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التحليل الاحصائي وتفسير النتائج

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الجامعـــــــــة الإســـــلاميــة بغـزة
عمادة البحث العلمي والدراســات العليا
كـــــليـــــــــــة العـــــلـــــوم
مـاجســـتـيـــــــر الـكـيـمـيـاء

Synthesis and Characterization of Novel Series of tetra Hydrazide-Hydrazones of Ethylenediamine-N,N,N',N'-tetra- Acetic Acid, and their Conversion into tetra N-acetyl-dihydro-1,3,4-Oxadiazoles

تحضير وتشخيص سلسلة جديدة من مركبات الهيدرازايد–هيدرازون الرباعية المشتقة من الإيثلين ثنائي أمين رباعي حمض الأستيك وتحويلها إلى رباعي أستيل–ثنائي هيدرو–4,3,1–أكسادايزول

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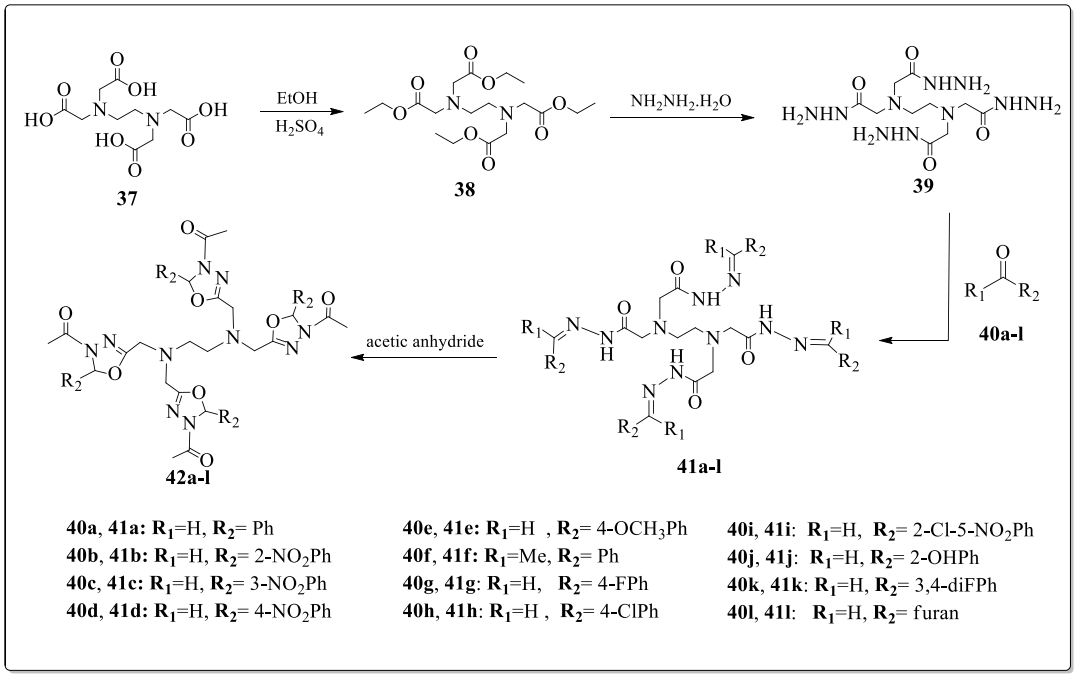
Abstract

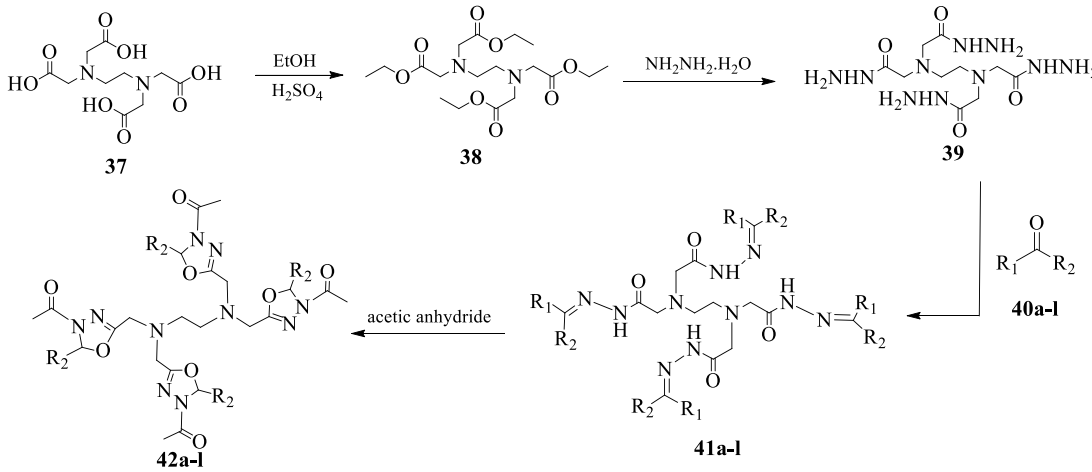
A new series of novel Tetra Hydrazide-Hydrazones of Ethylenediamine-N,N,N',N'-tetraacetic acid **41a-l** was synthesized *via* condensation of Ethylenediamine-N,N,N',N'-tetra-hydrazide **39** with different carbonyl compounds **40a-l**, The synthesized *N*-acylhydrazones **41k** were reacted with acetic anhydride to produce the Tetra N-Acetyl 1,3,4-oxadiazole derivitives **42k** in good yield.



The obtained compounds were fully characterized by MS, HRMS, IR, ^{1}H-NMR, and ^{13}C-NMR. The structure of compound **39** was confirmed by X-ray analysis.

ملخص الدراسة

تحضير سلسلة جديدة من مركبات الهيدرازايد هيدرازون الرباعية **41a-l** من خلال تكثيف الإيثلين ثنائي أمين رباعي هيدرازايد **39** مع بعض الألدهيدات والكيتونات المختلفة **40a-l** ، ومن ثم مفاعلة أحد هذه المشتقات **41k** مع أنهيدرايد حمض الأستيك لينتج مشتقات رباعي أستيل- ثنائي هيدرو-4,3,1- أكسادايزول **42k** بنسبة جيدة.



40a, **41a: R_1**=H, **R_2**= Ph
40b, **41b: R_1**=H, **R_2**= 2-NO_2Ph
40c, **41c: R_1**=H, **R_2**= 3-NO_2Ph
40d, **41d: R_1**=H, **R_2**= 4-NO_2Ph
40e, **41e: R_1**=H , **R_2**= 4-OCH_3Ph
40f, **41f: R_1**=Me, **R_2**= Ph
40g, **41g**: **R_1**=H, **R_2**= 4-FPh
40h, **41h**: **R_1**=H , **R_2**= 4-ClPh
40i, **41i**: **R_1**=H, **R_2**= 2-Cl-5-NO_2Ph
40j, **41j**: **R_1**=H, **R_2**= 2-OHPh
40k, **41k**: **R_1**=H, **R_2**= 3,4-diFPh
40l, **41l**: **R_1**=H, **R_2**= furan

تم تشخيص المركبات المحضرة بشكل كامل من خلال أطياف الكتلة ، والكتلة عالية الدقة ،والرنين المغناطيسي بشقيه البروتون والكربون 13 ،وبالإضافة إلى ذلك تم تحديد شكل المركب **39** باستخدام أشعة إكس .

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List of Schemes

List of Abbreviations

DEPT	Distortionless Enhancement by Polarization Transfer
DMSO	Dimethyl sulfoxide
EDTA	Ethylenediaminetetraacetic acid
ES	Electrospray
ES-MS	Electron spray Ionization Mass Spectrometry
EtOH	Ethanol
FT-IR	Fourier-transform Infrared Spectrometer
GPR	General Purpose Reagent
HBV	hepatitis B virus
HIV-1	human immunodeficiency virus-1
HRMS	High Resolution Mass Spectrometry
IR	Infrared
LRMS	Low Resolution Mass Spectrometry
MHz	Megahertz
Mp	Melting Point
MS	Mass spectrometry
NMR	Nuclear Magnetic Resonance
ppm	parts per million
THF	Tetrahydrofuran
TLC	Thin layer Chromatography
TOF-ES	Time-of-flight Electrospray
TOF-MS	Time-of-flight Mass Spectrometer
UK	United Kingdom
UV	Ultraviolet

Chapter 1

Introduction & Literature Survey

Chapter 1
Introduction

1.1 Background and Literatures

The chemistry of heterocyclic compounds is an interesting field of study since a long time (Pangal & Shaikh, 2013). Literature survey revealed that the history of heterocyclic chemistry began in the 1800's, in step with the development of organic chemistry. After World War II, there was an enormous explosion of research in the field of heterocycles. Heterocyclic chemistry is one of the most complex and intriguing branch of organic chemistry, and heterocyclic compounds constitute the largest and most varied family of organic compounds. Hetrocyclic compounds are indispensable structural units for both the chemists and the biochemists. (Kushwah, Mehta, Gupta, Das, & Kaur, 2013). Heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agent (Asundaria, 2014). They have a wide range of application. They are predominantly used as pharmaceuticals, as agrochemicals and as veterinary products. They also find applications as sanitizers, developers, antioxidants, as corrosion inhibitors, as copolymers, dye stuff. They are used as vehicles in the synthesis of other organic compounds (Arora, Arora, Lamba, Wadhwa, & Research, 2012). In the family of heterocyclic compounds, nitrogen containing heterocycles with an oxygen atom , especially five-membered rings, are considered to be an important class of compounds which are used frequently in medicinal chemistry possess diverse biological properties that have led to intense study and research of these compounds (Ilango, Valentina, Umarani, & Kumar, 2009; Karabelyov, Kondeva-Burdina, & Angelova, 2021; Pangal & Shaikh, 2013). In the field of synthetic organic chemistry, major challenges are to develop new methods for the synthesis of five member heterocyclic compounds (Namera & Bhoya, 2014). One of these compounds is Oxadiazole.

1.2 Oxadiazole

Oxadiazole is a monocyclic ring system, have occupied a unique place in the field of medicinal chemistry due to its wide range of activities and applications. Although the 1,3,4-oxadiazole ring system was known in 1880, the proper study of its

chemistry, structure, physical properties and application of various derivatives began only in 1950. Oxadiazole is a five membered heterocycle having two carbons, two nitrogens, one oxygen molecule and two double bonds having molecular formula $C_2H_2N_2O$ and –N=C-O- linkage, Oxadiazole moiety is derived from furan by replacing two methine groups (–CH=) group with two pyridine type nitrogen (-N=), as aresult of this substitution the aromaticity of oxadiazole ring is reduced. So, there should be possibility of four oxadiazole isomers depending on the position of nitrogen. The four isomers of oxadiazoles are 1,3,4-oxadiazole **1**; 1,2,4-oxadiazole **2**; 1,2,3-oxadiazole **3**; 1,2,5- oxadiazole **4**, as shown in (**Figure 1.1)** (Karabelyov et al., 2021; Kushwah et al., 2013; Nagaraj, Chaluvaraju, Niranjan, & Kiran, 2011).

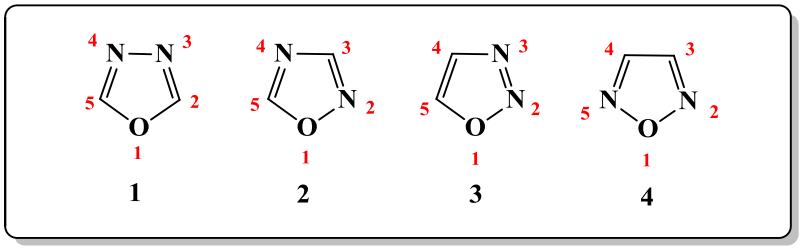


Figure (1.1): Oxadiazole isomers depending on the position of nitrogen.

1.2.1 1,3,4-oxadiazoles

Amongst oxadiazole isomers, The greatest interest is involved with 1,3,4-oxadiazole **1** (**Figure 1.1**) It is always used as synthesized intermediate and it is also termed as bioisoesters of amides and esters that can engage in hydrogen bonding interactions with receptors (Jadhav, Deshmukh, Medhane, Gaikwad, & Bholay, 2016; Karabelyov et al., 2021).

The privileged structure of 1,3,4-oxadiazole heterocyclic compounds made them be the target of many works held in the last years, concerning drugs designing (Taha, Tapabashi, & Ghaleb, 2020); due to their diverse and broad spectrum biological activity including, anti-fungal, anti-inflammatory, analgesic, antiviral, antibacterial, antituberculosis, anticonvulsant ,anti-HBV activity, anti-Alzheimer activity, anticancer, antidiabetic properties, and as HIV-1 integrase inhibitors. Several examples of compounds containing the 1,3,4-oxadiazole moiety utilized in clinical medicine are Raltegravir **5** an antiretroviral drug for HIV infection treatment; Tiodazosin **6** and Nesapidil **7** as antihypertensive agents; as well Zibotentan **8** as an

experimental anti-cancer drug candidate. Furamizole **9** as an antibiotic and Ataluren **10** for treatment of cystic fibrosis (**Figure 1.2)** (Karabelyov et al., 2021).

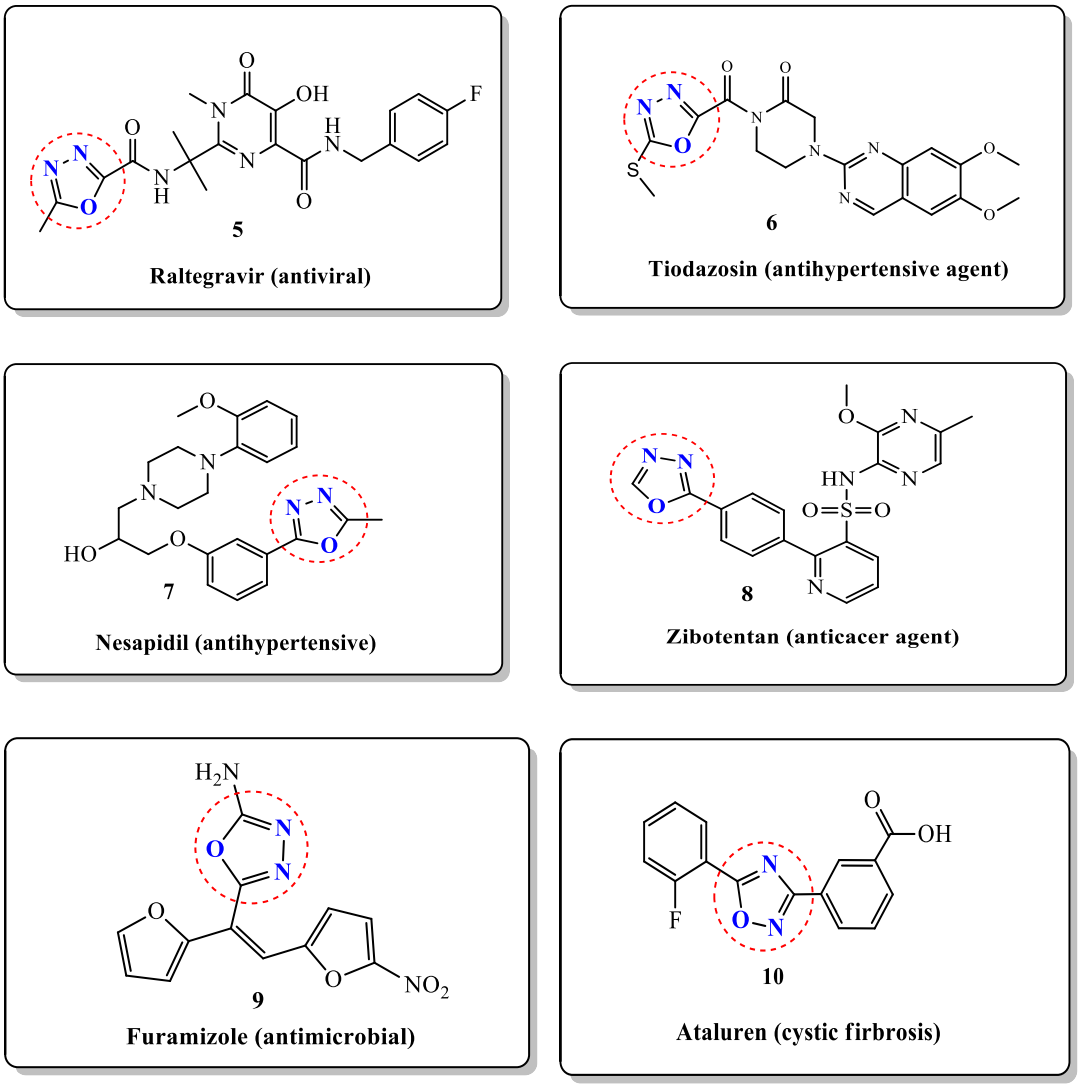
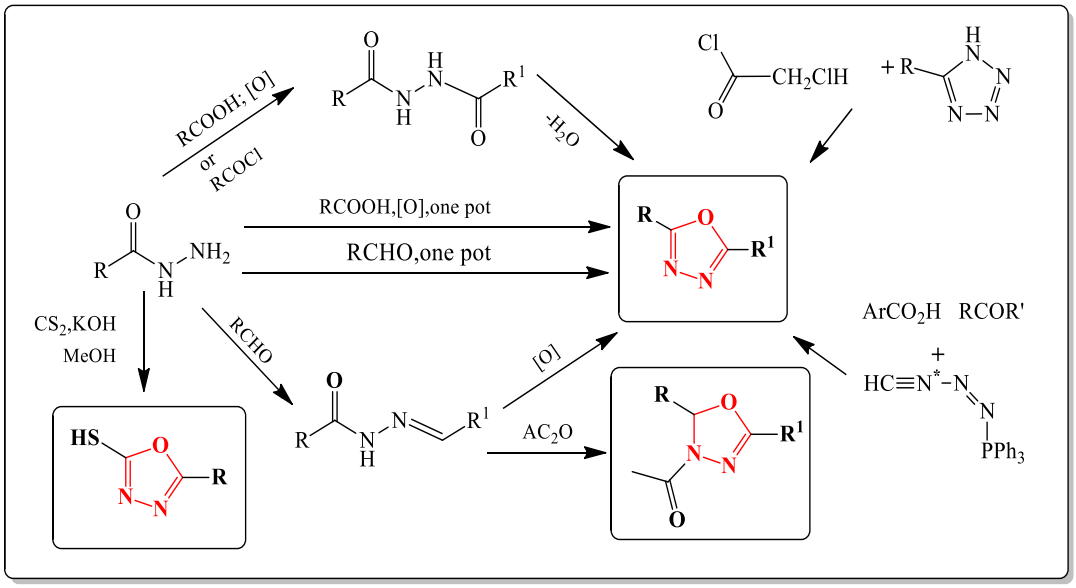


Figure (1.2): Commercially available drugs containing 1,3,4-oxadiazole moiety.

1.2.1.1 Methods of Synthesis of 1,3,4-oxadiazoles

At the end of the nineteenth century, the first derivatives of 1,3,4-oxadiazole were synthesized (Pinner & Caro, 1894), The methods of obtaining the new structures were multidirectional, including reactions of appropriate hydrazides and phosgene (Pinner & Caro, 1894), thermal cyclization of 1-acylsemicarbazides (Rupe & Labhardt, 1900) or cyclization of 1,2-diacylhydrazines by the action of dehydrating agents (Stollé, 1899). Currently, scientists use various routes for the preparation of

1,3,4-oxadiazole derivatives, some of them are improved previous methods , e.g., cyclization oxidative reactions of N-acylhydrazones, cyclodehydration reactions of diacylhydrazines or hydrazide reactions with carbon disulfide (Patel, Prajapati, Panchal, & Patel, 2014).The synthetic routes have been categorized on the basis of the chemical scaffold found in oxadiazole derivatives and on that in the chemical reagents. **Scheme 1.1** summarizes the most used synthetic approaches to an un-symmetrical 2,5-diaryl and 2,5- alkyl/aryl-substituted 1,3,4- oxadiazoles (Karabelyov et al., 2021).



Scheme(1.1): The most used pathways to the synthesis of unsymmetrical 2,5-aryl/alkyl and diaryl-substituted 1,3,4-oxadiazoles.

The commonly used synthetic route for 1,3,4-oxadiazoles includes reactions of acid hydrazides (or hydrazine) with acid chlorides/carboxylic acids and direct cyclization of diacylhydrazines using a variety of dehydrating agents such as phosphorous oxychloride, thionyl chloride, phosphorous pentoxide, triflic anhydride, polyphosphoric acid, and direct reaction of acid with (Nisocyanimino-triphenylphosphorane) (Bala, Kamboj, Kajal, Saini, & Prasad, 2014). Looking at the importance of 1,3,4-oxadiazole nucleus, as an essential building unit for the creation of new drugs where a literature survey showed that a slight systemic change in 1,3,4-oxadiazole moiety structure could lead to qualitative as well as quantitative changes in 1,3,4-oxadiazole derivative activity, which convinced us to start synthesizing different new 1,3,4-oxadiazole derivatives hoping to increase their activity and lower their toxicity (Abdelrehim, 2021; Koçyiğit-Kaymakçıoğlu et al., 2012) .One of the most

promising structures of 1,3,4-oxadiazole derivatives we will have been highlighted in this study is N-3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazole derivatives.

1.3 N-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazole (Tri substituted oxadiazoles)

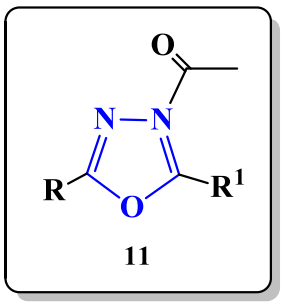


Figure (1.3): General chemical structure of 3-*N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4- oxadiazole.

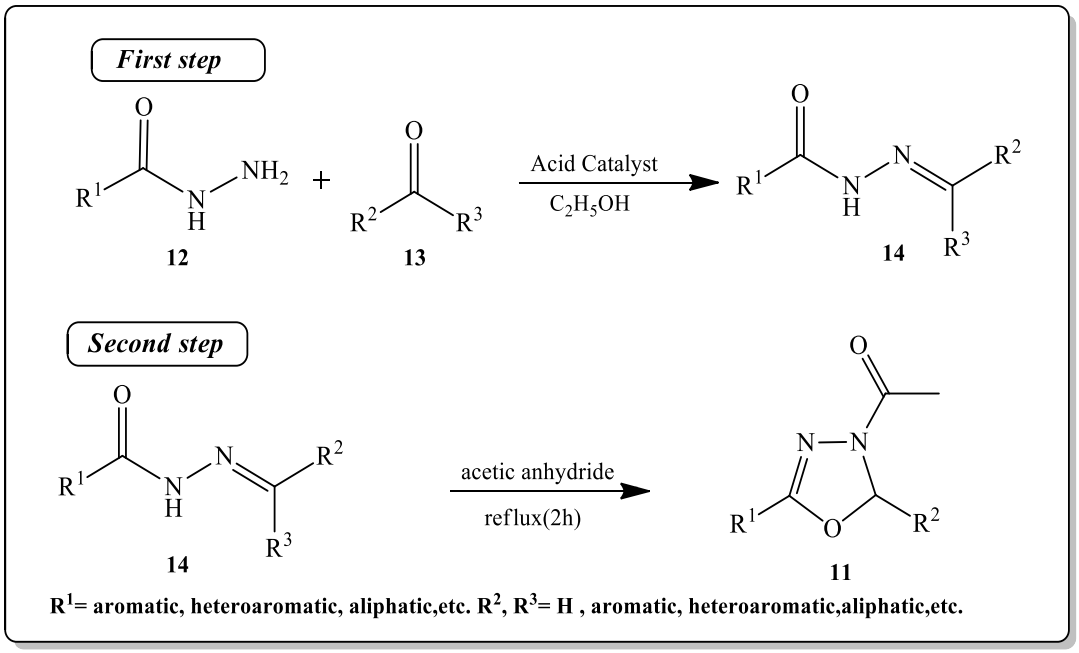
Chawla et al. confirmed that acetyl substituent is crucial to increase antibacterial activity of synthesized 1,3,4- oxadiazole derivatives. Conducted antimicrobial activity research against four species of bacteria revealed that 1,3,4-oxadiazole compounds with acetyl substituent possessed much higher antibacterial activity in comparison with the non-substituted 1,3,4-oxadiazole derivatives (Paruch, Popiołek, & Wujec, 2020) . The main advantage of the cyclization step, in synthesis, and the introduction of an acetyl group is the presence of an oxadiazole ring that may improve pharmacokinetic efficacy due to its increased ability to establish hydrogen bonding interactions and confer enhanced metabolic stability. Because of that, it could be considered as an important structural motif for designing new drugs (Ishii et al.).

1.3.1: Methods of Synthesis of 3-acetyl-2,3-dihydro-1,3,4-oxadiazoles

The 3-acetyl-2,3-dihydro-1,3,4-oxadiazoles **11** are usually obtained as a result of the cyclization reaction of the corresponding hydrazones in an acetic anhydride medium(Paruch, Popiołek, Biernasiuk, et al., 2020).

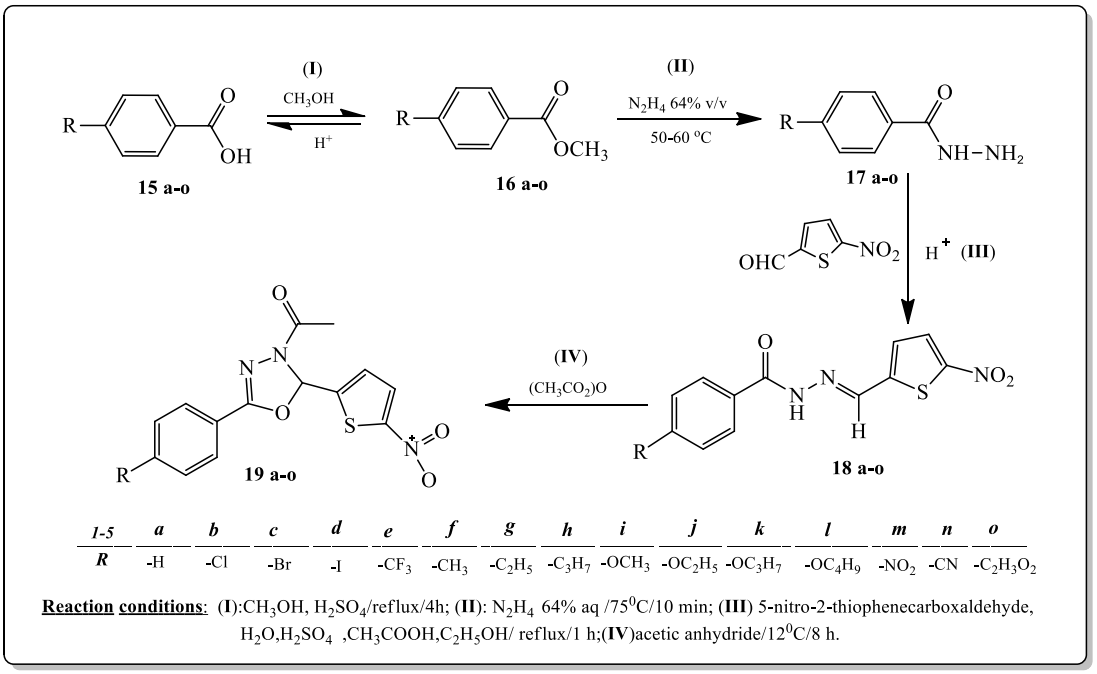
Their mechanism of synthesis is usually based on two step reactions. Firstly, the condensation reaction between appropriate carboxylic acid hydrazide **12** and aldehydes or Ketones **13** is performed and subsequently obtained hydrazones **14** are

subjected to cyclization reaction with acetic anhydride (Paruch, Popiołek, & Wujec, 2020). **(Scheme 1.2)**



Scheme (1.2): synthesis of *N*-acetyl 1,3,4-oxadiazole derivatives from N-Acylhydrazones.

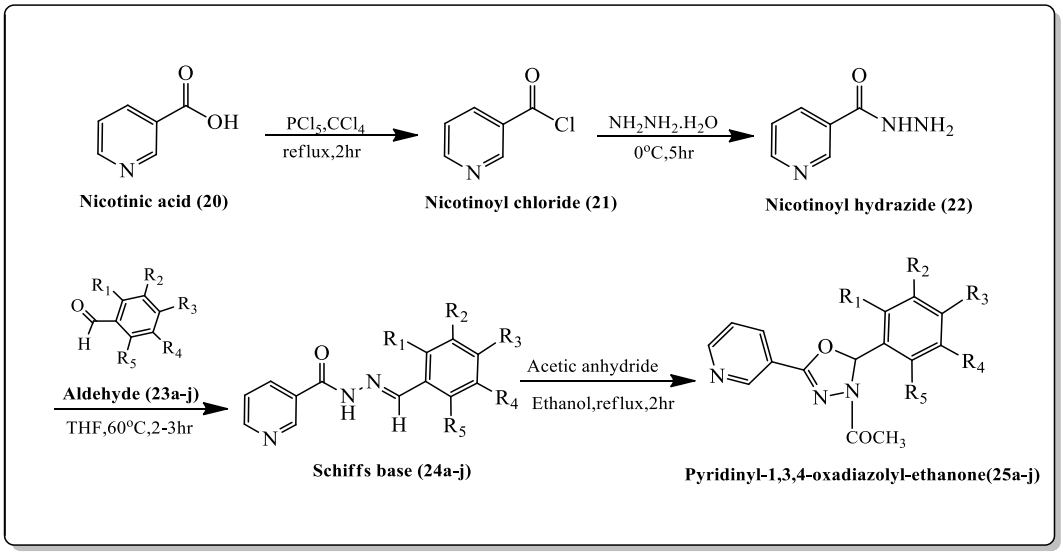
The synthesis of N-acetyl 1,3,4-oxadiazole was reported in many publications along with their biological activities. For example; Ishii et al. reported, the Synthesis of fifteen 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazole derivatives was performed in four steps : the synthesis of 4-substituted methyl esters (**16a–o**) from commercially available substituted benzoic acids (**15a–o**), synthesis of 4-substituted benzhydrazides (**17a–o**) from those methyl esters, synthesis of Schiff's bases (**18a–o**) from reaction with 5-nitro-2-thiophene carboxaldehyde ,and synthesis of 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazole derivatives (**19a–o**) from the Schiff's bases **(Scheme 1.3)** (Ishii et al.).



Scheme (1.3): Synthesis of 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazoles derivatives.

Another example about employing acetic anhydride as cyclooxidative reagent was recently reported by Mansoori et al., who reported the synthesis of a group of N-acetyl-2,3-dihydro-1,3,4 oxadiazoles **25 a-j** starting from nicotinic acid, Different acetylated nicotinic acid derivatives **25a–j** were synthesized by the acetylation of Schiff base with different substituents. The desired synthesized nicotinyl derivatives were achieved in good yield by reacting aromatic aldehydes i.e., benzaldehyde **23a**, dimethylaminobenzaldehyde **23b**, 2-chlorobenzaldehyde **23c**, 2-nitrobenzaldehyde **23d**, 4-methoxybenzaldehyde **23e**, 3-chloro-4-nitrobenzaldehyde **23f**, 3-nitrobenzaldehyde **23g**, 4-hydroxy-3-methoxybenzaldehyde **23h**, 4-methylbenzaldehyde **23i**, and 3,4-dimethoxybenzaldehyde **23j** with nicotinoyl hydrazide in ethanol and acetic anhydride (**Scheme 1.4**). The nicotinic acid was converted to nicotinoyl chloride by refluxing with phosphorus pentachloride (PCl_5) in

carbon tetrachloride (CCl_4) and thereafter it was reacted with hydrazine at low temperature to afford nicotinoyl hydrazide (Mansoori, Khatik, & Mishra, 2018).



Scheme (1.4) :Synthesis of acetylated nicotinic acid derivatives.

1.4 N-acylhydrazones

N-acylhydrazones belong to the azomethine class of compounds, have the general formula of $(R_1)CONHN=C(R_2R_3)$, where R_1 can be any group except hydrogen. The two groups R_2 and R_3 can be identical or different groups and one of them at maximum can be H (**Figure 1.4)** (Oliveira et al., 2013).

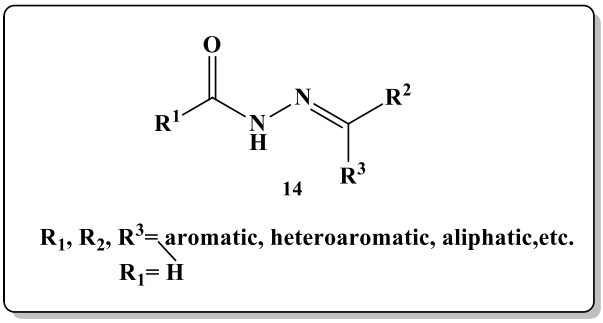


Figure (1.4): General chemical structure of *N*-acylhydrazones

they are extremely stable and mimic peptide portions, which are more sensitive to biological conditions as first observed by Kenyon et al., (dos Santos Filho & Pinheiro, 2017). Over the last two decades, N-acylhydrazone have been proven to be a very versatile and promising motif in drug design and medicinal chemistry (Thota et al.,

2018) several NAH derivatives have been reported with different pharmacological activities (de Miranda et al., 2012), such as Some widely used antibacterial drugs such as furacilin **26**, furazolidone **27** and ftivazide **28** that are known to contain such kind of moieties.(**Figure 1.5)**

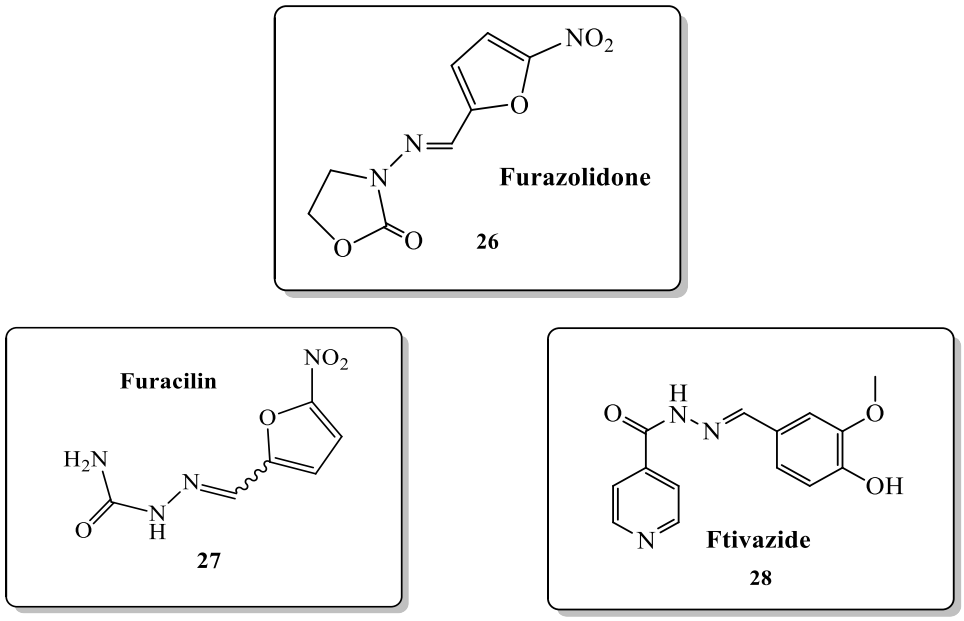
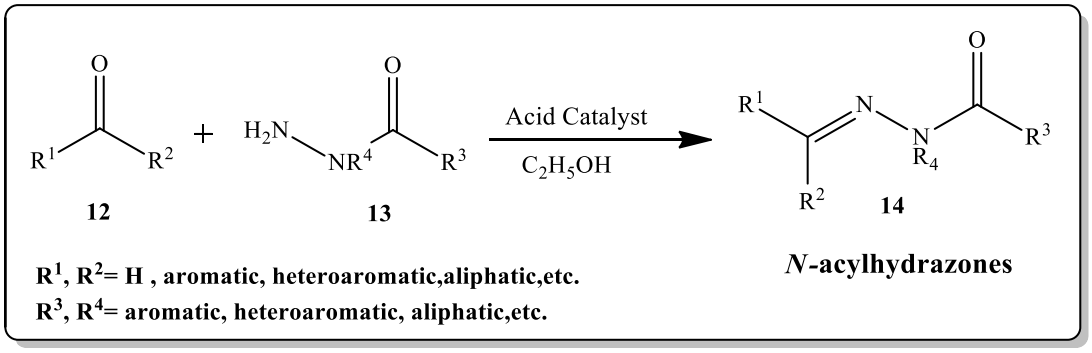


Figure (1.5) :antibacterial drugs containig N-acylhydrazones unite.

In addition, many N-acylhydrazone derivatives have been reported to exhibit an array of biological activities such as antimalarial, antiviral, antitumor, anti-inflammatory, anticonvulsant, antidepressant and vasodilative activities (Gu et al., 2012). In addition to their significant biological and pharmacological properties, N-acylhydrazones are excellent source for synthesis of many other nitrogen containing compounds due to their behavior as electrophiles. They serve as storable, stable imine equivalents which can react with various nucleophiles leading to syntheses of a large verity of useful organic compounds. Organic chemists have only quite recently focused on utility of *N*-acylhydrazones as electrophiles.

1.4.1 Synthesis of N-acylhydrazones

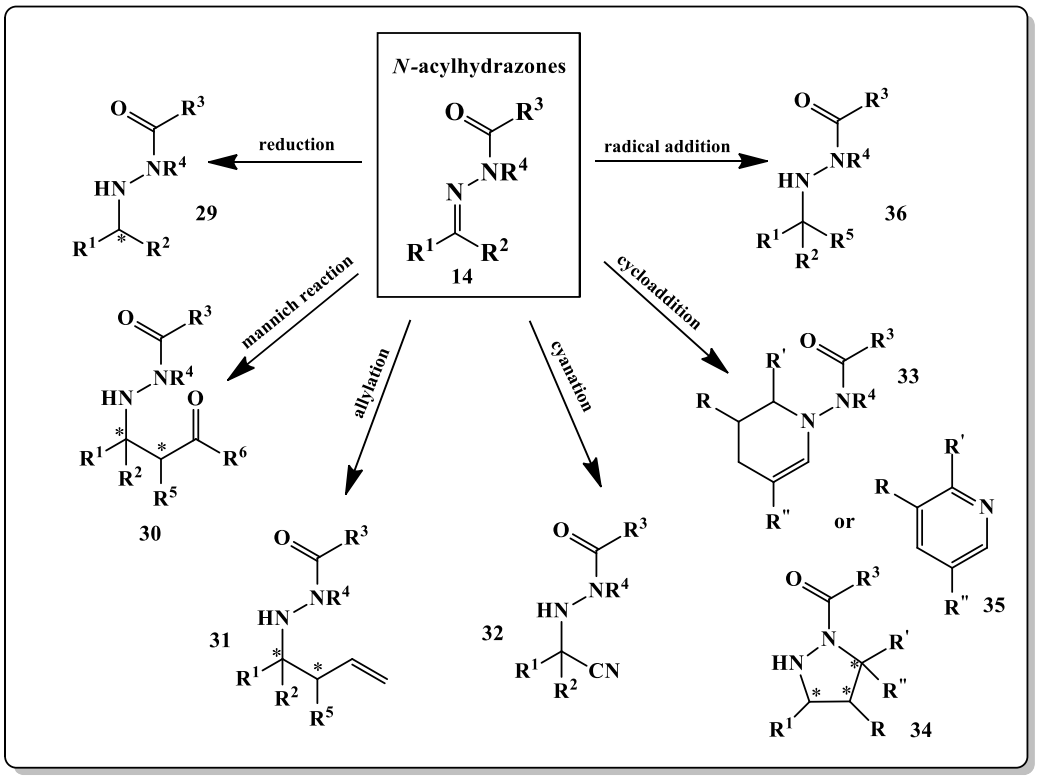
N-acylhydrazones **14** are readily obtained by the condensation of aldehydes or ketones **12** with acylhydrazines **13** in the presence of an acid catalyst according to **Scheme1.5** (Sugiura & Kobayashi, 2005)



Scheme (1.5): synthesis of N-acylhydrazone.

1.4.2 Reactions of N-acylhydrazones

The outcome of the different research activities in this field led to synthesis of many important nitrogen containing compounds that either cannot be made by other reaction pathways or it's hard to be made. For examples; researchers have utilized N-acylhydrazones as electrophiles in reduction, radical addition reactions, cycloaddition reactions, allylation, cyanation and Mannich reactions (**Scheme 1.6)** (Sugiura & Kobayashi, 2005).



Scheme (1.6): reactions of N-acylhydrazones.

1.5 Ethylenediamine-N,N,N',N'-tetra-Acetic Acid

EDTA ,or 2,2',2",2"'-(Ethane-1,2-diyldinitrilo)tetraacetic acid **37** is a molecule having molecular formula ($C_{10}H_{16}N_2O_8$) , was patented in Germany in 1935 by F. Munz (Oviedo & Rodríguez, 2003). It is a polyprotic acid containing four carboxylic acid groups and two amine groups with lone pair electrons. The molecule is a substituted diamine (**Figure 1.6**) usually marketed as its sodium salts (Banfi, Salvagno Gl Fau - Lippi, & Lippi). It is a powerful complexing agent of metals and a highly stable molecule because of its role as a hexadentate ("six-toothed") ligand and chelating agent, offering a considerable versatility in industrial and household uses.

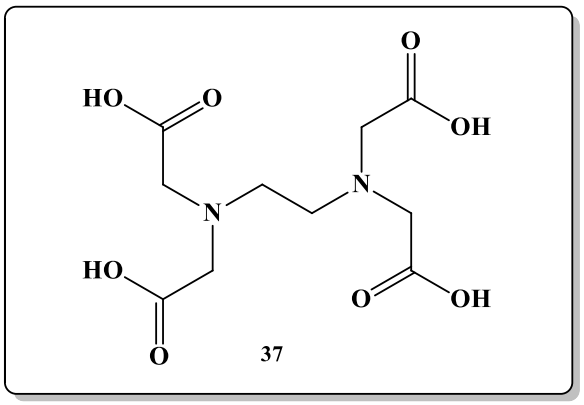


Figure (1.6): General chemical structure of Ethylenediaminetetraacetic acid.

EDTA has antibacterial activity and metal chelation of the ligand reduces this activity. The effect of chelating agents upon gram negative bacteria has been reported. EDTA causes disruption of the outer membrane, since it is capable of removing its calcic and magnesic divalent cations, with the consequent loss of substantial amounts of lipopolysacharide, which in turn, make cells susceptible to the action of many substances such as detergents, proteases, lipasesand lysozymes (Oviedo & Rodríguez, 2003).

In manufacturing, EDTA **37** is used to improve stability of some pharmaceutical products, detergents, liquid soaps, shampoos, agricultural chemical sprays, contact lens cleaners and cosmetics. It is also used in certain blood collection tubes used by medical laboratories. In foods, EDTA also used to help preserve food; and to promote the colour, texture, and flavour of food EDTA is a prescription medicine, given by

injection into the vein (intravenously) or into the muscle (intramuscularly), to treat lead poisoning and brain damage, to treat poisonings by radioactive materials such as plutonium, thorium, uranium, and strontium; for removing copper in patients with a genetic disease called Wilson's disease; and for reducing levels of calcium in people whose levels are too high. EDTA is also used intravenously for heart and blood vessel conditions including irregular heartbeat due to exposure to chemicals called cardiac glycosides, "hardening of the arteries" (atherosclerosis), chest pain (angina), high blood pressure, high cholesterol, stroke, and blood circulation problems. Other intravenous uses include treatment of cancer, rheumatoid arthritis, osteoarthritis, an eye condition called macular degeneration, diabetes, Alzheimer's disease, multiple sclerosis, Parkinson's disease, and skin conditions including scleroderma and psoriasis (Escolar et al.)

Chapter 2

Statement & Objective of The Problem

Chapter 2
Statement & Objective of The Problem

2.1. Purpose of the present work

2.1.1 The major aims of the project

Synthesis and characterization of a new Series of tetra N-Acyl Hydrazones of Ethylenediamine-N,N,N',N'-tetracetic acid and their Conversion into N-Acyl oxadiazole.

2.1.2 Work Plan

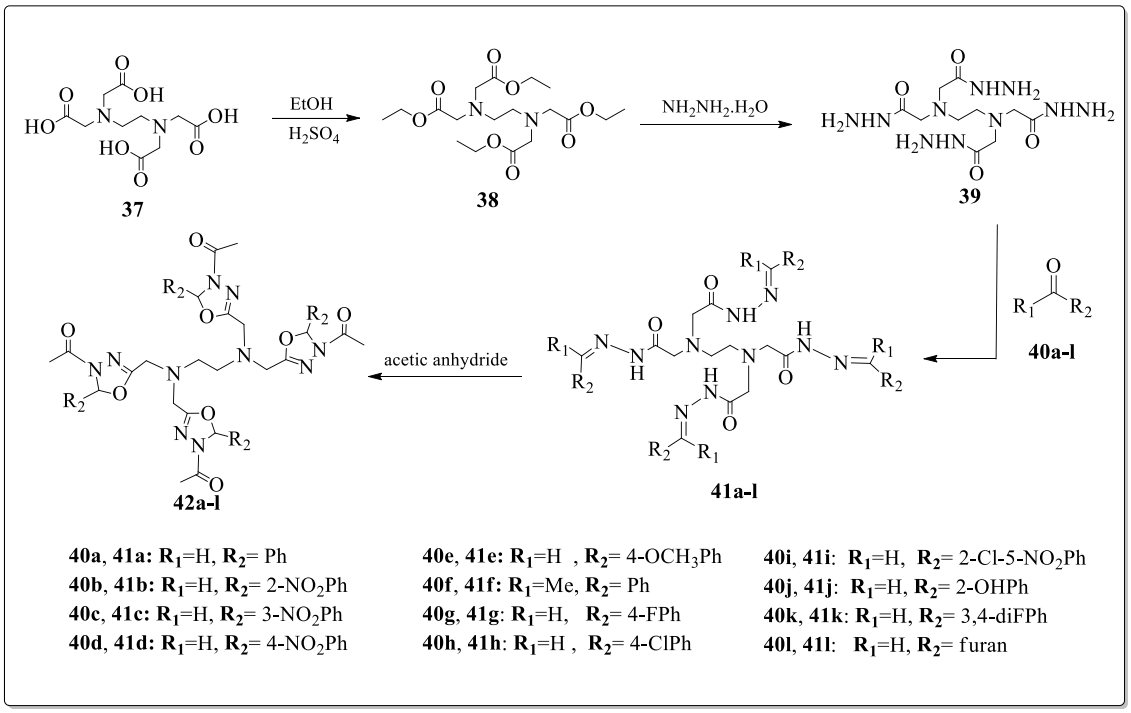
The advantage of using EDTA relies on its chemical structure where four terminal carboxylic groups are possessed in this compound. These four carboxylic acid that located in the molecule can be used to make the tetra- N-acylhydrazone and then conversion into tetra N-acyl oxadiazole. We expected strong antimicrobial activity in these compounds in comparison with others have one, two or three terminal groups.

2.2 Research Methodology

To achieve the project goals, the synthesis work is divided into two parts;

The first step of synthesis will involve the esterification of the commercially available starting material, Ethylenediamine-N,N,N',N'-tetracetic acid **37** to produce the Tetrethyl Ester of Edta **38**, The obtained ester **38** will be allowed to react with hydrazine hydrate in appropriate solvent to produce the tetrahydrazide of Edta **39**.

The second step; N-acyl hydrazone **41a-l** compounds are achievable via the reaction of carbonyl compounds **40a-l** with the hydrazide **39** in a suitable solvent. The Tetra-N-Acyl oxadiazole **42a-l** of Ethylenediaminetetracetic acid target compounds are achievable via the reaction of N-acyl hydrazone **41a-l** compounds with acetic anhydride. The proposed chemistry for syntheses of starting materials and the target compounds is described in **Scheme 2.1** .



Scheme (2. 1): The proposed chemistry for the target compounds.

2.3 Literature Survey

The literature survey for the current project has been accomplished. The Scifinder data base was used to ensure the authentic of the project. All the required papers and articles needed were obtained from the University of Manchester electronic library as well other recognized and trusted sources.

2.4 Materials

The starting materials have been purchased from Aldrich Company. Commercially available solvents and chemicals will also be used are obtained from local companies. No further purification neither for the starting material nor for the solvent were made unless otherwise specified .

2.5 Products Characterization:

Spectral analysis including (Mass Spectroscopy, Elemental Analysis, ^{1}H-NMR, ^{13}C-NMR, X-ray and any other required analyses) for all obtained products have been carried out through cooperation with Manchester Univ-UK.

Chapter 3

Results and Discussion

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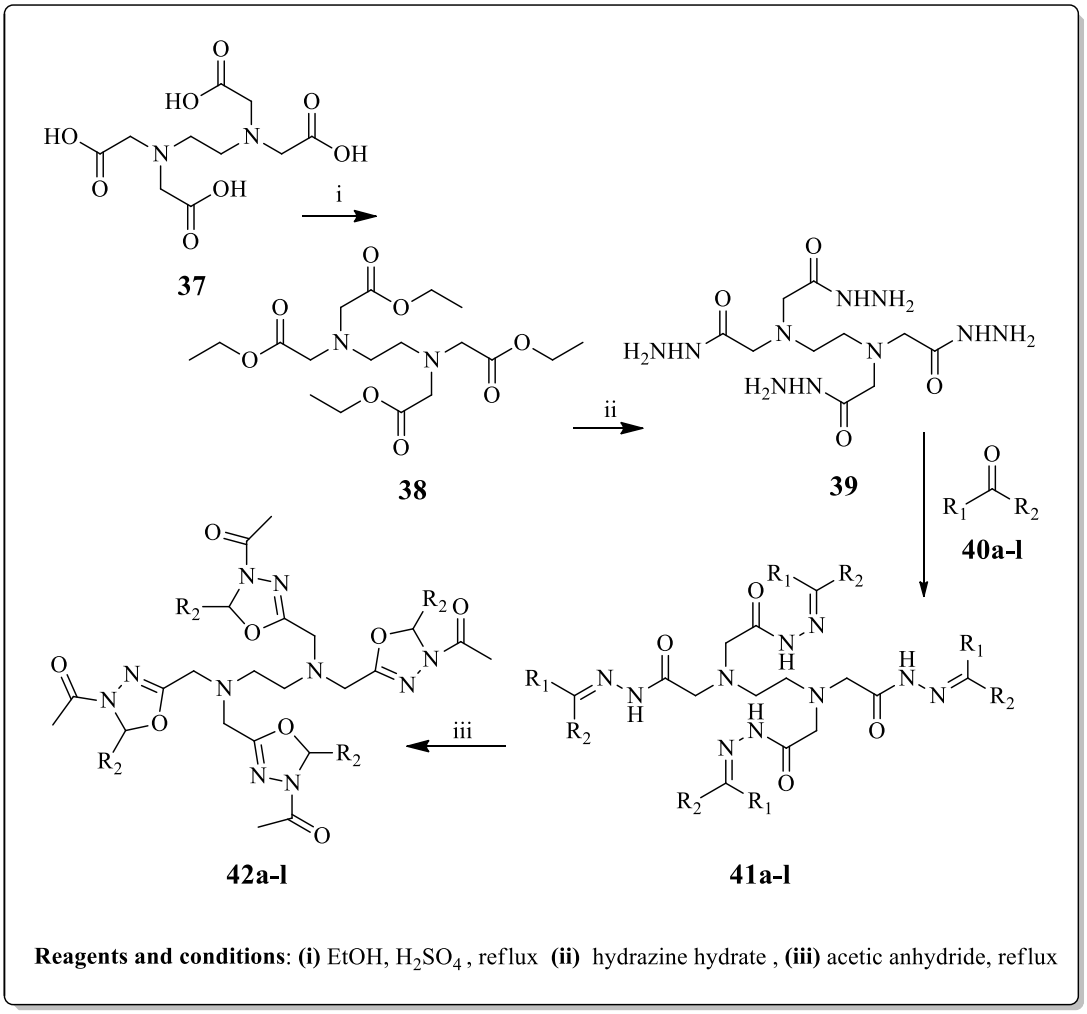
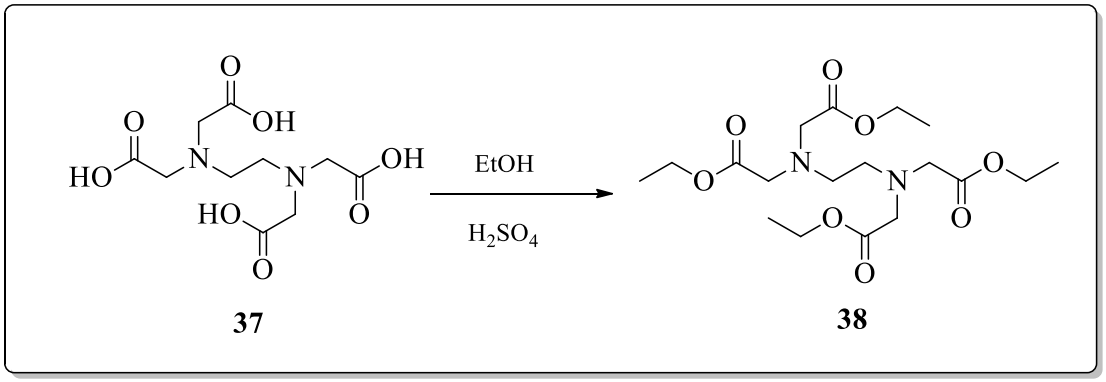
3.1 Results and Discussion

The primary aim of this project was to investigate the possibility of synthesis of a novel series of tetrahydrazide hydrazone of EDTA and their conversion of *N*-acetyl-dihydro-1,3,4-oxadiazole derivatives. Basically the project aim is achievable through two stages. For the first stage; there are two major requirements for this syntheses which are EDTA-tetrahydrazide and carbonyl compounds *i.e.* aldehydes and ketones and the second stage depends on utilizing the hydrazide hydrazone obtained from the first stage and acetic anhydride in order to obtain the target products (**Scheme 3.1**).



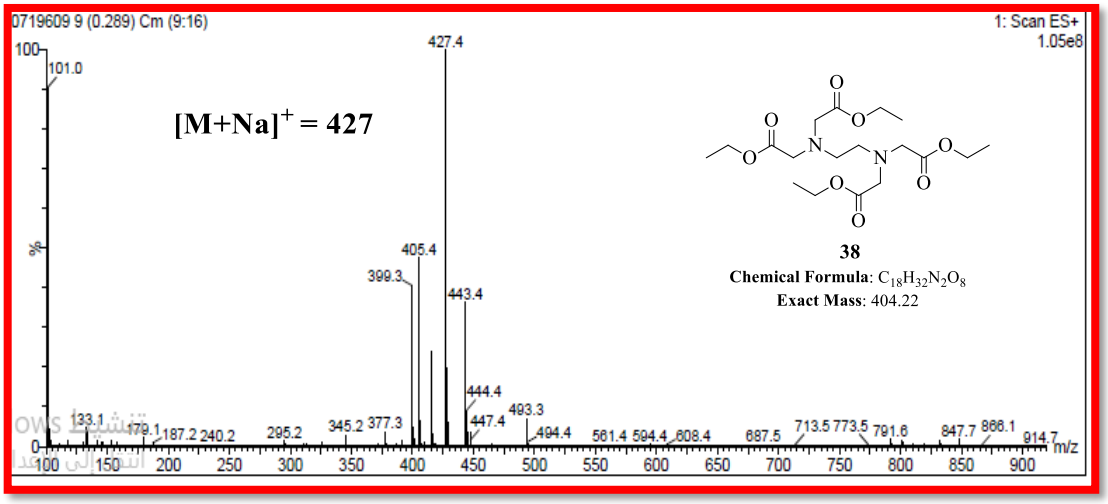
Scheme (3. 1): The proposed chemistry for the target compounds.

In order to achieve the project goal; EDTA **37** was first converted to ester **38** *via* reaction with ethanol in the presence concentrated s ulfuric acid (H_2SO_4) (**Scheme 3.2**).



Scheme (3. 2): Synthesis of tetraethyl EDTA 38

To the best of our knowledge; the only published data for the ester **38** was the melting point and LRMS. In our work; we obtained the ester as viscous oil but not as awhite crystalline solid. The structure of compound **38** was confirmed by both LRMS and HRMS as well as ^{1}H-NMR. the molecular formula for the compound **38** is $C_{18}H_{32}N_2O_8$ and the calculated molecular weight corresponding to the chemical formula is 404. The analysis was done using electrospray technique (ES). The required molecular ion for compound **38** was shown in the positive ion mode. In the positive ion mode ES^+ a peak was shown for ($C_{18}H_{32}N_2O_8Na$) $[M+Na]^+$= 427 (100%) **(Fig. 3.1)**.



Figure(3. 1): The LRMS spectrum for compound 38.

The purity of the synthesized compound **38** was confirmed by the high resolution mass spectroscopy (HRMS). Using HRMS (TOF-ES$^-$) technique, the analysis result showed good accordance between the value of the calculated exact mass 427.2051 for ($C_{18}H_{32}N_2O_8Na$) $[M + Na]^+$ and the value obtained from the experimental analysis 427.2031 **(Figure. 3.2)**.

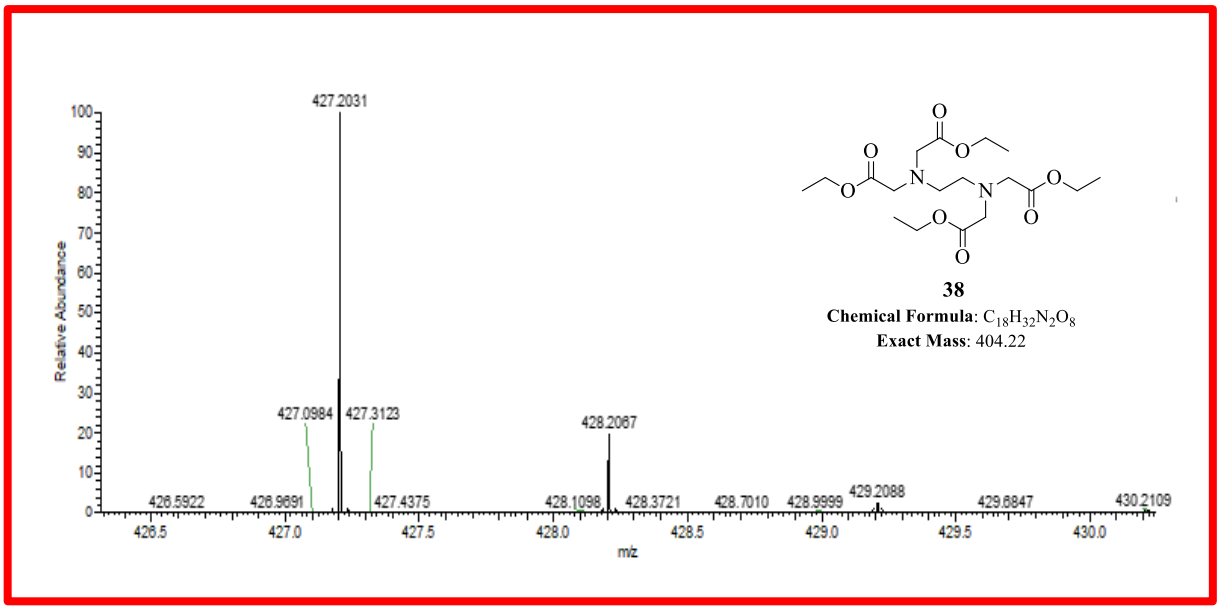
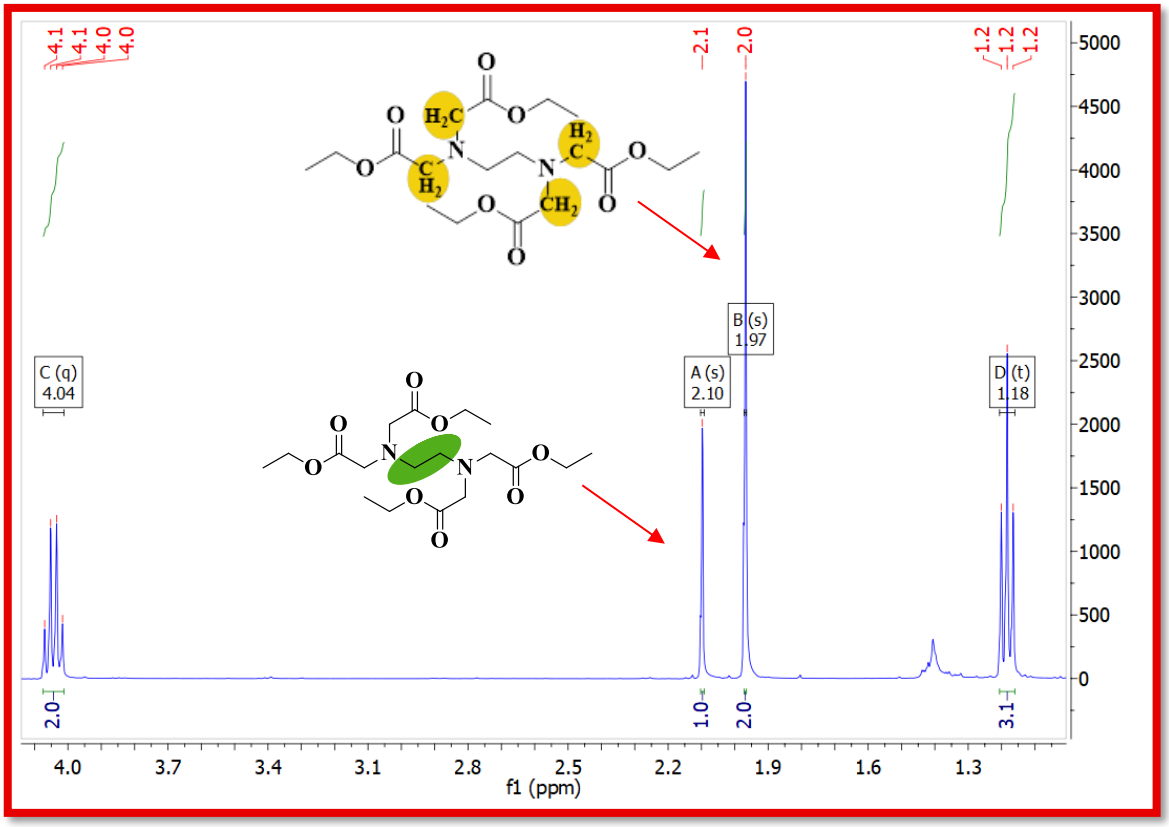


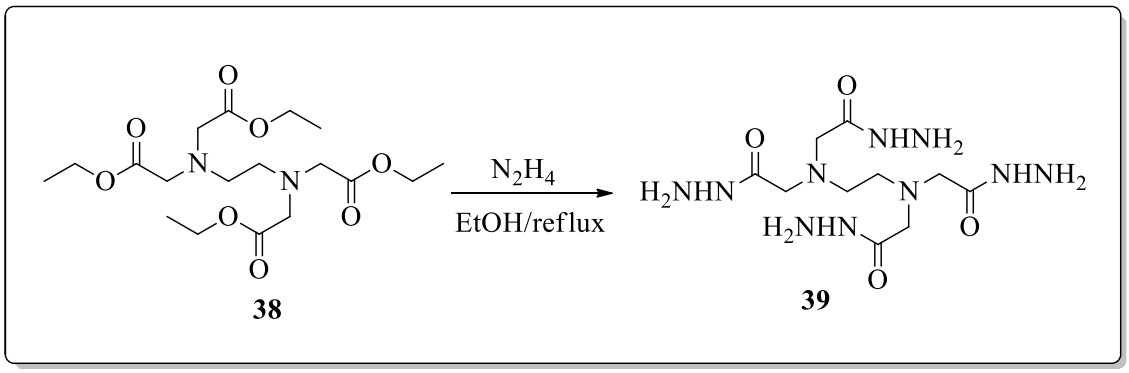
Figure (3. 2): The HRMS spectrum for compound 38.

The structure of compound **38** was also confirmed by ^{1}H-NMR spectroscopy. In the ^{1}H-NMR spectrum for compound **38** the appearance of the quartet peak at δ 4.0 ppm (OCH_2, J = 7.1 Hz) with integration value corresponding to 8 protons along with the triplet peck at δ 1.2 (CH_3, J = 7.1 Hz) with integration value corresponding to 12 protons confirmed the presence of OCH_2CH_3 group. The singlet peck with integration value corresponding to 4 protons at δ 2.1 ppm is assigned to the four identical protons of ($N-CH_2-CH_2N$). The singlet peak at δ 2.0 ppm with integration value corresponding to 8 protons is assigned for the protons of the 4 CH_2. The ^{1}H-NMR spectrum for compound **38** is shown in (**Figure 3.3)**.



Figure(3. 3): ^{1}H-NMR for compound 38

With the EDTA-tetraester **38** in hand; the next step was the conversion of the ester **38** into EDTA-tetrahydrazide **39** (**Scheme 3.3**). Compound **39** was synthesized according to the reported procedures and the obtained physical and spectroscopic data were in good accordance with the reported data (Bersworth, 1970).



Scheme (3.3): Synthesis of EDTA-tetrahydrazide 39

We tried and luckily succeeded to obtain suitable crystal for single crystal determination for compound **39** and that was done by dissolving small amount of

compound **39** in DMSO. The sample tube was partially sealed and left undisturbed for five days at room temperature. Few crystals were collected and submitted to analyses. The X-ray crystal structure for compound **39** is shown in **(Figure 3.4)**.

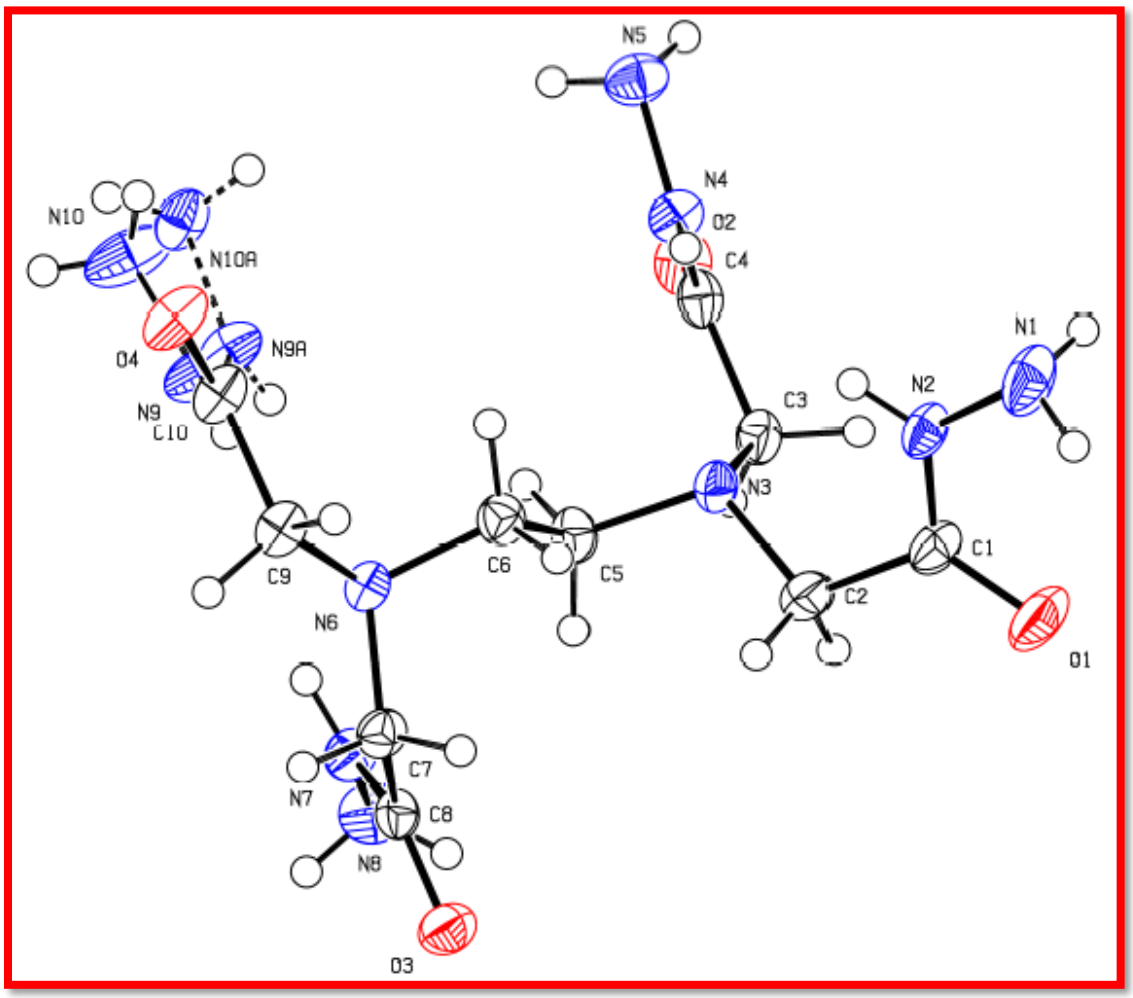
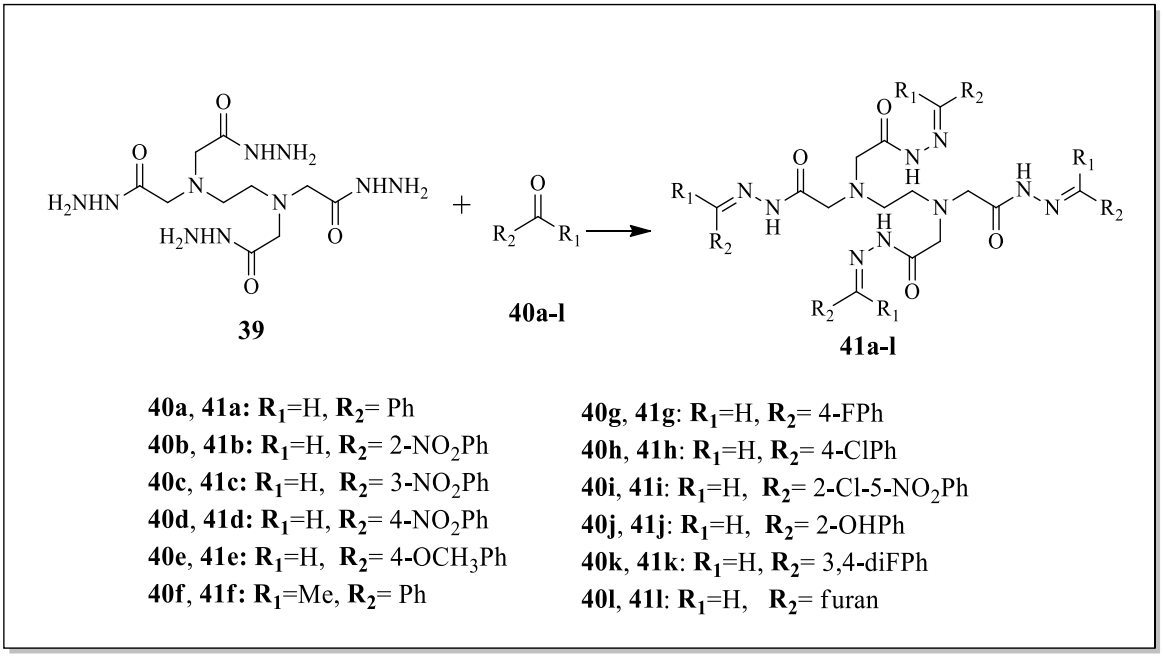


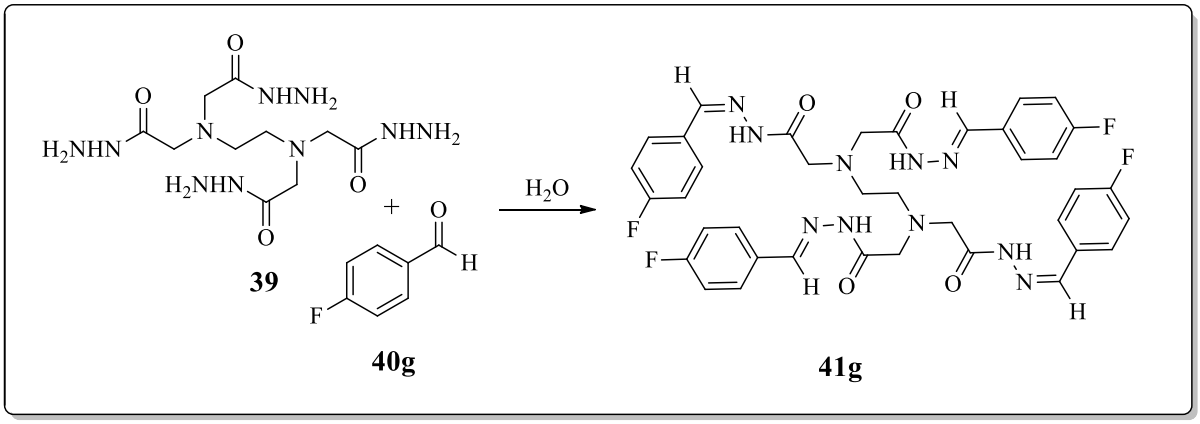
Figure (3. 4): X-ray structure for compound 39.

The next step in the project was to react the obtained EDTA-tetrahydrazide **39** with different aldehydes and ketones to obtain the required hydrazide-hydrazones. Both aliphatic and aromatic aldehydes and ketones were tested. However; only aromatic carbonyl compounds gave the required products, but none of aliphatic ketones gave the required products. The tested aldehydes are shown in **Scheme 3.4**.



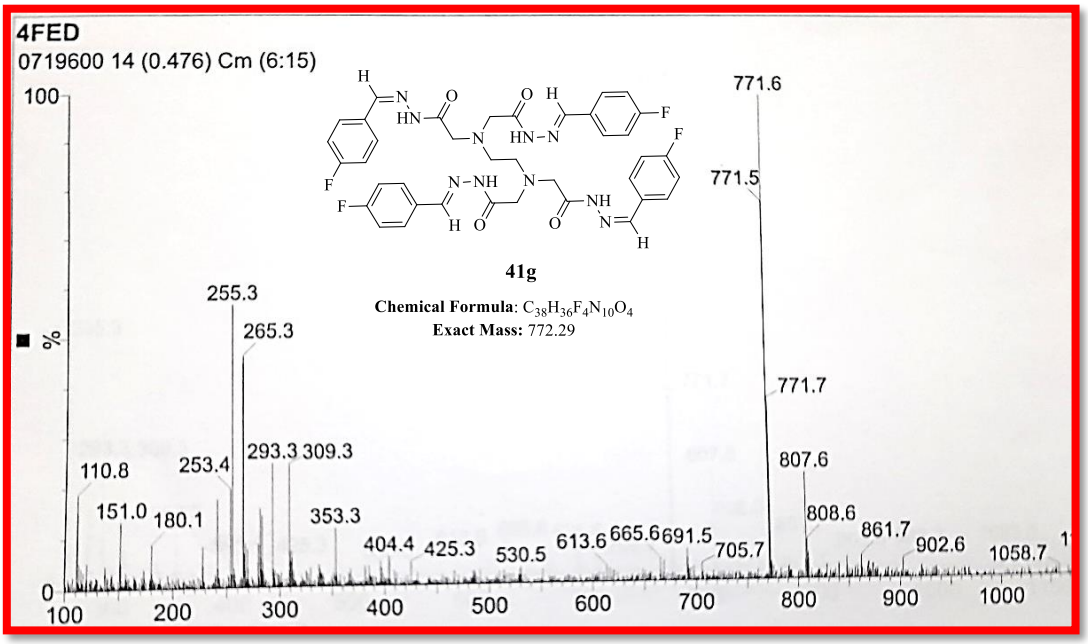
Scheme (3.4): Syntheses of *N*-acylhydrazones of EDTA-tetrahydrazide

The condensation of 1.3 equivalent of EDTA-tetrahydrazide **39** with 4.0 equivalent of aromatic carbonyl compounds **40a-l** in water as solvent led to the formation of hydrazide-hydrazones of EDTA **41a-l** in 50-60% yield. The structure of the products was confirmed by MS, HRMS, ^{1}H-NMR and ^{13}C NMR. Compound **41g** produced from the reaction EDTA-tetrahydrazide **39** with 4-florobenzaldehyde **40g** will be discussed as represented example (**Scheme 3.5**).



Scheme (3.5): Syntheses of 41g from tetrahydrazide 39 and 4-florobenzaldehyde 40g.

The structure of compound **41g** was confirmed by LRMS and its purity was confirmed by HRMS. The molecular formula for compound **41g** is $C_{38}H_{36}O_4N_{10}F_4$ and the calculated molecular weight corresponding to the chemical formula is 772. The analysis was done using electrospray technique (ES). The required molecular ion for compound **41g** was shown in the negative ion mode. In the negative ion mode ES^- a peak was shown for ($C_{38}H_{35}N_{10}O_4F_4$) $[M-H]^+$= 771 (100%) **(Figure 3.5)**.



Figure(3. 5): The LRMS spectrum for compound 41g.

The purity of the synthesized compound **41g** was confirmed by the high resolution mass spectroscopy (HRMS). Using HRMS (TOF-ES^-) technique, the analysis results showed good accordance between the value of the calculated exact mass 771.2784 for (C_{38} H_{35} O_4 N_{10} F_4) $[M - H]^+$ and the value obtained from the experimental analysis 771.2798 **(Figure 3.6).**

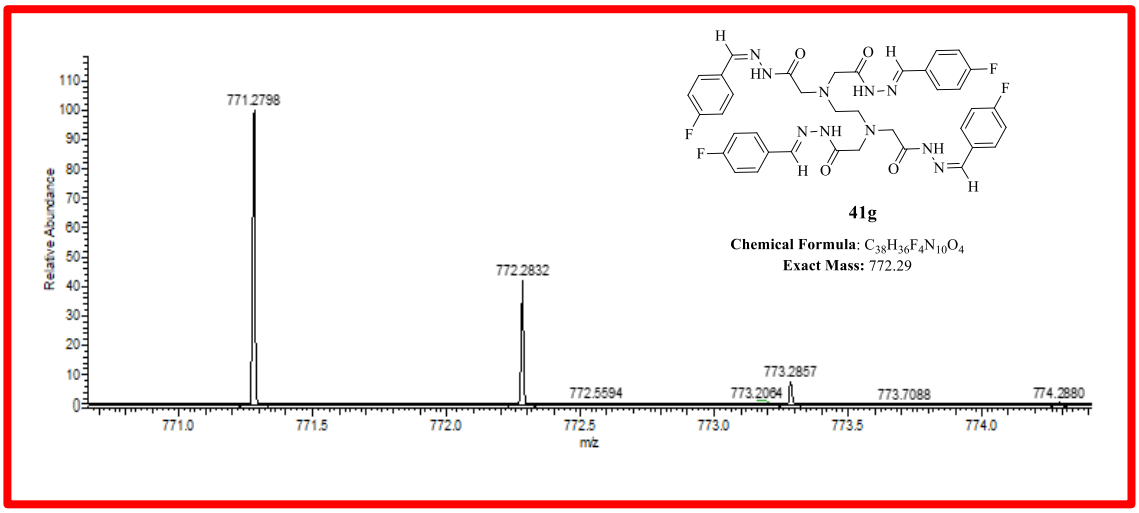


Figure (3. 6): The HRMS spectrum for compound 41g.

The structure of compound **41g** was also confirmed by ^{1}H-NMR spectroscopy . However; it is well known that acylhydrazones exist on either *E* or *Z* configuration at the imine bond *i.e.* (NHN=C) and in most of cases they exist on the *E* isomer due to its superior stability over the *Z* isomer. In addition; these compounds can adopt different conformation at the amide bond (CO-NHN) *i.e. syn* and *anti*-conformations as there are many different examples reported in literature describing this behavior of amide bond. In the reported studies; acylhydrazones containing only one amid bond lead to only two possible conformers *i.e*. *syn* and *anti*. In the *tetra*-acylhydrazones there are four possible conformers (*syn, syn*), (*anti, anti*), (*syn, anti* and *anti, syn*). In both cases *i.e.* conformations and configurations the ratio of isomers is depending on different factors notably nature of solvent used and temperature. The study of ^{1}H-NMR spectrum for compound **41g** shown clearly the formation of the different possible isomers. In the ^{1}H-NMR spectrum for compound **41g** the NH peak appeared as seven singlet peaks at δ 10.9-10.5 ppm with integration value corresponding to 4 protons (**Figure 3.7**).

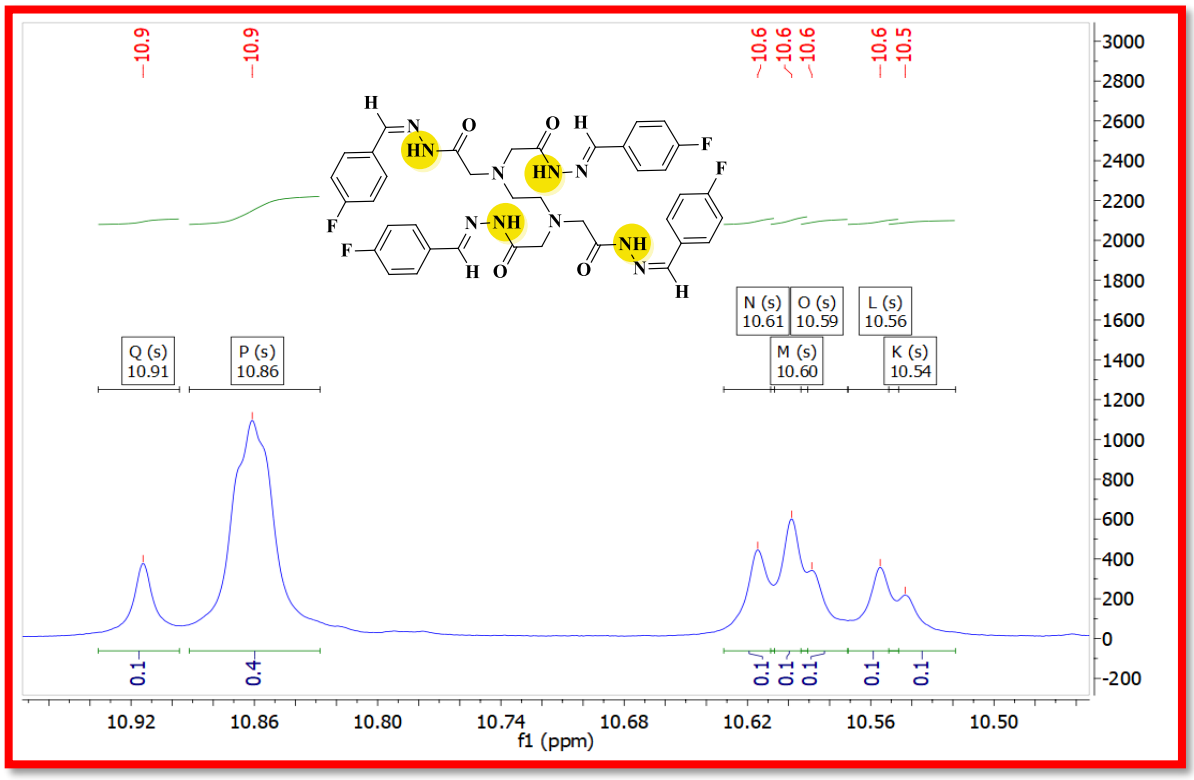


Figure (3.7): The signals of NH in the ^{1}H-NMR for compound 41g .

The proton of the imine bond (C**H**=NNH) resonated at 7.58-7.1 ppm and appeared as seven single peacks with integration values corresponding to 4 protons **(Figure 3.8)**.

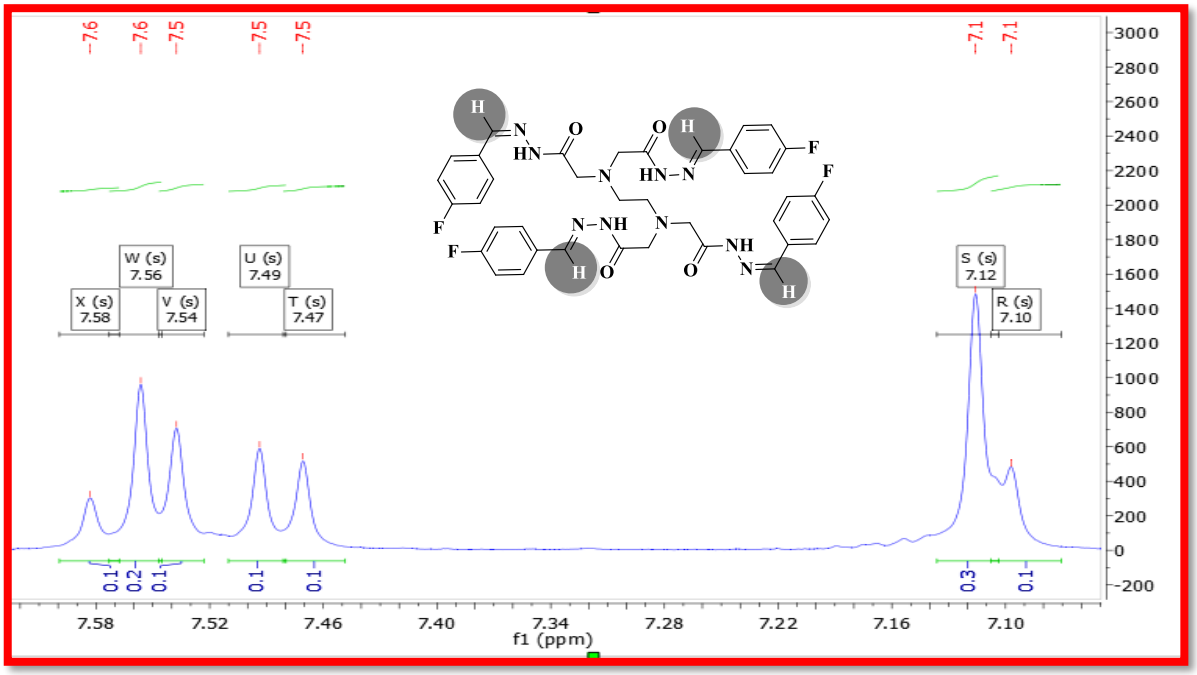


Figure (3.8): The signals of imine CH in the ^{1}H-NMR for compound 41g.

The aromatic protons resonated at 7.01 – 6.69 ppm and appeared as multiplet peaks with integration values corresponding to 16 protons **(Figure 3.9)**.

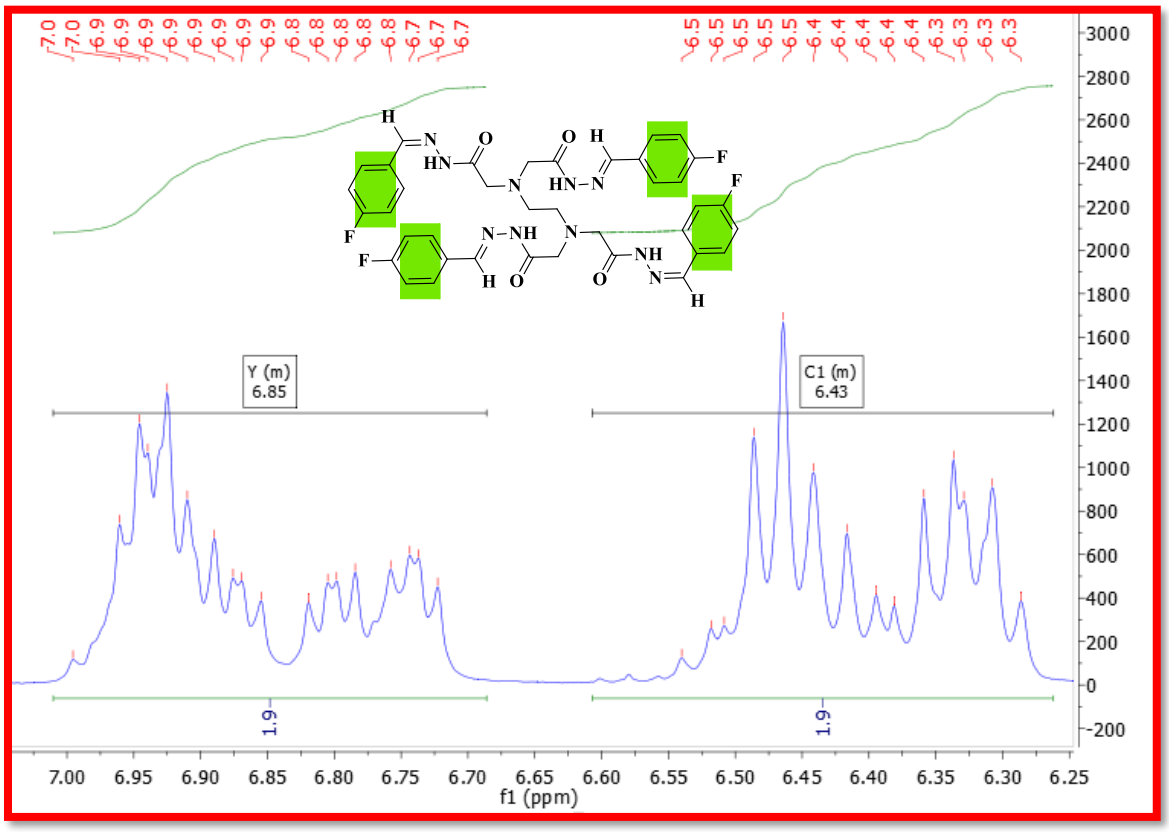


Figure (3.9): The signals of aromatic protons in the ^{1}H-NMR for compound 41g.

In the aliphatic region of the ^{1}H-NMR spectrum the 8 singlet peaks at 3,3-2,6 ppm with integration value corresponding to 8 proton were assigned to the protons of the core EDTA (4 x NC**H**$_2$C=ONH) and the four singlet peaks at 2.2-2.0 ppm with integration value corresponding to 4 H were assigned to the four protons of the EDTA (NC**H**$_2$C**H**$_2$N) (**Figure 3.10**).

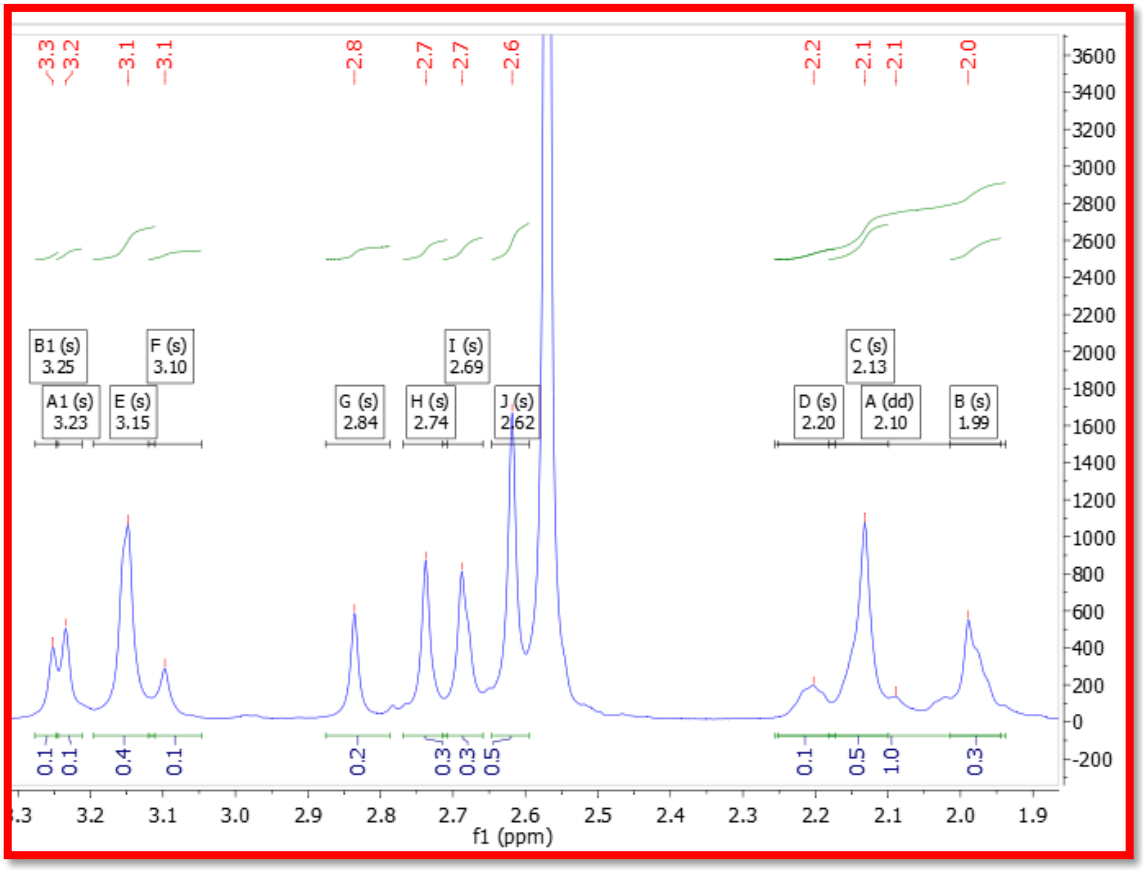
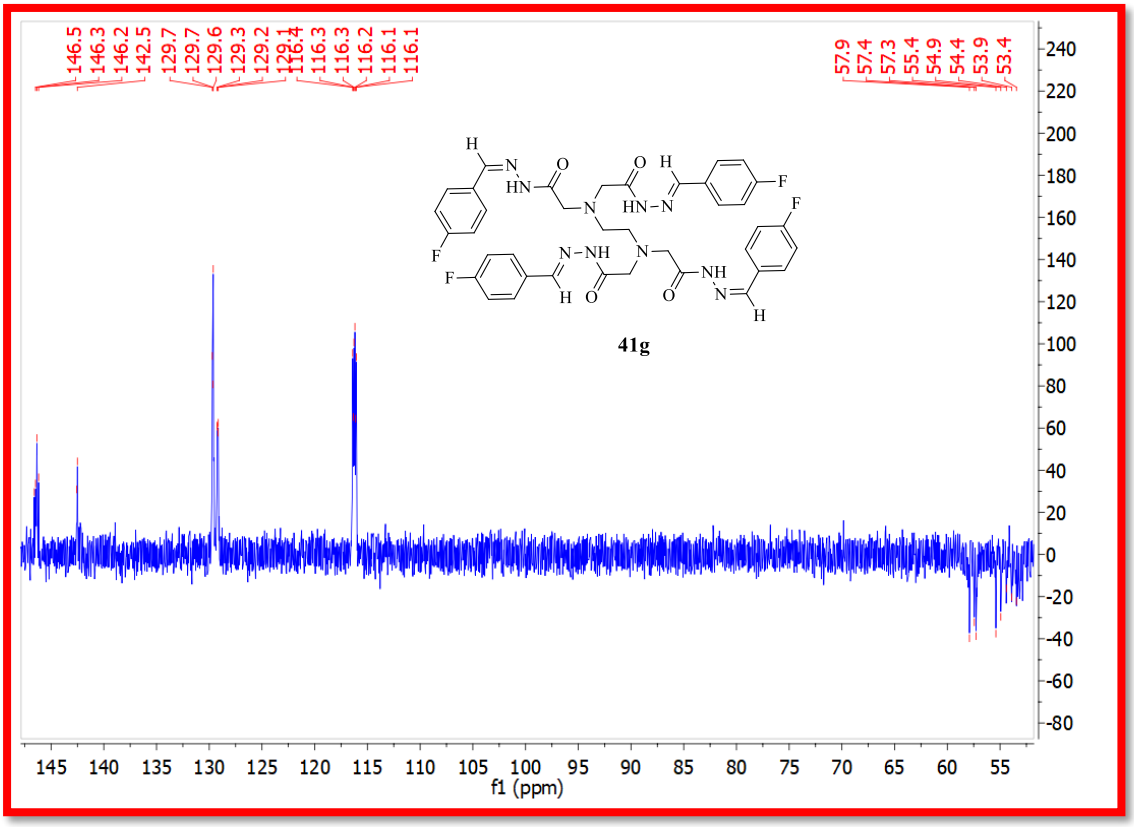


Figure (3.10): The signals of aliphatic protons in the ^{1}H-NMR for compound 41g.

The structure of compound **41g** was also confirmed with ^{13}C-NMR as the major peak were observed in the spectrum. However; the ^{13}C-NMR spectrum was weak and the DEPT spectrum was used to enhance the confirmation of the compound **41g** structure. In principle the structure of **41g** has a total of six different types of carbons that must appear in the aromatic region of the spectrum and two different carbons that must appear on the aliphatic region of the spectrum. Among the six carbons; there are three carbons that are quaternary carbons and will not appear in the DEPT 135 spectrum and only three carbons bonded to hydrogen are expected to appear in the aromatic region of the DEPT spectrum and this indeed what the DEPT spectrum has shown (**Figure 3.11**). In the same spectrum; the two different carbons bonded to two hydrogen atoms i.e. **C**H_2 were also seen in opposite phase to the aromatic carbons holding single proton *i.e.* **C**H .

In the DEPT 135 spectrum of compound **41g**; the carbon of the imine bond (**C**H=NNH) appeared as four peaks in the range of 142-146 ppm as these multiplications of signals is a clear indication about the formation/existence of different isomers *i.e.* either *E/Z* geometrical isomers and / or different conformational isomers at the amide bond (CO-NHN) *i.e. syn* and *anti*-conformations.

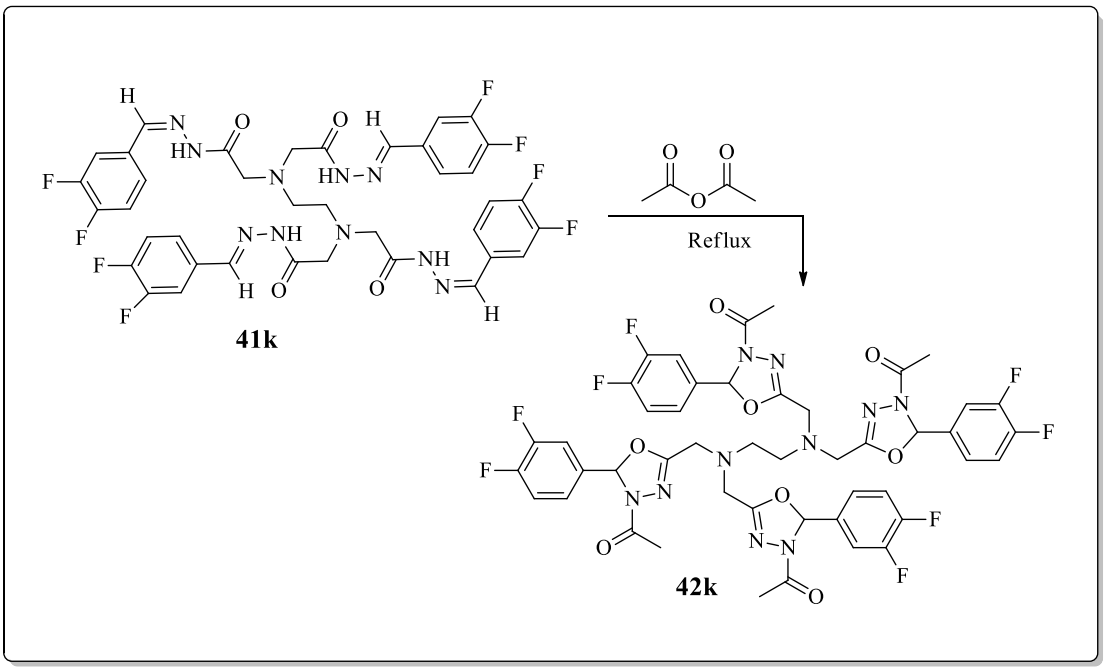


Figure(3.11): The DEPT 135 spectrum for compound 41g.

In the same spectrum; the two set of carbon signals resonated at 129.7-129.1 ppm and 116.4-116.1 were assigned to the carbon of the aromatic ring. In the aliphatic region of the spectrum; the carbon atoms of the EDTA core were clearly seen as two different sets of signals. The first set at 57.9-57.3 ppm was assigned for the (N**C**H_2C=ONH) carbon while the second set at 55.4-53.4 ppm was assigned for (N**C**H_2**C**H_2N) carbons. The two sets appeared in an opposite phase to the CH carbons of the imine and aromatic carbons.

3.2 Synthesis of *N*-acetyl oxadiazole

In the first part of the current project we have synthesized and characterized the first examples of tetra-hydrazide-hydrazones of ethylenediamine-*N,N,N',N'*-tetra-acetic acid as to the best of our knowledge; this work has not been reported before based on Sci-finder data base search. However; with this set of compounds in hand, we thought to convert the obtained hydrazide-hydrazones into *N*-acetyl-dihydro-1,3,4-oxadiazoles. The attempt was accomplished *via* refluxing of compound **41K** in acetic anhydride (**Scheme 3.6**). The reaction was followed up by TLC After approximately 45 min; the TLC indicated that the starting materials was consumed. The reaction mixture was poured in water to hydrolyze the excess acetic anhydride to acetic acid, followed by the addition of $NaHCO_3$ solution to convert the acetic acid to water soluble sodium acetate. The crud mixture was transferred to aseparatory funnel and the organic layer was extracted by ethyl acetate. The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuum. The crude product was purified by column chromatography using a mixture of hexane to ethyl acetate (1:3) gradually changed to neat ethyl acetate to give the pure product in 45% yield. The obtained product **42k** was analyzed by the different spectroscopic techniques.



Scheme (3.6): Syntheses of *tetra*-*N*-acetyl-dihydro-1,3,4-oxadiazoles 42k.

The molecular formula of compound **42k** is $C_{46}H_{40}F_8N_{10}O_8$ and the molecular weight corresponding to this formula is 1012. In the high resolution mass spectrum analysis of compound **42k** a molecular ion of 1035.2777 was observed and its corresponding to $[M+Na]^+$= 1035. 2795 (**Figure 3.12**).

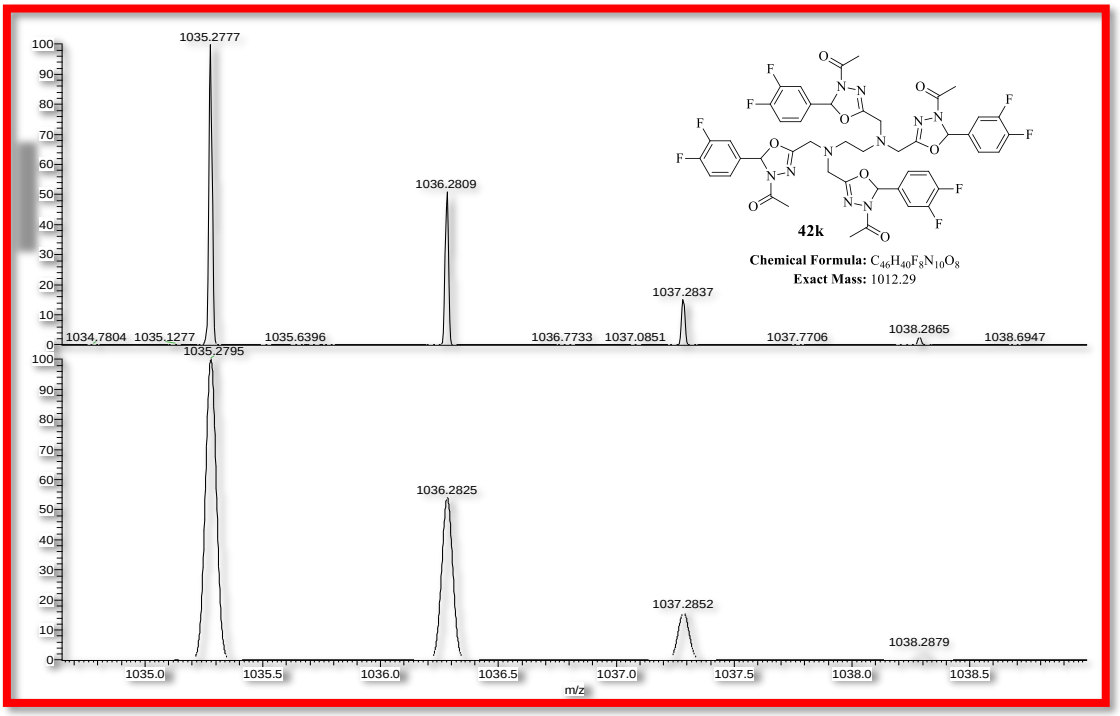


Figure (3.12): The high resolution mass spectrum for compound 42k.

The ^{1}H-NMR spectrum was sort of complicated and unclear due to the presence of 2 F atoms that make the spectrum sort of complicated due to the coupling with the protons in the compound. In addition the sample was not dry enough so the signals of the solvent were dominant and make the signals unobvious. The unprocessed ^{1}H-NMR for compound **42k** is shown in (**Figure 3.13**).

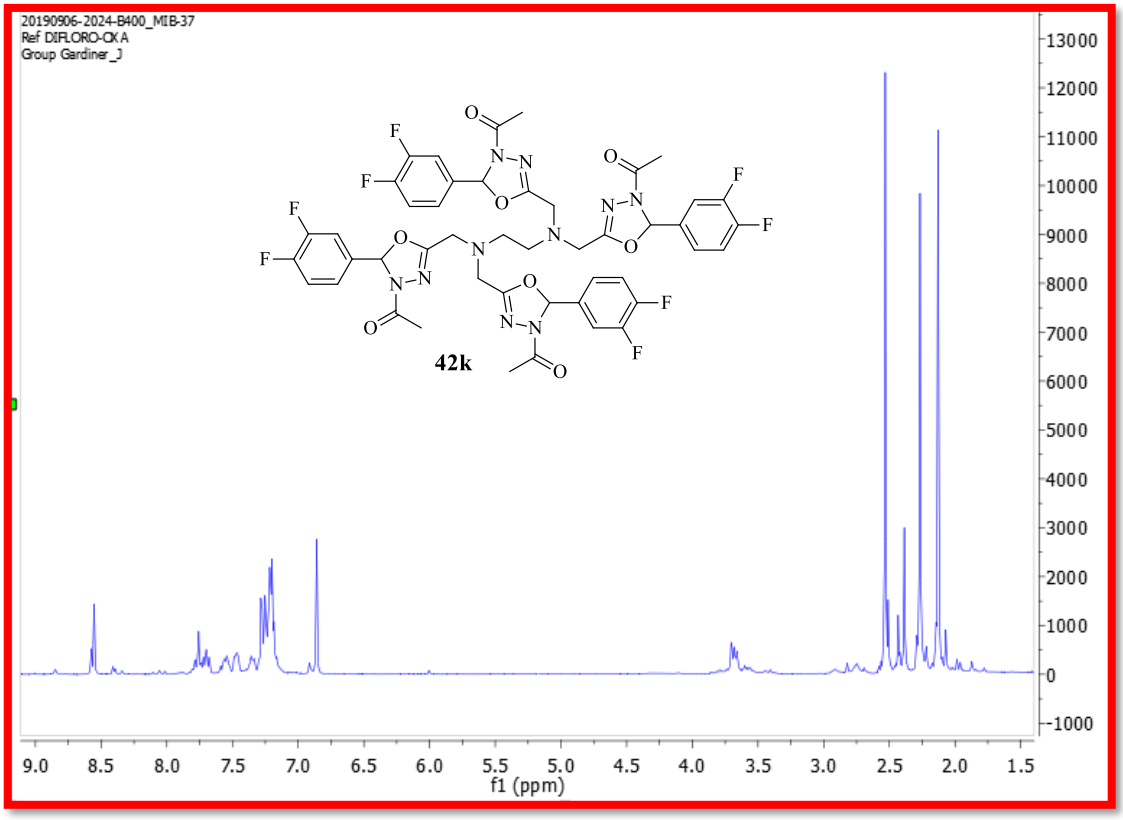


Figure (3.13): The unprocessed ^{1}H-NMR spectrum for compound 42k.

The structure of compound **42k** was confirmed by ^{13}C-NMR spectrum. The four signal at lower filed of the spectrum at 171.5-141.1 ppm were assigned for the quaternary carbons of C=O, C=N, the two C-F carbons and the quaternary carbon of the aromatic ring. The aromatic carbons resonated at 125.7-115.6 ppm for three CH carbons and one quaternary carbons. These aromatic carbons were influenced by the existence of the F atoms that caused the multiplication of the signals due to F-C coupling. The duplication of signals was clearly seen in the ^{13}C-NMR spectrum and was strong for the carbons that are closed to the F atoms (**Figure 3.14**). In the same spectrum, the formation of the oxadiazole ring was confirmed by a significant peck for the CH carbon of the oxadiazole ring. It is well known that the formation of the oxadiazole ring is always indicated in ^{13}C-NMR by appearance of a peak at about 85-105 ppm as this peak is a strong evidence about the formation of the oxadiazole ring. For compound **42k** this peak resonated at about 90.4 ppm and it's considered as an evidence about the formation of the oxadiazole ring.

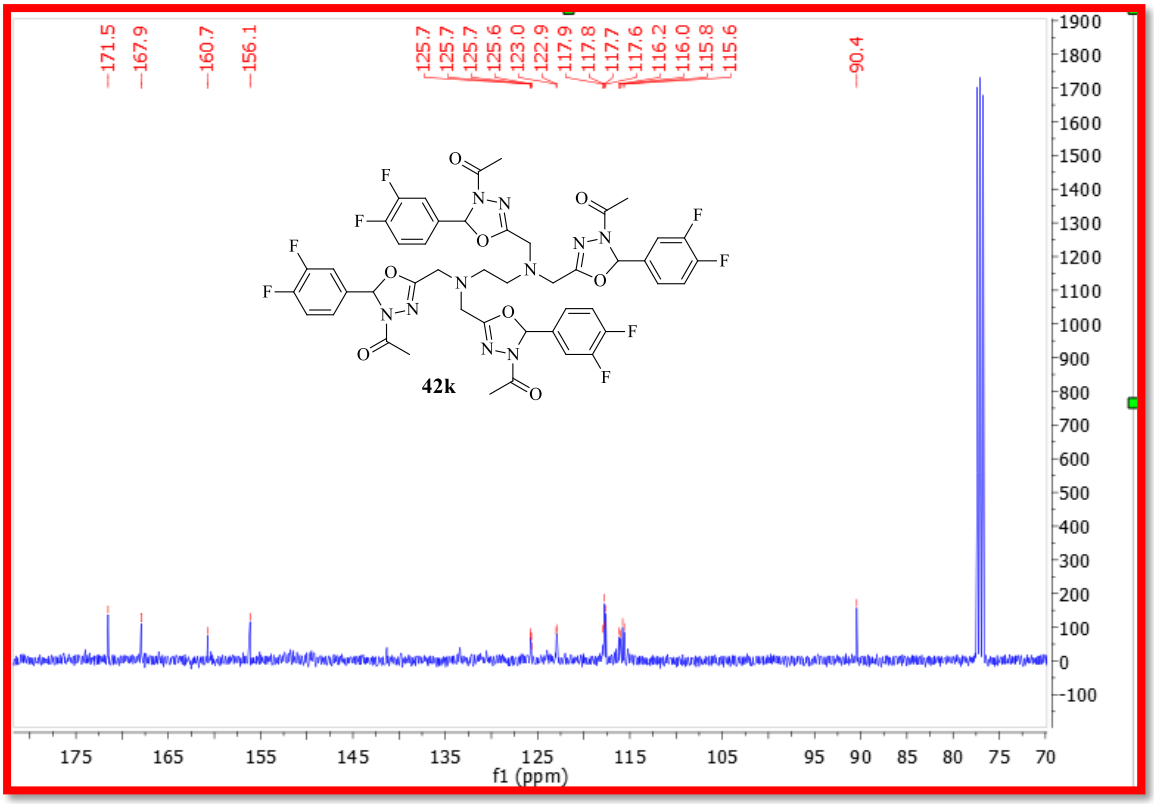


Figure (3.14): The aromatic region of ^{13}C-NMR spectrum for compound 42k.

In the aliphatic region of the spectrum; in addition to some solvent peaks, the carbon signals of the CH_2 that belongs to the core EDTA were very weak and the spectrum just showed the carbon pecks of the CH_3 at about 21-20 ppm. The carbon of CH_3 was duplicated as this was due to the free rotation of C-N bond that led to the adoption of different conformation of the amide bond (**Figure 3.15**).

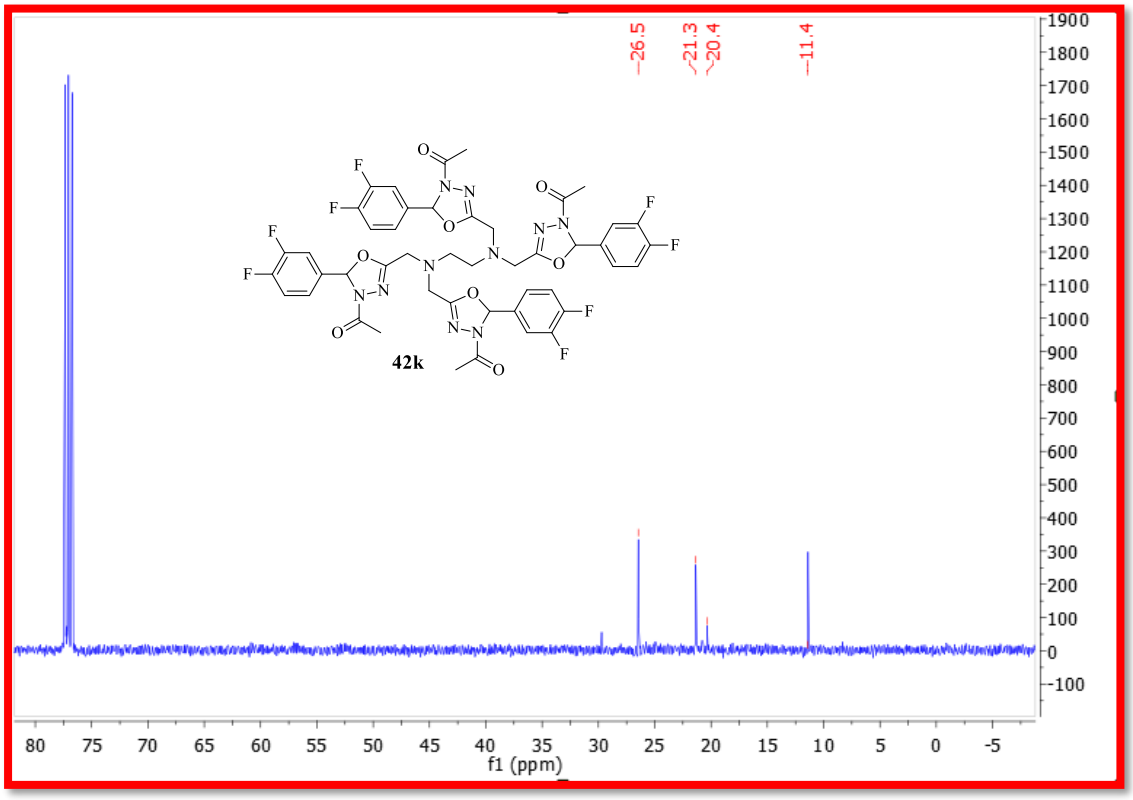


Figure (3.15): The aliphatic region of ^{13}C-NMR spectrum for compound 42k.

The DEPT 135 spectrum provided a further confirmation for the structure of **42k**. The five quaternary carbons disappeared in the DEPT spectrum. The three CH carbons were strongly coupled with the F atoms and they appeared as three sets of multiple pecks in the range of 115-125 ppm. The unique C atom of the oxadiazole appeared at 90.5 ppm. The carbon signals of the two different types of CH_2 which belongs to the EDTA core resonated on opposite direction of CH carbons at 57.0 and 52.9 ppm. The carbon signals of the CH_3 groups resonated at 20.4-21.4 ppm. The extra pecks at 29.7, 26.5, 25.0 and 11.4 ppm were attributed to impurities or solvents residuals (**Figure 3.16**).

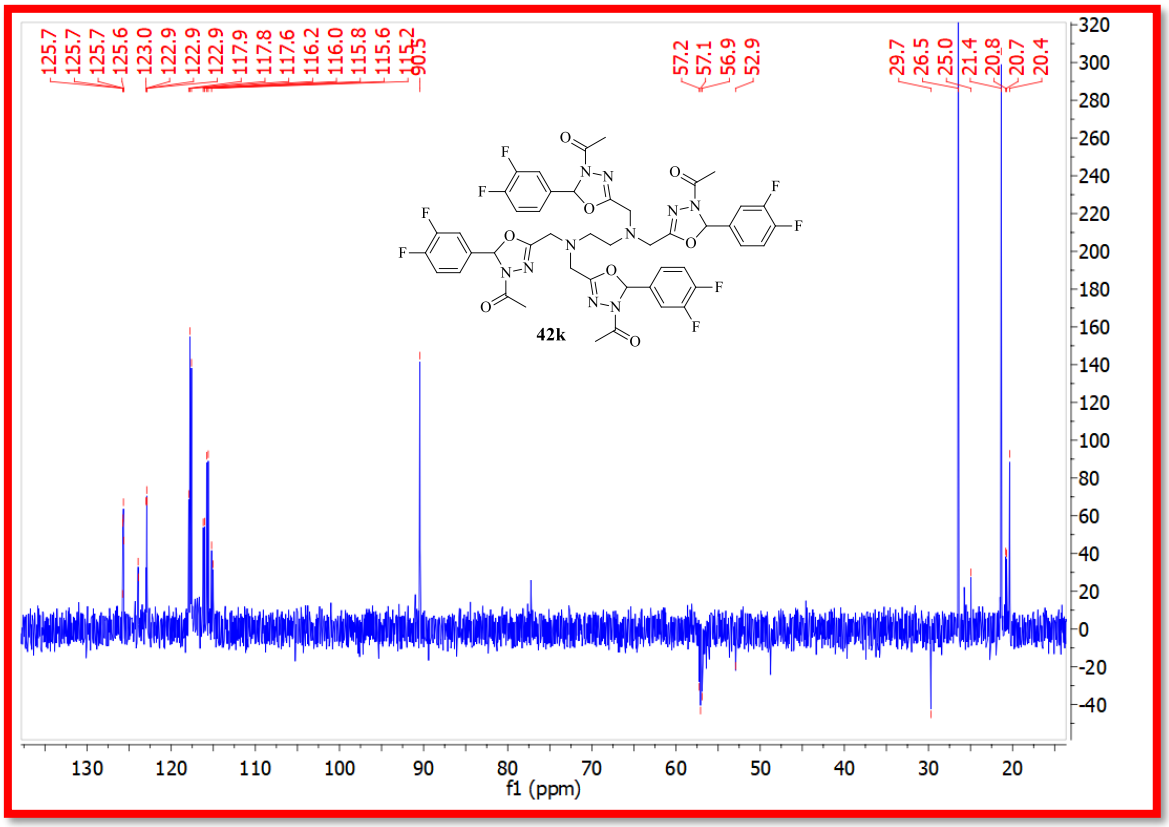


Figure (3.16): The DEPT 135 spectrum for compound 42k.

Chapter 4

Experimental Part

Chapter 4
Experimental Part

4.1 Experimental

^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100.0 MHz on a Bruker AC400 spectrometer. Chemical shifts are denoted in ppm (δ) relative to internal solvent standard. The splitting patterns for NMR spectra are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or combinations thereof. Coupling constants (J) are designated in Hz. Assignments were made with the aid of DEPT135, experiments. Mass spectra were recorded on a VG 70/70 Hybrid or a Kratos MS-50 mass spectrometer by ES (positive ion and negative ion mode) with flow injection *via* a Waters 2790 separation module autosampler. IR spectra were obtained using a Nexus 670/870 FT-IR spectrometer. X-Ray structure determination was obtained using X-ray single crystal data and was collected at 230 K using graphite monochromated Mo Kα λ = 0.7107 Å radiation on a Bruker SMART APEX CCD diffractometer. Data reduction was carried out using SAINT and the structure was solved using SHELXS-97. Melting point determinations were made using a Stuart Scientific SMP1 apparatus and are uncorrected. Analytical TLC was performed on Fluka or Merck silica gel aluminium backed plates containing a 254 nm fluorescent indicator. The plates were visualised under UV light. Column chromatography employed Apollo (for flash chromatography) silica gel, using GPR hexane, GPR diethyl ether and GPR ethyl acetate. THF was dried by distillation from sodium benzophenone ketyl. All reactions were conducted in dry glassware, unless otherwise stated. All chemicals were used directly from supplier's vessel without further purification, unless otherwise stated.

4.2 General Procedures:

4.2.1 Method for the syntheses of Tetraethyl 2,2',2'',2'''-(ethane-1,2-diylbis(azanetriyl))tetraacetate 38

Ethylendiaminetetraaceticacid (EDTA) **37** (0.068 mol, 20.0 g) was dissolved in absolute ethanol (800 mL) .To this solution, 12.8 ml (.252 mol) concentrated sulfuric acid (H_2SO_4) was added to the reaction in one portion. This reaction mixture was refluxed for 3 hours. After the reaction completed and cooling to room temperature ethanol was removed by vacuum. Then the mixture was neutralized by $NaHCO_3$ followed by extracted process with Chloroform two times ,organic phases were combined and dried over magnesium sulfate, to yield 16.0 g (80%) of the title compound as viscious oil .

4.2.2 Method for the syntheses of EDTA-tetrahydrazide 39

A mixture of tetraethyl 2,2',2",2"'-(ethane-1,2-diylbis(azanetriyl))tetraacetate **38** and hydrazine hydrate (51% in H_2O; 1 ml, 17.1 mmol, 4 equiv.) was heated in EtOH (20 ml) under reflux overnight . The solution was cooled down to room temperature to obtain white crystals precipitate. The precipitate was filtered off and the residue dried under vacuum to produce 0.85 g (85%) of the EDTA-tetrahydrazide **39**.

4.2.3 General method for the syntheses of N-acylhydrazones of EDTA tetrahydrazide 41a-l

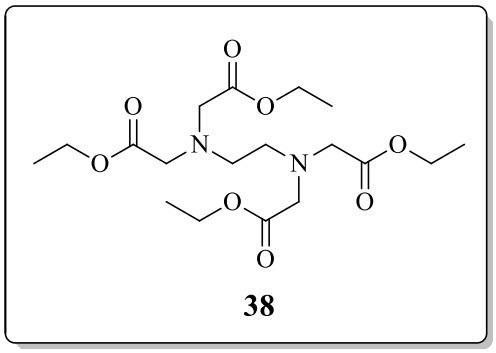
The EDTA-tetrahydrazide **39** (3.3 g, 9.5 mmol) was dissolved in distilled H_2O (200 ml) and the corresponding carbonyl compound **40a-l** (4.0 equiv.) was slowly added to the EDTA tetrahydrazide. The reaction mixture was left under stirring for 3 h. The formed precipitate was filtered and the residue washed with H_2O and then crystalized from ethanol to give the solid products **41a-l** .

4.2.4 General method for The syntheses of N-acetyl-dihydro-1,3,4-oxadiazoles 42k

A mixture of **41K** and acetic anhydride was refluxed and the reaction was followed up by TLC. After approximately 45 min; the TLC indicated that the starting materials were consumed. The reaction mixture was poured in water to hydrolyze the excess acetic anhydride to acetic acid, followed by the addition of $NaHCO_3$ solution

to convert the acetic acid to water soluble sodium acetate. The crud mixture was transferred to separatory funnel and the organic layer was extracted by ethyl acetate. The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuum. The crude product was purified by column chromatography using a mixture of hexane to ethyl acetate (1:3) gradually changed to neat ethyl acetate to give the pure product in 45% yield.

Tetraethyl 2,2',2'',2'''-(ethane-1,2-diylbis(azanetriyl))tetraacetate 38

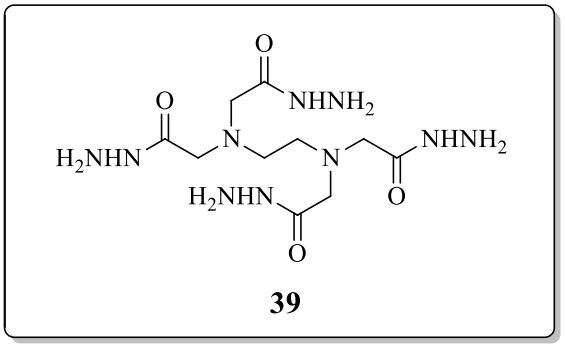


38

Yield (80%); oily compound; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (q, *J* = 7.1 Hz, 8H, OC**H**$_2$), 2.10 (s, 4H, N-C**H**$_2$C**H**$_2$-N), 2.0 (s, 8H, NC**H**$_2$), 1.18 (t, *J* = 7.1 Hz, 12H, OCH_2C**H**$_3$).

LRMS (ES^+) 427 $[M + Na]^+$; HRMS (TOF-ES^-) *m/z* calcd. for $C_{18}H_{32}N_2O_8Na$ $[M + Na]^+$ 427.2051, found 427.2031.

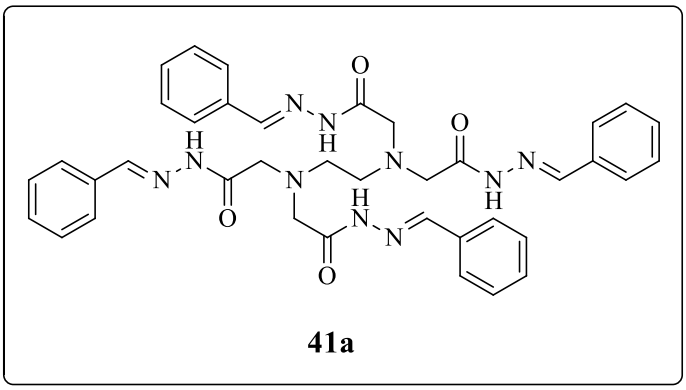
2,2',2'',2'''-(ethane-1,2-diylbis(azanetriyl))tetra(acetohydrazide) 39



39

M.p. (164-165 ^{o}C); white crystal; Yield (85%); ^{1}H NMR (400 MHz, D_2O) δ 3.2 (s, 8H, 4 x NC**H**$_2$CONHNH$_2$), 2.6 (s, 4H, 2 x NC**H**$_2$ C**H**$_2$N). ^{13}C NMR (100 MHz, D_2O) δ 171.8 (**C**=O), 56.7 (N**C**H$_2$CONHNH$_2$), 52.6 (N**C**H$_2$ C**H**$_2$N). LRMS (ES^+) 371 $[M + Na]^+$; HRMS (TOF-ES^-) *m/z* calcd. for $C_{10}H_{24}O_4N_{10}Na$ $[M + Na]^+$ 371.1874, found 371.1877.

(*N'E,N'''E,N'''''E,N'''''''E*)-2,2',2'',2'''-(ethane-1,2 diylbis(azanetriyl))tetrakis(N'-benzylideneacetohydrazide) 41a

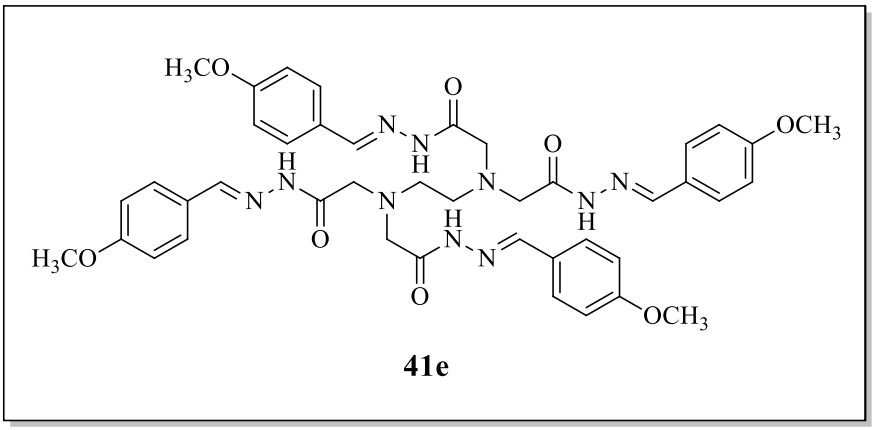


41a

M.p. (182-185 ^{o}C); Yield (55%); ^{1}H NMR (400 MHz, DMSO-H_6) δ 10.91, 10.85, 10.84, 10.82, 10.76, 10.55, 10.52, 10.49 (8s, 4H, CH=NN**H**), 7.55, 7.51, 7.48, 7.46, 7.13, 7.11, 7.08, 7.07 (8s, 4H, C**H**=NNH), 6.88 – 6.60 (m, 10H, **Ar**), 6.59 – 6.41 (m, 10H, **Ar**), 3.23, 3.22, 3.12, 3.07, 2.82, 2.73, 2.71, 2.65, 2.62 (8s, 8H, 4 x NC**H**$_2$CONHN), 2.58, 2.19, 2.18, 2.10, 1.99, 1.95, 1.95, 1.91 (8s, 4H, 2 x NC**H**$_2$N). ^{13}C NMR (100 MHz, DMSO-H_6) δ 172.86, 172.69, 168.17, 167.82, 167.73, 167.47 (**C**=O), 147.86, 147.67, 147.56, 147.50, 147.36, 147.34, 143.75 (N=**C**H), 134.85, 134.79, 134.65, 134.45, 134.43, 134.26, 133.33, 131.26, 130.46, 130.18, 129.74, 129.40, 129.22, 129.04, 128.85, 127.54, 127.17, 127.11, 127.07, 127.03, 125.59 (**C** and **C**H aromatic C), 58.20, 58.09, 57.97, 57.48, 57.29, 57.15 (N**C**H$_2$CONHN), 55.39, 54.95, 54.30, 53.93, 53.54, 53.42, 52.78 (N**C**H$_2$C**H**$_2$N).

LRMS (ES$^-$) 669 [M - H]$^+$; HRMS (TOF-ES$^-$) *m/z* calcd. for $C_{38}H_{39}O_4N_{10}$ [M - H]$^+$ 699.3161 found 699.3172.

(*N'E,N'''E,N'''''E,N'''''''E*)-2,2',2'',2'''-(ethane-1,2-diylbis(azanetriyl))tetrakis(*N'*-(4-methoxybenzylidene)acetohydrazide) 41e

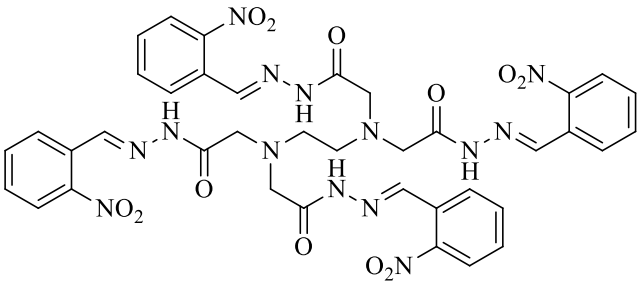


41e

M.p. (240-242 ºC); Yield (50%); ^{1}H NMR (400 MHz, DMSO) δ 11.60, 11.57, 11.55, 11.53, 11.25, 11.24, 11.21, 11.18 (8s, 4H, CH=NN**H**), 8.32, 8.28, 8.24, 8.22, 7.86, 7.85, 7.84 (7s, 4H, C**H**=NNH), 7.69 – 7.25 (m, 8H, **Ar**), 7.05 – 6.73 (m, 8H, **Ar**), 4.02, 4.00, 3.90, 3.86, 3.79, 3.78, 3.76 (7s, 12H, OC**H**$_3$), 3.76, 3.75, 3.74, 3.62, 3.50, 3.44 (7s, 8H, 4 x NC**H**$_2$CONHN) , 3.00, 2.91, 2.79, 2.79, 2.75, 2.73 (6s, 4H, 2 x N C**H**$_2$C**H**$_2$N). ^{13}C NMR (100 MHz, DMSO) δ 167.33, 167.16 (**C**=O), 161.88, 161.58, 161.20, 160.93 (**C**-OCH$_3$) 147.51, 147.37, 147.19 (N=**C**H), 129.14, 129.07, 128.62, 114.72, 114.63, 114.57 (Ar-C), 58.21, 57.55, 57.25, 55.72, 55.68, 55.65, 55.05, 54.73, 54.59 (N**C**H$_2$CONHN, O**C**H$_3$, N**C**H$_2$N).

LRMS (ES$^-$) 819 [M - H]$^+$; HRMS (TOF-ES$^-$) *m/z* calcd. for $C_{42}H_{47}O_8N_{10}$ [M - H]$^+$ 819.3584 found 819.3602.

2,2',2'',2'''-(ethane-1,2-diylbis(azanetriyl))tetrakis(*N*'-(2-nitrobenzylidene)acetohydrazide) 41b

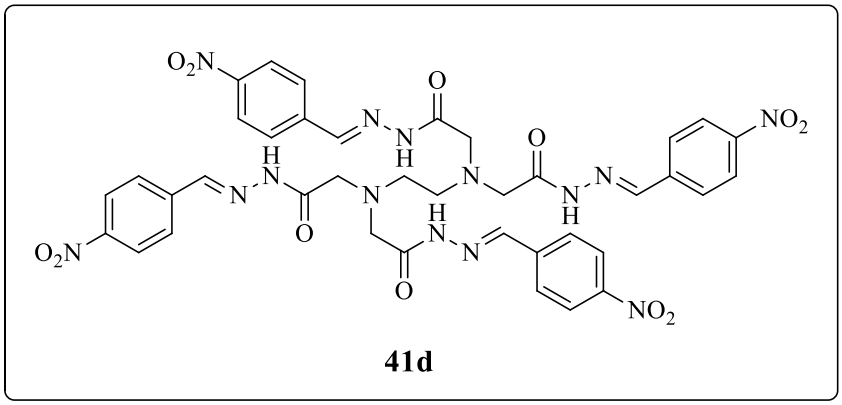


41b

M.p. (220-222°C); Yield (60%); ^{1}H NMR (400 MHz, DMSO-H_6) δ 11.20, 11.16, 10.89, 10.88, 10.85, 10.84, 10.81 (7s, 4H, CH=NN**H**), 7.92, 7.90, 7.89, 7.87, 7.52, 7.49 (6s, 4H, C**H**=NNH), 7.39 – 7.05 (m, 8H, **Ar**), 7.04 – 6.68 (m, 8H, **Ar**), 3.25, 3.23, 3.19, 3.14, 2.84, 2.78, 2.76, 2.70 (8s, 8 H, 4 x NC**H**$_2$CONHN), 2.17, 2.14, 2.09, 2.03 (4s, 4H, 2 x NC**H**$_2$N). ^{13}C NMR (100 MHz, DMSO-H_6) δ 168.42, 168.11, 168.00, 167.77 (**C**=O), 148.49, 148.36 (NO_2-**C**), 143.00, 142.80, 142.60,142.40, 142.20 (**C**H=NNH) , 139.10, 138.99, 138.92, 138.65, 134.12, 134.07, 133.96, 133.86, 133.81, 131.02, 130.94, 130.75, 130.69, 128.46, 128.40, 128.33, 128.18, 128.06, 125.12, 125.00 (Aromatic C), 57.60, 57.29, 57.16 (NC**H**$_2$CONHN), 54.76, 54.43, 53.85, 53.52, 53.13 (N C**H**$_2$C**H**$_2$N).

LRMS (ES^+) 881 $[M + H]^+$; HRMS (TOF-ES^-) *m/z* calcd. for $C_{38}H_{37}O_{12}N_{14}$ $[M + H]^+$ 881.2710, found 881.2705.

(*N'E,N'''E,N'''''E,N'''''''E*)-2,2',2'',2'''-(ethane-1,2-diylbis(azanetriyl))tetrakis(N'-(4-nitrobenzylidene)acetohydrazide) 41d

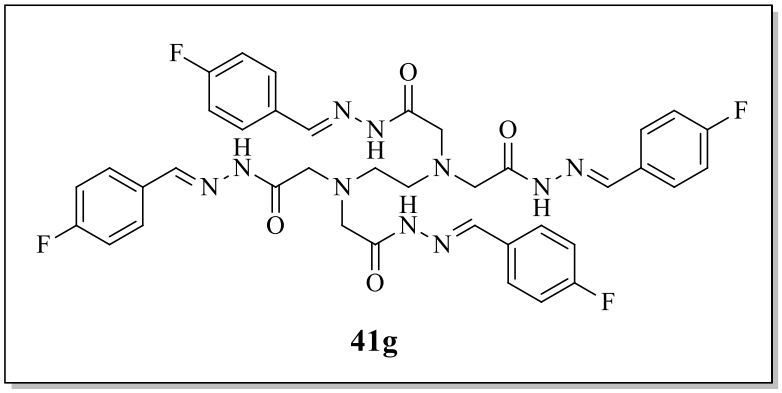


41d

M.p. (192-194 ºC); Yield (20%); ^{1}H NMR (400 MHz, DMSO) ^{1}H NMR (400 MHz, DMSO-H_6) δ 11.90, 11.85, 11.69, 11.67, 11.64, 11.61 (6s, 4H, CH=NN**H**), 8.66, 8.46, 8.41, 8.38, 8.32, 8.30, 8.28, 8.27, 8.25, 8.25 (10s, 4H, C**H**=NNH), 8.24 – 7.96 (m, 8H, **Ar**), 7.97 – 7.64 (m, 8H, **Ar**), 4.09, 4.07, 4.04, 4.00, 3.99, 3.93, 3.63, 3.57, 3.53, 3.53, 3.50, 3.488 (12s, 8H, NC**H**$_2$C=ONH), 3.04, 2.95, 2.81 (3s, 4H, NC**H**$_2$C**H**$_2$N).

LRMS (ES$^+$) 879 [M - H]$^+$; HRMS (TOF-ES$^-$) *m/z* calcd. for $C_{38}H_{35}O_{12}N_{14}$ [M - H]$^+$ 879.2564, found 879.2580.

2,2',2'',2'''-(ethane-1,2-diylbis(azanetriyl))tetrakis(N'-(4-fluorobenzylidene)acetohydrazide) 41g

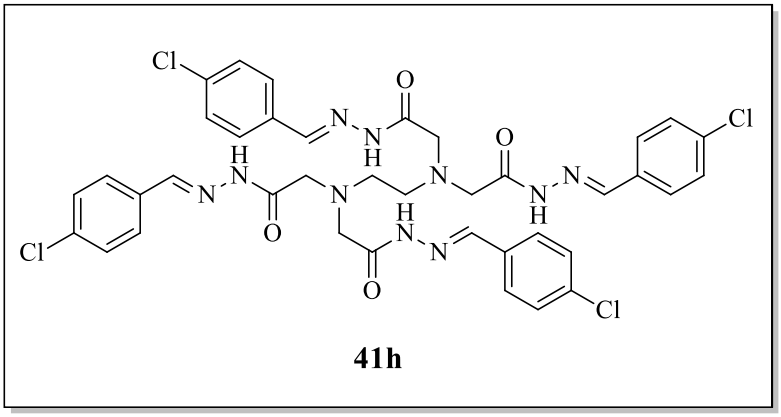


41g

M.p. (228-230 °C); Yield (63%); ^{1}H NMR (400 MHz, DMSO-H_6) δ 10.91, 10.86, 10.61, 10.60, 10.59, 10.56, 10.54 (7s, 4H, CH=NN**H**), 7.58, 7.56, 7.54, 7.49, 7.47, 7.12 , 7.10 (7s, 4H, C**H**=NNH), 7.01 – 6.69 (m, 8H, **Ar**), 6.61 – 6.26 (m, 8H, **Ar**), 3.25, 3.23, 3.15, 3.10, 2.84, 2.74, 2.69, 2.62 (8s, 8H, NC**H₂**C=ONH), 2.20, 2.13, 2.10, 1.99 (4s, 4H, NC**H₂**C**H₂**N). ^{13}C-NMR (100 MHz, DMSO) δ 169.80, 167.40 (**C**=O), 163.88 (**C**-F aromatic) 146.6, 146.30, 146.20 (N=**C**H), 129.70, 129.60, 129.30, 129.10, 116.90, 116.60, 116.30, 116.10 (Ar-**C**), 56.4(N**C**H_2CONHN), 52.2 (N**C**H_2N).

LRMS (ES^+) 771 $[M - H]^+$; HRMS (TOF-ES^-) *m/z* calcd. for $C_{38}H_{35}O_4N_{10}F_4$ $[M - H]^+$ 771.2798, found 771.2784.

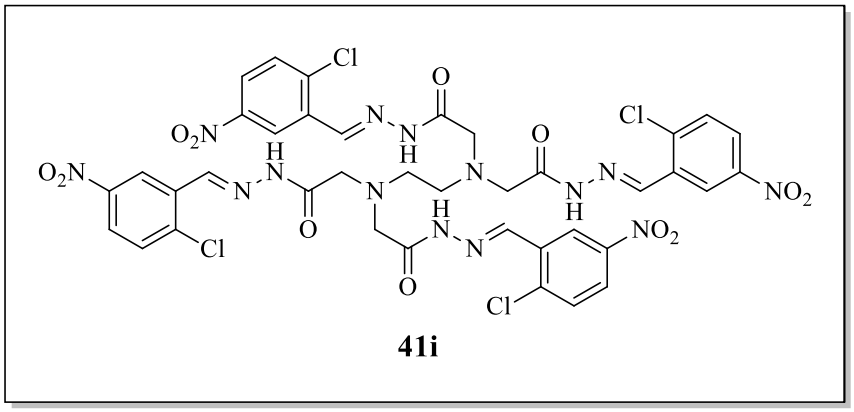
(*N'E,N'''E,N'''''E,N'''''''E*)-2,2',2'',2'''-(ethane-1,2-diylbis(azanetriyl))tetrakis(*N*'-(4-chlorobenzylidene)acetohydrazide) 41h



41h

M.p. (196-198 ^{o}C); Yield (40%); ^{1}H-NMR (400 MHz, DMSO-H_6) δ 11.21, 10.95, 10.71, 10.60, 10.59, (5s, 4H, CH=NN**H**), 7.45, 7.66, 7.57, 7.47, 7.12 (5s, 4H, C**H**=NNH), 7.01 – 6.69 (m, 8H, **Ar**), 6.61 – 6.26 (m, 8H, **Ar**), 3.25, 3.23, 3.15, 3.10, 2.84, 2.74, 2.69, 2.62 (8s, 8H, NC**H**$_2$C=ONH), 2.20, 2.13, 2.10, 1.99 (4s, 4H, NC**H**$_2$C**H**$_2$N). ^{13}C-NMR (100 MHz, DMSO) δ 169.80, 165.10 (**C**=O), 146.7, 146.50, 146.20 (N=**C**H), 137.8, 137.6, 137.2 (**C**-Cl), 130.20, 129.80, 129.50, 129.10, 116.80, 116.50, 116.30, 116.10 (Ar-**C**), 56.4(N**C**H$_2$CONHN), 52.2 (N**C**H$_2$N). LRMS (ES$^+$) 771 [M - H]$^+$; HRMS (TOF-ES$^-$) *m/z* calcd. for $C_{38}H_{35}O_4N_{10}Cl_4$ [M - H]$^+$ 835.1675, found 836.1942. .

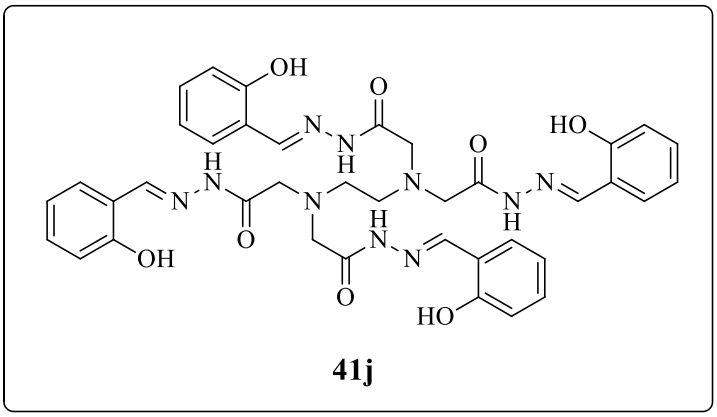
(*N'E,N'''E,N'''''E,N'''''''E*)-2,2',2'',2'''-(ethane-1,2-diylbis(azanetriyl))tetrakis(*N*'-(2-chloro-5-nitrobenzylidene)acetohydrazide) 41i



41i

M.p. (250-252 ºC); Yield (50%); ^{1}H NMR (400 MHz, DMSO) δ 12.11, 12.08, 12.05, 12.04, 11.86, 11.83, 11.76 (7s, 4H, CH=NN**H**), 8.73, 8.71, 8.70, 8.68, 8.67, 8.62, 8.60 8.59 (7s, 4H, C**H**=NNH), 8.56 – 8.53 (m, 6H, **Ar**), 8.42 – 8.10 (m, 6H, **Ar**), 4.16, 4.13, 4.10, 4.06, 3.69, 3.65, 3.62, 3.59 (8s, 8H, NC**H$_2$**C=ONH), 3.13, 3.06, 2.94, 2.89 (3s, 4H, NC**H$_2$**C**H$_2$**N). LRMS (ES$^+$) 1015 [M - H]$^+$; HRMS (TOF-ES$^-$) *m/z* calcd. for C_{38} H_{31} O_{12} N_{14} Cl_4 [M - H]$^+$ 1015.1027, found 1015.1005.

(*N'E,N'''E,N'''''E,N'''''''E*)-2,2',2'',2'''-(ethane-1,2-diylbis(azanetriyl))tetrakis(N'-(2-hydroxybenzylidene)acetohydrazide) 41j

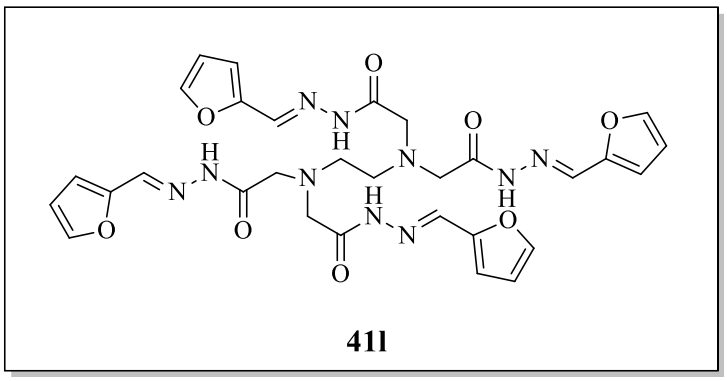


41j

M.p. (188-191 ºC); Yield (70%); ^{1}H NMR (400 MHz, DMSO) δ 11.95, 11.9, 11.87, 11.84 (4s, 4H, ArO**H**), 11.37, 11.31, 11.24, 11.12, 11.08 (5s, 4H, CH=NN**H**), 8.53, 8.50, 8.25, 8.24 (4s, 4H, C**H**=NNH), 7.73 – 7.11 (m, 8H, **Ar**), 7.08 – 6.59 (m, 8H, **Ar**), 4.05, 3.97, 3.95, 3.65, 3.58 , 3.54, 3.48 (8H, NC**H**$_2$C=ONH), 2.93, 2.83 (2s, 4H, NC**H**$_2$C**H**$_2$N). ^{13}C NMR (100 MHz, DMSO) δ 168.47, 168.14, 167.92, 167.55, 167.39 (**C**=O), 157.89, 157.79, 156.76 (**C**-OH aromatic), 148.28, 147.98, 147.88 (**C**H=NNH, 131.80, 131.44, 130.11, 129.77, 120.43, 120.09, 119.71, 119.16, 119.10, 119.01, 116.81, 116.77, 116.48 (Ar-**C**), 57.34, 56.91, 55.36 (N**C**H$_2$C=ONH), 52.94, 52.90 (N**C**H$_2$**C**H$_2$N).

LRMS (ES$^+$) 763 [M - H]$^+$; HRMS (TOF-ES$^-$) *m/z* calcd. for $C_{38}H_{39}O_8N_{10}$ [M - H]$^+$ 763.2958, found 763.2970.

(*N'E,N'''E,N'''''E,N'''''''E*)-2,2',2'',2'''-(ethane-1,2-diylbis(azanetriyl))tetrakis(*N'*-(furan-2-ylmethylene)acetohydrazide) 41l

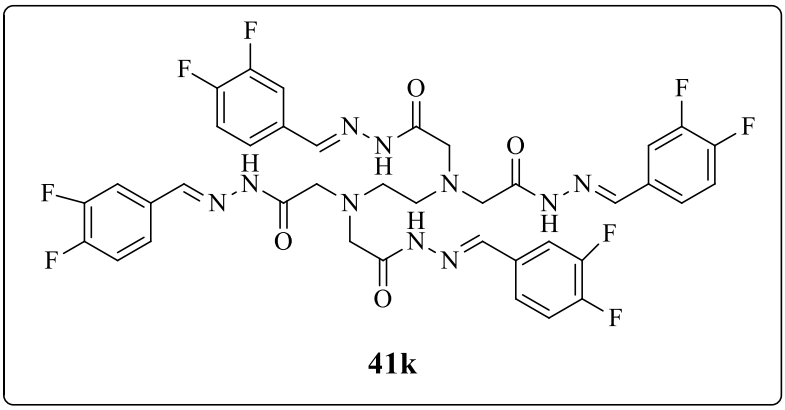


41l

M.p. (188-191 ºC); Yield (56%); ^{1}H NMR (400 MHz, DMSO) δ 11.62, 11.59, 11.58, 11.56, 11.34, 11.33 , 11.31 (7s, 4H, CH=NNH), 8.21, 8.17, 8.14, 7.96 (4d, *J* = 2.9 Hz, 4H, OC**H**CHCH, Furan ring), 7.82, 7.73 (2s, C**H**=NNH), 7.77, 7.73, 6.86, 6.83, 6.77, 6.75 (6d, *J* = 3.1 Hz, 4H, OCHCHC**H**, Furan ring), 6.66 – 6.50 (m, 4H, OCHC**H**CH, Furan ring), 3.92, 3.84, 3.84, 3.55, 3.48, 3.43, 3.37 (7s, 8H, NC**H**$_2$C=ONH), 2.89, 2.87, 2.86, 2.83, 2.74, 2.72 (6s, 4H, NC**H**$_2$C**H**$_2$N). ^{13}C NMR (100 MHz, DMSO) δ 168.36, 168.12, 167.92, (**C**=O), 149.73, 149.52, 149.31 (O**C**CH, furan ring), 145.66, 145.52, 147.31 (**C**H=NNH), 137.50, 137.44, 137.31 (CO**C**H, furan ring), 113.97, 113.85, 113.6 (**C**HCH, furan ring), 112.74, 112.62, 112.57 (CH**C**H, furan ring), 57.7, 57.51, 57.2 (N**C**H$_2$C=ONH), 54.84, 54.50, 53.7 (N**C**H$_2$**C**H$_2$N).

LRMS (ES^{+}) 659 [M - H]$^{+}$; HRMS (TOF-ES^{-}) *m/z* calcd. for $C_{30}H_{31}O_8N_{10}$ [M - H]$^{+}$ 659.2332, found 659.2344.

(*N'E,N'''E,N'''''E,N'''''''E*)-2,2',2'',2'''-(ethane-1,2-diylbis(azanetriyl))tetrakis(*N'*-(3,4-difluorobenzylidene)acetohydrazide) 41k

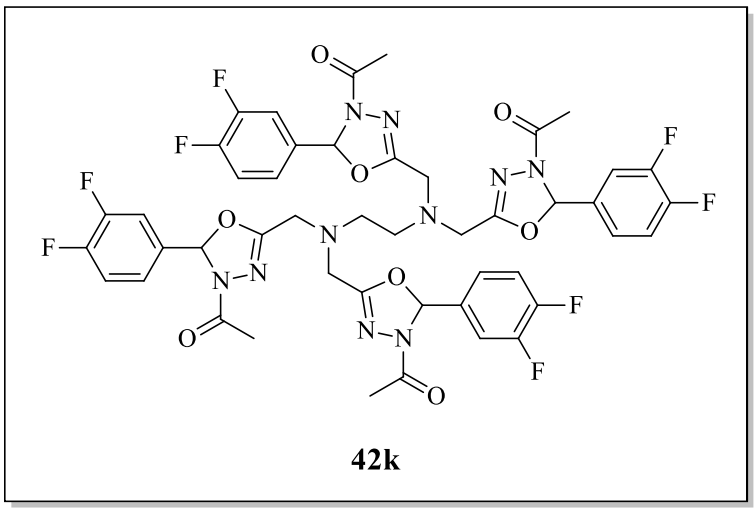


41k

Yield (56%); ^{1}H NMR (400 MHz, DMSO) δ 11.73, 11.69, 11.50, 11.48, 11.45, 11.42 (6s, 4H, NH), 8.30, 8.28, 8.26, 8.23, 8.20, 7.84 (6s, 4H, C**H**=NNH), 7.93-7.44 (m, 12 H, aromatic **H**) 4.04, 4.01, 3.95, 3.93, 3.60, 3.54, 3.5, 3.47, 3.41 (9s, 8H, NC**H**$_2$C=ONH), 2.98, 2.91, 2.76 (3s, 4H, NC**H**$_2$C**H**$_2$N).

LRMS (ES$^+$) 843 [M - H]$^+$; HRMS (TOF-ES$^-$) *m/z* calcd. for $C_{38}H_{31}O_4N_{10}F_8$ [M - H]$^+$ 843.2480, found 843.2950.

1,1',1'',1'''-(5,5',5'',5'''-((ethane-1,2-diylbis(azanetriyl))tetrakis(methylene))tetrakis(2-(3,4-difluorophenyl)-1,3,4-oxadiazole-5,3(2H)-diyl))tetraethanone 42k



42k

Yield (45%); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.52 (**C**=O), 167.94, 160.73 (**C**-F), 156.14 (**C**=N), 125.75, 122.97, 117.92, , 115.79, (aromatic **C**), 90.44 (O**C**HN), 21.35, 57.1 (N**C**H_2C=ONH), 52.9 (N**C**H_2**C**H_2N). LRMS (ES^+) 1035 $[M + H]^+$; HRMS (TOF-ES^-) *m/z* calcd. for $C_{46}H_{40}F_8N_{10}O_8Na$ $[M + Na]^+$ 1035.2777, found 1035.2795.

Chapter 5

Conclusion

Chapter 5
Conclusion

5.1 Conclusion and Future Work

A series of novel hydrazide hydrazone of EDTA were synthesized and characterized by MS, ^{1}H-NMR, ^{13}C-NMR and DEPT 135. Attempts to convert the hydrazide hydrazone into *N*-acetyl-1,3,4-oxadiazole led to one successful example compound **42** and its structure was confirmed by spectroscopic analyses data. In this work; we demonstrated that the syntheses of the target compounds are achievable. However; more time is required to improve and expand the conversion of the hydrazide hydrazone into *N*-acetyl-1,3,4-oxadiazole. The biological activity evaluation of both hydrazide hydrazone and their 1,3,4-oxadiazole derivatives will be considered in our future work.

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