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جامعة ديالى/ كلية العلوم
قسم الكيمياء

تحضير وتشخيص مركبات عضوية جديدة مشتقة من 2(1,1-ثنائي مثيل-1,3- ثنائي هيدرو-H٢- بنزواندول-2-يليدين) مالونالديهايد وقياس فعاليتها الحيوية

رسالة مقدمة الى
مجلس كلية العلوم / جامعة ديالى
وهي جزء من متطلبات الحصول على شهادة الماجستير في علوم الكيمياء
من قبل الطالب

داليا عبد الستار جميل

بكالوريوس علوم الكيمياء / جامعة تكريت ٢٠١٥

بإشراف

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CHAPTER ONE

INTRODUCTION

1. 1. Heterocyclic Compounds

Heterocyclic compounds probably constitute the most varied and largest family of organic compounds. Every carbocyclic compound (homocyclic compound), despite of structure and functionality, may in principle be changed over into a collection of heterocyclic analogs by replacing one of the ring carbon atom or more with a different element. Even if we restrict our consideration to oxygen, nitrogen and sulfur (the most well-known heterocyclic elements), the permutations and combinations of such a replacement are various.[1] Heterocyclic compounds can be aromatic in nature as indicated by their chemical structure such as pyrrole, furan and thiophene figure (1. 1). Or aliphatic like pyrrolidine and tetrahydrofuran, figure (1. 2).

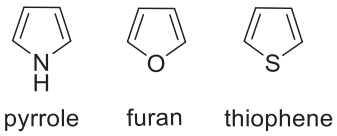


figure (1. 1): The chemical structure of pyrrole furan, and thiophene

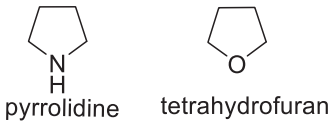


figure (1. 2): The chemical structure of pyrrolidine and tetrahydrofuran

The aromatic heterocyclic rings can be five-membered. They may include one heteroatom such as pyrrole, furan, and thiophene, or two heteroatom as in oxazole ring which comprises of one oxygen atom and one nitrogen atom, or in thiozole which contains

one nitrogen atom and one sulfur atom, and in imidazole ring which comprises of two nitrogen atoms figure (1. 3).

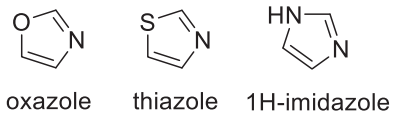


figure (1. 3): The chemical structure of oxazole, thiozole and 1*H*-imidazole

These heterocyclic rings could be fused with benzene ring to give compounds like indole, benzofuran, and benzothiophene.[2] figure (1. 4).

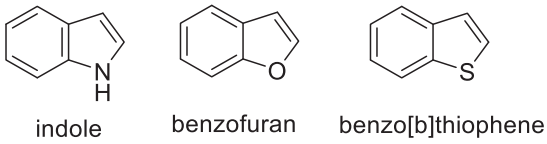


figure (1. 4): The chemical structure of indole, benzofuran, and benzothiophene

Most of pharmaceuticals and biologically active agrochemicals are heterocyclic while countless additives and modifiers utilized in industrial applications running from cosmetics, reprography, information storage and plastics are heterocyclic in nature.[3] One striking structural feature inherent to heterocycles, which continue to be exploited to great advantage by the drug industry, lies in their ability to manifest substituents around a core scaffold in defined three-dimensional representations. Between them, nitrogen and sulfur -containing heterocyclic compounds have kept up the interest of researchers through decades of historical development of organic synthesis.[4]

1.2. Indole

Indole is a bicyclic aromatic heterocyclic organic compound[5] Consisting of a six membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring figure (1. 5). In 1866, Baeyer and knop,[6] in the course of a study of the structure of indigo, reduced isatin and obtained two products, C_8H_7NO and $C_8H_7NO_2$ (oxindole and dioxindole), which they considered as hydroxyl derivatives of C_8H_7N; they named the latter indole. The work was proceeded by Baeyer and Emmerling, proposed in 1869 the formula which is generally accepted.[7-9]

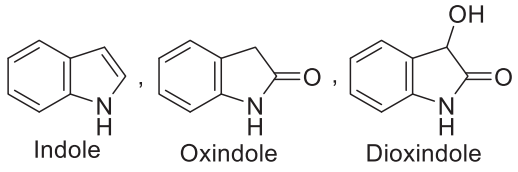


figure (1. 5): The chemical structure of indole, oxindole, and dioxindole

Indole derivatives occur widespread in many natural products has been produced, usually in small amount, by extraction from naturally occurring materials by methods which recommend that the indole so obtained is in many cases the result of breakdown of its derivatives. Different plants have yielded indole, among them the following: Robinia pseudacacia,[10] the jasmines,[11,12] certain citrus plants, and orange blossoms. [13] Indole is also found after putrefactive processes have occured. It's found in the animal body wherever pus formation occurs and in the pancreas, and liver, the bile, and brain. It's formed in the putrefaction of milk, of blood fibrin, of albumin, and possibly of vegetable protein. Formation of indole is probably the result of the decomposition of tryptophan in these cases of putrefaction of protein material. Indole has also been

found to be present in coal tar in the fraction boiling between 240° 260° C. [14,15]

The discovery of indomethacin [16] figure (1. 6) as a successful agent for clinical treatment of anti-inflammatory disorders has led to the investigation of indole moiety to obtain better anti-inflammatory agents.

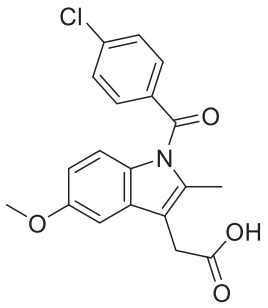


figure (1. 6): The chemical structure of Indomethacin

Furthermore indole and its analogs possess wide range of biological activities, such as anti-inflammatory [17-20], anti-microbial [21,22], anti-bacterial [23,24], anticonvulsant [25,26] and cardiovascular activity. [27]

The Indole is an important heterocyclic system because it provides the skeleton of indole alkaloids—biologically active compounds from plants including strychnine figure 1. 7 and Lysergic acid diethylamide (LSD) (figure 1. 8), because it is the basis of drugs like indomethacin, and because it is built into proteins in the form of amino acid tryptophan.[28]

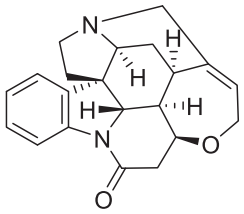


Figure (1. 7): The chemical structure of strychnine

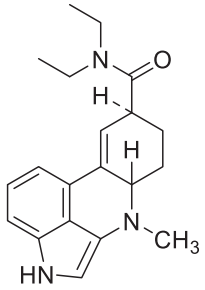


figure (1. 8): The chemical structure of Lysergic acid diethylamide (LSD)

1. 2. 1. Properties of Indole

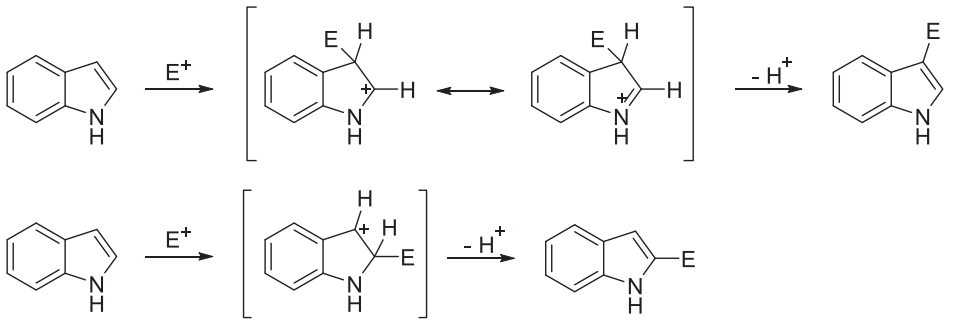
Indole is a colorless crystalline solid in the form of shinning leaflets. It is volatile with steam. indole melts at 52°C and boils at 253°C. It is soluble in hot water and in hot alcohol, and it is also soluble in benzene and in ether. The compound in the impure state has unpleasant odor.(29)

The indole nucleus is a planar bicyclic molecule containing 10π electrons (8π electrons from double bonds and 2π electrons from lone pair of electrons from nitrogen), thus it is aromatic according to Huckel's rule. It acts as a weak base and protonates only in the presence of strong acids.(30)

1. 2. 2. General Reactivity of Indole

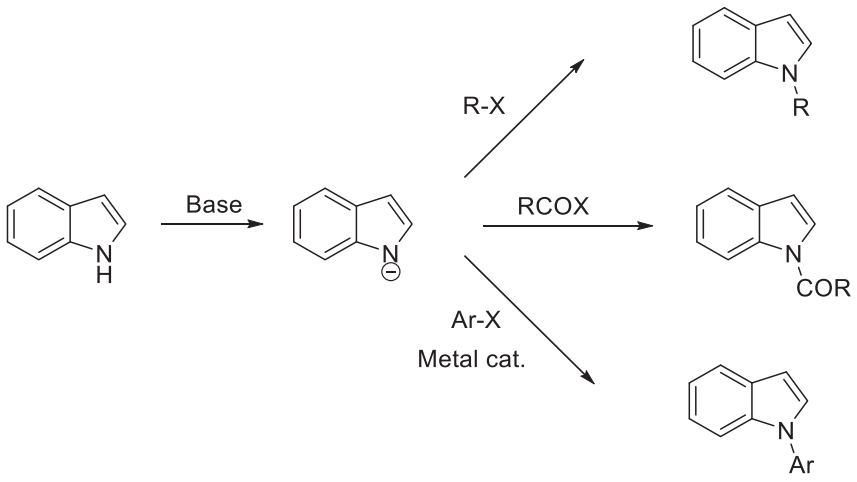
Indole is a π-excessive aromatic heterocycle with ten π-electrons. The lone pair of the nitrogen atom (which features sp2 hybridization) completes the ten π-electrons delocalized across the

ring. As in pyrrole, the π-excessive nature of the aromatic ring detects its reactivity and chemical properties. Indole is a weak base (pKa -2,4 for the conjugated acid), as protonation of the nitrogen atom would deactivate the aromaticity of the five-membered ring. In contrast, as a π-excessive aromatic heterocycle, electrophilic aromatic substitution (EAS) is one of the most characteristic reactions. Unlike pyrrole, addition of electrophiles occures preferentially at C3.[31] Indole shows up high EAS reactivity, which is estimated to be orders of magnitude greater than benzene. This is due to electron-rich nature of indole, and the high electron density at its 3-position is responsible for indole's regioselectivity toward EAS reactions [32] scheme (1. 1)



scheme (1. 1): Possible regioisomers in the electrophilic attack on the indole ring

The indole N-H is weakly acidic, so can be deprotonated by strong bases (pka 16.7 in water) to provide the indolyl anion. Therefore, substitution at the nitrogen can be done through base-promoted processes, such as acylations, alkylations, and, more recently transition metal catalyzed arylations[31,33] scheme (1. 2).



Scheme (1. 2): Deprotonation of indole by strong base

1. 2. 3. Tautomers and Isomers of Indole

The 2H-indole and 3H-indole are tautomers of 1H-indole figure(1. 9). Both systems are highly unstable, although 3H-indole has been characterized spectroscopically, and its derivatives have been isolated.(34) High level quantum chemical Discrete Fourier Transform (DFT) calculations predict an energy difference of 5.20 and 24.10 Kcal.mol^{-1} between 1H-indole and 3H-indole, and 1H-indole and 2H-indole respectively. The other isomeric benzopyroles are isoindole and indolizine. (31) figure (1. 9).

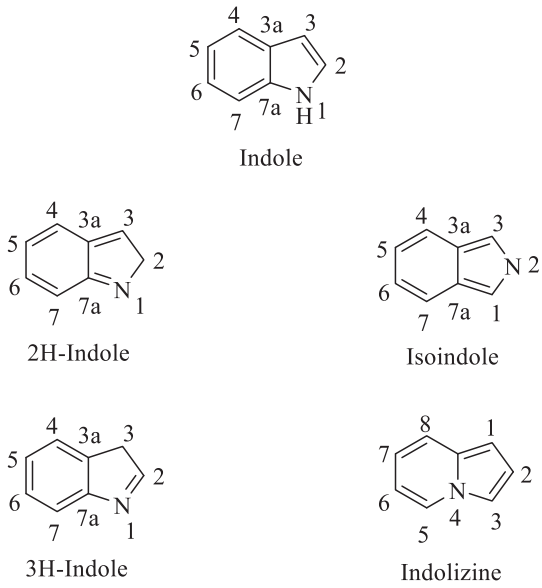
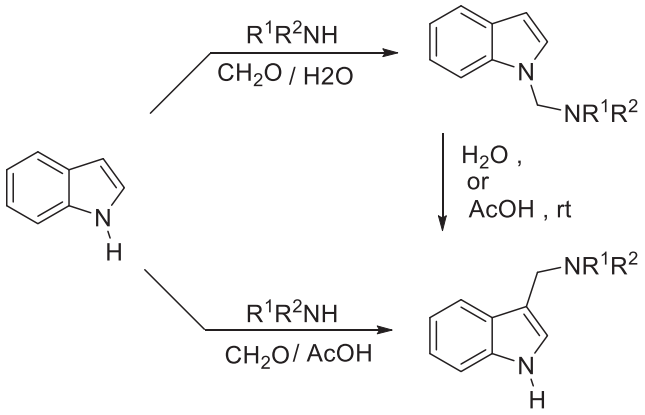


figure (1. 9): Indole, tautomers and isomers with conventional numbering

1.2.4. Reactions of Indole

1.2.4.1. Mannich Reaction

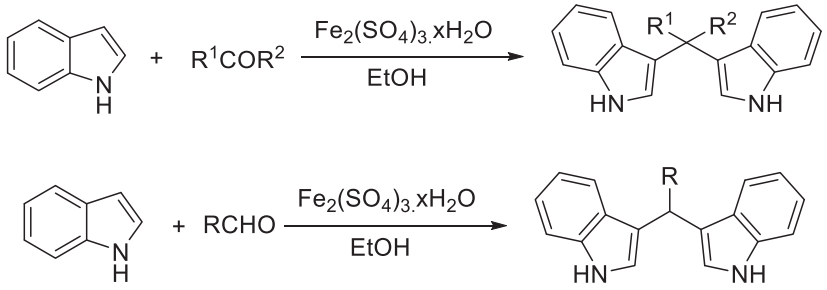
Under typical Mannich's conditions, indole undergoes alkylation at C3. This reaction leads to the synthesis of gramines which are significant intermediates for the preparation of substituted indoles. When the reactions are conducted in water at low temperatures, the kinetically controlled N-alkylation product is produced , the resulting N-aminal indoles are relatively stable but convert into the thermodynamically more stable C3-substituted aminomethyl indoles via heating at neutral pH or acid treatment at room temperature[35] scheme (1. 3).



scheme (1. 3): Mannich's Reaction of Indole

1. 2. 4. 2. Reactions of indole with aldehydes, ketones in the presence of (a) Hydrated ferric-sulfate, (b) Silica gel.

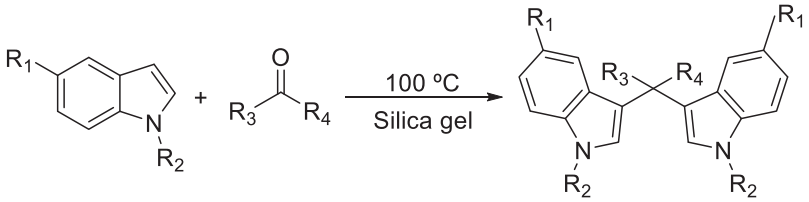
Hydrated ferric sulfate [$Fe_2(SO_4)_3.xH_2O$] has been found to be an Effective catalyst for condensation of bisindoles with aliphatic or aryl aldehydes and ketones including methyl and ethyl-alkyl ketones, methyl aryl ketones, cyclic ketones. [36]



scheme (1. 4): Reactions of indole with aldehydes, ketones in the presence of hydrated ferric-sulfate

A simple, clean, and effective solvent-free protocol were described for the synthesis of bis(indolyl)methanes promoted by silica gel. The products were gained in good to excellent yields through the reaction of indoles with cyclohexanone and a range of

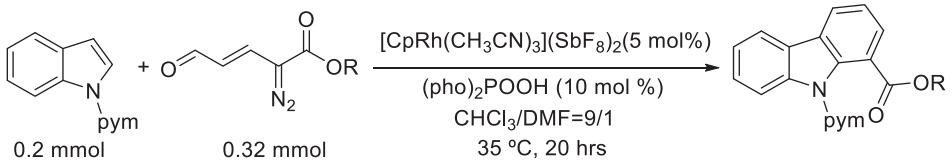
aldehydes. The silica gel was easily recovered and used for further reactions without activity lossing . (37)



scheme (1. 5): Reactions of indole with aldehydes, ketones in the presence of silica gel

1. 2. 4. 3. Reaction of Indoles with Enaldiazo Esters in the presence of tandem catalyst.

A tandem CpRh(III)-catalyzed C−H activation/Bronsted acid-catalyzed intramolecular cyclization lets a facile synthesis of carbazoles from easily obtainable indoles. The reaction proceeds under rather mild reaction conditions with the generation of water and N_2 as the only byproducts. Broad substrate field, excellent functional group tolerance, and high yields were obtained. (38)

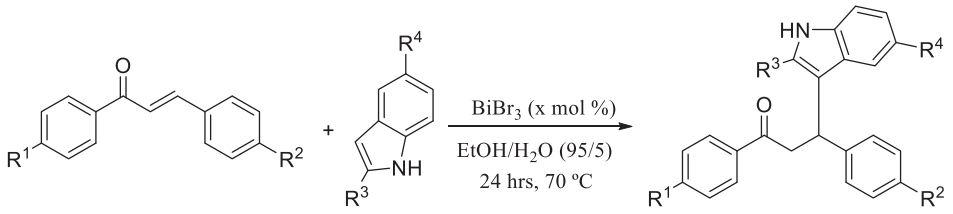


scheme (1. 6): Reactions of indole with Enaldiazo Esters in the presence of tandem catalyst.

1. 2. 4. 4. Conjugate Addition of Indoles to α,β-Unsaturated Ketones by Using Bismuth (III) Bromide.

An effective method for the conjugate addition of indoles to a Different of chalcones using $BiBr_3$ in ethanol is reported. Products are isolated by a simple method that avoids an aqueous

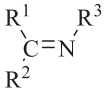
work up and extensive chromatography, thus decreasing waste. Bismuth (III) compounds are especially attractive from a green chemistry perspective because they are remarkably nontoxic, non-corrosive and relatively inexpensive. (39)



scheme (1. 7): Reactions of indole with Conjugate α,β-Unsaturated Ketones by Using Bismuth (III) Bromide.

1. 3. Schiff bases

Schiff bases, named after Hugo Schiff ,(40) are produced when any primary amine reacts with an aldehyde or a ketone under specific conditions. Structurally, a Schiff base (also known as azomethine or imine) figure (1. 10) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (C=O) has been exchanged by an azomethine or imine group. (41)



R^1, R^2 and/or R^3=alkyl, aryl or H

Figure (1. 10): General structure of a Schiff base

Schiff bases are some of the most broadly used organic compounds. They are used as dyes and pigments, catalysts, intermediates in organic synthesis, and as polymer stabilisers (42) , Schiff bases have also been shown to exhibit a wide range of biological activities, including antibacterial, antifungal, anti-

inflammatory, antimalarial, antiviral, antiproliferative, and antipyretic properties. [42-44]

Azomethine or imine groups are exsist in various natural, natural-derivatives, and non-natural compounds. The azomethine group present in such compounds has been shown to be critical to their biological activities. [45-47] (figure 1. 11)

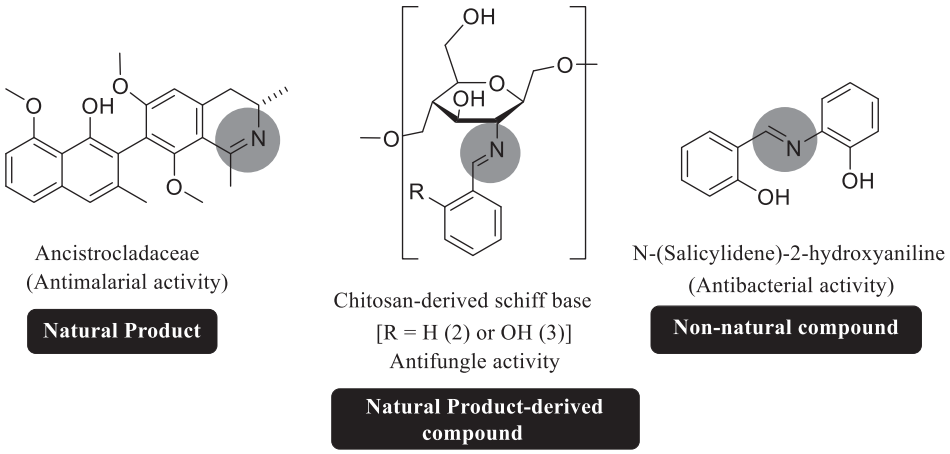
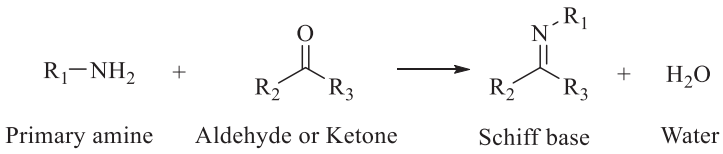


figure (1. 11): Example of bioactive Schiff bases

1. 3. 1. Synthesis of schiff bases

The first preparation of schiff base was achieved in the 19th century by Schiff (1864). Since then a Different of methods for the synthesis of schiff bases have been described,[48] A Schiff base reaction is a reversible, acid-catalysed condensation between a primary amine (not ammonia) and an aldehyde or ketone, which is shown in scheme (1. 8) where R may be an alkyl or an aryl group.

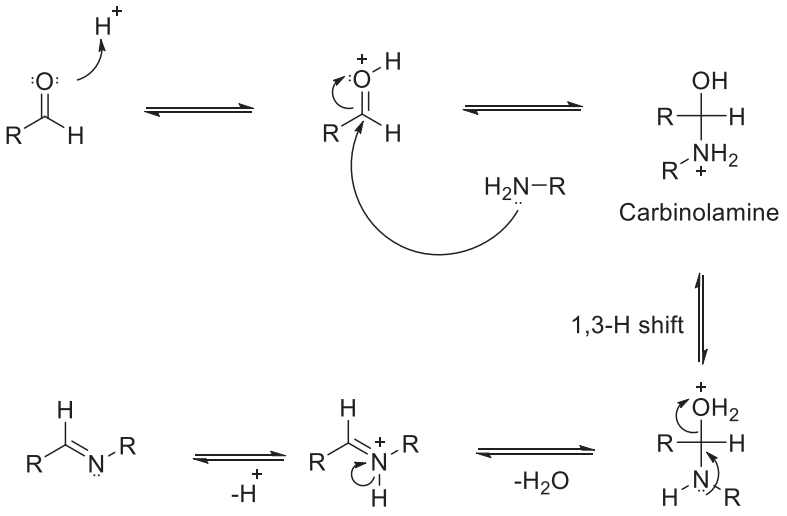


scheme (1. 8): Preparation of Schiff base

Usually, the formation of Schiff bases from aldehydes or ketones requires a protic solvent which is sufficiently dry in order to avoid potential hydrolysis of the newly formed imine bond. The formation is generally undertaken under acid or base catalysis, or via heating. The completion of imine formation is controlled by the separation of the product or removal of water, or both. [49]

1. 3. 2. Mechanism of Schiff bases formation

The general concept of the mechanism of Schiff base formation, as shown in scheme (1. 9) is nucleophilic addition to the carbonyl group. During Schiff base formation, the primary amine is the nucleophile. In the first part of the mechanism, the lone pair of electrons in the amine nitrogen attacks the aldehyde or ketone to give an unstable addition compound called a (carbinolamine).[50] Then a 1,3-hydrogen shift follows which simplify losing water by either acid or base catalysis. Since the carbinolamine is an alcohol, it undergoes acid catalysed dehydration.

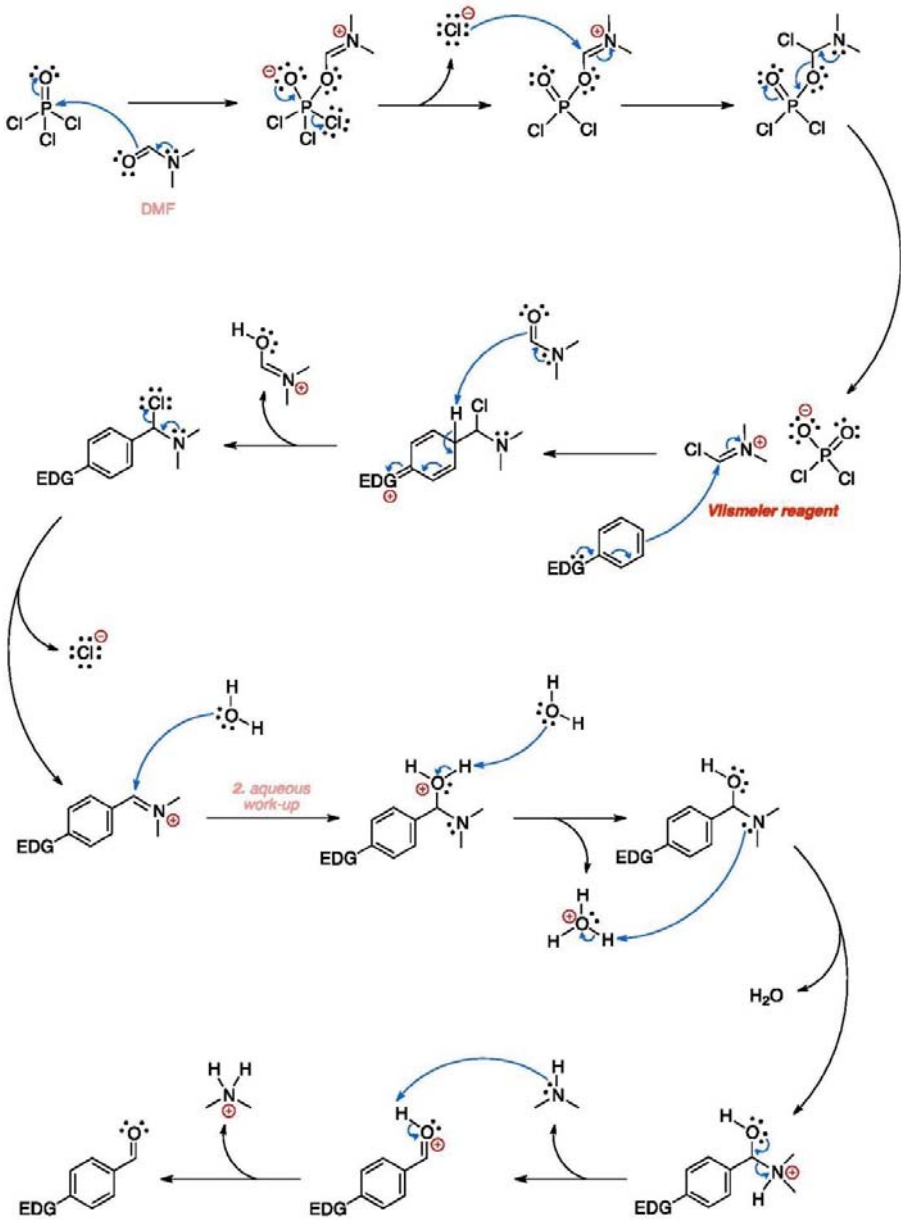


scheme (1. 9): Mechanism of Schiff base formation

1. 4. Vilsmeier – Haack Reaction

The Vilsmeier-Haack reagent is an effective, economical and mild reagent for the formylation of reactive aromatic and heteroaromatic substrates[51]. in the precent time used as a powerful synthetic tool for the construction of many heterocyclic compounds.[52-54] The classical Vilsmeier-Haack reaction[55], however, includes electrophilic substitution of an activated aromatic ring with a halomethyleniminium salt to get the corresponding iminium species, which facilitates easy entry into different nitrogen and oxygen based heterocycles. [56]

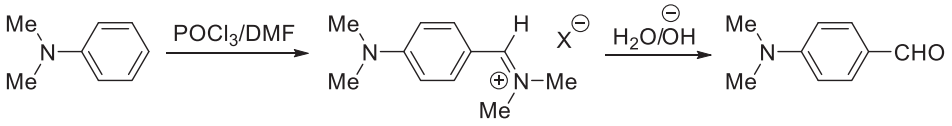
The reaction of an N,N-disubstituted formamide, like di methylformamide (DMF) or N-methylformanilide, with acid chlorides, such as phosphoryl chloride or phosgene, leads to the formation of adducts. These adducts which are usually referred to as the Vilsmeier-Haack reagent find important applications in synthetic organic chemistry specially in the formylation of electron rich aromatic compounds or alkenes. In the present time it is well established that the reaction proceeds by the attack of the carbonyl oxygen of the amide to form the adduct at first which reacts further to give chloromethylene iminium salt scheme (1. 10). [57]



Scheme (1. 10): Vilsmeier Haack mechanism

The classical vilsmieir-Haack reaction involves the reaction of electron rich aromatic compounds or alkenes with the iminium salts produced from formamides and acid chlorides.

The vilsmieir-Haack reaction is an important method for the synthesis of sevsral aromatic aldehydes and α,β-unsaturated aldehydes Scheme (1. 11). [58]



Scheme (1. 11): Vilsmieir-Haack reaction for the synthesis of aromatic aldehydes

1. 5. Biological activity of indole Schiff bases

The indole ring system is probably t Widespread heterocycle in nature. Owing to the great structural diversity of biologically active indoles, it is not surprising that the indole ring system has become an significant structural component in many natural products with high structural complexities and biologically active molecules. For this reason, indole and its derivatives have been utilized, continuously, in different research areas such as fragrances, pharmaceuticals, pigments, agrochemicals, and material science. [59] Schiff bases are important type of compounds in pharmaceutical and medicinal field. They exhibit biological applications including antibacterial [60-64], antifungal [61-64] and antitumor activity [65,66]. Identically indole derivatives are prepared for a long time for a variety of biological activities such as treatment of CNS, anticancerous, antidepressant, antihistaminic, antibiotic, anticonvulsants and many others. Electron-rich nitrogen

heterocyclic compounds play an important role in varied biological activities. (67)

Fadhil L. Faraj *et al* synthesized 2-(5-Chloro-3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-3-(2,4-disubstituted phenylimino)-propionaldehyde and were evaluated for their in vitro against– AMJ breast cancer cell line. The appeared data showed that compounds have promising anticancer activity toward AMJ13 cell line at low concentrations figure (1. 12). (68)

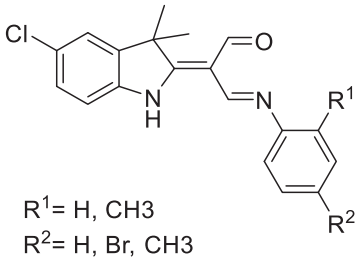


figure (1. 12): 2-(5-Chloro-3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-3-(2,4-disubstituted phenylimino)-propionaldehyde

Anand R. Saundane *et al* synthesized N'-[(5-substituted-2-phenyl-1H-indol-3-yl)methylene] 2-oxo-2H-chromene-3-carbohydrazides and were screened for their antimicrobial and antioxidant activities. The synthesized derivatives showed acceptable activities as antimicrobial and antioxidant agents figure (1. 13). (69)

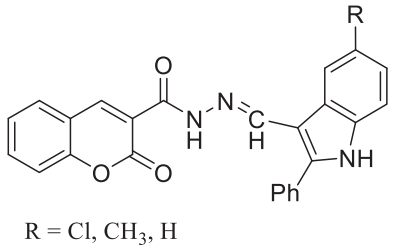


figure (1. 13): N'-[(5-substituted-2- phenyl-1H-indol-3-yl)methylene] 2-oxo-2H-chromene-3-carbohydrazides

Syahrul Imran *et al* synthesized bisindolylmethane Schiff base derivatives and evaluated them for their antibacterial activity against selected Gram-positive and Gram-negative bacterial strains (*Salmonella typhi*, *S. paratyphi* A and *S. paratyphi* B). The synthesized derivatives showed moderate to good antibacterial activity against bacteria strains used. [70]

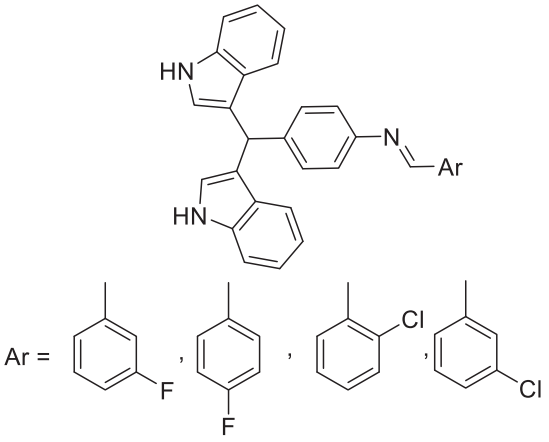


figure (1. 14): (E)-N-(4-(di(1H-indol-3-yl)methyl)phenyl)-1-(substituted phenyl)methanimine

Gokce Gurkok *et al* synthesized new series of (E)-3-((2-(substituted phenyl)hydrazono)methyl)-1H-indole derivatives, and were evaluated for their antimicrobial activity. Tested compounds displayed significant activity against used microorganisms. [71]

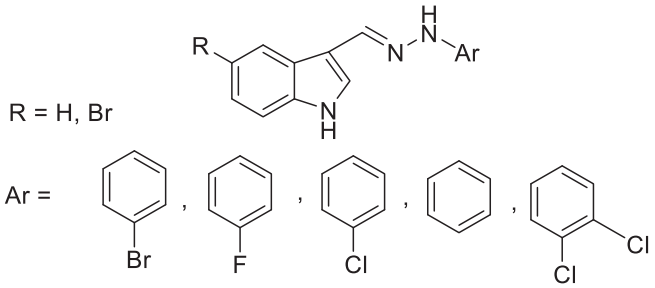


figure (1. 15): (E)-N-(4-(di(1H-indol-3-yl)methyl)phenyl)-1-(substituted phenyl)methanimine

1. 5. 1. Cancer

Cancer considered to be one of the major reasons of deaths in the 20st century and increasing occurrence in 21st century. This represents main world health problem. Almost 7.6 million deaths are usually caused by cancer which represents (13%) of all deaths.(72) The cancer represents abnormal cell growth which means that some of the cells start to divide without stopping chance by ignoring the usual rules of normal cell division and these cells begin to invade to the surrounding tissues and this is called as "metastasis". (73)

There are several causes of cancer: family history, age, bacterial infection, viral infection, smoking, contact to radiation and chemicals, alcohol use and drinking, eating, touching or breathing harmful materials, these cancer causing are called "carcinogens" and contact to these carcinogen does not mean you will get cancer but depends on how many times you are exposed to it. (74)

There are many types of cancer such as breast, blood, prostate, lung, brain and colon cancer which is considered the most common cancer types appears in Iraq.(75)

Breast cancer was considered one of the most common diagnosed type in the women around the world. (76) In each year about 600,000 women around the world were death because of it. (77) American Cancer Society's estimated that breast cancer is the most common type in American women. In 2017 About 252,710 new cases of breast cancer in women were diagnosed and about 40,610 were died from it. (78) Also the percentage deaths of cancer in Asian women has increased more rapid rate in every year.(79)

Aim of the work

The main objectives of the present study are :

1- Synthesis new derivatives of indole based Schiff bases.

2- Characterization the chemical structure of the synthesized compounds by spectral techniques (FT-IR, ^{1}H, APT ^{13}C NMR).

3- Evaluating anticancer activity of the synthesized derivatives against AMJ-13 breast cancer cell line.