جمهورية العراق
وزارة التعليم العالي والبحث العلمي
جامعة ديالى
كلية العلوم
قسم الكيمياء

تحضير،تشخيص،تقييم الفعالية ضد الخلايا السرطانية لبعض المركبات الحلقية غير المتجانسة المشتقة من مشتق الاندول

رسالة مقدمه الى

مجلس كلية العلوم - جامعة ديالى
كجزء من متطلبات نيل درجه الماجستير
في علوم الكيمياء

من قبل
ضحى صالح محمد

بكالوريوس علوم كيمياء 2018

كلية العلوم - جامعة ديالى

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Chapter One

(Preface & Literature review)

1.1. Preface

Heterocyclic compounds constitute the largest and most varied family of organic compounds. their number is increasing rapidly due to the enormous synthetic research and also their synthetic utility [1]. In a number of biologically active natural compounds, N-heterocycles have been found to play an important role: Antibiotics like penicillin and cephalosporin, alkaloids such as vinblastine and morphine, as well as fungal natural products including cyclosporine, are biologically important substances [2]. They are classified into three, four, five, and six-membered rings. The most common heterocycles are those having five or six-membered rings and containing heteroatoms of nitrogen (N), oxygen (O), or sulfur (S) [3]. Heterocyclic compounds classified into aliphatic and aromatic compounds. Although, a variety of highly efficient methodologies for synthesis of aromatic heterocyclic and their derivatives have been reported in the past, the development of novel methodologies is in continuous demand. Particularly, development of new synthetic approaches toward heterocyclic, aiming at achieving greater levels of molecular complexity and better functional groups. Indole ring in is a typical example of the heterocyclic organic [4] .

Indole is an organic compound with the formula C_8H_7N. The indole ring enters into the structure of many natural products. These compounds are very plenty in nature, are an important source of pharmacologically active vehicles. Indole alkaloids have anticancer activity via different anti-proliferative mechanisms, and some of them, such as *Vinblastine* and *Vincristine*, have already utilized in clinics or under clinical estimations for the therapy for cancer [5]. Indole and many of its derivatives are the most interesting heterocycles class containing nitrogen due to their variety of biological actions, which include antitumor [6], antiviral [7] and anti-inflammatory properties [8].

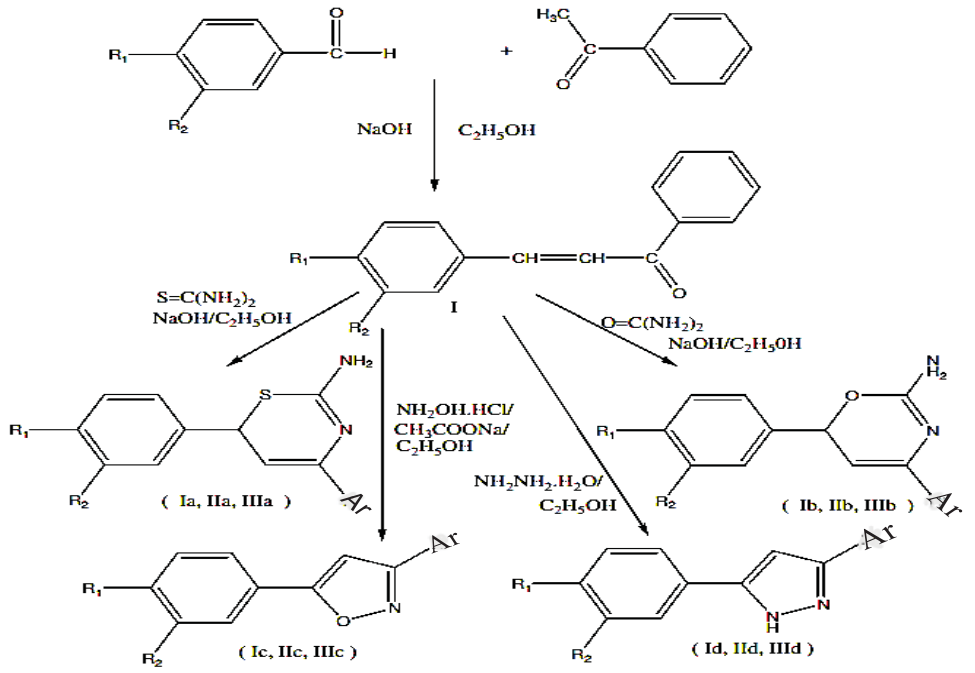
Chalcones are an important class of compounds found in various natural products [9]. The synthetic methods for chalcone containing compounds are simple,

efficient, convenient, and high yielding [10]. Synthetic and natural chalcones show various interesting medicinal activities [11]. Chalcone is comprising of two aromatic rings connected together by a three carbon α,β unsaturated carbonyl bridge. It is one of the most privileged scaffolds in medicinal chemistry that can be synthesized in the laboratory and can be converted into several therapeutically active heterocyclic scaffolds. It exhibits multifarious pharmacological activities and also plays a key role in several non-pharmacological scientific applications [12].

Pyrazoline is a five-membered heterocyclic compound having two adjacent nitrogen atoms within the ring. It has only one endocyclic double bond and is basic in nature. Pyrazole derivatives have a long history of application in agrochemicals and pharmaceutical industry as herbicides and active pharmaceuticals [13]. They have been widely explored by the scientific community and are reported to possess wide spectrum of biological activities. For combating unprecedented diseases and worldwide increasing drug resistance, 2-pyrazoline has been tackled as a fascinating pharmacophore to generate new molecules with improved potency and lesser toxicity along with desired pharmacokinetic profile [14].

1.2. Literature review

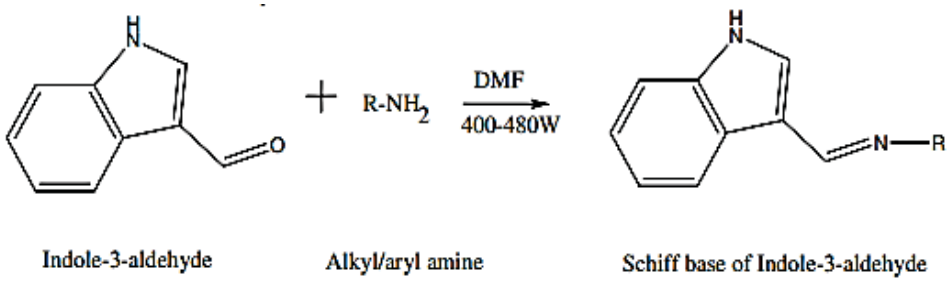
Kalirajan R. *et al.* (2009) some novel heterocyclic derivatives such as Thazines, Oxazines, Isoxazoles and Pyrazoles were synthesized from various chalcones. These compounds were screened for their anti inflammatory, anti bacterial and antifungal activities [15]



Compound Code	R_1	R_2	Ar
(I), (Ia), (Ib), (Ic) & (Id).	OCH_3	H	C_6H_5
(II), (IIa), (IIb), (IIc) & (IId).	H	Cl	C_6H_5
(III), (IIIa), (IIIb), (IIIc) & (IIId).	H	NO2	C_6H_5

Scheme (1.1) :Synthesized some new heterocyclic derivatives of chalcones.

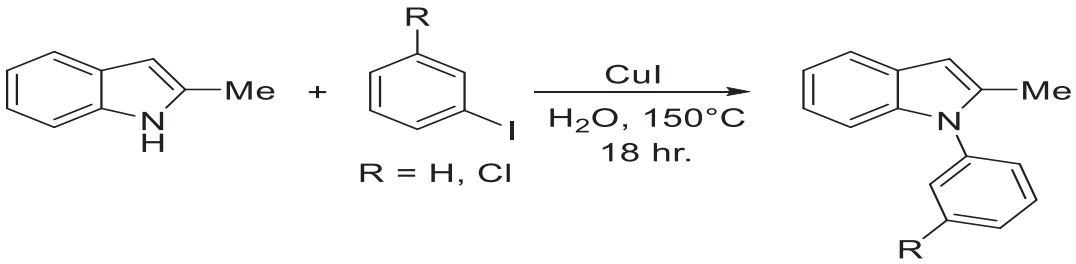
Kamaria P. *et al.* (2011) synthesized Schiff bases by reacting indole-3-aldehyde with aniline under microwave irradiation, which demonstrated excellent antibacterial action, as shown in equation (1.1). The antimicrobial activity of synthesized compounds was examined against one gram-positive and one gram-negative bacteria. Synthesized Schiff bases exhibited moderate antibacterial activity against *S. aureus* and *B. subtilis* [16].



Indole-3-aldehyde Alkyl/aryl amine Schiff base of Indole-3-aldehyde

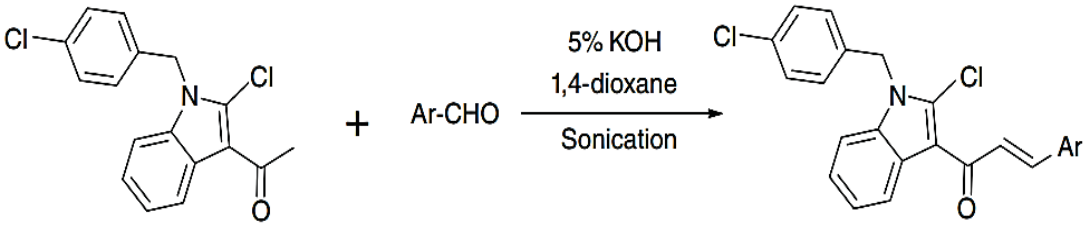
Equation (1.1): Synthesis of Schiff bases.

Abele E. *et al.* (2013) have developed a new protocol for N-arylation of heterocycles including indole in the presence of CuI as a catalyst system and water as an efficient medium, as illustrated in the equation (1.2) [17].



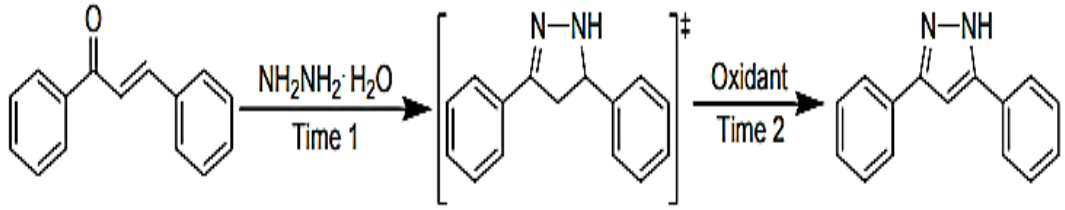
Equation (1.2): Synthesis of N-substituted indole derivatives.

Gao W. *et al.* (2014) two powerful methods for the synthesis of indole-based chalcone derivatives, namely 1-(2-chloro-1-(4-chlorobenzyl)-1H-indol-3-yl)-3-aryl(hetaryl)prop-2-en-1-ones are described, involving the ultrasound-assisted or solvent-free Claisen–Schmidt condensation reaction of 3-acetyl-2-chloro-1-(4-chlorobenzyl) indole and various aromatic aldehydes. The ultrasound-assisted reaction was carried out using 1,4-dioxane as solvent and KOH as base at room temperature to give the corresponding products in yields ranging from 75 to 88 % [18].



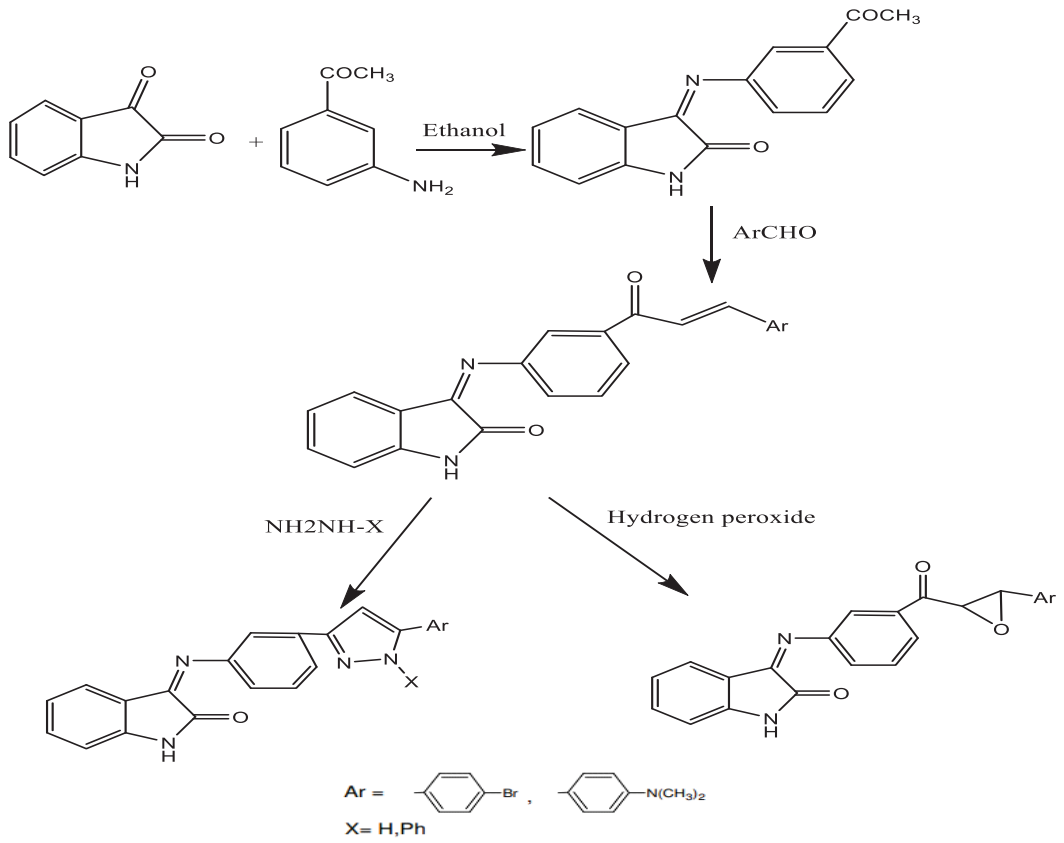
Equation (1.3) :Ultrasound-assisted synthesis of indole-based chalcone derivatives.

Zhang Z. *et al*.(2014) a highly efficient and environmentally friendly method has been developed for facile synthesis of 3,5-diphenyl-1H-pyrazoles under mechanochemical ball-milling conditions [19].



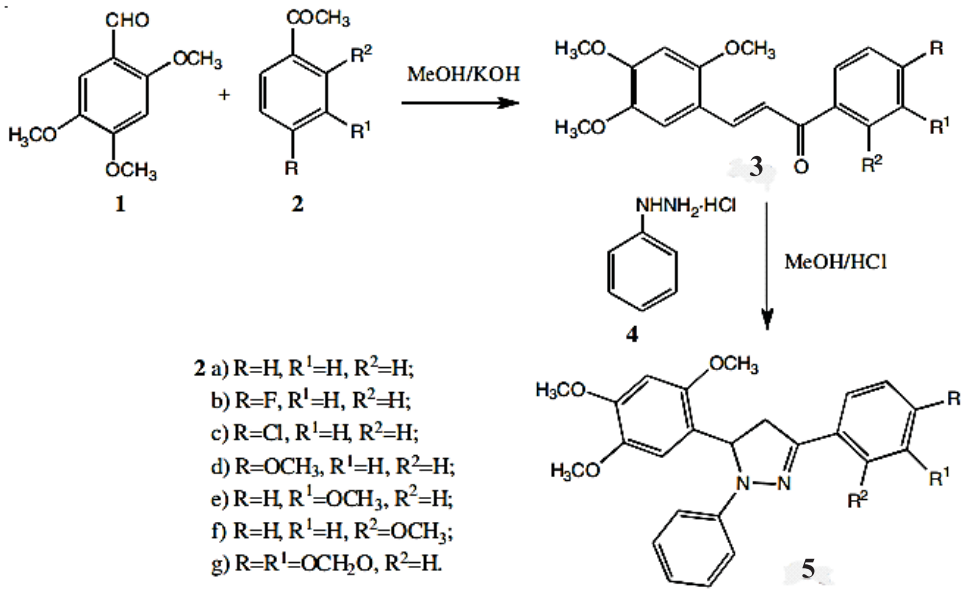
Scheme(1.2) :Synthesis of pyrazole derivatives.

Ali W. B. *et al*. (2016) synthesis of new chalcones derived from isatin compound. In the first Schiff base compound was prepared through the reaction of isatin compound with 3-amino acetophenone and then chalcones were synthesized by reaction of Schiff base with different aryl aldehyde in the presence of potassium hydroxide. However cyclization compounds were synthesized from condensation of chalcones compounds with hydrazine hydrate, phenyl hydrazine and hydrogen peroxide [20].



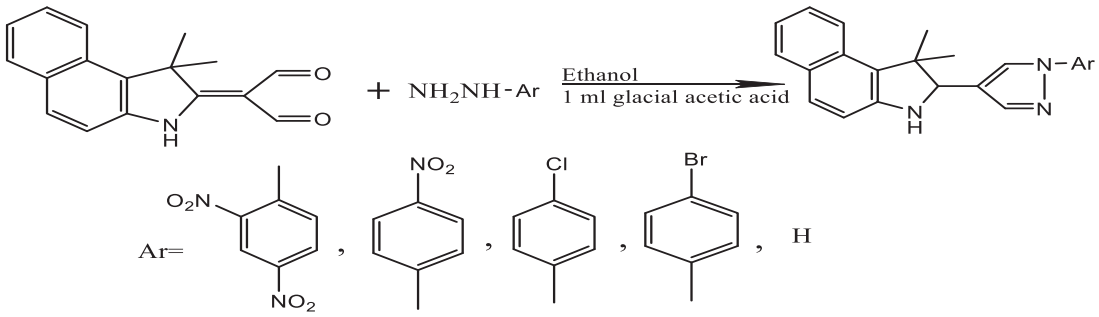
Scheme(1.3):Synthesis of new chalcones derived from isatin compound.

Ramyashree D. *et al.* (2017) an efficient procedure for the synthesis of trisubstituted pyrazoles was developed. Claisen Schmidt condensation of 2,4,5-trimethoxybenzaldehyde and substituted acetophenone in the presence of aqueous alkaline bases produced chalcones. The cyclocondensation reaction of chalcones and phenyl hydrazine hydrochloride catalyzed by an acid produced trisubstituted pyrazolines in good yields. The synthesized new compounds were characterized by spectral studies and elemental analysis and some of the intermediate chalcones by single crystal X-ray diffraction studies. The compounds were screened in vitro for their antimicrobial susceptibilities against different bacteria and fungi species [21].



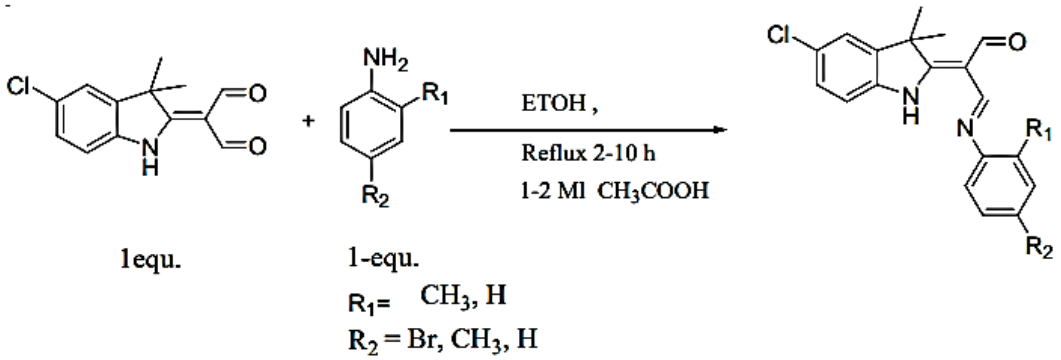
Scheme(1.4): Diagram for the synthesis of pyrazolines.

Ali W.B. *et al.* (2018) synthesized new series of pyrazole derivatives by refluxing hydrazine derivatives with 2-(1,1-Dimethyl1,3- dihydro-benzo[e]indol-2-ylidene) malonaldehyde as shown in equation (1.4)**.** The compounds were identified by FTIR and ^{1}HNMR spectral data [22].



Equation (1.4) : Synthesized new series of pyrazole derivatives.

Ghaidan A. F. *et al.* (2018) synthesized 2-(5-Chloro-3,3-dimethyl1,3-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 equation (1.5) [23].



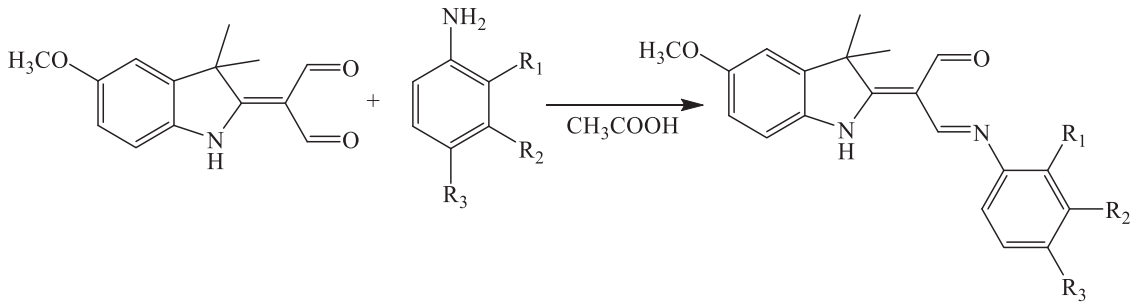
1equ. 1-equ.

R_1= CH_3, H

R_2 = Br, CH_3, H

Equation (1.5) : Synthesis of new Schiff bases.

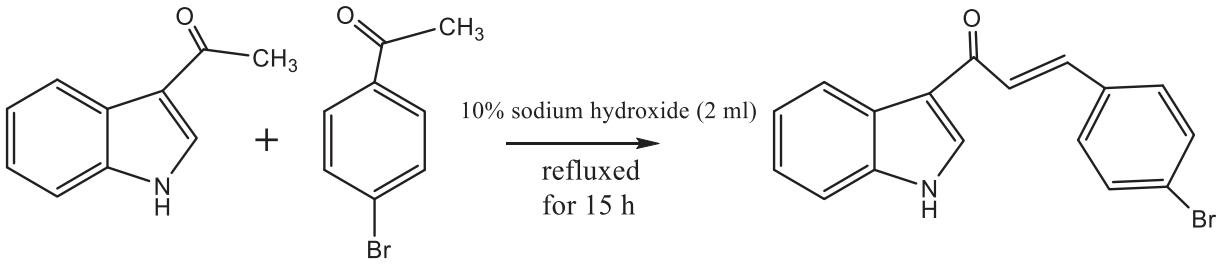
Nafia R. A. *et al*.(2019) synthesized three new Schiff bases by the reaction of 2-(5-methoxy-3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-malon aldehyde with substituted aniline as shown in equation (1.6).The chemical structures were characterized by FTIR, 1H ,and ^{13}C NMR .The biological activity of the new synthesized compounds screened on Lymphatic cell in metaphase in human blood ,which was revealed different results [24].



R_1=OH or CH3,R_2=CH_3,R_3=OH

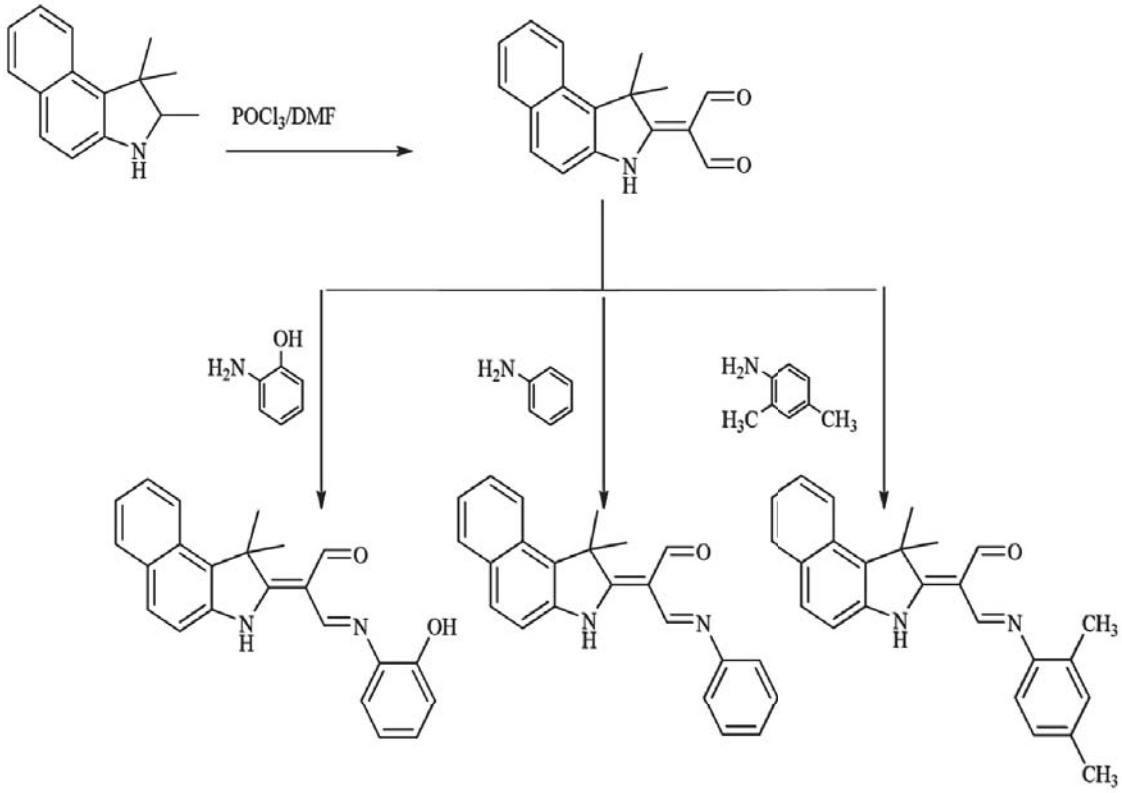
Equation (1.6): Synthesized three new Schiff bases.

Sasidharan R. *et al*. (2019) This study evaluates the anti-inflammatory effect of indole based chalcone derivative 3-(4-bromophenyl)-1-(1H-indol-3-yl) prop-2-en-1-one on lipopolysaccharide (LPS) activated murine macrophages RAW264.7 cells and carrageenan-induced acute model in rats [25].



Equation (1.7): Synthesis of indole based chalcone derivative.

Jameel D. A. *et al.* (2020) series of new indole based Schiff base derivatives were designed and synthesized by reacting 2-(1,1-dimethyl- 1,3-dihydro (2H) benzo[e]indole-2-ylidene)malonaldehyde with different substituted aniline. Spectroscopic techniques were used to confirm and characterize the chemical structure of the substances (FT-IR, ^{1}H-NMR and ^{13}C-NMR). The cytotoxicity activity of the target compounds at various doses was tested against the AMJ-13 breast cancer cell line [26].



Scheme (1.5): General reaction for synthesis of the three new indole Schiff bases derivatives.

The aim of the study

The aim of the present study can be summarized in:

1. the core of the current project was on synthesis a new series of Schiff bases, chalcone and pyrazoline derivatives from indole derivative
2. Characterization of the synthesized compounds by FTIR and ^{1}HNMR
3. investigated them against cancer cells (MCF7) and normal cells (MEF) then compared the effect to find out the extent of their effect on the used cells.