جمهورية العراق

وزارة التعليم العالي والبحث العلمي

جامعة المثنى / كلية العلوم

قسم الكيمياء

تحضير وتشخيص مركبات حلقية غير متجانسة تحتوي على حلقات1,2,3-ترايازول و 1,3,4-ثاياديازول

رسالة مقدمة الى كلية العلوم-جامعة المثنى كجزء من متطلبات نيل درجة الماجستير في الكيمياء

من قبل الطالبة

نور حميد عمران

بكالوريوس علوم كيمياء ٢٠٠٩

بإشراف

أ.م. د. رياض جليل ناهي

١٤٤٠ هـ ٢٠٠٩ م

الخلاصة

تم في هذه الرسالة تحضير وتشخيص و دراسة الأستقراية الحرارية لسلسلة جديدة من مركبات حلقية غير متجانسة تحتوي على ٣,٢,١-ترايازول وحلقة ٤,٣,١-ثايادايزول ومجموعة الايمين (قواعد شف). تضمن الجزء الاول من البحث تحضير مشتقات ٣,٢,١-التراياأزول ٥٣-٥٧ باستخدام تفاعل الإضافة الحلقية بين الأزايد والألكاين بوجود مركبات النحاس الأحادي كعامل مساعد. لذا تم تحضير سلسلة من مركبات الأزايد الاروماتي ٤٨-٥٢ كمكونة الأزايد المطلوب في تفاعل الاضافة الحلقية بينما تم استخدام حامض البروباينويك المتوفر تجاريا كمكونة الالكاين. إن استخدام حامض البروباينويك في هذا التفاعل يؤدي الى تعويض حلقة ٣،٢،١-التراياأزول بمجموعة كاربوكسيل وبالتالي يمكن استغلالها في الكثير من التفاعلات لتحضير مركبات مشتقات جديدة لتطبيقات مختلفة.

بعد تحضير مشتقات ٣,٢,١-الترايازول، تم التركيز على استغلال مجموعة الكاربوكسيل في تحضير حلقة٤,٣,١- ثايادايزول متجمعة مع حلقة ٣,٢,١-التراياأزول وذلك من خلال مشتقات الترايازول ٥٣-٥٧ المحضرة مع ثايوسيمي كاربازايد بوجود زيادة من $POCl_3$ وبالتالي الحصول على سلسلة جديدة من المركبات الحلقية الجديدة تحتوي على٤,٣,١- ثايادايزول متجمعة مع حلقة ٣,٢,١-الترايازول في جزيئة واحدة ٥٣-٥٧. بسبب احتواء المركبات الناتجة على مجموعة امين معوضه مباشرة على حلقة الثايادايزول في الموقع C2, لذا تم استغلال هذه المجموعة لتحضير سلسه جديده من مشتقات قواعد شف وذلك بالتفاعل مع اثنين من الالديهايدات الاروماتية بارا برومو بنزالديهايد وبارا نايترو بنزالديهايد.

وتم تشخيص جميع المركبات المحضرة بمقياس الاشعة تحت الحمراء FT-IR ومطيافية الرنين النووي المغناطيسي ومطيافية الكتلة.

علاوة على ذلك تم دراسة السلوك الحراري للمركبات المحضرة بتقنية التحليل الحراري الوزني TGA والتحليل الحراري التفاضلي الوزني DTG.

Republic of Iraq

Ministry of Higher Education

& Scientific Research

Al-Muthanna University

College of Science

Department of Chemistry

Synthesis and Characterization of New Heterocyclic Compounds Containing 1,2,3-Triazole and 1,3,4-Thiadiazole Rings

A Thesis Submitted in Partial Fulfillment of the Requirements

For the Master Degree in Chemistry Science

By

Noor Hameed Imran

B.Sc. 2009

Supervisor

Assist. Prof. Dr. Riyadh Jaleel Nahi

2019 A.D 1440 A

Certification of the Supervisor

I certify that this thesis entitled " **Synthesis and Characterization of New Heterocyclic Compounds Containing 1,2,3-Triazole and 1,3,4-Thiadiazole Rings** " was done by " **Noor Hameed Imran** " under my supervision in the Department of Chemistry /College of Science /Al-Muthanna University, in partial fulfillment of the requirements for the Master's degree in Chemistry.

Signature:

Supervisor: Assist. Prof. Dr. Riyadh Jaleel Nahi

Data: / / 2019

Department of Chemistry /Collage of Science /Al-Muthanna University

In view of the available recommendations, I forward this thesis for debate by the examining committee.

Signature:

Assist. Prof. Dr. Riyadh Jaleel Nahi

Head of Department

Data: / / 2019

Dedication

To my father

"May God bless his soul"

To my dear mother

To my lovely husband

and my darling children
"Yousif and Ameer"

Noor / 2019

Acknowledgements

Thanks to God (Allah) for giving me this blessing and helping me to complete my MSc Study. Initially, I would like to thank and appreciate my supervisor Assist. Prof. Dr. Riyadh Jaleel Nahi for his supervision and support me by important scientific information and valuable discussion which help me to complete my research. I would also like to thank the dean of the College of Science, Al Muthanna University, and I would like to thanks the head and the staff members of the department of chemistry. I would also like to thank the staff of central Lab. Mr. Ahmed Rezag and Mr. Hyder Radhi and Mr. Murad chuder for their efforts in the FT-IR and TGA analysis measurements. I would also like to thank member staff of Chemical store Mr. Mohammed Adil. I would also like to thank Assist. Prof. Dr. Adil Muala Dhumad, Basrah university, collage of Education for pure Sciences, Department of chemistry for his efforts in the NMR and Mass spectroscopy measurement. Finally, I would like to thank my beloved husband " Hazem" for standing with me in every moment of sadness and joy; "I thank God for your presence in my life".

Noor / 2019

Abstract

This thesis describes the synthesis, characterization and thermal study of new heterocyclic compounds containing 1,2,3-triazole, 1,3,4-thiadiazole and imine moieties at the same molecule. Firstly, the copper (I) catalyzed azide-alkyne cycloaddition (CuAAC) was the method choice for the synthesis of the target 1,2,3-traizole derivatives **53-57**. Thus, a series of *p*-substitution phenyl azides **48-52** was designed as azido components of this reaction which was synthesized via reaction of diazonium salts with sodium azide. The propiolic acid was chosen as an alkyne building block in CuAAC reaction. Importantly, choosing propiolic acid as a second moiety of CuAAC reaction is allowed to functionalize the target 1,2,3-triazole derivatives **53-57** with a carboxyl group. The latter, can be exploited in different reactions and applications. The main efforts are focused to exploit their carboxyl function groups for the combination of 1,2,3-triazole ring system with 2-amino-1,3,4-thiadiazole ring system. However, new series of heterocyclic compounds containing 1,2,3-triazole and 1,3,4-thiadiazole moieties at the same molecule was synthesized through condensation reaction between the synthesized 1,2,3-triazole derivatives **53-57** with thiosemicarbazide in the presence of $POCl_3$. Furthermore, as the synthesised compounds **57-62** containing an amino function group attached into the C_2 position of 1,3,4-thiadiazole ring, it was exploited for the synthesis of new heterocyclic compounds containing 1,2,3-triazole, 1,3,4-thiadiazole and imine moieties in one

molecule. All the synthesized compounds were characterized by the FT-IR, NMR and Mass spectroscopies. For further investigations, the thermal behavior of the synthesised compounds was studied by TGA and DTG techniques.

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List of Appreviations	
Appreviation	**Term**
t-But	tert-Butyl
℃	Degrees Celsius
DMF	Dimethylformamide
cm	Centimeter
DMSO	Dimethyl sulfoxide
FT-IR	Fourier transforms infrared
^{1}H -NMR	Proton nuclear magnetic resonance
mL	Mili Liters
mmole	Mili Mole
min	Minutes
m.p.	Melting point
m	Multiple
MS	Mass spectrometry
^{13}C-NMR	Carbon nuclear magnetic resonance
P	Para
S	Single
NMP	N-methyl-2-pyrrolidone

DCM	Dichloromethane

1.0 Introduction

1.1 Motivation

Heterocyclic compounds are widely distributed in the nature and many are of fundamental importance to living systems, furthermore it is striking how often a heterocyclic compound is found as a key component in biological processes. A large number of heterocyclic compounds such as thiazoles, thiadiazoles, indoles, oxadiazole, benzisoxazoles and pyrroles have been successfully used as antibacterial, anticancer, antipyretic, schistosomicidal, hypoglycemic, antihypertensive, antitubercular, anti-inflammatory and anti-HIV agents [1-3]. In addition, they have been used in agriculture, plastics, polymers, industry of dyes and textiles [4,5]. However, heterocyclic chemistry is still continues to draw the attention of synthetic organic chemists, due to their use as protecting groups, synthetic intermediates, chiral auxiliaries, and organic catalysts. Nowdays, heterocyclic chemistry represents a separate field of chemistry with a long history present society and future prospects. Thus, the work presented in this thesis is based entirely on the chemistry of heterocyclic compounds containing 1,2,3-triazole and 1,3,4-thiadiazole combination in one molecule.

1.2 Heterocyclic Chemistry

Heterocyclic compounds have practical applications ranged from extensive clinical use to diverse fields such as agriculture, biocide formulation, photography and polymer science [6]. Chemistry of heterocyclic compounds has been continued to be one of the most active areas of organic chemistry due to its diversity important in different fields and the most natural products containing them [7]. Literatures survey is showed that the history of heterocyclic chemistry started in the 1800's as a promising step with the development of chemistry as a separate field of organic chemistry [8]. In general, the prefix hetero indicates that is at least one non-carbon atom such as oxygen (O), nitrogen (N) and sulphur (S) is incorporated into either aromatic or partially or fully saturated cyclic system. Structurally, the cyclic system may comprise in one ring or more in fused ring system [9]. The simplest and most common heterocyclic rings are a five-membered ring such as pyrrole **1**, thiophene **2** and furan **3** [10] or six-membered ring such as pyridine **4 (**Figure 1.1). Moreover, these ring systems can be containing two or more heteroatoms such as imidazole **5**, oxadiazole **6**, thiazole **7**, isothiazole **8** and triazine **9** [11-14].

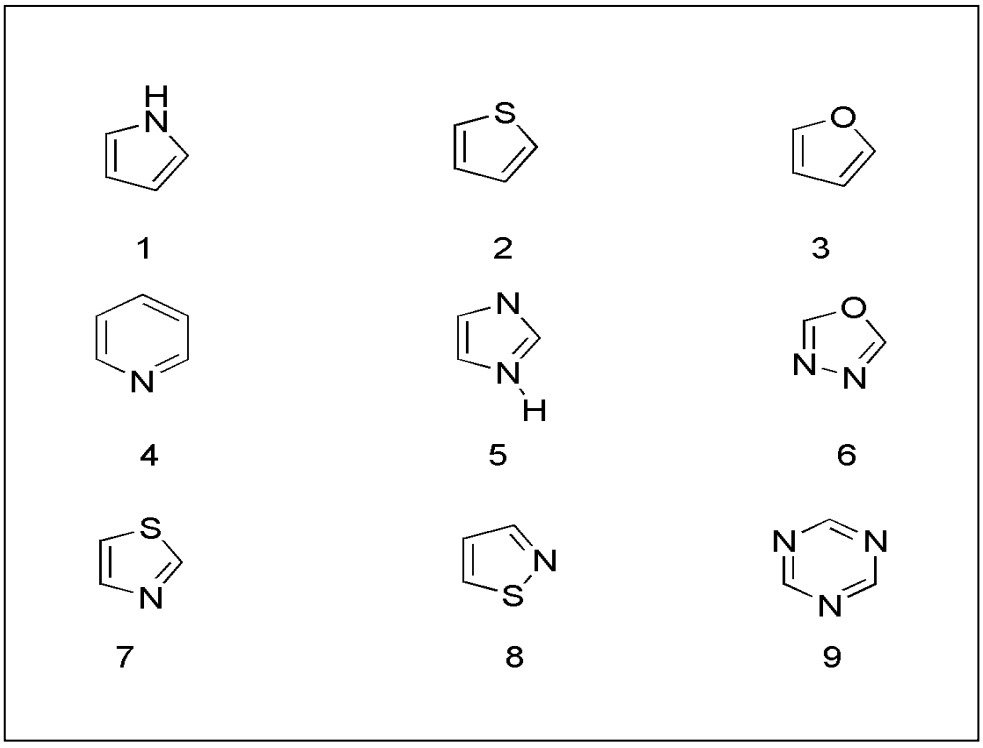


Figure 1.1: Structure of selected heterocyclic compounds.

Nowdays, heterocyclic chemistry has invaded almost all aspects of modern organic chemistry, medicinal chemistry and material science to present a wide range of compounds can be used in different applications such as pharmaceuticals [15], agrochemicals [16], veterinary products [17], antioxidants [18], corrosion inhibitors [19], monomers and additives of polymers [20] and dye stuff [21], [22]. A large number of compound containing five membered ring systems, such as triazole, thiadiazole with three heteroatoms at symmetrical or asymmetrical positions have been synthesised and studied due to its interesting pharmacological properties and industrial applications [23],[24]. Moreover, there are many heterocyclic ring structures which have been designed in such a way that their properties and applications improved after structural modifications [25]. Thus, this thesis emphasises on the synthesis of a series of new heterocyclic compounds containing 1,2,3-triazole derevatives and combine these compounds with 1,3,4-thiadiazole ring system as a new compounds.

1.2.1 Triazole Ring System: Structural and Properties

Triazole is an interesting sort of nitrogen containing compounds belongs to a family of organic compounds called azoles [26]. The origin of the name 'triazoles' was first reported by Bladin in 1885 for carbon-nitrogen five membered rings with the molecular formula $C_2H_3N_3$ [27]. In addition, the triazole ring system is an analogue to pyrrole ring, it was given an alternative name called pyrrodiazole [28]. Structurally,

depending on the arrangement of the three nitrogens in the ring system, there are two isomeric structures of triazole ring systems i.e.,1,2,3-triazoles **10** or called 'v'-triazole and 1,2,4- triazoles **11** or called 's'-triazole as shown in Figure 1.2 [29].

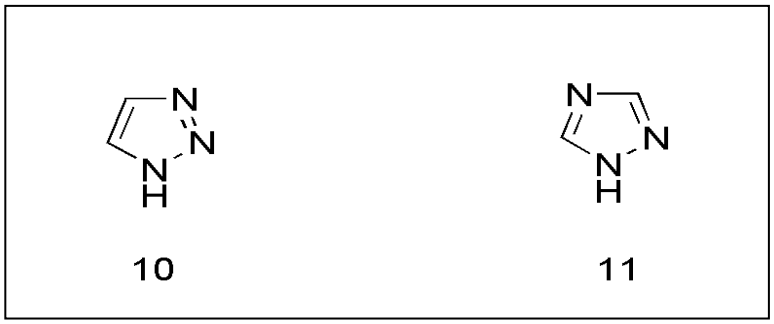


Figure 1.2: Isomeric structures of triazole ring system.

For 1,2,4-triazole isomer, two nitrogens are adjusted one to another in positions labeled N1 and N2, whereas the third nitrogen atom is labeled as N4 of the ring system, all respect to the two carbon atoms that are labeled at C3 and C5. While in the 1,2,3-triazole isomer, the three nitrogen atoms are adjusted to one another in positions labeled as N1, N2 and N3 of the triazole ring system [30]. Both triazole isomers **10** and **11** can be found in different forms (Tautomers) depending on the position of the hydrogen that is attached to the nitrogen particle as shown in Figure 1.3 [31].

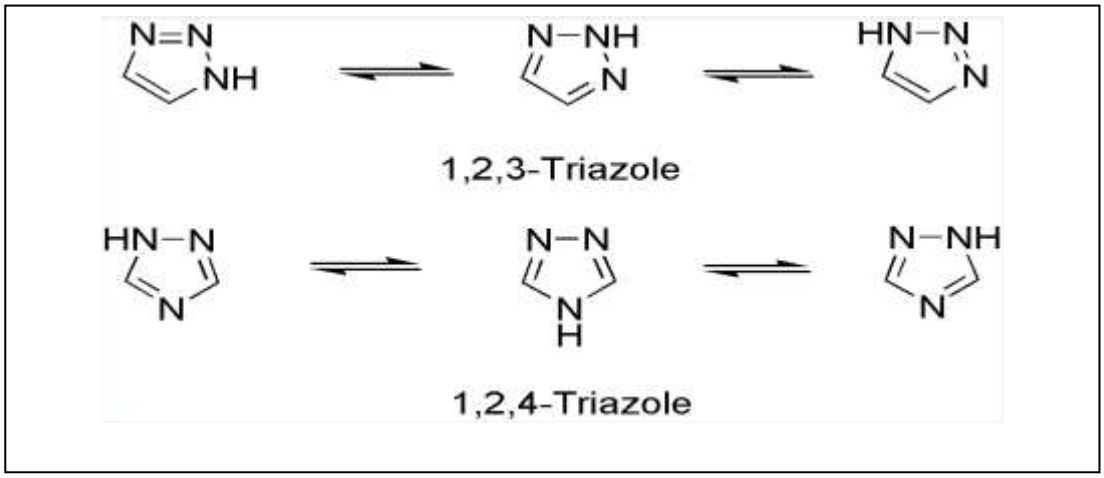


Figure 1.3: Different tautomeric structures of the both triazole isomers.

In both isomers, the triazole ring system is considered an aromatic system that has three electron pairs contribution from two pairs of π-electrons that come from the two double bonds and the remaining one pair come from a nitrogen atom. Thus, it obey Hückel's rule [32]. Such a system is stabilized by delocalization of π-electrons and though the triazole nucleus may be represented by tautomeric forms as shown in Figure 1.4 [33].

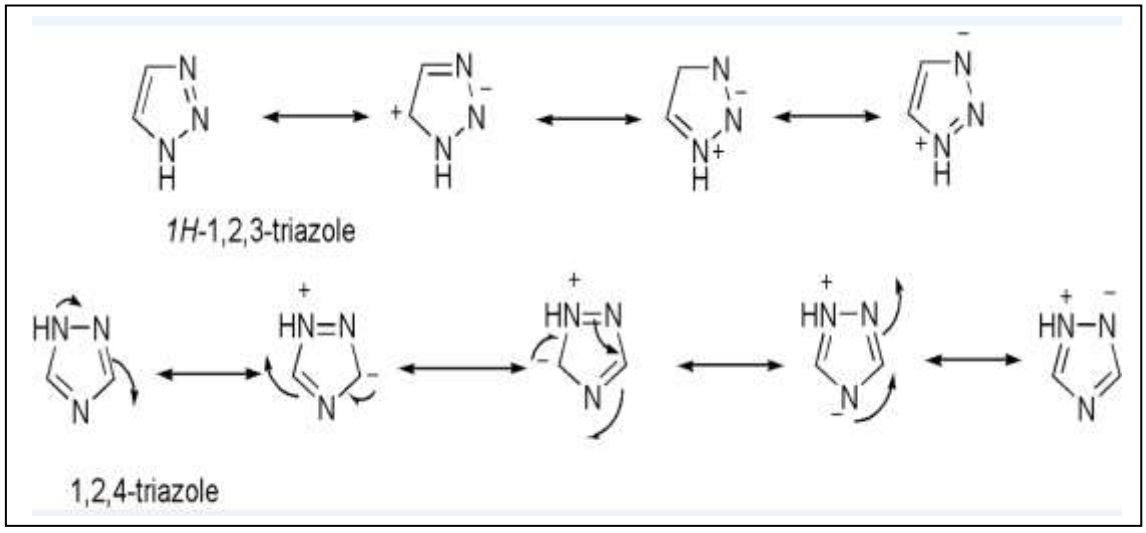


Figure 1.4: Tautomeric form of 1,2,3-triazole and 1,2,4-triazole ring.

The aromatic nature and delocalization of π-electrons is the main reason of the stability of triazole nucleus [34]. Therefore, triazole derivatives are capable to bind to

diverse biological and chemical systems via different interactions and forces such as coordination bonds, hydrogen bonds, hydrophobic effect cation π, π-π stacking, vander-waals forces, So, displaying a wide spectrum of applications [35]. Due to these factors, triazole units have attracted a considerable attention in fields, such as medicinal and agrochemical research as well as in the material sciences. During the last few decades, a considerable interest has been devoted to synthesise of triazole derivatives due to their wide spectrum of biological activities such as anticonvulsant [34], antidepressant [36], antibacterial [34], antifungal [37], anti-inflammatory [38], analgesic [39], anticancer [40], and anti-viral activities. Furthermore, 1,2,4-triazole derivatives are also useful as analytical reagents [41], photographic chemicals [42] and in polymer synthesis [43], [44]. However, the chemistry of 1,2,3-triazoles derivatives have received a considerable attention owing to their synthetic and effective biological importance.

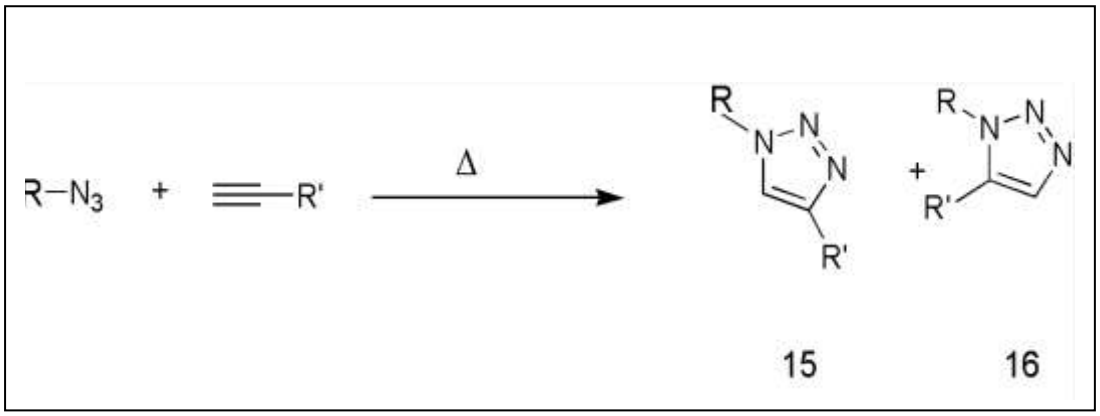
1.2.1.1 1,2,3-Triazole Ring System: Structure and Properties

1,2,3-Tiazole ring is an ubiquitous structural feature of many synthetic compounds, especially with diversified therapeutic efficacy [45]. Since 1,2,3-traizole structure contains three neighboring nitrogen atoms, there are three obtainable substitution sites found at their positions, resulting three different structures of 1,2,3-triazole. These structures include two aromatic structures and named as *1H*-1,2,3-triazole **12** and 2*H*-1,2,3-triazole **13**, while the third one is not aromatic and named as 4*H*-1,2,3-triazole **14** [46]. In addition, the different substitution in the isomers of 1,2,3-triazole ring

system leads to many differences in their chemical and biological properties [31]. 1,2,3-Triazole derivatives are attractive connecting units because they are not oxidized or reduced, stable towards biological and chemical degradation and able to form hydrogen bonding, which can be favorable in the binding of bio molecular targets and can improve their water solubility [47]. Moreover, 1,2,3-triazole ring system has an acidic and basic behavior due to the strong polarization of its aromatic π-system which attributed to the presence of three nitrogen atoms [48]. Thus, when considering that the relevant contributing structures as well as inductive, the carbon atoms and the nitrogen atom at N1 are estimated to be positively charged, whereas 2- and 3-nitrogen atoms should appearance negative partial charges [49]. The *1H*-1,2,3-triazoles **12** is the most common isomer of 1,2,3-triazole ring system and can be considered as not electron-rich, However, it can be nitrated and brominated, but the relative rates are on a par just below that of benzene [50]. Neucleophilic transpositions of halide atoms from halogenated triazoles can be occurred but at rates slower than with halogenated other aromatic heterocyclic such as pyridines [51]. In general, the 1*H*-1,2,3-triazoles **12** can experience both electrophilic and neucleophilic reactions, but at a modest rate [52]. In overall, there are three isomers of *1H*-1,2,3-triazole compound with diverse possibilities in the site of the substituents attached of the heterocyclic ring. Those are 1,5-disubstituted and 1,4 disubstituted-1,2,3-triazole. Clearly, the structural, electronic properties,and applications of these isomers are diverse [53]. However, in the current work, we concerned in synthesizing a series of different *1H*-1,4-disubstituted-1,2,3-triazole derivatives copper catalyzed azide-alkyne cycloaddition reaction "CuAAC" [54].

1.2.1.2 Synthesis of 1,4-disubstituted-1,2,3-Triazole Derivatives by Click Chemistry

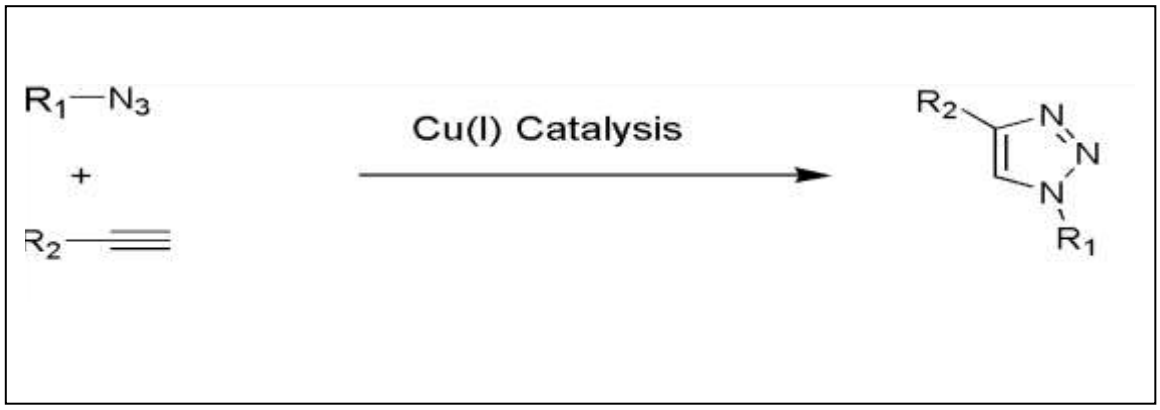
The first synthesis of 1,4-disubstituted-1,2,3-triazole derivatives using azide and alkyne reaction was first reported by Arthur Michael in 1893 [55]. However, the full synthetic study of reaction that was achieved by Rolf Huisgen in 1961 showed that this reaction is relatively is a slow 1,3-dipolar cycloaddition reaction. Furthermore, it also found that this reaction can be achieved at high temperatures to obtain a reasonable yield. However, with lossing a regioselectivity to generate a mixture of 1,4-disubstituted and 1,5-disubstituted-*1H*-1,2,3-triazole isomers **15** and **16**, respectively as shown in Scheme1.1.



Scheme 1.1: Classical thermal 1,3- dipolar cycloaddition.

In 1984, copper metal was used as a catalyst for the synthesis of azidoallene complex. It was observed that a Huisgen azide-alkyne 1,3-dipolar cycloaddition product is formed as a side reaction [56]. However, this observation was left without an interest until 2001, when a renewed interest in azide-alkyne 1,3-dipolar cycloaddition was reported by Sharpless et al, when they published a paper include introducing a new synthetic strategy used in organic synthesis termed "click chemistry". In addition, they defined and described this strategy as modular, broad in scope, generating only safe by-products, stereospecific, simple to perform and giving high yields. In 2002, in an attempt to apply the principles of click chemistry in the organic synthesis,

independently two groups; Sharpless in the US [57] and Meldal in Denmark [58] used the copper (I) species as a catalyst for azide-alkyne cycloaddition. Both observed that this reaction proceeds exclusively to give any 1,4-disubstituted 1,2,3-triazole as shown in Scheme1.2.



Scheme 1.2: Synthesis of 1,4-disubstituted-1,2,3-triazole ring system.

In addition, the copper catalyzed azide-alkyne reaction (CuAAC) can be described as a fast reaction that requires low temperatures in high yield products without being affected by the steric or electronics of the substrates [59]. Importantly, the discovery of copper (I) catalyst for regioselective [3+2] cycloaddition of azides with alkynes opened its broad exploitation in medicinal and material science. Moreover, CuAAC "click chemistry" can be proceeded according to the general mechanism that is described in Figure1.5.

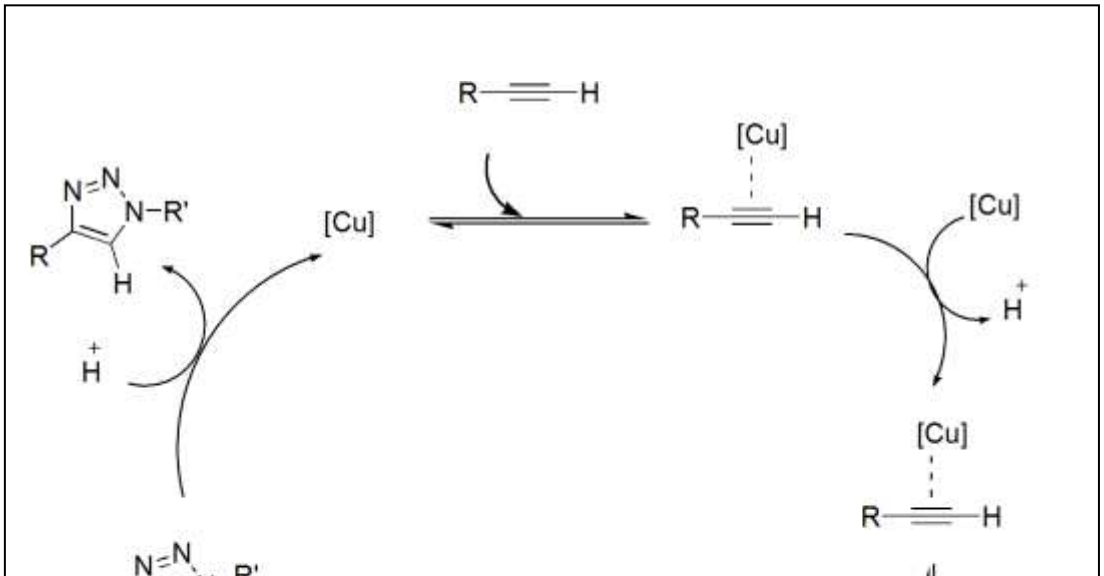


Figure1.5: A general mechanism of click chemistry.

In this mechanism, the (copper catalysed azide-alkyne 1,3-dipolar) cycloaddition (CuAAC) proceeds through the coordination between Cu (I) and the terminal alkyne to form an active (copper acetylide). This intermediate in turn reacts with the azide component to generate the copper acetylide-azide complex. This complex then cyclizes to form a metallocycle intermediates, following by rearrangement to form a cyclic compound. Finally, after protonation and dissociation, the reaction ends to produce the final products regenerating the Cu (I) catalyst [60]. Practically, the conventional sources of Cu (I) that is required for the click reaction are copper (I) halide and Cu (I) acetate. Furthermore, it also was found that Cu (I) can be produced *in situ* from a Cu (II) salt, such as copper sulphat ($CuSO_4$) in the presence of a reducing agent such as sodium ascorbate [61]. Although the standard (CuAAC) reaction solvent is *tert*-BuOH:H_2O (1:1), this reaction can be achieved in other solvents such as DMF, H_2O, NMP, DMSO, $CHCl_3$, MeOH, DCM and only *tert*-BuOH [62].

1.2.1.3 Importance of 1,4-disubstituted 1,2,3-Triazole Compounds

1,2,3-Triazole derivatives have been an interestingly special attention due to wide potential applications as medicinal agents [63], agrochemicals [64], materials science [65], super molecular ligands [66], artificial acceptors [67], and biomimetic catalysts [68]. Thus, a large number of compounds containing 1,2,3-triazole derivatives are known as antimicrobial and antifungal drugs like Triazolam, Alprazalam, Etizolam, Furacylin, Ribavirin, Hexaconazole, Triadimefon, Mycobutanil, Rizatriptan, Propicaconazole, Fluotrimazol and Fluconazole [69], [70]. 1,2,3-Triazole also can act as intermediate for preparation of substituted caprolactum useful for treatment of HIV disease [71] and also find applications in the preparation of photographic plates, polymers and as analytical agent [72]. In general, the importance of triazolic compounds in medicinal chemistry is undeniable. Particularly, 1,2,3-triazoles ring system can actively participate in hydrogen bonding and dipole-dipole interactions because of their strong dipole moments and are extremely stable to hydrolysis and oxidative/reductive conditions [73]. Therefore, 1,2,3-triazole moieties are attractive connecting units which are favorable in binding of bio molecular targets and improve their solubility [74]. Moreover, as 1,2,3-triazole ring system is poor basicity, it is not protonated at physiological pH [75].

1.3 Thiadiazoles: Chemical Structure and Properties

Thiadiazole ring system was first described in 1882 by Fischer as a five-membered heterocyclic compound containing one sulfur atom and two nitrogen atoms with a molecular formula $C_2N_2H_2S$ as member of azoles family [76]. Structurally, depending on the arrangement of the two nitrogen atoms respect to the sulphur atom. There are

four possible isomers of thiadiazole ring system such as 1,2,3-thiadizole **17**, 1,2,4-thiadiazole **18**, 1,2,5-thiadizole **19** and 1,3,4-thiadizole **20** [77].

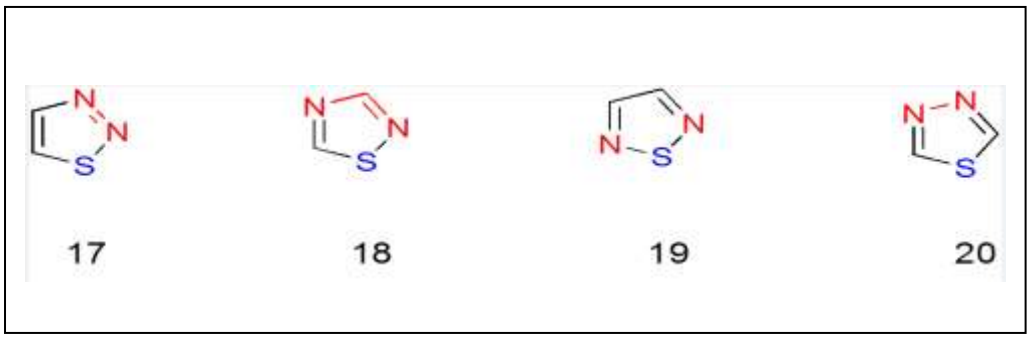


Figure 1.6: Structural isomers of thiadiazole ring system.

In general, the aromaticity is an important parameter for determining the physical properties and chemical reactivity of heterocyclic compounds and thus, their potential applications [78]. Since five-membered heterocycles such as thiophene and thiazoles have played an important role in different research area, therefore, thiadiazole ring system, which has similar electronic properties to these compounds has been started to be under the spotlight. In general, thiadiazole ring system is less aromatic than benzene, pyridine and thiophene and the aromatic character which measured by π-electron delocalization which decreases as 1,2,5-thiadiazole > 1,2,3-thiadiazole > 1,2,4-thiadiazole > 1,3,4-thiadiazole [79]. Furthermore, the electrophilic attack at carbon of thiadiazole ring system is very rare and neucleophilic substitution reactions are common due to the electron withdrawing nature of the nitrogen atoms [80]. In general, the thiadiazole ring acts as a scaffold between different molecule due to its electron-deficient nature. So, thiadiazole derivatives play a major role in advanced applications ranging from pharmaceutical chemistry to materials science. Interestingly, thiadiazoles ring system continuously draws an interest for the development of new drug moiety. Among all thiadiazoles structures, the chemistry of

1,3,4-thiadiazole ring system has attracted a special interest and a literature survey has indicated that 1,3,4-thiadiazole and its derivatives have been most promised isomer than other isomer of thiadiazole rings system [82].

1.3.1 1,3,4-Thiadiazole Ring System: Chemical Structure and Properties

1,3,4-Thiadiazole moiety is one of the most common isomer of thiadiazole ring system and can be considered as an analogue of thiophene by replacement of both its C4 and C5 by the electronegative nitrogen atom. The fully 1,3,4-thidiazole nature was first demonstrated by Goerdler and et al in 1956 [81]. 1,3,4-Thiadiazole ring system **20** is looked upon as 4-azathiazole or 3,4-diazathiophene, so far as they are electronically isosteric [1]. The studies that achieved on the chemical activities and the spectral features have revealed that 1,3,4-thiadiazole structure **20** is a typical pseudo-aromatic molecule with dipole moment value of 3.25D [82]. It was also found that 1,3,4-thiadazole ring **20** is stable toward strong acids but cleaved by strong bases [83]. Unlike thiophene, it resists electrophilic substitution reactions, however, facile neucleophilic attack takes place at 2- and 5-positions [84]. Groups like alkyl groups, mercapto, hydroxyl, amino, halogens and carboxyl group are presented in these positions are reactive and exhibits their typical reactions. In addition, 2-mercapto-, 2-hydroxy and 2-amino-1,3,4-thiadiazole derivatives such as **21** display a tautomeric behavior such as **22** that described in Figure: 1.8 [1].

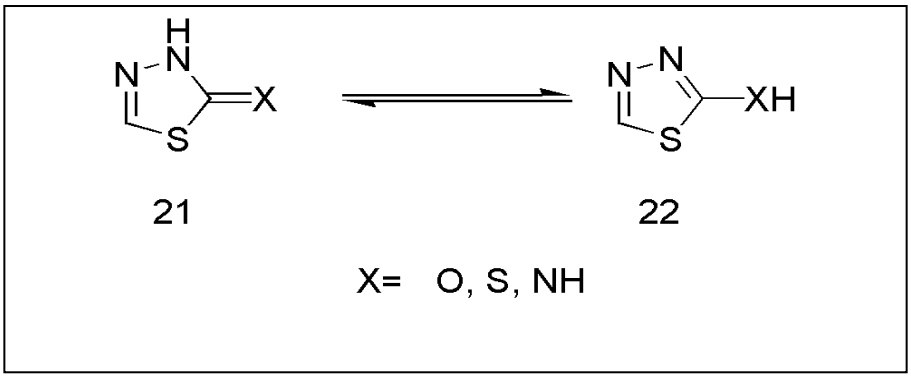
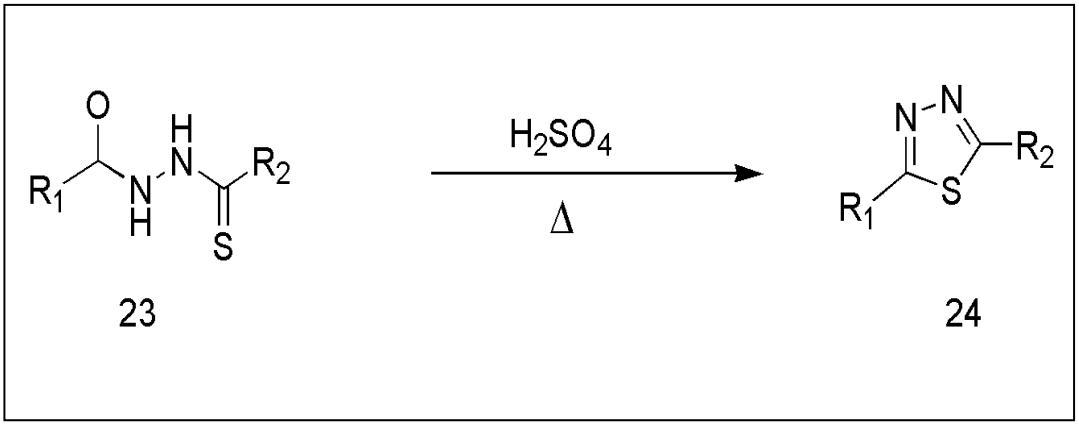


Figure 1.7: The tautomeric form of thiadiazole system.

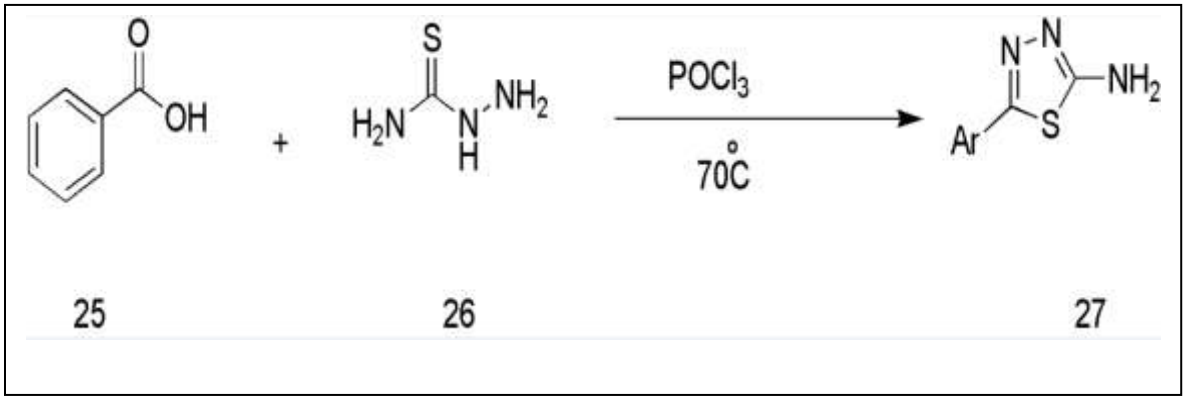
1.3.2 Synthesis of 2-5-Disubstituted-1,3,4-Thiadiazole Derivatives

There are various procedures that have been used for the synthesis of 2,5-disubstituted-1,3,4-thiadiazole ring system and the type of substituent group that are attached at C2 and C5 positions depends on the chemical structure of the starting material. The common method that has been used to synthesize 1,3,4-thiadiazole ring system such as **24** is a cyclo-dehydration reaction of the intermediate acyl thiosemicarbazide such as **23** as described in Scheme 1.3 [85]. This intermediate is prepared *in situ* by heating the appropriate carboxylic acid and thiosemicarbazide in the presence of acidic conditions.



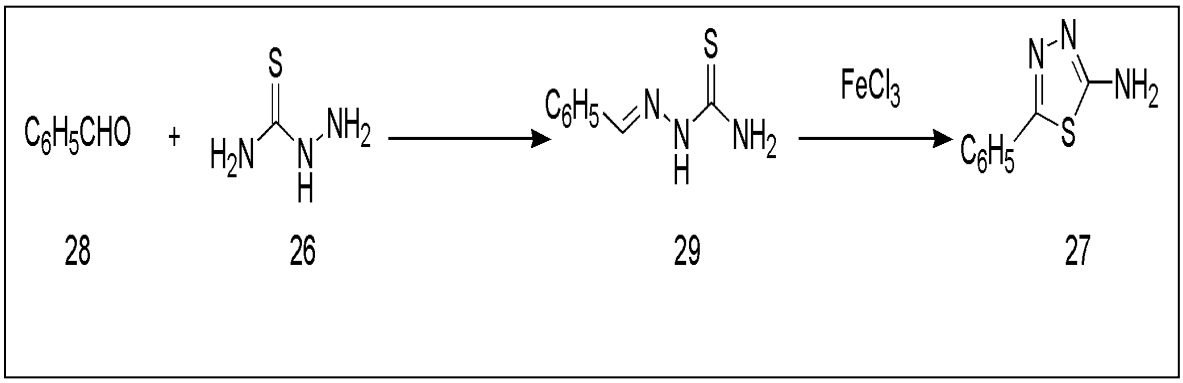
Scheme 1.3: Synthesis of 2,5-disubistitution 1,3,4-thiadiazole derevatives.

In this synthetic route, different acidic reagents are used such as sulfuric acid, phosphoric acid, acetic anhydride, and phosphorus halides as cyclization agents [86]. The common application for this synthetic route is the condensation reaction of carboxylic acids such as **25** with thiosemicarbazide **26** in the presence of phosphorus halides such as $POCl_3$ under reflux conditions to give 5-phenyl-2-amino-1,3,4-thiadiazole derivative [87], such as **27** as described in Scheme 1.4.



Scheme 1.4: Synthesis of 5-substituted 2-amino-thiadiazole **27**.

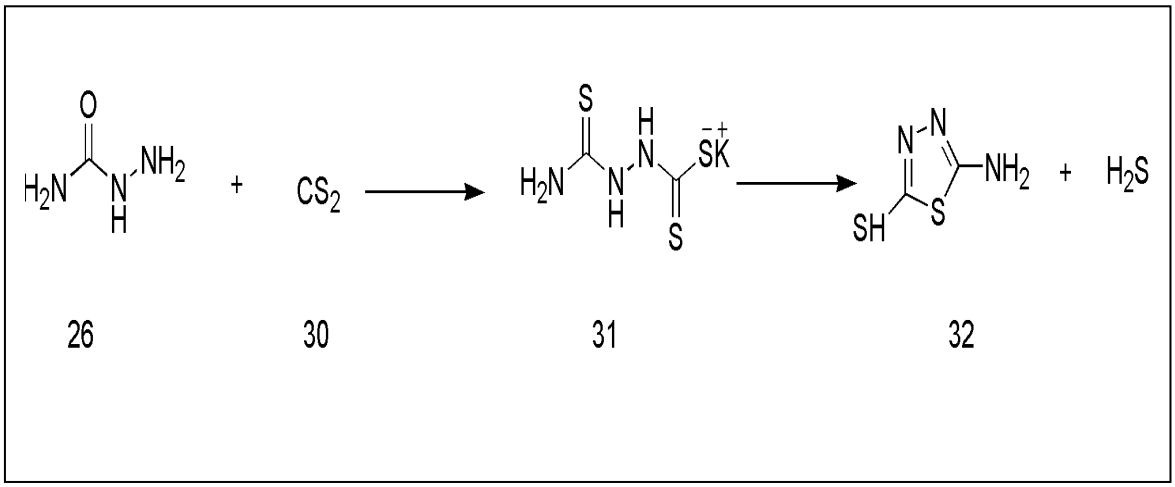
Moreover, the compound **27** can be prepared in a different synthetic method which is involved an oxidative cyclization of the corresponding benzaldehyde thiosemicarbazone such as **29** in the presence of ferric chloride. In this method, the intermediate **29** is prepared by the reaction of thiosemicarbazide **26** with benzaldehyde **28** or its derevatives as described in Scheme 1.5 [88].



Scheme 1.5: Synthesis of 5-substituted 2-amino-thiadiazole ring.

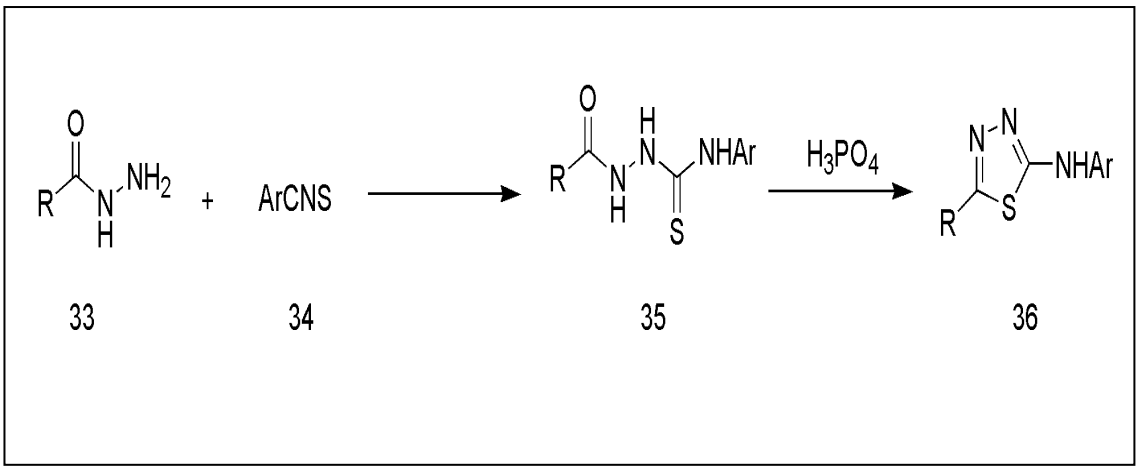
Also, it was found that the reaction of thiosemicarbazide **26** with carbon disulfide **30** in the presence of KOH yields the intermediate potassium dithiocarbazate salt **31**. Being followed by heating, 2-amino-1,3,4-thiadiazole ring system containing a

mercapto group attached at position C5 will be formed such as **32** as described in Scheme1.6 [89].



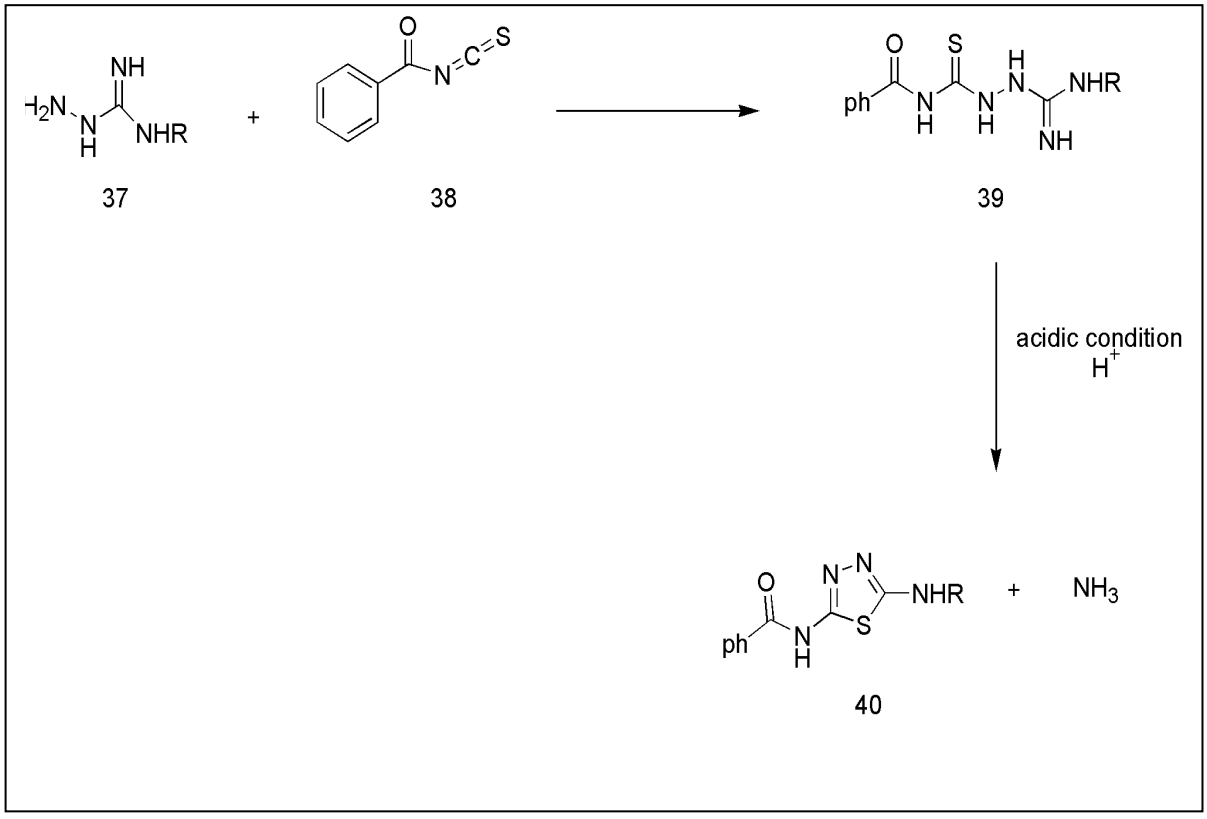
Scheme 1.6: Synthesis of 5-mercabto-2-amino-1,3,4-thiadiazole ring.

Furthermore, arylthioisocynate **34** can be used as a precursor to introduce sulfur atom into 1,3,4-thiadiazole ring system through its reaction with acylhaydrazone such as **33**. The key step for this reaction is the formation of substituted acyl thiosemicarbazide such as **35**. Followed by a cyclization step in the presence of H_2SO_4 or H_3PO_4 to produce 2-N-arylamino-1,3,4-thiadiazole derivative such as **36** as described in Scheme 1.7 [90].



Scheme 1.7: Synthesis of 2-N-arylamino-1,3,4-thiadiazole derivative.

In addition, 1,3,4-thiadiazoles derivatives such as **40** were prepared by cyclization of amidinothiosemicarbazides **39** under acidic conditions. In this reaction, the key intermediate compound **39** is obtained by reaction of aminoguinidine **37** with benzoylisothiocyanates **38** as described in Scheme 1.8 [91].



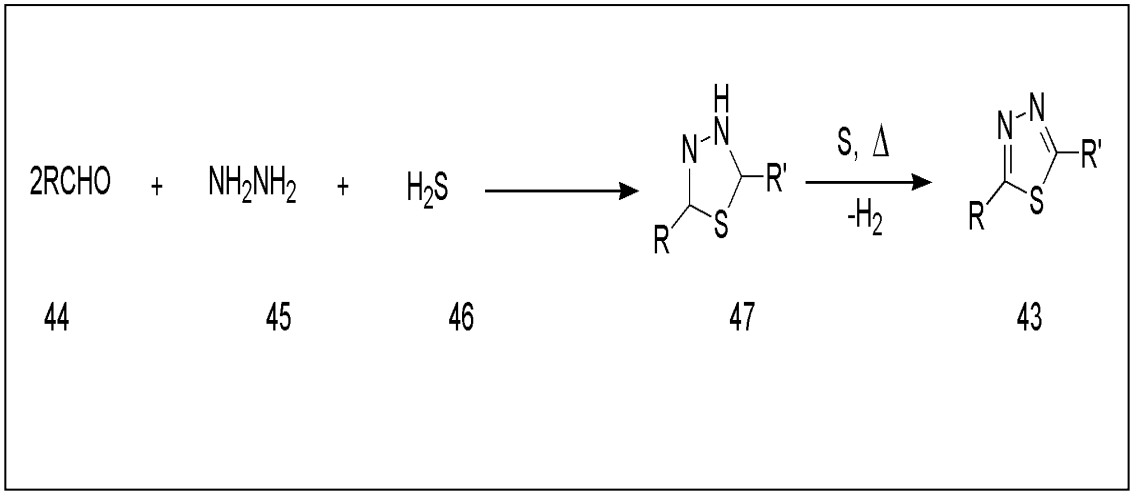
Scheme 1.8: Cyclization of acyl thiosemicarbazide under acid conditions.

In addition, 2,5-dialkyle-1,3,4-thiadiazole **43** was synthesised from a cyclization reaction of 1,2-diacylhydrazines such as **41** in the presence of P_2S_5 **42** as described in Scheme 1.9 [1].



Scheme1.9: Synthesis of 2,5-dialkyl-1,3,4-thiadiazoles derevatives.

Also, 2,5-disubstituted-1,3,4-thiadiazole **43** can be prepared in a high yield via dehydrogenation reaction of thiadiazolidines **47** in the presence of sulpher. The intermediate compound **47** is prepared from reaction of aliphatic aldehyde **44** with hydrazine **45** in the presence of hydrogen sulphide **46**. The latter is an agent to introduce the sulphur atom into the thiadiazolidines structure as described in Scheme1.10 [76, 92].



Scheme 1.10: Synthesis of 2,5-disubstituted-1,3,4-thiadiazole via dehydrogenation of thioacylation.

In the present work, we have adopted the method of Hoggarth [87], for the synthesis of new derivatives of 1,3,4-thiadiazoles starting from synthesised 1,2,3-triazole derivatives and thiosemicarbazide in the presence of $POCl_3$ for the synthesis of 2-amino-1,3,4-thiadiazole ring system.

1.3.2.1 Importance of 2,5-Disubstituted-1,3,4-Thiadiazole Derivatives

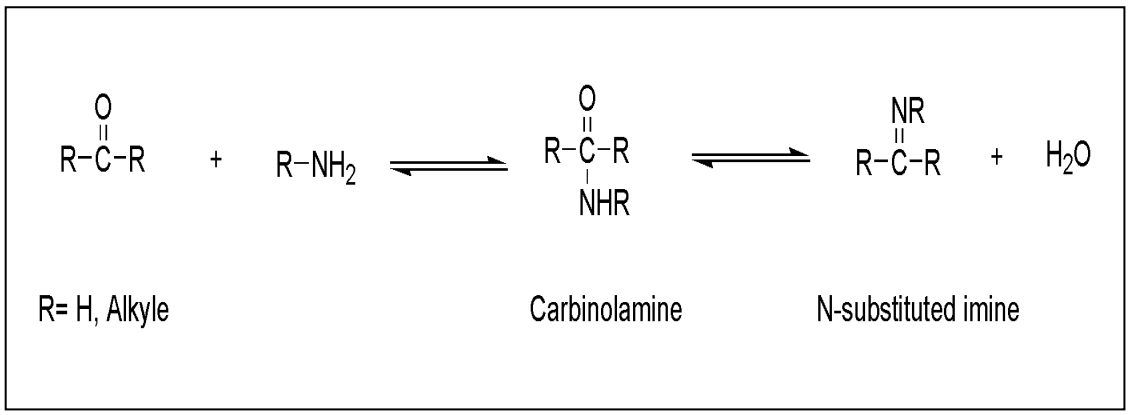
In general, 2,5-Disubstituted-1,3,4-thiadiazoles derivatives are an important class of heterocyclic compounds which display diverse applications in the organic synthesis, pharmaceutical and biological applications. Thus, during the recent years, there has been intense investigation of different classes of 2,5-disubstituted-1,3,4-thiadiazole compounds, many of which have wide-ranging pharmacological activities [93]. These compounds have a promising biological activity probably conferred the strong aromaticity of this ring system and virtue of a toxophoric -N=C-S- group [80]. Thus, it has a great stability *in vivo* and a lack of toxicity for higher vertebrates including humans. Thus, 2,5-disubstituted-1,3,4-thiadiazole derivatives are used for different biological activities such as antiviral [94,95], antibacterial [96], antifungal [97] and antitubercular [98]. Interestingly, the 1,3,4-thiadiazole derivative have displayed an ability to reduce the proliferations activity of cell line tumor [99]. In the other hand, 2,5-disubstituted-1,3,4-thiadiazole derivative also known to useful as cyanine dyes [100], oxidation inhibitors [101], anti-corrosion agents [102] and metal chelating agents [103].

1.4 Schiff's Bases: Chemical Structure and Properties

Schiff's bases (also known as imine or azomethine compounds) were first discovered by Hugo Schiff in 1864 [104] as the product of the condensation reaction of a primary amine with an aldehyde or a ketone.

Schiff bases that contain aryl substituents are substantially more stable and more readily synthesized, while those which contain aliphatic alkyl substituents are relatively unstable [105]. In addition, Schiff bases of aliphatic aldehydes are relatively

unstable and readily polymerizable, while those of aromatic aldehydes having effective conjugation are more stable [106]. In general, the synthesis of Schiff's base is a reversible reaction and takes place under acid or base catalysis upon heating as described in Scheme 1.12 [107].



Scheme 1.11: Synthesis of Schiff base.

The formation of Schiff base is generally driven to the completion by separation of the product or removal of water, or both. However, Schiff bases can be hydrolyzed back to their aldehydes or ketones and amines by aqueous acid or base [108]. The mechanism of the synthesis of imine group is included a neucleophilic addition of an amine to the carbonyl group of aldehyde or ketone [109]. In the first part of this mechanism, the amine reacts with the aldehyde or ketone to give an unstable addition compound called carbinolamine. This intermediate carbinolamine loses water by either acid or base catalyzed pathways. Since the carbinolamine is an alcohol, it

undergoes acid catalyzed dehydration [110]. Naturally the dehydration of the carbinolamine is the rate-determining step of Schiff base formation and that is why the reaction is catalyzed by an acid. In addition, the acid concentration cannot be too high because amines are basic compounds. If the amine is protonated and converts non-neucleophilic, equilibrium is drawn to the left and carbinolamine formation cannot happen [111]. Therefore, many Schiff bases synthesis are finest carried out at slightly acidic pH. The dehydration of carbinolamine is also catalyzed by base. This reaction is somewhat analogous to the (E_2 elimination) of alkyl halides except that it is not a concerted reaction. It proceeds in two steps through an anionic intermediate [112]. Schiff bases can be synthesized from aromatic or aliphatic amines and a carbonyl compound by a neucleophilic addition forming a hemiaminal, followed by a dehydration to generate an imine. Schiff bases have a chelating structure and are in demand because they are easy to prepare and are moderate electron donors [113]. Schiff bases are a widely used and the most appreciated organic (building blocks) to have a different range of pharmacological importance, as well Schiff base interred in many other fields as biological, inorganic, and analytical chemistry [114]. Schiff bases are reported to explain awide range of pharmacological activities and used as anti-microbial, anti-oxidant, anti-viral, anti-malarial, anti-cancerous, and anti-inflammatory agents [101,102].

1.5 Objectives of The Current Work

1- Synthesis of new 1,2,3-triazole compounds containing a carboxyl functional group that can be utilized as biological active compounds.

2- Combination of the synthesised 1,2,3-triazole ring with 1,3,4-thiadiazole ring system in the same molecules that can be exploited as biological active and electron-transporting materials.

3- Synthesis a new series of Schiff base by exploited The primary amino group that attached directly on 1,3,4-thiadiazole ring. That can be used as appreciated organic (building blocks) to have a different range of pharmacological importance.

4- Study thermal stability of all newly heterocyclic compounds by TG-DTG technique.

2.0 Experimental

2.1 Materials and Instruments

Chemicals and Solvents

All starting materials and solvents were purchased from different commercial available sources such as, BDH, Fluka, Riedel-de Haen, GCC, Thomas Baker Alpha and Merck companies and they were directly used without further purification.

NMR Spectroscopy

All ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 500 MHz and 125 MHz, spectrometer at Tehran University. Chemical shifts are given in respectively on Inova parts per million and the abbreviations were mentioned as: s= singlet and m=

multiple. All spectra were calibrated using chemical shifts reported relative to the residual deuterated solvent signals in DMSO-d_6 [2.50 ppm for ^{1}H-NMR spectra (central signal of quintuplet) and 39.7 ppm for ^{13}C-NMR spectra (central line of septuplet)].

FT-IR Spectroscopy

FT-IR measurements were recorded on an FT-IR Shemidzo–8400S plus spectrometer operating from 4000–500 cm^{-1} as KBr disc at Al-Muthanna University/College of Science/ Department of Chemistry.

GC-Mass Spectroscopy

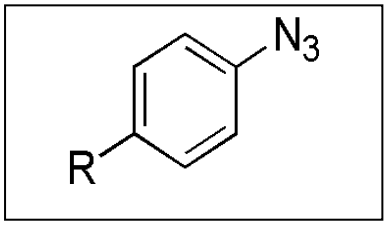
All GC-MS data were measured by Direct Probe instrument at Tehran University, MS Model: 5973 Network Mass Selective Detector, with Ion source: Electron Impact (EI) 70 eV.

Thermal Analysis

DTG measurements were done on using a Perkin Elmer TG 4000 at /All TG Department of Chemistry/ College of Science / Al-Muthanna University.

2.2 Procedures

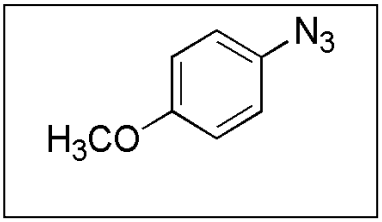
2.2.1 General procedure for the synthesis of para-substitution phenyl azide (48-52)



R = *p*-Methoxy, *p*-methyl, *p*-Hydroxy, *p*-bromo, *p*-chloro.

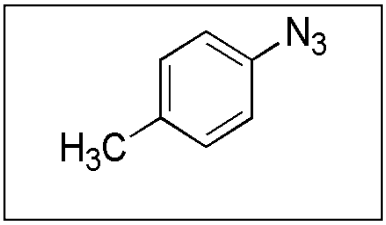
p-Substituted aniline (40.0 mmole) was dissolved in a solution of HCl (16.0 ml was dissolved in distilled water 80.0 ml). The resulting solution was cooled in an ice bath (0-5°C) before being treated slowly with a solution of sodium nitrite(4.0 g, 60.0 mmole) over 15 minutes with a sufficient stirring at the same temperature. To the mixture reaction, sodium azide (3.9 g, 60.0 mmole) was added slowly over 15 minutes under continues stirring with maintaining the temperature below 5 °C, then stirred for further 30 minutes before being worked up. The solid product was collected directly by filtration under vacuum, while the oily compounds were extracted with diethyl ether (3×50 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum to obtain the target products.

Synthesis of 4-methoxy phenyl azide 48



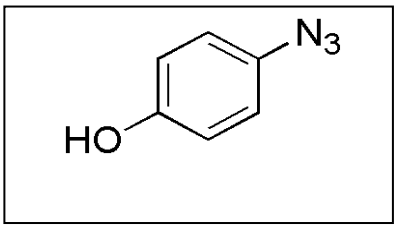
It was prepared according to general methods by using 4-methoxyphenylamine (5.0 g, 40.0 mmole). The molecular formula of compound **48** is **$C_7H_7N_3O$**: Yield (4.7 g, 80 %) as a green oil. **FT-IR** (KBr disc, cm^{-1}): 3120 (CH-aromatic), 2963 (CH-aliphatic), 2115 (-N_3 group) and 1593 (C=C) (Figure 1, p. 81).

Synthesis of 4-methyl phenyl azide 49



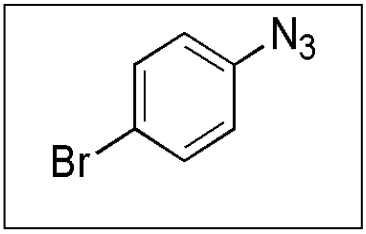
It was prepared according to general methods by using 4-methyl phenyl amine (4.28 g, 40.0 mmole). The molecular formula of compound **49** is **$C_7H_7N_3$**: Yield (2.9 gm, 60 %) as a brown oil. **FT-IR** (KBr disc, cm^{-1}): 3032 (CH- aromatic), 2928 (CH-aliphatic), 2120 (-N_3 group) and 1510 (C=C), (Figure 2, p. 81).

Synthesis of 4-hydroxy phenyl azide 50



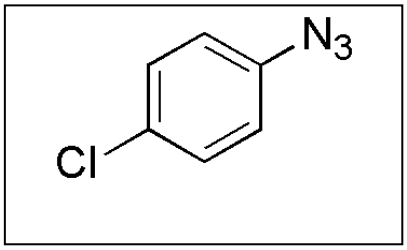
It was prepared according to general methods by using 4-hydroxy phenyl amine (4.4 g, 40.0 mmole). The molecular formula of compound **50** is **$C_6H_5N_3O$**: Yield (4.5 g, 77 %) as a black oil. **FT-IR** (KBr disc, cm^{-1}): 3396-3500 (OH, phenol), 3076 (Ar, H), 2995 (CH-aliphatic), 2115 (-N_3 group) and 1510 (Ar, C=C), (Figure 3, p. 82).

Synthesis of 4-bromo phenyl azide 51



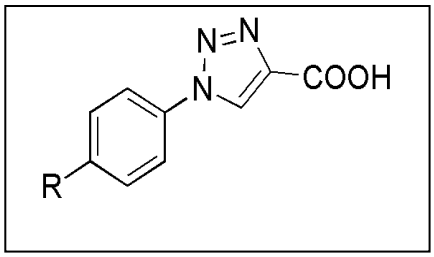
It was prepared according to general methods by using 4-bromo phenyl amine (6.8 g, 40.0 mmole). The molecular formula for compound **51** is **$C_6H_4N_3Br$**: Yield (7.15 g, 90 %) as a pale yellow precipitate at room temperature. **FT-IR** (KBr disc, cm^{-1}): 3220 (Ar, H), 2992 (CH-aliphatic), 2128 (-N_3 group) and 1500 (Ar, C=C), (Figure 4, p. 82).

Synthesis of 4-chloro phenyl azide 52



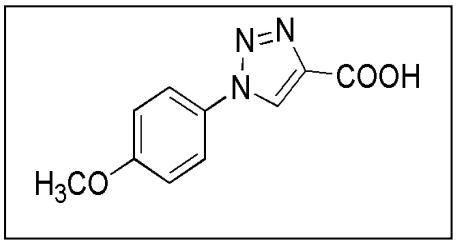
It was prepared by using 4-chloro phenyl amine (5.1 g, 40.0 mmole), sodium nitrite (4.1 g, 60.0 mmole), sodium azide (3.9 g, 60.0 mmole). The molecular formula for compound **52** is **$C_6H_4N_3Cl$**: Yield (5.8 g, 94 %) as a white precipitate at room temperature. **FT-IR** (KBr disc, cm^{-1}): 3242 (Ar, H), 2960 (CH-aliphatic), 2133 (-N_3 group) and 1500 (Ar, C=C), (Figure 5, p. 83).

2.2.2 General procedure to synthesise of 1,2,3-triazol derevatives (53-57)



A solution of sodium ascorbate (0.8 g, 4.0 mmole was dissolved in water 0.5 ml) was added to a stirred solution of $CuSO_4.5H_2O$ (0.65 g, 3.0 mmole was dissolved in water 0.5 ml). Followed by addition a mixture of *tert*-butanol:water (2:1). To the resulting solution were sequentially added propiolic acid (30.0 mmole, 2.1 ml) and an appropriate azide compound (30.0 mmole). The reaction mixture was then stirred at 60 °C for overnight. The reaction mixture was cooled to room temperature before addition of water (100 ml). The formed precipitate was filtered, washed with ether and dried to obtain the target compound.

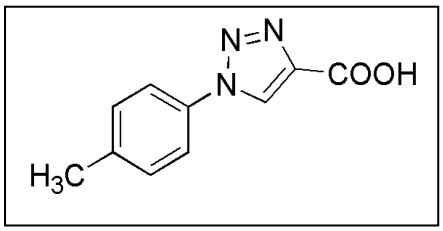
Synthesis of 1-(4-methoxyphenyl)-1H-[1,2,3]-triazolyl-4-carboxylic acid 53



It was prepared according to general procedure by using compound **48** (4.47 g, 30.0 mmole). The molecular formula of compound **53** is **$C_{10}H_9N_3O_3$**: Yield (5.0 g, 75 %) as a brown solid, m.p. (220-223°C). 3293-2500 (OH, COOH), 3151 (CH-aromatic), 2930 (CH-aliphatic), 1730 (C=O), 1610 (C=C, triazole), 1564 (Ar, C=C) and 1437 (N=N) (Figure 6, p. 83). **^{1}H-NMR** (500 MHz, DMSO-*d6*): δ= 3.8 (s, 3H, OCH_3), 7.1-7.8 (dd, 4H, Ar-H) and 9.1 (s, 1H, C=CH, triazole ring). (Figure 19, p.90). **HP-MS-**

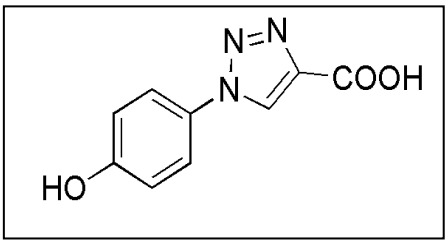
EI$^+$ (m/z): Calc. for $C_{10}H_9N_3O_3$ = 219.0, Found = 219.1. (Figure 36, p. 99).

Synthesis of 1-(4-methylphenyl)-1H-[1,2,3]-triazolyl-4-carboxylic acid 54



It was prepared according to general procedure by using compound **49** (3.9 g, 30.0 mmole). The molecular formula of compound **54** is **$C_{10}H_9N_3O_2$**: Yield (3.5 g, 50 %) as a pale brown solid, m.p. (200-204°C). **FT-IR** (KBr disc, cm^{-1}): 3332-2560 (-OH, COOH), 3134 (CH-aromatic), 2883 (CH-aliphatic), 1720 (C=O), 1640 (C=C, triazole), 1606 (Ar, C=C) and 1471 (N=N, triazole) (Figure 7, p. 84). **^{1}H-NMR** (500 MHz, DMSO-*d6*): δ= 2.3 (s, 3H, CH_3), 7.3-7.7 (dd, 4H, Ar-H) and 8.7 (s,1H, C=CH triazole). (Figure 20, p. 90). **HPMS-EI$^+$ (m/z):** Calc. for $C_{10}H_9N_3O_2$ = 203.2, Found = 203.0. (Figure 37, p. 100).

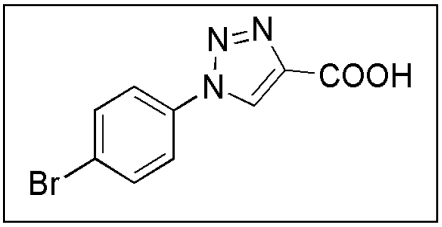
Synthesis of 1-(4-hydroxyphenyl)-1H-[1,2,3]-triazolyl-4-carboxylic acid 55



It was prepared by using of compound **50** (4.0 g, 30.0 mmole). The molecular formula of compound **55** is **$C_9H_7N_3O_3$**: Yield (6.3 g, 76 %) as a black precipitate, m.p. (213-216 °C). **FT-IR** (KBr disc, cm^{-1}): 3500-2800 (-OH, COOH), 3134 (CH-aromatic),

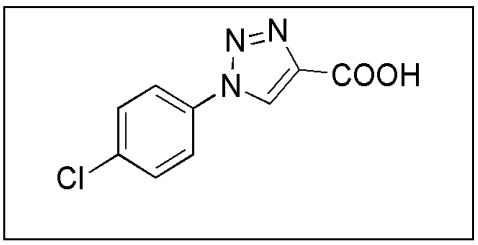
2970 (CH-aliphatic), 1727 (C=O), 1608 (C=C, triazole), 1573 (Ar, C=C) and 1470 (N=N) (Figure 8, p. 84). **^{1}H-NMR** (500 MHz, DMSO-*d6*): δ= 9.1(s, 1H, C=CH-triazole), 6.9-7.7 (dd, 4H, Ar). (Figure 21, p. 91). **HPMS-EI$^+$ (m/z):** Calc. for $C_9H_7N_3O_3$ = 205.0, Found = 205.1. (Figure 39, p. 101).

Synthesis of 1-(4-bromophenyl)-1H-[1,2,3]-triazolyl-4-carboxylic acid 56



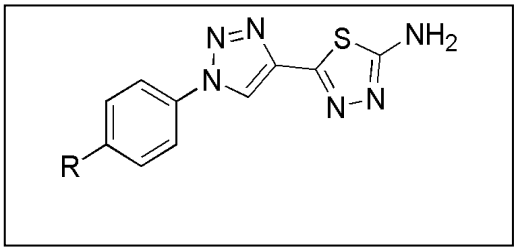
It was prepared according to general procedure by using compound **51** (5.9 g, 30.0 mmole). The molecular formula of compound **56** is **$C_9H_6N_3O_2Br$**: Yield (7.5 g, 93 %) as a brown precipitate, m.p. (225-227 °C). **FT-IR** (KBr disc, cm^{-1}): 3475-2400 (OH, COOH), 3028 (CH-aromatic), 2930 (CH-aliphatic), 1695 (C=O), 1614 (C=C, triazole), 1585 (Ar, C=C), 1402 (N=N) and 734 (C-Br) (Figure 9, p. 85). **^{1}H-NMR** (500 MHz, DMSO-*d6*):δ= 7.8-8.3 (dd, 4H, Ar-H), 8.7 (s, 1H, C=CH, triazole ring) (Figure 22, p. 91). **HPMS-EI$^+$ (m/z):** Calc. for $C_9H_6N_3O_2Br$ = 268.0, Found = 267.0. (Figure 38, p.100). .

Synthesis of 1-(4-chlorophenyl)-1H-[1,2,3]-triazolyl-4-carboxylic acid 57



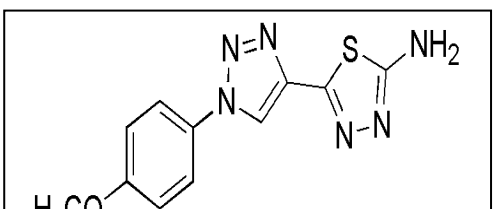
It was prepared according to general procedure by using compound **52** (4.6 g, 30.0 mmole). The molecular formula of compound **57** is **$C_9H_6N_3O_2Cl$**: Yield (6 g, 89 %) as a wight precipitation; m.p. (219-221 °C). **FT-IR** (KBr disc, cm^{-1}): 3468-2570 (-OH, COOH), 3100 (CH-aromatic), 2852 (CH-aliphatic), 1702 (C=O), 1552 (C=C, triazole), 1500 (Ar, C=C) and 1431 (N=N) (Figure 10, p. 85). **^{1}H-NMR** (500 MHz, DMSO-*d6*): δ= 7.7-8.1 (dd, 4H, Ar-H), 8.8 (s, 1H, C=CH, triazole ring). (Figure 23, p. 92). **HPMS-EI$^+$ (m/z):** Calc. for $C_9H_6N_3O_2Cl$= 223.02, Found= 223.0. (Figure 40, p. 102).

2.2.3 General procedure to Synthesis of 1,3,4-thiadiazol derevatives (58-62)



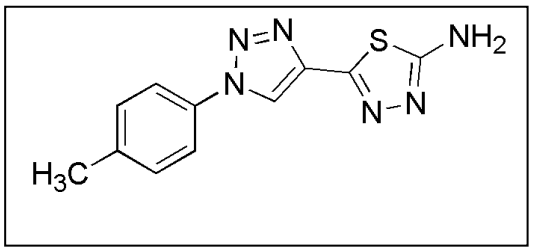
An appropriate compound of 1,2,3-triazole derivatives **(53-57)** (20.0 mmole) and thiosemicarbazide (1.8 g, 20.0 mmole) were dissolved in $POCl_3$ (20.0 ml). The resulting solution was refluxed for 7 hour. Then the mixture reaction was cooled to room temperature and poured onto a crush-ice with stirring. The resulting solution was then treated with sodium hydroxide solution 50 % under stirring. The precipitate was then collected by filtration under vacuum as detailed below.

Synthesis of 2-amino-5-[1-(4-methoxyphenyl)-1H-[1,2,3]-triazol-4-yl]-1,3,4-thiadiazole 58



It was prepared according to general procedure by using of compound **53** (4.3 g, 20.0 mmole). The molecular formula of compound **58** is **$C_{11}H_{10}N_6SO$**: Yield (5.0 g, 92 %) as a dark green precipitate; m.p. (255-258 °C). **FT-IR** (KBr disc, cm^{-1}): 3287-3130 (-NH_2), 2962 (CH-aromatic), 2864 (CH-aliphatic), 1665 (-C=N-), 1612 (C=C, triazole), 1518 (Ar, C=C) and 1440 (-N=N) (Figure 11, p. 86). **^{1}H-NMR** (500 MHz, DMSO-*d6*): δ= 3.8 (s, 3H, OCH_3), 8.1-8.4 (dd, 4H, Ar-H) and 9.2 (s, 1H, C=CH, triazole ring). (Figure 24, p. 92). **HPMSEI$^+$ (m/z):** Calc. for $C_{11}H_{10}N_6SO$ = 274.0, Found = 274.1. (Figure 41, p. 103).

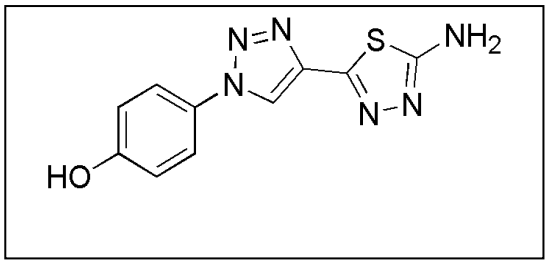
Synthesis of 2-amino-5-[1-(4-methylphenyl)-1H-[1,2,3]-triazolyl-4-yl]-1,3,4-thiadiazole 59



It was prepared according to general procedure by using the compound **54** (4.0 g, 20.0 mmole). The molecular formula of compound **59** is **$C_{11}H_{10}N_6S$**: Yield (3.5 g, yield 78 %) as a brown precipitate, m.p. (248-252 °C). **FT-IR** (KBr disc, cm^{-1}): 3414-3100 (-NH_2), 3144 (CH-aromatic), 2937 (CH-aliphatic), 1647 (-C=N), 1610 (C=C, triazole), 1504 (Ar, C=C) and 1440 (-N=N- triazole) (Figure 12, p. 86). **^{1}H-NMR** (500 MHz, DMSO, *d6)* δ= 2.4 (s, 3H, CH_3), 6.9-7.7 (dd, 4H, Ar-H) and 9.7 (s, 1H, C=CH, triazole ring) (Figure 25, p. 93). **^{13}C-NMR** (125 MHz, DMSO-*d6*): δ= 190.9, 163.3,

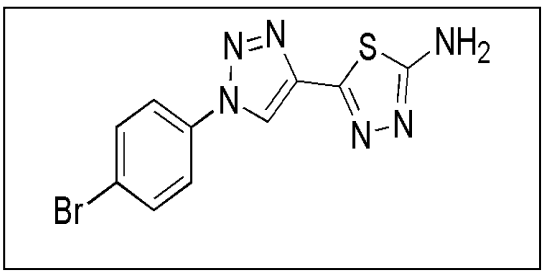
132.1, 130.7, 128.4, 115.8 and 115.6. (Figure 31, p. 96). **HPMS-EI$^+$ (m/z):** Calc. for $C_{11}H_{10}N_6S$ = 258.0, Found = 258.0 (Figure 42, p. 104).

Synthesis of 2-amino-5-[1-(4-hydroxyphenyl)-1H-[1,2,3]-triazolyl-4-yl]-1,3,4-thiadiazole 60



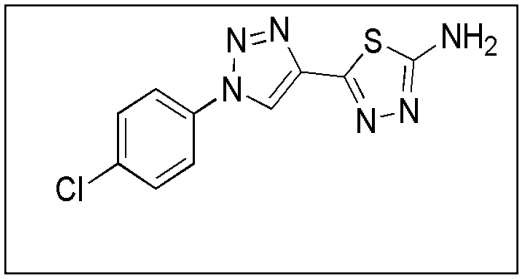
It was prepared by using the compound **55** (4.1 g, 20.0 mmole). The molecular formula of the compound **60** is **$C_{10}H_8N_6SO$**: Yield (4.6 g, 88 %) as a black precipitate, m.p. (220-224 °C). **FT-IR** (KBr disc, cm^{-1}): 3445-3150 (-NH_2), 3306 (-OH), 3010 (CH-aromatic), 2744 (CH-aliphatic), 1643 (-N=C-), 1606 (C=C, triazole) and 1512 (Ar, C=C), (Figure 13, p. 87). **^{13}C-NMR** (125 MHz, DMSO-*d6*): δ= 168.7, 153.3, 152.1, 147.1, 132.2, 122.3, 120.1 and 116.2 (Figure 32, p. 96). **HPMS-EI$^+$ (m/z):** Calc. for $C_{10}H_8N_6SO$ = 260.0, Found = 260.0 (Figure 43, p. 104).

Synthesis of 2-amino-5-[1-(4-bromophenyl)-1H-[1,2,3]-triazole-4-yl]-1,3,4-thiadiazole 61



It was prepared by using of the compound **56** (5.3 g, 20.0 mmole). The molecular formula of the compound **61** is **$C_{10}H_7N_6SBr$:** Yield (5.5 g, 85 %) as a gray precipitate; m.p. (270-274 °C). **FT-IR** (KBr disc, cm^{-1}): 3400-3320 (NH_2), 3009 (CH-aromatic), 2901 (CH-aliphatic), 1653 (-N=C-), 1620 (C=C, triazole), 1552 (Ar, C=C) and 1420 (-N=N-) (Figure 14, p. 87). **^{1}H-NMR** (500 MHz, DMSO-*d6*): δ= 7.5-8.0 (dd, 4H, Ar-H), 9.3(s, 1H, C=CH, triazole ring), 4 (s, 2H, NH_2). (Figure 26, p. 93). **^{13}C-NMR** (125 MHz, DMSO-*d6*): δ= 168.5, 157.5, 147.4, 140.8, 135.4, 132.8, 122.5 and 120.3 (Figure 33, p. 97). **HPMS-EI$^+$ (m/z):** Calc. for $C_{10}H_7N_6SBr$ = 323.9, Found = 324.0 (Figure 44, p. 105).

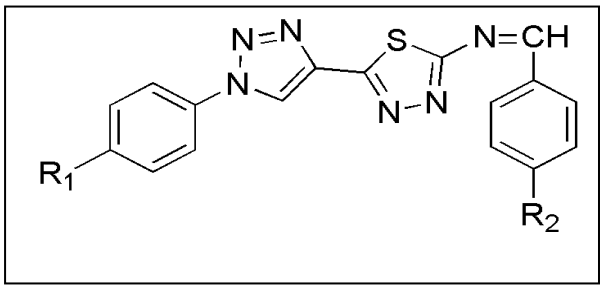
Synthesis of 2-amino-5-[1-(4-chlorophenyl)-1H-[1,2,3]-triazole-4-yl]-1,3,4-thiadiazole 62



It was prepared by using of the compound **57** (5.3 g, 20 mmole). The molecular formula of compound **62** is **$C_{10}H_7N_6ClS$**: Yield (5 g, 85%) as a dark green precipitate; m.p. (219-223 °C). **FT-IR** (KBr disc, cm^{-1}): 3466-3120 (NH_2), 2936 (CH-aliphatic), 1676 (-N=C-), 1590 (C=C, triazole), 1502 (Ar, C=C) and 1417 (-N=N-) (Figure 15, p. 88). **^{1}H-NMR** (500 MHz, DMSO-*d6*): δ= 7.4-8.1 (dd, 4H, Ar-H) and 9.3 (s, 1H, C=CH, triazole), 3.3 (s, 2H, NH_2) (Figure 27, p. 94). **^{13}C-NMR** (125

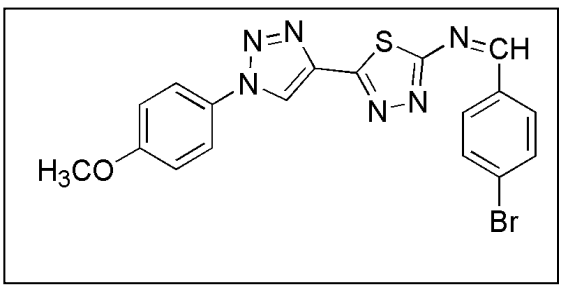
MHz, DMSO-*d6*): δ= 161, 140.7, 135.4, 133.4, 129.8, 125.9, 122.3 and 120.3 (Figure 34, p. 97). **HPMS-EI$^+$ (m/z):** Calc. for $C_{10}H_7N_6ClS$ = 278.7, Found = 278.0 (Figure 45, p. 106).

2.2.4 General procedure for the synthesis of Schiff base derevatives (63-65)



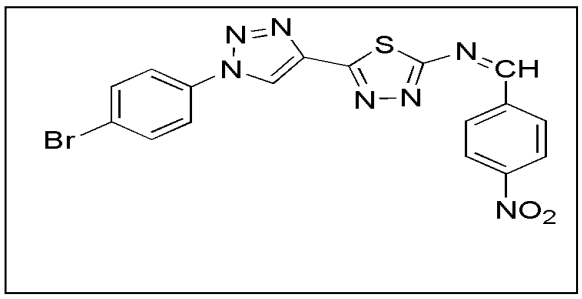
To a solution of compounds **58, 61, 62** (1.0 mmole dissolved in DMF 10 ml) was added to an appropriate 4-subustituted benzaldehyde (1.0 mmole) with a few drops of glacial acetic acid, and the reaction mixture was refluxed for overnight. The solid product was collected directly by filtration under vacuum, washed with ethanol, diethylether, and dried to obtain the target compounds.

Synthesis of 2-(4-bromobenzylidene)-5-[1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl]-1,3,4-thiadiazole 63



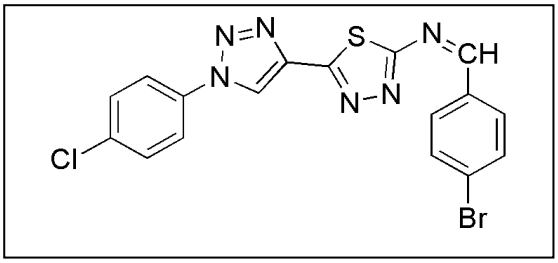
It was prepared by using compound **58** (0.5 g, 1.9 mmole), 4-bromobenzaldehyde (0.36 g, 2.0 mmole). The molecular formula of compound **63** is **$C_{18}H_{13}BrN_6OS$**: Yield (0.7 g, 51 %) as a brown solids; m.p. (267-270 °C). **FT-IR** (KBr disc, cm^{-1}): 3078 (CH-aromatic), 2824 (CH-aliphatic), 1616 (N=CH), 1591 (N=N), 1560 (Ar, C=C), 1396 (C-O) and 819 (C-Br) (Figure 16, p. 88). **^{1}H-NMR** (500 MHz, DMSO-d_6) δ = 9.5 (s, 1H, C=N), 9.2 (s, 1H, C=CH triazole), 7.1-7.9 (dd, 4H, Ar-H) and 3.8 (s, 1H, CH_3O) (Figure 28, p. 94). **^{13}C-NMR** (125 MHz, DMSO-d_6) δ=159.5, 140.4, 129.6, 122.2, 122.0, 120.1, 114.8 and 55.6 (Figure 35, p. 98). **(HPMS-EI$^+$ (m/z):** Calc. for $C_{18}H_{13}N_6OSBr$ = 441.3, Found = 442.0 (Figure 46, P. 107).

Synthesis of 2-(4- nitro benzylidene)-5-[1-(4-bromophenyl)-1H-1,2,3 -triazol-4-yl]- 1,3,4-thiadiazole 64



It was prepared by using compound **61** (0.5 g, 1.6 mmole), 4-nitro-benzaldehyde (0.25 g, 1.7 mmole). The molecular formula of compound **64** is **$C_{17}H_{10}BrN_7O_2S$**: Yield (0.6 g, 59 %) as a dark red solids; m.p. (240-243°C). **FT-IR** (KBr disc, cm^{-1}): 3078 (CH-aromatic), 2875 (CH-aliphatic), 1616 (N=CH), 1583 (C=C), 1406 (N=N) and 748 (C-Br) (Figure 17, p. 89). **^{1}H-NMR** (500 MHz, DMSO-d_6) δ = 10.1 (s, 1H, CH=N), 8.8 (s, 1H, C=CH-triazole) and 7.5-8.4 (dd, 4H, Ar-H) (Figure 29, p. 95). **HPMS-EI$^+$(m/z):** Calc. for $C_{17}H_{10}N_7O_2SBr$ = 456.2, Found = 456.0 (Figure 47, p. 108).

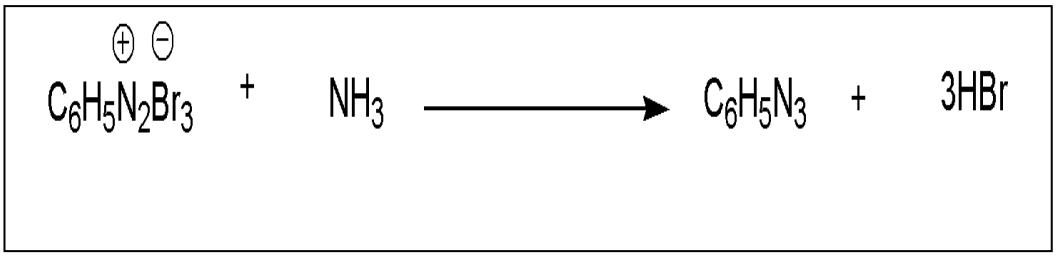
Synthesis of 2-(4-bromobenzylidene)-5-[1-(4-chlorophenyl)-1H-1,2,3 - triazol-4-yl]- 1,3,4-thiadiazole 65



It was prepared by using compound **62** (0.5 g, 1.8 mmole), 4-bromo-benzaldehyde (0.35 g, 1.9 mmole). The molecular formula of compound **65** is **$C_{17}H_{10}BrClN_6S$**: Yield (0.6 g, 60 %) as a pale yellow solids; m.p. (271-273 °C). **FT-IR** (KBr disc, cm^{-1}): 3111 (CH-aromatic), 2900 (CH-aliphatic), 1614 (N=CH), 1585 (C=C), 825 (C-Br) and 513 (C-Cl), (Figure 18, p. 89). **^{1}H-NMR** (500 MHz, DMSO-d_6) δ = 9.9 (s, 1H, N=CH), 9.4 (s, 1H, C=CH-triazole) and 7.6-7.9 (dd, 4H, Ar-H) (Figure 30, p. 95). **HPMS-EI$^+$ (m/z):** Calc. for $C_{17}H_{10}N_6BrClS$ = 445.7, Found = 446.0 (Figure 48, p. 109).

3.1 Synthesis of para-substituted phenyl azide compounds

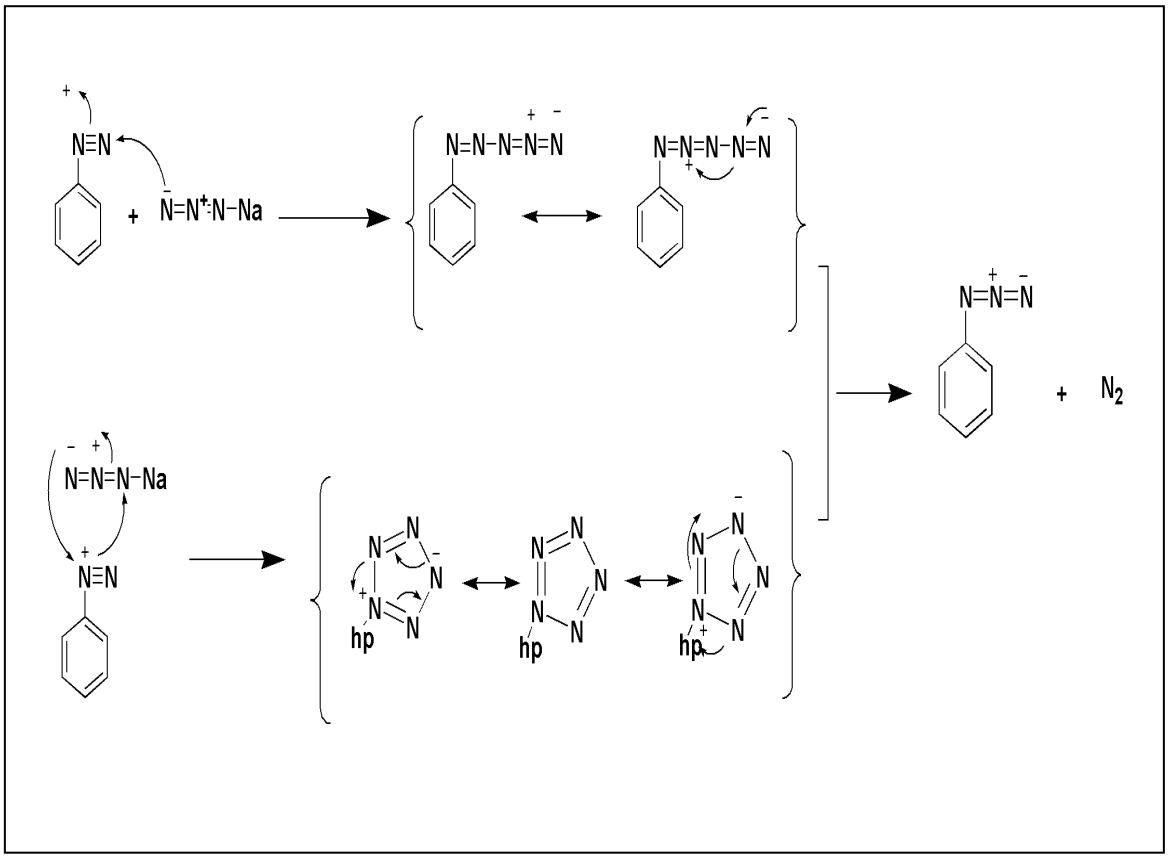
In general, the chemistry of organic azides began with the synthesis of azido benzene by Peter Griess in 1864 [117] via a reaction of benzene diazonium per bromide with ammonia as described in Scheme 3.1.



Scheme 3.1: synthesis of azido benzene by reaction ammonia with diazonium bromide.

Overall, organic azides are identified as good and valuable intermediates for the synthesis of nitrogen having cyclic compounds such as triazoles [118]. Since their discovery, organic azides have received a renewed interest due to its diversity of potential organic transformations with different applications in chemistry, biology and materials science [119]. The chemical behavior of the azido group ($-N_3$) strongly depends on its electronic structure, which in a ground state, is characterized by three nitrogen atoms linearly linked by bonding and nonbonding electron pairs [120]. Synthetically, there are several synthetic routes are available for the synthesis of aryl azides, including the reaction of diazonium salts with hydrazine, or azide ions [121, 122]. However, the latter reaction has been the most commonly used. In principle, at least there are three possible mechanisms that can be used to explain this reaction. However, previous studies suggested that the most predicated mechanism is involved the neucleophilic attack of the azide anion on the diazonium ion with formation of aryl pentazenes and/or pentazoles, which subsequently lose nitrogen.

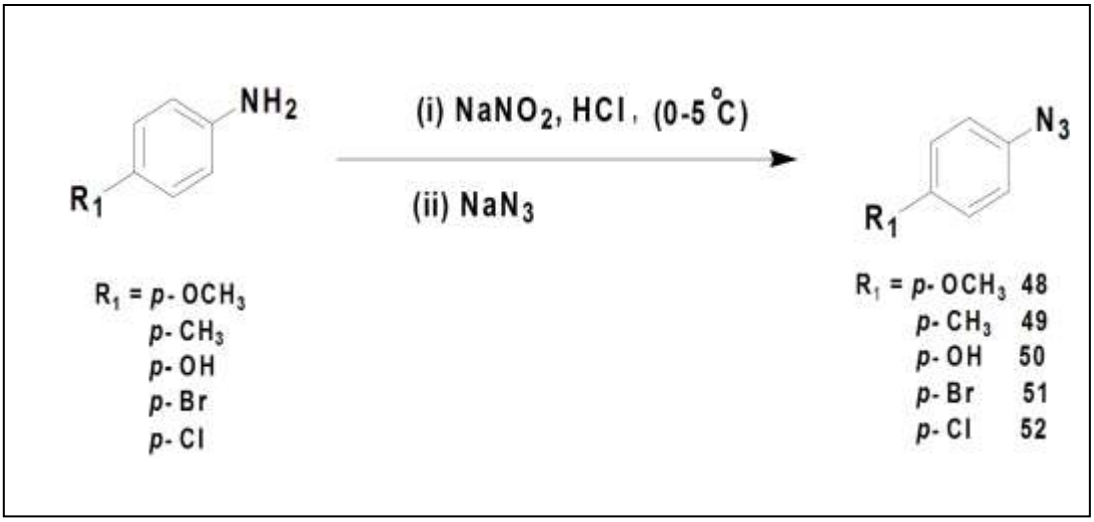
Whether the mechanism occurs through a concerted (3+2) mechanism or takes place stepwise. In general, two reaction pathways are competing to form phenyl azide from phenyl diazonium chloride and sodium azide (Scheme 3.2).



Scheme 3.2: General mechanism of reaction diazonium salt with azide anion.

The reaction attitude to the right proceeds according to 1,3-dipolar cycloaddition. This cycloaddition provides phenyl pentazole as an intermediate at low temperature. This intermediate decays above 0 °C through a 1,3-dipolar cycloreversion to produce the 1,3-dipole phenyl azide as the targeted product, and molecular nitrogen as a byproduct. The rest of the phenyl azide obtained in this reaction produced from an intermediate called 1-phenylpentazene, which is afforded in competition with phenyl pentazole. followed by elimination of nitrogen molecule from the central N atom of pentazenes by unavoidably ensuing reaction, which leads to the same product (phenyl azide) as the phenyl pentazole path. These two possible mechanisms were confirmed

by the experimentally isotopic labeling reviewed in the literature [121,123]. In the current research, a series of electron-rich and poor *p*-substituted phenyl azides were synthesized as azide components for the copper (I) catalysed azide-alkyne cycloaddition reaction (CuAAC). The synthetic route that has been established to synthesise the target azides **48-52** is based on the reaction of diazonium salts with sodium azide according to procedure that was described in the literature [124]. The first step of this synthetic route is involved diazonium salts formation according to the standard procedure that was described in the literature [125]. Typically, this procedure involves a conversion of the starting material *p*-substituted aniline compounds into their corresponding diazonium salts as outlined in Scheme 3.3.

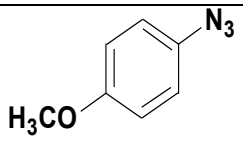
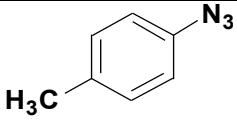
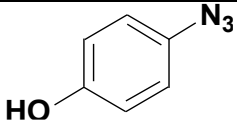
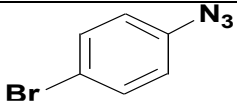
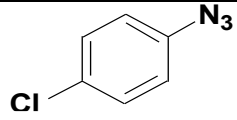


Scheme 3.3: Synthesis of phenyl azide **(48-52)**.

In this synthetic route, the commercially available *p*-substituted aniline was first protonated with a solution of hydrochloric acid before being treated with an excess of sodium nitrate at (0-5℃). The azido group was then introduce to the formed diazonium salts via the azido transfer reaction through the addition of sodium azide as a solid with maintaining the temperature below 5℃. By a simple, highly yield and cheap synthetic route the target *p*-substituted phenyl azide **48-52** were obtained as

pure oily compounds at room temperature. All the synthesised were characterized by FT-IR spectroscopy. The FT-IR spectra showed the appearance of a strong absorption band at range (2115-2133 cm^{-1}) (fig 1-5, p.p.) which is returned to the ($-N_3$) group. In addition to the disappearance the band of amino group of aromatic amines ($-NH_2$) that can be seen at range (3400-3500 cm^{-1}) of aromatic amines as shown in Table (3.1).

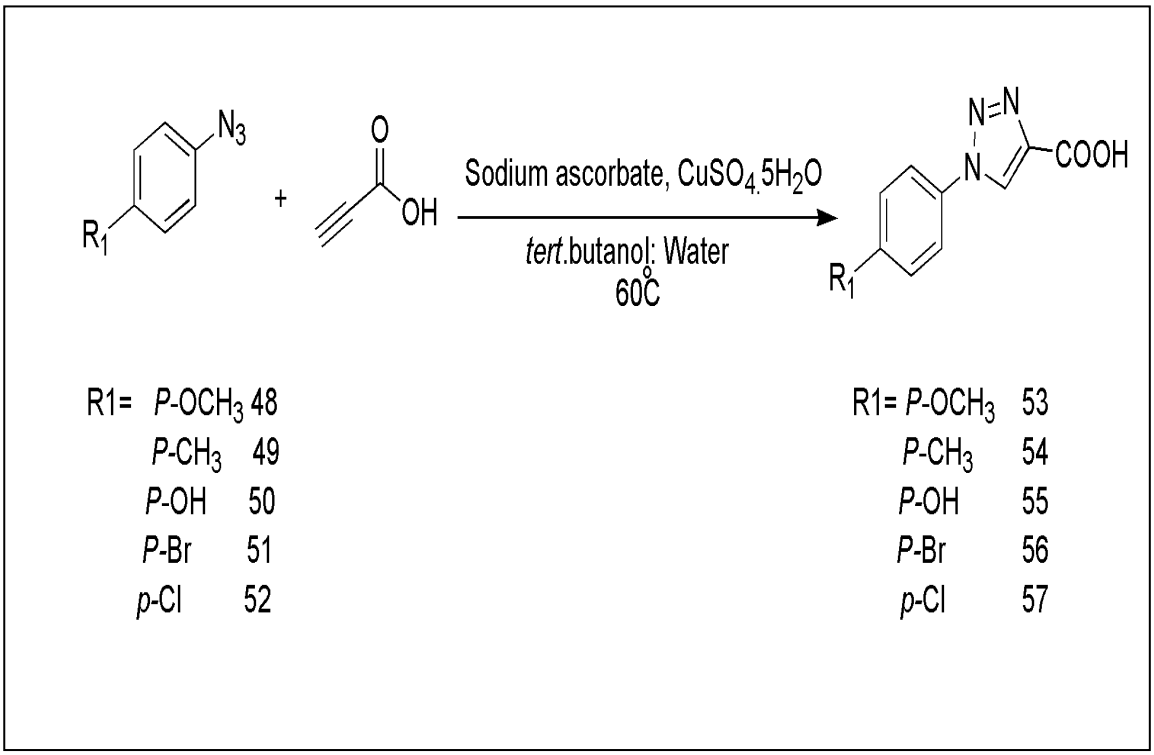
Table 3.1: Physical and spectral data for aromatic phenyl azide (**48-52**).

Comp. NO.	Structure	FT-IR value (υ, cm^{-1})
48		3030 (CH, Ar), 2963 (CH_3), 2115 ($-N_3$), 1590 (Ar, C=C).
49		3032 (CH, Ar), 2962 (CH_3), 2120 ($-N_3$),1506 (Ar, C=C).
50		3396 (OH, phenol), 3076 (CH, Ar), 2112 ($-N_3$), 1510 (Ar, C=C).
51		2990 (CH, Ar), 2128 (N_3), 1500 (Ar, C=C), 692 (C-Br).
52		3242 (CH, Ar), 2133 ($-N_3$), 1559 (Ar, C=C).

As the phenyl azides generally are not stable at room temperature and should be stored below 0℃, therefore, the synthesised azide **48-52** were used in the next step without further purification and spectroscopic characterization.

3.2 Synthesis of 1,2,3-Triazole Derivatives 53-57

The first aim of the current study is the synthesis of a new series of 1,2,3-triazole derivatives **53-57** for potential biological applications. Also**,** these compounds can be used as starting materials to synthesise new a series of heterocyclic compounds containing 1,2,3-triazole combination with another heterocyclic structure in one molecule. Thus, After completing the synthesis of the intermediate azide compounds **48-52**, efforts are turned on verifying their reactivity as azide components in the CuAAC reaction. In the current project, the commercially available propiolic acid was selected to be the alkyne component of this reaction. Furthermore, choosing of the propiolic acid as an alkyne component takes advantage that this compound will introduce a carboxyl group attached directly to the 1,2,3-triazole ring. This carboxyl group can be exploited in combination of 1,2,3-triazole with different species. Our initial attempt to synthesise the target 1,2,3-triazole derivatives **53-57** involved the addition of azide compounds **48-52** and propiolic acid to a solution of (*tert*-butanol: water, 1:1 v/v) containing $CuSO_4 \cdot 5H_2O$ in the presence of sodium ascorbate. The latter is a reducing agent to produce Cu (I) that is required to achieve CuAAC reaction as outlined in Scheme 3.4. The resulting reaction mixture was left stirring at room temperature for overnight.



Scheme 3.4 : Synthesis of compounds **(53-57)** by click chemistry (CuAAC).

At the beginning, the expected challenge for this reaction was that this reaction may be not proceed successfully because the alkyne group of propiolic acid is attached to a strong withdrawing group of electrons (COOH) which may reduce the reactivity of the alkyne function group toward making a complex with the copper (I) that is required for the click reaction to progress successfully. In addition, the azido function is attached to aromatic system which can be described as a withdrawing electrons system and also containing a strong drawing group such as ($-NO_2$) thereby reducing the reactivity of the azido group to attack the formed copper complex. However, the starting materials azide compounds **48-52** displayed a limited solubility in the standard click solvent reaction mixture (*tert*-butanol:water, 1:1 v/v) at room

temperature and the titled compounds **53-57** were obtained in a very low yield. When the ratio of *tert*-butanol: H_2O was changed to 2:1 v/v, it was enough to dissolve the azide compounds **48-52**. The new solvent system was used with the same reaction constituent as before and left to stir at room temperature. In this attempt, the target compounds **53-57** were formed in a yield ranged (20-35 %). Since the yield was not optimal, we investigated whether the yield can be improved. Thus, the reaction mixture was heated up to 60 °C and left to stir for overnight, and this was enough to afford the desired products **53-57** in relatively high yield ranged (55-80 %). Our synthetic pathway highlighted that the target compounds **53-57** are separated as a precipitate from the reaction mixture and collected by filtration without a further hard work up and was pure enough to not require column chromatography. The structure of the synthesized compounds (**53-57)** was confirmed by FT-IR, ^{1}H-NMR and GC-MS spectroscopies as described in chapter two and appendix. The FT-IR spectra of all synthesized compounds **(53-57)** were showed disappearance of absorption band of the azido group that is ranged at 2104-2133 cm^{-1} and by the same time new significant two bands were appeared at 1691-1725 cm^{-1} and 2500-3400 cm^{-1} which were attributed to the carbonyl and hydroxyl group, respectively. While the ^{1}H-NMR spectra that were recorded for compounds **53-57** showed appearance of singlet signal ranged at 8.7-9.3 ppm which is belonging to triozolyl proton C (5). Furthermore, the GC-MS spectra of all the synthesized compounds **53-57** gave the expected M^+ peaks corresponding to their molecular mass, such as GC-Mass spectrum of compound **53** shown in Figure 3.1

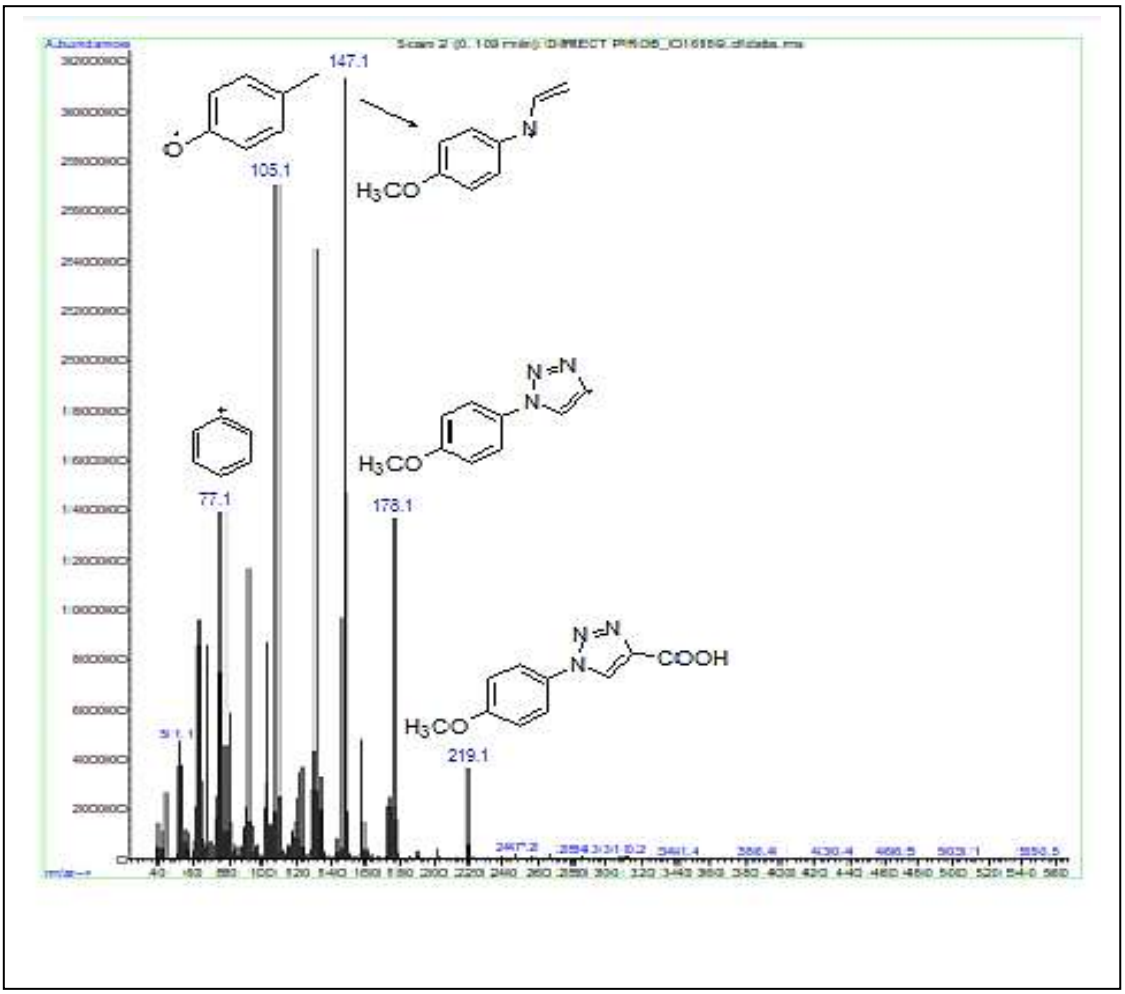
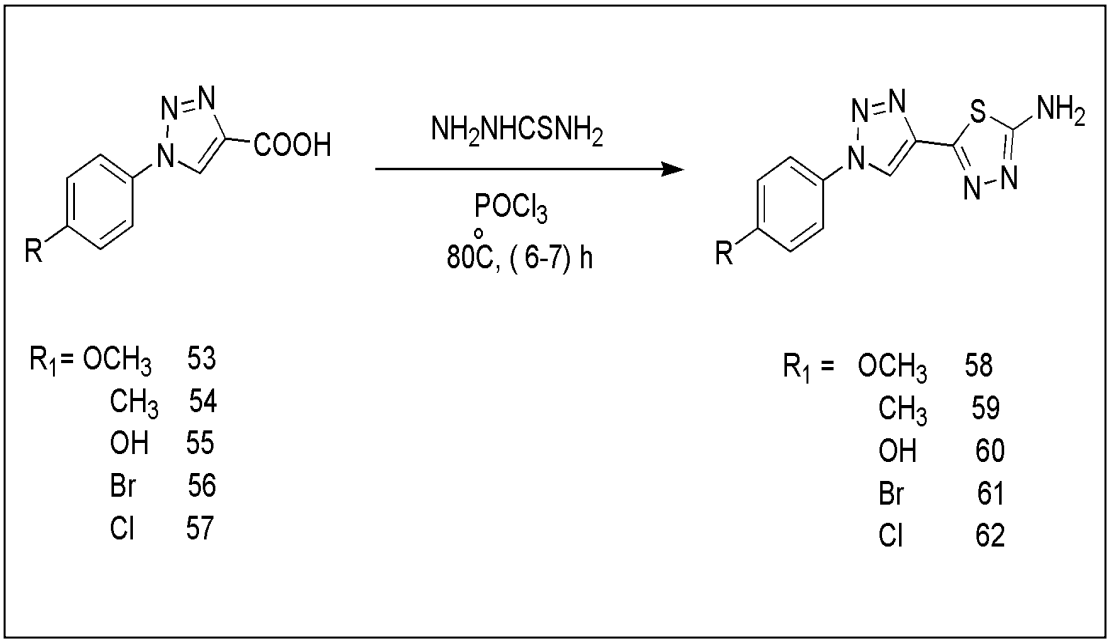


Figure 3.1 : GC-Mass fragments of compound **53**.

3.3 Synthesis of 1,3,4-Thiadiazole Derevatives 58-62

In general, many procedures have been reported for the synthesis of 1,3,4-thiadiazole derevatives [126],[127], after having the synthesis of 1,2,3-triazole derevatives, we turned our attention to exploited their carboxyl functional group to extend the 1,2,3-triazole ring system for the synthesis of new heterocyclic compounds. In the recent

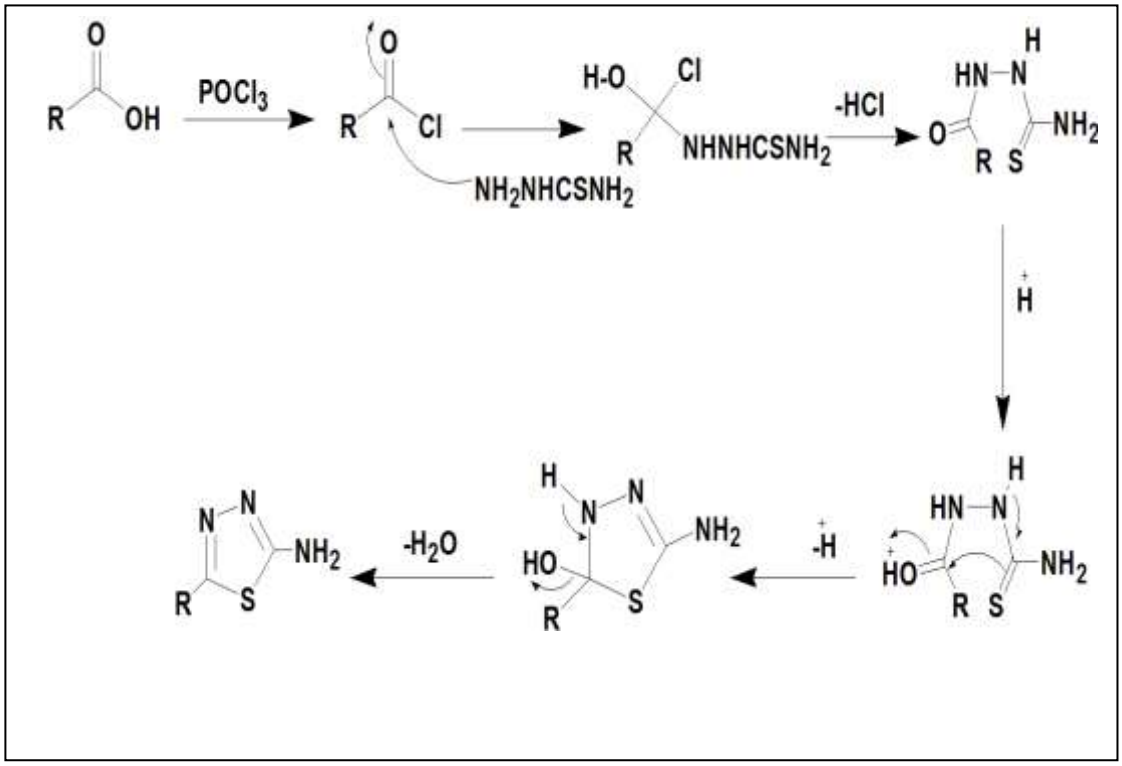
project, it is interested in the combination of 1,2,3-triazole ring system with 2-amino-1,3,4-thiadiazole moiety.



Scheme 3.5 : Synthesis of compounds **(58-62)**.

Thus, a new series of 5-amino-2-substituted-1,3,4-thiadiazole derivatives **(58-62)** was synthesised by a condensation reaction of the synthesised 1,2,3-triazole derevatives **(53-57)** and thiosemicarbazide in the presence of $POCl_3$, as outlined in Scheme: 3.5. In general, this reaction involves two steps; initially, the carboxyl group of the synthesised 1,2,3-triazole derevatives to react with $POCl_3$ to product an acyl chloride that is reacted concurrently with thiosemicarbazide to produce *in situ* the intermediate acyl thiosemicarbazide. Secondly, the intermediate acyl thiosemicarbazide will goes toward dehydro-cyclization reaction, also in the presence of $POCl_3$ as a dehydrating agent to give the corresponding 1,3,4-thiadiazole derevatives **(58-62)** as outlined in (Scheme 3.6). Due to the low water solubility of the 1,2,3-triazole starting material

53-57 the target compounds **58-62** could be polluted with the unreacted starting material. So, to avoid this problem, the crude reaction mixture was treated with an aqueous solution of NaOH (50%) to convert the remaining starting material **53-57** to soluble species.



Scheme 3.6: General mechanism of cyclization reaction.

The target compounds **58-62** were collected by filtration under vacuum. The current synthetic route highlighted that the obtained compounds **58-62** were obtained in good yields and pure enough. Does not need to further purification by chromatography. The structure of compounds **58-62** were characterized by FT-IR, NMR and Mass spectroscopies as described in chapter two as described in chapter two and appendix, where the FT-IR spectra of all synthesized compounds **(58-62)** were showed disappearance of absorption band of the carbonyl and hydroxyl group that is ranged at

1691-1725 cm^{-1}, 2400-3500 cm^{-1} respectively and by the same time new significant two bands were appeared at 3414 cm^{-1} and 3300 cm^{-1} which were attributed to the primary amino group. The ^{1}H-NMR spectra that were recorded for compounds **58-62** showed appearance of singlet signal ranged at 8.7-9.3 ppm which is belonging to triozolyl proton C(5), While, ^{13}CNMR spectra that were recorded for compounds **58-62** showed appearance of band at ranged 150-160 ppm attributed to carbon in thiadiazole ring. Furthermore, the GC-MS spectra of all the synthesized compounds **58-62** gave the expected M^{+} peaks corresponding to their molecular mass such as fragments of compound **58** shown in Figure 3.2.

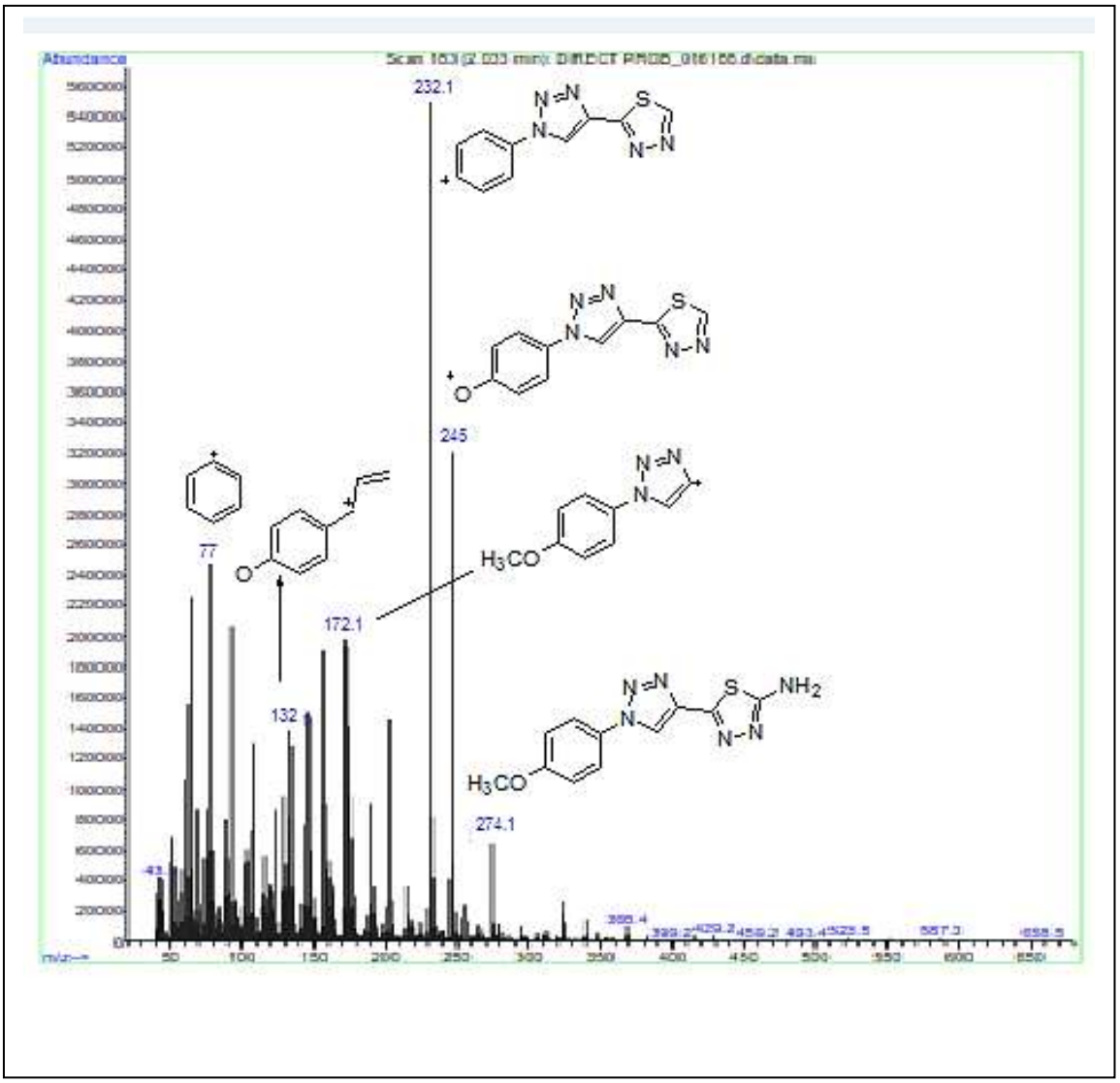
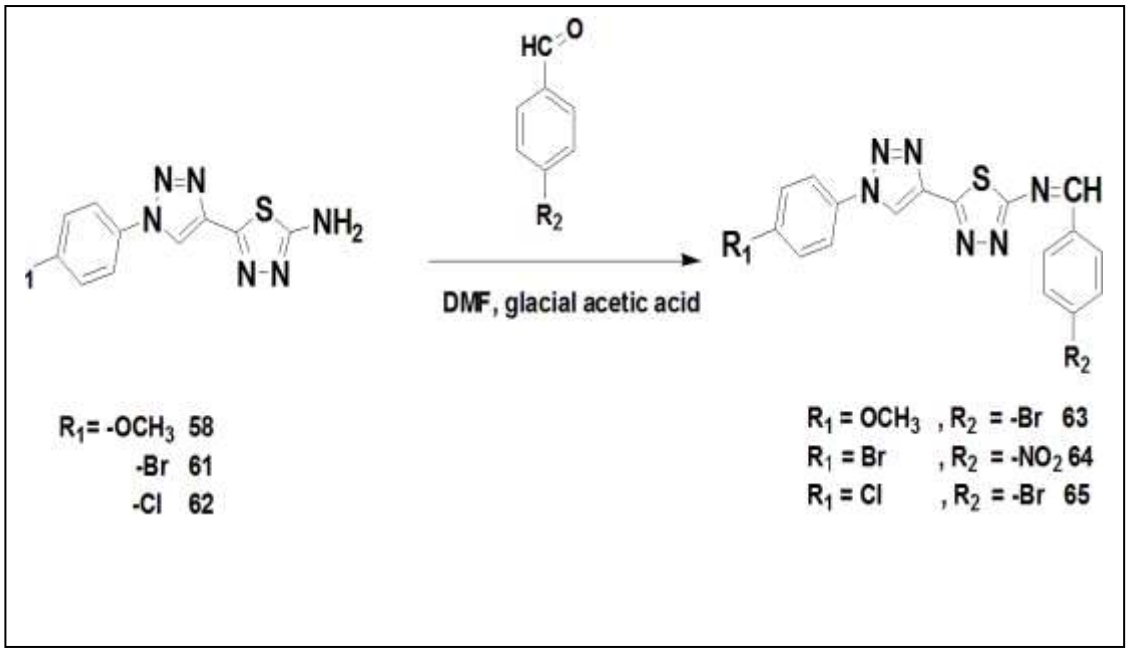


Figure 3.2: GC-Mass fragments of compound **58**.

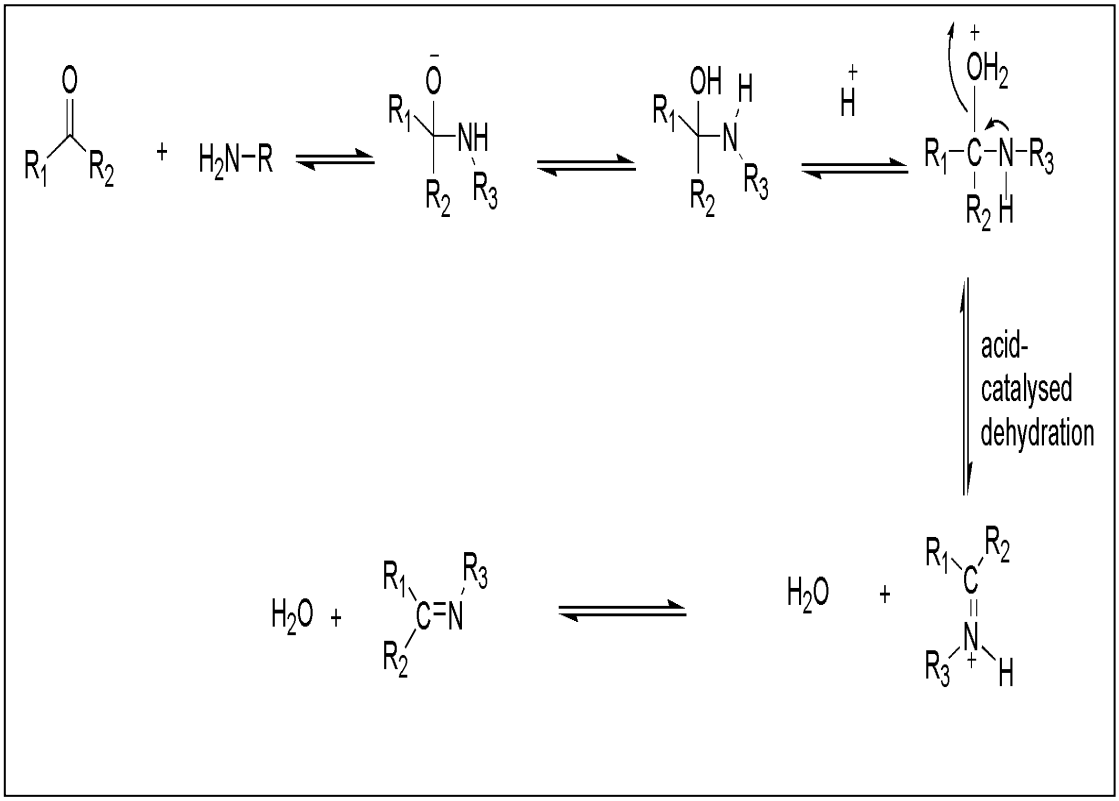
3.4 Synthesis of Schiff Bases 63-65

Since the synthesised heterocyclic compounds **58-62** contain an amino group attached directly in the 1,3,4-thiadiazole ring at position C2. Thus, we interested in verifying its reactivity toward neucleophilic addition in a condensation reaction with aromatic aldehydes. To obtain new heterocyclic compounds containing 1,2,3-triazole, 1,3,4-thiadiazole and imine moieties in one molecule. To achieve this aim, compounds **58**, **61** and **62** were selected as models to react with two aromatic aldehydes such as *p*-bromo and *p*-nitro benzaldehyde in the presence of glacial acetic acid according to the standard procedure that has been used to prepare Schiff bases as described in the literature [128]. However, the synthesised compounds **58-62** have a low solubility in the common solvents that are used in the synthesis of Schiff base such as ethanol and methanol, thus, the first attempt was failed to give the target compounds. As Dimethylformamide (DMF) is high polar solvent, it was enough to dissolve the starting materials compounds **58-62**. Thus, the first attempt was successful to give the target compounds **63**, **64** and **65** as described in scheme 3.6.



Scheme 3.7: synthesis of compounds **(63-65)**.

The formation of Schiff base is generally driven to the completion by separation of the product or removal of water, or both. However, Schiff bases can be hydrolyzed back to their aldehydes or ketones and amines by aqueous acid or base [108]. The mechanism of the synthesis of imine group as outlined in Scheme 3.7 is included a neucleophilic addition of an amine to the carbonyl group of aldehyde or ketone [109]. In the first part of this mechanism, the amine reacts with the aldehyde or ketone to give an unstable addition compound called carbinolamine. This intermediate carbinolamine loses water by either acid or base catalyzed pathways. Since the carbinolamine is an alcohol, it undergoes acid catalyzed dehydration [110].



Scheme 3.8: Acid catalysed dehydration of the carbinolamine.

Naturally the dehydration of the carbinolamine is the rate-determining step of Schiff base formation and that is why the reaction is catalyzed by an acid. In addition, the acid concentration cannot be too high because amines are basic compounds. If the amine is protonated and converts non-neucleophilic, equilibrium is drawn to the left and carbinolamine formation cannot happen [111]. Therefore, many Schiff bases synthesis are finest carried out at slightly acidic pH. The dehydration of carbinolamine is also catalyzed by base. This reaction is somewhat analogous to the (E_2 elimination) of alkyl halides except that it is not a concerted reaction. It proceeds in two steps through an anionic intermediate [112]. Schiff bases can be synthesized from aromatic or aliphatic amines and a carbonyl compound by a neucleophilic addition forming a hemiaminal, followed by a dehydration to generate an imine. Schiff bases have a chelating structure and are in demand because they are easy to prepare and are moderate electron donors [113]. Schiff bases are a widely used and the most appreciated organic (building blocks) to have a different range of pharmacological importance, as well Schiff base interred in many other fields as biological, inorganic, and analytical chemistry [114]. Schiff bases are reported to explain awide range of pharmacological activities and used as anti-microbial, anti-oxidant, anti-viral, anti-malarial, anti-cancerous, and anti-inflammatory agents [101, 102]**.** The structure of the target products **63-65** was confirmed by FT-IR, NMR and Mass spectroscopies as described in chapter two. where the FT-IR spectra of all synthesized compounds **(63-65)** were showed disappearance of absorption band of the amino group that is ranged at 3400-3305 cm^{-1} and by the same time new significant band was appeared at 1620-1640 cm^{-1} which were attributed to the imine bond,. While the ^{1}H-NMR spectra that were recorded for compounds **63-65** showed appearance of singlet signal ranged at 9.4-9.9 ppm which is belonging to imine bond proton, while

the ^{13}C-NMR spectra that were recorded for compounds **63-65** showed appearance of band in 159 ppm that returned to carbon imine bond for compound **63**.

4.0 Introduction

Different substances decompose over different ranges of temperatures yielding different proportion of volatile and residues. Basically, thermal analysis allows to study of all chemicals processes that are associated with heating of samples such as decomposition, phase change, pyrolysis, calorimetry, etc. [129]. The thermal analysis has been become an accepted tool in the chemistry to study the thermal behavior of important products such as organic compounds, polymers, pharmaceuticals, minerals, clays, alloys, metals and various complex in inorganic chemistry [130]. In the organic synthesis field, thermal analysis is a very important tool to obtain information about the stability of target products, where, the stability is normally measured as a function of temperature [131]. Several thermal techniques have been recognized in which differ in temperature programs and the properties measured [132]. The most frequently used of these being differential thermal analysis (DTA), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA)and thermo mechanical analysis (TMA), dimensional changes versus temperature or time. In the current study, the thermo gravimetric analysis (TGA) and differential thermal analysis (DTG) were used to investigate the thermal stability of the synthesised compounds [133]. In more details, the TG–DTG technique is capable to detecting lossing of the

weight and heat flow of a given compound when it loses weight of the order of few micrograms which ultimately releases significant amount of heat, these two combined technique were used to estimate the thermal stability of the synthesized compounds.

4.1 Thermo Gravimetric Analysis (TGA)

Thermo gravimetric (TG) is a useful analytical technique used for recording weight loss of a test sample as a function of temperature, which may be used for understanding the chemical nature of the substance. Thus, the weight of a substance in an environment heated at a controlled rate is recorded as a function of time or temperature [134]. Although there are three types of thermogravimetry such as static or isothermal thermogravimetry, quasistatic thermogravimetry and dynamic thermogravimetry. The most studies of the chemical substance are carried out with dynamic thermogravimetry [135]. In this technique, "the sample starts losing weight at a very slow rate up to a particular temperature and then the rate of loss becomes large over a narrow range of temperature [131]. While, the corresponding 1st derivative of the TGA curve provides the decomposition rate and is helpful for evaluating the mass-loss steps accurately. TGA-DTG curves are characteristic for a given substance because of unique sequence of physico-chemical reactions, which occur over definite temperature ranges. The change in weight is a result of the rupture and/or formation of various physical and chemical bonds at elevated temperatures that lead to evaluation of volatile products in the formation of heavier reaction products [126]. The weight of the sample decreases slowly as reaction begins and then decreases rapidly over a comparatively narrow range of temperature and finally levels off as the reaction is completed. The shape of the curve depends on the kinetic parameters: order of reaction (n), frequency factor (A) and activation energy (Ea.).

The values of these parameters have been shown to be of major importance to elucidate the mechanism of degradation [136]. In general, several temperature characteristics were described for qualitative assessment of relative thermal stability of target compounds such as; Initial decomposition temperature (T_o), Temperature for 10% weight loss (T_{10}), Temperature for maximum rate of decomposition (T_{max}), Half volatilization temperature (T_s), Differential decomposition temperature and Integral procedural decomposition temperature (IPDT) with dynamic heating [127]. However, T_o and T_{10} are some of the main criteria of the thermal stability of a given substance [130]. The thermal stability studies have been carried out on all the synthesised compounds explored in earlier chapters. The measurement of the TG-DTG losing wight (%) as a function of the temperature is the standard approach to investigate the thermal properties of the synthesised compounds **(53-65)** as outlined in the next sections.

4.2 Thermal stability study of the synthesised 1,2,3-triazole derivatives (53-57)

Looking the importance of the subject to our work in the field of thermal analysis of newly synthesized heterocyclic compounds, we are interested in the study of the thermal behavior of the synthesised 1,2,3-triazole derivatives **53-57**. For these compounds, *p*-substituted phenyl group was introduced at position N1 of 1,2,3-triazole ring in order to investigate its effect on thermal stability of 1,2,3-triazole ring system. The thermal stability of the synthesised 1,2,3-tirazole derivatives **53-57** was evaluated by TG–DTG techniques. The TG-DTG measurements (Figure 4.1) that were recorded for compound **53** which is containing a methoxy group (-OCH_3) showed that this compound **53** is thermally stable up to 252.3 ^{o} C. Followed by a main

single decomposition stage ranged 252.3-402.8 ˚C and the maximum mass losses occurred at 350.7 ^{o}C with 42.9 %.

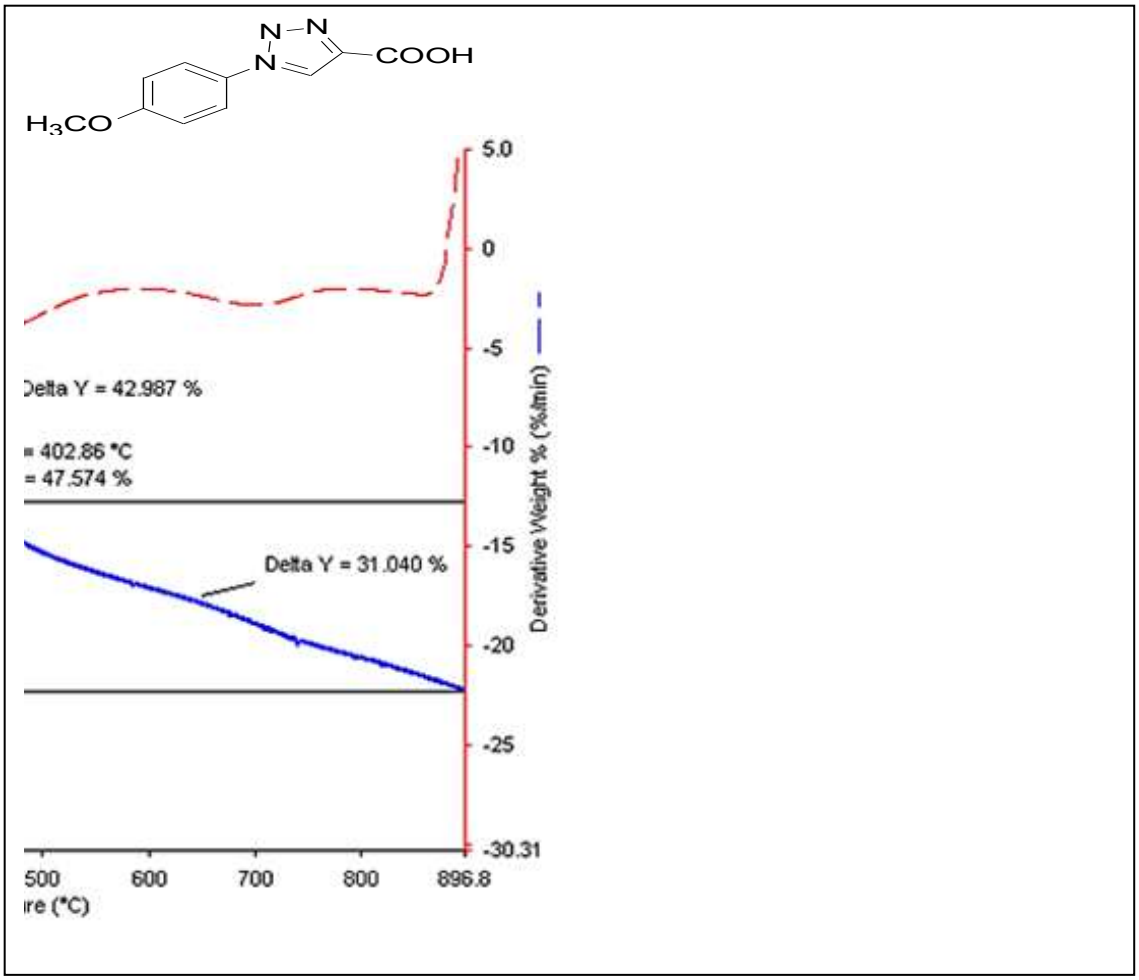


Figure (4.1): TG-DTA curves of compound **53**. X1,X2 is temperatures, Delta Y= Ratio of losing mass, Delta Y1, Y2 = Ratio of residual mass.

While compound **54** which is substituted with methyl group (-CH_3), the TG-DTG measurements (Figure 4.2) indicated that this compound displayed slightly less thermally stable is up to about 243.7 ºC. Decomposition of compound **54** takes place in a main single narrow decomposition stage ranged 243.7-272.3 ºC and the maximum mass losses occurred at 259.6 º C with 46.07% as shown in Figure 4.2.

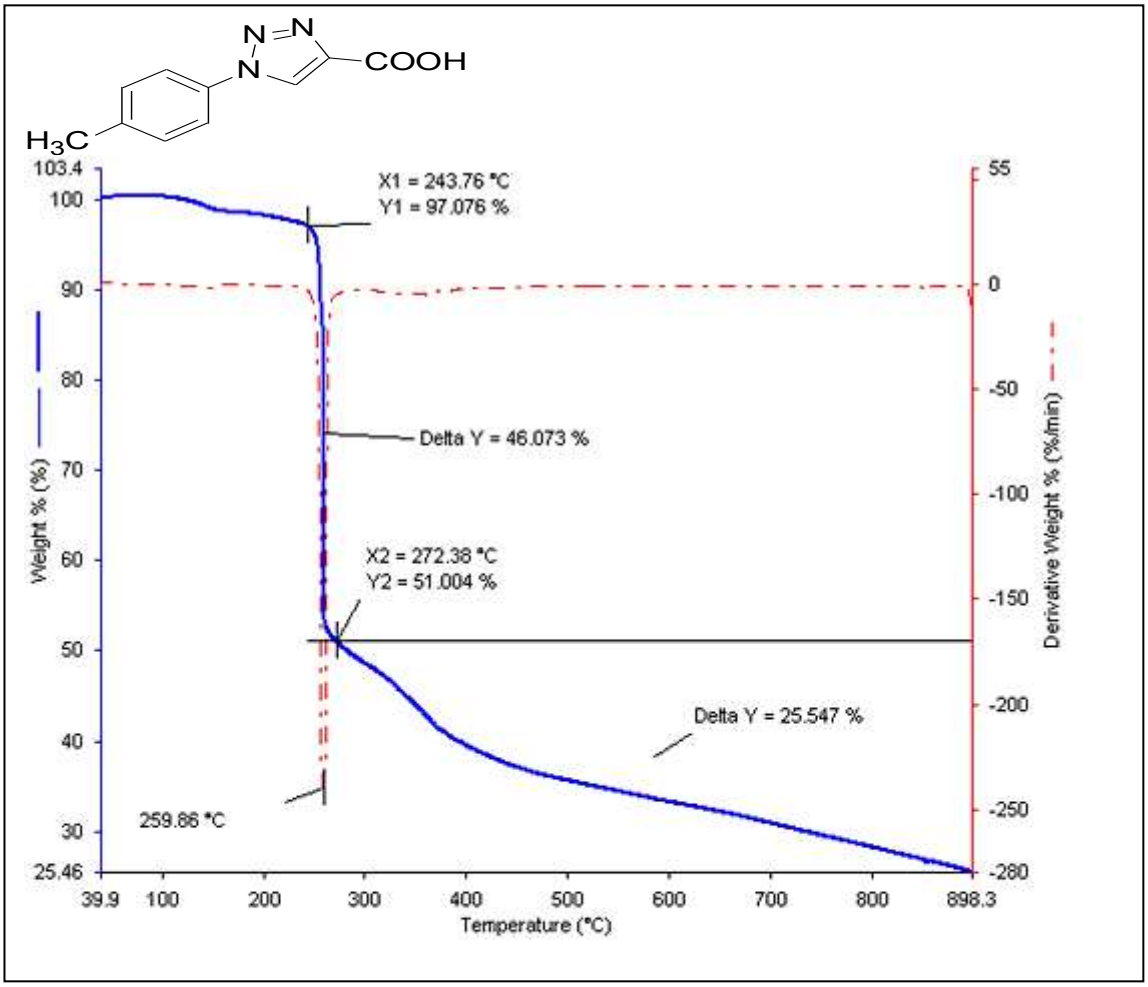


Figure (4.2):TG-DTA curves of compound **54**. X1,X2is temperatures, Delta Y= Ratio of losing mass, Delta Y1, Y2 = Ratio of residual mass.

By the shape of the TG-DTG curves that are shown in figure 4.3, it could be concluded that compound **55** which is substituted with hydroxyl group (-OH) is thermally stable up to 277.6 ºC. Compound **55** decomposed at one stage ranged 277.6-317.6 ºC and the maximum mass losses is about 42.4 % at 290.5 ºC as shown in Figure 4.3.

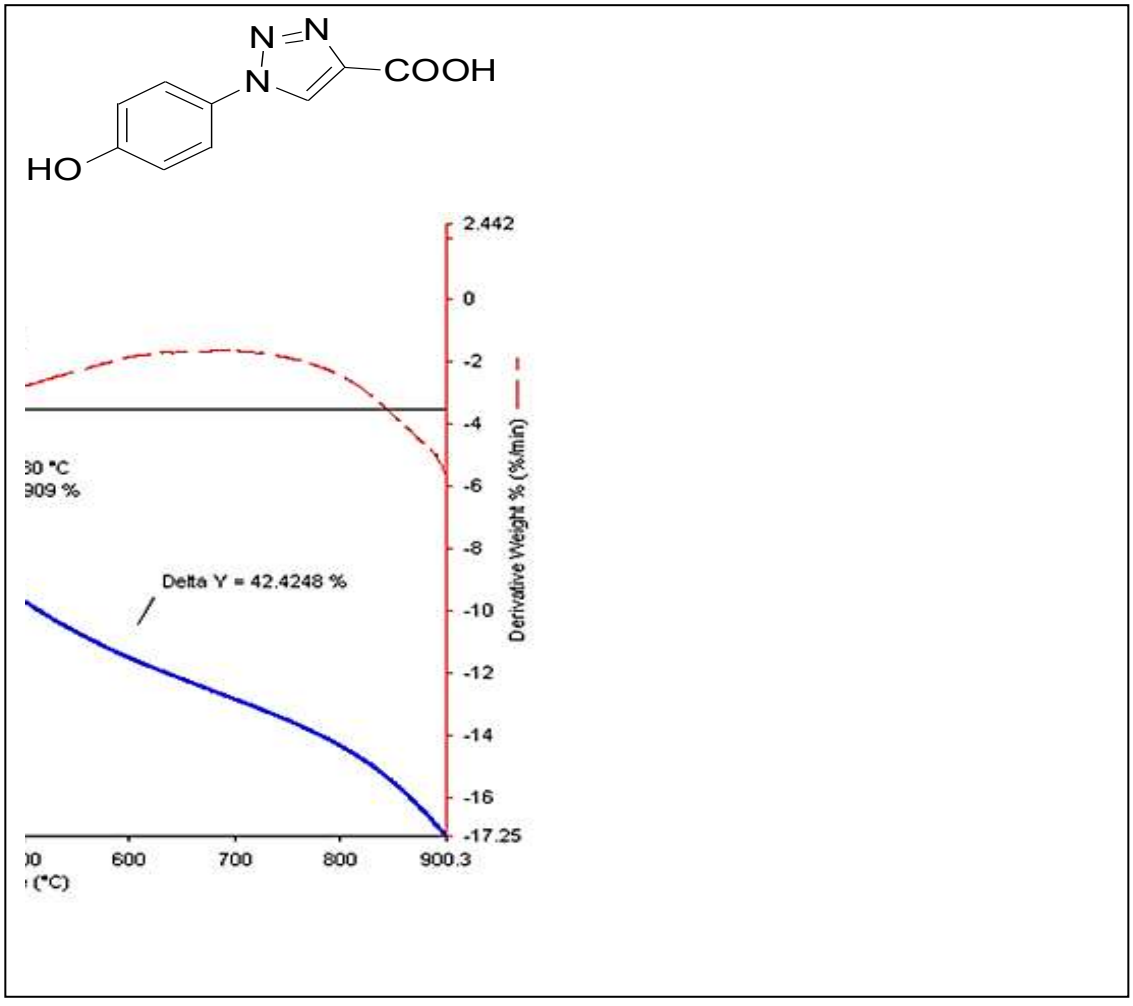


Figure (4.3): TG-DTA curve for compound **55**. X1,X2is temperatures, Delta Y =Ratio of losing mass, Delta Y1, Y2 = Ratio of residual mass.

For further investigation, the effect of halogen group such as bromo and chloro verified on the thermal stability such as in compounds **56** and **57**, respectively. TG-DTG measurements (Figure 4.4) that were recorded form compound **56** explained that this compound is the lowest thermal stability up to 208.1 ºC compared to the synthesised 1,2,3-triazole derivatives **53-57**. This compound also decomposed in a single decomposition stage ranged 208.1-278.0 ºC and its maximum mass losses is 29.4% at about 233.0 ºC as shown in Figure 4.4.

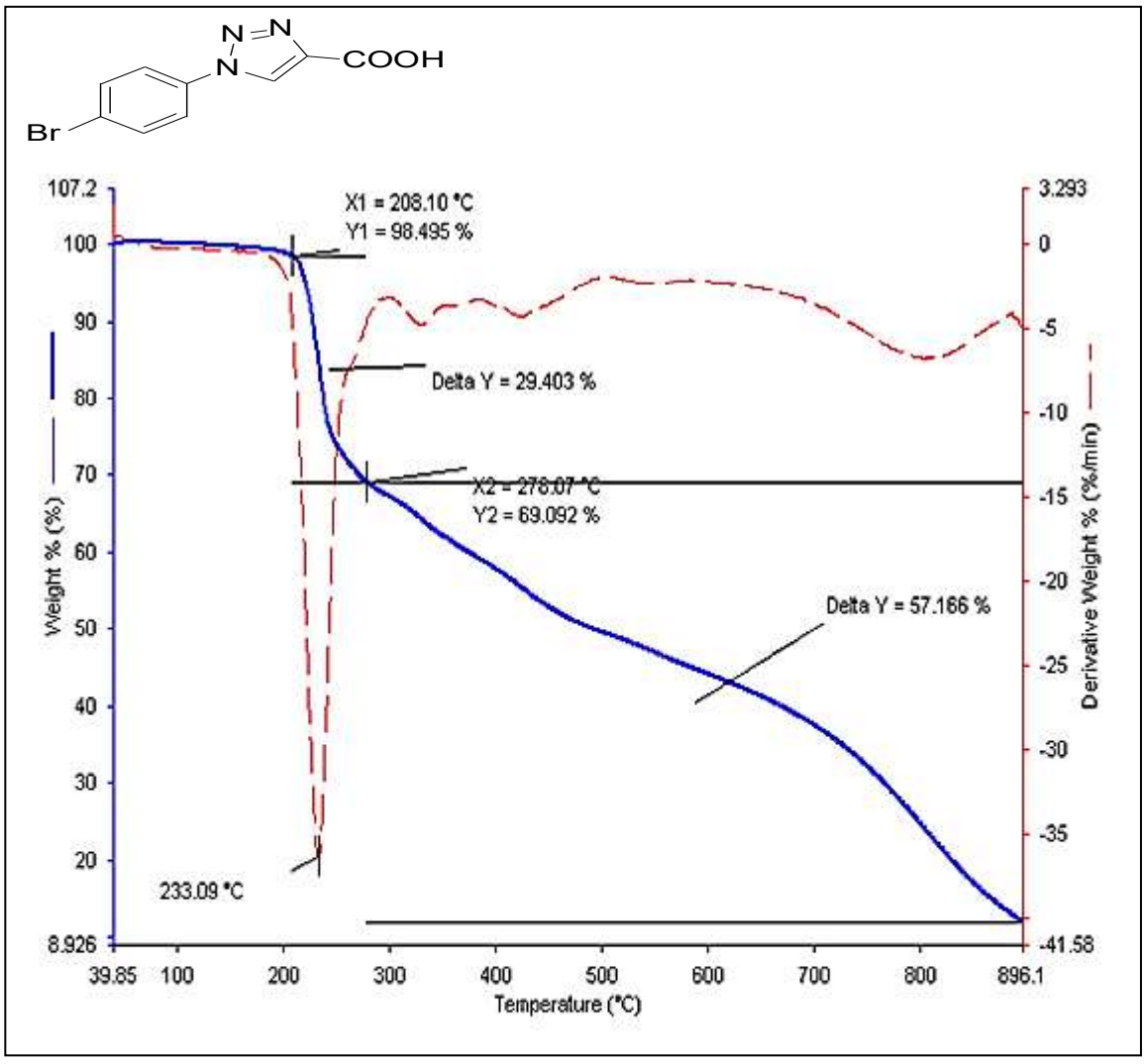


Figure: (4.4): TG-DTA curve for compound **56**. X1,X2 is temperatures, Delta Y =Ratio of losing mass, Delta Y1, Y2 = Ratio of residual mass.

While, TGA-DTG measurements that recorded for compound **57** showed that this compound is has higher the same thermally than that was described for compound **56** which is containing bromo group. Decomposition of this compound occurred also in one single stage ranged 270.5-390.3 ºC and the maximum mass losses takes place at 361.24 ºC with about 41.6 %, as shown in Figure 4.5.

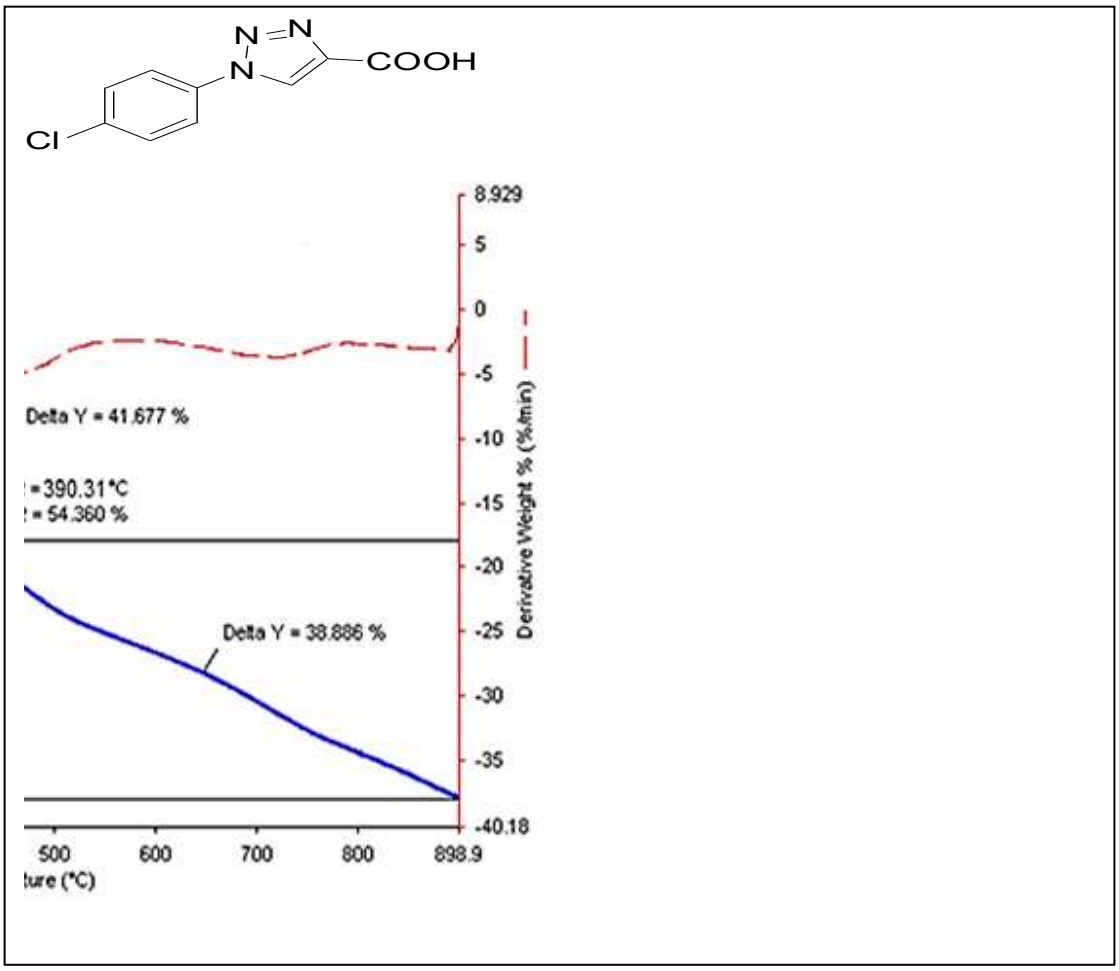


Figure: (4.5): TG-DTG curve for compound **57** X1,X2 is temperatures, Delta Y =Ratio of losing mass, Delta Y1, Y2 = Ratio of residual mass.

4.3 Thermal study of 1,3,4-thiadiazole derevatives (58-62)

The main second part of our project involves the combination the 1,2,3-triazole ring system of the synthesised 1,2,3-triazole derivatives **53-57** with 2-amino-1,3,4-thiadiazole moiety in one molecule. Since 1,3,4-thiadiazole ring system is thermally stable and its stability is increased on substitution, particularly by withdrawing system or group. Thus, the thermal behavior of the synthesised 2-amine-5-(substituted phenyl 1H-[1,2,3]-triazol-4-yl)-[1,3,4]-thiadiazole derivatives **58-62** was studied by thermal analysis using TG-DTA technique under same operational conditions that were used for their 1,2,3-triazole precursors. In general, the TG-DTG measurements indicate that compounds **58-62** are more thermally stable than their precursors **53-57**. Thus, according to TG-DTG curves (Figure 4.6) that were recorded for compound **58** shows that this compound is thermally stable up to about 263 °C. However, after this temperature, there is a rapid of losing weight happened in a single stage at temperature ranged about (263.8-403.1℃) with loosing mass about 37.9%. Furthermore, the maximum mass losses takes place at about 359.0 °C as shown in Figure 4.6

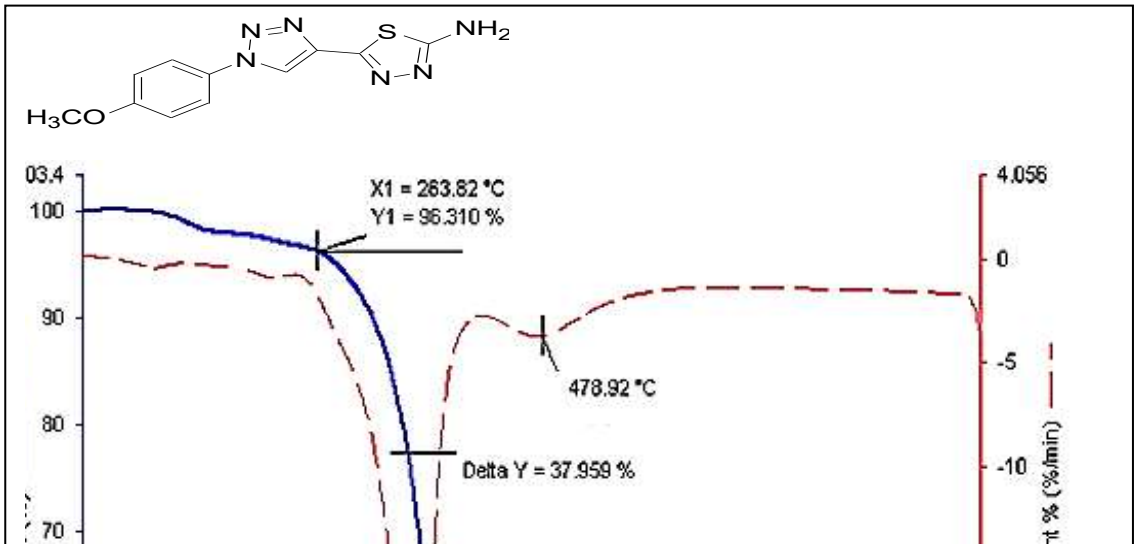


Figure: (4.6): TG-DTG curve for compound **58**. X1,X2 is temperatures, Delta Y =Ratio of losing mass, Delta Y1, Y2 = Ratio of residual mass.

While, from TG-DTG curves (Figure 4.7) that were recorded for compound **59**, it is easily concluded that this compound is less thermal stability than compound **58**, which is thermally stable at about 203.8℃. However, it decomposed in one stage ranged at 203.8- 406.7 ºC which is a wide range compared to that described for compound **58**, the maximum losses of weight about 34.8 % at 364.4℃, as shown in

Figure 4.7

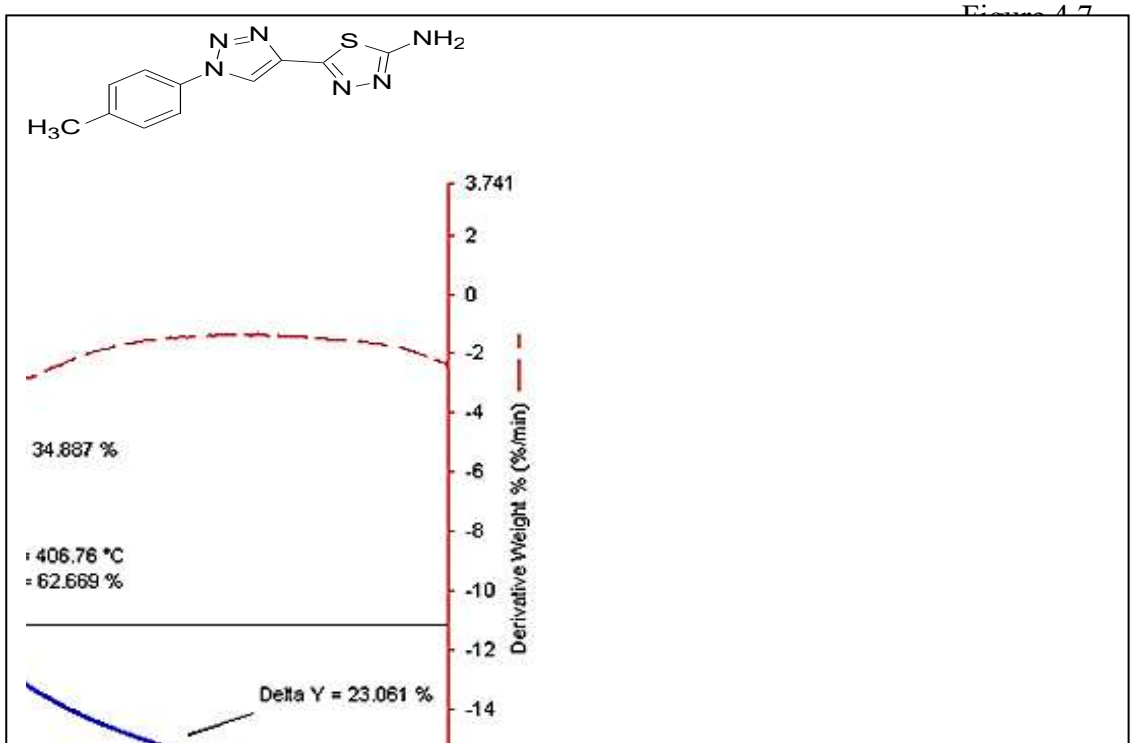


Figure: (4.7): TG-DTG curve for compound **59** X1,X2 is temperatures, Delta Y =Ratio of losing mass, Delta Y1, Y2 = Ratio of residual mass..

On the other hand, TG-DTG curves for the compound **60** which is shown in Figure 4.8 showed the presence of the hydroxyl group reduced the thermal stability of compound **60** to about 269.8 ^{o}C, however, is still higher thermally stable than its precursor **55**. The compound **60** decomposed in one stage ranged from 269.8-358.9 ^{o}C. Furthermore, the maximum mass losses occurs at 299.0 ^{o}C as shown in Figure 4.8.

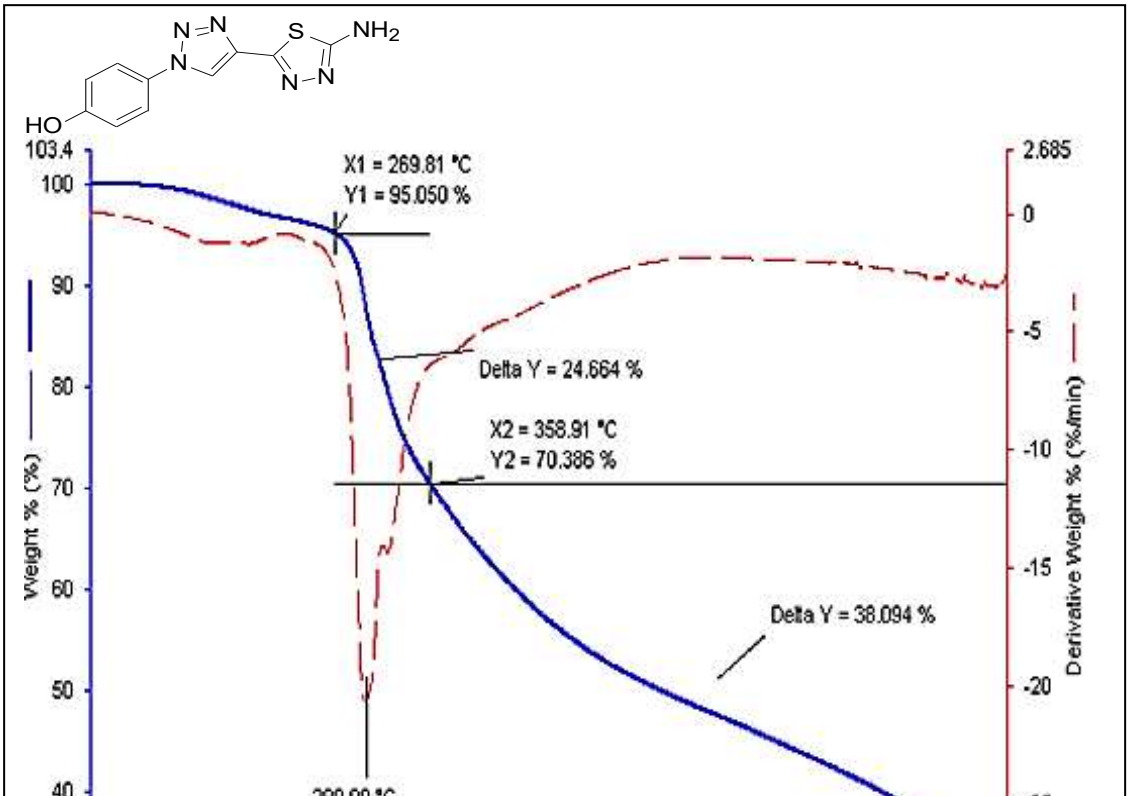


Figure: (4.8): TG-DTG curve for compound **60**. X1,X2 is temperatures, Delta Y =Ratio of losing mass, Delta Y1, Y2 = Ratio of residual mass.

While, the thermal stability of compound **61** which is containing bromo group as a substituent attached to the phenyl group, the TG-DTG measurements that were recorded for compound **61** showed no changing in its weight until about 280℃, followed by broad week decomposition stage ranged from 280.33–350.97 ºC as shown in figure 4.9. the maximum losing of weight at 313.20 ºC about 25.25 % as shown in Figure 4.9.

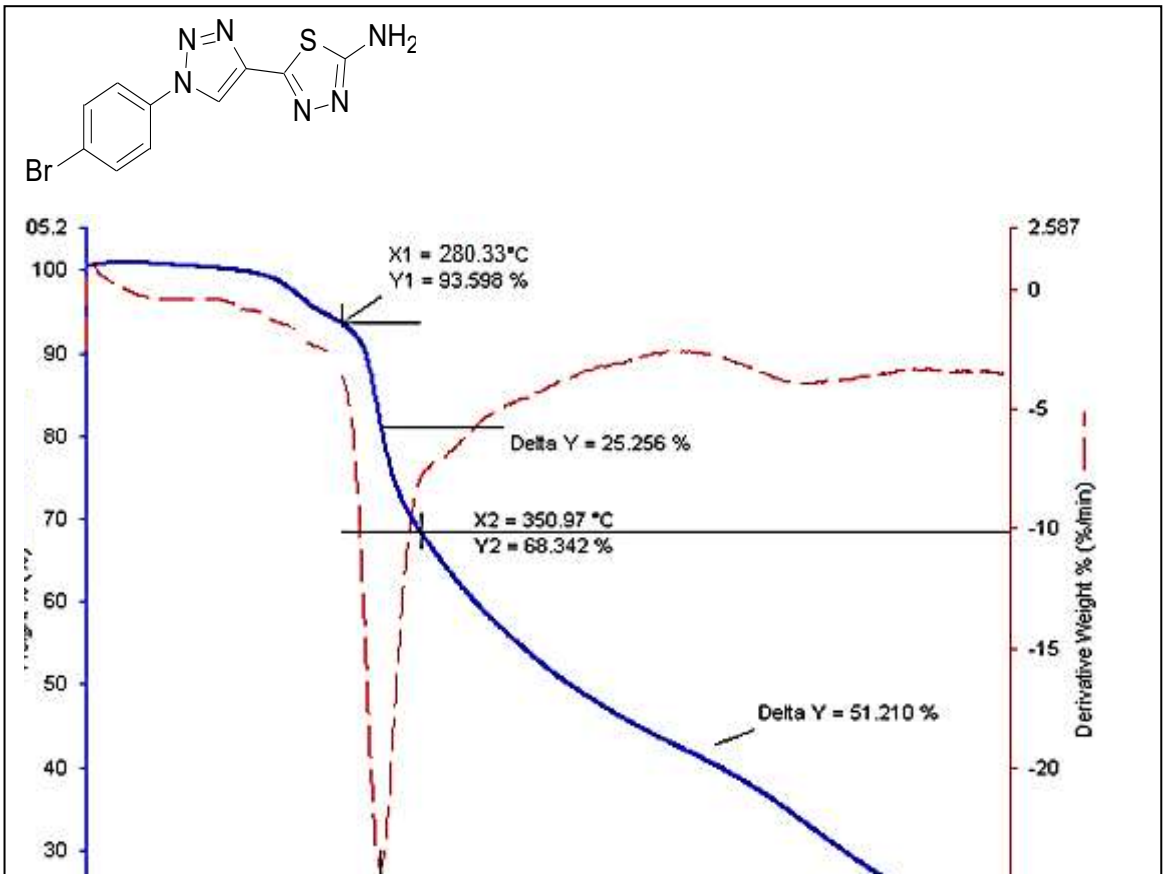


Figure: (4.9): TG-DTG curve for compound **61**. X1,X2 is temperatures, Delta Y =Ratio of losing mass, Delta Y1, Y2 = Ratio of residual mass.

While compound **62** which containing a chloro group instead of the other group that were discussed previously, it displayed thermal stability up to 227 ° C, followed a single stage decomposition ranged about from 227.2-388.1 °C which refers to the maximum losing of weight at 336.8 °C about 34.5 % as shown in Figure 4.10.

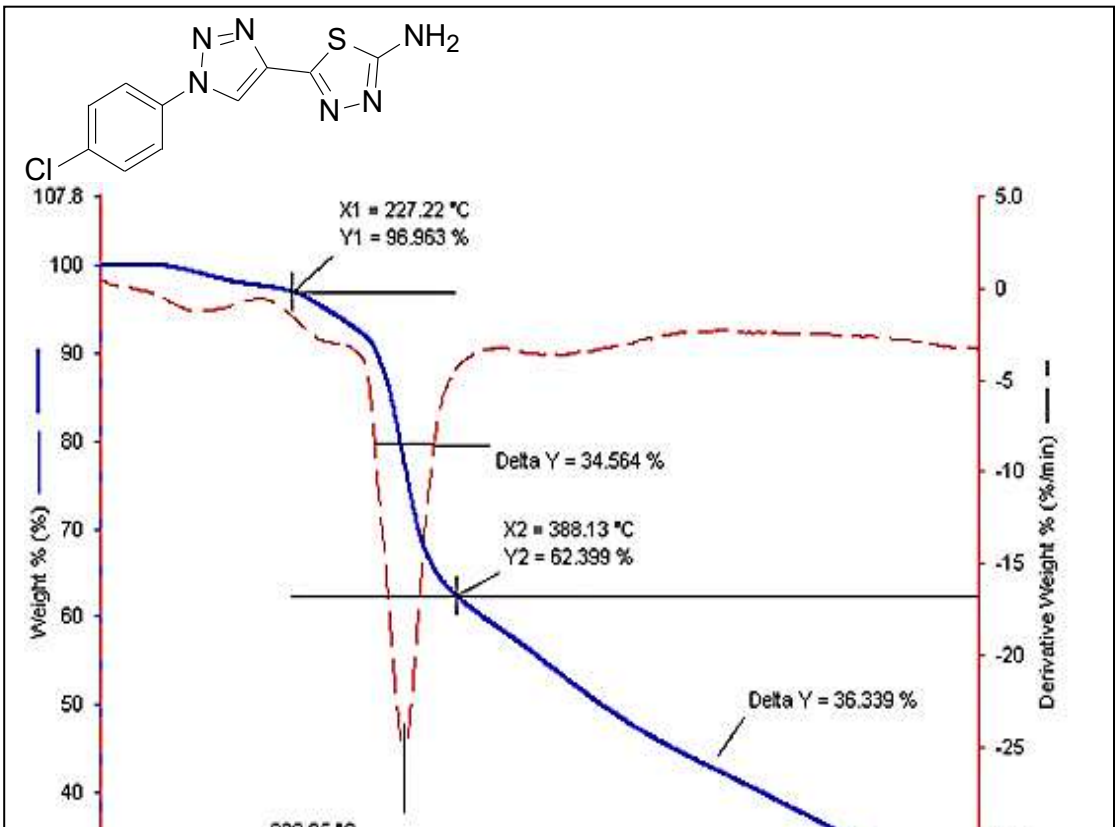


Figure: (4.10): TG-DTG curve for compound **62**. X1,X2 is temperatures, Delta Y= Ratio of losing mass, Delta Y1, Y2 = Ratio of residual mass.

4.4 Thermal stability study of synthesis Schiff base

This part of the present study focused on the synthesis compound **(63-65)** and their thermal behavior at elevated temperature. Generally, Schiff base displayed a highly thermal stability. According to TG-DTG curve in figure 4.11 that were recorded for compound **63** that Schiff base derived from compound **58** showed that this compound **63** has a high thermal stability up to 291˚C. after this temperature there is a rapid of lossing weight happened in a single stage at temperature ranged about (291.9-409.8℃) with 42.6 %, that maximum mass losses takes place at about 359.0℃ as shown in figure 4.11.

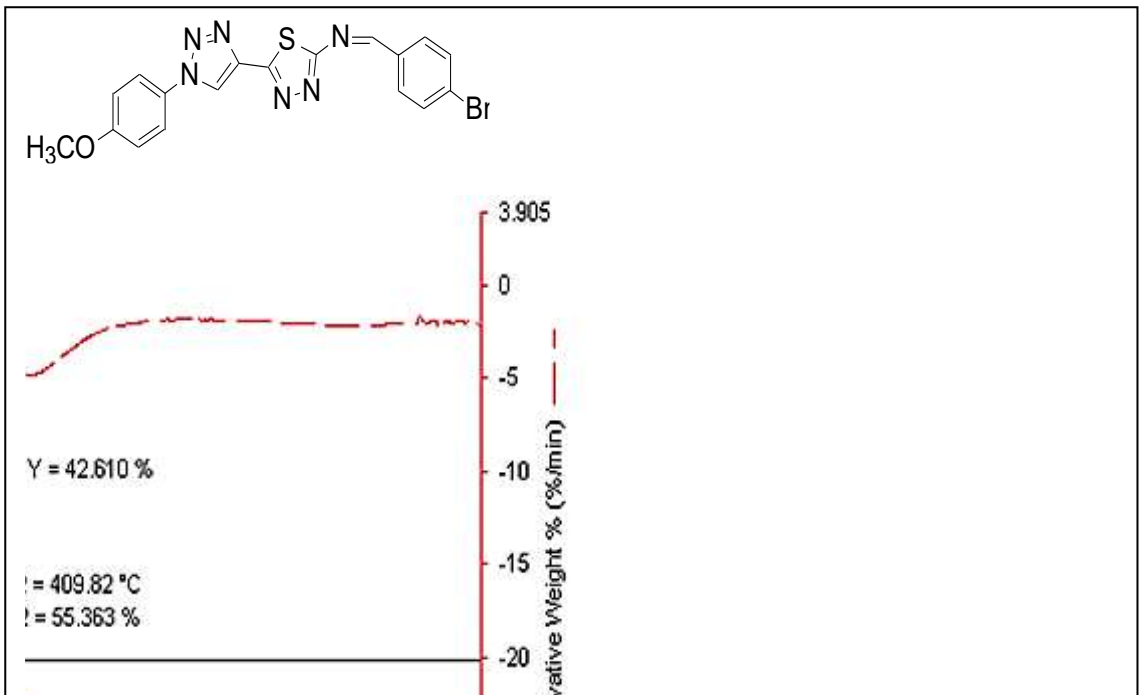


Figure: (4.11): TG-DTG curve for compound **63**. X1,X2 is temperatures, DeltaY=Ratio of losing mass, Delta Y1, Y2 = Ratio of residual mass.

According to the TG-DTG measurements in figure 4.12, that were recorded for compound **64** that derived from compound **61** showed no changing in its weight and very high thermal stability until about 293℃, then occurred decomposition in about (293.6-384.3℃), the maximum lossing of weight at about 326.3˚C.

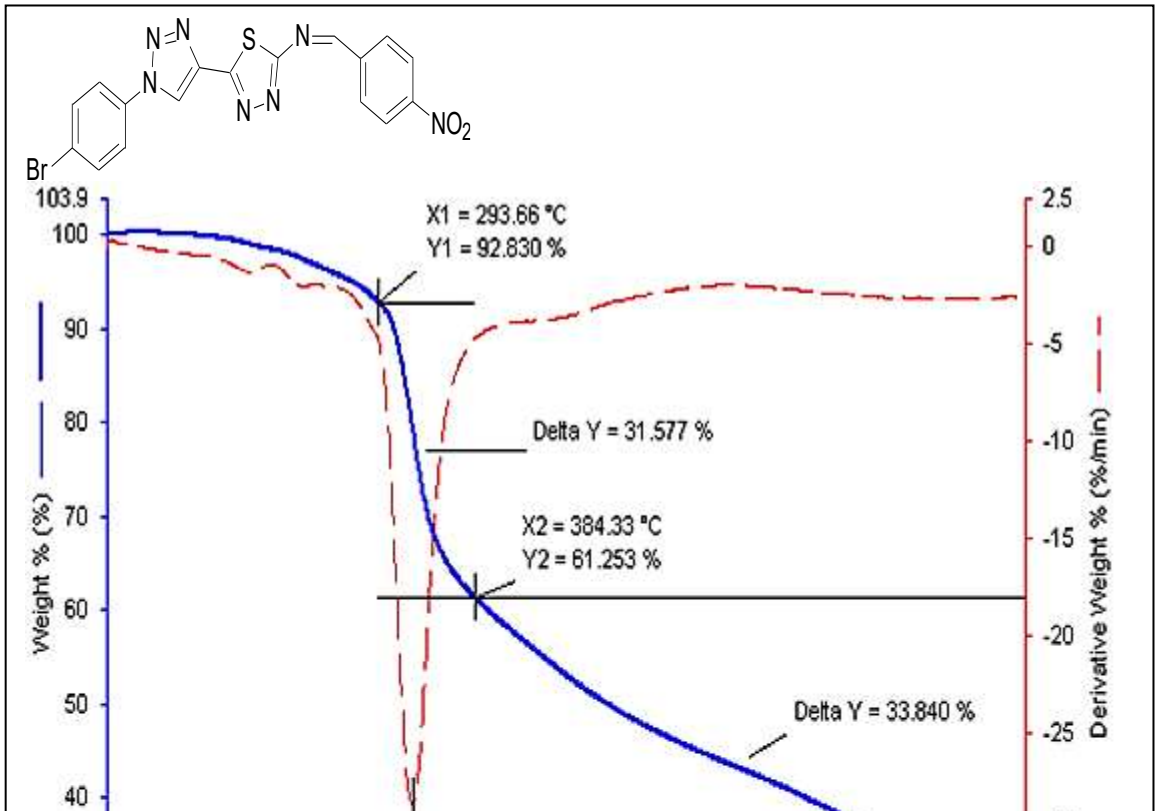


Figure: (4.12): TG-DTG curve for compound **64** X1,X2 is temperatures, DeltaY =Ratio of losing mass, Delta Y1, Y2 = Ratio of residual mass

While the Schiff base **65** that derived from compound **62** displayed a thermal stability up to 260.3℃, followed by decomposition one stage ranged 266.3-384.1℃. The maximum lossing from weight about 31.2 % takes place 313.4℃. that shown in figure 4.13.

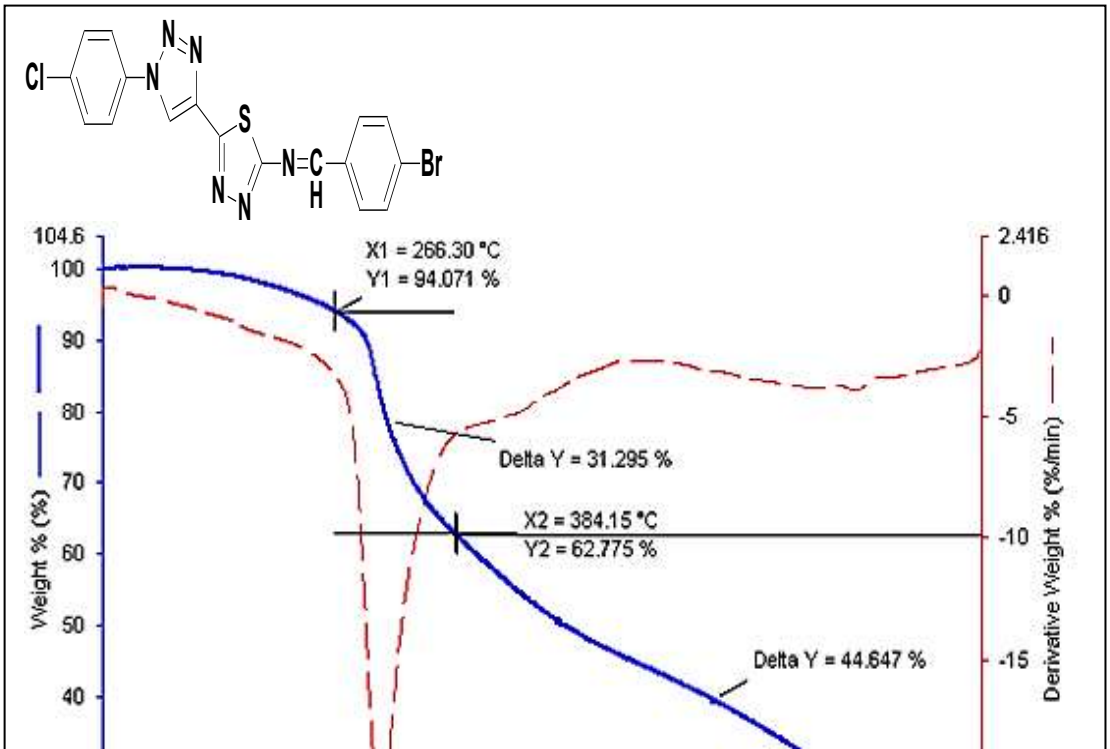


Figure: (4.13): TG-DTG curve for compound **65**. X1,X2 is temperatures, DeltaY= Ratio of losing mass, Delta Y1, Y2 = Ratio of residual mass.

5.1 Conclusions

The work that is described in this thesis mainly deals with the synthesis and characterization of three series of heterocyclic compounds containing 1,2,3-triazole, 1,3,4-thiadiazole and imine moieties as well as study their thermal stability. Since the azide compound being considered as a substrate for the copper (I) catalysed azide-alkyne cycloaddition. We successfully used the synthesised *p*-substituted phenyl azido and the commercially available propiolic acid for the synthesis of new series of 1,2,3-triazole derivatives **(53-57)** in a simple, high yield and cheap synthetic pathway. Furthermore, since choosing the propiolic acid led to functionalize the target 1,2,3-triazole derivatives with a carboxyl function. Thus, in the current project, the synthesised 1-(p-substituted phenyl)-*1H*-1,2,3-triazoyl-4-carboxylic acid derivatives have shown an ability to react with thiosemicarbazide in the presence of $POCl_3$ an agent for the conversion the carboxyl function group to acyl group which is more reactive toward

acylation of the thiosemicarbazide. Followed by dehydro-cyclization step to synthesize a series of new compounds containing 1,2,3-triazole and 1,3,4-thiadiazole moieties combine in the same molecule **58-62**. As the new synthesised heterocyclic compounds **58-62** containing an amino group attached to position C2 of 1,3,4-thiadiazole ring system, this amino group displayed a reactivity toward Schiff's bases formation. Furthermore, all the target synthesised compounds displayed relatively a good thermal stability.

5.2 Future work

As the target compounds 1-(*p*-substituted-phenyl)-1,2,3-triazolyl-4-carboxylic acid derivatives **53-57** were successfully synthesised in a simple and cheap synthetic route, future investigations for biological applications can be achieved. As the synthesised compounds containing 1,3,4-thiadiazole moieties **(58-62)** displayed a very low solubility in water and the most organic solvent that have lower polarity, this poor solubility may make them are not favorable in the biological application. However, due to their relatively good thermal stability they can be investigated as additives of polymer to improve their industrial properties. Furthermore, as the synthesised heterocyclic compounds **58-65** are considered a big aromatic system, so, it can be investigated in the semiconductors field.

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