An-Najah National University
Faculty of Graduate Studies

VANILLIN-BASED THIAZINE, OXAZINE, AND PYRAZOLE AS A NON-COMPETITIVE AMPA RECEPTOR ANTAGONISTS

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Dedication

To the teacher of the nation, the intercessor of creation, Muhammad, may God bless him and grant him peace.

I dedicate my graduation to those whom God has entrusted me with, my dear father and mother, may God protect and care for them. I also dedicate it to my constant support, my beloved brothers, and the comfort of my heart, my beautiful sister.

To those who provided me with knowledge and advice, my esteemed teachers. I also dedicate it to my friends and classmates.

Acknowledgment

The grace of God was great. Praise be to God for His great generosity in granting me the ability to carry out this work.

I would like to express my gratitude to Professor Othman Hamed for his guidance, support, and supervision of the thesis, and to Dr. Wassim Abu Aoun and Dr. Muhammad Qanibi, who contributed to helping me to complete this research to the fullest extent.

Finally, I am honored to express my sincere gratitude to everyone who helped complete this effort in one way or another.

Declaration

I, the undersigned, declare that I submitted the thesis entitled:

VANILLIN-BASED THIAZINE, OXAZINE, AND PYRAZOLE AS A NON-COMPETITIVE AMPA RECEPTOR ANTAGONISTS

I declare that the work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

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Date: **27/07/2024**

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Abstract

Background: Heterocyclic derivatives have received much attention from researchers because they are important components of natural compounds and synthetic drugs, as they are considered safe, abundant, and available at a reasonable cost.

Objictive: This work aims to create an anti-alzheimer's disease and anti-microbial drug with enhanced efficacy and lower toxicity based on heterocyclic derivatives including oxazine, thiazine, and pyrazole. The objective of this work is to manufacture a drug from the aforementioned derivatives aimed at alleviating and treating alzheimer's disease, and the drug has very few side effects.

Methodology: To achieve the goal of the study, several compounds derived from oxazine, thiazine, pyrazole, phenyl pyrazole, and pyrazole with semicarbazide were synthesized. The synthesis was performed in a two-step process. It is considered a condensation reaction. In the first step, chalcone is prepared from the reacting benzophenone with vanillin in an alkaline medium. The α-H of the benzophenone is extracted, and this creates a nucleophilic center (enolate) that attacks the carbonyl of the aldehyde. Neutralization followed by dehydration results in the production of the target compound.

Results: The structures of the prepared compounds were identified by FT-IR and by ^{1}H-NMR spectroscopy. The productivity of the compounds ranged from 80 to 90%. The compounds showed clear activity in treating alzheimer's disease vanillin-based noncompetitive antagonists of AMPA receptors, reducing amyloid plaques, reducing tau tangles, and improving brain functions.

Conclusion: The study concluded that the compounds were successfully manufactured by condensation reaction and their anti-alzheimer's activity as well as the anti-microbial results are pending. They are expected to show promising results. There is still more work to be done to determine the most potent of the prepared derivatives and their mechanism of action.

Keywords: Alzheimer's, condensation reaction, heterocycles, oxazine, thiazine, pyrazole, phenyl pyrazole.

Chapter One

Introduction

1. Background

1.1 Heterocyclic Compounds

Heterocycles are those with a ring moiety with one or more of the elements O, N, and S and at least one carbon atom. The most common heterocycles contain five and six atoms of those mentioned above and are more stable than three, four, or seven rings or higher. Heterocyclic rings are classified as aromatic and non-aromatic. Most heterocycles are non-aromatic, and the chemical properties they have are like linear compounds. Heterocyclic compounds are among the largest organic compounds, as they exist naturally, and a wide group of heterocycles have large number of applications. Examples of heterocyclic systems, include all nucleic acids, anti-biotics, and many industrial and natural drugs and dyes [1].

Heterocyclic compounds also have unique properties and diverse applications. Among the heterocyclic compounds, simple compounds containing S, O, and N and known to have unique properties are pyrrole (1), furan (2), thiophene (3), pyrazole (4), isoxazole (5), imidazole (6), oxazole (7), thiazole (8), thiazine (9), and oxazine (10). The chemical structures of these heterocycles are shown in Figure 1.1 [2].

1.1.1 Imidazole

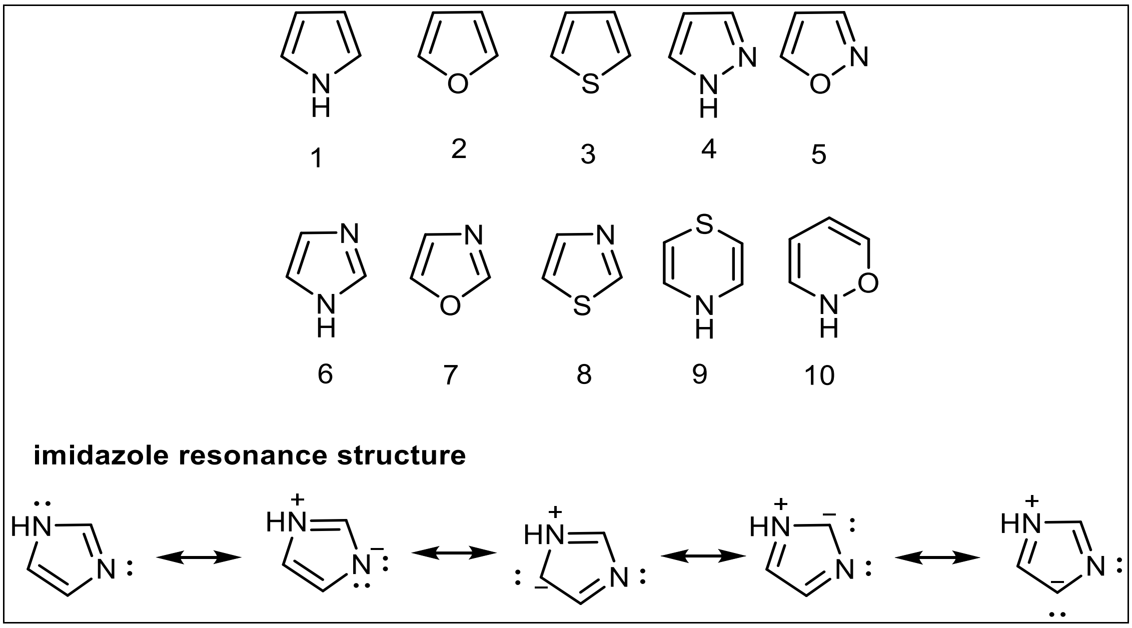
1.1.1.1 Physical and chemical properties

German chemist Arthur Rudolf Hantzsch came up with the term "imidazole" in 1887 [3]. It is a pentagonal heterocyclic aromatic ring that contains nitrogen and carbon atoms in its ring structure. It has a chemical formula of $C_3N_2H_4$, as shown in Figure 1.1 compound 6. It has a colorless appearance at room temperature and is highly soluble in water and many other solvents. It is also known as an important component with many biological activities such as an anti-bacterial, anti-fungal, and anti-microbial agent, as well as an anti-histamine and anti-allergic agent, purine bases, and the amino acid histidine. It is present as an active ingredient in many medications including midazolam, anti-depressants, astemizole (antihistamine), and some other anti-biotics [4].

The imidazole ring available in two tautomeric forms and hydrogen can be attached to both or one N atoms. It is a strongly polar molecule, with high solubility in water [5]. The compound is also classified as an aromatic compound that has six electrons in a planar ring with a resonance energy of 14.2 cal/mol [6]. Figure 1.1 shows the number of imidazole resonances and their structure.

Figure 1.1

Examples of simple heterocyclic systems and imidazole resonance structure



When the ring is free of polar substituents, the dipole moment ranges from 3.8-4.0 D for imidazole. The value is increased by a factor of 2-2.5 D by adding a nitro substituent to the ring, but by N-arylation the dipole moment decreases. The reason is due to the coupling of the imidazole and aryl rings [7]. They are tautomeric compounds with a melting temperature of 90 °C, and they are weak bases compared to other heterocyclic compounds that consist of 5-members. Also, their boiling point is higher, with a value of 256 °C. Because of the H-bonding that exists between the molecules, which is a linear bond between the molecules, it is an odorless liquid.

1.1.1.2 Methods of preparation for imidazole

Imidazole can be prepared using multiple synthetic processes, done by changing the functional groups of the reactants, to produce imidazole and different imidazole derivatives. There are several ways in which it is synthesized, such as Wallach synthesis method, in this method, imidazole was prepared from aminonitrile and aldehyde. Other synthesis methods include Dipo synthesis, Markwald synthesis, Radeszewski synthesis, and Imidazoline dehydrogenation [8]. The following are summaries of the synthetic methods and their mechanism of action. They are all summarized in Figure 1.2 and 1.3 (appendix A).

a. Wallach method

In this method, N, N-dimethyloxamide (18) was modified using phosphorus pentachloride to form compound (19) that contained chlorine which was then reduced with HI (hydroiodic acid) to make N-methyl imidazole (20). Under the same conditions shown in Figure 1.2, N, N- diethyloxamide was substituted to chlorine, and when reduced produces 1-ethyl-2-methylimidazole [9].

b. Debus method

Imidazole was first invented by Heinrich Debus in 1858, although imidazole derivatives have been around since the 1840s. Imidazole (1) is the final product of its production known as glyoxalene, which started with formaldehyde (3) and glyoxal (2) in ammonia as shown in Figure 1.2. This synthesis has been used to make C-substituted imidazoles despite the reaction produced imidazole at very low yield [10].

c. α-Halo ketone method

This reaction depends on the interaction of alpha- halo ketones (17) with imidine (18). The method resulted in the synthesis of 2,4 or 2,5-diphenylimidazole (19). Also similarly, imidazoles (22) are produced when acylolein (20) was reacted with imides (21) or alpha-halo ketones. Figure 1.2 shows the reaction [11].

d. Radiszewski method

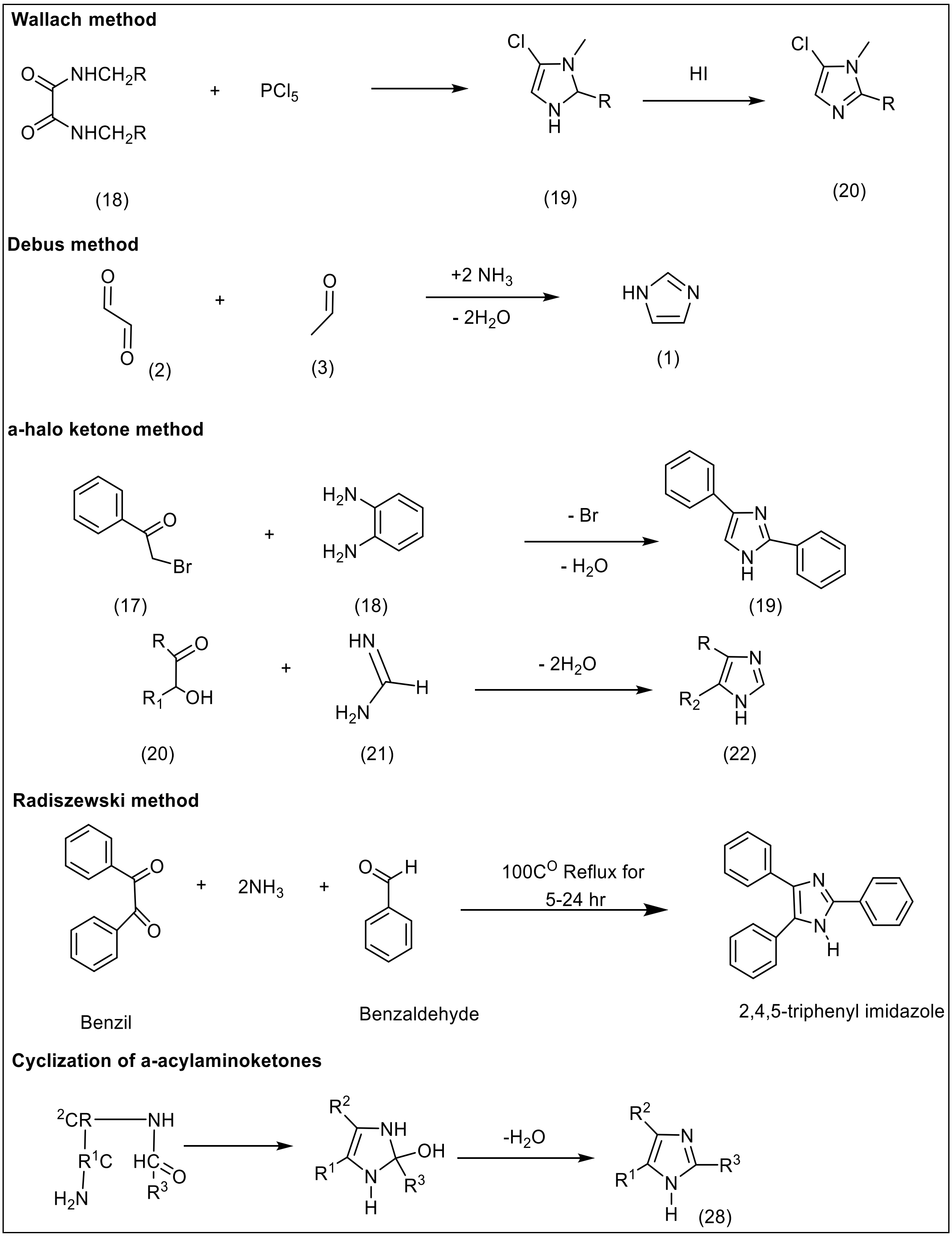
According to the method, 2,4,5-triphenylimidazole is produced when alpha-ketobenzyl aldehyde, benzaldehyde, or alpha-diketones are condensed in the presence of ammonia. Figure 1.2 shows the reaction mechanism for the Radiszewski method [12].

e. Cyclization of α-acylaminoketones method

α-acylaminoketones (26) exhibit,1,4-diketo properties as well (27). When ammonium acetate and anhydride are present, this molecule leads to easy cyclization and formation of compound (28), Figure 1.2 shows the reaction mechanism of making imidazole from the cyclization of α-acylaminoketones [11].

Figure 1.2

Methods of preparation for imidazole



f. Dehydration of imidazoline method

Conversion of imidazoline to imidazole by using barium chromate was reported by Knapp and colleagues. Running the reaction with $BaMnO_4$, imidazolines made from alkyl nitriles and 1,2-ethane-diamine produce 2-substituted imidazoles as shown in Figure 1.3 (appendix A) [13].

g. Markwald method

It involves the synthesis of 2-mercapto imidazole by reacting potassium thiocyanate or alkyl isothiocyanate with an aldehyde or amino ketone. It is considered the most widely used method, but there is a drawback in this method, which is the use of distant bonds, such as amines, aldehydes, or ketones, for various oxidation procedures that help in removing sulfur from 2-mercapto imidazole easily. Figure 1.3 (appendix A) shows a summary of the method [14].

h. From formaldehyde and tartaric acid dinitrate method

The method of preparing imidazole is to heat quinoline dicarboxylic acid with copper, after which dinitrophenolic acid and formaldehyde react based on ammonia. Figure 1.3 (appendix A) shows the reaction mechanism for making imidazole from formaldehyde and tartaric acid dinitrate [14].

i. From aminonitrile and aldehyde method

To produce a substituted imidazole such as (31), the aldehyde (29) and aminonitrile (30) react under appropriate conditions as shown in Figure 1.3 (appendix A) [8].

j. Formation of one bond method

The reaction of imides and amino aldehyde or aminacetal leads to the generation of imidine, which is converted to imidazole, using the Akabori method, which provides amino aldehydes from amino acids that can be easily reduced. Figure 1.3 (appendix A) shows a summary of the reaction [4].

k. Condensation reaction method

Condensation of 1, 2-diaminobenzene (40) with a carboxylic acid for example (41) when heated in an acidic solution produces benzimidazole (42). The reaction is summarized in Figure 1.3 (appendix A) [15].

Many imidazole derivatives are prepared through other reactions using the microwave method, because they are easy to prepare and their reactions are clean, increasing productivity and increasing energy efficiency.

1.1.2 Oxazine

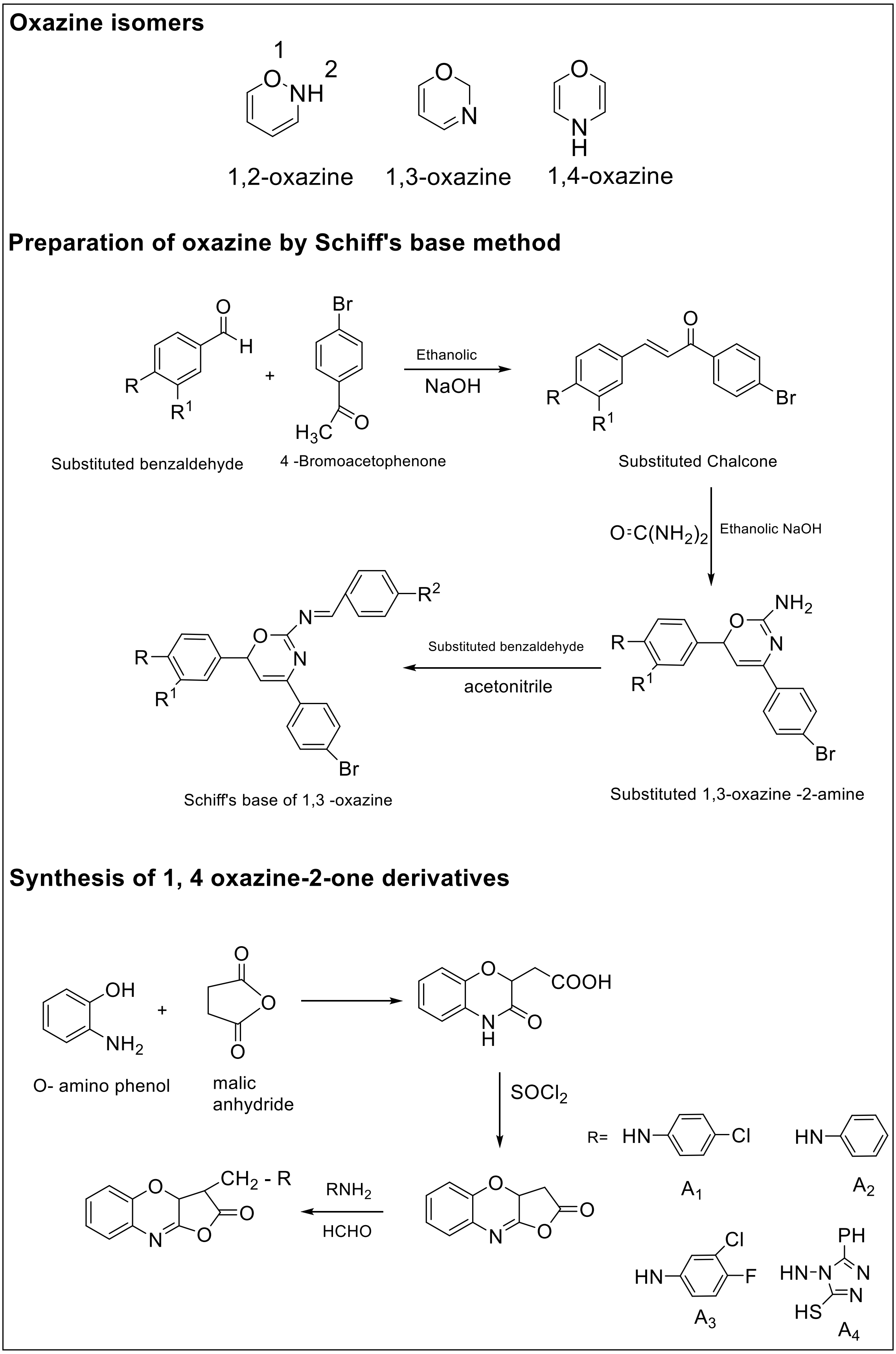
Oxazines, which are classified as heterocyclic compounds, were synthesized for the first time by Holly-Cobb and the Manib method in 1944. They are considered an important category of heterocycles due to the diversity of their pharmacological and biological activities. They are an important industrial intermediate that possesses anti-convulsant, anti-microbial, anti-cancer, anti-malarial, and anti-inflammatory properties. They are also used as sedatives, analgesics, and anti-pyretic [16]. Oxazine compounds are extracted from gasoline, that is, they are made by replacing carbon and hydrogen atoms with nitrogen and oxygen atoms [17]. Oxazine compounds can be used to develop new medicines and therapeutic methods.

1.1.2.1 Structures and properties

Oxazines are weak bases that undergo various reactions, including oxidation-reduction reactions and nucleophilic addition, which allows the N atom in the heterocyclic ring to be nucleophilic and interact with electrophiles. In terms of the structure of oxazine, it has one nitrogen in addition to one oxygen. It also contains three isomers that are determined based on the relative positions of the oxygen and nitrogen atoms within the ring and the double bonds. 1,2-oxazine is the simplest isomer, and there are 1,3-oxazine and 1,4-oxazine isomers, Figure 1.4 shows the oxazine isomers. [18]. Oxazine is a colorless liquid or solid, with different melting and boiling points depending on the specific isomer. Oxazine compounds have different properties. They have properties that are sensitive to light and absorption and emission properties near-infrared. They have the largest wavelength of oxazine compounds, 660 nm, and in other cases, 690 nm [19]. It also has the ability, under a beam of light and ultrasound, to produce oxygen species with high efficiency [20]. It has good thermal stability and low molecular weight, which allows it to cross the blood-nerve barrier and has the physical performance of resins containing oxazine. This is achieved with an initial storage coefficient and high glass transition temperatures, in addition to possessing thermal stability.

Figure 1.4

Oxazine isomers and methods of preparation



1.1.2.2 General methods of preparation for oxazine

Several examples of synthesis of Oxazines are shown in Figure 1.4, and Figure 1.5 (appendix A). Among these methods is the Schiff's base method, Sawant and co-workers reported that a group of Schiff reagent consisting of 1,3-oxazines were produced from reacting 1,3-oxazine-2-amine and modified benzaldehyde. Figure 1.4 shows a summary of the reaction. Its anticoagulant activity was studied by measuring the prothrombin time using the Quick method. The identified compounds were analyzed using infrared and nuclear magnetic resonance techniques, and was determined that the material produced exhibited anti-coagulant activity [21].

1.1.3 Thiazine

Thiazine is considered a heterocyclic compound that contains nitrogen and sulfur atoms. It has great interest in the medical community because of its pharmaceutical importance. It is also considered the focus of attention of science because it contains nitrogen and sulfur atoms in its ring, which has led to its biological importance in the manufacture of medicines [22]. It is involved in the synthesis of compounds that have anti-psychotic, anti-cancer, and anti-proliferative activities. It is also considered an anti-inflammatory, anti-bacterial, anti-viral, anti-fungal, and analgesic [23].

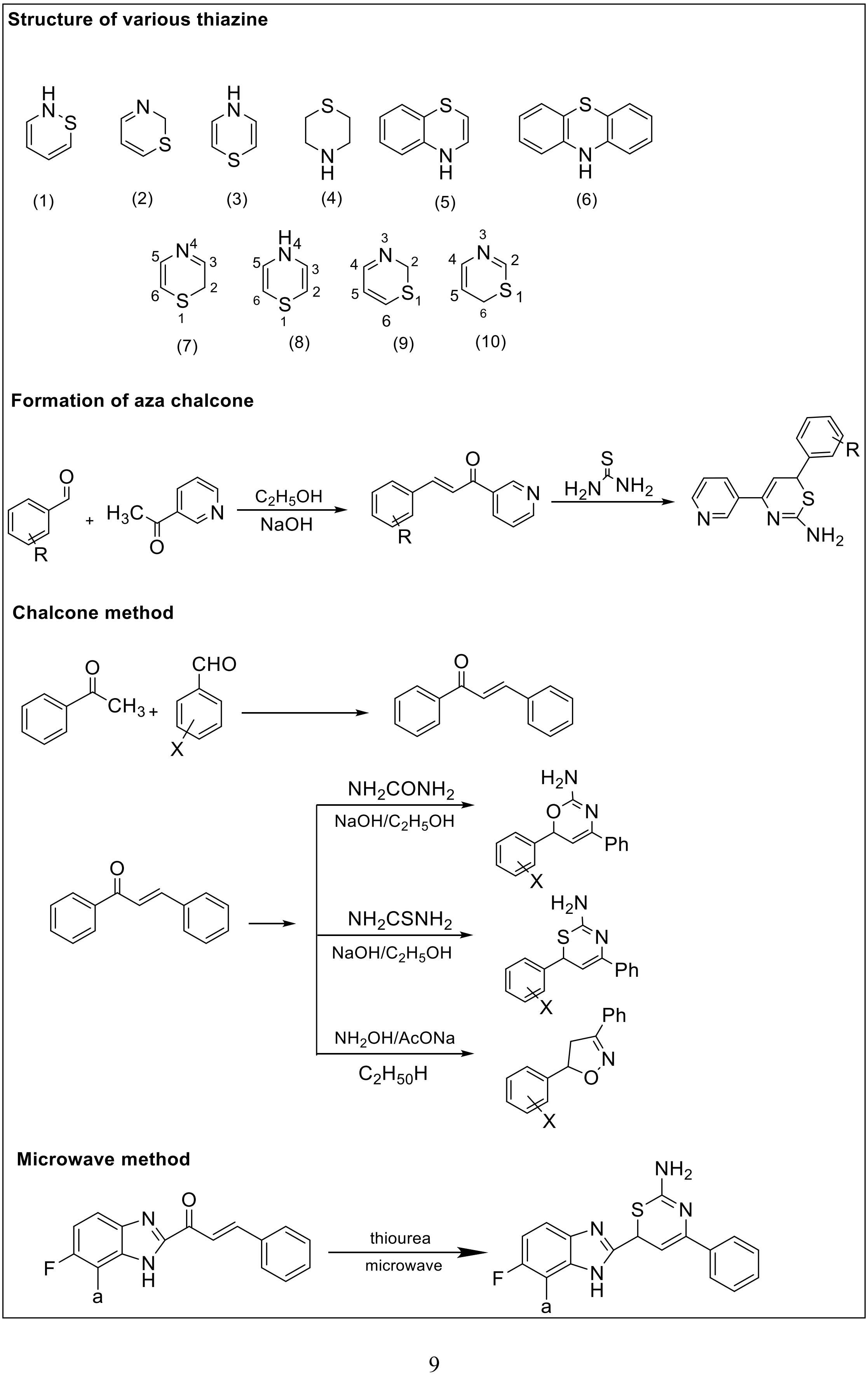
The nitrogen and sulfur atoms present in heterocyclic compounds possess unique properties such that they are considered important raw materials in medicinal chemistry and pharmaceuticals. They also possess biologically active behavior and act as anti-microbial agents [24].

1.1.3.1 Structures and properties of thiazine

Thiazine contains three isomers, which are classified according to the arrangement of the nitrogen and sulfur atoms Figure 1.6. Thiazine is present in the form of the isomer 1,2-thiazine (1), 1,3-thiazine (2), and 1,4-thiazine (3), due to the different arrangement of the nitrogen and sulfur in the ring, and thus the different numbering of the compound. Thiomorpholine (4) is the analogue compound of morpholine with the thiazine formula and the molecular formula C_4H_9NS. Benzothiazine derivatives of thiazines, such as benzothiazines (5) with the molecular formula C_8H_7NS, and phenothiazines (6), which contain an additional benzene ring with the molecular formula $S(C_6H_4)_2NH$, showed a high interest due to their special dynamic and therapeutic properties [25].

Figure 1.6

Structure of various thiazine and Preparation of various thiazine



In addition, there are two tautomeric forms of 1,4-thiazine (2H-1,4-thiazine (7), 4H-1,4-thiazine (8)) and 1,3-thiazine (2H-1,3-thiazine (9), 6H-1,3-thiazine (10)), Figure 1.20 shows the compounds [26].

1.1.3.2 Physical properties of thiazine

Thiazine compounds have been widely studied to know their chemical and physical properties. using chemical quantum calculations, to predict and know the behavior and interactions of phenothiazine derivatives, in addition to knowing the simulation of the molecular fusion with a variety of proteins. Through the theory and analysis of the functional density, it was found that in the thiazine cycle, there are sulfur and nitrogen atoms as electrophilic and nucleophilic sites, respectively [27]. The hydrophobic triple rings found in sedative drugs of the phenothiazine class contribute to their interesting binding properties [28]. Thioridazine hydrochloride, which is used as a drug to treat psychiatric illnesses, has been investigated for its physical and chemical properties in various settings. The drug is considered a hydrophobic compound, which forms spontaneous aggregations when it is present in solutions [29]. The thermodynamic properties of thioridazine hydrochloride in aqueous solutions were measured to understand its process mechanism, including conductivity, density, and surface tension.

1.1.3.3 General methods of preparation for thiazine

The new compound aza chalcone was prepared by Kazem et. al. by reacting acetylated pyridine with 4-hydroxybenzaldehyde [30]. While azachalcone was pretreated with thiourea for a high yield of thiazine derivative ((E)-3-(4-hydroxyphenyl)-1-(pyridine-3-yl) prop-2-en-1-one). The reaction is shown in Figure 1.6. Material from pyridine with acetyl group and benzaldehyde are used for the synthesis of a thiazine heterocyclic where R means one of the following substituents p-OH, m-NO_2, m-OCH_3, m-Br, p-$N(CH_3)_2$.

Elarfi and a group of researchers reported that chalcone derivatives were prepared by reacting some benzaldehyde derivatives with acetophenone, Figure 1.6. The products produced from the reaction of urea, thiourea, and hydroxylamine form heterocyclic derivatives of oxazine, thiazine, and isoxazole sequentially [31].

Gayathri and colleagues showed that thiazine heterocycles with chlorine, fluorine, and benzimidazole can be prepared via microwave reaction. So, 1-(7-chloro-6-fluoro-1H-benzo[d]imidazol-2-yl)-3-arylprop- 2-en-1-one was reacted with thiourea in a microwave oven leading to the production of derivative 1, 3-thiazine-6-(7-chloro-6-fluoro-1H-benzo-2-yl)-4 -phenyl-6H-1,3- thiazine-2-amine, Figure 1.6 [32].

In 2005, Zia-ur-Rahman and other researchers working at the Applied Chemistry Research Center of PCSIR Laboratories reported that using ionic liquids with high efficiency to prepare derivatives of 1,2- benzothiazine 1,1-dioxide. They used an environmentally friendly method to synthesize 2-alkyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxides starting Nalkylation of sodium O-benzosulfimide in an ionic liquid for the first time in synthesis. In a single step, ring undergoes cleavage and then closure of the products was performed in an active solvent (methanol), which was then followed by alkylation at N atom resulted in the formation of 4-hydroxy-2H-1 alkyl, 2-benzothiazine-3- carboxylate Figure 1.7 (appendix A), in an ionic solution. Using liquid boron trifluoride as a catalyst in the carboxamide formation step with molecular sieves [33].

Dighade et. al. reported that six (Ia-IF) chalcones were variously prepared by condensation of 2-hydroxy-3-iodo-5-methyl acetophenone with six aromatic aldehydes using NaOH and different in ethanol. This chalcone was converted using diphenyl-thiourea in ethanol, leading to the synthesis of compounds (IIa-IIF). The method is summarized in Figure 1.7 (appendix A) [34].

Yadav and co-researchers report a new three component preparation of 3,6-diaryl-5-mercaptoperhydro-2-thiooxo-1,3-thiazine-5-one from 2-methyl 2-phenyl-1,3-oxathiolane-5-one. An aryl aldehyde and an N-phenyl dithiocarbamic acid as shown in Figure 1.7 (appendix A). This reaction is classified as selective and contains Knoevenagel and Michael conversion reactions, using microwave radiation, and is solvent-free in a single tandem ring procedure [35].

Wang and his group reported the preparation of a new group of polyether derivatives, which were synthesized by mixing thiazolines, and thiazines with dibromide, the method is summarized in Figure 1.7 (appendix A) [36].

El-Shehry and other researchers claimed that 1,4-thiazine compounds can be prepared by reacting 2-bromopropenone derivatives with O- amino thiophenol in an ethanol solution of KOH. The method is summarized in Figure 1.7 (appendix A) [37].

1.1.4 Pyrazole

Pyrazole is classified as a heterocyclic aromatic compound. It is a pentagonal ring containing two N atoms and 3 carbons in near positions. It has also been noted with great interest for the compound pyrazole due to its pharmacological and medicinal properties. It has many pharmacological efficacies like anti-convulsant, anti-bacterial, anti-microbial, anti-oxidant, anti-inflammatory, anti-depressant, and anti-cancer. It is also classified as an analgesic and anti-pyretic, which makes it important in drug design and development as well [38].

pyrazole is also considered a scaffold that has the advantage of possessing effective pharmacological activities. It has multiple therapeutic classes, such as anti-inflammatory (Celecoxib), anti-psychotic (CDPPB), anti-obesity (Rimonabant), and analgesic (Difenamizole). It also can interact with several receptors and H_2 receptor agonists (Pythazole), the anti-depressant agent (Vizolamide), and enzymes in the biological system present in the target cells [39]. shows some drugs containing the Pyrazole unit. Examples of Pharmaceutical drugs containing pyrazole units are shown in Figure 1.8a.

1.1.4.1 Physical and chemical properties of pyrazole

Pyrazole is an organic compound consisting of an unsaturated ring with two N atoms at 1 and 2 positions. Pyrazole also has 3 partially reduced forms that depend on the distribution of electrons, which makes it a chemically stable compound.

It is considered with no color and solid material, with a melting point of 69.0-70.0 °C, and a boiling of 186-188 °C, resulting from the presence of hydrogen bonds between the molecules of the compound. Pyrazole exists in the form of tautomer that are identically shaped, and due to the rapid interconversion of tautomer, they are indissociable. Pyrazole has a low basicity due to the aromaticity (pKa = 2.52) and this is due to increased destabilization of the π bond after protonation. It is a very weak acid (pKa = 14.21), and when an electron withdrawing functional group (-I) or a one electron transfer group (-M) is added to the pyrazole, its acidity increases. This occurs due to the ability of the groups to pull the electronic density away from the ring, so the proton positive becomes more reactive with the positive electrons [40].

1.1.4.2 Methods of making pyrazole

a. From 1,3-diketones

It is a quick and simple method is the cyclo-condensation of 1,3-dicarbonyl compounds with hydrazine derivatives to produce multi-substituted pyrazoles. In 1883, Knorr and other researchers [41] reported the first synthesis of substituted pyrazoles, which consisted of reacting with β-diketone with various hydrazine's to produce two isomers 3 and 2 as shown in Figure 1.8b.

b. From the acetylenic ketones

In another method pyrazole was formed by a cyclo-condensation reaction of hydrazine derivatives (17) with acetylene ketones (16) [42], producing two regioisomers (18) and (19), the reaction scheme is shown in Figure 1.8b.

c. From the vinyl ketones

Pyrazole was also produced by a cyclo-condensation reaction that occurs between an alpha, beta-ethylenic ketone, and various hydrazines, which leads to the production of various pyrazolines, which produces pyrazole after an oxidation process Figure 1.8b [43].

d. From vinyl ketones with a leaving group

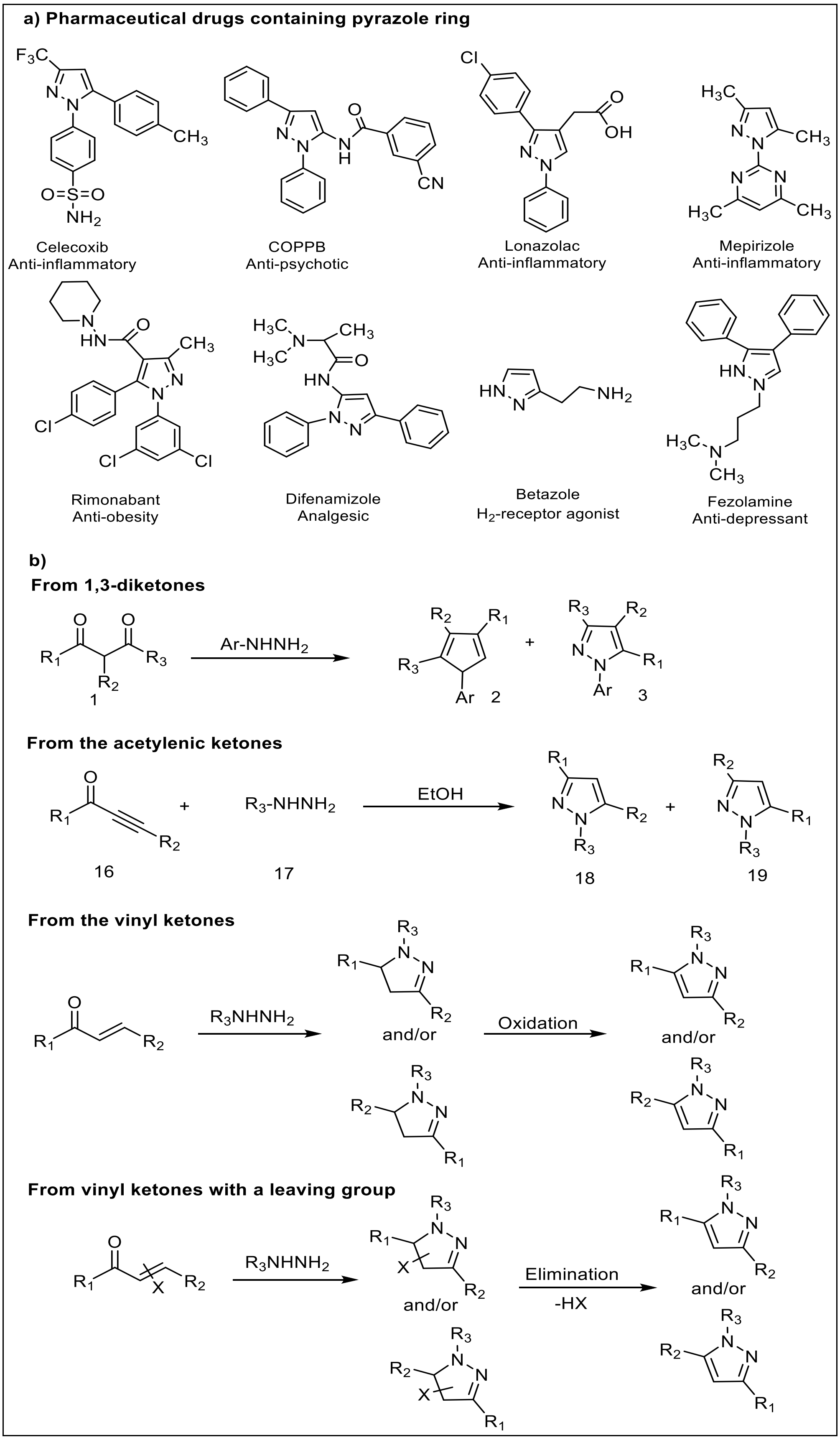
Pyrazoles were also produced by reacting alpha, beta ethylenic ketones containing a departing group with hydrazine compounds, leading to the formation of pyrazolines, that were converted to pyrazoles when the leaving group was removed Figure 1.8b [44].

e. Cycloaddition of diazocarbonyl compounds

He and colleagues reported the procedure that led to the production of pyrazole (57), by reacting phenyl propargyl (55) with ethyl alpha diazoacetate (56) in the presence of triethylamine and a catalyst which is zinc trinitrate Figure 1.9 (appendix A). The reaction produced pyrazole using a 1,3-dipolar cycloaddition reaction, the yield was about 89%, and it is considered a simple reaction [45].

Figure 1.8

a) pharmaceutical drugs containing pyrazole ring and b) method of making various pyrazoles



f. The Sydnones

Delaunay and researchers carried out a reaction known as cycloaddition that involved alkyne and sydnone to synthesize two tetra-substituted pyrazoles (71) and (70). The reaction time took approximately 15 hours. This caused the production of a mixture (3:1) of the regioisomers 5-iodopyrazole (70) and (71), with a yield value of 84%. However, the pyrazoles were separated from each other by chromatographic analysis, and the structure of the required main isomer (70) was determined, and the yield value was 63%. It was determined based on the ^{1}H-NMR spectrum [46]. The reaction scheme is shown in Figure 1.9 (appendix A).

g. Nitrilimines

Dadiboyena and the research team prepared the 1,3,5-polysubstituted pyrazole using a 1,3-dipole cyclic reaction between the diphenyl nitrileimine (75) and the alkene (76) in CH_2Cl_2, triethylamine was present as a base. This caused the production of polysubstituted pyrazole (78), which was obtained instead of the expected product of spiro-pyrazoline (77) [47] as shown in Figure 1.9 (appendix A).

h. Preparation of carbonyl derivatives

Harigae with his colleagues published a simple synthetic method for making di-substituted pyrazole (86) at 3 and 5 positions in very good yield with excellent selectivity by treating terminal alkenes (83) with aromatic compound (aldehydes, 84) as well as the substituents iodine and hydrazine Figure 1.9 (appendix A) [48].

i. Preparation of β-aminoenones

Kovacs and others showed that there is a new mechanism for the preparation of disubstituted pyrazole (97) at 3 and 5 positions which is by cupro-catalyzed coupling of an alkyne (95) with the oxime (94) in the polar solvent N,N-dimethylformamide, that leads to the production of aminoinone (96) and is converted to pyrazoles by the addition of hydrazine directly, the product yield was (97) 70%. The reaction is summarized in Figure 1.9 (appendix A) [49].

j. In-situ formation of a hydrazone

Dang and other researchers reported a reaction mechanism for the preparation of pyrazole-3-carboxylate (100) by reacting the dihydrazone (98) cycle with diethyl oxalate (99), resulting in a good yield of 53% pyrazole. The reaction is summarized in Figure 1.9 (appendix A) [50].

k. From heterocyclic systems pyranones

Pyranones are heterocyclic rings that have been widely used for the preparation of pyrazole. The manufacturing mechanism is by condensing 2,3-dihydro-4H-pyran-4-one (110) containing aryl hydrazine in absolute ethanol which contains a catalyst, that is montmorillonite KSF, which leads to the production of 5-substituted pyrazoles (111) with a production rate of 57-86% [51]. Xie and his colleagues also developed a method for producing pyrazole, which involved using Suzuki coupling of aryl boronic acids with chromone (112), and subsequently hydrazine hydrate. Which led to the production of pyrazole 3,4-diaryl (113) at a rate of 48-95%. The reaction is summarized in Figure 1.10 (appendix A).

l. Preparation from using pyrimidines and pyrimidones

3-cyano-4-tri-fluoro methyl-6-aryl-2(1H)-pyridone (126) reacts with hydrazine that is hydrated, to produce 5-tri-fluoromethyl-3-aryl pyrazole (127) with a yield of 45-65%. 3,5-Diacyl-1,4-dihydropyridine (128) is also reacted with a hydrazine compound in methanol at a temperature of 140 °C to produce (129) di-pyrazolyl methane in high yield. The reaction is depicted in Figure 1.10 (appendix A) [52].

m. From using imidazole

(5Z)-1-acyl-5- (cyanomethylidene)-3-methyl imidazolidine-2,4-dione (compound 130) was cyclized under basic conditions with arylhydrazonyl chloride to produce pyrazole-5-carboxamide (compound 131) in an average yield of 27-40%. The reaction is summarized in Figure 1.10 (appendix A) [53].

n. From oxazoles

Phenyl hydrazine and 4-tri-fluoroacetyl-1,3-oxazolium-5-oleate (132) were reacted by heating and under benzene reflux to produce 5-tri-fluoro methyl-3-hydroxy pyrazole (133) with excellent yields up to 95%. The reaction is summarized in Figure 1.10 (in appendix A) [54].

o. From tetrazoles

Tetrazolyl acroleins (compound 134) in xylene was reacted with fumaronitrile at 140 °C, forming pyrazole (135) Figure 1.11 (appendix A). Where cyanopyrazole (135) was prepared in an easy way from tetrazolo [1,5-a] pyrimidines, tetrazolo [1,5b] pyridazines, and tetrazolo [1,5-a] pyridines [55].

p. From triazines

Rykowski and colleagues [56] reported, explaining the manufacture of pyrazoles, this was done based on the mechanism of condensation reaction of 3-chloro-6-phenyl- 1,2,4-triazines compound (136) with alpha-chlorosulfonyl with the addition of potassium hydroxide (KOH) to give pyrazoles (137), the reaction is summarized in Figure 1.11 (appendix A).

q. From 1,5-benzodiazepin-2-one

Ferfra and colleagues [57] reported that the mechanism of pyrazole preparation is through a single step of benzodiazepine-2-thione, opening the 7-membered heterocyclic from reacting benzodiazepine-2-thione (compound 138) with hydrazine to produce O-aminophenyl aminopyrazole (139). The reaction is summarized in Figure 1.11 (appendix A).

1.2 Biological significance of heterocycles

Medicinal chemistry is an important field in organic chemistry because the link between medical life and organic chemistry is through studying and understanding common diseases and their solution. This branch of chemistry, which is considered modern, appeared when researchers around the world studied the isolation and purification of active substances that they obtained from tissues of animals and plants, tissues also taken from microorganisms and their fermentation products. Medicinal chemistry has a strong reliance on traditional types of chemistry, especially synthetic organic type of chemistry and some physics and biology areas as well as the literature study indicates, heterocyclic compounds have an important place and role in the fields of medicinal chemistry [58].

It was noted that the majority of medicines belong to the category of heterogeneous materials. Heterocycles also have a major place in the metabolism of all creature cells. It is composed of 5 or 6-members, and in its nucleus, there are one to three heterogeneous atoms. Purine- and pyrimidine-based compounds can be found in DNA in the genetic material. These compounds can be isolated or combined. Many common compounds have been used in pharmaceutical preparations, including amino acids such as histidine, proline, and tryptophan, as well as coenzymes such as riboflavin, pyridoxine, thiamin, biotin, folic acid, and a group of vitamins such as E and B12 [59].

A review published in the literature shows that a portion of heterocycles with a condensed ring type system have a different set of physiological functions. Anti-microbial [60], anti-fungal [61], anti-alzheimer's [62], anti-inflammatory [63], anticonvulsant [64], anti-cancer [65], anti-bacterial [66] and anti-allergic [67].

Studies have shown that heterocyclic compounds that contain nitrogen constitute more than 75% of the compounds that have physiological activity. They are considered the most widespread and have an important role in pharmaceutical preparations, medicinal chemistry, and the discovery and development of new drugs [68].

Imidazole, oxazine, pyrazole, and thiazine are some of the heterocyclic nitrogen-containing chemicals that have retained special attention from scientists due to the broad biological activities they have. They are considered the most important heterocycles with many medical applications.

1.2.1 Biological significance of imidazole

In terms of pharmacological activity and biological importance, heterocyclic imidazoles are of great importance, as they are considered a planar five-ring polar compound. It can be highly soluble in water and polar solvents. Imidazole derivatives have many different pharmacological performance, such as anti-depressant, anti-microbial, anti-cancer. They also have many beneficial properties such as good tissue permeability. The occurrence of negative side effects is very low, indicating It has great development potential in medicinal and pharmaceutical chemistry and materials science [69].

Anti-depressant activity

N-[(4-morpholinyl) ethyl)]-1-benzyl 2-(alkylthio)- 1H-imidazole-5 -carboxamides was generated and evaluated as anti-depressant activity by a test known as a forced swim in rats. Its analogues (10), (11), and (12) Figure 1.12 (appendix A) were found to be more effective than moclobemide. Moclobemide analogues are manufactured by changing the moclobemide benzene ring with functionalized imidazoles. Moclobemide compound (9) is a selective and showed to be as a reversible inhibitor of monoamine oxidase A and also used as an anti-depressant [70].

Anti-microbial activity

The anti-microbial activities of imidazoles such as 4-(phenyl)1H-imidazole-2(5H)-one/thione/imine were identified to be good against bacteria such as Escherichia- coli, Salmonella typhi, Proteus and Staphylococcus aureus. Compounds (17), (18), and (19) are analogues that have been replaced by chlorine Figure 1.12 (appendix A). The results showed that P. vulgarius bacteria were sensitive to all the heterocyclic compounds studied, while S. aureus was less sensitive to them. In addition, it was found that imidazoles were well effective against Escherichia- coli

bacteria, but their activity was moderate against S. typhi. The reported results have highlighted the potential of the compounds in developing new treatments for the diseases associated with the aforementioned bacteria [71].

Anti-cancer activity

Ten new compounds containing aryl imidazoles Figure 1.12 (appendix A) combined with chemotherapy compounds were reported, and their anti-bacterial and anti-cancer efficacy were evaluated. All imidazole reported compounds showed good anti-bacterial activity against Klebsiella pneumoniae and Escherichia- coli strains. The derived imidazole compounds possess significant cytotoxic activity against the cell lines Dalton's lymphoma (DLA) and Ehrich's ascites (EAC). Compound (13) shows anti-cancer efficacy with CTC values of 31.3 and 98.6 μg ml compared to DLA and 150 EAC cells [72]. A group of imidazoles containing the single substitution were also synthesized by replacing the aniline with various sulfonamides. The compounds were studied to evaluate their anti-microbial and anti-cancer activity. Compound (14) showed the excellent activity against cervical cancer, while compound (15) showed acceptable anti-fungal activity and also compound (16) showed good anti-bacterial activity.

1.2.2 Biological significance of oxazine

Oxazine derivatives have industrial importance due to their biological activities like, anti-depressant [16], anti-microbial and anti-alzheimer. As have a great interest in medicinal organic compounds due to their wide range of pharmacological activities. Oxazine derivatives can also, be extracted from gasoline by replacing carbon atoms with nitrogen and oxygen atoms. The compounds have been extensively studied as industrial intermediates and have shown activity against various diseases. The development of drug resistance has become a challenge in the field of medicine [73]. Some of the applications of Oxazines as drugs are shown below

Anti-alzheimer's activity

Alzheimer's disease was classified as a research priority and one of the main concerns of global health [74]. Scientific studies have also shown that the prevalence of the disease will double in all parts of the world by approximately 2050 [75]. Alzheimer's illness, or AD for short, is a neurodegenerative illness that begins first with a slight loss of memory, then increases gradually. It is also classified as continuous and affects several areas in the cerebral cortex and hippocampus [76]. Difficulty remembering recent events is considered one of the symptoms associated with the disease, and the symptoms increase as the disease progresses, including language problems, mood swings, confusion, and behavioral problems. As the disease increases further, it may lead to loss of body functions and death [77].

AD is often caused by a protein defect that results from the buildup of abnormally elongated amyloid beta in amyloid plaques in the brain or neurofibrillary tangles in the brain, related to the accumulation of tau protein. Plaques are small peptides with a length of approximately 39-43 amino acids and they form the amyloid beta protein (AB). It is considered part of amyloid-beta precursor protein (APP). The larger amyloid beta protein has great importance in the growth, repair, and survival of nerve cells. Gamma and beta-secretase enzymes also work together in proteolysis, which leads to the division of APP into many small parts, and these parts lead to the appearance of beta-amyloid fibrils, causing the formation of deposited masses on nerve cells in the outer part [78].

AMPA receptors play an important role in brain function, and for this reason, research has linked AMPA receptor dysfunction to the development of AD[79]. AMPA receptors[80], also known as AMPARs, are ionotropic glutamate receptors that play a crucial role in facilitating rapid excitatory synaptic transmission in the central nervous system [81][82]. They have a vital role in synaptic plasticity, as well as in learning and memory processes. AMPARs consist of tetrameric complexes composed of subunits GluA1-GluA4, each of which possesses extracellular, transmembrane, and intracellular domains [83]. as receptors activated by the binding of glutamate, ligand-gated ion channels facilitate the movement of positively charged ions, specifically sodium and potassium. Regulation of AMPAR is an intricate modification by several auxiliary proteins that impact receptor trafficking, location, and kinetics. This includes the subunit composition, post-translational changes, and interactions with auxiliary proteins [84]. The dynamic behavior of AMPARs, which involves their continuous migration in and out of synapses through exocytosis, endocytosis, and lateral diffusion, plays a vital role in synaptic plasticity. Their ability to move and change shape, especially in the N-terminal domain, affects the speed at which they open and close, which is crucial for the correct functioning of synapses [85]. Gaining a comprehensive understanding of these systems is crucial for developing effective therapy strategies for neurological illnesses and obtaining valuable insights into the processes of learning and memory.

Alzheimer's disease is characterized by changes in AMPARs, which are strongly associated with the development of the illness. Researchers have found notable alterations in AMPAR expression, trafficking, and function in AD. These factors include lower levels of AMPAR in brain tissue affected by AD and neurons treated with Aβ, problems with transport due to amyloid-β oligomers, higher ubiquitination that breaks down receptors, and changes in acetylation that lowers AMPAR levels. These modifications decrease the amount of synaptic AMPAR, which hinders the ability of synapses to undergo plasticity. Synaptic dysfunction is an early pathological characteristic of AD that plays a crucial role in causing cognitive impairments [86]. Changes in AMPAR function and expression might also modify neuronal excitability, potentially leading to disturbed network activity typical of AD. Although the significance of AMPAR kinetics (activation, desensitization, and deactivation) for synaptic function is widely recognized, further research is needed to understand the particular abnormalities in these kinetics in AD [87].

However, the significant changes in AMPAR dynamics that are found in AD are likely to affect the speed at which AMPARs function, therefore worsening synaptic dysfunction. Comprehending these changes offers possible areas to focus on for medical treatments that attempt to protect synapse function and reduce cognitive loss in AD [88].

Chemical interventions have been observed to prepare medicinal drug compounds related to AD and aim to prevent or slow the progression of the disease's stages, i.e. alleviate it. Studies have shown that medications containing heterocyclic compounds derived have an effective role in reducing the symptoms of the disease.

Low et al in 2018 [89], reported a combinatorial and structural relationship of a group of β-Site APP-cleaving enzyme (BACE) inhibitors containing oxazines, where the Aβ peptide is considered to be responsible for AD, and through which the enzyme β-secretase and BACE inhibitors can be produced, which act on Reducing Aβ levels in the brain. Derivative (76) was found to be a strong stabilizer of BACE (IC_{50} = 15 nM) with acceptable absorption, distribution, metabolism, and excretion properties [90]. Fuchino and colleagues also reported in 2018 that new BACE1 inhibitors based on oxazine (77a) and (77b), were synthesized to improve brain penetration by reducing the basality of the two intermediates. The compounds also showed a significant reduction in Aβ [90]. It also caused the formation of potent inhibitors of 5-fluoro-1,3-dihydrooxazine beta-secretase BACE1 through the study of Nakahara and colleagues. By its stabilized active conformation, compound (78) inhibited HERG and showed high efflux of P-gp with a strong reduction of Aβ. It also significantly reduced Aβ. As reported by Rombouts and colleagues in 2015, the new synthesis of 1,4-oxazine analogues. It has been shown that these components have strong inhibition in BACE1 enzymatic and cellular assays as well. The synthetic derivatives (79a) and (79b) are orally bioavailable, centrally active, and have a strong reduction in brain and cerebrospinal fluid levels [91] Figure 1.13 (appendix A).

Anti-depressant activity

It lies in the formation of compounds that can potentially be used in treating neurological disorders related to low serotonin activity. Two new classes of analogues represent the discovery: benzoxazine-3-in PAdole alkylamine (19) and benzoxazine-3-indole tetra hydro pyridine analogues (20) Figure 1.13 (appendix A). Which is used to contain the drug compound 5-HT1A with SSRI and 5-HT1A receptor activities, and in some compounds, selective it has been improved on the α1 receptor, and most of the compounds in these two categories are agonists for 5-HT1A receptors [92].

Anti-microbial activity

Peena and his colleagues reported on a method for synthesizing a series of [6-(p-aminophenyl)-4-(p-substituted phenyl)-6H-1, 3-oxazin-yl]-acetamides by claisen-schmidth condensation, and these compounds were examined, which was prepared and known for its activity against microbes. One powerful anti-bacterial and anti-fungal derivative of chloro-1,3-oxazinyl acetamide Figure 1.13 (appendix A) [93]. In 2013, Didoag and co-workers reported the preparation of a group of 6-chloro-2,4-diphenyl-3,4-dihydro-2H1,3-benzoxazines Figure 1.13 (appendix A) from reacting 4-chlorophenol and the substituted phenyl aldehyde in solution of methanol/ammonia. Their anti-microbial activities were examined, and it was noted that the methoxy-substituted derivatives were more anti-microbial than the standard drugs [94]. Sawant and his colleagues reported on the synthesis of a series of Schiff molecules that formed 1,3-oxazines from p-bromoacetophenone and a substituted phenyl aldehyde in the presence of NaOH to produce chalcones which then treated with urea to produce its analogues. P-(4-Bromophenyl)-6- (substituted phenyl)- 6H -1, and its analogues are also 3-oxazine 2-amine. These formed compounds were also reacted with substituted aromatic aldehydes to produce 4-(4-bromophenyl)-6-(substituted phenyl)-2-[(1E) (phenyl) methyl adenine]-6H-1,3-oxazine- Amen. The study also showed that the compound 4-(4-bromo phenyl)-6-(N, N-dimethyl aminophenyl)-N-[(E)(4-chlorophenyl) methyl idine]-6H-1, 3-oxazine-2-amine It is considered one of the most anti-microbial compounds [95].

1.2.3 Biological significance of thiazine

The heterocyclic compounds thiazines and benzothiazines are classified as a very important section of the organic medicinal, due to the importance of their unique medicinal activities. It has many pharmacological activities and is classified as anti-psychotic [101], anti-alzheimer [97], and anti-microbial [99]. Thiazines have many beneficial properties. Also, alternative thiazines explored in various ways for pharmaceutical activities are based on their structure-activity relationship (SAR) data. Thiazines have been classified as a lead molecule in some pathological conditions such as microbial infections, central nervous system disorders, cancer, viral diseases, epilepsy, and tuberculosis [96].

Anti-alzheimer's activity

It has recently been reported that thiazines with bicyclic can be used to control AD illness, as the beta-secretase enzyme (BACE1) found in bicyclic thiazines is an important protein targeted in combating AD. Highly effective thiazine derivatives are still being designed that can bond to different types of the BACE1-enzyme. 1,3-thiazine Spiro analogues are neuroprotective that can inhibit the absorption of calcium ions that result from amino acids in the functional parts related to the cerebral cortex Rats. The inhibitory activities of these drugs are due to the specific structure of the side chain that is bonded to the N atoms outside the ring [97]

Another activity of thiazines in treating AD has also been reported. The red thiazine dye is used to identify specific areas affected by AD in laboratory rat brains. Its analogues have been recorded, including 2,6-dicarbethoxy-3,5-diaryltetrahydro-1,4-thiazine-1,1-dioxide, which works better in cases of electric shock [98].

Anti-microbial activity

These compounds have been detected as having good performance against illness caused by viruses, bacteria, protozoa, molluscs, and fungi. The action of these heterocycles is examined by testing them on different living organisms, like mammals infested with viruses, bacteria, etc. [99].

The 1,3-thiazine cyclic is considered the active part of cephalosporins and is classified as a beta-lactam antibiotic. It is active against bacteria that cause gram-negative and gram-positive diseases. Cephalosporins also have the same mode of treatment as penicillin and identical to beta-lactam ring. Most of the bacteria that are resistant to penicillin are sensitive to cephalosporins. Resistance bacteria is also considered a major issue with cephalosporins. For instance, intestinal bacteria have resistance to most 3rd - and 4th - generation drugs, but many strains of Staphylococcus aureus are resistant to 5th generation of cephalosporins, such as Ceftaroline and ceftobiprole [100]. A broad-spectrum antibacterial action method was developed in the laboratory, and the results showed that it was active against many types of bacteria that caused Gram-negative and Gram-positive diseases. Imides and N-carboxymethyl imides based on N-substituted 2-acyl phenothiazines also had antibacterial activities. Thiazine and derivatives are also classified as reactive substances in the synthesis of anti-biotics such as quinolones. Barai and other researchers reported the manufacture of a number of analogues of 1,4-thiazine and (S) -3-methyl-1,4-benzoxazine.

Anti-psychotic agent's activity

The mechanism of anti-psychotic activity of both thiazines and phenothiazines lies in the process of electron donation of the basic N of the thiazine compound. Which works to transfer charge by donating electrons to biological receptors. The hydrogen bonded to the N is replaced by other substitutes that stimulate pharmaceutical activities. New pentacyclic systems with 13H-5,14-dihydroquinoxalino[2,3-a] phenothiazines are being prepared and investigated for neuro pharmacological and neuro sedative properties. It was shown that the antagonistic effect of the compounds against the climbing behavior induced by Ortwin in rats was demonstrated. Compound (88) shown below Figure 1.14 (appendix A) is the first pentacyclic phenothiazine used in nerve anesthesia [101].

Blokhina and other researchers reported in 2014 that the manufacture of some of the compounds spiro-1,3-thiazine were classified as neuroprotectants. The mechanism of action of these materials is to block the absorption of calcium ions that are caused by glutamate in the cerebral cortex. The SAR investigation showed the existing alternatives nature. The nitrogen atoms outside the ring are important in its antipsychotic efficacy. The permeability of the materials is through a phospholipid membrane that has the property of donor receptors. SAR also showed that the alkyl group consisting of ethyl and isopropyl, which is located in the orthographic positions and close to the phenyl ring that is linked to the outer ring nitrogen, worked to increase the inhibitory ability and reduce the lanaryl group, and the groups Polar ones, such as nitrogen, halogen, and oxygen, reduce their effectiveness [102].

1.2.4 Biological significance of pyrazole

Pyrazole is of great importance due to its important and diverse pharmacological activities. Heterocyclic compounds possess important properties such as anti-microbial, anti-depressant, anti-alzheimer's, anti-fungal, anti-inflammatory, anti-tumor, and anti-cancer. The biological activity makes the compounds one of the most promising compounds in the field of medical research and drug discovery. Incorporating pyrazole with other structures increased its biological importance and potential, and helped pave the way for the development of new targeted compounds.

Anti-alzheimer's Activity

Chimenti and his colleagues reported on the preparation of a group of 3,5-diaryl pyrazoles, which were tested for their performance to inhibit monoamine oxidase B and monoamine oxidase-A. Many heterocycles are active with concentration values in the nano molar range. Compound (428) for example showed that it had good inhibitory against monoamine oxidase B and monoamine oxidase-A, but with low selectivity. Kodok and his colleagues also reported that compound (429) was classified as a powerful and completely selective with agonist M_1 positive allosteric rates, which gave high activity, giving M1IP with low free fraction of 10% in mice and humans [103]. Malamas and other researchers created new thienyl and pyrazolyl aminohydates as powerful BACE1 inhibitors. The compound with the most effective analogue was n-butyl (430), it showed an IC_{50} value of about 8.0 nM. While Probst et al reported that they produced amyloid radicals and compound (431) was present in human clinical trials, it worked to reduce alpha-beta in the cerebrospinal fluid of healthy volunteers. By Zou and his group prepared a group of pyrazole-based compounds that were classified as C-terminus and Beta-secretase 1 (BACE1). In addition, the pyrazole was modified to identify a new compound (432), which is considered a strong inhibitor of BACE1. In many attempts to develop new inhibitors for receptors for advanced glycation (RAGE) to treat AD illness. Through Han and other researchers, a group of pyrazole-5-carboxamides was prepared, and their performance was studied, and the obtained results showed that (433) is an isotope. It is considered the most active, and the activities of the inhibitors were higher, there was a significant effect in reducing alpha and beta in the brain, in addition to the presence of aqueous solubility [104].

Silva and his group also reported the existence of a new group of pyrazolotacrines as acetylcholinesterase (AChE) inhibitors. It was found that compound (434) is the most powerful AChE inhibitor, with an IC_{50} [105]. Meanwhile, Khoubi and other researchers have synthesized novel tetracyclic tacrine analogues with pyrano[2,3-c] pyrazole and have also been tested for acetyl cholinesterase (AChE) inhibition. It was also found that compound (435), which has a 3,4-dimethoxybenzene group, is considered the most effective against AChE because it is more effective than the drug tacrine [106]. Zanaletti and his co-worker, have developed novel α 7nicotinicacetylcholinereceptors (α7 nAChR), a promising treatment for cognitive impairment related to schizophrenia and AD. Compound (436) is considered a powerful with high selectivity agonist α7 nAChR, which has been shown to improve plasma stability and brain levels [107]. Synthesis and an α7 nAChR inhibitor of pyrazole derivatives has a new class of activity. Compound (437) was found to be both powerful and selective, with fair pharmacokinetics and cognitive efficacy. It has also been reported that a hybrid series of pyrazole has been manufactured with strong and selective agonists for α7 nicotinic acetylcholine receptors. The results showed that compound (438) was the most effective inhibitor against alpha7 nicotinic acetylcholine receptor (α7nAChR). Astrazeneca AB has also developed a variety of pyrazole compounds as positive allosteric modulators (PAMs) it is a type of medication that works to increase the speed at which a neurotransmitter is released from its receptor. That is, it makes the neurotransmitter separate from the receptor faster, which shortens the duration of its effect. Pyrazole compounds also bind at specific sites on the neurotransmitter receptors, which leads to a change in the shape of the receptor, and this change causes the neurotransmitter to slip more easily. From the future, which increases its emptying speed. Compound (439) showed excellent activity by working against nicotinic acetylcholine receptors (n-AChRs), these are ligand-gated ion channels found in the nervous system. Acetylcholine is the natural ligand for nAChRs, and when it binds, it opens a channel allowing ions to flow through it, which transmits signals through neurons [108]. Janssen as a Pharmaceutica also created a novel tri-substituted pyrazole compounds of PAM types 1-4 related to their kinetic properties by using the agonist choline at a concentration of 1.0 mM. Tri-substituted compound (440) also showed remarkable activity with an efficiency of 68% [109] Figure 1.15 (appendix A).

Anti-microbial activity

Boussalah and group developed a set of new functional pyrazolyl compounds from amino acids, to determine their anti-fungal activity against Fusarium oxysporum f. sp. albedinis fungi and the yeast Saccharomyces cerevisiae. It was determined that the pyrazolyl compounds showed high activity against the microorganisms that were studied Figure 1.15 (appendix A) [110].

Bendaha and other researchers reported the synthesis of a pyrazolic (37) from 1a and the amine. Compounds (1) and (37) are shown in Figure 1.16 (appendix A) were also examined to study their anti-fungal activity against the yeast Saccharomyces cerevisiae [111]. It was also found that the two materials had a toxic side effect. The suggestion was that this compound stimulates DNA damage and therefore its mechanism of working is different compared to other derivatives such as azole.

Radi and his colleagues reported pyrazole derivatives (38), (39), (40), (41) that can act against the fungal strains Saccharomyces cerevisiae and Fusarium oxysporum f. sp albedinis and the bacterial strain Escherichia-coli four new, and based on the preliminary results that These are some compounds that showed strong activity against microbes [112], Figure 1.17 (appendix A).

As another study [113] showed, by testing compounds 3 to 16 shown in Figure 1.18 (appendix A), the test was against a single strain fungus Fusarium oxysporum f. sp. albedinis, and also the bacterial strains: Micrococcus luteus, Bacillus subtilis, and Escherichia-coli. The results showed that some of the heterocycles containing an Oh group and the vinyl anion had a significant effect against bacteria, and also that compounds containing a group of (-Br) had higher activity against fungi. Also, the composition and anti-microbial effect of some of the tetramer compounds. The new based pyrazole compounds and proto-diamines, had a tested anti-fungal and bactericidal action on the budding yeast Saccharomyces cerevisiae and the bacteria Escherichia-coli [114].

The results were that no compound appeared against the Gram-negative strain when using 500 μM, but some of the synthesized compounds had a strong rate of inhibition in budding yeast when using 500 μM, specifically compound (46) Figure 1.18 (appendix A).

Anti-depressants activity

Adriana Bolasco and other researchers carried out the process of synthesizing a new and diverse group of analogues compounds to pyrazole and examining their inhibitory ability against monoamine oxidase (MAO) A and B. It was shown that the prepared compounds 152a and b are more effective Figure 1.19 (appendix A), and are considered selective and also reversible dimers of MAO-A compared to MAO-B as shown in Table 1.1 [115].

Table 1.1

Monoamine oxidase inhibitory activity of the compound (152a and 153b)

Compound	MAO IC_{50}	MAO-A IC_{50}	MAO-B IC_{50}	SI selectivity[a]
152a	$3.0 \times 10^{-5} \pm 0.05$	$8.8 \times 10^{-9} \pm 0.01$	$1.0 \times 10^{-4} \pm 0.06$	11363
152b	$4.0 \times 10^{-5} \pm 0.02$	$8.0 \times 10^{-9} \pm 0.01$	$1.3 \times 10^{-4} \pm 0.06$	13250

[a]SI: selectivity index = IC_{50} (MAO-B)/IC_{50} (MAO-A).

Abdel-Aziz and researchers also reported the existence of a new group of pyrazole isotopes (153a, b, and c) [116]. These materials have been shown to have anti-depressant activity by means of a behavioral despair method, i.e. via a tail suspension, and anticonvulsant activity against seizures caused by pentylenetetrazole (PTZ) in rats. The isotopes (153a, b, and c) also showed a good protective performance against tonic clonic seizures resulting from intraperitoneal (IP) injection of the PTZ at a dose of 20.0 mg/kg Table 1.2 [117].

Table 1.2

Anti-depressant activities of the compounds (153a–153c) as compared to imipramine

Compound[a]	Duration of immobility (s) (mean ± S.E.M.)	Change from control (%)
153a	283.90 ± 9.30	-24.41
153b	198.70 ± 6.80	-18.33
153c	153.30 ± 4.60	-36.99
Imipramine	132.00 ± 2.60	-45.75

Values represent the mean ± S.E.M. (n = 6); [a]Compounds and imipramine were tested at 10 mg/kg dose level, ip.

1.3 Aims of the work

The objective of this work is to create various heterocycles derivatives composed of imidazoles, oxazines, thiazines, and pyrazoles moieties using simple approach and natural based starting materials that are available at low cost. The compounds are anticipated to have good antimicrobial activity and are effective against AD

The general objectives of the current work are:

1. Synthesize of a new type of imidazoles, thiazines, oxazines, and pyrazoles based on biobased principles. Vanillin was selected for this purpose.
2. Analyze the prepared heterocycles by the spectroscopic methods FT-IR, and NMR (^{1}H and C-13).
3. Evaluate the activity of the prepared heterocycles as effective drugs against AD
4. Evaluate the anti-microbial activities of the prepared heterocycles against various gram positive and gram negative bacteria.

1.4 Long Term Objectives

Provide multi-gram quantities of drug derivatives to interested pharmaceutical companies for large-scale testing in large animal models, evaluation in clinical testing, and subsequent commercial development.

Chapter Two

Experimental

2.1 Materials

All materials used in the experimental part were of analytical grade and used as received (Alderich Chemical Company) include Acetophenone ($C_6H_5CCH_3$), 2-Bromoacetophenone (C_8H_7BrO), 2,4-Dibromoacetophenone ($C_8H_6Br_2O$), 4-Fluoro phenyl hydrazine hydrochloride ($C_6H_7FN_2$.HCl), 2-Bromo phenyl hydrazine hydrochloride ($C_6H_8BrClN_2$), 2-Chlorophenyl hydrazine hydrochloride ($C_6H_8Cl_2N_2$), Ethylene diamine ($C_2H_8N_2$), Semicarbazide (CH_5N_3O), Phenyl hydrazine ($C_6H_8N_2$), Hydroxyl amine hydrochloride(NH_2OH.HCl), Hydrazine hydrate (H_6N_2O), Sodium acetate ($CH3COO^-Na^+$), Urea (NH_2CONH_2), Thiourea (NH_2CSNH_2), Vanillin ($C_8H_8O_3$), Sodium hydroxide (NaOH), Ethanol (C_2H_6O).

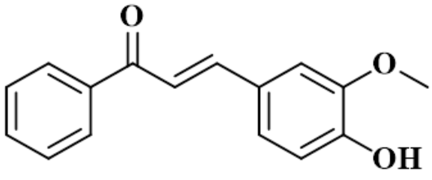
2.2 Instrumentation

A Stuart Scientific Melting Point SMP3 apparatus was used for the melting point determinations, all melting points are reported in Celsius (°C). (FT-IR) was performed on Nicolet iS5 (Thermo Fisher Scientific Company, USA). Nuclear Magnetic Resonance (NMR) spectra were obtained using Bruker Avance (500 spectrometers, Switzerland, University of Jordan, Amman).

2.3 General procedures for synthesis of chalcones

Synthesis of (E)-3-(4-hydroxy-3-methoxyphenyl)-1-phenylprop-2-en-1-one (1):

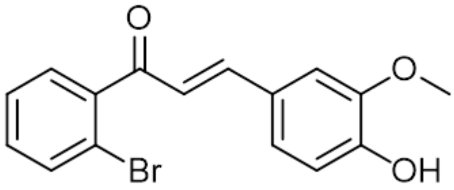
A solution of vanillin (0.02 mol, 3.0 g) and acetophenone (0.02 mol) was prepared in absolute ethanol (50 mL). The solution was treated with Sodium hydroxide solution 10% (10.0 mL) by dropwise addition dropwise over a period of 10 min. The produced reaction mixture was stirred at room temperature for 6hrs then place in the Refrigerator for overnight. The produced precipitate was collected by suction filtration washed with ethanol (3 x 20 mL) and dried.



(E)-3-(4-hydroxy-3-methoxyphenyl)-1-phenylprop-2-en-1-one

Synthesis of (E)-1-(2-bromophenyl)-3-(4-hydroxy-3-methoxyphenyl) prop-2-en-1-one (2):

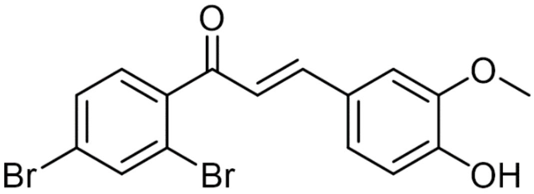
A solution of vanillin (0.02 mol, 3.0 g) and 2-bromo acetophenone (0.02 mol) was prepared in absolute ethanol (50 mL). The solution was treated with Sodium hydroxide solution 10% (10.0 mL) by dropwise addition dropwise over a period of 10 min. The produced reaction mixture was stirred at room temperature for 6 hrs then place in the Refrigerator for overnight. The produced precipitate was collected by suction filtration washed with ethanol (3 x 20 mL) and dried.



(E)-1-(2-bromophenyl)-3-(4-hydroxy-3-methoxyphenyl) prop-2-en-1-one

Synthesis of (E)-1-(2,4-dibromophenyl)-3-(4-hydroxy-3-methoxyphenyl) prop-2-en-1-one (3):

A solution of vanillin (0.02 mol, 3.0 g) and 2,4-dibromo acetophenone (0.02 mol) was prepared in absolute ethanol (50 mL). The solution was treated with Sodium hydroxide solution 10% (10.0 mL) by dropwise addition dropwise over a period of 10 min. The produced reaction mixture was stirred at room temperature for 6 hrs then place in the Refrigerator for overnight. The produced precipitate was collected by suction filtration washed with ethanol (3 x 20 mL) and dried.



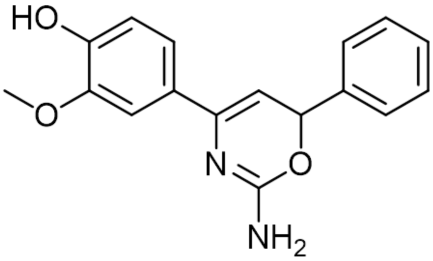
(E)-1-(2,4-dibromophenyl)-3-(4-hydroxy-3-methoxyphenyl) prop-2-en-1-one

2.4 General procedure for synthesis of oxazine

Part of the above prepared chalcone (1) (0.01 mol, 2.7 g, MW 269.0 g/mol) was mixed with urea (0.01 mol, 0.6 g) in ethanol (30 mL) and treated with sodium hydroxide solution 10% (5 mL). The mixture was stirred for 4 hr (the reaction progress was followed by TLC using hexane/ethyl acetate (80/20) as an eluting solvent) then to a 20 mL of ice water with continuous stirring for 1 hr, then left overnight in the refrigerator. The produced solid was collected by filtration, washed with ethanol (2 x 10 mL), and recrystallized from ethanol.

4-(2-amino-6-phenyl-6H-1,3-oxazin-4-yl)-2-methoxyphenol (4):

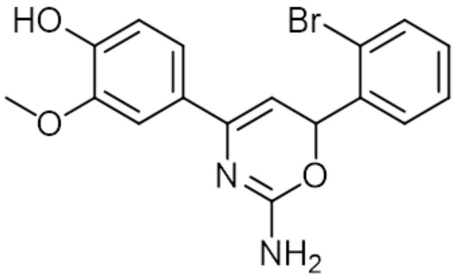
Chalcone 1 was used for making this compound Product solid powder was obtained (orange colored) with a yield of 77%, mp 349.7 °C. IR (ν in cm^{-1}):3360–3225 (N-H, O-H), 3030 (=C-H), 1625 (N-H), 1602 (C=C), 1598 (C=C), 1280 (C-N), 1235 (C-O, OH), 1270–1110 (Ar-O-CH_3), 760 (N-H). ^1H NMR (500 MHz, MeOH) δ in ppm: 7.66 (s, 1, OH), 7.39 (m, 5H, aromatic), 7.06 (1H, aromatic), 7.02 (2H, NH_2), 6.86 (1H, d, aromatic), 6.8 (d, aromatic, 1H), 6.8 (d, 1H), 5.5 (d, 1H, vinylic), 3.86 (3H, S, OCH_3) *m*/*z*: (M+) for $C_{17}H_{16}N_2O_3$ Calcd.: 296.12, Found: 296.63



4-(2-amino-6-phenyl-6H-1,3-oxazin-4-yl)-2-methoxyphenol

4-(2-amino-6-(2-bromophenyl)-6H-1,3-oxazin-4-yl)-2-methoxyphenol (5):

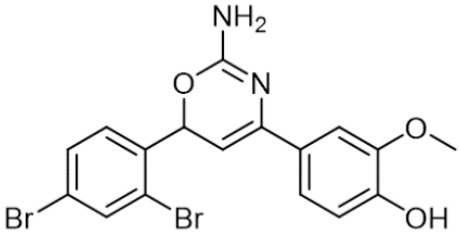
Chalcone 2 was used for making this compound Product solid powder was obtained (Beige colored) with a yield of 77%, mp 281°C. IR (ν in cm^{-1}): 3360–3225 (N-H, O-H), 3030 (=C-H), 1625 (N-H), 1625 (C=N), 1602 (C=C), 1598 (C=C), 1280 (C-N), 1235 (C-O, OH), 1270–1110 (Ar-O-CH_3), 760 (C-Br). ^1H NMR (500 MHz, MeOH) δ in ppm: 7.66 (s, 1, OH), 7.6 (dd, 1H, aromatic), 7.45 (dd, 1H, aromatic), 7.30 (m, 2H, aromatic), 7.05 (dd, 1H, aromatic), 7.02 (2H, NH_2), 6.89 (1H, d, aromatic), 6.82 (d, aromatic, 1H), 5.92 (d, 1H), 5.6 (d, 1H, vinylic), 3.84 (3H, S, OCH_3) *m*/*z*: (M+) for $C_{17}H_{15}BrN_2O_3$ Calcd.: 374.02, Found: 374.12.



4-(2-amino-6-(2-bromophenyl)-6H-1,3-oxazin-4-yl)-2-methoxyphenol

4-(2-amino-6-(2,4-dibromophenyl)-6H-1,3-oxazin-4-yl)-2-methoxyphenol (6):

Chalcone 3 was use for making this compound Product solid powder was obtained (gray colored) with a yield of 77%, mp 190°C. IR (ν in cm^{-1}): 3360–3225 (N-H, O-H), 3030 (=C-H), 1625 (N-H), 1625 (C=N), 1602 (C=C), 1598 (C=C), 1280 (C-N), 1235 (C-O, OH), 1270–1110 (Ar-O-CH_3), 760 (C-Br). ^{1}H NMR (500 MHz, MeOH) δ in ppm: 7.80 (s, 1, OH), 7.7 (s, 1H, aromatic), 7.5 (s, 2H, aromatic), 7.04 (dd, 1H, aromatic), 7.04 (2H, NH_2), 6.90 (d, 1H, aromatic), 6.80 (d, 1H, aromatic), 5.96 (d, 1H, aromatic), 5.55(1H, d, vinylic), 3.84 (3H, S, OCH_3) *m/z*: (M+) for $C_{17}H_{14}Br_2N_2O_2$, Calcd.: 453.94, Found: 454.12



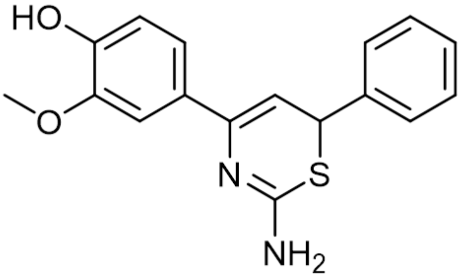
4-(2-amino-6-(2,4-dibromophenyl)-6H-1,3-oxazin-4-yl)-2-methoxyphenol

2.5 General procedure for synthesis of thiazine

Part of the above prepared chalcone (1) (0.01 mol, 2.7 g, MM 269) was mixed with thiourea (0.01 mol, 0.76 g) in ethanol (30 mL) and treated with sodium hydroxide solution 10% (5 mL). The mixture was stirred for 4 hr (the reaction progress was followed by TLC using hexane/ethyl acetate (80/20) as an eluting solvent) then to a 20 mL of ice water with continuous stirring for 1 hrs, then left overnight in the refrigerator. The produced solid was collected by filtration, washed with ethanol (2 x 10 mL), and recrystallized from ethanol.

4-(2-amino-6-phenyl-6H-1,3-thiazin-4-yl)-2-methoxyphenol (7):

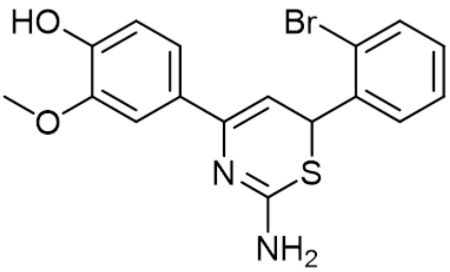
Chalcone 1 was used for making this compound Product solid powder was obtained (orange colored) with a yield of 77%, mp 330°C. IR (ν in cm^{-1}): 3360–3225 (N-H, O-H), 3030 (=C-H), 1625 (N-H), 1625 (C=N), 1602 (C=C), 1598 (C=C), 1280 (C-N), 1235 (C-O, OH), 1270–1110 (Ar-O-CH_3), 760 (N-H). ^{1}H NMR (500 MHz, MeOH) δ in ppm: 7.66 (s, 1, OH), 7.39 (m, 2H, aromatic), 7.33 (m, 3H, aromatic), 7.06 (d, 1H, aromatic), 6.90 (s, 1H, aromatic), 6.86 (1H, d, aromatic), 6.8 (d, aromatic, 1H), 6.6 (s, 2H. NH), 6.2 (d, 1H, vinylic), 3.84 (3H, S, OCH_3) *m*/*z*: (M+) for $C_{17}H_{16}N_2O_2S$ Calcd.: 312.29, Found: 311.83.



4-(2-amino-6-phenyl-6H-1,3-thiazin-4-yl)-2-methoxyphenol

4-(2-amino-6-(2-bromophenyl)-6H-1,3-thiazin-4-yl)-2-methoxyphenol (8):

Chalcone 2 was used for making this compound Product solid powder was obtained (light brown colored) with a yield of 77%, mp 289°C. IR (ν in cm^{-1}): 3360–3225 (N-H, O-H), 3030 (=C-H), 1625 (N-H), 1625 (C=N), 1602 (C=C), 1598 (C=C), 1280 (C-N), 1235 (C-O, OH), 1270–1110 (Ar-O-CH_3), 760 (C-Br). ^{1}H NMR (500 MHz, MeOH) δ in ppm: 7.68 (s, 1, OH), 7.6 (dd, 1H, aromatic), 7.45 (dd, 1H, aromatic), 7.34 (m, 2H, aromatic), 7.07 (dd, 1H, aromatic), 6.90 (d, 1H, aromatic), 6.80 (d, 1H, aromatic), 6.68 (2H, NH), 6.45(1H, d, vinylic), 5.08 (d, 1H), 3.84 (3H, S, OCH_3) *m*/*z*: (M+) for $C_{17}H_{15}BrN_2O_2S$, Calcd.: 390.02, Found: 390.43.



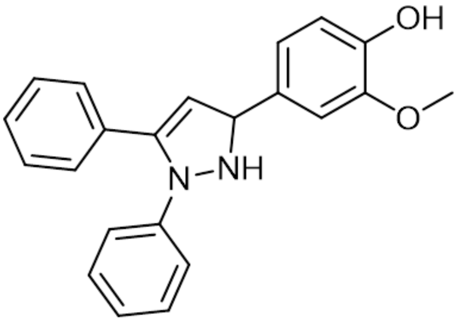
4-(2-amino-6-(2-bromophenyl)-6H-1,3-thiazin-4-yl)-2-methoxyphenol

2.6 General procedure for synthesis of phenyl pyrazole

a mixture of chalcone (1) (0.01 mol, 2.7 g) and phenyl hydrazine (0.01mol, 1.0 g) in 50 mL absolute ethanol was refluxed for 12 hr. The reaction progress was followed by TLC using hexane/ethyl acetate (80/20) as an eluting solvent. The reaction mixture was cooled down to room temperature and the produced precipitate was collected by filtration and recrystallize from ethanol.

4-(1,5-diphenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (9):

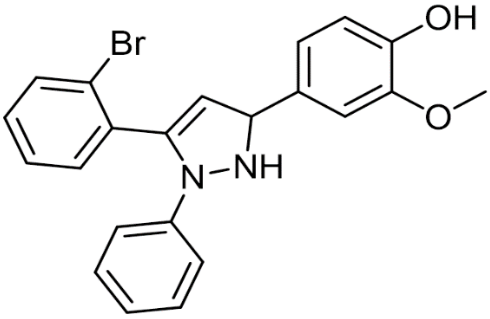
Chalcone 1 was used for making this compound Product solid was obtained (light brown colored) with a yield of 77%, mp 349.4°C. IR (v in cm^{-1}): 3350-3220 (O-H), 2900 (=C-H), 1760 (C=O, lactam), 1635 (C=N), 1625-1510 (C=C), 1300 (C-N), 1235 (C-O, OH), 1270-1110 (CO, Ar-O- CH3). H NMR (500 MHz, MeOH) 8 in ppm: 8.30 (s, 1, OH), 7.5 (m, 4H, aromatic), 7.4 (m, 6H, aromatic), 7.36 (dd, 1H, aromatic), 7.3 (d, 1H, aromatic), 7.18 (d, 1H, aromatic), 6.96 (d, IH, aromatic), 5.10 (1H, d), 3.87 (bs, 1H, NH), 3.87 (s, 3H, OCH3); (m/z: (M+) for C22H20N2O2, Calcd.: 344.14, Found: 344.28.



4-(1,5-diphenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol

4-(5-(2-bromophenyl)-1-phenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (10):

Chalcone 2 was used for making this compound Product solid powder was obtained (brown colored) with a yield of 77%, mp 195°C. IR (v in cm^{-1}): 3350-3220 (Q-H), 2900 (=C-H), 1760 (C=O, lactam), 1635 (C=N), 1605-1590 (C=C), 1300 (C-N), 1235 (C-O, OH), 1270-1110 (CO, Ar-O-CH3), 765 (C-Br). H NMR (500 MHz, MeOH) 8 in ppm: 8.30 (s, 1, OH), 7.6 (m, 2H, aromatic), 7.51 (m, 4H, aromatic), 7.40 (m, 3H, aromatic), 7.30 (m, 3H, aromatic), 6.92 (d. 1H, aromatic), 5.12 (1H, d), 3.87 (bs, 1H, NH), 3.87 (s, 3H, OCH3) m/: (M+) for C22H19BrN2O2, Calcd.: 422.29, Found: 422.12.



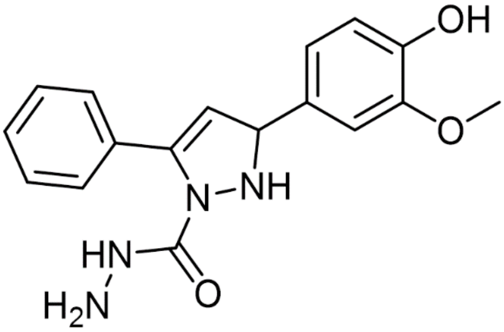
4-(5-(2-bromophenyl)-1-phenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol

2.7 General procedure for synthesis of pyrazole with semicarbazide

a mixture of chalcone (1) (0.01 mol, 2.7 g) and semicarbazide (0.01mol, 0.75 g) in 50 mL absolute ethanol was refluxed for 12 hr. The reaction progress was followed by TLC using hexane/ethyl acetate (80/20) as an eluting solvent. The reaction mixture was cooled down to room temperature and the produced precipitate was collected by filtration and recrystallize from ethanol.

3-(4-hydroxy-3-methoxyphenyl)-5-phenyl-2,3-dihydro-1H-pyrazole-1-carbohydrazide (11):

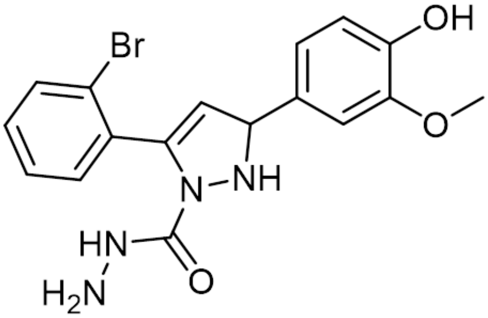
Chalcone 1 was used for making this compound Product solid powder was obtained (white colored) with a yield of 77%, mp 224°C. IR (ν in cm^{-1}): 3360–3225 (N-H, O-H), 3030 (=C-H), 1625 (N-H), 1640 (C=O amide), 1625 (C=N), 1602 (C=C), 1598 (C=C), 1280 (C-N), 1235 (C-O, OH), 1270–1110 (Ar-O-CH_3). ^{1}H NMR (500 MHz, MeOH) δ in ppm: 9.02 (s, 1H, NH), 8.28 (s, 1, OH), 7.63 (d, 2H, aromatic), 7.4 (m, 4H, aromatic), 7.27 (s, 2H, aromatic), 6.95 (d, 1H, aromatic), 4.82 (s, 3H, NH and NH_2), 5.14 (1H, d), 3.87, 3.87 (s, 3H, OCH_3) *m/z*: (M+) for $C_{17}H_{18}N_4O_2$, Calcd.:326.34, Found: 326.76.



3-(4-hydroxy-3-methoxyphenyl)-5-phenyl-2,3-dihydro-1H-pyrazole-1-carbohydrazide

5-(2-bromophenyl)-3-(4-hydroxy-3-methoxyphenyl)-1H-pyrazole-1-carbohydrazide (12):

Chalcone 2 was used for making this compound Product solid powder was obtained (Light brown colored) with a yield of 77%, mp 255°C IR (ν in cm^{-1}): 3360–3225 (N-H, O-H), 3030 (=C-H), 1625 (N-H), 1640 (C=O amide), 1625 (C=N), 1602 (C=C), 1598 (C=C), 1280 (C-N), 1235 (C-O, OH), 1270–1110 (Ar-O-CH_3), 760 (C-Br). ^1H NMR (500 MHz, MeOH) δ in ppm: 9.02 (s, 1H, NH), 8.28 (s, 1, OH), 7.70 (d, 1H, aromatic), 7.63 (d, 1H, aromatic), 7.4 (m, 1H, aromatic), 7.34 (m, 3H, aromatic), 7.29 (s, 1H, aromatic), 6.95 (d, 1H, aromatic), 5.18 (1H, d), 4.82 (bs, 2H, NH, NH_2), 3.87 (3H, s, OCH_3) *m*/*z*: (M+) for $C_{17}H_{17}BrN_4O_3$, Calcd.:404.34, Found: 404.76.



5-(2-bromophenyl)-3-(4-hydroxy-3-methoxyphenyl)-1H-pyrazole-1-carbohydrazide

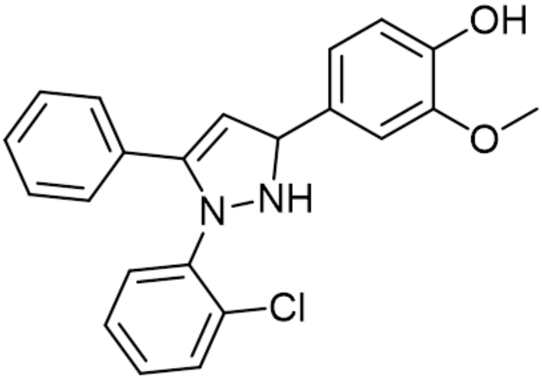
2.8 General procedure for synthesis of 2-chloro phenyl hydrazine hydrochloride

a mixture of chalcone (1) (0.01 mol, 2.7 g) and 2-chloro phenyl hydrazine hydrochloride (0.01mol, 1.79 g) in 50 mL absolute ethanol was refluxed for 12 hr. The reaction progress was followed by TLC using hexane/ethyl acetate (80/20) as an eluting solvent. The reaction mixture was cooled down to room temperature and the produced precipitate was collected by filtration and recrystallize from ethanol.

4-(1-(2-chlorophenyl)-5-phenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (13):

Chalcone 1 was used for making this compound Product solid powder was obtained (white colored) with a yield of 77%, mp 349 °C. IR (ν in cm^{-1}): 3350–3220 (O-H), 2900 (=C-H), 1760 (C=O, lactam), 1635 (C=N), 1605-1590 (C=C), 1300 (C-N), 1235 (C-O, OH), 1270–1110 (CO, Ar-O-CH_3), 800–600 (C-Cl). ^1H NMR (500 MHz, MeOH) δ in ppm: 8.30 (s, 1, OH), 7.7 (m, 1H, aromatic), 7.51 (m, 1H, aromatic), 7.46 (m, 2H, aromatic), 7.42 (m, 4H, aromatic), 7.38 (m, 2H, aromatic), 7.28 (d, 1H, aromatic), 7.24

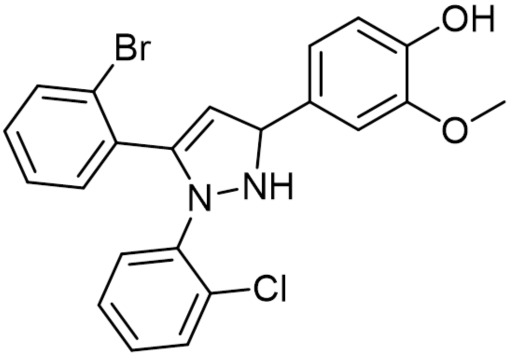
(S, 1H, aromatic), 6.90 (d, 1H, aromatic), 5.52 (1H, d), 4.71 (bs, 1H, NH), 3.87 (s, 3H, OCH_3) *m*/*z*: (M+) for $C_{22}H_{19}ClN_2O_2$, Calcd.: 378.14, Found: 378.42.



4-(1-(2-chlorophenyl)-5-phenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol

4-(5-(2-bromophenyl)-1-(2-chlorophenyl)-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (14):

Chalcone 2 was used for making this compound Product solid powder was obtained (Light brown colored) with a yield of 77%, mp 348.6 °C. IR (ν in cm^{-1}): 3350–3220 (O-H), 2900 (=C-H), 1760 (C=O, lactam), 1635 (C=N), 1605-1590 (C=C), 1300 (C-N), 1235 (C-O, OH), 1270–1110 (CO, Ar-O-CH_3), 650-800 (C-Cl, C-Br).^{1}H NMR (500 MHz, MeOH) δ in ppm: 8.30 (s, 1, OH), 7.70 (m, 3H, aromatic), 7.50 (m, 1H, aromatic), 7.45 (m, 2H, aromatic), 7.40 (m, 2H, aromatic), 7.30 (m, 3H, aromatic), 6.93 (d, 1H, aromatic), 5.56 (1H, d), 4.77 (bs, 1H, NH), 3.87 (s, 3H, OCH_3) *m*/*z*: (M+) for $C_{22}H_{18}BrClN_2O_2$, Calcd.: 456.05, Found: 456.36.



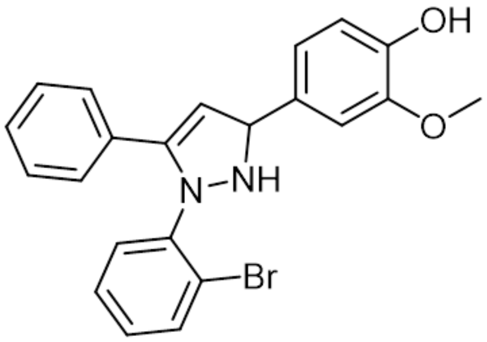
4-(5-(2-bromophenyl)-1-(2-chlorophenyl)-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol

2.9 General procedure for synthesis of 2-bromo phenyl hydrazine hydrochloride

a mixture of chalcone (1) (0.01 mol, 2.7 g) and 2-bromo phenyl hydrazine hydrochloride (0.01mol, 2.24 g) in 50 mL absolute ethanol was refluxed for 12 hr. The reaction progress was followed by TLC using hexane/ethyl acetate (80/20) as an eluting solvent. The reaction mixture was cooled down to room temperature and the produced precipitate was collected by filtration and recrystallize from ethanol.

4-(1-(2-bromophenyl)-5-phenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (15):

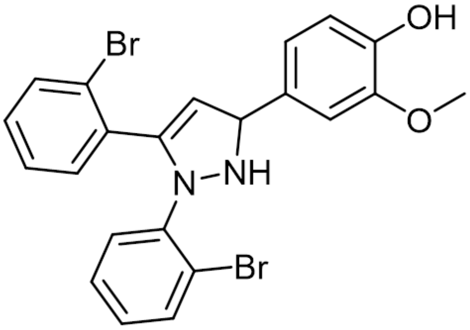
Chalcone 1 was used for making this compound Product solid powder was obtained (dark brow colored) with a yield of 77%, mp 350 °C. IR (v in cm^{-1}): 3350-3220 (O-H), 2900 (C-H), 176 (C=O, lactam), 1635 (C=N), 1605-1590 (C=C), 1300 (C-N), 1235 (C-O, OH), 1270-1110 (CC Ar-O-CH3), 765 (C-Br). H NMR (500 MHz, MeOH) 8 in ppm: 8.30 (s, 1, OH), 7.6 (m, 2F aromatic), 7.51 (m, 1H, aromatic), 7.40 (m, 5H, aromatic), 7.37 (m, 2H, aromatic), 7.25 (m, 2 aromatic), 6.92 (d, 1H, aromatic), 5.51 (1H, d), 4.67 (, 1H, NH), 3.87 (s, 3H, OCH3) m/z: (M+ for C22H19BrN2O2, Calcd.: 422.29, Found: 422.62.



4-(1-(2-bromophenyl)-5-phenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol

4-(1,5-bis(2-bromophenyl)-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (16):

Chalcone 2 was used for making this compound Product solid powder was obtained (light brown colored) with a yield of 77%, mp 340 °C. IR (v in cm^{-1}): 3350-3220O-H), 2900 (=C-H), 1760 (C=O, lactam), 1635 (C=N), 1605-1590 (C=C), 1300 (C-N), 1235 (C-O, OH), 1270-1110 (CO, Ar-O-CH3), 765 (C-Br). H NMR (500 MHz, MeOH) 8 in ppm: 8.30 (s, 1, OH), 7.60 (m, 4H, aromatic), 7.48 (t, 1H, aromatic), 7.38 (m, 2H, aromatic), 7.33 (m, 4H, aromatic), 6.90 (d, IH, aromatic), 5.53 (1H, d), 4.78 (bs, 1H, NH), 3.87 (3H, s, OCH3) m/:: (M+) for C22H18Br2N2O2, Calcd.: 499.96, Found: 452.08.



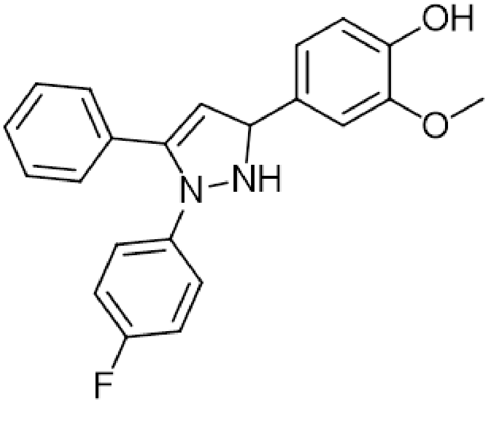
4-(1,5-bis(2-bromophenyl)-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol

2.10 General procedure for synthesis of 4-fluoro phenyl hydrazine hydrochloride

a mixture of chalcone (1) (0.01 mol, 2.7 g) and 4-fluoro phenyl hydrazine hydrochloride (0.01mol, 1.63 g) in 50 mL absolute ethanol was refluxed for 12 hr. The reaction progress was followed by TLC using hexane/ethyl acetate (80/20) as an eluting solvent. The reaction mixture was cooled down to room temperature and the produced precipitate was collected by filtration and recrystallize from ethanol.

4-(1-(4-fluorophenyl)-5-phenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (17)

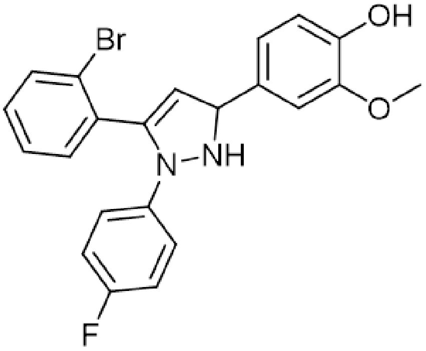
Chalcone 1 was used for making this compound Product solid powder was obtained (gray colored) with a yield of 77%, mp 233 °C. IR (ν in cm^{-1}): 3350–3220 (O-H), 2900 (=C-H), 1760 (C=O, lactam), 1635 (C=N), 1605-1590 (C=C), 1300 (C-N), 1235 (C-O, OH), 1270–1110 (CO, Ar-O-CH_3). ^{1}H NMR (500 MHz, MeOH) δ in ppm: 8.30 (s, 1, OH), 7.65 (dd, 1H, aromatic), 7.63 (dd, 1H, aromatic), 7.55 (m, 4H, aromatic), 7.40(m, 2H, aromatic), 7.37 (dd, 1H, aromatic). 7.30 (m, 2H, aromatic), 7.25 (s, 1H, aromatic), 6.93 (d, 1H, aromatic), 5.46 (1H, d), 4.68 (bs, 1H, NH), 3.87 (3H, s, OCH_3) *m*/*z*: (M+) for $C_{22}H_{19}FN_2O_2$, Calcd.: 362.15, Found: 362.26



4-(1-(4-fluorophenyl)-5-phenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol

4-(5-(2-bromophenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-2-methoxyphenol (18)

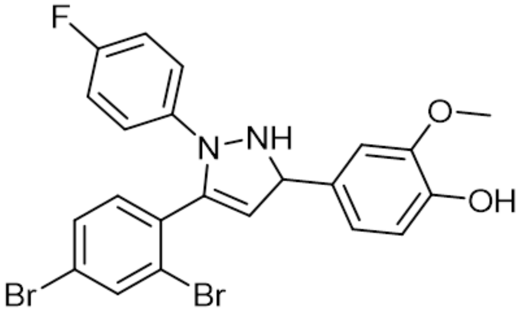
Chalcone 2 was used for making this compound Product solid powder was obtained (beige Shiny colored) with a yield of 77% mp 310°C. IR (ν in cm^{-1}): 3350–3220 (O-H), 2900 (=C-H), 1760 (C=O, lactam), 1635 (C=N), 1605-1590 (C=C), 1300 (C-N), 1235 (C-O, OH), 1270–1110 (CO, Ar-O-CH_3), 765 (C-Br). ^{1}H NMR (500 MHz, MeOH) δ in ppm: 8.28 (s, 1, OH), 7.62 (m, 4H, aromatic), 7.38 (m, 4H, aromatic), 7.28 (m, 1H, aromatic), 7.30 (m, 2H, aromatic), 6.92 (d, 1H, aromatic), 5.51 (1H, d), 4.78 (bs, 1H, NH) 3.87 (3H, s, OCH_3) *m*/*z*: (M+) for $C_{22}H_{18}BrFN_2O_2$, Calcd.: 440.04, Found: 440.18



4-(5-(2-bromophenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-2-methoxyphenol

4-(5-(2,4-dibromophenyl)-1-(4-fluorophenyl)-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxypheno (19)

Chalcone 3 was used for making this compound Product solid powder was (White shiny colored) obtained with a yield of 77%, mp 311°C. IR (ν in cm^{-1}): 3350–3220 (O-H), 2900 (=C-H), 1760 (C=O, lactam), 1635 (C=N), 1605-1590 (C=C), 1300 (C-N), 1235 (C-O, OH), 1270–1110 (CO, Ar-O-CH_3). ^{1}H NMR (500 MHz, MeOH) δ in ppm: 8.28 (s, 1, OH), 7.7 (m, 1H, aromatic), 7.6 (m, 2H, aromatic), 7.38 (m, 3H, aromatic), 7.26 (d, 1H, aromatic), 7.14 (d, 1H, aromatic), 7.08 (m, 2H, aromatic), 6.95 (d, 1H, aromatic), 5.48 (1H, d), 4.82 (bs, 1H, NH) 3.87 (s, 3H, OCH_3) *m*/*z*: (M+) for $C_{22}H_{17}Br_2FN_2O_2$, Calcd.:517.11, Found: 517.53



4-(5-(2,4-dibromophenyl)-1-(4-fluorophenyl)-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxypheno

Chapter Three

Results and Discussion

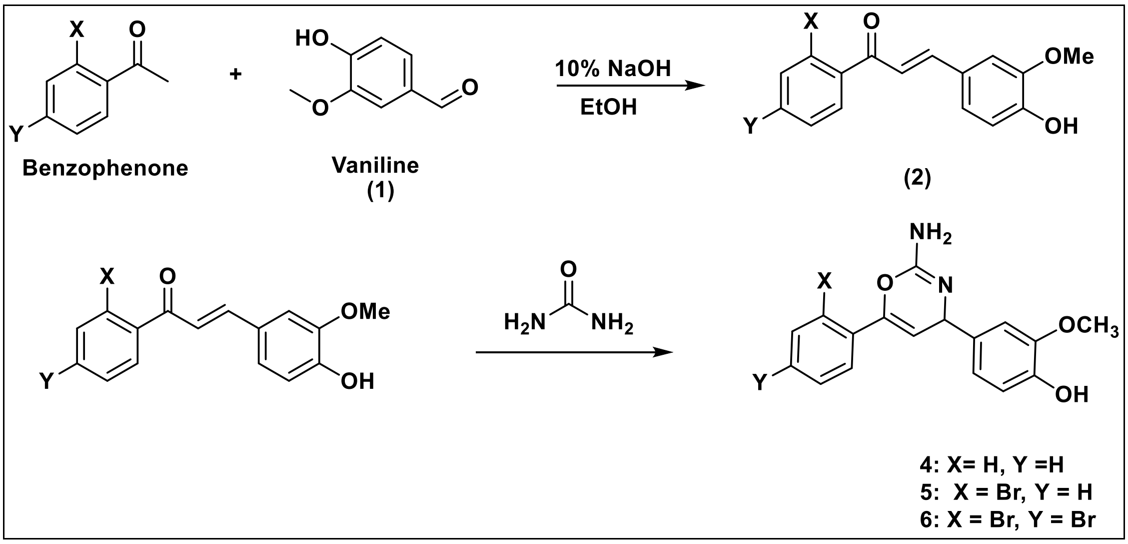
Heterocycles are important components of natural compounds and synthetic drugs and are known to play a crucial role in several biochemical and chemical processes. Derivatives of oxazine, thiazine, pyrazole, and some other compounds have attracted the attention of many scientists, as they have shown compounds with various biological activities ranging from antimicrobial to anti-alzheimer's. In this work, several derivatives of the heterocyclic rings of oxazine, thiazine, and pyrazole in addition to some of the following compounds were prepared using a simple two-step process. The antimicrobial activity of the prepared derivatives was evaluated.

3.1 Oxazine derivatives

Several oxazine derivatives were prepared, a summary of the prepared compounds is shown in Figure 3.1. The process of making oxazine derivatives involved a two-step process, in the first step chalcone 2 was prepared from reacting benzophenone and vanillin in alkaline medium.

Figure 3.1

Preparation of oxazine derivatives

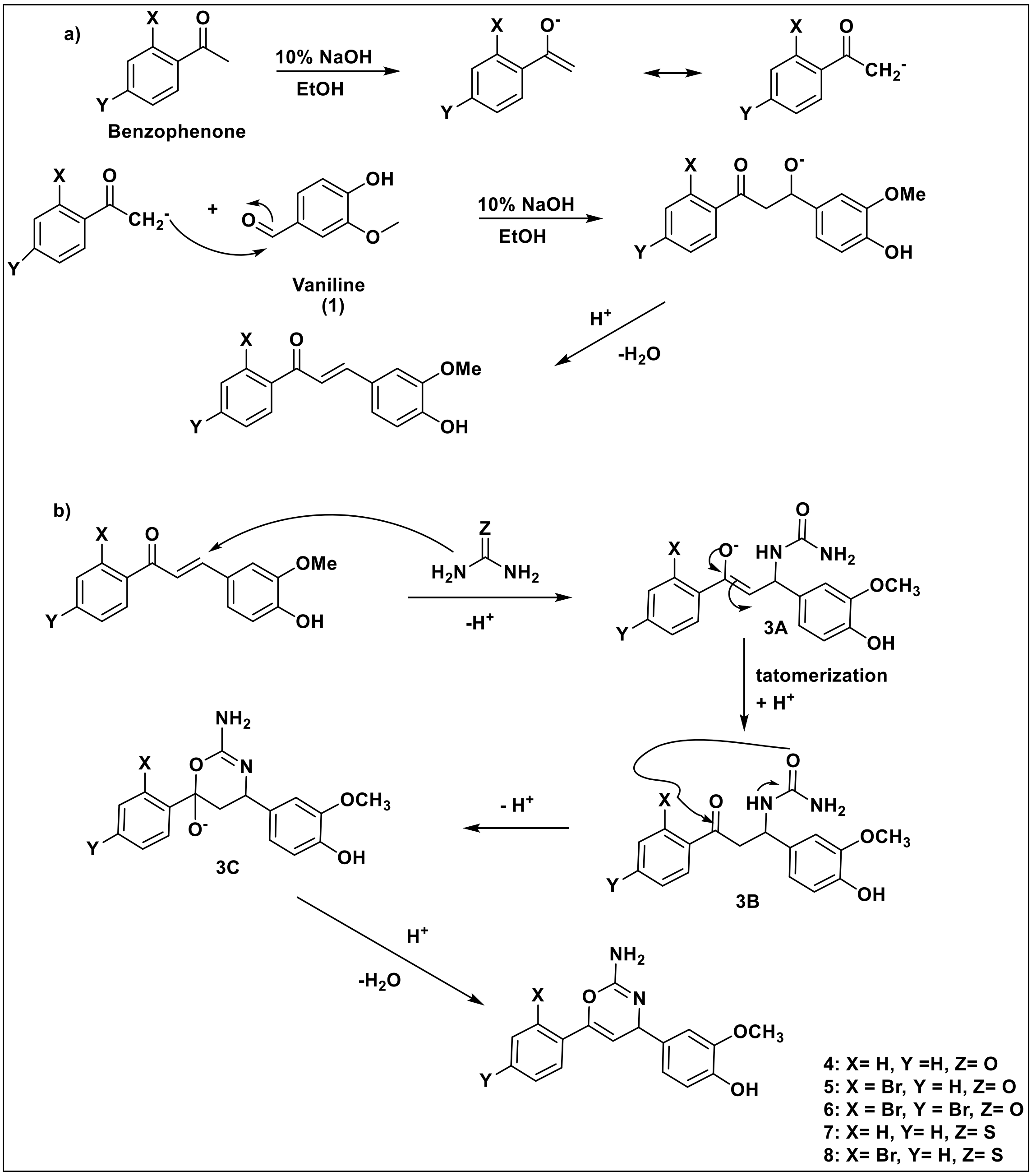


The reaction is a condensation reaction shown in Figure 3.2. In the first step an α-H is abstracted from benzophenone, and that creates a nucleophilic center (enolate) which attacks the carbonyl of the aldehyde. Neutralization followed by dehydration produces the target chalcone Figure 3.2a.

The formation of oxazine involves reacting the produced lactone with urea. In the first step of the reaction mechanism urea molecules makes Micheal addition on chalcone to form the addition product 3A. Tautomerization in compound 3A, followed by protonation leads to the formation of compound 3B. Which undergoes internal nucleophilic addition reaction to form intermediate 3C. Then 3C undergoes protonation and dehydration to form the target product Figure 3.2b.

Figure 3.2

Preparation and mechanism for making oxazine and thiazine derivative



The yield of the compounds ranged from 80 to 90%. The acetophenone with the bromide showed higher yield, which could be related to the higher reactivity due to the formation of more stable enolate. The proton NMR shown in Figure 3.3 (appendix A) and the IR shown in Figure 3.4 (appendix A) results showed the formation of the target compounds. The IR spectra of the compounds showed the presence of N-H stretching band, C=N stretching bands, C=C of aromatic and =C-H vinylic starching bands.

3.2 Thiazine derivatives

Several thiazine derivatives were prepared, and a summary of the prepared compounds is shown in Figure 3.5 (appendix A). The process of preparing thiazine derivatives involves a two-step process. In the first step, chalcone 2 was prepared from the reacting benzophenone with vanillin in an alkaline medium. The second step involved reacting chalcone 2 with thiourea. The preparation and mechanism for making thiazine derivative Figure 3.2.

The yield of the compounds ranged from 80 to 90%. The acetophenone with the bromide showed higher yield, which could be related to the higher reactivity due to the formation of more stable enolate. The proton NMR shown in Figure 3.6 (appendix A) and the IR shown in Figure 3.7 (appendix A) results showed the formation of the target compounds. The IR spectra of the compounds showed the presence of N-H stretching band, C=N stretching bands, C=C of aromatic and =C-H vinylic starching bands.

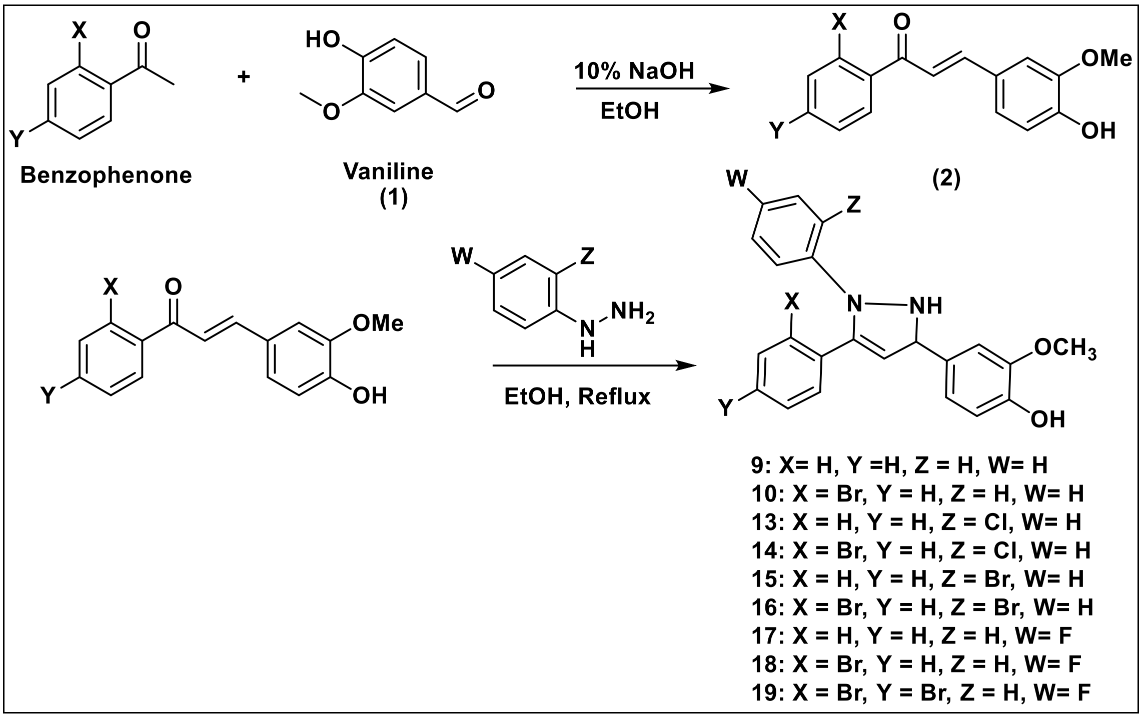
3.3 Phenyl pyrazole derivatives

The process of preparing phenyl pyrazole derivatives involves a two-step process. In the first step, chalcone 2 was prepared from the reaction of benzophenone or 4-bromo benzophenone or substituted phenyl hydrazine and vanillin in an alkaline medium as shown on Figure 3.8 the yield of the compounds ranged from 80 to 90%. In the second step chalcone 2 was reacted with phenyl hydrazine to form the target product.

The proton NMR results shown in Figure 3.9 (appendix A) and IR results shown in Figure 3.10 (appendix A) showed the formation of target compounds for the phenyl pyrazole derivatives. The IR spectra of the compounds showed the presence of N-H stretching bands, C=N stretching bands, C=C aromaticity bands and C-H vinylic bands of starch. Figure 3.11 - 3.16 (appendix A) shows IR and proton NMR for each of the phenyl hydrazine (2-chloro phenyl hydrazine hydrochloride and 2-bromo phenyl hydrazine hydrochloride, 4-flouro phenyl hydrazine hydrochloride) compounds.

Figure 3.8

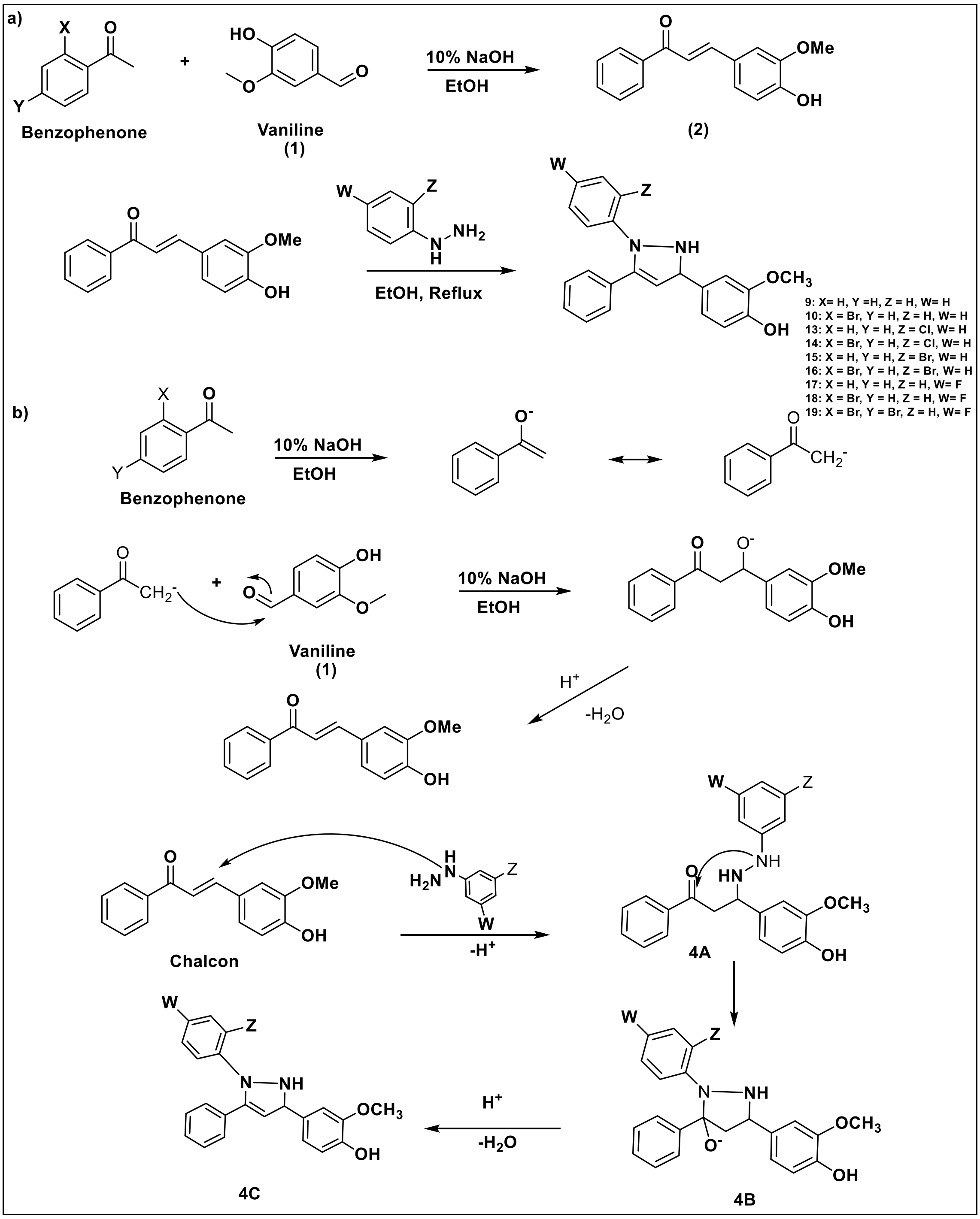
Preparation of phenyl pyrazole and phenyl hydrazine derivatives



The reaction mechanism involves a condensation reaction as shown in Figure 3.17 in the first step an α-H is abstracted from benzophenone, and that creates a nucleophilic center (enolate) which attacks the carbonyl of the aldehyde to form the chalcon Figure 3.17a. The formation of pyrazole involves reacting the produced lactone with various hydrazine. In the first step of the reaction mechanism hydrazine molecules makes Micheal addition on chalcone to form the addition product 4A. Tautomerization in compound 4A, followed by protonation leads to the formation of intermediate 4B. Which undergoes internal nucleophilic addition reaction to form intermediate 4C. Then 4C undergoes protonation and dehydration to form the target product Figure 3.17b.

Figure 3.17

Preparation and mechanism for making phenyl pyrazole and phenyl hydrazine derivative

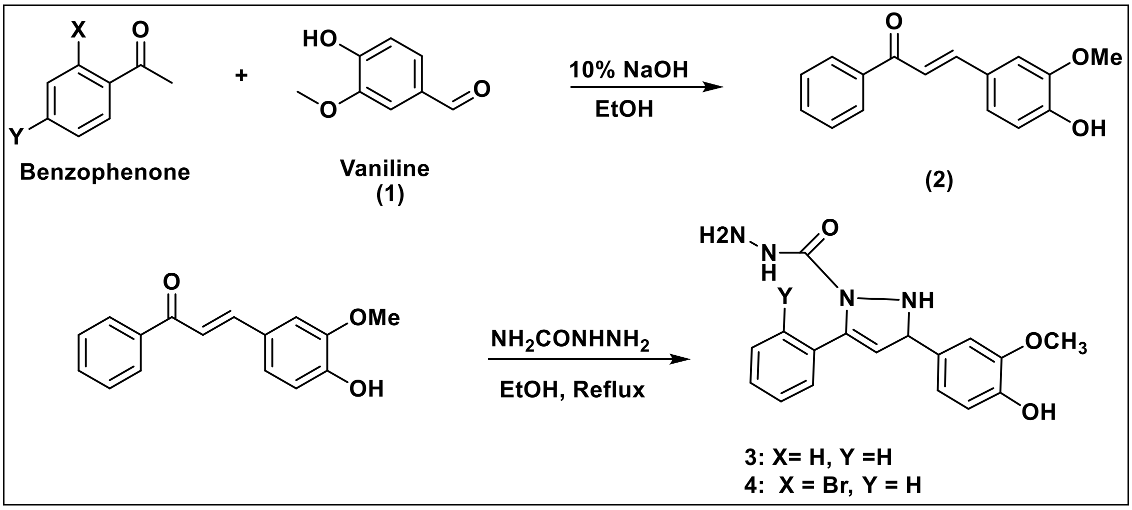


3.4 pyrazole with semicarbazide derivatives

The process of preparing pyrazole with semicarbazide derivatives involves a two-step process. In the first step, chalcone 2 was prepared from the reaction of benzophenone or 4-bromobenzophenone and vanillin in an alkaline medium as shown in Figure 3.18. In the second step Chalcone 2 was reacted with semicarbazide to form the final product.

Figure 3.18

Preparation of pyrazole with semicarbazide derivatives



The yield of the compounds ranged from 80 to 90%. The acetophenone with the bromide showed higher yield, which could be related to the higher reactivity due to the formation of more stable enolate. The proton NMR Figure 3.19 (appendix A) and the IR results Figure 3.20 (appendix A) showed the formation of the target compounds. The IR spectra of the compounds showed the presence of N-H stretching band, C=N stretching bands, C=C of aromatic and =C-H vinylic starching bands. The reaction is a condensation reaction shown in Figure 3.21 (appendix A) in the first step an α-H is abstracted from benzophenone, and that creates a nucleophilic center (enolate) which attacks the carbonyl of the aldehyde. Neutralization followed by dehydration produces the target compound.

3.5 Anti-microbial and Alzheimer activity

The compounds were synthesized for two purposes as shown in the introduction section (thesis scope) to evaluate the activity of the compounds as effective drugs against Alzheimer disease; and to evaluate the anti-microbial activities of the compounds against various gram positive and gram negative bacteria.

3.6 Conclusion

In this work, heterocyclic compounds were prepared with various heterocyclic rings were prepared. The heterocyclic rings include oxazine, thiazine, pyrazole, and pyrazole with semicarbazide, phenyl pyrazole, 2-chloro phenyl hydrazine hydrochloride, 2-bromo phenyl hydrazine hydrochloride, and 4-fluoro phenyl hydrazine hydrochloride. The reaction mainly involves a condensation reaction, α-H is extracted from benzophenone, which leads to the synthesis of a nucleophilic center (enolate), which attacks the carbonyl of the aldehyde. Neutralization followed by dehydration leads to the production of the target chalcone which then reacted with various amines to form the target compounds in moderate to excellent yield.

These compounds are expected to have several biological activities, including antimicrobial, anti-Alzheimer's, and anti-depressant, and they have an important role in medicinal and pharmaceutical chemistry. The compounds structures were confirmed by proton nuclear magnetic resonance (NMR) and infrared (IR).

List of abbreviation

Abbreviation	Meaning
AMPA	α-amino-3-hydroxy-5-methyl-4- isoxazole propionic acid
FT-IR	Fourier-Transform Infrared Spectrophotometer
H-NMR	Proton nuclear magnetic resonance
D	Factor dipole moment
NaOH	Sodium hydroxide
CDPPB	3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl) benzamide
PKa	Acid dissociation constant
KSF	Montmorillonite Catalyst Key Success Factor
DNA	Deoxyribonucleic acid
DLA	Dalton's lymphoma
EAC	Ehrich's ascites
CTC	Circulating tumor cells
AD	Alzheimer's disease
APP	Amyloid-beta precursor protein
BACE	β-Site APP-cleaving enzyme
Aβ	Amyloid beta
IC_{50}	Half maximal inhibitory concentration (a measure of the potency of a substance in inhibiting a specific biological or biochemical function).
HERG	human ether-a-go-go related gene
P-gp	P-glycoprotein
5-HT1A	hydroxytryptamine 1A receptor
SSRI	Selective Serotonin Reuptake Inhibitor
α1	alpha-1
SAR	Structure-Activity Relationship
MAO-A	Monoamine oxidase -A
MAO-B	Monoamine oxidase -B
M1	Classified as a powerful and completely selective agonist of M1-positive allosteric rates.
RAGE	Receptors for advanced glycation end products
AChE	Acetylcholinesterase
α7 nAChR	Alpha7 nicotinic acetylcholine receptor
PAMs	Positive allosteric modulators
nAChRs	Inhibitors nicotinic acetylcholine receptor
MAO	Monoamine oxidase
NMR	Nuclear magnetic resonance
mp	Melting point
TLC	Thin layer chromatography

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Appendices

Appendix A

Figures

Figure 1.3

Other methods of synthesis imidazole

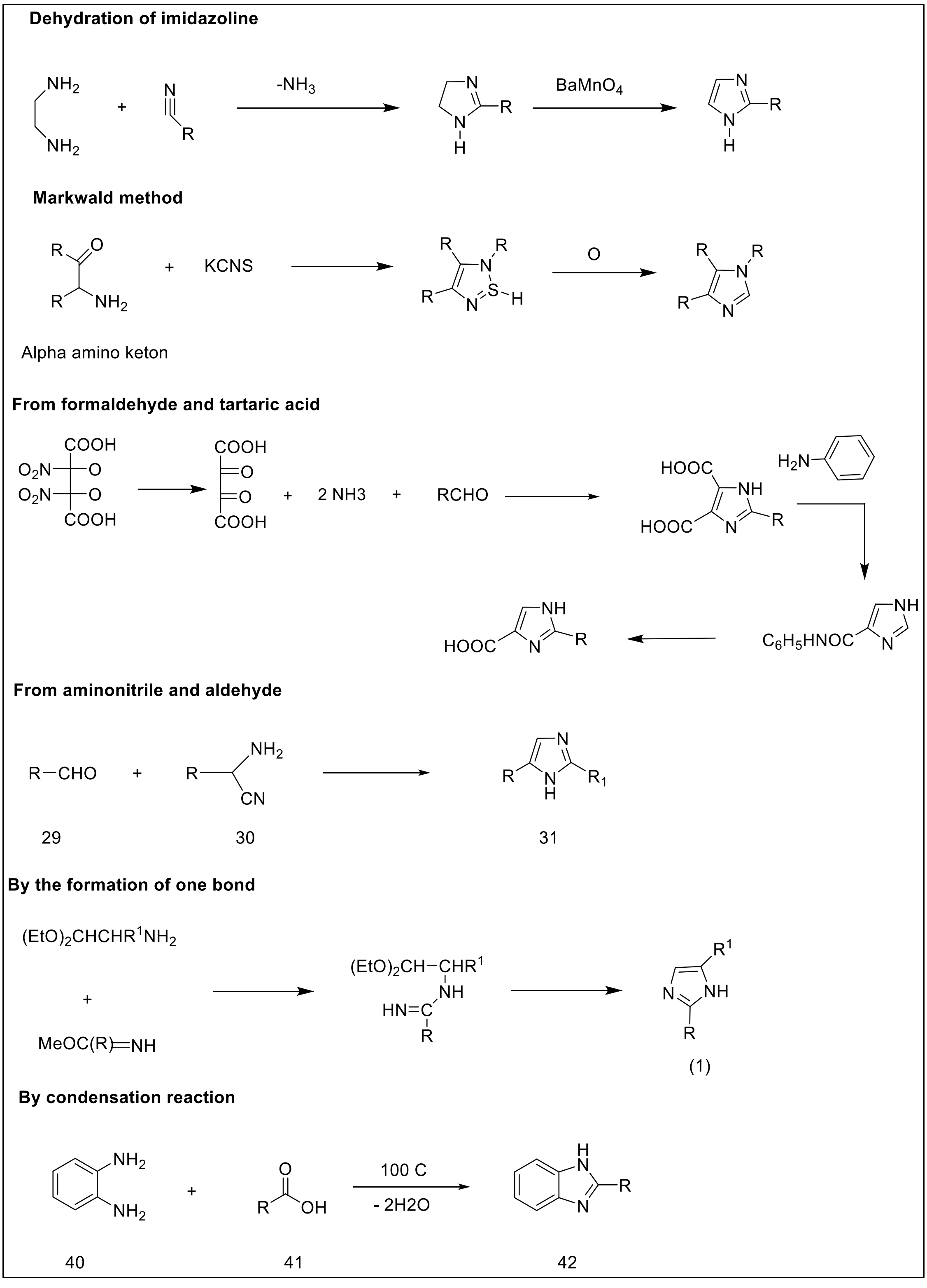


Figure 1.5

Other methods of synthesis of oxazine

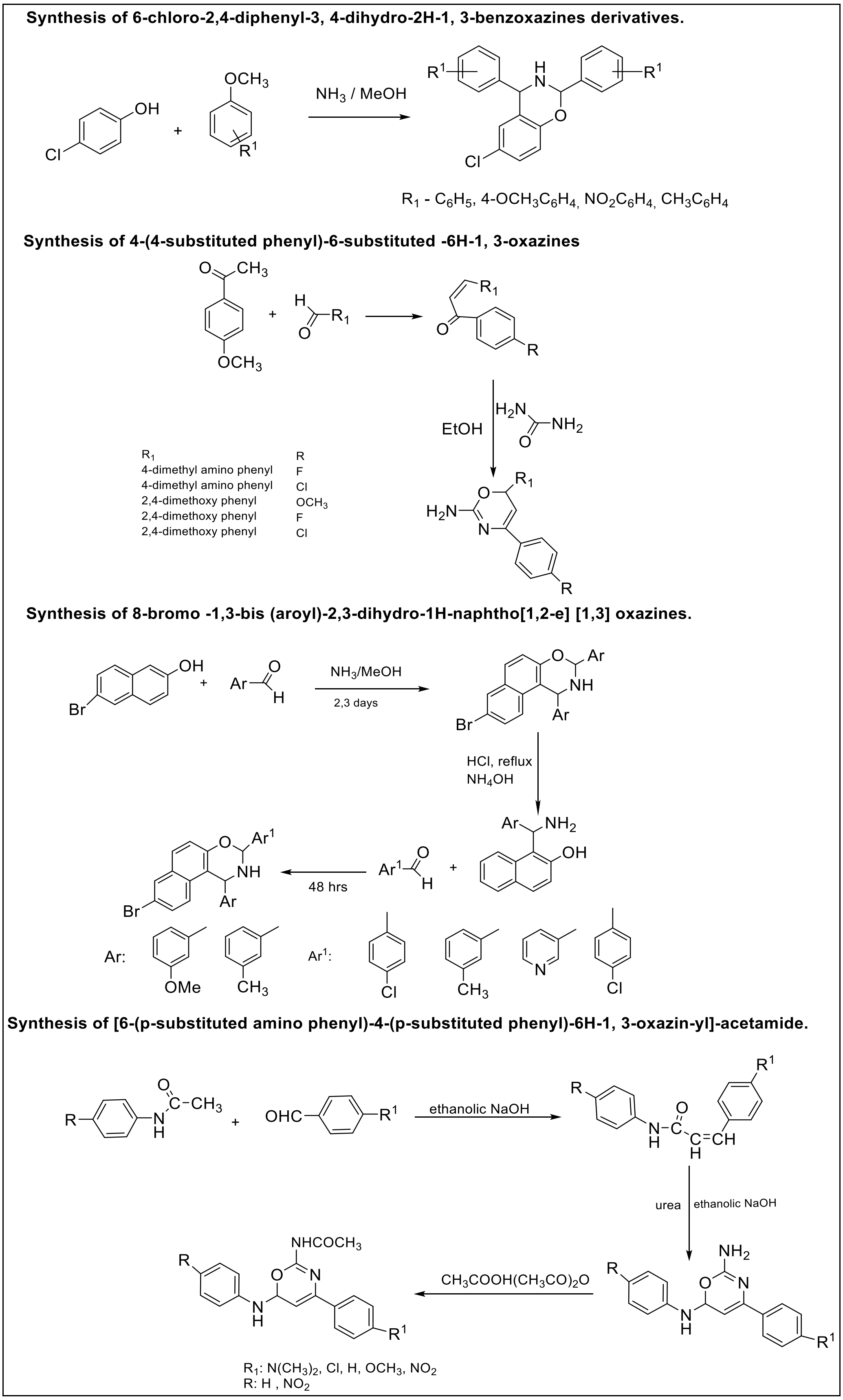
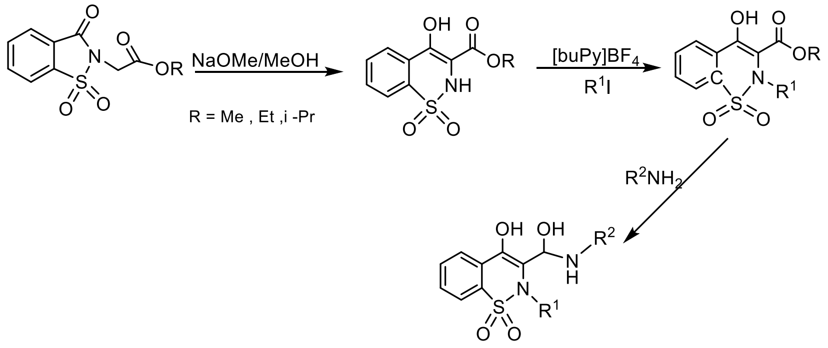


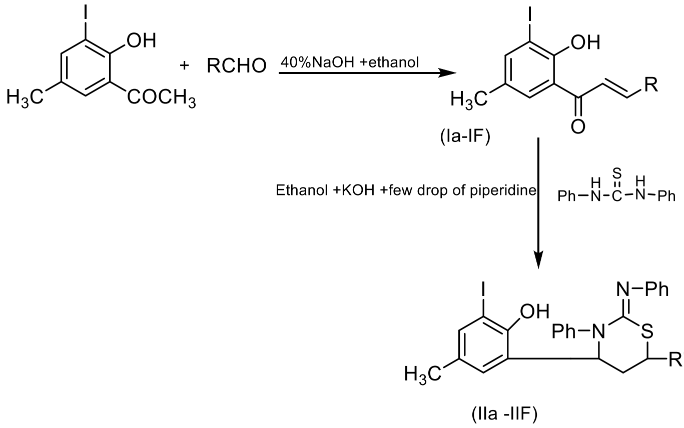
Figure 1.7

Other methods of preparation of various thiazine

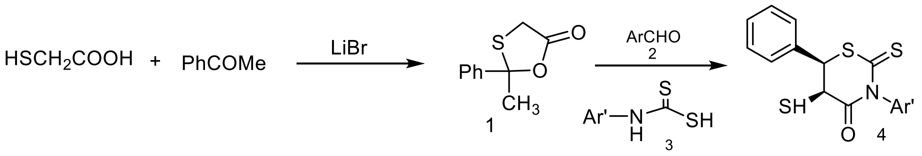
Synthesis of different N-[(1E)-aryl methylidene]-4-hydroxy 2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxides derivatives



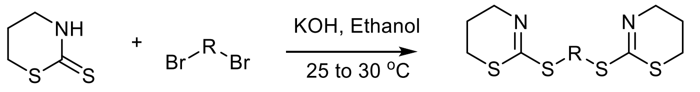
Diphenyl-thiourea reagent



Three-component expeditious method for the synthesis of 1,3-thiazine derivatives



Synthesis of multithioether derivatives of thiazine



R= -CH$_2$CH$_2$- , -CH$_2$CH$_2$CH$_2$- , -CH$_2$CH$_2$CH$_2$CH$_2$-

Synthesis of 1,4-thiazine derivatives from alpha-bromopropenone

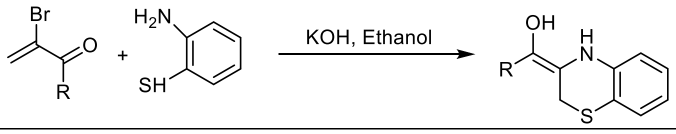


Figure 1.9

Other methods of preparation of pyrazole (a)

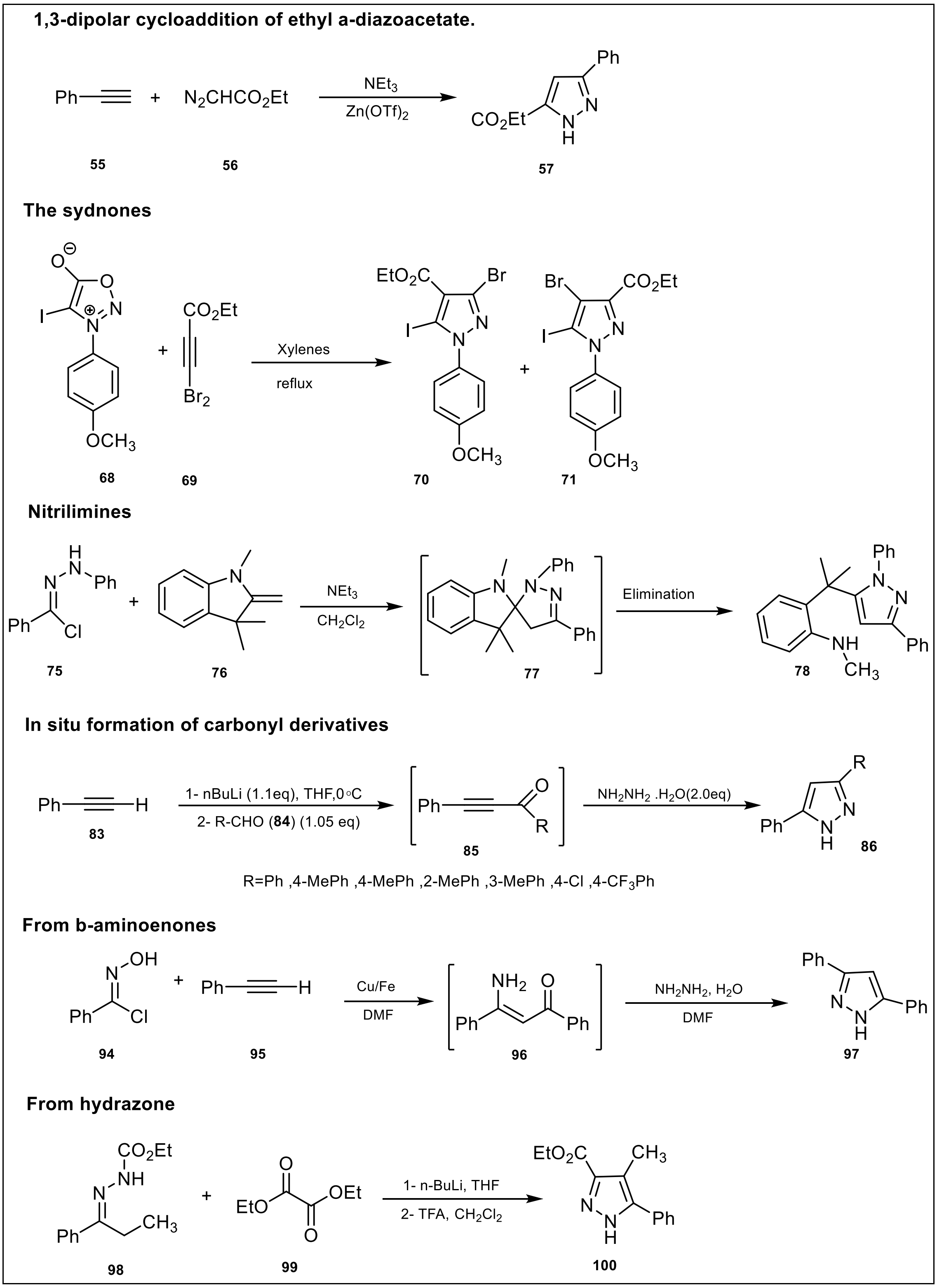


Figure 1.10

Other methods of preparation of pyrazole (b)

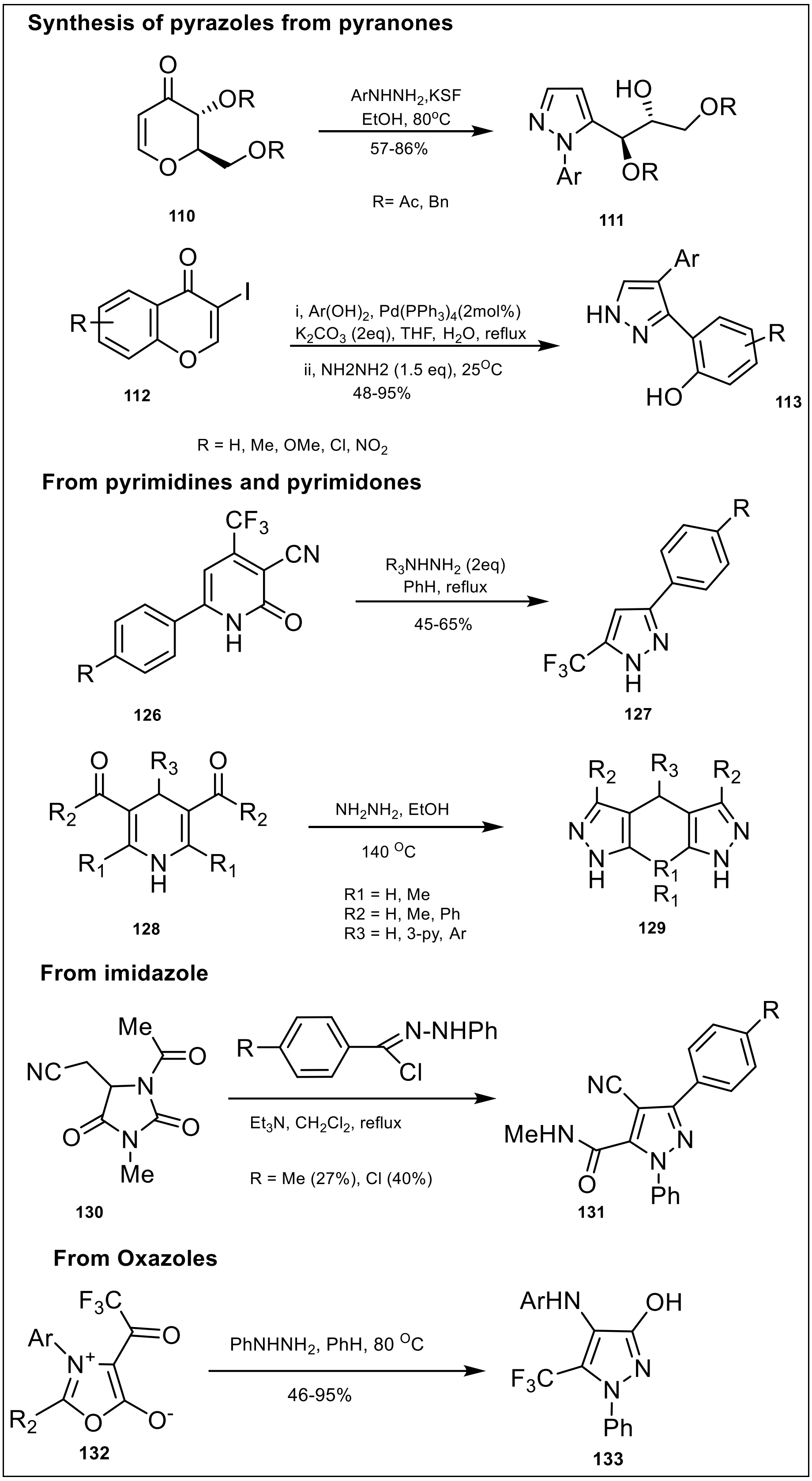


Figure 1.11

Other methods of preparation of pyrazole (c)

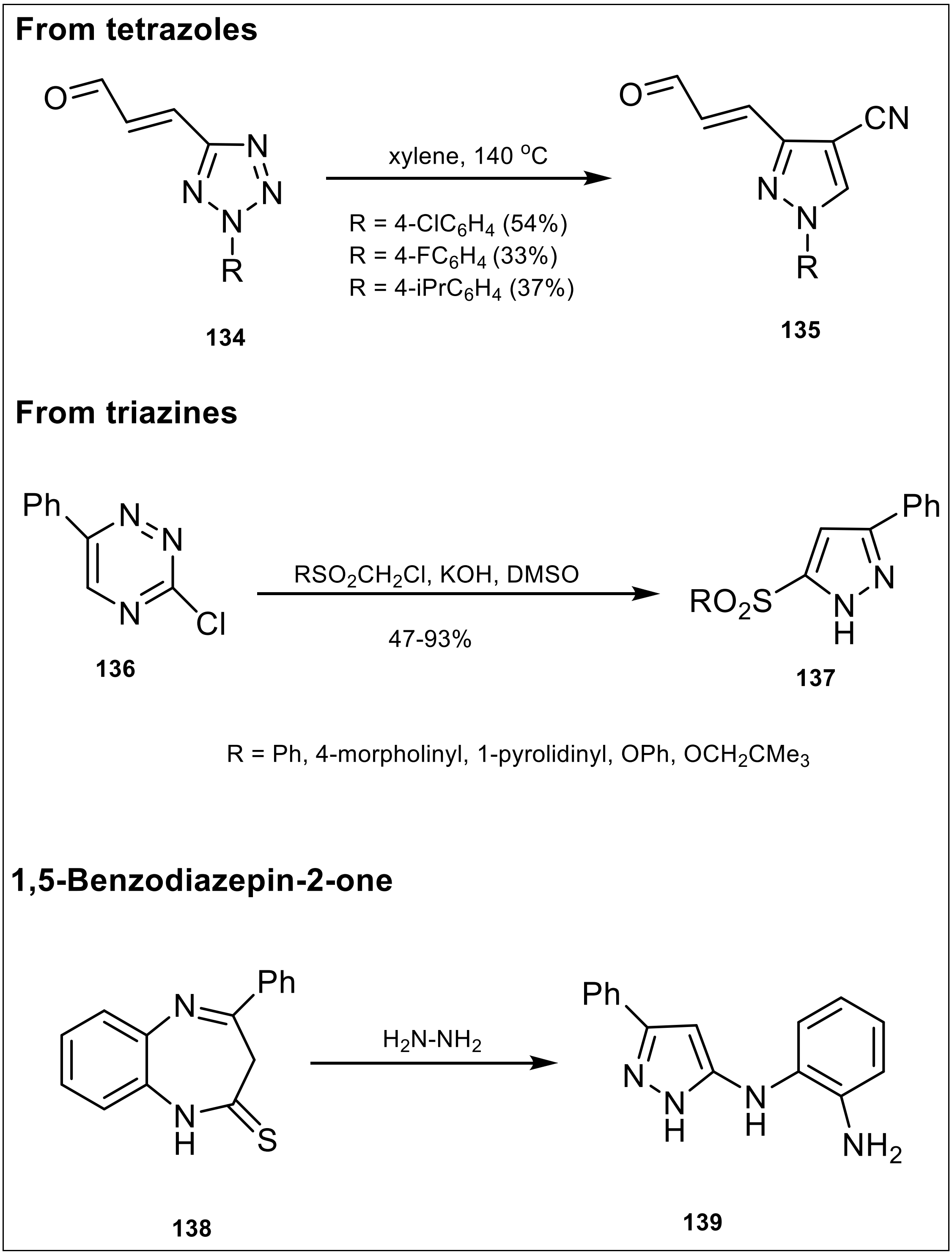
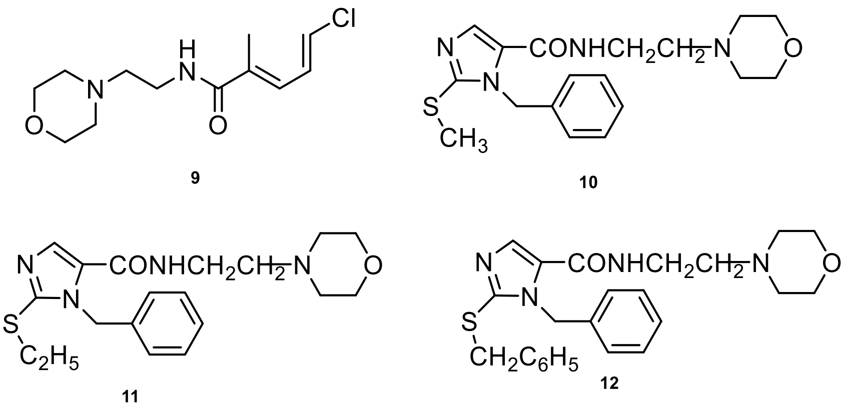


Figure 1.12

Various biological activities of various heterocycles for imidazole

Imdazoles as anti-depressants



Anti-cancer and anti-microbial compounds with imidazole moiety

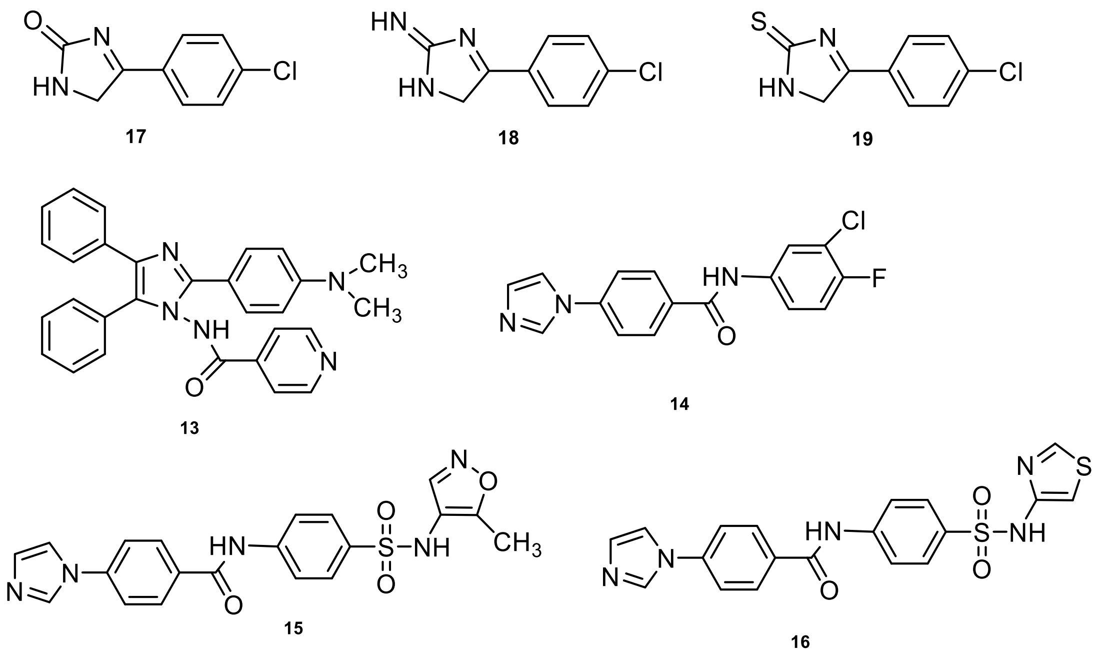


Figure 1.13

Examples of oxazine compounds various biological activities for oxazine

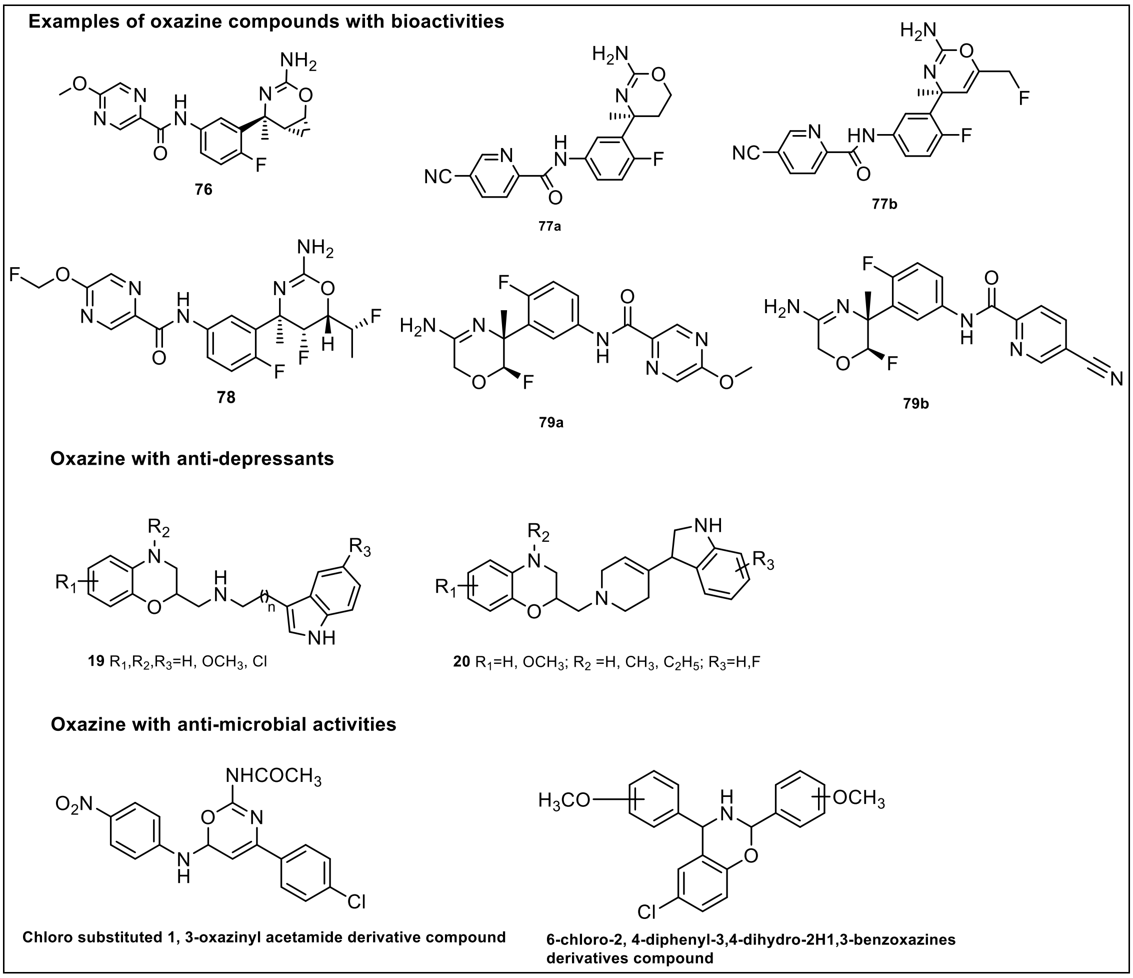
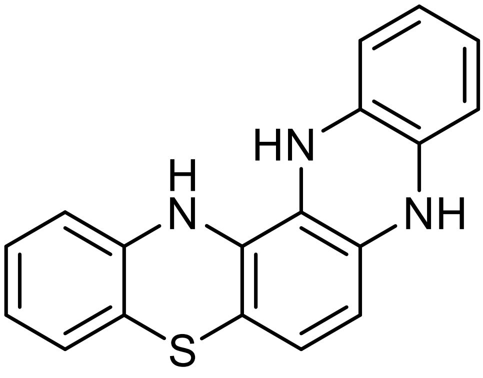


Figure 1.14

A pentacyclic phenothiazine compound for nerve anesthesia

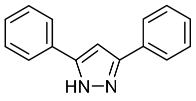


(88)

Figure 1.15

Pyrazole derivatives with anti-alzheimer activity and Amino acid ester functional pyrazole compounds

Pyrazole derivatives with anti-azheimer activity.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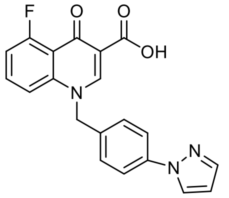
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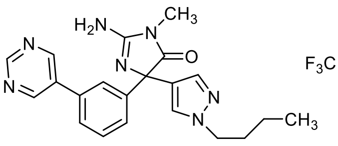
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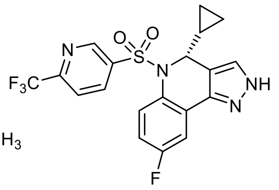
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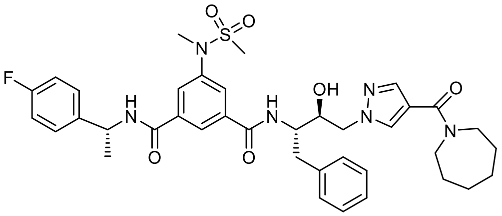
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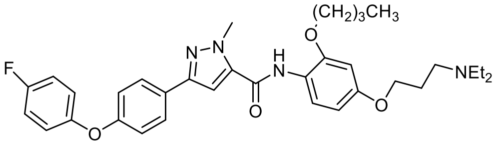
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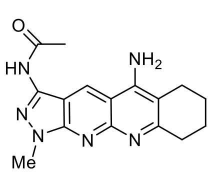
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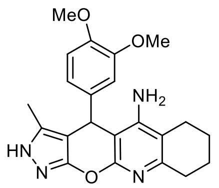
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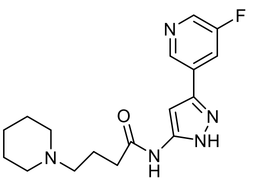
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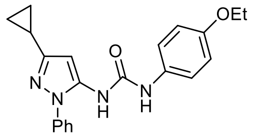
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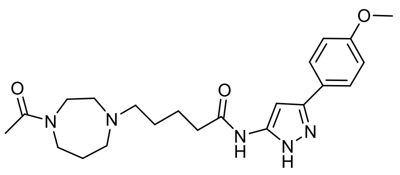
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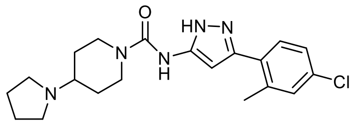
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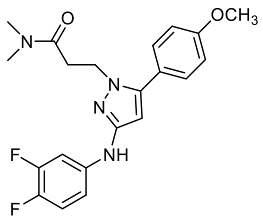
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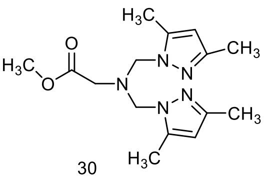
Amino acid ester functional pyrazolyl compounds.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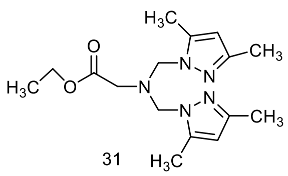
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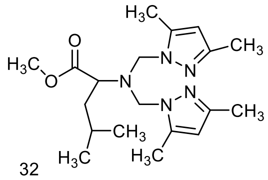
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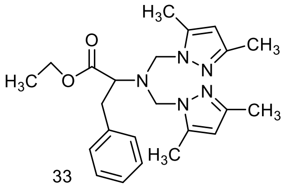
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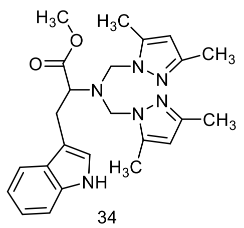
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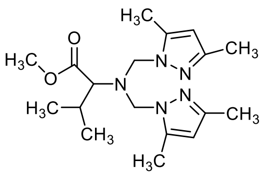
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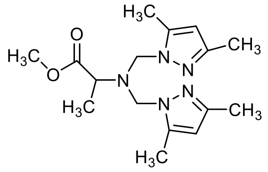
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Figure 1.16

synthesis of a pyrazole compound

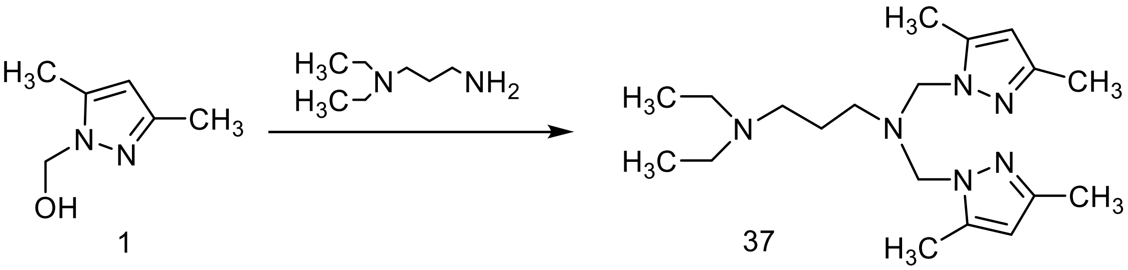

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Figure 1.17

The pyrazole derivatives screened

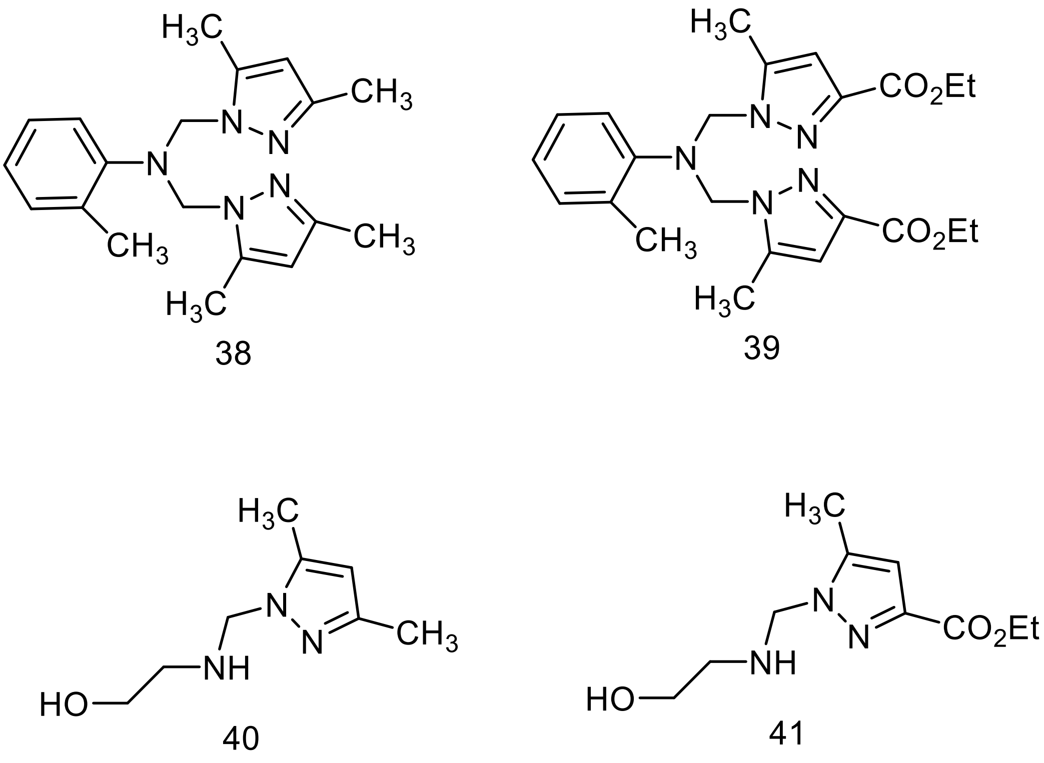

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Figure 1.18

Molecular structure for the bidentate compounds tested

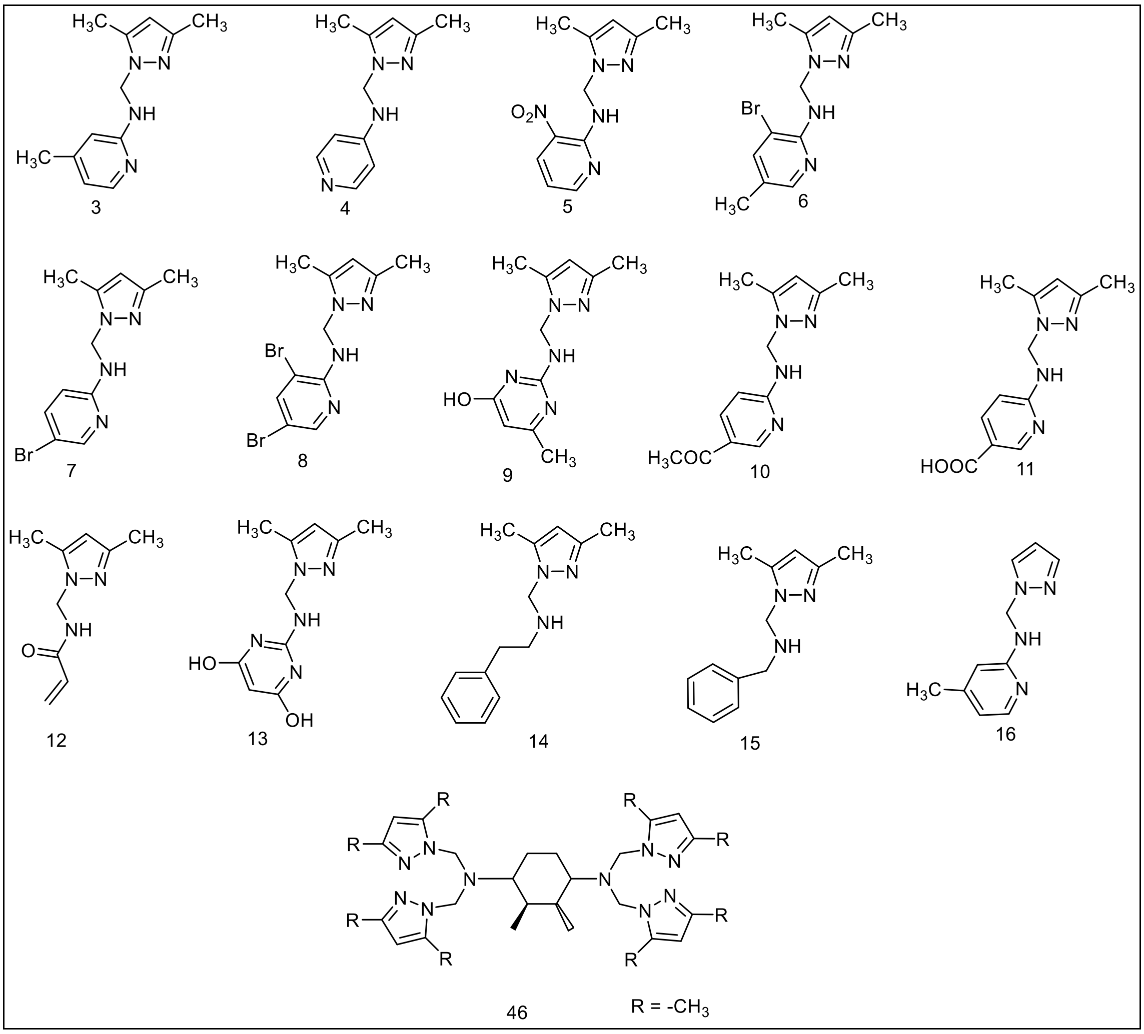


Figure 1.19

Structures of pyrazole-mediated anti-depressants

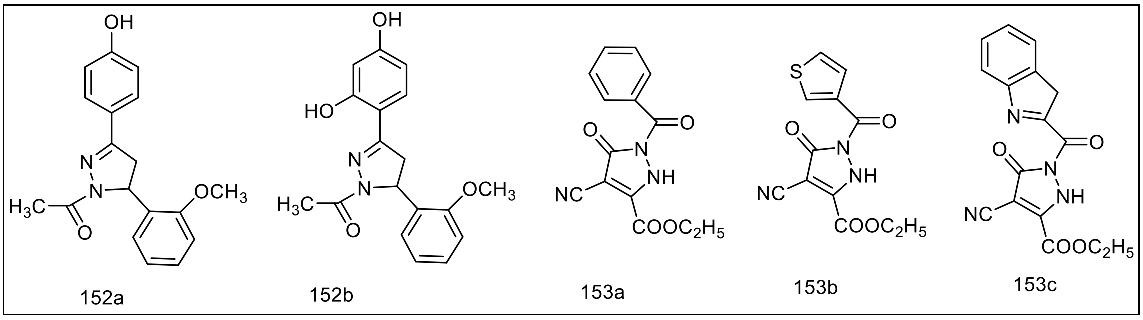
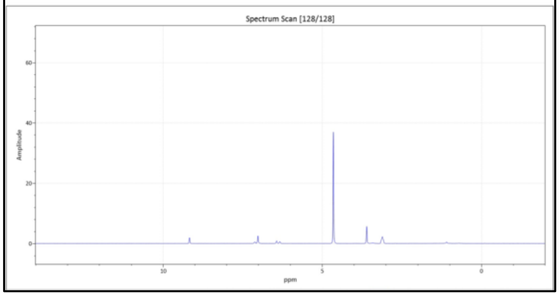


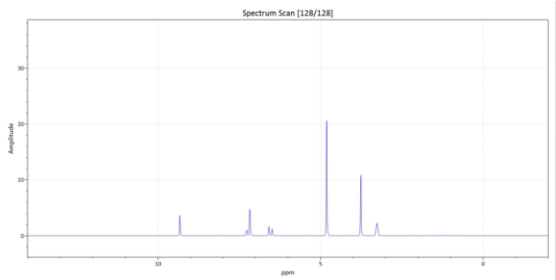
Figure 3.3

Proton NMR of oxazine derivatives

4-(2-amino-6-phenyl-6H-1,3-oxazin-4-yl)-2-methoxyphenol (4)



4-(2-amino-6-(2-bromophenyl)-6H-1,3-oxazin-4-yl)-2-methoxyphenol (5)



4-(2-amino-6-(2,4-dibromophenyl)-6H-1,3-oxazin-4-yl)-2-methoxyphenol (6)

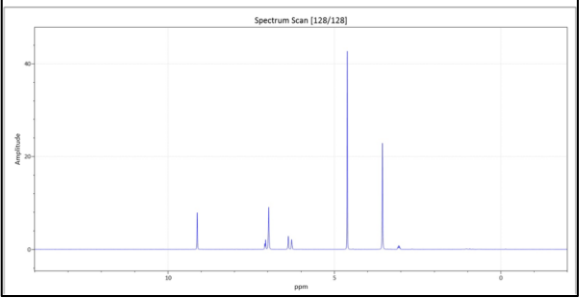
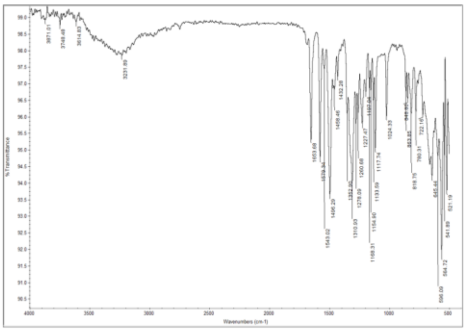


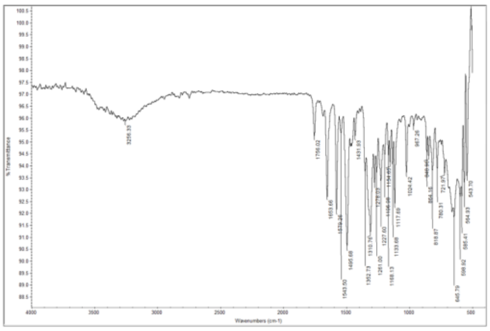
Figure 3.4

IR spectrum of oxazine derivatives

4-(2-amino-6-phenyl-6H-1,3-oxazin-4-yl)-2-methoxyphenol (4)



4-(2-amino-6-(2-bromophenyl)-6H-1,3-oxazin-4-yl)-2-methoxyphenol (5)



4-(2-amino-6-(2,4-dibromophenyl)-6H-1,3-oxazin-4-yl)-2-methoxyphenol (6)

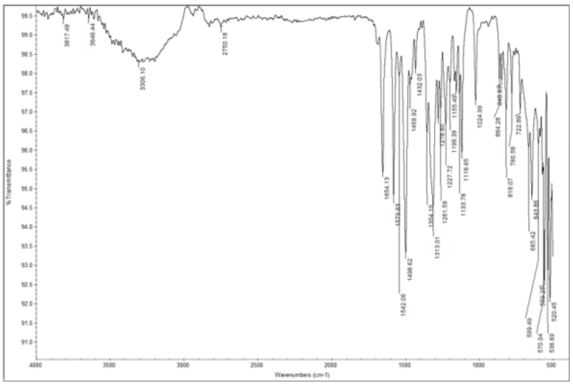


Figure 3.5

Preparation of thiazine derivatives

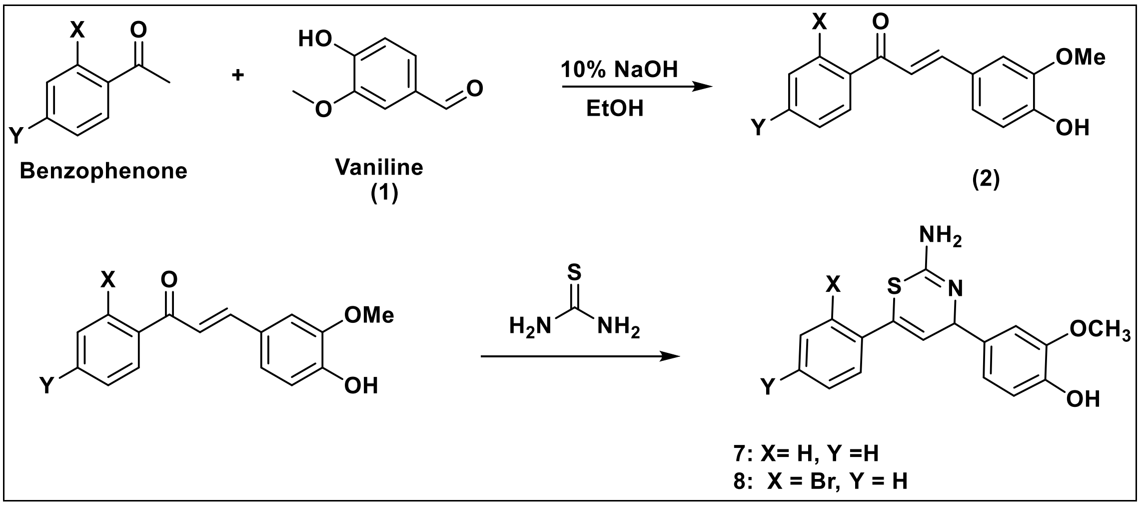


Figure 3.6

Proton NMR of thiazine derivatives

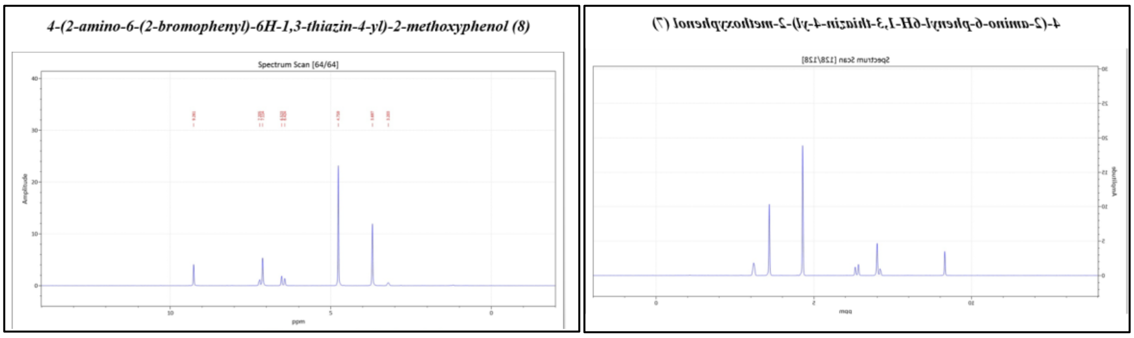


Figure 3.7

IR spectrum of thiazine derivatives

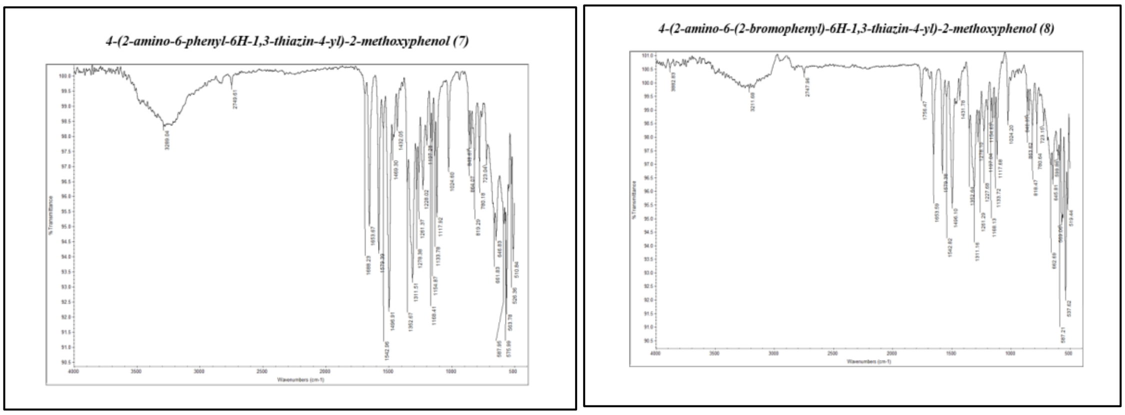
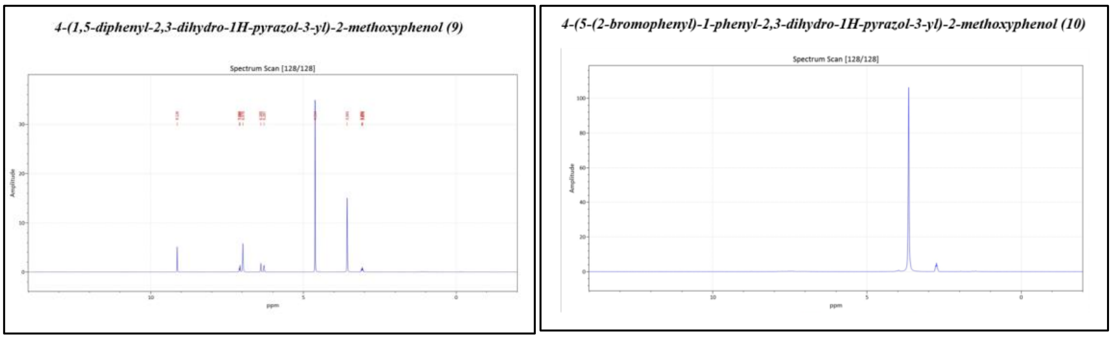


Figure 3.9

Proton NMR of phenyl pyrazole derivatives

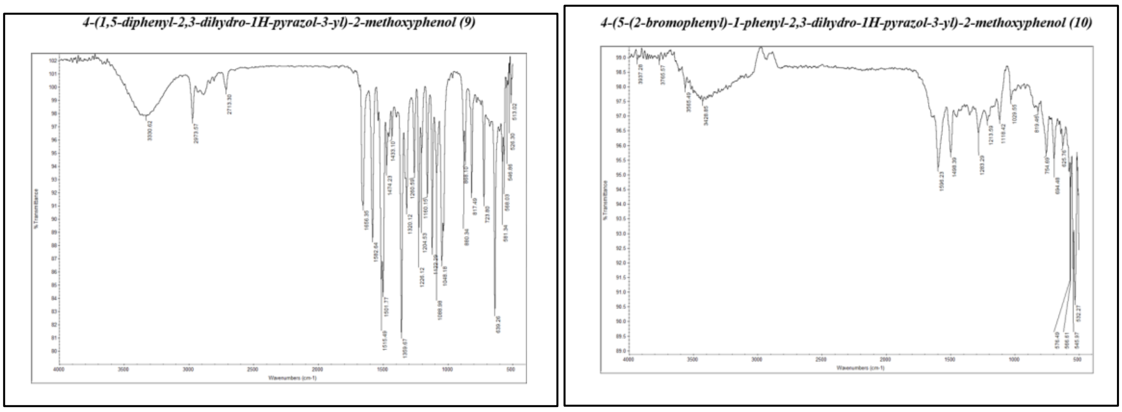


4-(1,5-diphenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (9)

4-(5-(2-bromophenyl)-1-phenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (10)

Figure 3.10

IR spectrum of phenyl pyrazole derivatives

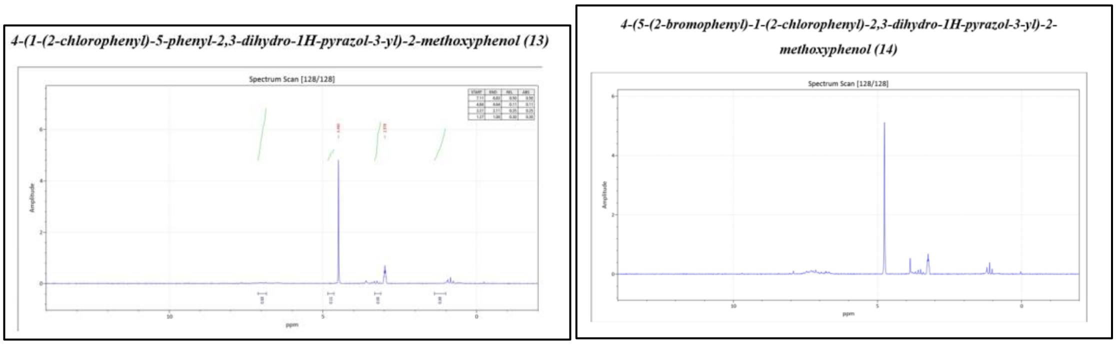


4-(1,5-diphenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (9)

4-(5-(2-bromophenyl)-1-phenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (10)

Figure 3.11

Proton NMR of 2-chloro phenyl hydrazine hydrochloride derivatives

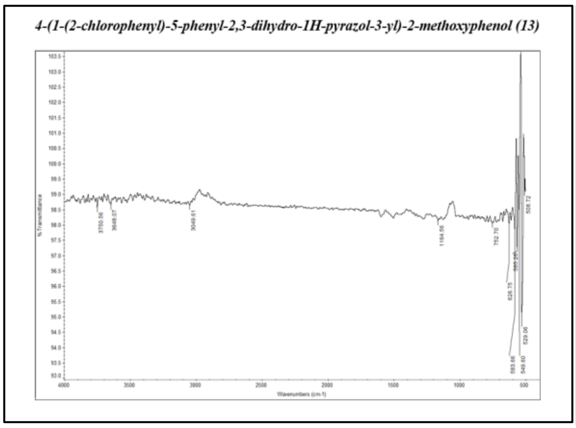


4-(1-(2-chlorophenyl)-5-phenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (13)

4-(5-(2-bromophenyl)-1-(2-chlorophenyl)-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (14)

Figure 3.12

IR spectrum of 2-chloro phenyl hydrazine hydrochloride derivatives


4-(1-(2-chlorophenyl)-5-phenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (13)

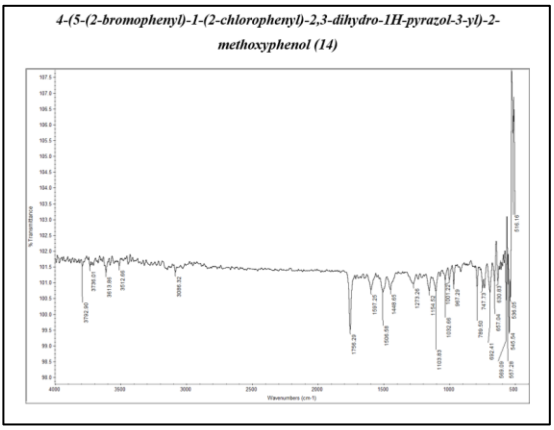
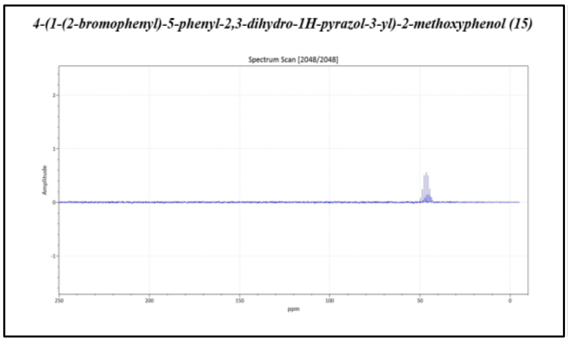

4-(5-(2-bromophenyl)-1-(2-chlorophenyl)-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (14)

Figure 3.13

Proton NMR of 2-bromo phenyl hydrazine hydrochloride derivatives


4-(1-(2-bromophenyl)-5-phenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (15)

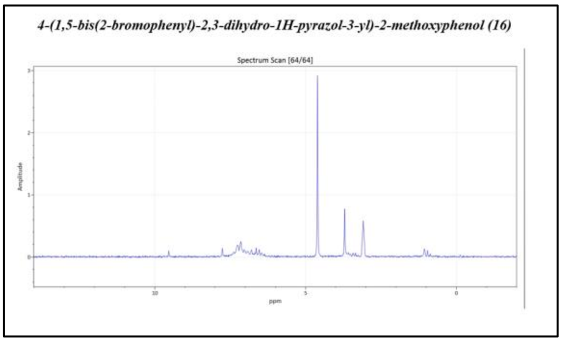
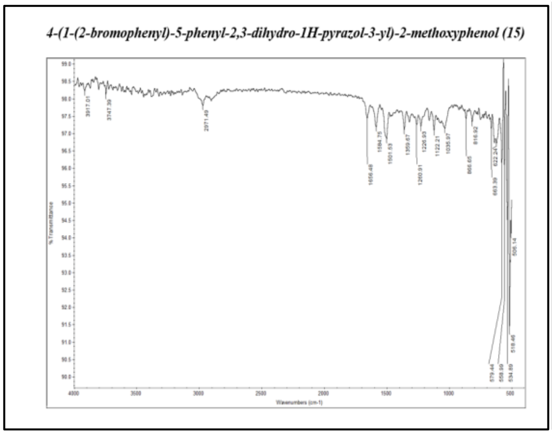

4-(1,5-bis(2-bromophenyl)-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (16)

Figure 3.14

IR spectrum of 2-bromo phenyl hydrazine hydrochloride derivatives


4-(1-(2-bromophenyl)-5-phenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (15)

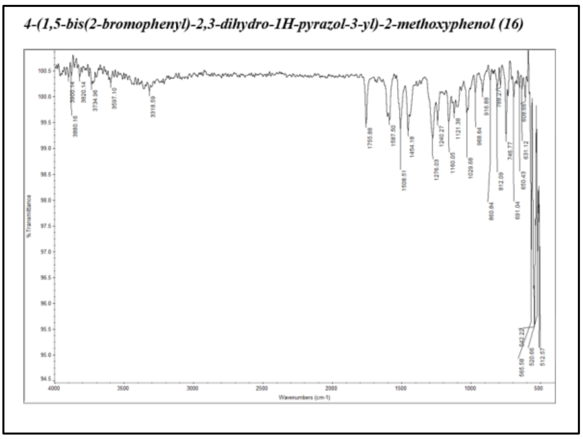
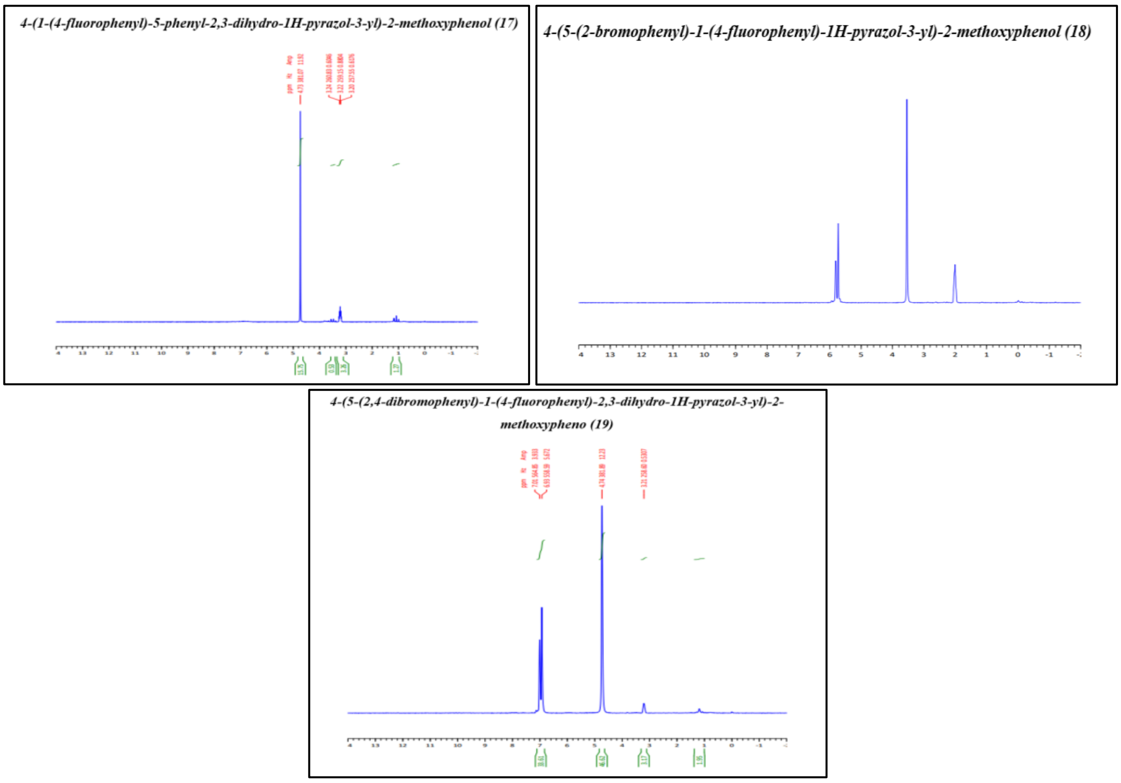

4-(1,5-bis(2-bromophenyl)-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (16)

Figure 3.15

Proton NMR of 4-flouro phenyl hydrazine hydrochloride derivatives



4-(1-(4-fluorophenyl)-5-phenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (17)

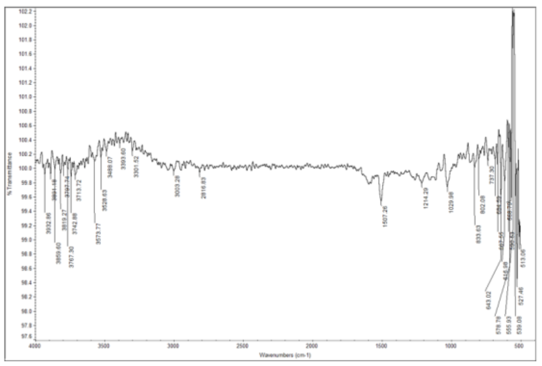
4-(5-(2-bromophenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-2-methoxyphenol (18)

4-(5-(2,4-dibromophenyl)-1-(4-fluorophenyl)-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxypheno (19)

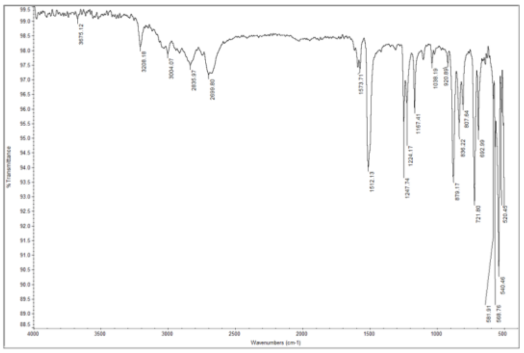
Figure 3.16

IR spectrum of 4-flouro phenyl hydrazine hydrochloride derivatives

4-(1-(4-fluorophenyl)-5-phenyl-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxyphenol (17)



4-(5-(2-bromophenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-2-methoxyphenol (18)



4-(5-(2,4-dibromophenyl)-1-(4-fluorophenyl)-2,3-dihydro-1H-pyrazol-3-yl)-2-methoxypheno (19)

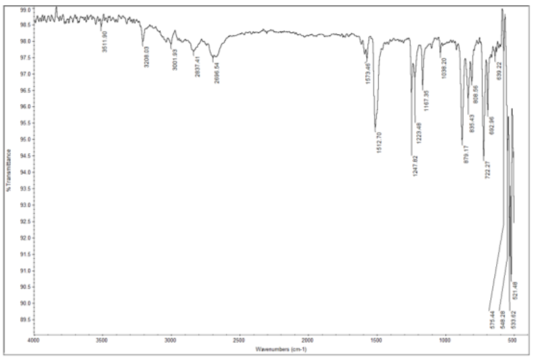
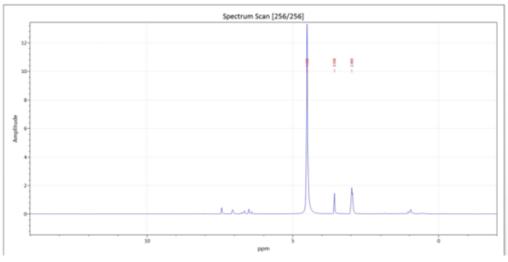


Figure 3.19

Proton NMR of pyrazole with semicarbazide derivative

3-(4-hydroxy-3-methoxyphenyl)-5-phenyl-2,3-dihydro-1H-pyrazole-1-carbohydrazide (11)



5-(2-bromophenyl)-3-(4-hydroxy-3-methoxyphenyl)-1H-pyrazole-1-carbohydrazide (12)

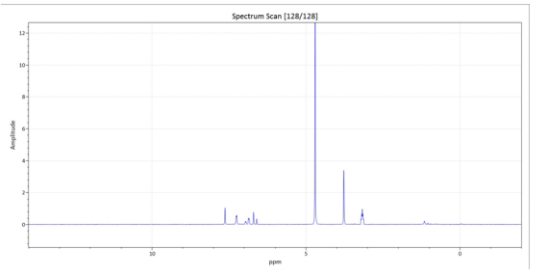
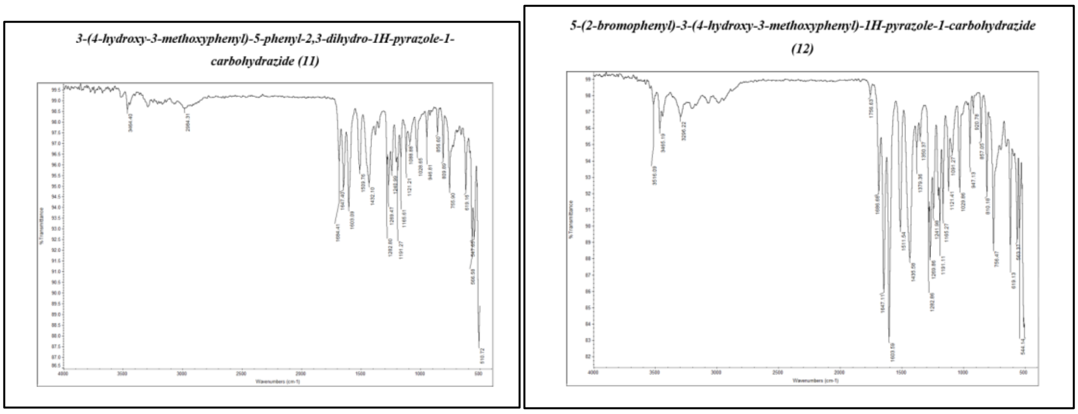


Figure 3.20

IR spectrum of pyrazole with semicarbazide derivative

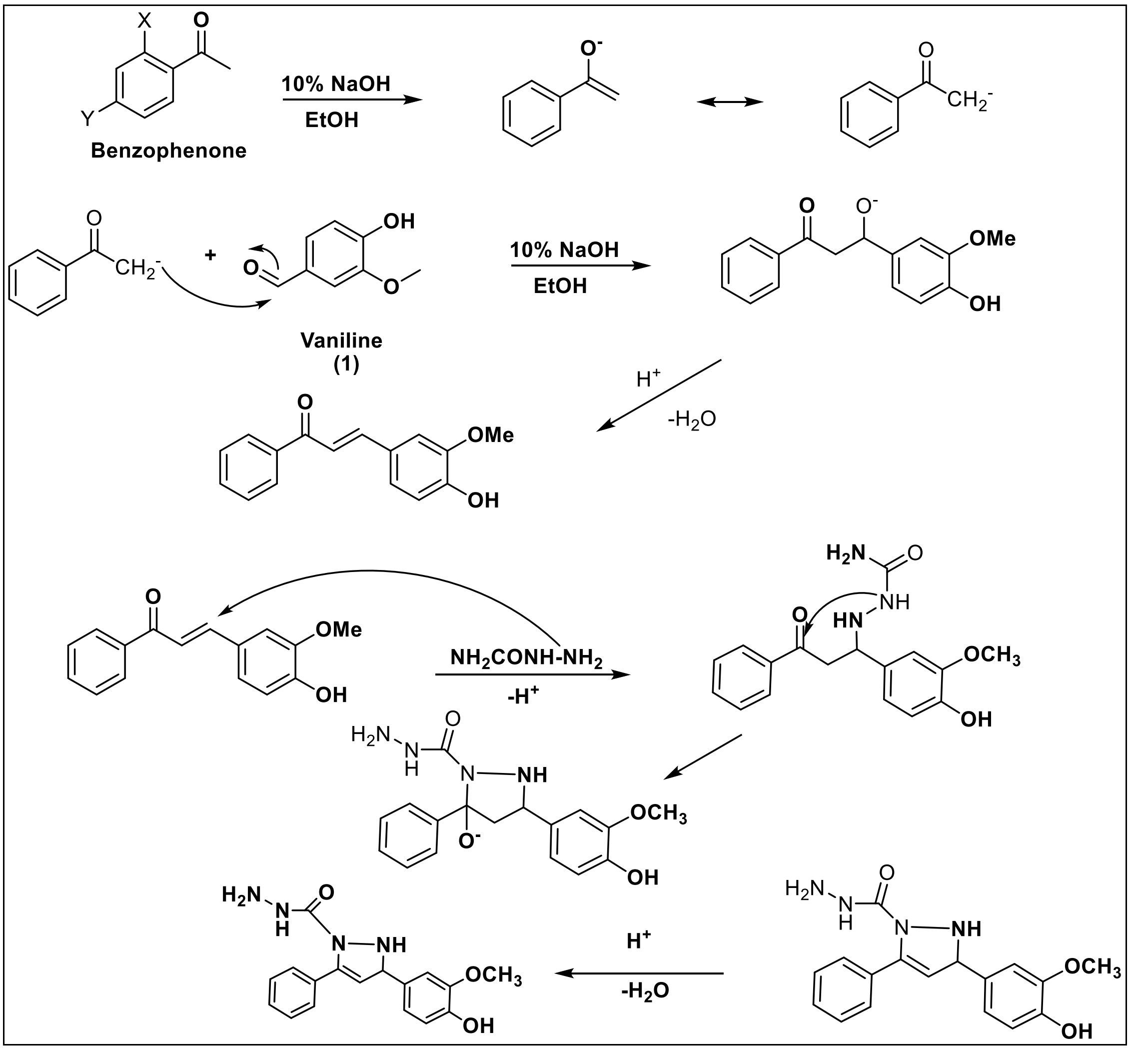


3-(4-hydroxy-3-methoxyphenyl)-5-phenyl-2,3-dihydro-1H-pyrazole-1-carbohydrazide (11)

5-(2-bromophenyl)-3-(4-hydroxy-3-methoxyphenyl)-1H-pyrazole-1-carbohydrazide (12)

Figure 3.21

Mechanism pyrazole with semicarbazide derivative condensation reaction



جامعة النجاح الوطنية
كلية الدراسات العليا

الثيازين والأوكسازين والبيرازول المعتمد على الفانيلين كمضادات غير تنافسية لمستقبلات أمبا

إعداد
عطاء جاسر عرفات عوادة

إشراف
أ. د. عثمان حامد
د. محمد قنيبي

قدمت هذه الرسالة استكمالا لمتطلبات الحصول على درجة الماجستير في الكيمياء، من كلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس – فلسطين.

2024

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الملخص

حظيت المشتقات الحلقية غير المتجانسة باهتمام كبير من الباحثين لأنها مكونات مهمة للمركبات الطبيعية والأدوية الاصطناعية، كما أنها تعتبر آمنة ووفيرة ومتوفرة بتكلفة معقولة. يهدف هذا العمل إلى إنشاء دواء مضاد لمرض الزهايمر ودواء مضاد للميكروبات بكفاءة أكبر وسمية أقل استنادًا إلى مشتقات الحلقية غير المتجانسة بما في ذلك مشتقات الأوكسازين والثيازين والبيرازول، وبيرازول فينيل، وبيرازول مع سيميكاربازيد، و2-كلورو فينيل هيدرازين هيدروكلوريد، و2-برومو. فينيل هيدرازين هيدروكلوريد، 4-فلوروفينيل هيدرازين هيدروكلوريد. الهدف الرئيسي من هذه الدراسة هو تصنيع دواء من المشتقات المذكورة أعلاه بهدف التخفيف من مرض الزهايمر وعلاجه، كما أن آثار الدواء الجانبية قليلة جداً. ولتحقيق هدف الدراسة تم تصنيع عدة مركبات مشتقة من أوكسازين، ثيازين، بيرازول، فينيل بيرازول، بيرازول مع سيمي كاربازيد، 2-كلورو فينيل هيدرازين هيدروكلوريد، 2-برومو فينيل هيدرازين هيدروكلوريد، 4-فلور فينيل هيدرازين هيدروكلوريد، وتم تصنيع تم إجراء التوليف في عملية من خطوتين. ويعتبر رد فعل التكثيف. في الخطوة الأولى، يتم تحضير الجالكون من تفاعل البنزوفينون والفانيلين في وسط قلوي. يتم استخراج α-H من البنزوفينون، وهذا يخلق مركزًا محبًا للنواة (إينولات) يهاجم كربونيل الألدهيد. يؤدي التحييد الذي يتبعه الجفاف إلى إنتاج المركب المستهدف.

تم التعرف على تركيب المركبات المحضرة بواسطة FT-IR ومطياف .H-NMR وتراوحت إنتاجية المركبات من 80 إلى 90%. أظهرت المركبات نشاطًا واضحًا في علاج مرض الزهايمر، حيث تحتوي

على مضادات غير تنافسية لمستقبلات AMPA ، مما يقلل من لويحات الأميلويد، ويقلل من تشابكات تاو، ويحسن وظائف المخ.

وخلصت الدراسة إلى أن المركبات تم تصنيعها بنجاح بطريقة تفاعل التكثيف وتم تقييم نشاطها المضاد لمرض الزهايمر. لقد أظهروا نتائج واعدة. لا يزال هناك المزيد من العمل الذي يتعين القيام به لتوضيح بنية وأنشطة المشتقات الدورية ضد مرض الزهايمر.

الكلمات المفتاحية: الزهايمر، تفاعل التكثيف، الحلقات الحلقية غير المتجانسة، أوكسازين، الثيازين، بيرازول، فينيل بيرازول، بيرازول مع سيمي كربازيد، 2-كلورو فينيل هيدرازين هيدروكلوريد، 2-برومو فينيل هيدرازين هيدروكلوريد، 4-فلور فينيل هيدرازين هيدروكلوريد.