Ministry of Higher Education
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University of Diyala
College of Science
Department of Chemistry

New Heterocyclic Derivatives with Potential Biological Activity

A Thesis Submitted to the
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CHAPTER ONE

PREFACE AND LITERATURE REVIEW

1.1 Preface

Heterocyclic compounds are organic compounds that contain at least one carbon atom and one difference element carbon, such as sulfur, oxygen and nitrogen within or inside the ring structure. The most common heterocyclic loops are those that have five- or six-membered rings. It contains one or more heteroatoms such as nitrogen (N), oxygen (O), or sulfur (S) in their chemical structures [1]. Heterocyclic play an important role in sciences fields such as medicinal chemistry [2]**.** Heterocyclic compounds are the largest type of organic chemistry which has a great importance in biological and industrial sectors. Most pharmaceuticals and biologically active agrochemicals are heterocyclic [3]. Among the various clinical applications, heterocyclic compounds contain significant active role as anti-bacterial, anti-viral, anti-fungal, and anti-inflammatory and anti-tumor drug [4]**.**

Heterocyclic compounds with nitrogen-atoms have special importance because they are participating in the formation of most natural and synthetic products used in daily life. Most of these compounds exhibit beneficial biological activities while, others have curial roles in industry. It may allow the development of new therapies for epilepsy, pain and other neurological disorders [5]. Heterocyclic compounds, particularly those with five and six member rings, have attracted the attention of the pharmaceutical world in recent years due to their therapeutic potential. [6]

Indole is an aromatic heterocyclic organic compound. It is a bicyclic structure, containing a benzene ring and pyrrole nucleuses fused in 2,3 positions of the pyrroie ring. A name indole is consisting of the two words in dingo and oleum. Indole is non-important nitrogenous compounds.

Indole began to develop with study of a dye in dingo. The word indole is derivative from a word India; a blue dye there is in India known as name indigo [7].

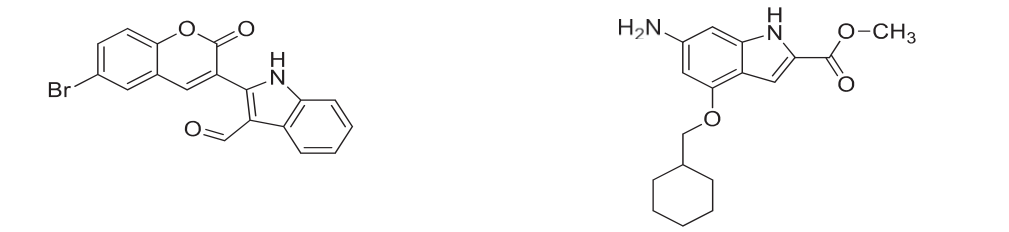
The indole shiff bases were known a significant class of heterocyclic organic compounds which have wide applications in many fields for example anti-inflammatory[8],anti-bacterial, anti-tumor activity[9], anti-applications microbial xactivity [10]and anti-oxidant[11].

Cancer is one of the leading causes of death worldwide. The most recent advances in nitrogen-containing heterocyclics as possible chemotherapy agents for cancer. More than 90% of the novel drugs bear heterocyclics and among them, nitrogencontaining heterocyclic compounds show superior pharmaceutical effect than non-nitrogen compounds. Nitrogen-containing compounds, the heart of drug discovery, present a significant and valuable group of molecules that play a chief and vital role in the metabolism of living cells[12].

The data on the synthesis and properties of benzo[g]indoles accumulated mainly over a period of the past 15 – 20 years are integrated. Various variants of pyrrole ring and naphthalene nucleus closure are considered. It is demonstrated that, in addition to the expected similarity between benzo[g]indoles and indoles, there are noticeable differences between them as well, especially where the synthesis of the benzo-indole system is concerned. Practical applications of benzo[g]indoles are discussed [13].

Extensive research has been carried out on indole and its derivatives, which led to the presence of many indole- containing drugs, approved in the global market in addition to many of them in the preparation stages. They were synthesized many heterocyclic compounds contain indole rings which

have biological activity against cancer, some examples of them as shown in Figure (1. 1) [14].



2-(6-bromo-2-oxo-2H-chromen-3-yl)-1H-indole-3-carbaldehyde

methyl 6-amino-4-cyclohexylmethoxy-1Hindole-2-carboxylate

Figure (1. 1). Some examples of anti-cancer compounds

Vislemer reaction: Vilsmeier- Haak reagents ($POCl_3$, DMF), has been used to form a heterocyclic and variety of aromatic pillars well [15]. The can be applied to enter a aldehyde groups to aromatic compounds, but many can be achieved using the technique to other transformations [16].

Schiff bases: Schiff base also known called Imines are characterized by the azomethine group and are it usually made up of primary amine with ketone or condensation of aldehyde, the condensation reaction between primary amine and carbonyl compound to the configure Schiff base. Schiff base are mainly excellent factors, especially when forming a functional groups such as –SH or OH which, is close to the groups to of form a five or six –member rings of metal ion [17]. Heterocyclic compounds of Schiff bases used to employ as ligands in a metal complex, such as Ni (II), Co (II), Pd (II), Cu (II) and Pt (II) (III). These complexes are important in medicinal applications, supra molecular chemistry and bio inorganic chemistry [18].

1.2. Previous studies.

Gurkok et. al. (2009): Investigated the antibacterial activity of hydrazone and hydrazide of indole-3-aldehyde derivatives, as shown in Figure (1.2), *against bacterial strains E. coli, B. subtilis,* and *S. aureus,* as well as the *fungal strain C. albicans.* Almost all of the compounds demonstrated promising antibacterial activity with MIC values in the range of 6.25-50 µg/ml [19].

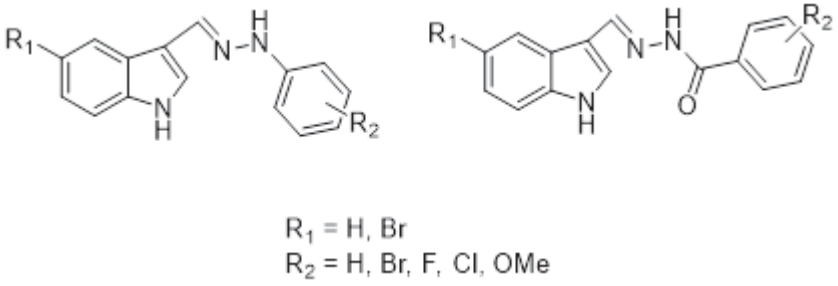
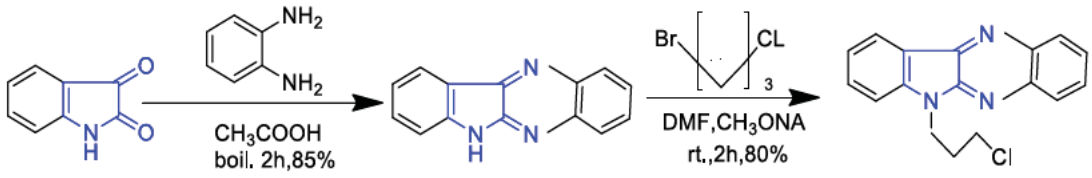


Figure (1.2): Some hydrazone and hydrazide of indole derivatives.

Shibinskaya M. O. et al. (2012): Synthesized 6-(3-chloropropy1)-6H-indolo-[2,3- b] quinoxaline with 80% yield via indolo quinoxaline alkylation by 1-bromo-3- chloropropane. Alkylation of 6*H*-Indolo-[2,3-b] quinoxaline was carried out in dimethylformamide at room temperature in the presence of equimolar quantity of sodium methylate as shown in Scheme (1.1)[20].



Scheme (1.1): Synthesis of 6-(3-chloropropyl)-6*H*-indolo [2,3-b] quinoxaline.

Syahrul Imran (2014): Declared bisindolylmethane Schiff base derivatives and evaluated 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 [21].

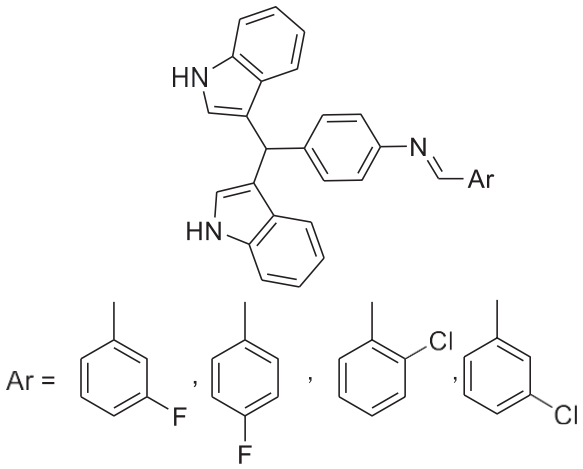


Figure (1.3): (E)-N-(4-(di(1*H*-indol-3-yl)methyl)phenyl)-1-(substituted henyl)methanimine

Rasa Steponavičiūtėa et al (2014): Announced the reaction of 1,1,2-trimethyl-1H-benzo[e]indole with acrylic acid and its derivatives was employed for the preparation of novel fluorescent building blocks [22].

Mhaske et. al. (2015): Synthesized 1*H*-indole-3-carbaldehyde by reacting indole with phosphorus oxychloride in DMF and a solution of sodium hydroxide in water as shown in Figure (1.4). The synthesized compound was found to be an excellent antibacterial agent against *E. coli* and *S. auerus* when they were compared with known antibacterial agents [23].

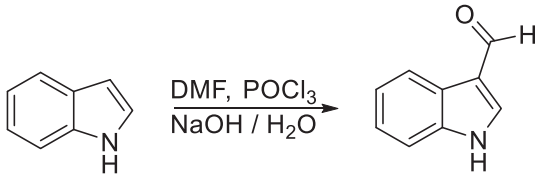
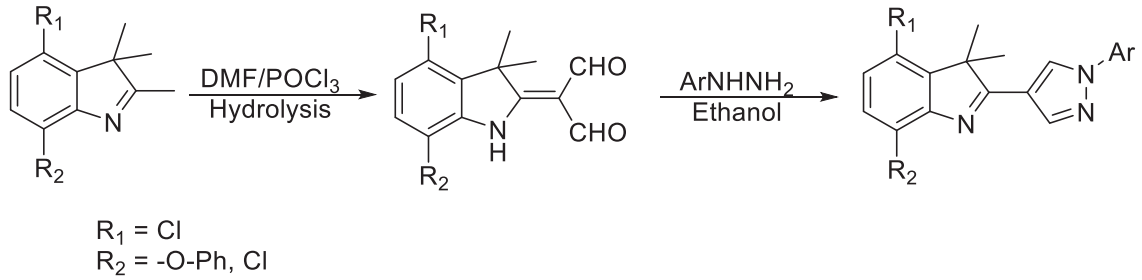


Figure (1.4): Synthesis of 1*H*-indole-3-carbaldehyde

Khezri M. et. al. (2016): Demonstrate the Vilsmeier-Haack reaction with 2,3,3-trimethyl-3*H*-benzo [g] indole and its conversion in to 2-(1-aryl-1*H*-pyrazol-4-yl)-3,3-dimethyl-3*H*-benzo[g]indoles, as shown in Scheme (1.2)[24].



Scheme (1.2): Synthesis pathway of some indole derivatives

Fatemeh H. et aI. (2017): Prepared 2-(1,1-Dimethyl-1,3-dihydro-benzo[e]indol-2-ylidene)-3-(2-hydroxyphenylimino)-propionaldehyde, DBID from 2-(1,1-dimethyl-1,3-dihydro-benzo[e]indol-2-ylidene) malonaldehyde with 2-aminopheno1. The chemical was tested for anti-proliferative activity against the HCT 116 colorectal cancer cell line, and a putative mechanism of action was discovered. The MTT assay was performed to estimate the IC_{50} value, and its apoptosis-inducing impact was studied [25].

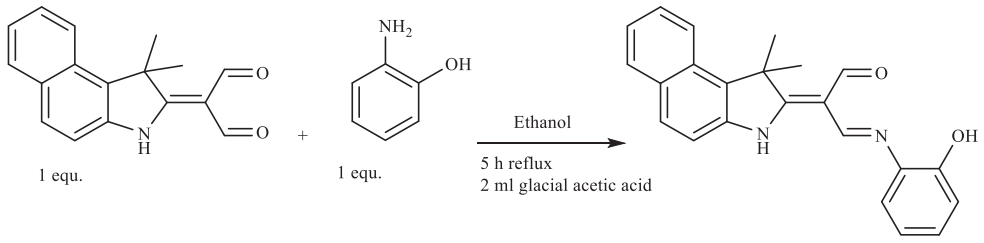


Figure (1.5): Synthesis of (DBID).

Halawa A. H. (2017): Developed and synthesized a number of new heterocyclic schiff bases comprising the indole moiety via condensation of indole-3/2/5-carboxaldehyde with various aromatic and heterocyclic primary amines via traditional and/or microwave irradiation methods [26].

Some important heterocyclic compounds such as tryptophan and serotonin contain indole rings have been synthesized by *Nagendra Kumar Kaushik at el.* Figure (1. 6) [27].

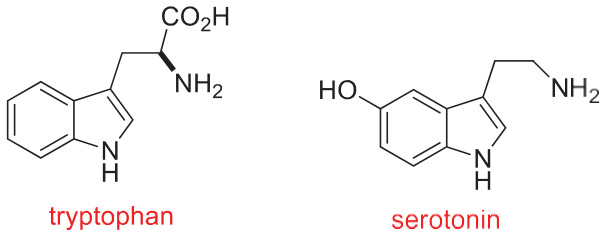


Figure (1. 6). Structures of some naturally occurring indoles

Al-Azawi K.F. (2018): Synthesized successfully new compound, ethyl 4-amino N-(3-isatinyl) benzoate in high yield from reaction of ethyl 4-aminobenzoate with isatin in (1:1) molar ratio as illustrated in the Figure (1.7), and its inhibition impact on corrosion of MS (mild steel) in hydrochloric acid as corrosive solution was examined via weight loss and scanning electron microscope techniques [28].

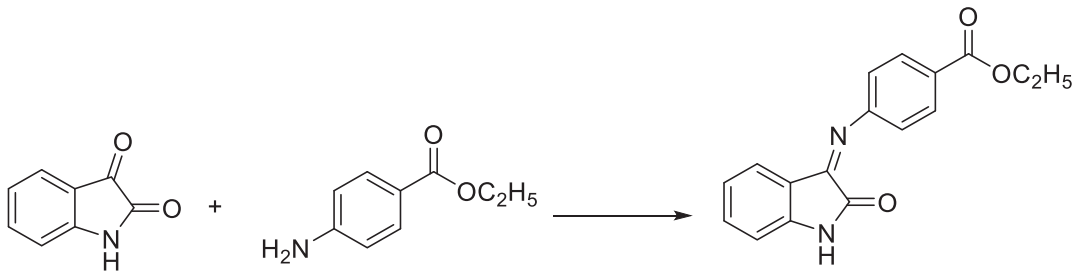
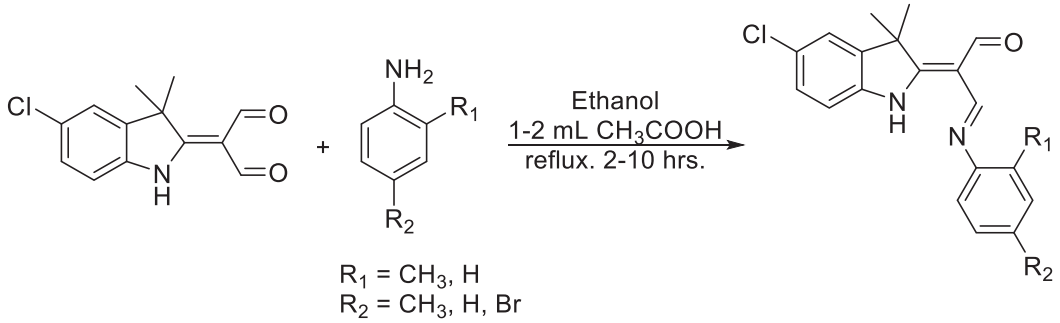


Figure (1.7): Synthesis of (ethyl 4-amino N-(3-isatinyl) benzoate) inhibitor.

Ghaidan A. et. al. (2018): Synthesized a series of novel indole Schiff bases by the reaction of 2-(5-chloro-3, 3-dimethyl-1, 3-dihydro-indol-2-ylidene)malonaldehyde with aniline substituted, as illustrate in Scheme (1.3). The anticancer activity of the new synthesized compounds was tested in vitro against– AMJ13 breast cancer cell line. The revealed data showed that compounds have promising anticancer activity against AMJ13 cell line at low concentrations [29].



Scheme (1.3): Synthetic pathway of novel indole Schiff bases with aniline substituted.

Fadhil L. Faraj et al (2018): Published 2-(5-Chloro-3,3-dimethyl- 1,3-dihydro-indol-2-ylidene)-3-(2,4-disubstituted phenylimino)- propion aldehyde and were evaluated their inhibition against AMJ breast cancer cell line *in vitro*. The appeared data proven that compounds have promising anti-cancer activity toward AMJ13 cell line at low concentrations Figure (1. 8)[30].

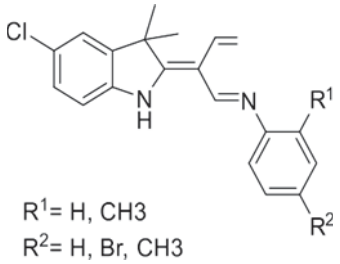


Figure (1.8): Some halogenated indole derivatives.

Ali W.B. (2018): Synthesized new series of pyrazole derivatives by refluxing hydrazine derivatives with 2-(1,1-Dimethy11,3- dihydro-benzo[e]indol-2-ylidene) malonaldehyde as shown in Figure(1.9). [31].

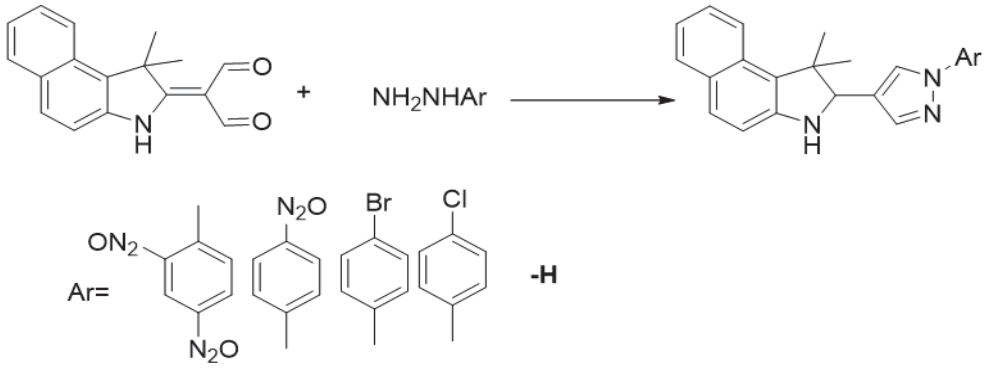
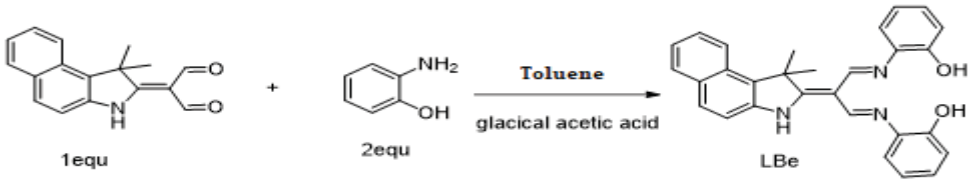


Figure (1. 9): Synthesis of pyrazol derivatives.

Hameed R. F. et aI. (2019)**:** Synthesized new ligand 2-(1,1-dimethyl-1,3- dihydro-2*H*-benzo[e] indol-2-y1idene) propane-1,3-diylidene) bis (azanylylidene) diphenol LBe by the condensation reaction of 2-hydoxy aniline with 2-(1,1- dimethyl-1,3- dihydro-2*H*-benzo[e]indol-2-y1idene) malonaldehyde in ratio 2:1 as illustrated in the Figure (1.10). This compound used as ligand to synthesis a series of metal complexes by its reaction with different metal chlorides in a molar ratio 1: 1 and 1:2 of M:L in ethanol. Cytotoxicity effect of ligand and its complexes have been evaluated against Hella cell line (cervical cancer) in two exposure times 24 and 48 hours [32].



Figure(1.10): Synthesis ofh2-(1,1-dimethyl-1,3-dihydro-2H-bend fe]indol-2-ylidene)propane-1,3- diylidene)j bis (azanylylidene) diphenol.

Guangkuan Zhao. Et.al (2019): An efficient and selective C–H activation method of readily available β-*N*-aryl glycosides with various alkynes has been established. Using $[Cp^*RhCl_2]_2$ as a catalyst and $AgSbF_6$ in DCE, this protocol proved to be general to prepare a variety of 2,3-substituted *N*-glycosyl indoles in good yields [33].

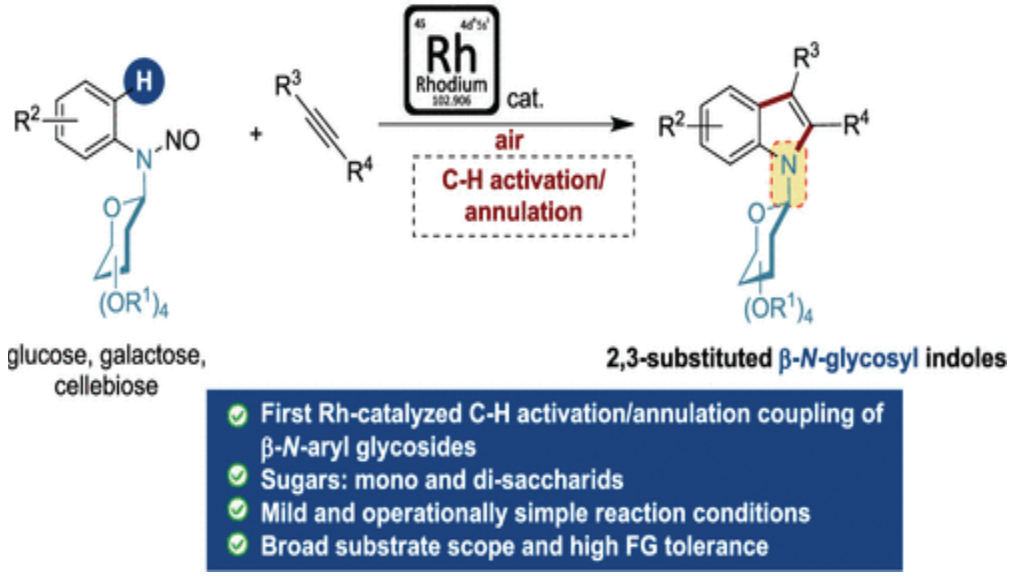


Figure (1. 11). Synthesis of some indoles based N-glycoside linkage.

Xingchao Dai. et.al (2019): Pd supported on natural palygorskite was developed for amine formylation with CO_2 and H_2. Both secondary and primary amines with diverse structures could be converted into the desired formamides at < 100 °C, and good to excellent yields were obtainedas [34].

Nafia R. A. et. al. (2019): Synthesized three novel Schiff bases by the reaction of 2-(5-methoxy-3, 3-dimethyl-1, 3-dihydro-indol-2-ylidene)-malonaldehyde with substituted aniline, as shown in the Figure (1.12). The

biological activity of the new synthesized compounds was screened on lymphatic cell in metaphase in human blood, which revealed different results [35].

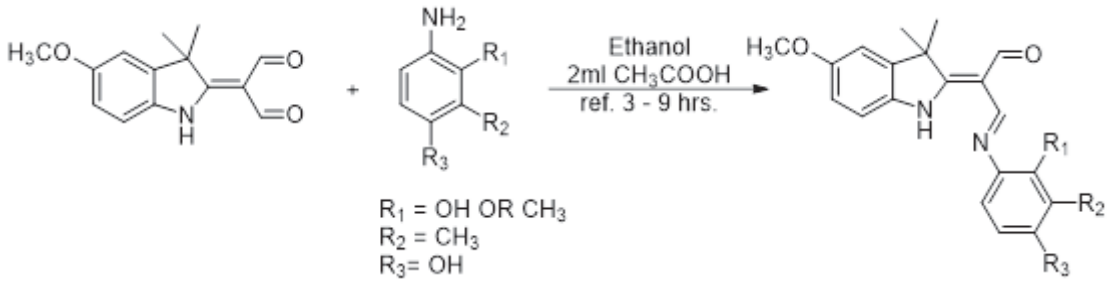
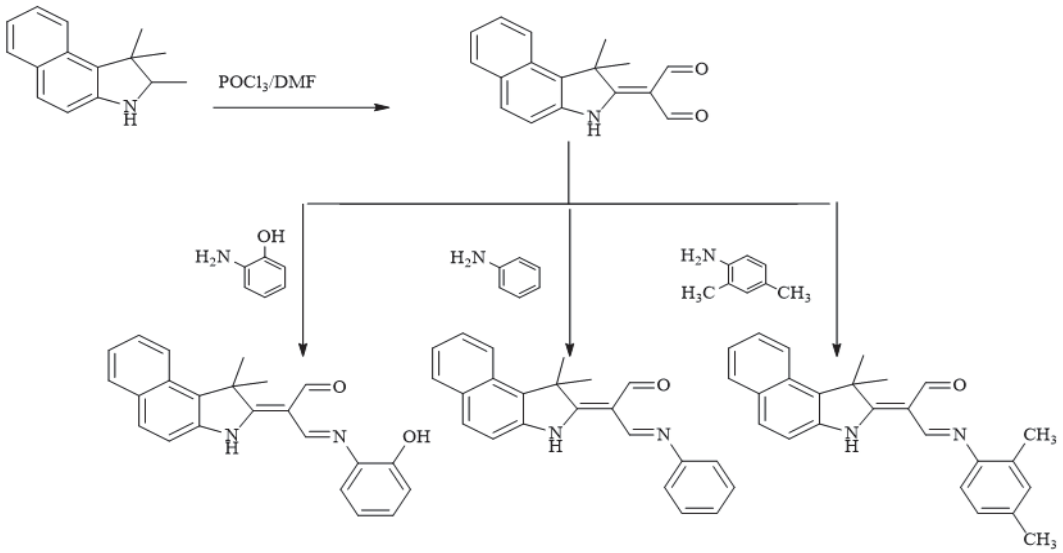


Figure (1.12): Synthetic pathway of novel indole Schiff bases

Jameel D. A et al.(2020): Designed and synthesized a series of new indole based Schiff base derivatives by reacting 2-(1,1-dimethyl- 1,3-dihydro-2*H*- benzo[e]indole-2-ylidene)malonaldehyde with different substituted aniline. The cytotoxicity activity of the target compounds at various was tested against the AMJ-13 breast cancer cell line. The findings revealed that compounds have promising cytotoxic activity against AMJ13 cell line at different concentration Scheme (1.4)[36].



Scheme (1.4): The general scheme of indole Schiff bases derivatives

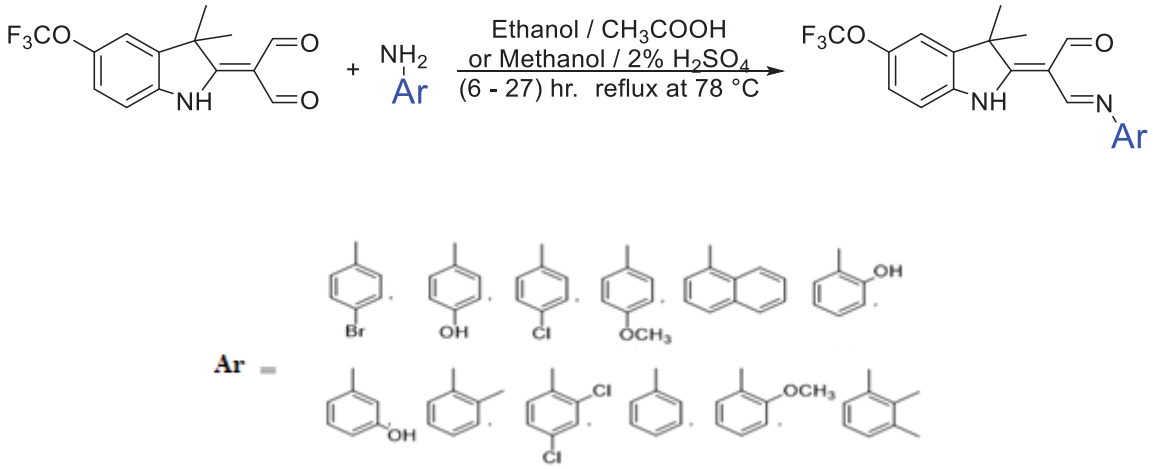
Mohammed Gawi. et.a l (2021): The synthesis new indole Schiff base compound of benzo[e]indol-2-ylidene)-3-(4-methoxyphenyl) imino propanal] (2P) was investigated for antioxidant, toxicity and anti-tumor activity for A547 cell, PC3 cell and WRL 68 cell. This compounds show a good antitumor ability that may be used 2P a new anticancer drug [37].

Yury A. Sayapina and coworkers (2021): Reported the synthesis of chemosensors based on 1*H*-indole, 1*H*-benzo[e]indole, and 1*H*-benzo[g] indole as fluorescence [38].

$R^1 = R^2 = R^3 = R^4 = H$ **(a)**; $R^1 + R^2 = C_4H_4$, $R^3 = R^4 = H$ **(b)**;
$R^1 = R^2 = H$, $R^3 + R^4 = C_4H_4$ **(c)**

Figure (1. 13): Florescence activity of some indole derivatives.

Ismail A. (2021): Designed and synthesized a diformyl of indole derivative by using the Vilsmeier- Haack reagent, which consists of $POCL_3$ with DMF acting as an electrophile attacked by the indole core compound Figure (1.14)[39].



Figure(1.14) Synthesis of indole derivatives via Vilsemer-Haack Reaction.

Vanesa S.D.Gomes .et.al (2022): Report four squaraine dyes derived from 2,3,3-trimethylindolenine at and 1,1,2-trimethyl-1*H*-benzo[*e*]indole with different combinations of barbituric groups attach to the central ring, having ester groups and alkyl chains in the nitrogen atoms of heterocyclic rings were synthesized, and their photo-physical behavior was studied in ethanol and phosphate-buffered solution. The interaction of synthesized dyes with human serum albumin (HSA) was also evaluated. The antifungal potential of the dyes against the yeast *Saccharomyces cerevisiae* was evaluated using a broth microdilution assay. The results showed that the interaction of dyes with HSA and the antifungal activity depends on the different structural modifications of the dyes [40].

1.3 Aim of the work

The objectives of this study are to:-

1- Synthesis new derivatives of indole Schiff bases.
2- Characterization of the synthesized compounds by spectroscopic techniques (FTIR, ^{1}H, ^{13}C NMR).
3- Evaluating anticancer activity of the new derivatives against HepG2 and RD cancer cell line
4- Investigation of the biological activity of the synthesized derivatives toward some kinds of bacteria.