An-Najah National University

Faculty of Graduate Studies

SYNTHESIS AND BIOLOGICAL EVALUATION OF COPPER COMPLEXES WITH ORGANIC LIGANDS BASED ON (*E*)-3-(4-(DIMETHYLAMINO)PHENYL)-1-(PYRIDIN-2-YL)PROP-2-EN-1-ONE

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Dedication

To my parents

To my wife

To my brothers

To my sister

To my son

And my friends

I dedicate this work

Acknowledgment

Praise and thanks to my God, the most merciful for assisting and directing me to the right path, without his help my effort would have gone astray.

Special thanks are due to my research supervisors, Dr. Nawaf Al-Maharik, Prof. Ismail Warad for the opportunity to work with them in their research group.

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My family and wife have my sincere gratitude and appreciation for their assistance, prayers, and support during my studies.

Declaration

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

SYNTHESIS AND BIOLOGICAL EVALUATION OF COPPER COMPLEXES WITH ORGANIC LIGANDS BASED ON (*E*)-3-(4-(DIMETHYLAMINO) PHENYL)-1-(PYRIDIN-2-YL)PROP-2-EN-1-ONE

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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Abstract

Background: Chalcone is an organic compound found in a variety of plants and fruits; it is classified as a phytochemical, specifically a polyphenol. Chalcone is important in the synthesis of many compounds, especially polyphenol derivatives. In addition, it has great medical importance as it is used as an antibiotic to treat cancer. What distinguishes it is that it is non-toxic or has very little toxicity towards normal cells, depending on the source of synthesis. Organic compounds and chalcones, in particular, with metals form complexes with greater activity from their origin; these properties can be used in many fields.

Objectives: The thesis aims to synthesize new organic compounds and their copper complexes formed based on (*E*)-3-(4-(dimethylamino)phenyl)-1-(pyridin-2-yl)prop-2-en-1-one (**102**), then evaluate them biologically.

Methodology: Under basic conditions, the condensation reaction was used to prepare compounds. Chalcone (**102**) was prepared and then reacted with compounds (**106**, **108**, **110**, **112** and **Dichloromethane**) to prepare organic compounds (**105**, **107**, **109**, **111**, and **118**). It then reacted with a solution of copper (II) to prepare the copper complexes. The reactions were monitored using TLC. The prepared compounds were purified and then characterized using NMR, IR, and UV/VIS spectroscopies. In the end, their toxic activity was examined on MEF-1 and B16F10 cells.

Results: The results show that most of the compounds possess pigment properties. Chalcone (**102**) and its complexes were found to be more bioactive. While the other compounds were toxic to normal cells.

Conclusion:

- Chalcone (**102**) and compound (**105**) are produced in basic conditions, but (**107**, **109**, and **111**) require acidic conditions.
- The interaction of dichloromethane with chalcone (**102**) has been confirmed.
- All organic compounds that are synthesized have a conjugated chemical system that enables them to bind and interact with copper II, normal cells, and cancer cells.
- The best anticancer is chalcone (**102**) and its copper complex (**113**).
- The activity of copper complexes is greater than that of their constituent organic ligands.
- This research advances our understanding of the reaction conditions required for the synthesis of the aforementioned compounds.

Keywords: Chalcone, Chemical synthesis, Organometallic Complexes', Copper (II) complexes, Cancer, Anticancer.

Chapter One

Introduction

1.1 Phytochemicals

Phytochemicals that are found in phyto-foods and have some nutritional value, particularly in connection to maintaining human health and preventing diseases, are referred to as phytonutrients. Their frequent and sufficient use may provide protection against serious chronic diseases, such as cancer, cardiovascular and neurological illnesses [1]. Walnuts, blueberries, carrots, soybeans, tomatoes, and apples are examples of phyto-foods that contain a variety of phytonutrients. More than twenty five thousand phytochemicals have been identified in plant foods, such as polyphenols, anthocyanins, flavonoids, carotenoids, diarylalkanoids, lignans, phenolic acids and coumarins [1].

Non-nutritive substances called phytochemicals have the ability to maintain health and resist future diseases. Since they are not necessary nutrients, the body does not require them to maintain life. The fact that plants create these compounds to defend themselves is well known, but new research has shown that they can also prevents the human body from getting sick and from diseases. Several thousand phytochemicals are known. Lycopene in tomatoes is an example of a well-known phytochemicals [1].

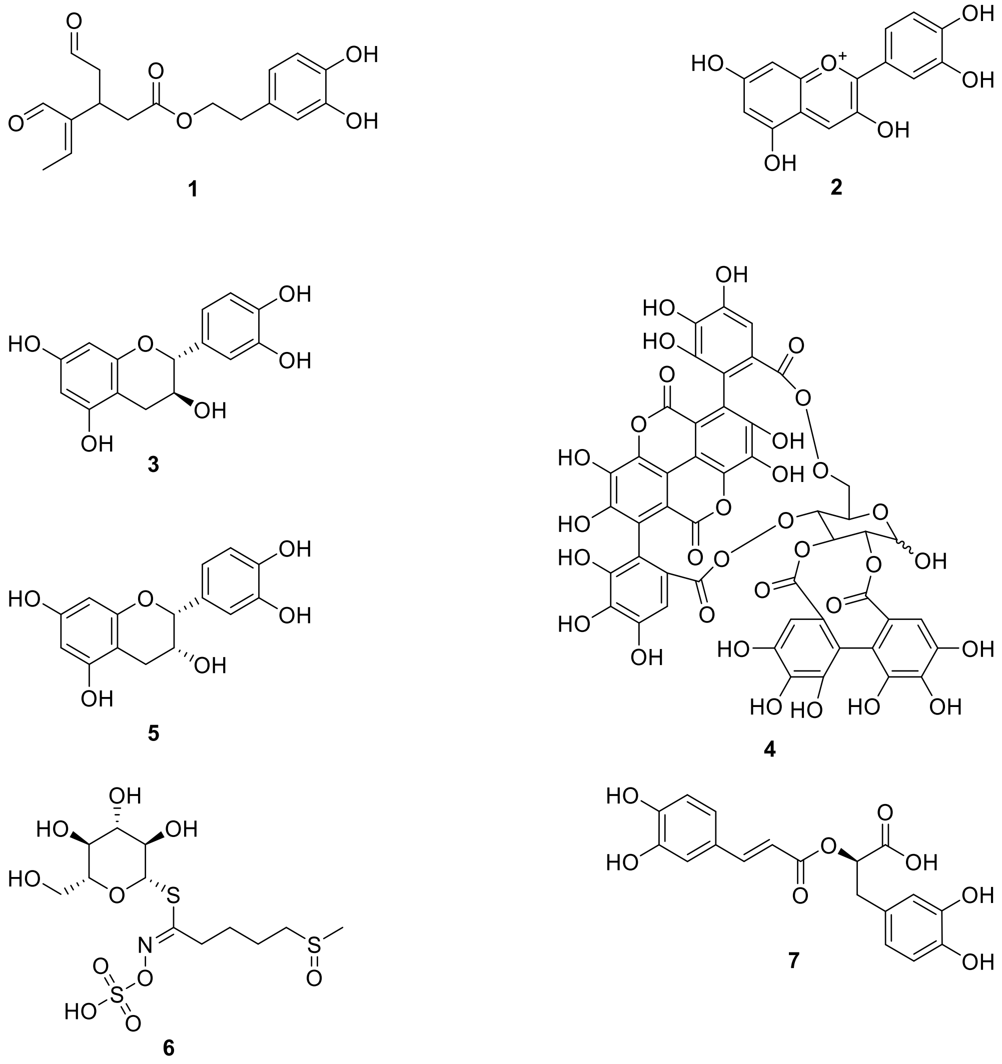
The majority of modern pharmaceuticals and medicines are not derived from plants, but it’s a new compounds made and form by chemical synthesis [1]. Many laboratories started locating plant phytochemicals that may be turned into medicines in the 1980s. Many of the newly identified phytochemicals seem to be cancer, heart disease, and stroke preventatives or treatments [1].

1.2 polyphenols

Polyphenols are naturally synthesized molecules that have many phenolic moieties.[1]. In addition of that this broad category of phytonutrients frequently includes a large variety of phenolic chemicals [1]. The major polyphenol classes for the most representative compounds found in the majority of foods with antioxidant properties that were in nature, as Secoiridoids, phenylethanoids, phenolic acids, flavonoids and their classes and derivatives, hydroxy-isocromans, lignans, catechins, phenolic acids, phenylpropanoids, tannins, gallotannins, ellagitannins, proanthocyanidins, hydroxybenzoic acids, hydroxycinnamates, stilbenes, terpenes, triterpenoids, stilbenes, stilbenoids, phytosterols, and glucosinolates for example : Oleuropein-aglycone mono-aldehyde (3,4-DHPEA-EDA) (**1**) that is found in extra virgin olive oil, cyanidin (**2**) that is found in edible berries, catechin (**3**) that is found in grapes, punicalagin(**4**) that is found in pomegranate, epicatechin (**5**) that is found in nuts, glucoraphanin (**6**) that is found in brassicaceae, and rosmarinic acid (**7**) that is found in spices (Figure 1.1) [1].

Figure 1.1

*Chemical structure of 3,4-DHPEA-EDA (**1**), Cyanidin (**2**), Catechin (**3**), Punicalagin (**4**), Epicatechin (**5**), Glucoraphanin (**6**) and Rosmarinic acid (**7**)*



Most of these positive health impacts, such as anticancer activity, are provided about by the polyphenolic chemicals' antioxidant characteristics [2]. The interaction of chemicals with polyphenols is another factor that affects its bioavailability. According to certain reports, transport proteins such serum albumin and quercetin metabolites can form intermolecular interactions, which can inhibit the metabolite removal. The high affinity that epigallocatechin-3-*O*-gallate has for blood proteins may also extend the plasma half-life for this blood [1].

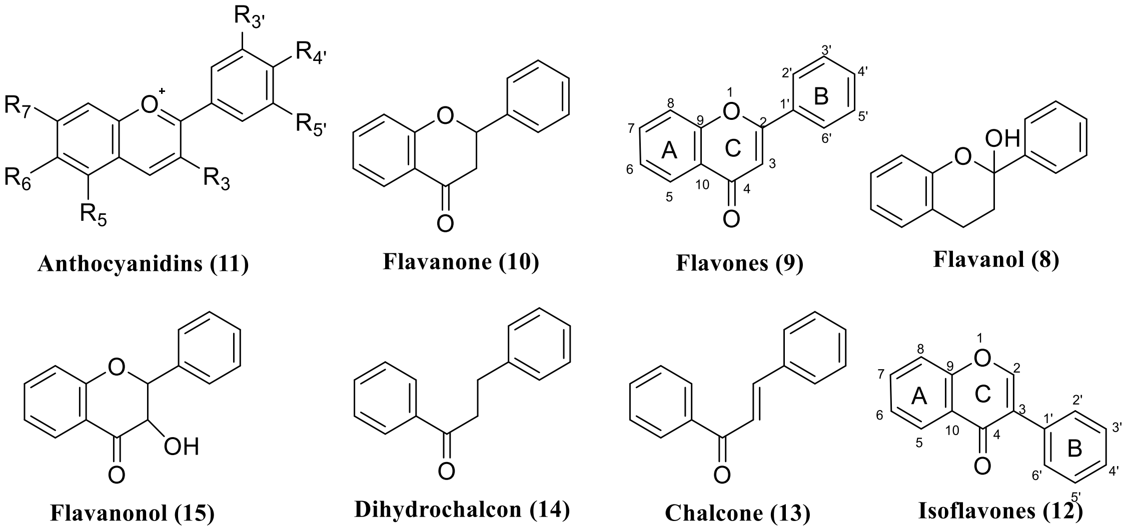
1.3 Flavonoids

Flavonoids, a type of polyphenolic compound, are found in plants, common fruits and vegetables, wine, tea, and so on. Furthermore, flavonoids are classified as plant secondary metabolites [1,3–5].

Flavonoids are classified into many major groups as flavanols (**8**), flavones (**9**), flavanone (**10**), anthocyanidins (**11**), and isoflavonoids (**12**), and they are divided into some subclasses, [1,3,4] and flavonoid monomers, such as chalcone (**13**) as it can consider a main class as we can include dihydrochalcones (**14**) and (α- and β-OH-dihydrochalcones). In addition to flavanonol (**15**). Their fundamental chemical structure is known as 2-phenylbenzopyrane. as can be seen in (Figure 1.2) [1].

Figure 1.2

Basic chemical structure of major classes of flavonoids



Anthocyanidins (11) **Flavanone (10)** **Flavones (9)** **Flavanol (8)**

Flavanonol (15) **Dihydrochalcon (14)** **Chalcone (13)** **Isoflavones (12)**

Basic structure ((R4' = -OH),(R3,R5,R6,R7,R3',R5'= -OH, -OCH$_3$,-H)

Flavonoids have many beneficial human health effects, and for thousands of years, they have been widely utilized in traditional medicine [1,4,6,7]. Flavonoids could act as antioxidants and have many biological activities, such as antiproliferative and anticarcinogenic activity, as well as reducing osteoporosis and cardiovascular disease.

They are also used to alleviate menopausal symptoms [5,8–11]. They are chemicals that may protect against oxidative stress, which is connected to inflammation and the risk of macromolecule damage, and because of that, they are traditionally classified as dietary antioxidants. In addition, these risks result from free radicals and other oxidizing agents such as oxygen or nitrogen species [8].

1.4 Isoflavonoids

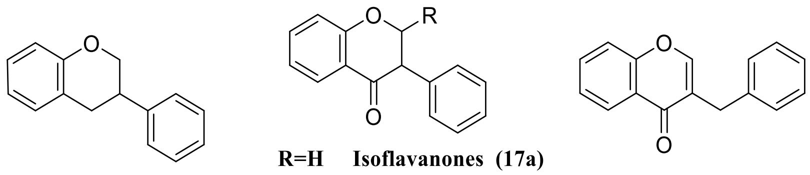
Isoflavonoids (**9**) or as it known as (3-phenylchromans) are produced when the aromatic ring moves from its major skeleton's C-2 to C-3 position. as can be seen in (Figure 1.2) [1,12]. Since isoflavonoids (**9**) are an isomerized form of flavones (**8**) and a subclass of flavonoids [4,12,13], isoflavonoids are relatively rare in the plant world in comparison to other classes of flavonoids, presumably due to the infrequent presence of isoflavone synthase. It has been reported that the bulk of natural isoflavonoids (**9**) (more than 2000 by the end of 2018) come from the Leguminosae subfamily Papilionoideae. In addition, isoflavonoids (**9**) have been discovered in non-leguminous plants such as Iridaceae, Moraceae, and Melicacea. [14].

Because several isoflavonoid molecules have biological effects via the estrogen receptor, isoflavonoids and their derivatives are frequently referred to as phytoestrogens. Isoflavonoids have many benefits as flavonoids had that are indicated by vitro experiments such as antioxidant, antiproliferative, antimutagenic additionally, cancer prevention benefits [12,15]. In addition, there are many benefits indicated by a few isoflavonoid metabolites that are produced by human microflora [16].

Based on ring C's oxidation state and the coupling between this ring and ring B, isoflavonoids (**9**) are divided into several subclasses. With similar skeletons for both isoflavones and isoflavanones, in addition to isoflavans, isoflavan-4-ol, homo isoflavonoids, and isoflav-3-ene are one of the subclasses free of ring D. Pterocarpans and rotenoids are examples of subclasses with extra ring D development [12] (Figure 1.3 on the next page) . Moreover, they could be divided into separate classes [12,17].

Figure 1.3

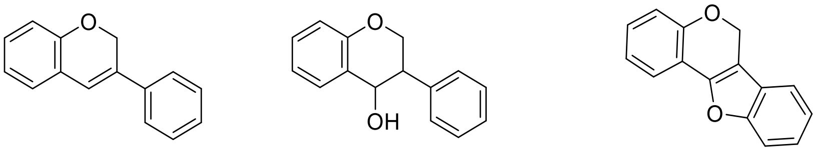
Chemical structure of major classification of isoflavonoids (9)



Isoflavan (16)

R=H Isoflavanones (17a)
R=OH Isoflavanonols (17b)

Homoisoflavonoids (18)



Isoflav-3-ene (19)

Isoflavan-4-ol (20)

Pterocarpans basic structure (21)

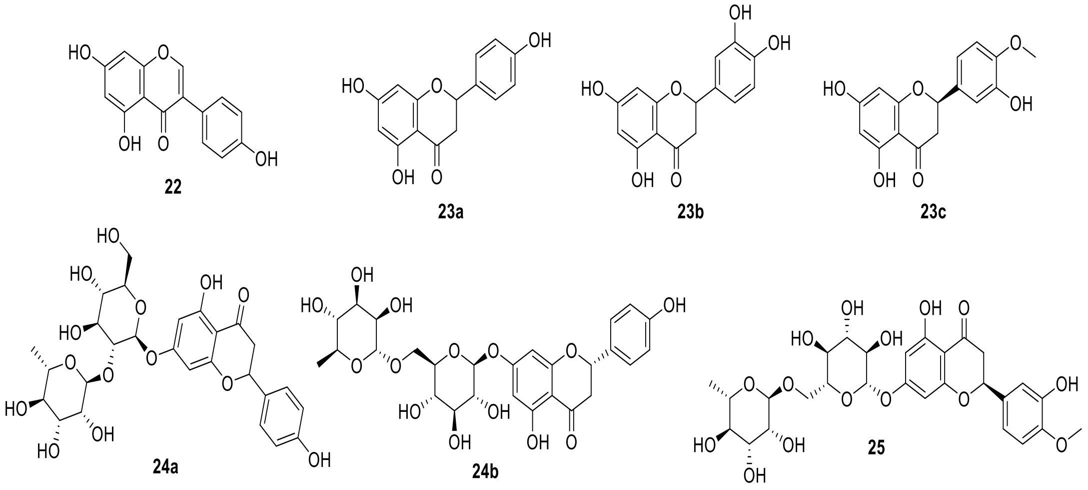
The most common example of isoflavonoid is genistein (**22**) (Figure 1.4) that is present in soybeans, and it's found also in fava beans, and other significant stable foods. Genistein (**22**) has many benefits as the capability to prevent the development of new blood vessels in various cancer cell types [3,7,12,15,17] .

Flavanones

Flavanones (**15**) are another important class that may be found in many fruits, such as oranges, lemons, grapes, and other citrus fruits. Common flavanones found and synthesized in segment membranes and peels as in flavedo and albedo, as naringenin (**23a**), and eriodictyol (**23b**), hesperetin (**23c**) (Figure 1.4) [1,8]. For instance, sweet orange, often known as citrus sinensis, contains a total flavanones level ranging from 35 to 147 mg/100 g. Naringin (**24a**) and narirutin (**24b**) (Figure 1.4) concentrations in grapefruit, also known as the paradisi fruit. It was shown to have a concentration of 44–106 mg/100 g. However, because the albedo and membranous sections are typically eliminated during juice processing, citrus juice flavanone levels are decreasing. The juice of the paradisi fruit included levels of naringenin **(23a)** that ranged from 17 to 76 mg/100 mL, and the juice of the sweet orange contained levels of hesperidin (**25**) and narirutin (**24b**) (Figure 1.4) that ranged from 13 to 77 mg/100 mg [1,8]. Because of their ability to remove free radicals, flavanones are associated with a number of health advantages. The peel of citrus fruits and their juice have a bitter taste due to flavanone compounds. Citrus flavonoids also have interesting pharmacological benefits and properties, such as antioxidant effects, anti-inflammatory effects, blood lipid-lowering effects, and acting as cholesterol-lowering drugs [8].

Figure 1.4

*Chemical structure of Genistein (**22**), naringenin (**23a**), eriodictyol (**23b**), hesperetin (**23c**), Naringin (**24a**), narirutin(**24b**) and hesperidin (**25**)*



The fundamental chemical structural variation between the two subclasses of flavonoids (flavanone and flavone) is that in flavanones, also known as dihydroflavones, the double bond between sites 2 and 3 is saturated, but not in flavones (**8**) (Figure 1.2). Over the last 15 years, the amount of flavanones has increased dramatically [8].

Flavanones can be synthesized from chalcone in the same manner that naringenin **(23a)** can be synthesized from naringenin chalcone, where Naringenin **(23a)** is a common precursor for all flavonoid classes [1].

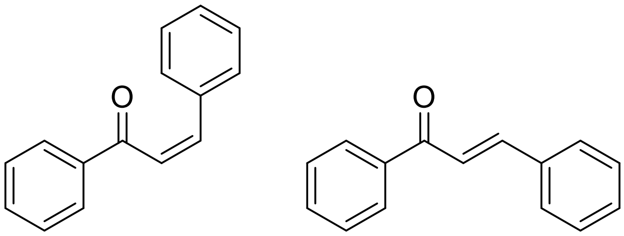
1.5 Chalcone

Chalcones are widely present in fruits, vegetables, teas, and other plants and are simple chemical framework of various naturally occurring chemicals. This name is due to the color of the majority of naturally occurring chalcones , that the word "chalcone" is a derivation form that is taken from "chalcos," which in the Greek language "bronze" [18].

Chalcones are polyphenolic molecules that come from plants. Chalcones' yellow to orange color is caused by their chemical structure, which consists of aromatic rings joined to another aromatic ring by a linker of three-carbons made up of (-C=O-CH=CH-) as an α, β-unsaturated. As a result, it has delocalized π -electron system and conjugated double bonds in the two rings. Because the structure contains a double bond (-C=C), chalcone tends to be found in both configuration cis- or trans and has a virtually planar form [1,18].

Figure 1.5

Chemical structure of traditional chalcone in cis- and trans-configuration

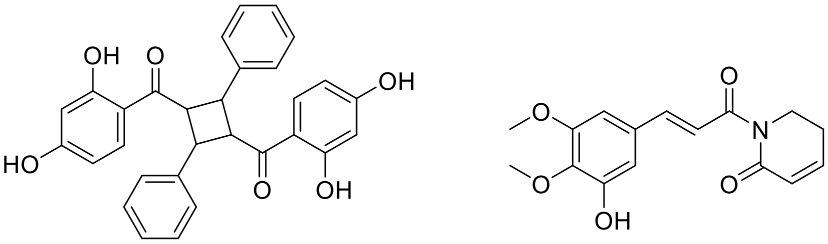


cis chalcone (13a) **trans chalcone (13b)**

Despite having a wide range of structural variations, the chalcone family can be generally divided into two groups: the first one is a simple/classical chalcones (traditional), and the second one is a hybrid that has a skeleton of 1,3-diaryl-2-propen-1-one. In addition of above nontraditional chalcone (subclass of hybrid chalcones) could be a class such as fused chalcones (as oxyfadichalcones (**26**)) and chalcone mimics (as piperlongumines (**27**)) (Figure 1.6). Despite the fact that they contain a comparable system of ketone that is α, β-unsaturated or forms that are fused, that produced from chalcones by specific biosynthetic routes [18].

Figure 1.6

*Chemical structure of oxyfadichalcones (**26**) and piperlongumines (**27**)*



26 **27**

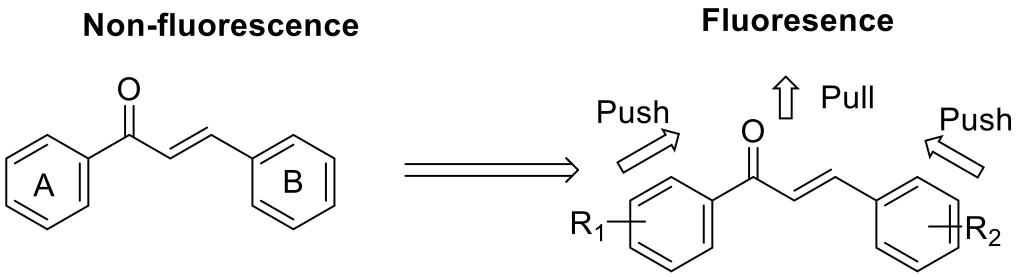
Chalcones, both natural and synthetic, have demonstrated remarkable biological characteristics and a low toxicity profile. According to several researchs, the removal of the keto-ethylenic group reduces these biological activities, which supports the theory that the presence of this group is the major contributors to these biological activities. The effect of conjugation between the (-C=O) and the (-C=C) next to it is provided by the keto-ethylenic group [1].

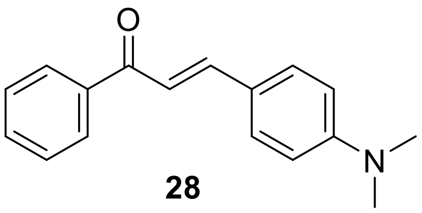
Due to resonance, which results in free electron mobility around atoms of functional groups, both functional groups are located next to one another. Resonance thereby increases the ability for nucleophilic addition while the double bond reactivity for electrophilic addition decreases, making the keto-ethylenic group more vulnerable to attacked by nucleophile [1]. The (-C=C) that is next to other groups that classified as electron withdrawing like carboxylate (-COO), amine, ester (-COOR), ether (-COR), and nitro (-NO2) groups do not undergo the aforementioned addition reaction. Therefore, based on the strength of the nucleophile and the conditions of reaction, the keto-ethylenic group is cyclized easily, forming heterocyclic molecules that are biologically active in chalcones through Michael addition as (1,4-addition) or Claisen addition as (1, 2-addition). Many compounds based on chalcone can be synthesized, like pyrazoline-based development of chalcone [1].

if the Chalcones have the suitable functional groups as electron-pulling or electron-pushing or both of them on the benzene ring(s) (Figure 1.7), it can be fluorescent due to their conjugated structure, making them suitable as chemical probes or chemical sensor for mechanistic studies and investigations, and for imaging/diagnosis [18].

Figure 1.7

*Electron push −pull pairs for fluorescent chalcones, and the chemical structure of 4-dimethylaminochalcone (**28**)*





28

However, the ability of fluorescent chalcones to identify various diseases has been studied. Both fluorescent chalcone compounds and influorescent probes frequently use the dimethylamino group as a substituent. For example the compounds of 4-N,Ndimethylaminochalcone (**28**) (Figure 1.7), shows an absorption (Abs) at range of λ_m (390 – 460) nm and an emission (Emi) at range of λ_m (450- 620) nm [18].

1.5.1 Chalcone Synthesis

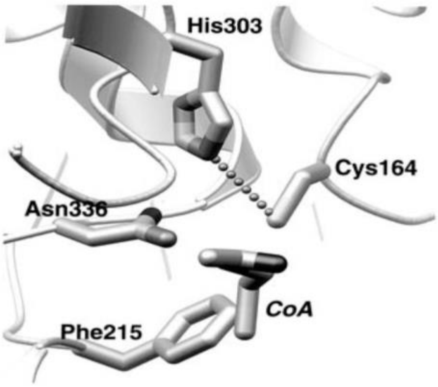
1.5.1.1 Biosynthesis

Chalcone synthase (CHS), the chemical is structurally linked to flavanone and anthraquinone and is biosynthesized via the CHS route [1,18]. Higher plants frequently contain PKS, which is type III polyketide synthase for the chalcone plant superfamily; the first type was found in the 1970s. Moreover, CHS in the liverwort Marchantia polymorpha has been detected in lower plants, as it could be found in other examples of lower plants. For this family, the remaining members are "CHS-like" enzymes, as they are all referred to. In conclusion, the major responsible for the biosynthesis of chalcones is CHS [18].

The production of several secondary metabolites, including flavonoids, stilbenes, and others, is mediated by enzymes belonging to the CHS superfamily. There is a homodimer of CHS. The essential residues of the active site are amino acids (His303, Phe215, Cys164, and Asn336) that in all CHS members, in addition to CHS-like enzymes, they have been conserved (Figure 1.8), (Scheme 1.1) [18–20].

Figure 1.8

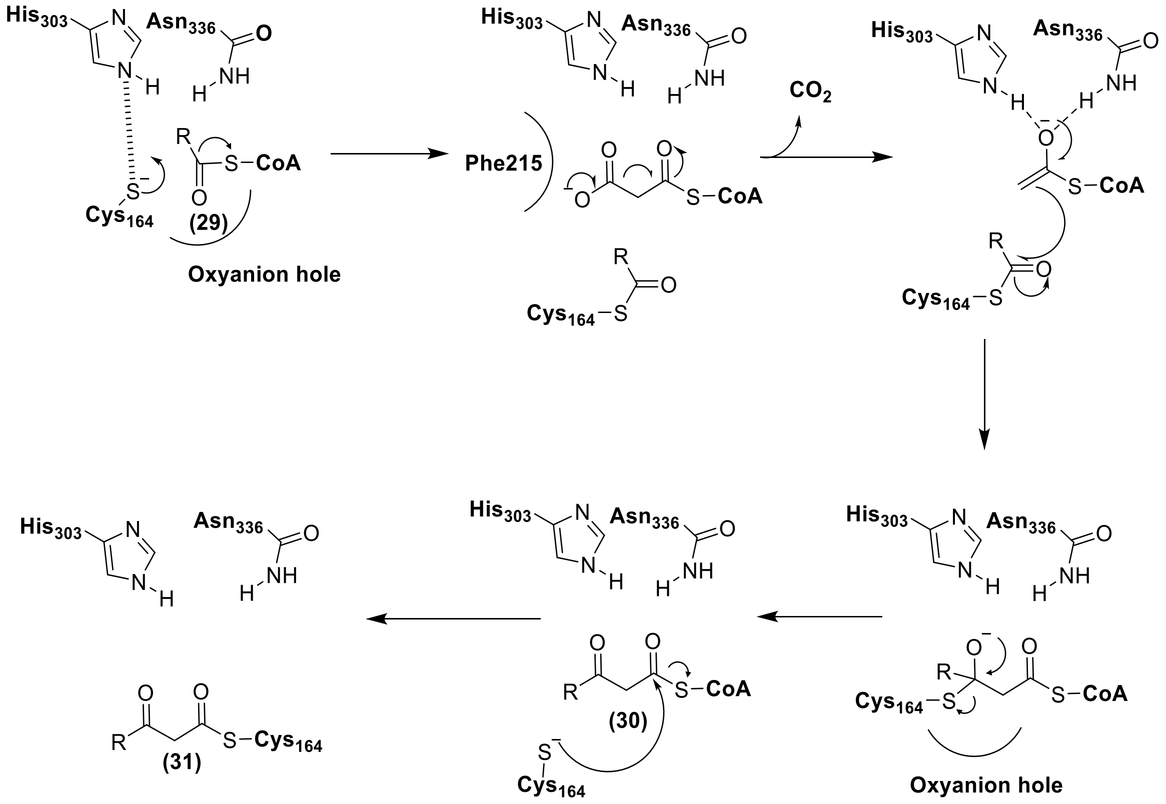
CHS active site and reaction mechanism



Jez, Ferrer et al 2001 [19]

Scheme 1.1

Proposed mechanism for first step in CHS

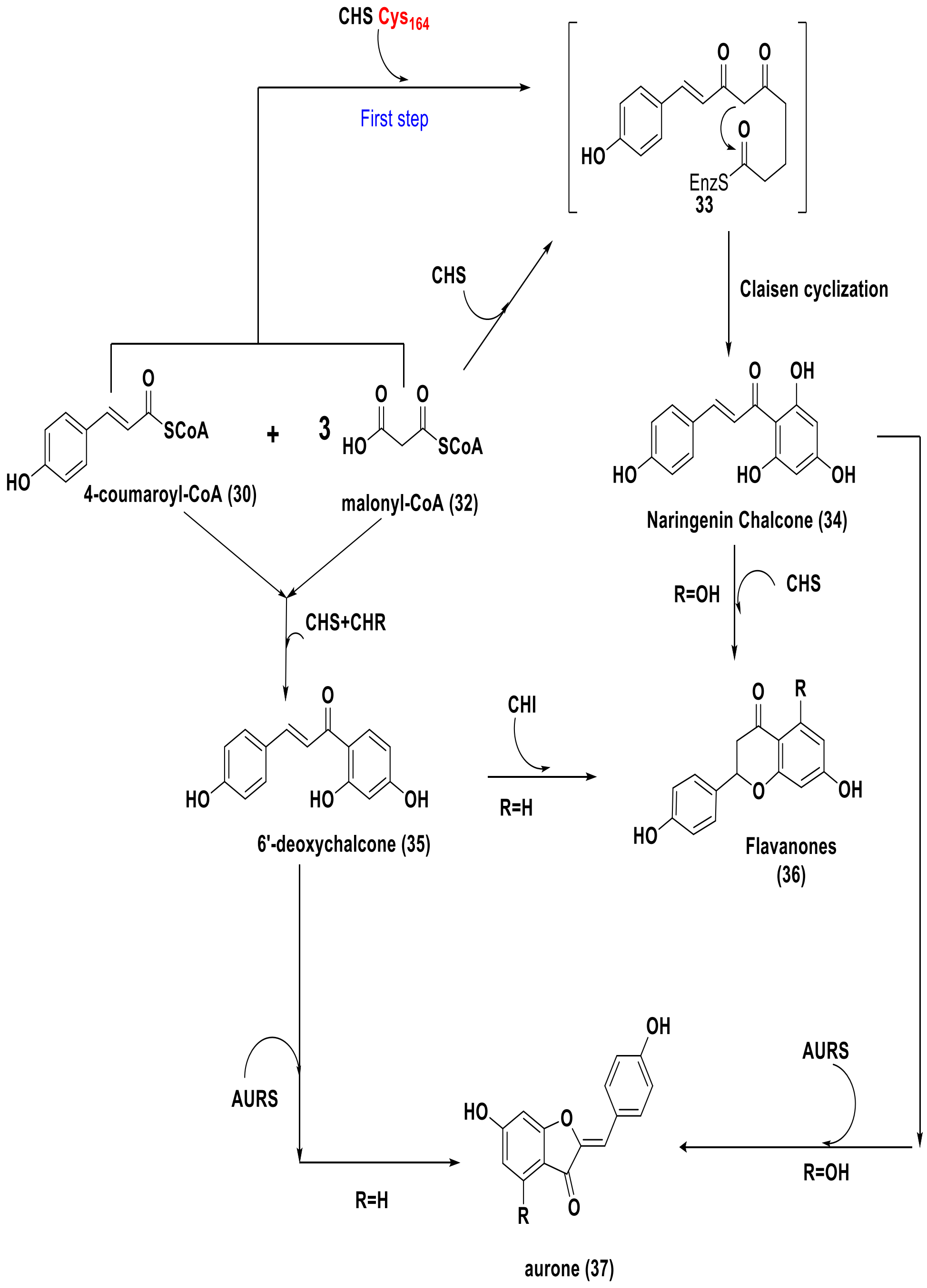


As the first step (Scheme 1.1), from one 4-coumaroyl-coenzyme A (CoA) (**30**) CHS transfers the moiety of coumaroyl (**29**) to Cys164 (**31**) Three malonyl-CoA thioesters (**32**) then undergo a polyketide reaction to create an intermediate (Scheme 1.2). Production of naringenin chalcone (**34**) by formation of a new ring system that is produced from thioester-linked tetraketide (**33**) by cyclization of type Claisen regiospecific [18–20].

6′-deoxynaringenin chalcone (**35**) as seen next page is produced by the changing of naringenin chalcone (**34**) by chalcone reductase (CHR) and CHS, in association with specific catalytic enzymes. In the same way, secondary metabolites from plants could be biosynthesized, such as phloroglucinols, stilbenes, and benzophenones. Using naringenin chalcones as substrates, CHS and chalcone isomerase (CHI) generate flavonoids, and its flavonoids molecules, such as (**36**) A aurone synthase (AURS) which is plant enzyme that use naringenin chalcones as basic structure unite in production of aurone molecules (Scheme 1.2). Chemical processes could also be used to achieve the conversions mentioned from chalcones to aurones, flavanones, or other compounds [18–20].

Scheme 1.2

Pathways of biosynthesis of Chalcones



1.5.1.2 Chemical Synthesis

Chalcones are often produced through condensation processes catalyzed by bases or acids. Despite the fact that chalcones are a form of α,β-unsaturated ketone that is simple to synthesize, not long ago, many innovative procedures and methods were documented because of the creation of various interesting catalysts or reaction circumstances and their activities that are biological [18].

1.5.2 Methods and strategies for chemical chalcone synthesis

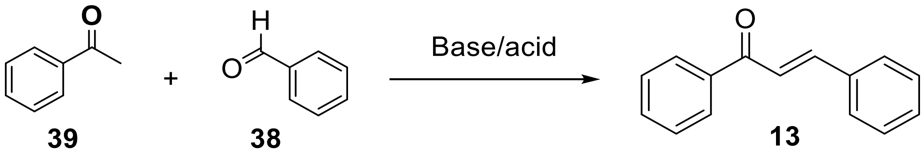
1.5.2.1 Claisen–Schmidt Condensation

In the presence of catalysts such as strong bases or acids, the process of this reaction explains the condensation of a benzaldehyde (**38**) with acetophenone (**39**) which is an example of a methyl ketone, and this reaction is the most traditional in organic chemistry (Scheme 1.3) [18].

In acid catalysis, the production of chalcone from the aldol product occurs via an enol mechanism, but it occurs via an enolate mechanism in base catalysis via dehydration, whereas it is produced. Unfortunately, this reaction rate is slow; it often takes a long time that reaches several days to complete [18].

Scheme 1.3

*Claisen–Schmidt condensation benzaldehyde (**38**) with acetophenone (**39**) for the formation of chalcone (**13**).*

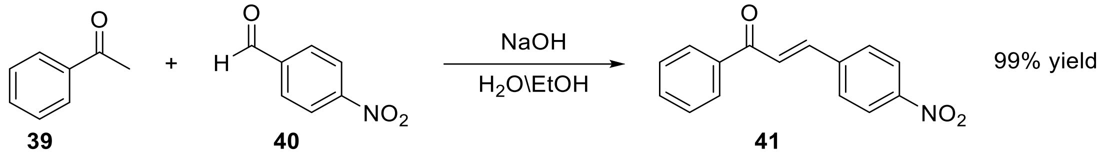


The desired product, as well as byproducts and occasionally starting ingredients, could all be present in the complicated mixture formed by the reaction. Hence, the yield could range from 10% to nearly 100% conversion, depending on which reactants and catalysts are used. Nonetheless, due to its ease of experimentation and very effective production of the (C=C) with little constraint on the molecule's complexity, this reaction has been used in the majority of publications. It was discovered that in the synthetic chalcones, under acidic conditions Aldehyde encourages condensation when electron-donating groups are in, whereas the presence of electron-withdrawing substituents favored condensation under basic circumstances. In chalcone synthesis, the base condition is more frequent [18].

A quantifiable yield of 4'-nitrochalcone (**41**) (enone) is produced from the reaction of 4-nitrobenzaldehyde (**40**) with acetophenone (PhCOMe) (**39**) under NaOH catalysis in aqueous ethanol (Scheme 1.4) which is an example of a condensation process that produces chalcone. They make up a very small portion of all known aldol reactions [21].

Scheme 1.4

*Synthesized 4-nitrochalcone (**41**) by condensation reaction between 4-nitrobenzaldehyde (**40**) and acetophenone (**39**)*



Cross-condensations are those that take place between two carbonyl compounds that are separate, where one is acting as an electrophile and the other as an enol or enolate nucleophile. Compared to self-condensations, they are more intriguing, but understanding how they function requires more thought [21].

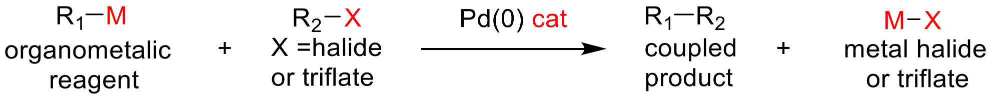
A complex mixture could be produced by Claisen–Schmidt condensation, but it was found to be difficult to purify to have the desired product as chalcone [18].

1.5.2.2 Cross-Coupling

Cross-coupling reactions typically involve triflate or organic halide and a palladium (II) intermediate reagent (Scheme 1.5) [21].

Scheme 1.5

General coupling for organic synthesis

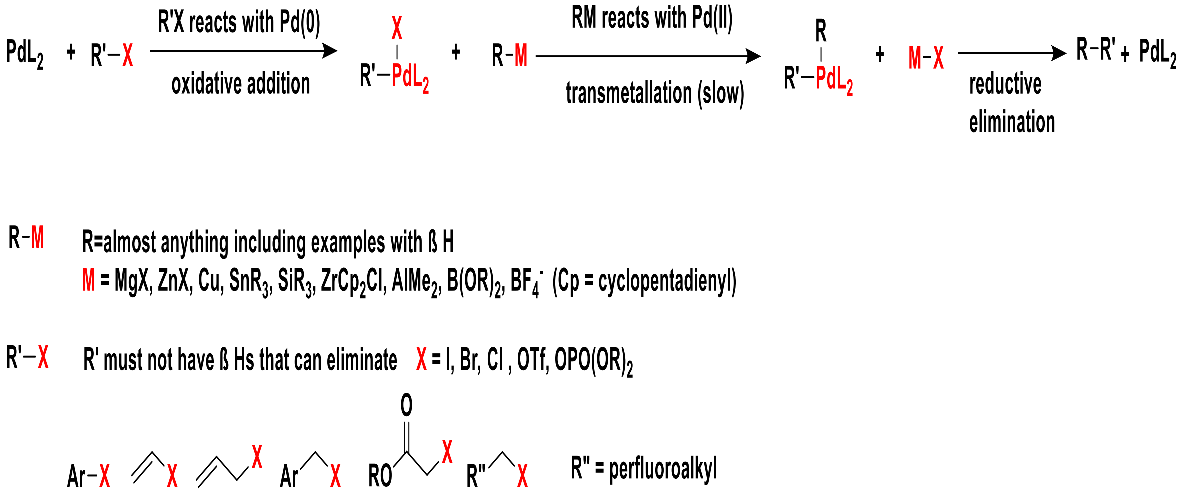


Although the yields of this reaction are quite low when there is no catalyst of transition metal, it appears to be a very interesting process for synthesis. Nevertheless, coupling happens stereospecifically and in high yield when a transition metal exists, such as Pd (0) for Sn and Cu(I) for Li [21].

Particularly significant palladium-catalyzed interactions with partners of organometallic that is based on Zn that is known as Negishi coupling, B that is known as the Suzuki coupling, Mg that is known as Kumada coupling, and Sn that is known as Stille coupling (Scheme 1.6) [21].

Scheme 1.6

Mechanism for cross coupling



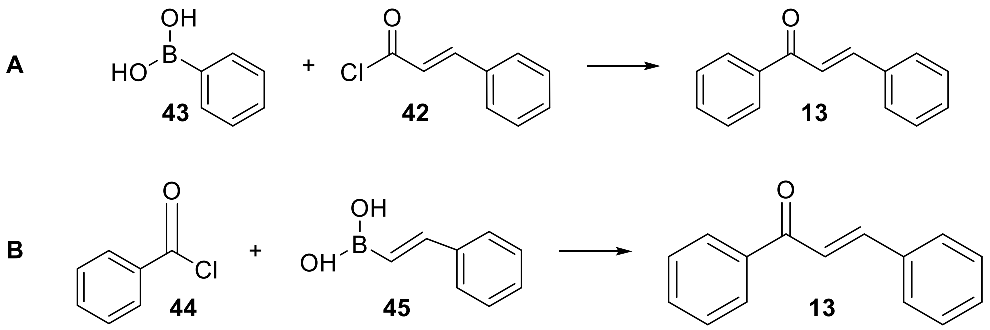
1.5.2.2.1 Suzuki Coupling

Akira Suzuki revealed the existence of the Suzuki coupling in 1979. In this type of coupling, the palladium catalyzes the formation of a carbon-carbon bond [18].

According to the retrosynthetic study, two methods may be used to produce chalcones (**13**), coupling phenylboronic acid (**43**) with cinnamoyl chloride (**42**) (Scheme 1.7 A) or phenylvinylboronic acid (**45**) with benzoyl chloride (**44**) being coupled (Scheme 1.7 B) [18].

Scheme 1.7

Suzuki coupling reaction for chalcone synthesis

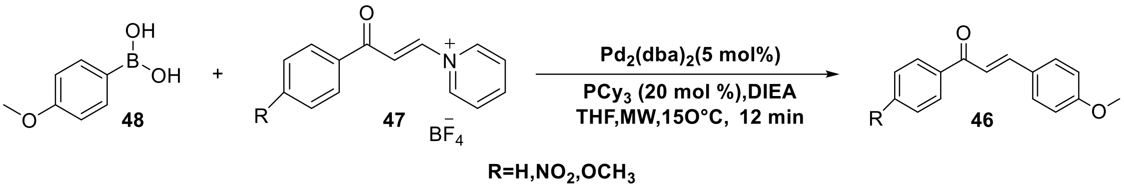


The reaction circumstances have an expected impact on the reaction yield. The coupling of cinnamoyl chloride (**42**) with phenylboronic acids (**43**) under Bumagin's conditions results in a yield of (23–37%), but under McCarthy's conditions provide about fifty percent and ninety percent isolated yields for the method mentioned in the previous scheme, respectively. There are many factors that affect the reaction of the Suzuki coupling, such as electronic property, which has a limited impact on the benzene rings for its substituents, as shown by the extension of this reaction to produce chalcones with electron-donating such as 4-methoxychalcone (**46**) or withdrawing substituents [18].

An intriguing example of Suzuki-Miyaura coupling is the production of N-vinylpyridinium tetrafluoroborate salt (**47**) for chalcone synthesis, which gives yields in the range of 60% to 81% (Scheme 1.8). These salts are a new family of electrophilic coupling partners that palladium catalyzes and react with a variety of boronic acids to form 4-methoxy phenylboronic acid (**48**) (Scheme 1.8). The salts can also be produced quantitatively in a single step using pyridinium or trialkylammonium-tetrafluoroborates in addition to activated acetylenes, and they are nonhygroscopic crystals that are air-stable [18].

Scheme 1.8

Chalcone Synthesis by Suzuki–Miyaura Coupling



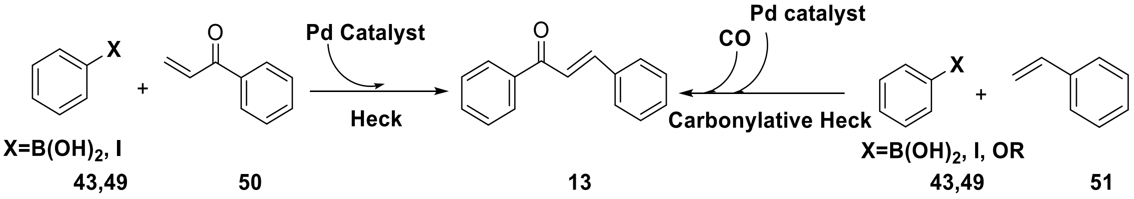
1.5.2.2.2 Heck Reaction

Chalcone is structurally similar to stilbene and is produced by the traditional Heck reaction between an unsaturated ketone and an aryl iodide as iodobenzene (**49**) or arylboronic acid (**43)** when a palladium catalyst in the base solvent exists (Scheme 1.9). Using catalytic circumstances [CH_3CN, TEA, Ph_3P, $Pd(OAc)_2$]], it has been reported that the synthesis of derivatives of chalcone using a direct coupling of aryl iodides with aryl vinyl ketones (**50**) ,which is quickly and give a yields of 75% to 96%. Using a phosphine-rhodium catalyzed conjugate addition reaction by competitive side reaction, Heck coupling can also be accomplished, the production of carbon-carbon bonds, which is catalyzed by rhodium. Moreover, a method for creating the chalcone moiety by competing with the conjugate addition and Heck coupling process has been reported. For instance, phenyl vinyl ketone as 1-phenylprop-2-en-1-one (**50**) react with phenylboronic acid (**43**) in a biphasic system of toluene-water, using $RhCl_3$ (3 percent) or $(PPh_3)_3RhCl$ (3 percent) −(±)2,2-bis- (diphenylphosphino)-1,1binaphthalene (15 percent) as the catalyst. With $(PPh_3)_3RhCl$, the resultant dihydrochalcones and chalcones were produced in an equivalent ratio, but when we use the second catalyst, the ratio will be > 99:1 as opposed to conjugate adduct selectivity [18].

Chalcones can also be produced through carbonylative Heck coupling (Scheme 1.9). At a yield of only 8%, the required chalcone was initially produced using conditions of palladium-catalyzed. As anticipated, under optimal circumstances(toluene, $[(cinnamyl)PdCl]_2$, NEt_3, dppp, 100 °C, 20 h), phenyl triflate with carbon monoxide and various derivatives of styrene (**51**) produced the respective chalcones in a range of yields from 71% to 95%. Moreover, this approach was used to aryl iodide (**49**) and arylboronic acid (**43**), producing chalcones in acceptable yields [18].

Scheme 1.9

Chalcone Synthesis by Carbonylative Heck Coupling and Heck Coupling



Although in Heck reaction the metal-catalyzed is thought to be a highly effective method for producing chalcones, its use is restricted due to the requirement for carbon monoxide that is pressurized and the scarcity of aryl-vinyl-ketones. The work was nonetheless noteworthy, though, for a number of reasons: It represents a connection, as a relationship between the well Known carbonylative Sonogashira and carbonylative Suzuki reactions; A powerful tool that is used to label isotopes that are compounds of chalcone derivatives by using a simple isotope-labeling gas; Although easily explained, the variation in CO as a function of oxygen had not before been proven [18].

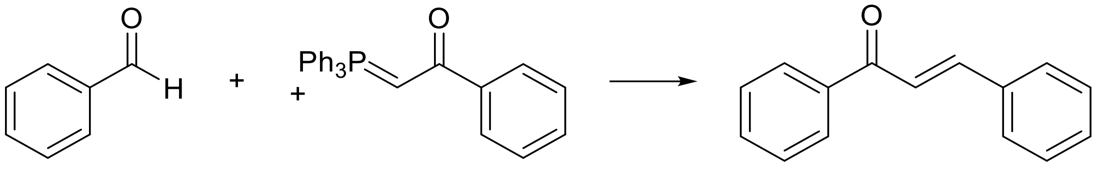
1.5.2.2.3 Wittig Reaction

This technique is used for producing alkene compounds and could be called Wittig olefination; According to (Scheme 1.10). The chalcone is an alkene template that is suitable for approaching the Wittig reaction. The first attempt, which had a decent yield of 70% and took 3 days of reflux triphenylbenzoylmethylenephosphorane (**52**) and benzaldehyde (**38**) in benzene or 30 hours in THF [18].

Additional research has suggested that microwave irradiation could considerably increase the response rate. For instance, it was reported that eight aromatic aldehydes were used in the synthesis of different chalcones. For all of the substrates investigated, good yields (>80%) were obtained, and the reaction could be completed utilizing microwave irradiation techniques in 5–6 min [18].

Scheme 1.10

Chalcone Synthesis by Wittig Reaction



38 **52** **13**

1.5.2.2.4 Julia–Kocienski Olefination

Olefination Julia-Kocienski (Scheme 6.1 in Appendix B). Heteroaryl-sulfonyl phenylethanone (**53**) or the Julia reagents and benzaldehyde (**38**) were olefinated in basic medium to produce a large number of chalcones. Many variables, including the Julia reagent, base, solvent, and temperature, had an impact on this reaction. Heteroaryl, such as benzothiazole (**54**) (Scheme 6.1 in Appendix B) with The Julia reagent was the most effective, whereas was the most effective base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [18].

The yields generally decreased throughout the sequence THF > DCM > $CHCl_3$ > CH_3CN > MeOH, with nonpolar solvents being more advantageous than polar solvents. When the temperature reached 78 °C, the yield drastically reduced. Although the Newman projection might explain stereoselectivity at such low temperatures, the predominant product was still the *trans*-isomer [18].

1.5.2.2.5 Other Cross-Couplings

Metal-catalyzed that is direct cross-coupling (using, for instance, palladium or silver) has recently received extensive research as a means of producing chalcones, in addition to the aforementioned cross-couplings. Benzoyl chlorides (**44**) and potassium styryltrifluoroborates (**55**) were used in a reaction of direct cross-coupling with $PdCl_2$(DTBPF) as the catalyst and K_2CO_3 to produce the appropriate chalcones, as shown in (Scheme 6.2 A in Appendix B). This process took use of microwave irradiation [18]. This circumstance allowed to synthesis several chalcones with a yields of range from (56-96%) [18].

Another recent method for producing chalcones uses 3-benzoylacrylic acids (**56**) and is called palladium-catalyzed decarboxylative coupling (Scheme 6.2 B in Appendix B). According to one study, chalcone derivatives are produced when aryl halides (**49**) or arylboronic acids (**43**) interact with 3benzoylacrylic acids when palladium catalysts exist, in addition to [Cu(OAc)2H_2O], which is a salt of copper oxidant. Using 3-acylacrylic acids directly is much better than using vinyl ketones that are corresponding due to their availability and stability. It has been found by a mechanistic investigation that ArPdX mediated decarboxylation generated chalcone or by using a Heck-type reaction, and a limitation for Heck coupling was demonstrated. Building chalcone scaffolds using the procedure of double-decarboxylation catalyzed by silver is another option (Scheme 6.2 C in Appendix B) [18].

Chalcones have been produced with high yields from readily available α-keto acids (**57**) and cinnamic acids (**58**) when $AgNO_3$, $Na_2S_2O_8$, and K_2CO_3 exist in aqueous solution under mild conditions. A potential mechanism has been put forth. From α-keto acid peroxodisulfate oxidation of Ag(I) to Ag(II) produces an aryl radical, which releases one mole of an Ag(I) cation and carbon dioxide. At the α-position when the cinnamate anion is joined to the aryl radical, a further molecular carbon dioxide loss and silver occurs, resulting in the creation of chalcone (I). By combining decarboxylation and dehydrogenation, the method of employing saturated propiophenones (**59**) to create chalcones that are unsaturated, which has also been established (Scheme 6.2 D in Appendix B). Beyond the constraints of Heck's starting materials, the researchers extended the Heck reaction by cross-coupling aryl carboxylic acids (**60**) with a - palladium catalyst that is supported by PCy3 to produce chalcones in reasonable yields ds [18].

In conclusion, the aforementioned traditional cross-coupling techniques have been established to create (c=c) under benign conditions, and the yield is good, resulting in a variety of valuable chalcone derivatives for synthetic chemistry and medicinal chemistry. Depending on the particulars, which are solvents, starting materials, and catalyst conditions, in addition to the ease of purification, these strategies can be chosen and used. Each has advantages and disadvantages of its own [18].

1.5.2.3 Friedel–Crafts Acylation by using Cinnamoyl Chloride

By acylation of cinnamoyl chloride (**42**) and an aromatic ether (**61**) through Friedel-Crafts chalcones can be made by using a potent of aluminum trichloride or any other Lewis acid catalyst (Scheme 6.3 in Appendix B). Four chalcones manufactured using this method were reported with reasonable yields. Nonetheless, the synthesis of chalcones has not frequently utilized this reaction [18].

1.5.2.4 Photo-Fries Rearrangement using Phenyl Cinnamates

The main intermediate flavonoid for biosynthesis in nature are 2′-hydroxychalcones (**62**), and because of that, the photochemistry of chalcones has garnered a lot of attention. The photosynthesis of these chalcones is sometimes referred to as the Fries rearrangement (Scheme 6.5 in Appendix B), wherein phenyl cinnamate (**63**) goes through a practical rearrangement reaction to get a hydroxy aryl ketone (**62**) takes place when Lewis acids exist [18]. which is considered a para- or ortho-selective reaction, and the solvents and temperature of the reaction have an impact on the reaction. According to one study, phenyl cinnamates could be exposed to high-pressure mercury arc radiation under nitrogen using benzene as the solvent to produce 10% 2′hydroxychalcone (**63**) and 2% 4 hydroxychalcone. This reaction has since been expanded to include several substituted chalcones from natural sources, such as dihydroxychalcones, dihydroxychalcones that are protected by O-methoxymethyl and the chalcones that are multisubstituted. Methanol, chloroform, and ethanol are also favorable for this rearrangement, according to Ramakrishnan and Kagan. Although switching the solvent could increase the yield by around 50%, phenyl cinnamates haven’t yet achieved full conversion. This approach is rarely frequently used because of the reaction's limitations, a low yield, a prolonged reaction time, and a challenging operation [18].

1.5.2.5 One-Pot Synthesis

It is a technique for enhancing reaction efficiency and avoiding intermediary purification to shorten reaction times and boost total yield. One-pot synthesis using ketone and alcohol has recently been used to create the chalcone scaffold [18].

A ketone as (39) and a primary alcohol as phenylmethanol (64) form a mixture in addition to the slowly added chromium (VI) oxide, as shown in (Scheme 6.5 A, condition I in Appendix B), resulting in a yields of range from (65-98%) of the chalcone. It is clear that the appropriate aldehyde is converted in situ from the alcohol, and then the ketone reacts with it to produce the end result. By varying the temperature of reaction from ten to hundred °C for 10 to 96h with a catalyst that made from (TEMPO) 2,2,6,6-tetramethylpiperidine-1-oxylcopper iodide ,and 2,2′-bipyridine, and that was how several ketones and alcohol react through one-pot reaction that reported by a researcher (Scheme 6.5 A, condition II in Appendix B). Furthermore, according to another study, a new water-soluble nano-palladium (nano-Pd-V) synthesized from PdCl2 efficiently catalyzed the process, and from ketones and alcohols, the chalcones were produced in a yield of 92% (Scheme 6.5 A, condition III in Appendix B). Another research reported that the alkylation of ketones with primary alcohols, catalyzed by a palladium catalyst that is recyclable and heterogeneous (Pd/AlO(OH)) (Scheme 6.5 A, condition IV in Appendix B) [18].

Without ligands or other additions, this catalyst was functional. In the presence of oxygen, enones such as chalcones can be generated in a selective manner (1 atm O_2). Ketones were the main result, though, when argon was present [18].

A recyclable gold catalyst was used to construct this method, which produced chalcones under an oxygen balloon in high yields and with great selectivity. Mechanically, the aldehyde is converted from an alcohol and subsequently undergoes condensation reaction with a ketone. This application's strength is its extension of the traditional Claisen-Schmidt condensation employing benzyl alcohols (**64**) as starting materials rather than aldehydes [18].

Also, benzyl alcohols (**64**) in addition to phenols (**65**) have been employed in one-pot synthesis. A documented example involved the one-pot activation of phenol (**65**) to extend the aforementioned carbonylative Heck coupling and produce chalcones from phenols (**65**) (Scheme 6.5 B in Appendix B) [18].

1.5.3 Synthesis of cis-Chalcones

Contrary to the more stable trans-chalcones, only few investigations have documented the synthesis of the thermodynamically less stable cis-chalcones (**66**). Siloxypropynes (**67**) were combined at temperature of 78 °C with (t-BuOK) potassium tert-butoxide to make siloxyallenes (**68**), a crucial intermediate that was then processed with 1,2-dimethoxyethane (DME) and (H_2SO_4) as a strong acid to create cis-chalcones (**66**)

(Scheme 6.6 in Appendix B). Great preference for geometry with a yield that reaches 85% and a ratio that reaches 99 cis: 1trans were both achieved in the cis-chalcone preparation [18].

1.5.4 Chalcone in Nature

Natural chalcones from food have already been linked to several biological processes, and it has been established that the group keto-ethylenic in the compound's primary structure is responsible for these actions. Anti-neuroprotective, antioxidant, hepatoprotective antimicrobial, antihypertensive, anticancer, antidiabetic, anti-inflammatory, and anti-obesity properties are among the biological activities documented [1]. Also, these chalcones have a great profile for food safety because numerous animal and human clinical investigations have demonstrated that they are not harmful to normal cells. The overall positive benefits of chalcones showed that these substances are very nutritive, safe to take, and highly promising Pb compounds to treat many diseases; they need to be further developed as alternative medications for that [1].

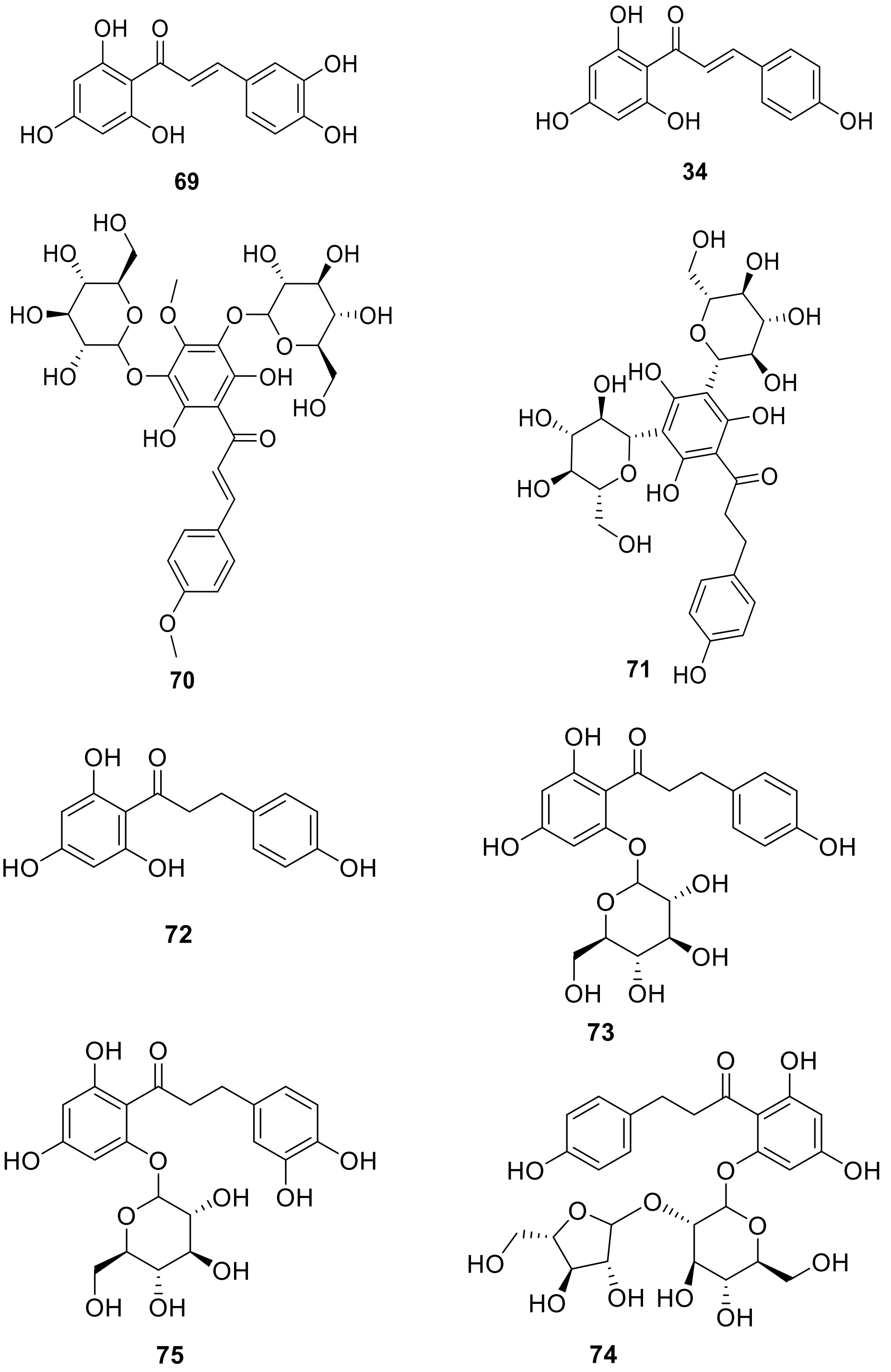
Several plants and fruits, such as the tomato and apple, contain polyphenol including flavanones, dihydroxy-cinnamates, dihydrochalcones, hydroxycinnamates, and chalcone with health advantages. Chalcones are frequently found in tomatoes (Solanum lycopersicum), particularly naringenin chalcone (**34**) and its conjugates [1].

Naringenin chalcone (**34**) is one of the main bioactive substances found in tomatoes. Eriodictyol chalcone (**69**) and dihydroxy-chalcones are two more chalcones that have been discovered in tomatoes in addition to their conjugates. There is very little production of these chalcones in the tomato's other components of the fruit, which is virtually entirely its skin or peel. Phloretin-3',5'-di-C-glucoside (**71**) and dihydroxy-dimethoxy-chalcone-C-diglucoside (**70**) are the two dihydroxy-chalcones discovered in tomatoes. Phloretin-3',5'-di-C-glucoside (**71**) is the first C-glycoside and dihydrochalcone discovered in tomatoes (Figure 1.9) [1].

Dihydrochalcones, a major component of polyphenols, are concentrated in the apple’s fruits, shoots, bark, leaves, and roots. Phloretin (**72**) and phloridzin or phlorizin (**73**) as its conjugates, which make up to ninety percent of the polyphenols that are soluble and detected in apple tree leaves, are the primary dihydrochalcones present. Phloretin 2'-O-xylosylglucoside (**74**) ($C_{26}H_{32}O_{14}$) and 3-hydroxyphloridzin (**75**) are the additional dihydrochalcones that have been discovered in apples and their derivatives (Figure 1.9) [1].

Figure 1.9

*Chemical Structure of (**34**), (**69**), (**70**), and (**71**) that found in Tomato, and chemical Structure of compounds (**72**), (**73**), (**74**), and (**75**) are found in Apple*



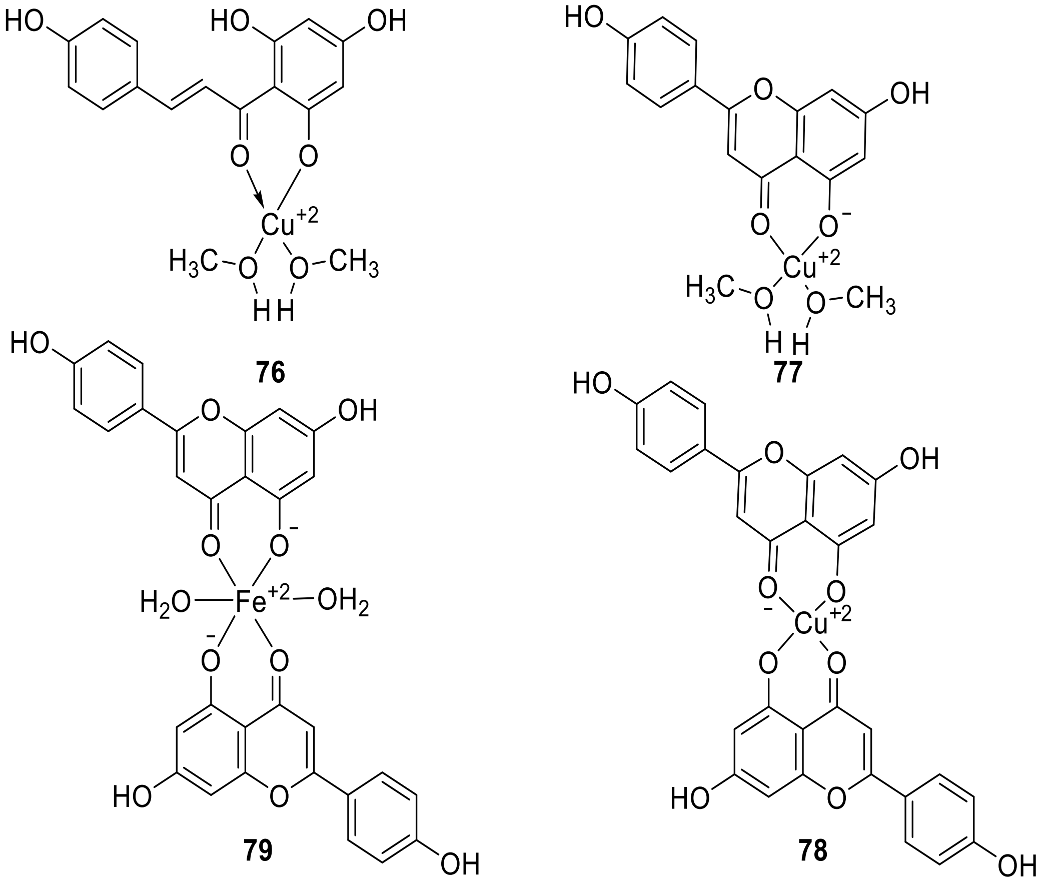
1.6 Organometallic complexes

Given their presence in a variety of biologically relevant processes, metal complex synthesis is a growing field of research in organometallic and bioinorganic chemistry [15,22–24]. Schiff bases are regarded as a significant class of ligands in coordination chemistry with a diverse range of uses [25]. The application of Schiff base ligands in the areas of biology, analytical chemistry, the dye industry, and the food industry is expanded by the introduction and incorporation of the ions of transition metals such as Co^{+3}, Cu^{+2}, Fe^{+3} [26,27].

The free ligand was shown to be less active than the organometal complexes [28]. On the other hand biological activity has been reported to increase and fluctuate in organometal complexes such those in (Figure 1.10) compared to free equivalent organic ligands [2,7,29,30]. (Organometal complexes have greater activity and selectivity) [6].

Figure 1.10

Chemical Structure for plausible Organometallic complexes based on chalcone



76 **77** **79** **78**

Due to their exceptional physicochemical, electrochemical, structural, and catalytic capabilities, complexes of transition metal of Schiff base ligands show phenomenal expansion [31,32]. Many complexes of Schiff bases have exceptional activity that is catalytic for both heterogeneous and homogeneous catalysis through other types of processes [33]. Because of their physiological and pharmacological properties, the ligands of Schiff bases that contain imine groups are extremely important [34].

Organometal complexes demonstrated positive impacts on health, such as anticancer activities [2]. For instance, Genistein (**22**) binding to copper(II) or gold nanoparticle (Figure 6.1 in Appendix A) has been found to boost the rate of scavenging [7,35]. Nephrotoxicity, gametogenesis, neurotoxicity, and the establishment of drug resistance are all potential side effects of metal complexes [6].

Before creating new metal complexes, it should be taken into account that they must possess certain characteristics in order to fulfill the intended function.

1. Have stable molecules and good inherent characteristics.
2. exhibit strong binding characteristics, such as solubility, bond type, and others.
3. engage in selected behavior.
4. serve as effective anticancer metal complexes that interact with blood and membrane transport proteins and, ideally, have activity against tumor cells [2].

Organometallic complexes that can be divided into two categories based on the type of bonding: Complexes with a direct metal-carbon link and those with coordinated metal-ligands [36–38].

The polarity of the carbon-metal link affects an organometallic compound's reactivity: (the compound will be more reactive as a nucleophile when the polarity of the bond is greater) [37].

If the metal of an organometallic compound is less electronegative than the metal of a metal halide and these compounds are combined with each other, transmetallation (metal exchange) will occur (Transmetallation occurs if the alkyl group can be transferred to a more electronegative metal) [37].

1.6.1 Syntheses and Preparation

The characteristics and reactivity of organometallic compounds vary greatly, just like the elements from which they are made. These substances may be transition metal or main group metals like lithium alkyls. There is therefore no one approach that can be used for all substances, but some typical methods include:

1. Metals and Alkyl Halides Reacting.
2. Reactions of 2-Alkyl Group Transfer
3. Metal Halide and Grignard Reagent Reaction
4. Olefin and Hydrogen Reaction with a Metal [38].

It has been determined that the most widely used method for creating organometal complexes is to first dissolve the salt of an organic in an alcoholic or water-based solution, then add the metal salt, likewise in an alcoholic or water-based solution [6,15,28,29,39]. A base is typically employed to enable metal coordination and to make the hydroxyl groups deprotonated. The reaction can be conducted under various stirring and/or heating conditions. Typically, the complex is filtered before being air dried after it separates from the solution [6,15,28,29,39].

The oxygen back-bonding propensity of the metal and the symmetry of the AC of the compounds are two factors that affect how organic compounds attach to metal surfaces [35].

The reactivity and likelihood of forming organometallic compounds increased when a group such as sulfur trioxide or amine was added to an organic ligand, for example, sodium 6,4'-dimethoxyisoflavone-3'-sulfonate (**80**) and amino isoflavones (**81**). In addition to having superior activity than their parent compounds when sulfo-groups are added to isoflavones, isoflavone-sulfonates can also connect with various metal ions in a variety of ways, such as isoflavone-3'-sulfonate binding to cesium ion (**82**) as shown in (Figure 6.3 in Appendix A) [15,40].

Also, their chelation is influenced by the solvent type that is used, the pH levels, the presence of specific sites of chelation in the isoflavonoid's structure, and other factors. The 4-keto and 5-hydroxy groups in the isoflavones would be the most likely metal chelation sites. Chelation with species of transition metals like Ni(II) and Cu(II) has been successful [29].

Examples of techniques to synthesis of organometal complexes as chalcone ligand and organic compound based on chalcone have been studied (Scheme 6.7 in Appendix B).

According to several articles, some chemical ligands, such as isoflavones, hardly ever bind with metal ions [15]. For instance, genistein (**22**) binds to Fe(III) and Cu(II), whereas daidzein was discovered by UV/Vis experiments not to chelate with any of the metals [29].

Because Fe(III) and Cu(II) are two prevalent metal species found in the body of humans and interact with organic ligands and organometal complexes, understanding these interactions is important for determining whether or not the metal interactions will have a positive impact on health [29].

The ability of isoflavones with sites of chelation for 5-hydroxy-4-keto to chelate cupric, ferrous, and ferric ions has been demonstrated and validated, but the cuprous ions Cu(I) didn’t chelate with them. However, compared to other active isoflavonoids or well-known chelators of copper/iron, for all of the aforementioned ions, the affinity was typically lower [13].

1.7 Mechanism

Two pathways have been described for the mechanisms of substitution for organometallic complexes based on chalcone as (isoflavonoid metal complexes). In the first, the outgoing group departs from the metal's coordination sphere before the entering group affixes to it. In addition, they apparently employed an aquation-anation mechanism with the same dissociative properties as the S_N1 method. In consequence, the transition state complex has a lower coordination number than the reactant [38]. In these situations, the concentration of the introducing group has little to no impact on the pace of the reaction throughout a broad concentration range. Because only the complex is involved in the transition state, first-order is the reaction in the complex, and the complex's coordination number in the transition state is one lower than it is in the reactant (Figure 6.4) as shown below [38].

$$ML_nX \xrightleftharpoons{\text{Slow}} \left[ML_n + X\right]^+ \xrightarrow{\text{fast} + Y} ML_nY + X$$

The substitution reaction can be demonstrated in the second, where the entering group begins to connect to the metal before the outgoing group leaves the coordination sphere. It is also described as being associative as the S_N2 mechanism as shown below [38].

$$ML_nX + Y \xrightleftharpoons{\text{Slow}} \left[Y\text{- - -}ML_n\text{- - -}X\right]^+ \xrightarrow{\text{fast}} ML_nY + X$$

The product that contains a portion of organic of the compound of organometallic is interesting in isolating, not the portion of the metal-containing [36]; In organometallic compound synthesis from bonding theoretical work, this is true of many reactions involving organometallic compounds. Lewis acids and bases form coordinate bonds in coordination compounds, which is their key characteristic. Any species with unshared pairs of electrons (one or more) can be nearly Lewis bases, and the Lewis acids can be ions of metal or atoms of metal [38].

Complexes, coordination complexes, or just complexes are several names for coordination chemicals. The formation of coordinate bonds between acceptors of electron pair, or ions of metal or atoms of metal, and electron pair donors, or ligands, is the key characteristic of coordination compounds (Scheme 6.8, Scheme 6.9 in Appendix B) [38].

1.8 Cytotoxic activity of organometallic complexes based on chalcone

The cytotoxic activity of organic molecules like chalcone and flavonoids has been described, and this could also occur in organometallic complexes based on these ligands, despite the fact that organometallic compounds offer many benefits [39]. These complexes' metal atoms can interact with nucleotides of DNA by covalent binding to nucleobases or electrostatic interactions with groups of phosphate (Figure 6.5 in Appendix A). Hence, the isoflavonoids' auto-oxidation produces reactive oxygen species (ROS) and free radicals close to the DNA. This results in DNA oxidative damage and triggers apoptosis [39].

Yet, it has been shown that the complexes of metal can interact with DNA in a non-covalent or covalent manner [28]. The cleavage activity of the complexes is another feature of DNA interaction. This characteristic may enhance their anticancer effectiveness, but it may also harm normal cells' DNA through oxidative stress, leading to cell death. Hence, attempts to improve the complexes selectivity towards cells of cancer are of the utmost significance [2].

In most cases, the metal complexes show higher antioxidant activity than the parent flavonoids; however, the metal complexes with higher antioxidant activity were typically explained by the acquiring an extra radical-scavenging metal core by the complexes [2]. The lower antioxidant activity of the metal (e.g., Cd^{2+}, Sn^{2+}) Complexes can be explained by metal ion chelation, which causes a significant change in the chemical attributes of the organic ligand or may increase oxidation potentials in comparison to the free organic ligand; some metal complexes, particularly those of ions of Fe(III), exhibit prooxidant activity [2].

Organometallic complexes' redox processes are influenced via a number of variables, including the type of metal centers, the positions at which substituents are bound, and potential molecular interactions including axial coordination and aggregation [41].

Some dependant factor has been demonstrated as drugs have showed positive control and growth inhibitory action that is dose-dependent in various cancer cell lines [28].

1.9 Cancer Overview

In the world now, cancer continues to be the second-biggest cause of death [42]. According to the World Health Organization (WHO), there were over 10 million deaths in 2020 [43]. A Disease as cancer occurs when some body cells spread to other body regions and grow without control. In millions of millions of cells that constitute the human body, practically anywhere cancer can be developed [44].

Cells of human often divide (through a cell cycle process, or cell-division cycle) to produce new cells when the body needs them. When old cells die, they are replaced by new ones due to aging or damage. When this process that is systematic fails, cells begin to proliferate and divide when they shouldn't. The tissue masses that formed the tumors can develop from these cells that are aberrant or damaged. Tumors can be either malignant or benign [44].

Malignant tumors can spread and move far in the body to produce new tumors and disseminate into or invade neighboring tissues. On the other hand, benign tumors do not penetrate or spread into the tissues around them. While benign tumors typically don't come back after being removed, the dangerous ones do. However, sometimes the benign can be extremely enormous if left to grow. Some of them, like tumors of the brain, could produce severe symptoms or even be fatal[44].

1.9.1 Cancer Causes

It is regarded as a genetic disease caused by genetic alterations (mutated genes) that affect how the cells grow and divide, and other behaviors. It does have a role in both cell growth and death [4,44]. The inheritance's fundamental building blocks are genes, which could be changed in many ways to cause cancer. The genes are organized in chromosomes, which are tightly packed DNA long strands. The structure of genes and DNA shown in (Figure 6.6 in Appendix A) [44].

The DNA alterations are a reason to change the genes that are involved in the growth of cells regularly to become oncogenes, which are abnormal genes, and because of that, the cell's development becomes uncontrolled [44].

Genetic alterations can occur for many reasons; some of them are:

1. DNA mistakes that happen while cells divide as a result of endogenous sources (cellular metabolic activities). Alkylation, Hydrolysis, base mismatching, and oxidation are all examples of sources of endogenous of DNA damage.
2. DNA damage is brought on by outside sources (environmental factors). One of the most famous sources of exogenous DNA damage are radiation of ionizing (IR), UV radiation from the sun (ultraviolet), and other compounds, such as dangerous elements in the environment and chemicals in tobacco smoke [44,45].
3. They were transmitted to us by our parents [44].
4. Various viruses can also cause cancer in people [46].

Significant evidence that a range of viruses in humans can cause cancer started to emerge in the 1980s. According to the International Agency for Research on Cancer (IARC), there is currently enough proof that human T-cell lymphotropic virus, hepatitis B, virus of human immunodeficiency, human papillomavirus, hepatitis C, virus of human herpes(8), and Epstein-Barr virus are carcinogenic to humans [46].

The emergence of human cancer is influenced by both genetic and epigenetic alterations. It is widely known that the gradual accumulation of genetic alterations plays a role that is significant in the etiology of cancer [47].

The ability of organisms to effectively respond to DNA damages has evolved. Significant impact of apoptosis, senescence, and genomic instability on organismal development speed that could result from DNA damage that is not repaired effectively at the beginning of cellular level. More essential, a loss of genetic integrity puts the organism at risk for cancer, neurological problems, and immunodeficiency [45].

In order for cells to respond effectively to DNA damage, repair pathways and checkpoints for DNA damage must be integrated and coordinated [45].

1.9.2 Comparison between cancerous and normal cells

Cancer cells are different from normal ones. For example:

1. Cancer cells proliferate when there are no signals instructing them to do so. Unlike normal cells, they only do so when they receive a signal.
2. Stop dividing signals.
3. To various parts of the body cancerous cells spread by invading neighboring regions. The bulk of normal cells do not travel throughout the body and halt their growth when cells interact with one another [44].
4. Arteries are ordered to develop toward tumors by cancer cells. These arteries provide nutrition and oxygen to the tumors and transport tumor waste from them.
5. Cancer cells are hiding from the system of immune and avoiding it. Normally, the immune system destroys damaged or abnormal cells [44].
6. Cancer cells fool the immune system into allowing them to survive and thrive. For instance, some cells of tumor convince the immune cells to protect the tumor instead of fighting it.
7. Multiple chromosome alterations, such as duplications and partial deletions, build up in cancer cells' chromosomes. Some cells of cancer contain double the number of chromosomes of normal cells [44].

Cancer cells that have broken off from the initial tumor and spread to distant regions of the body via lymphatic system or the blood, where they depart the arteries to form new tumors, are said to have metastasized [44].

1.10 Cancer treatment

Cancer cells frequently engage in aberrant behaviors that are crucial to their survival. Researchers have developed medicines that target the aberrant properties of cancer cells using this fact. For instance, Some cancer treatments prevent blood vessels from growing toward tumors by targeting specific growth factors, such as cell signaling, angiogenesis, or preventing protein breakdown, effectively denying the tumor of the nutrition it needs [44,48].

There are several cancer treatment options. The most common ones are hormone therapy, chemotherapy, hyperthermia, photodynamic therapy, immunotherapy, radiation therapy, targeted therapy, surgery, and stem cell transplants. The type of cancer a person has and how advanced it is determine the treatment type that person will receive [49].

Only one treatment may be given to some cancer patients. But most patients have a mix of treatments, such as radiation and chemotherapy therapy along the surgery [48,49].

Finding genes, proteins, and other elements (sometimes referred to as biomarkers or tumor markers) that can provide information about cancer is possible by doing a biomarker test. People and their doctors can choose a cancer treatment by using biomarker testing [49].

1.10.1 Cancer treatment side effect

Both cancer and its therapies can cause negative effects. Problems known as “side effects” happen when a treatment affects healthy tissues or organs, such as appetite loss, anemia, (thrombocytopenia) bruising and bleeding, diarrhea, constipation, delirium, sleep issues, urinary and bladder problems, and many other side effects, and its can differ from person to another, even among cancer patients undergoing the same type of cancer treatment [50].

1.11 Chemotherapy treatment

The term "chemotherapy" ("chemo") is usually used to describe treatments for cancer. However, not all cancer medications function the same way. The medications used in standard or traditional chemotherapy are cytotoxic, which means they can destroy tumor cells. Understanding how it functions and what to expect can frequently assist patients in preparing for therapy and making wise choices about their medical care and treatment [51].

Paul Ehrlich, a German chemist who researched how drugs were used to treat infectious diseases is credited with creating the term "chemotherapy." In addition to that, he was the first researcher to use animal models to test a range of compounds for potential disease-fighting properties. Apparently, arsenicals were first used in the 1900s, according to historical records [48].

The use of mustard gas in the Middle East, notably its deployment against people in Syria and Iraq, has recently made headlines. Mustard gas was so named because of its yellow-brown color and mustard scent. The use of mustard agents in American medical research dates back to the World War I (WWI) study of Dr. Edward and Helen Krumbhaar [52].

At least twenty medical researchers had developed mustard chemicals into cancer chemotherapy by World War II(WWII) end. Sulfur mustard (**94**), sometimes called mustard gas, in addition to nitrogen mustard (**95**) (Figure 6.7 in Appendix A), a mustard gas derivative, were both developed as innovative cancer therapies in the 1940s. Until the year 1970, mustard chemicals were still being looked for as potential medical treatments [52]. According to an article, the development of cancer chemotherapy, particularly derivatives of oral like chlorambucil and eventually cyclophosphamide, was significantly influenced in the beginning by the nitrogen mustard effectiveness in the lymphoma treatment [48].

Chemotherapy aims to stop cell division and growth of tumor, preventing metastasis and invasion in the process. However, in addition to the fact that chemotherapy has an effect on normal cells, this also results in hazardous side effects. There are various ways for a cell and its surroundings to stop a tumor from growing [48,52].

Chemotherapy attempts to prevent invasion and metastasis by reducing tumor growth and cell division. However, since chemotherapy also affects normal cells, this causes hazardous side effects. At several levels, both surrounding the cell and inside it,tumor growth can be slowed down [48].

Chemotherapy combination is a popular option to generate suitable responses as well. They seem to promote cytotoxicity in dividing and resting cells, which appears to stop the emergence of resistant clones.[48].

Based on the following fundamental ideas, the chemotherapeutic drugs combination is administered cyclically:

1. No matter how many tumor cells are present, a steady therapy dose only eliminates a consistent portion of them.

2. Neoplastic tumor cells respond linearly to the dose given and the effectiveness.

3. Cancer cells develop spontaneous mutations that lead to medication resistance, according to Goldie-Coldman [48].

1.11.1 Chemotherapy Mechanisms and Their Common Drug Mechanisms

The macromolecular synthesis and function of malignant cells are substantially disrupted by conventional chemotherapy medications, which affect the normal functioning of the preformed molecule or interfere with the production of RNA, DNA, or proteins [48]. The induction of apoptosis or the direct effect of chemotherapeutic agents causes cell death when interference in function or macromolecular synthesis is sufficient. The death of cell may be delayed with conventional medicines. As a fraction of the cells that die as a result of a given treatment, Therefore, to produce a result, the medication may need to be taken again.

Chemotherapeutic drugs, based on their mechanism of action (MOA), can be categorized:

1. **Alkylating Agents** such as: Alkyl sulfonate, Nitrogen mustard (**95**), and analogs of platinum, Ethyleneimine.

- MOA: These medications react with nucleophilic sites on proteins and nucleic acids to produce an unstable alkyl group, R-CH_2^+. prevent transcription and replication of DNA as shown in (Scheme 6.10 in Appendix B) [48,53].

- Toxicity: toxicology that is dose-limited: myelosuppression (neutropenia nadir: 6 to 10 days with recovery in 14 to 21 days). nausea, alopecia, neurotoxicity, and mucositis Chronic side effects include lung fibrosis, infertility, and secondary cancerous tumors [48].

2. **Miscellaneous** as Arsenic trioxide:

- MOA: promotes cells differentiate
- Toxicity: replacement of K and Mg, abnormal heartbeat, and APL differentiation syndrome [48].

3. **Antimetabolites** in general MOA such as methotrexate (**97**) and other foliate antagonists can prevent DNA replication (Figure 6.8 in Appendix A).

- MOA: decreases folate, which is necessary for the synthesis of thymidylate and purine nucleotides.
- Toxicity: Hepatotoxicity, nephrotoxicity, bone marrow suppression, mucositis, and coriaceous sensitivity and reactions
- Toxicity prevention: Leucovorin or folinic acid rescue, hydration, and urine alkalinization [48].

4. **Antimicrotubular agents** such as Topoisomerase I inhibitors: Irinotecan, Topotecan (**98**) (Figure 6.9 in Appendix A)

- MOA: blocks the release of Top I from the cleavable complex and creates a ternary complex to prevent relegation.
- Toxicity: Irinotecan caused diarrhea that is dose-limited. Topotecan caused thrombocytopenia and dose-limiting neutropenia [48,54].

5. **Antibiotics** are agents used in chemotherapy such as actinomycin D (**99**) (Figure 6.10 in Appendix A), bleomycin, and daunomycin:

- MOA: in general inhibiting RNA and DNA synthesis, Single-strand and double-strand DNA breaks are caused by bleomycin's binding to DNA.
- Toxicity: increasing pulmonary toxicity over time and hyperpigmentation [48,55].

1.11.2 Chemotherapy drug resistant and side effect

Chemotherapy resistance: is a complicated process that results from changing the medication targets [56]. It starts after drug exposure but already exists prior to drug exposure or secondary resistance [48].

Several mechanisms of resistance to chemotherapeutic drugs as : drug inactivation, drug target alteration, epigenetic impacts, drug efflux, repairing damaged DNA, inherent cell heterogeneity, cell death inhibition, Epithelial-mesenchymal transition (EMT), any combination of the mechanisms [48,57],and Multi-drug resistance (MDR).

It has been noted in cancer chemotherapy that MDR refers to the ability of cancer cells to survive against a variety of anticancer medications. A decrease in medication absorption in these cells can be a result of increased drug release outside of the cells and may lead to the development of MDR mechanisms[56].

The synthesis of tumor glycoprotein, a molecule that essentially removes the drug from the tumor cell, is carried out through a specific efflux mechanism.

Another mechanism that refers to the Goldie-Coldman theory is tumor cell heterogeneity, in which every tumor cell has a varied degree that is inversely proportionate to the tumor growth [48].

Cell Death Inhibition: Apoptosis and autophagy are two significant regulatory processes that cause cell death. Despite being in opposition to one another, these activities both lead to cell death. Phagolysosomal death, which occurs at an acidic lysosomal pH, initiates autophagy. Drugs like chloroquine (**100**) (Figure 6.11 in Appendix A) and its derivatives stop this process by increasing pH levels in lysosomes, which renders the digestive enzymes inactive. These medications have generally been used to treat malaria, but studies have shown that they can also help cancer cells become more responsive to other medications. For example, chloroquine combined with fluorouracil (**101**) (Figure 6.11 in Appendix A) is more successful in treating cancer cells than fluorouracil alone.[57]

Drug-drug interactions (DDIs) are frequently observed in routine clinical practice, especially while treating cancer patients. Antiepileptic drugs (AEDs) are frequently recommended for individuals with brain malignancies and brain metastases who frequently experience storks or seizures. The chance for DDIs caused between anticancer drugs and AEDs is very big [58].

Administration of chemotherapy medications could be intravenously, intrathecally, subcutaneously, orally, or intrathecally (IT). Most chemotherapy medications are given intravenously due to their 100% absorption rate. Some chemicals, like paclitaxel, must be coupled with solvents like cremophor for more good absorption [48]. Doctors need to understand the factors that influence absorption, particularly for patients with cancer taking opioids, because of their side effects on surgery and stomach motility.

The kidneys or liver are, in general, responsible for the excretion of chemotherapeutic drugs and the body's metabolism. many chemotherapy medications are cytotoxic to the liver or kidneys. There are often many side effects accompanied by the use of therapeutic drugs. Typically, Chemotherapy side effects are a direct reflection of how chemotherapy works as MOA. Cytotoxic chemotherapy frequently targets the DNA and proteins in both healthy host cells and cancer cells [48].

The most common anticancer drug-AED were discovered that caused DDIs are carbamazepine, phenytoin, phenobarbital, primidone, and valproic acid. When AEDs and anticancer medications are provided simultaneously, doctors need to take caution. By choosing alternate AEDs that are less probable to interact, DDIs can be avoided or reduced. To avoid patient toxicity and to guarantee chemotherapeutic adequate and antiepileptic coverage, serum medication concentrations should be constantly monitored if it is necessary and must be to use the combinations of drugs for therapy [58].

In individuals with advanced and/or refractory solid tumors, combining natural medicines with chemotherapy medications may decrease the toxicity risk it produces and offer a practical way of managing and controlling cancer [59].

1.12 Objectives of this study

1. To synthesize the chalcone (E)-3-(4-(dimethylamino)phenyl)-1-(pyridin-2-yl)prop-2-en-1-one (**102**).
1. To synthesize organic ligands based on chalcone (**102**).
2. To synthesize the copper complexes with organic ligands based on chalcone (**102**).
3. To study the effect of organic ligands on cancer cells and compare them with their copper complexes.

Chapter Two

Experimental section

2.1 Chemicals and Instruments

All reagents and materials were obtained from commercial suppliers Sigma-Aldrich. The progress of the reaction was monitored by thin-layer chromatography (TLC) using silica gel. Analytical thin layer chromatography was carried out using aluminum-supported Merck TLC silica gel 60 F254 plates. These plates were visualized using UV light at 254 nm and 365 nm wavelength, colored by potassium permanganate or phosphomolybdic acid, followed by air dryer heating. Flash column chromatography was done with Sigma-Aldrich silica gel, 60 Å pore size and 230-400 mesh, 40-63 µm particle size under 5 psi compressed air.

NMR Spectra were acquired on Bruker AvIII 500 and AVIII-HD 500 spectrometers. NMR analyses were carried out at room temperature in deuterated solvents. Chemical shift measurements are presented as δ in units of ppm relative to the corresponding deuterated NMR solvent (TMS). Coupling constant J was recorded in Hz.

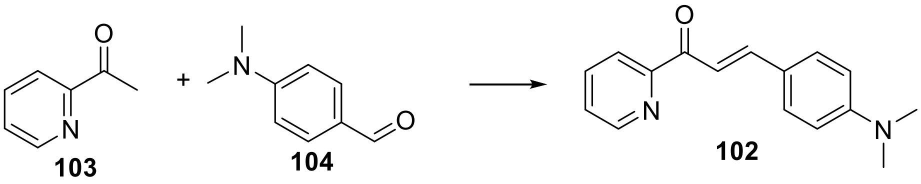
IR spectra were obtained from Fourier-Transform Infrared Spectrophotometer (FT-IR) (Nicolet iS5, iD3 ZnS, Thermo-scientific). HPLC was also used in this study (Waters 1525 binary HPLC pump, Waters 2998 photodiode array detector) to examine the purity of the sample. All reactions were carried out under a nitrogen environment.

The reaction glassware was flame dried or oven dried and cooled under vacuum. Commercially accessible chemicals were used as received unless otherwise noted.

All the samples were evaporated by using Hiedolph, Rotary Evaporator, Vacuo relates to the rotary evaporator with membrane pump at 30-50 mbar. The melting point (m.p.) was determined using digital electro thermal melting point device, were (need to be corrected). The metal complexes were identified and confirmed of existence by Shimadzu UV-Visible Spectrophotometer at range (350-800) nm.

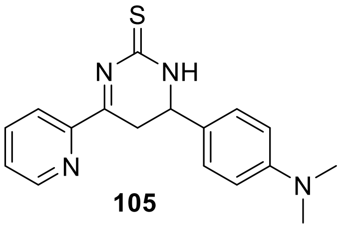
2.1.1 Synthetic procedures

(*E*)-3-(4-(dimethylamino)phenyl)-1-(pyridin-2-yl)prop-2-en-1-one .(102(R1)):



To a solution of 2-Acetylpyridine **103** (2.16 g, 2ml, 17.83 mmol) in methanol (30 mL), 4-N,N-dimethylaminobenzaldehyde **104** (2.66 g, 17.83 mmol) and (5.002 g, 17.83 mmol) KOH were added with stirring. The mixture was stirred for 2h at room temperature (RT). The progress of the reaction was monitored by TLC (ratio of 1:9 ethyl acetate/ n-hexane). Water (20 mL) was added in the end. The yellowish-orange precipitate was filtered after being washed with cold water and then extracted with ethyl acetate (50 ml) three times (the ethyl acetate extract was washed with water and brine and dried over $MgSO_4$). The solvent was removed in vacuo, to obtain desired yellow-orange product **102** (4.48g, 17.77 mmol, 99%), m.p. 138-139.3°C; IR: 2901.26 cm^{-1} (C-H)-sp^2 stretching, 2802.44 cm^{-1} (C-H)-sp^3 stretching, 1685.35 cm^{-1} (C=O) stretching, 1595.87 cm^{-1} (C=C)conj stretching, 1522.22 cm^{-1} (C=C)Ar stretching, 1371.43 cm^{-1} (C-N) stretching (Figure 6.23 in Appendix A). ^{1}H NMR (600 MHz, DMSO-D_6) δ ppm: 8.78 (dd, *J* = 1.8, 0.9 Hz, 1H), 8.77 (dd, *J* = 1.8, 0.9 Hz, 1H), 8.08 (dt, *J* = 7.8, 1.2 Hz, 1H), 8.05 – 8.00 (m, 1H), 8.00 (s, 1H), 7.79 (d, *J* = 15.8 Hz, 1H), 7.68 – 7.62 (m, 3H), 6.79 – 6.73 (m, 2H), 3.01 (s, 6H) (Figure 6.30 in Appendix A). ^{13}C NMR (151 MHz, DMSO-D_6) δ ppm: 188.55 (C=O), 154.67(C-N(Ar)), 152.70(C-$N(CH_3)_2$, 149.56(C=N), 145.82(C=C-Ar), 138.14, 131.29, 127.67, 122.73, 122.45, 115.22, 112.42, 40.18 $N(CH_3)_2$. (Figure 6.31 in Appendix A)

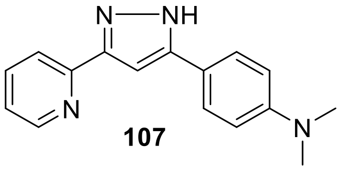
6-(4-(dimethylamino)phenyl)-4-(pyridin-2-yl)-5,6-dihydropyrimidine-2(1H)-thione (105):



105

To a solution of thiourea **106** (0.502 g, 6.59 mmol) in ethanol (20 mL), **102**(**R1**) (1.664 g, 6.59 mmol), and NaOH (0.791 g, 19.7 mmol) were added with stirring. The mixture was refluxed for 2h. The progress of the reaction was monitored by TLC (ratio of 1:9 ethyl acetate/ n-hexane). Water (15 mL) was added in the end. The dark orange precipitate was filtered after being washed with cold water and then extracted with ethyl acetate (30 ml) three times (the ethyl acetate extract was washed with water and brine and dried over $MgSO_4$). The solvent was removed in vacuo, to obtain desired dark orange product **105** (2g, 6.45 mmol, 98%); IR: 3373.19 cm^{-1} (N-H) stretching, 3179.91 cm^{-1} (C-H)-sp^2 stretching, 3059.38 cm^{-1} (C-H)-sp^3 stretching, 1612.66 cm^{-1} (C=NCS) stretching, 1546.76 cm^{-1} (C=NC) stretching, 1523.18 cm^{-1} (C=C)Ar stretching, 1461.21 cm^{-1} (C-N(CH_3)$_2$) stretching, 1414.03 cm^{-1} (SC-N) stretching (Figure 6.24 in Appendix A), ^{1}H NMR (600 MHz, DMSO-*D*$_6$) δ ppm: 9.25 (s, 1H), 8.91 (s, 1H), 8.62 (t, *J* = 0.1 Hz, 1H), 7.93 (ddt, *J* = 8.2, 2.5, 1.1 Hz, 1H), 7.87 (tt, *J* = 7.8, 2.0 Hz, 1H), 7.42 (dddd, *J* = 7.3, 5.0, 2.1, 1.1 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.72 (t, *J* = 1.6 Hz, 2H), 6.10 (t, *J* = 4.8 Hz, 1H), 5.09 (td, *J* = 4.8, 1.8 Hz, 1H), 3.38 (s, 6H), 3.36 (d, *J* = 3.1 Hz, 1H), 2.86 (s, 3H). (Figure 6.32 in Appendix A), ^{13}C NMR (151 MHz, DMSO-*D*$_6$) δ ppm: 174.11(C=S), 150.76(C=N-CS), 149.00 (C-N(Ar)), 148.91 (C-N(CH_3)$_2$, 148.53 (C=N-C), 138.00, 131.47, 130.74, 128.43, 127.99, 127.82, 124.50, 119.91, 113.52, 113.32, 103.19, 55.35 (C-N-H), 54.55,40.65 N(CH_3)$_2$. (Figure 6.33 in Appendix A)

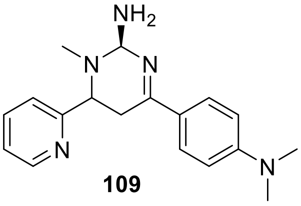
N,N-dimethyl-4-(3-(pyridin-2-yl)-4,5-dihydro-1H-pyrazol-5-yl)aniline (107):



107

To a solution of **R1 102** (0.2 g, 0.79 mmol) in ethanol (10ml), hydrazine $N_2H_4.H_2O$ (**108)** (0.0436 g, 6.879 mmol) and NaOH (0.94 g, 23.7mmol) were added. The mixture was refluxed for three days under nitrogen and the reaction was monitored by TLC (ratio of 2:8 n-hexane/ ethyl acetate). After cooling, water (10 ml) was added and was then extracted with ethyl acetate (20 ml) three times. The ethyl acetate extract was washed with water and brine and dried over $MgSO_4$. The solvent was removed in vacuo, then it was purified by silica gel column chromatography using n-hexane/ ethyl acetate solvent systemin in ratio of (15:85) to obtain grey product **107** (0.01 g, 0.0378 mmol, 4.8%); IR: 3598.36 cm^{-1} (N-H) stretching, 3279.80 cm^{-1} ((C-H)-sp^2 beside NH) stretching, 2879.16 cm^{-1} (C-H)-sp^2 stretching, 2800.00 cm^{-1} (C-H)-sp^3 stretching, 1615.19 cm^{-1} (C=C) Ar stretching, 1540.05 (C=CNH) stretching, 1480.67 cm^{-1} (C=N) stretching, 1356.32 cm^{-1} ($C-N(CH_3)_2$) stretching (Figure 6.25 in Appendix A). ^{1}H NMR (600 MHz, DMSO-D_6) δ ppm: 8.58 (d, *J* = 4.7 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.84 (t, *J* = 7.7 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.30 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.08 (s, 1H), 6.77 (d, *J* = 8.8 Hz, 2H), 2.93 (s, 6H), 1.21 (d, *J* = 4.7 Hz, 1H) (Figure 6.34 in Appendix A). ^{13}C NMR (151 MHz, DMSO-D_6) δ ppm: 150.59 (C-N(Ar)), ($C-N(CH_3)_2$, 149.81(C=N-N), 149.67(C=N-C), 137.43(C-N-H), 126.60, 123.10, 119.94, 113.27, 112.94, 112.82, 112.34, 40.26 $N(CH_3)_2$ (Figure 6.35 in Appendix A).

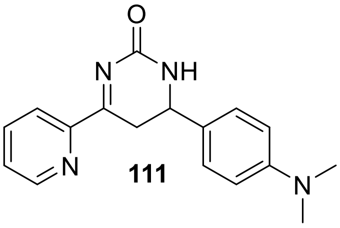
(2R)-4-(4-(dimethylamino)phenyl)-1-methyl-6-(pyridin-2-yl)-1,2,5,6-tetrahydropyrimidin-2-amine (109):



109

As the previous procedure for compound (**107**), except that to a solution of 1-methylguanidin hydrochloride **110** (0.043 g, 0.396 mmol) in ethanol (10 mL), R1(0.1 g ,0.396 mmol) and NaOH (0.0475, 1.18mmol) were added. It was purified by silica gel column chromatography using the diethyl ether/ ethyl acetate solvent system in ratio of (7:3) to obtain brownish purple product **108** (0.03 g, 0.097 mmol, 24.52%); IR: 2918.98 cm^{-1} (C-H)-sp^2 stretching, 2852.81 cm^{-1} (C-H)-sp^3 stretching, 1664.09 cm^{-1} (C=N) stretching, 1523.18 cm^{-1} (C=C)Ar stretching, 1432.9 cm^{-1} (C-N(CH$_3$)$_2$) stretching, 1359.76 cm^{-1} (HNC-N) stretching (Figure 6.26 in Appendix A).

6-(4-(dimethylamino)phenyl)-4-(pyridin-2-yl)-5,6-dihydropyrimidin-2(1H)-one (111):



111

As the procedure for compound (**107**), except that to a solution of Urea **112** (0.0476 g, 0.79 mmol) in ethanol (10 mL), **R1 (102)** (0.2 g, 0.79 mmol) and NaOH (0.94g, 2.3 mmol) were added. It was purified by silica gel column chromatography using the diethyl ether/ ethyl acetate solvent system in ratio of (8:2) to obtain brown product **111** (0.0464 g, 0.158 mmol, 20%); IR: 3355.64 cm^{-1} (N-H) stretching, 2901.71 cm^{-1} (C-H)-sp^2 stretching, 2858.88 cm^{-1} (C-H)-sp^3 stretching, 1733.70 cm^{-1} (C=O) stretching, 1630.20 cm^{-1} (C=NCO) stretching, 1595.19 cm^{-1} (C=C)Ar stretching, 1554.01 cm^{-1} (C-N(Ar)) stretching, 1521.64 cm^{-1} (C-N(CH$_3$)$_2$) stretching, 1463.25 cm^{-1} (CH$_3$)$_2$ bending, 1204.09 cm^{-1} (N-CO) stretching (Figure 6.27 in Appendix A).

2.1.2 Organometallic reaction procedures

To prepare the desired complexes **113**, **114**, **115**, **116**, **117**, and **119**, 2 equiv. of **105**, **107**, **109**, and **111** ligand**s** were dissolved individually in 15-ml ethanol then added dropwise to 5 mmol of $CuCl_2.2H_2O$ dissolved in 20 ml of ethanol solution, the reaction mixture was placed under vigorous stirring for 3-6h. The completeness of the reaction was monitored by color changes from yellow to purple. The reaction mixture was left for 2 days until all the solvent was evaporated; the residue was then washed well with 20 ml ethyl acetate and filtered to have 80-92% yields.

2.1.3 Cell line cell culture

Mouse embryonic fibroblast-1 (MEF-1) cells from the American Type Culture Collection (ATCC, Manassas, VA, USA) were cultured in McCoy's 5a Medium Modified, Wako, Japan) containing 10% fetal bovine serum (FBS. HyClone. Logun. UT. USA) and 1% penicillin streptomycin (P/S) (Nacalai Tesque, Kyoto, Japan). Melanoma cell line (B16F10) were cultured in Dulbecco's Modified Eagle Medium (DMEM, Gibco, Waltham, Massachusetts, USA) supplemented with 10% (v/v) FPS and P/S.

(MEF-1) cells maintained in DMEM high glucose with L-glutamine, phenol red (Wako, Japan) medium containing 10% of FBS. And 1% (P/S).

2.1.4 Drug treatment in vitro

Each of the compounds (**102**, **105**, **107**, **109**, **111**, **113**, **114**, **118, and 119**) was dissolved in sterile DMSO and diluted in DMEM to make the desired concentrations. These compounds, with concentrations of 5-50 µm range, were added to in vitro cultures.

2.1.5 Cell Proliferation Assay

Melanoma cell line B16F10 cells (1 x 10^5 cells/ well) were seeded in 24-well plates (TPP, Switzerland) and kept overnight. Then, cells were cultured for an additional 24 hours after the addition of each compound in DMSO in four concentrations (0, 5 µM, 10 µM, 50 µM) and control, and the number of viable cells (after trypan blue staining) were determined but counting as a measure of cell viability.

Chapter Three

Result and Discussion

3.1 Chemical Result and Discussion

The first step in the synthesis of organometallic complexes based on chalcone is to synthesize a chalcone (**102**). The key chalcone was prepared via condensation of (**103**) with (**104**) followed by dehydration. The first step in the mechanism was formation an enolate anion by KOH as a base. The yield of chalcone (**102**) was 99% as a sole yellowish orange product because there's only one site for enolization, as there is only one position for α protons (Scheme 6.11 in Appendix B).

It was observed that compound (**102**) reacts with dichloromethane (DCM) as the color changes quickly to a reddish purple while working in the lab, and that was confirmed using IR (Figure 6.28 in Appendix A), NMR (Figure 6.36, Figure 6.37 in Appendix A), UV-Vis (Figure 6.43 in Appendix A), and by measuring the m.p. which was for **R5** (**118**) 249-259 °C while **R1** (**102**) was 138-139.3°C .The product **R5** (**118**) (Figure 6.12) was obtained by a reaction of DCM with the basic nitrogen of the pyridine ring in the chalcone (**102**).

This reaction needs a long time to be completed and may produce a long chain-based **102** compound, but the major product is compound **118**. DCM was then prohibited from being used in extraction processes for the rest of the experiments.

All reactions were done in basic media. The yield for the product of compounds (**105**, **107**, **109**, and **111**) was low in the basic condition, and that was discovered and confirmed by repeating the experiments under the same conditions again, and the same thing was observed. Some experiments took a week or more in the beginning, so when there was no change in the rate of reaction, the reactions were stopped early when they were repeated.

Compounds (**105**, **107**, **109**, and **111**) can be produced in reactions via 1,2 or 1,4 addition mechanisms (Scheme 6.12 - Scheme 6.16 in Appendix B). The reaction can be reversible or irreversible depending on the charge, the nature of the reactant, and each side of the reaction.

The compounds (**105**, **107**, **109**, and **111**) obtained through the same procedure but with different yields as brown product **111** (0.0464 g, 0.158 mmol, 20%), brownish purple product **109** (0.03 g, 0.097 mmol, 24.52%), grey product **107** (0.01 g, 0.0378 mmol, 4.8%), dark orange product **105** (2g, 6.45 mmol, 98%).

The reason for the high yield of compound (**105**) that resulted from reacting compound **106** with chalcone (**102**) is that compound **106** has less basicity and behaves like an acid that donates a proton in basic media, which increased the charge and polarity of the compound **106** and produced a strong nucleophile that increased the rate of reaction and yield. In this case, the nucleophile adds irreversibly, the reaction is kinetically controlled, and the compound **105** is the kinetic product, and it's the only product.

It was observed that when the basicity increased for the compounds (**107**, **109**, and **111**) in basic media, the rate of reaction and yield decreased, and these compounds added reversibly. The reaction is thermodynamically controlled, so it is recommended to use an acidic catalyst such as sulfuric acid to increase the rate of the reaction and the yield.

Chalcone **102** showed an Abs at a range of λ_{m}(432 – 432.5) nm (Figure 6.38 in Appendix A) that differs from compounds (**105**, **107**, **109**, **111**, **and 118**)(Figure 6.39, Figure 6.40, Figure 6.41, Figure 6.42, Figure 6.43 in Appendix A), and the closest Abs to it was compound (**111**) with a range of λ_{m}(414 – 415).

All compounds have the ability to be fluorescent as they contain a dimethylamino group and have electron push-pull pairs, but as the compounds can form hydrogen bonds with the solvent, their fluorescent intensity decreases. In addition, the compounds were able to be detected in TLC at 254 nm and 365 nm wavelengths.

Another factor to consider is that because the compounds have conjugate systems, they have the ability to produce resonance. For example, compound (**105**) could exist in tautomeric forms (Figure 6.13 in Appendix A) as was shown in the NMR spectra as (S-H) could be in ^{1}H NMR at δ 1.23, and ^{13}C NMR at δ 174.11 for (C-S). Density functional theory (DFT) calculations may confirm the existence of tautomerization.

Yellow to purple products (80-92%) were obtained in the synthesis of organometallic compounds (**113**, **114**, **115**, **116**, **117**, and **119**) based on chalcone (**102**). A sharp change in color and the production of precipitate were indicators of the starting and occurrence (Figure 6.14 in Appendix A).

The chemical structure for each compound was determined (Figure 6.15 - Figure 6.20 in Appendix A) based on the chelating site in the organic ligand (**105**, **107**, **109**, **111**, **and 118**), the chelating effect of these ligands, less steric hindrance, and checked by silver nitrate ($AgNO_3$). For the best structural characterization, X-ray crystallography is needed, which needs to produce crystals for each compound and complex.

Plausible structure for copper (Cu(II))complex (**113**, **114**, **115**, **116**, **117**, and **119**)are listed in the figures below

The complex **117** was discovered to be neutral (Figure 6.19 in Appendix A), which means that the Cl was removed in the first step, the oxygen was attracted with copper in the center, and this was checked by $AgNO_3$, resulting in no precipitate.

The production of complexes (**113**, **114**, **115**, **116**, **117**, and **119**) was confirmed using UV-VIS (Figure 6.38, Figure 6.39, Figure 6.40, Figure 6.41, Figure 6.42, and Figure 6.43 in Appendix A).The results for both IR and NMR were compatible for the compounds .The copper complexes was synthesized via $S_N1$or S_N2 mechanism, but S_N2 associative mechanism is favored here, as the solvent is polar and the charge of metal. In addition, it was observed that these compounds need to be saved in the desiccator as they react with water.

3.2 Biology

We use HPLC to ensure the purity of each compound before using it in the biology experiments.

After adding each compound to normal cells as MEF cells in four concentrations (0.5 µM, 10 µM, 50 µM), it was found that all compounds are toxic to MEF cells, and the compounds that are best for use and have less toxicity are: urea (**111**), chalcone (**102**), and chalcone complex (**113**), as shown in the (Figure 6.21 in Appendix A), where urea is the less toxic one.

In the second part, after adding each compound to cancer cells as Melanoma cell (B16F10) cells in four concentrations (0.5 µM, 10 µM, 50 µM), it was found that the toxicity to melanoma cell (B16F10) cells is lees than to MEF cells, and the compounds that are best for use and have higher toxicity are: chalcone (**102**), and chalcone complex (**113**), as shown in (Figure 6.22 in Appendix A).

It is obvious that the reactivity of the complex is greater than that of the ligand, and it must be taken into consideration that the type of metal has an impact on the ligand's antioxidant or anticancer ability, as copper has an antioxidant effect.

From these results, the product (**118**) differs from chalcone (**102**) in behavior, and this confirmed the reaction of chalcone (**102**) with DCM.

3.3 Conclusion

- 10 novel compounds were synthesized and characterized based on the chalcone (**102**); 5 of them are organic ligands, and the other is their copper complex.
- They were synthesized by condensation reactions in basic media.
- They were synthesized by nucleophilic addition as 1,2 or 1,4.
- The reaction of DCM with the chalcone (**102**) was confirmed.
- All organic compounds have a conjugated chemical system that enables them to bind and interact with copper II, normal cells, and cancer cells.
- All compounds have shown toxicity to normal cells and less toxicity to melanoma cells; it's been found that the chalcone (**102**) and its copper complexes are best to use as anticancer agents.
- Copper complexes with chalcone have shown potent biological activities, making them promising drug candidates. Their ability to inhibit the growth of cancer cells has garnered attention for their potential use as therapeutic agents.
- This research advances our understanding of the reaction conditions required for the synthesis of the aforementioned compounds and improves their behavior.
- This study needs to be supported by X-ray crystallography.
- To determine their toxicity and pharmacokinetic properties, as well as optimize their biological activities and improve their stability, more research is required.
- Furthermore, more research is needed to investigate their potential use in combination with other therapeutic agents.

List of Abbreviations

Abbreviations	Meanings
$h\nu$	Sunlight, Photon Energy
t-BuOK	tert-butoxide
DME	1,2-dimethoxyethane
rfx	Reflux
S_N1	Nucleophilic substitution associative reaction mechanism
S_N2	Nucleophilic substitution dissociative reaction mechanism
DPPH	2,2-diphenyl-1-picrylhydrazyl
$PdCl_2$(DTBPF)	1,1′-Bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II)
ROS	Reactive oxygen species
WHO	World Health Organization
NMR	Nuclear magnetic resonance
HPLC	High Performance Liquid Chromatography
UV	Ultraviolet
UV-Vis	Ultraviolet-Visible
IR	Infrared spectroscopy
IARC	International Agency for Research on Cancer
IT	Intrathecally
RNA	Ribonucleic acid
DNA	Deoxyribonucleic acid
WWI	World war one
WWII	Second world war
TOP1	Topoisomerase I
5-FU	Fluorouracil
AEDs	Antiepileptic drugs
DDIs	Drug-drug interactions
EMT	Epithelial-mesenchymal transition
MDR	Multi-drug resistance
MOA	mechanism of action
DMEM	Dulbecco’s Modified Eagle Medium
ATCC	American Type Culture Collection
MEF-1	Mouse embryonic fibroblast-1
B16F10	Melanoma cell line

P/S	Penicillin Streptomycin
VA	Virginia
USA	United Stat of America
UT	Utah
TPP	Techno Plastic Products
DMSO	Dimethyl sulfoxide
v	Volume
w/v	Weight by volume
H, h	Hour
TLC	Thin-layer chrootography
CC	Column chromatography
m.p	Melting point
TBDMSCl	Tert-butyldimethylsilyl chloride
MACIR	Microwave-assisted coupling isomerization reaction
TEA	Triethyl amine
Min	Minute
nm	Nanometer
^{o}C	Celsius
G, g	Gram
%	Percent
mL	Milliliter
mg	Milligram
µL	Micro-liter
µg	Micro-gram
M	Molar concentration
TBFA	Tetra-n-butylammonium fluoride
µM	Micro-Molar
Fig.	Figure
Temp.	Temperature
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy

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Appendices

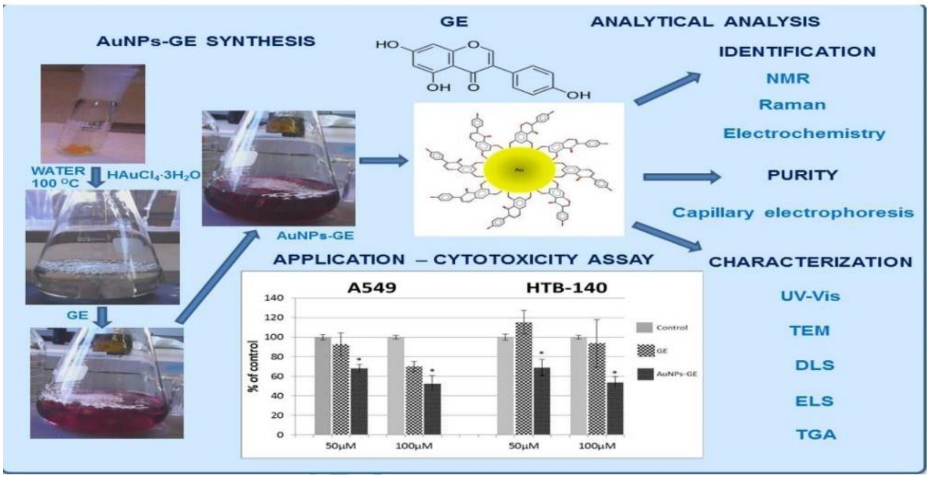
Appendix A

Figures

Figures of Chapters 1–3

Figure 6.1

*Structural and methods to characterization and synthesis of conjugated Genistein (**22**) with gold nanoparticles*



Stolarczyk, Stolarczyk et [35]

Figure 6.2

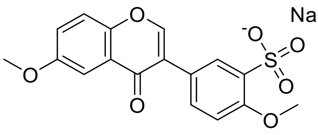
Plausible carbon-metal bond could be formed

$\overset{\delta-}{\mathrm{C}}-\overset{\delta+}{\mathrm{Cd}}$ $\overset{\delta-}{\mathrm{C}}-\overset{\delta+}{\mathrm{Pd}}$ $\overset{\delta-}{\mathrm{C}}-\overset{\delta+}{\mathrm{Li}}$ $\overset{\delta-}{\mathrm{C}}-\overset{\delta+}{\mathrm{Cu}}$ $\overset{\delta-}{\mathrm{C}}-\overset{\delta+}{\mathrm{Mg}}$

$\overset{\delta-}{\mathrm{C}}-\overset{\delta+}{\mathrm{Hg}}$ $\overset{\delta-}{\mathrm{C}}-\overset{\delta+}{\mathrm{Ru}}$ $\overset{\delta-}{\mathrm{C}}-\overset{\delta+}{\mathrm{Al}}$ $\overset{\delta-}{\mathrm{C}}-\overset{\delta+}{\mathrm{Pb}}$ $\overset{\delta-}{\mathrm{C}}-\overset{\delta+}{\mathrm{Zn}}$

Figure 6.3

Plausible Chemical structure for some isoflavonoids metal complexes synthesized



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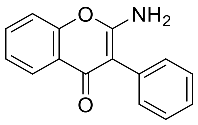
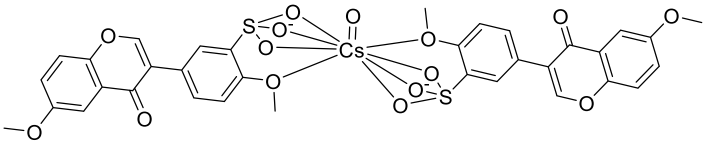


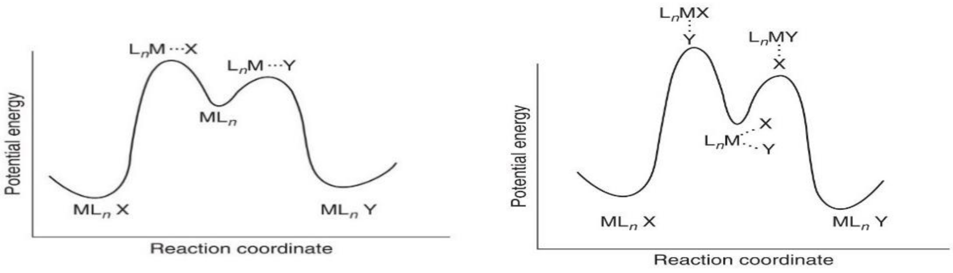
81



isoflavone-3'-sulfonate binding to cesium ion (**82**)

Figure 6.4

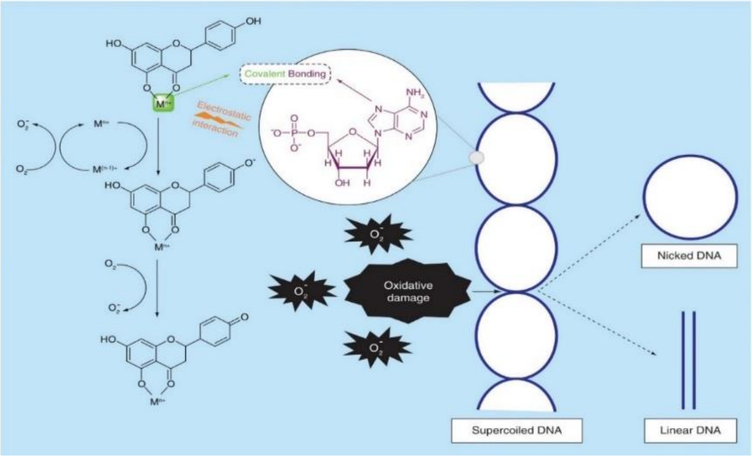
Energy profile for dissociative as S_N1 mechanism (left) and associative as S_N2 mechanism (right)



House 2008 - Inorganic ch (3)[38]

Figure 6.5

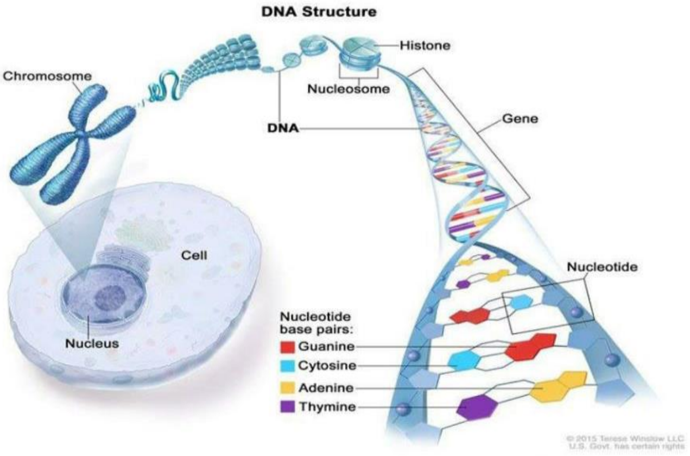
Plausible oxidative DNA damage mechanism by organometal complexes



Khater, Ravishankar et al [39]

Figure 6.6

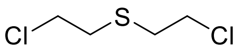
Genes and DNA structure



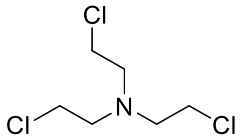
National Cancer Institute [44]

Figure 6.7

*Chemical structure of sulfur mustard (**94**) and nitrogen mustard (**95**)*



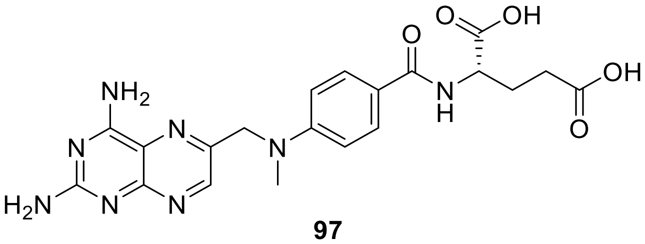
94



95

Figure 6.8

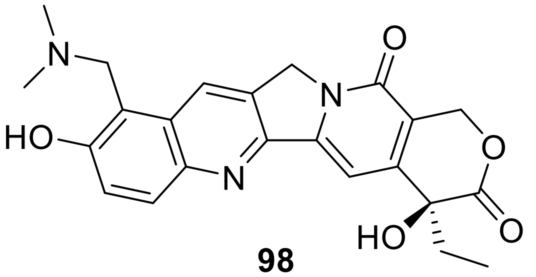
*Chemical structure of methotrexate (**97**)*



97

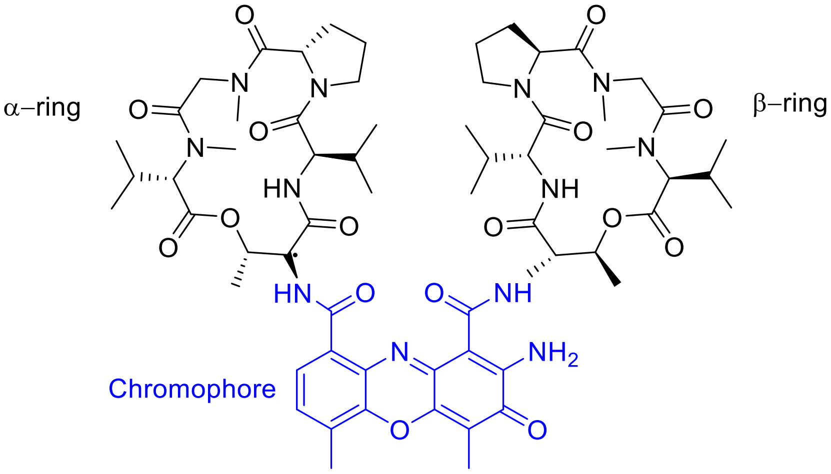
Figure 6.9

*Chemical structure of Topotecan (**98**)*



98

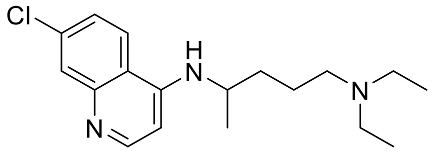
Figure 6.10
*Chemical structure of actinomycin D (**99**)*



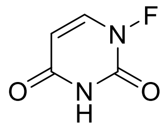
99

Figure 6.11

*Chemical structures of chloroquine (**100**) and fluorouracil (**101**)*



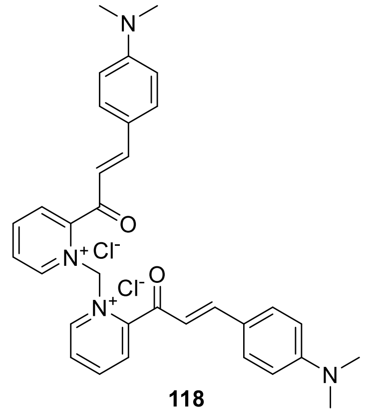
100



101

Figure 6.12

*Plausible chemical structure for compound (**118**) 1,1'-methylenebis(2-((E)-3-(4-(dimethylamino)phenyl)acryloyl)pyridin-1-ium)*



118

Figure 6.13

*Plausible tautomeric compounds for compound **105***

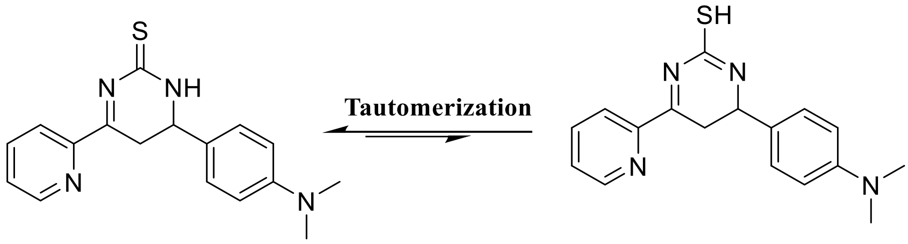


Figure 6.14

Color change and the production of precipitate in the synthesis of organometallic compounds ***(113, 114, 115, 116, 117, and 119)***

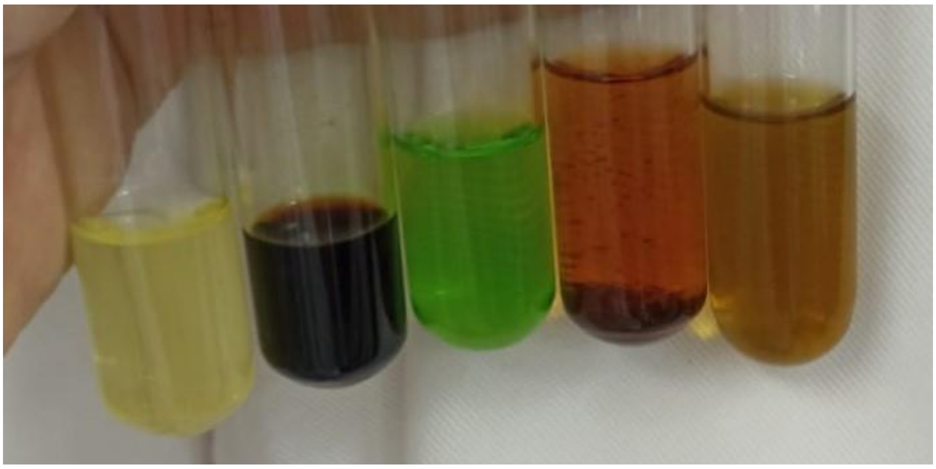
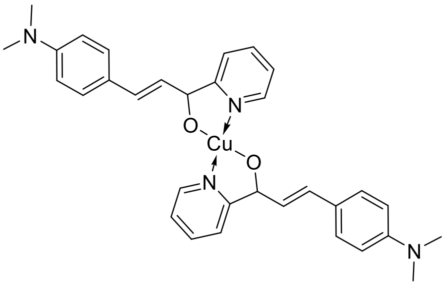
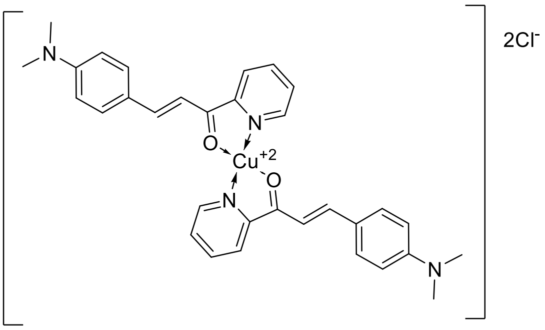


Figure 6.15

*Plausible structure for complex (**113**)*



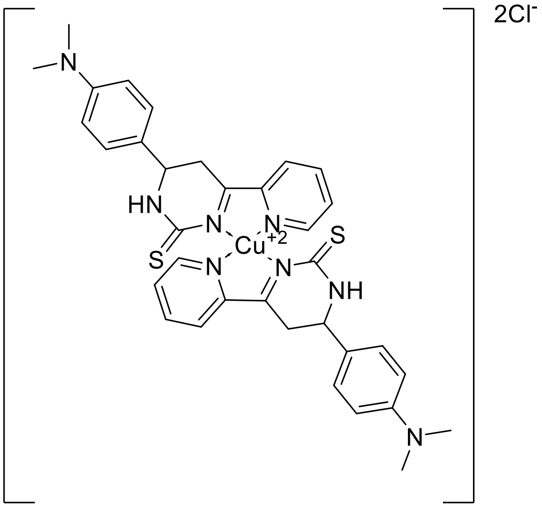
113 neutral



113 Ion

Figure 6.16

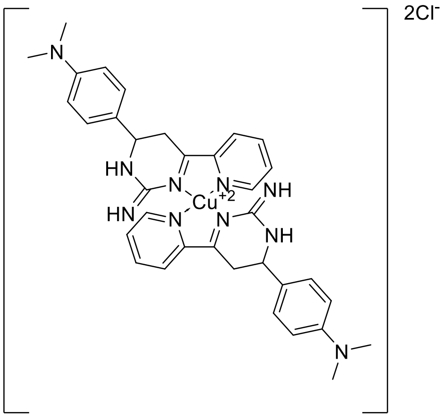
*Plausible structure for complex (**114**)*



114

Figure 6.17

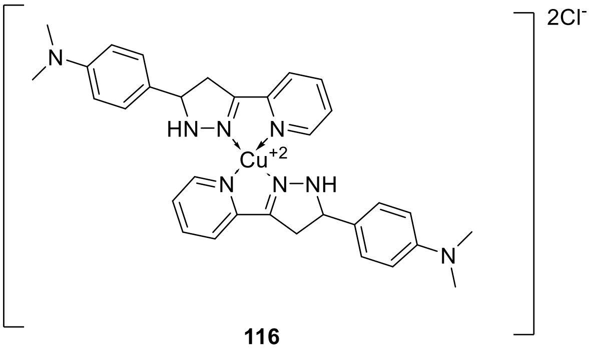
*Plausible structure for complex (**115**)*



115

Figure 6.18

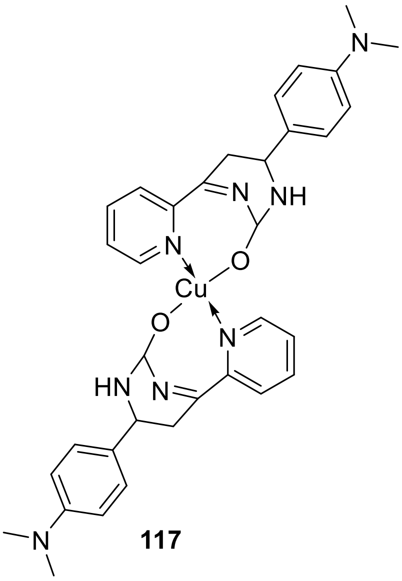
*Plausible structure for complex (**116**)*



116

Figure 6.19

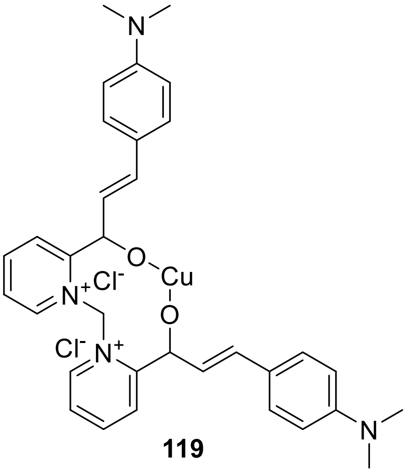
*Plausible structure for complex (**117**)*



117

Figure 6.20

*Plausible structure for complex (**119**)*



119

Figure 6.21

*Cell proliferation assay after adding compounds (**102 ,105 ,107 ,109 ,111 ,113 ,114 ,118 , and 119**) to MEF cells*

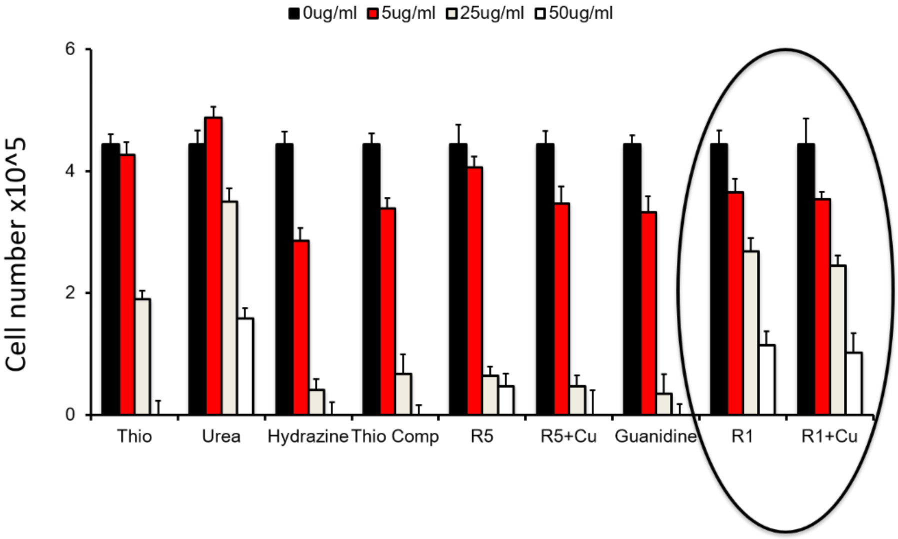
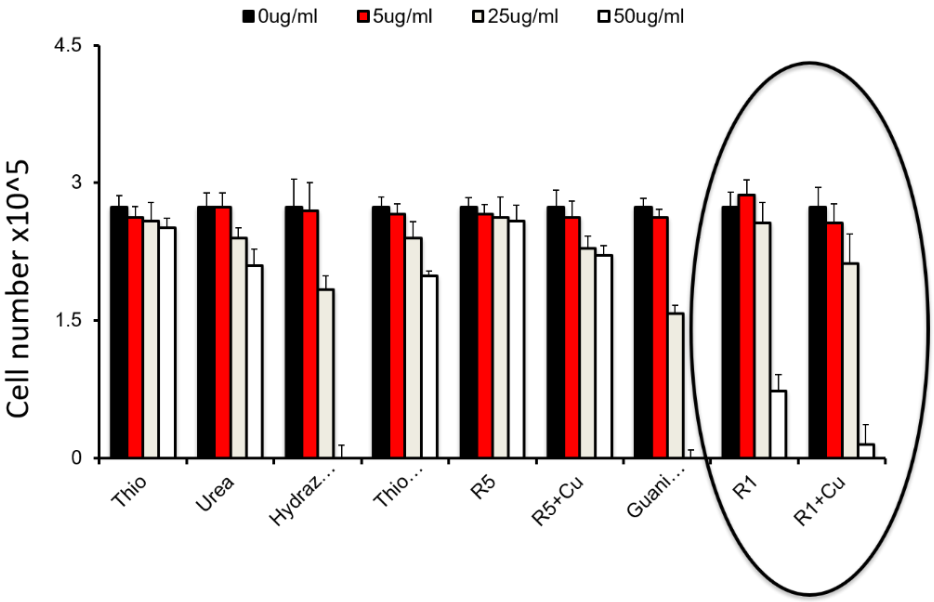


Figure 6.22

*Cell proliferation assay after adding compounds **(102,105, 107, 109, 111, 113, 114,118 ,and 119**) to Melanoma cell **(B16F10**) cells*



IR Spectra:

Figure 6.23

*IR Spectra for compound (**102**) **R1***

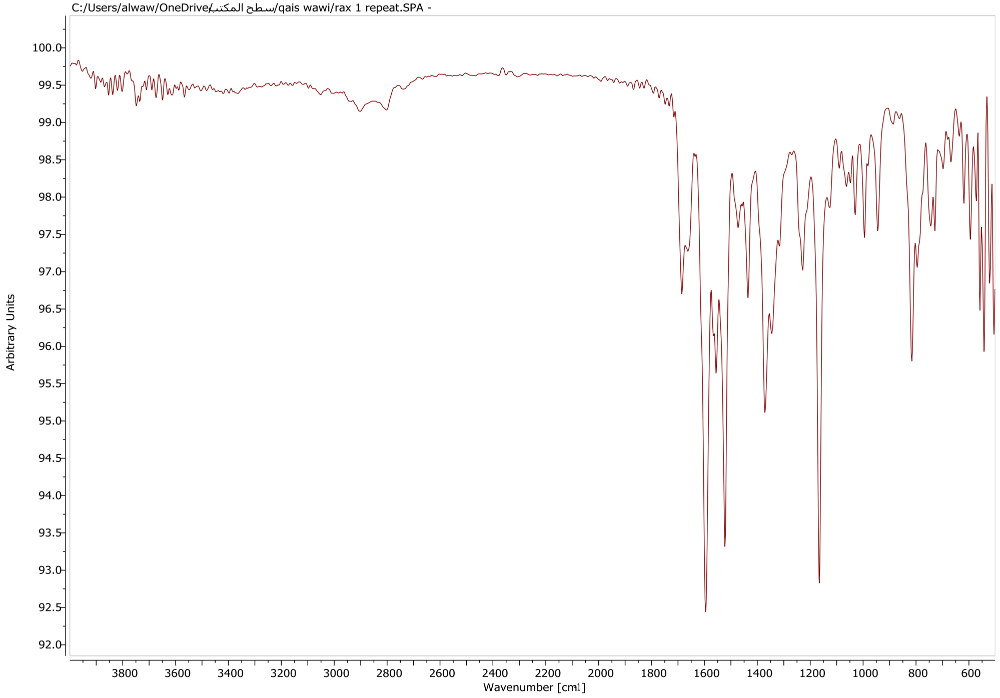


Figure 6.24

*IR Spectra for compound (**105**) **Thio***

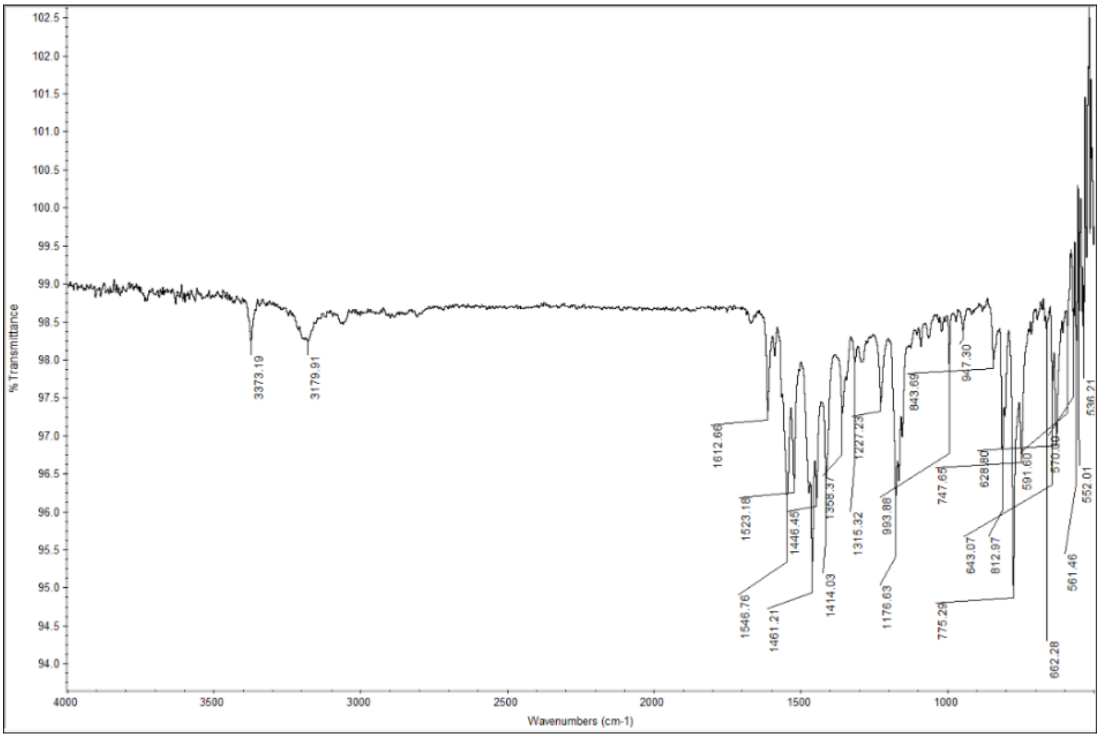


Figure 6.25

*IR Spectra for compound (**107**)*

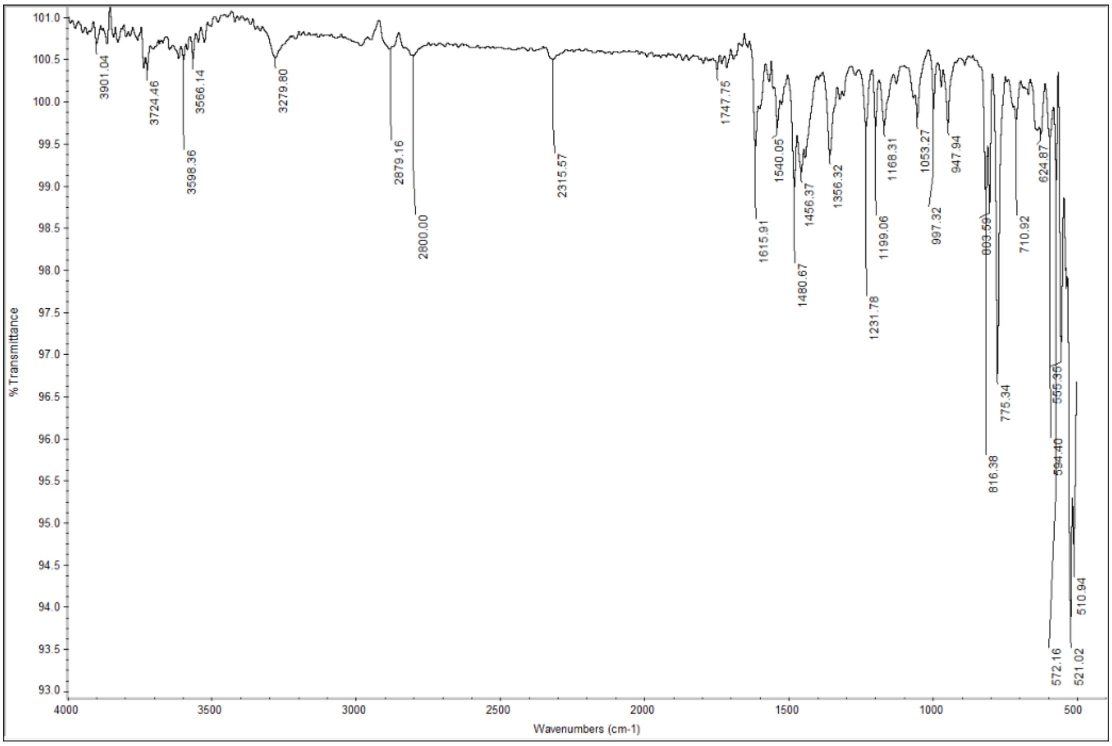


Figure 6.26

*IR Spectra for compound (**109**) Guanidine*

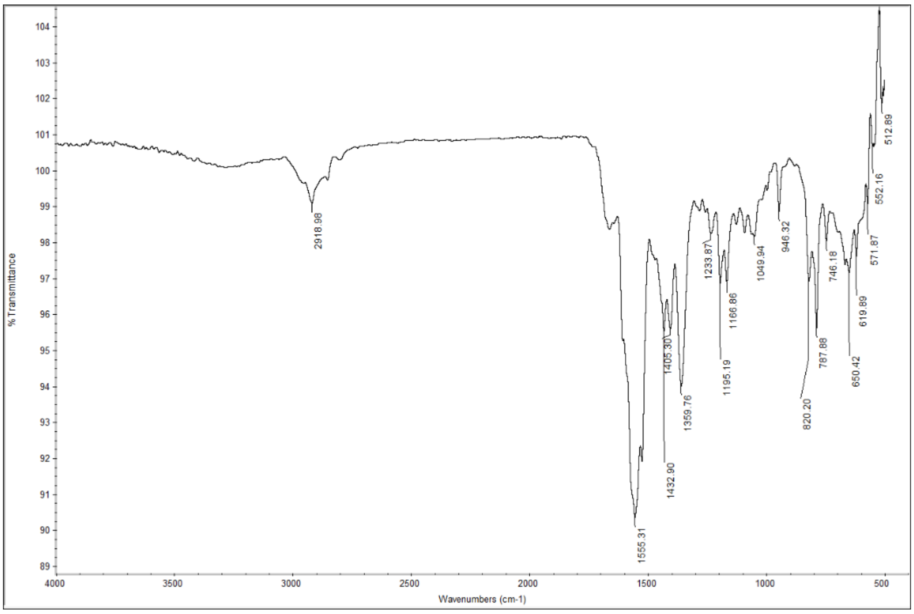


Figure 6.27

*IR Spectra for compound (**111**) **Urea***

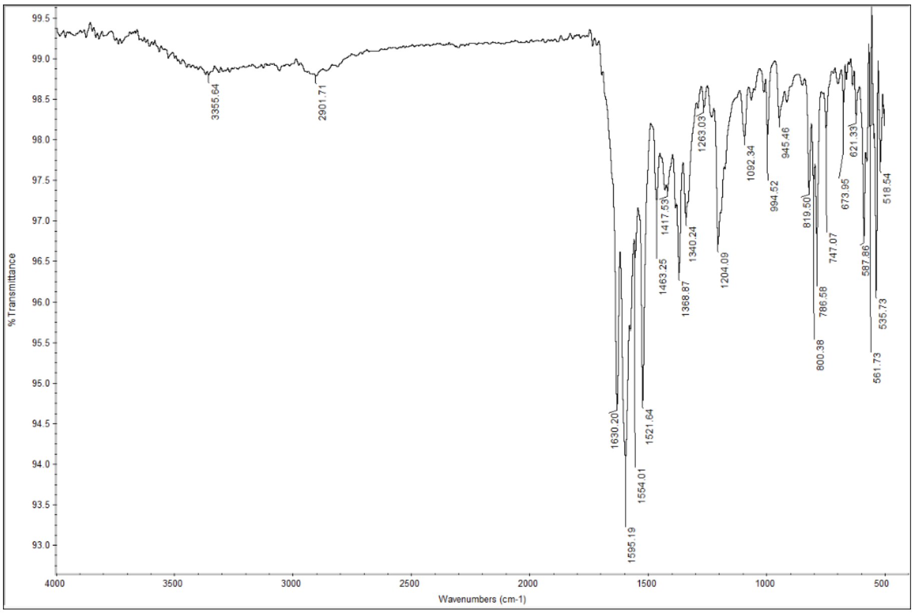


Figure 6.28

*IR Spectra for compound (**118**) **R5***

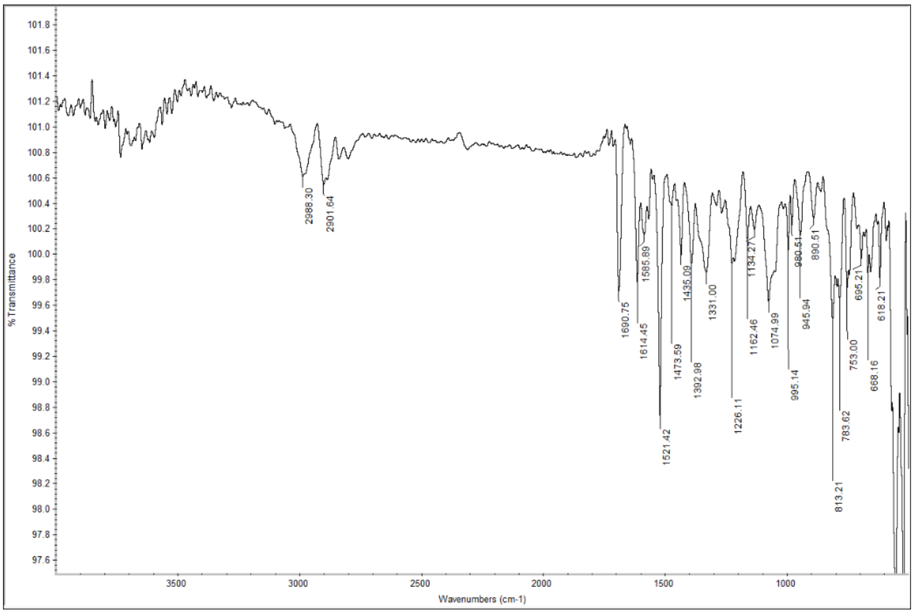
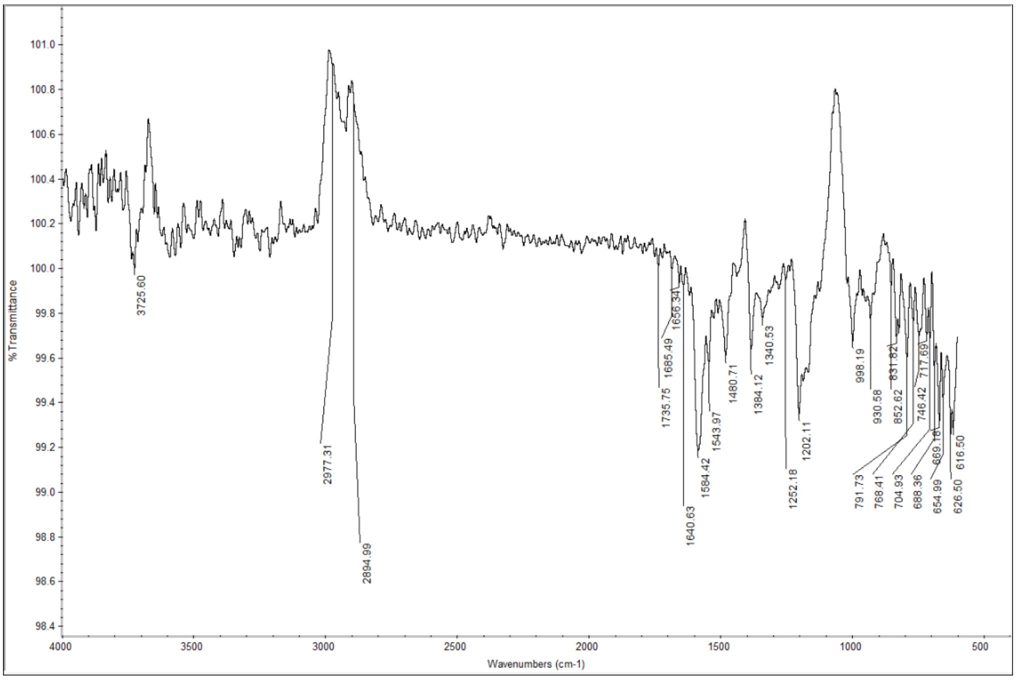


Figure 6.29

*IR Spectra for compound (**114**) **Thiocomplex***



NMR Spectra

Figure 6.30

*^{1}H-NMR spectra for compound (**102**) **R1***

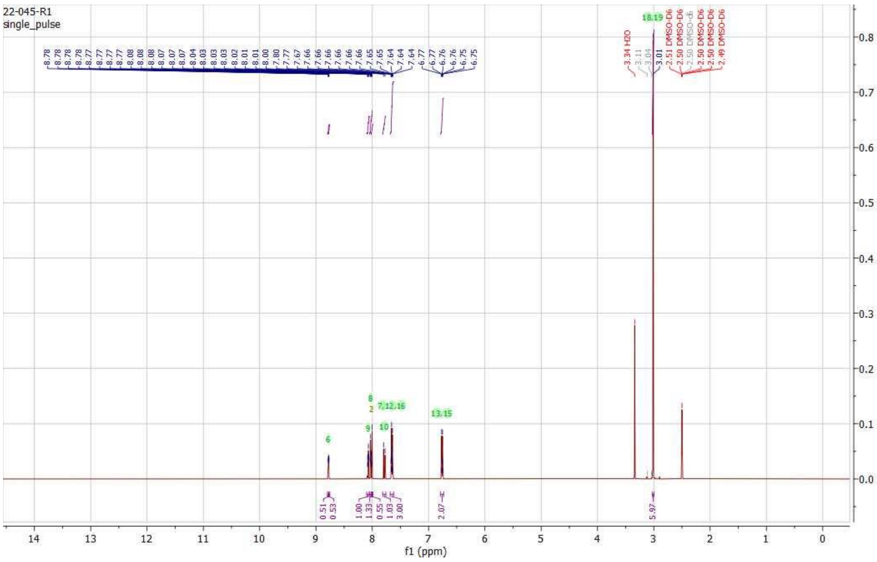
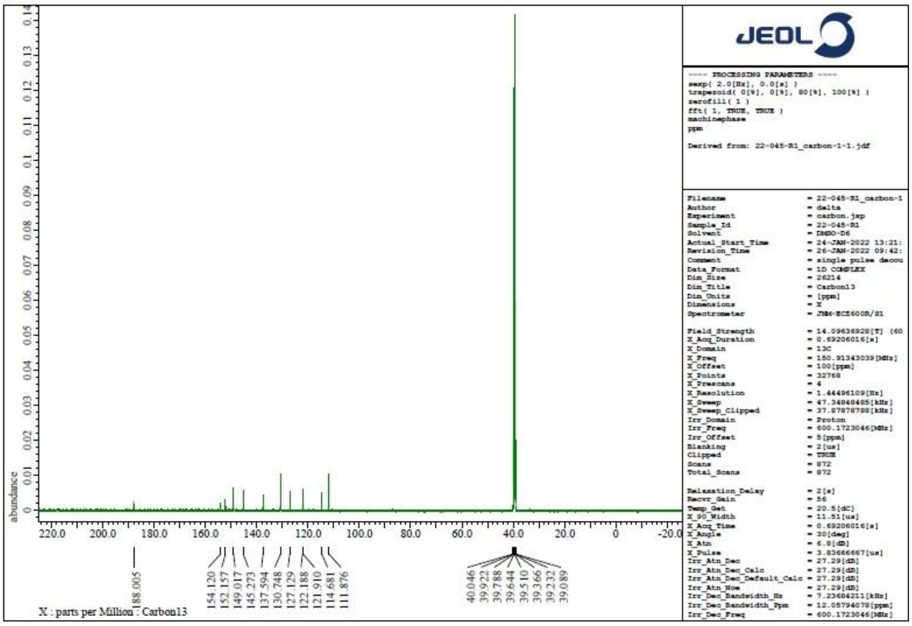


Figure 6.31

*^{13}C-NMR spectra for compound (**102**) **R1***



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fft( 1, TRUE, TRUE )
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ppm

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Figure 6.32

*^{1}H-NMR spectra for compound (**105**) **Thio***

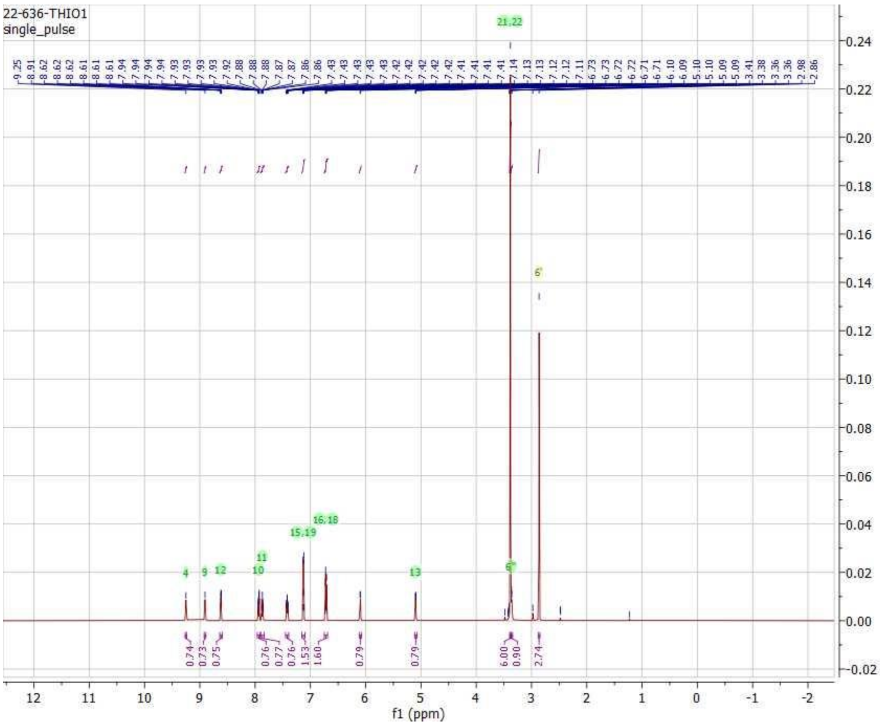


Figure 6.33

*^{13}C-NMR spectra for compound (**105**) **Thio***

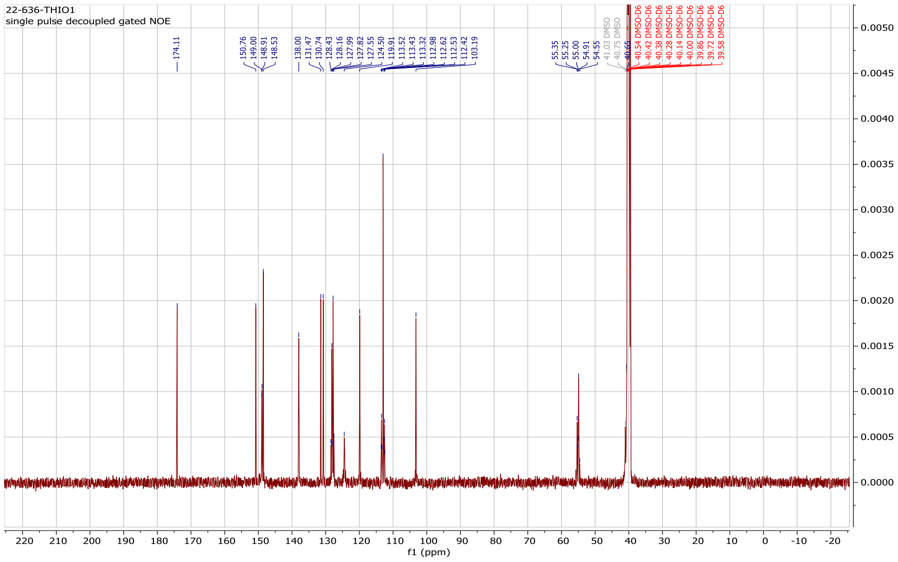


Figure 6.34

*^{1}H-NMR spectra for compound (**107**)*

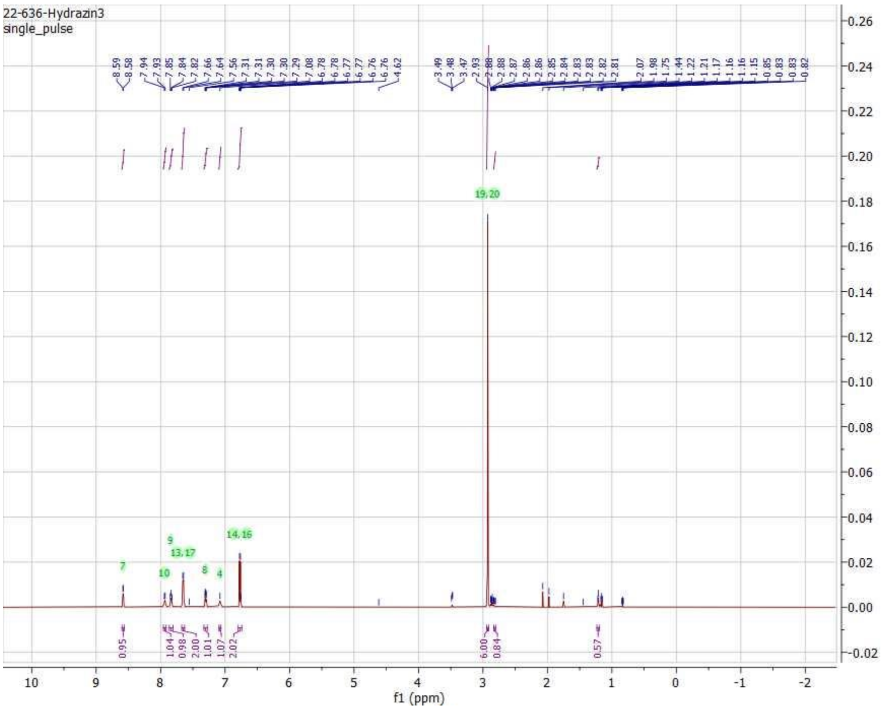
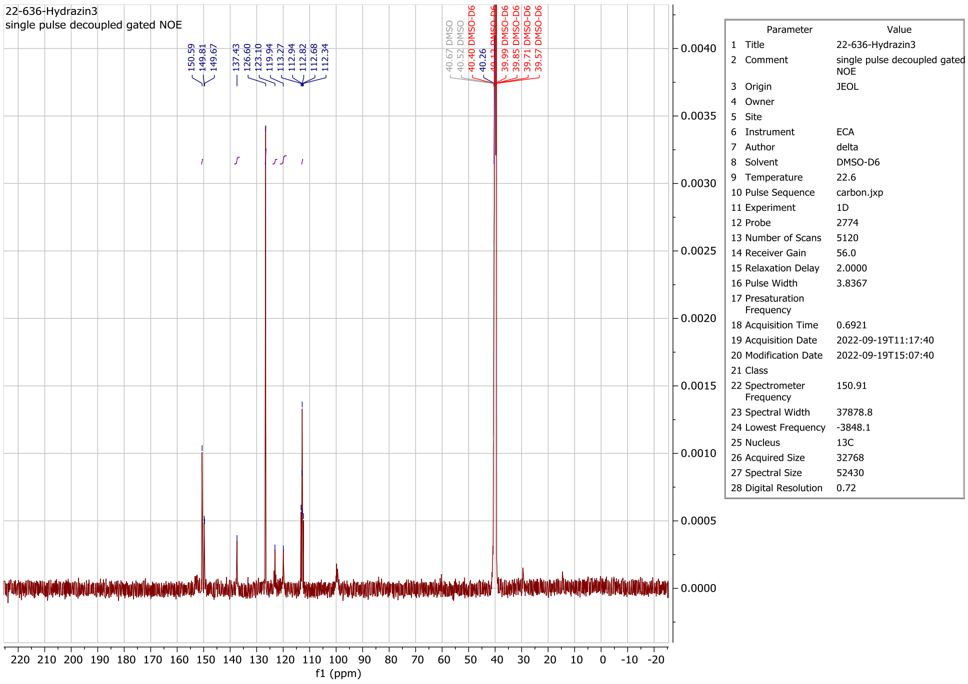


Figure 6.35

*^{13}C-NMR spectra for compound (**107**)*



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5	Site	
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7	Author	delta
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9	Temperature	22.6
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11	Experiment	1D
12	Probe	2774
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24	Lowest Frequency	-3848.1
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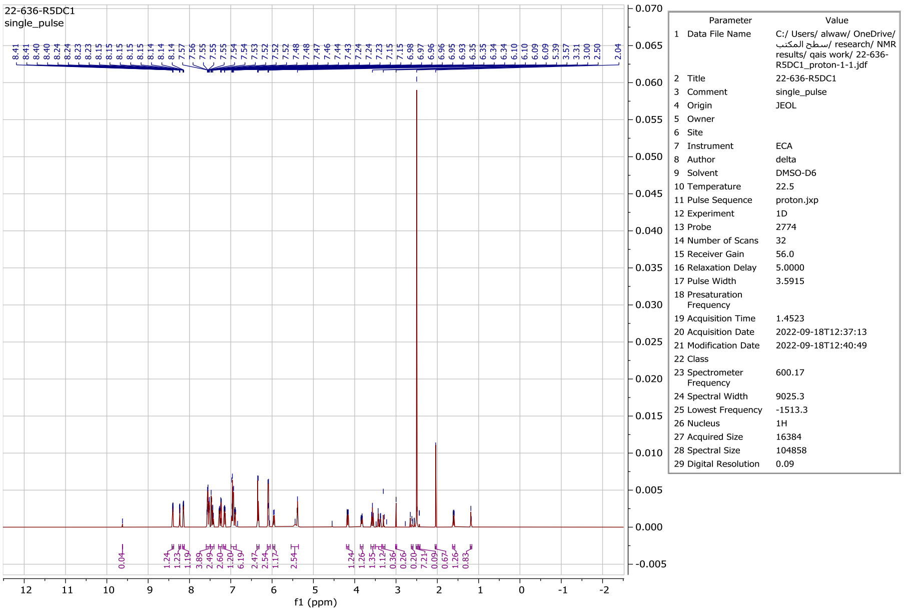
28	Digital Resolution	0.72

Figure 6.36

*^{1}H-NMR spectra for compound (**118**) **R5***



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6	Site	
7	Instrument	ECA
8	Author	delta
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13	Probe	2774
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23	Spectrometer Frequency	600.17
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26	Nucleus	1H
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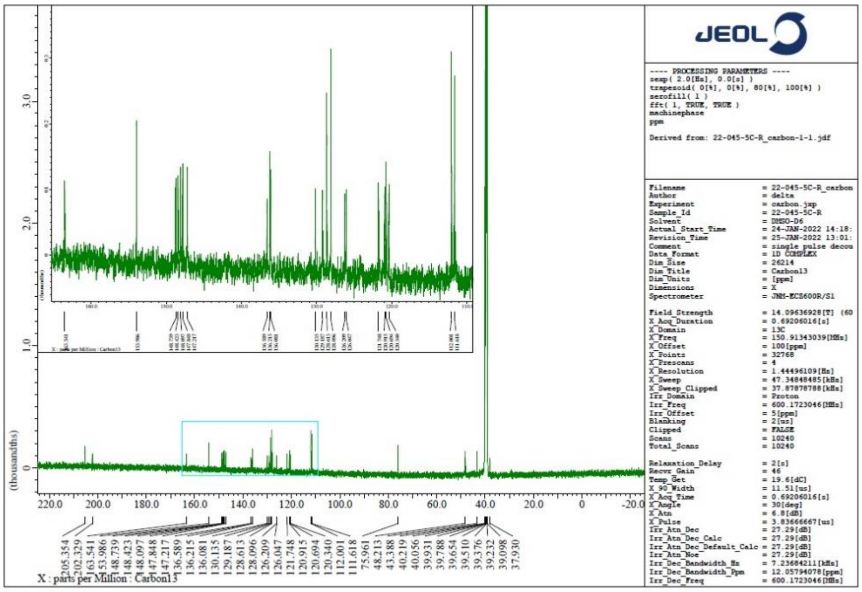
29	Digital Resolution	0.09

Figure 6.37

*^{13}C-NMR spectra for compound (**118**) **R5***



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UV-Visible Spectra

Figure 6.38

*Visible spectra for Compound (**102**) **R1** and its metal complex (**113**)*

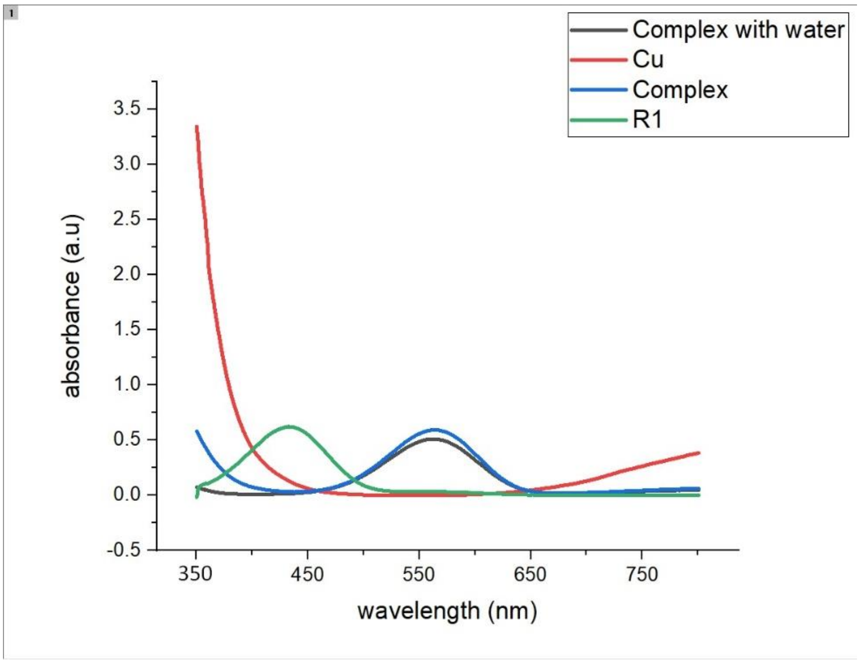


Figure 6.39

*Visible spectra for Compound (**105**) **Thio** and its metal complex (**114**)*

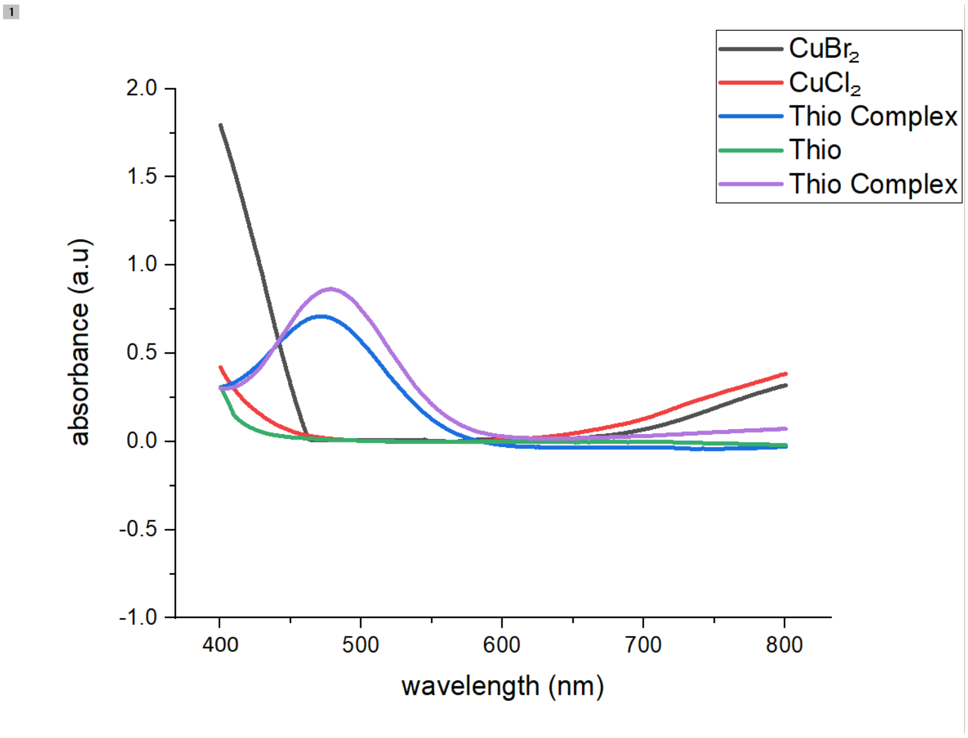


Figure 6.40

*Visible spectra for Compound (**107**) and its metal complex (**115**)*

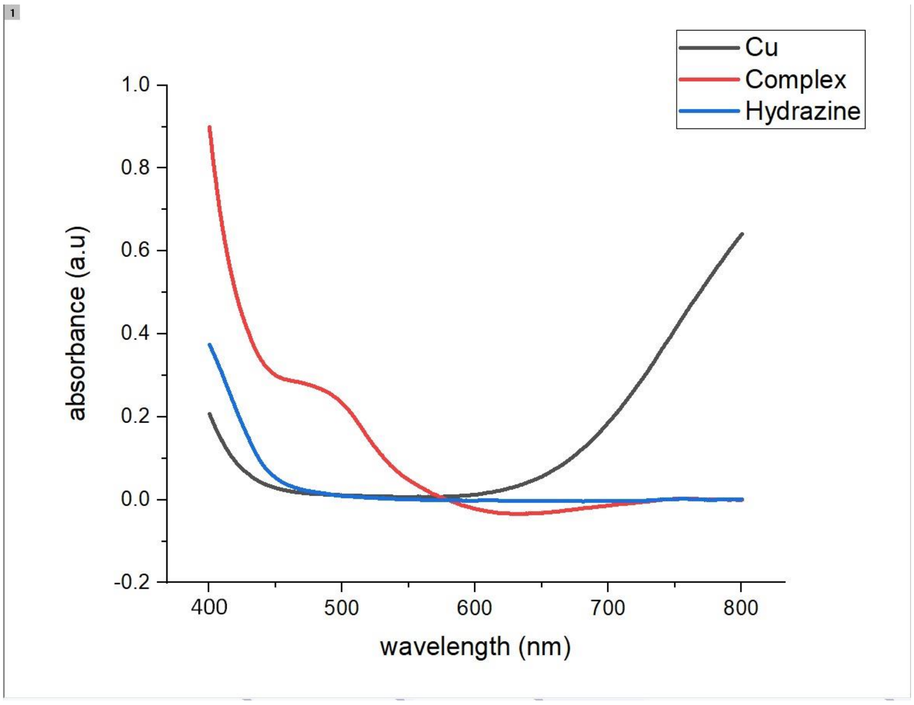


Figure 6.41

*Visible spectra for Compound (**109**) **Guanidine** and its metal complex (**116**)*

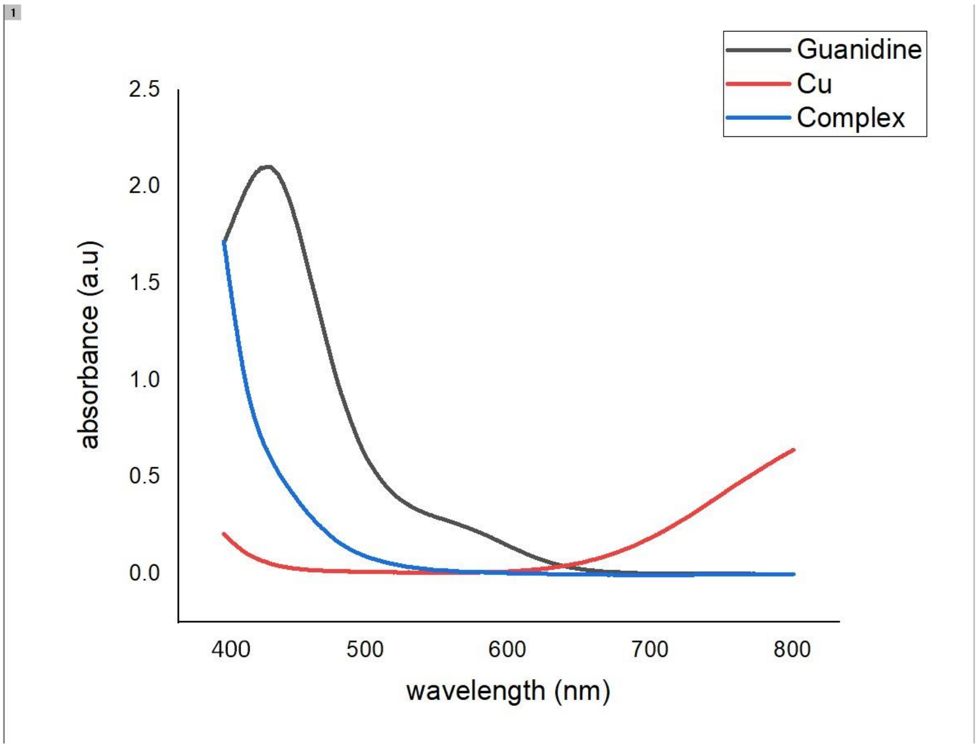


Figure 6.42

*Visible spectra for Compound (**111**) Urea and its metal complex (**117**)*

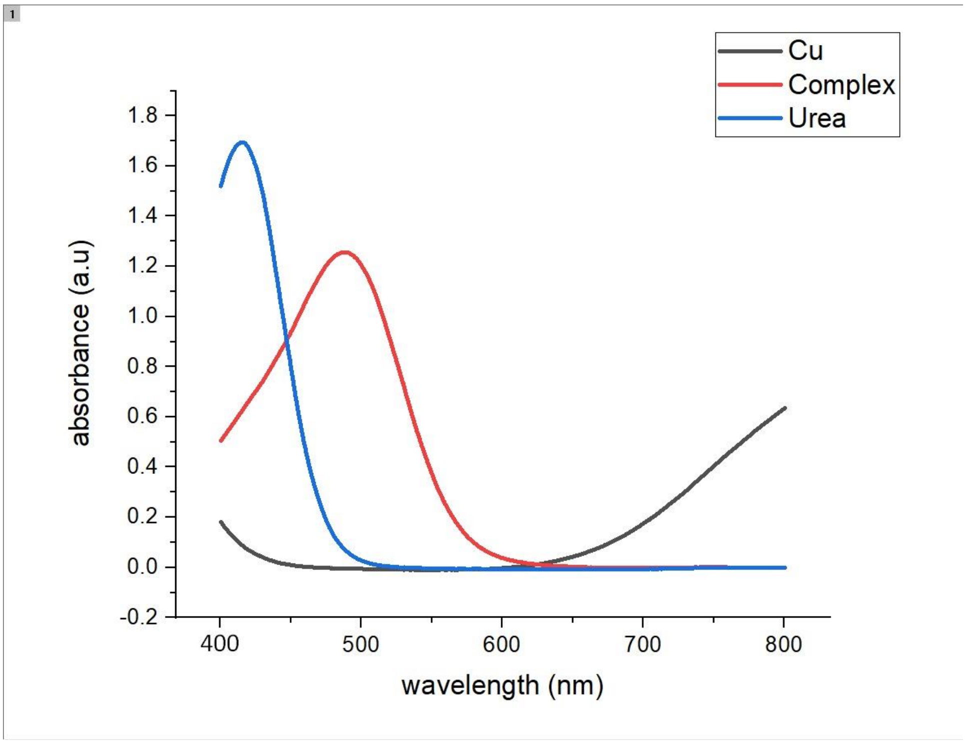
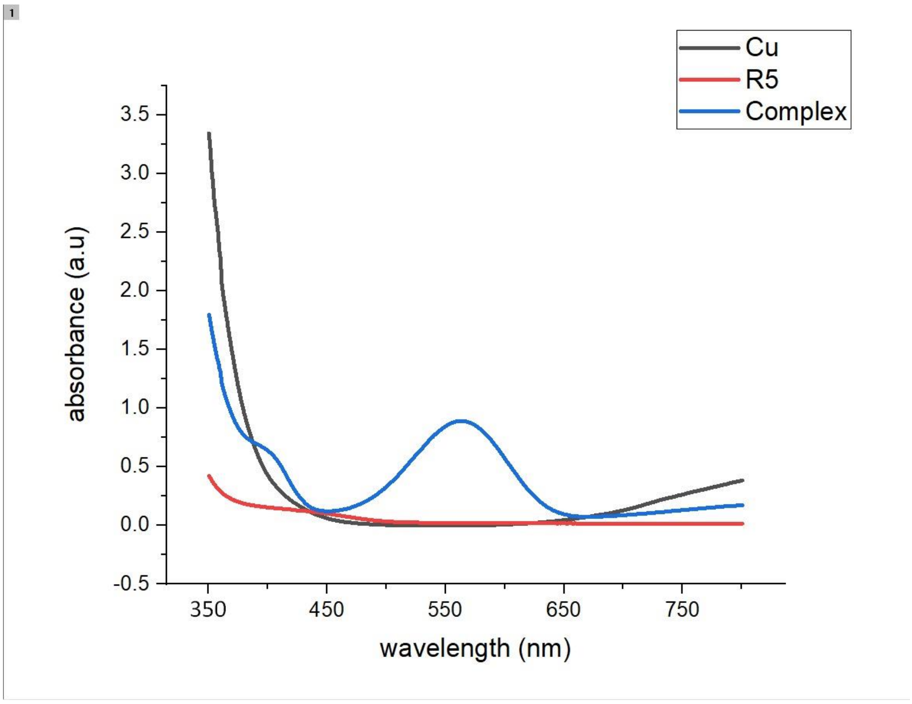


Figure 6.43

*Visible spectra for Compound (**118**) **R5** and its metal complex (**119**)*

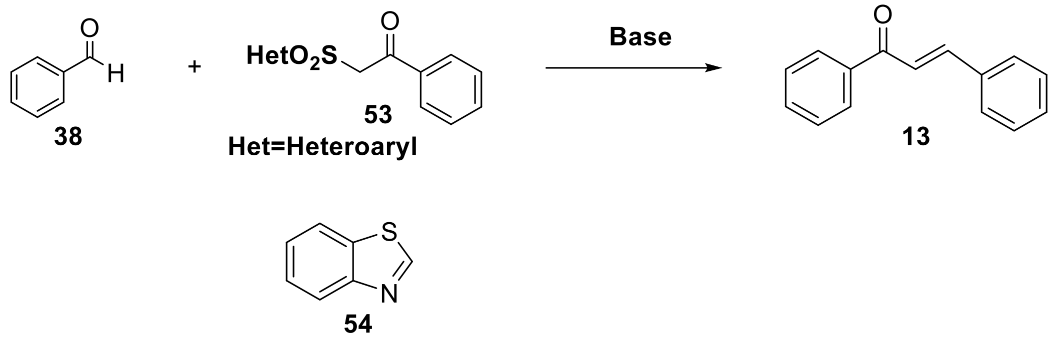


Appendix B

Schemes

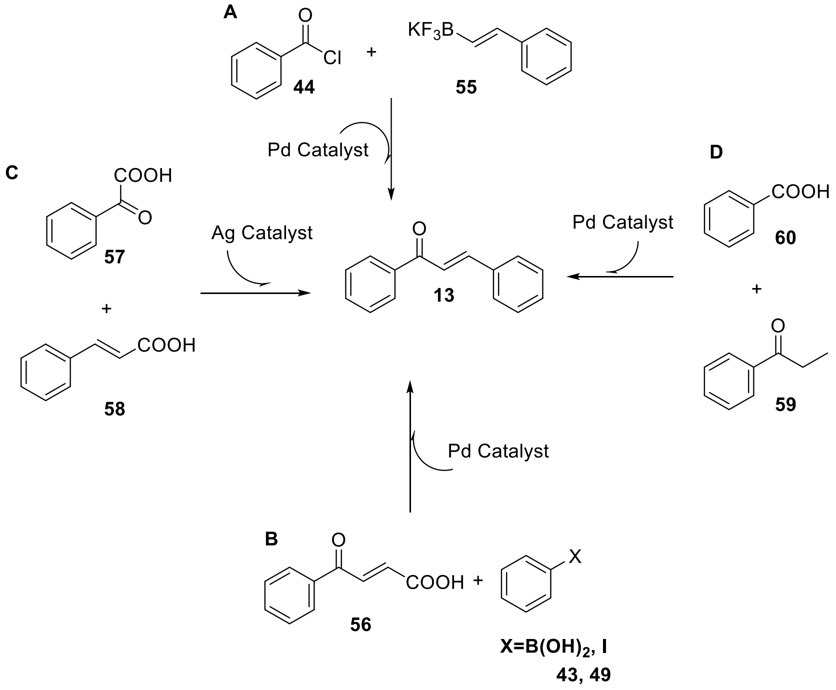
Scheme 6.1

Chalcone Synthesis by Julia–Kocienski Olefination, and Chemical Structure for benzothiazole



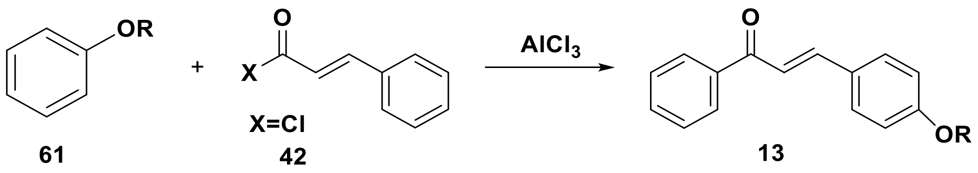
Scheme 6.2

Chalcone Synthesis by Cross-Couplings



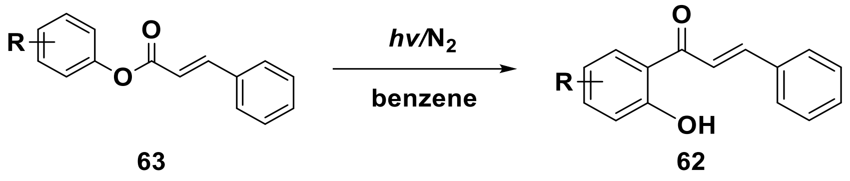
Scheme 6.3

Chalcone Synthesis by Friedel–Crafts Acylation



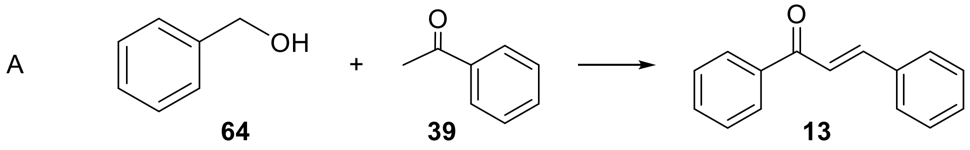
Scheme 6.4

*Chalcone Synthesis by Photo-Fries Rearrangement using Phenyl Cinnamates (**63**)*

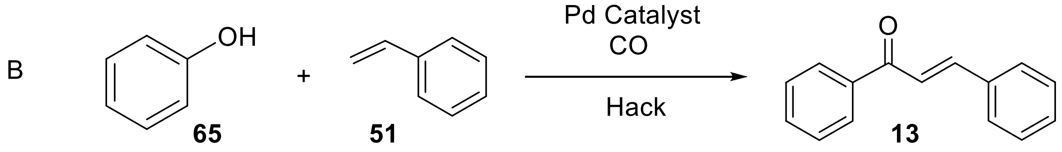


Scheme 6.5

Chalcone Synthesis by One-Pot Reaction

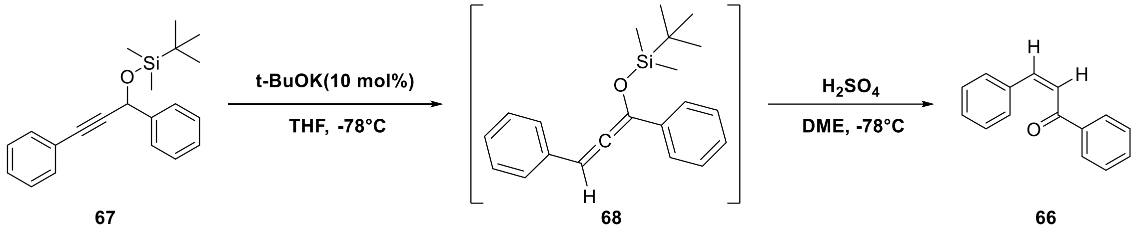


Condition I:CrO_3, 58°C
Condition II:CoI, 2,2'-bipyridine,TEMPO, -10 - 100°C
Condition III:nano-Pd-V,$Ba(OH)_3$, O_2, H_2O, 80°C
Condition IV: toluene, 1 mol%, Cs_2CO_3, O_2 , rt



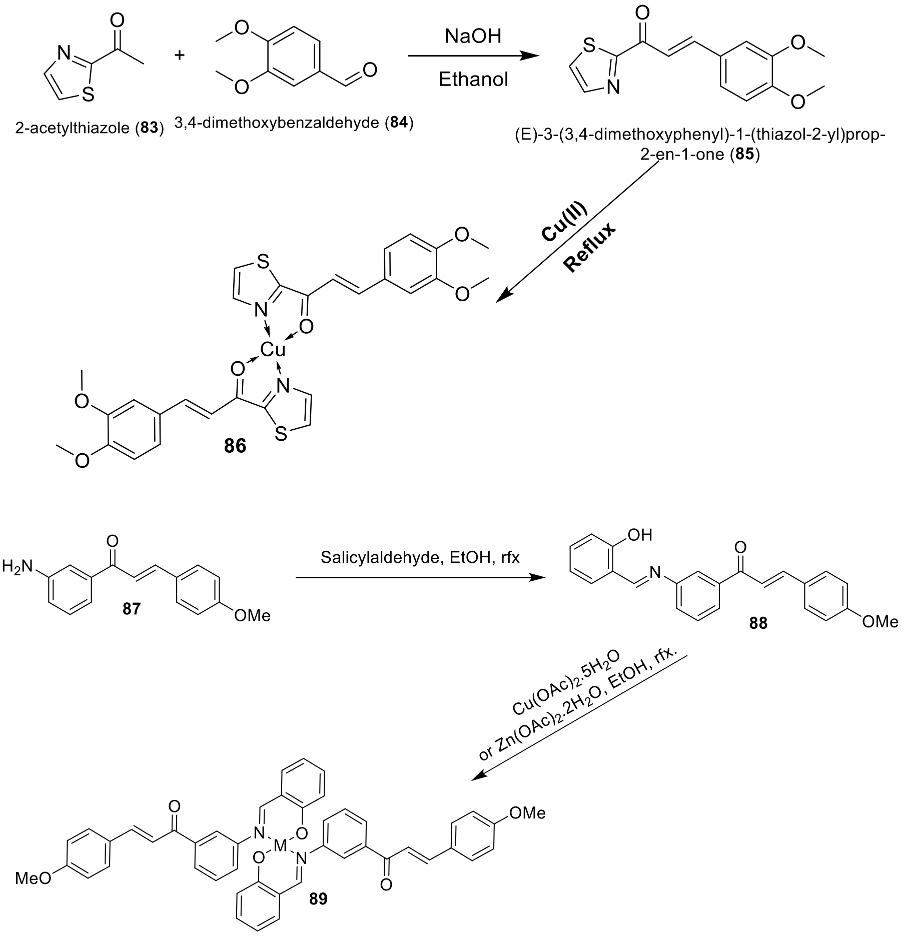
Scheme 6.6

Synthesis of Cis-Chalcones



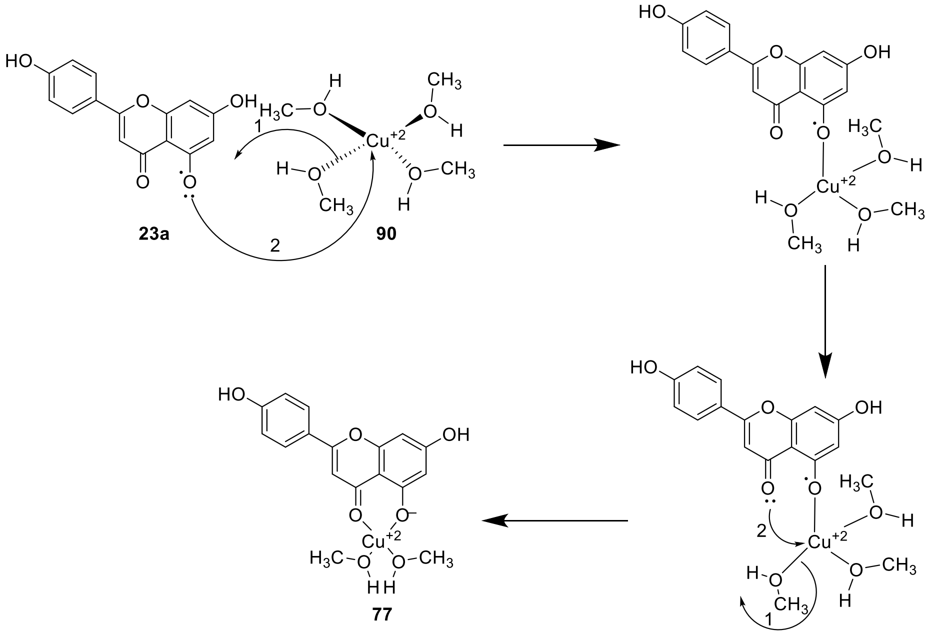
Scheme 6.7

Summary of examples for the synthesis of organic metal complexes based on chalcone



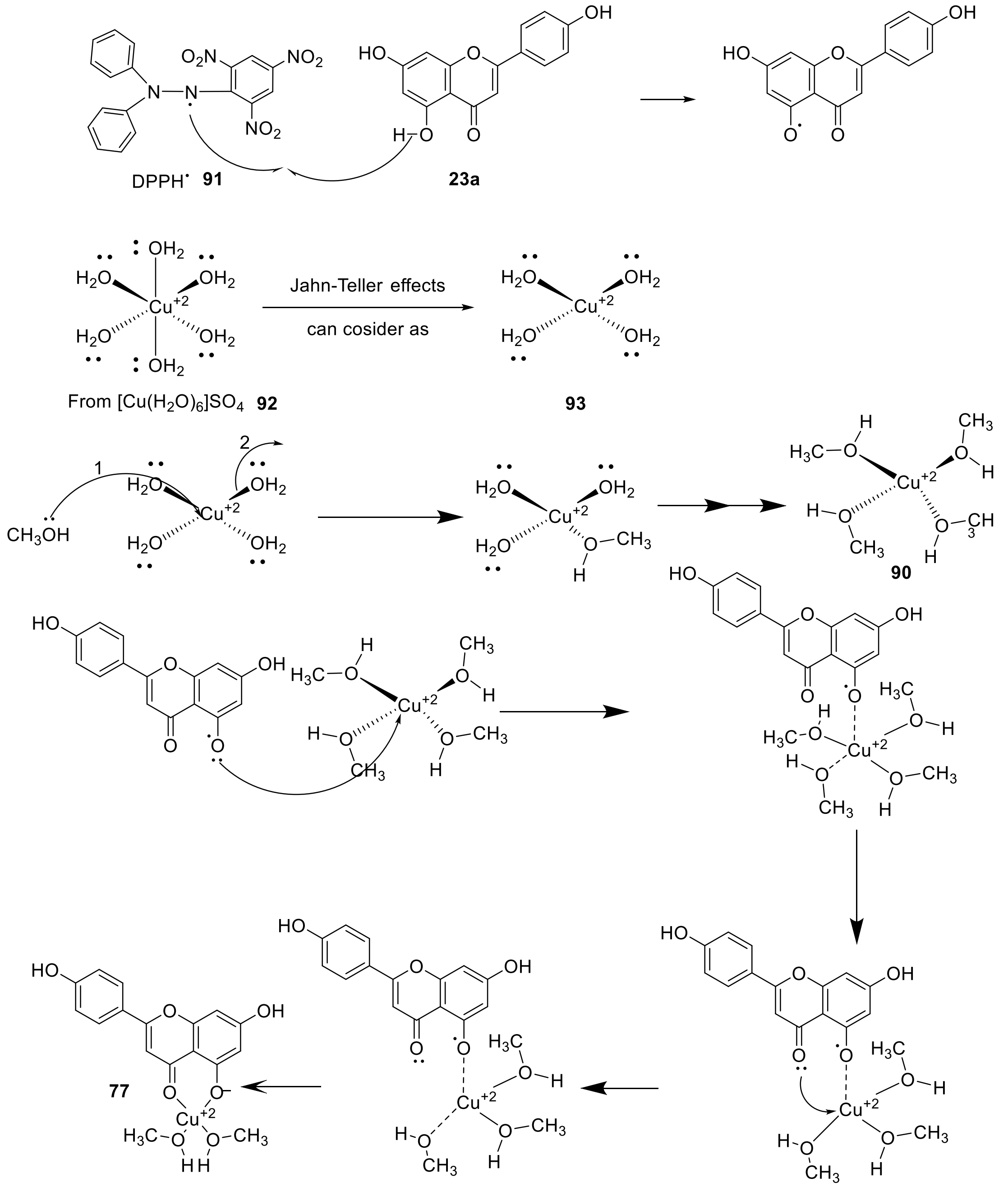
Scheme 6.8

Summary of plausible S_N1 dissociative mechanism of synthesis copper(II)naringenin complex



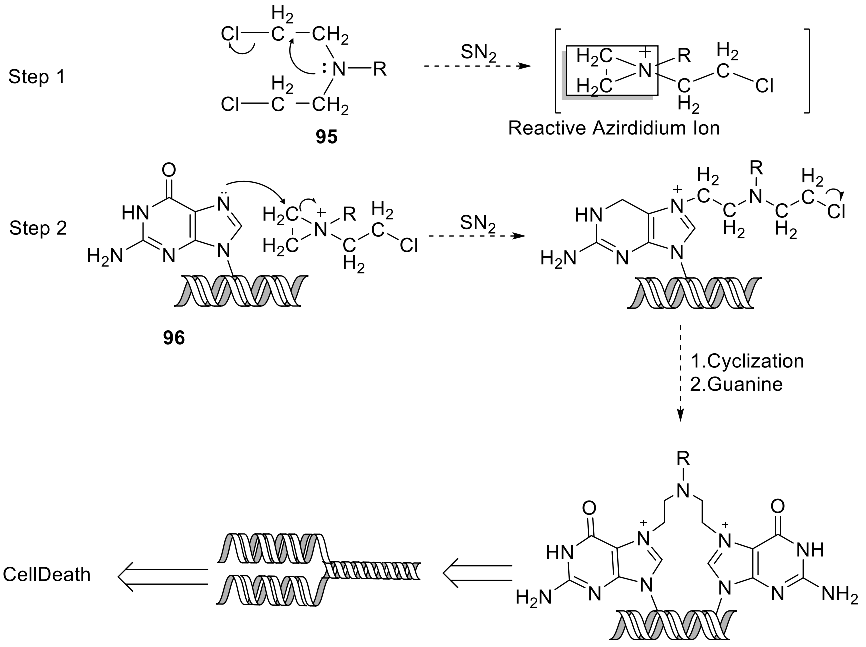
Scheme 6.9

Summary of S_N2 associative mechanism of synthesis copper(II)naringenin complex



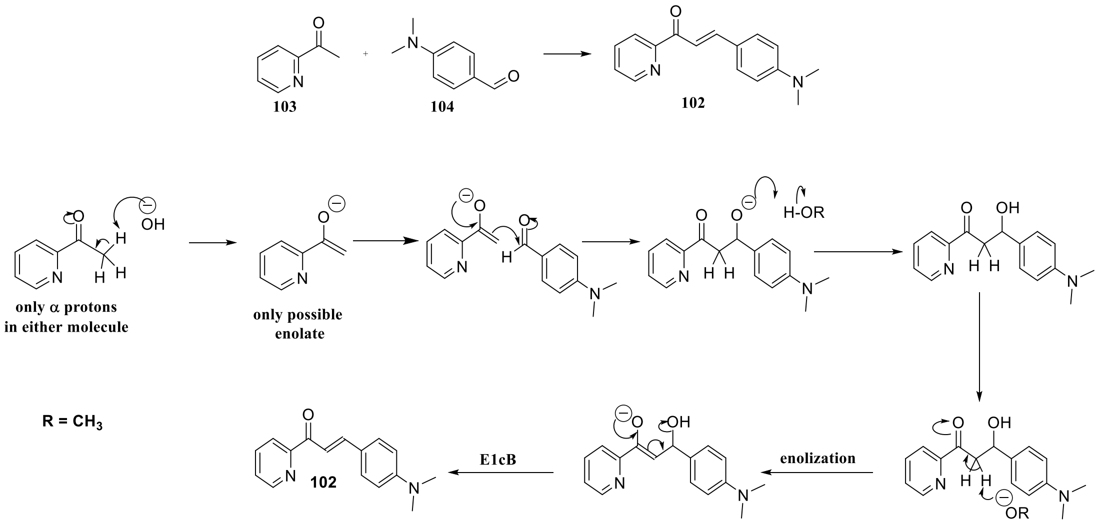
Scheme 6.10

*Alkylating mechanism of nitrogen mustard (**95**) agent with guanine base of DNA (**96**) leading to cell death*



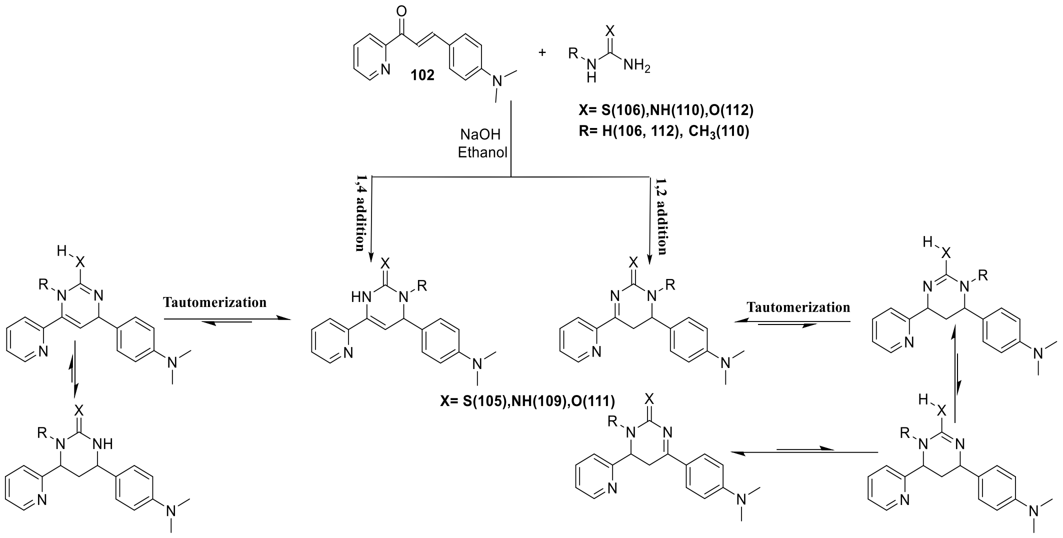
Scheme 6.11

Mechanism for synthesis of chalcone



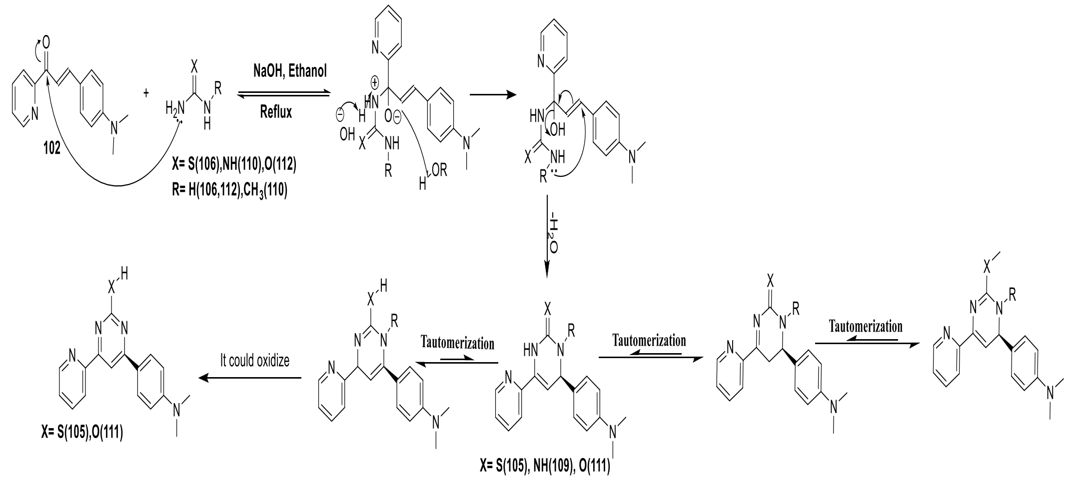
Scheme 6.12

Pathway for synthesis compound ***(105**, **109**, and **111)***



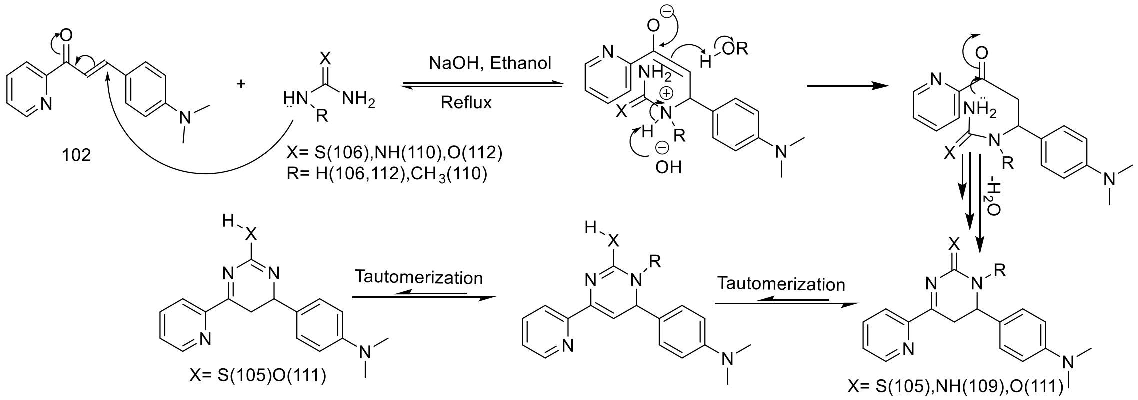
Scheme 6.13

Mechanism for synthesis compound ***(105, 109, and 111)*** *via 1,2 additions*



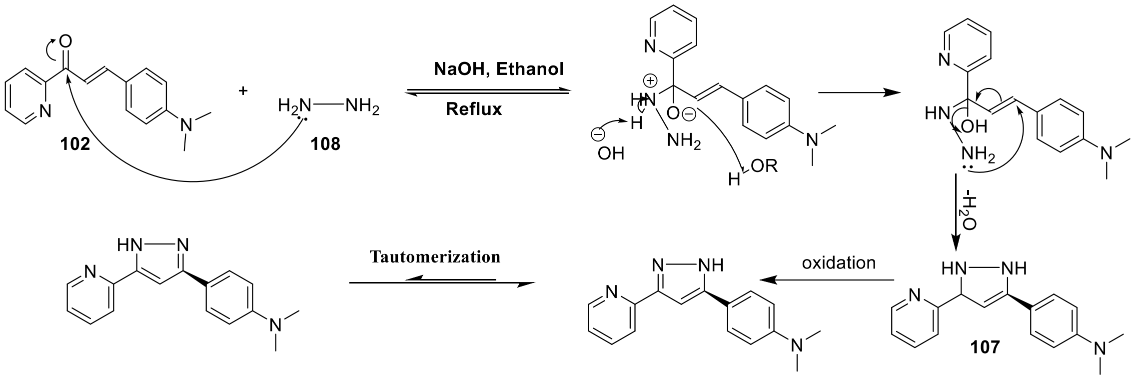
Scheme 6.14

Mechanism for synthesis compound ***(105, 109, and 111)*** *via 1,4 additions*



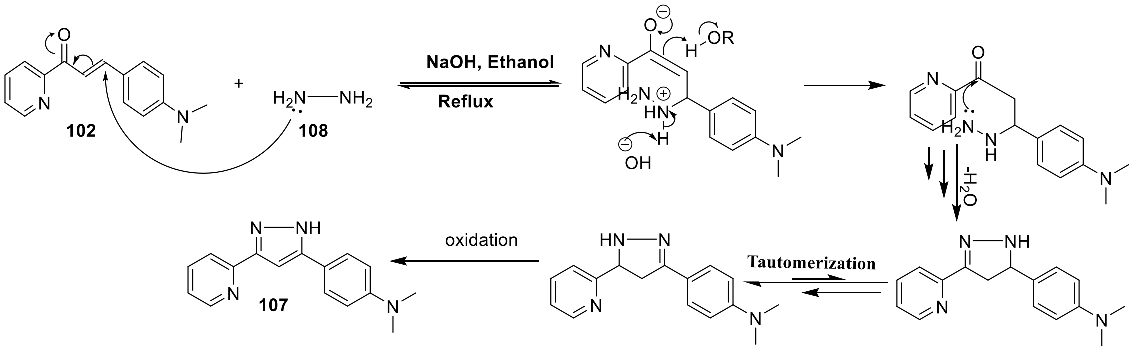
Scheme 6.15

*Mechanism for synthesis compound (**107**) via 1,2 additions*



Scheme 6.16

*Mechanism for synthesis compound (**107**) via 1,4 additions*



جامعة النجاح الوطنية

كلية الدراسات العليا

التصنيع والتقييم البيولوجي لمجمعات النحاس مع الروابط العضوية بناءً على الكالكون (E)-3-(4-(ثنائي ميثيل أمينو) فينيل)-1-(2-بريدينيل)-2-بروبين-1-أون

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

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الملخص

خلفية الدراسة: الكالكون مركب عضوي منتشر في العديد من النباتات والثمار الطبيعية ، وينتمي بشكل عام للفايتوكيميكالات (الكيميائيات النباتية) وبشكل خاص للبولي فينولات. يعتبر الكالكون مهماً في صناعة العديد من المركبات وخاصة مشتقات البولي فينولات. بالإضافة إلى ذلك فإن له أهمية طبية كبيرة حيث يستخدم كمضاد حيوي وفي علاج السرطان ، وما يميزه أنه غير سام أو يمتلك سمية قليلة جدا تجاه الخلايا الطبيعية حسب مصدر التصنيع . وتشكل المركبات العضوية مع الفلزات مجمعات ذات نشاط أكبر من الأصل المشكل له خاصة الكالكون، ويمكن الاستفادة من هذه الخصائص في العديد من المجالات.

أهداف الدراسة: هدفت هذه الرسالة إلى تصنيع مركبات عضوية جديدة ، والمجمعات النحاسية لها المتكونة على أساس (E)-3-(4-(ثنائي ميثيل أمينو) فينيل)-1-(2-بريدينيل)-2-بروبين-1-أون **(102)** ، وتقييمها بيولوجياً.

منهجية الدراسة: تم استخدام تفاعل التكاثف لتحضير المركبات في ظروف قاعدية. حيث تم تحضير الكالكون **(102)**، ثم تمت مفاعلته مع كل من المركبات **(106، و108، و110، و112** ، **وثنائي كلورو ميثان)** لتحضير المركبات العضوية **(105، و107، و109, و111، و118)** ومن ثم تمت مفاعلتُهنَّ مع محلول النحاس (II) لتحضير المجمعات النحاسية لها. وتمت مراقبة التفاعلات باستخدام كروماتوغرافيا

الطبقة الرقيقة ، ثم تمت تنقيتها. وتم تشخيص المركبات المحضرة باستخدام عدد من الأجهزة أهمها جهاز NMR و جهاز مطيافية الاشعة تحت الحمراء. بعد ذلك، تم التحقق من نقاوة المركبات ثم فحص نشاطهم السام للخلايا الليفية الجنينية للفأر (MEF-1) و خلايا سرطان الجلد (B16F10).

نتائج الدراسة: أظهرت النتائج امتلاك معظم المركبات خصائص صبغية. وتبين أن الكالكون (**102**) ومجمعه النحاسي يمتلك أفضل نشاطا بيولوجياً. بينما كانت المركبات الأخرى سامة للخلايا الطبيعية.

الاستنتاجات:

- ينتج المركب الكالكون(**102**) والمركب (**105**) في ظروف قاعدية وبنسبة عالية، ولكن المركبات (**107**، و**109**, و**111**) تحتاج إلى ظروف حمضية.
- تم تأكيد تفاعل مركب **ثنائي كلورو ميثان** مع الكالكون (**102**) .
- تمتلك جميع المركبات العضوية نظام كيميائي مترافق تمكنها من الارتباط والتفاعل مع كل من النحاس(II) والخلايا الطبيعية والخلايا السرطانية.
- الأفضل للعمل به في معالجة السرطان هو الكالكون(**102**) والمجمع النحاسي الخاص به(**113**).
- نشاط المجمعات النحاسية أكبر من نشاط المركبات العضوية المكونة له.
- تساهم هذه الدراسة في فهم أعمق لظروف التفاعل المناسبة لتصنيع المركبات السابق ذكرها.

كلمات مفتاحية: كالكون، التصنيع الكيميائي، المركبات الفلزية العضوية, مجمعات النحاس (II)، السرطان، مضادات السرطان.