Ministry of Higher Education
and Scientific Research
University of Diyala
College of Science
Department of Chemistry

Synthesis, Characterization and Cytotoxic Activity of Some New Schiff Bases and Thiazolidinone Compounds

A Thesis Submitted to the
Council of College of Science, University of Diyala in
artial Fulfillment of the Requirements for the Degree
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by

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بسم الله الرحمن الرحيم

وَتَرَى الْجِبَالَ تَحْسَبُهَا جَامِدَةً وَهِيَ تَمُرُّ مَرَّ السَّحَابِ ۚ صُنْعَ اللَّهِ
الَّذِي أَتْقَنَ كُلَّ شَيْءٍ ۚ إِنَّهُ خَبِيرٌ بِمَا تَفْعَلُونَ ٨٨

(سورة النمل / الأية 88)

Dedication

Dedicated To you . . .

To my parents whose prayers are the secret of my success, may God protect them and take care of them . . .

To my husband and dear son Ibrahim, who was the source of strength, persistence and support, may God protect him . . .

To everyone who stood beside me . . .

Acknowledgement

I am grateful to my parents for this experiment, to my brothers for their help, and to all those who contributed directly or indirectly towards the completion of this thesis.

Finally, I must express my very profound gratitude to my husband and my son darling (Ibraheem) for providing me with unfailing support and continuous encouragement throughout my interval of study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them.

I would like to express my special thanks of Dr. Iuma salman who gave me the excellent opportunity to do this wonderful project , which helped me in doing alot of Research and I came to know about so many new things.

Thank you...

Abstract

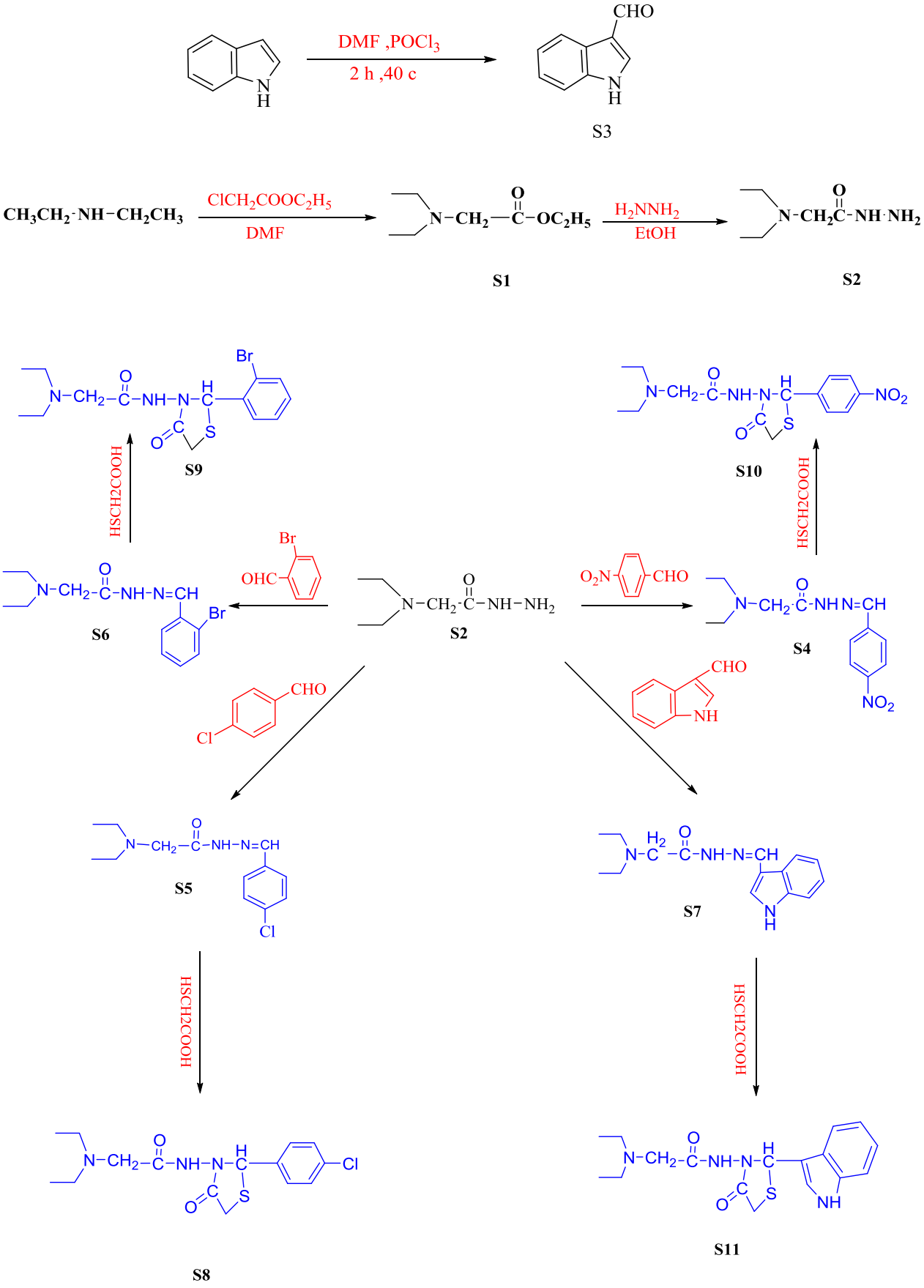
The work described in this thesis describes approaches towards synthesis of substituted hydrazone-hydrazide as intermediates in the synthesis of precursor for the synthesis of thiazolidinones compounds.

The initial approach to the synthesis of thiazalidinone focused on the synthesis of ethyl diethylglycinate on a suitable scale that would enable the synthesis of the require target 2-(diethylamino) acetohydtazid.

- The first step started from inexpensive diethylamine with chloroethylacetate in presence of potassium hydroxide as catalyst.
- Synthesis of 2-(diethylamino)acetohydrazid was accomplished in one step by reaction of ethyl diethylglycinate with hydrazine hydrate in yield of 66%.
- The required Schiff base derivatives was obtained after subjected 2-(diethylamino) acetohydrazid to reaction with variable aldehyde under mild acid conditions to give the imine compounds in variable yield .
- The key cyclization step was achieved by treatment Schiff base derivative with Thioglycolic acid in toluene as a solvent for (10-20 hrs) gave the target compounds in low to moderate yield.

The chemical structures of all new compounds have been characterized and confirmed by spectroscopic techniques such as, (FT- IR, ^{1}H-NMR, ^{13}C-NMR and APT ^{13}C-NMR). Their purity was tested by thin layer chromatography (TLC). Two new synthesized compounds (S7 and S9) was evaluated for their cytotoxicity activity against HepG2 liver cancer cell line and SK-GT2 esophageal cancer cell line revealed increased inhibition compare to the normal cell line.

The general scheme shown synthesized compounds



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List of Schemes

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List ofAbberviations

°C	Degree Celsius
Eπ	Ione pair of orbital P electrons
EAS	Electrophilic Aromatic Substitution
DFT	Discrete Fourier Transform
Kcal.mol	Kilo calories.Mole
α	*Alfa*
ß	*Beta*
DMF	Dimethyle formamide
CNS	Central nervous system
TLC	Thin Layer Chromatography
FTIR	Fourier-Transform Infrared
^{1}H -NMR	Proton Nuclear Magnetic Resonance Spectrometer
^{13}C -NMR	Carbon Nuclear Magnetic Resonance Spectrometer
APT ^{13}C	Attached Proton Test ^{13}C- Nuclear Magnetic
NMR	Resonance Spectrometer
Ml	Milliliters
Mmol	Millimole
h, hrs	Hour, Hours
G	Gram
M.p.	Melting point
Cm	Centimeter
MHz	Megahertz
DMSO	Dimethyl Sulfoxide
δ	Chemical shift
ppm	Part per million
s	Singlet
d	Doublet
t	Triplet
m	Multiplet
TMS	Tetramethylsilane
Ar	Aromatic ring
Rf	Retetion factor
ICCMGR	Iraqi Center for Cancer and Medical Genetics Research
HepG2	Liver cancer cell line
SK-GT2	Esophageal cancer cell line
MLT	Medical laboratory technicians
BHT	Butylated hydroxyl toluene
IC_{50}	inhibitory concentration
DPPH	Di phenyl pecral hydrazil
TB	Mycobacterium tuberculosis
DPA	Diphenylamine
DEA	Diethylamine

Chapter One

Introduction and Literature Survey

1. 1 Introduction

The amide bond is perhaps the most significant in modern science, with applications in drug, agrochemical, and polymer preparation . Recently, the most well- known strategies for amide synthesis rely upon activation of a carboxylic corrosive with a coupling factor and reaction with an amine. However, this strategy has a characteristic drawback including a stoichiometric amount of waste product. Additionally, enzymatic techniques can be used, although the isolation costs are higher and the substrate range is slightly limited. At present, most recent research is directed towards developing catalyzed amide bond formulations. The use of metallic catalysis in amide synthesis makes it possible to start from substrates rather than carboxylic acids.[(1)]

Hydrazide and hydrazones are available in a significant number of the bioactive hetrocyclic compounds that are of wide interest due to their organic and clinical properties .Because of their properties ,these compounds has received much attention from synthetic chemists in the past few years .During the past years, compounds with a variety of hydrazide derivatives were synthesized and evaluated for their various biological activities such as anticancer, anti-HIV, anthelntic antimycobacterial , trypanocidal and antimalarial activitives. [(2)]

Schiff base is a chemical compound formed by condensation reaction of carbonyl compound with primary amine and their derivatives in which the carbonyl group replaced by azomethine group. These compounds are also known as imines. Schiff bases of aliphatic aldehydes are generally unstable and easily polymerizable while those of aromatic aldehydes, having active conjugation, are more stabillzed. [(3)]

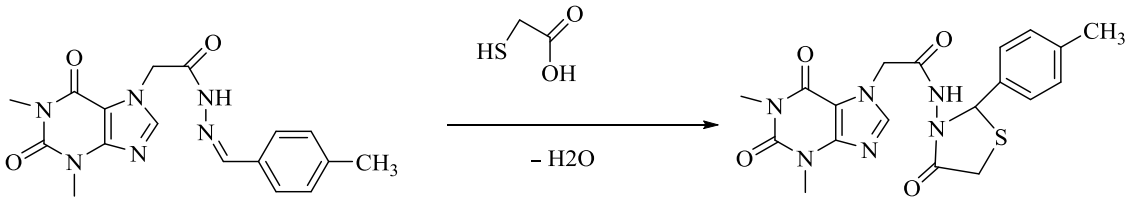
Thiazolidine ring is a uniqu heterocyclic five-membered ring present in various natural and bioactive compounds having sulfur at the first position and nitrogen at the third position. The presence of sulfur atom improve their pharmacological properties, and, therefore, they are utilized as a vehicles in synthesis of valuable organic compounds . They show varied biological and medical activities, for example ,anti-cancer, anti-infammatory, neuroprotective, anticonvulsant, and antioxidant activity. (4)

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and the fourth most common cause worldwide of cancer-related death. Liver cancer most often develops in the context of cirrhosis. Difficulties in finding early diagnosis in the early stage of disease contribute to poor response of patients to current clinical treatments. Currently, one-third of newly diagnosed liver cancer patients are in early stage (0 or A), according to the Barcelona Clinic Liver Cancer Staging System (BCLC), and these will be eligible for potential curative treatments such as local resection, resection or bone endoscopy.(5)

1. 2 Literature Survey

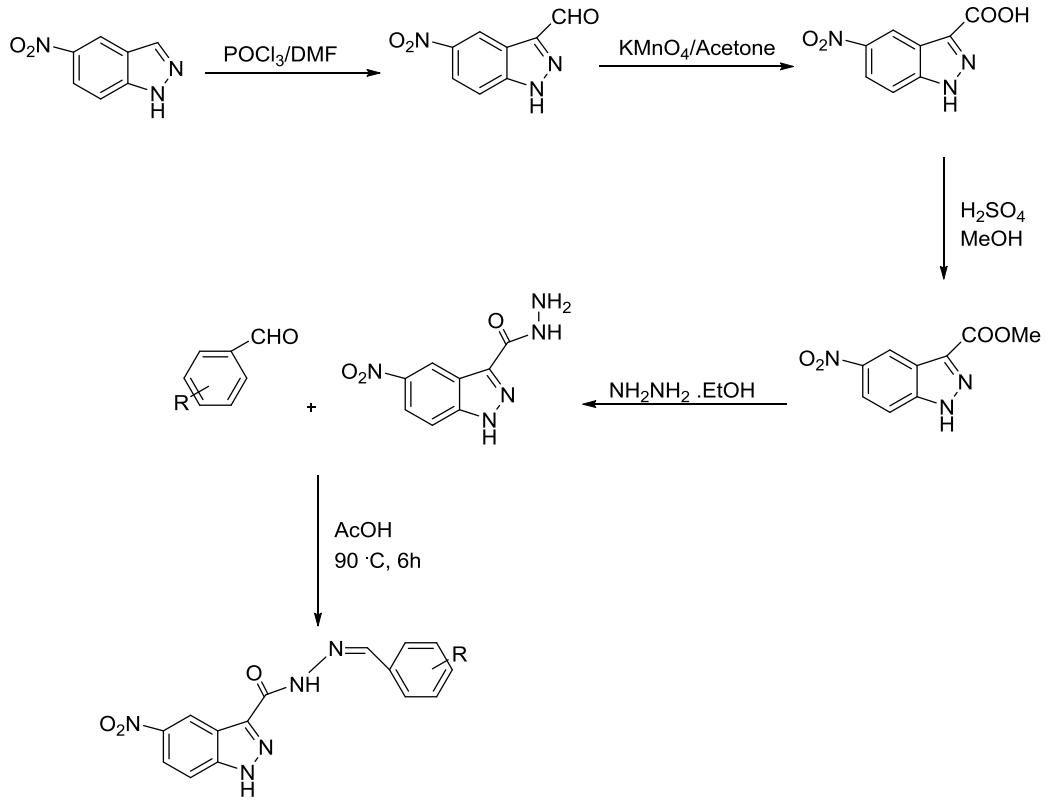
Sandra Constantin et al (2017) was studied some new synthesis of thiazolidine-4-one derivatives with xanthine scaffold were developed by of the reaction between N-(4-methylbenzylidene)-2-(1,3-dimethylxanthin-7-yl)acethydrazide and thioglycolic acid in order to obtain 2-(4- methylphenyl) -3- [(1,3-dimethylxanthin-7-yl) acetamido]thiazolidine-4-one in high yeild and purity. The optimization

was performed by varying different reaction parameters such as: molar ratio between reagents, time and temperature of reaction, solvent, catalyst and type of method. The best result was obtained using excess of 20 equivalents of thioglycolic acid to 1 equivalent of hydrazone in freshly distilled toluene as solvent, under reflux for 18 hrs.[(6)]



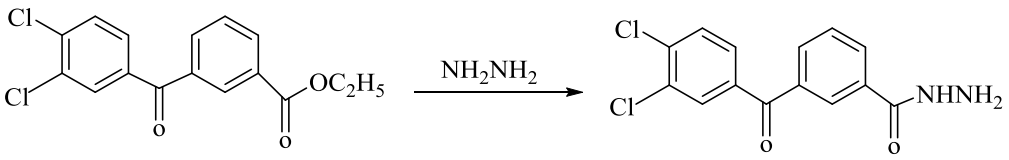
Scheme (1. 1): Synthesis of 2-(4-methylphenyl)-3-[(1,3-dimethylxanthin-7-yl) acetamido]thiazolidine-4-one.

Durgesh Rudavath et al (2018) was synthesized a new series of hydrazide-hydrazones linked between indazole and substituted benzaldehydes . The prepared compounds were evaluated for cytotoxicity against A549 - human alveolar adenocarcinoma cell line, HLa - human cervical cancer cell line, MCF-7 - human breast adenocarcinoma cell line, K562 - human chronic myeloid leukemia cell line and HEK- 293 - Human normal embryonic cell line .[(7)]



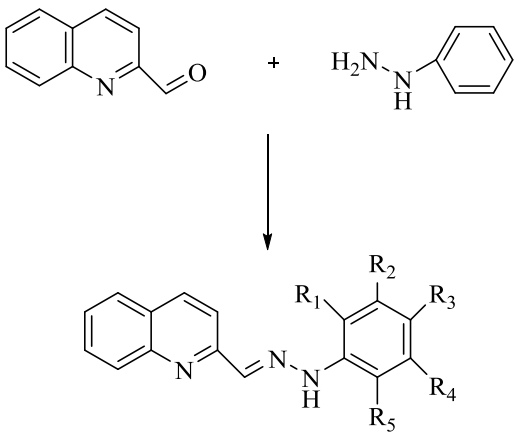
Scheme (1. 2): Formation of the of novel hydrazide-hydrazones.

Bushra P. and Arvind K. (2020) synthesized new hydrazone derivatives, starting from 2-(3,4-Dichloro-benzoyl)-benzoic acid to 2-(3,4- Dichloro-benzoyl)-benzoic acid ethyl ester that converted into 2-(3,4-Dichloro-benzoyl)-benzoic acid hydrazide with substituted aromatic ketones.[8]



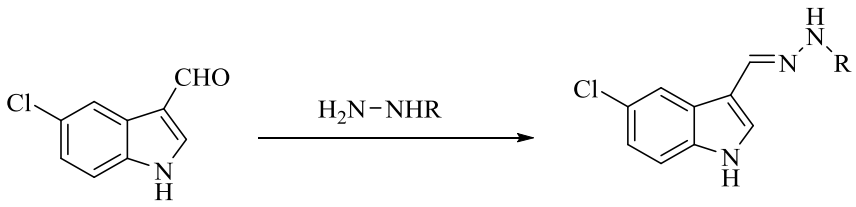
Scheme(1. 3): Synthesis of 2-(3,4-Dichloro-benzoyl)-benzoic acid hydrazide.

M. Orhan Puskullu et al (2016) was reported a series of new quinoline-2-carbaldehyde hydrazones using simple reaction strategies that was developed as an isotope biosynthesis for MLT. Targeted hydrazones derived from quinoline-2-carboxaldehyde and suitable hydrazine derivatives were heated in the presence of EtOH and the new compounds was characterized using IR, ^{1}H-NMR ,^{13}C-NMR and elemental analyses. (9)



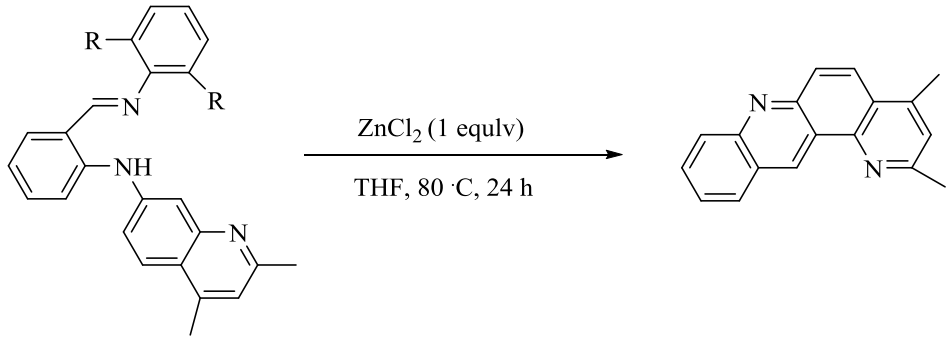
Scheme (1. 4): Synthesis of quinoline-2-hydrazones carboxaldehyde.

Ayse D. Yılmaz et al *(2012)* was reported melatonin analogue indole hydrazide / hydrazone derivatives. All the compounds characterized on the basis of ^{1}H and ^{13}C-NMR, Mass, FT-IR spectra and elemental analysis, and antioxidant activity was investigated in vitro against MLT and BHT. Most of the compounds showed a strong inhibitory effect on the superoxide radical scavenging assay at 1 µm concentration (79-95%).Almost all tested compounds possessed a robust cleaning activity against DPPH radical scavenging activity at values of IC_{50} (2 to 60 µm).(10)



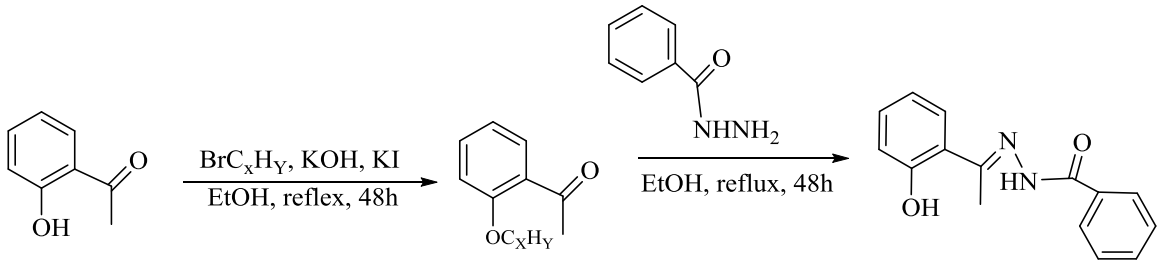
Scheme (1. 5): Synthesised 5-chloro indole derivatives.

Qing Su. et al (2014) was reported an efficient method for a wide range of acridine derivative compounds from readily available o-arylaminophenyl schiff base compounds and $ZnCl_2$ that found an enhanced cycling reaction under favorable conditions. The new cyclization reaction was also applied to the synthesis of complex polycyclic aromatic compounds by double cyclization of bis (o-arylaminophenyl Schiff base) substrate but this time with 4 equ. of $ZnCl_2$.(11)



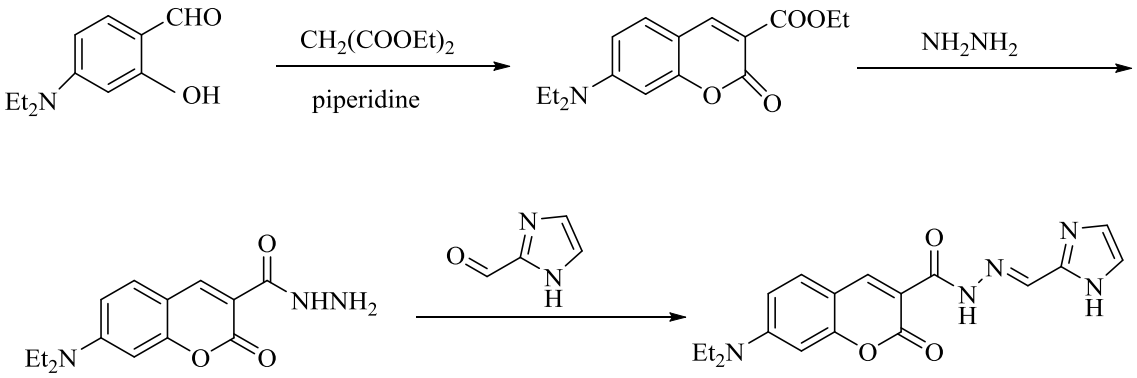
Scheme (1. 6): The Cyclization Reaction by $ZnCl_2$.

Ruwaidad et al (2017) was designed three hydrazine schiff base compounds carrying carbon chains of C_8H_{17}, $C_{10}H_{21}$ and $C_{12}H_{25}$. The compounds were prepared by reacting effecting ketones with benzhydrazide via a condensation reaction. (12)



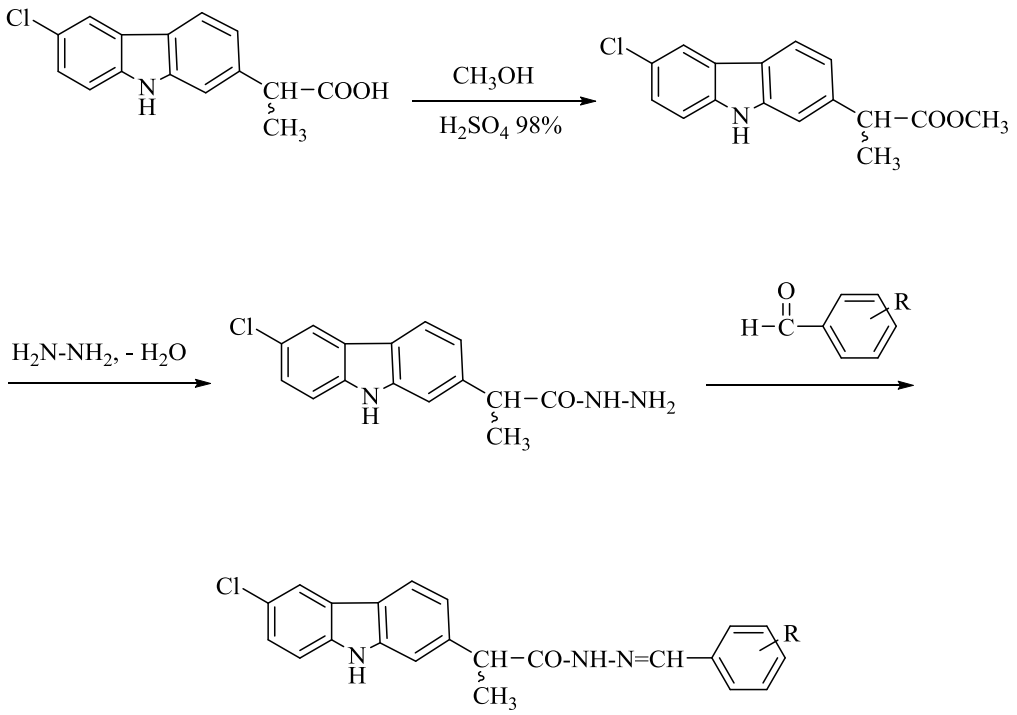
Scheme (1. 7): Synthesis of hydrazone Schiff base compound and its derivatives.

Guangjie et al (2019) was designed a new fluorescent compound that synthesized by coumarin hydrazine and imidazole-2 formaldehyde. A fluorescent schiff base derivative compound then alloyed coordination with copper ions to form a fluorescent probe (Cu^{+2} complex), which has selectivity to GSH relative to Cys and Hcy biothiols. The mechanism of the reaction was also examined by means of UV / VIS spectroscopy, fluorescence spectroscopy and mass spectrometry. (13)



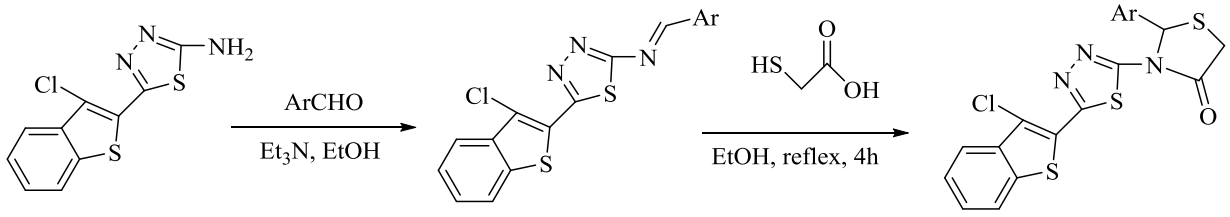
Scheme (1. 8): Synthetic route of fluorescent Schiff base.

Alexandra T. Bordei et al (2019) was published a new series of Schiff bases that synthesized by treating (2RS) -2- (6-chloro-9H-carbazol-2-yl) propanehydrazide (carprofen hydrazide) with few benzaldehyde derivatives under microwave irradiation.[14]



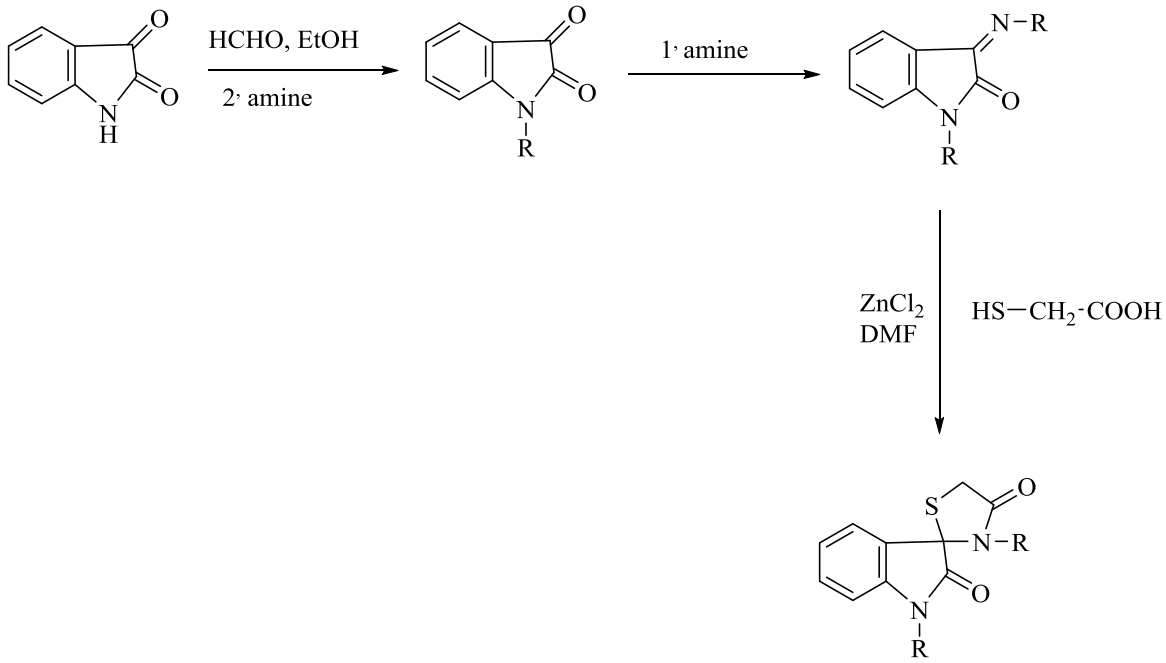
Scheme (1. 9): Synthesis of novel Schiff bases from carprofen hydrazide.

Maryan Lelyukh et al (2018) was synthesized of 5-unsubstituted 2-arylthiazolidine-4-ones based on condensation of benzo[b]thiophene containing Schiff bases with thioglycolic acid in ethanol medium. [15]



Scheme (1. 10): Synthesis of 5-unsubstituted 2-arylthiazolidine-4-ones.

Krishna Srivastava et al (2020) was polished a route to synthesis and characterization of spiro isatin derivatives compounds. They started from 1- (substituting 1-ylmethyl) indoline-2,3-dione that was converted into (Z) 3- (4-subitutedphenylimino) -1- (substituted-1-ylmethyl) indolin-2-one by treatment with different types of primary amines. The interaction of indoline-2-one with thioglycolic acid and chloro acetylchloride leads to a cyclization process to give the compound spiroisatin derivative compounds with a yield of 84-71 according to the type of substrate. All synthesized compounds were tested in the laboratory against bacteria and demonstrated has been showed mide to moderate activity against tested bacteria.[16]



Scheme (1. 11): Synthesis of thiozale.

Mustafa et al (2019) was published a new derivatives of mefenamic acid by conventional method. The first step was a acylation of secondary amine of mefenamic acid with chloracetyl chloride to give acetamidobenzoic acid followed reaction with hydrazine hydrate to form hydrazine derivative. The target compounds 4-thiazolidinone heterocyclic ring was obtained through reaction of thioglycolic acid with schiff base that derived from reaction of hydrazine derivative with benzaldehyde deravatives. The anti-inflammatory effect of the synthesized compounds was evaluated in rats using an edema-induced egg white-inflammatory model, the compounds contain [OH, F, $N(CH_3)_2$] groups which are electron donating groups that showed superior anti- inflammatory activity to mefenamic acid. [17]

1.3 Aim of this project

1- Synthesis a series of new Schiff Bases and thiazolidinones derivatives.
2- Identification the chemical structures of the synthesizd compounds by various spectroscopic techniques such as Nuclear Magnetic Resonance Spectroscopy ^{1}H-NMR, APT ^{13}C-NMR and Fourier Transform infrared Spectroscopy (FT-IR).
3- Evaluation the biological activity of some newly synthesized compounds to against HepG2 liver cancer cell line , SK-GT2 esophageal cancer cell line and WRL68 normal cell line for the human liver.

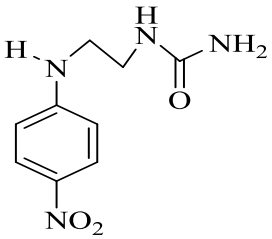
Chapter Two

Theoretical Part

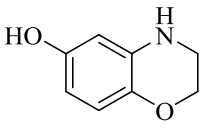
2. Theoretical part

2. 1 Secondary amines

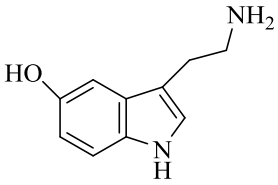
Secondary amines are important intermediates in the formation of high value chemicals produced by the organic synthesis. These amines are important pharmaceuticals, dyes, agrochemicals, surfactants, fine chemicals, and functional chemicals [18] . The most common and direct method for the formation of the secondary amines is N-alkylation of primary amines with alkyl halides in the presence of an equivalent amount of base. An example of such compounds are illustrated in Figure **(2. 1)**. The major limitation of this method is that the excessive alkylation occurs at the same time, and leads to large production of by-products.[19]



4-Nitrophenyl aminoethylurea



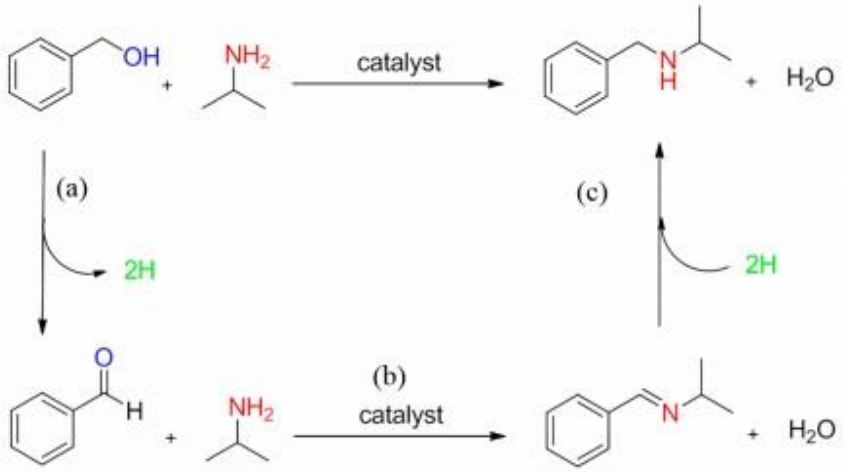
Hydroxybenzomorpholine



Serotonin

Figure(2. 1): Example of secondary amines.

The secondary amines can also be obtained in the presence of reducing agent or hydrogen gas through the reduction amines of carbonyl compounds (such as aldehyde or ketones) with primary amines by forming an imine [20]. However, the alcohol reductive amine is preferred to the carbonyl group, and the latter is derived from alcohol oxidation. An alternative approach, which involves reducing amine from primary alcohols to produce secondary amines, is an environmentally friendly method with only water as a by-product.[21]

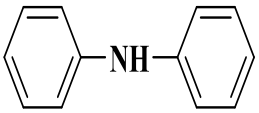


Scheme(2. 1): Preparation of secondary amines.

The secondary amine is considered as a derivative of ammonia where two hydrogen atoms are replaced by two organic groups (they may be equal or different from each other and may carry other substitutes), bound to nitrogen by single bonds. These carbon atoms cannot be double or triple bonded, or bonded to other heterocyclic atoms, such as oxygen or nitrogen.[22]

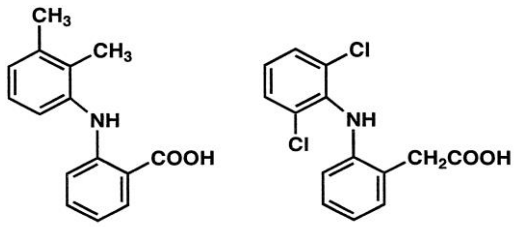
2. 1. 1 Diphenylamine

Diphenylamine (DPA),chemical formula $(C_6H_5)_2NH$, is a dimer of aniline synthesized by heating the parent monomer in the presence of aniline hydrochloride.[23]



Figure(2. 2): Diphenylamine.

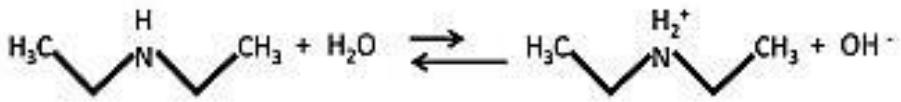
DPA is a highly reactive compound due to the imine hydrogen atom, which can easily be replaced electrophilically. For example , the alkali metals can be substituted, a reaction which can be used to detect potassium (as N-potassium DPA). Also, minerals (for the moment aluminum) are able to displace hydrogen under the metal formation (for example aluminum) diphenylamide. Several other derivatives are known to form when N-hydrogen is replaced by alkyl-, aryl-, or an acyl group. DPA and its derivatives are still entering the environment by used as intermediates in manufacturing agricultural that leads to the formation of harmful substances which represent public health problems spicily in the Environment.[24]



Figure(2. 3): Diphenylamine derivatives.

2. 1. 2 Diethylamine

Diethylamine(DEA) is a colorless, room-temperature liquid with a fishy, ammonia-like odor. molecular formula($C_4H_{11}N$). DEA is used as an organic medium in industry to produce a corrosion inhibitor, N, N-diethylethanolamine .DEA is widely used in rubber, medicine, resins, pesticides, insecticides, and dyes processing. Additionally, DEA can be used as a polymerase inhibitor. When amines with a high pKa content come into contact with tissues or liquids at physiological pH, they become protonated and the hydroxide ion is liberated, causing local necrosis. [25]



Scheme(2. 2): Reaction of DEM with physiologic pH.

2.1.3 N-Alkylation of secondary amines

The direct activation of amino groups in complex organic molecules is one of the main techniques in modern organic synthesis, especially in the synthesis of biologically active chemicals and pharmaceuticals. While many chemical reactions of amines have been developed to date, a selective and practical method for recruiting complex amines is still in great demand [26]. Alkylamine represents an important class of functions in the representative of valuable and complex molecules, examples are shown in Figure (2. 4). The alkylamino's function is essential for drug design, as it often improves oil-water inter-partitioning (log P), reduces their toxicity, and increases their bioavailability.[27]

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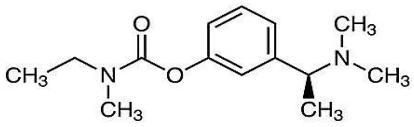
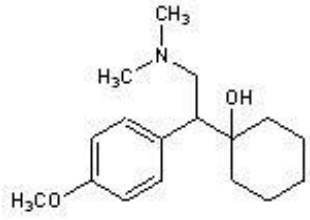
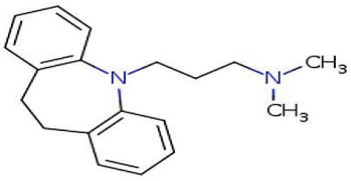


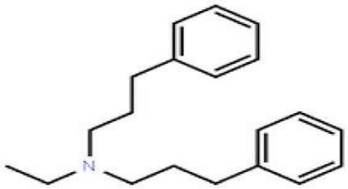
Rivastigmine



Venlafaxine



Alverine

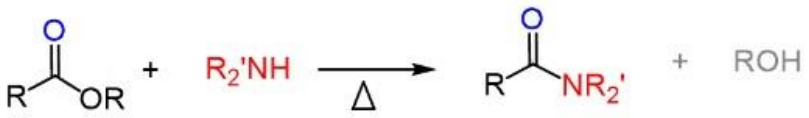


Imipramine

Figure (2. 4): Representative pharmaceuticals with N-alkylated groups.

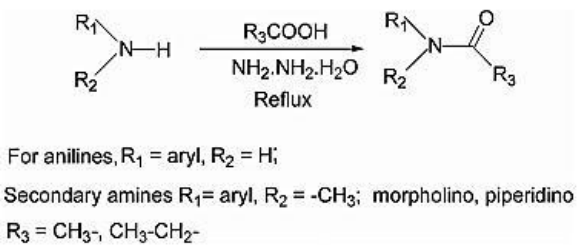
2. 1. 4 N-Acylation of secondary amines

Amides are common functional groups that have been well studied for more than a century. They represent a building blocks of proteins and present in a wide range of other natural and synthetic compounds. Amides are known to be weak electrical materials, which are usually attributed to the resonance stability of the amide bond.[28]



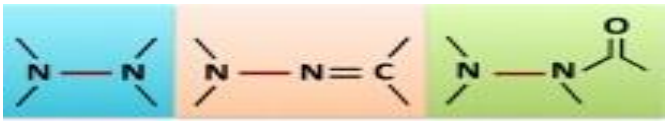
Scheme(2. 3): Reaction ester with secondary amine. [29]

N-acetylation is generally caused by using of acetic anhydride (which is a currently classified chemical), in the presence of bases or by using of tear acetyl chloride. Hence, a simple method of acetylation of the amines without using of these two reagents would be beneficial. However, several methods known to date suffer from some drawbacks. The catalysts are somewhat expensive and require reagents that are not readily available. ***Mahantesha Basanagouda et al,*** developed a comfortable and light method scheme (2.4) for N-acylation of anilines and secondary amines in good yields using hydrazine hydrate, which is a very useful reagent for the synthesis and transformations of many organic compounds.[30]



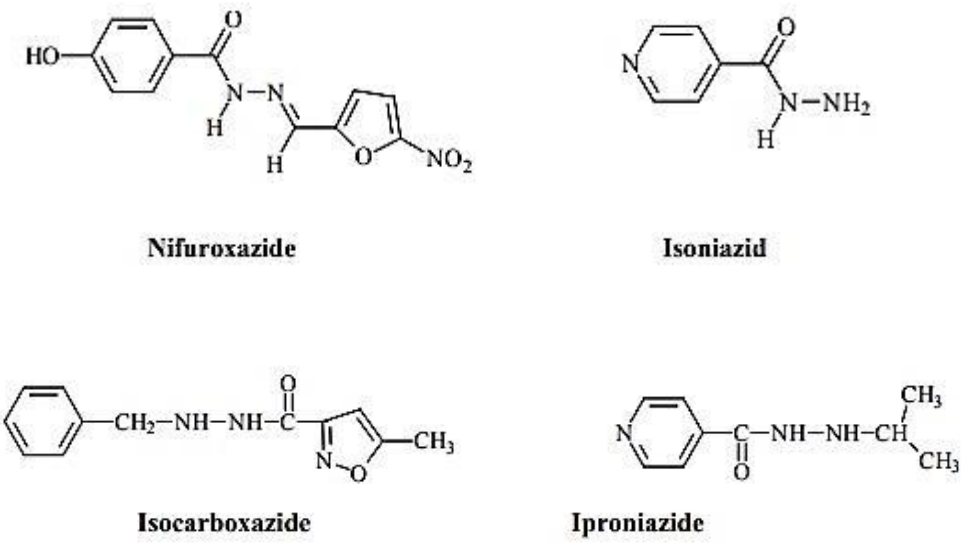
Scheme(2. 4): Acylation of amines.

2. 2. 1 Hydrazine derivatives



Hydrazine Hydrazon Hydrazide

The derivatives of Hydrazine, Hydrazone, and Hydrazide are nitrogen-nitrogen-containing bonding compounds. These particles are relatively rare in nature and have been isolated from plants, marine organisms, and microorganisms. These compounds display remarkable structural diversity and related biological activities. N-N bonds, N-acylases catalyze the formation of C-N bonds contribute to the chemical diversity of natural N-N-containing (N_2NP) products. The natural derivatives of Hydrazine are extremely rare, and so far only four non-acylated compounds are known. Three of the plants and the fourth, were isolated from marine slugs. Hydrazine HN_2-NH_2 is a highly reactive base with reducing properties that has been used for more than a century in organic synthesis. Hydrazine has been used to produce many medicines such as nifuroxazide, carbidopa, hydralazine, dihydralazine, isocarboxazid, isoniazid and iproniazide Figure(2. 5). Hydrazine itself, as a sulfate salt, is used to treat tuberculosis, sickle cell anemia, and many chronic diseases.[31]



Figure(2. 5): Example of drugs.

2. 2. 2 Biological activity of Hydrazine Derivatives

Hydrazonone nuclei exhibited enormous pharmacological activities. Hydrazones are found in many bioactive heterocyclic compounds that have of an important use due to their various biological and clinical applications. Hydrazone-based conjugation methods are used in medical biotechnology to bind drugs to target antibodies. For example, antibodies against a specific type of cancer cell. In most of the major reactions of hydrazones is the nucleophilicity of the hydrogen atom of carbon [(32)]. Hydrazones have two connected nitrogen atoms of different nature and a double carbon-nitrogen bond paired with a single electron pair of the terminal nitrogen atom. These structural parts are mainly responsible for the physical and chemical properties of hydrazones. Each of the nitrogen atoms in the hydrazone group are nucleophilic, although nitrogen of the amino type is more reactive. The carbon atom in the hydrazone group has both electrophilic and nuclear properties.[(33)]

According to the literature review, isonicotinic acid hydrazide (isoniazid, INH) has a very high inhibitory activity against tuberculosis H37Rv. hydrazide-hydrazones INH Figure (2. 6) was synthesized by interacting INH with various aldehydes and ketones . These compounds have been reported to have an inhibitory activity in an infected mice with different strains of *Mycobacterium tuberculosis*(TB). It also showed less toxicity in these mice than INH of hydrazone and development of vitamin B6.

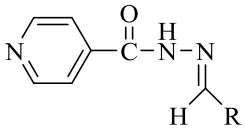
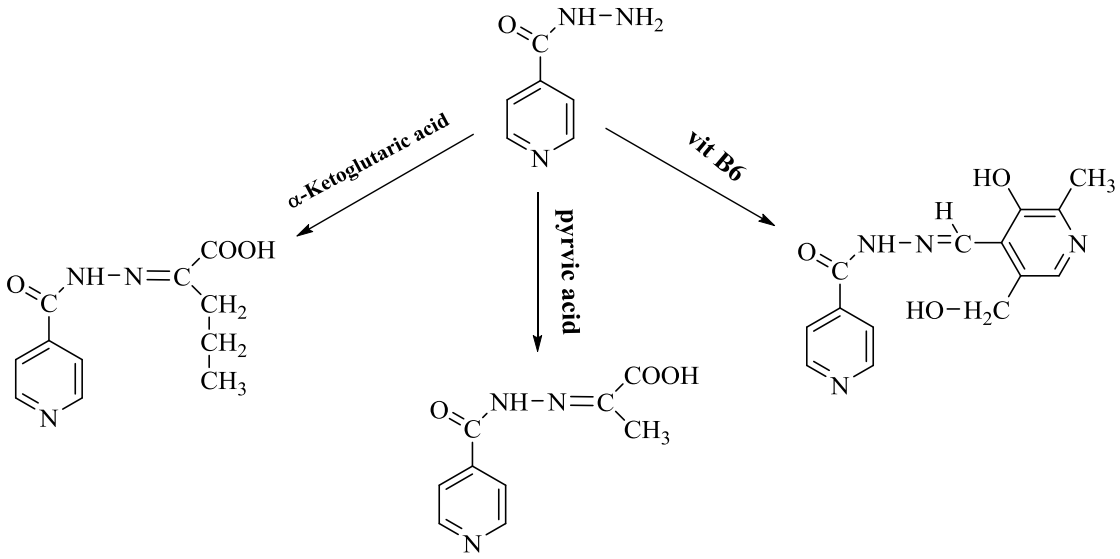


Figure (2. 6): Hyrazide-Hydrazones.

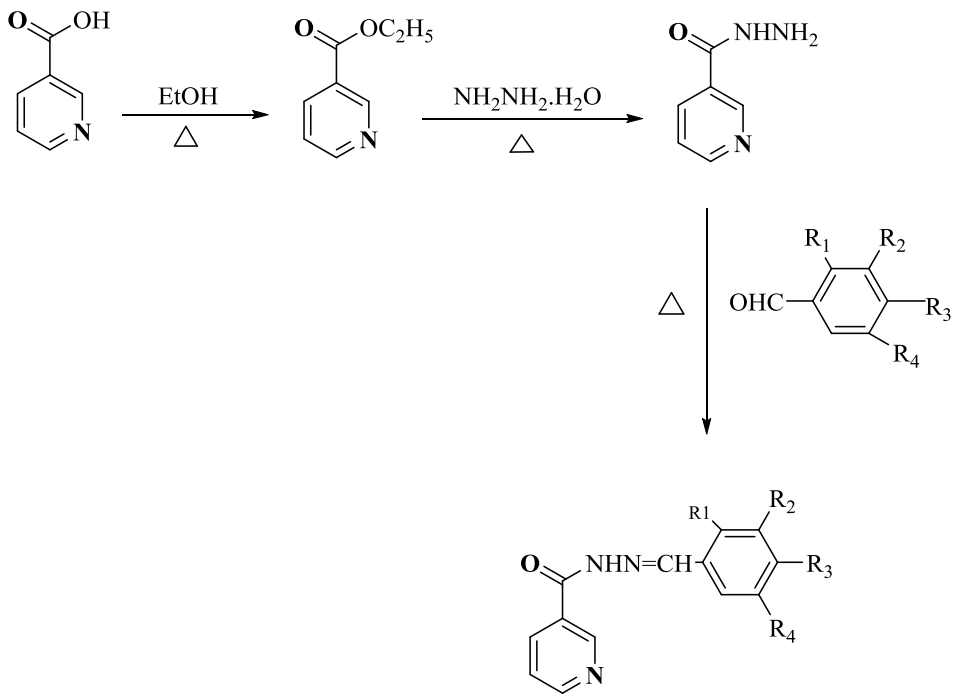
On the other hand, some of the synthesized hydrazide-hydrazones have been reported to be less toxic than hydrazide due to blockage of the NH2-group. These results support the increasing importance of hydrazide-hydrazone synthesis .

Hydrazides (as INH) are known to form alpha-ketoglutaric acid and hydrazone with vitamin B6 and pyruvic acid. It is clinically important that when treating TB patients with INH. The interaction of INH with vitamin B6 leads to hydrazone formation and vitamin B6 deficiency, so patients treated with INH should be given vitamin B6 Scheme (2. 5).[34]



Scheme(2. 5): Pharmacological activity of hydrazones.

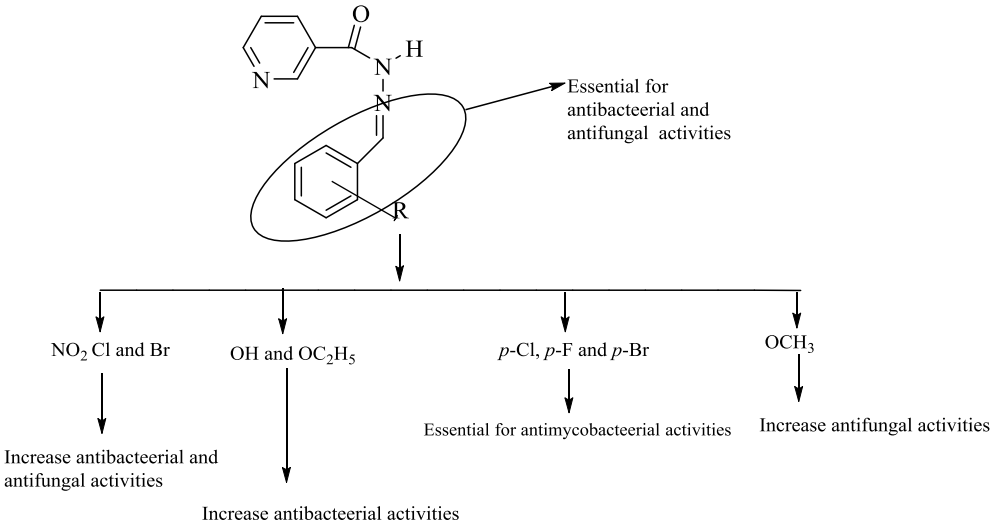
In 2011, ***Narang et al*** ,reported a series of nicotinic acid benzylidene hydrazide derivatives. The compound was tested in the laboratory for biological assessments. The results of the anti-fungal activity showed that the presence of the halogen groups pulling an electron in the ***p***-position of the phenyl ring improved its activity . The results of the antiviral evaluation indicated that none of the combined derivatives inhibited the viral replication at sub-toxic concentration. Moreover, the results of the antimicrobial assay indicated that the compounds containing the OCH_3 and NO_2 substitutes were more effective. Scheme(2. 6).



Scheme (2. 6): Synthesis of intermediate and target compounds.

R1= OCH_3 R2=NO_2 R3=OH R4=Cl

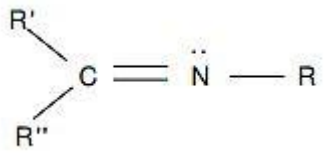
(QSAR, Quantitative structure–activity relationship) investigations showed the QSAR multi-target models were effective in describing bacterial activity. [35]



Scheme(2. 7): Structural requirements for antibacterial and antimicrobial activities of nicotinic acid hydrazide derivatives.

2. 3 Schiff's Bases

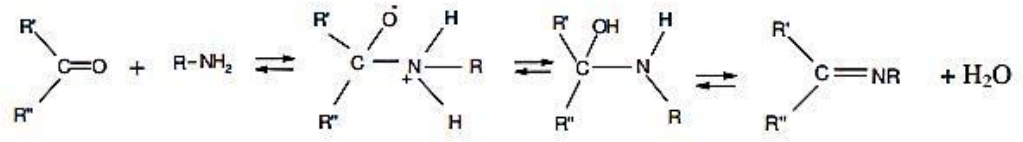
A Schiff base is a type of chemical compounds that contains a double carbon-nitrogen bond as a functional group, wherein the nitrogen atom binds to an aryl group or alkyl group (R) but not hydrogen. Schiff's base is synonymous with azomethene. These compounds are named after Hugo Schiff and have the following general structure: [36]



Figure(2. 7): Stracture of Schiff Base genral

There are many interaction pathways to form Schiff rules. The most common way is the acid-catalyzed condensation reaction of a primary amine with an aldehyde or ketone under diffrent conditions, Scheme (2. 8). The first step in this reaction is the attack of the nucleophilic nitrogrn atom of amine on the carbonyl carbon, resulting in the usually unstable intermediate carbinolamine. The reaction can be reversed to the starting materials, or when the hydroxyl group is eliminated and HC=N bond is formed and the product is called an imine .Many factors are influence the condensation reaction, for example the pH of the solution as well as the steric and electronic effects. In acidic solutions, the amine protons are made, and thus it cannot act as nucleophilic and the reaction cannot continue.

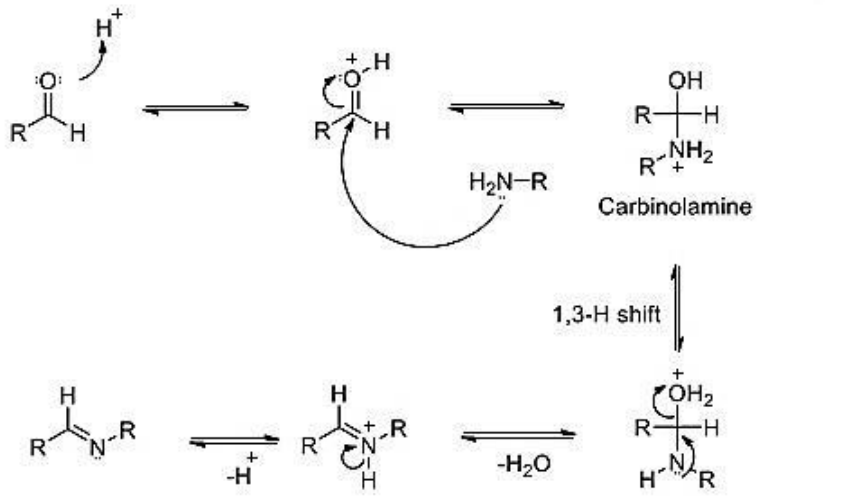
Moreover, in a very basic conditions, the reaction is impeded due to insufficient protons available to stimulate elimination of the carbenolamine hydroxyl group.[37]



Scheme(2. 8): Reaction of aldehyde or ketone with amine to form Schiff base.

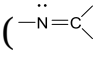
2. 3. 1 Mechanism of Schiff Bases formation

The mechanism of schiff base formation is another variation on the topic of the nucleophilic addition of the carbonyl group. In this case, the nucleophile is an amine. In the first part of the mechanism, the amine reacts with an aldehyde or a ketone to give an unstable addition compound called carbenolamine. Carbinolamine loses water either via acid or base catalyzed pathways. Since carbenolamine is alcohol, it undergoes acid-induced dehydration.[38]



Scheme(2. 9): Mechanism of Schiff Base Formation

2. 3. 2 Reactions of Schiff`s Bases

Schiff`s bases undergo an addition reactions of azomethine, the reagents add to polarized double bond () therefore, nucleophilic reagents attack the carbon atom of the azomethine [39]. Schiff's bases have a large number of industrial uses in organic chemistry. Acetylation of Schiff bases is initiated by acid anhydrides, acid chlorides, and acyl cyanides by attacking the nitrogen atom and leads to net addition of the acyl agent to the double bond between carbon and nitrogen. Reactions of this type have been used well in synthesizing natural products. [40]

2. 3. 3 Biological Activities of Schiff`s Bases

Different Schiff bases derivatives of amines and aromatic aldehydes are mainly employed for purposes in biology, analytical and inorganic chemistry . Some reported showed novel significant of biological activities with an good results on synthesized Schiff bases such as lipid oxidation potency, antitumor , anti-inflammatory and antioxidant activity. In pharmaceutical medicinal field, Schiff bases are most widely used and play a key role in different types of activities . The inhibition of urease for example, was also reported on Schiff bases with excellent effects . Due to lower side effects of Schiff bases ,they also show a novel nature a many other synthesized compounds. Throughout the world in the twenty first century in major health problem is the diabetic disease and approximately fifteen million people affected from it which is concerned with nephropathy, hyperglycemia and hypertension . Recently ,diabetes is clinically treated through synthetic drugs like similar to Schiff bases due to the novel imine or azomethine heteroatom groups .Schiff bases compounds biological activities rates either enhance or decreased by donating or electron withdrawing groups . The highest noticeable

biological activity of certain compounds is due to various aromatic or hetero atom linkages.[41-44]

2. 4 4-Thiazolidinones

Thaizolidinone is a heterocyclic compound consisting of five membered atoms consisting of three carbon atoms, nitrogen and sulfur atom in non-contiguous positions. The chemistry of thiazolidinediones was of great interest due to the presence of such heterocyclics in a large variety of biologically important molecules.[45]

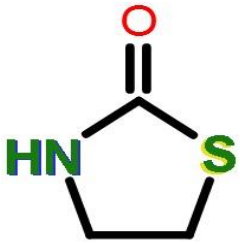
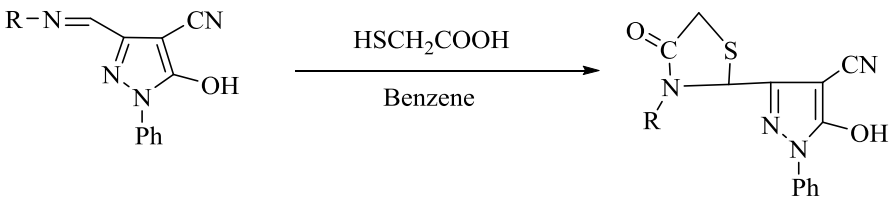


Figure (2. 8): 4-Thiazolidinones.

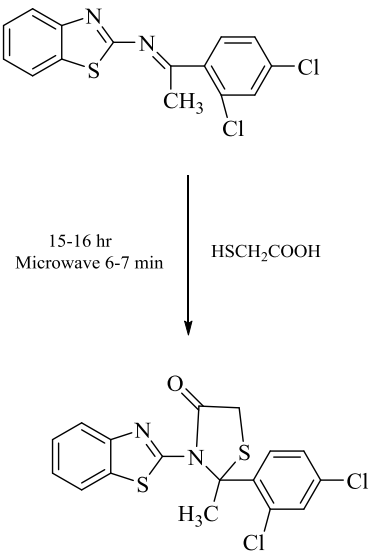
2. 4. 1 Cycloaddition reaction of thioglycolic acid with Schiff Bases

For several years, the Diels-Alder reaction was the only widely useful example of the so-called cycloaddition reactions[46]. In **2013**, ***Elkanzi*** published a short review on the cycloaddition of thioglycolic acid with derivatives of Schiff bases in boiling benzene. [47]



Scheme (2. 10): Synthesis of the cycloaddition reaction of thioglycolic acid to Schiff's Bases.

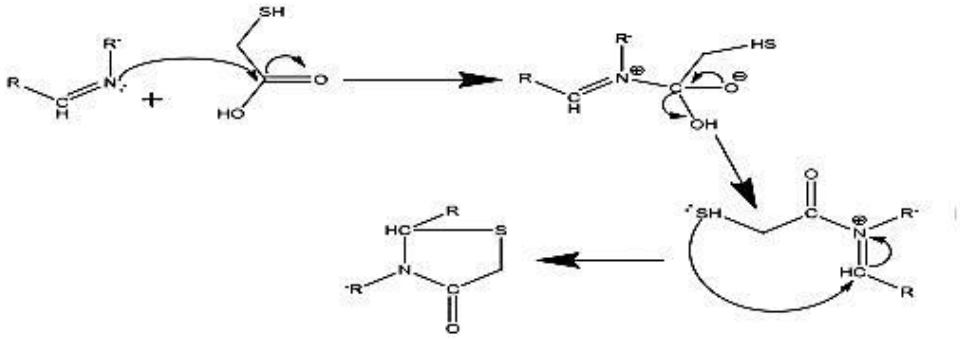
Schiff's bases obtained by the condensation of ketones and amines also react with mercaptoacetic acid to give 2,2-disubstituted-4-thiazolidinones. ***Desai KR et al*** has carried out the microwave assisted synthesis of thiazolidinone from the Schiff's bases Scheme(2. 11) by using thiolactic acid. The products were synthesized by conventional and microwave synthesis and the yield were compared with each other. They concluded that the percent yield with the microwave irradiated synthesis was better than the conventional. (48)



Scheme (2. 11): Synthesis of thiazolidinone derivatives by microwave irradiation.

2. 4. 2 Mechanism of thaizolidinone

The mechanism of the reaction around the ring between the imine group and thioglycolic acid was systematically investigated to prepare a thiazolidinone ring . The breaking and formation of bonds takes place simultaneously and thus the reaction continues through one periodic loop as shown in the Scheme (2. 12). (49)



Scheme (2. 12): mechanism for the synthesis of 4-thiazolidinediones derivatives.

2. 4. 3 Biological activities of thiazolidinediones derivatives

Heterocyclic compounds containing nitrogen and sulfur are widespread in nature and are very important due to their uses in pharmaceuticals and agrochemicals. Substituted 4-thiazolidinediones are one of the most important heterocyclic compounds with some macromolecules making them pseudo nucleotide; this enables them to exhibit interesting biological activities.[50] Small heterocyclic rings containing a strange nucleus due to their important biological properties. Among the wide range of heterocyclics that have been explored to develop biologically active molecules, thiazoles were played the most important role in medicinal chemistry [51]. A review of the literature showed that the compounds containing a thiazole nucleus possess a wide range of biological activities such as antibacterial and anti-fungal properties. Among these types of molecules, 4-thiazolidinedione were shown to have various important biological activities such as antibacterial[52], antifungal[53], antiviral[54], antidiabetic[55], anti tuberculostatic[56], anti-HIV[57], antimalarial[58], anticancer[59], anticonvulsant[60],antimicrobial[61], anti-inflammatory and analgesic

properties[62] Recently, a study reported on the large-scale biosynthetic and chemical properties of a series of 4-thiazolidinedone molecules. Some of these compounds showed moderate to good biological properties. The interesting biological properties observed for this class of compounds have prompted us to manufacture new derivatives with potentially improved medicinal properties with practicalities.[63]

2. 5 Cancer

Cancer considered to be one of the major reasons of deaths in the 20st century and increasing occurrence in 21st century. This represents main world health problem. Almost 7.6 million deaths are usually caused by cancer which represents (13%) of all deaths[64]. Cancer is an abnormal cell growth which means that some of the cells start to divide continuously compare with the controlled cell division and these abnormal cells begin to invade the surrounding tissues which is called "metastasis" [65]. Although many chemotherapy agents are available, there is no effective treatments can provide to deal with the cancer sequelae and the disease is still persistent and fatal. [66]

There are several causes of cancer: family history, age, bacterial infection, viral infection, smoking, contact to radiation and chemicals, alcohol use and drinking, eating, touching or breathing harmful materials, these materials that cause cancer are called "carcinogens" and contact to these carcinogen does not mean people will get cancer because it depends on how many times you are exposed to it . [67]

There are many types of cancer such as breast, leukemia , prostate ,liver , lung, brain and colon cancer which is considered the most common cancer types appears in Iraq .[68]

Liver cancer is one of the major reason of cancer-linked death in the world; actually, this malignancy is the second most combined reason of cancer-linked death and its happening and mortality average are increasing [(69)]. Hepatocellular tumor accounts for 75% of liver tumor status . Surgical intervention is a common treatment for liver cancer. But at present the emphasis has been on genetic therapies and the use of advanced treatments[(70)] . Chronic alcohol consumption is a risk factor for certain types of cancers of the esophagus, larynx, pharynx, liver, colon, rectum and breast .[(71)]

Esophageal cancer is a common malignancy of the gastrointestinal tract. It is mainly divided into esophageal adenocarcinoma (EAC), and esophageal squamous cell carcinoma (ESCC) according to the different aetiology and pathology. However, due to frequent recurrence after surgery, the effect is not satisfactory after chemotherapy or radiotherapy, and the overall 5-year survival rate is less than 20% . Therefore, the development of new therapeutic drugs or the search for new therapeutic targets is extremely urgent for the clinical treatment of esophageal cancer.[(72)]. Although esophageal cancer is not among the common cancers such as prostate, lung, breast, or colon malignant cancer, it has a very high mortality rate, as its incidence is close to that associated with cancer. [(73)] Cirrhosis of the liver is occasionally encountered in patients with esophageal carcinoma intended for surgery. However, the effect of liver cirrhosis on surgically treated esophageal cancer patients remains unclear. [(74,75)]

Chapter Three

Experimental Part

3. EXPERIMENTAL

3. 1 Chemicals

The chemical used are listed in (Table 3. 1)

Table(3. 1): The chemicals and their manufactures

No	Chemicals	Supplied from	Purity
1	Acetone	G.C.C	**99%**
2	2-bromobenzaldehyde	Aldrich	**99 %**
3	4-chloro benzaldehyde	Aldrich	**97%**
4	Diethylamine	Thomas baker	**99%**
5	4-dimethylaminobenzaldehyde	Aldrich	**98 %**
6	Dimethylformamide (DMF)	Merck	**99.5%**
7	Dimethylsulfoxide (DMSO)	BDH	**98%**
8	Diphenylamine	Analar	**97%**
9	Ethanol	Scharlu	**99.9%**
10	Ethyl acetate	Aldrich	**99%**
11	Ethyl chloroacetate	Aldrich	**99%**
12	Glacial Acetic acid	BDH	**99.9%**
13	Hexane	BDH	**99%**
14	Hydrazine hydrate	Merck	**80%**
15	4-nitro benzaldehyde	Aldrich	**98 %**
16	Phosphoryl chloride	Merck	**99.5 %**
17	Potassium carbonate	BDH	**99%**
18	Potassium hydroxide	Fluka	**98%**
19	Sodium hydroxide	Merck	**97%**
20	Tetrahydrofuran (THF)	Riedel-de Haën	**99%**
21	Thioglycolic acid	Merk	**99%**
22	Toluene	Merck	**99%**
23	Zinc (II) chloride	Aldrich	**99.9%**

3. 2 Experimental Techniques

- **FT-IR** spectrum was recorded on **(Perkin Elmer spectrum-65** at the Department of Chemistry / College of Science / University of Diyala) by using KBr disk.

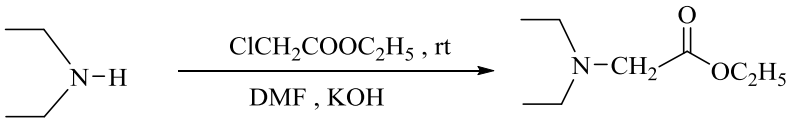
- **^{1}H and ^{13}C-NMR** spectra were recorded on **(Bruker 300 MHz** at Al-Albayt University / Jordan) and **(Bruker 400 MHz** at the Jordan University for science and technology / Jordan) by using tetramethylsilane as an internal reference and DMSO-d_6 as a solvent.

- **Thin layer chromatography (TLC)** analyses were performed using alumina plates (size 20×20 cm) percolated with silica gel with fluorescent indicatr. TLC plates were developed either by the quenching of UV fluorscence at 254 nm or by treatment with basic $KMnO_4$ solution or vanillin, and heating.

- **Melting Point:** The melting points of the synthesized compounds were determined by using the stuart SMP10 electronic apparatus, at the Department of Chemistry, College of Science, University of Diyala.

3. 3 Synthetic methods of the compounds.

3. 3. 1 Synthesis of ethyl diethylglycinate (1) as illustrated in Scheme (3. 1)

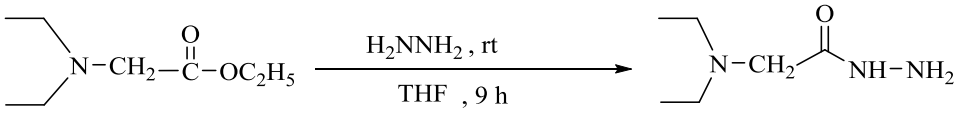


Scheme (3. 1): The Synthetic pathway of ethyl diethylglycinate **(1)**

A mixture of diethylamine (2g, 27.34mmol) and chloroethylacetate (5.8ml) in DMF (30ml) was treated with a catalytic amount of potassium hydroxide (1.5g, 26.73mmol) was left stirring at r.t. for 11 hrs .The organic layer was separated and the aqueous layer was extracted with ethylacetate (3 × 30ml) .The comboined organic extracts were dried over Na_2SO_4 and concentrated in under vaccum to afford the product as a brown oil. Yield (74 %) .

FT-IR-data in $(cm)^{-1}$ 2979, 2877, 1625, 1384, 1276, 868 and 781 cm^{-1}. ^{1}H-NMR (400MHz, DMSO, δ in ppm) δ= 4.48 (2H, OCH_2), 4.26 (2H, NCH_2CO), 2.8(q, 2H, NCH_2CH$_3$) and 1.18(t, 3H, 2CH$_3$). ^{13}C-NMR (400MHz, DMSO, δ in ppm) δ= 167.46 (*C*=O), 62.14(N-*C*HCO), 56.89(O*C*H$_2$), 41.21 (N-*C*H$_2$CH$_3$) and 13.74-10.00 (2*C*H$_3$) .

3. 3. 2 Synthesis of 2-(diethylamino)acetohydrazid (2) as illustrated in Scheme (3. 2)

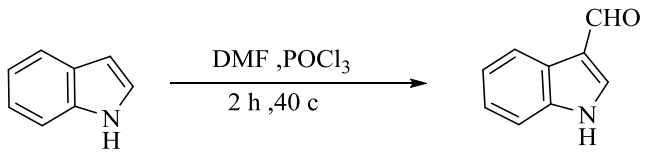


Scheme (3. 2): The Synthetic pathway of 2-(diethylamino)acetohydrazid **(2)**

A mixture of ethyl diethylglycinate (0.5 g, 3.14mmol) and (5.5 ml) of hydrazine hydrate 80% in THF (30 ml) was left stirring at r.t. for 9 hrs .The organic layer was separated and the aqueous layer was extracted with ethylacetate (3×30 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated in under vaccum to afford the product as yellow oil.Yield (66 %) .

FT-IR-data in $(cm)^{-1}$ 3444, 3303, 3064, 1667, 1615, 1528, 1378, 1318, 1147, 1040, 993, 917 and 648 cm^{-1} . ^{1}H-NMR (400MHz, DMSO, δ in ppm) δ= 10.06(s, 1H, NH), 4.23 (s, 2H, N$\underline{CH_2}$CO), 3.88 (2H, N$\underline{CH_2}CH_3$), 2.39(s, 2H, NH$\underline{NH_2}$) and 1.05(t, 3H, CH_3) . ^{13}C-NMR (400MHz, DMSO, δ in ppm) δ= 174.68 (*C*=O), 61.98(N-*C*H_2CO), 48.16 (N-*C*H_2CH_3) and 12.04 (2*C*H_3) .

3. 3. 3 Synthesis of 1H-indole-3-carbaldehyde (3) as illustrated in Scheme (3. 3)



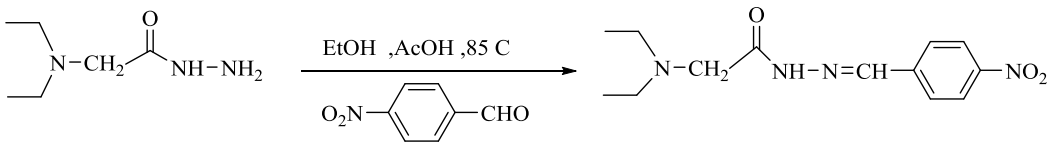
Scheme (3. 3): The Synthetic pathway of 1H-indole-3-carbaldehyde **(3)**

Phosphoryl chloride($POCl_3$) (4.7ml) was slowly added to a solution of pre-cooled indole (2g, 17.07 mmol) in DMF (15 ml) at 5 °C . After completion of addition, the temperature was a raise to 40 °C and the reaction mixture was stirred at 40°C for 2 hrs. , before quenched with crushed ice followed by NaOH (1-2 ml, 1M). The resulting was heated rapidly to the boiling point and then allowed to cool to r.t. ,before placed in refrigerator overnights. The precipitate was filtered off and wash three time with (100 ml) water to furnish the title compound as red solid.Yield (88%). M.p 195-196 °C.

FT-IR-data in $(cm)^{-1}$ 3411, 3201, 3171, 3105, 3045, 2931, 2817, 1697, 1634, 1613, 1577, 1519, 1495, 1448, 1393, 1333, 1243, 1126, 1084, 1006 and 787 cm^{-1}. ^{1}H-NMR (400MHz, DMSO, δ in ppm) δ= 12.21 (s, 1H, *NH*), 9.93 (s, 1H, *COH*) and 8.28-7.21 (5H, indole and *ArH*) . ^{13}C-NMR (400MHz, DMSO, δ in ppm) δ= 184.85 (*C*=O) and 138.28-112.30 (Ar-C and C-indole).

3. 3. 4 Synthesis of Schiff Bases

3. 3. 4. 1 Synthesis of 2-(diethylamino)-N'-(4-nitrobenzylidene) Acetohydrazide (4) as illustrated in Scheme (3. 4)

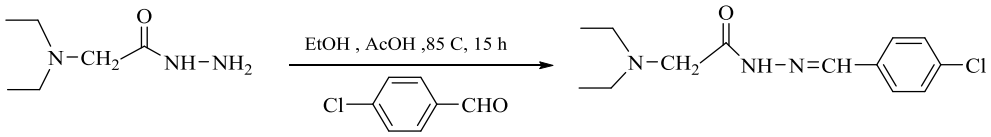


Scheme (3. 4): The Synthetic pathway of 2-(diethylamino)-N'-(4-nitrobenzylidene) Acetohydrazide **(4)**

To stirred solution of 2-(diethylamino)acetohydrazid (0.3g, 2.06 mmol) and 4-nitro benzyaldehyde (0.3g, 1.9 mmol) in ethanol (10 ml) at 85 ° C was added glacial acetic acid (10 drops). The resulting solution was heated at reflux in oil bath for 11hrs .The reaction was cooled to r.t., before being placed in refrigerator overnight. The precipitated solid thus obtained was filtered, washed with ethyl acetate then with ice-cold water and recrystallized from hot EtOH (50 ml) to give the title compound as a yellow crystals. Yield (87%).

FT-IR-data in $(cm)^{-1}$ 3177, 3093, 2973, 2838, 1751, 1682, 1643, 1604, 1522, 1477, 1390, 1345, 1333, 1288, 1222, 1135, 1093, 1078, 1030 , 952, 877, 817 and 736 cm^{-1}. ^{1}H-NMR (400MHz, DMSO, δ in ppm) δ= 11.65 (s, 1H, N*H*), 8.51-7.73 (s, 1H, N=C*H*), and (d, 4H, Ar-*H*), 2.25(s, 2H, N-CH_2), 1.24(t, 3H, NCH_2CH_3). ^{13}C-NMR (400MHz, DMSO, δ in ppm) δ= 172.24 (C=O), 148.19(N=*C*H), 143.35-120.66(Ar-*C*) and 20.25(CH_3) .

3. 3. 4. 2 Synthesis of N'-(4-chlorobenzylidene)-2-(diethylamino) acetohydrazide (5) as illustrated in Scheme (3. 5)

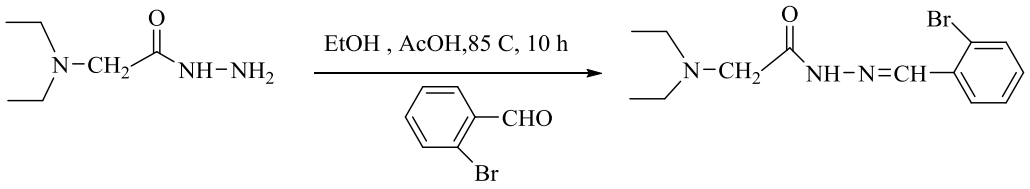


Scheme (3. 5): The Synthetic pathway of N'-(4-chlorobenzylidene)-2-(diethylamino)acetohydrazide **(5)**

To stirred solution of 2-(diethylamino)acetohydrazid (0.45g, 3 mmol) and 4-chloro benzyaldehyde (1 g, 7.11 mmol) in ethanol (30 ml) at 85 ° C was added glacial glacial acetic acid (10 drops). The resulting solution was heated at reflux in oil bath for 15hrs.The reaction was cooled to r.t. , before being placed in refrigerator overnight. The precipitated solid thus obtained was filtered, washed with ethyl acetate then with ice-cold water and recrystallized from hot EtOH (50 ml) to give the title compound as a bright yellow crystals. Yield (75%).M.p 215-216 °C .

FT-IR-data in $(cm)^{-1}$ 3500, 1646, 1625, 1592, 1565, 1487, 1401, 1293, 1090, 1012, 958, 824 and 701 cm^{-1} . ^{1}H-NMR (400MHz, DMSO, δ in ppm) δ= 8.73 (s, 1H, N=C*H*), 7.92-7.59 (2d, 4H, Ar-*H*), approximately 4.40 (s, 2H, N-CH_2CO), 2.09 (2H, NC$H_2$$CH_3$) and 1.06(3H, NCH_2CH_3).

3. 3. 4. 3 Synthesis of N'-(2-bromobenzylidene) -2- (diethylamino) acetohydrazide (6) as illustrated in Scheme (3. 6)

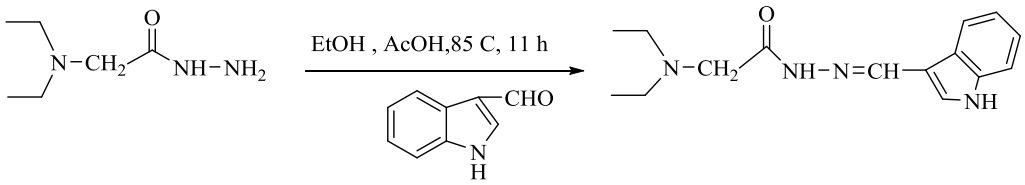


Scheme (3. 6): The Synthetic pathway of N'-(2-bromobenzylidene)-2-(diethylamino)acetohydrazide **(6)**

To stirred solution of 2-(diethylamino)acetohydrazid (0.56g, 3.8 mmol) and 2-bromo benzyaldehyde (1 ml) in ethanol (30 ml) at 85 ° C was added glacial glacial acetic acid (10 drops). The resulting solution was heated at reflux in oil bath for 10 hrs. The reaction was cooled to r.t., before being placed in refrigerator overnight. The precipitated solid thus obtained was filtered, washed with ethyl acetate then with ice-cold water and recrystallized from hot EtOH (50 ml) to give the title compound as a yellow solid. Yield (67 %) .M.p 181-182 °C.

FT-IR-data in $(cm)^{-1}$ 3515, 3444, 3330, 3205, 2995, 2948, 1655, 1628 , 1610, 1589, 1556, 1464, 1431, 1314, 1269, 1024, 952, 749 and 639 cm^{-1}. ^{1}H-NMR (400MHz, DMSO, δ in ppm) δ= 8.94-8.90 (s, 1H, NHCO and s, 1H, N=C*H*), 8.17-7.49 (d-t, 4H, *Ar-H*), 2.09 (2H, N$CH_2$$CH_3$) and 1.13(3H, NCH_2CH_3).

3. 3. 4. 4 Synthesis of N'- (1H-indol-3-yl)methylene) -2-(diethylamino) acetohydrazide (7) as illustrated in Scheme (3. 7)



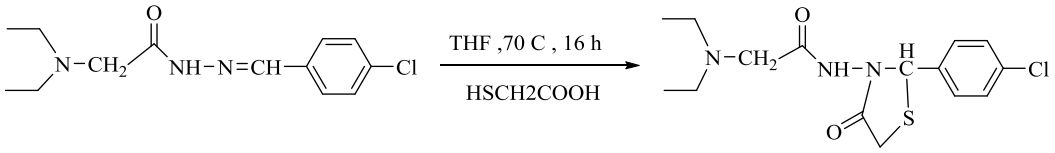
Scheme (3. 7): The Synthetic pathway of N'-((1H-indol-3-yl)methylene)-2-(diethylamino)acetohydrazide **(7)**

To stirred solution of 2-(diethylamino)acetohydrazid (0.6g, 4.1 mmol) and 1H-indole-3-carbaldehyde (1.5 g, 10.33 mmol) in ethanol (30 ml) at 85 °C was added glacial glacial acetic acid (10 drops). The resulting solution was heated at reflux in oil bath for 11hrs.The reaction was cooled to r.t. , before being placed in refrigerator overnight. The precipitated solid thus obtained was filtered, washed with ethyl acetate then with ice-cold water and recrystallized from hot EtOH (50 ml) to afford the title compound as a brown solid. Yield (72 %).

FT-IR-data in $(cm)^{-1}$ 3193, 3109, 3061, 2930, 1672, 1622, 1242, 1120, 955, 806, 707 and 603 cm^{-1}.

3. 3. 5 Synthesis of Thio Compounds

3. 3. 5. 1 Synthesis of the N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-2-(diethylamino)acetamide (8) as illustrated in Scheme (3. 8)

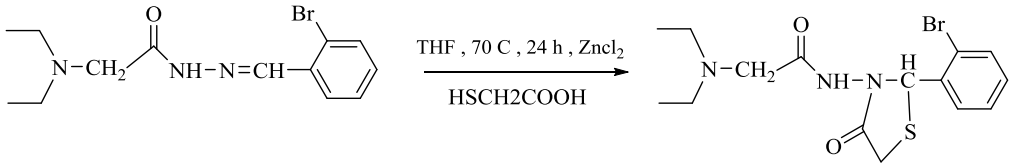


Scheme (3. 8): The Synthetic pathway of N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-2-(diethylamino)acetamide **(8)**

A solution of N'-(4-chlorobenzylidene)-2-(diethylamino)acetohydrazide (0.6 g, 2.24 mmol) and thioglycolic acid (0.50 ml) in (30 ml) of tetrahydrofurane(THF) was left stirring under refluxed in oil bath at 70 °C for 16 hrs. The resulting solution was quenched with distilled water and neutralized with an aqueous solution of NaOH 10%. The resulting of white precipitate was filtered off, washed with distilled water and dried in an oven. Yield (52 %).

FT-IR-data in $(cm)^{-1}$ 2938, 2659, 2564, 1714, 1491, 1407, 1289, 1176, 1176, 1088, 1015, 901, 832, 751 and 656 cm^{-1}. ^{1}H-NMR (400MHz, DMSO, δ in ppm) δ=10.33 (s, 1H, CO-N*H*), 8.74-7.48 (d-dd, 4H , Ar*H*) 6.50 (s, 1H, N-C*H* thiazolidine ring), 4-3.85 (s, 2H, N-CH_2), 3.36 (2d, 2H, CH_2S thiazolidine ring), 2.21(2H, NCH_2-CH_3) and 1.24(3H, NCH_2-CH_3). APT ^{13}C-NMR (400MHz, DMSO, δ in ppm) δ= 167.35 (C=O), 160.36(C=O), 149.07-138.31(Ar-C), 59.56(CH-N), 29.69(CH_2S) and 19.97(CH_3).

3. 3. 5. 2 Synthesis of N-(2-(2-bromophenyl)-4-oxothiazolidin-3-yl)-2-(diethylamino)acetamide (9) as illustrated in Scheme (3. 9)

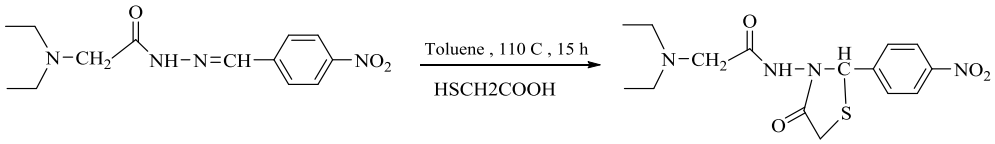


Scheme (3. 9): The Synthetic pathway of N-(2-(2-bromophenyl)-4-oxothiazolidin-3-yl)-2-(diethylamino)acetamide **(9)**

A mixture of N'-(2-bromobenzylidene)-2-(diethylamino) (diethylamino)acetohydrazide (0.4 g, 1.28 mmol) and thioglycolic acid (0.75 ml) in (30 ml) of tetrahydrofurane(THF) was treated with catalytic amount of anhydrous $ZnCl_2$. The mixture was left stirring under refluxed in oil bath at 70 °C. for 24 hrs. The resulting solution was quenched with distilled water and neutralized with an aqueous solution of NaOH 10 %. The resulting of white precipitate was filtered off, washed with distilled water and dried in an oven. Yield (66 %) .

FT-IR-data in $(cm)^{-1}$ 3062, 2923, 2674, 2564, 1718, 1465, 1396, 1293, 1176, 1022, 901 and 747 cm^{-1} . ^{1}H-NMR (400MHz, DMSO, δ in ppm) δ=8.99 (s, CO-N*H*), 7.21–8.21 (d-dd, 4H, Ar*H*) 6.68 (s, 1H, N-C*H* thiazolidine ring), 5.37(s, 2H, N-CH_2), 4.06-3.89(2d, 2H,CH_2S thiazolidine ring), 2.04(2H, NCH_2-CH_3) and 1.28(3H, NCH_2-CH_3) .

3. 3. 5. 3 Synthesis of 2-(diethylamino)-N-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)acetamide(10) as illustrated in Scheme (3. 10)

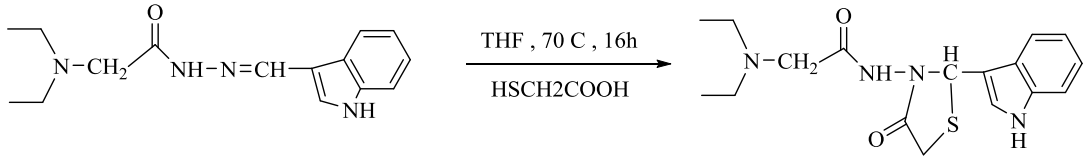


Scheme (3. 10): The Synthetic pathway of 2-(diethylamino)-N-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)acetamide **(10)**

A solution of 2-(diethylamino)-N'-(4-nitrobenzylidene) acetohydrazide (0.5 g, 1.79 mmol) and thioglycolic acid (0.50 ml) in (30 ml) of toluene, was left stirring under refluxed in oil bath at 110 °C for 15 hrs. The resulting solution was quenched with distilled water and neutralized with an aqueous solution of NaOH 10 %. The resulting of light brown precipitate was filtered off, washed with distilled water and dried in an oven. Yield (47 %).M.p 119-120 °C.

FT-IR-data in $(cm)^{-1}$ 3245, 3076, 2979, 2925, 2864, 1722, 1689, 1598, 1523, 1390, 1345, 1266, 1224, 1173, 1106, 1058, 1013, 997, 928, 898, 849, 810 and 735 cm^{-1}. ^{1}H-NMR (400MHz, DMSO, δ in ppm) δ=10.16 (s, CO-N*H*), 8.41-7.69 (d-dd, 4H, Ar*H*) 6.64 (s, 1H, N-C*H* thiazolidine ring), 5.94 (s, 2H, N-CH_2), 4.04-3.73 (d, and dd, 2H, CH_2S thiazolidine ring), 2.30(2H, NCH_2-CH_3) and 1.07(3H, NCH_2-CH_3). APT ^{13}C-NMR (400MHz, DMSO, δ in ppm) δ= 167.73(C=O), 170.00(C=O), 130.35-123.60(Ar-*C*), 60.30(*N*-*C*H), 29.59(CH_2S) and 20.04(CH_3).

3. 3. 5. 4 Synthesis of N-(2-(1H-indol-3-yl)-4-oxothiazolidin-3-yl)-2-(diethylamino)acetamide (11) as illustrated in Scheme (3. 11)

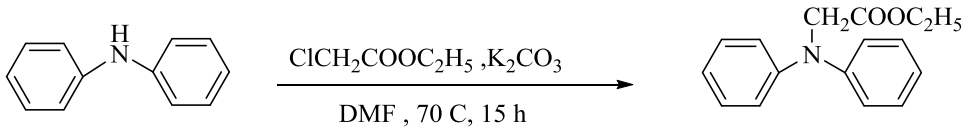


Scheme (3. 11): The Synthetic pathway of N-(2-(1H-indol-3-yl)-4-oxothiazolidin-3-yl)-2-(diethylamino)acetamide **(11)**

A solution of N'-((1H-indol-3- yl)methylene)-2-(diethylamino) acetohydrazide (0.8 g, 2.93 mmol) and thioglycolic acid (1 ml) in (30 ml) of tetrahydrofurane ,was left stirring under refluxed in oil bath at 70 °C. for 16 hrs. The resulting solution was quenched with distilled water and neutralized with an aqueous solution of NaOH 10 %. The resulting a pink precipitate was filtered off, washed with distilled water and dried in an oven. Yield (75 %).

FT-IR-data in $(cm)^{-1}$ 3398, 3212, 3110, 3056, 2924, 2875, 2725, 1719, 1671, 1623, 1578, 1518, 1494, 1437, 1361, 1337, 1283, 1244, 1154, 1121, 1010 and 956 cm^{-1}. ^{1}H-NMR (400MHz, DMSO, δ in ppm) δ=11. 68 (s, 1H, CO-N*H*), 8.90 (s, 1H, NH), 8.34-7.18 (Ar-H) 6.17 (s, 1H, N-C*H* thiazolidine ring), 4.69(s, 2H, N-CH_2), 3.87-3.69 (m, 2H, CH_2S thiazolidine ring), 2.28(2H, NCH_2-CH_3) and 1.07(3H, NCH_2-CH_3) .

3. 3. 6 Synthesis of the ethyl diphenylglycinate (12) as illustrated in Scheme (3. 12)



Scheme (3. 12): The Synthetic pathway of ethyl diphenylglycinate **(12)**

A mixture of diphenylamine (1g, 5.9 mmol) in DMF (30ml) and chloroethylacetate (0.8ml) was treated with a catalytic amount of potassium carbonate (1g, 7.2 mmol) .The reaction mixture was left stirring and heating at 70 °C. in water bath for 15hrs. After cooling to r.t. , the resulting mixture was extracted with ethylacetate/water and then dried with sodium sulphate (Na_2SO_4).The solvent was evaporated and the resulting liquid was purified by colume chromatography on silica gel and eluted with hexane/ethylacetate (4:1) furnished the title compound as a brown oil . Yield (3 %)

FT-IR-data in $(cm)^{-1}$ 2987, 2933, 1751, 1661, 1592, 1427, 1382, 1298, 1271 ,1190, 1142, 1101, 1029, 858 and 756 cm^{-1} .

Table (3. 2): Showed the newly synthesized compounds

Comp. Symbol	Molecular Formula	M. Wt ($g.mol^{-1}$)
S1	$C_8H_{17}NO_2$	159.23
S2	$C_6H_{15}N_3O$	145.21
S3	C_9H_7NO	145.16
S4	$C_{13}H_{18}N_4O_3$	278.31
S5	$C_{13}H_{18}ClN_3O$	26.76
S6	$C_{13}H_{18}BrN_3O$	312.21
S7	$C_{15}H_{20}N_4O$	272.35
S8	$C_{15}H_{20}ClN_3O_2S$	346.45
S9	$C_{15}H_{20}BrN_3O_2S$	352.41
S10	$C_{15}H_{20}N_4O_4S$	346.45
S11	$C_{17}H_{22}N_4O_2S$	341.85
S12	$C_{16}H_{17}NO_2$	255.32

3. 4 Biological part:

3. 4. 1 Materials

All chemicals used in the biological part were obtained from different company suppliers as listed in Table (3. 3).

Table (3. 3): Chemicals and solvents used in the biological part

Materials and chemicals	Company	Origin
Ascorbic acid	Sigma	U.S.A
Crystal violate	BDH	England
DMSO	Sigma	U.S.A
DPPH	Sigma	U.S.A
Fetal Bovine Serum	Sigma	U.S.A
Giemsa stain	Thomas Baker	India
MTT Dye Sigma Aldrich	Sluka	Germany
Roswell Park Memorial Institute -1640	Sigma	U.S.A
Trypsin\Versine	Sigma	U.S.A

3. 4. 2. Instruments:-

The instruments used in this study are found in Iraqi Center for Cancer and Medical Genetics Research (ICCMGR) / University of Mustansiriya, and their Manufacturers are listed in Table (3. 4).

Table (3. 4): Instruments and Manufacturers are used in the biological part

Equipment'	Company	Origin
96 – well Microtiter Plate	SantaCruz	U.S.A
Autoclave	Gallenkamp	U.K
CO_2 Incubator	Gallenkamp	England
Deep Freezer	The Electron Cotporation	U.S.A
ELISA	Quik Fit	Germany
Filter unit 0.22 µm	Millipore	Spain
Incubator	Memert	Germany
Inverted Microscope	Oltmpus	Japan
Laminar Flow Hood	K & K	Korea
Micro Centrifuge	Hermle	Germany
Micropipette	Volac	England
Oven	Memaret	Germany
pH-Meter	Radiometer	Denmark
Plastic Flasic For Tissue Culture	Falcon	U.S.A
Sensitive Balance	Sartorius	Germany
Shaker Incubator	Selecta	Spain
Vortex	Griffin	England
Water Bath	Gallenkamp	England

3. 4. 3. Cytotoxicity test [76]

The cytotoxicity assay was carried out using the crystal violate stain according to the method of ***Freshney, R. I. (2012)***. In brief, the synthesized organic compounds were dissolved in DMSO and diluted by serum free media (SFM) to prepare different concentrations range of (15.1, 31.2, 62.5, 125, 250, 400 and 500) µg/ml. Three types of cell lines were used in this test included human liver cancer (HepG2), human esophageal cancer (SK-GT2) and normal human liver (WRL-68) cell lines. The tumor cells (1 x 10^5 cell/ml) were seeded in 96-well microplate and incubated for 24 hrs at 37 ^oC, then was changed with a new serum-free medium (SFM) containing serial concentrations of each compound. Plate was incubated for 24 hrs in humidified incubator at 37 ^oC containing 5% CO_2. After incubation period, the culture medium was discarded and 100 µl of crystal violate dye was added into each well and re-incubated 20 min at 37 ^oC. Then, the wells were washed with phosphate buffered saline (PBS), and left for 15 min at r.t. The absorbance was measured Microplate reader at 492 nm. The inhibition percentage was calculated by the following formula:

Inhibition (%) = (A-B/A) x 100

Where:

A= Absorbance of the control

B= Absorbance of the sample

Media and solutions for tissue culture were prepared and as explained in the following paragraphs mentioned:

3. 4. 3. 1. Antibiotics

3. 4. 3. 1. 1 Penicillin, Benzyl Pencillin

The content of a vial containing 1 million international units was dissolved in 5 ml of sterile distilled water, A solution of (200,000) µm / ml was prepared, and kept at -20 °C.

3. 4. 3. 1. 2 Streptomycin

The contents of a package containing 1g were dissolved in 5 ml of sterile distilled water, and a storage solution of (200,000) µm/ ml was prepared and kept at -20 °C.

3. 4. 3. 1. 3 Phosphate buffered saline (PBS) (pH 7.2)

NaCl	8 g
KCl	0.2 g
Na_2HPO_4	0.1 g
KH_2PO_4	0.2 g

The materials were dissolved in 1000 ml of distilled water and sterilized by autoclaving at a temperature of 121 °C for 15 minutes and kept at 4 °C.

3. 4. 3. 1. 4 Trypsin solution

1 g of trypsin powder was dissolved in 100 ml of PBS solution and sterilized with a filter 0.22 µm and keep at 4°C.

3. 4. 3. 1. 5 Versine solution

It was prepared by dissolving 1 g of (EDTA) powder in 100 ml of distilled water and sterilized in autoclave at 121°C for 10 minutes and stored at 4°C.

3. 4 .3. 1. 6 Trypsin-Versine solution

Prepared by mixing 20 ml of trypsin solution and 10 ml of alfresin solution and 370 ml of (PBS) solution before use under an aseptic conditions and kept at 4°C.

3. 4. 3. 1. 7 Hanks balanced salt solution (HBSS)

10X off-the-shelf solution from Flow laboratories, Irvine, Scotland.

3. 4. 3. 1. 8 Trypan blue stain solution

1 g of the dye was dissolved in 100 ml of Hanks' solution (HBSS), then filtered using (Whatman No. 1) filter paper and kept at 4°C .The solution was diluted simultaneously with a ratio of (10: 1).

3. 4. 3. 1. 9 Crystal violet stain solution

Prepared by dissolving 5 g of the dye powder in 200 ml of methyl alcohol absolute and filtered using filter paper and 50 ml of formalin (40%) was addedand the volume completed 1000 ml with distilled water and kept in a sterile vial at room temperature.

3. 4. 3. 2. Preparation of culture media

RPMI-1640 medium (Roswell park memorial institute)

This medium was used in cultivation and growth of cancer cell lines and called Complete Growth Media.

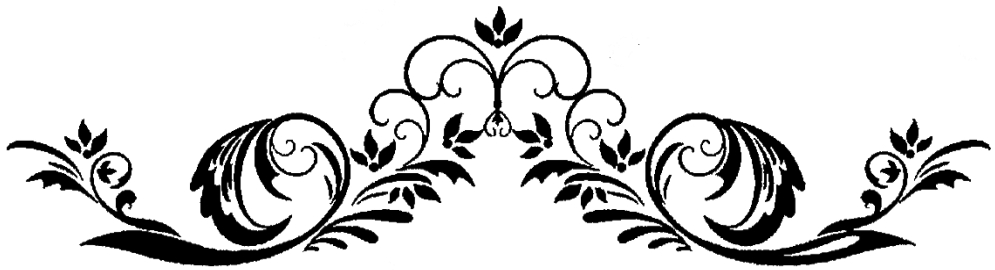
The culture medium consists of :

RPMI-1640 with hepes buffer, L-glutamin	10.4 g
$NaHCO_3$ (4.4%)	15ml
Fetal Calf serum (% 10)	100ml
Benzyl penicillin	0.5ml
Streptomycin	0.5ml

Complete to a volume of 1 L by adding distilled water and the pH was adjusted to 7.2 , then sterilized using membrane filters 0.22 µm and distribute in sterile containers and kept at 4 $^{\circ}$C until use.

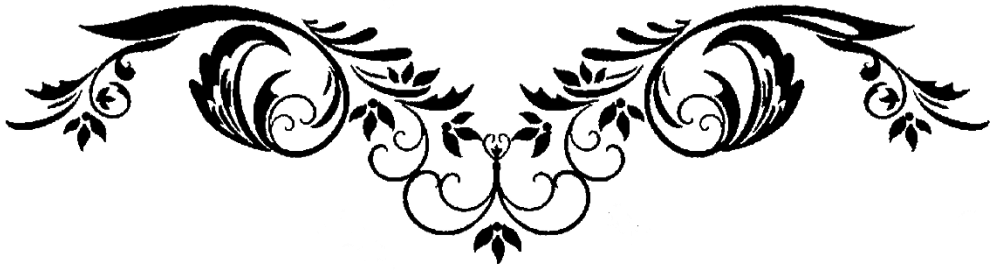
3. 4. 3. 3. DMSO solution

Prepared by mixing 0.2 ml of DMSO with 100 ml of distilled water and sterilized using a perforated filter with a diameter of 0.22 µm , and kept at $4^{\circ}C$ until use.



Chapter Four

Results and Discussion



4. 1 Chemistry Part

4. 1. 1 Methodology

The main goal of this work is an approach to the total synthesis of 4-thiazolidinones by the cyclo-condensation of Schiff base and thioglycolic acid using toluene as solvent . Four Schiff bases were synthesized in order to investigate the mechanism of cyclisation.

4. 1. 2 Study FT-IR results of the ethyl diphenylglycinate (12)

Our initial studies focused on obtaining the best reaction conditions for N-alkylation of secondary aromatic amine using diphenylamine as substrate. The rout started from commercial diphenyl amine that was converted into ethyl diphenylglycinate in too small amount by the procedure of *Reddy et al*. [77]

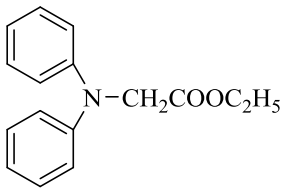


Figure (4. 1): The chemical structure of compound S12

A mixture solution of diphenyl amine (2 g, 11.8 mmol) and (0.8 ml)chloroethyl acetate**,** and (4 g, 28.9 mmol) K_2CO_3 in N,N-dimethyl formamide (DMF) was left heating at 70°C for 15 hrs. The TLC analysis showed that a new compound had been formed, after work-up and column chromatography eluting with (hexane –ethyl acetate) (4:1). The

FT-IR spectrum (Fig4.2) of the first compound isolated from the column indicated it to be recovered starting material and the second compound. Disappearance of stretching vibration of NH_2 group this a good an evidence to formation of new compound.

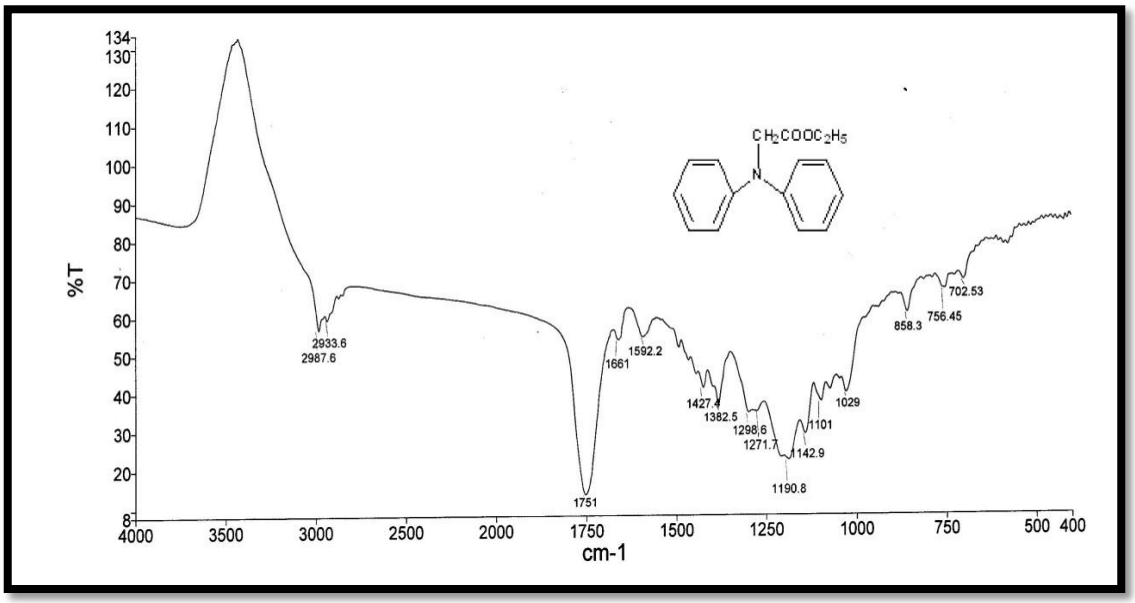


Figure (4. 2) : FT-IR spectrum of compound [S12]

The yield and result obtained for the synthesis of ethyldiphenylglycinate are summarized in Table (4. 1)

Table (4. 1): Study of the formation of ethyl diphenylglycinate

No.	Starting material	Ethylchloro acetate	Base	Time/ condations	Solvent	Yield
1	DPA	2 equiv.	2 equiv. of K_2CO_3	15 h / 70 °C	DMF	Low
2	DPA	2 equiv.	2 equiv. of K_2CO_3	20 h/ 25 °C	Acetone	*
3	DPA	2 equiv.	2 equiv. of K_2CO_3	5 h	DMSO	*
4	DPA	2 equiv.	2 equiv. of NaOH	10 h	DMSO	Low

* Only Starting Material Recover

4. 1. 3 Study FT-IR, ^{1}H-NMR and ^{13}C-NMR results of the compound ethyl diethylglycinate (1)

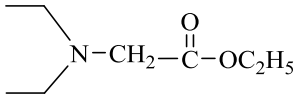


Figure (4. 3): The chemical structure of compound S1

The first step in the synthesis of ethyl diethylglycinate started from diethyl amine with chloroethylacetate in presence of different kinds of base as catalyst. The TLC analysis of each attempt showed that a new compound had been formed .

The FT-IR spectrum (Fig 4. 4) shows strong absorption corresponding to the carbonyl group of ester at 1745cm^{-1} .

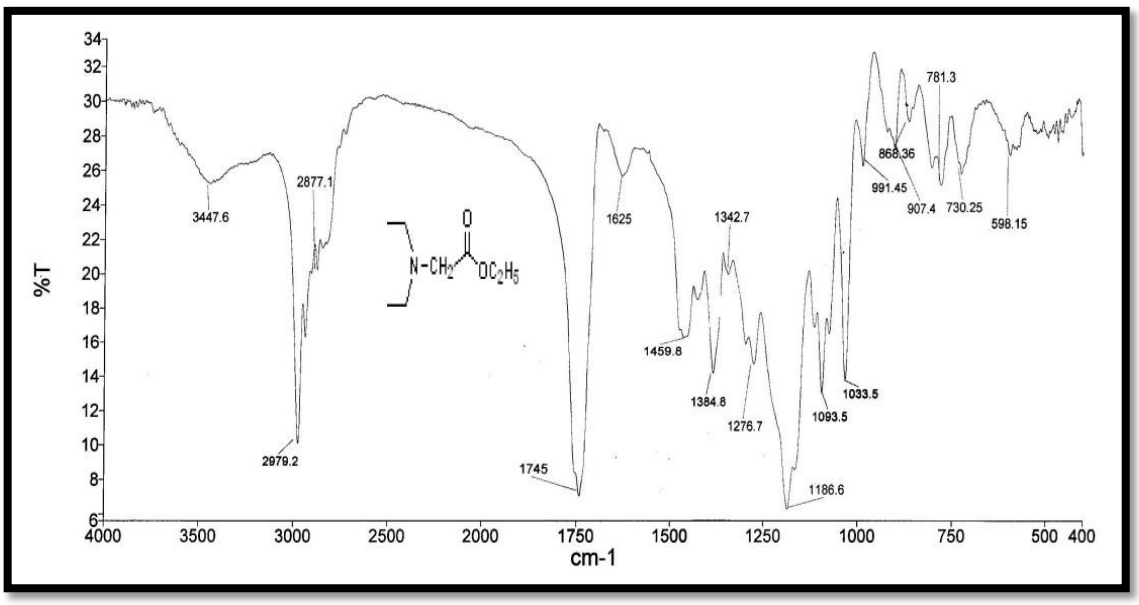


Figure (4. 4): FT-IR spectrum of compound [S1]

Analysis of the ^{1}H-NMR spectrum (Fig 4. 5) of crude materials obtained after work showed two new signals characteristic at δ 4.48 and 4.26 ppm corresponding to protons of O-CH_2 and (N-CH_2CO) group.

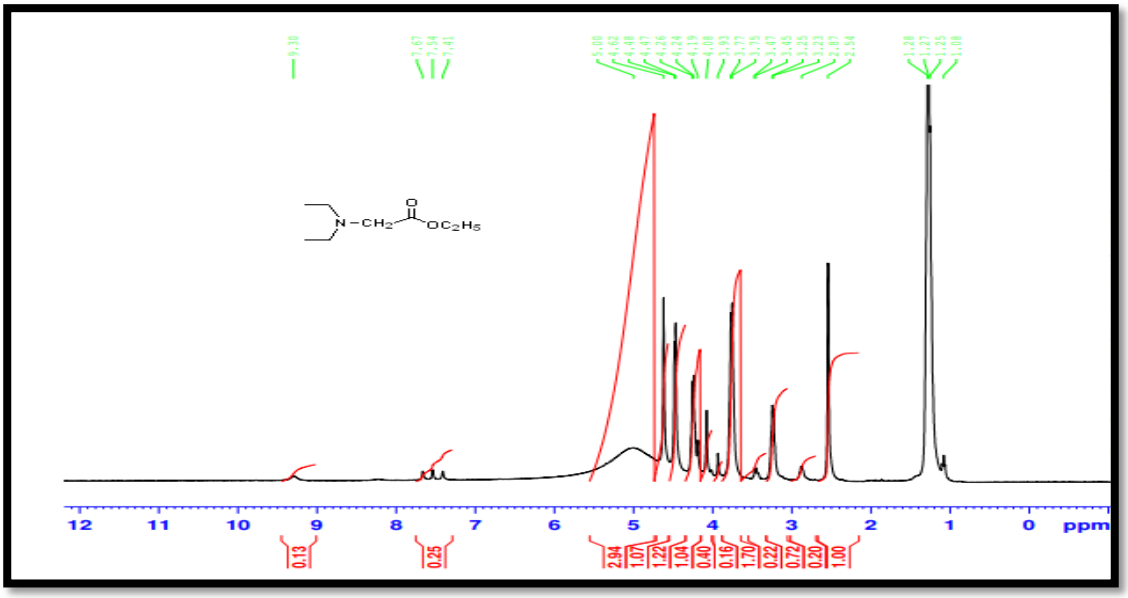


Figure (4. 5): ^{1}H-NMR spectrum of compound [S1]

Furthermore appearance series of signals at δ 167.46, 56.89, 62.14, 41.21 and 13.74 ppm ^{13}C-NMR spectrum (Fig 4. 6) corresponding to the resonances of the carbon of C=O of ester, O-CH_2, N-CH_2C=O, N$CH_2$$CH_3$ and 2CH_3 confirmed our assumption.

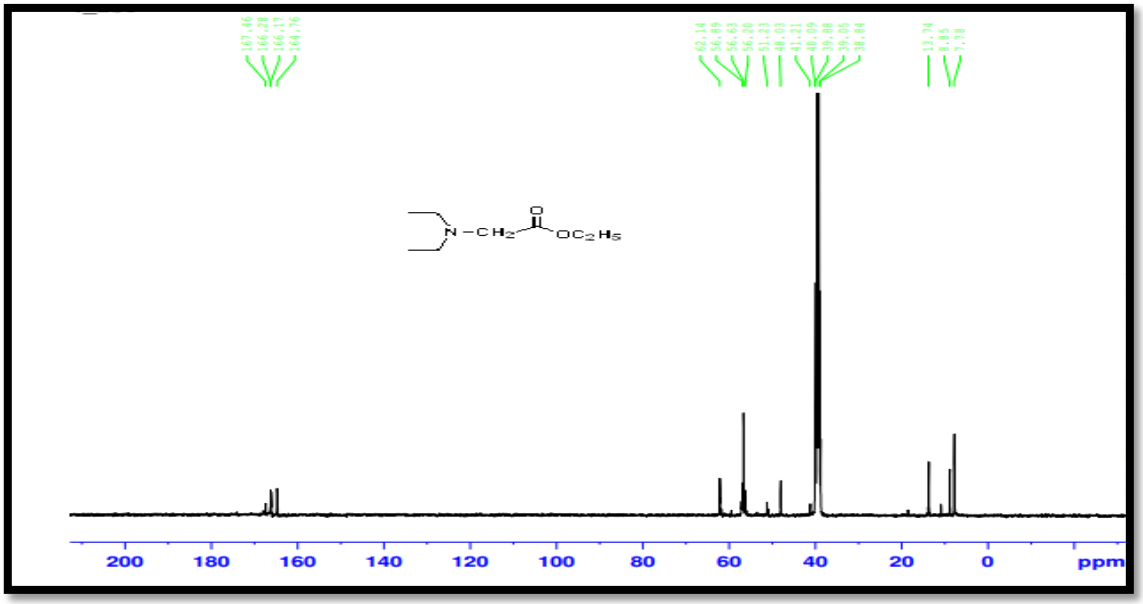


Figure (4. 6): ^{13}C-NMR spectrum of compound [S1]

It was found that, when the reaction was conducted on a larger scale 10 g, of substrate the reaction afforded only low yield of desire compound. The best yield obtained with KOH as base in THF. The data in Table (4. 2) illustrate our efforts to optimize the yield of the reaction.

Table (4. 2): Study of the formation of ethyl diethylglycinate

No.	Starting material	Ethylchloro acetate	Base	Time	Solvent	Yield
1	DEA	2 equiv.	2 equiv. of K_2CO_3	10 h	DMF	63%
2	DEA	1 equiv.	1 equiv. of K_2CO_3	10 h	DMF	60%
3	DEA	1 equiv.	1 equiv. of KOH	15 h	THF	74%
4	DEA	1 equiv.	1 equiv. of $NaHCO_3$	9 h	DMSO	40%

4. 1. 4 Study FT-IR, ^{1}H-NMR and ^{13}C-NMR results of the compound 2-(diethylamino)acetohydrazid (2) (78)

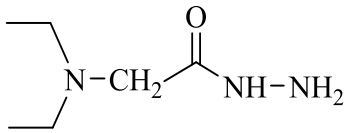


Figure (4. 7): The chemical structure of compound S2

The next step in our route was synthesized the critical intermediate 2-(diethylamino)acetohydrazid. Excess of hydrazine hydrazine hydrate 80% was treated with 20 ml of THF . The reaction mixture was left stirring at room temperature for 9 hrs. The TLC analysis showed the presence of a new material with complete consumption of starting material . FT-IR and ^{1}H-NMR allowed the identification of the desired new compound .

The FT-IR spectrum (Fig 4. 8) displayed two stretching bands at 3444 and 3302 cm^{-1} belong to amine group, in addition absorption band at 1667 and 1615 cm^{-1} belonged to (C=O) and NH bending .

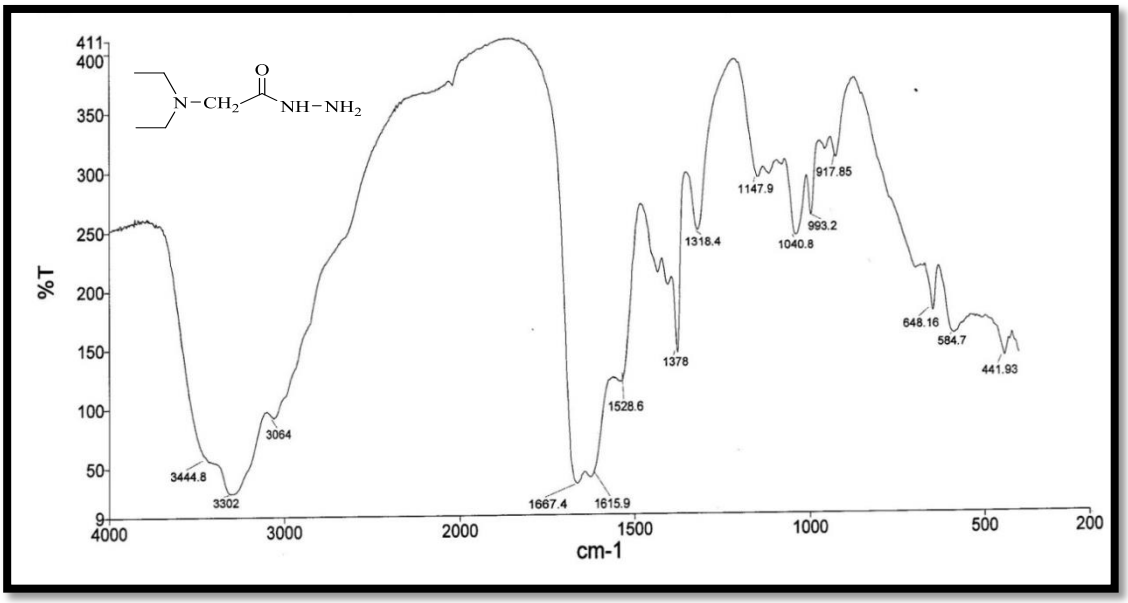


Figure (4. 8): FT-IR spectrum of compound [S2]

A new feature in the ^{1}H-NMR spectrum (Fig 4. 9) was a signal at δ= 10.06 and δ 2.39 ppm corresponding to the protons of NH and NH_2 respectively along with resonances at δ 4.2 and δ 3.88 ppm corresponding to the protons of ($N-CH_2CO$) and $N-CH_2CH_3$ groups.

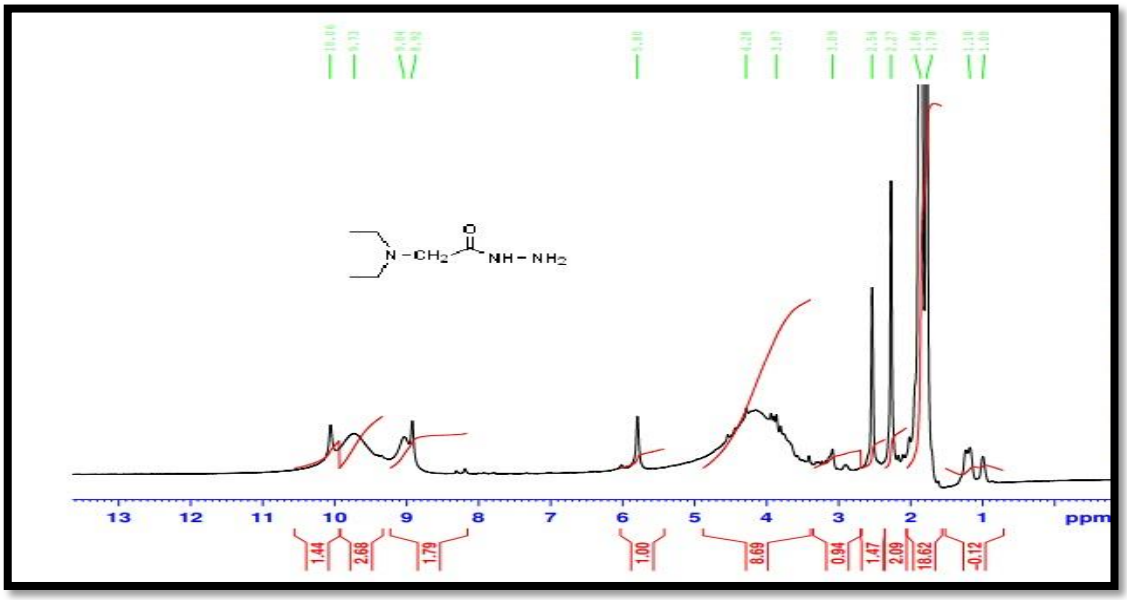


Figure (4. 9): ^{1}H-NMR spectrum of compound [S2]

Furthermore, analysis of ^{13}C-NMR spectrum (Fig 4. 10) allowed to identified the carbonyl group of amide at δ 174.68 ppm.

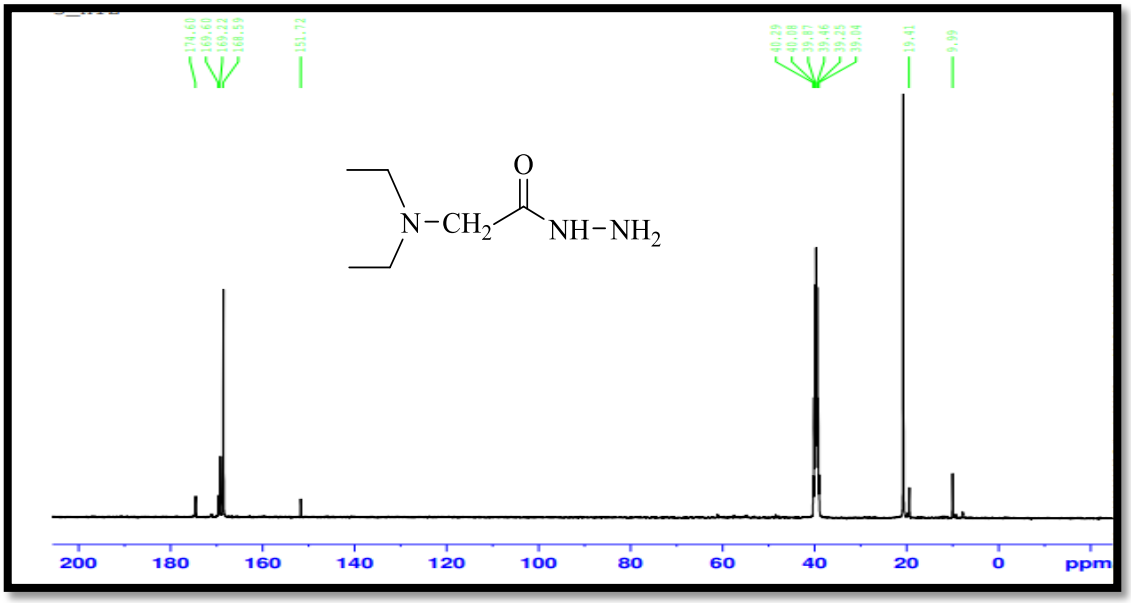


Figure (4. 10): ^{13}C-NMR spectrum of compound [S2]

4. 1. 5 Study FT-IR, ^{1}H-NMR and ^{13}C-NMR results of the compound 2-(diethylamino)-N'-(4- nitrobenzylidene) acetohydrazide (4) [79]

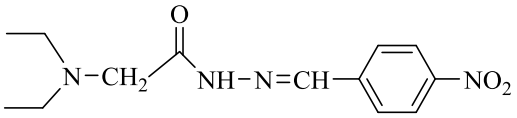


Figure (4. 11): The chemical structure of compound S4

Having synthesised the desired 2-(diethylamino)acetohydrazid the next task was investigate the reaction of *p*- nitrobenzaldehyde compound with (diethylamino)acetohydrazid as reported in our synthetic proposal According to the procedure of *Mehtap et al.* (diethylamino)acetohydrazid was treated with catalyst amount of glacial acetic acid before addition to the mixture of (0.3gm) of 4-nitrobenzaldehyde in 10 ml of ethanol . The resulting mixture was left sttiring at 85C^{o} for11 hrs, and work up . The FT-IR spectrum (Fig 4. 12) showed a strong absorption corresponding to the carbonyl group of amide at 1682 cm^{-1} along with of 1643 cm^{-1} corresponding to C=N group. The structure also was confirmed by analysis of the ^{1}H-NMR and ^{13}C-NMR spectrum .

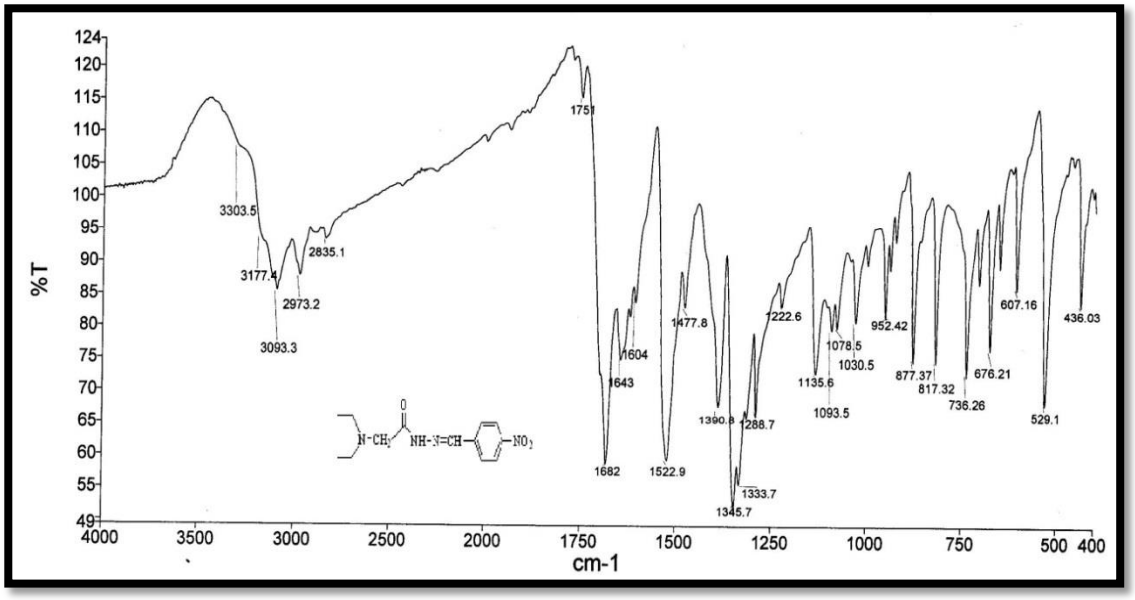


Figure (4. 12): FT-IR spectrum of compound [S4]

^{1}H-NMR spectrum (Fig 4. 13) showed doubling up of all peaks signal such as NH proton at δ 11.65 and δ 11.49 ppm along with two signals in aliphatic region at δ 2.52-1.07 ppm tentatively assigned to the methylene and methyl groups. All these a new feature indicated that there is a mixture of two isomers of the desired compound.

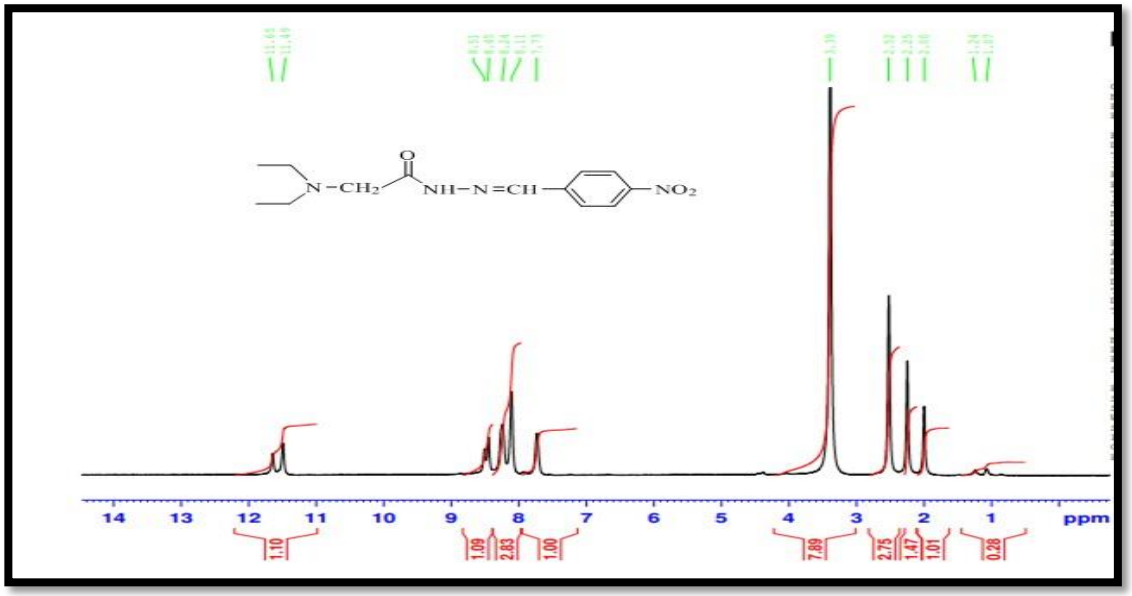


Figure (4. 13): ^{1}H-NMR spectrum of compound [S4]

In ^{13}C-NMR spectrum (Fig 4. 14) , two signals for amide carbon at δ 172.24 and 165.98 ppm along with two carbon resonances for each carbon of the desired compound were also observed. This informations confirm the result that obtained from ^{1}H-NMR and led us to conclude that we had Z and E isomers. It is imported to write that, the ^{1}H NMR of the product did not showed any signal of N-CH_2 which attribute either the weakness of this bond or overlapping with water peak of solvent .

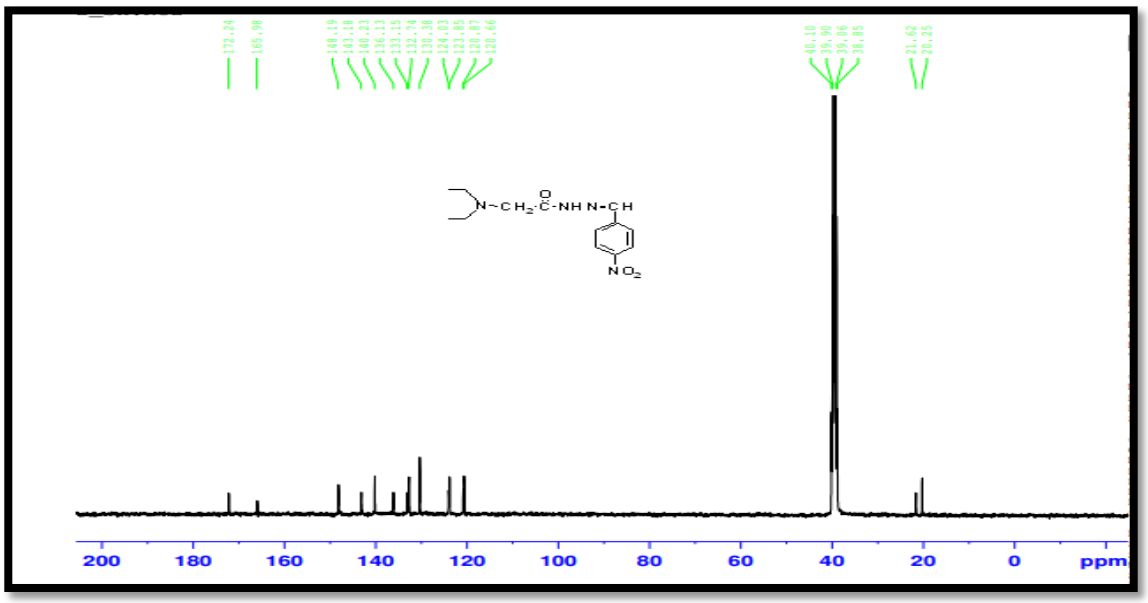


Figure (4. 14): ^{13}C-NMR spectrum of compound [S4]

4. 1. 6 Study FT-IR, ^{1}H-NMR and APT ^{13}C-NMR results of the compound 2-(diethylamino)-N-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)acetamide (10) (80)

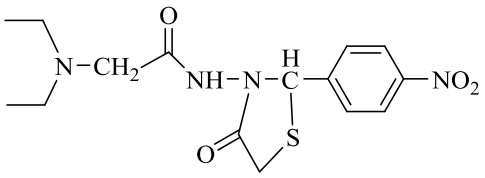


Figure (4. 15): The chemical structure of compound S10

With the two procurser in hand condensation 2-(diethylamino)-N'-(4-nitrobenzylidene) acetohydrazide with thioglycolic acid as cyclising agent, was the next task to prepare the desired 4-thiazolidinone ring. According to the literature procedure of *Hoan, D. Q*. After 15 hrs refluxing in oil bath the TLC analysis showed the presence of new material.

Furthermore, the FT-IR spectrum (Fig 4. 16) allowed to identification of all the functional group. The presence of two peaks at 1722.6 and 1689.4 cm^{-1} are corresponding to the carbonyl group of thiazolidinone ring and amide with a broad peak at 3245cm^{-1} which assign to the NH group confirm the proposal compound.

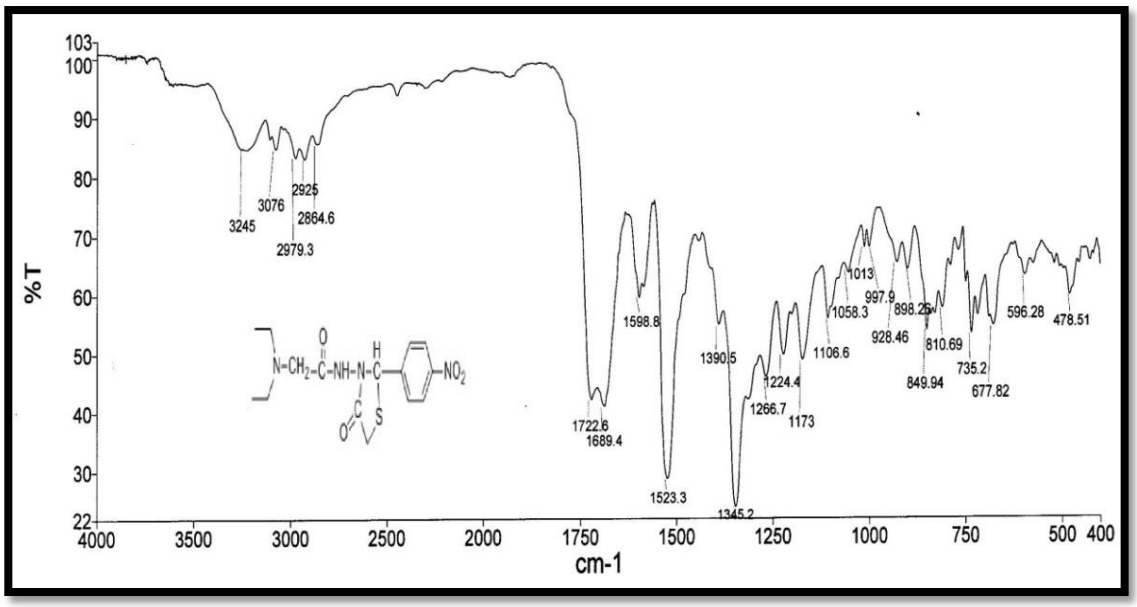


Figure (4. 16): FT-IR spectrum of compound [S10]

The ^{1}H-NMR spectrum (Fig 4. 17) of this compound showed signal characteristic proton of CO-NH in aromatic region at δ 10.16 ppm . Signals at δ 6.64 ppm corresponding to the resonance of N-CHAr of thiazolidine ring along with a clean signals of protons of CH_2S at δ 4.04-3.73 ppm as d and dd indicating the formation of thiazolidine ring.

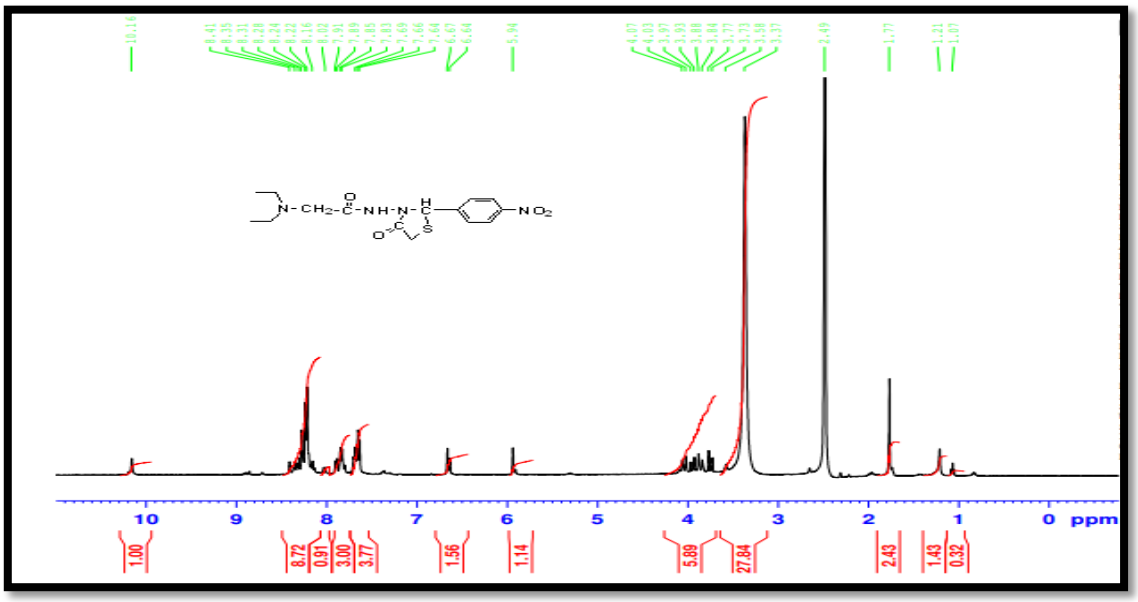
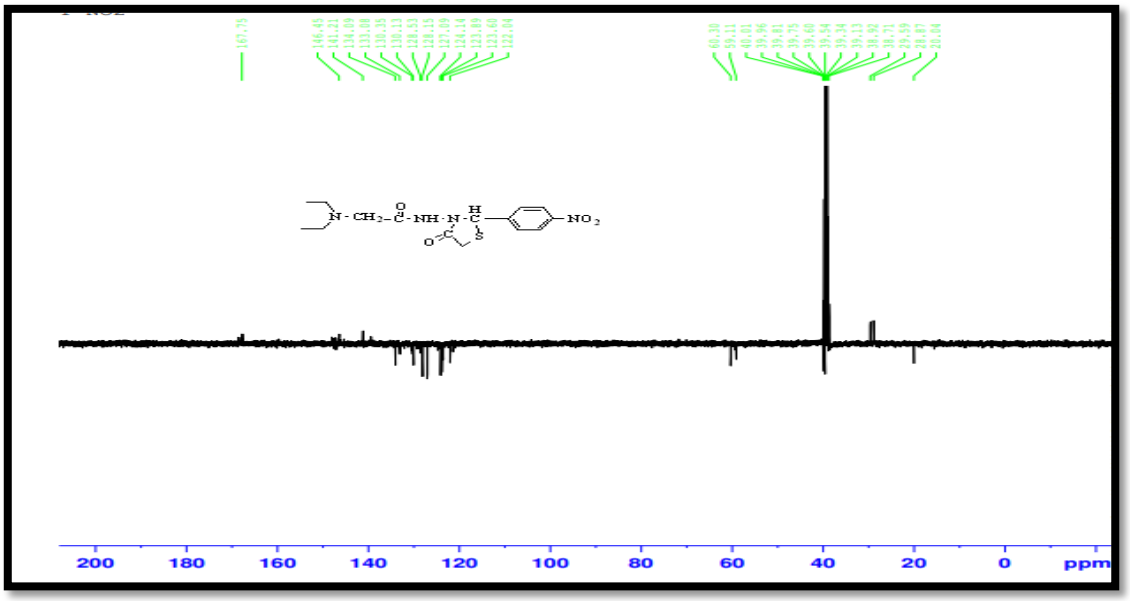


Figure (4. 17): ^{1}H-NMR spectrum of compound [S10]

A signal in the APT ^{13}C-NMR spectrum (Fig 4. 18) at δ 167.73 ppm corresponding to the carbonyl carbon of thiazolidinone ring was observed along with two carbon signals at δ 60.30 and 29.59 ppm which were attributed to the carbons of the N-<u>C</u>H and <u>C</u>H_2-S for thiazolidinone ring



.**Figure (4. 18):** APT ^{13}C-NMR spectrum of compound [S10]

4. 1. 7 Study FT-IR, ^{1}H-NMR and ^{13}C-NMR results of the compound 1H-indole-3-carbaldehyde (3) (81)

The 1H-indole-3-carbaldehyde was synthesized using procedure described by *Praveen Choppara et al* .

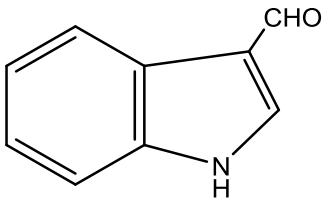


Figure (4. 19): The chemical structure of compound S3

Phosphorous oxychloride (1.1 eq.) was added dropwise to previous cooling solution of N,N-dimethylformamide and indol in ice bath. After completion the addition the reaction mixture was left sttiring for 2 hrs. After work up the TLC analysis suggested that new compound had been formed with completely consume of starting material.

FT-IR spectrum (Fig 4. 20) of the new compound showed absorption at 3411 ,and 1697 cm^{-1} that referred to NH and C=O respectively . Two absorption bands of starching vibration at 2817 and 2931cm^{-1} assignd to CHO. This is agood evidanse to formation of desired compound.

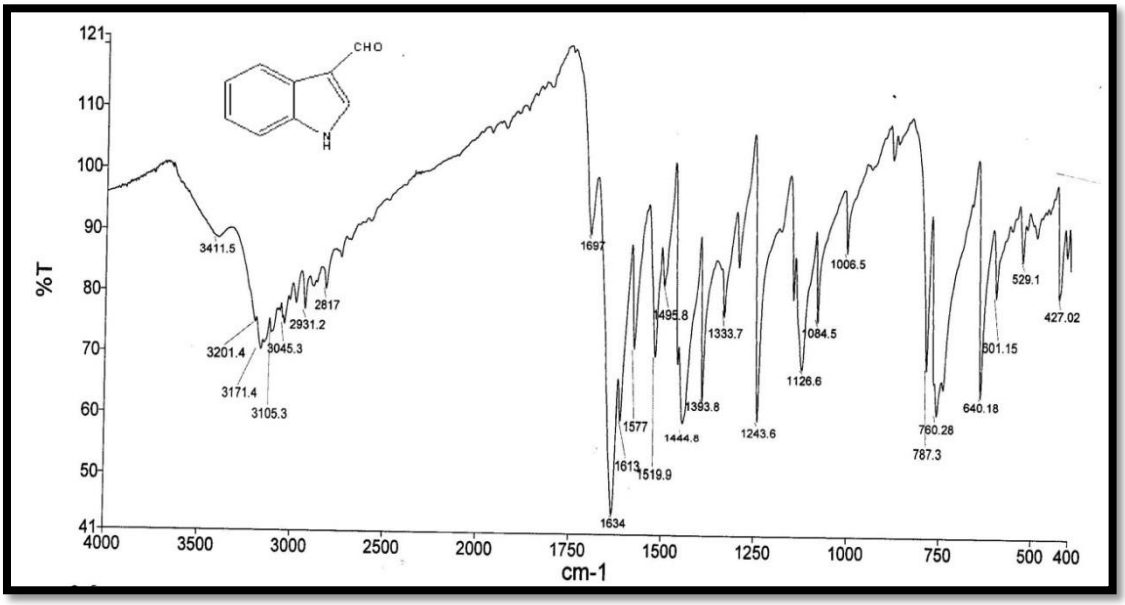


Figure (4. 20): FT-IR spectrum of compound [S3]

The ^{1}H-NMR spectrum (Fig 4. 21) of the new product obtained after work up showed peaks corresponding to the proton of aldehyde group and NH of indole at δ 9.93 and δ 12.21 ppm respectively with additional peaks in aromatic region belong to the protons of rings.

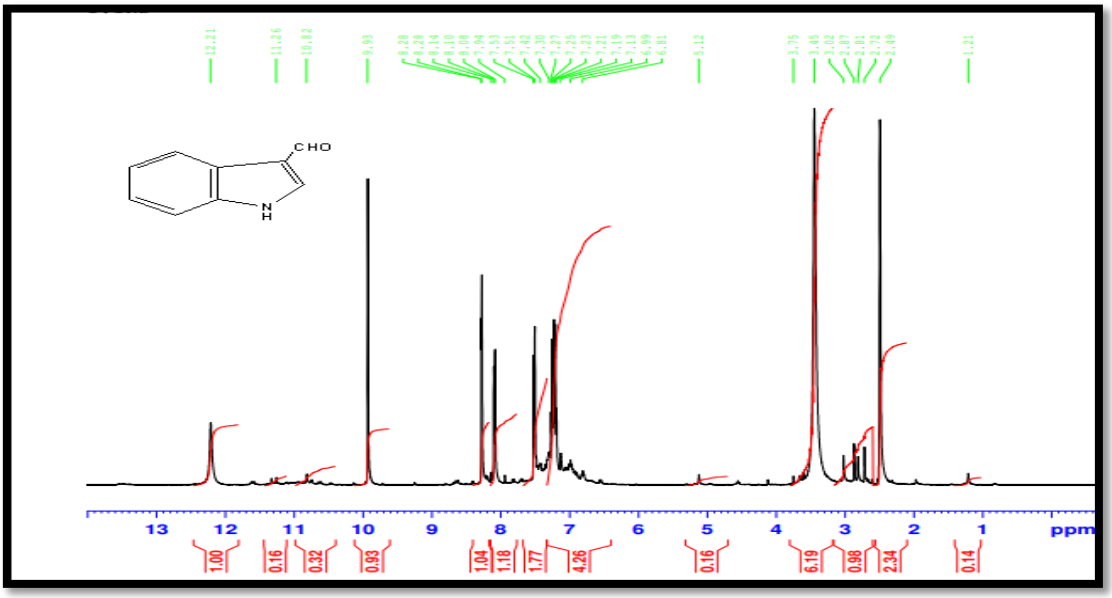


Figure (4. 21): ^{1}H-NMR spectrum of compound [S3]

A signal in the ^{13}C-NMR spectrum (Fig 4. 22) at δ 184.85 ppm corresponding to the carbonyl carbon of aldehyde group was observed along with eight carbon signals at δ 138.28 - 112.30 ppm which were attributed to the carbons of the rings .

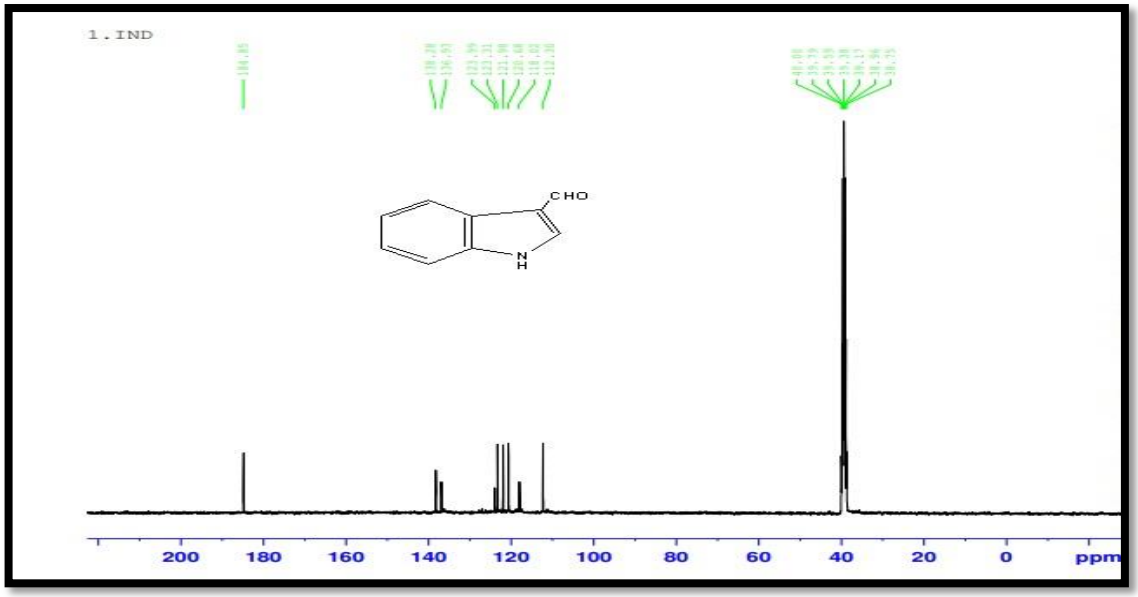


Figure (4. 22): ^{13}C- NMR spectrum of compound [S3]

4. 1. 8 Study FT-IR results of the compound N'-((1H-indol-3-yl) methylene) -2- (diethylamino) acetohydrazide (7) (82)

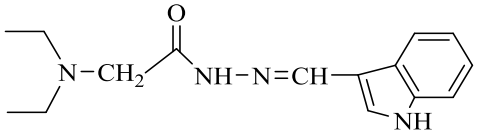


Figure (4. 23): The chemical structure of compound S7

The new compound N'-((1H-indol-3-yl)methylene)-2-(diethylamino)acetohydrazide was synthesized from the literature method *Singh et al* as evidenced by the FT-IR spectrum (Fig 4. 24) showed a peak at 3193 cm^{1} due to indole NH groups and absorption band corresponding to the carbonyl group of amide at 1622cm^{-1} and 1577 cm^{-1} for C=N .

4. 1. 9 Study FT-IR and ^{1}H-NMR results of the compound N-(2-(1H-indol-3-yl)-4-oxothiazolidin-3-yl)-2-(diethylamino) Acetamide (11)

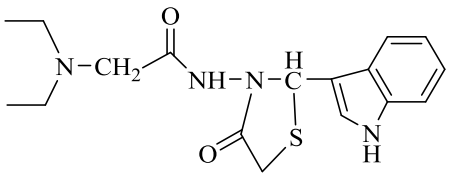


Figure (4. 25): The chemical structure of compound S11

The new compound was synthesized from cyclocondensation of N' -((1H-indol-3-yl)methylene)-2-(diethylamino)acetohydrazide with thioglycolic acid in tetrahydrofurane.

The FT-IR spectrum (Fig 4. 26) spectrum for 4-oxothiazolidin also confirmed the cyclization showing the expected CO group of five member cyclic amide stretch at 1719 cm^{-1}. Other peaks were observed at,3398, 3212 and 1671 cm^{-1} which assign to NH of indole, CO- NH and carbonyl group of amide.

The ^{1}H-NMR spectrum (Fig 4. 27) showed that a three of signals at δ 11.68, 8.90 and 8.34-7.8 ppm belong to the CO-NH, NH of indole and aromatic protons. N-CH was observed at δ 6.51 ppm. The resonance corresponding to the protons of S-CH_2- of thiazolidinone ring appeared at 3.69 ppm.

4. 1. 10 Study FT-IR and ^{1}H-NMR results of the compound N'-(2-bromobenzylidene)-2-(diethylamino)acetohydrazide (6)

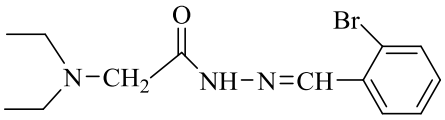


Figure (4. 28): The chemical structure of compound S6

Formation of Schiff base was investiged this time with 2-bromo benzyaldehyde in ethanol with catalytic amount of glacial acetic acid. After 10 hrs the TLC analysis indicated that the reaction had produced a new one spot very close to gather.

In the FT-IR spectrum (Fig 4. 29) it was possible to observed the stretching at 1655.2 and 1556.6 cm^{-1} corresponding to C=O and C=N respectively. In the ^{1}H-NMR spectrum (Fig 4. 30) of the above compound **S6** showed two resonance as a singlet at δ 8.94 and δ 8.90 ppm corresponding to the protons of N*H*CO and N=C*H* also 8.17-7.49 ppm to the aromatic protons with other peaks at δ 2.09 and δ 1.13 which belong to the NC$\underline{H}_2$ and $NCH_2C\underline{H}_3$. In the same spectra we could not distinguish proton of CH_2N group.

4. 1. 11 Study FT-IR and ^{1}H-NMR results of the compound bromophenyl)-4-oxothiazolidin-3-yl)-2-(diethylamino)acetamide (9) (83)

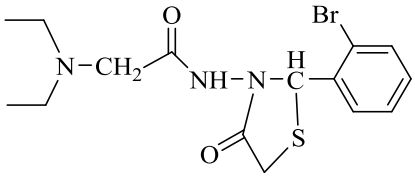


Figure (4. 31): The chemical structure of compound S9

The final compound 4thiazolidin was synthesized by equimolar ratio of N'-(2-bromobenzylidene)-2-(diethylamino)acetohydrazide . Thioglycolic acid and catalytic amount of zinc chloride anhydrous in tetrahydrofuran .The reaction mixture was refluxed for 24 hrs. The formation of the new compounds confirmed by their spectral as follows;

FT-IR spectrum (Fig 4. 32) showed characteristic peaks at 3068 cm^{-1} for NH, and at 1725 cm^{-1} to five member cyclic amide C=O stretching . Appearance strong absorption peak at 751.68 cm^{-1} for C-S group of cyclized thiozolidinone ring.

^{1}H-NMR spectrum (Fig 4. 33) of the new compound exhibits signal peak for N-H proton at **δ** 8.99 ppm , and series of multiple in the region 8.21–7.21 ppm is due to the aromatic protons. Two signals proton 3.89 – 4.06 ppm accounted for a proton of N-C*H* and CH_2S [(84)] of thiazolidinone ring.

4. 1. 12 Study FT-IR and ^{1}H-NMR results of the compound N'-(4-chlorobenzylidene)-2-(diethylamino)acetohydrazide (5)

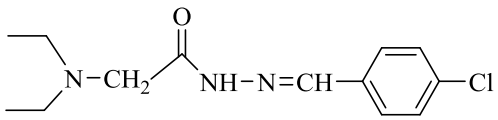


Figure (4. 34): The chemical structure of compound S5

In this experiment hydrazide was allowed to react with commercially available *para* chlorobenzaldehyde in ethanol for 15 hrs. After re-crystallized the structure of new compound was first inspection by its The FT-IR spectrum (Fig 4. 35) that showed the presence a peaks at 1658.2 and 1592.4 cm^{-1} corresponding to C=O and C=N respectively. The ^{1}H-NMR spectrum (Fig 4. 36) showed signals in the region δ 8.9-8.2 ppm corresponding to the resonances of protons of aromatic, and at 8.5-6, 2.09 and 1.06 ppm to CH=N group, NCH_2 and NCH_2CH_3. It is important to write that when the experiment was repeated second time the same result was observed with absence resonance of NH group .

4. 1. 13 Study FT-IR, ^{1}H-NMR and APT ^{13}C-NMR results of the compound N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-2-(diethylamino)acetamide (8)

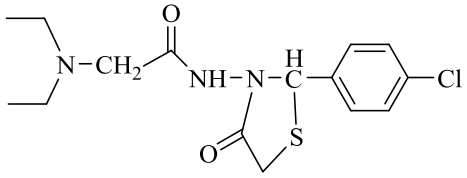


Figure (4. 37): The chemical structure of compound S8

The FT-IR spectra (Fig 4. 38) of the compounds showed several bands beginning with NH stretching band which appeared at 3188 cm^{-1}, stretching bands of aromatic and aliphatic C-H was observed at about 3086 cm^{-1} and 2978, 2863 cm^{-1} respectively, whereas stretching bands of C=O of thiazolidinone and C-S appeared at the region 1683 and 823 cm^{-1}. The ^{1}H-NMR spectrum (Fig 4. 39) of this compound displayed two signals at 11.47-11.33 ppm was belonged to proton of NH . A signal at 8.74-7.48 ppm was referred to protons of aromatic ring and single signal at 6.50 ppm was attributed to proton of C-H thiazolidine ring. Also signal was appeared in the region 3.36 ppm were belonged to protons of CH_2S and appearse signal at 2.21 to protons CH_2 .Finally peak at 1.24 ppm was belonged to protons of CH_3.

A signal in the APT ^{13}C-NMR spectrum (Fig 4. 40) at δ 167.35 and 160.36 ppm corresponding to the carbonyl carbon of $CH_2\underline{C}ONH$ and thiazolidinone ring was observed along with two carbon signals at δ 59.56 and 29.69 ppm which were attributed to the carbons of the N-$\underline{C}$H and $\underline{C}H_2$-S for thiazolidinone ring provided further evidence for the formation of desire compound.

4. 2 Biological part

4. 2. 1. Cytotoxicity effect toward HepG2 and SK-GT2 cell line

Cancer cell lines HepG2 and SK-GT2 were seeded as (1 x 10^5 cell/ml) in 96-well microplate and incubated for 24 hrs at 37 ^oC. when the cells become confluent monolayer, they were exposed to the compound's concentrations at (15.1, 31.2, 62.5, 125, 250, 400 and 500) µg/ml and incubated in 37℃ for 24 h, then stained with crystal violate dye and calculated the inhibition rate (%) for each compound.

4 .2 .1. 1 Cytotoxic activity of N-(2-(2-bromophenyl)-4-oxothiazolidin-3-yl)-2- (diethylamino)acetamide

This compound showed an increased inhibition rate after 24 hrs. of HepG2 cancer cell line at concentrations 15.1, 31.2, 62.5,125 , 250, 400 and 500 µg/ml were 10 , 22, 47 , 50, 51, 62 and 64 % , respectively. Concentration 500 µg/ml represent the ideal concentration prepared from compound that inhibited 64.5% of HepG2 cell line after 24 hrs. exposure with no significant differences. As presented below in Table (4. 3), while the same compound (S9) showed higher level of inhibition (86.4) against SK-GT2 cancer cell line at concentration 500 µg/ml .At concentration 500 µg/ml of the same compound showed the highest inhibition rate among the other tested compounds. When compared the effect of compound (S9) on normal cell line (WRL68) as control, there were no cytotoxic activity could be noticed at concentrations of 15.1, 31.2, 62.5 and 125 µg/ml , which means that these concentrations could be safe to the normal cells .However , the effect of toxicity start to appear at concentrations 250, 400 and 500 µg/ml . The ideal concentration for both

cell lines could be 125 µg/ml because it inhibits SK-GT2 and HepG2 cancer cell line growth and not harmful to WRL68 normal cell.

4. 2. 1. 2 Cytotoxic activity of N'-((1H-indol-3- yl)methylene)-2-(diethylamino)acetohydr azide

The inhibition of this compound and its dilutions was showed in Table (4. 3). The concentrations 15.1, 31.2, 62.5,125 , 250, 400 and 500 μg/ml in 24 hrs., of exposure time were represented the ideal concentrations that inhibited HepG2 cell lines growth with inhibition rates ranges from 5-60%. The resultes of compound (S7) on SK-GT2 cancer cell line are allustrated in Table (4. 3) that shows their dependence on concentration at 24 hrs. The inhibition rates were range from 6 to 63 % for 24 hrs. When examined these concentrations on WRL68 (control) cell lines the results seems to be much different. The concentration 500 µg/ml has the lower cytotoxicity toward this cell line even after 24 hrs., of exposure. The cytotoxicity rates reach 8 % .While the concentrations 15.1, 31.2, 62.5,125, 250 and 400 µg/ml at 24 hrs.,did not show any cytotoxicity . The optimum concentration for this compound suggested that 500 µg/ml even when treated for 24 hrs. also appear to be safe to WRL68 (control)cell line.

Table (4. 3): Percentage inhibition values of different cell lines treated with two prepared organic compounds at different concentrations. Inhibitions (%) values are expressed as Mean±SD.

Compound	Cell line	Concentrations (µg/ml)						
		Inhibition (%)						
		15.1µg/ml	31.2µg/ml	62.5µg/ml	125µg/ml	250µg/ml	400µg/ml	500 µg/ml
S9	WRL68 (control)	0 c	0 c	0 c	0 c	13.7±2.6b	20.2±2.5a	22.3±2.6a
	HepG2	10.5±5.6c	22.1±3.9c	47.7±2.6b	50.6±3.3a	51.2±3.3a	62.3±3.7a	64.5±3.7a
	SK-GT2	8.6±0.1d	26.6±0.2c	28.8±0.1c	29.8±1.2c	62.9±1.1b	67.8±0.2b	86.4±0.2a
S7	WRL68 (control)	0 c	0 c	0 c	0 c	0 c	0 c	8.4±1.3a
	HepG2	5.4±4.2d	8.5±3.8d	13.6±4.9d	26.2±6.5c	51±4.1b	59.5±4.3b	60.1±3.9a
	SK-GT2	6.8±1.2c	9±1.8c	10±2.4c	21.3±3.6b	26.7±2.2b	59.3±2.4a	63.2±3.6a

S9: N-(2-(2-bromophenyl)-4- oxothiazolidin-3-yl)-2- (diethylamino)acetamide

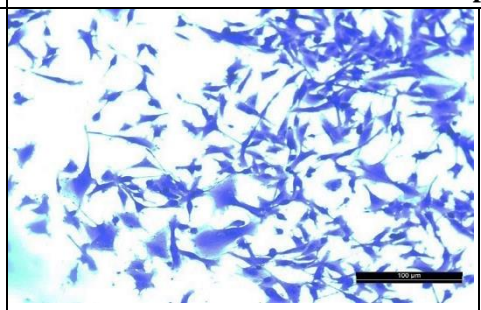
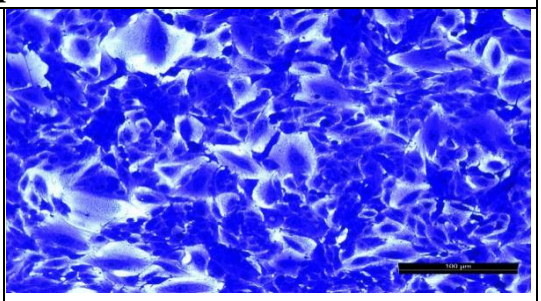
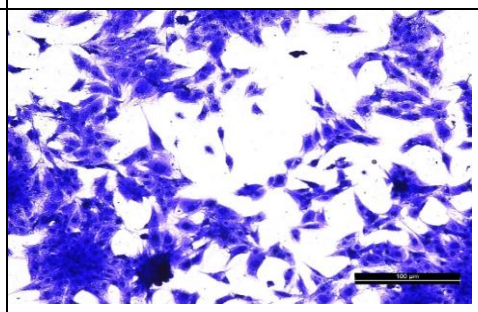
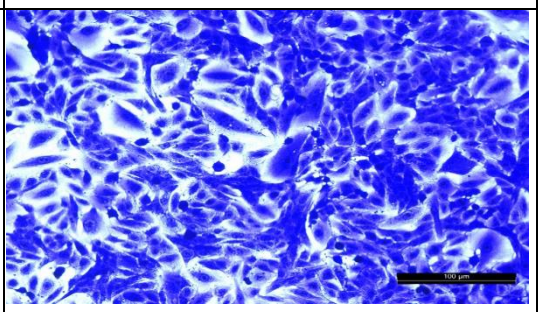
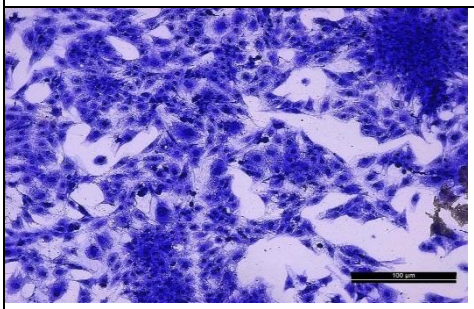
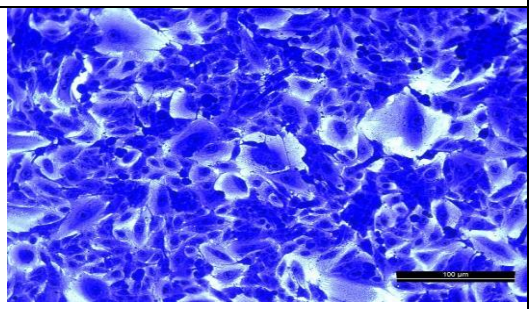
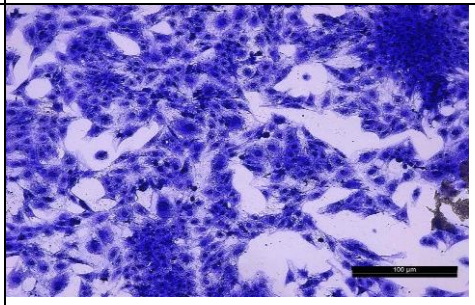
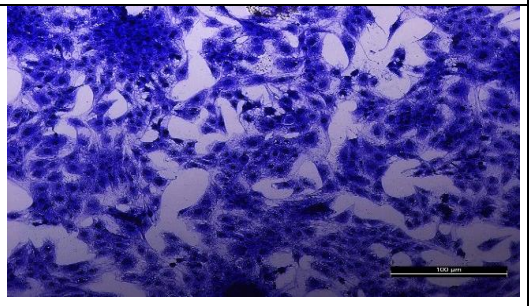
S7: N'-((1H-indol-3- yl)methylene)-2- (diethylamino)acetohydr azide

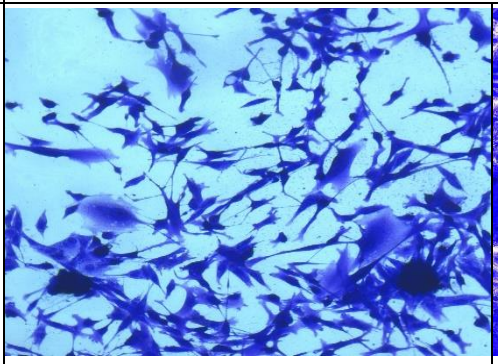
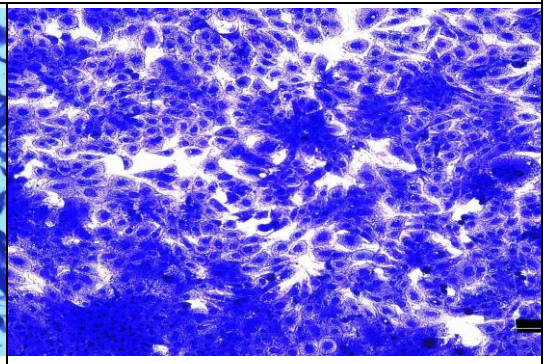
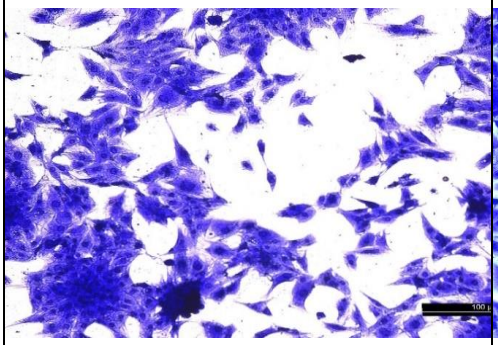
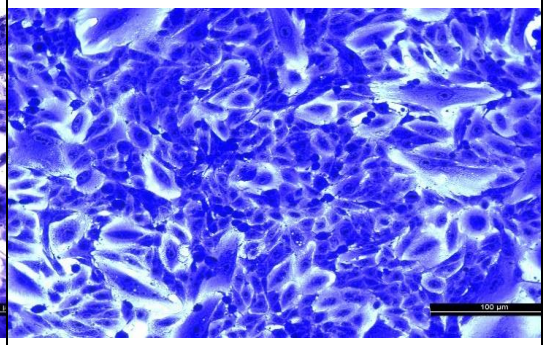
HepG2 : Liver cancer cell line

SK-GT2 : Esophageal cancer cell line

WRL68 : A nrmal cell line for the human liver

Table (4. 4): The in vitro cytotoxicity effect of prepared organic compounds on different cell lines at 15.1 and 500 µg/ml after 24 hrs incubation at 37 C.

Compound	Concentration (µg/ml)	
	500 µg/ml	15.1 µg/ml
	HepG2 cell line	
S9		
S7		
	WRL68 cell line	
S9		
S7		

Compound	Concentration (µg/ml)	
	500 µg/ml	15.1 µg/ml
	SK-GT2 cell line	
S9		
S7		

Conclusion

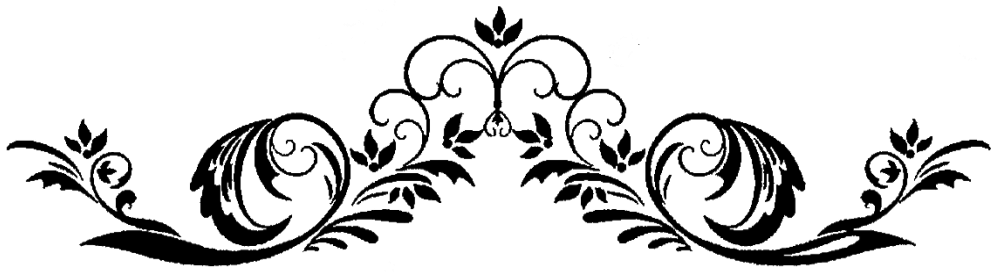
1. The synthesis of 2-(diethylamino)acetohydrazid as precursor from ethyl diethylglycinate to built the key step schiff base was successful that used to form five member ring skeleton of 4-oxothiazolidin .
2. These compounds were obtained as solid and oily state and the purity of each synthetic compounds were confirmed by thin layer chromatography.
3. Their chemical structures were identified by inspection of its spectral techniques for instant FT-IR, ^{1}H-NMR ^{13}C-NMR and APT ^{13}C-NMR .
4. Various yield were obtained in attempts to carry out the alkylation step with diethyl amine and the pest result was obtained in THF and KOH as base in yield of 74% .
5. Attempt to synthesis ethyl diethylglycinate from Dipheny amine , was successful as indicated by IR spectrum after column chromatography eluting with hexane - ethyl acetate (4:1), but unfortunately the low yield led us to abandon this substrate .
6. 2-(diethylamino)-N'-(4-nitrobenzylidene) acetohydrazide was synthesized as a mixture of two isonmer E/Z as indicated by ^{1}H-NMR and ^{13}C-NMR
7. Synthesis of 1H-indole-3-carbaldehyde in good yield engorged us to use it as a substrate to complete the cyclization step with thioglygolic acid.
8. Two new compound.N'-((1H-indol-3-yl)methylene)-2-(diethylamino)
9. acetohydrazide.and.N-(2-(2-bromophenyl)-4-oxothiazolidin-3-yl)-2-(diethylamino)acetamide was investigated against two kinds of cancer HepG2,SK-GT2 and WRL68(control) at (15-500µg/ml) for 24 hrs , and exhibited increased inhibition in both compound .

Suggestions for Future work

1 - We have achieved an efficient (3 steps) route to the key precursor Schiff base derivatives from ethyl diethylglycinate.

2- Now we would seek to apply this route to synthesis different heterocyclic compounds on large scale and evaluation their biological activity against different kind of cancer cells, bacteria or fungus.

3- It may will be that the specific reaction conditions developed in this area could be applied with success to this work.



APPENDIXE

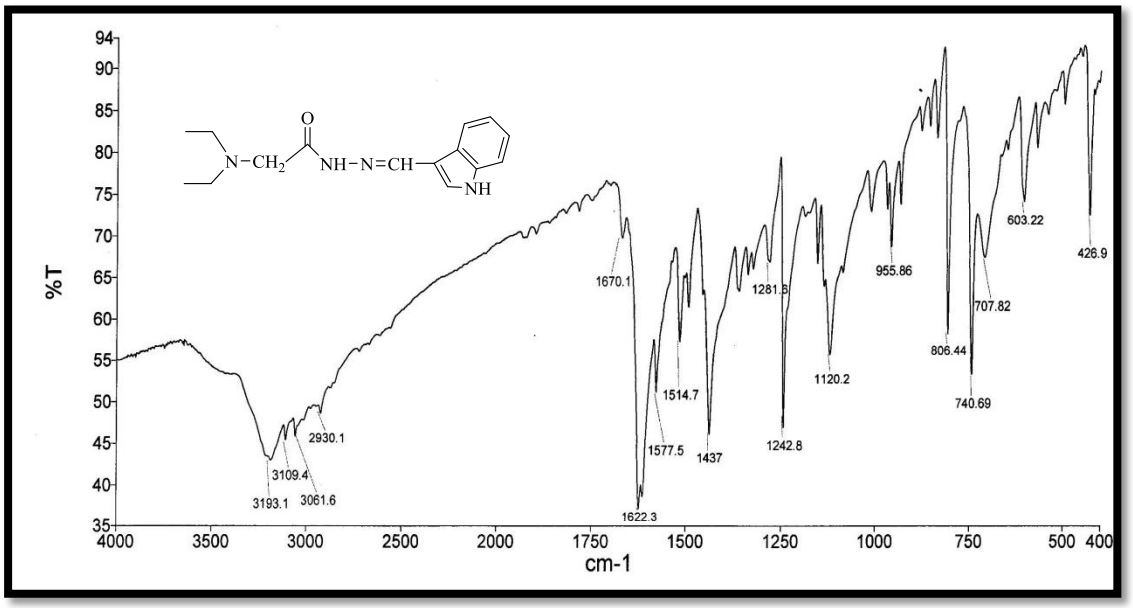


Figure (4. 24): FT-IR spectrum of compound [S7]

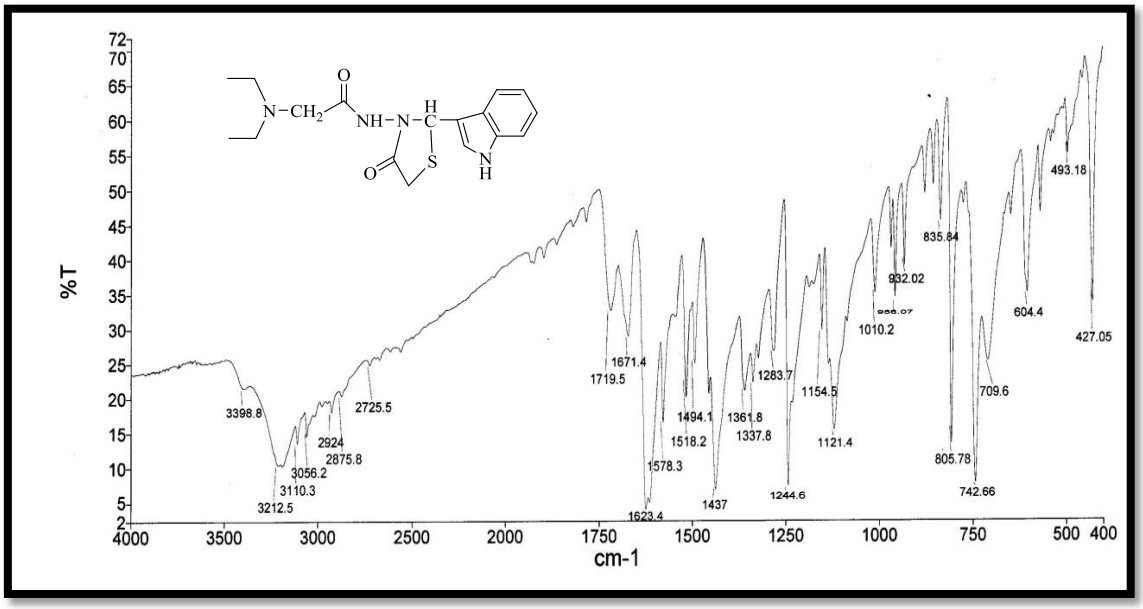


Figure (4. 26): FT-IR spectrum of compound [S11]

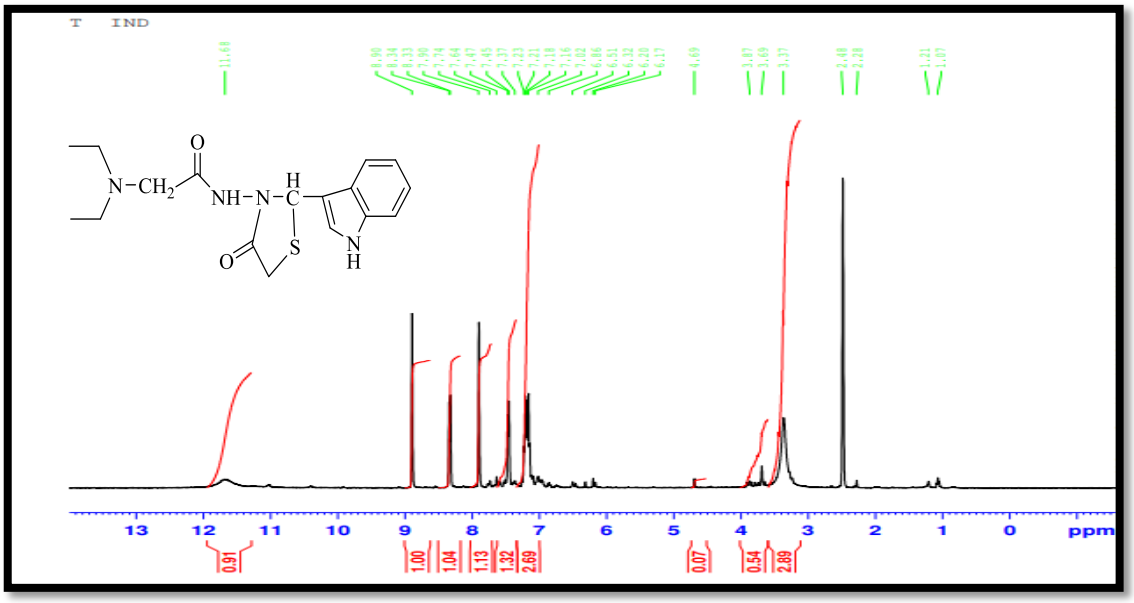


Figure (4. 27): ^{1}H-NMR spectrum of compound [S11]

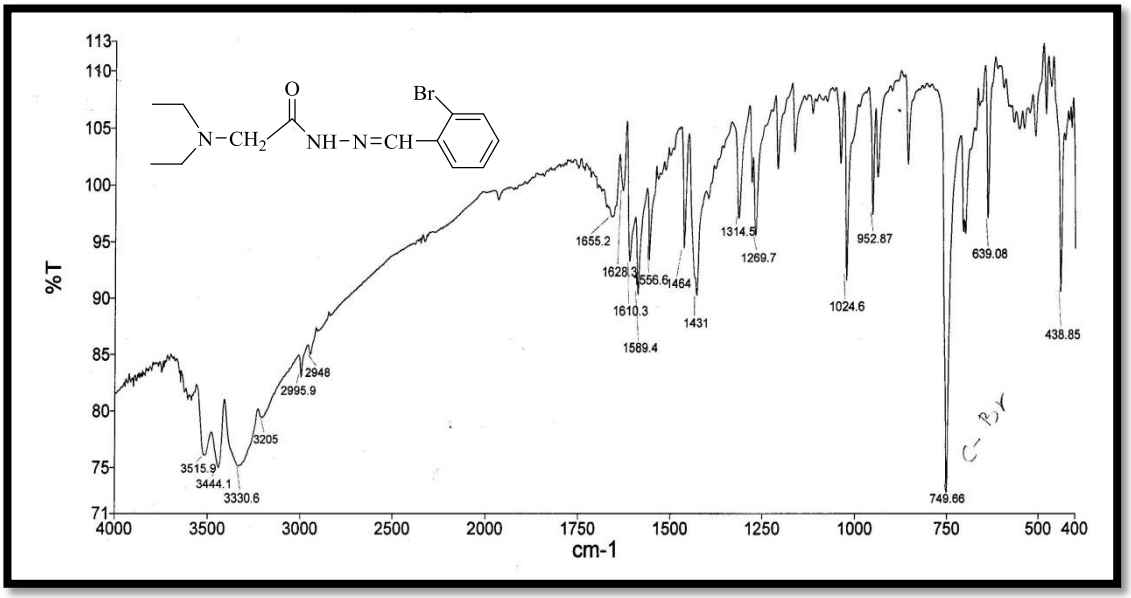


Figure (4. 29): FT-IR spectrum of compound [S6]

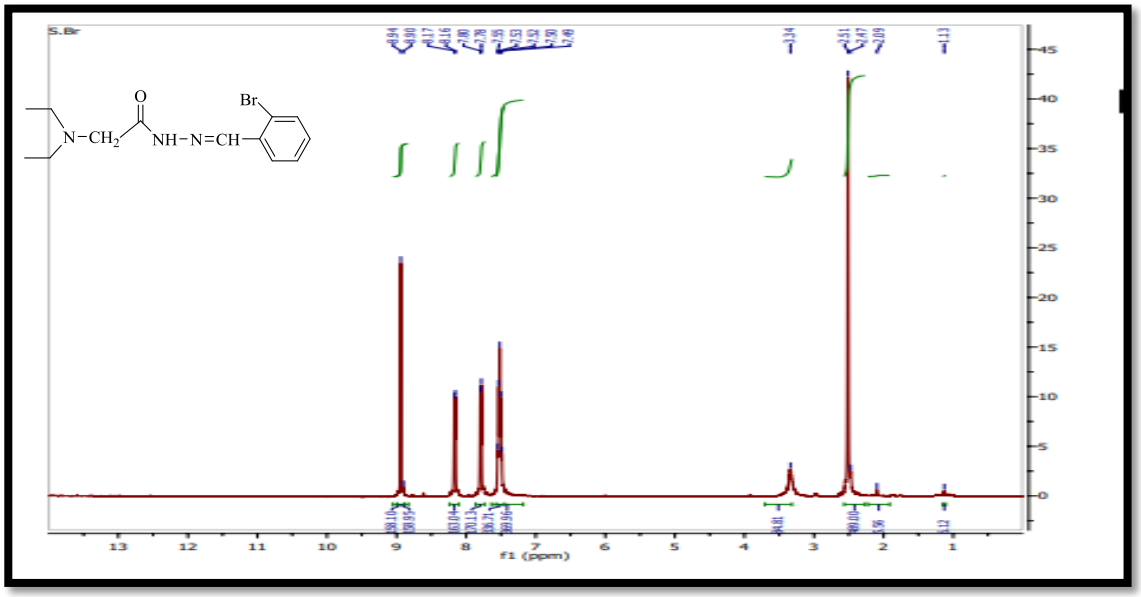


Figure (4. 30): ^{1}H-NMR spectrum of compound [S6]

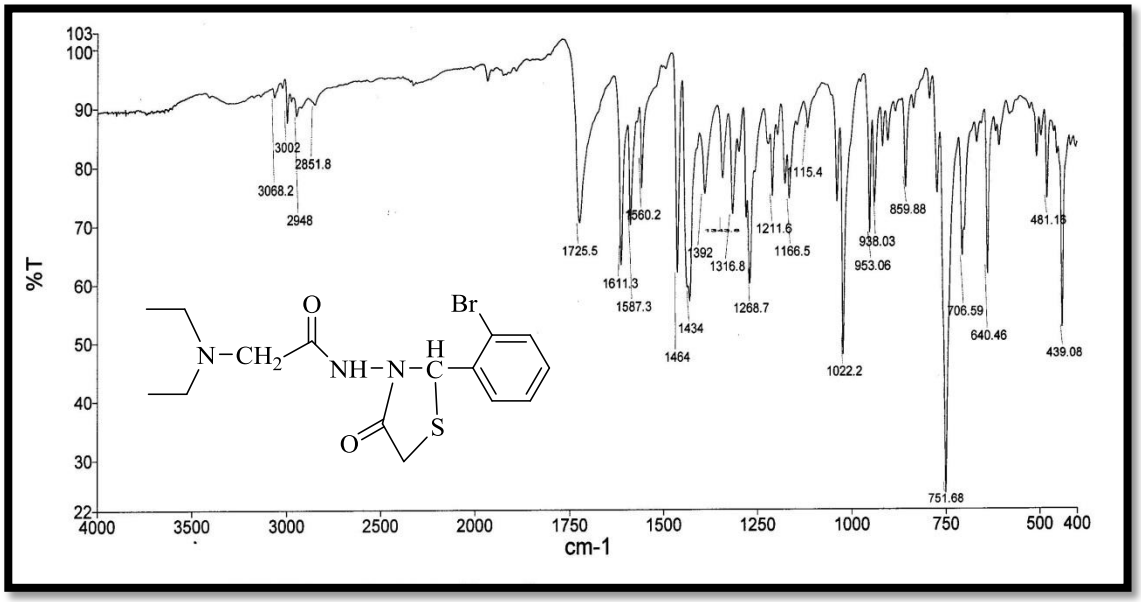


Figure (4. 32): FT-IR spectrum of compound [S9]

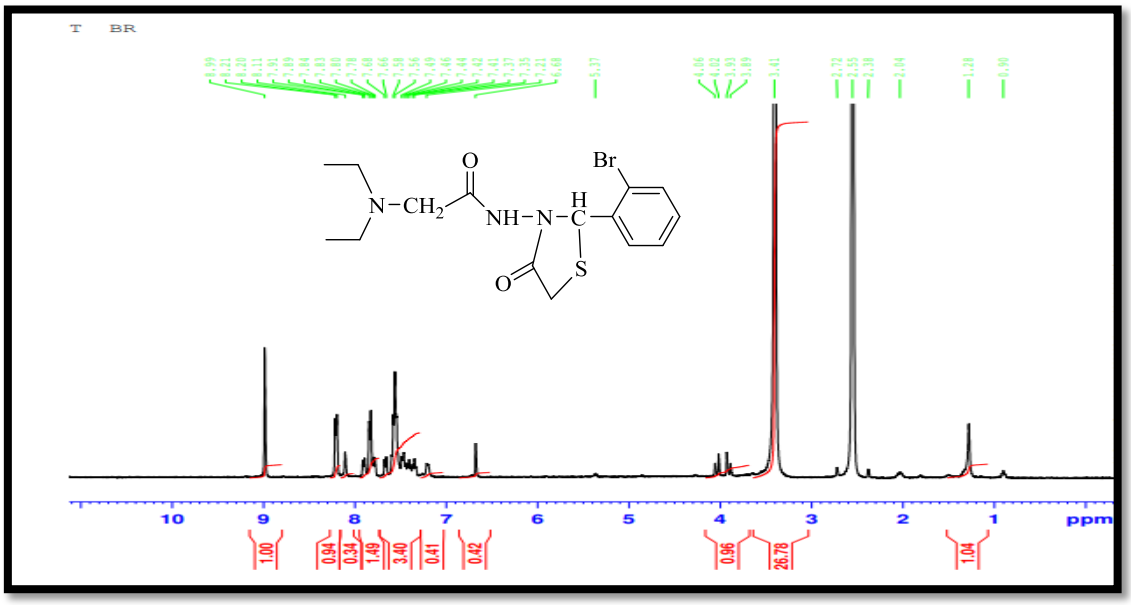


Figure (4. 33): ^{1}H-NMR spectrum of compound [S9]

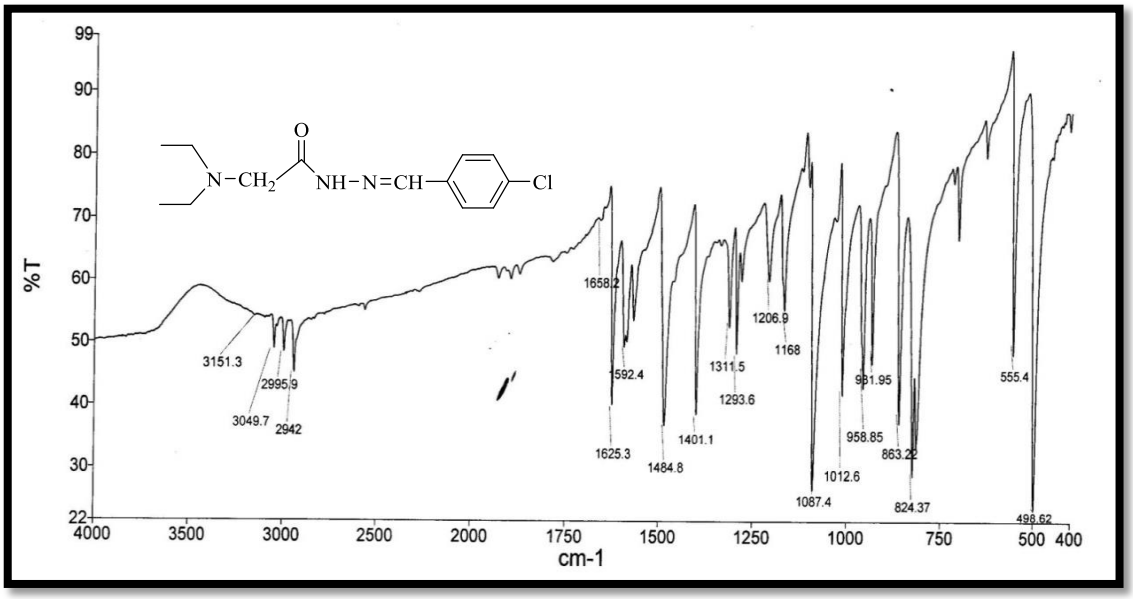


Figure (4. 35): FT-IR spectrum of compound [S5]

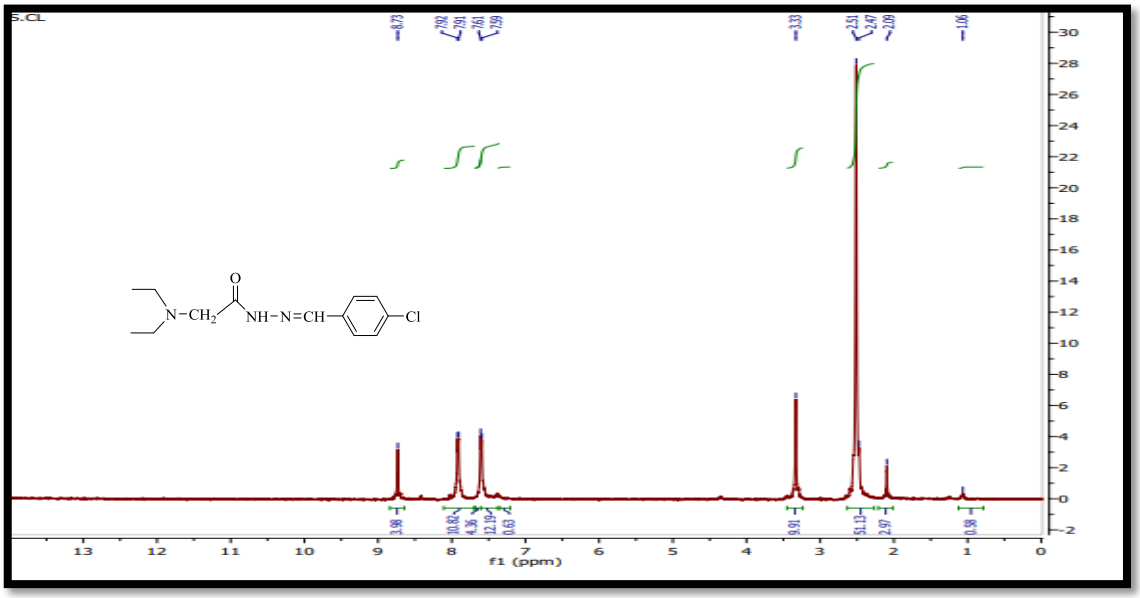


Figure (4. 36): ^{1}H-NMR spectrum of compound [S5]

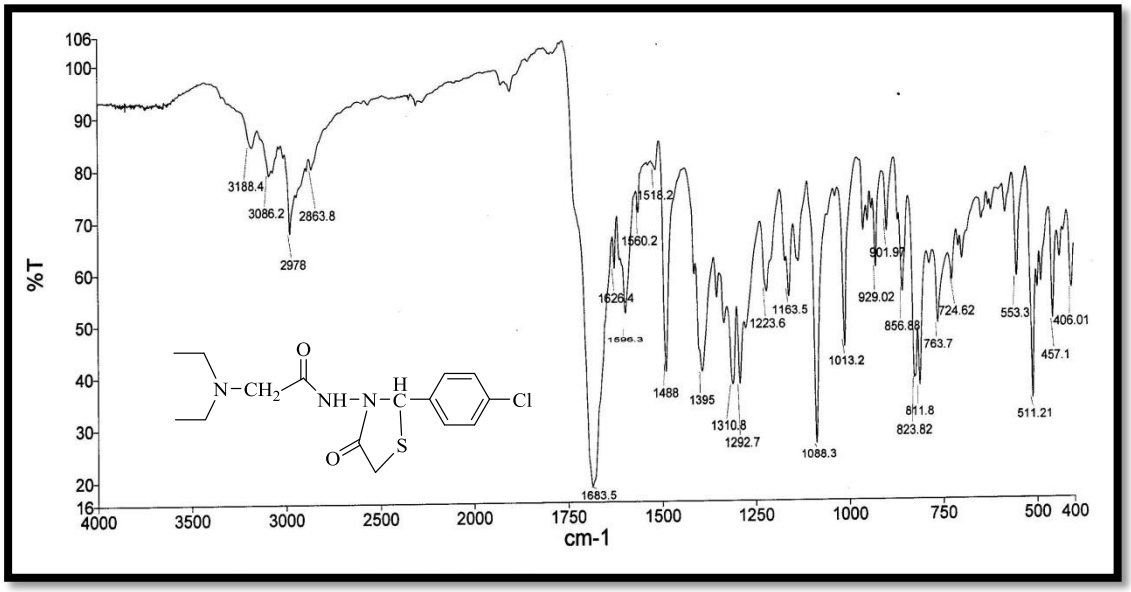


Figure (4. 38): FT-IR spectrum of compound [S8]

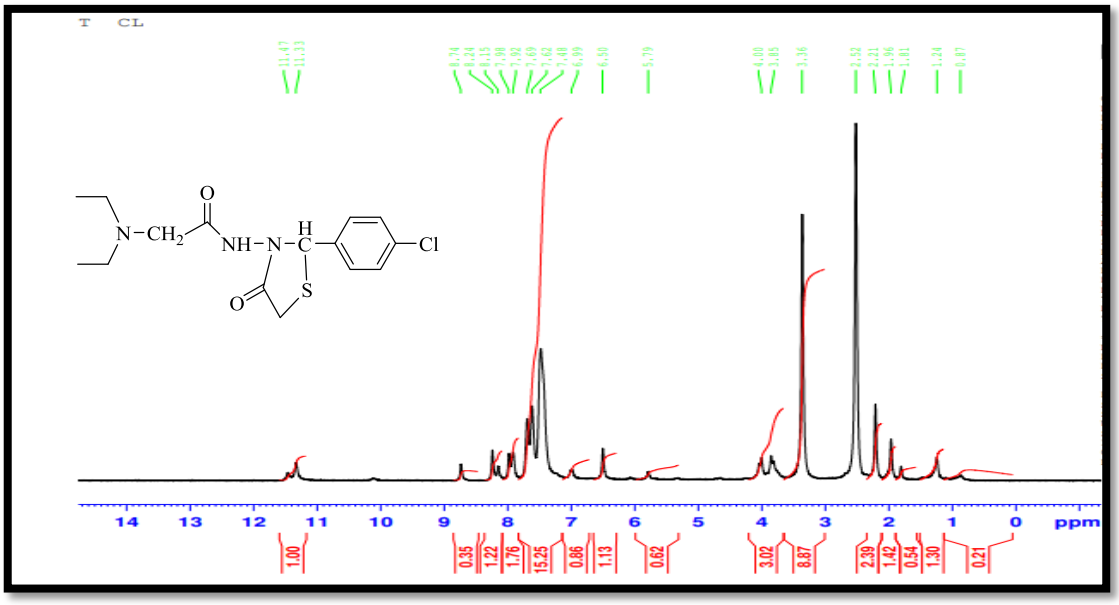


Figure (4. 39): ^{1}H-NMR spectrum of compound [S8]

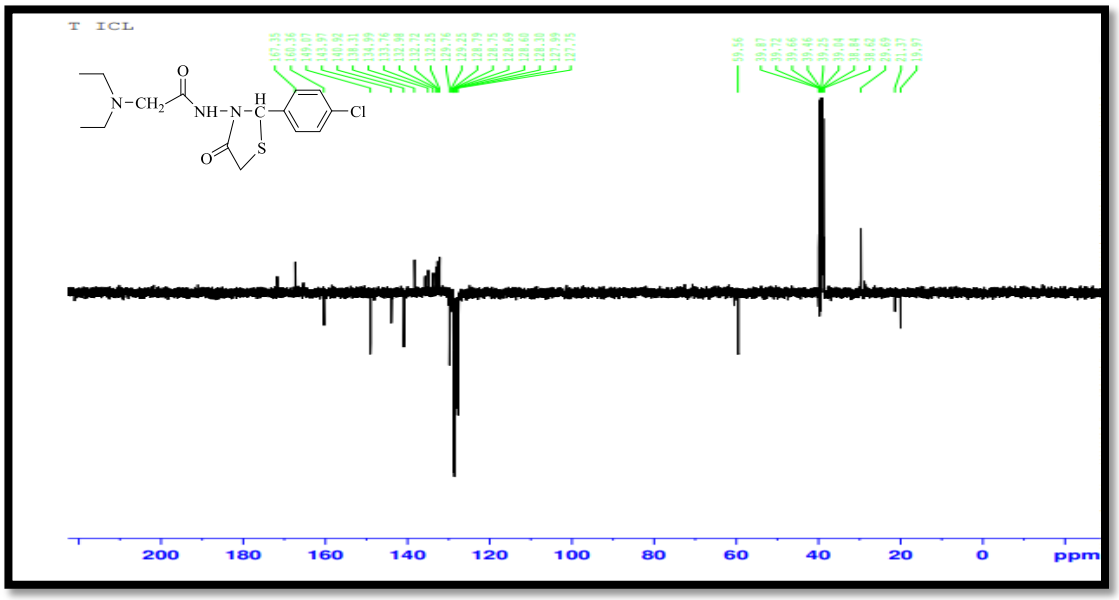
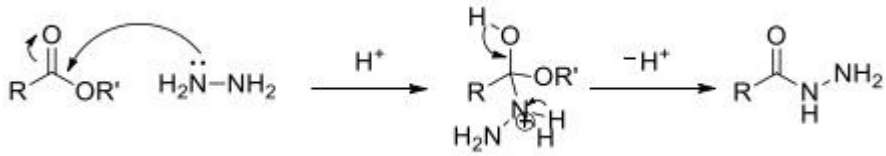
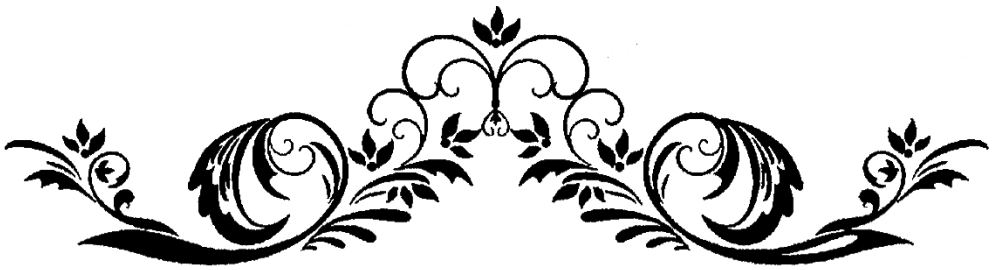


Figure (4. 40): APT ^{13}C-NMR spectrum of compound [S8]



Scheme (4. 1): The mechanism of the compounds S2 [87]



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الخلاصة

يصف العمل في هذه الأطروحة مناهج بناء هيدرازون-هيدرازيد المستبدلة كوسائط في تخليق السلائف لتخليق مركبات ثيازوليدينون.

ركز النهج الأولي لتخليق ثيازاليدينون على تحضير إيثيل جلايسينات الإيثيل الذي من شأنه أن يتيح تخليق المركب المطلوب ٢- (داي إيثيل أمينو) أسيتوهيدتازيد .

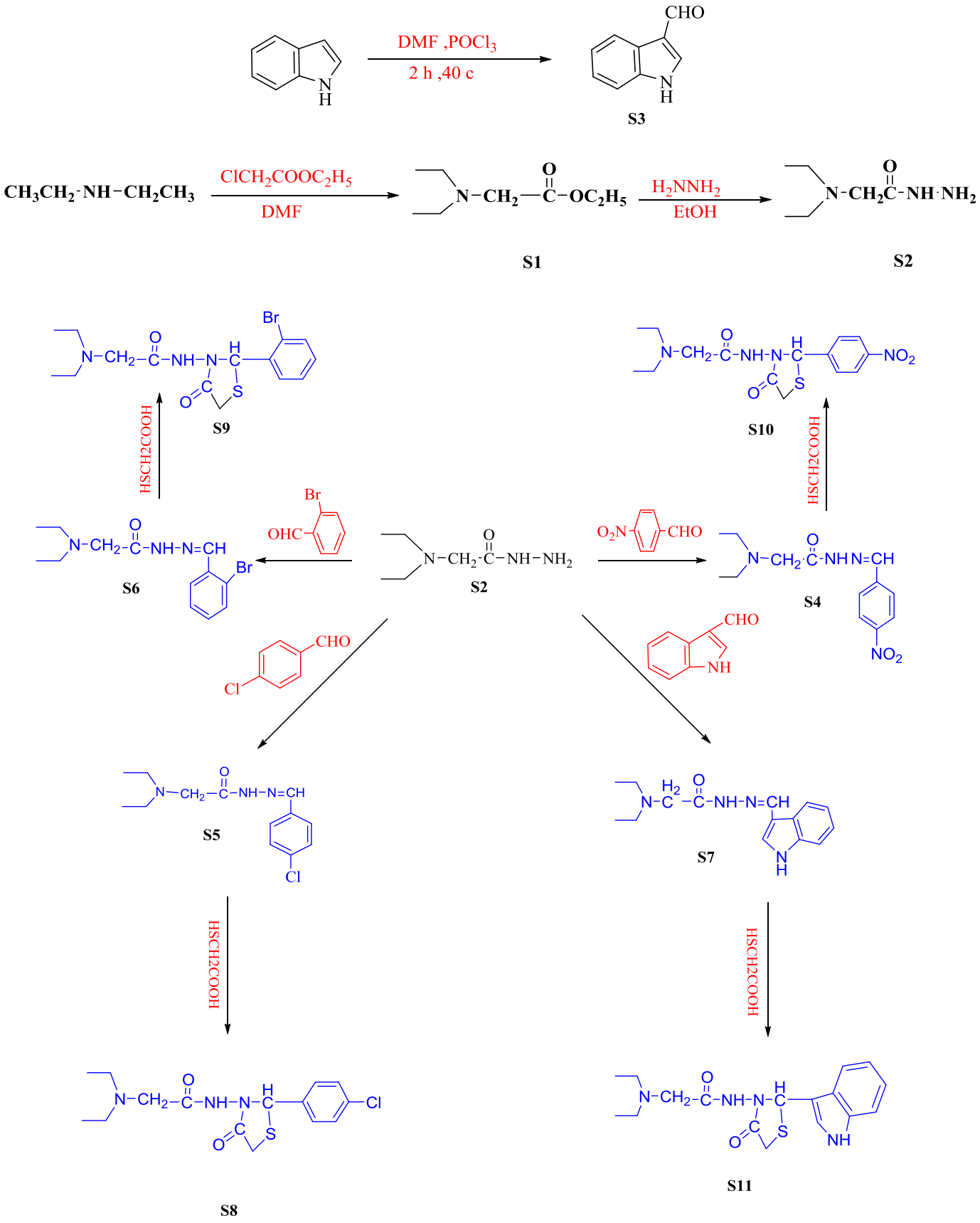
بدأت الخطوة الأولى من ثنائي إيثيل أمين مع كلورو إيثيل أسيتات في وجود هيدروكسيد البوتاسيوم كعامل مساعد.

تم تصنيع ٢- (داي إيثيل أمينو) أسيتوهيدرازيد في خطوة واحدة بتفاعل إيثيل داي إيثيل جلايسينات مع هيدرات الهيدرازين بحاصل ٦٦٪ .

تم الحصول على مشتقات قاعدة شيف المطلوبة بعد تفاعل ٢- (ثنائي إيثيل أمين) أسيتوهيدرازيد مع ألدهيد عطري متغير تحت ظروف حمضية خفيفة لإعطاء مركبات الإيمين ذات العائد المتغير.

تم تحقيق خطوة الغلق الحلقي الرئيسية بمعالجة مشتق قاعدة شيف مع حمض الثيوجليكوليك في التولوين كمذيب لمدة (١٠-٢٠ ساعة) أعطت المركبات المستهدفة ذات العائد المنخفض إلى المتوسط .

هذه المركبات تم تشخيصها واثبات تركيبها الكيمياوي بالتقنيات الطيفية مثل طيف الاشعة تحت الحمراء(FT- IR) وطيف الرنين المغناطيسي للبروتون والكاربون (^{1}H-NMR, APT ^{13}C-NMR)، تم اختبار نقاوتها بواسطة كروموتوكرافيا الطبقة الرقيقة وتم تقييم مركبين جديدين لنشاطهما السمي ضد خط خلايا سرطان الكبد و المريء. وكشف عن نتائج متوسطة مقارنة بالخلايا الطبيعية.



مخطط يوضح المركبات التي تم تحضيرها

وزارة التعليم العالي والبحث العلمي

جامعة ديالى / كلية العلوم

قسم الكيمياء

تحضير وتشخيص الفعالية السمية لبعض قواعد شف الجديدة ومركبات ثايازوليدينون

مجلس كلية العلوم / جامعة ديالى

وهي جزء من متطلبات نيل درجة الماجستير في علوم الكيمياء

كيمياء عضوية

من قبل الطالبة

صبا عبدالقادر حميد

بكالوريوس في علوم الكيمياء ٢٠١٣

جامعة ديالى ـ كلية العلوم

بأشراف

أ.م.د. لمى سلمان عبد

١٤٤٢ هجرية **٢٠٢١ ميلادية**