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Synthesis, Characterization, Coordination Compounds, Molecular Orbital study and Biological activity of 1,2,4-triazolo[1,5-c]pyrimidine-5(6H)-ones

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Thesis Approval

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Dedication

I dedicate my dissertation work to my family, many friends, and my students, who have always been supportive and encouraging. A special feeling of gratitude for my dear mother and the soul of my father.

To Dr. Mohammad Abul Haj who was like a father to me during my studies, whose words of encouragement and push for tenacity ring in my ears.

My friend Ruwaa, has never left my side and is very special.

With respect and love

Declaration:

I certify that this thesis submitted for the degree of Master, is the result of my own research, except where otherwise acknowledged, and that this study (or any part of the same) has not been submitted for a higher degree to any other university or institution.

Signed: 

Sali Ali Ahmad Al-Asmar

Date : 04/06/2022

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The research mentioned in this thesis was carried out at Al-Quds University's Department of Chemistry between 2018 to 2022. Throughout this time, many people have backed me up in my efforts.

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I‘m grateful to everyone who helped make this project a success.

Abstract

The condensation of a 1,2,4-triazole ring with a pyrimidine ring produces 1,2,4-triazolopyrimidines, which are bicyclic heterocycles. Because the relative orientation of each ring can take four different forms, four separate isomeric families of compounds can be established. The 1,2,4-triazolo[1,5-a]pyrimidine derivatives are the most investigated because they are thermodynamically more stable and same goes to 1,2,4-triazolo[1,5-c]pyrimidine, but there is not enough research on it. There have also been revisions on the synthesis, reactivity, spectroscopic characterization, and crystallographic studies of 1,2,4-triazolo[1,5-c]pyrimidines, 1,2,4-triazolo[4,3-a]pyrimidines, and 1,2,4-triazolo[4,3-c]pyrimidines. However, it's worth noting that combining the two rings into a single molecule may boost biological activity.

Our thesis is focusing on researching and investigating triazolopyrimidine coordination chemistry. We synthesized and characterized 1,2,4-triazolo[1,5-c]pyrimidine-5(6H)-ones. In this thesis, we adopted the optimal approach through synthesis and modification to reach the highest yield. The substance was identified using standard procedures, with positive results. The Spartan program was also used to investigate the computational chemistry of this molecule; two models were utilized: semi-empirical and Hartree-Fock. Using heat of formation, the most stable tautomer has been discovered. Aside from that, Molecular Orbital Calculation and Electrostatic Atomic Charge were determined. The results showed that the possibility of binding the ligand with metal will be as follows: N3>N4>O1. This theoretical study was corroborated by X-ray analysis of the complex and showed that bonding occurred through the nitrogen atom in position 3 of the pyrimidine ring and the nitrogen atom in position 4 of the triazole ring as well.

The coordination chemistry of 1,2,4-triazolo[1,5-c]pyrimidines has never been studied before. Metal complexes of the first and second raw transition metals: Silver(I), Copper(II), Nickel(II), Cobalt(II), Fe(II), platinum(II), palladium(II), and Ruthenium(III) were synthesized and used to manufacture and study the capacity to build coordination compounds from the ligand. Some of these coordination compounds were isolated in single crystal form, while others require more examination; X-ray crystallography was used to characterize the coordination compounds.

The biological activity of 1,2,4-triazolo[1,5-c]pyrimidine and coordination compounds as antibacterial and antimalarial agents were investigated; it was found to have good antibacterial activity and minor effects as antimalarials, except for platinum(II) coordination compound, which showed high efficacy as an antimalarial compared to the chloroquine drug. its antimalarial effect has been maintained even at low concentrations. This could be a good sign to introduce it as an alternative treatment. Other biological functions of these chemicals are possible. However, it is recommended investigating these coordination compounds as anticancer activity especially for platinum(II) coordination compound.

تحضير، تشخيص، المركبات التناسقية والدراسة المدارية الجزيئية والفعالية الحيوية لمركب

1,2,4-triazolo[1,5-c]pyrimidine-5(6H)-ones

اعداد الطالبة: سالي علي احمد الاسمر

بإشراف: د محمد ابو الحاج

الملخص

مركبات الترياز ولوبيرميدين هي مركبات عطرية غير متجانسة وتتكون من حلقتين الاولى هي حلقة سداسية البرميدين والاخرى خماسية ترياز ول، ينتج عن ارتباط الحلقتين اربع مجموعات من المتشكلات، اثنين من هذه المتشكلات هي مركبات تتكون بسرعة وهي& 3,4-a 3,4-c مع العلم انها غير مستقرة من ناحية الديناميكا الحركية، والمجموعتان 1,5-a & 1,5-c وهما مستقران حراريا. ومع ذلك ، تجدر الإشارة إلى أن الجمع بين الحلقتين في جزيء واحد قد يعزز النشاط البيولوجي.

في هذه الرسالة تم تحضير وتمييز (1,2,4-triazolo[1,5-c]pyrimidine-5(6H)-ones) تم اعتماد النهج الأمثل من خلال التحضير والتعديل للوصول إلى أعلى عائد. خلال هذا البحث تم بداية دراسة هذا المركب من ناحية النظرية باستخدام طريقة (semiempirical and Hartree-Fock)، والتي هي جزء من موضوع الكيمياء المحوسبة (Computational chemistry)، وقد تم التعرف على (tautomer) الاكثر استقرارا، وتم احتساب الكثافة الالكترونية وحسابات الافلاك الجزئية لهذا المركب. تم اكتشاف ذرة النيتروجين في حلقة البيريدين لتكون الموقع المفضل لعمل روابط تشاركية في المعقدات.

لم يتم دراسة كيمياء التنسيق لـ (1,2,4-triazolo[1,5-c]pyrimidine-5(6H)-ones) من قبل. تم تصنيع المعقدات المعدنية من المعادن الانتقالية الأولى والثانية (الفضة (I) والنحاس (II) والنيكل (II) وغيرها) بالإضافة إلى ذلك ، تم استخدام العديد من المعادن الانتقالية مثل البلاتين (II) والبلاديوم (II) لتصنيع ودراسة القدرة على بناءالمعقدات.

تكوين هذه المجمعات يتأثر بعدة عوامل ، بما في ذلك النسبة المولية بين الليجاند (ligand) والمعدن، درجة الحموضة ونوع المذيب. تم عزل بعض هذه المعقدات في شكل بلوري نقي ، بينما يتطلب البعض الآخر مزيدًا من الفحص ؛ تم استخدام علم البلورات بالأشعة السينية لتشخيص المعقدات بما في ذلك معقدات النحاس (II) والفضة (I) .

تم التحقيق في النشاط البيولوجي لـ (1,2,4-triazolo[1,5-c]pyrimidine-5(6H)-ones) ومعقداته، كعوامل مضادة للبكتيريا والملاريا. حيث تم اكتشاف أن لديهم نشاطات ممتازة كمضادات للبكتيريا بتركيزات منخفضة جدا. لكن عندما يتعلق

الامر بتأثيراتها كمضادات الملاريا وجدنا ان هناك تأثيرات طفيفة لهذه المركبات، باستثناء البلاتينيوم ، الذي كان له تأثير مرتفع جدا بالمقارنة مع دوار كلوروكوين حتى عند استخدام تركيز اقل بقي محافظ على تأثيره. وهذا قد يكون بداية لامكانيه استخدامه كعلاج بديل.

قد يعد هذا نقطة بداية لتحسين الفعالية الحيوية، حيث يمكن أن تمتلك هذه المواد فعاليات حيوية أخرى من خلال إجراء علاقة الشكل بالفعالية. مع ذلك نوصي باختبار هذه المركبات كمضادات للسرطان.

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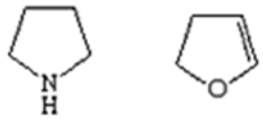
Chapter one

Introduction

Heterocyclic chemistry is a discipline of organic chemistry concerned with the synthesis, characteristics, and applications of heterocyclic cycles. Its molecules` atoms are bound in rings containing at least one non-carbon atom. Many biological materials are found in heterocyclic compound, Nucleic acids for example, are lengthy chains of heterocyclic units bound together by other sorts of molecules that carry genetic information that controls heredity (1) Furthermore, many naturally occurring vitamins and medicines as well as most hallucinogens are heterocyclic compounds. Synthetic heterogeneous cycles are used in modern culture as medications, plastics, insecticides, dyes, and other products (2). Heterocyclic nitrogen cycles are found in 59 percent of FDA-approved medications, accounting for more than half of the known compounds are heterocyclic (3)

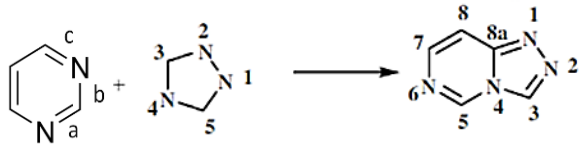
Most frequent heterocycles contain nitrogen (N), oxygen (O), or sulfur (S), and have rings with five or six members. Pyridine, pyrrole, furan, and thiophene are the most well-known chemicals. Heterocycles can be saturated, unsaturated, or aromatic. the following structural formulas demonstrate: 4,5-dihydrofuran is an unsaturated heterocyclic molecule, while pyrrolidine is a saturated heterocyclic compound.



pyrrolidine 4,5-dihydrofura

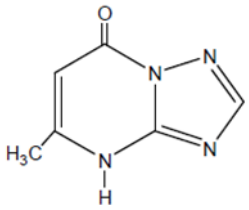
Triazolopyrimidine, a biheterocyclic aromatic chemical molecule that is a pervasive structural component in numerous active drugs with varying pharmacological activity (4) is one of the nitrogenous heterocyclic systems. Many researchers are interested in developing novel compounds with anticancer, anti-inflammatory, antibacterial, and other properties based on these architectures

(5) (6)The triazolopyrimidine ring is generated when the triazole unit, a five-membered aromatic ring system with three nitrogen atoms, and the pyrimidine ring are fused together (six-membered aromatic ring system containing two nitrogen atoms in positions 1 and 3). The structure of 1,2,4-triazolo[4,3-c]pyrimidine is shown below **Scheme 1**



Scheme 1 Structure of 1,2,4-triazolo[4,3-c]pyrimidine

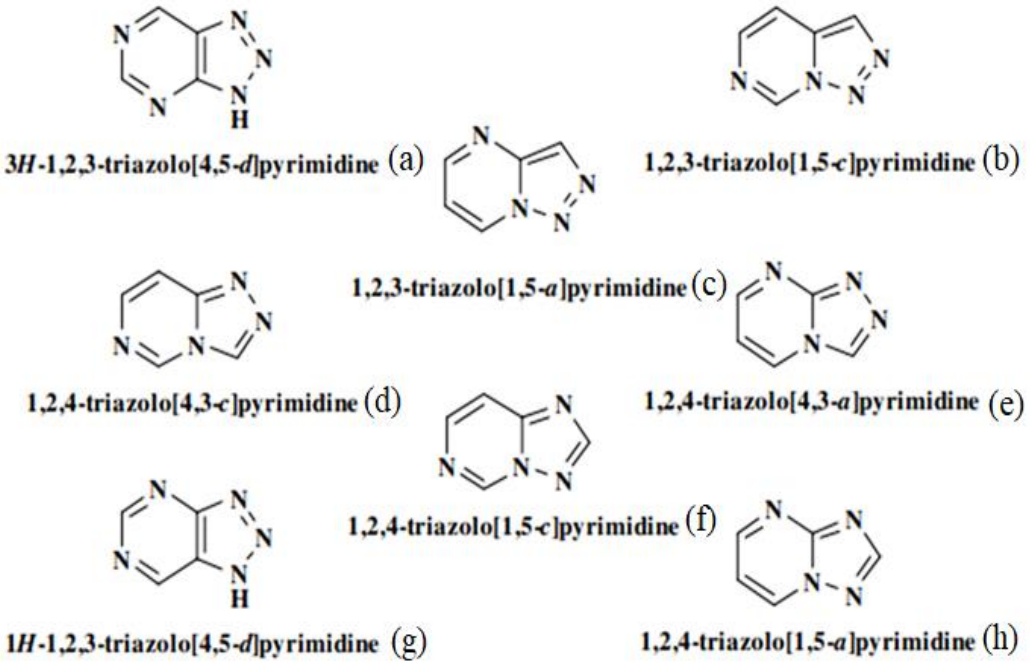
In 1909, Hass et al. published the synthesis of 5-methyl-1,2,4-triazolo[1, 5-a]pyrimidine-7-one, which launched the chemistry of 1, 2, 4-triazolopyrimidine derivatives (7) **(Scheme 2).** Due to its chemistry, which has exhibited several biological activities in addition to medical, pharmacological, agrochemical, and photographic uses, many efforts have been made toward the synthesis of triazolopyrimidines.



Scheme 2: Structure of 5-methyl-1, 2, 4-triazolo [1, 5-a] pyrimidine-7-one

Few articles and patents on triazolopyrimidine systematic investigations were published throughout the previous fifty years (8)-(15) yet, Fischer study revisions are the most recent and comprehensive. (10)

Special characteristics of syntheses and reactivity have been discussed in multiple reviews (16)-(20) and in a useful comparative analysis of various azaindolzines (21) It should be noted that the triazolopyrimidine unit can occur in the form of 8 isomers illustrated in **Scheme3.** 1,2,4-triazolopyrimidine systems can occur in four different ways resulting in the isomeric structures shown in **Scheme 3** (d, e, f, and h) all of which have a nitrogen bridgehead atom. (22)



Scheme 3: Isomers of triazolopyrimidine.

Furthermore, due to its diverse pharmacological effects, the triazolopyrimidine ring has been widely exploited as a well-known scaffold in medicinal chemistry (22) (23). According to the survey, triazole derivatives have been extensively researched and have shown to be effective

corrosion inhibitors under a variety of operating situations in addition to its non-toxic characteristic. (24) (25). (26) (27)This diversity in biological effects is because triazolopyrimidine consists of two rings, each ring has different biological effects that when combined increase the benefit.

Triazolopyrimidines are synthetic heterocycles with valuable bioactivity. they are effective therapies for the treatment and prevention of cardiovascular disorders, and are also known as smooth muscle cell growth inhibitors . (28) (29). Numerous metabolites with unusual structures and significant bioactivity have been identified from bacterial and fungal strains collected from a variety of marine settings, including animals, plants, and sediments. in recent years, The bacteria produced a triazolopyrimidine derivative with an unusual skeleton among natural products which was given the name essramycin, the first Triazolopyrimidines antibiotic isolated from nature. (30)

Researchers from a wide range of industries have been drawn to studies on preventing steel corrosion in acidic conditions and the resulting hazardous chemical processes (31). Steel corrosion prevention has become more significant in a variety of industries, particularly in the chemical and petrochemical processing industries. A variety of studies have been carried out to look into effective corrosion prevention strategies.

The main objectives of the research are:

- To synthesize 1,2,4-Triazolo[1,5-c]pyrimidine-5(6H)-ones by using simple convenient and good yielding method .

- To synthesize Nickel(II), Copper(II), Cobalt(II), Fe(II). Palladium(II), Platinum(II), and Ruthenium(III), Ag(I) coordination compound by using 1,2,4-Triazolo[1,5-c]pyrimidine-5(6H)-ones as ligand .

- To characterize all synthesized compound using FTIR, NMR , X-ray and thermal studies.

- To determine biological activity such as anti-malarial and anti-bacterial for 1,2,4 Triazolo[1,5-c]pyrimidine-5(6H)-ones and coordination compounds.

Chapter two

Literature review

2.1 Introduction

The objective of this review is to present the different synthetic routes of 1,2,4-triazolopyrimidines, their reactivities, as well as their biological properties.

2.2 Synthesis

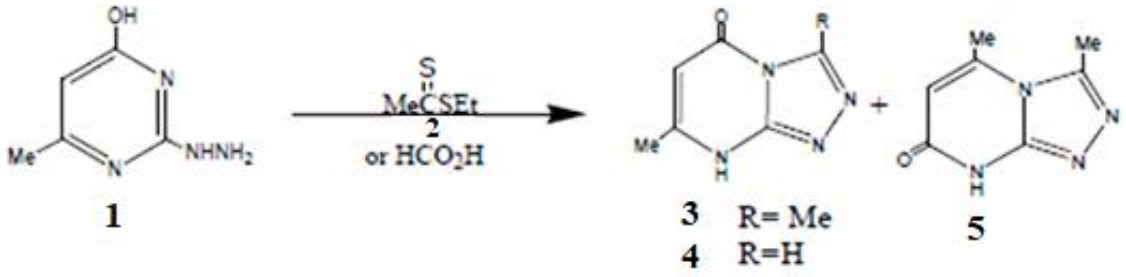
The majority of triazolopyrimidines are made from 1,2,4-triazolo derivatives or from a pyrimidines (need the annulation of a second heterocyclic ring). 5-amino-1,2,4-triazololes and 2-hydrazinopyrimidines are preferred. These synthesizes can be classed as cyclocondensation, oxidative cyclizations or cyclizations depending on the reaction type (17)

In some circumstances, the kinetically preferred [4,3-c] and [4,3-a] products are generated first, then Dimroth rearrangement transforms them into the thermodynamically more stable [1,5-c] and [1,5-a] pyrimidines, respectively (32)

2.2.1 Synthesis of 1,2,4-triazolo[4,3-a]pyrimidine

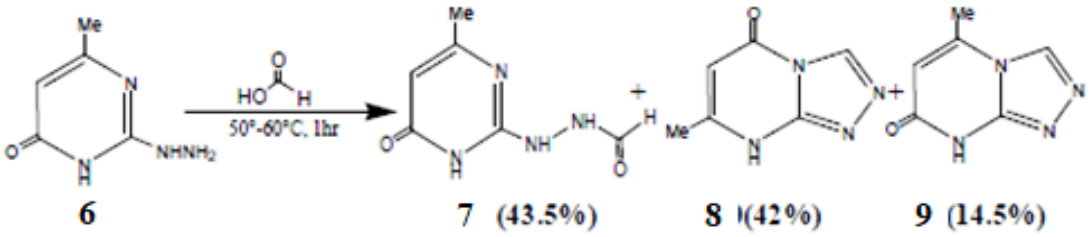
2.2.1.1 Synthesis from pyrimidine

When the first compound is reacted with formic acid the following compound will form (33) whereas Reaction of 1 with ethyl dithioaectate 2 gave a mixture of 3,7(3,5) dimethyltriazolo[4,3-a]pyrimidinones 3 and 5 (34) As shown below **Scheme 4.**

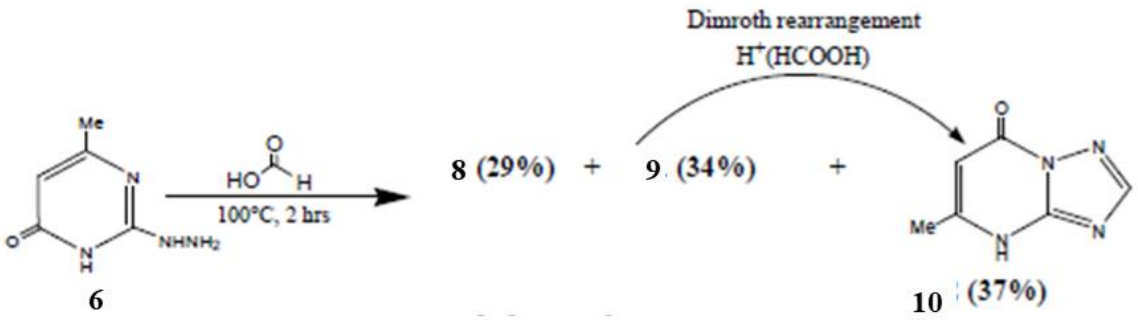


Scheme 4

Cyclization of formic acid with 2-hydrazino-6-methylpyrimidin-4-one (structure 6) represents an interesting case, depending on the reaction circumstances (pH, temperature, and time), mixtures of products were formed that varied in quantity, structure, and relative amounts (35) The reaction of the structure with formic acid was carried out for 1 hour at 50-60°C, yielding a mixture of formylhydrazine (7, 43.5%), 7-methyl-5-oxo-1,2,4-triazolo[4,3-a]pyrimidine (8, 42%), and 5-methyl-7-oxo-1,2,4-triazolo[4,3-a]pyrimidine (9, 14.5 %). Dehydrocyclization of hydrazide (7) was achieved by nucleophilic attack of the pyrimidine N1 or N3 onto the formylhydrazino carbonyl carbon, resulting in compounds 8 and 9. **(Scheme 5).** The separated products were (8, 29%), (9, 34%), and 7-methyl-5-oxo-1,2,4-triazolo[1,5-a] pyrimidine (10, 37%) when this reaction was carried out at 100°C for 2 hours. Acid-induced Dimroth-like rearrangement of 8 resulted in the formation of the final **(Scheme 6).**

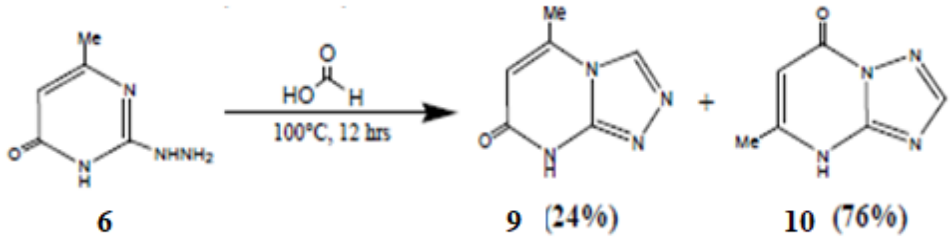


Scheme 5



Scheme 6

When the reaction duration was increased in 12 hours, the presence of extra formic acid, (9, 24%) and (10, 76%) of the reactions. (35)**(Scheme 7)**.

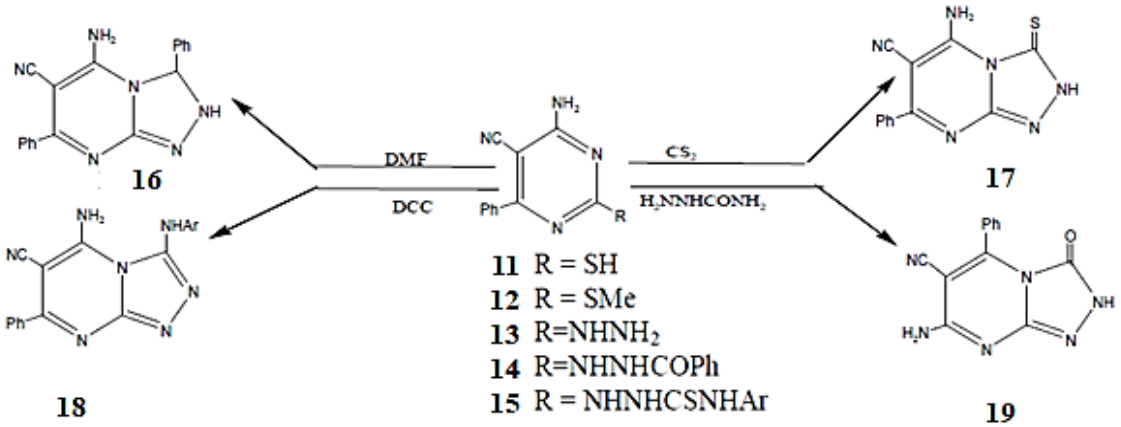


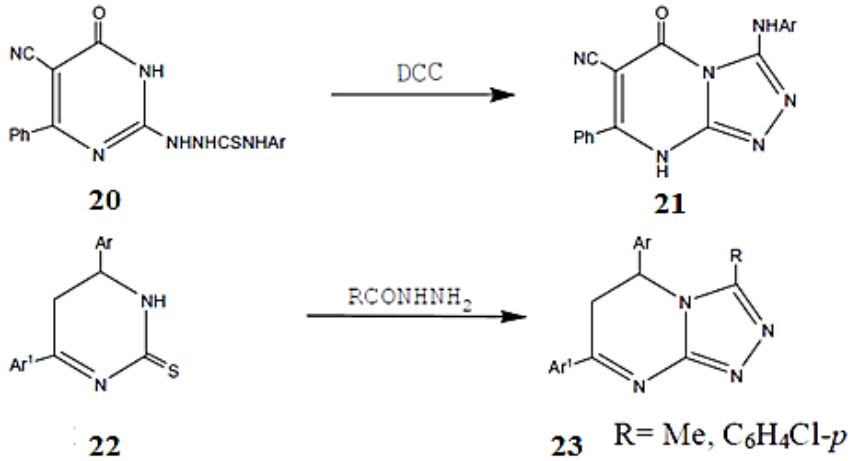
Scheme 7

The 4-aminopyrimidines 11 and 12 were made by reacting benzylidene malononitriles with either thiourea or S-methylisothiourea. The 2-hydrazino derivative 13, which was treated with carbon disulfide yielded the triazolopyrimidine 17 rather than its isomeric compound , was obtained via nucleophilic substitution at the 2-position of 12 with hydrazine (36).The N-benzoyl derivative 14 was obtained by heating 13 with benzoyl chloride anhydrous dioxane, and the ring closure was achieved by heating in DMF to yield 5-amino-6-cyano-3,7-diphenyl-1,2,4-triazolo[4,3 a]pyrimidine 16. By reacting 12 with semicarbazide, the isomeric 1,2,4-triazolo-[4,3-a]pyrimidin-3-one 19 was produced (37). 13 was reacted with isocyanates to produce thiosemicabazides 15,

which were then cyclodesulfurized with DCC to produce 18 in the same way, cyclocondesulfurization of 20 yielded 21. (38)

The triazolopyrimidine 23 was obtained by cyclizing the dihydropyrimidinethione 22 with acetylhydrazine or pchlorobenzoylhydrazine (39)**(Scheme 8)**.



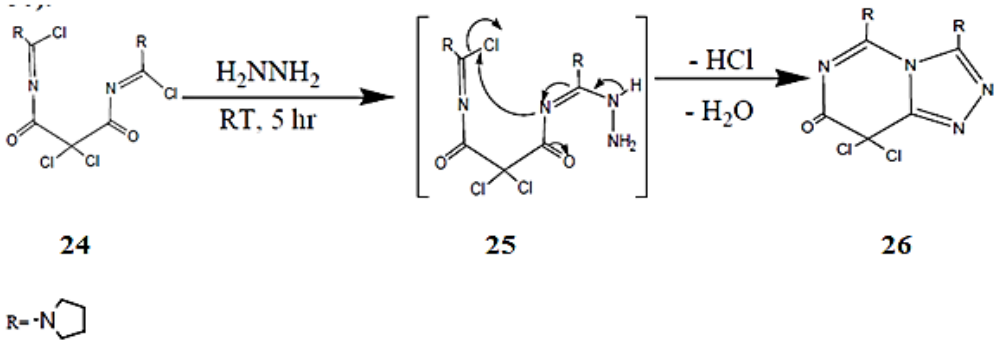


Scheme 8

2.2.2 1,2,4-triazolo[4,3-c]pyrimidine

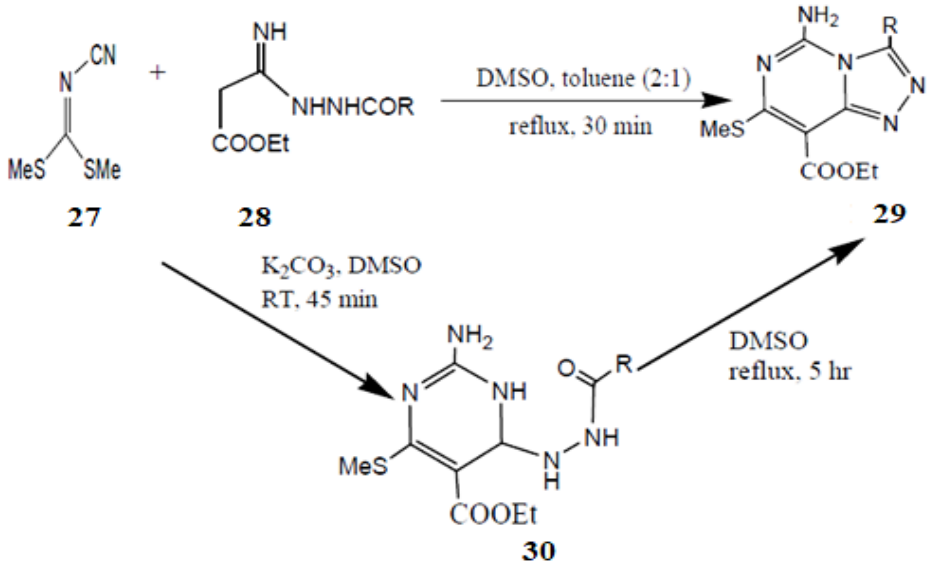
2.2.2.1 Synthesis by concurrent formation of both of the 1,2,4-triazole and pyrimidine rings

The 8,8-dichloro-3,5-dipyrrolidino-1,2,4-triazolo[4,3-c]pyrimidin-7(8H)-one 26 was obtained by cyclizing the 2,2-dichloromalonic acid dipyrrolidine diimidoyl dichloride 24 with hydrazine hydrate, as reported in (40) **(Scheme 9)**.



Scheme 9

At increased temperatures, the reaction of N-[bis(methylthio)methylene]cyanamide 27 with N1-acylamidrazones 28 generated the corresponding 1,2,4-triazolo[4.3-c]pyrimidines 29. The 4-acylhydrazino pyrimidines 30 were obtained by performing the reaction between 27 and 28 at room temperature in the presence of potassium carbonate, which were then dehydratively cyclized to 29 by heating in dimethylsulfoxide (41)**(Scheme 10)**.



R = Me, Me_2CH, $PhCH_2$, 4-$ClC_6H_4CH_2$, Ph, 4-$O_2NC_6H_4$, 4-pyridyl

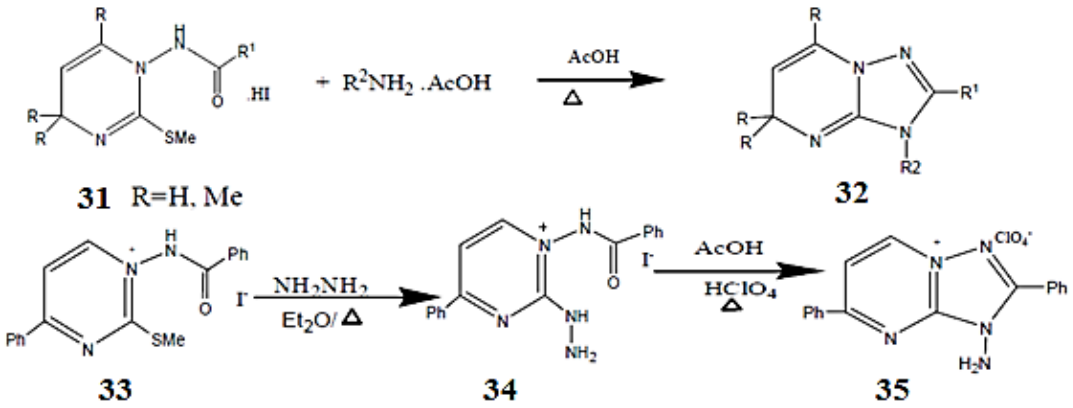
Scheme 10

2.2.3 Synthesis of 1,2,4-Triazolo[1,5-a]pyrimidine

These compounds are made via either Dimroth rearrangement of 1,2,4-triazolo[4,3-a] pyrimidines or by constructing one of the heterocycles and then utilizing it as a base to create the other ring onto it. 1-amino or 2-aminopyrimidines are used to make 1,2-diaminopyrimidines. Alternative precursors that can provide three carbons to complete the pyrimidine ring are 3- and 5-amino-1,2,4-triazoles.

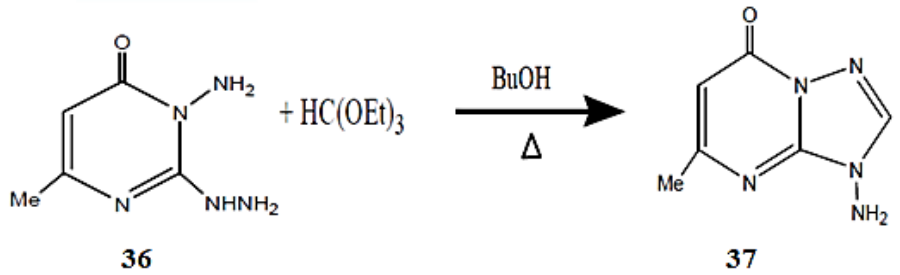
2.2.3.1 Synthesis from 1-Aminopyrimidines

3H,5H-1,2,4-triazolo[1,5-a]pyrimidines 32 were obtained by cyclizing l-(acylamino)pyrimidine hydroiodides 31 with alkyl ammonium acetates (42) The 1-(acylamino)pyrimidinium salt 33 was condensed with hydrazine hydrate to give 34, which was then cyclized with acetic acid in the presence of perchloric acid to give the 3-amino-1,2,4-triazolo[1,5-a]pyrimidinium salt 35 (43)**(Scheme 11).**



Scheme 11

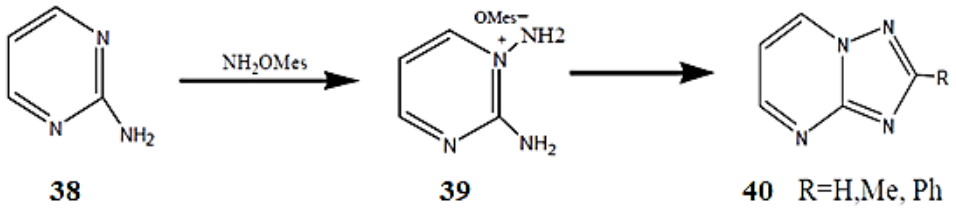
With triethyl orthoformate, the 1-amino-2-hydrazinopyrimidine 36 can be cyclized to 37 (44)**(Scheme 12).**



Scheme 12

2.2.3.2 Synthesis from 2-Aminopyrimidines

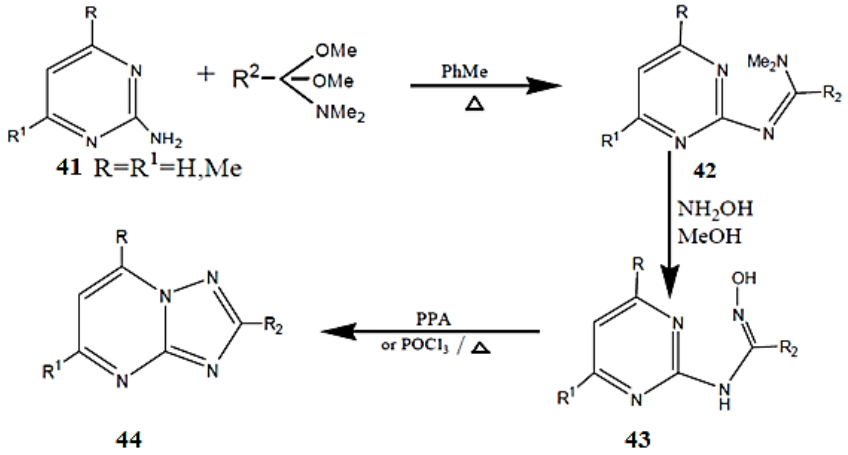
The N-aminopyrimidinium salt 39 was obtained by amination of 2-aminopyrimidine 38 with O-mesitylenesulfonylhydroxyamine (NH2OMes), which may be converted into 1,2,4-triazolo[1,5-a]pyrimidines 40 by heating with formic acid, acetic anhydride, and benzoyl chloride (45)**(Scheme 13)**.



38 39 40

Scheme 13

The cyclization of 2-aminopyrimidines by fusing of a C-N fragment can be used to make triazolopyrimidines. Thus, the triazolopyrimidines 44 were synthesized by first condensation of 2-aminopyrimidines 41 with (MeO)2CR2NMe2, then reaction of the resultant derivative 42 with NH2OH to provide the hydoxyiminomethyleneaminopyrimidine 43, which was then cyclized by polyphosphoric acid (PPA). (46) When using 2-amino-4-methylpyrimidine as a starting molecule, cyclization involved either an N-1 or N-3 pyrimidine atom, resulting in the formation of both isomers in a 1:5 ratio; the predominant one having R1 = Me (47)**(Scheme 14)**.

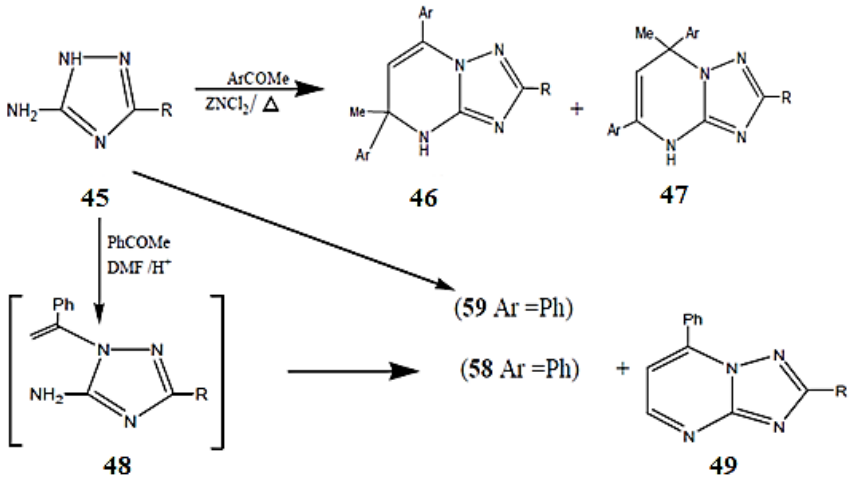


41 R=R1=H,Me 42 43 44

Scheme 14

2.2.3.3 Syntheses from 5(3)-Amino-1,2,4-Triazoles

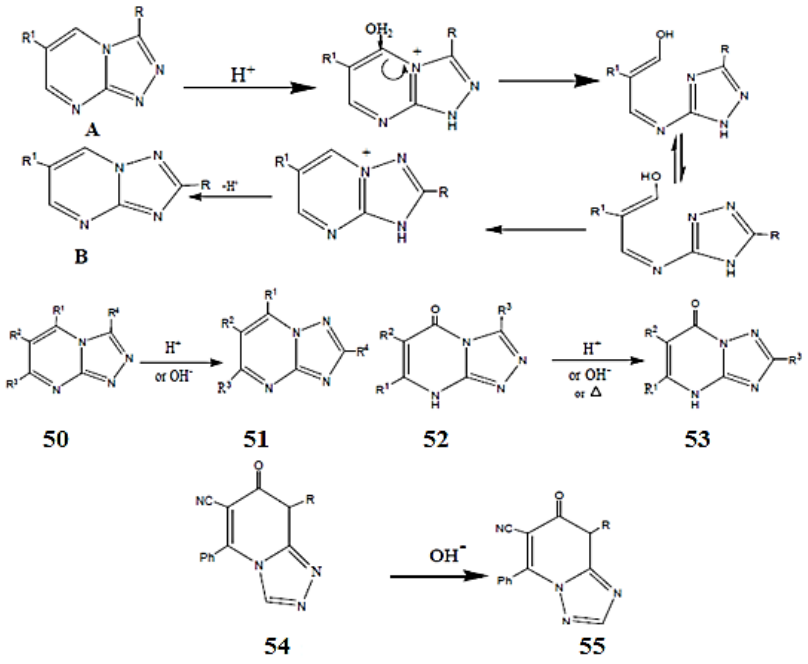
By reacting with appropriate carbonyl compounds, 5-amino-1H-1,2,4-triazole and its derivatives are widely employed as precursors for this ring. The dihydrotriazolopyrimidines 46 and 47 were formed by reacting the 5-amino-1,2,4-triazoles 45 produced from calcium cyanide with the appropriate acetophenone in the presence of ZnCl2 (48) By involving either a second acetophenone molecule or a DMF molecule in the cyclocondensation of 45 with acetophenone in DMF, the triazolopyrimidines 46 (Ar=Ph) and 49 were produced via the intermediate 48. In the absence of a catalyst, the reaction of 45 with PhCMe=CHCOPh yielded the dihydrotriazolopyrimidines 47 (Ar=Ph) (49)**(Scheme 15).**



Scheme 15

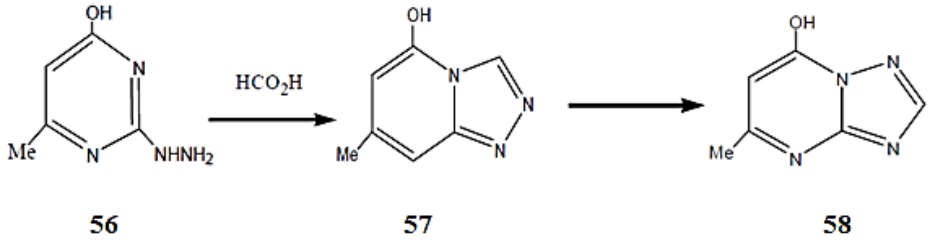
2.2.3.4 Dimroth Rearrangement of 1,2,4-triazolo[4,3-a]pyrimidine

Dimroth rearrangement of 1,2,4-triazolo[4,3-a]pyrimidines (A) gave the 1,2,4-triazolo[1,5-a]pyrimidines (B) the triazolopyrimidines with various substituents on the ring, as in 50,52, or 54, underwent rearrangement to generate 51, 53, and 55 respectively, upon treatment with acid, alkali, or triethyamine, or upon fusion (50)**(Scheme 16)**.



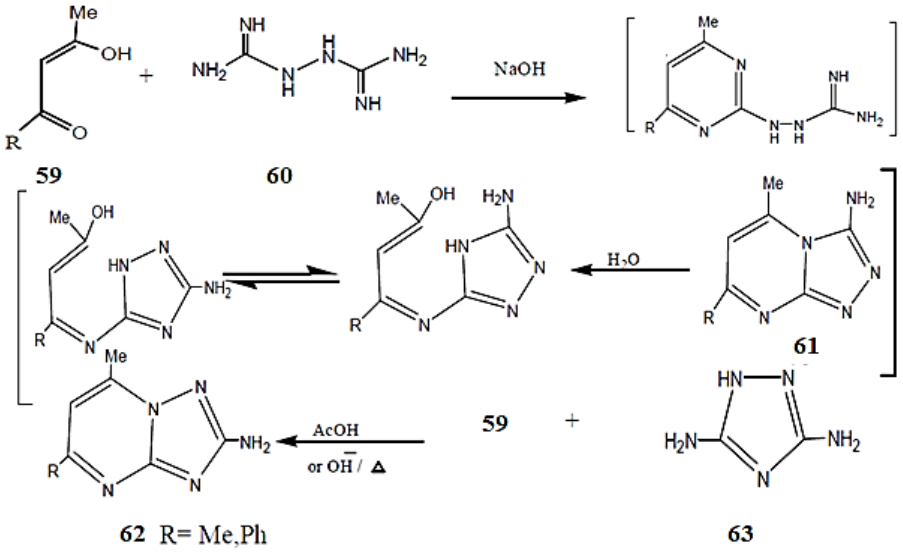
Scheme 16

Because the [4,3-a] ring system cannot be separated, Dimroth rearrangement may be regarded a disadvantage during its synthesis. It is, nonetheless, useful when the [1,5-a] ring system is required. As a result of the reaction of the hydrazine 56 with formic acid, 58 was obtained via 57 (11)**(Scheme 17)**.



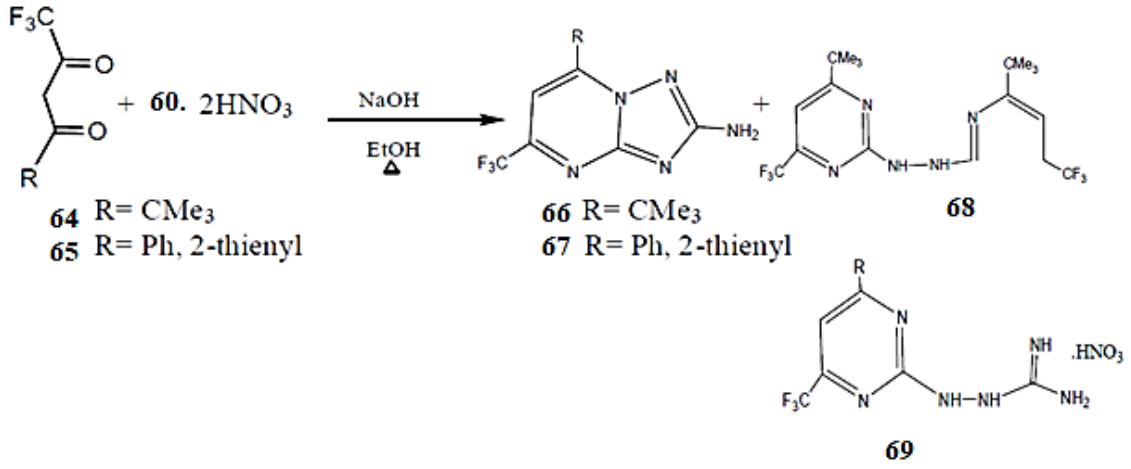
Scheme 17

The production of l,2,4-triazolo[1,5-a]pyrimidine 62 was achieved by cyclizing the diamidine 60 with acetyl- or benzoyl-acetone 59. Alternatively, 62 can be made by combining 59 with diaminotriazole 63 (13)**(Scheme 18)**.



Scheme 18

The trifluoromethyl substituted *B*-diketone 76 produced a mixture of triazolopyrimidine 78 and pyrimidine 80 when it was reacted with 60 nitrates, whereas the aromatic *B*-diketones 77 produced a mixture of triazolopyrimidines 79 and pyrimidines 81. (13) (51)**(Scheme 19)**

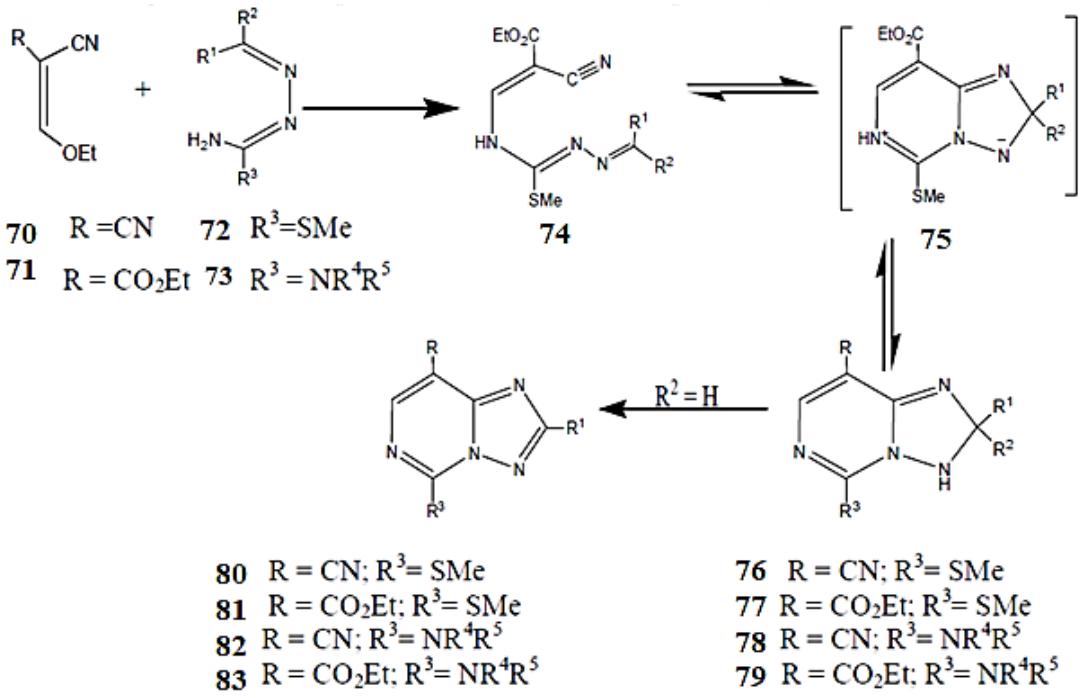


Scheme 19

2.2.4 1,2,4-triazolo [1,5-c]pyrimidine

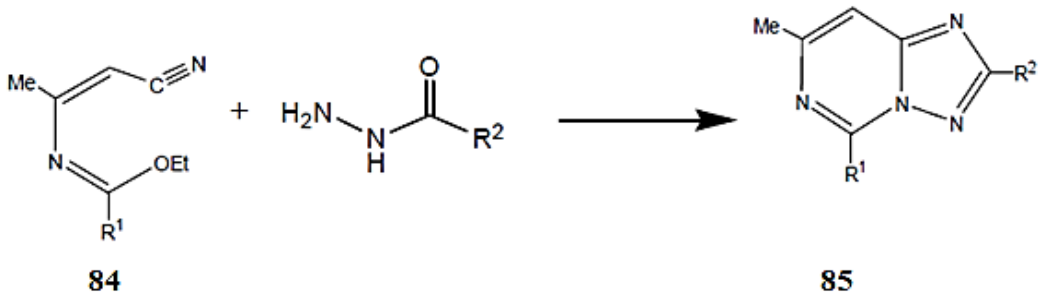
2.2.4.1 Open Chain Precursors for Synthesis

This ring can be made by cyclizing 4-[2-cyano-2-(ethoxycarbonyl)vinyl]-3-methylisothiosemicarbazones of aromatic aldehydes (74; R2=H), which can be created by heating 71 with 72 in BuOH/DMF/dioxane or pyridine to provide triazolopyrimidines 81 in reasonable yields. Ethyl 4-amino-2-(methylthio)-pyrimidine-5-carboxylate is formed through a competitive process. Intermolecular cycloaddition of 74 via the intermediate 75 produced 2,2,5-trisubstituted 2,3dihydrotriazolopyrimidine-8-carboxylates77 by treating the corresponding aromatic ketones with heated acetic acid or pyridine.A 10-electron cyclic transition state may be involved in the ring closure of 74. (52) The dihydrocyano analogs 76 were easily oxidized in DMSO to give the triazolopyrimidines 80 after condensation of ethoxymethylenemalonontrile 70 with isothiosemicarbazones 72. (52). Similarly, in the presence of MeCN/Et3N, condensation of diaminomethylenehydrazones 73 with 71 and 72 yielded the 2,3-dihydro-1,2,4-triazolo[1,5-c]pyrimidines 78 and 79, respectively. The attack of the amino group of 73 on the ethoxymethine carbon of 70 or 71 started the reaction, which was then followed by an electrocyclic reaction. The triazolopyrimidines 82 and 83 were obtained by oxidizing compounds 78 and 79 with FeCl3/AcOH or I2/EtOH, respectively (53)**(Scheme 20)**.



Scheme 20

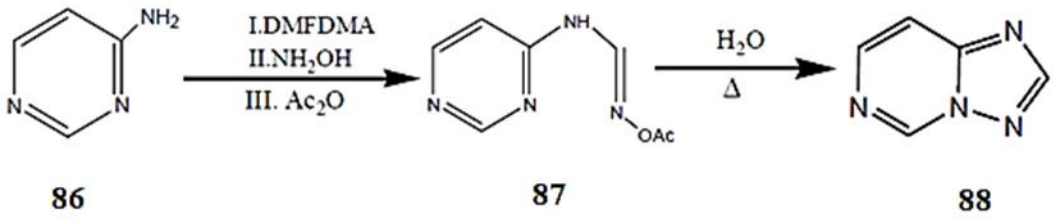
The imidates 84 were condensed with hydrazides to yield 1,2,4-triazolo[1,5-c]pyrimidines 85 (54)**(Scheme 21)**.



Scheme 21

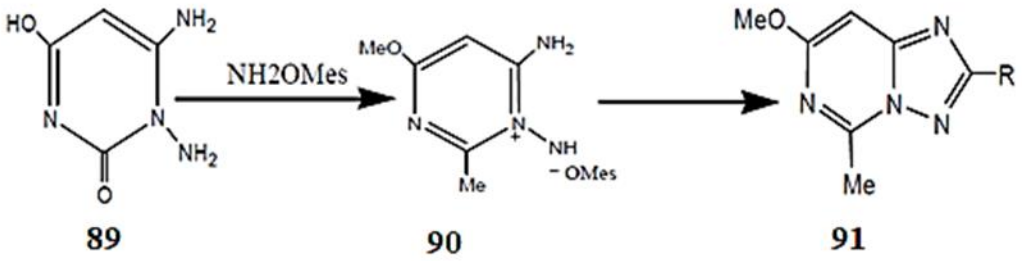
2.2.4.2 Synthesis from pyrimidine

The acetoxyiminomethyleneaminopyrimidine 87 was obtained by reacting amine 86 with DMF/DMA, followed by hydroxylamine and then acetylation, and then heating in water (55) **(Scheme 22)**.

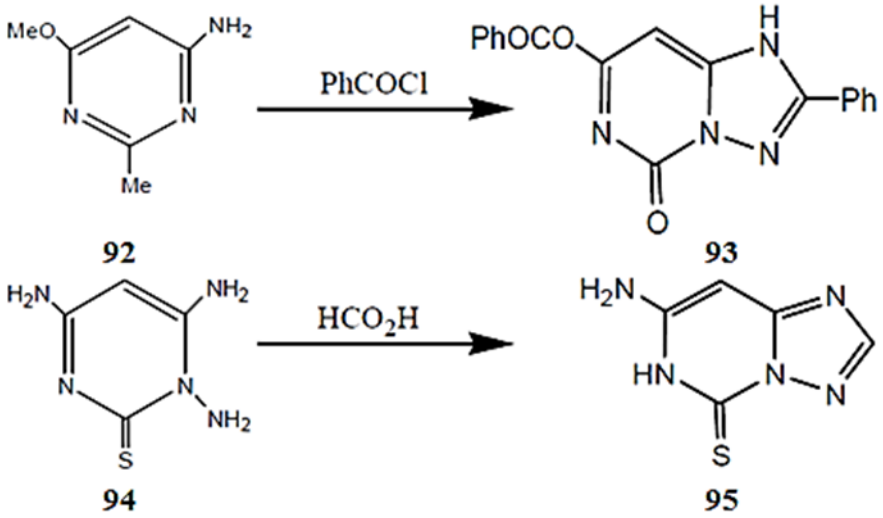


Scheme 22

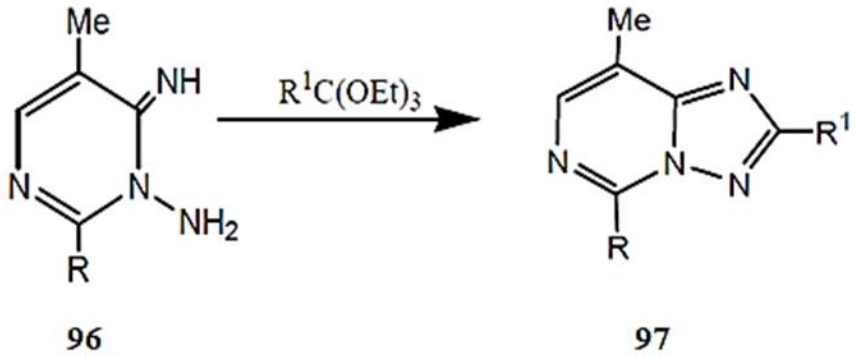
The N-aminopyrimidinium salt 90 was obtained via amination of the 4-aminopyrimidine 89 with O-mesitylenesulfonylhydroxylamine. By heating with formic acid, acetic anhydride, or benzoyl chloride, 1,2,4-triazolo[1,5-c]pyrimidines 91 were produced. (56) Similarly, the triazole[1,5-c]pyrimidines 93, 95, and 97 were obtained by reacting 1,6-diaminopyrimidine 92 with benzoyl chloride (57) triamine 94 with formic acid (58) and aminoiminopyrimidine 96 with orthoesters (54)**(Schemes 23-25)**.



Scheme 23



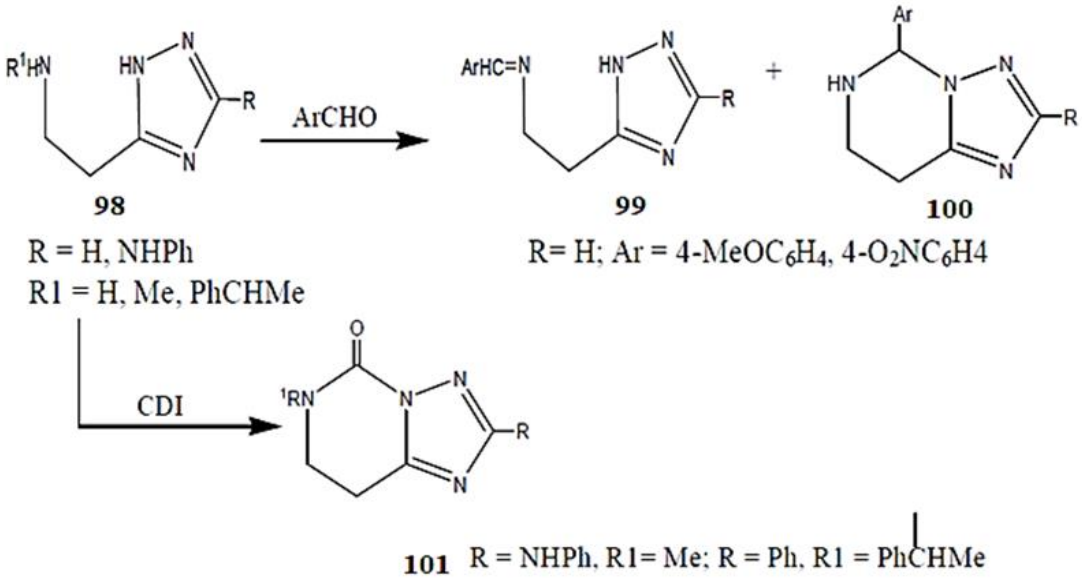
Scheme 24



Scheme 25

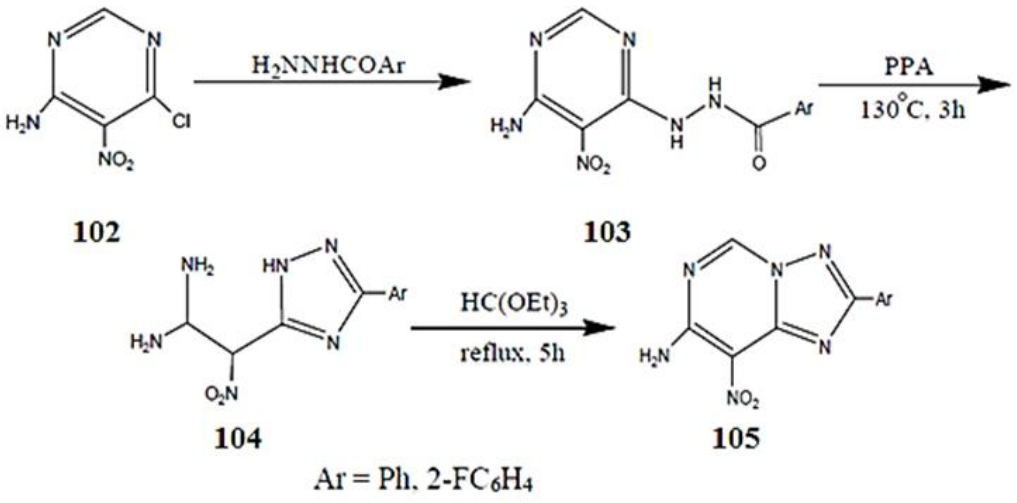
2.2.4.3 Synthesis from triazoles

The related Schiff bases 99 and the 5,6,7,8-tetrahydro-1,2,4-triazolo[1,5-c]pyrimidines 100 were obtained by cyclizing the 3-(2-aminoethyl)-1,2,4-triazoles 98 with aromatic aldehydes. The 5-oxo analogs 101 were obtained by cyclizing 98 with carbonyl-1,1'-diimidazole (CDI) (59) **(Scheme 26)**.



Scheme 26

By heating the 6-acylhydrazinopyrimidine 103 with polyphosphoric acid, the pyrimidine ring ruptured, generating the 1,1-diamino-2-nitro-2-(3-phenyl-1,2,4-triazol-5-yl)ethene 104 instead of dehydrocyclization. The completely aromatic triazolopyrimidine 105 was obtained by cyclocondensing the latter with triethyl orthoformate **(Scheme 27)** (60).



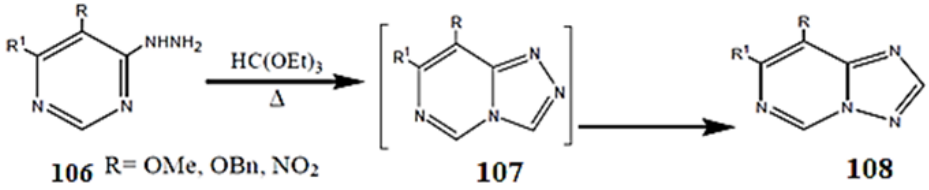
Scheme 27

The assignment of the 1,2,4-triazolo[1,5-c]pyrimidine structures to the products obtained from the previously described cyclizations rather than the alternative [4,3-c] structures has been rationalized and corroborated on the basis of: (I) The products' X-ray crystallographic analysis (61).(II) The inability of the generated products to undergo acid- or base-catalyzed Dimroth rearrangement, which is a property of the thermodynamically less stable [4,3-c] isomers (62)(III) the preference for cyclization at the more nucleophilic triazole ring N2 rather than the less nucleophilic N4. (IV) a comparison to authentics that have been prepared without ambiguity (63)

2.2.4.4 Dimroth Rearrangement of 1,2,4-Triazolo[4,3-c]pyrimidine

The rearrangement of the triazolo[4,3-a]pyrimidine intermediate to the triazolo[1,5-c]pyrimidine product is a common phenomenon found during the cyclization of various hydrazino derivatives of pyrimidines.

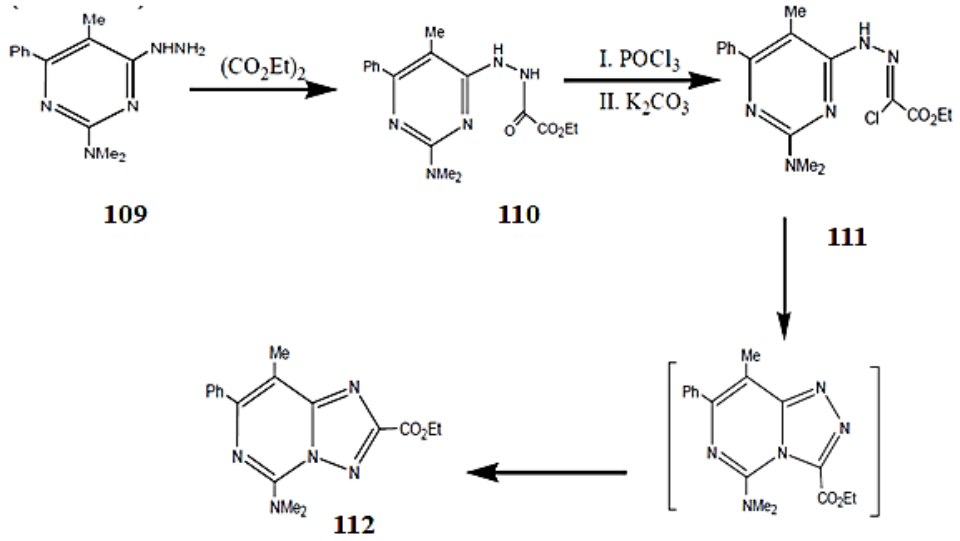
The l,2,4-triazolo[4,3-c]pyrimidine intermediate 107 was produced via cyclization of 5-methoxy(nitro)-4-hydrazinopyrimidines 106 with triethyl orthoformate, but it could not be isolated since it was converted to its [l,5-c]isomer 108 by a Dimroth rearrangement. However, under the same conditions, the 5-benzyloxypyrimidine derivative yielded a mixture of the 8-benzyloxy derivatives of both [4,3-c] and [1,5-c]isomers 107 and 108, respectively (64)**(Scheme 28)**.



Scheme 28

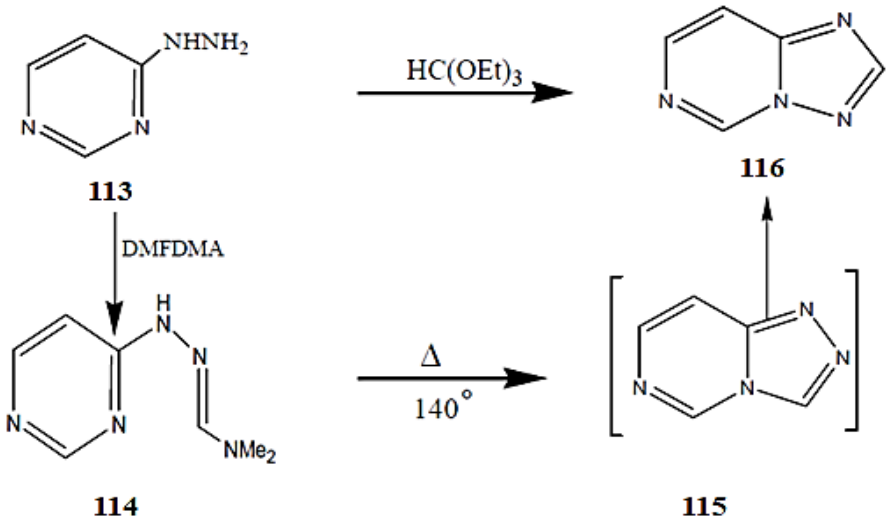
When hydrazinopyrimidine 109 was heated in diethyl oxalate, it produced 110, which was chlorinated with phosphorus oxychloride to produce (2-ethoxycarbonyl) triazolo[l,5-c]pyrimidine

112. Under mild circumstances, the intermediate hydrazidoyl chloride 111 can be separated (65)**(Scheme 29)**.



Scheme 29

Although the reaction of hydrazinoazines with triethyl orthoformate yields unrearranged products, the 4-hydrazinopyrimidine 113 yielded the rearranged product 1,2,4-triazolo[1,5-c]pyrimidine 128 with the same reagent (B. Jenko et al. 1976). The identical heterocycle 116 was synthesized by reacting 113 with DMF/DMA to produce the N,Ndimethylaminomethylenehydrazono derivative 114, which thermally cyclized to the 1,2,4-triazolo[4,3-e]pyrimidine 115, which rearranged into 116. (66)**(Scheme 30)**. Arrangement).



Scheme 30

2.3 Biological effect

In this chapter, the most important biological effects of Triazolopyrimidine compounds will be reviewed, especially in terms of Anti-cancer, Anti-malarial activities, Anti-inflammatory activities, Anti-microbial activities, Antifungal activities, Anti parasites (pest) activities, Agents active on the central nervous system and others.

Cancer is a huge public health issue that kills people all over the world, thus finding new chemical molecules that could lead to the discovery of new antitumor medicines is vital. The extensively documented anticancer action of Triazolopyrimidine derivatives is the focus of this research.

In 2019, B. Lucero et al. (127), produced triazolpyrimidine derivatives, such as compound 117 **(Figure 1)**, that shown significant effectiveness against a variety of plant diseases. Following that, Wyeth Pharmaceuticals examined molecules in this class as possible chemotherapeutic treatments. A triazolopyrimidine derivative, also known as cevipabulin 118 **(Figure 1)**, has been found as having significant anticancer action in vitro and in vivo after thorough Structure-Activity Relationship analyses (SAR). Other investigations SAR and mode of action with a series of

triazolopyrimidine structural congeners related, however, show that triazolopyrimidine derivatives without the alkoxy side chain in the para position of the fluorinated phenyl ring 119 have good activity **(Figure 1)** (67) (68)

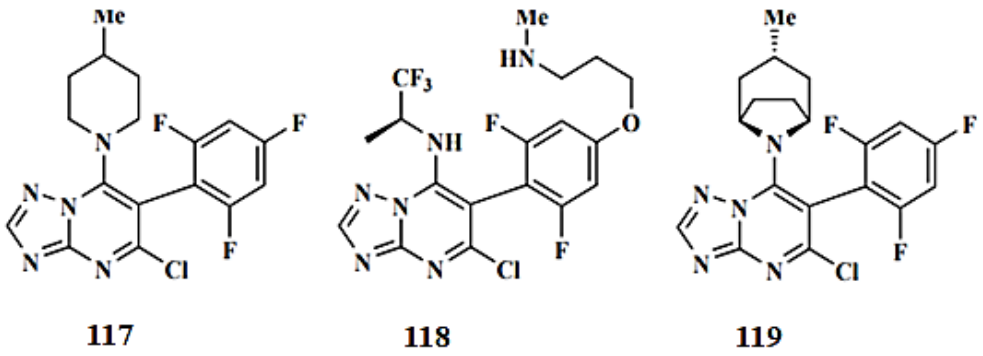


Figure 1 Structure produced triazolpyrimidine derivatives 117-119

In 2017, R. Kumar et al.(126) investigated triazolopyrimidine-pyrazole hybrids 120, which are effective apoptosis inducers **(Figure 2)**. Their research demonstrated that the newly discovered hybrids have a high potential for inducing cell death in Capra hircus goat testicular germ cells. The most cytotoxic compounds for inducing the death of apoptotic cells were discovered to have phenyl and naphthyl groups. (69)

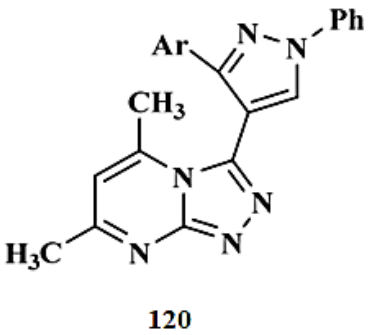
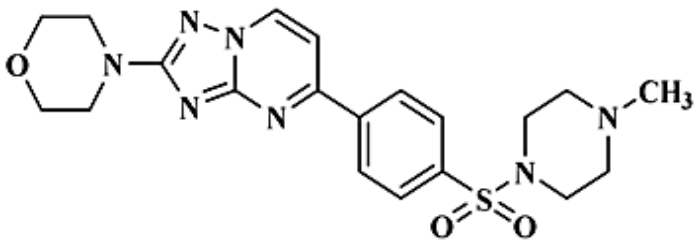


Figure 2 triazolopyrimidine-pyrazole hybrids structure 120

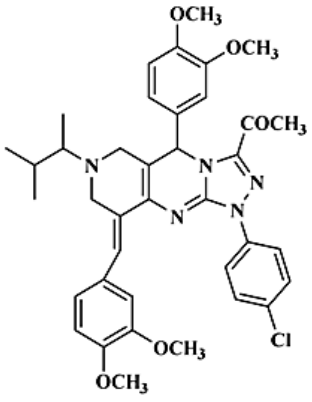
In addition, in the same year, Maarouf et al (128) investigated the antitumor potential of a triazolopyrimidine 121 derivative in 2017. **(Figure 3)**. They tested these chemicals for anticancer action by looking at how well they interacted with DNA. The researchers discovered that compounds with the morpholine ring had higher activity than derivatives with the N-methylpiperazine unit. In vitro, the phenylazo group was discovered to be a pharmacophore that increased activity, especially when attached to a group electron attractor in para position.



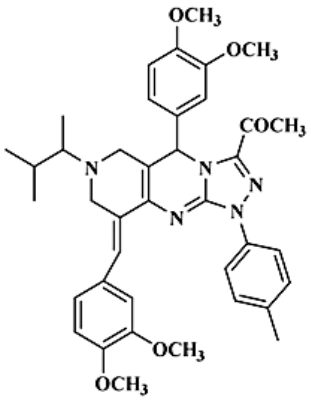
121

Figure 3 Product structure 121 of a triazolopyrimidine

Abdel-Hafez et al., revealed the anticancer potential of triazolopyrimidine derivatives in 2019(129) .There have been several novel fused heterocyclic compounds created. The anticancer activity of products 122 and 123 **(Figure 4)** is particularly high.



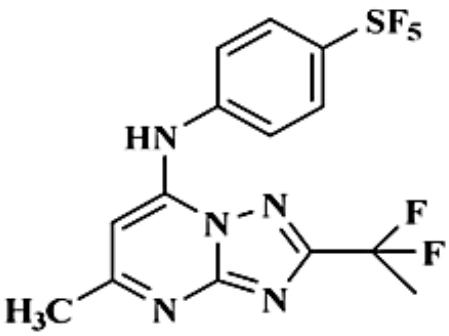
122



123

Figure 4 Structure of products 122 and 123 as anticancer activity

To increase their medicinal qualities, X. Deng et al., produced dihydroorotate inhibitors triazolopyrimidine dehydrogenase (136). They used SF5-aniline derivatives, which led to the discovery of compounds with improved therapeutic characteristics and improved species selectivity while preserving efficacy and pharmacokinetic features, all while maintaining a similar product profile. Compound 124's physical and chemical qualities have been improved as a result of the research as anti-malarial activities **(Figure 5)**



124

Figure 5 Product structure of dihydroorotate inhibitors triazolopyrimidine dehydrogenase 124.

As Anti-inflammatory activities, Adam et al., presented novel receptor agonists 1,2,3-triazolopyrimidine derivatives 125-128 as a viable therapy for inflammatory kidney disorders (137). They began by screening heterocyclic small compounds for novel CB2 receptor agonists using high-throughput screening. As CB2 receptor agonists, a novel highly powerful and selective triazolopyrimidine (relative to CB1) was produced. A benzyl tetrazole at position 3 of the triazolopyrimidine boosts the activity, according to the SAR of compounds. Of Similarly, the 3-pyrrolidine substituent at position 7 of the bicyclic system boosts the compound's efficacy **(Figure 6)**.

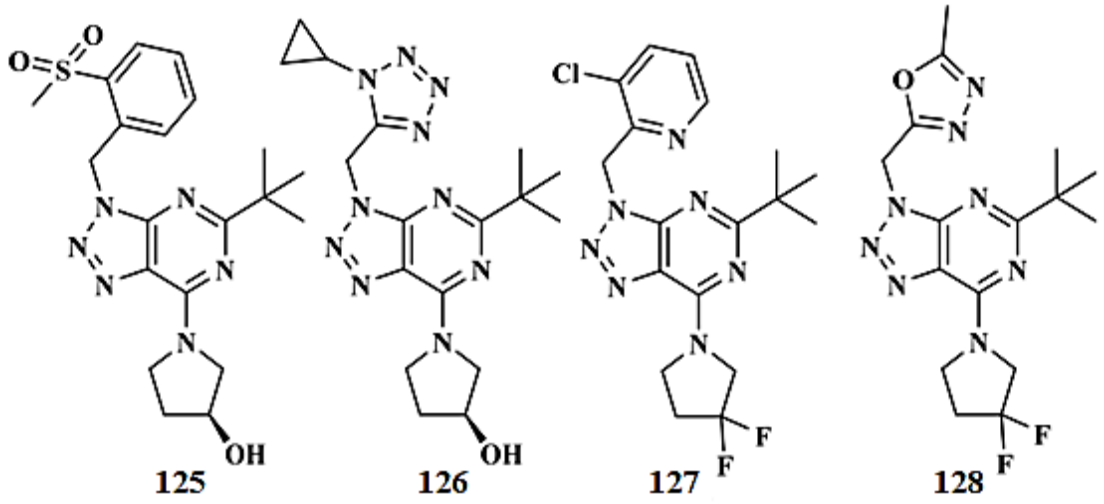


Figure 6 Structure of products 1,2,3-triazolopyrimidine derivatives 125-128

In 2019, Ibrahim et al., demonstrated that compound 129 was higher or nearly equivalent to the reference drugs against COX-2, using the formalin-induced claw edema protocol as a model of acute inflammation (Subramanium in 2015) and the granulation protocol, induced by granuloma, as a model of chronic inflammation **(Figure 7)**, (Fahmy in 2018), for a more in-depth evaluation of its anti-inflammatory activity. In 2018, Sleem et al., tested the newly synthesized compounds for anti-inflammatory action in rats, utilizing the paw edema generated by carrageenan as a model and indomethacin as a control medication. The findings show that the novel chemicals investigated have a broad range of anti-inflammatory effects in rats. Compounds 130-132 are also the most active **(Figure 7)**, (70)

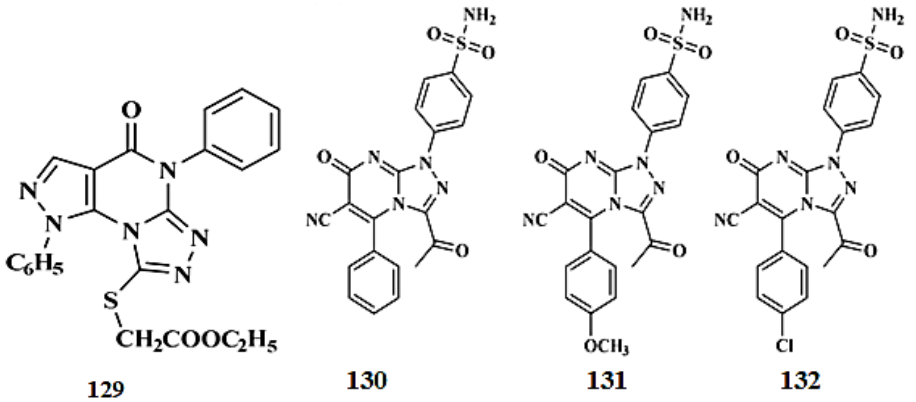
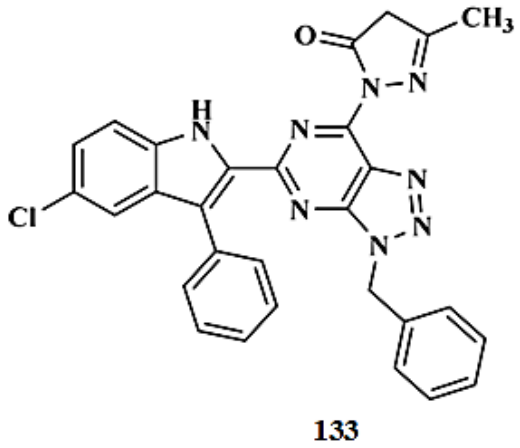


Figure 7 Structure of products as anti-inflammatory effects 129-132

Halu et al. reported on the study of certain novel indole analogues containing the triazolopyrimidine unit 133 **(Figure 8)** as antibacterial agents in 2017(130). The occurrence of chloro and methoxy substitutions in hybrids may be responsible for their antibacterial and antioxidant properties, according to their research. In contrast to compounds with no substitution, the inclusion of these substituents increased activity. In addition, the triazolopyrimidine system 144 boosts activity in general. Furthermore, it has been demonstrated that the indole motif is required for antibacterial action.



133

Figure 8 certain novel indole analogues containing triazolopyrimidine structure 133.

T.A. Farghaly et al., investigated the antibacterial properties of triazolopyrimidines 134 and 135 **(Figure 9)** in 2018. Four fungus strains and four bacterium species were used in an in vitro antibacterial study of compounds 134 and 135. The antimicrobial activity results for 134 revealed that it had the greatest antibacterial activity against the most pathogens tested.

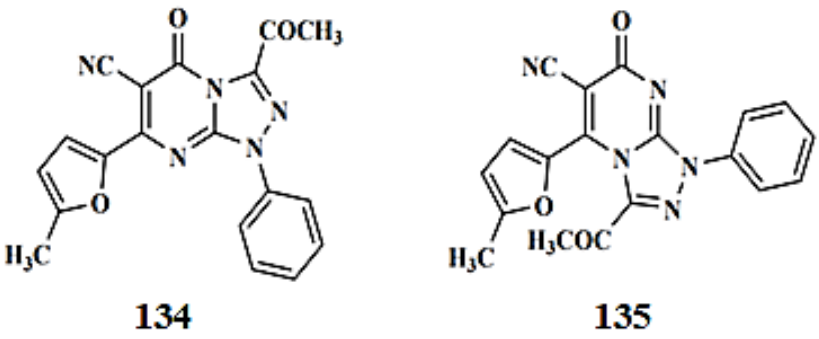


Figure 9 Structure of products 134-135

Hassan et al., published a study in 2019 that evaluated some novel triazolopyrimidine 136 and 137 **(Figure 10)** derivatives as antibacterial agents. They were examined for antibacterial effectiveness against a variety of bacterial and fungal strains, as well as for safety and hemolysis potential. The most effective compounds were tested for their method of action as DNA Gyrase inhibitors. (71)

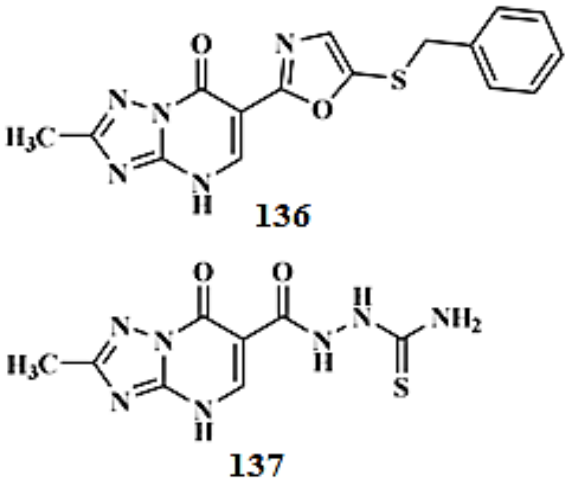


Figure 10 Structure of products novel triazolopyrimidine derivatives 136-137

Anouar et al., reported on the antibacterial assessment of a novel triazolopyrimidine 139 **(Figure 11)** in 2019. Gram-negative microbial strains such Escherichia coli, Pseudomonas and Staphylococcus aureus, aeruginosa were tested, with results demonstrating Compound 139 had higher antibacterial efficacy than the reference (72) (73). In 2019, Hekal et al., published a review of the antibacterial efficacy of various novel derivatives of triazolopyrimidine 138 **(Figure 11)**. The antibacterial activity of the compounds produced was measured using the broadcast method on agar wells. In addition, several antibacterial medicines use the 1,2,4-triazolo[1,5-a]pyrimidine motif as a core (74) (75) (76) (77)

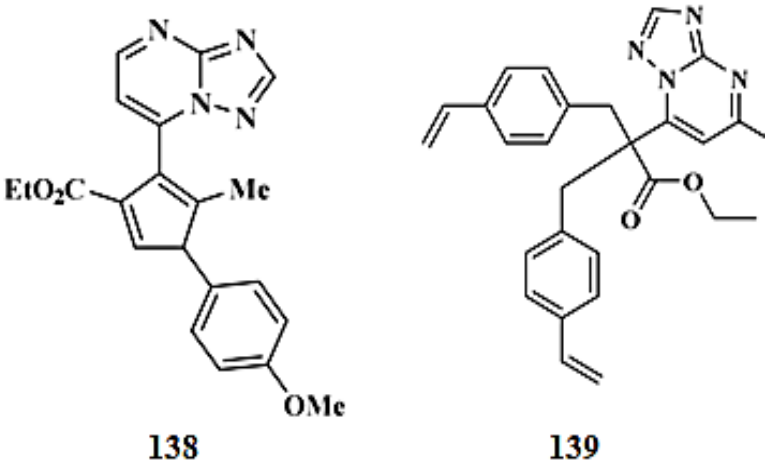
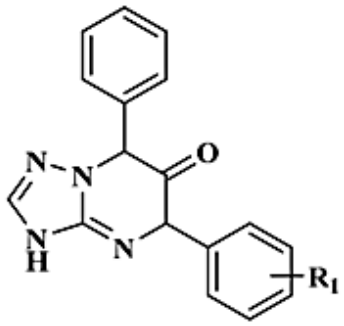


Figure 11 Structure of products 138 and 139

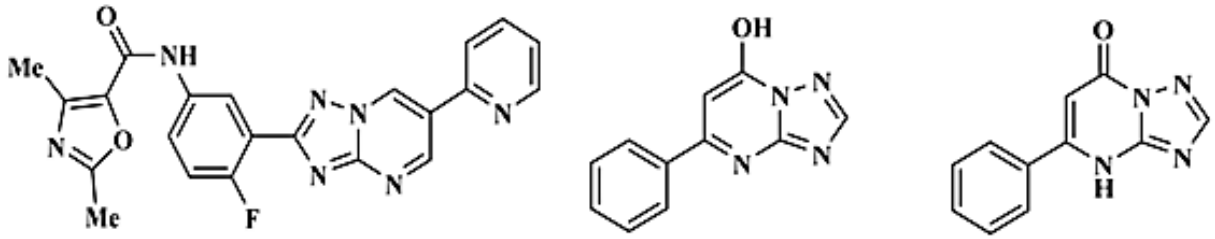
Kalita et al., synthesized triazolopyrimidines 140 and described their assessment utilizing cycloaddition processes in 2015(138). **(Figure 12)**. The produced compounds exhibit fair to moderate antifungal activity, according to antifungal investigations.



140

Figure 12 Product structure 140

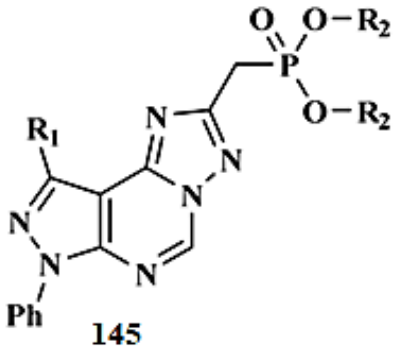
Triazolpyrimdine 157 was created by Luceroet al., in 2019. **(Figure 13)**. In vivo investigations of compound 141 in mice models of kinetoplastid infections demonstrated that the compound is both well tolerated and efficient against numerous parasite infections (Salas et al. in 2014), because it doesn't interfere with the mammalian proteasome. Esteban-Parra et al., synthesized triazolpyrimdine derivatives 142 and 143 in 2017. **(Figure 13)**. They discovered that these chemicals have anti-parasitic properties (78) (79) (80) (81)



141 142 143

Figure 13 Structure of products 141-143

In 2016, Romdhane et al. revealed that derivatives of pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidines 145 had anti-acetylcholinesterase action (131)**(Figure 14)**. They discovered that all of the compounds examined inhibited acetylcholinesterase significantly. They discovered that phosphonate derivatives form a covalent adduct with serine in the enzyme acetylcholinesterase's catalytic region.

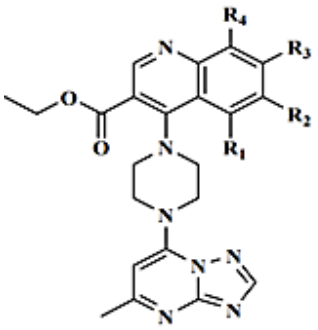


145

Figure 14 Product structure of derivatives of pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidines 145

The AchE inhibitory potential of the triazolopyrimidine connected to the substituted triazine via a piperazine ring was investigated by Maqbool et al., in a similar study published in 2017. They came to the conclusion that triazolopyrimidines combined with triazine have a higher Ache inhibitory potential and that overall in vitro findings in Alzheimer's disease have improved.

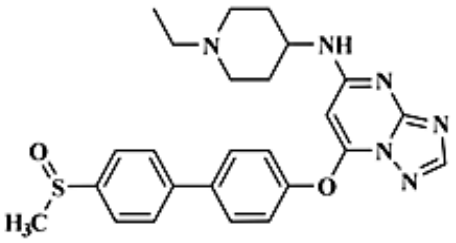
Kumar andMeena et al., in 2016, found AchE inhibitory action of a variety of triazolopyrimidine 146 compounds. They discovered that compounds with a quinolone motif and a piperazine ring in position 7 of the triazolopyrimidine inhibited both ChE (AchE and BuChE) in vitro in the sub-micromolar range **(Figure 15)**, Yenjai et al., (132). In 2018, they repeated the experiment, keeping the triazolopyrimidine motif but substituting a pyrimidine nucleus for the quinoline nucleus. There was no substantial improvement in the intended activity (82)



146

Figure 15 Product structure of AchE inhibitory 146

Chen et al., developed and produced various piperidine-ring-containing derivatives of 1,2,4-triazolo [1,5- a]pyrimidine components of novel non-nucleoside transcriptase inhibitors in 2015. They tested their antiviral inhibitory activity in MT-4 cell cultures. Compound 147 **(Figure 16)** was the most powerful of the compounds produced against the wild type double mutant HIV-1 strain HIV-1 (K103N and Y181C).



147

Figure 16 Product structure of novel non-nucleoside transcriptase 147

Y. Tian et al., investigated the crystal structure of the human immunodeficiency type 1 (HIV-1 RT) reverse transcriptase in interaction with diarylpyrimidines (133). They developed and produced

various 1,2,4-triazolo[1,5-a]pyrimidine derivatives based on their findings. In MT-4 cells, the latter were tested for anti-HIV activity. Compound 148 **(Figure 17)** had the strongest inhibitory action against HIV-1 wild-type and K103N/Y181C double resistance mutant strains, and it was shown to be better than (or similar to) nevirapine and delavirdine. Furthermore, compounds 149 and 150 **(Figure 17)** demonstrated considerable inhibitory effect, supporting the notion that this kind of nitrogen heterocycles can be produced and modified to obtain non-nucleoside reverse transcriptase inhibitors with improved antiviral activity.

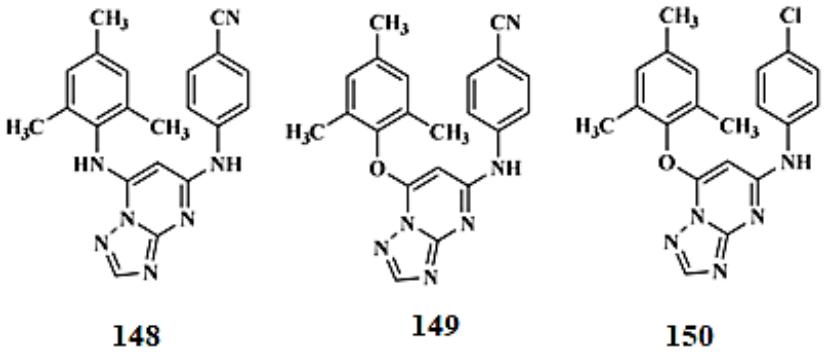


Figure 17 Product structure of non-nucleoside reverse transcriptase inhibitors 148-150

In other studies, they found that Pyrimidines and purines are the main bases of nucleic acids. Novel biological ability, in addition to other pyrimidine core rings, is projected to result in Purine as a analogs, primarily triazolopyrimidines, are therefore required (83) (84) (85). Because of their diverse effects, triazolopyrimidine-integrating compounds have been studied in a variety of fields. Because of their unique pharmacology, which includes antibacterial properties (86)

Triazolopyrimidines, a subtype of purine analogs, are the topic of chemical and biological investigations, also antihypertensive and antileishmanial (87) (88) Anticonvulsant (89), antitumor (90)cytotoxicity (91)and therapeutic potential (92). Furthermore, triazolopyrimidines are flexible ligands that, along with their derived coordination compounds, can be used as model systems for

metal-ligand interactions seen in biological systems (10). We are currently reporting on the synthesis and antimicrobial assessment of novel triazolepyrimidines, as well as our growing interest in the field of physiologically active heterocycles, based on these facts (93) (94). In hybirds, the inclusion of trizole and pyrimidine moieties in the same molecule is expected to boost bioactivity. Some chemicals in this system have been shown to enhance the antibiotic (7-amino-3-[2-amino-3-[2-amino-3-[2-amino-3-[2-amino-3-[2-amino-3-[2-amino-3 (3,4dihydroxybenzenesulfonylmethyl) -5-methyl-1,2,4-triazolo[1,5a] pyrimidin-7-ylsulfanylmethyl] pyrimidin-7-ylsulfanylmethyl] pyrimidin-7-ylsulfanylmethyl] pyrimidin-7-ylsul oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid) Antiallergic agents (2,5,6-trialkyl-1,2,4-triazolo[1,5-a]pyrimidine-7-ylamine), antihistaminic agents (5,7,8-triazolo[1,2,4]triazolo[1,5-c]pyrimidine-2-one), and bronchodilator agents (8-(4-chlorophenyl)-1,2,4-triazolo[4,3-c]pyrimidine.

2.4 Applications of Triazolopyrimidines

2.4.1 Agrochemical Uses

Pesticides, fungicides, nitrification inhibitors, growth regulators, and especially herbicides are all made from triazolopyrimidines. 1,2,4-triazolo[1,5-a] Pyrimidinesulfonamides are utilized as herbicides and plant growth inhibitors (95), and they have anti-acetolactate synthase action In beets, the compound (7-Methoxymethyl-5-methyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonic acid arylamide) is a selective herbicide against dicotyledonous weeds as Galium, Matricaria, Galinsoga, and Mercurialis Spp. The agrochemical fungicides (2,5,6-trialkyl-1,2,4-triazolo[1,5-a]pyrimidin-7-ylamine) and (5,7-dihalo-1,2,4-triazolo[1,5-a]pyrimidines) protect against Plasmopara viticola.(its herbicidal activities vary with the position of the substituent on the phenyl ring). (96) (97)

Herbicides such as (2-(Arylthio)-1,2,4-triazolo[1,5-a]pyrimidines) and (5,7-Dichloro-[1,2,4]triazolo[1,5-a]pyrimidines) are also available (98).Where (5,7-Dialkyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-sulfonic acid phenylamide) are employed as herbicides and nitrification inhibitors in soil, and they are utilized to suppress Echinochioa crusgalli without causing rice damage.

Fungicides that contain (7-amino-2-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carbonitrile) are superior (Eichen et al. 1983). Pigweed can be controlled by 5-fluoromethyl-7-methoxy-1,2,4-triazolo-[1,5-a]pyrimidine-2-sulfonamides (96)

2.4.2 Photographic uses

Birr discovered 5-methyl-1,2,4-triazolo[1,5-a]pyrimidine-7-one (MOT) in 1935, and it was utilized as a "stabilizing" activity for the first time, making it feasible to stabilize the sensitometric qualities of photographic materials during storage for the first time. Many compounds have been created, however none are significantly more effective than MOT. Even today, practically every photography product contains some form of MOT.

As a photosensitive photographic element, 2,5,6-Trialkyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-one was in 1989 and 1991, 5-or-7-one-1,2,4-triazolo[1,5-a]pyrimidines derivatives added to silver halide photographic materials to offer strong contrast and good shelf life under high temperature and high humidity by (Nakazawa et al. and Hosoi et al.), respectively. synthesized (99) (100). As a photosensitive photographic material, silver halide emulsion layers containing substituted 5(7)-one-1,2,4 triazolo[4,3-a]pyrimidine derivatives are utilized, There is no comprehensive theory of stabilization. (101)

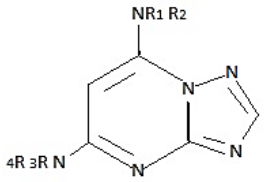
2.4.3 Pharmaceutical uses

Many triazolopyrimidines have been studied for their potential biological activity as microorganism growth inhibitors, including antiviral (7-pyrrolyl(indolyl)triazolopyrimidinum salts) by (Pilicheva et al. in 1990) (102) , antifungal (6,7-dihydrotetrazolo-[1,5-a]pyrimidine) and antibacterial (6,7-dihydrotetrazolo-[1,5-a]pyrimidine) activities (El Ashry et al. 1999) (103). Some compounds from this system were discovered to enhance the antibiotic's action (7-Amino-3-[2-(3,4-dihydroxybenzenesulfonylmethyl)-5-methyl-1,2,4-triazolo[1,5-a]pyrimidin-7-ylsulfanylmethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid) (Nakazawa et al. 1989), Nucleosides bearing a1,2,4-triazolo[1,5-c] triazolo[1,5-c] triazolo[1,5-c] triazolo[1,5-c] triazolo[1,5-c] triazolo[1,5-c] triazolo[1,5-c] triazolo[1,5-c] tria The nucleosides base pyrimidin-5(6H)-one showed antiprotozoal efficacy against Leishmania donovani amastigotes (104). They showed antiallergic

(2,5,6-trialkyl-1,2,4-triazolo[1,5-a]pyrimidin-7-ylamine), antihistaminic (5,7,8-Trimethyl-[1,2,4]triazolo[1,5-c]pyrimidin-7-ylamine) and antihistaminic (5,7,8-Trimethyl-[1,2,4]triazolo[1,5-c]pyrimidin bronchodilator (8-(4-Chloro-phenyl)-1,2,4-triazolo[4,3-c]pyrimidine) pyrimidin-2-one . (103) (105) (106)

Oral antihypertensive (8-aryl-1,2,4-triazolo[1,5-c]pyrimidine-2-thiol) and angiotensine II receptor antagonist (1,8a-Dihydro-2H-1,2,4-triazolo[4,3-c]pyrimidin-3-one) decreases aortic smooth muscle proliferation -5-methyl-1,2,4-triazolo[1,5-a]pyrimidin-7-yl-diethylamine, treatment of circulatory disease such as stroke and arteriosclerosis (5-butyl-4(2'-triazolylbiphenylmethyl-1,2,4-triazolo[1,5-a]pyrimidine-7one) and used to treat cardiac insufficiency and arterial wall disease (5-butyl-4(2`-triazolylbiphynylmethyl)-1,2,4-triazolo[1,5-a]pyrimidine-7-one). (107)-(110)

Antiulcer agents (2,5,6-trialkyl-1,2,4-triazolo[1,5-a] triazolo[1,5-a] triazolo[1,5-a] triazolo[1,5-a] triazolo[The amine derivatives of 1,2,4-triazolo[1,5-a]pyrimidine-5,7-diamine, pyrimidin-7-ylamine, show antineoplastic action. Thus, (NR1R2 = NHBn; NR3R4 = NHNH2) is effective against AK755, (NR1R2 = NHBn; NR3R4 = morpholino) is effective against sarcoma 37, and (NR1R2 =NR1R2 = phthalmidoethylthio) is effective against Lewis Lung Cancer (111). In addition, 7-phynoxyalkyl-1,2,4-triazolo[1,5-a]pyrimidines were created in the hopes of treating seizures and neurological disorders (112)



The effect of adding (cis-[Pt(4,7-dihydro-7-oxo-1,2,4-triazolo[1,5-a]pyrimidine)2Cl2]) to cultured human cell lines MCF-7 breast carcinoma and A121 ovarian carcinoma at various concentrations was investigated (113). The findings show that this compound has a considerable antitumour activity against the latter, being less active than cisplatin but more active than carboplatin. Antitumor efficacy of 5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidinecomplexes with Ru(II) is also being investigated by (Velders et al. 1998) (114).

Chapter three

Materials and Instruments

3.1 Materials

Phosphorus pentasulfide, Uracil, Anhydrous pyridine, Hydrazine hydrate, ethanol >99.9%, Methanol > 99.9%, Formic acid 98%, Deuterated DMSO(Dimethyl sulfoxide-d6 with TMS (0.03 vol.%)), Deionized (DI) water, Acetone 99.9%, Ethyl acetate, Hexane, Ammonia, Nickel(II) nitrate hexahydrate 98%, Copper(II) nitrate trihydrate 98%, Cobalt(II) nitrate hexahydrate 98%, Ammonium iron(II) sulfate hexahydrate 98%, Dimethyl sulfoxide (DMSO), Nitric acid, Potassium tetrachloropalladate(II) 98%, Potassium tetrachloroplatinate(II) 98%, Hydrochloric acid (HCl) 0.1M, Silver nitrate ≥99.0%, Copper(II) perchlorate hexahydrate 98%, Acetonitrile ≥99.5%, Nickel(II) perchlorate hexahydrate, Hydrogen hexachloroplatinate(IV) 8wt%, Ruthenium(III) chloride trihydrate. (*Sigma-Aldrich provided all of the chemical materials and solvent*).

Muller-Hinton Agar, distilled water, saline solution, Sterile discs of 6 mm filter paper (Whatman, UK), Gram-positive bacteria: MRSA, Staphylococcus aureus, Gram-negative bacteria: Escherichia coli and Pseudomonas, sterile cotton swap and Petri Dishes (10 cm diameter).

Hemin chloride, ultra-pure water, sodium acetate buffer (pH 4.4), anti-malarial medication solution, 0.1 M NaOH, and chloroquine (CQ).

3.2 Instrumentation

Bruker ALPA FTIR Spectrophotometer, Oxford/ Pulsar-Benchtop NMR (60MHz using DMSO-d6), Analytical balance SHIMADZU ATx324 320g in Balances (S-841), Recirculating Cooler (SRC4), Rockyvac 300 Vacuum Pump, SANYO/ GALLENKAMP Melting point apparatus,

ONiLAB Magnetic Hotplate Stirrer (MS-H-S-Pro), Stuart Rotary Evaporator (RE 400) with Digital Water Bath (RE 400 DB), Perkin Elmer Jade Differential scanning calorimetric (DSC), X-ray (XtaLAB Synergy, Single source at offset/far, HyPix diffractometer).

Chapter four

Synthesis and Characterization

4.1 Introduction

The coordination compounds of the 1,2,4-triazolo[1,5-c]pyrimidine in this thesis are a first time subject. Prior to doing this research, we had to prepare and describe this derivative using standard techniques as well as conduct a theoretical investigation to round out the experimental work.

The compounds were investigated using nuclear magnetic resonance (NMR); which is the most essential approach for obtaining precise information about a molecule's physical, chemical, and structural properties. Differential scanning calorimetry (DSC); a thermal technique used to investigate a compound's physical, chemical, oxidative, thermal properties (i.e. melting range) and figure out impurities. And Fourier-transform infrared spectroscopy (FT-IR) –one of the most essential techniques for determining the structure of a molecule; Infrared light is absorbed by organic molecules and turned into energy in the shape of molecule vibration (stretching and bending). As a result, it is utilized to evaluate functional groups and bonding in a solid product.

4.2 Experimental Synthesis and characterization of Organic Compounds

4.2.1 Synthesis of Organic Compounds

To obtain 1,2,4-Triazolo[1,5-c]pyrimidine-5(6H)-ones, 4-thiouracil and hydrazinopyrimidinone must be prepared beforehand. In this chapter, preparation method based on Brown et al. study to obtain the intended compound will be presented. (115)

4.2.1.1 Synthesis of 4-thiouracil

Starting with 1L round-bottom flask containing 12.0 grams of uracil and 600 ml of pyridine added together and stirred at room temperature for an entire day. phosphorus pentasulfide (7.0 g) was gradually added to the heated solution and boiled under reflux while stirring for 18 hours. after

cooling down to room temperature, the solution was evaporated to dryness using a rotary evaporator adjusted to 25 mmHg pressure and 80℃ then recrystallized with around 15 ml of boiling ethanol. This procedure was repeated until full amount of filtrate was produced then put in the refrigerator until fully precipitated to give 4-thiouracil. m.p 320 ℃, The yield was 85%.

4.2.1.2 Synthesis of hydrazinopyrimidinone

To 250ml round-bottom flask containing 7.0g of 4-thiouracil, 14 ml hydrazine hydrate and 100 ml ethanol were added and the solution was Boiled under reflux with stirring for 1.5 hours. After cooling down to room temperature, the solution was evaporated to dryness on the same adjusted rotary evaporator (25 mmHg, 80 ℃) Then recrystallized with 15 ml of methanol. This procedure was repeated until full amount of filtrate was obtained then was put in the refrigerator until fully precipitated to give hydrazinopyrimidinone. m.p 305 ℃, The yield was 60%.

4.2.1.3 Synthesis of 1,2,4-Triazolo[1,5-c]pyrimidine-5(6H)-ones

To the 250ml round-bottom flask containing 3.5g hydrazinopyrimidinone , 50 ml of 98% formic was added and heated under reflux while stirring for 5 hours. After cooling down to room temperature, the solution was evaporated on the same adjusted rotary evaporator (25 mmHg, 80 ℃) then recrystallized with 15 ml of ethanol. This procedure was repeated until full amount of filtrate was obtained then put it in the refrigerator until fully precipitated to give s-Triazolo[1,5-c]pyrimidine-5(6H)-ones. Total eathanol 60ml . M.p 353℃, The yield was 86%.

4.2.2 Characterization of Organic Compounds

4.2.2.1 FTIR

In this experiment, IR spectra was recorded in the 4000-500 cm^{-1} range.

4.2.2.1.a FTIR for 4-Thiouracil

As in **Figure 18** the IR spectrum of the free 4-Thiouracil; the absorption of C=S was shown in 1240-1110 cm^{-1} range while in 3154-3000 cm^{-1} range for C-H aromatic stretch. the absorption aliphatic C-H appeared at rang of 2963-2883 cm^{-1} while for C=C and C=N stretch in 1586-1551cm^{-1} range. In 1403-1383 cm^{-1} for CH2 bending. And C-N stretching appeared at 1196 cm^{-1}

Spectrum 1062-1006 cm^{-1} for C-H in-plane bending, while 846-620 cm^{-1} for C-H out-plane bending.

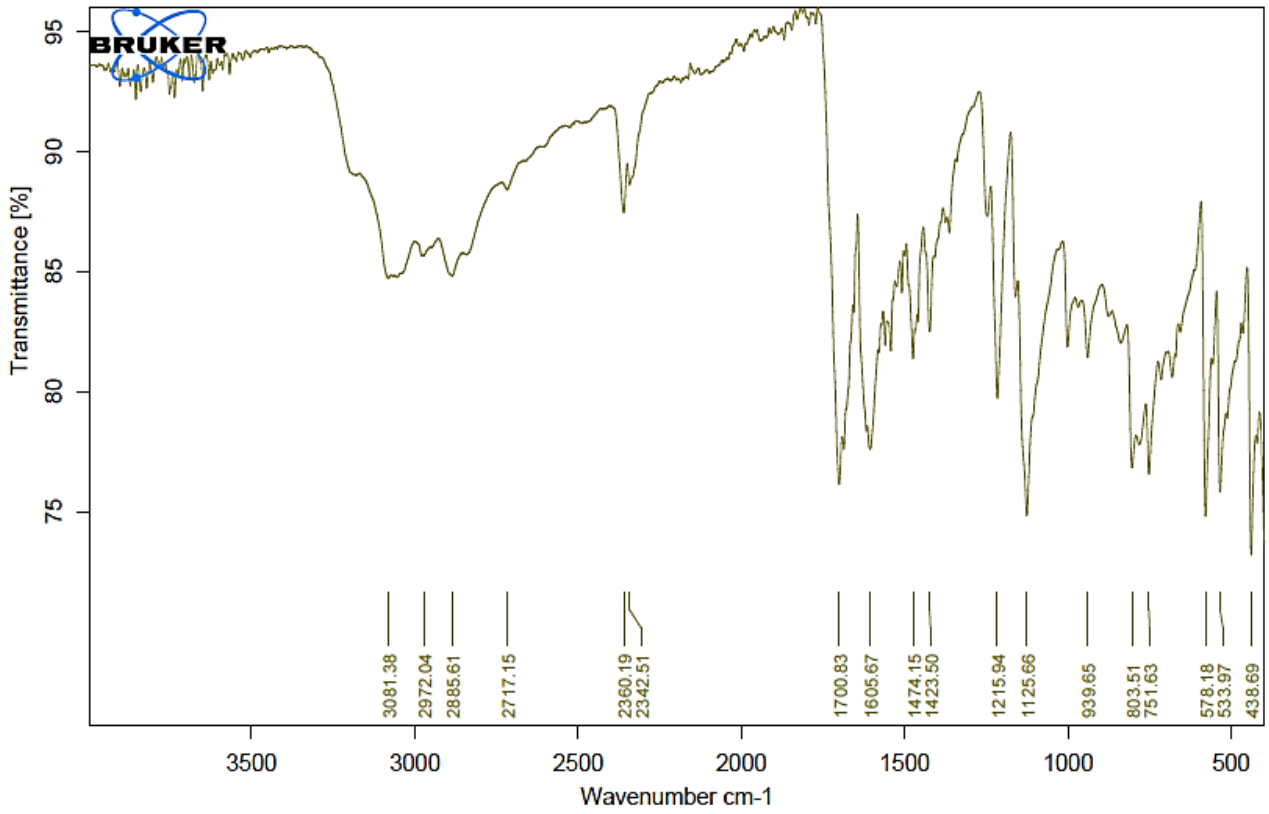


Figure 18 FTIR for 4-Thiouracil

4.2.2.1.b FTIR for hydrazinopyrimidinone

As in **Figure 19** the IR spectrum of the free hydrazinopyrimidinone; the absorption of N-H was shown 1339 cm^{-1} , 3058 cm^{-1} for C-H aromatic stretch, the absorption aliphatic C-H appeared at 2929 cm^{-1} , 1586-1500 cm^{-1} for C=C and C=N stretch, too, 1403-1383 cm^{-1} for CH2 bending. C-N stretching appeared at 1196 cm^{-1} . Spectrum 1058-1000 cm^{-1} for C-H in-plane bending, while 885-620 cm^{-1} for C-H out-plane bending.

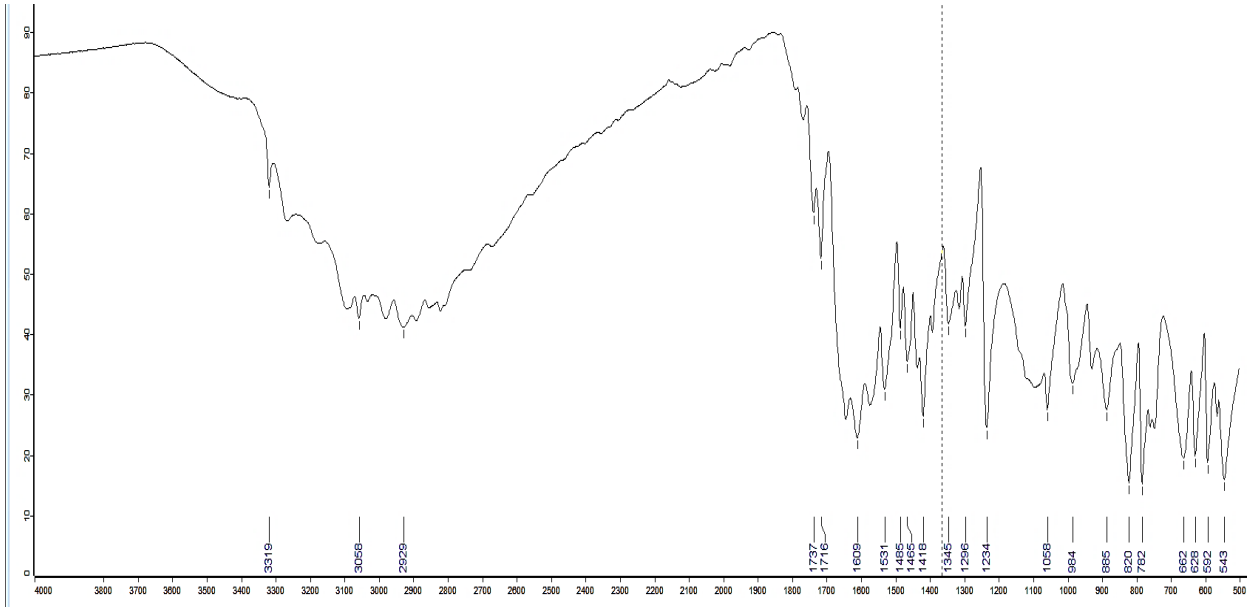


Figure 19 FTIR for hydrazinopyrimidinone

4.2.2.1.c FTIR for 1,2,4-Triazolo[1,5-c]pyrimidine-5(6H)-ones

As in **Figure 20.** the IR spectrum of the free 1,2,4-Triazolo[1,5-c]pyrimidine-5(6H)-ones ligand, a single band at 3114-3000 cm^{-1} are assignable for the C-H aromatic stretch, the absorption C=C stretch appeared at 1565 cm^{-1} , C-H bending in plane at 1165-929 cm^{-1} , C=O stretch at 1717 cm^{-1} , C-N stretch at 1341-1270 cm^{-1} , C-H bending out of plane at 899-524 cm^{-1} , C=N stretch at 1661-1617 cm^{-1} . N-H stretch didn't appeared due to intermolecular hydrogen bonding.

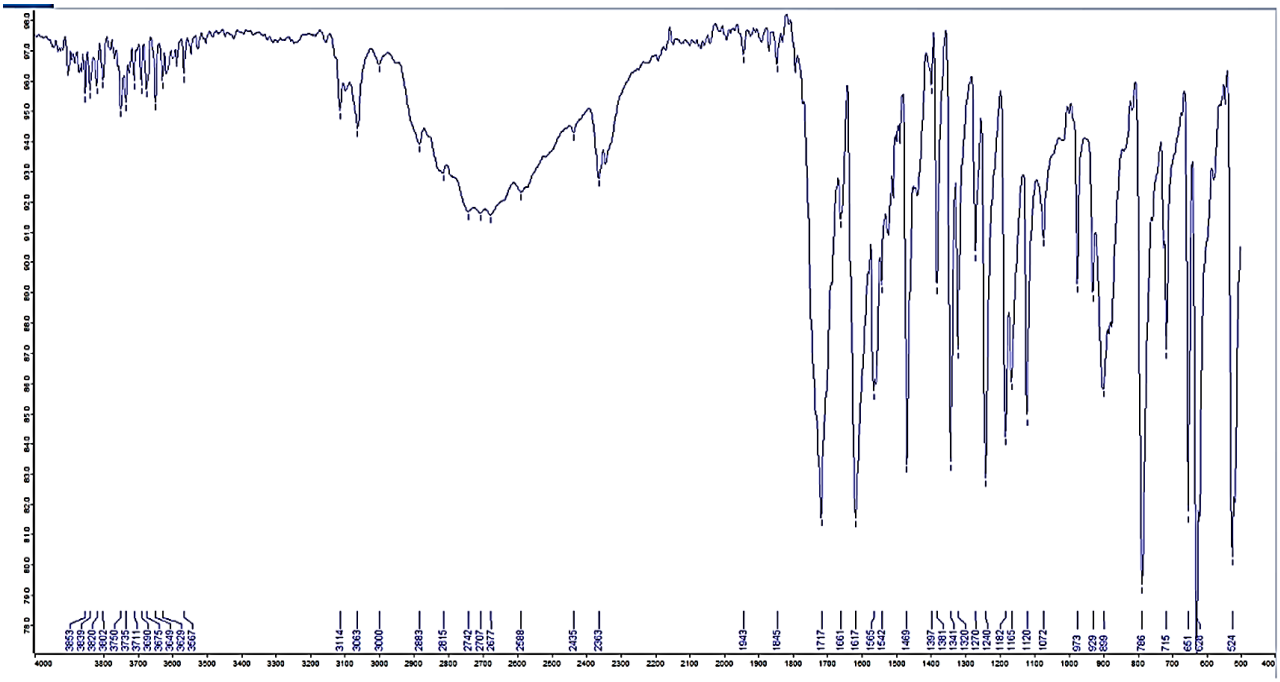


Figure 20 FTIR for 1,2,4-Triazolo[1,5-c]pyrimidine-5(6H)-ones

4.2.2.2 DSC

4.2.2.2.a DSC for 4-Thiouracil

Through DSC two peaks were found; the first one at 278.98℃ of which indicates the melting point of the compound (4-Thiouracil), and the second one was decomposed at 303.92℃.

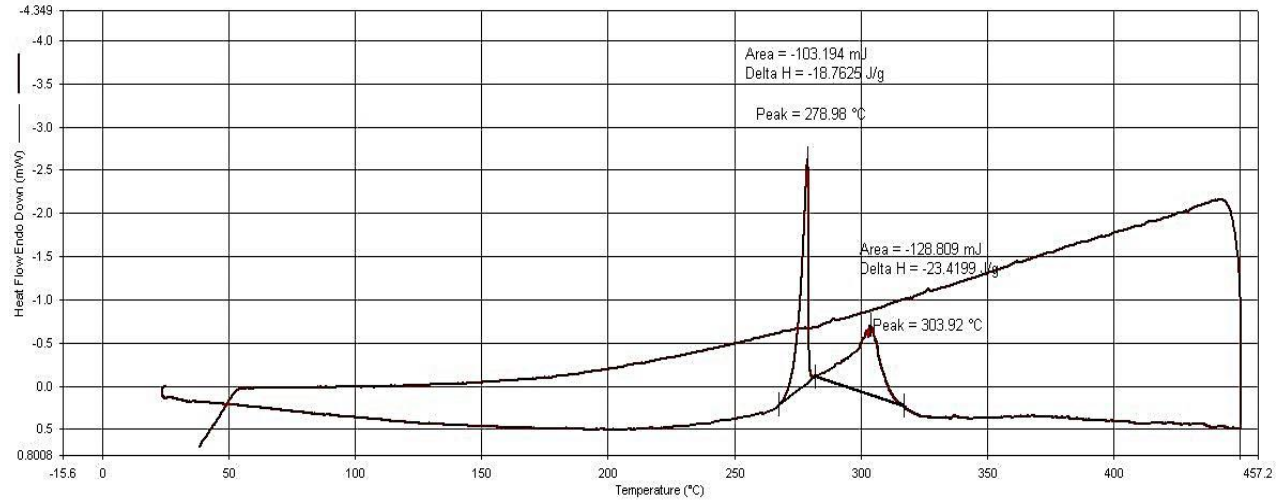


Figure 21 DSC for 4-Thiouracil

4.2.2.2.b DSC for hydrazinopyrimidinone

Hydrazinopyrimidinone was thermodynamically stable, it decomposed at 337.61℃.

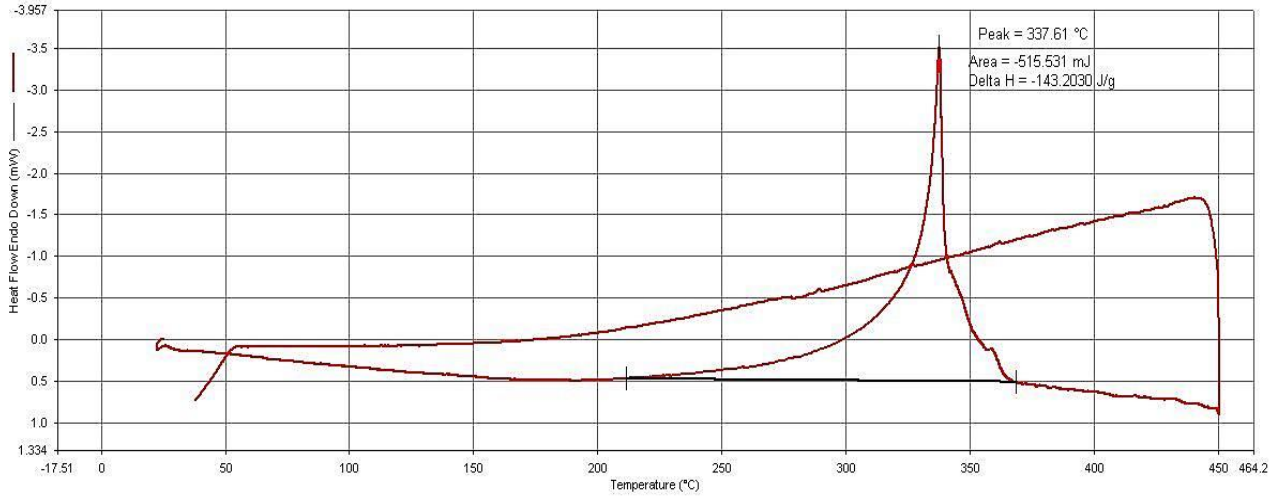


Figure 22 Thermal transition for hydrazinopyrimidinone obtained by DSC analysis

4.2.2.2.c DSC for 1,2,4-Triazolo[1,5-c]pyrimidine-5(6H)-ones

Shown in **Figure 23** at 311.43 ℃ is a stable endothermic peak. decomposed after.

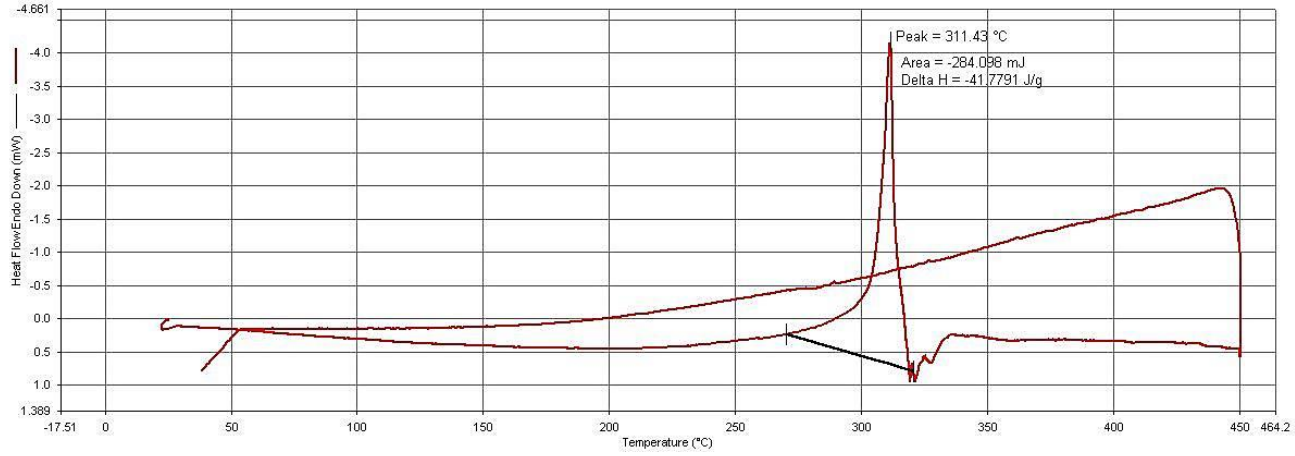


Figure 23 DSC for 1,2,4-Triazolo[1,5-c]pyrimidine-5(6H)-ones

4.2.2.3 H-NMR

4.2.2.3.a H-NMR for 1,2,4-Triazolo[1,5-c]pyrimidine-5(6H)-ones

The analysis was done for (1,2,4-Triazolo[1,5-c]pyrimidine-5(6H)-ones) compound which is the ligand, and the results were as follows: : 6.79, d, H8; 7.62,d, H7; 8.51,s, H2.

2.26,d, H; 3.5,s, H refers to dimethyl sulfoxide (DMSO-d6) and tetramethylsilane (TMS) acetone respectively. this study peaks are very close to Brown. et al. which were 6.71, d, H8; 7.43,d, H7; 8.34,s, H2. (115)

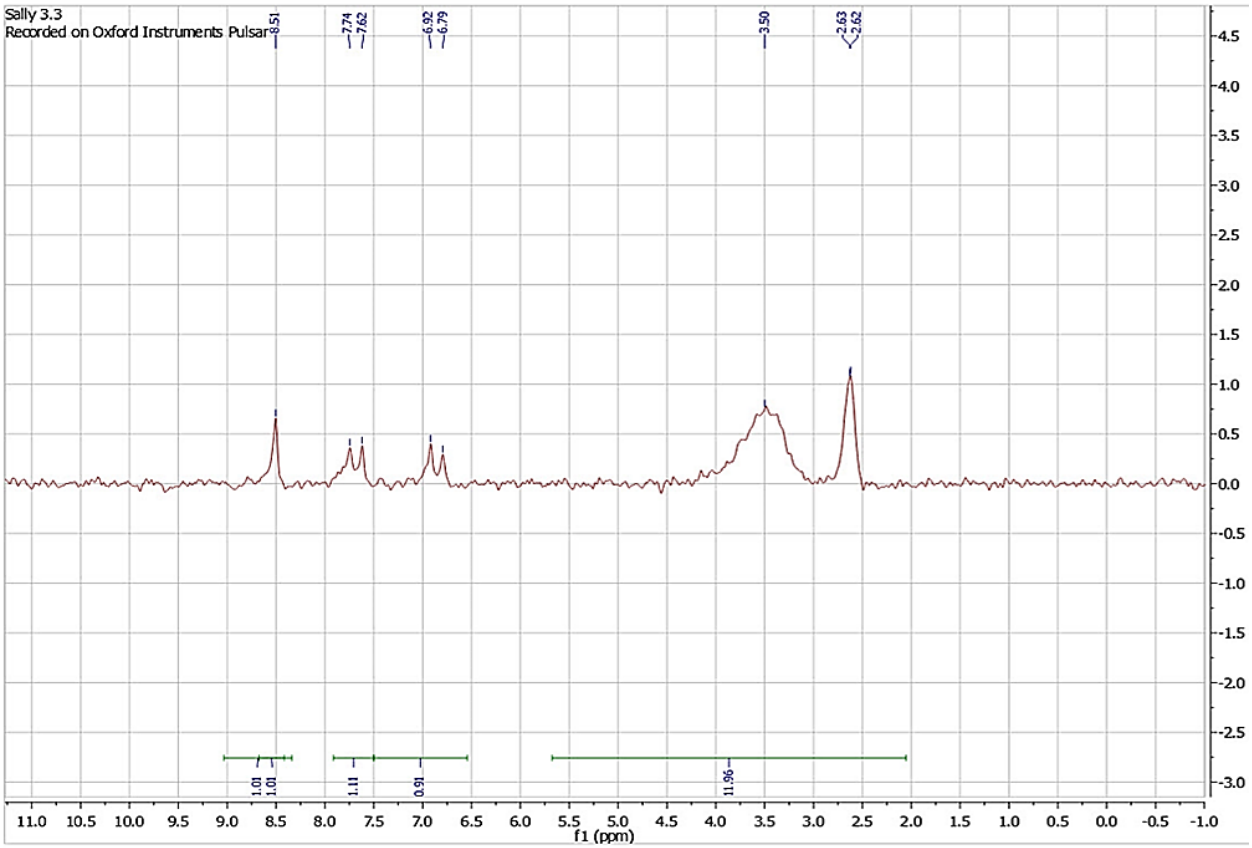


Figure 24 H-NMR for 1,2,4-Triazolo[1,5-c]pyrimidine-5(6H)-ones

4.3 Experimental Synthesis and characterization of Coordination Compounds

4.3.1 Synthesis of Coordination Compounds

4.3.1.1 Synthesis of Copper (II) complexes

4.3.1.1.A

1,2,4-Triazolo[1,5-c]pyrimidine-5(6H)-ones as a ligand (0.272g, 2mmol) was dissolved in 15ml of water, (0.2416g, 1mmol) of $Cu(NO_3)_2.3H_2O$ was dissolved in 5ml of water, first solution was added to the second while stirring. 2ml of concentrated ammonia then added to the mixture. gravity

filtration was done for the resulting solution and was evaporated at room temperature. blue crystals were formed after 3 days. M.p >290°C.

4.3.1.1.B

(0.136g, 1mmol) of ligand was dissolved in 15ml of water, (0.12g, 0.5mmol) of $Cu(NO_3)_2.3H_2O$ was dissolved in 5ml of water and first solution was added to the second while stirring. gravity filtration was done for the resulting solution and was evaporated at room temperature. No precipitate appeared.

4.3.1.1.C

(0.136g, 1mmol) of ligand with (0.12g, 0.5mmol) of $Cu(NO_3)_2.3H_2O$ was dissolved in 30ml of 0.1M nitric acid with stirring. gravity filtration was done for the resulting solution and was evaporated at room temperature. No precipitate appeared.

4.3.1.2 Synthesis of Nickel (II) complex

(0.272g, 2mmol) of ligand was dissolved in 10 ml water. (0.29g, 1mmol) of $Ni(NO_3)_2.6H_2O$ was dissolved in 5ml of methanol, first solution was added to the second while stirring and 3ml of ammonia added. gravity filtration was done for the resulting solution and was evaporated at room temperature. Pale purple crystals were formed after 3 days. M.p 212.8 °C.

4.3.1.3 Synthesis of Cobalt (II) complexes

4.3.1.3.A

(0.272g, 2mmol) of ligand was dissolved in 15 ml of water. (1mmol, 0.291g) of $Co(NO_3)_2 \cdot 6 H_2O$ was dissolved in 5ml of methanol, first solution was added to the second while stirring, 3ml of ammonia were added. gravity filtration was done for the resulting solution and was evaporated at room temperature. Shiny brown crystals were formed after 5 days. M.p >250°C .

4.3.1.3.B

(0.068g, 0.5 mmol) of ligand was dissolved in 10 ml acetonitrile. 0.5ml DMSO added. (0.072g, 0.25 mmol) of $Co(NO_3)_2 \cdot 6H_2O$ was dissolved in 5ml of methanol, first solution was added to the second while stirring . gravity filtration was done for the resulting solution and was evaporated at room temperature. No precipitate appeared.

4.3.1.4 Synthesis of Silver (I) complex

(0.068g, 0.5 mmol) of ligand was dissolved in 10ml 1M ammonia, (0.0425g, 0.25mmol) of $AgNO_3$ was dissolved in 7ml of 1M ammonia, first solution was added to the second while stirring. gravity filtration was done for the resulting solution and was evaporated at room temperature. A white crystal precipitate was formed after 1 week.

4.3.1.5 Synthesis of Platinum(II) and Palladium(II) complexes

4.3.1.5.A Synthesis of Pd(II)complex

(0.136g, 1mmol) of ligand was dissolved in 11ml 0.1M HCl. (0.163g, 0.5 mmol) Potassium tetrachloropalladate2 K_2PdCl_4 was dissolved in 11 ml of 0.1M HCl, then ligand solution was added to Pd solution. Shiny yellow microcrystals were immediately formed. The transparent solution was kept. After 5 days, Brown crystals were formed. They were collected through filtration and were air-dried. M.p 280 °C.

4.3.1.5.B Synthesis of Pt (II) complex

(0.136g, 1mmol) of ligand was dissolved in 11ml 0.1M HCl, K_2PtCl_4 (0.207g, 0.5 mmol) was dissolved in 11 ml of 0.1M HC. Ligand solution was added to Pt solution. Yellow microcrystals were formed after 3 days. The transparent solution was kept. After one week, yellow-orange crystals solid were formed. They were collected through filtration and were air-dried. M.p 290 °C

4.3.1.6 Synthesis of Ammonium iron (II) sulfate complex

4.3.1.6.A

(0.136g, 1mmol) of ligand was dissolved in (0.196 g, 0.5 mmol) of $(NH_4)_2Fe(SO_4)_2 \cdot 6H_2O$ was dissolved in 20ml of 0.1M ammonia with stirring. gravity filtration was done for the resulting solution and was evaporated at room temperature. Two types of crystals precipitates have formed after 2 weeks. Further analysis to be done on these precipitates.

4.3.1.6.B

(0.068g, 0.5 mmol) of ligand was dissolved in (0.098g, 0.25 mmol) of $(NH_4)_2Fe(SO_4)_2 \cdot 6H_2O$ was dissolved in 10ml acetonitrile with stirring. Gravity filtration was done for the resulting solution and was evaporated at room temperature. No precipitate appeared.

4.3.1.7 Synthesis of Nickel (II) perchlorate hexahydrate complex

(0.068g, 0.5 mmol) of ligand was dissolved with (0.072 g, 0.25 mmol) of $Ni(ClO_4)_2 \cdot 6H_2O$ was dissolved in 10ml acetonitrile and 0.5ml DMSO with stirring. Gravity filtration was done for the resulting solution and was evaporated at room temperature. A green precipitate was formed. M.p 212 °C

4.3.1.8 Synthesis of Ruthenium (III) chloride complex

In a 100 ml Round bottom flask, 0.207g of $RuCl_3 \cdot 3H_2O$, 50ml 0.1M HCl, and 0.272g of ligand were added and Boiled under reflux with stirring for 3h. After cooling down to room temperature, Gravity filtration was done for the resulting solution and precipitate was obtained from the filtration. shiny black precipitate formed after 5 days. M.p 290 °C.

4.3.2 Characterization of Coordination Compounds

4.3.2.1 DSC

The following is the thermal behavior of our complexes: first complex is copper, it has two peaks for dehydration (water loss) at temperatures of 121.45°C and 187.93°C **(figure 25)**. When

temperature is raised to 306.06°C, the aromatic component decomposes –the oxidative step which refers to the exothermic peak where copper nitrate is conversed to copper oxide.

Cobalt complex is shown to be stable till 352.60°C. in a higher degree, the aromatic component begins to decompose **(figure 26)**. Iron complex shows four endothermic peaks, 79.37℃ and 107.67℃ for dehydration (water loss). 311.12°C When the aromatic component decomposes. and at 396.02℃ that refers to Iron oxide oxidative step **(figure 27)**. when it comes to Nickel(II) perchlorate complex **(figure 28)** it has two peaks, endothermic indicating water loss at temperature of 118.00℃, and exothermic at temperature 212.86℃ for decomposition of the aromatic component.

DSC for Ni(II) complex shows two peaks; endothermic and exothermic. first peak at 208.73℃ for aromatic decomposition and second peak at 357.53℃ due to oxidation of Nickel. The complex didn't have a dehydration peak where It could be anhydrous compounds **(figure 29)**. platinum, palladium, Ruthenium, and silver complexes were thermally stable till temperatures above 450℃, **(figures 30-33)**.

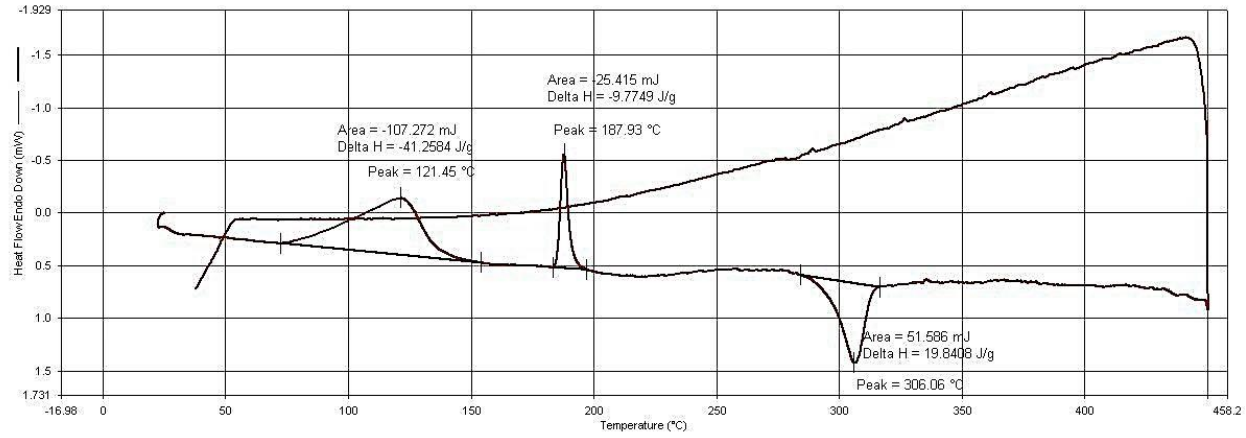


Figure 25 Thermal transition for Copper complex obtained by DSC analysis

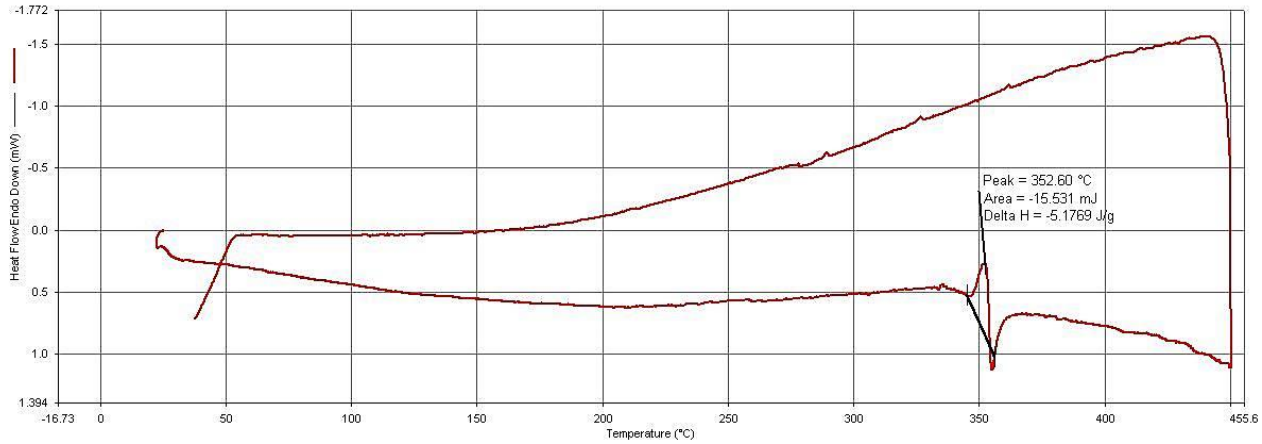


Figure 26 Thermal transition for Cobalt complex obtained by DSC analysis

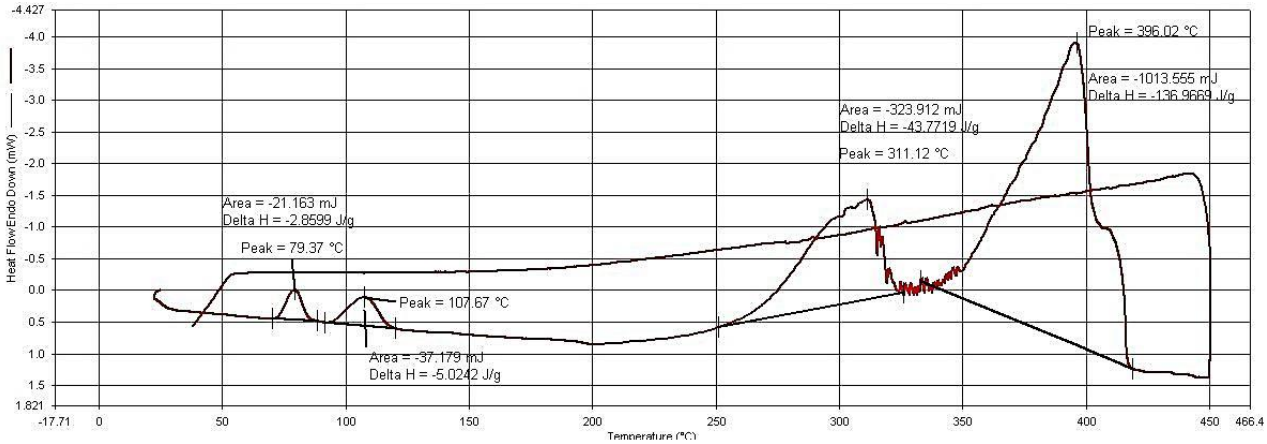


Figure 27 Thermal transition for Iron complex obtained by DSC analysis

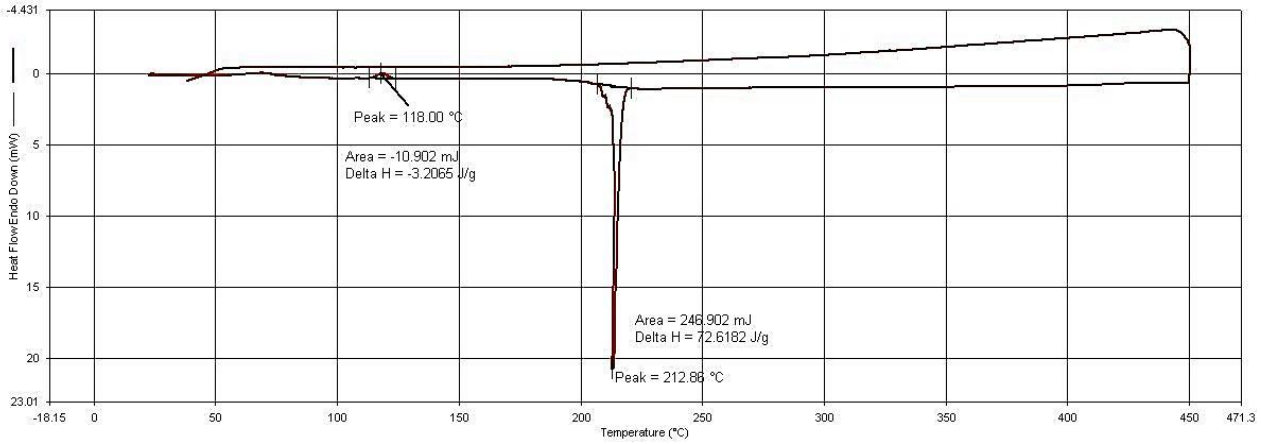


Figure 28 Thermal transition for Nickel (II) perchlorate complex obtained by DSC analysis

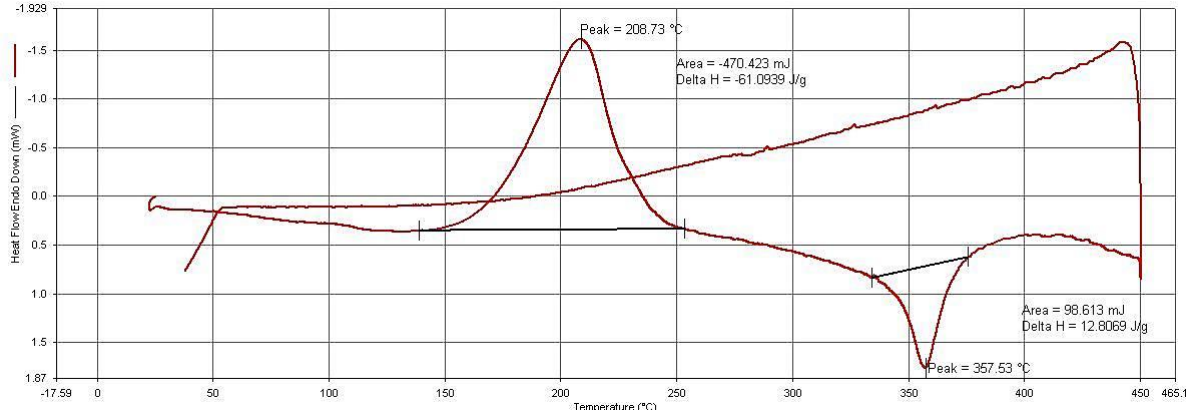


Figure 29 Thermal transition for Nickel complex obtained by DSC analysis

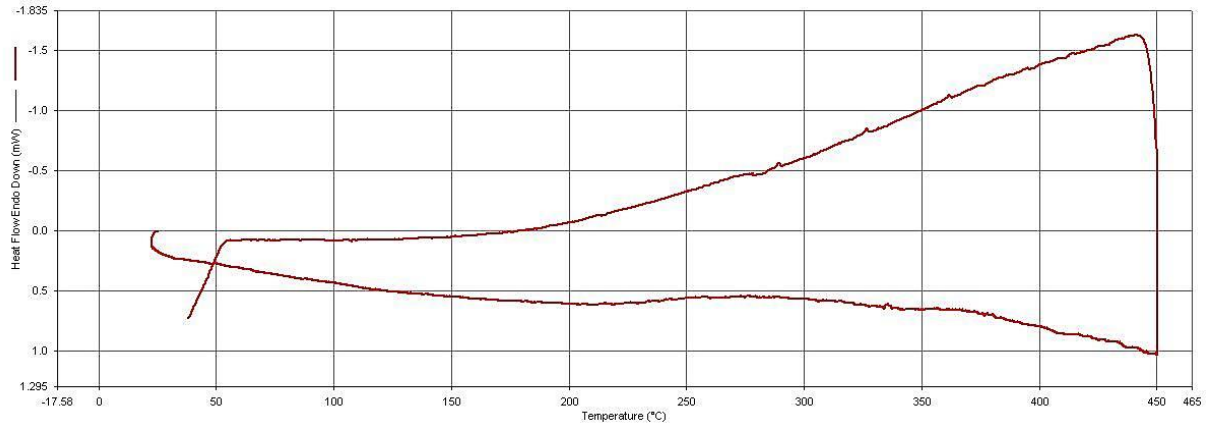


Figure 30 Thermal transition for Pd complex obtained by DSC analysis

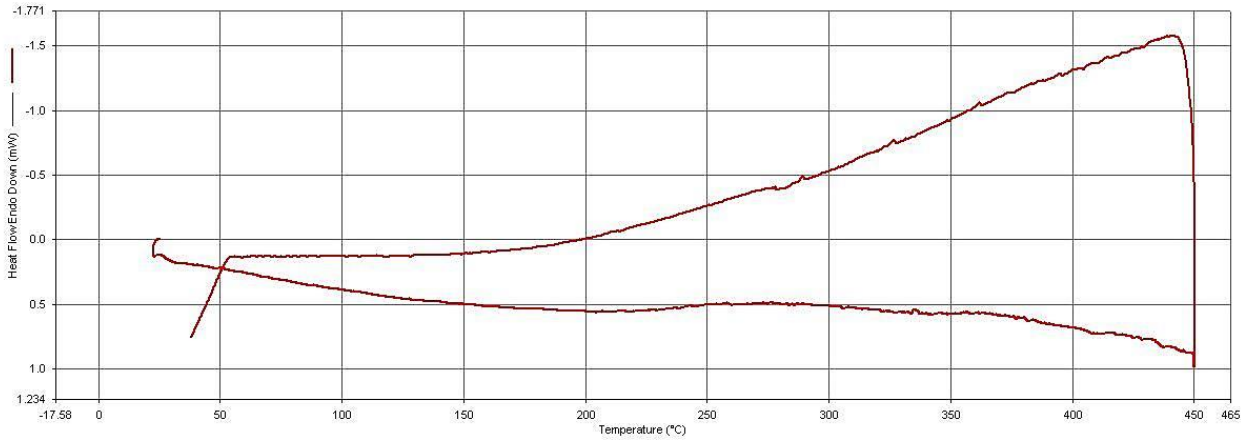


Figure 31 Thermal transition for Pt complex obtained by DSC analysis

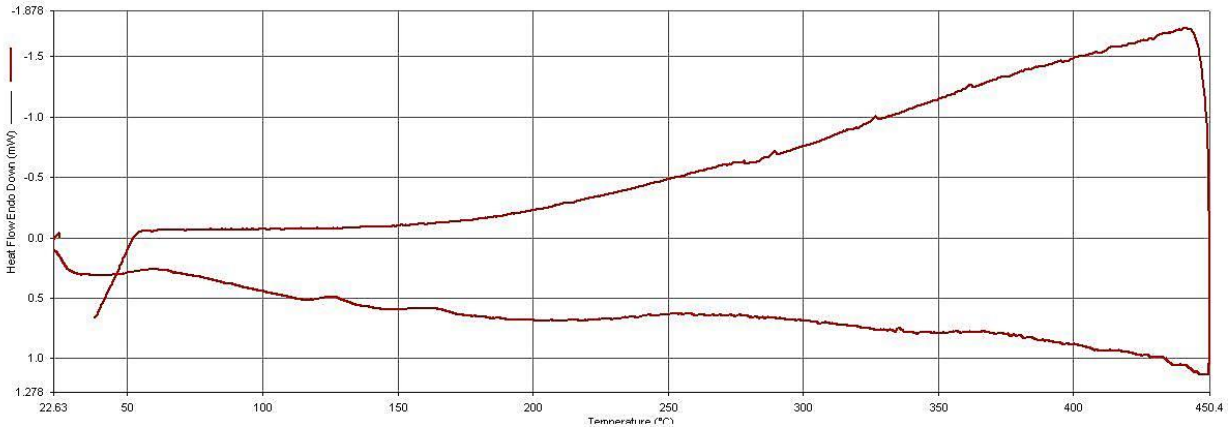


Figure 32 Thermal transition for Ru complex obtained by DSC analysis

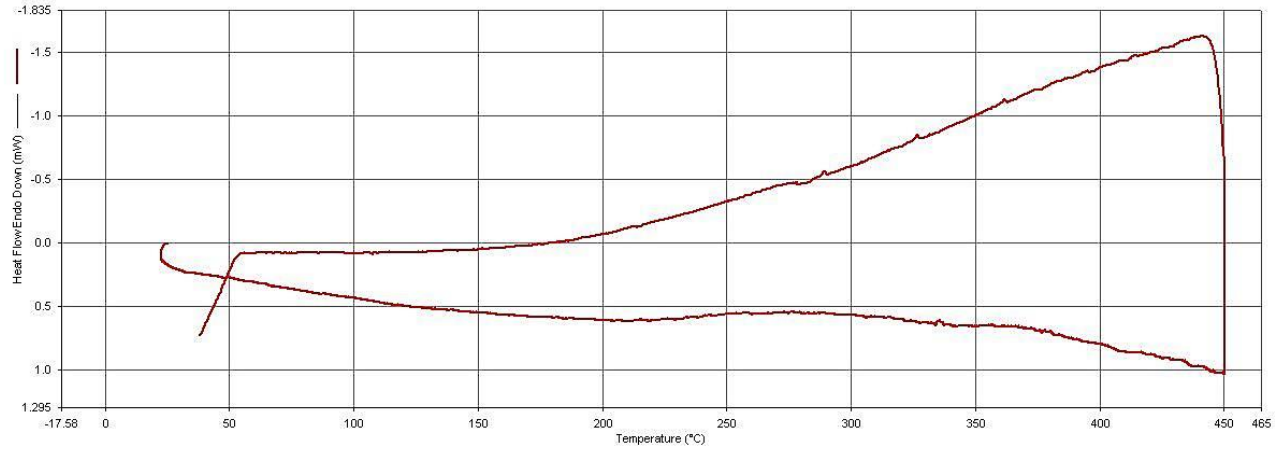


Figure 33 Thermal transition for Silver complex obtained by DSC analysis

4.3.2.2 FTIR

4.3.2.2.1 FTIR of Copper (II) complex

(**figure 34**) shows spectrum changes between the ligand and Cu, and shifts between them creating new peaks. The most pronounced change occurred in C=O region where peak turned from sharp-strong to broad-weak peak at 1304 cm^{-1}. C-H aromatic downfield shift from 3064-3154 to 3306-

3332cm^{-1}. C=N is less strong, and shifted from 1620-1660 to 1586-1619cm^{-1}. C-H plane and N-H disappeared from the complex at peak1120 cm^{-1} . The spectrum also showed peak at 1022 cm^{-1} indicating copper(II)- nitrogen interaction, and peak at 782 cm^{-1} indicates Cu-OH vibrations.

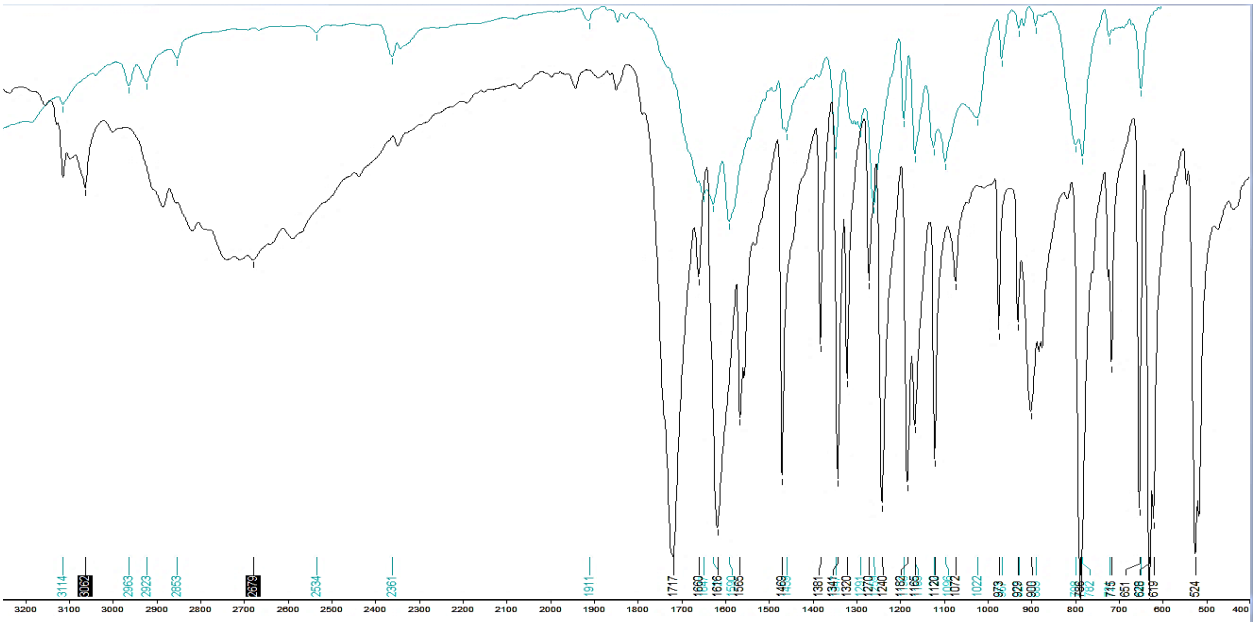


Figure 34 Upper FTIR spectrum for Cu complex, Lower spectrum for the ligand

4.3.2.2.2 FTIR of Nickel (II) perchlorate hexahydrate complex

IR in (**Figure 35**). Complex was formed because of some changes in FTIR; some of the peaks were shifted Due to bonding, the C-H aromatic peaks were displaced downfield from 3064-3154 to 2343-22360 cm^{-1}. Furthermore, C=N and C=C stretching became weaker and C=C shifted from 1566 to 1319 cm^{-1} which could be attributed to nitrogen binding Ni(II). In addition, the N-H peak has become very strong-broad at 3318 cm^{-1}. New peaks appeared as well at 997 cm^{-1} for Cl-O stretching. asymmetric stretching was noted by a large-broad peak at 1010 cm^{-1} , and a new weak-sharp peak at 684 cm^{-1} . The unfiled was observed for the ClO_4- spectra, and it could be coordinated with the ligand (Cl-O—H-N).

As a result of this finding, the expected coordination environment for Ni(II)ion is 2-N donor ligand coordination and oxygen coordination with counter ion. As a result, [Ni(II)(ligand)ClO_4]ClO_4 is the predicted formula.

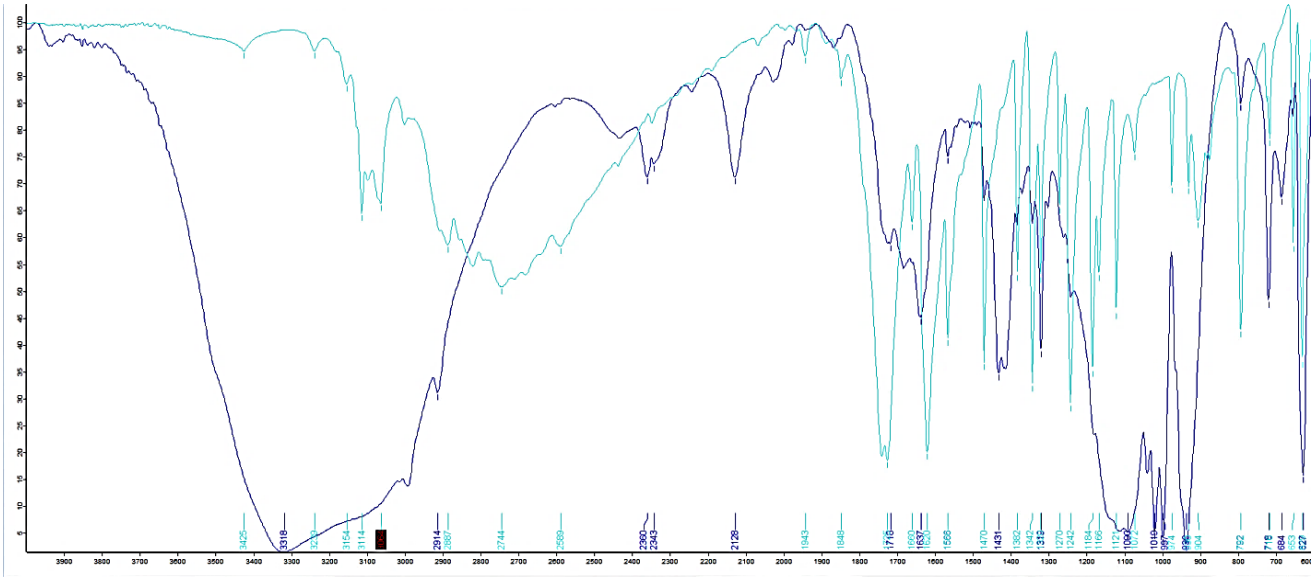


Figure 35 FTIR for Nickel(II) perchlorate hexahydrate complex (Lower).

4.3.2.2.3 FTIR of Nickel (II) complex

As the resulting from IR in **Figure 36**. Complex was formed because a change in FTIR occurs; some of the peaks were shifted. Due to bonding the C-H aromatic peaks were displaced downfield from 1166 to 1233 cm^{-1}. Furthermore, C=N shifted from 1660 to 1607 cm^{-1}, and stretching became weak to medium level. Also, C=O shifted from very strong peak 1725 cm^{-1} to 1644 cm^{-1} a medium level, which could be attributed to nitrogen binding with Ni (II). In addition, the N-H peak has become very strong - broad at 3331 cm-1.

In addition to the disappearance of the peak of the ligand at the following peaks: 1184, 1270 and 1660 cm-1. Even more, new peak was appeared at 1132 and 807 cm-1 referred to interaction Nickel (II) with Nitrogen.

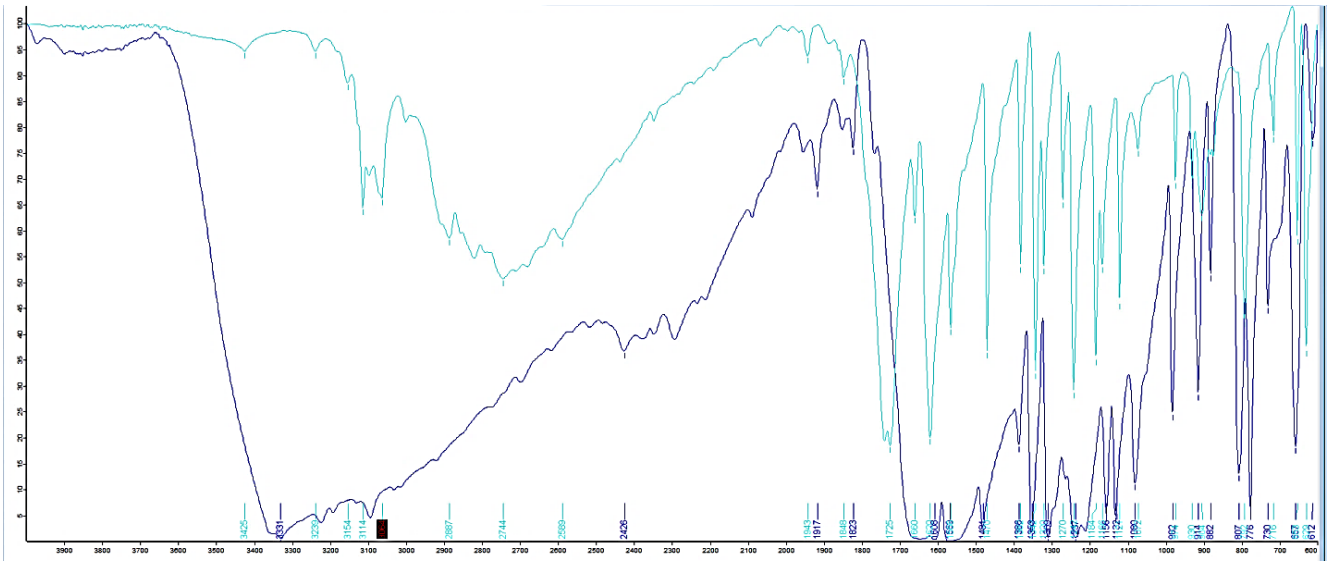


Figure 36 FTIR for Nickel (II) complex (Lower).

4.3.2.2.3 FTIR of Cobalt (II) complex

As the resulting from IR in the **Figure 37**, we see that there was no significant difference, as most of the differences were as follows: some of the peaks were shifted. Due to bonding, the C-N peaks were displaced downfield from 1342-1270 to 1380-1319 cm-1. Furthermore, C=N shifted from 1620 to 1614 cm-1, and stretching became v. strong to medium. Also, C=O shifted from 1725 to 1722 cm-1, and stretching became v. strong to medium, which could be attributed to nitrogen binding with Cobalt (II). Even more, new peak was appeared at 514 and 618 cm-1 referred to interaction Cobalt (II) with Nitrogen.

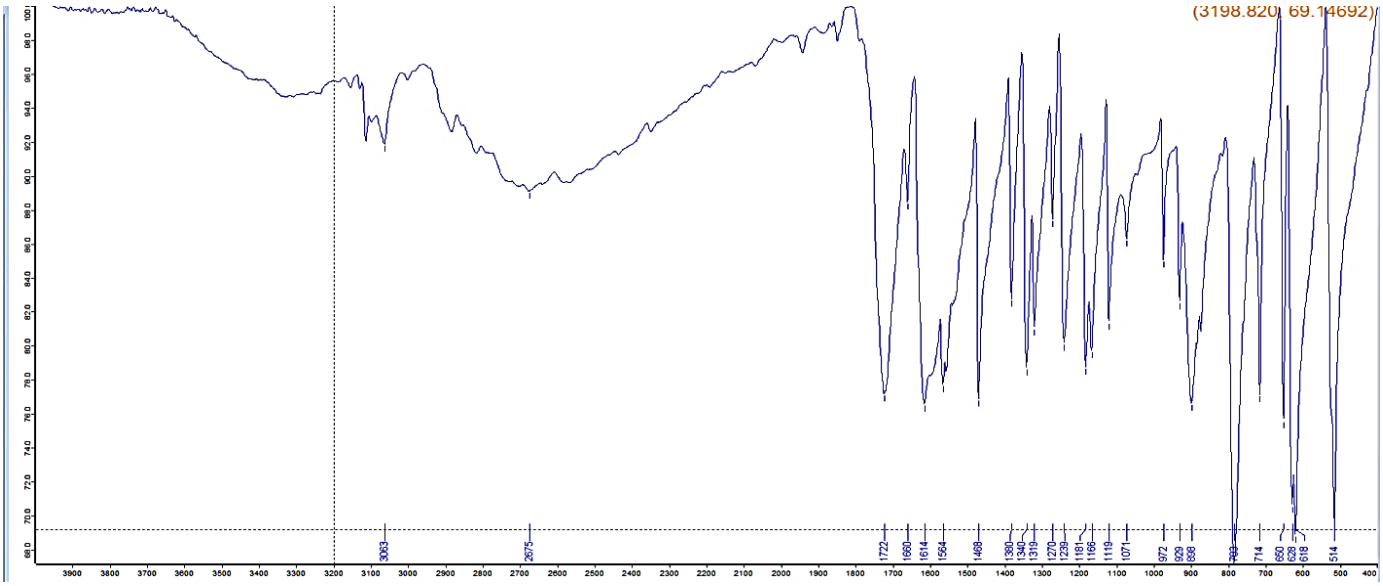


Figure 37 FTIR for Cobalt (II) complex.

4.3.2.2.4 FTIR of Platinum(II) and Palladium(II)

Chemical shifts in IR were found in the FTIR for Pt(II) and Pd(II) complexes. The absorption peaks for C-H aromatic were shifted from 3064-3154 to 3090-3105 cm-1 in the FTIR for Pt(II) **(Figure 38)** complex, while the absorption peaks for C-N stretch were shifted from 1320 to 1328 cm-1. C=O moved the spectra from 1725 to 1731-1758 cm-1, while C-H in-plane and out-plane bending shifted the spectrum at 1121-1159 to 1066-1121 cm-1 and 792-785 cm-1, respectively. New peak appearance at 1132 cm-1.

In the same way as Pd(II) acts, the FTIR of the Pd(II) complex) **(Figuree 39)** was: C-H aromatic stretching showed sharp to broad at 3112 cm-1, C-N stretching appeared at 1344 cm-1 and faded at 1270 cm-1, C=C and C=N stretching appeared v. strong at (1557 and 1617) cm-1, and C=C and C=N stretching appeared v. strong at (1557 and 1617) cm-1, respectively. In addition, C-H in-plane bending went shifted from strong to weak at 1072 to 1074 & 974 to 994 cm-1, while C-H out-plane bending shifted from strong to weak at 653-629 to 649-628 cm-1, and disappeared at 716 cm-1. Furthermore, at 776 cm-1, a new peak has appeared.

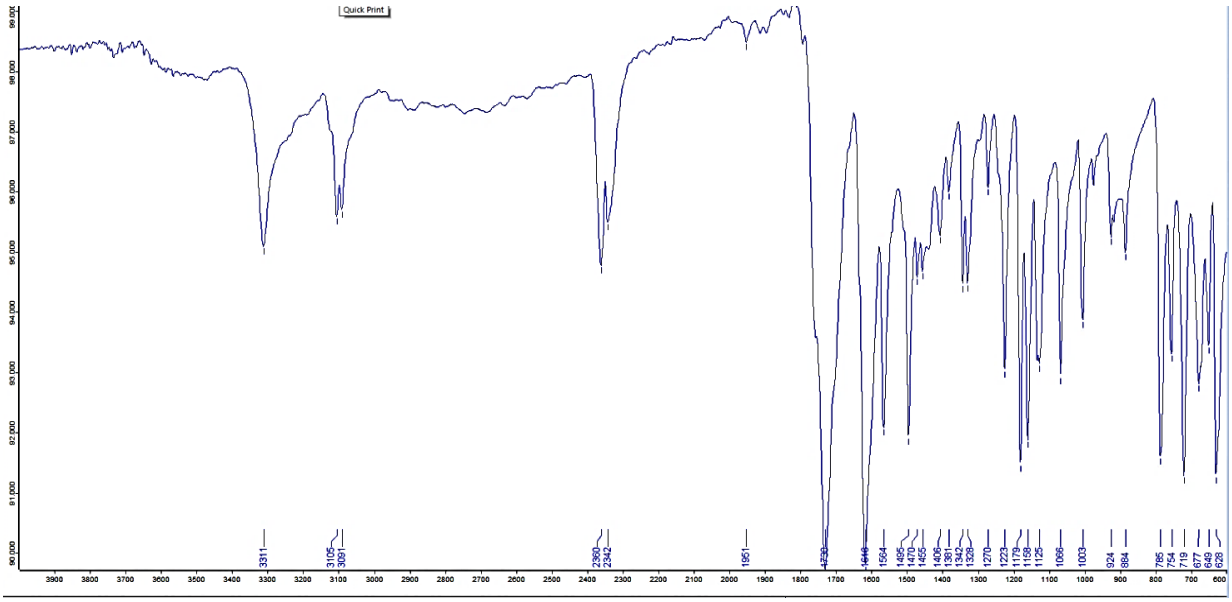


Figure 38 FTIR for Pt (II) complex.

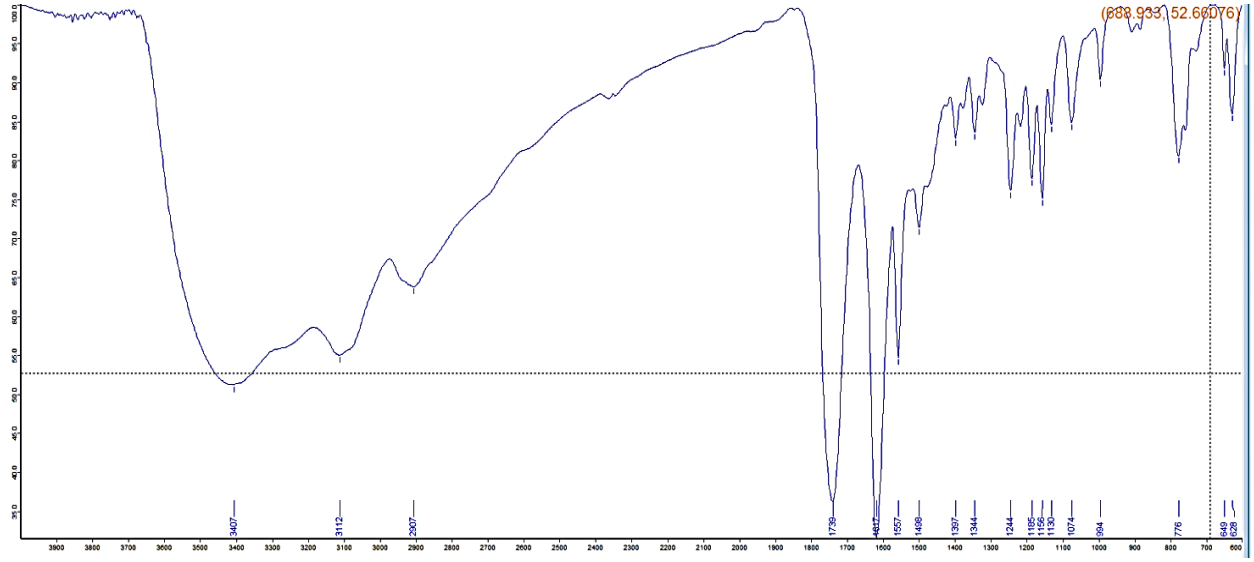


Figure 39 FTIR for Pd (II) complex.

4.3.2.2.5 FTIR of Ruthenium (III) chloride complex

In the same manner, FTIR of Ru(III) complex in (fig**ure** 40) was : The C-H aromatic stretch was appeared at 3112 cm-1 and it was shifted from 2887 to 2907 cm-1, N-H was shifted from 3425 to 3407 cm-1 from sharp to v. broad. C-N stretching was shifted from 1342-1320 to 1344-1244 cm-1, C=C and C=N stretch were appeared at (1557 and 1617) cm-1 respectively, and disappeared C=N at 1660 cm-1 from complex. Even more, C-H in-plane bending was shifted from 1166-974 to 1156-994 & 974-930 to 900 cm-1 from strong to weak, while, C-H out-plane shifted from strong to weak at 792 to 776 & from 716 to 649-628 cm-1.

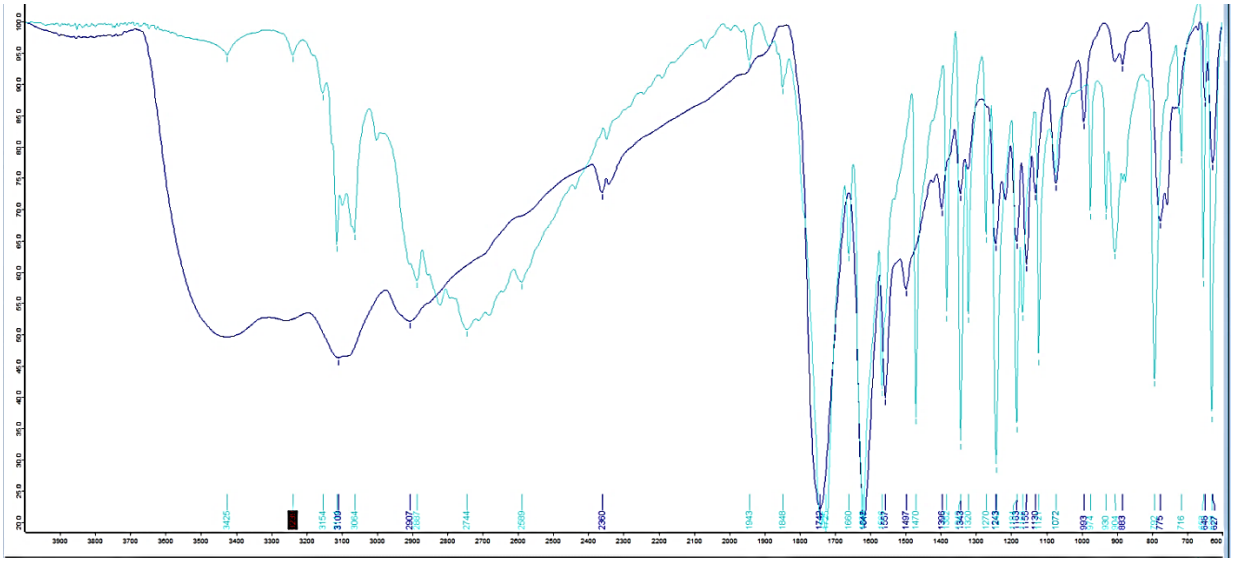


Figure 40 FTIR for Ru (III) complex (Lower).

4.3.2.3 X-Ray

4.3.2.3.1 X-Ray of Copper coordination compound

The copper complex displays a mononuclear coordination compound, this compound is composed of two ligands, and three water molecules, one of them is in axial position, forming a distorted square pyramid geometry, the distortion is usually due to two factors, the first is steric factor and the second is energy requirement, can be seen in the **figure 41.a.** The hydrogen bonding affects

the arrangement in a way it orders the array. The molecules arrangements can be seen in the **figure 41.b**. Also the unit cell is verified in the **figure 41.c**.

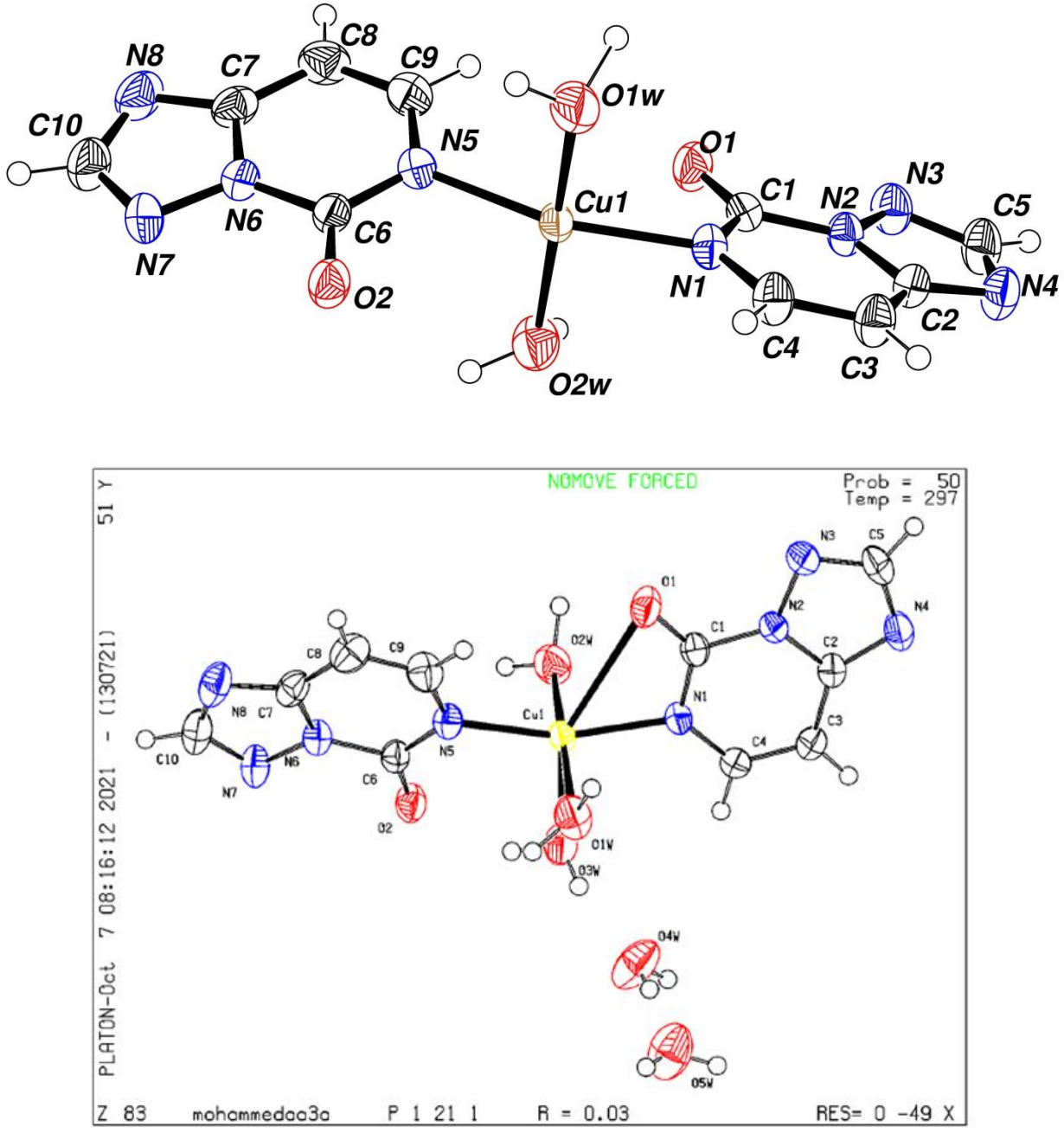


Figure 41.a X-Ray of Copper coordination compound

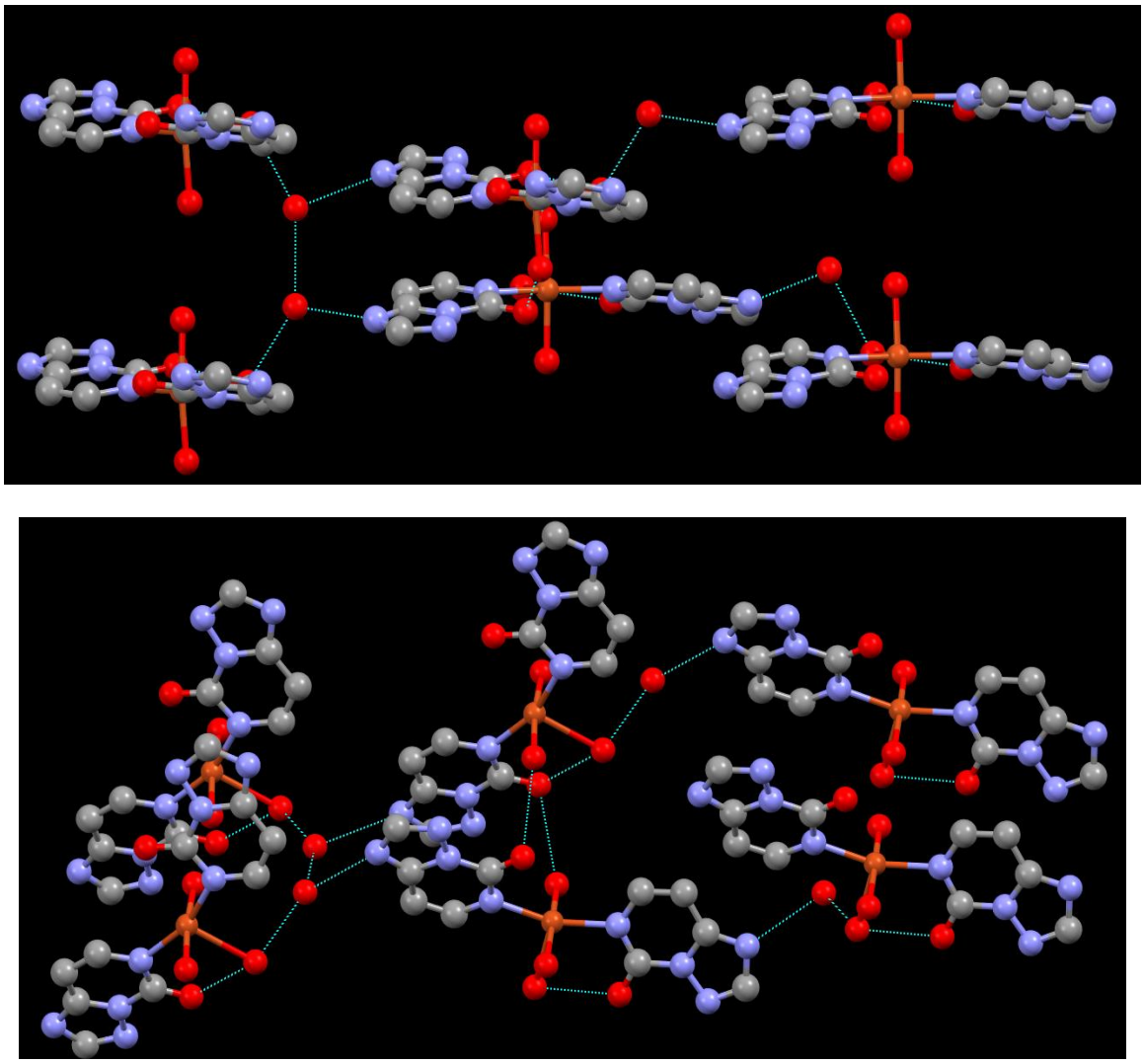


Figure 42.b X-Ray of Copper coordination compound

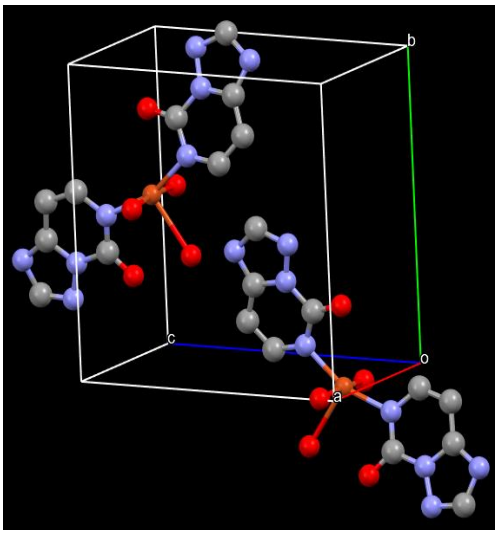


Figure 41.c unit cell of Copper coordination compound

Table 1 Crystal data and structure of Copper (II) complex

Empirical formula	$C_{10}H_{16}CuN_8O_7$
Formula weight	423.85
Temperature/K	296.7(8)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	7.2526(2)
b/Å	10.7188(3)
c/Å	11.1036(3)
α/°	90
β/°	97.539(2)
γ/°	90
Volume/Å^3	855.72(4)
Z	2
ρ_{calc}g/cm^3	1.645
μ/mm^{-1}	1.33
F(000)	434
Crystal size/mm^3	0.234 × 0.205 × 0.068
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.304 to 64.62
Index ranges	$-8 \leq h \leq 10$, $-15 \leq k \leq 15$, $-16 \leq l \leq 16$
Reflections collected	14478
Independent reflections	5038 [R_{int} = 0.0233, R_{sigma} = 0.0282]
Data/restraints/parameters	5038/1/248
Goodness-of-fit on F^2	1.05
Final R indexes [I>=2σ (I)]	R_1 = 0.0349, wR_2 = 0.0903
Final R indexes [all data]	R_1 = 0.0383, wR_2 = 0.0923
Largest diff. peak/hole / e Å^{-3}	0.61/-0.55
Flack parameter	-0.001(9)

Table 2 Bond Lengths of Copper (II) complex:

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Cu1	O1W	1.980(3)	N4	C5	1.346(5)
Cu1	O2W	1.995(2)	N5	C6	1.339(4)
Cu1	N1	2.012(3)	N5	C9	1.367(5)
Cu1	N5	2.025(3)	N6	N7	1.368(4)
O1	C1	1.238(4)	N6	C6	1.400(4)
O2	C6	1.243(4)	N6	C7	1.363(4)
N1	C1	1.346(4)	N7	C10	1.309(5)
N1	C4	1.365(4)	N8	C7	1.333(5)
N2	N3	1.374(4)	N8	C10	1.357(6)
N2	C1	1.402(4)	C2	C3	1.413(5)
N2	C2	1.372(4)	C3	C4	1.344(5)
N3	C5	1.327(4)	C7	C8	1.410(5)
N4	C2	1.335(4)	C8	C9	1.348(5)

Table 3 Bond Angles of Copper (II) complex:

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1W	Cu1	O2W	173.5(2)	C10	N7	N6	101.0(3)
O1W	Cu1	N1	90.70(12)	C7	N8	C10	102.9(3)
O1W	Cu1	N5	91.41(12)	O1	C1	N1	124.0(3)
O2W	Cu1	N1	89.74(13)	O1	C1	N2	121.0(3)
O2W	Cu1	N5	90.45(11)	N1	C1	N2	114.9(3)
N1	Cu1	N5	159.42(12)	N2	C2	C3	117.7(3)
C1	N1	Cu1	110.1(2)	N4	C2	N2	108.4(3)
C1	N1	C4	121.4(3)	N4	C2	C3	133.8(3)
C4	N1	Cu1	128.3(2)	C4	C3	C2	116.5(3)
N3	N2	C1	124.7(3)	C3	C4	N1	124.6(3)
C2	N2	N3	110.5(3)	N3	C5	N4	116.8(4)
C2	N2	C1	124.8(3)	O2	C6	N5	125.1(3)
C5	N3	N2	100.8(3)	O2	C6	N6	119.4(3)
C2	N4	C5	103.5(3)	N5	C6	N6	115.6(3)
C6	N5	Cu1	118.1(2)	N6	C7	C8	117.7(3)
C6	N5	C9	120.4(3)	N8	C7	N6	108.5(3)
C9	N5	Cu1	121.3(3)	N8	C7	C8	133.9(4)
N7	N6	C6	124.2(3)	C9	C8	C7	116.1(4)
C7	N6	N7	110.8(3)	C8	C9	N5	125.2(4)
C7	N6	C6	125.0(3)	N7	C10	N8	116.8(3)

4.3.2.3.2 X-Ray of silver coordination compound

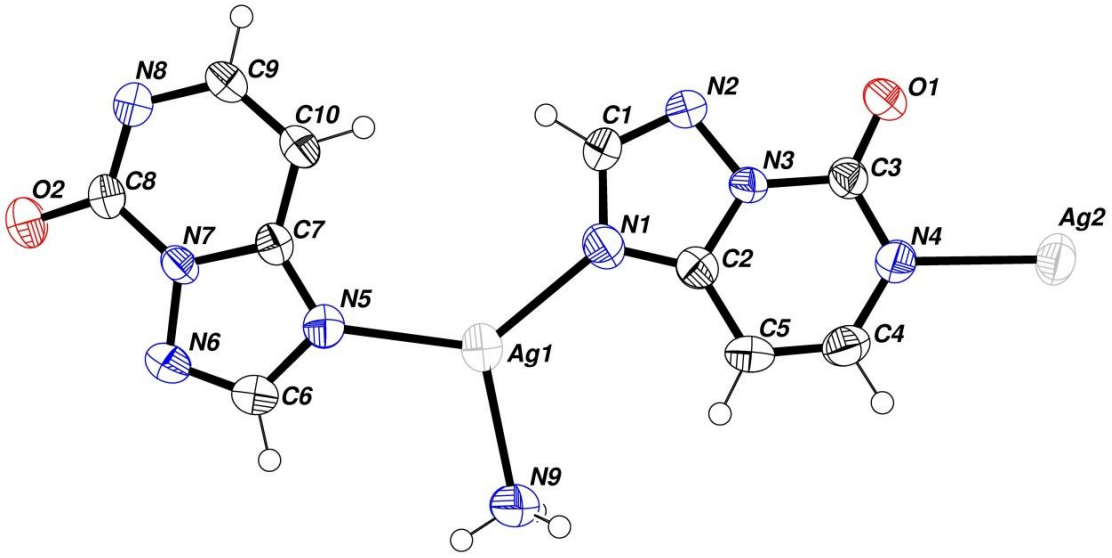
The single crystal of the silver coordination compound was solved by the heavy-atom method, the structure comprises a metal-organic framework (MOF), the structure composed of silver atom coordinated to the ligand through the nitrogen 4 of the triazole and nitrogen 8 of the pyrimidine, and another silver atom connected to nitrogen 1 and nitrogen 5 forming a linear polymer. These linear polymers are crosslinked through the silver atoms.

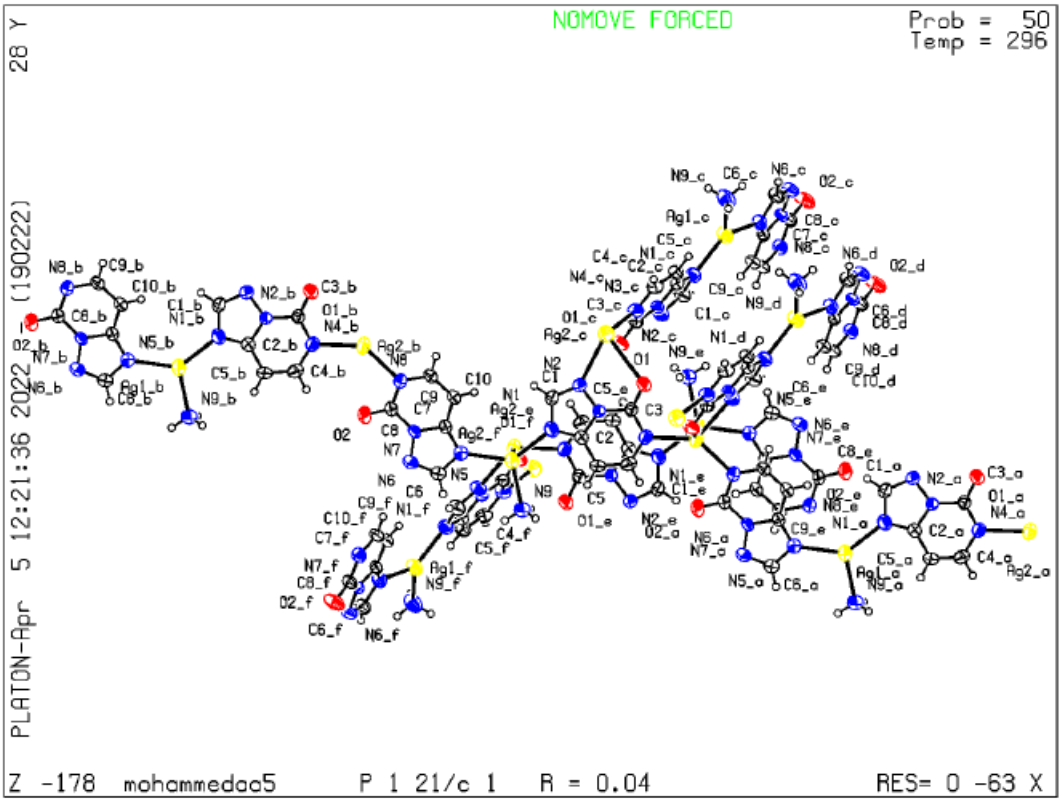
These silver atoms that connect these ligands have two alternating geometries, as shown in **Figure 42.a.**

- The first in distorted tetrahedral geometry connected to three nitrogen atoms N1 and N5 forming linear polymer and the third with N 9 from another crosslinked chain this silver atom is also connected with another silver atom from another chain in an antiparallel fashion. This kind of framework ends up with a three-dimensional network

- The other silver is in the center of a distorted triagonal bipyramid connected to two nitrogen atoms N4 and N8 connecting the linear polymer on the other hand the silver is also connected to N 2 from and crosslinked chain, the axial positions are connected first to silver ion from another chain in an antiparallel fashion the fifth position (axial) is occupied by nitrogen from ammonia.

The network has fixed and well-defined spaces at equal intervals and distances in the plane that upon looking at several layers these spaces are still available and in a fashion of molecular sieves, as shown in **figure 42.b**


N8
C9
C10
O2
C8
N7
C7
N6
N5
C6
Ag1
N9
C1
N2
O1
N3
C3
N1
C2
N4
Ag2
C5
C4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28 Y
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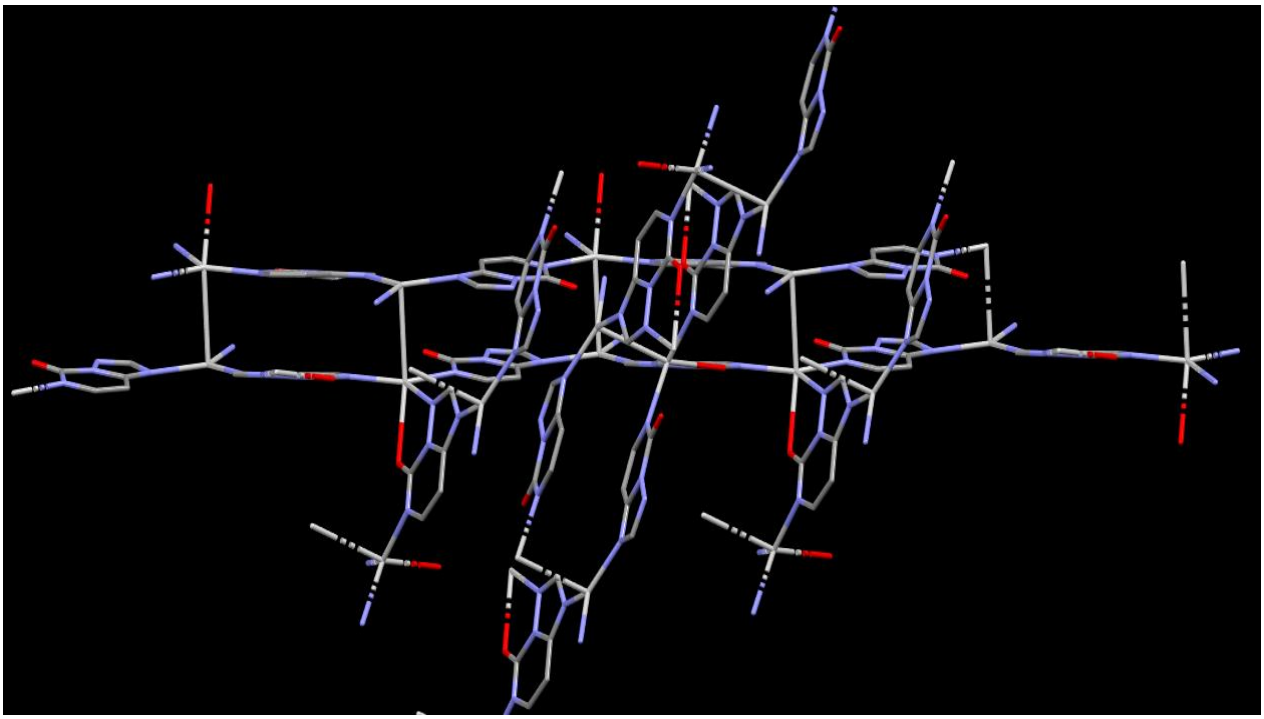
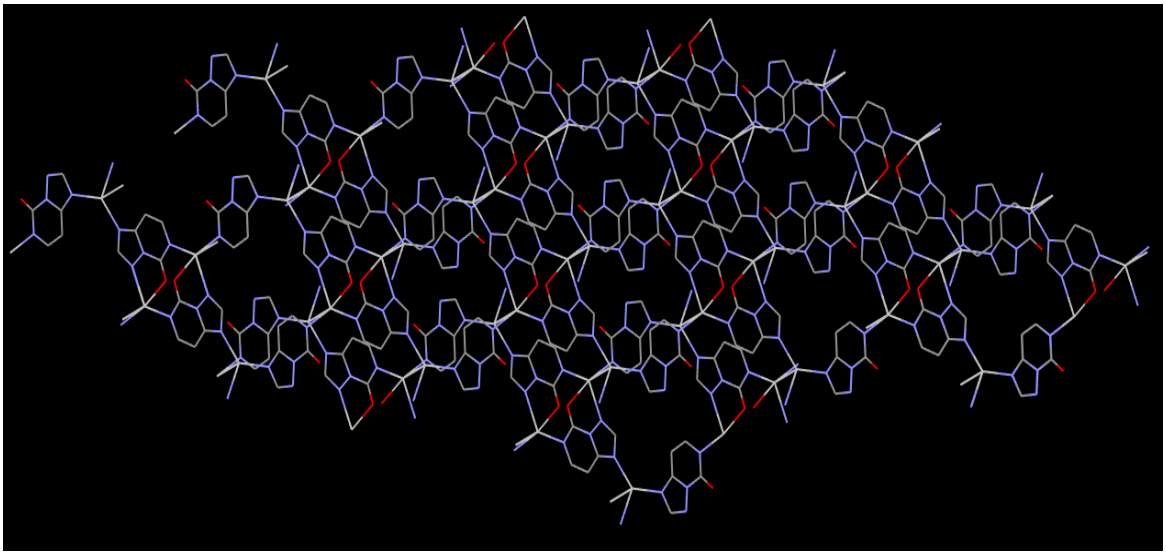
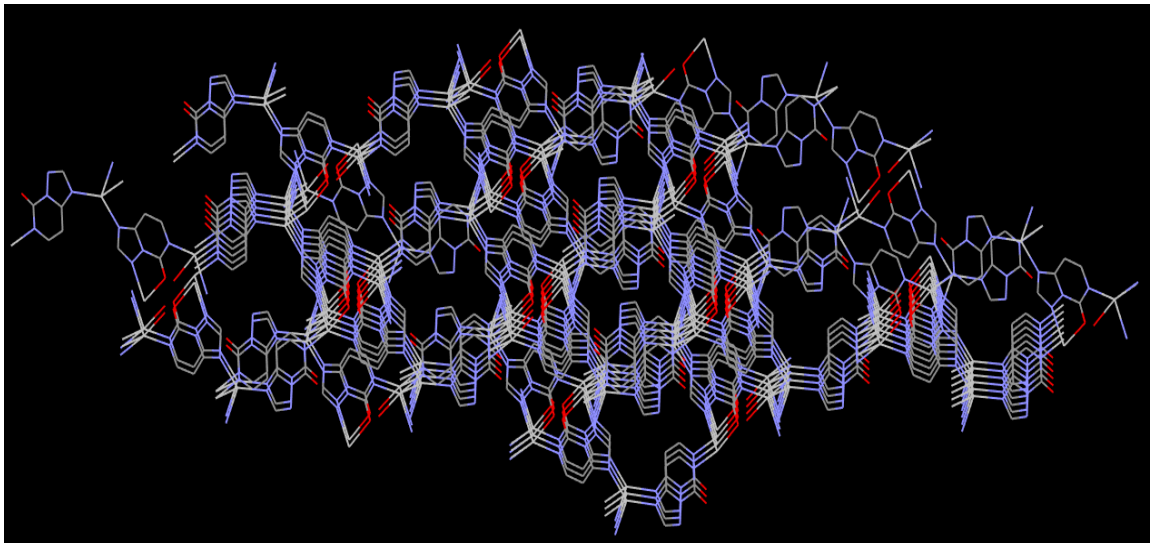


Figure 43.a Molecular structure of C10H9Ag2N9O2 according to X-ray analysis





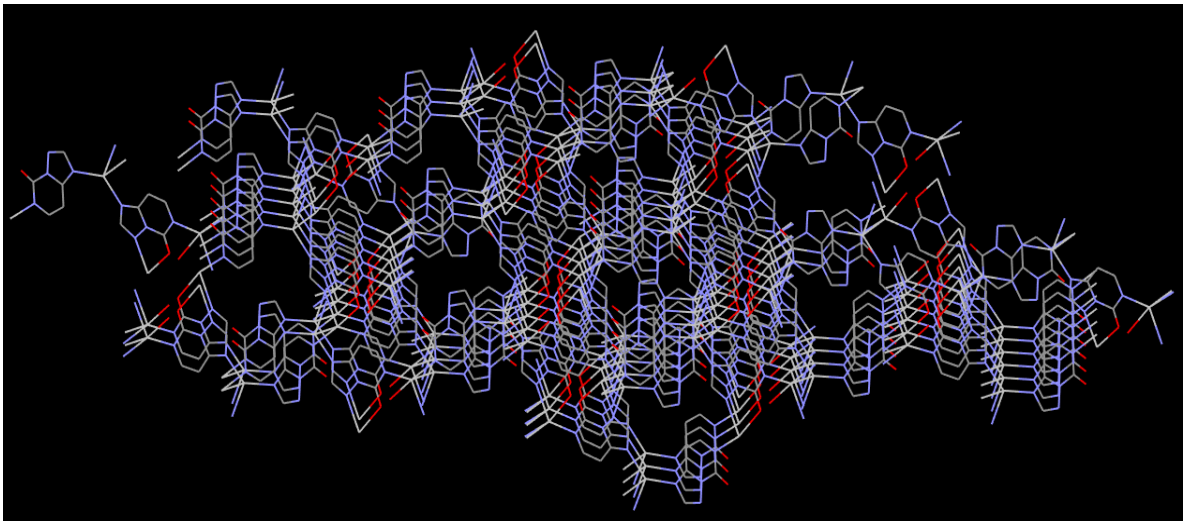


Figure 44.b Molecular structure of C10H9Ag2N9O2

Table 4 Crystal data and structure of Silver (I) complex:

Empirical formula	$C_{10}H_9Ag_2N_9O_2$
Formula weight	503.00
Temperature/K	296.1(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	12.7546(4)
b/Å	7.6651(2)
c/Å	14.0792(4)
α/°	90
β/°	102.536(3)
γ/°	90
Volume/Å^3	1343.64(7)
Z	4
ρ_{calc}g/cm^3	2.487
μ/mm^{-1}	2.942
F(000)	968.0
Crystal size/mm^3	0.21 × 0.14 × 0.09
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.928 to 64.914
Index ranges	$-18 \leq h \leq 16$, $-10 \leq k \leq 10$, $-19 \leq l \leq 18$
Reflections collected	25870
Independent reflections	4196 [R_{int} = 0.0349, R_{sigma} = 0.0237]
Data/restraints/parameters	4196/0/209
Goodness-of-fit on F^2	1.036
Final R indexes [I>=2σ (I)]	R_1 = 0.0401, wR_2 = 0.0976
Final R indexes [all data]	R_1 = 0.0535, wR_2 = 0.1041
Largest diff. peak/hole / e Å^{-3}	2.16/-1.18

Table 5 Bond Lengths of Silver (I) complex:

Atom-Atom	Length/Å	Atom-Atom	Length/Å
Ag1-Ag2[1]	3.1764 (5)	N4-C3	1.338 (5)
Ag1-N1	2.209 (3)	N4-C4	1.373 (5)
Ag1-N5	2.223 (3)	N5-C6	1.369 (5)
Ag1-N9	2.281 (4)	N5-C7	1.332 (5)
Ag2-N2[2]	2.481 (3)	N6-N7	1.381 (4)
Ag2-N4	2.201 (3)	N6-C6	1.301 (5)
Ag2-N8[3]	2.229 (3)	N7-C7	1.370 (4)
O1-C3	1.231 (4)	N7-C8	1.402 (5)
O2-C8	1.227 (4)	N8-C8	1.344 (5)
N1-C1	1.373 (5)	N8-C9	1.360 (5)
N1-C2	1.333 (5)	C2-C5	1.404 (5)
N2-N3	1.382 (4)	C4-C5	1.342 (6)
N2-C1	1.309 (5)	C7-C10	1.400 (5)
N3-C2	1.371 (5)	C9-C10	1.356 (5)
N3-C3	1.394 (4)		

Table 6 Bond Angles of Silver (I) complex:

Atom-Atom-Atom	**Angle/°**	**Atom-Atom-Atom**	**Angle/°**
N1-Ag1-Ag2[1]	95.65 (10)	C7-N5-C6	103.4 (3)
N1-Ag1-N5	131.76 (12)	C6-N6-N7	102.5 (3)
N1-Ag1-N9	118.15 (14)	N6-N7-C8	125.3 (3)
N5-Ag1-Ag2[1]	94.35 (9)	C7-N7-N6	109.5(3)
N5-Ag1-N9	110.00 (13)	C7-N7-C8	125.2 (3)
N9-Ag1-Ag2[1]	81.25 (13)	C8-N8-Ag2[5]	116.5 (2)
N2[2]-Ag2-Ag1[1]	102.84 (8)	C8-N8-C9	120.6 (3)
N4-Ag2-Ag1[1]	83.57 (9)	C9-N8-Ag2[5]	122.7 (3)
N4-Ag2-N2[2]	129.45 (12)	N2-C1-N1	115.3 (3)
N4-Ag2-N8[3]	135.26 (12)	N1-C2-N3	108.9 (3)
N8[3]-Ag2-Ag1[1]	86.84 (9)	N1-C2-C5	134.0 (4)
N8[3]-Ag2-N2[2]	95.29 (12)	N3-C2-C5	117.1 (3)
C1-N1-Ag1	128.3 (3)	O1-C3-N3	119.5 (3)
C2-N1-Ag1	127.4 (3)	O1-C3-N4	125.4 (3)
C2-N1-C1	103.6 (3)	N4-C3-N3	115.1 (3)
N3-N2-Ag2[4]	116.0 (2)	C5-C4-N4	126.1 (4)
C1-N2-Ag2[4]	141.4 (3)	C4-C5-C2	115.8 (3)
C1-N2-N3	102.6 (3)	N6-C6-N5	115.8 (3)
N2-N3-C3	124.4 (3)	N5-C7-N7	108.9 (3)
C2-N3-N2	109.6 (3)	N5-C7-C10	133.3 (3)
C2-N3-C3	126.0 (3)	N7-C7-C10	117.7 (3)
C3-N4-Ag2	118.6 (2)	O2-C8-N7	119.9 (4)
C3-N4-C4	119.9 (3)	O2-C8-N8	125.2 (4)
C4-N4-Ag2	121.4 (2)	N8-C8-N7	114.9 (3)
C6-N5-Ag1	126.1 (3)	C10-C9-N8	125.5 (3)
C7-N5-Ag1	128.7 (2)	C9-C10-C7	115.9 (3)

Chapter five

Computational Calculations

5.1 Introduction

Computational chemistry is a relatively recent field. Its introduction and popularity have coincided with advances in computing power over the last several decades. Computational chemistry, like other branches of chemistry, use techniques to better understand chemical reactions and processes. Computational theoretical chemistry is one of the most advanced and modern disciplines of chemistry today and scientific research in this field are diverse and comprehensive. It is used to estimate some important variables whose calculation necessitates extensive laboratory work, as well as to provide scientific support for practical calculations and to explain some phenomena that are difficult or impossible to demonstrate through laboratory work, all of which necessitates the use of precise and sophisticated devices. Although computational chemists build and update software tools on a regular basis, their main focus is on using software to improve chemical knowledge.

In general, software programs calculate using two methods: molecular mechanics and quantum mechanics. Semiempirical and ab initio quantum mechanics approaches are available. In comparison to ab initio approaches, molecular mechanics and semi-empirical quantum mechanics have significant advantages. Above all, these procedures are quick. While this may not be critical for tiny molecules, it is crucial for biomolecules. Another advantage is that these approaches can calculate values that are closer to experiment than lower level ab initio techniques for specialized and well-parameterized molecular systems. The database used to parameterize a molecular mechanics or semi-empirical quantum mechanics approach determines its accuracy. This is true for the types of molecules in the database, as well as the physical and chemical data. These strategies frequently produce the best results for a specific class of chemicals or events. The fact that you must have parameters accessible before executing a calculation is a disadvantage of these approaches. It takes time to develop parameters. The ab initio approach may be able to solve this issue.

Ab initio refers to the first principle, and it is one of the most accurate methods for finding an exact solution to a Schrödinger equation. However, they are only useful for tiny molecules. It takes a long time to calculate, sometimes up to three days; this long period is one of the reasons why people prefer to use other procedures that take less time. Methods for ab initio quantum mechanics have been evolving for decades. The development of new algorithms and the introduction of better basis functions have substantially improved the speed and accuracy of ab initio computations.

Quantum mechanics is a basic technique for describing the characteristics of molecules. Many different quantum mechanics-based computation methods are utilized, including spectrum (UV-visible, infrared and NMR) and molecular structures. Ab initio, Hartree-Fock (HF), semi-empirical technique (116) and Density functional theory (DFT) are only a few examples (117)

The Schrödinger **eq. (1)** describes the wave functions and energy of a molecule in quantum mechanics.

$$\mathbf{H\Psi = E\Psi} \qquad \mathbf{(1)}$$

The molecular Hamiltonian is H, the wave function is Ψ, and the energy is E. The kinetic energy of nuclei (N) and electrons (E), nuclear-nuclear (NN) and electron-electron repulsions (EE), and the attraction between nuclei and electrons (NE) make up the molecular Hamiltonian **(eq. 2)**.

The kinetic energy of the particles that make up the molecule (nuclei and electrons) as well as the columbic interaction between individual particles are described by the Hamiltonian operator (118)

H = (Kinetic energy)N + (Kinetic energy)E + (repulsion)NN + (repulsion)EE + (attraction)NE (2)

The mass of nuclei is several times that of electrons. Electrons move so fast that their distribution is smooth within a relatively short period of time when heavy nuclei mobility is negligible. As a result, the electron distribution is approximated to be dependent solely on the fixed positions of

nuclei and not on their velocities. The molecular Hamiltonian can be simplified in two ways using this approximation. The term "nuclear kinetic energy" is no longer used **(eq. 3)**.

H = (Kinetic energy)E + (repulsion)NN + (repulsion)EE + (attraction)NE (3)

This phrase is also dropped since the nuclear-nuclear repulsion is constant for a specific configuration of atoms. The Hamiltonian has now been reduced to a completely electronic state. To calculate a potential energy surface after solving the electronic Schrödinger equation **(eq. 4)**, you must subtract nuclear nuclear repulsions **(eq. 5)**.

H = (Kinetic energy)E + (repulsion)EE + (attraction)NE (4)

Helectronic Ψ electroni = E electronic Ψ electroni

VPES = E electronic + (repulsion)NN (5)

This equation necessitates solutions for a large number of nucleus configurations in order to generate the potential energy surface (PES). The electronic energy is not explicitly evaluated in molecular mechanics.

Instead, these methods use a force field equation to solve the potential energy surface. Electronic energy is represented by the force field equation.

Molecular mechanics doesn't begin with the Schrödinger equation; it is also known as force-field since it is used to define the geometry and conformation of molecules in a chemically plausible manner. The nature of molecules determines the type of force Van der Wall force between both crowded molecules, bonded force between connected molecules Opposed molecule (nuclei and electrons), which are formed up of molecules, and bond length and bond angle (atom position was utilized to obtain structural data). (119)

The semi-empirical technique is the most straightforward; it is less precise than Hartree-Fock, but it is particularly effective for large molecules. Because more approximations were utilized, it takes

less time to calculate: Introduce a value based on experimental data (135), ignore the Differential Diatomic Overlap (NDDO) approximation, and eliminate overlap between functions on distinct atoms (120)

5.2 Heat of Formation

The following is the basic strategy for theoretical research: first, we build the molecule using Spartan, an interactive molecular graphics application for generating and editing Molecular mechanical equations. These are used to improve molecular geometry (optimization) and to provide information about isolated molecules' structures, relative stabilities, and other features. Molecular mechanics calculations including molecular orbital computations using the Hartree–Fock method.

There are 4 different tautomers for 1,2,4-Triazolo[1,5-c]pyrimidine-5(6H)-ones. The heat of formation was calculated by using the Spartan program. the formation energy was calculated and the most stable compound among the compounds was determined. According to these results, **figure 43.b** was the most stable tautomeric form which has a heat of formation of 318.62 KJ/mol. While **Figure 43.a and Figure 43.d** compounds showed the same heat of formation (350 KJ/mol). **Figure 43.c** had the highest value of heat of formation (398.146 KJ/mol) in addition to being the least stable among the tautomers.

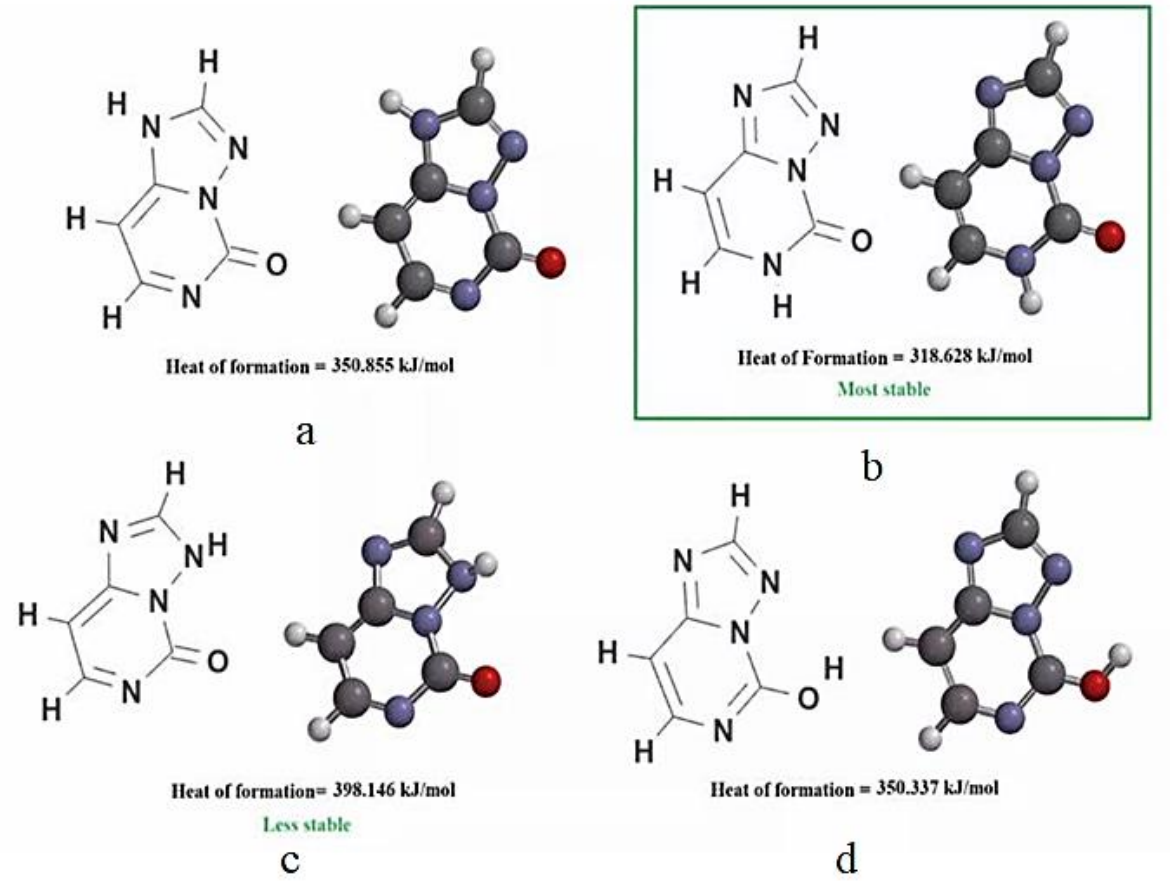


Figure 45 Theoretical Tautomers & heat of formation of 1,2,4-triazolo[1,5-c]pyrimidine-5(6H)-ones

5.3 Molecular orbital Calculation

Probability of finding an electron (Ψ2) in a Molecular orbital for 1,2,4-Triazolo[1,5-c]Pyrimidine-5(6H)-ones –the most stable tautomer, was computed using two methods: semi-empirical and Hartree-Fock which were utilized to determine the ligand-metal bonding area. Spartan program is used to construct the Molecular orbital Calculation.

Theoretically, 1,2,4-Triazolo[1,5-c]Pyrimidine-5(6H)-one is a ligand that has different possible binding sites. **Table 7** shows the highest values of metal-ligand binding sites that were detected: 0.40215(N3), 0.25852(N4), and 0.2301(O1). **Figure 44** shows the locations of nitrogen 3,4 and

oxygen 1. N3 is the nitrogen atom at position 3 of the pyrimidine ring and N4 is the nitrogen atom at position 4 of the triazole ring.

The nitrogen atom (N3) in the pyridine ring is the most favorable location for Metal coordination binding followed by (N4). semi-empirical method is consistent with Hartree-Fock, because nitrogen in pyridine acts as a sigma-donor.

Hartree-Fock showed that 1,2,4-Triazolo[1,5-c]Pyrimidine-5(6H)-ones can be bonded with metal with σ bond at O1 which exist in pyridine ring. In addition, there is a possibility of the compound linking to a σ bond at N2. The sigma bond will be significantly stronger if the kind of interaction is σ donor- π donor, while the total bond will be weak if the type of interaction is σ donor- π acceptor.

Despite the multiple metal coordination binding sites shown in **table 7.** Yet, the most prominent atoms are: N3 > N4> O1.

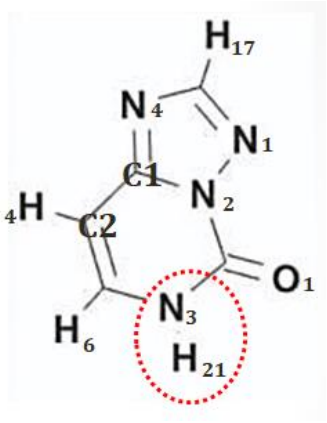


Figure 46 The favored region in 1,2,4-Triazolo[1,5-c]Pyrimidine-5(6H)-ones to binding with Metals

Table 7 Calculated Ψ2 for most stable Tautomer of 1,2,4-Triazolo[1,5-c]Pyrimidine-5(6H)-ones using Semi-empirical/AM1 & Hartree-Fock.

Ψ2 energy	Ψ221	Ψ222	Ψ223
	-0.453	-0.43049	-0.42952
Type of symmetry	σ	π	π
Ψ2	Ψ221	Ψ222	Ψ223
C1	0.04156	0.14654	0.05902
C3	0.00684	0.000016	0.00483
C5	0.00305	0.00193	0
N2	0.02531	0.10713	0.10254
N1	0.06154	0.12889	0.25211
C2	0.0027	0.05387	0.08863
H6	0.00589	0	0
H4	0.00043	0	0
N3	**0.40215**	0.23783	0.10298
N4	**0.25852**	0.15666	0.07774
C9	0.05822	0.000035	0.30394
H17	0.000014	0	0
H21	0.00362	0	0
O1	**0.2301**	0.16706	0.00816

Ψ2 energy	Ψ224	Ψ225	Ψ226
	-0.453	-0.43049	-0.42952
Type of symmetry	π	π	π
Ψ2	Ψ224	Ψ225	Ψ226
C1	0.05902	0.06635	0.18309
C3	0.00483	0.1508	0.32743
C5	0	0.00802	0.00356
N4	0.10254	0.14421	0.06839
N1	0.25211	0.0293	0.09129
C2	0.08863	0.23812	0.10966
H6	0	0	0
H4	0	0	0
N3	0.10298	0.09904	0.10656
N2	0.07774	0.14864	0.09634
C9	0.30394	0.04316	0.01136
H17	0	0	0
H21	0	0	0
O1	0.00816	0.07232	0.00227

Ψ2 energy	Ψ227	Ψ228
	-0.453	-0.43049
Type of symmetry	π	σ
Ψ2	Ψ227	Ψ228
C1	0.06797	0.07527
C3	0.09105	0.04641
C5	0.30411	0.27235
N4	0.00827	0.13673
N1	0.000037	0.16907
C2	0.17142	0.00538
H6	0	0.01078
H4	0	0.01298
N3	0.00044	0.01504
N2	0.08545	0.11415
C9	0.12392	0.00888
H17	0	0.0097
H21	0	0.08676
O1	0.14727	0.03642

5.4 Electrostatic atomic charge

The computed net charges on the atoms of the 1,2,4-Triazolo[1,5-c]Pyrimidine-5(6H)-ones as ligand using semi-empirical/AM1 & Hartree-Fock method which are theoretically the most stable tautomers of the isomer in neutral and anion forms, are shown in **Figure 45**.

The negative charge density for neutral forms follows the pattern N4>N3>O1>N1 (-0.619, -0.477, -0.464 and -0.458, Respectively), but for anionic forms follows the sequence N3>>N4>O1 (-0.825, -0.734, and -0.595, Respectively). The metal binding would be expected to follow a similar pattern based on this result.

Metal-binding to oxygen (O1), on the other hand, is less prevalent –soft and intermediate metals prefer nitrogen as a coordination site.

Because of the use of ammonia (that is when a hydrogen atom has been removed), theoretical results will be considered for the anionic forms, the possibility of binding the ligand with metal for anionic forms will be as follows: N3>>N4>O1.

The results of the Molecular Orbital Calculation are in agreement with the results of the Electrostatic atomic charge. In addition, the theoretical study (Molecular orbital Calculation and Electrostatic Atomic Charge) was corroborated by an X-ray analysis of the complex and showed that bonding occurred through the nitrogen atom in position 3 of the pyrimidine ring and the nitrogen atom in position 4 of the triazole ring as well.

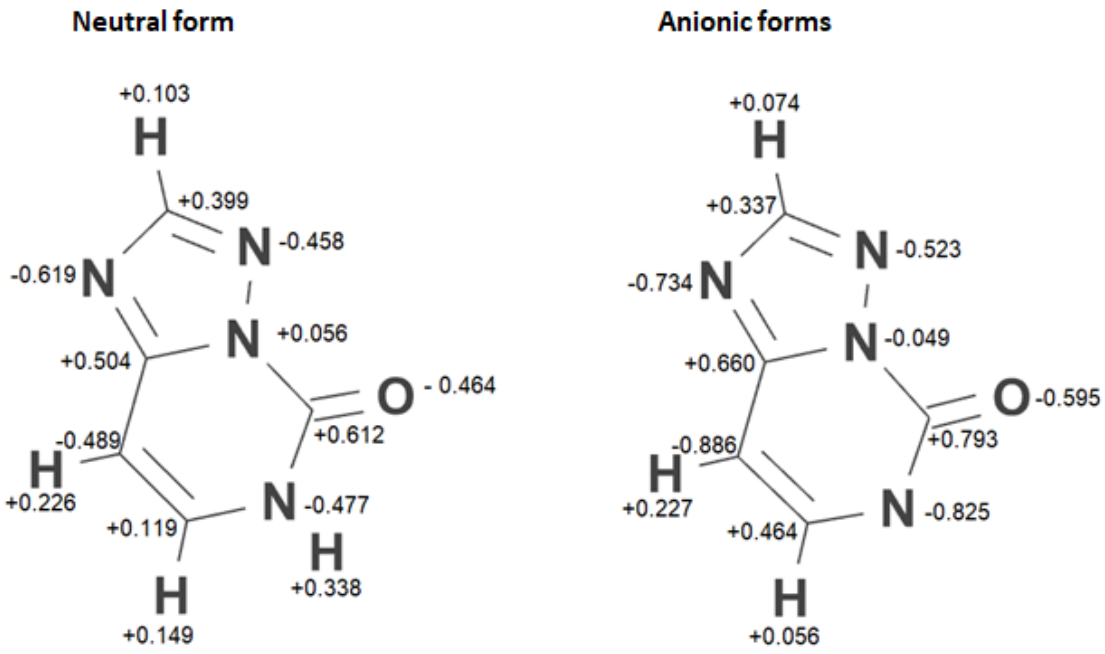


Figure 47 Electrostatic atomic charge using Hartree-Fock method

Chapter six

Biological Testing

6.1 Anti-bacterial Testing

6.1.1 Experimental

6.1.1.1 Material

Muller-Hinton Agar, distilled water, saline solution, Sterile discs of 6 mm filter paper (Whatman, UK), bacteria, Antibiotics, sterile cotton swap, Petri Dishes (10 cm diameter), 1,2,4 Triazolo[1,5-c]pyrimidine-5(6H)-ones as ligand, (Copper(Cu), Iron(Fe), Palladium(Pd), Platinum(Pt), and Nickel(Ni) coordination compounds).

6.1.1.2 Preparation of Agar media

Muller-Hinton Agar (37g) was dissolved in 1L distilled water, autoclaved for 1 hour at 15 Ibs pressure (121℃), cooled, and then poured into sterile petri plates.

6.1.1.3 Preparation of compound solutions

A series of solutions (ligand, Cu, Ni, Pt, Pd, and Fe) were prepared at a concentration of 0.01mg and dissolved in 1ml distilled water.

6.1.1.4 Disc Diffusion Method

Sterilized disc paper with a 6mm diameter was immersed in each solution, then placed on a petri dish containing bacteria and agar substrate, and incubated for 24 hours to determine the diameter of the zone of inhibition.

6.1.2 Result and Discussion

The disc diffusion method was used to screen 1,2,4-Triazolo[1,5-c]Pyrimidine-5(6H)-ones and its complexes for anti-bacterial activity against Gram-positive and negative bacteria, and the zone of inhibition were illustrated in **Table 8.a and Figure 46**.

As results in **Table 8.a** and **Figure 46**, the complexes have higher and more anti-bacterial activity compared to the starting ligand (1,2,4-Triazolo[1,5-c]Pyrimidine-5(6H)-ones). As no anti-bacterial was found for the ligand without the metals. Triazolo-Pyrimidine was not enough alone to effect as anti-bacterial It might be N-alkylated and increased the chain length of it (raising the number of carbon to nine) to improve the biological activities (125) or substituted with functional groups such as halogens to improve the biological activities. This may be a starting point for improving antibacterial activity.

The results were as shown in **Figure 47** as follows: About MRSA, as shown, there was no effect of the ligand, while Pt obtained the largest result, followed by Cu, Ni, Pd, and Fe, respectively. Regarding S. aureus, there were similar results for Pt and Pd (the highest result), followed by Fe. Cu and Ni got the lowest result. Whereas in E. coli, there were significant differences between the complexes, where Pt had the strongest antibacterial effect, while Pd, Ni, and Cu got the same effect and their effect was much less than Pt. And there was no effect as an anti-bacterial with Fe. Finally, with the Pseudomonas, Pt also had the highest effect, while there was no effect concerning Cu. While Fe, Ni, and Pd got the same effect.

The inhibition zone(IZ) was measured to assess the antibacterial activity of selected antibiotics against MRSA, S. aureus, E. coli, and Pseudomonas available bacterial strains in the initial screening **(Table 8. b)**. As shown, Bacitracin exhibited the highest inhibition zone against MRSA (11 mm), then Gentamicin (10mm). While the rest antibiotics had no effect. And when we compare it to the complexes, we notice that Pt has the same value as the antibiotic Bacitracin. The other results of the complexes were comparable to the antibiotics mentioned in **Tables 8. a and 8. b**. The following complexes: Cu, Ni, Fe, and Pd have IZ, while the rest of the antibiotics had no effect.

Penicillin showed the highest IZ against S. aureus, at 29 mm, followed by Gentamicin at 27 mm, and Bacitracin at 10 mm. While all the complexes had a greater and the same effect of the Bacitracin.

Penicillin had the highest IZ of 25 mm in E. coli, followed by Gentamicin and Ampicillin with IZ of 25 and 21 mm, respectively. The Bacitracin has the smallest IZ, measuring 13mm. Compared to the complexes, Pt obtained the same IZ value for Ampicillin = 21 mm.

Gentamicin has the most activity against Pseudomonas, while the other antibiotics had no activity, as indicated in **Table 8. b**. For the complexes, there was less effect from Gentamicin. Where the complexes: Ni, Fe, Pt, and Pd showed minor effects that did not appear in the rest of the antibiotics (Penicillin, Ampicillin, and Bacitracin).

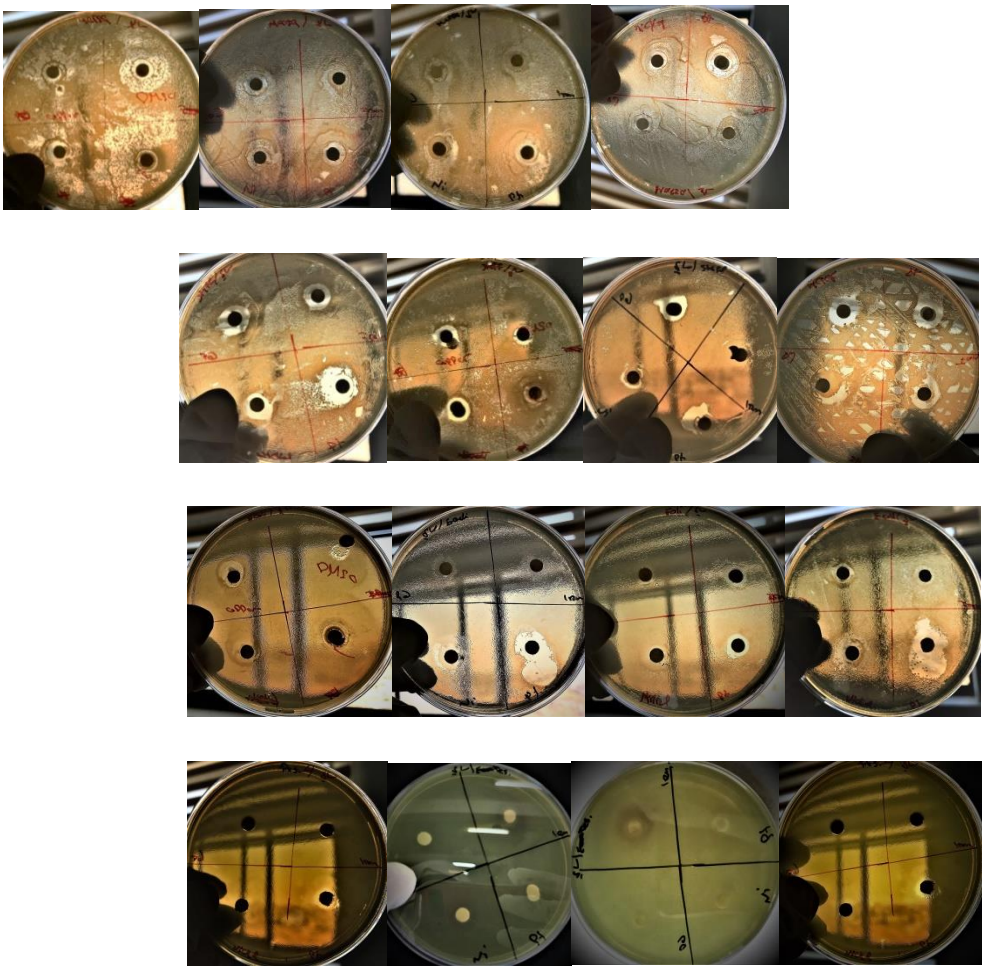


Figure 48 Antibacterial activity of ligand and its complexes using disc diffusion method

Table 8.a Inhibition zone of ligand and its complexes against all strains

Bacteria	**Samples**					
	ligand	Cu	Ni	Fe	Pt	Pd
	Inhibition Zone (mm)					
MRSA	0.0	9.0	8.0	5.0	11.0	7.0
S. aureus	0.0	10	10	11.0	12.0	12.0
E. coli	0.0	5.5	5.0	0.0	21.5	5.0
Pseudomonas	0.0	0.0	5.0	5.0	8.0	5.0

Table 8.b Evaluation of antibiotics activity against bacteria

Bacteria	**Antibiotics**			
	Gentamicin	Penicillin	Ampicillin	Bacitracin
	Inhibition Zone (mm)			
MRSA	10	0.0	0.0	11
S. aureus	27	29	15	10
E. coli	25	25	21	13
Pseudomonas	23	0.0	0.0	0.0

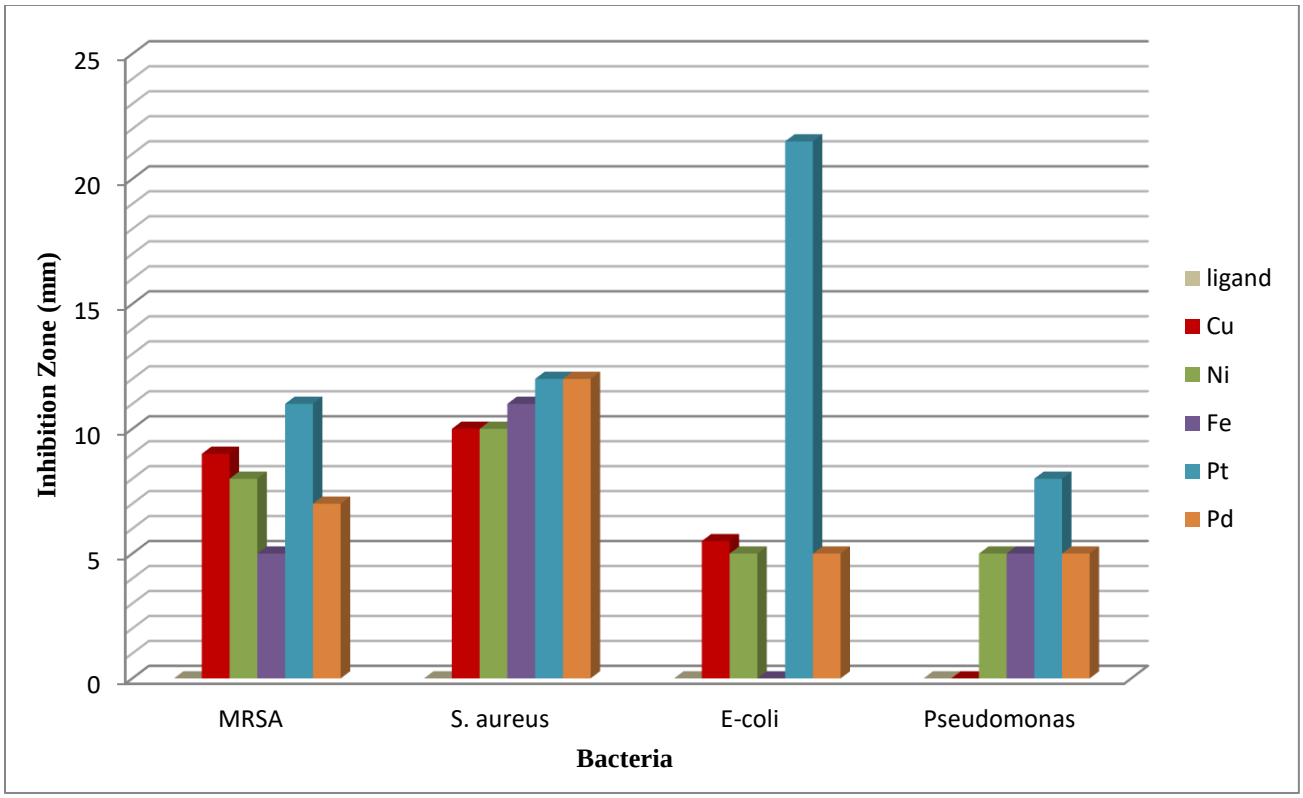


Figure 49 Inhibition zone (mm) of ligand and its complexes against MRSA, S.aureus, E coli and Pseudomonas.

6.2 Anti-malarial Testing

6.2.1 Material

Hemin chloride, ultra-pure water, sodium acetate buffer (pH 4.4), anti-malarial medication solution, 0.1 M NaOH, distilled water and chloroquine (CQ).

6.2.2 Semi-quantitative method

The solutions were prepared from Pt, Pd, Ni, and Fe (1 mg) and dissolved each of them in 1 ml of distilled water. The same solutions were prepared, but with lower concentrations, 0.5 mg / 1 ml in distilled water. Then using a semi-quantitative in-vitro method: According to Deharo et al. the approach was used (121)(135). A mixture of 50 µL of freshly dissolved 0.5 mg/mL hemin chloride in Dimethylsulphoxide (DMSO), 100 µL of 0.5 M sodium acetate buffer (pH 4.4), and 50 µL of prospective anti-malarial medication solution or solvent was incubated at 37°C for 18-24 hours in a non-sterile 96-well flat bottom plate. In the order listed above, the solutions were added to the plate. The plate was then centrifuged at 4000 rpm for 10 minutes. The reaction's pH was determined after the supernatant was removed. The mixture's final pH was in the range of (5.0-5.2). To eliminate free hemin chloride, the wells were rinsed with 200 µL DMSO per well. The dish was centrifuged one more before the supernatant was discarded. The leftover -hematin was dissolved in 200 µL of 0.1 M NaOH to produce an alkaline hematin that can be detected spectrophotometrically at 405 nm using an ELISA reader. The negative control was ultra-pure water, while the positive controls and tested extracts were also dissolved in ultra-pure water. Drug efficiency is inversely related to absorption, hence the lower the absorption, the more effective the drug.

6.2.3 Result and Discussion

Pt, Pd, Ni, and Fe coordination compounds were dissolved in distilled water, Chloroquine Drug (CQ) was employed as a positive control, and water was utilized as a negative control in semiquantitative tests of the prospective antimalarial medication. The figures of dissolved hematin (alkaline hematin) absorption at 405 are hilarious. Drug efficiency is inversely related to absorption, hence the lower the absorption, the more effective the drug.

Absorption results for the following Ni and Fe coordination compounds: 2.262, and 1.611, respectively. The results of their absorption are close to the negative control (water), which indicates that they have no antimalarial effect.

While there was a slight effect of the coordination compound Pd, as it obtained an absorption value = 0.778, which was close to the positive control (chloroquine), this indicates that there is an antimalarial effect, but it is slight compared to Pt.

Pt coordination compound with an absorbance value of 0.119 for a concentration of 1 mg /ml, It shows an absorption value lower than that of the chloroquine, where the chloroquine absorbance gave a result of 0.172. Drug efficiency is inversely related to absorption, hence the lower the absorption, the more effective the drug. The absorption value of Pt is lower than chloroquine, so Pt more effective than that of chloroquine as in the **Figure 52**.

The effect persists even when reducing the concentration. As it appears in **(Figure 53)** when using a lower concentration (0.5 mg/ ml) an absorbance value =0.112 for Pt and for chloroquine was 0.150. Where the absorption value of Pt decreased from 0.119 to 0.112.

When the concentration decreased from 1 to 0.5 mg/ ml, the efficiency of Pt increased further due to the decrease in its absorption from 0.119 to 0.112. Where absorption is inversely proportional to drug efficacy. Therefore, it could be used as an alternative treatment even at low concentrations.

Table 9 semi-quantitative test results of potential antimalarial drug Pt, Pd, Ni, and Fe complexes for a concentration for 1mg\ml and 0.5mg\ml compared to chloroquine (CQ), as positive controls,

while water was used as negative controls. Absorption is inversely proportional to drug efficiency; the lower absorption drug is considered to be more efficient. Results are the average of 24 tests.

water	**Conc. 1 mg/ml**				
	Fe	**Pt**	**Ni**	**Pd**	**CQ**
2.028	1.653	0.175	2.158	1.000	0.135
2.329	1.543	0.095	2.252	0.742	0.272
2.331	1.544	0.109	2.362	0.757	0.075
2.330	1.705	0.096	2.277	0.611	0.208
Average = 2.255	**1.611**	**0.119**	**2.262**	**0.778**	**0.172**

water	**Conc. 0.5 mg/ml**				
	Fe	**Pt**	**Ni**	**Pd**	**CQ**
2.209	1.838	0.123	1.971	0.949	0.079
2.159	1.994	0.099	2.331	1.285	0.220
2.025	1.975	0.103	2.302	1.291	0.212
1.871	1.589	0.120	2.275	1.672	0.091
Average= 2.066	**1.849**	**0.112**	**2.219**	**1.299**	**0.150**

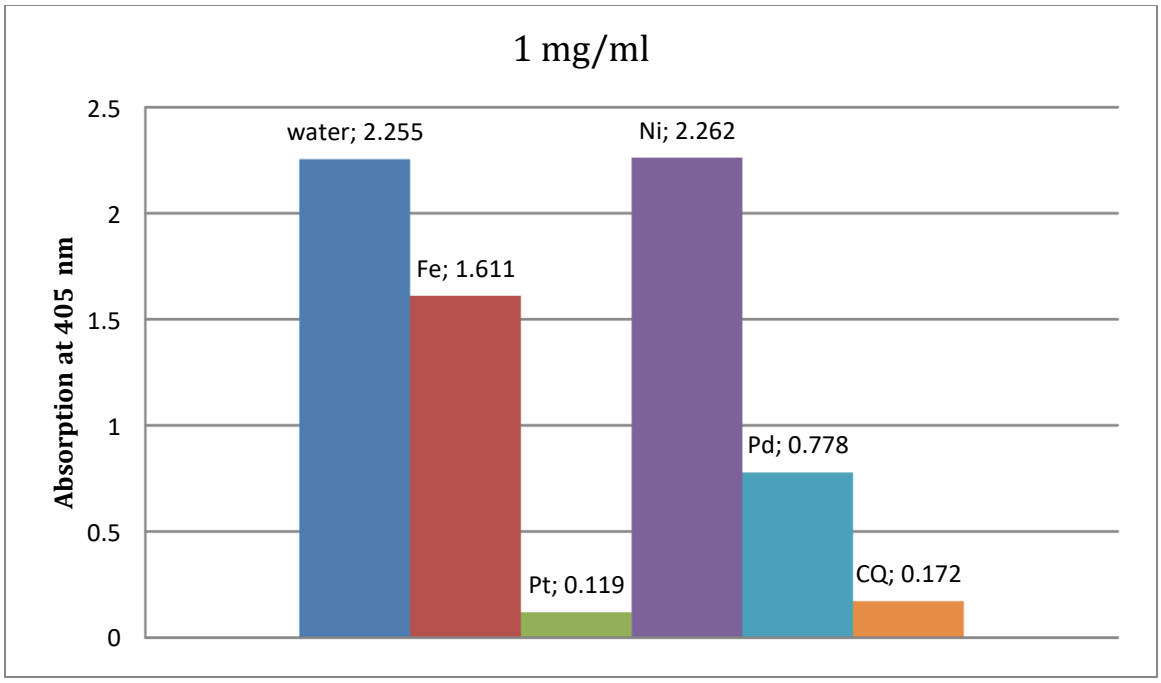


Figure 50 Column diagram representing semi-quantitative test results of potential antimalarial drug Pt, Pd, Ni, and Fe complexes for a concentration for 1mg\ml compared to chloroquine (CQ), as positive controls, while water was used as negative controls. Absorption is inversely proportional to drug efficiency; the lower absorption drug is considered to be more efficient.

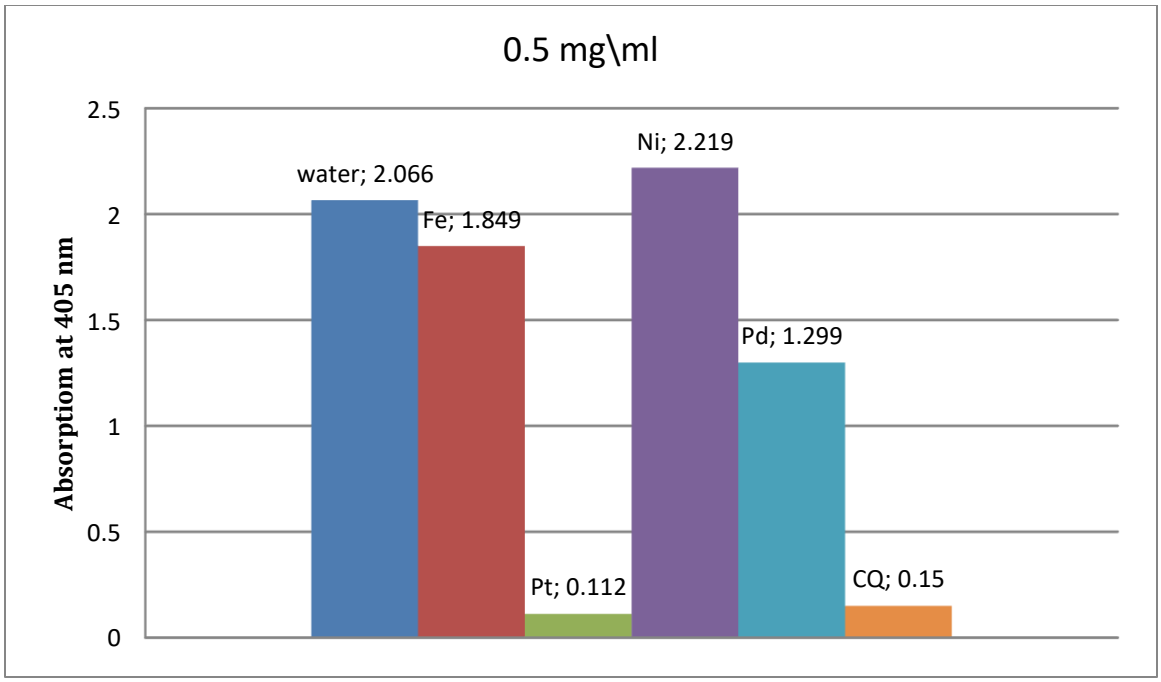


Figure 51 Column diagram representing semi-quantitative test results of potential antimalarial drug Pt, Pd, Ni, and Fe complexes for a concentration for 0.5 mg\ml compared to chloroquine (CQ), as positive controls, while water was used as negative controls. Absorption is inversely proportional to drug efficiency; the lower absorption drug is considered to be more efficient.

Chapter seven

Result and Discussion

Our thesis focused on research and examination of triazolopyrimidine coordination chemistry; a comprehensive revision was completed, incorporating all prior work of all inquiry groups in this field of study. We have not identified any references for the coordination compound of any of the other arrangements (1,5-c, 4,3-a, or 4,3-c), despite the fact that all previous work on coordination chemistry had concentrated on the 1,5-a derivative.

In the fields of organic, inorganic, and medicinal chemistry, triazolopyrimidine is a critical component. Since the development of several synthetic techniques, the research of triazolopyrimidine derivatives has increased significantly. Several innovative approaches have recently been described for accessing triazolopyrimidine derivatives that were previously unavailable through standard synthetic procedures, hence increasing the diversity of triazolopyrimidine-based compounds. We have tackled the numerous techniques of synthesis of triazolopyrimidine derivatives and showed their reactivities with respect to various reagents through this research. Finally, triazolopyrimidine derivatives have been proven to have crucial biological and pharmacological effects.

Comparing practical results and theoretical calculations for 1,2,4-Triazolo[1,5-c]pyrimidine-5(6H)-ones, it was discovered that there is a match between them, especially in the X-ray. the nitrogen atom in position 3 of the pyrimidine ring and the nitrogen atom in position 4 of the triazole ring is the most favorable sites for 1,2,4-Triazolo[1,5-c]pyrimidine-5(6H)-ones. The computerized chemistry study was matched by x-ray analysis, and the result showed that a 1,2,4-Triazolo[1,5-c]Pyrimidine-5(6H)-ones (as a ligand) was binding to the metal coordination through nitrogen 3 and 4. The theoretical results (molecular orbital calculation and electrostatic atomic charge) using semiempirical/AM1 and Hartree-Fock method were in agreement with the X-ray result Where it showed the binding of silver metal to the ligand through nitrogen 3 and 4. And copper metal through nitrogen 3. This is due to the high electron density in that region.

Furthermore, the complexes have higher and more anti-bacterial activity compared to the starting ligand (1,2,4-Triazolo[1,5-c]Pyrimidine-5(6H)-ones). As no anti-bacterial was found for the ligand without the metals. Triazolo-Pyrimidine was not enough alone to effect as anti-bacterial It might be N-alkylated and increased the chain length of it (raising the number of carbon to nine) to improve its biological activities (122) or substituted with functional groups such as halogens to improve the biological activities or using metals such as Cu, Pt, Pd, Ni, Mn, etc. because their DNA intercalating capacity was evidenced. So, the ligand has been modified by adding metals. This may be a starting point for improving antibacterial activity. Low concentrations were used; we expect when we increase the concentrations, the effect will be stronger for them than that. The results were shown in Chapter 6, where Bacitracin and Pt complex showed the same of inhibition against value of MRSA, which was 11 mm. Cu, Ni, Fe and Pd coordination compounds have IZ, while the rest of the antibiotics had no effect.
In S. aureus, all the complexes showed greater and the same effect of the Bacitracin.
In E. coli, Ampicillin with IZ 21 mm, Compared to the Pt complex obtained the same IZ value for Ampicillin. Where the coordination compounds: Ni, Fe, Pt, and Pd against Pseudomonas, showed minor effects that did not appear in the rest of the antibiotics (Penicillin, Ampicillin, and Bacitracin).

The results show that Pt coordination compound has a very high efficacy as antimalarial, and it was compared with chloroquine, using low concentrations of Pt, this is due to its ability to disable to disrupt the heme detoxification pathway of the malaria parasite. Where Mbaba et al.,(124) talked about Organometallic Platinum-Group Metal Complexes as Antimalarial Agents (123), The results showed that as a method of action, Ru(III) complexes can disrupt the malaria parasite's heme detoxification pathway, albeit this capability may be mostly dependent on the type of the coordinating ligand. To generate plasmodial efficacy, Ru(III) complexes interact with DNA. The proposed way of DNA binding via stacking interactions with AT-rich sections (The AT-rich region is exactly where a replication complex is created and DNA synthesis is initiated), which is unique to plasmodial DNA, could allow for more selectivity in targeting P. falciparum. So it could be expected the same thing happened with the pt complex and has reacted with DNA. While the other coordination compounds were not associated with DNA, so they do not have any antimalarial effect.

Conclusion

The current study showed that the coordination compounds of ligand have different biological activities and are of high value, especially when we use metals to improve the ligand. This could be the beginning of its use as an alternative treatment. Where Pt coordination compound showed high efficacy as an antimalarial compared to the chloroquine drug, its efficacy was higher than that of chloroquine, and it maintained the same efficacy even at low concentrations.

Future work

The study strongly recommends further research on Pt coordination compound used as an anti-cancer. The use of other metals, and examination of complexes for their biological effects and analyze them using X-rays

To boost biological activity, several modifications can be made to 1,2,4-Triazolo[1,5-c]pyrimidine-5(6H)-ones, such as increasing the number of carbons in the aliphatic sections of 1,2,4-Triazolo[1,5-c]pyrimidine-5(6H)-ones, and adding -Cl, -Br, -F, and NO2 to the aromatic rings. Other changes should also be made.

Complexes with other transition metals such as Zn(II), Re(I), Re(II), Co(II), and Au(III) might be synthesized using various counter ions and solvents. Furthermore, x-ray characterisation of all complexes to determine their structure could be carried out.

The spaces In the silver coordination compound could have application in several fields: adsorption, catalysis, photoluminescence, and molecular sieves, the size of the spaces would definitely be appropriate for the inclusion of certain metal ions or even organic molecules. It could be important in host-guest chemistry supramolecular chemistry the subject of molecular recognition. The "host" component can be considered the larger molecule, and it encompasses the smaller, "guest", molecule. In biological systems, the analogous terms of host and guest are commonly referred to as enzyme and substrate respectively. highly recommend calculating the size of these spaces.

Ouxilling ligand. Improving Pt by adding more than one group of ligands and testing it as an antimalarial, and comparing it with the results attached in the thesis.

Chapter eight

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