وزارة التعليم العالي والبحث العلمي
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قسم الكيمياء

تحضير وتشخيص بعض مشتقات الإندول ودراستها على مرضى احتشاء العضلة القلبية

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

من قبل
صابرين حسين كاظم
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Chapter One

Preface and Previous studies

1.1. Preface

Heterocyclic compounds are organic compounds that contain at least one carbon atom and at least one different element other than carbon, such as sulfur, oxygen and nitrogen is inside the ring structure. While homo cyclic organic compounds all atoms in the ring are carbon. The most common heterocyclic are those that have five- or six-membered rings. It contains hetero atoms of nitrogen (N), oxygen (O), or sulfur (S) in their chemical structures [1]. Heterocyclic compounds have a role at another fields of sciences [2]. Heterocyclic compounds considered one of the biological classes of organic compounds, which are used in many biological fields, given that it is of activity in multiple diseases. Heterocyclic contain nitrogen is of special importance because it is an important type of natural and synthysized and many exhibit beneficial biological activities, and some heterocyclic derivatives, may allow to the development of new therapies for epilepsy, pain and other neurological disorders [3].

In a number of biologically active natural compounds, N-heterocycles have been found to play an important role. Consider the following: Antibiotics like penicillin and cephalosporin, alkaloids such as vinblastine and morphine, as well as fungal natural products including cyclosporine, are biologically important substances. [4]

For a long time, medicinal chemistry has been fascinated by the chemistry and biology of heterocyclic molecules. A number of heterocyclic derivatives with a nitrogen atom serve as unique and adaptable scaffolds for drug development in the laboratory. Since indole was first extracted by treating indigo dye with oleum,the study of the dye indigo sparked the development of indole chemistry. [5]

Indole is a significant class of organic heterocyclic compounds which it has a two-ring structures, consisting of a six-membered benzene ring embedded in a five-pyrrole ring containing nitrogen. Indole is a common ingredient in perfumes and a precursor to many drugs. The compounds that contain an indole ring are called indoles. While, a tryptophan is amino acid which contains indole ring in its structure is the precursor of the neurotransmitter serotonin [6]. Tryptophan plays a substantial role as a building unit in protein biosynthesis. Proteins containing tryptophan have a reducing effect on hormone-related depression and insomnia [7].

Myocardial infarction (MI) is a term used for an event of heart attack which is due to formation of plaques in the interior walls of the arteries resulting in reduced blood flow to the heart and injuring heart muscles because of lack of oxygen supply.The symptoms of MI include chest pain, which travels from left arm to neck, shortness of breath, sweating, nausea, vomiting, abnormal heart beating, anxiety, fatigue, weakness, stress, depression, and other factors [8].

Critical myocardial ischemia may occur as a result of increased myocardial metabolic demand and/or decreased delivery of oxygen and nutrients to the myocardium via the coronary circulation [9]. An interruption in the supply of myocardial oxygen and nutrients occurs when a thrombus is superimposed on an ulcerated or unstable atherosclerotic plaque and results in coronary occlusion. A high-grade (> 75%) fixed coronary artery stenosis due to atherosclerosis or a dynamic stenosis associated with coronary vasospasm can also limit the supply of oxygen, nutrients and precipitate an AMI [10]. MI type was divided into ST elevation myocardial infarction

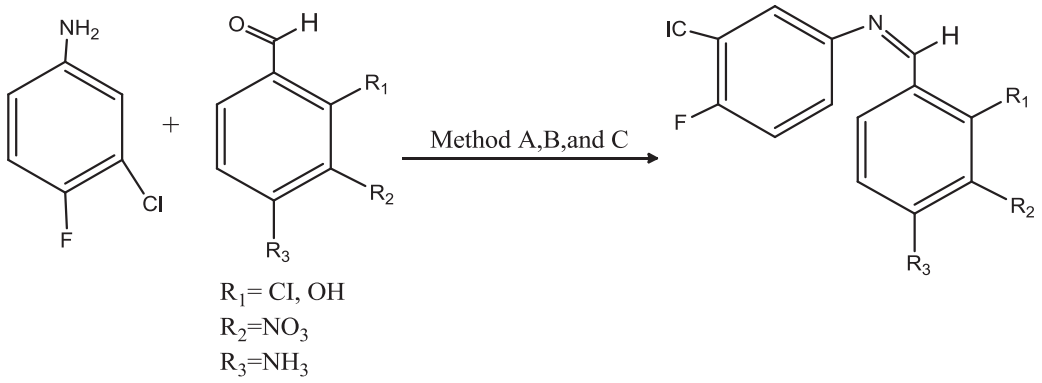
(STEMI) and non-ST elevation myocardial infarction (NSTEMI). STEMI was defined by the presence of ST segment elevation ≥ 1 mm (≥2 mm in V1-V3) in two or more adjacent leads. Whereas NSTEMI was defined by the presence of ST depression, T wave inversion, or non-significant ST-T changes [11].

Some enzymes and proteins are related to myocardial infarction, enzymes are proteins catalysts of biological origin [12]. Necrotic cardiac tissue releases several enzymes and proteins into the circulation, therefore, the appearance of an increased amount of enzymes in the blood stream can be detected with great sensitivity. Therefore, enzymes such as. aspartate transaminase (AST) , lactate dehydrogenase (LDH). Alkaline Phosphatase (ALP), alanine aminotransferase (ALT), creatine kinase (CK) and finally CK-MB have been indicators used for years a diagnosis of AMI [13] .

Previous studies have identified an association between higher ALP levels and mortality from all causes and with cardiovascular disease in subjects with previous myocardial infarction [14]. In AMI, AST and ALT are often elevated, especially in STEMI patients [15]. Lofthus *et al*. recently confirmed in their large study of 1783 patients the elevation of AST in 85.6% and ALT in 48.2% of patients at baseline [16]. Rapid laboratory testing for creatine kinase (CK)-MB greatly revolutionized the diagnosis and management of acute myocardial infarction, in the same study showed high serum levels of creatine kinase MB and lactate dehydrogenase in patients with AMI [17].

1.2 . Previous studies.

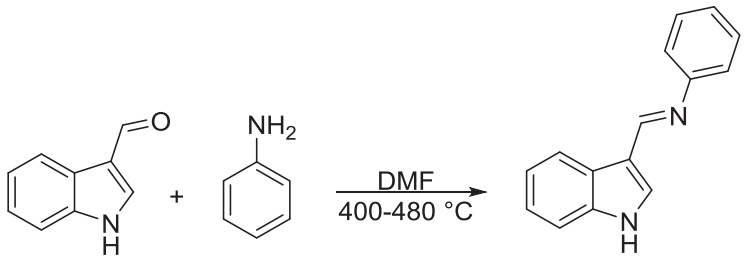
Naqvi A. et.al. (2009) designed and synthesized a series of novel derivatives of Schiff bases from 3-chloro-4-fluoraniline and substituted benzaldehydes using non-classical methods water based reaction (A), microwave (B), and grindstone chemistry (C), These methodologies constitute an energy-efficient and environ-mentally benign greener chemistry version of the classical condensation reactions for schiff bases formation. Scheme (1.1) [18]



Scheme (1.1) Synthesis of Schiff bases using non-classical method(A).

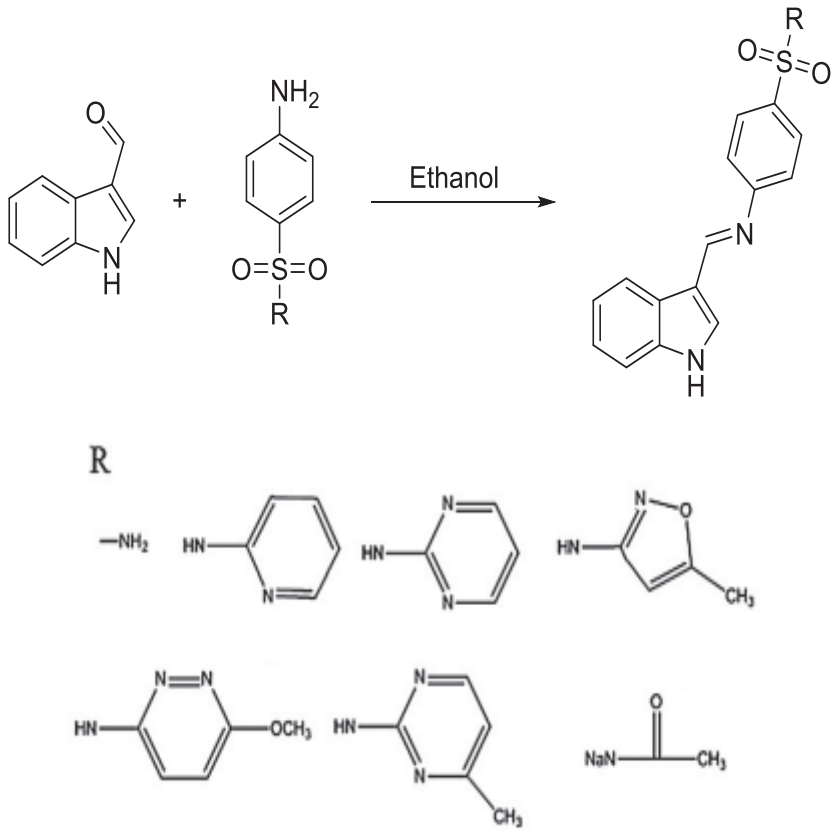
Kamaria, P. *et.al*.(2011) In order to develop new antimicrobial agents, a series of Schiff bases of indole-3-aldehyde Scheme (1.2) were synthesized by microwave assisted synthesis by taking DMF as solvent and evaluated for their antimicrobial activity. All the synthesized compounds were characterized by IR, ^{1}HNMR and mass spectral analysis. All compounds were tested against five gram positive and five gram negative bacterial strains and one fungal strain.The compounds exhibited better activity against

gram positive strains than against gram negative strains and the compounds were found more active against *S.aureus* and *B.subtilis*. [19]



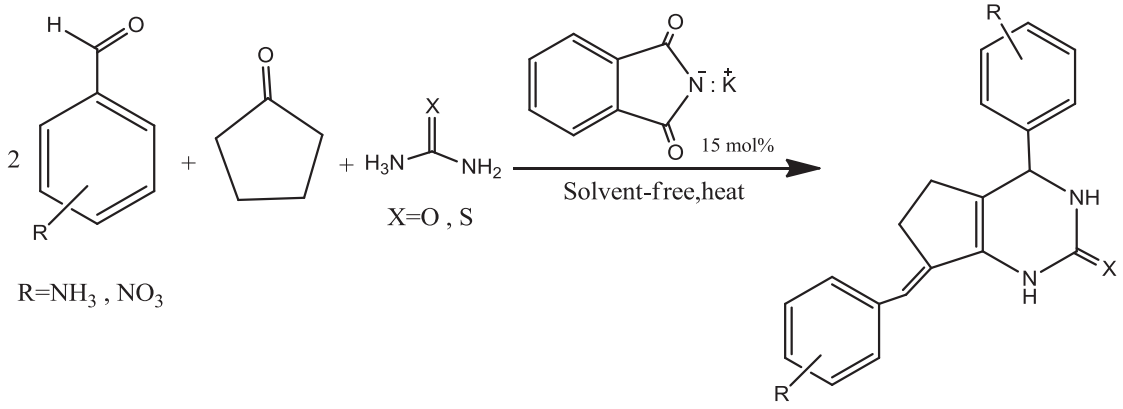
Scheme (1.2) Synthesis of indole based Schiff base derived from indole-3-aldehyde.

Ebrahimi H. et. al. (2013) synthesized a series of novel Schiff bases, as indicated in Scheme(1.3), by condensation of indole-3-carbox-aldehyde with various sulfa drugs in ethanol (1:1). [20]



Scheme (1.3) Synthesis of Schiff bases deiverd from indole-3-carboxaldehyde with various sulfa drugs.

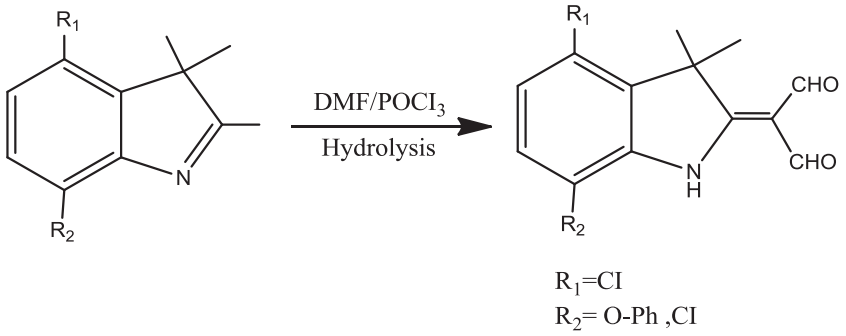
Kiyani, H., et al (2014) An synthesized efficient of Biginelli-type compounds using potassium phthalimide as a green, mild, and commercially available organocatalyst. In a one-pot, multi-component cyclocondensation reaction of cyclo pentanone, aldehydes, urea and thiourea was reported. The present methodology is a green approach to access-4-aryl-7-(arylmethylene)-3,4,6,7-tetrahydro-1*H*-cyclopenta[*d*]pyrimidin-2(5*H*)-ones thiones. It offers several merits such as simple operational procedures, no use of hazardous organic solvents, cheap and environmentally friendly solid basic catalyst. [21]



Scheme (1.4) Synthesis of 4-aryl-7-(arylmethylene)-3,4,6,7-tetrahydro-1H-cyclopenta[d]pyrimidin-2(5H)-ones/thiones catalyzed by PPI.

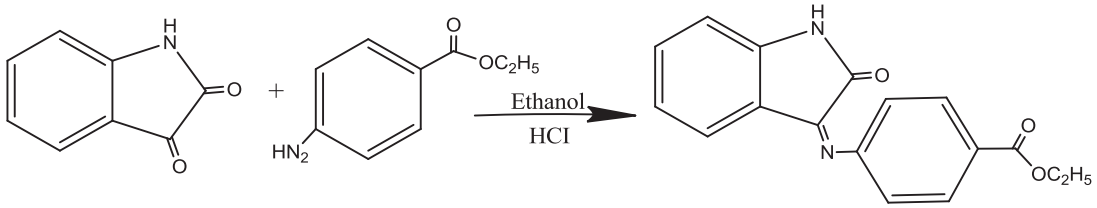
Derbali *et al*., (2015) Found isoproterenol injection showed changes in ECG pattern, including ST-segment elevation (diagnostic of myocardial infarction), increase in the serum levels of Troponin T and cardiac injury markers (creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), aspartate transaminase (AST), and alanine transaminase (ALT) [22-23].

Khezri , M. et. al. (2016) demonstrate the reaction of Vilsmier-Haack reagent with 2,3,3-trimethyl-3H-benzo [g] indole give 2-(1-aryl-1H-pyrazol-4-yl)-3,3-dimethyl-3H-benzo[g]indoles scheme (1.5). [24]



Scheme (1.5) Synthesis pathway of conversion 2, 3, 3-Trimethyl-3H-benzo [g] indole (1) into 2-(1-aryl-1H-pyrazol-4-yl)-3,3-dimethyl-3H-benzo [g] indoles.

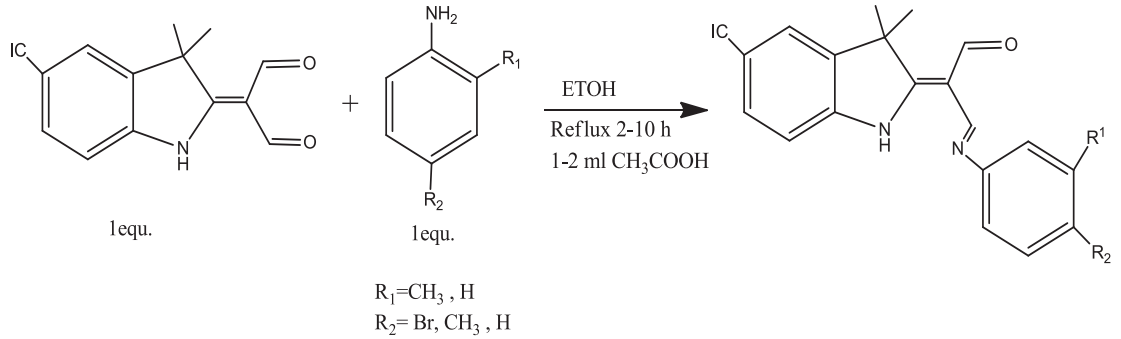
Khalida.F. Al-Azawi(2018) **s**ynthesized successfully new compound, ethyl 4-amino N-(3-isatinyl) benzoate in high yield from reaction of ethyl-4-aminobenzoate with isatin in (1:1) molar ratio Scheme (1.6). [25]



Scheme (1.6) Ethyl 4-amino-N-(3-isatinyl) benzoate

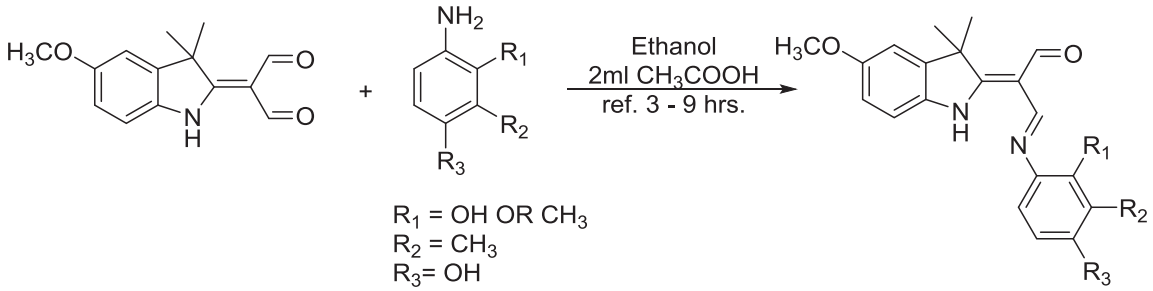
Ghaidan,A.F.et.al (2018). Synthesized a series of new compounds of indole Schiff base derivatives by reaction of 2-(5-Chloro-3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-malonaldehyde with aniline substituted Scheme (1.7).The in vitro anticancer activity of the new synthesized compounds tested against– AMJ breast cancer cell line. The revealed data

showed that compounds have promising anticancer activity against AMJ13 cell line at low concentrations. [26]



Scheme (1.7): 2-(5-Chloro-3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-3-(2,4-disubstituted phenylimino)-propionaldehyde derivatives

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. The biological activity of the new synthesized compounds was screened on Lymphatic Cell in metaphase in Human Blood, which revealed different results Scheme (1.8). [27]



Scheme (1.8): Synthetic pathway of novel indole Schiff bases by the reaction of 2-(5-methoxy-3,3-dimethyl-1, 3-dihydro-indol-2-ylidene)malonaldehyde with substituted aniline

Djakpo *et al* , (2020) found the mean ratio (AST/ALT) was higher in patients with ST-segment elevation myocardial infarction (STEMI) (3.2261 ±2.41379) than in non-ST-segment elevation myocardial infarction (NSTEMI) (2.2089 ±1.63177) patients. The difference was statistically significant (p = 0.002) [28].