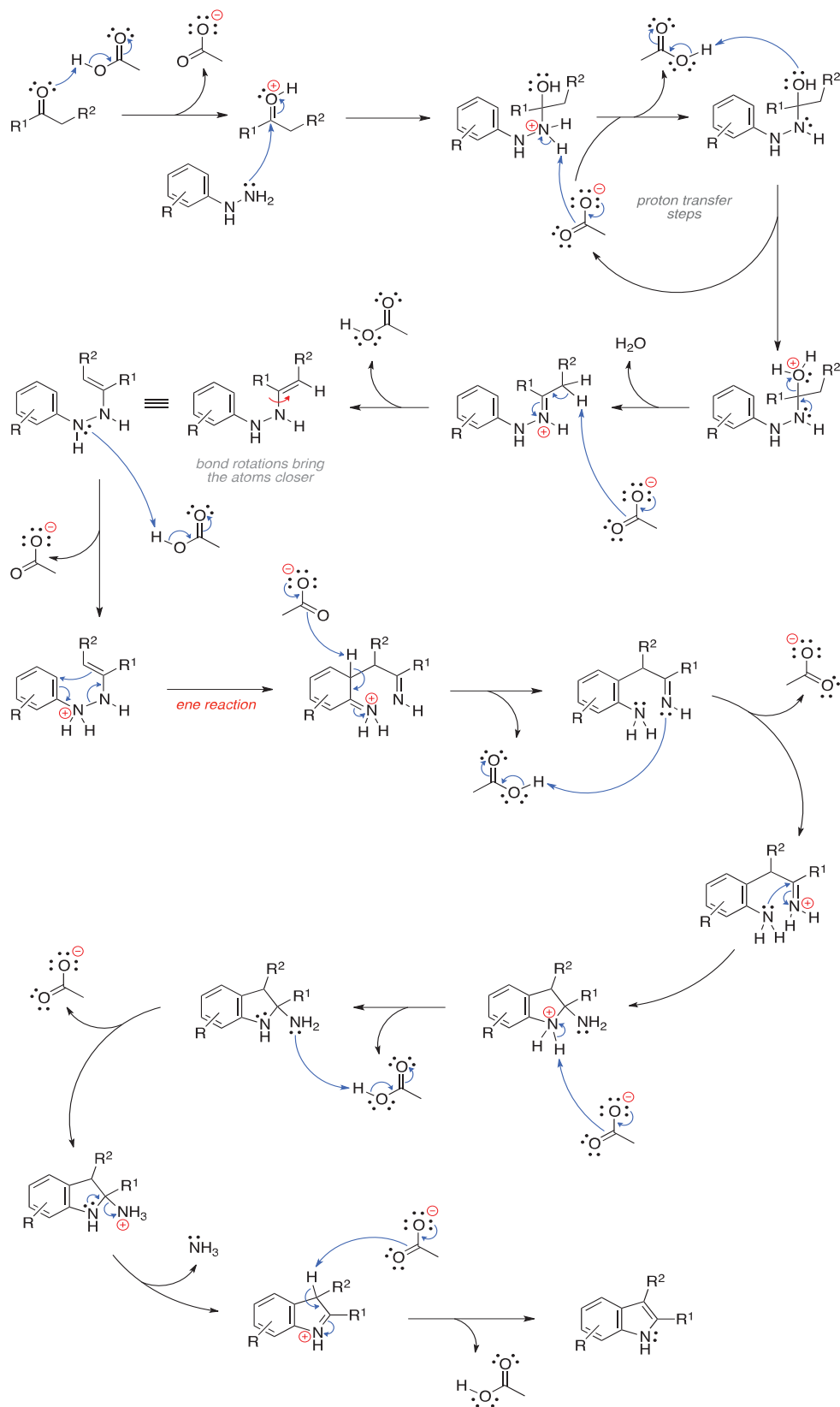
Scheme (1-1): Mechanism of Bartoli indole synthesis.

### 1. 2. 3. Fischer-Indole Synthesis.

In 1883, the Fischer reaction remained the superior method for the synthesis of indoles. Under acidic conditions and heat an arylhydrazine tautomerizes to the enehydrazine and undergoes a [3,3]-sigma tropic rearrangement that results in the functionalization of an inactivated aromatic C-H position. Imine exchange and further tautomerization give the desired indole, with ammonia eliminated as a side product. Equation (1-3) Although it is may be old-fashioned, this celebrated reaction addresses all the requirements of a modern indole synthesis in its convenience and simplicity coupling a mono functionalized arene with a readily available ketone or aldehyde, the only negative being the relatively small range of arylhydrazines that are commercially available [28]. The mechanism shown in the scheme (1-2)



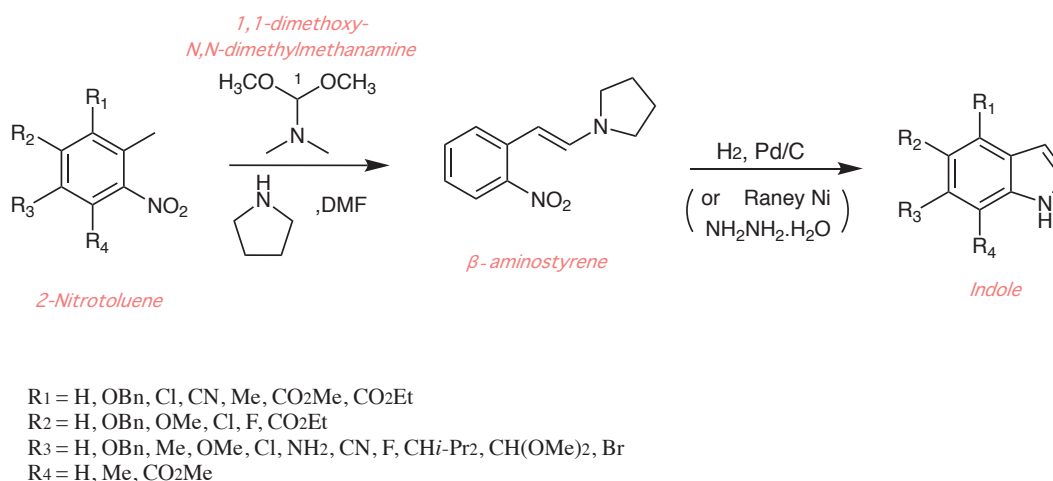
Equation (1-3): The Fischer indole synthesis.



Scheme (1-2): Mechanism of Fischer indole synthesis.

### 1. 2. 4. Leimgruber-Batcho indole synthesis.

The Leimgruber–Batcho indole synthesis is a relatively new method that has rapidly arisen as a weapon in the synthetic organic chemist. In 1971, Willy Leimgruber and Andrew Batcho reported at an international meeting the indole synthesis that now bears their name, followed soon thereafter in patents and then in organic syntheses an excellent review is available subsequent to the two main methods for reducing the  $\beta$ -amino styrene to indole (catalytic hydrogenation with palladium and Raney nickel–hydrazine), several other conditions have explored. The nitro enamine can often be isolated and purified before reduction, but it needs not being. The addition of pyrrolidine (or piperidine) is typically beneficial as it generates a more reactive formyl pyrrolidine acetal or a fused pyrrolidine dimethylamine amination. Leimgruber and Batcho synthesized a large number of indoles and employed several reduction conditions with and without the isolation of the nitro enamine. Scheme (1-3)[29].



Scheme (1-3): Leimgruber-Batcho Indole Synthesis.

### 1. 2. 5. Indole activity.

Indole is the active primary pharmacodynamic nucleus. This compound shows a variety of biological properties like anti-inflammatory, anticonvulsant, antibacterial, cardiovascular [30]. Antirheumatic [31]. Anticancer, anthelmintic, and an anti-hypertensive [32]. Indole is an important heterocyclic system because it has built into protein in the form of the amino acid tryptophan, indole derivatives remain to be a fascinated subject for studying and it has found that indole derivatives exhibit antimicrobial and antiviral activities, against several types of virus including Human Immunodeficiency Virus (HIV), Herpes Simplex Virus (HSV) types 1, 2. Flavivirus, Respiratory Syncytial Virus (RSV), and Coxsackie B virus. Besides, some indole derivatives have shown significant protect properties for red blood cells and DNA against radical-induced oxidation [33].

Additionally, such bicyclic heterocyclic structure provides an essential building block for many compounds including natural products, alkaloids, and drugs [34]. Many indole alkaloids recognized as one of the rapidly growing groups of marine invertebrate metabolites for their broad spectrum of biological properties. For example, new indole alkaloids, have been isolated from the tunicate *Aplidium meridianum*, which showed cytotoxicity toward murine tumor cell lines, the modified indole structure can produce a series of compounds with multiple activities when the introduction of different groups takes place on it. Various 3-substituted indoles had used as starting materials for the synthesis of many alkaloids, pharmaceuticals, agrochemicals, and perfumes. Also, its derivatives possess different types of broad-spectrum biological activities such as antitumor, antimicrobial, hypoglycemic, analgesic, and antipyretic activities [35].

### 1. 3. Vilsmeier– Haack.

Introduction of a formyl group into organic molecules attracts interest not only from the viewpoint of synthesis of new carbonyl compounds but also with the goal of extending their synthetic potential, in particular for obtaining new biologically active substances [34]. In 1896, Friedel noted the formation of a red dye on the treatment of N-methyl acetanilide with phosphoryl chloride, to which he assigned the questionable structure, figure (1-5) that was corrected by Fischer, Miller, and Vilsmeier in 1925. They appointed the Cyanine dye structure, and that's product derived from the self-condensation of the quinolinium salt [36]. Figure (1-6)

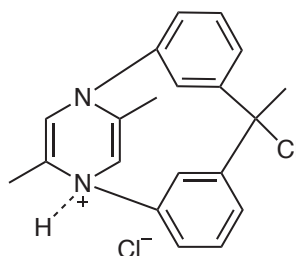


Figure (1-5): Dye discovered by Friedel in 1896.

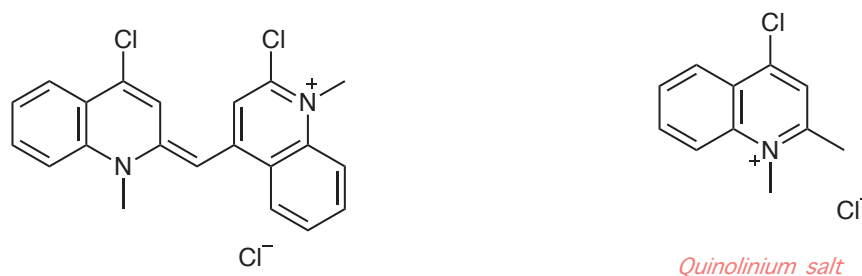


Figure (1-6): Cyanine dye.

### 1. 3. 1. The Vilsmeier– Haack constituting.

The Vilsmeier– Haack (VH) reagent is a Halomethyleniminium salt like  $\text{POCl}_3$ ,  $\text{COCl}_2$ , and  $\text{SOCl}_2$  and organic bases such as N-N'-dimethyl formamide (DMF), N-N'-dimethylacetamide (DMA), or analogous N-N'-dialkyl amides. VH reactions with organic compounds in general and hydrocarbons with excess pi-electrons, in particular, undergo formylation very readily on the synthetic scale [37]. In recent years the Vilsmeier–Haack reagent has found increasing use in domino reactions and particularly in the synthesis of heteroaromatic compounds. Due to the reagent, it has been possible to obtain a large number of various heterocyclic compounds under mild conditions and with high yields, and some of them have found practical application [38].

### 1. 3. 2. Some applications of Vilsmeier Haack reagent.

The most important application of the Vilsmeier-Haack (VH) reagent ( $\text{POCl}_3/\text{DMF}$ ) is the introduction of a formyl or acetyl group to various aromatic and heteroaromatic compounds. It's efficient, economical and mild reagent and now it's used as a powerful synthetic tool for the construction of many heterocyclic compounds [39]. It can be applied to add an aldehyde group to activate aromatic compounds and olefinic compounds. The formyl derivative obtained can further react to afford more complex molecules to be used as building blocks in biologically active compounds, supramolecular chemistry, and molecular electronics [40].

-A notable example that finds application in heterocyclic chemistry is the synthesis of pyrazole-4-carbaldehyde using the VH cyclization of hydrazone. The reaction exposure to 80–90 °C for four hours using three equivalent of the VH reagent [41].

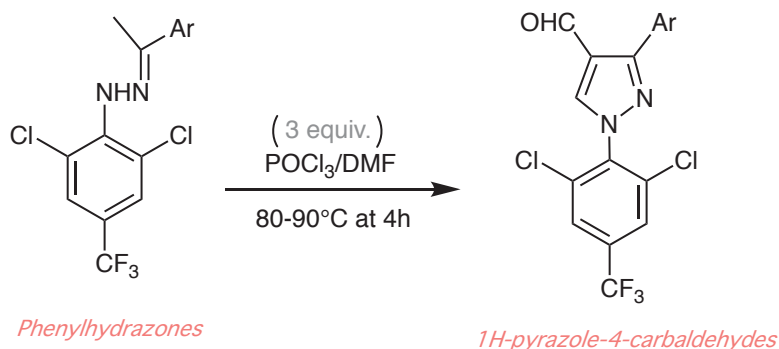
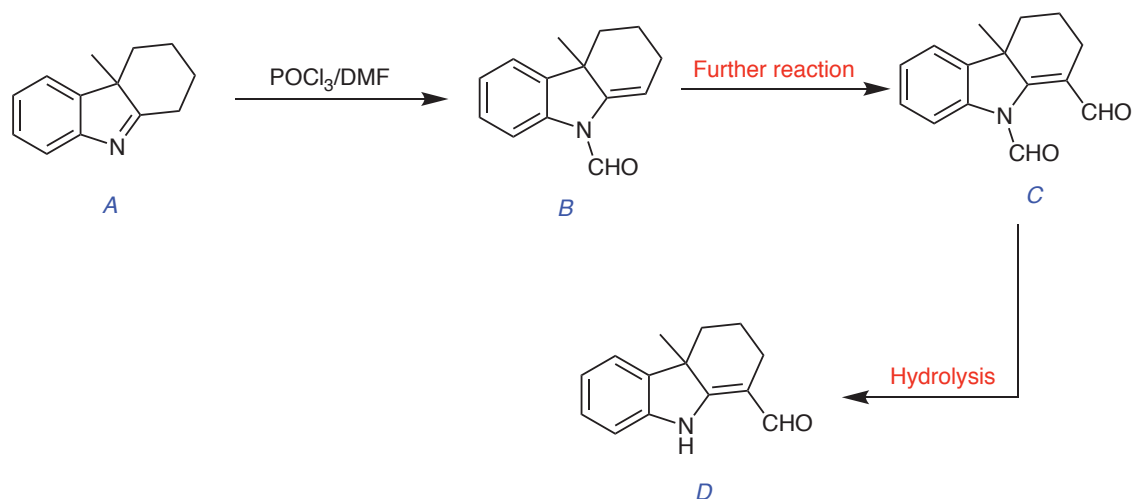


Figure (1-7): Synthesis of 1H-pyrazole-4-carbaldehydes.

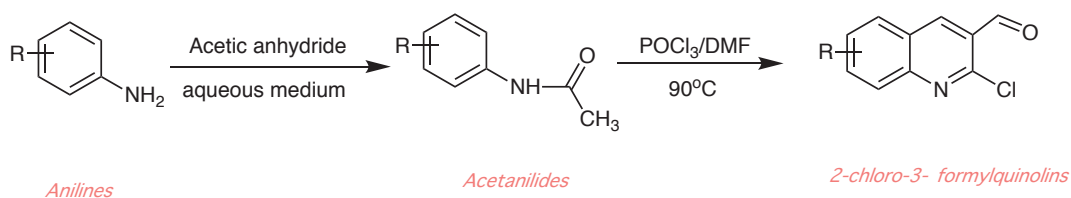
-According to Afghan and *et al.* says that in 1959 Fritz reported the reaction of indolenine (A) with Vilsmeier reagent formed from DMF and POCl<sub>3</sub> leading to (B). Further reaction of (B) under the same condition followed by, hydrolysis afforded compound (D). Formation of this product probably involves the intermediate (C), from which the N-formyl group hydrolytically removed during workup [42]. Scheme (1-4)





Scheme (1-4): The synthesis of 4a-methyl-3,4,4a,9-tetrahydro-2H-carbazole-1-carbaldehyde.

-In 2005, Singh and *et al.* reported the synthesis of 2-chloro-3-formylquinolines in different functionalities groups from cyclisation of acetanilide using  $\text{POCl}_3$  in DMF  $0-5^\circ\text{C}$  followed by heating to  $90^\circ\text{C}$  to afford in good moderate yield [43]. Scheme (1-5)



R= H, 4-CH<sub>3</sub>, 3-CH<sub>3</sub>, 2-CH<sub>3</sub>, 2-CH<sub>2</sub>CH<sub>3</sub>, 4-OMe, 3-OMe, 2-OMe, 4-Br, 3-Cl, 4-Cl.

Scheme (1-5): The synthesis of 2- chloro-3-formylquinolines.

-The reaction of 2,3,3-trimethyl-3*H*-indoles with the Vilsmeier reagent, producing amino methylene malondialdehydes [44]. Figure (1-8)

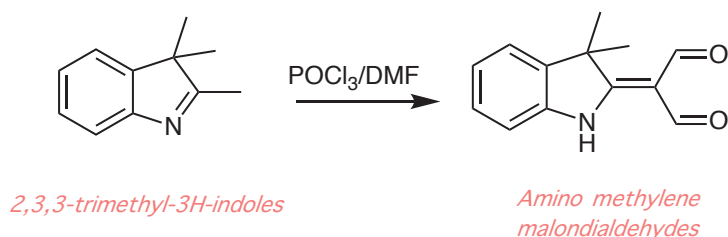


Figure (1-8): The synthesis of amino methylene malondialdehydes.

#### 1. 4. Pyrazole.

Pyrazole is important members of heterocyclic compounds with two adjacent nitrogens in a five-membered ring system. Among the two nitrogen atoms; one is primary, and the other is neutral. These are aromatic molecules due to their planar conjugated ring structures with six delocalized  $\pi$ -electrons. The aromatic nature arises from the four  $\pi$  electrons and the unshared pair of electrons on the  $-NH$  nitrogen. The partially reduced forms of pyrazole are named as pyrazolines; while the completely reduced form is pyrazolidine. Figure (1-9)

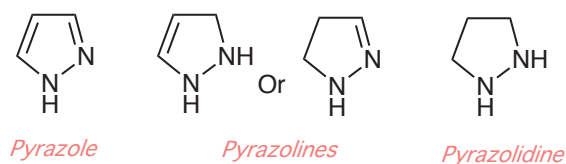


Figure (1-9): The chemical structures of pyrazole, pyrazoline, and pyrazolidine.

Pyrazole is a tautomeric substance the occurrence of tautomerism can't demonstrate pyrazole itself but can infer by the consideration of pyrazole derivatives. Unsubstituted pyrazole can represent in three tautomeric forms figure (1-10). For the pyrazole derivatives two carbon atoms are neighboring the nitrogen atoms on the ring have difference substituents, five tautomeric structures are possible [45]. Figure (1-11)

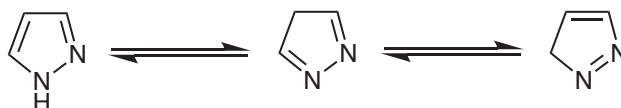


Figure (1-10): The tautomerism of pyrazole.

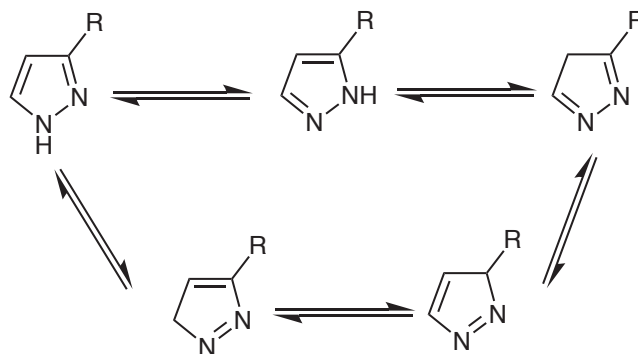


Figure (1-11): The tautomerism of pyrazole derivatives.

### 1. 4. 1. The important of pyrazole ring.

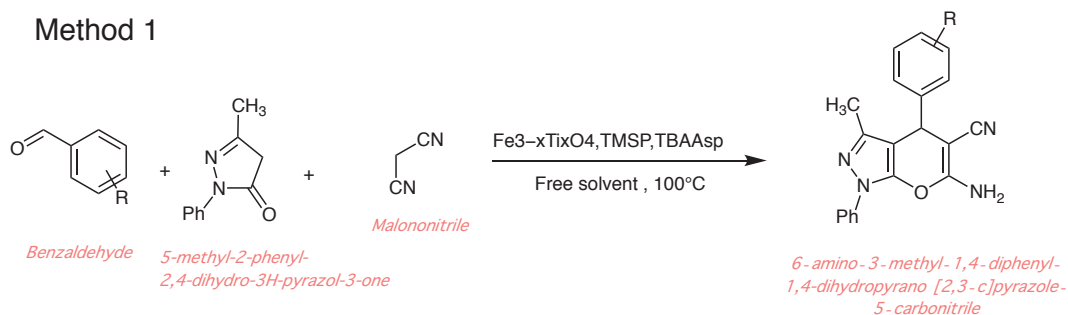
Pyrazole is one of the most studied group of compounds among the azole family, and its derivatives find particular use in agrochemical, pharmaceutical industry. These studies have involved a massive variety of synthesis methods and synthetic analogs, to support both discovery of active compounds and their preparation, among the many synthetic approaches to these heterocycles' compounds. Dipolar cycloaddition offers a convenient means to access complex pyrazoles from simple substrates [46-47-48]. They are also useful as synthons and building blocks for many heterocyclic products and can act as a bi nucleophile [49]. During the last decade, many molecules containing various azahetero cyclic rings including the pyrazole moiety in their structural framework have been designed, synthesized and investigated as potent inhibitors of angiogenesis [50].

### 1. 4. 2. Some important Reactions of pyrazole rings.

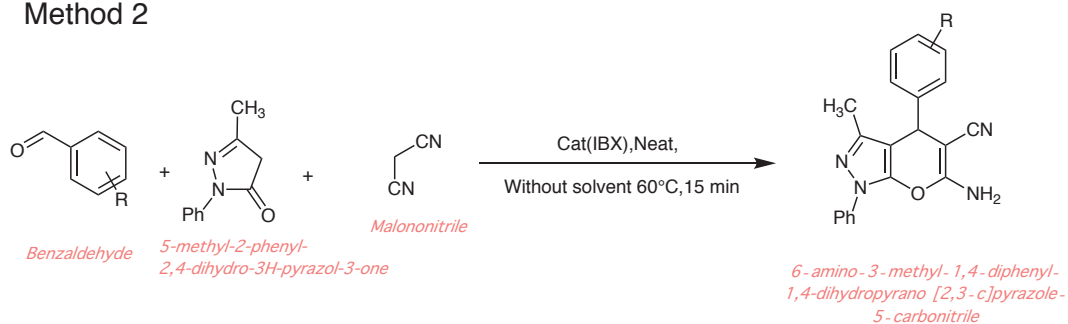
#### 1. 4. 2. 1. Synthesis of 1,4-dihydropyrano[2,3-c] pyrazole derivatives.

Dihydropyrano [2,3 c] pyrazoles and their derivatives are widely used in synthetic organic and bioorganic chemistry because of their pharmacological and therapeutic properties including insecticidal, diuretic, anticoagulant, anticancer, antibacterial, analgesic and anti-inflammatory activities [51-52-53]. They are generally prepared by one-pot three component condensations of aldehyde, malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one using a different condition. Figure (1-12)

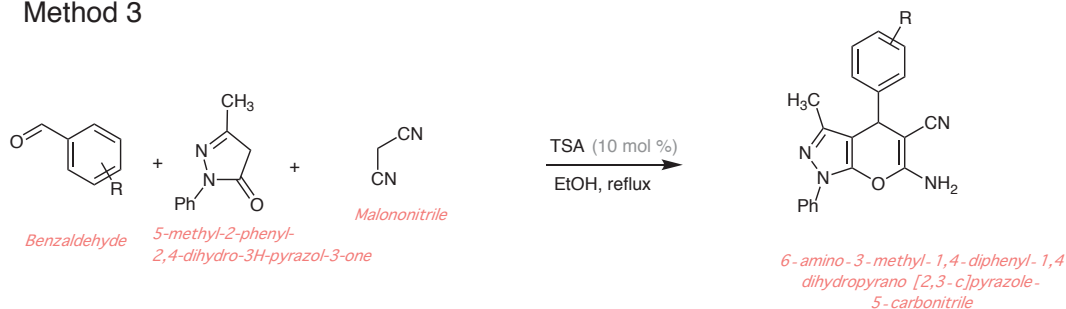
## Method 1



## Method 2



## Method 3



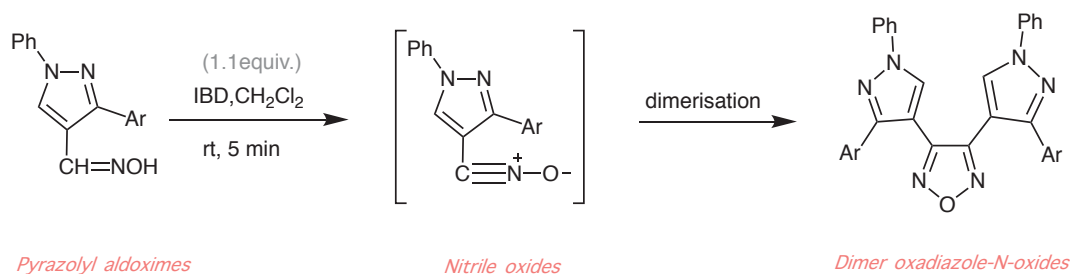
R= H, 3-NO<sub>2</sub>, 3Cl, 3-Br, 4-Me, 4-Cl, 4-Br, 4-OMe, 3-EtO-4-OH, 2,4-diCl.

Figure (1-12): The synthesis of 6-amino-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile.

These catalysts have widely used in organic reactions due to their environmental benignity, high thermal, stability, lack of toxicity, easy handling, and simple workup.

#### 1. 4. 2. 2. Synthesis of oxadiazole-*N*-oxides dimer.

Is a vital five-membered ring aromatic heterocycle compound [54]. In 2007, Prakash and *et al.* reported an efficient and straightforward synthesis of dimer oxadiazole-*N*-oxides. The formation of it was achieved by treatment of pyrazolyl aldoximes with iodobenzene diacetate (IBD) in dichloromethane at room temperature. For 5 min. The target compound obtained as a yellow solid confirmed by  $^1\text{H}$ ,  $^{13}\text{C}$ -NMR. Scheme (1-6)



Scheme (1-6): Synthesis of oxadiazole-*N*-oxides dimer.

The pyrazole-4-carboxaldehyde oximes needed in this study prepared by using a one-pot procedure involving Vilsmeier-Haack reaction of acetophenone phenylhydrazone followed by treatment with hydroxylamine hydrochloride and sodium bicarbonate [55]. Figure (1-13)

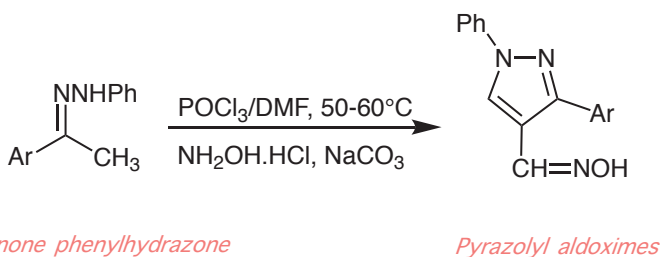
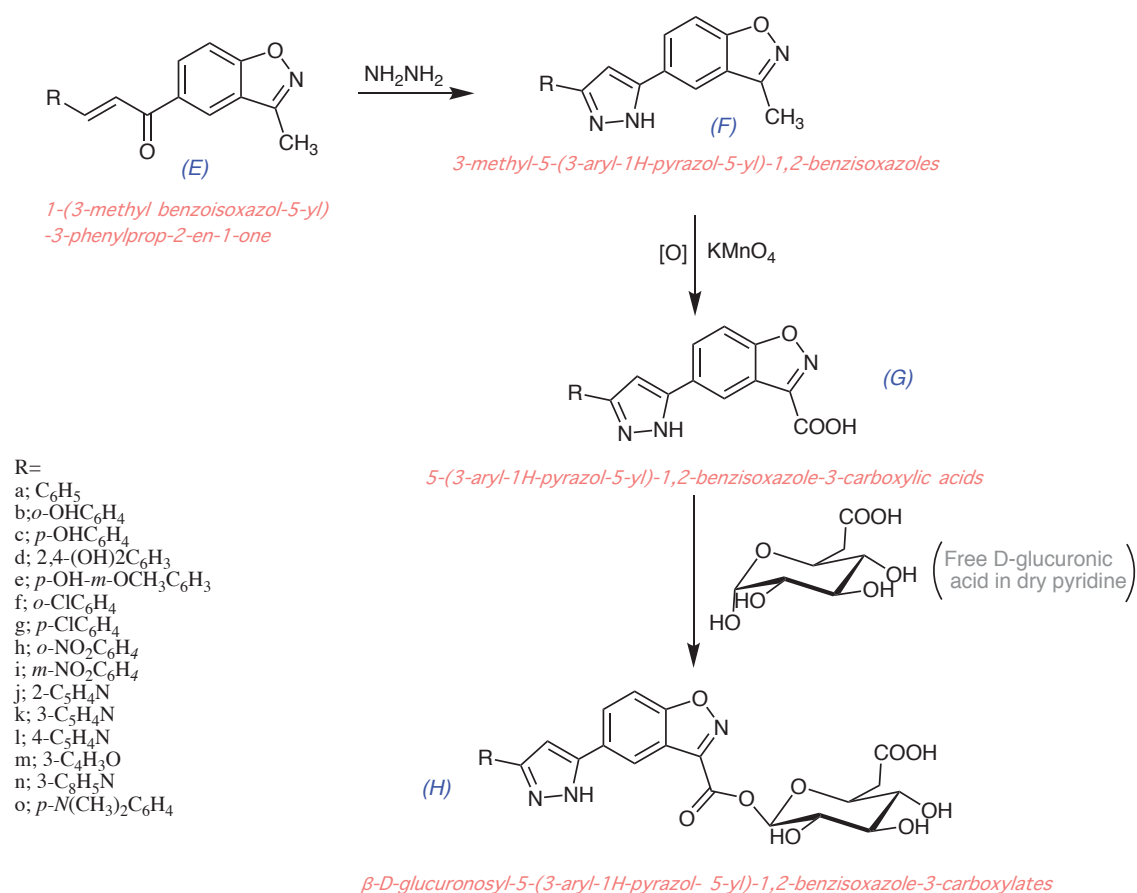


Figure (1-13): The synthesis of pyrazole-4-carboxaldehyde oximes.

### 1. 4. 2. 3. $\beta$ -D-glucuronides are containing pyrazole.

The synthesis of  $\beta$ -D-glucuronides has attracted a current interest in organic synthesis due to biological, pharmaceutical importance.  $\beta$ -D-Glucuronide is the conjugation products of compounds possessing a carboxylic acid functional group with free glucuronic acid. In 2011, Wanare started from (E) to build the hydrazine ring (F) through the cyclization of hydrazine hydrate. Oxidation of (F) with  $\text{KMnO}_4$  afforded benzisoxazole-3-carboxylic acid (G)  $^1\text{H-NMR}$  and IR spectrum confirmed the structure. Glucuronidation of (G) with free D-glucuronic acid in dry pyridine furnish (H) in moderated yield [56]. Scheme (1-7)



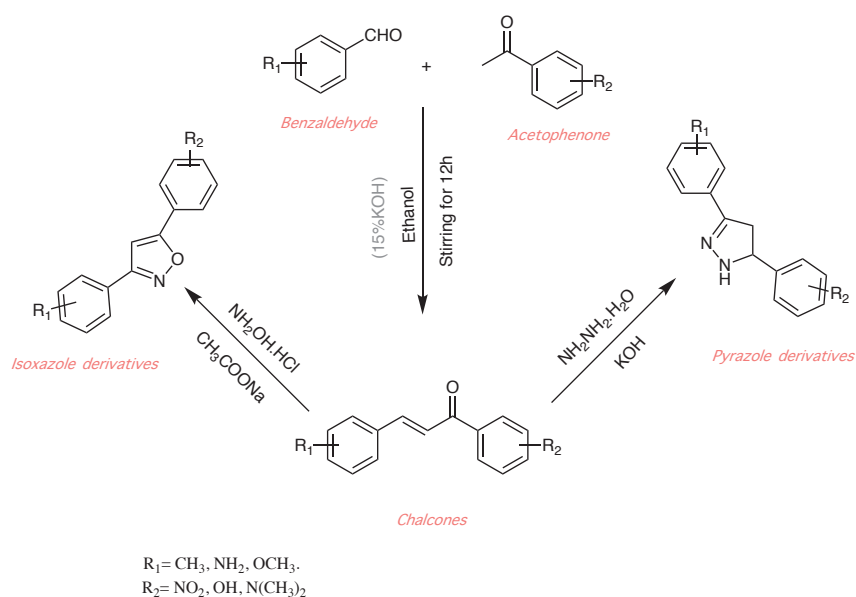
Scheme (1-7):  $\beta$ -D-glucuronosyl-5-(3-aryl-1H-pyrazol-5-yl)-1,2-benzisoxazole-3-carboxylates.

### 1. 4. 3. Pyrazole synthesis.

Pyrazole derivatives synthetic pathways represent an interesting topic since these compounds have many applications in the pharmaceutical and agrochemical industry [57].

#### 1. 4. 3. 1. From chalcones.

Chemically the Chalcones are 1,3-diphenyl-2-propene-1-one, in which two aromatic rings linked by a three-carbon with,  $\alpha,\beta$ -unsaturated carbonyl compound. Claisen Schmidt condensation of aromatic aldehydes with acetophenone synthesize this, by base or acid catalyzed followed by dehydration to yield Chalcones. Those Chalcones undergo a variety of chemical reactions, and its use in the synthesis of the array of heterocyclic compounds like isoxazole and pyrazole derivatives they are obtained by reacting Chalcones a starting material with hydroxylamine hydrochloride or hydrazine hydrate in refluxing alcohol [58].

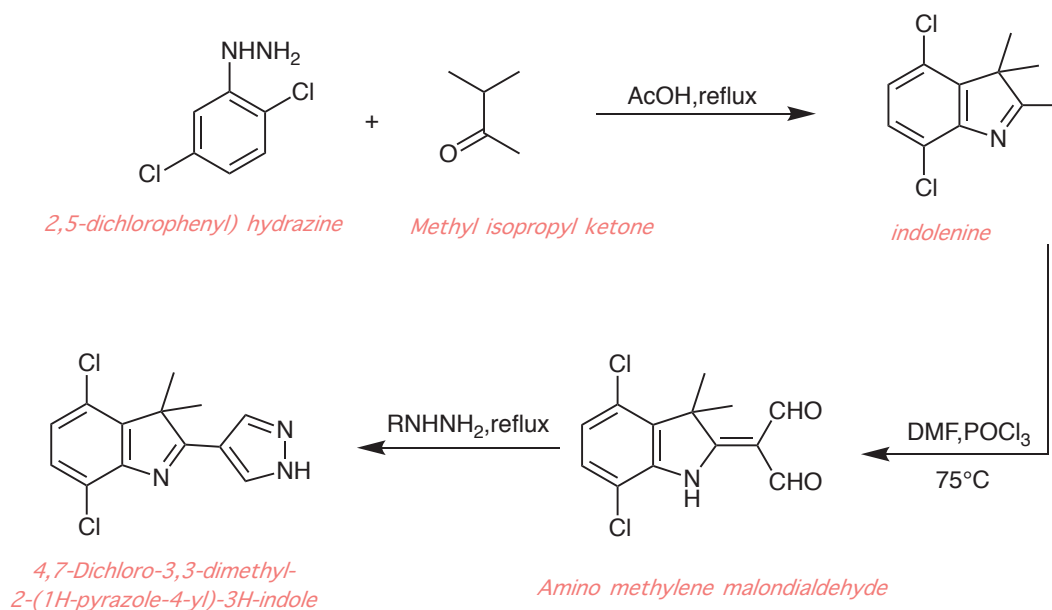


Scheme (1-8): The formation of isoxazole and pyrazole derivatives.



### 1. 4. 3. 2. From amino methylene malondialdehyde.

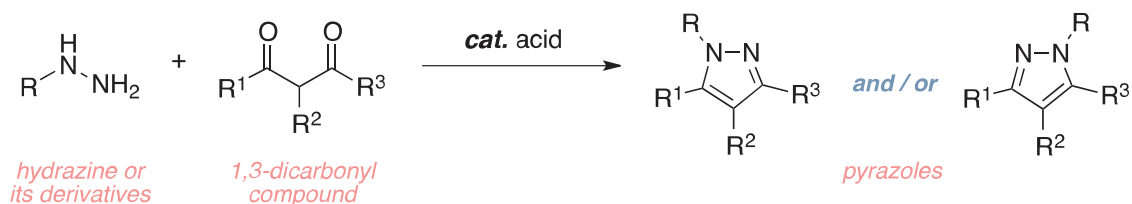
The reactions of (2,5-dichlorophenyl) hydrazine, with methyl isopropyl ketone in a Fischer reaction and hot acetic acid produced the indolenine the reaction of indolenine with the Vilsmeier reagent formed from dimethylformamide and phosphoryl chloride to produce amino methylene malondialdehyde. The reactions of amino methylene malondialdehyde with various aryl hydrazine led to form pyrazole ring on 3*H*-indole systems [59].



Scheme (1-9): The formation of pyrazole ring on 3*H*-indole.

### 1. 4. 3. 3. Knorr pyrazole synthesis.

It's one of the essential methods for synthesis involving the reaction of 1,3- dicarbonyls with hydrazine derivatives. The reaction proceeds by the initial composition of the mono hydrazine that converted to the pyrazoles by the action of acids or heat [60]. Equation (1-4)



Equation (1-4): Knorr synthesis for pyrazole ring.

#### 1. 4. 4. Pyrazole bioactivity.

Extensive utilization of chemotherapeutic agents for the administration of dangerous diseases leads to the evolution of microbial resistance to existing medicines [61]. The primary reason for the increase in microbial infections is the resistance improved by these microbial organisms. Consequently, the improvement of new antipathogenic agents or antimicrobial that work upon new microbial targets is required. Nowadays, many drugs developed from pyrazole derivatives, such as rimonabant that functions as a cannabinoid receptor inverse agonist and utilized in obesity treatment, celecoxib that demonstrates anti-inflammation effects and inhibits COX-2, fomepizole that inhibits alcohol dehydrogenase and sildenafil that inhibits phosphodiesterase [62]. And some pesticides like Cyenopyrafen, Fenpyroximate, and Tebufenpyrad [63]

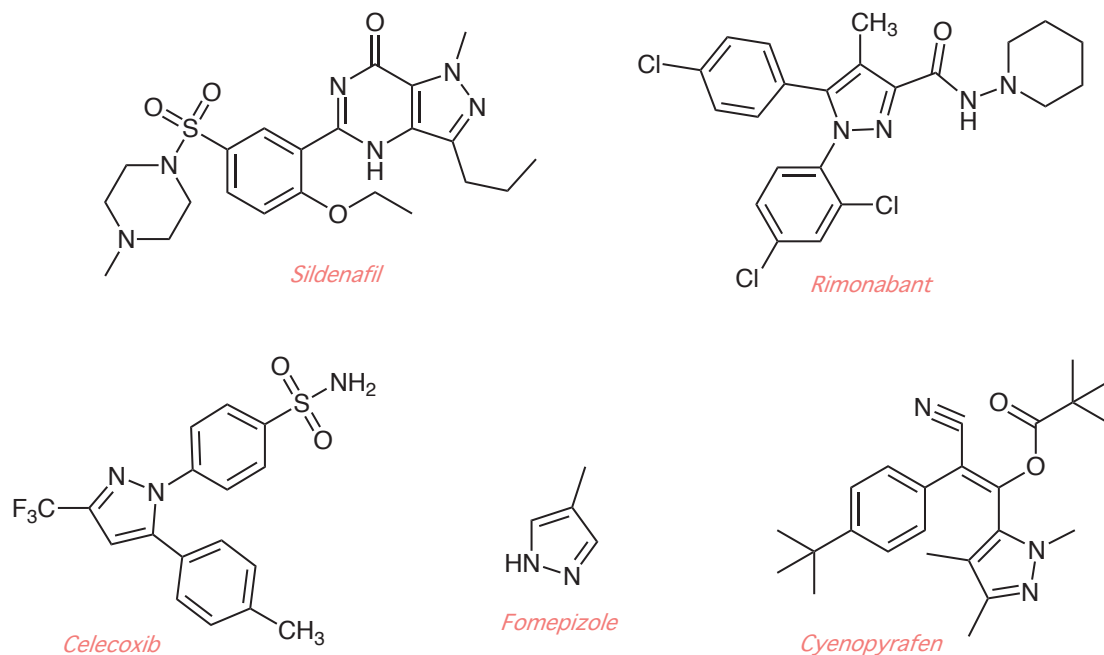


Figure (1-14): Some commercial drugs of bioactive pyrazole derivatives.

Heterocyclic compounds continue to attract considerable attention due to their several Bioactivities. The five-membered heterocyclic compounds occupy a unique position in the field of natural and synthetic organic chemistry. Like, pyrazoles have been found to display broad application as pharmaceutical agents. Now, attention has frequently given to the synthesis of pyrazole derivatives as a source of new agents. Pyrazole derivatives have reported to posse different biological activities [61]. Table (1-2)

Table (1-2): Some important biological activities for pyrazole derivatives.

NO.	Bioactivity	References
1	Anti-oxidant	[64]
2	Anticonvulsant	[65]
3	Antitumor	[66]
4	Anti-inflammatory	[67]
5	Hyperglycemic activity	[68]
6	Antimicrobial	[69]
7	Analgesia	[70]
8	Herbicidal	[71]
9	Anti-diabetic	[72]
10	Anti-arrhythmic	[73]
11	Ulcerogenic	[74]
12	Cardiotonic agents with vasodilator activity	[75]
13	Antidepressant	[76]
14	Potent antiparasitic	[77]
15	Antiproliferative	[78]
16	Cytotoxic	[79]
17	Antimetabolite	[80]
18	Selective enzyme inhibitory	[81]
19	Ruxolitinib	[82]
20	Antibacterial	[83]
21	Anti-leukemic	[84]
22	Anti-histaminic	[85]
23	Antivirus	[86]
24	Insect acaricides	[87]

There are many useful applications on crop protection chemistry one of them is from pyrazole derivatives, and there were many fungicidal, herbicidally and insecticidally working on pyrazole classes in this field [88]. Pyrazoles are explored to the maximum extent owing to their broad spectrum of photographic, and pharmacological activities such as lonazolac and difenamizole [89-90]. Figure (1-15)

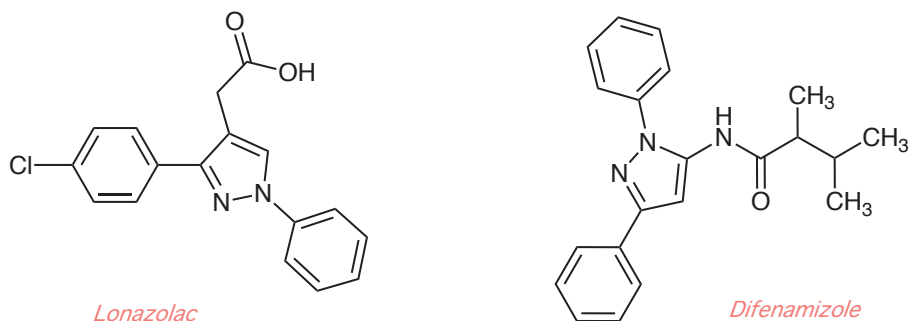


Figure (1-15): Some compounds contain pyrazole in their structure and having Photographic and pharmacological activities.

Also, Pyrazole derivatives have been shown great attention in agrochemicals because of their excellent bioactivities such as the commercialized herbicides pyrazolate, benzofenap, pyraflufen-ethyl, fluazolate, and pyrazosulfuron-ethyl. Figure (1-16) leading to exciting applications in the field of agricultural study. Combination of such pyrazole molecule with the additional heterocycles to form polycyclic systems to add functional diversity [91].

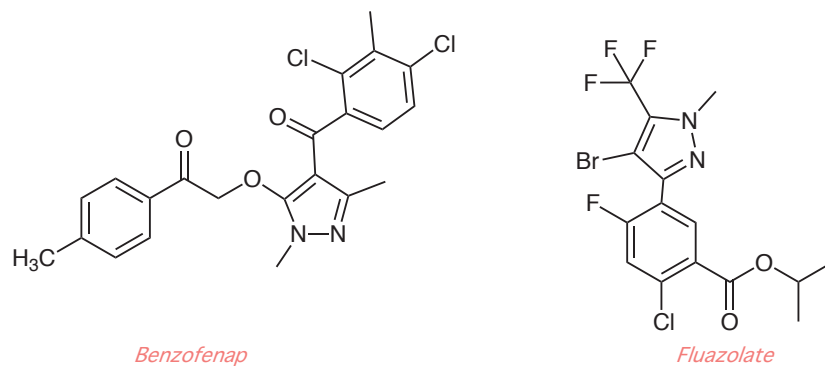
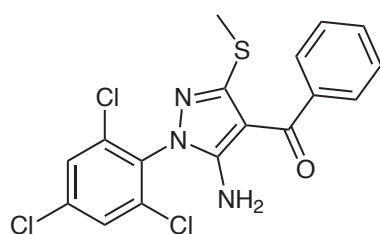
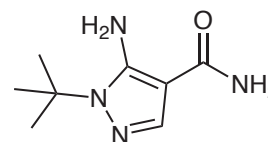


Figure (1-16): Some commercialized herbicides containing pyrazole.

Besides, pyrazole derivatives have different chemotherapeutic potentials including versatile antineoplastic activities such as antileukemic, and anti-proliferative in addition to their ability to exert remarkable anticancer effects through inhibiting various types of enzymes that play an essential role in cell division [92]. And there are important heterocyclic templates, which are the 5-aminopyrazole system, showed attracted considerable interest because of its long history of application in the agrochemical industries and pharmaceuticals, such as 5-amino-1-tert-butylpyrazole-4-carboxamide and 5-Amino-4-benzoyl-3-methylthio-1-(2,4,6- trichloro phenyl) pyrazole. Figure (1-17) These compounds have extensively investigated for over a hundred years, and their chemistry has reviewed in two books written in 1964 and 1967 [93].



*5-Amino-4-benzoyl-3-methylthio-1-(2,4,6- trichloro phenyl) pyrazole*



*5-amino-1-tert-butylpyrazole-4-carboxamide*

Figure (1-17): Some compounds were containing 5-aminopyrazole system.

And there are pyrazole derivatives have reported as nonnucleoside HIV-1 reverse transcriptase inhibitory activity like 1,5-Diarylpyrazole. Kees *et al.* have described (4-substituted benzyl) (trifluoromethyl)pyrazoles and pyrazolones which represent a new class of antidiabetic compounds. Cottine

*et al.* have reported substituted pyrazole-4-carboxylic acid and said the pharmacophore 3-methoxy-1*H*-pyrazole-4-carboxylic acid ethyl ester as a hypoglycemic agent. Das *et al.* have synthesized substituted pyrazole-3-one derivatives as a potential hypoglycemic agent [94].

Finally, Pyraclostrobin discovered by BASF is a commercial fungicide containing pyrazole structure as well as pyrazophos and penthiopyrad. Figure (1-18) it has potential antifungal activities, to control some plant diseases. It came to the market in 2002, and by 2012 the market of Pyraclostrobin reached 800\$ million which represent the second of the world fungicide market. So their applications are growing synthetically and biologically [95-96].

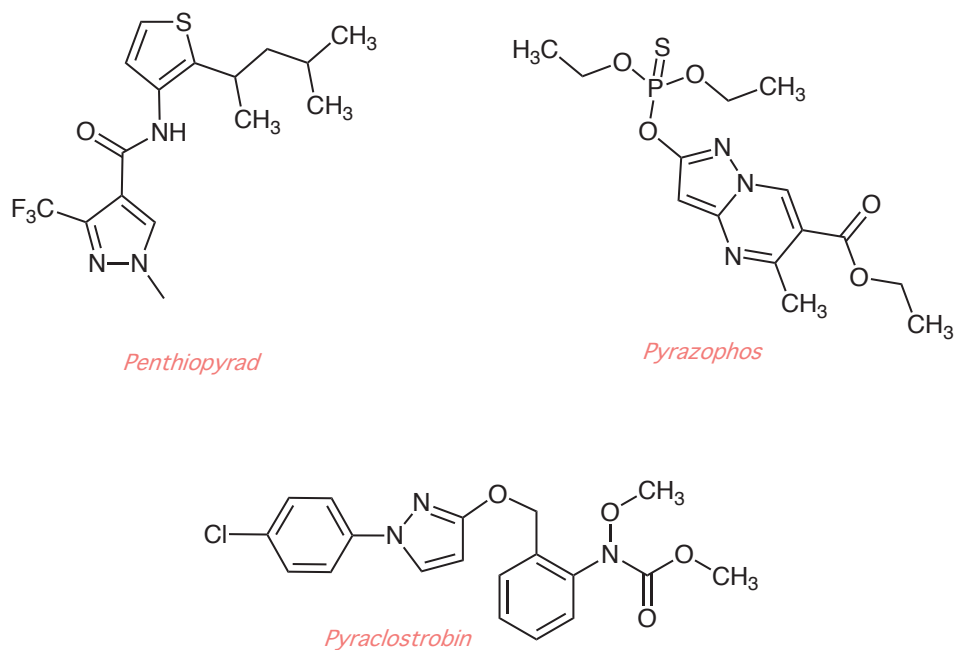


Figure (1-18): Some important antifungal pyrazoles derivatives.

## 1. 5. Research Outline.

### 1. 5. 1. Aims of this thesis.

The objectives of this study are: -

- 1) To synthesize a series of new pyrazole derivatives.
- 2) Identify the chemical purity and structures of the synthesized compounds; by various spectroscopic techniques like nuclear magnetic resonance spectroscopy  $^1\text{H}$ , APT $^{13}\text{C}$ -NMR and Fourier Transform infrared spectroscopy (FT-IR) as well as to confirm their physical properties.
- 3) To evaluate the biological activity of the newly synthesized compounds to inhibitory HeLa and RD cancer cells lines in the uterine and human muscle.