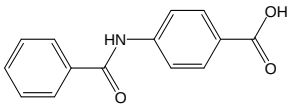
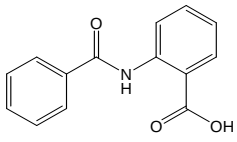
Abstract

New 2,5-disubstituted 1,3,4-oxadiazoles derived from amino acids carrying phenyl group at position (2) and benzamido, alkyl moieties at position 5 which were synthesized as outlined below :

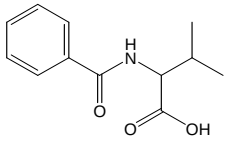
1. Synthesis of benzamido carboxylic acid [1-5]:- Condensation of appropriate amino acid (*p*- amino benzoic acid, *o*- amino benzoic acid, valine, leucine, phenyl alanin) with benzoyl chloride gave the corresponding benzamido carboxylic acids, having the following structure formula :-



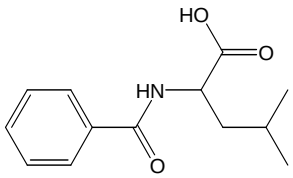
P-benzamido benzoic acid [1]



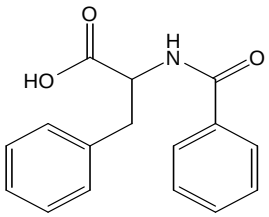
O-benzamido benzoic acid [2]



2-benzamido-3-methyl-butanoic acid [3]

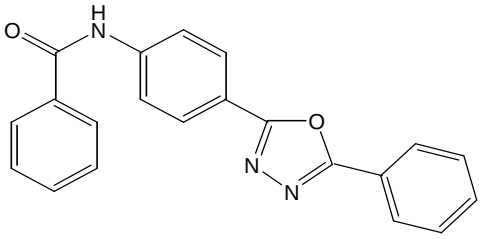


2-benzamido-4-methyl-pentanoic acid [4]

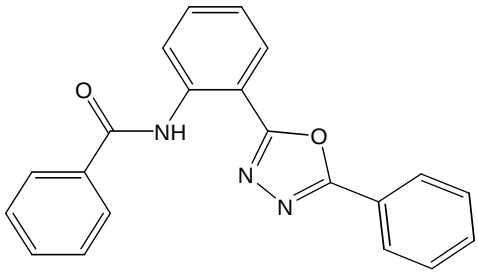


2-benzamido-3-phenyl-propanoic acid [5]

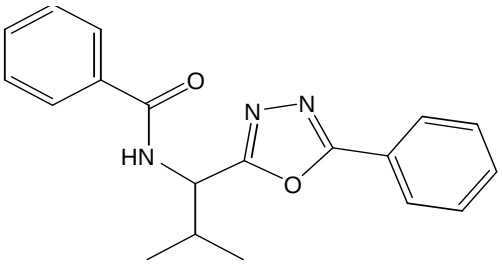
2. Synthesis of 2,5-disubstituted-1,3,4-oxadiazoles [6-10] Reaction of appropriate benzamido carboxlic acid with benzoyl hydrazine in the presence of phosphorous oxychloride furnished the corresponding 2,5-disubstituted 1,3,4-oxadiazoles [6-10] having the following structural formula :-



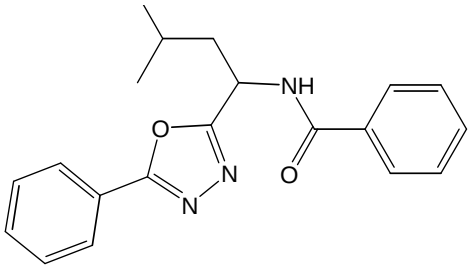
2-phenyl-5-[4-(benzamido)-phenyl]-1,3,4 -oxadiazole [6]



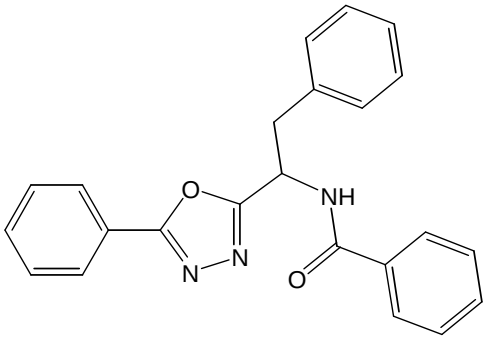
2-phenyl-5-[2-(benzamido)-phenyl]-1,3,4 -oxadiazole [7]



[1-benzamido-1-(5-phenyl-1,3,4 -oxadiazol-2yl)]2methyl)propane [8]



[1-benzamido-1-(5-phenyl-1,3,4-oxadiazol-2yl]-3methyl)butane [9]



[1-benzamido-1-(5-phenyl-1,3,4-oxadiazol-2yl]-2phenyl)-ethane [10]

The biological activity of the synthesized compounds [1-10] for their antimicrobial activity against two strains of pathogenic microorganism Gram positive bacteria *Staphylococcus aureus* and Gram negative bacteria *Escherichia coli*. Antifungal activity were also evaluated against *Trichophytone rubrum*. And finally, the cytotoxic effect were evaluated in normal cell line (Mouse embryo fibroblast) after 72 hrs of incubation. The results obtained revealed that all compounds showed measurable activity against the two type of bacteria using two concentration (0.005g/5ml) and (0.008g/5ml). The screening results

indicated that compounds [8] and [10] showed the highest inhibitory effect against *S. aureaus* while compounds [1] and [5] showed the highest inhibitory effect against *E. coli* **.** While in the fungus, The synthesized compounds showed an inhibition effect on the growth of *T. rubrum.* The inhibition of *T. rubrum* appeared at concentration (0.005g/5ml) except compounds [3] and [4] to which the pathogenic fungus was resistant in the same concentration.

For the cytotoxic effect, the synthesized compounds indicated that the compounds [1-5 and 10] have weak cytotoxic effect in lowest concentrations compared with solvent and control, and the compound [5] showed the highest cytotoxic effect on the treated cells, while compounds [6-9] have no cytotoxic effect in all concentrations.

Contents

Chapter One : Introducation

Chapter Two : Methodology

Chapter Three : Results and Discussion

Chapter Two

2. Methodology

2.1 Chemicals

The following chemicals and media were obtained from different companies, some of these were used directly from the bottle while others were purified to highest purity:

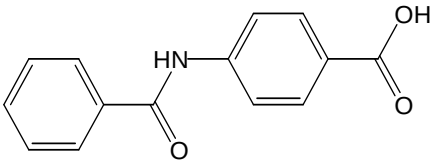
Table (2.1): Chemicals and media used in the experimental

Compounds and media	***Supplier***
Agar	Oxid
Benzoyl chloride	BDH
Chloroform	BDH
Dimethyl sulfooxide (DMSO)	BDH
Ethanol absolute	BDH
Ether	BDH
Hydrazine hydrate (85%)	Merck
Lucine	BDH
Methanol	BDH
Methyl benzoate	BDH
Nutrient broth	Oxid
o – amino benzoic acid	Merck
P – amino benzoic acid	Sherman chem. LTD
Phenylalanine	BDH
Phosphorus oxychloride	Fluka
Sodium bicarbonate	BDH
Sodium hydroxide	BDH
Tryptophan	Merck
Valine	BDH

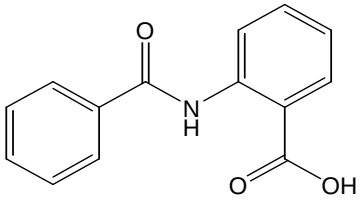
2.2 Instrumentation :-

- **Gallen Kamp** (England) was used to determine the melting point of the compounds.
- **Perkin – Elmer** (USA) 1310 infrared was used to recoreded the infrared spectra photometer, and FT-IR – 8300 Fourier transform infrared spectrophotometer SHIMADZU as potassium bromide disc.

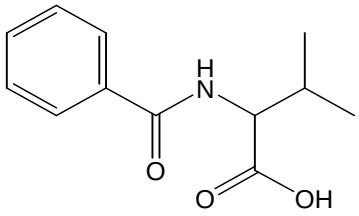
2.3.1 Preparation of benzamido carboxylic acids[82] [1-5]



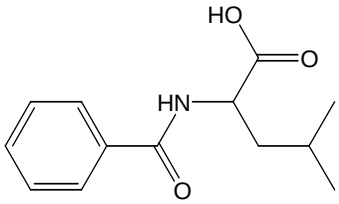
P-benzamido benzoic acid [1]
M.P = 278-279 °C, Yield (72%)



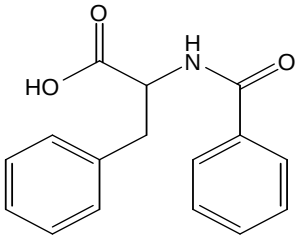
O-benzamido benzoic acid [2]
M.P = 270-272 °C , Yield (70%)



2-benzamido-3-methyl-butanoic acid [3]
M.P = 266-268 °C, Yield (72%)



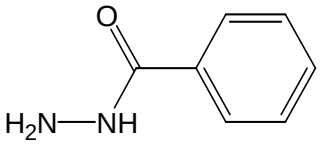
2-benzamido-4-methyl-pentanoic acid [4]
M.P = 265-266 °C, Yield (68%)



2-benzamido-3-phenyl-propanoic acid [5]
M.P = 260-262 °C, Yield (75%)

A one gram of appropriate amino acid was dissolved in (25ml) of 5% NaOH solution in a conical flask. To this mixture benzoyl chloride (2.25ml) was added in a five portions in (0.49 ml increments) and shaked vigorously until all the chloride has reacted, and the odors of benzoyl chloride has disappeared. acidified with diluted hydrochloric acid, and the crude product was washed with cold ether to remove any benzoic acid which may be present. And Finally, the desired product was recrystallized from Ethanol .

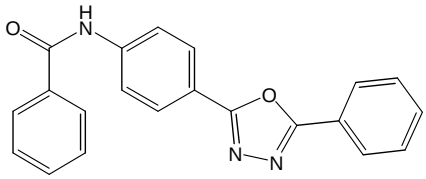
2.3.2 Preparation of Benzoyl hydrazine[77]



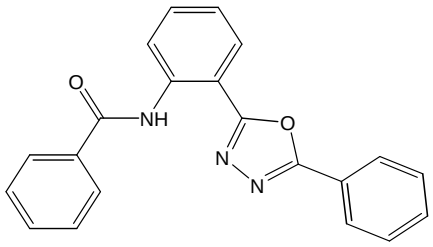
Benzoyl hydrazine
M.P = 135-136 °C, (68%)

A mixture of methyl benzoate (10ml) with 10ml of hydrazine hydrate were refluxed for 3 hours , Ethanol (15ml) was added and refluxed for 5 hours. After cooling, the precipitate was filtered and washed with cold absolute methanol to give the above compound and used without further purification.

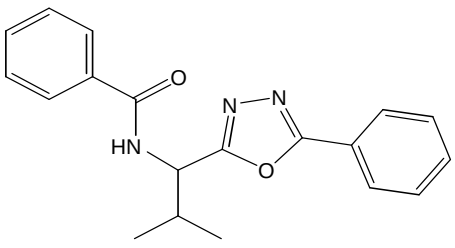
2.3.3 Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles[82] [6-10]



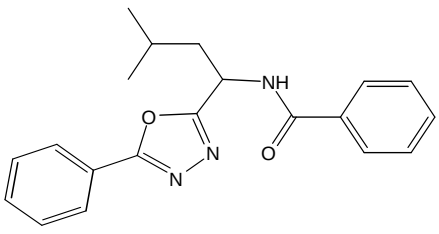
2-phenyl-5-[4-(benzamido)-phenyl]-1,3,4 -oxadiazole [6]
M.P = 259 -260 °C, Yield (70%)



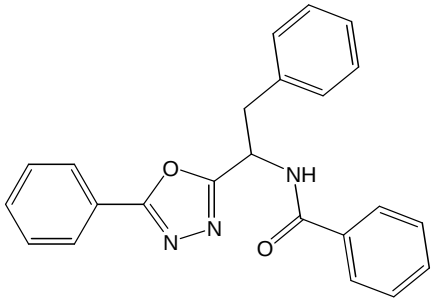
2-phenyl-5-[2-(benzamido)-phenyl]-1,3,4 -oxadiazole [7]
M.P = 250-252 °C, Yield (72%)



[1-benzamido-1-(5-phenyl-1,3,4 -oxadiazol-2yl)-2methyl]propane [8]
M.P = 109-111 °C, Yield (68%)



[1-benzamido-1-(5-phenyl-1,3,4-oxadiazol-2yl)-3methyl]butane [9]
M.P = 103-104 °C, Yield (70%)



[1-benzamido-1-(5-phenyl-1,3,4-oxadiazol-2yl)-2phenyl]-ethan [10]
M.P = 106-108 °C, Yield (72%)

To a mixture of benzoyl hydrazine (0.01 mole) with appropriate benzamido carboxylic acid (0.01 mole) in a round bottom flask 5ml of phosphorusoxychloride was added and refluxed for 8 hours, the cold reaction mixture was poured on crushed ice and made basic by adding sodium bicarbonate the resulting solid which was filtered, dried and recrystallized from chloroform to give the desired compound.

2.4 BIOLOGICAL ACTIVITY DETERMANTION

2.4.1 Antibacterial Activity:

All the synthesized compounds were evaluated for their *in vitro* antibacterial activity against the pathogenic bacteria, Gram positive *S. aureus* and Gram negative *E. coli* the were obtained from the Biotechnology Department , AL- Nahrain University.

2.4.1.1 Sterilization methods[78]:

Culture media were sterilized by autocleaving at 121°C , 15 pound / in^2 for 20 minutes. And glasswares were sterilized in the electric oven at 180 – 200°C for 3 hours.

2.4.1.2 Preparation of Nutrient Agar :

The bacteria were cultured on nutrient agar by mixing the following ingredients:[79]

Nutrient Broth	8g
Agar	20g
D.W.	1000ml

2.4.1.3 Antibacterial Evaluation :

Five milliliters of nutrient broth medium inoculated by loopful of fresh bacterial culture, incubated at 37°C for 18 hr, 0.1ml of the innoculant was spreaded on nutrient agar plates.

Sterile paper disks were soaked in the synthesized compounds at concentration (0.005g/5ml) and (0.008g/5ml) of DMSO then placed on

the inoculated plates then incubated at 37°C for 24 hours. After incubation the diameter (mm) of inhibition zones was measured.

2.4.2 Antifungal Activity :

All the compounds synthesized were evaluated for their *in vitro* antifungal activity against the pathogenic fungus, *Trichophyton rubrum* this fungus was obtained from the Biotechnology Department, Al-Nahrain University.

2.4.2.1 Preparation of Culture medium for antifungal activity:

Fungus was cultured on modified sabouraud dextrose agar (SDA) prepared according to Feingold et, al (1982)[80], by dissolving the following ingredients in one liter of D.W :-

Peptone	10g
Glucose	20g
Agar	20g
Cycloheximide	500mg
Cephalexin	500mg

and sterilized at 121°C , 15 pound / in^2 for 20 minutes. Cephalexin was added to the media to prevent the growth of bacteria, while cycloheximide was added to prevent the growth of saprophytic fungi

2.4.2.2 Antifungal Evaluation:

Concentrations of the synthesized compounds were prepared by dissolving 0.005g in 5ml of DMSO were added to modified sabouraud dextrose agar containing cephalexin and cycloheximide at a ratio 1.5 : 1.5ml. All pertidishes were inoculated with fungal spores and incubated at 30°C for 7 – 10 days[80].

The diameter (mm) of inhibition zone was determined after the period of incubation .

2.4.3 Cytotoxicity Evaluation :[74]

1. Mouse embryo fibroblast cells were grown in 96-well tissue culture plate until the log phase in concentration of at least 10000cells/ 100 µl.
2. 100 µl/ well of the synthesized compounds were added to the first, two wells in at least duplicate, two fold serial dilutions was made.
3. Plate was covered and incubated at 37 °C for 72 hr.
4. 100 µl of neutral red was added to the 96-wells, incubated for 1.5-2hr. at 37 °C.
5. The plate was washed with ethanol and elution buffer 150 µl/well was added.
6. The plate was read at ELISA reader system at 492nm wave length.

CHAPTER THREE

3. Results And Discussion

3.1 Synthesis of 2,5-disubstituted 1,3,4 – oxadiazoles [6-10]

Substituted 1,3,4-oxadiazoles have been described for their chemotheroputic importance and considerable pharmaceutical interest, which is documented by great number of publications and patents[81].

Different derivatives of 1,3,4-oxadiazole ring were synthesized and used as inhibitors for many bacteria , fungi and tumor.

Based on these findings, it was considered desirable to synthesize the title compounds with the hope that the incorporation of many different function groups presence with 1,3,4-oxadiazole unit might enhance it is biological activity.

For the synthesis of the target title heterocyclic compounds, different amino acids like (*P*–amino benzoic acid, *o*–amino benzoic acid, valine, lucien, and phenyl alanine) were as starting material.

The first step was the conversion of these amino acids to benzamido carboxylic acids [1-5] by their reactions with benzoyl chloride under ***Schotten – Baumman*** reaction conditions[82], this step was made firstly to prevent the amino group from reaction with carboxlic acid in the second step.

The second step in these sequenced reaction is the formation of the desired 1,3,4 – oxadiazoles by the reaction of benzamido carboxylic acid with benzoyl hydrazine in presence of phosphorus oxychloride to yield corresponding compounds [6-10]. The structures of the products were established by (FT – IR) spectral data.

With the FT–IR technique, a band –by– band correlation is an excellent evidence for identity. Thus we will follow the synthesis steps by FT–IR spectra of synthesized compounds.

For *P*–benzamido benzoic acid [1]. As shown in (figure 3.1) this compound shows absorbtion band at 3334.7 cm^{-1} which represent N–H stretching band. At 1652.9 cm^{-1} which represent C=O stretching of the amide carbonyl group, at 1687.6 cm^{-1} which represent C=O stretching of the carboxylic acid carbonyl group. Also, band at 859.5 cm^{-1} for the C–H out of plane bending of the phenyl group.

For 2– phenyl -5- (4– benzamido) phenyl–1,3,4–oxadiazole [6]. As shown in (figure 3.2) the FT–IR spectrum of this compound shows absorption band at 3421.5 cm^{-1} which represents N–H stretching. Band at 1640 cm^{-1} which represents C=O amide carbonyl group. While it showed the appearance of the bands at 1610.5 cm^{-1}, 1249 cm^{-1} and at 1070 cm^{-1} which represents C=N, asymmetrical and symmetrical C–O–C stretching

respectively. All of these bands indicate the formation of the oxadiazole ring.

For *o*-benzamido benzoic acid [2]. As shown in (figure 3.3) this compound shows absorption band at 3410 cm^{-1} which represent N-H stretching band, at 1640 cm^{-1} which represents C=O stretching of amide carbonyl group. At 1682.0 cm^{-1} which represents C=O stretching of the carboxylic acid carbonyl group.

For 2-phenyl-5-[2-(benzamido)-phenyl]-1,3,4-oxadiazole [7]. As shown in (figure 3.4) the FT–IR spectrum of this compound shows absorption band at 3446.1 cm^{-1} which represents N–H stretching band at 1677.7 cm^{-1} representing C=O amide carbonyl group. While it showed the appearance of the band at 1639.4 cm^{-1}, at 1267.1 cm^{-1} and at 1001.0 cm^{-1} which represents C=N, asymmetrical and symmetrical C–O–C stretching respectively. All of these indicate the formation of the oxadiazole ring.

For 2-benzamido-3-methyl-butanoic acid [3]. As shown in (figure 3.5) this compound shows absorption band at 3363.6 cm^{-1} which represents N-H stretching band, at 2966.3 cm^{-1} and 2835.2 cm^{-1} which represents the C-H stretching of alkane moiety, at 1629.7 cm^{-1} which represents C=O stretching of amide carbonyl group. At 1687.6 cm^{-1} which represents C=O stretching at the carboxylic acid carbonyl group.

For[1-benzamido-1-(5-phenyl-1,3,4-oxadiazol-2yl)-2methyl]-propane [8]. As shown in (figure 3.6) the FT–IR spectrum of this compound shows absorption band at 3380 cm^{-1} representing N–H stretching band at 1658.7 cm^{-1} which represents C=O amide carbonyl

group. at 2990 cm^{-1} and 2830 cm^{-1} which represents the C-H stretching of alkane moiety, While it showed the appearance of the band at 1612.4 cm^{-1}, at 1272.9cm^{-1} and at 1072.3 cm^{-1} which represents C=N, asymmetrical and symmetrical C–O–C stretching respectively. All of these indicate the formation of the oxadiazole ring.

For 2-benzamido-4-methyl-pentanoic acid [4]. As shown in (figure 3.7) this compound shows absorption band at 3307.7 cm^{-1} which represents N-H stretching band, at 1690 cm^{-1} which represents C=O stretching of amide carbonyl group. at 1640 cm^{-1} which represents C=O stretching at the carboxylic acid carbonyl group.

For2[1-benzamido-1-(5-phenyl-1,3,4-oxadiazol-2yl)-3-methyl]-butane [9]. As shown in (figure 3.8) the FT–IR spectrum of this compound shows absorption band at 3400 cm^{-1} which represents N–H stretching band at 1687.6 cm^{-1} which represents C=O amide carbonyl group. While it showed the appearance of the band at 1606.6 cm^{-1}, at 1263.3 cm^{-1} and at 1068.5 cm^{-1} which represents C=N, asymmetrical and symmetrical C–O–C stretching respectively. All of these indicate the formation of the oxadiazole ring.

For 2-benzamido-3-phenyl-propanoic acid [5]. As shown in (figure 3.9) this compound shows absorption band at 3375 cm^{-1} which represents N–H stretching band, at 1640 cm^{-1} which represents C=O stretching of amide carbonyl group. At 1680 cm^{-1} which represents C=O stretching at the carboxylic acid carbonyl group.

For[1-benzamido-1-(5-phenyl-1,3,4-oxadiazol-2yl)-2phenyl]-ethan [10]. As shown in (figure 3.10) the FT– IR spectrum of this compound shows absorption band at 3382.9 cm^{-1} which represents N–H stretching band at 1689.1 cm^{-1} which represents C=O amide carbonyl group. While it showed the appearance of the band at 1606.6 cm^{-1}, at 1293.2 cm^{-1} and at 1014.5 cm^{-1} which represents C=N , asymmetrical and symmetrical C–O–C stretching respectively. All of these indicate the formation of the oxadiazole ring.

Supervisors Certification

We certify that this thesis was prepared under our supervision at the Department of Chemistry, College of Science, AL-Nahrain University as a partial fulfillments of the requirement for the degree of master of science in chemistry.

Assistant Professor
Dr. Khulood Al-Samerai

Lecturer
Dr. Ayad S. Hameed

In view of the available recommendation, I forward this thesis for debate by the Examining Committee.

Assistant Professor
Dr. Shahbaz A. Maki
Head of the
Department of Chemistry
College of Science
Al-Nahrain University

Examining Committee's Certification

We, the Examining Committee, certify that we reads this thesis and examined the student ***Alaa Abbas Fadiel,*** in its contents and that, in our opinion, it is adequate as a thesis for the degree of Master of Science, in Chemistry.

Signature:
Name :
(Chairman)

Signature:
Name :
(Member)

Signature:
Name :
(Member)

Signature:
Name :
(Member/Advisor)

Signature:
Name :
(Member/Advisor)

I hereby certify upon the decision or the Examining Committee

Assist. Professor
Dr. Laith Abd Al-Aziz
Dean of
College of Science
Al-Nahrain University

بسم الله الرحمن الرحيم

ويسألونك عن الروح قل الروح من أمر ربي وما أوتيتُم مِن العِلمِ إلا قليلاً

صدق الله العظيم

سورة الاسراء الاية (٨٥)

Republic of Iraq
Ministry of Higher Education and
Scientific Research
Al – Nahrain University
College of Science
Department of Chemistry

SYNTHESIS AND BIOLIGICAL EVALUATION OF SOME NEW 1,3,4-OXADIAZOLE COMPOUNDS DERIVED FROM DIFFERENT AMINO ACIDS

A Thesis

Submitted to the College of Science of

Al-Nahrain University

In partial Fulfillment of the Requirements for the

Degree of Master of Sciences in Chemistry

By

Alaa Abbas Fadel Al – Haddad

B.Sc. Al-Nahrain University (2002)

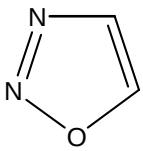
2005 **1426**

Chapter One

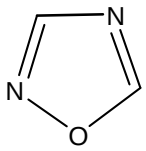
1. Introduction

1.1 Oxadiazoles :

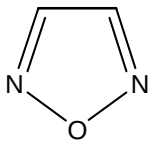
The oxadiazoles are five membered ring aromatic compounds with three heteroatoms one oxygen and two nitrogen atoms , which have four different isomers as shown bellow[1] :



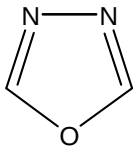
1,2,3 oxadiazole
(a)



1,2,4 oxadiazole
(b)

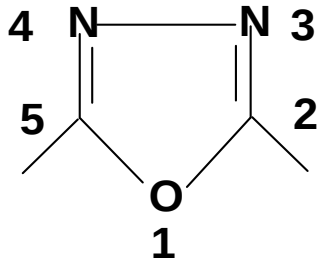


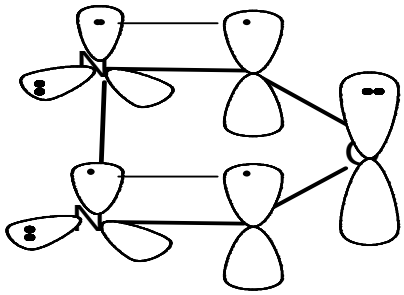
1,2,5 oxadiazole
(c)



1,3,4 oxadiazole
(d)

These isomers studied at a first time in (1962) from group of researchers[1]. The recent years demonstrates that the isomer (d) which is thermally stable and are becoming of great interest stems mainly from their wide range of application .





The structure of 1,3,4-oxadiazole is a ring with three heteroatoms one oxygen atom at position (1) and two nitrogen atoms at position (3 & 4).

This ring has three pairs of delocalizes π- electrons , two of the pairs are shown as π- bonds through the overlapping of unhybridized P- orbital of nitrogen atoms with P- orbital of carbon atom and one pair of non – bonding electrons on the hetero oxygen atom.

Derivatives of 1,3,4-oxadiazoles represent an important family of heterocyclic compounds, Since many of them display a remarkable biological activity like antibacterial[(2)], antifungal[(3)], antitumor[(4)] ,analgesic[(5)], anti-inflammatory[(6)] and anticonvulsant[(7)].

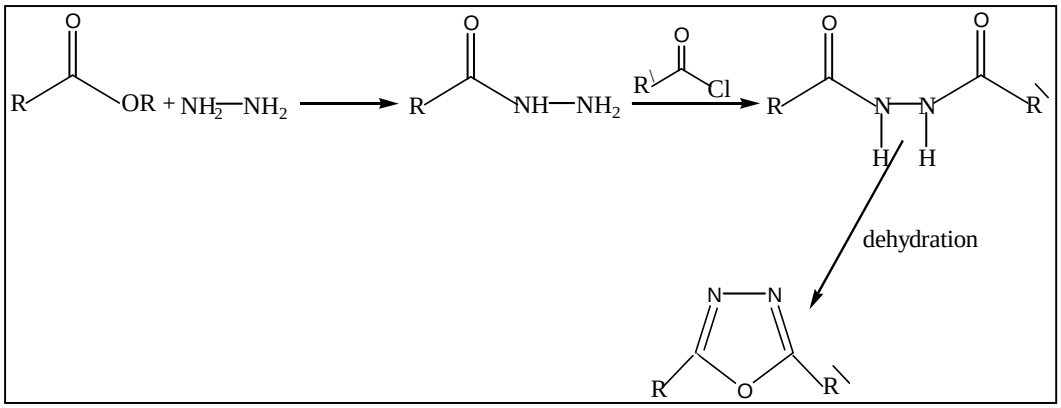
1.2 Methods for Synthesizing 1,3,4 – Oxadiazoles :

Several methods have been used to synthesize 1,3,4–oxadiazoles. Among these, the following are the most important methods :-

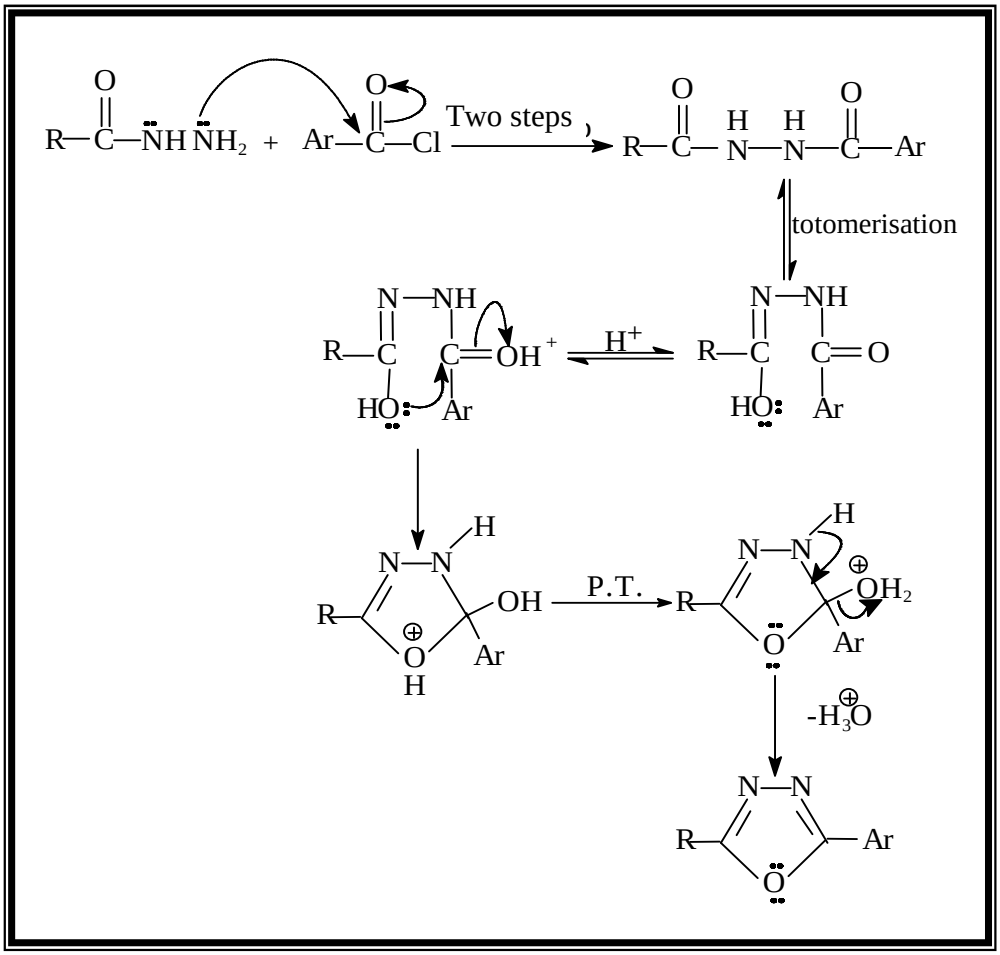
1.2.1 Dehydration of Acid Hydrazides :-

The common synthetic approach to oxadiazoles involve cyclization of diacid hydrazine . Hydrazides and related compounds have been described as useful building blocks for assembly of various heterocyclic rings[8].

Acid hydrazides are usually prepared from corresponding esters with hydrazine hydrate. These hydrazides are converted to di-acid hydrazides through their reaction with appropriate acid chlorides. The di-acid hydrazides are established to be the most convenient precursors for the synthesis of substituted 1,3,4 – oxadiazoles[9].



The mechanism of this reaction[10] is depicted in scheme (1.1)



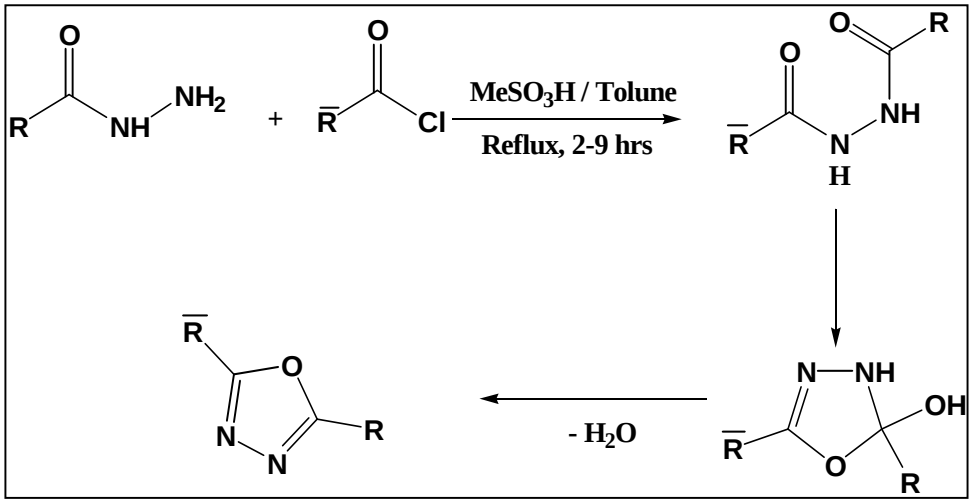
Scheme (1.1) Mechanism of formation of 1,3,4 oxadiazole ring by dehydration of di – acid hydrazide

A large number of aliphatic, alicyclic, aromatic and heterocyclic carbohydrazides, and related compounds are reported to present a plethora of biological activities[11] . Thus, different carbohydrazides were found to be useful as medicaments especially in the treatment of inflammatory and autoimmune diseases, osteoarthritis, respiratory diseases, tumors, cachexia, cardiovascular diseases, fever, hemorrhage and sepsis[12] . Carbohydrazides

and related compounds exhibited antifungal[11], antiviral[13] ,bacteriostatic[14], antiparasite[15], antituberculosis[16] , psychotrophic[11], and insecticidal[17] activities.

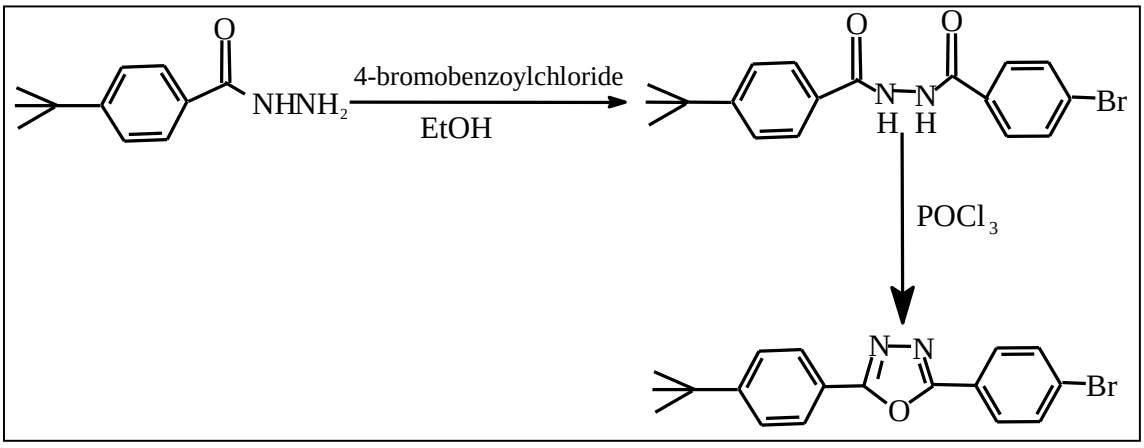
A variant conditions influence the dehydration reaction. Typically, the reaction promoted by heat and anhydrous agent including thionylchloride[18], phosphorus oxychloride[19], phosphorus pentoxide[20] , triphenyl phosphine[21] and triflic anhydride[22].

Recently, 1,3,4 –oxadiazoles derivatives have been synthesize using a new methods by treatment of a suspension of acid hydrazide with acid chloride in the presence of an equimolecular amount of methane sulfonic acid at room temperature , and then heating to reflux temperature gave 1,3,4-oxadiazoles[23] .

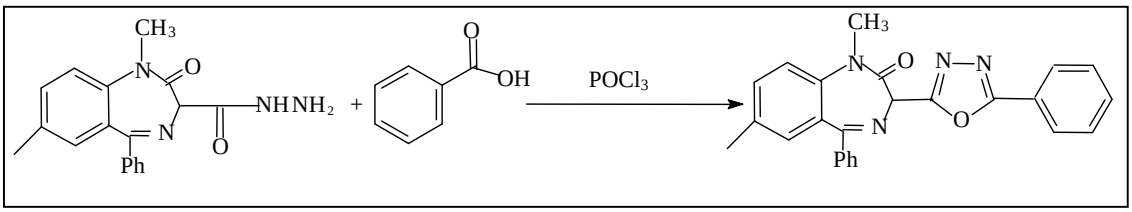


In the last years, a great number of 1,3,4 Oxadiazoles derivatives were prepared using different dehydrating agents, the following examples include some of these compounds :-

- **Lee et al.**[24] synthesized 2-(4-bromophenyl)-5-(4-tert-butylphenyl) 1,3,4-oxadiazole according to this equation :-

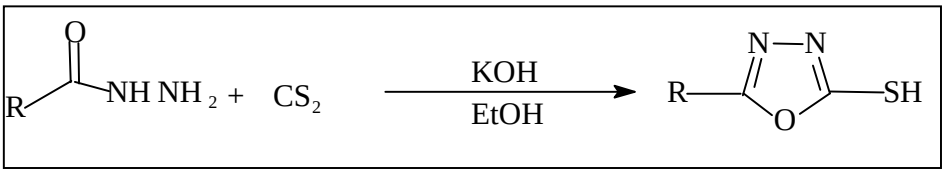


- **Berghot.**[25] synthesized a new 1,3,4-oxadiazole derivatives in one step reaction of an acid hydrazide with benzoic acid in the presence of phosphorusoxychloride.

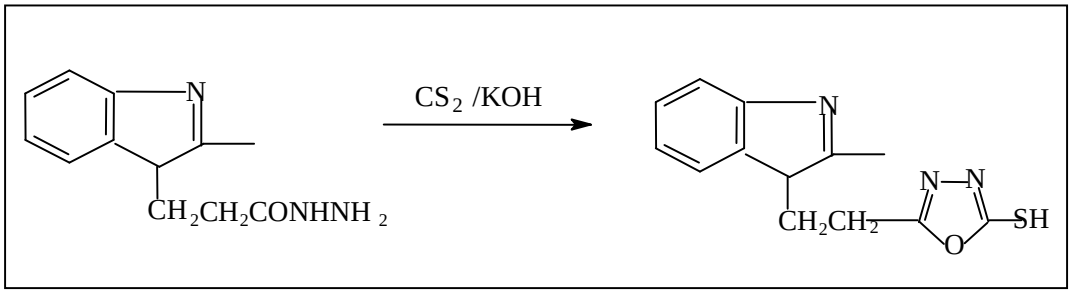


1.2.2 Reaction of acid hydrazide with carbon disulfide :

The oxadiazole ring is synthesized by following the general method of **Young** and **Wood** i.e. by refluxing ethanolic mixture of the appropriate acid hydrazide , carbon disulfide and potassium hydroxide[26].

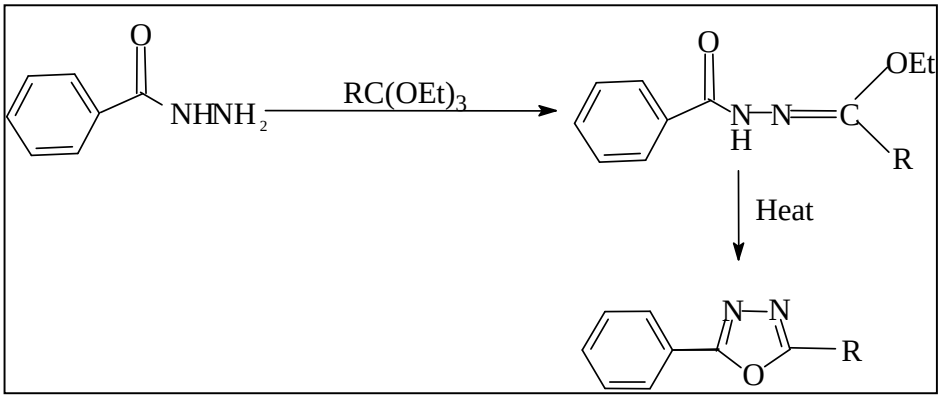


- **El–Masry et al.**[27] Synthesized 5-[2-(2-methylbenzimidazol-1-yl)ethyl]-[1,3,4]-oxadiazole-2(3H)-thione from the reaction of 3-(2-methylbenzimidazol-1-yl) propinoic acid hydrazide with carbon disulfide and potassium hydroxide.

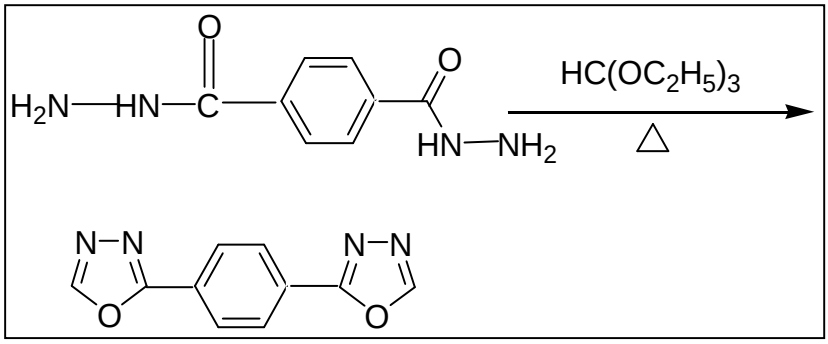


1.2.3 Reaction of acid Hydrazides with Orthoesters:

Treatment of the acid hydrazides with orthoesters $RC(OEt)_3$ gave N-aroylhydrazoic esters, which are cyclized upon heating to 1,3,4 – oxadiazoles.

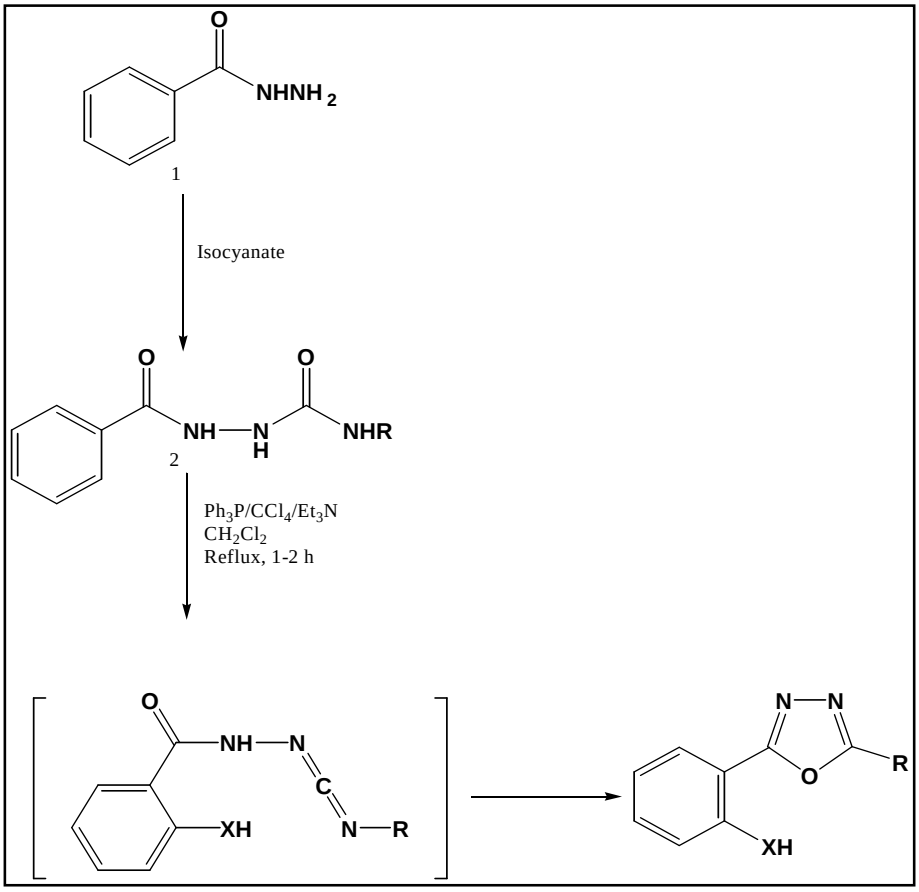


Also, bis(1,3,4-oxadiazol-2yl)-*p*-phenylene, was prepared by heating under reflux terphthalic acid dihydrazide in triethylorthoformate [28]



1.2.4 Reaction of acid hydrazide with isocyanates (Appel's Method)[29]*:*

The preparation of 2- substituted amino – 1,3,4-oxadiazoles from acid semicarbazide (2) was conducted. Thus, treatment of acid semicarbazide (2), Which were readily obtainable by the reaction of acid hydrazide with isocyanate , under Appel′s dehydration condition (Ph_3P/CCl_4 / Et_3N)[30] smoothly afforded 1,3,4-oxadiazoles via carbdiimide intermediate ($2'''$).



Where R = amino group

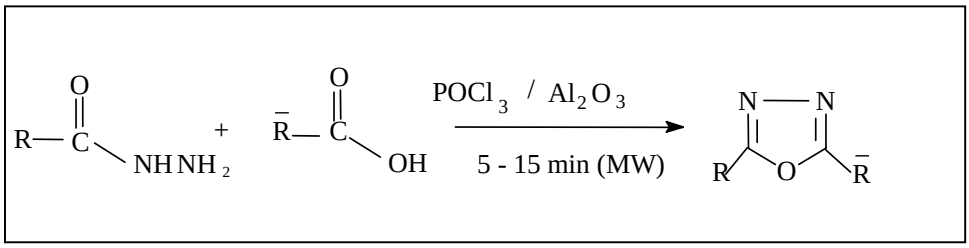
The advantage of the present method is cheap, non toxic, stable, and easy to handle.

1.2.5 Microwave method [31-34] *:*

Recent advances in technology have now made microwave energy a more efficient means of heating reactions. Chemical transformations that took hours, or even days , to complete can now be accomplished in minutes. Microwave energy offers numerous benefits for forming synthesis including increased reaction rates, yield enhancements, and cleaner chemistries.

The microwave technology has been applied to a number of useful research and development processes such as polymer technology, organic synthesis, application to waste treatment, drug release / targeting; ceramic and alkane decomposition.

- **Khalid M.Kham et. al**.[35] synthesized a number of 2,5-disubstituted 1,3,4 – oxadiazoles under microwave irradiation through the reaction of commercially available hydrazides with different carboxylic acids in the presence of phosphorous oxychloride.



Finally , this method provides an excellent approach for the safe, rapid, inexpensive and simple synthesis of medicinally important 2,5-disubstituted – 1,3,4 – oxadiazoles .

1.3 Biological Activity:

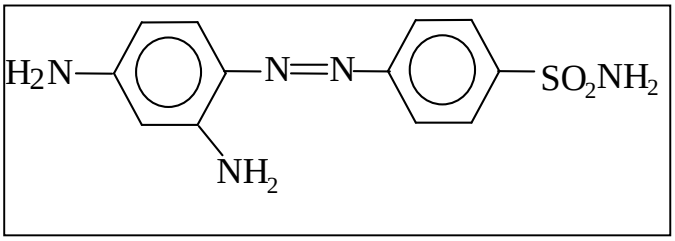
Antimicrobials:

Antimicrobial chemotherapeutic agents are chemical agents that have the ability to destroy the pathogenic microorganisms or inhibit their growth at concentrations low enough to avoid undesirable damage to the host[36]. Most of these agents are antibiotic microbial products or their derivatives that can kill susceptible microorganisms or inhibit their growth. The modern era of chemotherapy began with the work of the German physician ***paul Ehrlich*** (1854-1915) who began experimenting with dyes, ***Ehrlich's*** successes in the chemotherapy of sleeping sickness and syphilis established his concept of selective toxicity and led to the testing of hundreds of compounds for their therapeutic potential. In 1927, the German chemical industry began along-term search for chemotherapeutic agents under the direction of ***Cerhard Domagk*** who discovered that prontosil red [I] a new dye for staining leather, was nontoxic for animals and completely protected mice against pathogenic bacteria ***Streptococci*** and ***Staphylococci*** . In 1929 the scottish physician ***Alexander Fleming*** found that broth from ***penicillium*** culture contained penicillin, an antibiotic that could destroy a number of pathogenic bacteria.

The discovery of penicillin stimulated the search for other antibiotics[36]. ***Selman waksman*** and his associates lead to isolation of streptomycin in 1944 from ***streptomyces griseus***[37]**.**

The development of the broad spectrum antibiotics such as chloroamphenicol in 1947 which isolated from ***Streptomyces venzuelae***[38].

Chlorotetracycline in 1948 from ***Streptomyces aureofaciens***[39] and isolation of antifungal nystatin in 1951 from ***Streptomyces noursei***[40] ,this was led to broad screening programs that were set up to find agents which would be effective in the treatment of infections that had been resistant to chemotherapeutic agent, as well as to provide safer and more rapid therapy for infections. As a result large numbers of antibiotics were discovered such as erythromycin[41] , Lincomycin[42] , gentamycin[43] and the researches were continued in order to discover new antibiotics.



(I)

2,4-diamino azobenzene-4-sulfonamide
(prontosil red.)

1.3.1 Resistance To Antimicrobial agents:

Sooner or later bacteria develop resistance to virtually any antibiotic agents. Resistance has many consequences and also requires the use of more toxic or more expensive alternative drugs[44] .

Resistance thus affects the antibiotic options available to every practitioner and is no less a problem in the developing world[45].

Despite the versatility of antimicrobial agents and the evolution of new

ones, bacteria have a limited number of mechanisms of antimicrobial resistance; including: The production of detoxifying enzyme like β-lactamase which destroy β-lactam antibiotics, or the production of chloramphenicol acetyl-transferase in gram-negative chloramphenicol resistant bacteria[46-47]. In some cases the alteration in the target for the drug; which includes both reduction of receptor affinity and the substitution of an alternative pathway[46]. For example, resistance to some penicillins and cephalosporins may be a function of the loss or alternation of the penicillin binding proteins (PBP_S) of bacterial ribosome[48].

Resistance may arise by a mutation that reduces target affinity or allows the over production of a drug modifying enzyme, sometimes the insertion of foreign DNA by recombination accomplishes the same end[46].

Also decreased antibiotic uptake; which occurs through either diminished permeability or an active efflux system[46]. In ***Psedomonas aeruginosa,*** 50 to 85% of resistant strains produce chloramphenicol acetyl transferase[49] (CAT). In the remainder, resistance is caused by decreased outer membrane permeability[50-51] reported that the active efflux of tetracycline is mediated by new membrane transport system ***Psedomonas aeruginosa*** can also become resistant specifically to imipenem through the loss of an outer membrane protein (porin) that provides a channel for the entry of imipenem[52].

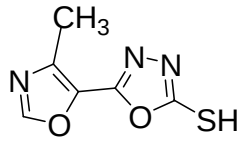
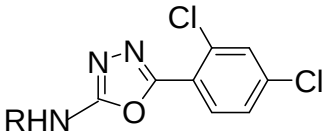
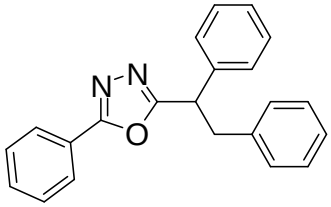
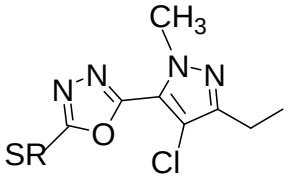
1.3.2 Antimicrobial Activity of 1,3 ,4-Oxadiazole Compounds:

Microorganism causes different kinds of diseases to human and animals. Discovery of antimicrobial agents played a very important role against infections caused by bacteria. For this reason searching for new antimicrobial agents is a continuous process and great efforts have been employed to find new antibiotics or new chemical compounds to show a high degree of selective toxicity toward microorganism. 1,3,4-oxadiazoles constitute an important class of compounds having a wide spectrum of biological activity. In the past years considerable evidence has been accumulated to demonstrate the efficacy of substituted 1,3,4-oxadiazole as antibacterial[53], antifungal[54], antimalarial[55], anticonversant[56] and anti-inflammatory[57] compounds.

When properly substituted in 2-and 5-positions.2-amino-5-substituted -l,3,4-Oxadiazoles were used as antimitotic[58] muscle relaxant[59] and tranquilizing agents[60].

Moreover, some schiff bases of 2-amino -1,3,4-Oxadiazole have also shown remarkable antibacterial and antifungal activities, 2-hydroxymethyl-5-aryl-1,3,4-Oxadiazole exhibit antiinflammatory and anticonvulsive activity.

Table (1-1) Summarize structures and biological activity of some these compounds

Compound Name	Structure	Biological Activity	References
2-(4-methyl-5-oxazolyl)-1,3,4-oxadiazole-5-thiol		Effective Drugs Against Tropical Diseases	61
2-sustituted-amino-5-(2,4-dichloro phenyl)-1,3,4-oxadiazole	 R= C_6H_5, P-$CH_3C_6H_4$, P-$CH_3OC_6H_4$	Anti Fungal Activity	62
2-phenyl-5-(1,2-diphenyl-ethyl)-1,3,4-oxadiazole		Anti Inflammatory	63
2-alkyl (alkylthio)-5-(4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-yl)-1,3,4-oxadiazole		Potential Fungicides	64

1.3.3 Pathogenesis of microorganisms

1.3.3.1 Staphylococcus aureus:

The Staphylococci is Gram positive bacteria, spherical usually arranged in grape-like irregular clusters. Some are members of the normal flora of the skin and mucous membranes of human, other cause suppuration, abscess formation, a variety of pyogenic infection and even fatal septicemia[(65)]. The pathogenic Staphylococci often hemolyse blood, coagulate plasma and produce variety of extra-cellular enzymes and toxins. The most common type of food poisoning is caused by a heat stable Staphylococcal Entero-toxin. Staphylococci rapidly develop resistance to anti-microbial agents and present difficult therapeutic problems[(65)].

S. aureus is a major pathogen for humans. Almost every person will have some types of *S. aureus* infection during poisoning or minor skin infections to sever life-threating infections. *S. aureus* infection can also result from direct contamination and a wound like the post operative Staphylococcal[(65)].

1.3.3.2 Escherichia coil:

E. coli is a Gram negative bacterium, rods belonged to the enterobacteriaceae family. *E. coli* is a member of the normal intestinal flora and also found as normal flora of the upper respiratory and gential tracts[(66)].

1. Urinary Tract Infection:

E. coli is the most common cause of urinary tract infection in young women. Urinary tract infection can result in bacteremia with clinical signs of sepsis. Nephro-pathogenic ***E. coli*** typically produces hemolysin[(66)].

2. ***E. coli - Associated*** **Diarrheal Diseases:**

E. coil that causes diarrhea is extremely common worldwide. Entero-pathogenic ***E. coil*** is an important cause of diarrhea in infants, especially in developing countries. Entero-pathogenic ***E. coil*** previously associated with outbreaks of diarrhea in nurseries in developed countries[(65)].

1.3.4 Pathogenic fungi:

Fungi cause direct harm to man and animals by means of toxins by inducing allergic reactions, or by progressive (Mycosis)[(67)]. About one-fifth of the world´s population suffers from mycosis. In man most infections involve the skin, hair and nail (Superficial mycosis). These mycosis are unpleasant and be difficult to cure, but will not normally be lethal. Infections inside the body (deep-seated mycosis) are much more dangerous. They may become generalized and fetal unless treated. The agents of most superficial mycosis are a group known as dermatophytes, belonging to the genera *microsporium*, *Epidermatophyton* and *Trichophyton*. The various dermatophytes usually cause virtually identical lesions if the infections involve the same part of the body[(67)].

Dermatophytosis refers to the infections of the skin, nails, or hairs that are caused by fungi classified as dermatophytes[(68)]. Normally, it is not considered that dermatophytic fungi can cause systemic disease, in fact with only one minor exception, non-of these fungi can grow at 37^0C. The dermatophytic fungi include numerous species of fungi, which contained in the three major genera. These organisms occur worldwide mainly in the soil and on certain animals. Dermatophytosis is some of the most common

diseases of man[64]. Although incidences of infection vary greatly, at least 10-20% of the world's population may be infected with these organisms. An outstanding feature of these organisms is that they are all keratinophilic which means that grow optimally in presence of Keratin[69].

Although fungal infections of skin were regarded as the most common and relatively begin of disease, their profile has taken a new and more direct aspect reflected in new pathological condition, particularly in immunocompromized hosts, which are examplified by malignant neoplasm, antineoplastic and acquired immunodifieiency syndrome[69]. It should be emphasized that distinctive skin lesion are occasionally the first manifestations of systemic mycoses and that superficial fungal infection of the skin and mucous membranes represent one of the earliest sign of deteriorating immune functions in HIV-infected individuals. Fungal infections of the skin can be classified according to their site of infection into the following three groups[70]:

1. Superficial Infection; Caused by fungi capable of utilizing keratin for their nutrition and invading such keratinized tissue as the stratum corneum of the skin, nail and hair[70].
2. Cutaneous and Subcutaneous Infection; produced by various mould and yeast.
3. Cutaneous Manifestation of life-threatening visceral or systemic fungal infections in immunologically competent[71-72].

1.3.4.1 Trichophyton rubrum:

Trichophyton rubrum spreads worldwide because of the severity and longevity of the disease and its refractivity to therapy, this organism causes many problems, very often *T. rubrum* is the cause of long-established foot and nail infection[(69)]. *T. rubnim* may also cause tinea corporis. Skin lesion caused by *T. rubrum* often have a red margin, the central portion appears to

be relatively clear, although scaling may be apparent. on rare occasions**,** this organism may cause tinea capitis. Primarily, these organisms are anthrophilic. Because cultures of *T. rubrum* are quite variable, identification can be frustrating[(69)]. This fungus is white and very fluffy and exhibits many aerial hyphae, this downy form is most commonly isolated from cases of chronic tinea pedis and tinea corporis. The other from of *T. rubrum* is called the granular form. This white colony is very flat, lacks aerial hyphae and has a pronounced granular appearance[(69)].

Trichophyton rubrum is the most common isolate from all regions except the scalp. Tinea pedis usually of the moccasin type is the most frequently seen form of disease[(73)].

1.3.5 Cytotoxicity[(74)]:

Many experiments carried out *in vitro* are for the sole purpose of determining the potential cytotoxicity of compounds under study, either because they are being used as a pharmaceutical or cosmetic and must be shown to be nontoxic, or because they are designed as anticancer agents, when cytotoxicity may be crucial to their action.

Current legislation demands that new drugs, cosmetics, food additives, etc., go through extensive cytotoxicity testing before they are released. This usually involves a large number of animal experiments, which are very costly and raise considerable public concern. There is therefore much pressure, both human and economic, to perform at least part of cytotoxicity testing *in vitro* . The introduction of specialized cell lines, as well as the continued use of long-established cultures, may make this a reasonable proposition.

Cytotoxicity is a complex event *in vivo*, where its expression may be manifest in a wide spectrum of effects, from simple cell death, as in the toxic effects of anticancer drugs on both cells of the tumor and normal cells of the bone marrow, skin, or gut, to complex metabolic aberrations such as neuro – or nephrotoxicity, where no cell death may occur, only functional change[(74)]. Definition of cytotoxicity will tend to very depending on the nature of the study, whether cells are killed or simply have their metabolism altered. While an anticancer agent may be required to kill cells (through it need not), the proof of the absence of toxicity of another pharmaceutical may require more subtle analysis of minor metabolic changes or an alteration in cell – cell signaling such as might give rise to an inflammatory or allergic response[(74)].

It is not possible here to define all the requirements of a cytotoxicity assay, so this study was concentrated on those aspects that influence growth or survival. Growth is generally taken to be regenerative potential, measured by clonal growth, net change in population size, as in a growth curve , or a change in cell mass (total protein or DNA) or gross metabolic activity such as respiration or DNA, RNA, or protein synthesis, usually plasma-membrane

integrity, or can use the same growth parameters as above, not to measure growth *per cell* but to say that capacity for growth implies survival[74].

1.3.6 Limitations of in vitro methods

It is important that any measurement can be interpreted in terms of the *in vivo* response, or at least with the understanding that clear differences exist between *in vitro* and *in vivo* measurements. Measurement of toxicity *in vitro* is a purely cellular event as presently carried out. It would be very difficult to re-create the complex pharmacokinetics of drug exposure, for example *in vitro,* and there will usually be significant differences in drug exposure time and concentration, rate of change of concentration, metabolism, tissue penetration, clearance, and excretion. Although it may be possible to simulate these parameters, e.g., using multicultural tumor spheroids for drug penetration, most studies concentrate on a direct cellular response. They are thereby gain their simplicity and reproducibility.

Many nontoxic substances become toxic after metabolism by the liver; in addition, many substances that are toxic *in vitro* may be detoxified by liver enzymes. For testing *in vitro* to be accept as an alternative to animal testing, it must be demonstrated that potential toxic reach the cells *in vitro* in the same form as they would *in vivo* this may require additional processing by purified liver microsomal enzyme preparations or co-culture with activated hepatocytes[74].

The nature of the response must also be considered carefully. A toxic response must also considered carefully. A toxic response *in vitro* may be measured by changes in cell survival or metabolism, while the major problem *in vivo* may be a tissue response, e.g., an inflammatory reaction or

fibrosis. For *in vitro* testing to be more effective, construction of models of these responses will be required, perhaps utilizing cultures reassembled from several different cell types and maintained in the appropriate hormonal milieu.

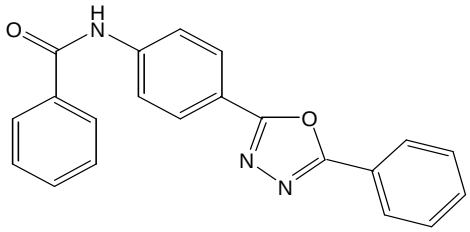
It should not be assumed that complex tissue and even systemic reactions cannot be simulated *in vitro.* Assays for the inflammatory response, teratogenic disorders, or neurological dysfunctions may be feasible *in vitro,* given a proper understanding of cell – cell interaction and the interplay of endocrine hormones with local paracrine and autocrine factors.

1.3.7 Normal cells

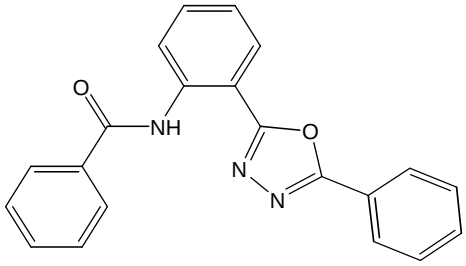
Most cells are specialized, they have a specific form and function that suit them to the role they play in the body. Normal cells are growing under controlled mechanisms, contact inhibition, one organized layer, and differentiated cells[(75)] , for example mouse embryo fibroblast cell line and chick embryo cell line. Normal cells can enter the cell cycle for about 50 times, and then they die, while cancer cells can enter the cycle repeatedly. In the body, a cancer cell divides to form an abnormal mass of cells called a ((tumor)), which invades and destroys neighboring tissue[(76)] .

1.4 Aim of the work :

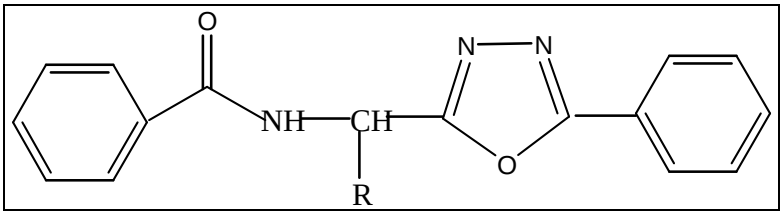
1. Synthesize some new 2-(phenyl)-5-substituted-1,3,4-oxadiazoles [6-10] derived from different amino acids (*P*-amino benzoic acid, *o*-amino benzoic acid, valine , phenyl alanine and leucine) having the following structural formula:



2-phenyl-5-[4-(benzamido)-phenyl]-1,3,4 -oxadiazole [6]



2-phenyl-5-[2-(benzamido)-phenyl]-1,3,4 -oxadiazole [7]



compound no :- [8], [9], [10]

R : $-CH(CH_3)_2$, $-CH_2-CH(CH_3)_2$, $-CH_2$-ph

2. Elucidate the biological activity of these synthesized compounds.

الاهداء

الى سبب وجودي وسر خلودي
... والدتي الحبيبة ...
الى مصدر قوتي وأقتداري
... والدي الحبيب ...
الى من رافقني في كل خطواتي
... زوجتي الحبيبة ...
والى كل من أوقد شمعة أنارت طريق
حياتي...

أهدي بحثي هذا
علاء الحداد

Acknowledgement

First of all thanks ALLAH who gave me the faith and health to accomplish this research.

My deep thank fullness and appreciation to my supervisor Dr. Ayad S. Hameed and Dr. Khulood Al – Samaraei for their suggestion and valuable advises during the whole period of research.

I wish to express my deep appreciation to the dean of college of science and the head of Chemistry department Dr. Shahbaz A. Maki to accomplish this study.

I wish to express my deep appreciation to all the staff of Chemistry department for their cooperation especially Dr. Eymad A. Yousif.

I am especially grateful to Mr. Farooq A. Mohammad for his great help in biological study and all the staff in Al-Nahrain Biotechnology research Center .

I would like to thank my nearest friends especially Mostafa Kattan, Bassam Fraoun, Adel Ahamed, Salah Mohammad, Nakțel abdel Hafeth, Moataz Adnan, Reny Khashaba and all friends that I hope will forgive me for not mentioning their names.

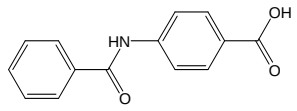
Alaa Al-Haddad

الخلاصة

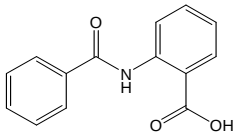
تـم تحضـير مركبـات جديـدة مـن ٢، ٥- ثنـائي التعـويض ١، ٣، ٤- أوكسـادايازول مشتقة من أحماض امينية مناسبة والتـي تحمل مجموعـة الفنيل فـي الموقـع (٢) وبنـز اميدو ومجموعة ألكيل عند الموقع (٥) وقد تضمنت طريقة التحضير خطوتين أساسيتين :

الخطوة الاولى : تحضير بنز اميدو حامض الكاربوكسيل

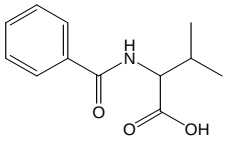
أن تكـاثف الحـامض الامينـي المناسـب (بـارا-أمينـو حـامض البنزويـك، أورثـو-أمينـو حامض البنزويك، الفالين، ليوسين، فنيل الانين) مـع بنزوايل كلورايد فـي وسط قاعدي يعطـي بنز أميد حامض الكاربوكسيل المقابل والتي لها الصيغة التركيبية التالية :-



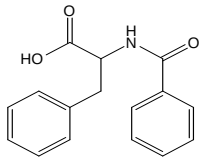
P-benzamido benzoic acid [1]



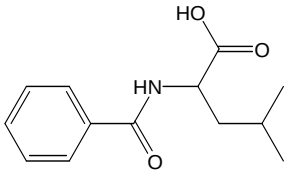
O-benzamido benzoic acid [2]



2-benzamido-3-methyl-butanoic acid [3]

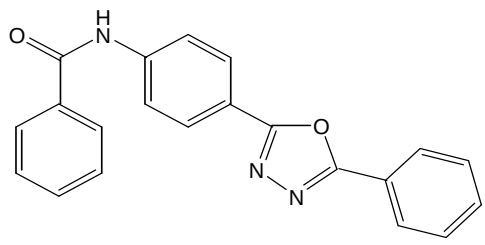


2-benzamido-3-phenyl-propanoic acid [5]

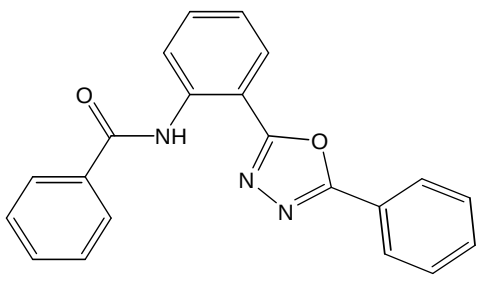


2-benzamido-4-methyl-pentanoic acid [4]

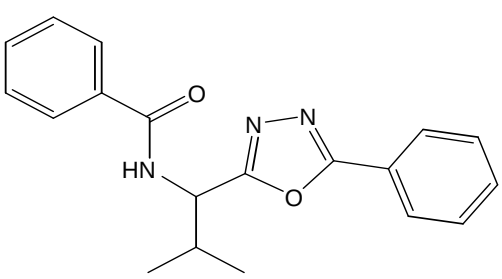
الخطوة الثانية: أن تكاثف بنز أميدو حامض الكاربوكسيل [١-٥] مـع بنزوايل كلوريد بوجود أوكسـي كلوريـد الفسـفوريل يُعطـي ٢، ٥ – ثنـائي التعـويض ١، ٣، ٤- أوكسـادايازولات المناسبة [٦-١٠] والتي لها الصيغة التركيبية التالية:



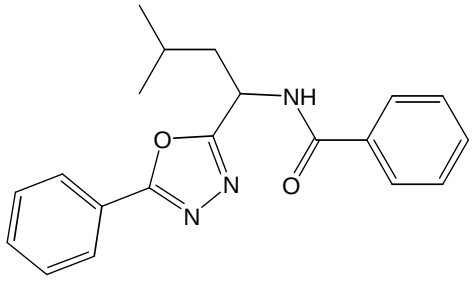
2-phenyl-5-[4-(benzamido)-phenyl]-1,3,4 -oxadiazole [6]



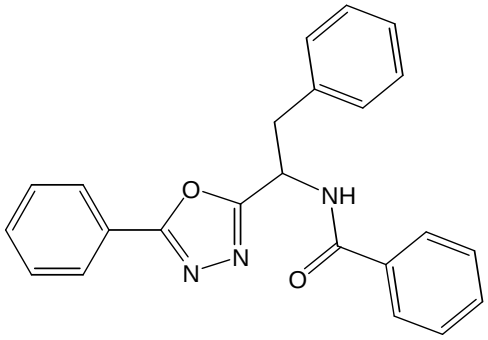
2-phenyl-5-[2-(benzamido)-phenyl]-1,3,4 -oxadiazole [7]



[1-benzamido-1-(5-phenyl-1,3,4-oxadiazole-2yl)-3methyl]butane [9]



[1-benzamido-1-(5-phenyl-1,3,4 -oxadiazole-2yl)-2methyl]propane [8]



[1-benzamido-1-(5-phenyl-1,3,4-oxadiazole-2yl)-2phenyl]-ethane [10]

لقد تم تقييم الفعالية البايلوجية للمركبات المحضرة ضد أنواع منتخبة من البكتريا وهما البكتريا الموجبة للصبغة (*Staphlococcus aureus*) و البكتريا السالبة للصبغة (*Escherichia. coli*) كذلك تم تقييم الفعالية البايلوجية للمركبات المحضرة على نوع واحد من الفطريات والتي تدعى (*Trichphytons rubrum*) واخيراً تم تقدير الفعالية السمية لهذه المركبات على الخلايا الطبيعية وهي (Mouse embryo fibroblast) في فترة تحضين ٧٢ ساعة في درجة حرارة ٣٧ م°.

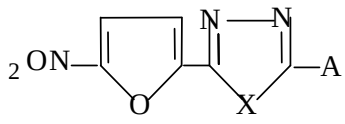
لقد دلت النتائج المستحصلة بأن المركبات المحضرة قد أظهرت فعالية معتبرة ضد البكتريا، (*S. aureus* و *E. coli*) وباستخدام تركيزين مختلفين، وجد ان المركب [٨] و [١٠] لهما فعالية بايولوجية عالية ضد البكتريا الموجبة للصبغة (*S. aureus*) وان المركبين

[١] و [٥] أظهرا فعالية بايولوجية عالية ضد البكتريا السالبة للصبغة (*E. coli*). وفيما يخص الفطريات، فقد بينت النتائج الاولية بأن المركبات المحضرة قامت بتثبيط نمو الفطر (*Trichphytons rubrum*)ما عدا مركب [٣] و [٤]. اما بالنسبة للتأثير السُمي للمركبات فقد وجد بأن المركبات [١-٥ ، ١٠] لهما تأثير سُمي قليل جداً على الخلايا الطبيعية، وان المركب [٥] اظهر اعلى سمية لها، اما المركبات [٦-٩] فليس لها تاثير سمي على نفس الخلايا.

3.2 Antibacterial Activity:

In agreement with 1944, ***Dodd and Stiliman***[83] who published their finding that furans with a nitro group in the 5- position possessed antibacterial activity. The 2- position of the 5-furan must be substituted, by a group of the general type -C=N-N=C-A (A=N,O, and S).

Scherman[84] found that the —C=N—N=C— system described. by (Dodd et al.) may be incorporated in heterocyclic systems, such compound is described in general terms by structure[85]



(X,A)= O,N or S

Applying the agar plate diffusion technique some of the synthesized compounds were screened *in vitro* for antibacterial activity against Gram positive *S. aureus* and Gram negative *E. coli*. The zone of inhibition of bacterial growth around the disc was observed the screening results given in table (3.1), (3.2) and shown in figures (3.11), (3.12), (3.13), (3.14), (3.15), (3.16), (3.17), (3.18) indicated that most of the synthesized compounds exhibited antibacterial activities against at least one of the two types of the tested bacteria. Almost all the compounds have an inhibitory action against *S. aureus* more than *E .coli*. And from the screening results given in table (3.2) indicated that compounds [8] and [10] showed highest inhibitory effect against *S. aureus* , while compounds [1] and [5] showed highest inhibitory effect against *E. coli* in the same concentration.

Table (3.1) Antibacterial activity of synthesized compounds in conc. 0.005/5ml of DMSO

Compound No.	*S. aureus* (G +ve)	*E. coli* (G –ve)
[1] *P*- benzamido benzoic acid	++	-
[2] *O*-benzamido benzoic acid	++	+
[3] 2-benzamido-3-methyl-butanoic acid	++	+
[4] 2-benzamido-4-methyl-pentanoic acid	++	+
[5] 2-benzamido-3-phenyl-propanoic acid	++	+
[6] 2-phenyl-5-[4-(benzamido)-phenyl]-1,3,4 -oxadiazole	+	+
[7] 2-phenyl-5-[2-(benzamido)-phenyl]-1,3,4 - oxadiazole	++	++
[8] [1-benzamido-1-(5-phenyl-1,3,4 -oxadiazole-2yl)-2methyl] propane	++	++
[9] [1-benzamido-1-(5-phenyl-1,3,4-oxadiazole-2yl)-3-methyl]butane	++	+
[10] [1-benzamido-1-(5-phenyl-1,3,4-oxadiazole-2yl)-2-phenyl]-ethan	++	++
Control (DMSO)	-	-

Note:

(-) = No inhibition
+ = 5-10 mm.
++ = 11-20 mm.
+++ = More than 20 mm

Table (3.2) Antibacterial activity of synthesized compounds in Conc. 0.008/5ml of DMSO

Compound No.	*S. aureus* (G +ve)	*E. coli* (G –ve)
[1] *P*- benzamido benzoic acid	++	+++
[2] *O*-benzamido benzoic acid	++	++
[3] 2-benzamido-3-methyl-butanoic acid	+++	++
[4] 2-benzamido-4-methyl-pentanoic acid	++	++
[5] 2-benzamido-3-phenyl-propanoic acid	+++	+++
[6] 2-phenyl-5-[4-(benzamido)-phenyl]-1,3,4 -oxadiazole	++	++
[7] 2-phenyl-5-[2-(benzamido)-phenyl]-1,3,4 - oxadiazole	+++	++
[8] [1-benzamido-1-(5-phenyl-1,3,4 -oxadiazole-2yl)-2methyl] propane	+++	+++
[9] [1-benzamido-1-(5-phenyl-1,3,4-oxadiazole-2yl)-3-methyl]butane	++	++
[10] [1-benzamido-1-(5-phenyl-1,3,4-oxadiazole-2yl)-2-phenyl]-ethan	+++	+++
Control (DMSO)	-	-

Note :
(-) = No inhibition
+ = (5-10)mm.
++ = (11-20)mm.
+++ = More than (20)mm

In general the activity of antibacterial agents are related to:

a) Inhibition of cell wall synthesis such as cycloserine[86] , penicillin Binding Protein[87] and bacitracin[88]

b) Alteration of cell membrane permeability or inhibition of active transport across cell membrane such as surfactants[89].

c) Inhibition of protein synthesis i.e. “Inhibition of translation and transcription of genetic material”., such as Erythromycin[90]. Streptomycine[91] and tetracycline[92].

d) Inhibition of nucleic acid synthesis such as sulfonamide[93] and nalidixic acid[94].

Thus, when screening for the antimicrobial activity of the synthesized substituted oxadiazole compounds against *S. aureus* and *E. coli* bacteria (Table 3.1, 3.2), It has been found that the drug was more active against *S. aureus* bacteria.

The difference in effectiveness of the drug between the two types of bacteria might be attributed to the difference in the cell wall structure. Bacterial cell wall consists of a branched chains of polysaccharide containing alternating units of N-acetylglucose amine and N-acetyl muramic acid connected by polypeptide cross linkage, this layers is called the peptidoglycan[(95)] In Gram positive bacteria, this basic layer is covered with teichoic acid which is ribitol phosphate, N-acetyl glucose amine polymer, and glycine, making up to 20% of cell weight. While in Gram nagative bacteria, lipopolysaccharides with lipoproteins were external to glycopeptides, which makes about 80% of the cell wall weight[(96)] this lipid containing layer of Gram negative bacteria cell wall keeps various small molecules from reaching the membrane[(95)] In addition to the fact that Gram positive bacteria cell wall is more permeable to molecules than Gram negative bacteria cell wall[(95)].

Figure (3.11) Effect of all synthesized compounds on *S. aureus* in conc. (0.005g/5ml) of DMSO at 37 °C for 24 hrs of incubation.

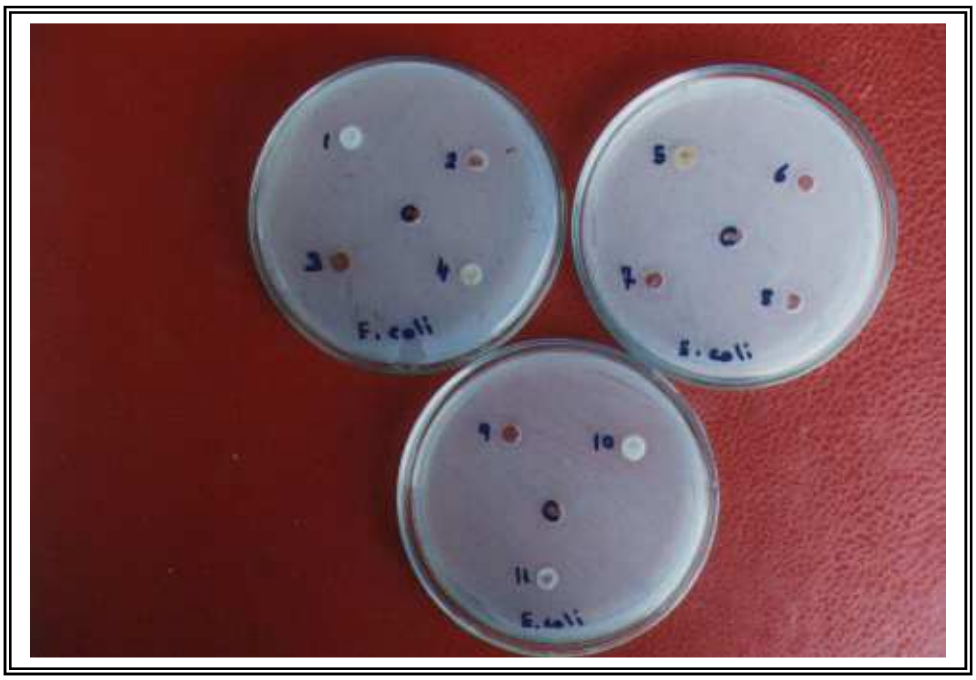


Figure (3.12) Effect of all synthesized compounds on *E. coli* in conc. (0.005g/5ml) of DMSO at 37 °C for 24 hrs of incubation

Figure (3.13) Effect of compounds [1], [2], [3], [4] on *S. aureus* in conc. (0.008g/5ml) of DMSO at 37 °C for 24 hrs of incubation.

Figure (3.14) Effect of compounds [5], [6], [7], [8] on *S. aureus* in conc. (0.008g/5ml) of DMSO at 37 °C for 24 hrs of incubation.

Figure (3.15) Effect of compounds [9], [10], [11] on *S. aureus* in conc. (0.008g/5ml) of DMSO at 37 ˚C for 24 hrs of incubation.

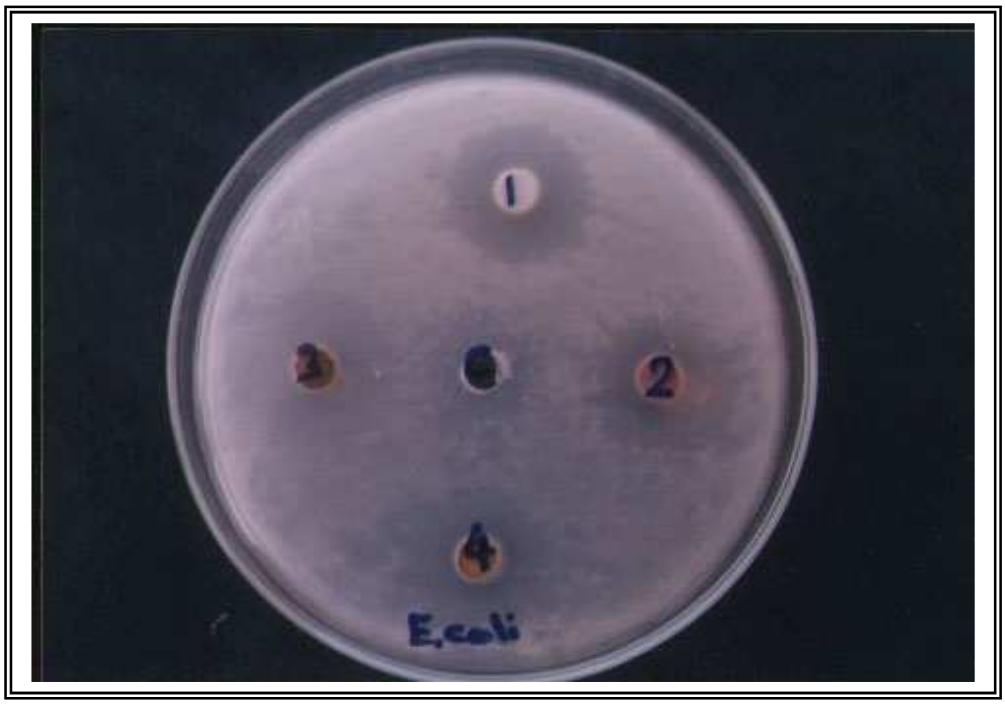


Figure (3.16) Effect of compounds [1], [2], [3], [4] on *E. coli* in conc. (0.008g/5ml) of DMSO at 37 ˚C for 24 hrs of incubation.

Figure (3.17) Effect of compounds [5], [6], [7], [8] on *E. coli* in conc. (0.008g /5ml) of DMSO at 37 °C for 24 hrs of incubation

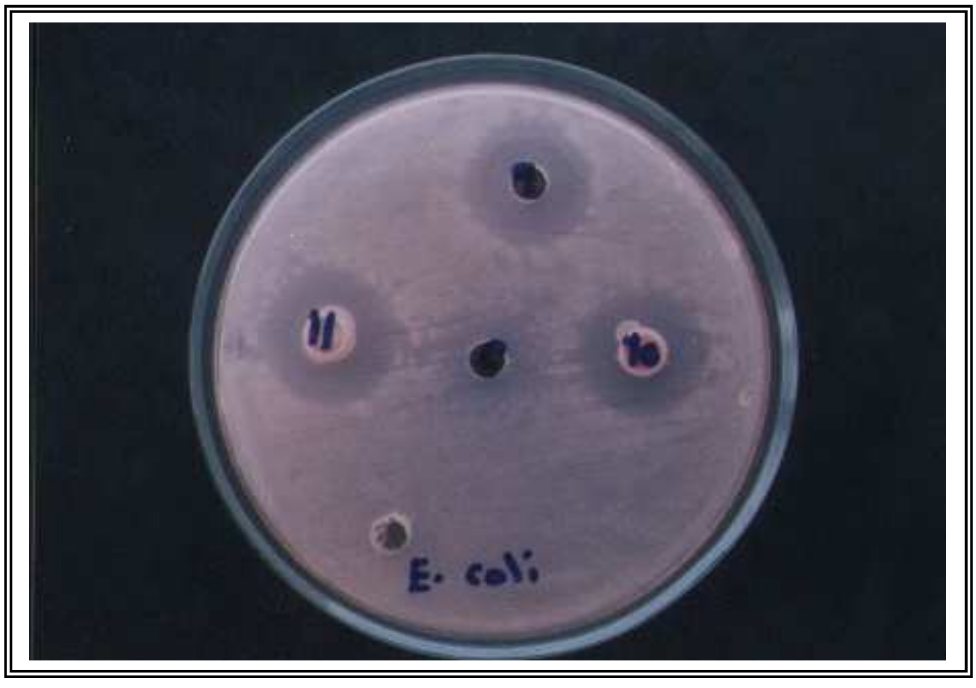


Figure (3.18) Effect of compounds [9], [19], [11] on *E. coli* in conc. (0.008g /5ml) of DMSO at 37 °C for 24 hrs of incubation

3.3 Antifungal Activity:

The synthesized compounds showed an inhibition effect on the growth of *Trichopytons rubrum.* The inhibition of *T. rubrum* appeared at concentration (0.005/5ml) of synthesized compounds was shown in table (3.3) and figures(3.19), (3.20), (3.21), (3.22), (3.23), (3.24) and observed that the *T. rubrum* appeared with resistance to compounds No. [3] and [4] at the same concentration. and from fig. (3.19) indicated that the solvent have no effect on the *T. rubrum* and did not inhibit the growth of it.

Table (3.3) Anti fungal activity of synthesized compounds in conc. (0.005/5ml) of DMSO

Compound No.	Diameter of inhibition zone (mm)
[1] *P*- benzamido benzoic acid	-
[2] *O*-benzamido benzoic acid	-
[3] 2-benzamido-3-methyl-butanoic acid	**30mm**
[4] 2-benzamido-4-methyl-pentanoic acid	**50mm**
[5] 2-benzamido-3-phenyl-propanoic acid	-
[6] 2-phenyl-5-[4-(benzamido)-phenyl]-1,3,4 -oxadiazole	-
[7] 2-phenyl-5-[2-(benzamido)-phenyl]-1,3,4 - oxadiazole	-
[8] [1-benzamido-1-(5-phenyl-1,3,4 -oxadiazole-2yl)-2methyl] propane	-
[9] [1-benzamido-1-(5-phenyl-1,3,4-oxadiazole-2yl)-3-methyl]butane	-
[10] [1-benzamido-1-(5-phenyl-1,3,4-oxadiazole-2yl)-2-phenyl]-ethan	-
Control	**Full growth**

Note:

(-) = No inhibition

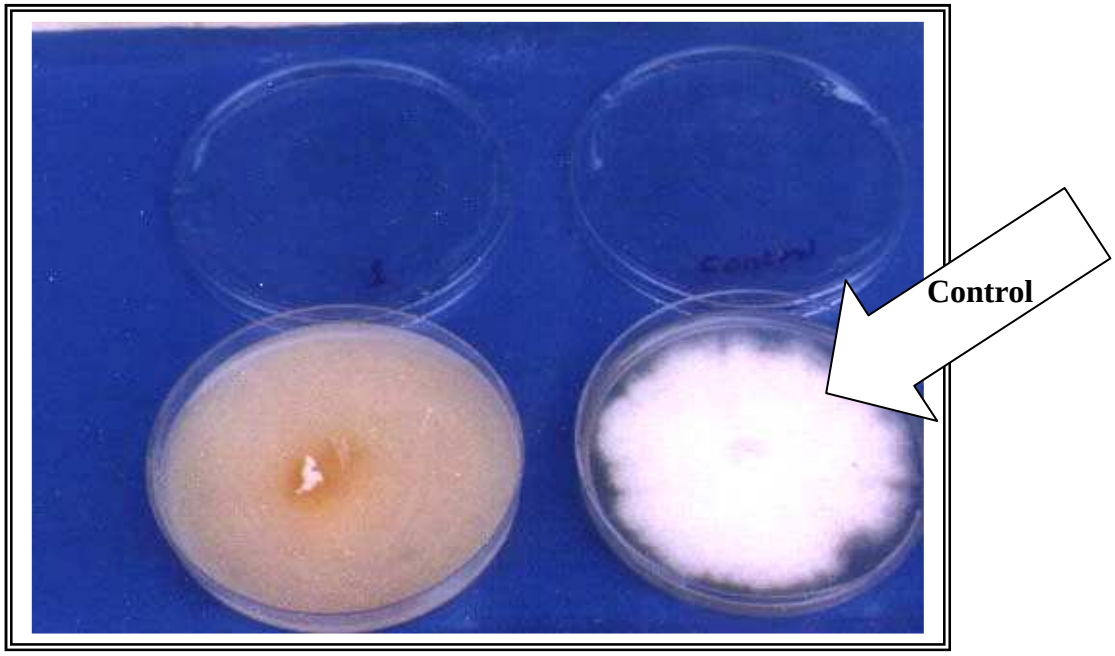


Figure (3.19) Effect of compounds [1] and [control] on *T. rubrum* in conc. (0.008g/5ml) of DMSO at 30 °C for 7-10 days of incubation

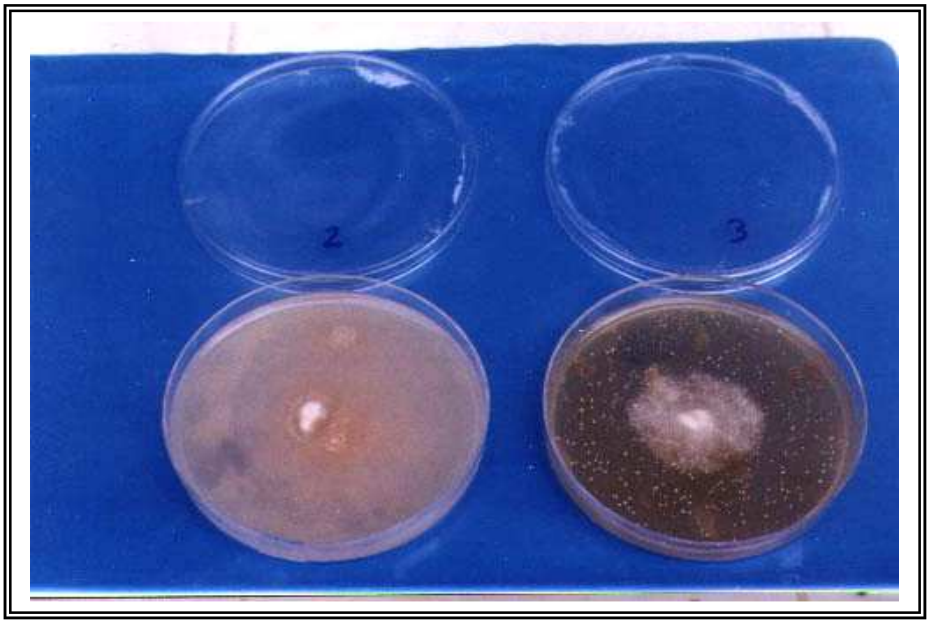


Figure (3.2٠) Effect of compounds [٢], [3] on *T. rubrum* in conc. (0.008g/5ml) of DMSO at 30 °C for 7-10 days of incubation

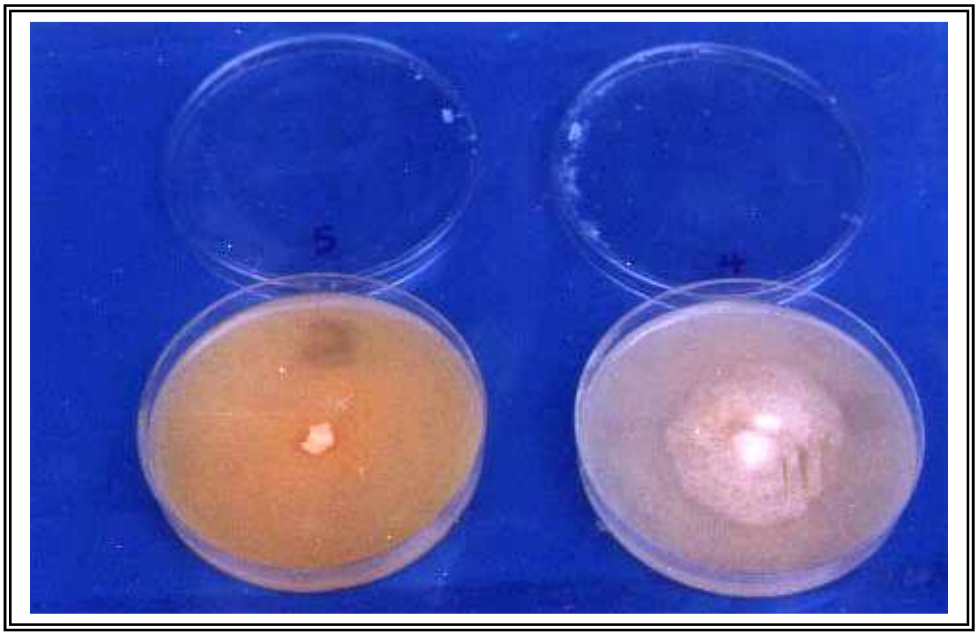


Figure (3.21) Effect of compounds [4], [5] on *T. rubrum* in conc. (0.008g/5ml) of DMSO at 30 °C for 7-10 days of incubation

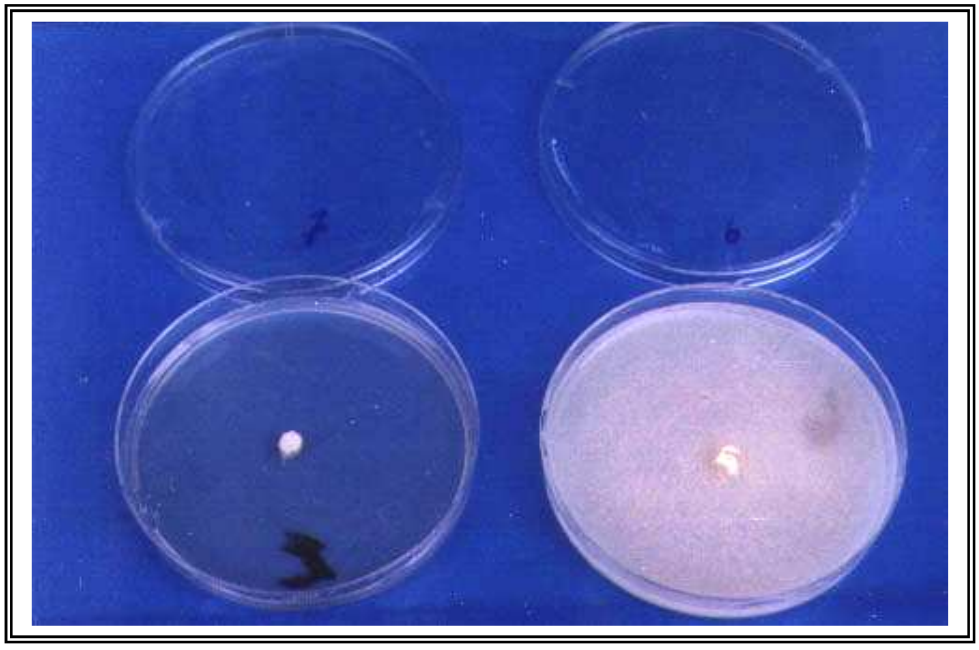


Figure (3.22) Effect of compounds [6], [7] on *T. rubrum* in conc. (0.008g/5ml) of DMSO at 30 °C for 7-10 days of incubation

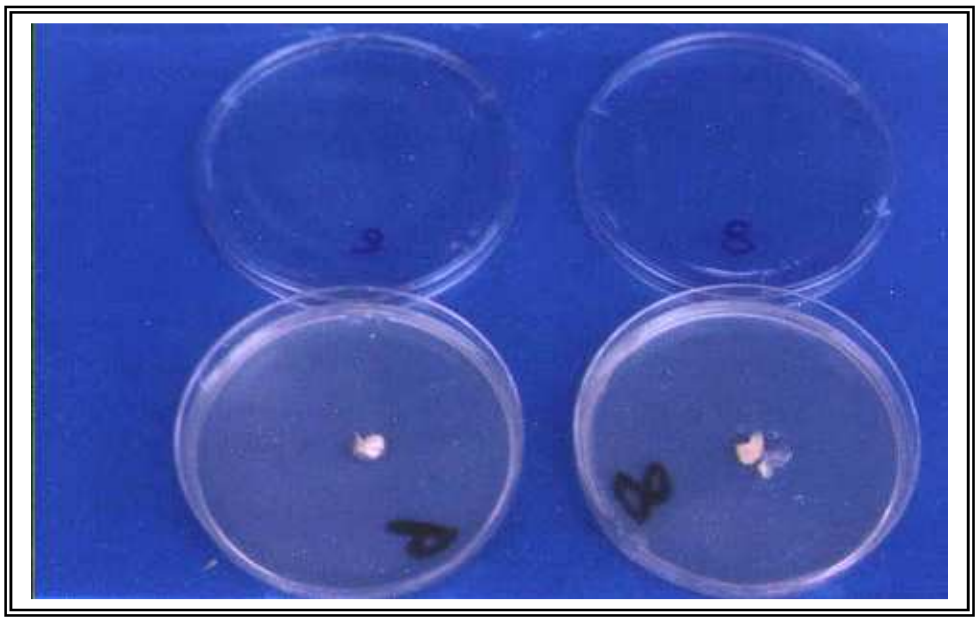


Figure (3.23) Effect of compounds [٨], [٩] on *T. rubrum* in conc. (0.008g/5ml) of DMSO at 30 °C for 7-10 days of incubation

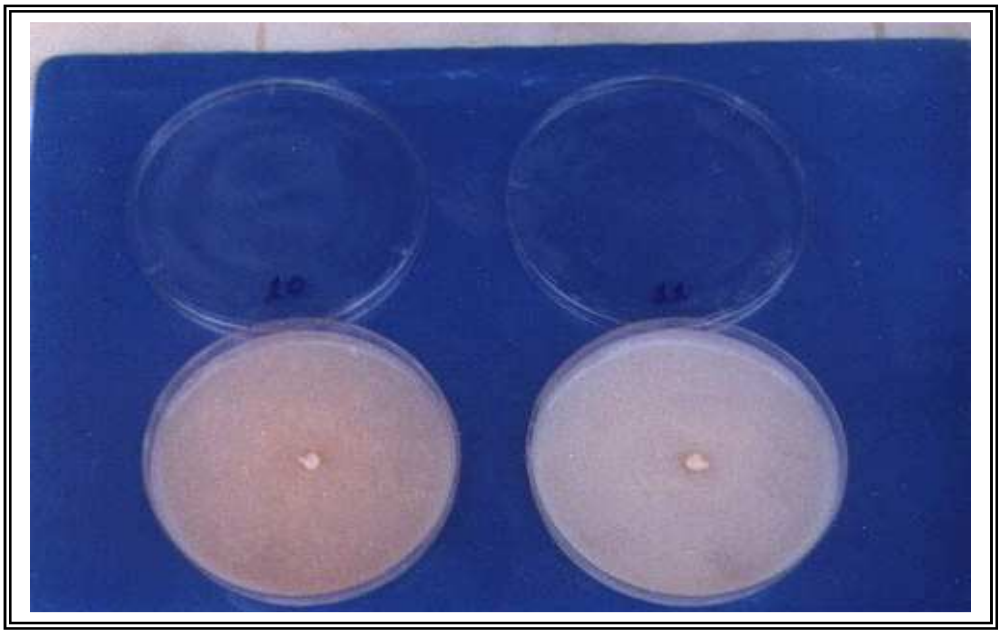


Figure (3.24) Effect of compounds [١٠], [١١] on *T. rubrum* in conc. (0.008g/5ml) of DMSO at 30 °C for 7-10 days of incubation

3.4 Cytotoxic activity:

Cytotoxicity is the *in vitro* determination of toxic effects of unknown compounds performed by counting viable cells after staining with a vital dye. Alternative methods used for measurement of radioisotope incorporation as a measure of DNA synthesis, counting by automated counters and others which rely on dyes and cellular activity.

The neutral red method, as originally developed by Borenfreund and Puerner[97] is simple, accurate and yields reproducible results. The key component is the vital dye, neutral red (Basic Red 5, Toluylene Red). Viable cells will take up the dye by active transport and incorporate the dye into lysosomes, whereas non-viable cells will not take up the dye. After the cells have been allowed to incorporate the dye they are briefly washed and fixed. The incorporated dye is then liberated from the cells in an acidified ethanol solution. An increase or decrease in the number of cells or their physiological state results in a concomitant change in the amount of dye incorporated by the cells in the culture. This indicates the degree of cytotoxicity caused by the test material[81].

Figures (3.25), (3.26), (3.27), (3.28), (3.29), and (3.34) show cytotoxic effect of synthesized compounds on normal cells (Mouse embryo fibroblast), at different concentration in 72hrs period of incubation.

Figure (3.25) can show weak cytotoxic effects of compound [1] on the treated cells at concentrations [0.01], [0.005], [0.0025] and [0.00125]M, while no effect have been observed in compared with (solvent) and control at the lowest concentrations [0.000625], [0.000313] and [0.000157] M.

Compound [2] figure (3.26) showed weak cytotoxic effects only in high concentrations [0.01] and [0.05]M on the treated cells in compared with control and solvent. In the lowest concentration this compound have no cytotoxic effects and can see only the effect of solvent on treated cells.

Figure (3.27) showed very weak cytotoxic effects of compound [3] only in the concentration [0.01]M on the treated cells and the remained concentrations have no cytotoxic effects and noted clearly the effect of solvent only.

Fig. (3.28) showed very weak cytotoxic effects of compound [4] in only the concentration [0.05]M on the treated cells, While the other concentration have no cytotoxic effects and noted clearly the effect of solvent only.

Figure (3.29) showed weak cytotoxic effects of compound [5] on the treated cells at concentrations [0.01], [0.005], [0.0025] and [0.00125] M, in compared with (solvent) and control, while no effect have been observed at the lowest concentrations [0.000625], [0.000313] and [0.000157] M.

Figures (3.30 [6]), (3.31 [7]), (3.32 [8]) and (3.33 [9]) can shows no cytotoxic effects on the treated cells in all concentrations, and noted clearly only effect of solvent on it.

Figure (3.34) showed weak cytotoxic effects of compound [10] on the treated cells at concentrations [0.01] and [0.005]M, while no effect have been observed in compared with (solvent) and control at the lowest concentrations [0.000625], [0.000313] and [0.000157] M.

These results indicated that compound [5] showed highest cytotoxic effect on the treated cells.

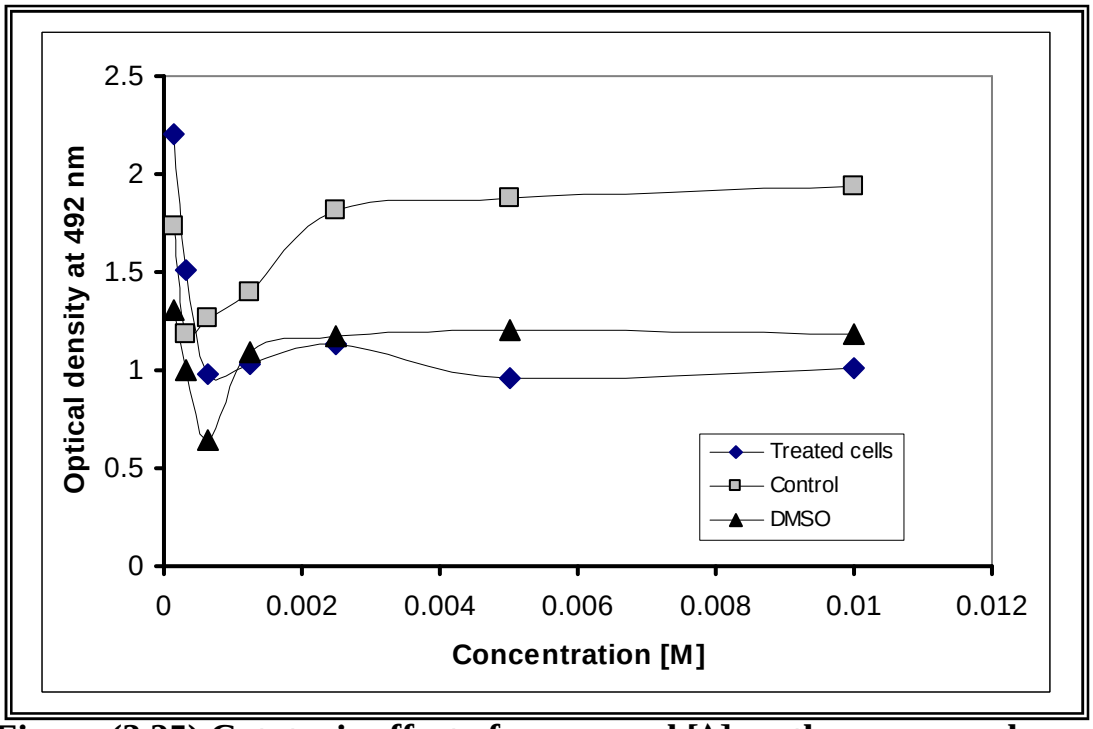


Figure (3.25) Cytotoxic effect of compound [١] on the mouse embryo fibroblast after 72hrs. of incubation at 37 °C

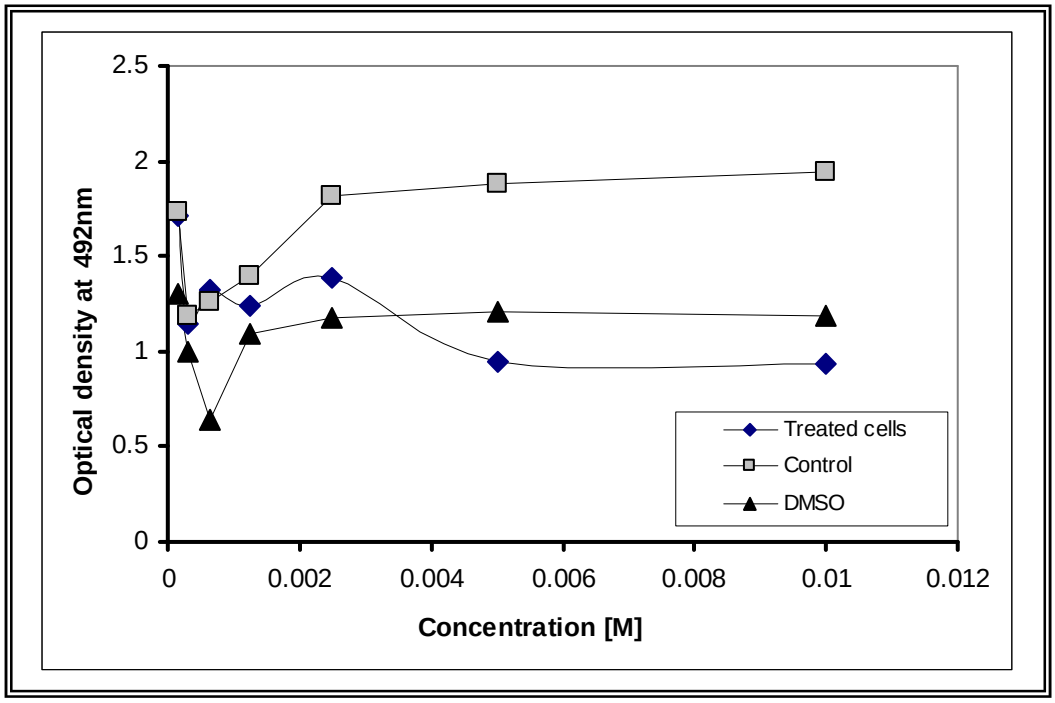


Figure (3.26) Cytotoxic effect of compound [٢] on the mouse embryo fibroblast after 72hrs. of incubation at 37 °C

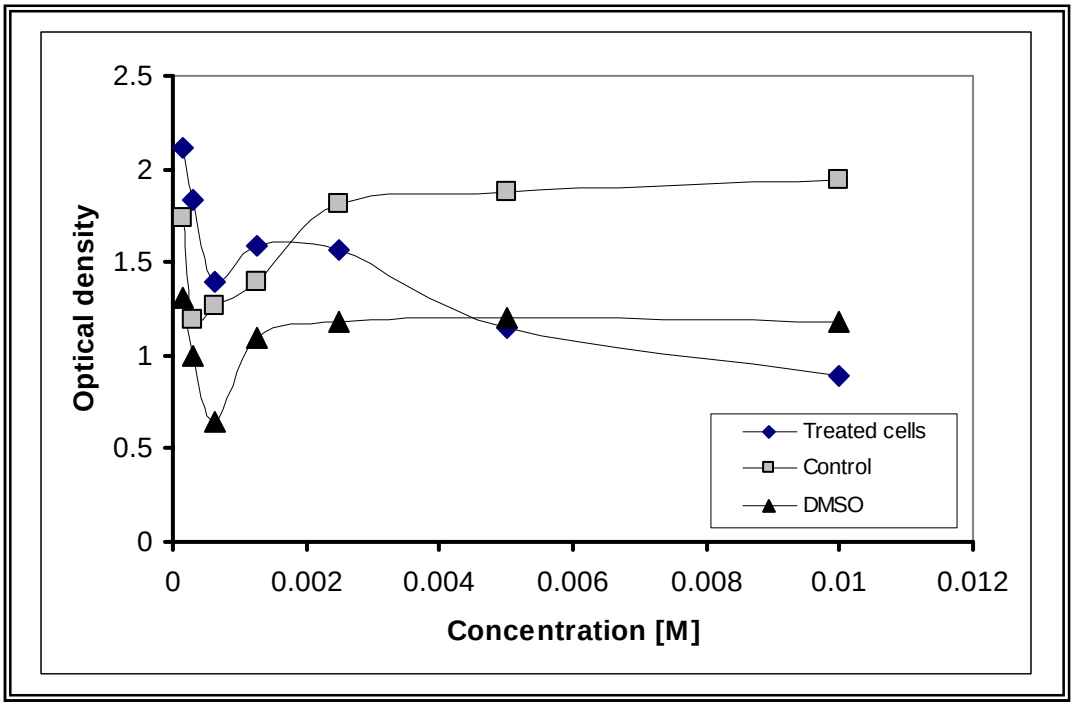


Figure (3.27) Cytotoxic effect of compound [٣] on the mouse embryo fibroblast after 72hrs. of incubation at 37 °C

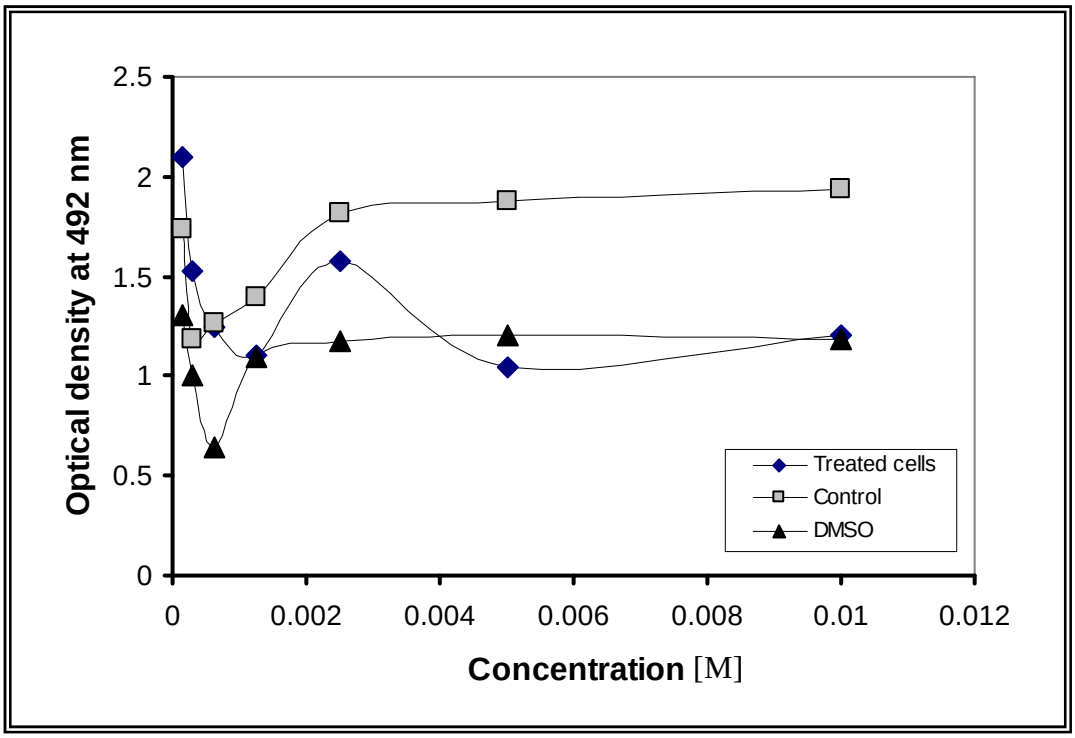


Figure (3.28) Cytotoxic effect of compound [٤] on the mouse embryo fibroblast after 72hrs. of incubation at 37 °C

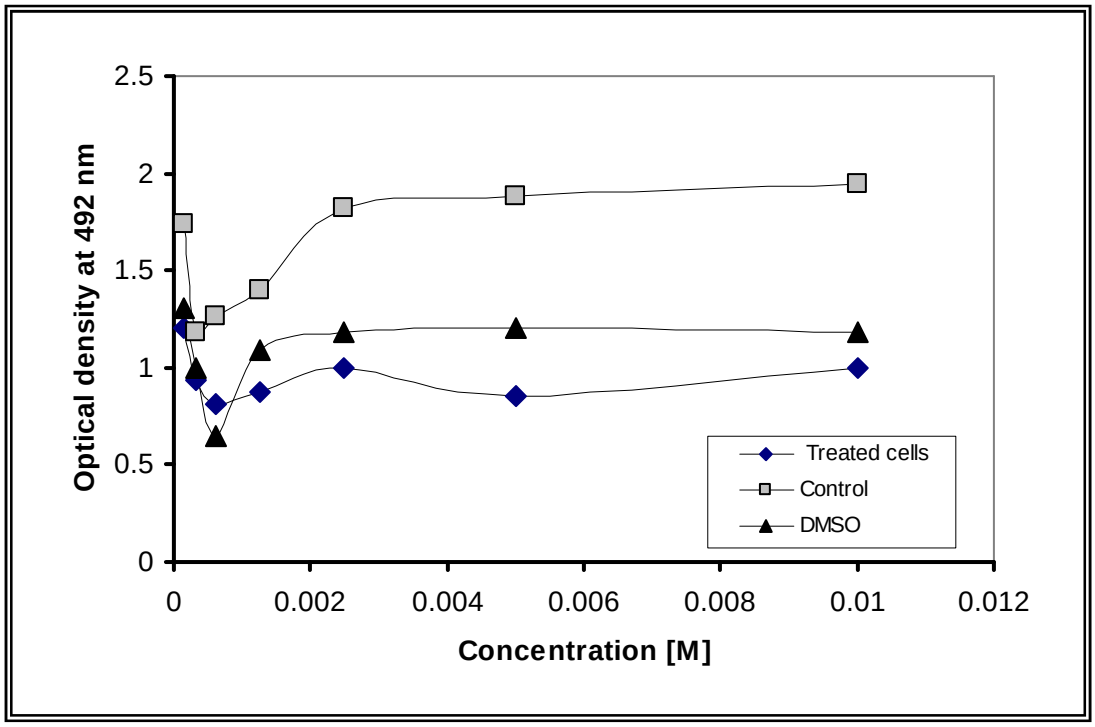


Figure (3.29) Cytotoxic effect of compound [٥] on the mouse embryo fibroblast after 72hrs. of incubation at 37 ˚C

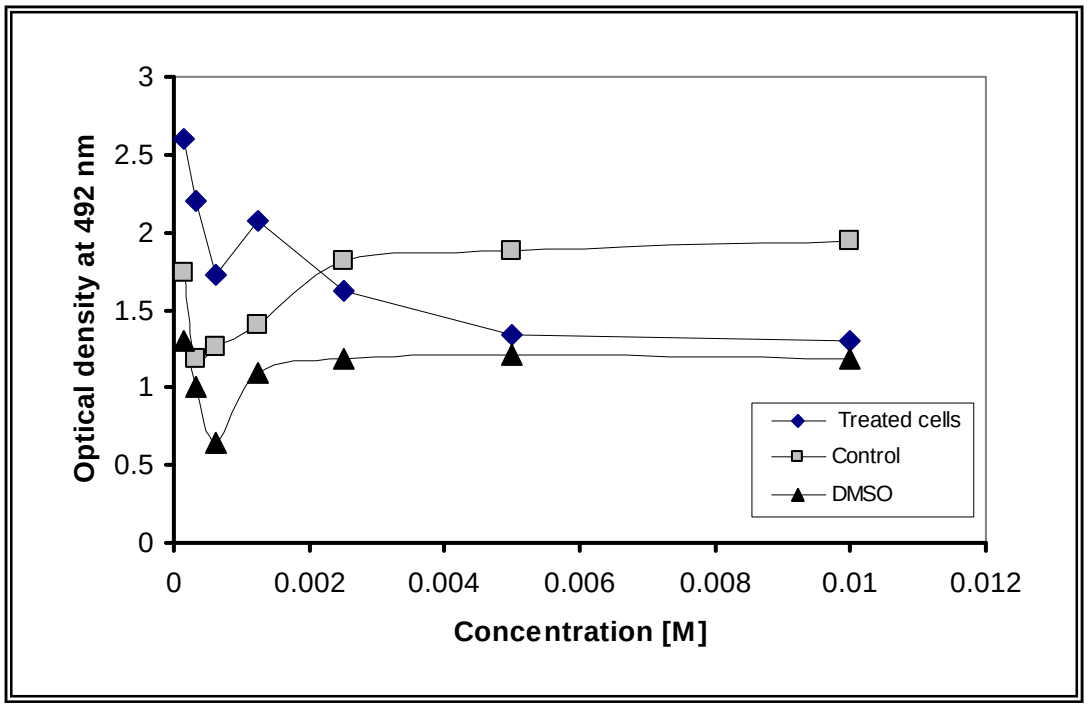


Figure (3.30) Cytotoxic effect of compound [٦] on the mouse embryo fibroblast after 72hrs. of incubation at 37 ˚C

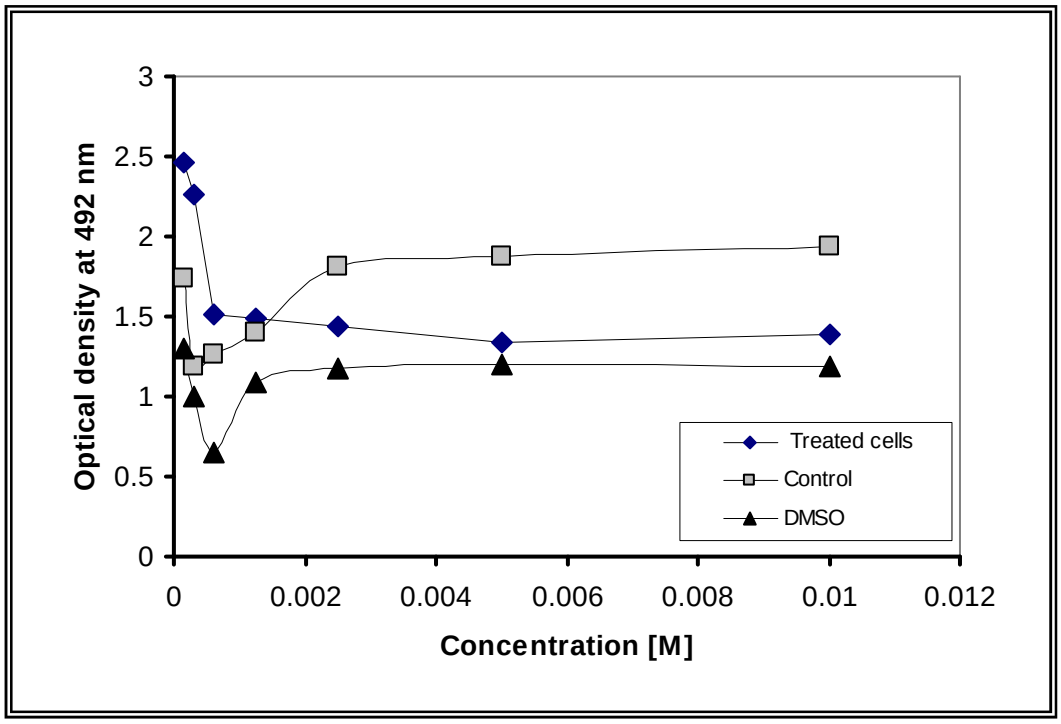


Figure (3.31) Cytotoxic effect of compound [٧] on the mouse embryo fibroblast after 72hrs. of incubation at 37 °C

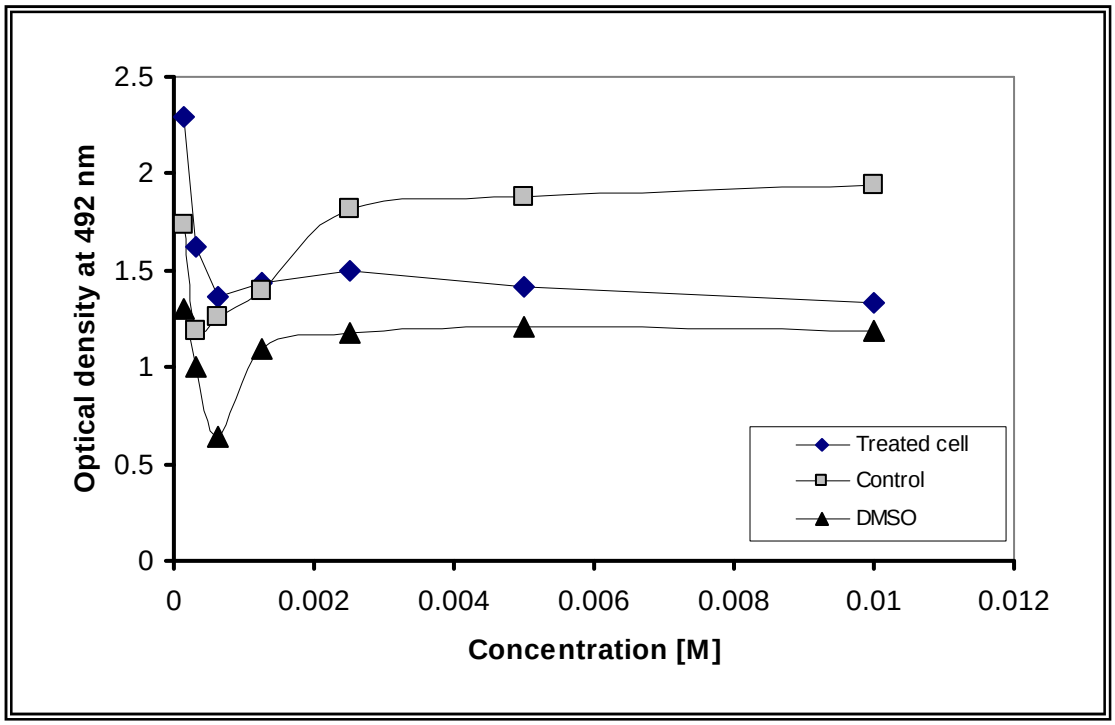


Figure (3.32)Cytotoxic effect of compound [٨] on the mouse embryo fibroblast after 72hrs. of incubation at 37 °C

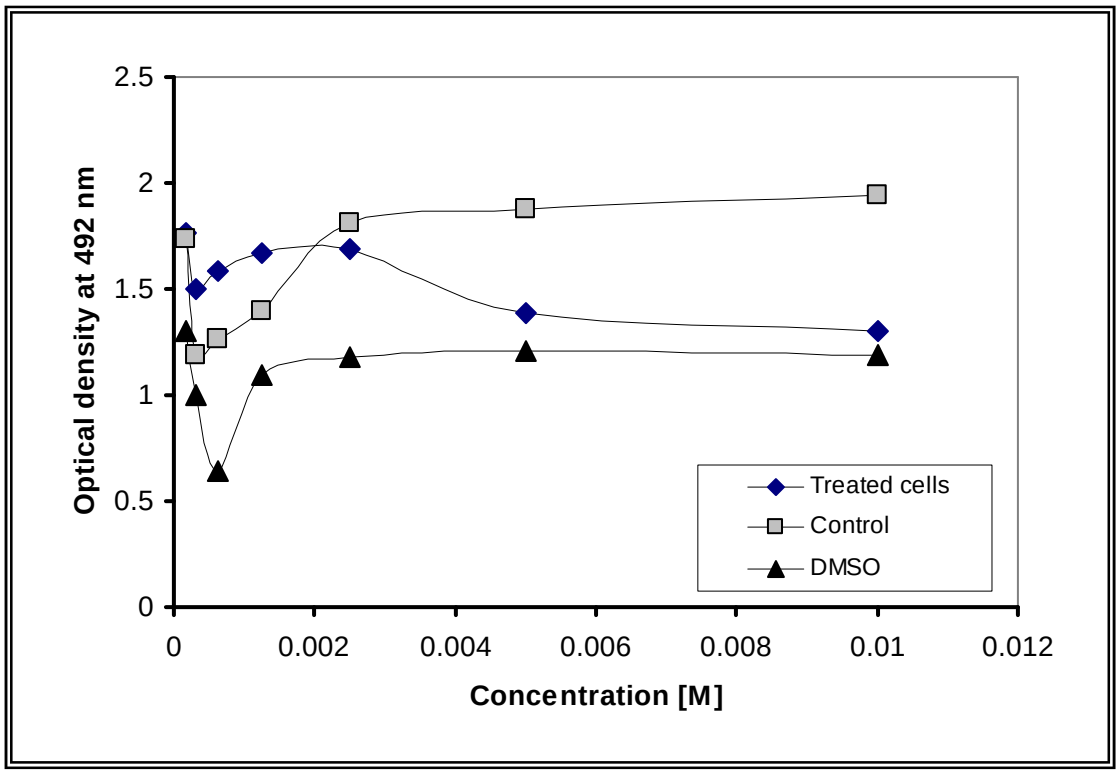


Figure (3.33)Cytotoxic effect of compound [٩] on the mouse embryo fibroblast after 72hrs. of incubation at 37 ˚C

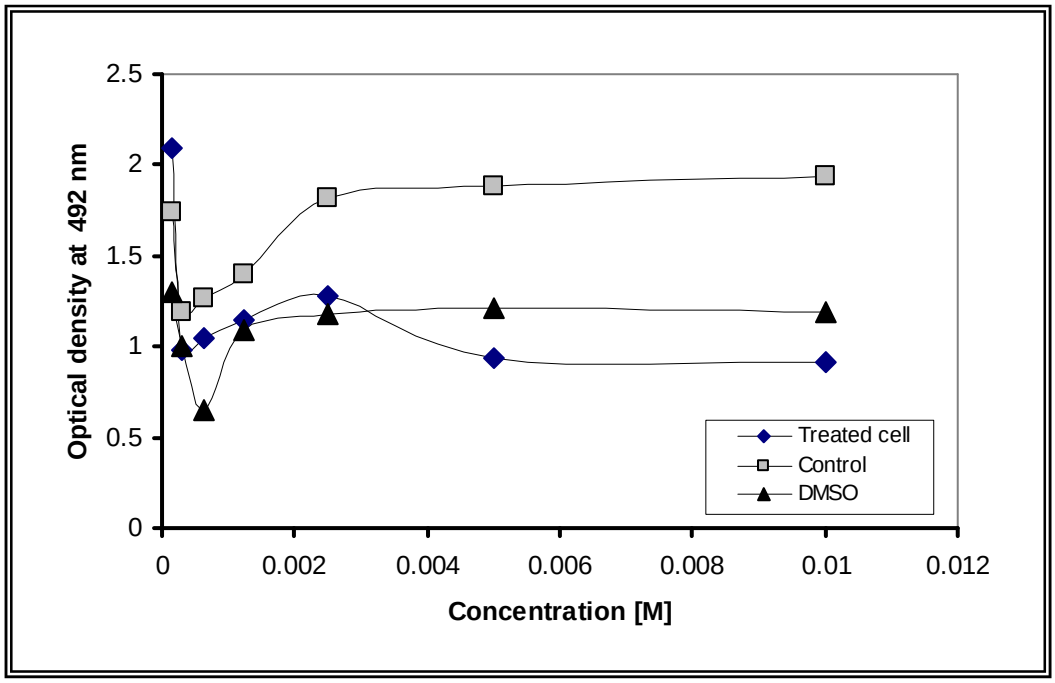
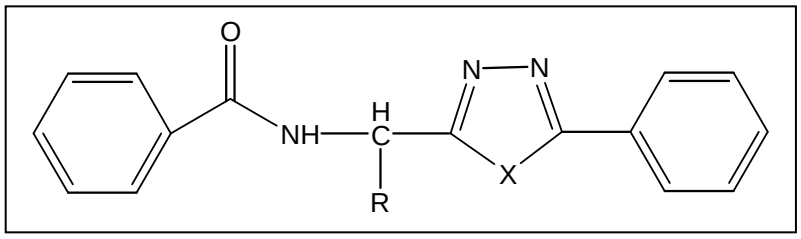


Figure (3.34) Cytotoxic effect of compound [١٠] on the mouse embryo fibroblast after 72hrs. of incubation at 37 ˚C

3.5 Suggestion for further work

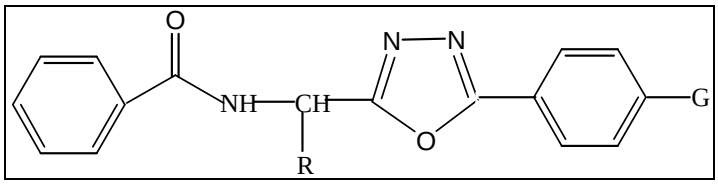
We hope to continue our extensive program directed towards the synthesis of novel heterocyclic compounds of potential biological application, a variety of modification will be done in order to synthesis the following compounds :

1. Synthesis of new heterocyclic compounds contain 1,3,4-thiadiazole and 1,2,4-triazol ring system and studying the effect of replacement of 1,3,4-oxadiazole by the ring on biological activities of synthesized compounds which studied.



X = S, N – H and N – Ph

2. Synthesis of other acid hydrazid and studying the effect of presence of substituent (G) on Biological activity of our synthesize compounds



G = OH, NO_2, CH_3, OCH_3

3. Compound [5] can be test in future and possible use as anti tumor.

جمهورية العراق
وزارة التعليم العالي والبحث العلمي
جامعة النهرين
كلية العلوم
قسم الكيمياء

تحضير و تقييم الفعالية البايولوجية لبعض مركبات ١، ٣، ٤- أوكسادايازول الجديدة والمشتقة من احماض امينية مختلفة

رسالة

مقدمة الى كلية العلوم – جامعة النهرين

وهي جزء من متطلبات نيل درجة الماجستير

في الكيمياء

من قبل

علاء عباس فاضل الحداد

بكلوريوس ٢٠٠٢ (جامعة النهرين)

١٤٢٦ هـ **٢٠٠٥ م**

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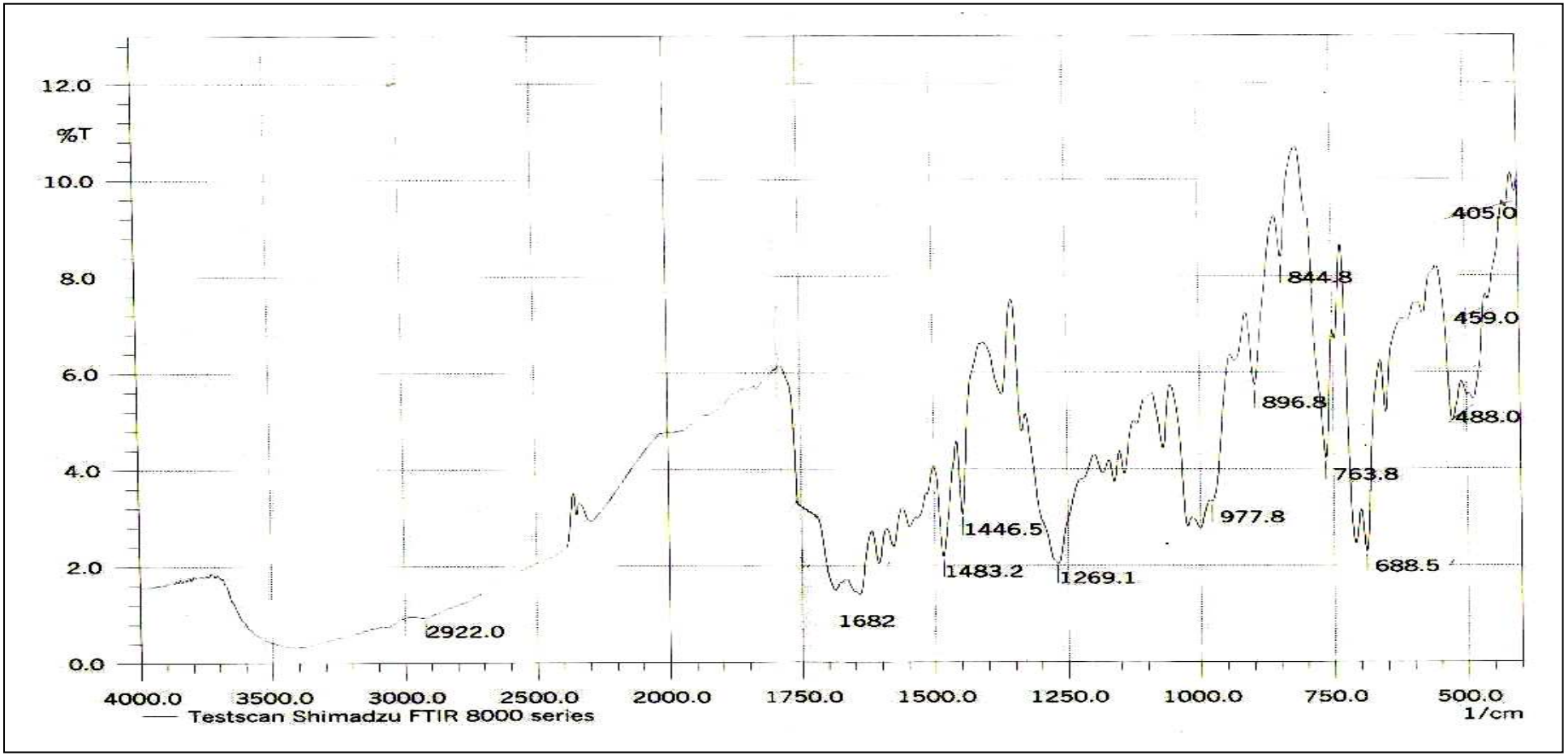


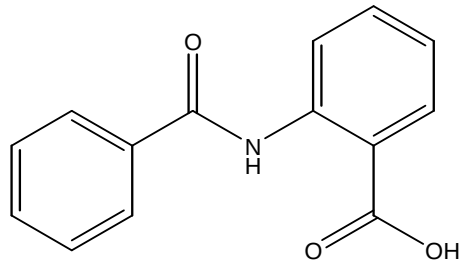
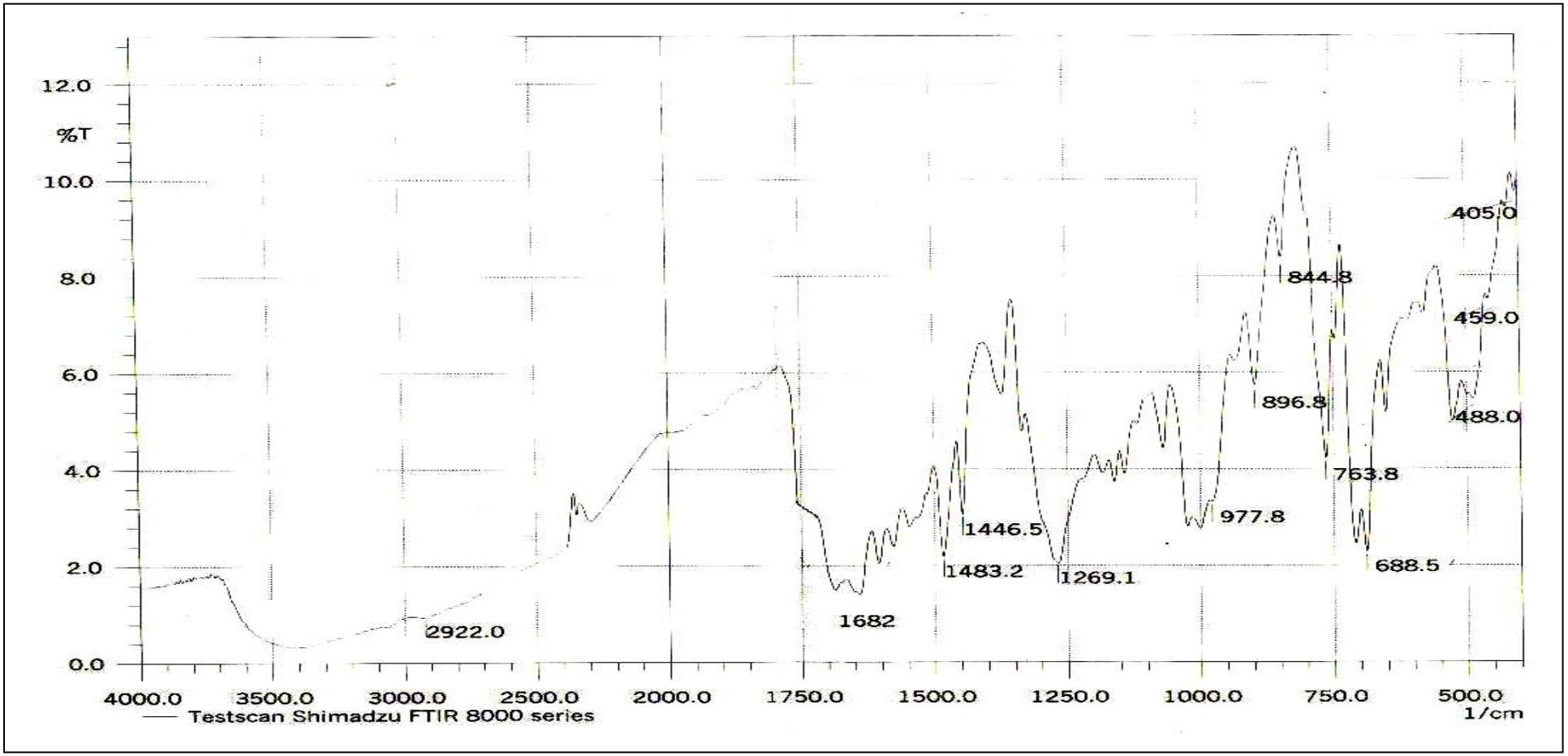
	Melting point (°C)	Characteristic bands (KBr, Cm^{-1})
	**122 - 124**	1. N-H stretch, 3410 2. Amide C=O stretch, 1612.3 3. Carboxylic C=O stretch, 1682.0

Fig. (3.3) FT-IR spectrum of *O*-benzamido benzoic acid [2]



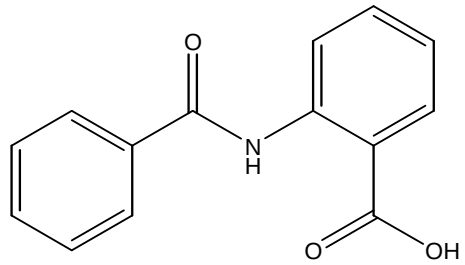
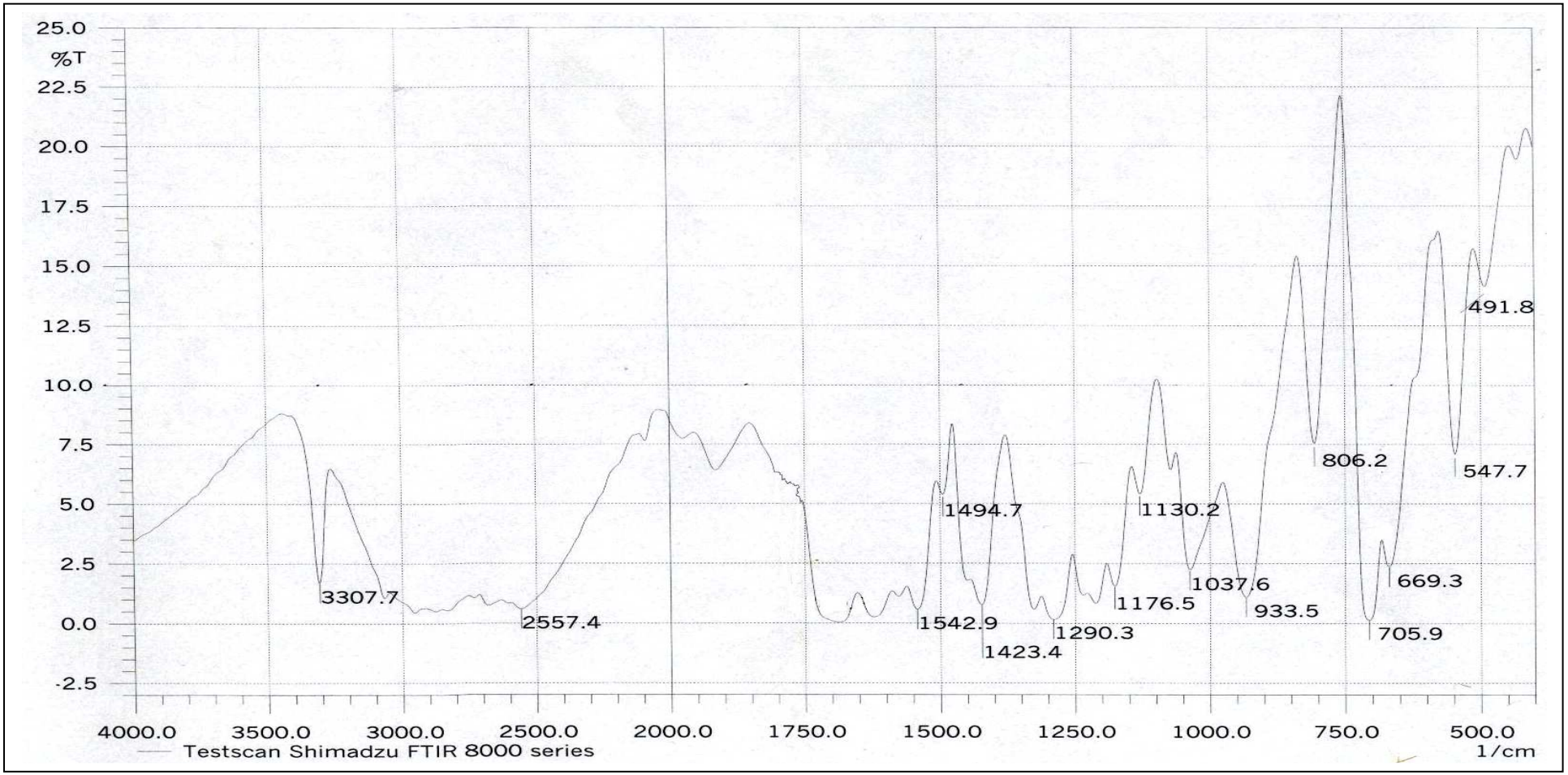
	Melting point (°C)	Characteristic bands (KBr, Cm^{-1})
	**122 - 124**	1. N-H stretch, 3410 2. Amide C=O stretch, 1612.3 3. Carboxylic C=O stretch, 1682.0

Fig. (3.3) FT-IR spectrum of *O*-benzamido benzoic acid [2]



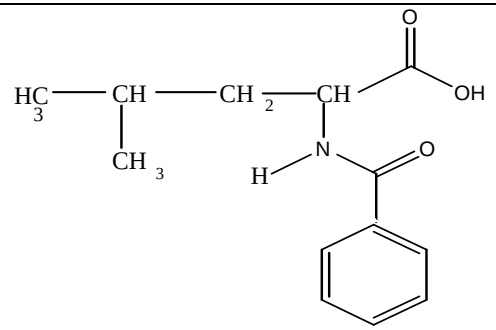
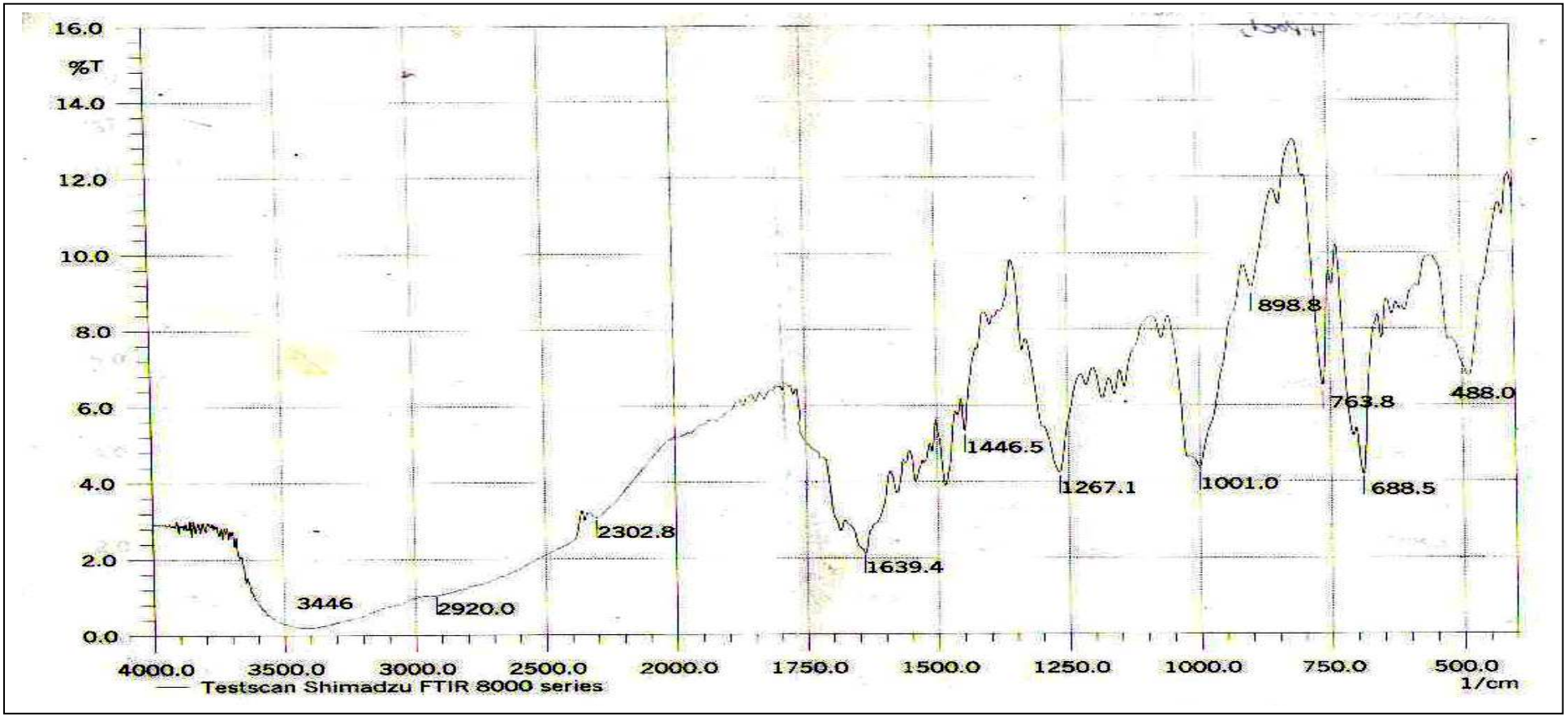
	Melting point (°C)	Characteristic bands (KBr, Cm^{-1})
	**94- 97**	1. N-H stretch, 3307.7 2. Amide C=O stretch, 1690 3. Carboxylic C=O stretch, 1640

Fig.(3.7) FT-IR spectrum of 2-benzamido-4-methyl-pentanoic acid [4]



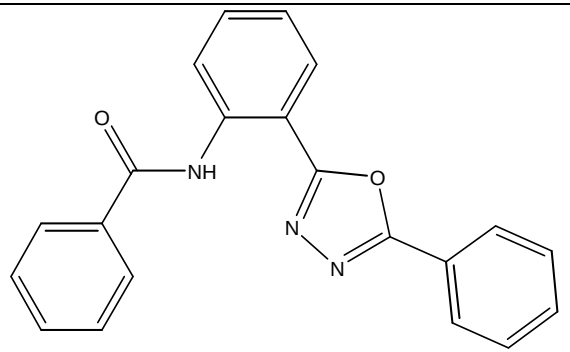
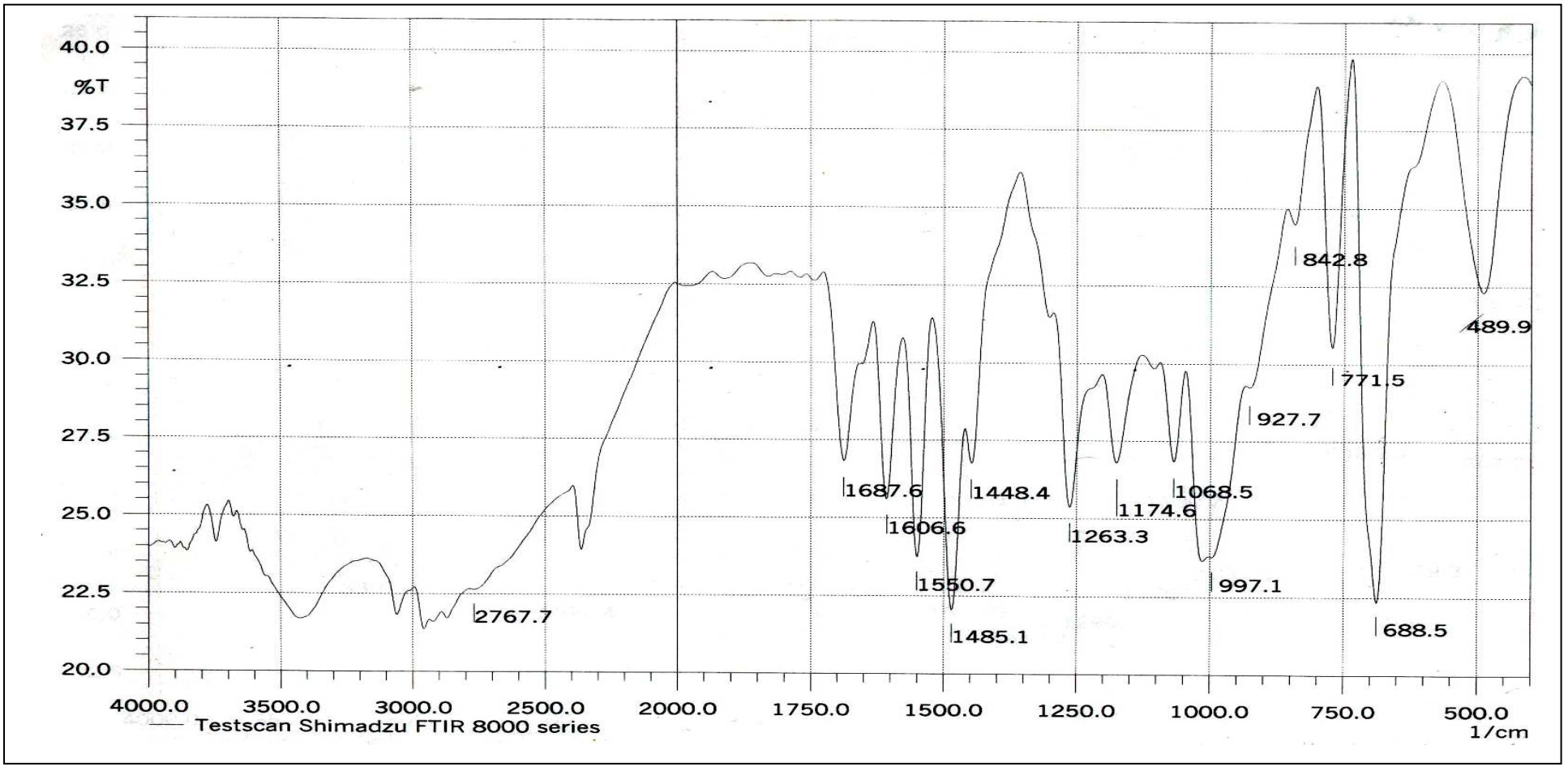
	Melting point (°C)	Characteristic bands (KBr, Cm^{-1})
	**275 - 277**	1. N-H stretch, 3446.0 2. Amide C=O stretch, 1677.7 3. C=N stretch, 1639.4 4. Asymmetric C-O-C stretch, 1267.1 5. Symmetric C-O-C stretch, 1001.0

Fig. (3.4) FT-IR spectrum of 2-phenyl-5-[2-(benzamido)-phenyl]-1,3,4 - oxadiazole [7]



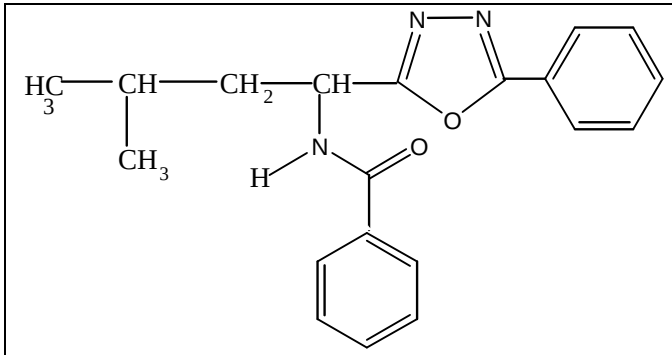
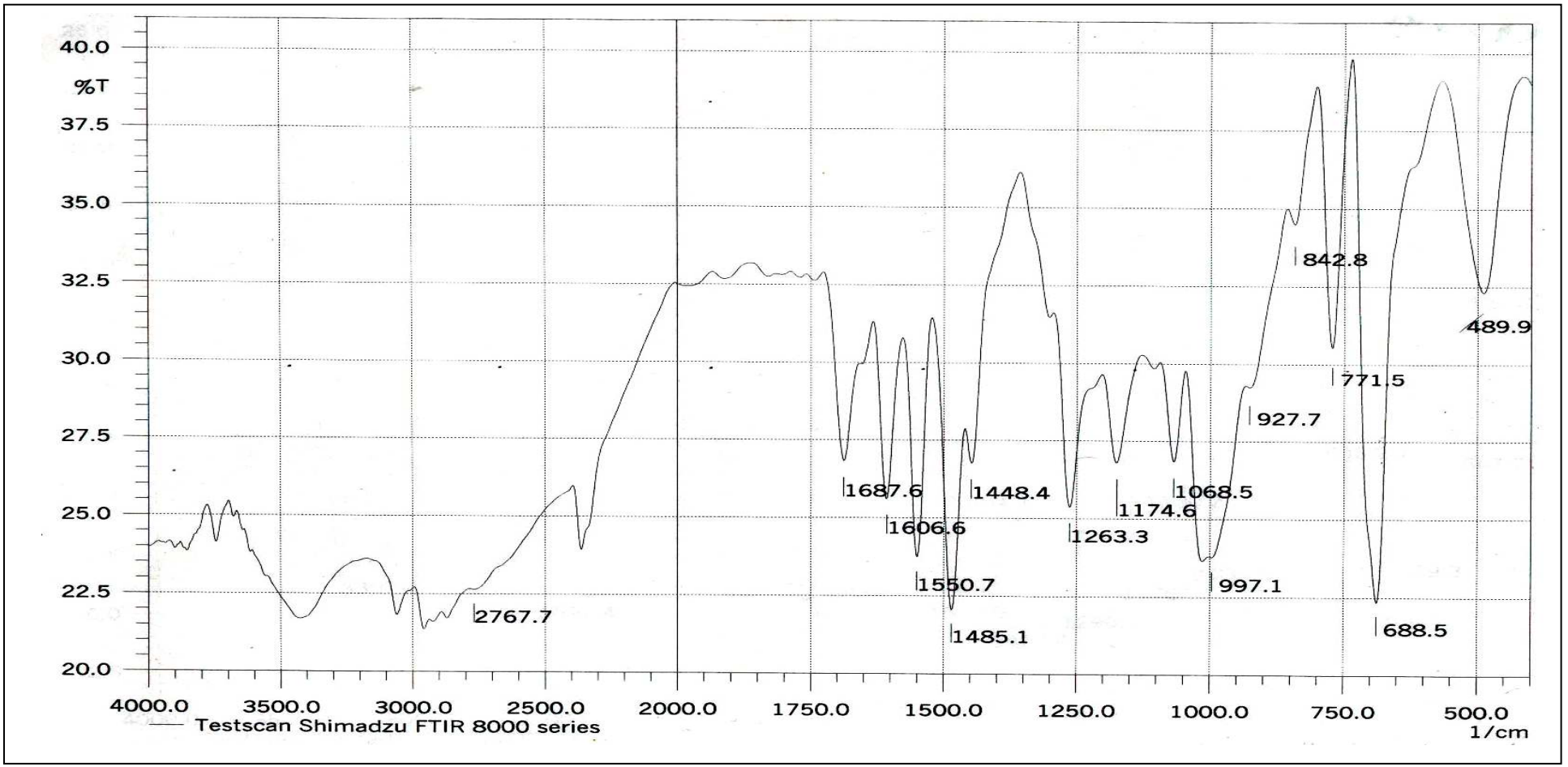
	Melting point (°C)	Characteristic bands (KBr, Cm^{-1})
	**103 - 104**	1. N-H stretch, 3400 2. Amide C=O stretch, 1687.6 3. C=N stretch, 1606.6 4. A symmetric C- 0-C stretch, 1263.3 5. Symmetric C–O-C stretch, 1068.5

Fig.(3.8) FT-IR spectrum of [1-benzamido-1-(5-phenyl-1,3,4-oxadiazole-2yl)-3-methyl]butane [9]



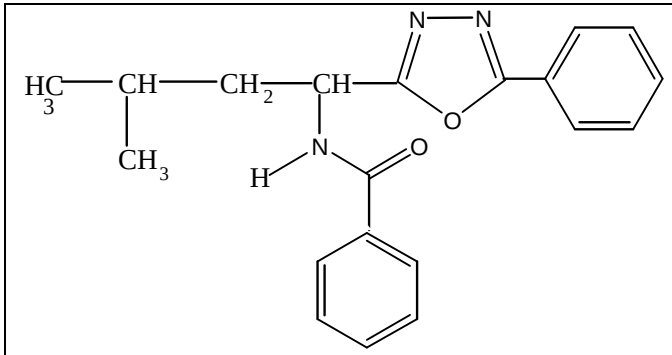
	Melting point (°C)	Characteristic bands (KBr, Cm^{-1})
	**103 - 104**	1. N-H stretch, 3400 2. Amide C=O stretch, 1687.6 3. C=N stretch, 1606.6 4. A symmetric C- 0-C stretch, 1263.3 5. Symmetric C–O-C stretch, 1068.5

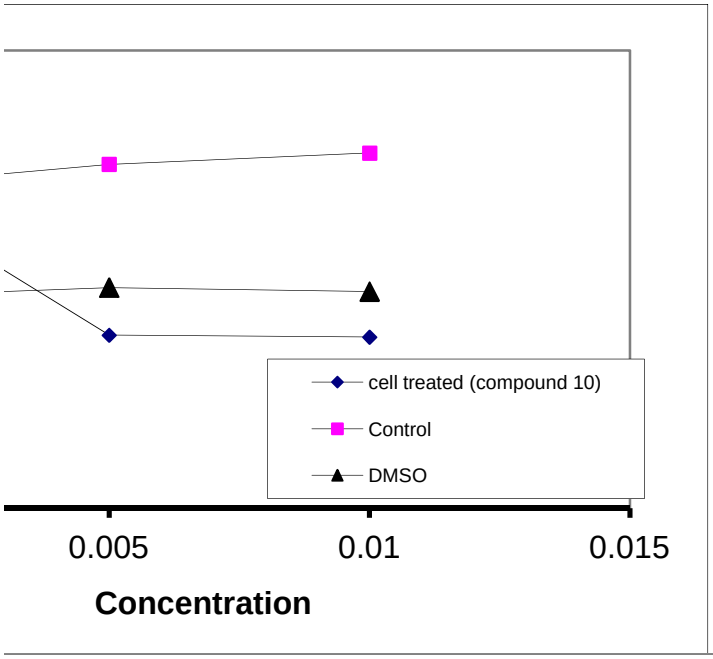
Fig.(3.8) FT-IR spectrum of [1-benzamido-1-(5-phenyl-1,3,4-oxadiazole-2yl)-3-methyl]butane [9]

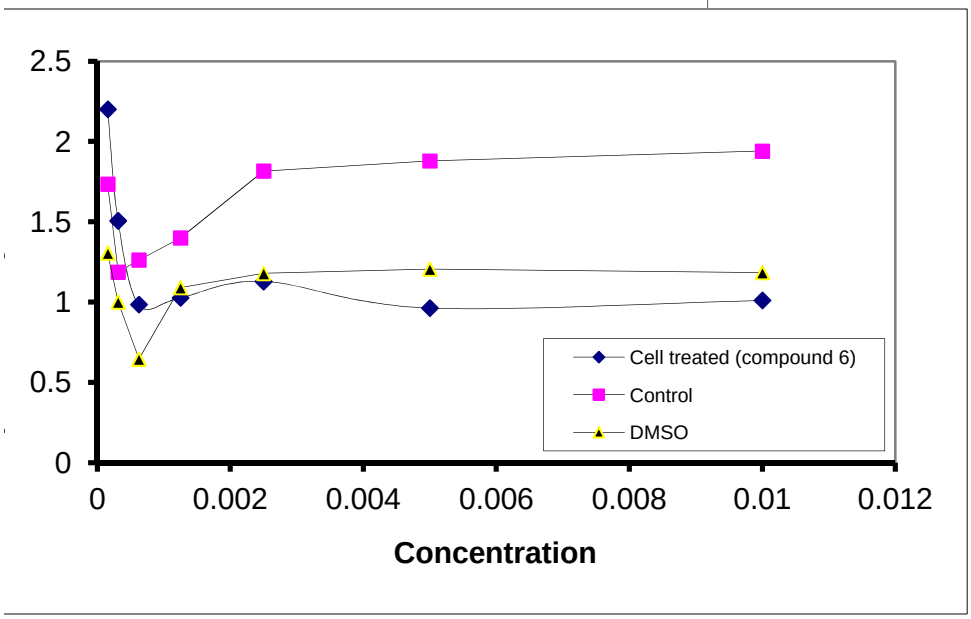
	8			**10**		**11**	
0.9	0.902	1.694	0.885	0.809	2.211	1.09	1.121
0.872	0.883	2.047	1.03	1.017	2.086	1.009	1.077
1.185	1.114	1.892	1.053	0.839	2.179	1.1	1.079
1.87	1.26	2.771	1.426	1.345	2.249	1.117	1.132
1.408	1.777	2.483	1.266	1.217	2.627	1.365	1.262
1.59	1.205	2.657	1.257	1.4	2.592	1.388	1.204
1.911	1.749	2.282	1.512	0.77	2.349	1.231	1.118
2.048	2.181	3.422	1.663	1.759	2.109	1.212	0.897

x	**11**
0.01	
0.005	1.07425
0.0025	1.0895
0.00125	1.1245
0.000625	1.3135
0.000313	1.296
0.000157	1.1745
	1.0545

		6			7	
2.061	0.912	1.149	2.187	1.33	0.857	1.802
1.98	0.916	1.064	2.619	1.22	1.399	1.755
1.926	1.005	0.921	2.079	0.825	1.254	2.299
2.258	1.092	1.166	3.146	2.14	1.006	3.13
2.054	1.125	0.929	2.208	1.016	1.192	3.185
1.969	0.902	1.067	2.49	0.96	1.53	2.795
3.013	1.311	1.702	3.055	1.199	1.856	3.66
4.402	2.455	1.947	4.189	2.09	2.099	4.229

6	7	8	10
1.01025	1.2015	0.88925	0.93525
0.963	1.0395	1.1495	0.946
1.129	1.573	1.565	1.3855
1.027	1.104	1.5925	1.2415
0.9845	1.245	1.3975	1.3285
1.5065	1.5275	1.83	1.141
2.201	2.0945	2.1145	1.711


cell treated (compound 10)
Control
DMSO
0.005
0.01
0.015
Concentration


2.5
2
1.5
1
0.5
0
Cell treated (compound 6)
Control
DMSO
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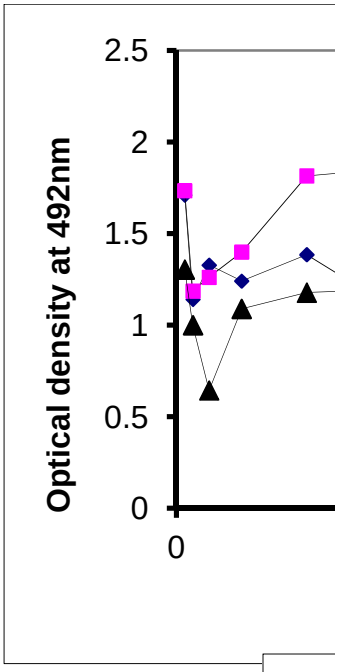
0.002
0.004
0.006
0.008
0.01
0.012
Concentration


Optical density at 492nm
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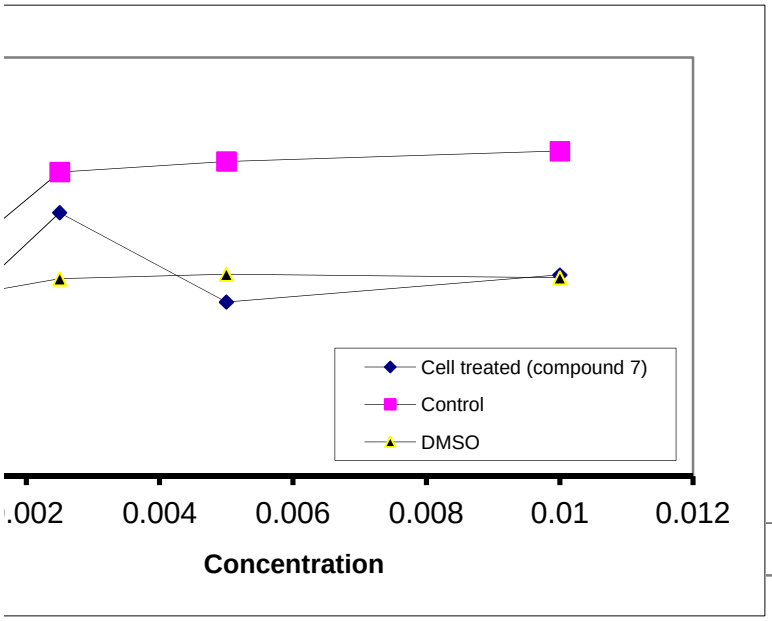
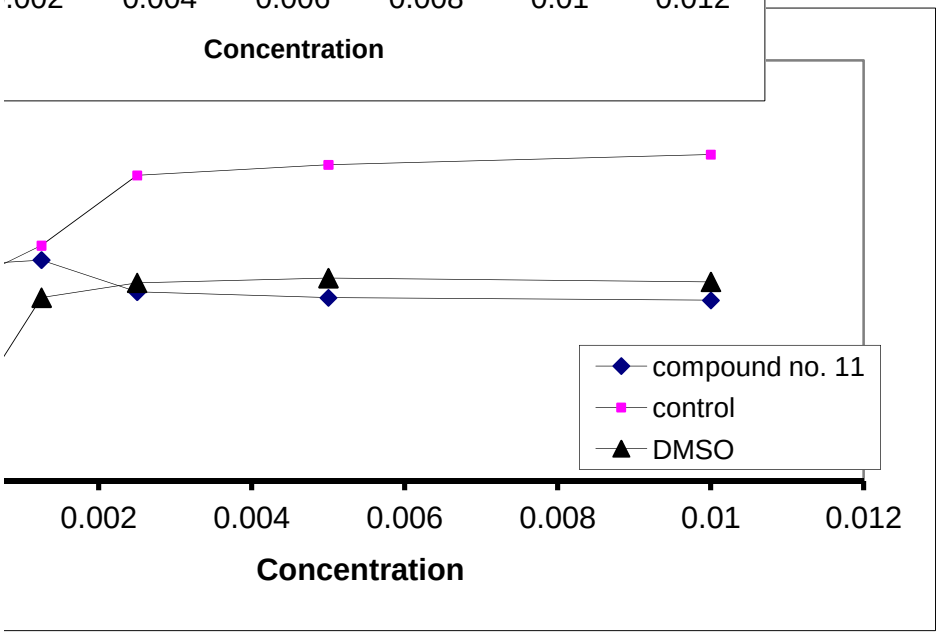
0.5
0
0


Cell treated (compound 7)
Control
DMSO
.002
0.004
0.006
0.008
0.01
0.012
Concentration


compound no. 11
control
DMSO
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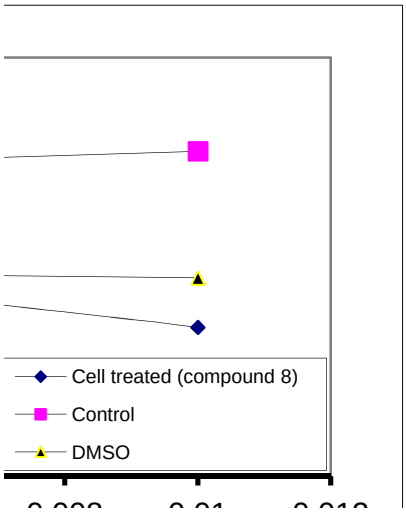
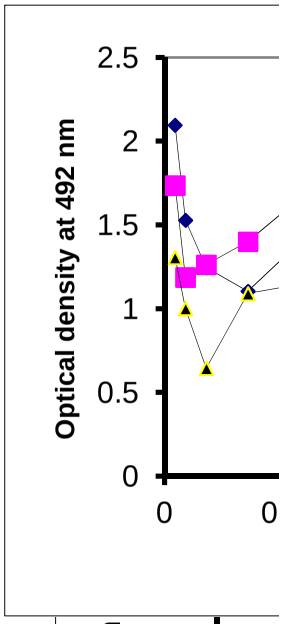
0.004
0.006
0.008
0.01
0.012
Concentration

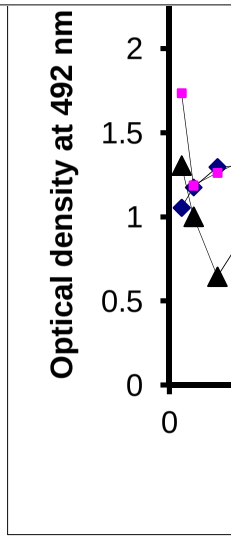

Optical density at 492 nm

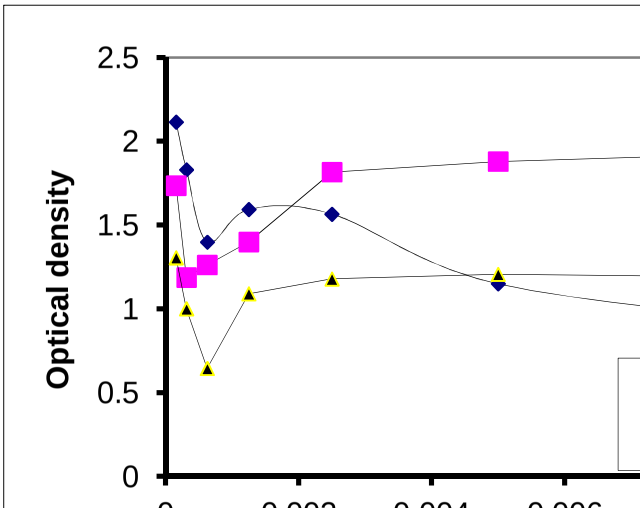

Cell treated (compound 8)
Control
DMSO

0.008	0.01	0.012

on


Optical density at 492 nm
2.5
2
1.5
1
0.5
0
0
0


Optical density at 492 nm
2
1.5
1
0.5
0
0


Optical density
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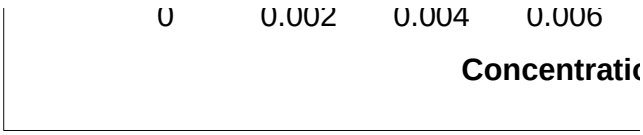
1.5
1
0.5
0


0
0.002
0.004
0.006
Concentrati

2				3				4
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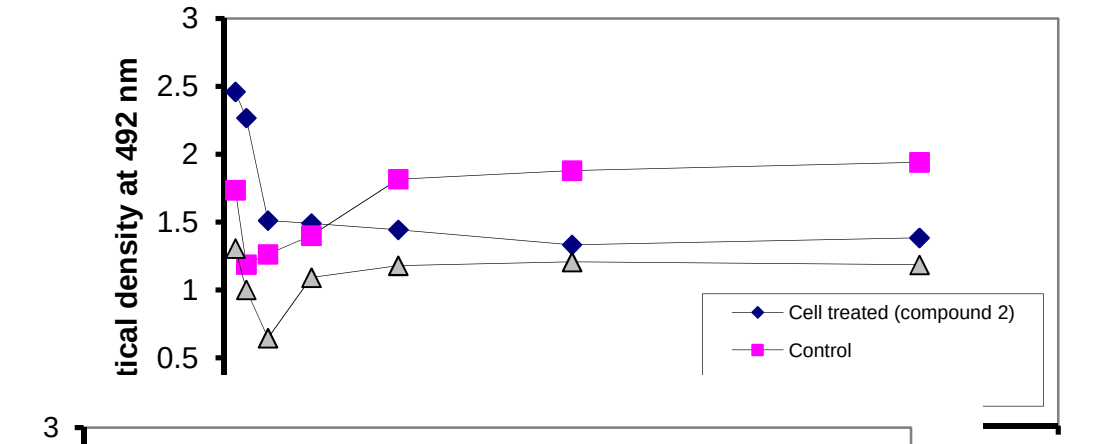
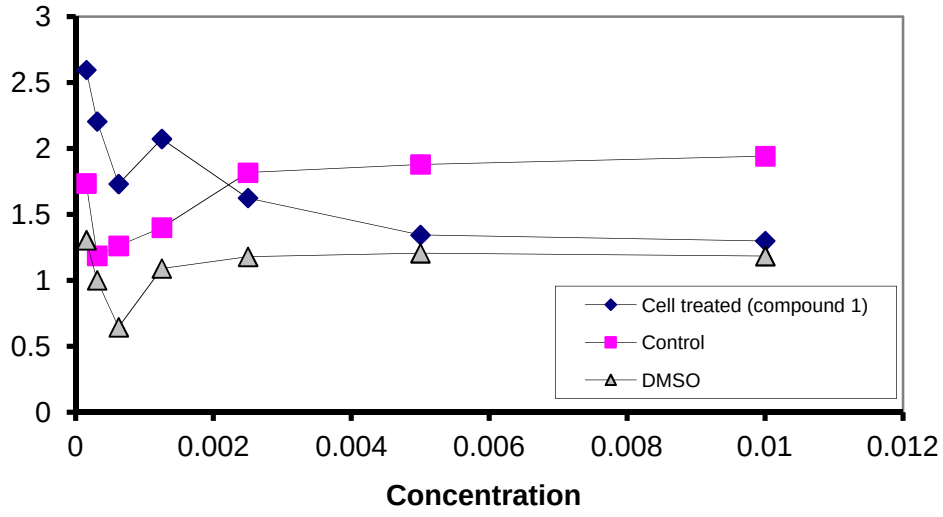
1.219	3.508	1.027	1.383	1.098	3.237	1.005	1.083	1.149
1.346	4.231	1.55	1.216	1.465	4.15	1.248	1.56	1.342
1.577	4.484	1.471	1.361	1.652	5.058	2.091	1.533	1.434
1.694	4.314	1.349	1.609	1.356	5.02	1.477	1.689	1.854
1.138	4.083	1.398	1.215	1.47	4.756	1.361	1.793	1.602
1.99	4.875	1.428	1.872	1.575	4.498	1.291	1.368	1.839
2.208	6.879	2.341	2.203	2.335	5.302	2.41	1.454	1.438

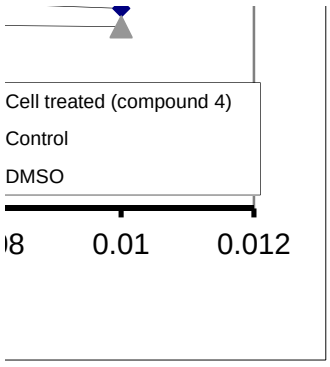
1	2	3	4
1.2985	1.383667	1.334167	1.304
1.343333	1.332333	1.410333	1.383333
1.624	1.443	1.494667	1.686
2.072	1.490333	1.438	1.673333
1.730667	1.510333	1.361	1.585333
2.204333	2.266333	1.625	1.499333
2.595	2.459667	2.293	1.767333

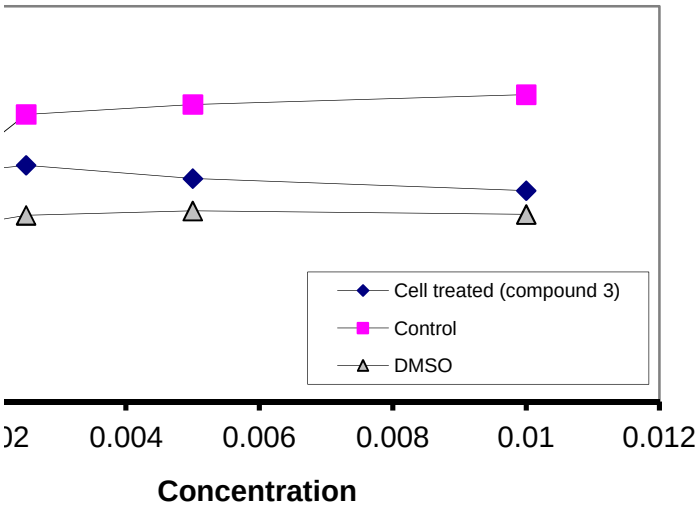
			1			
3.736	1.174	1.353	1.209	4.21	1.309	1.437
4.055	1.257	1.331	1.467	4.092	1.267	1.606
4.03	0.99	1.549	1.491	3.997	1.313	1.338
4.872	1.547	1.632	1.693	4.329	1.38	1.372
6.216	2.175	2.275	1.766	4.471	1.465	1.312
5.192	1.424	1.767	2.001	4.531	1.719	1.674
6.613	2.255	1.727	2.631	6.799	2.451	2.358
7.785	3	2.485	2.3	7.379	2.332	2.839

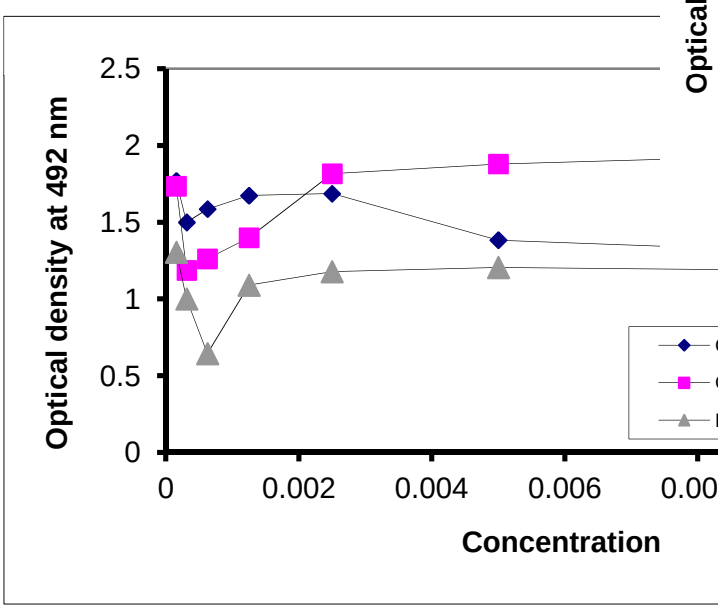
x
0.01
0.005
0.0025
0.00125
0.000625
0.000313
0.000157

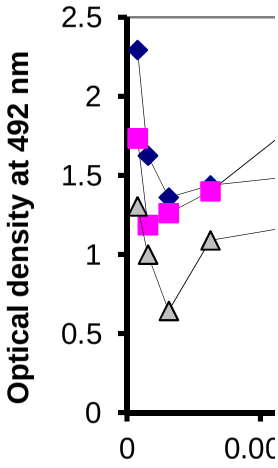

3
2.5
2
1.5
1
0.5
tical density at 492 nm
Cell treated (compound 2)
Control
0.012


3
2.5
2
1.5
1
0.5
0
0
0.002
0.004
0.006
0.008
0.01
0.012
Concentration
Cell treated (compound 1)
Control
DMSO


Cell treated (compound 4)
Control
DMSO
8
0.01
0.012


Cell treated (compound 3)
Control
DMSO
02
0.004
0.006
0.008
0.01
0.012
Concentration

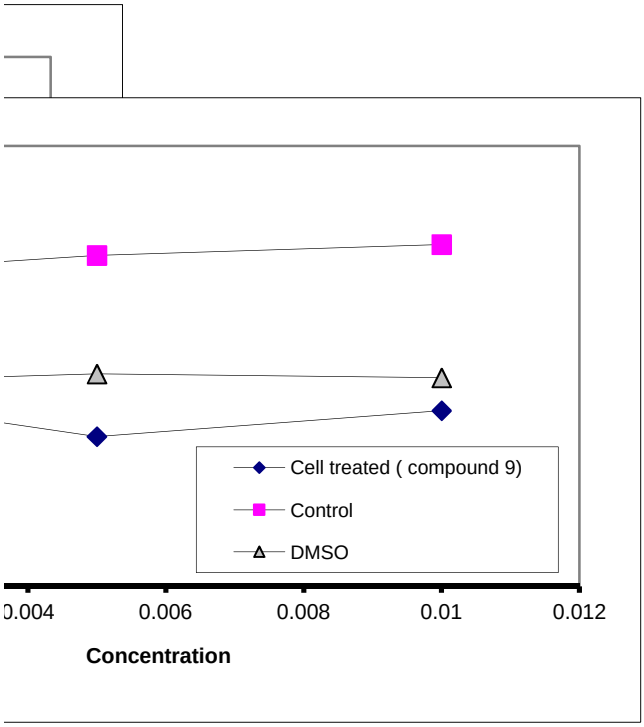

Optical density at 492 nm
2.5
2
1.5
1
0.5
0
0
0.002
0.004
0.006
0.00
Concentration
Optical density at 492 nm

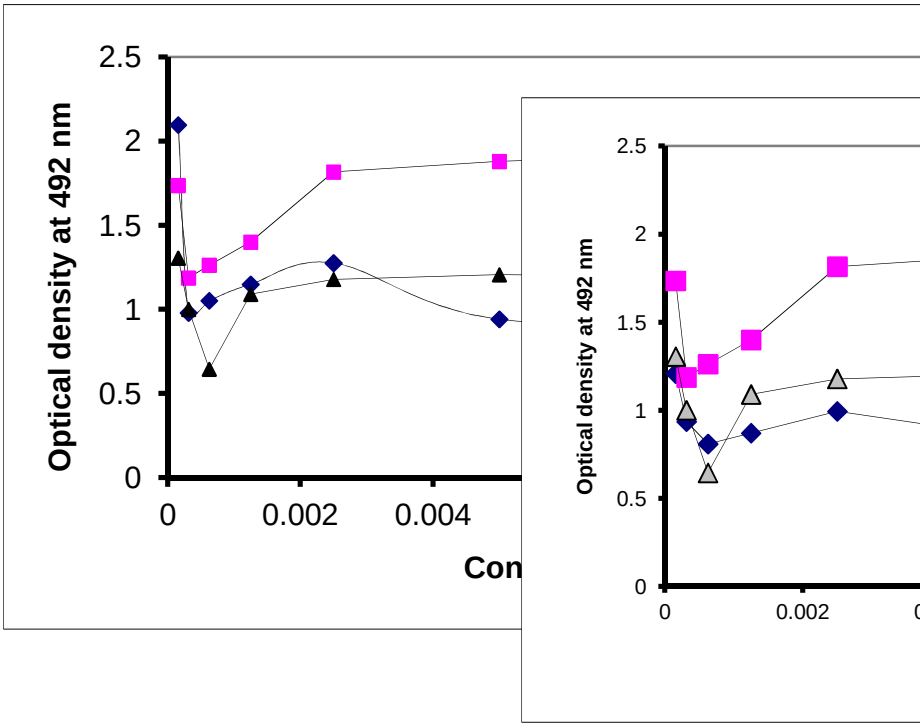

Optical density at 492 nm
2.5
2
1.5
1
0.5
0
0
0.00

		9			dmso			control
1.609	0.829	0.78	2.259	1.214	1.045	4.03	2.015	2.015
2.382	1.159	1.223	2.478	1.188	1.29	3.732	1.81	1.922
1.701	0.84	0.861	2.412	1.124	1.288	3.758	1.651	2.107
1.987	1.026	0.961	2.357	0.991	1.366	3.632	1.683	1.949
1.74	0.9	0.84	2.18	0.718	1.462	2.799	1.57	1.229
1.617	0.92	0.697	1.289	0.573	0.716	2.524	1.147	1.377
1.87	0.866	1.004	2.001	1.058	0.943	2.373	1.227	1.146
2.417	1.205	1.212	2.61	1.33	1.28	3.47	1.771	1.699

	5	9	dmso	control
	0.91475	0.99775	1.18425	1.9405
	0.941	0.8505	1.206	1.879
	1.275	0.9935	1.1785	1.816
	1.1485	0.87	1.09	1.3995
	1.0515	0.8085	0.6445	1.262
	0.9785	0.935	1.0005	1.1865
	2.0955	1.2085	1.305	1.735

		5
1.661	0.88	0.781
1.998	0.99	1.008
1.882	0.823	1.059
2.55	1.121	1.429
2.297	1.04	1.257
2.103	1.137	0.966
1.957	0.957	1
4.191	2.097	2.094


Cell treated (compound 9)
Control
DMSO
0.004
0.006
0.008
0.01
0.012
Concentration


Optical density at 492 nm
2.5
2
1.5
1
0.5
0
0
0.002
0.004
Con
Optical density at 492 nm
2.5
2
1.5
1
0.5
0
0
0.002

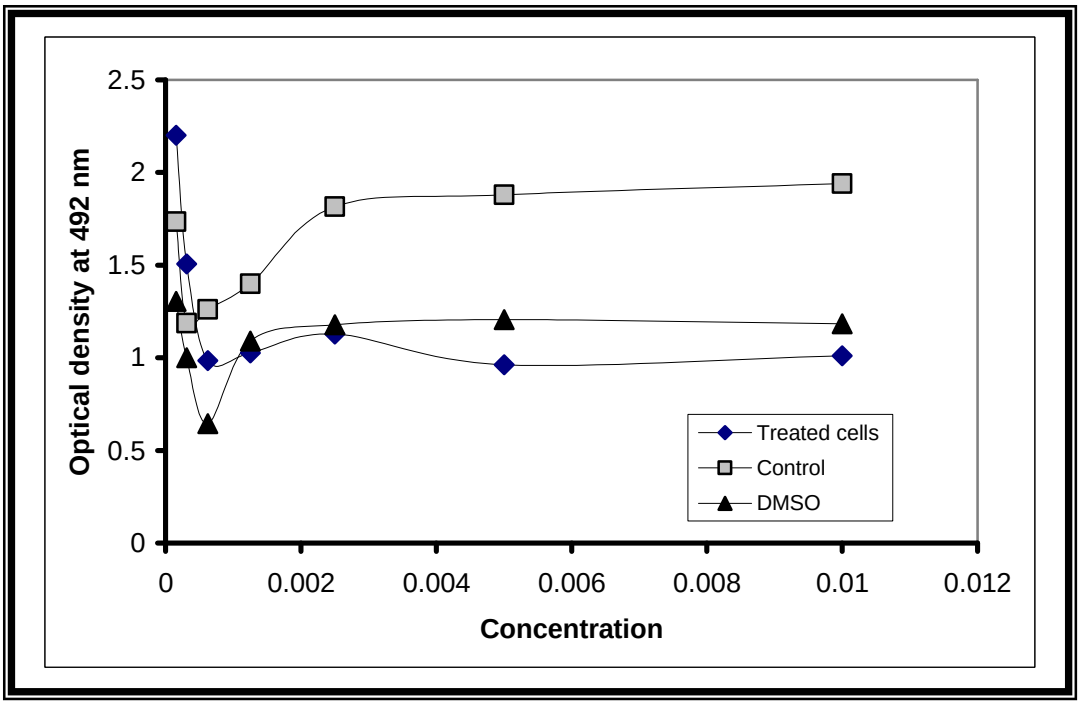


Fig. (3.29) Cytotoxicity effect of compound [١] on the mouse embryo fibroblast after 72hrs. of incubastion

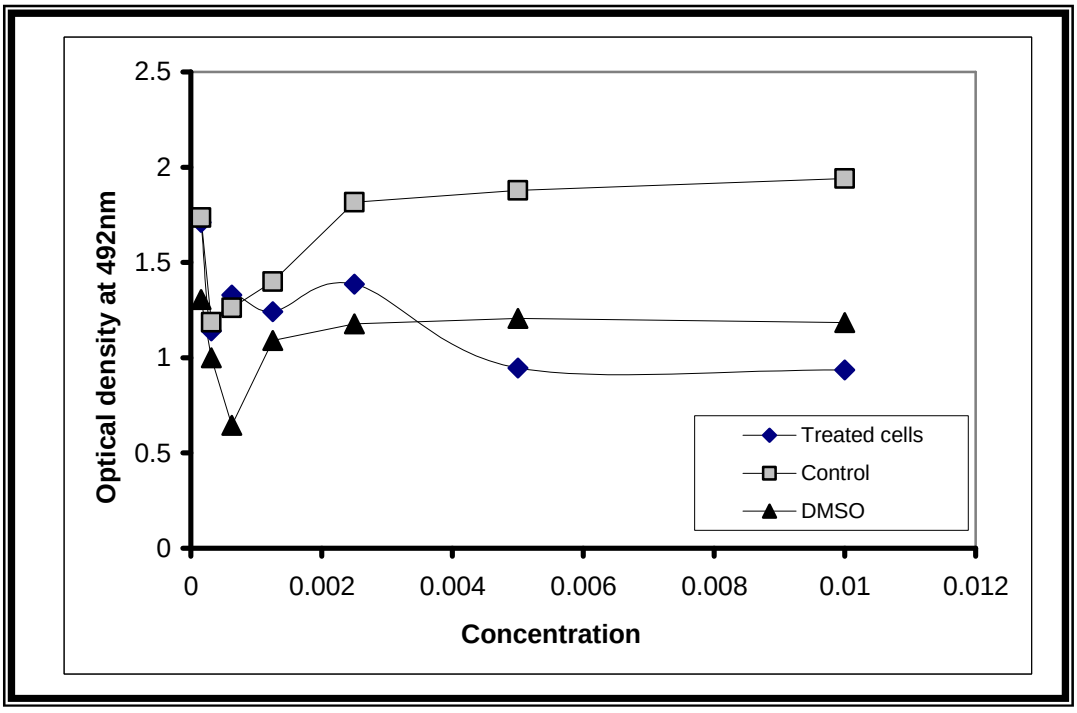


Fig. (3.26) Cytotoxicity effect of compound [٢] on the mouse embryo fibroblast after 72hrs. of incubastion

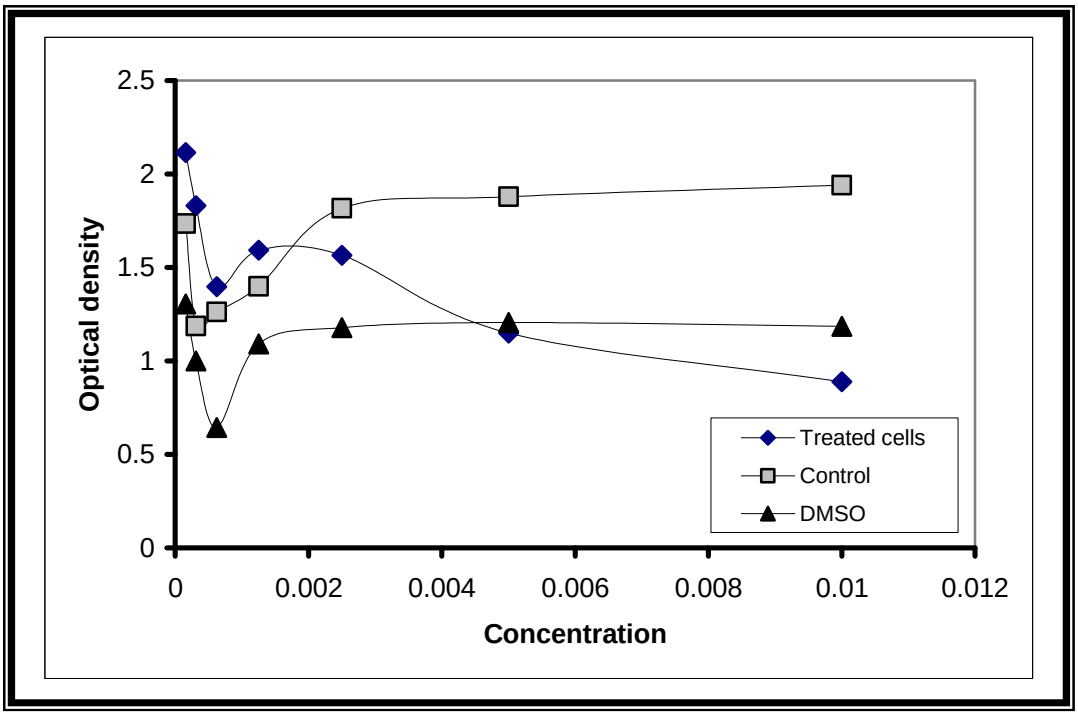


Fig. (3.28) Cytotoxicity effect of compound [٣] on the mouse embryo fibroblast after 72hrs. of incubastion

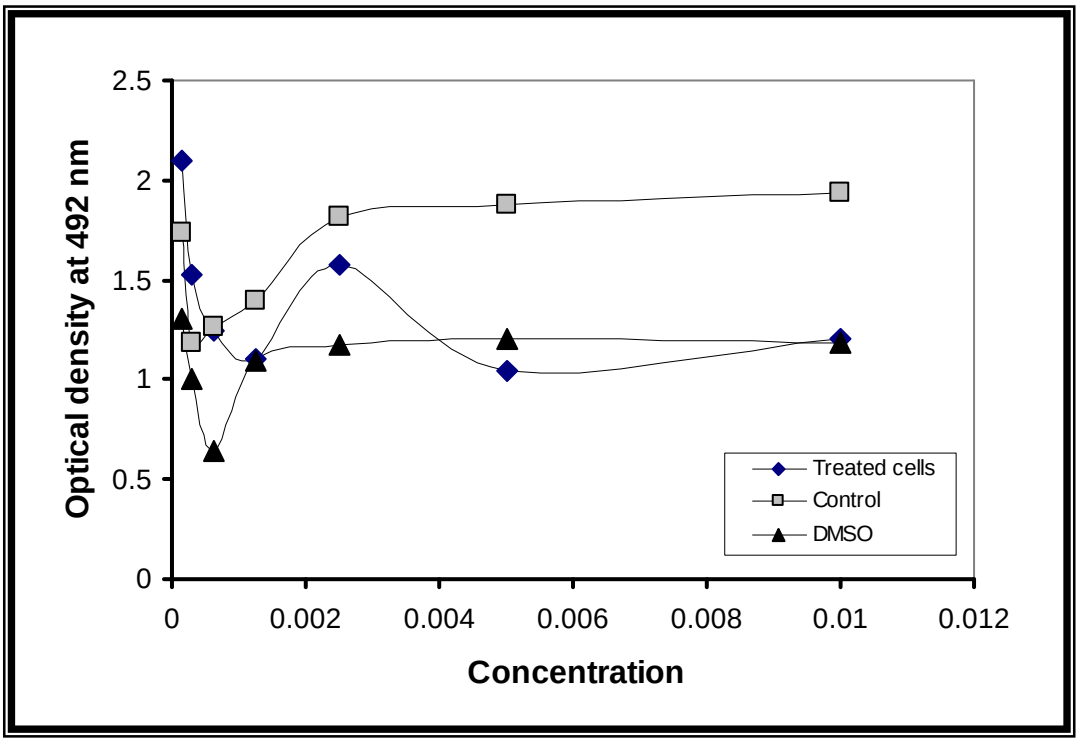


Fig. (3.29) Cytotoxicity effect of compound [٤] on the mouse embryo fibroblast after 72hrs. of incubastion

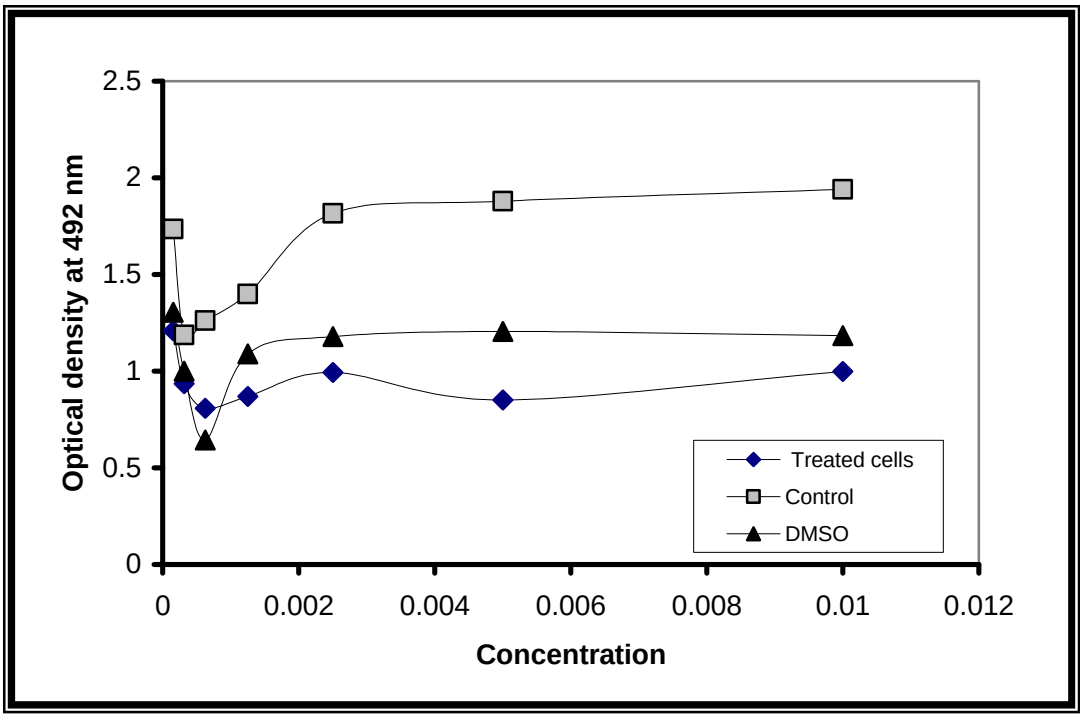


Fig. (3.28) Cytotoxicity effect of compound [٥] on the mouse embryo fibroblast after 72hrs. of incubation

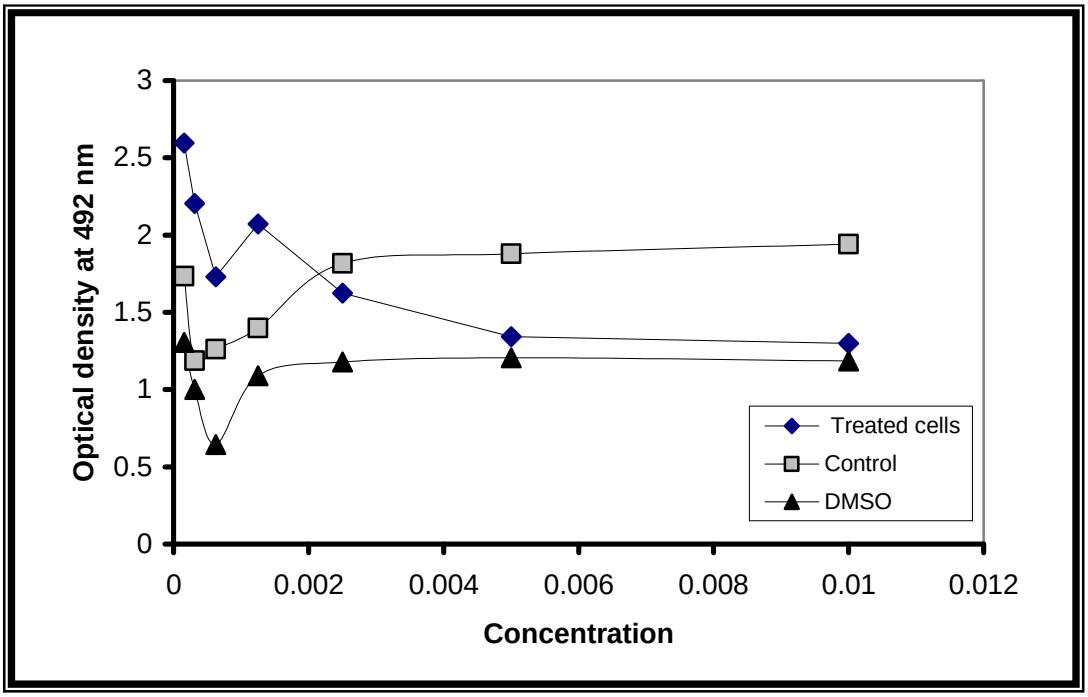


Fig. (3.34) Cytotoxicity effect of compound [٦] on the mouse embryo fibroblast after 72hrs. of incubation

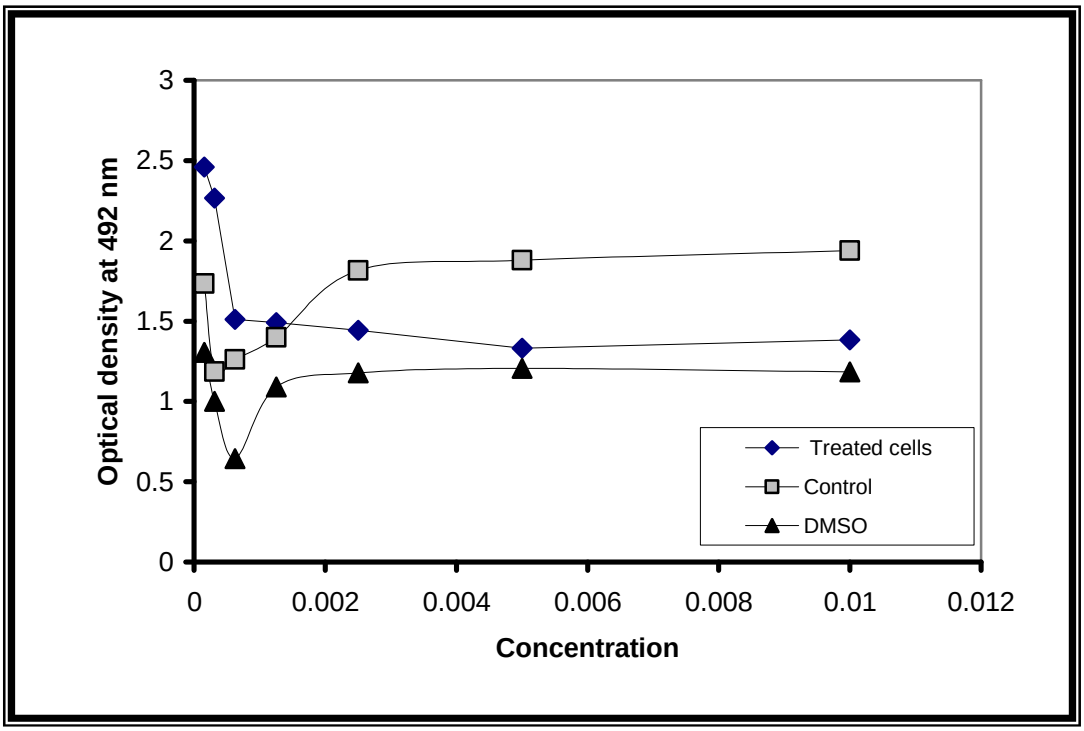


Fig. (3.27) Cytotoxicity effect of compound [ν] on the mouse embryo fibroblast after 72hrs. of incubation

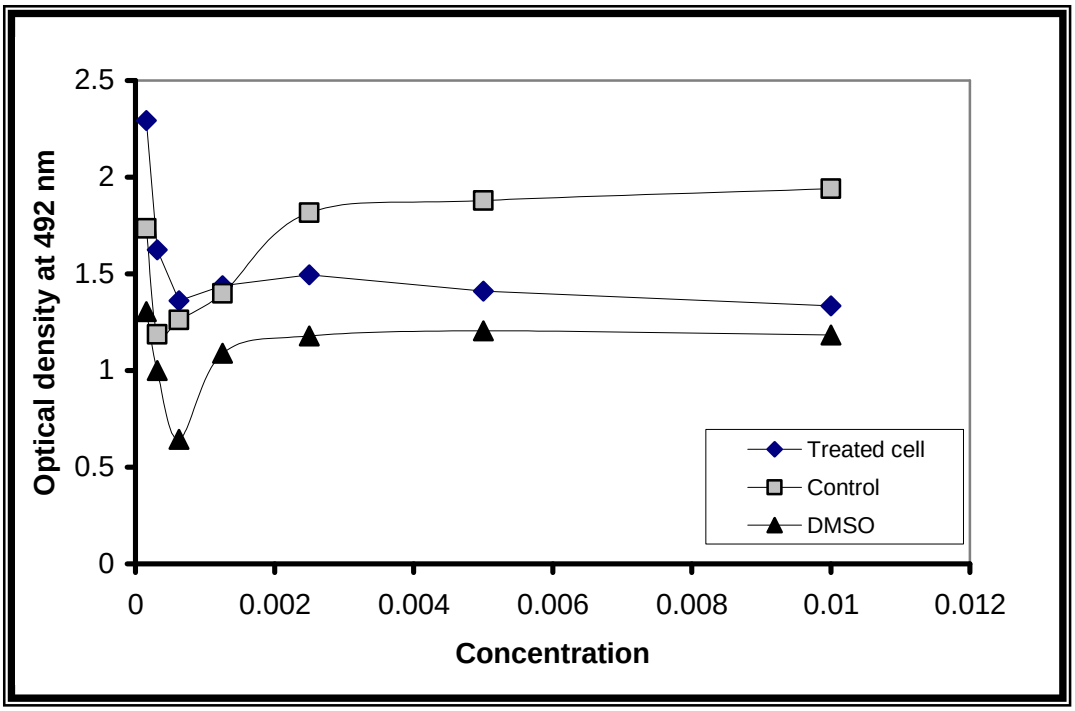


Fig. (3.32)Cytotoxicity effect of compound [ʌ] on the mouse embryo fibroblast after 72hrs. of incubation

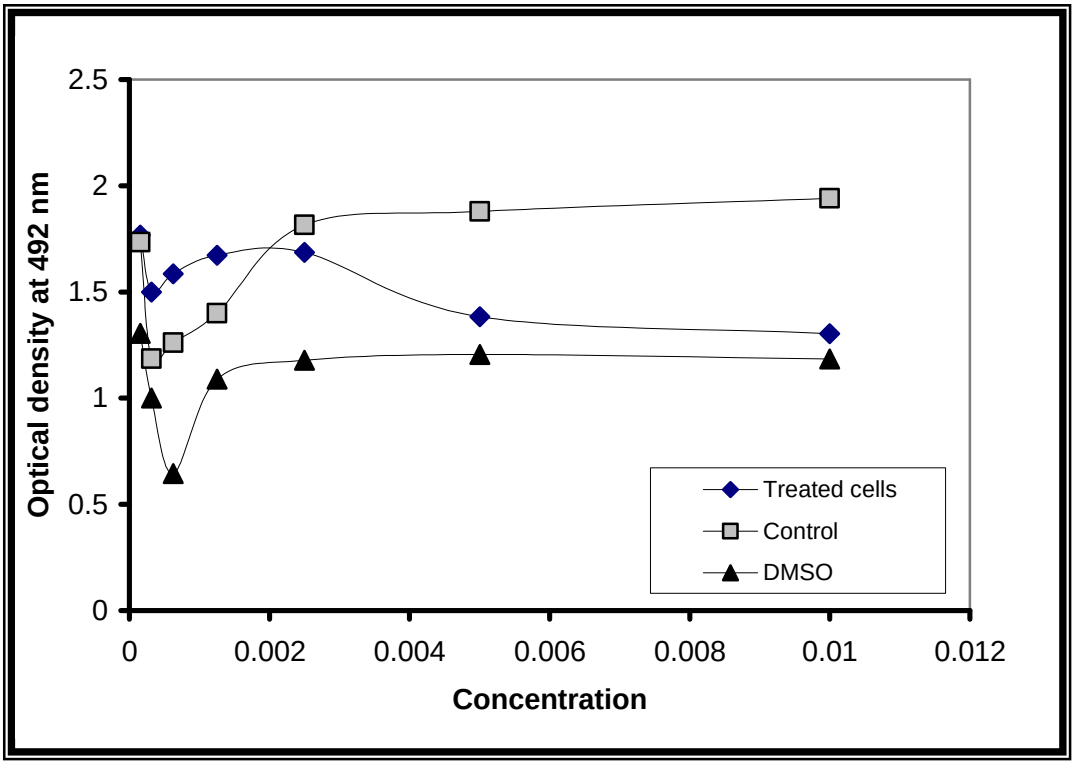


Fig. (3.31)Cytotoxicity effect of compound [٩] on the mouse embryo fibroblast after 72hrs. of incubation

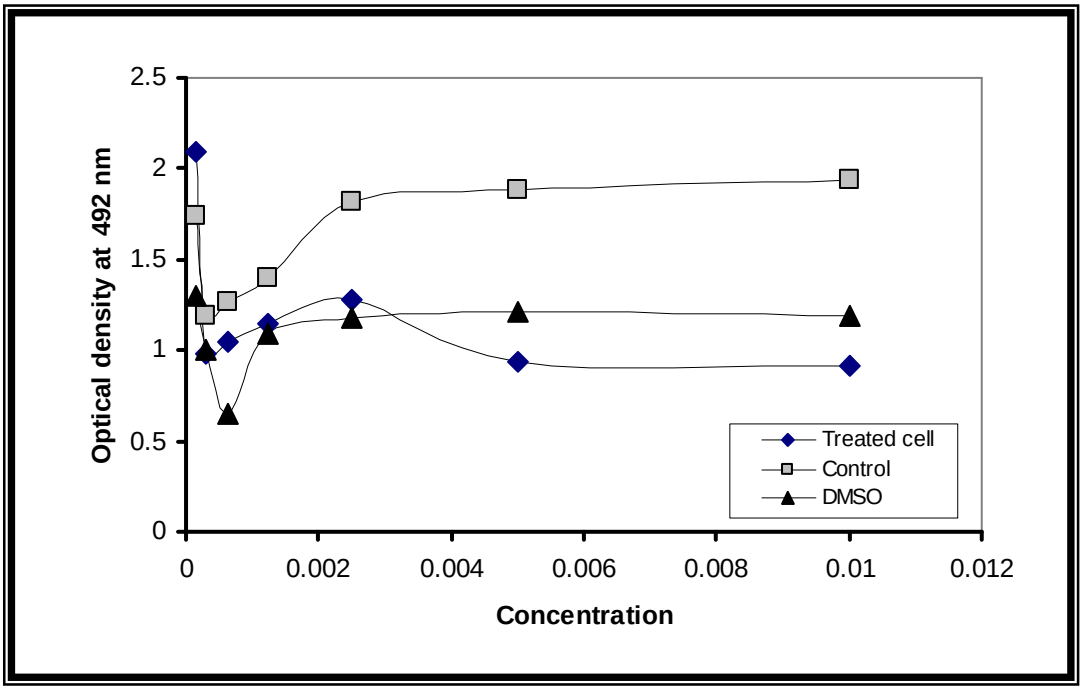
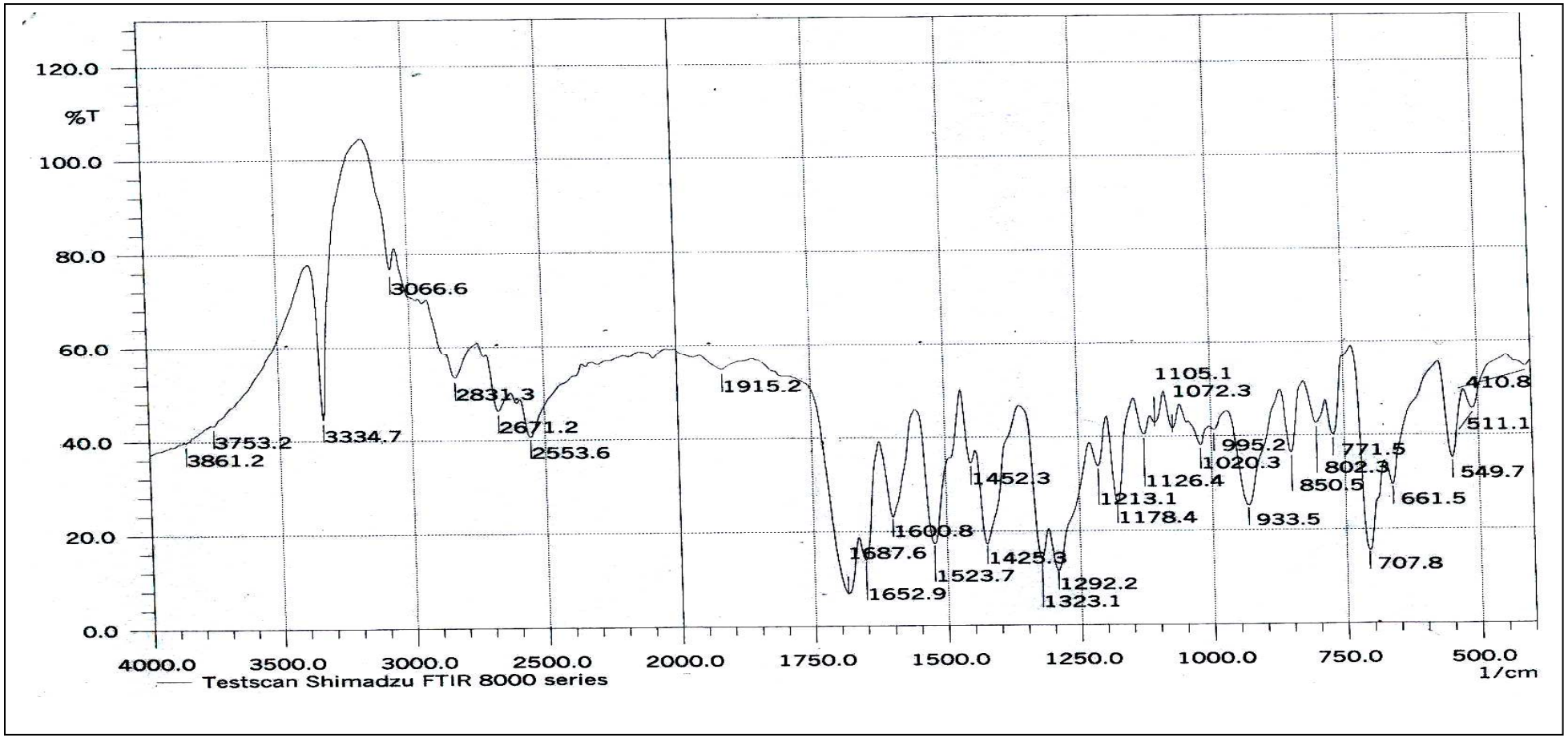


Fig. (3.30) Cytotoxicity effect of compound [١٠] on the mouse embryo fibroblast after 72hrs. of incubation



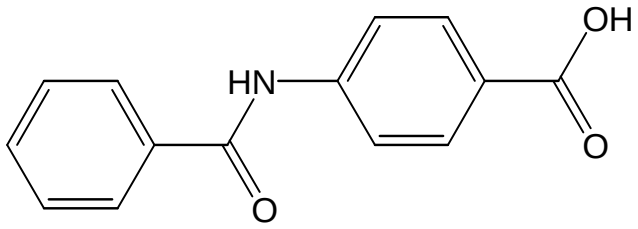
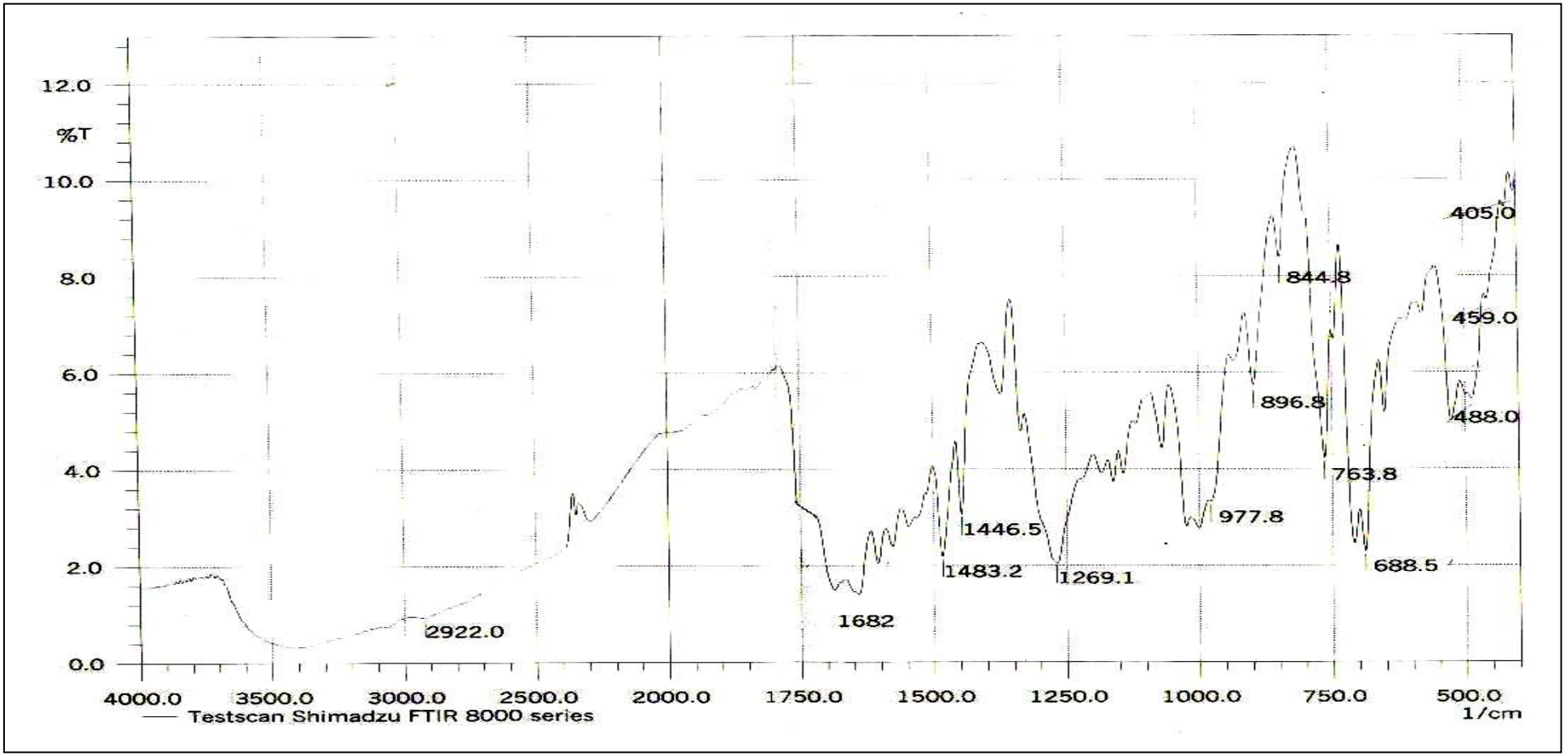
	Melting point (°C)	Characteristic bands (KBr, Cm^{-1})
	**278-279**	1. N-H stretch, 3334.7 2. Amide C=O stretch, 1652.9 3. Carboxylic C=O stretch, 1687.6 4. C – H out of plane bending, 850

Figure (٣،١) FT-IR spectrum of *P*- benzamido benzoic acid [1]



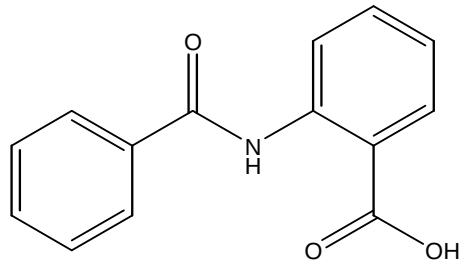
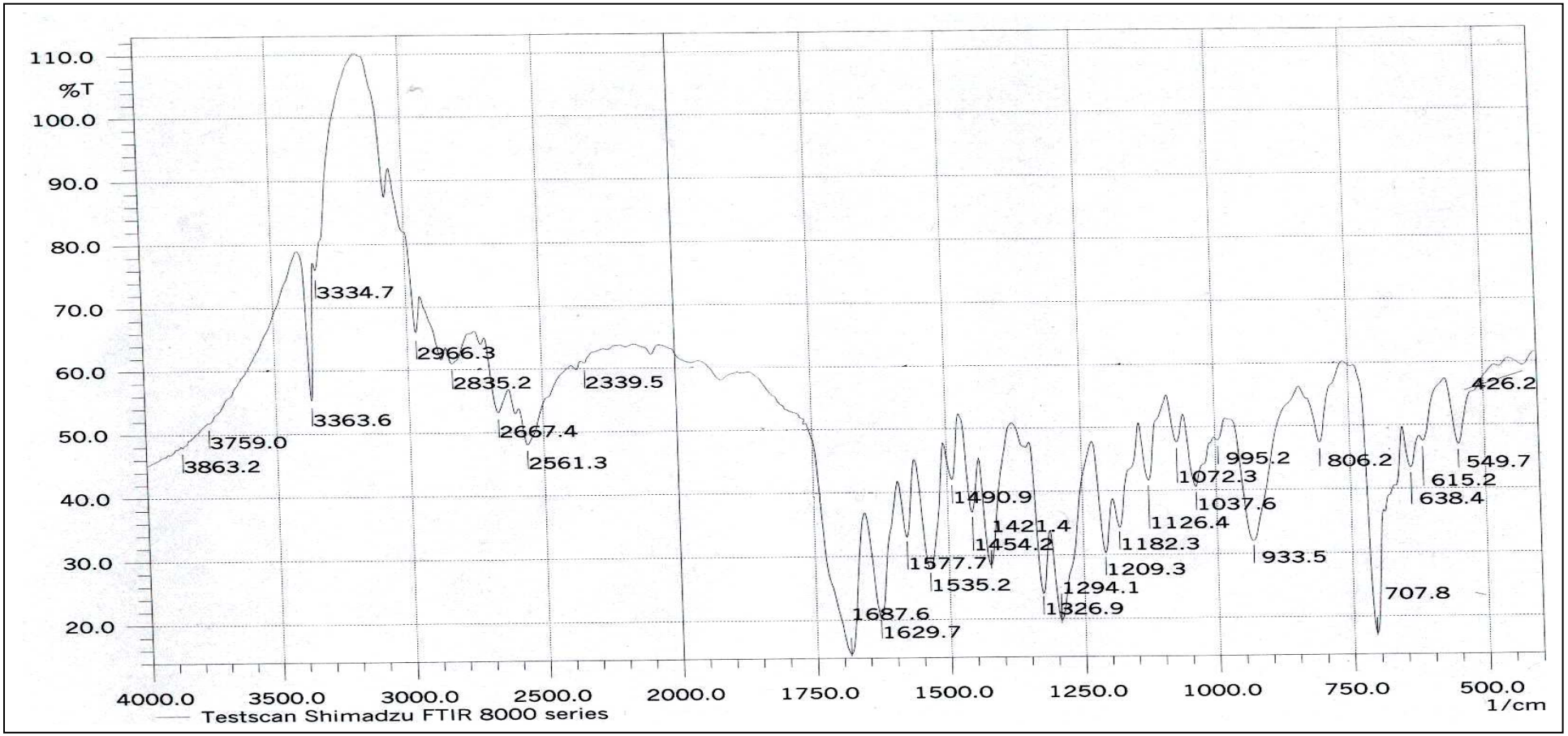
	Melting point (°C)	Characteristic bands (KBr, Cm^{-1})
	**122 - 124**	1. N-H stretch, 3410 2. Amide C=O stretch, 1612.3 3. Carboxylic C=O stretch, 1682.0

Figure (3.3) FT-IR spectrum of *O*-benzamido benzoic acid [2]



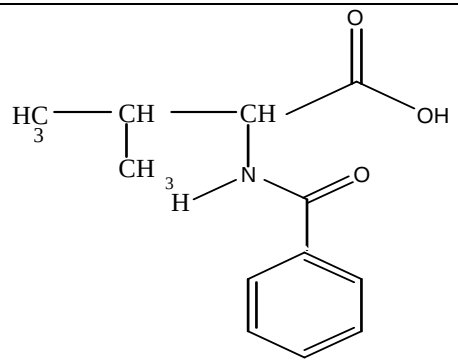
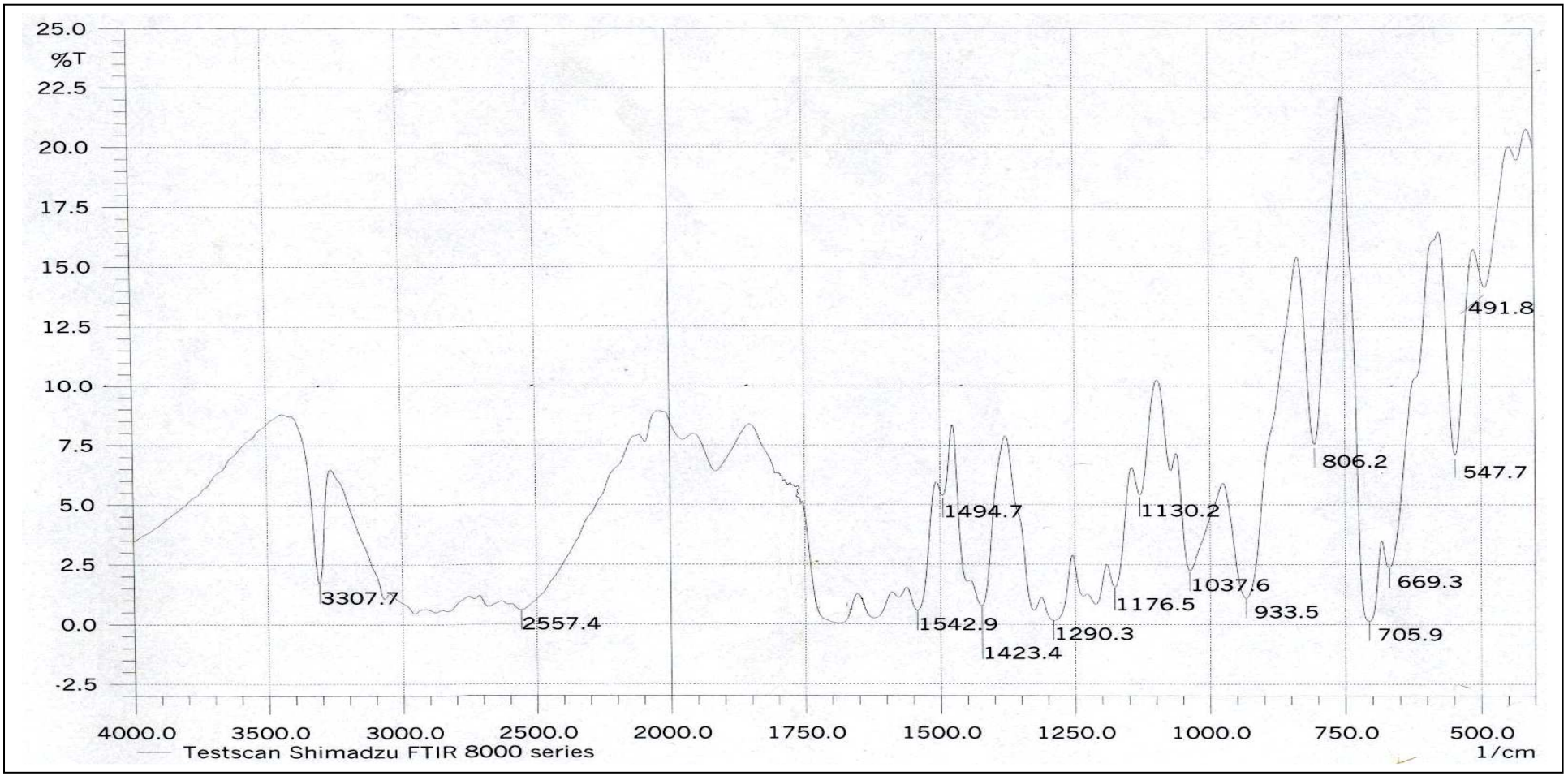
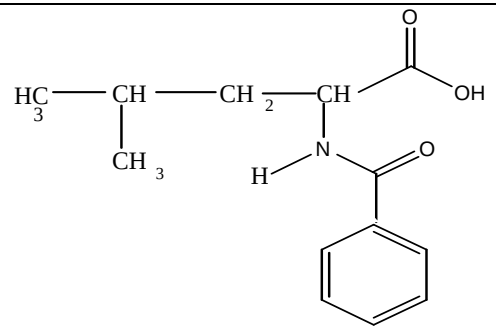
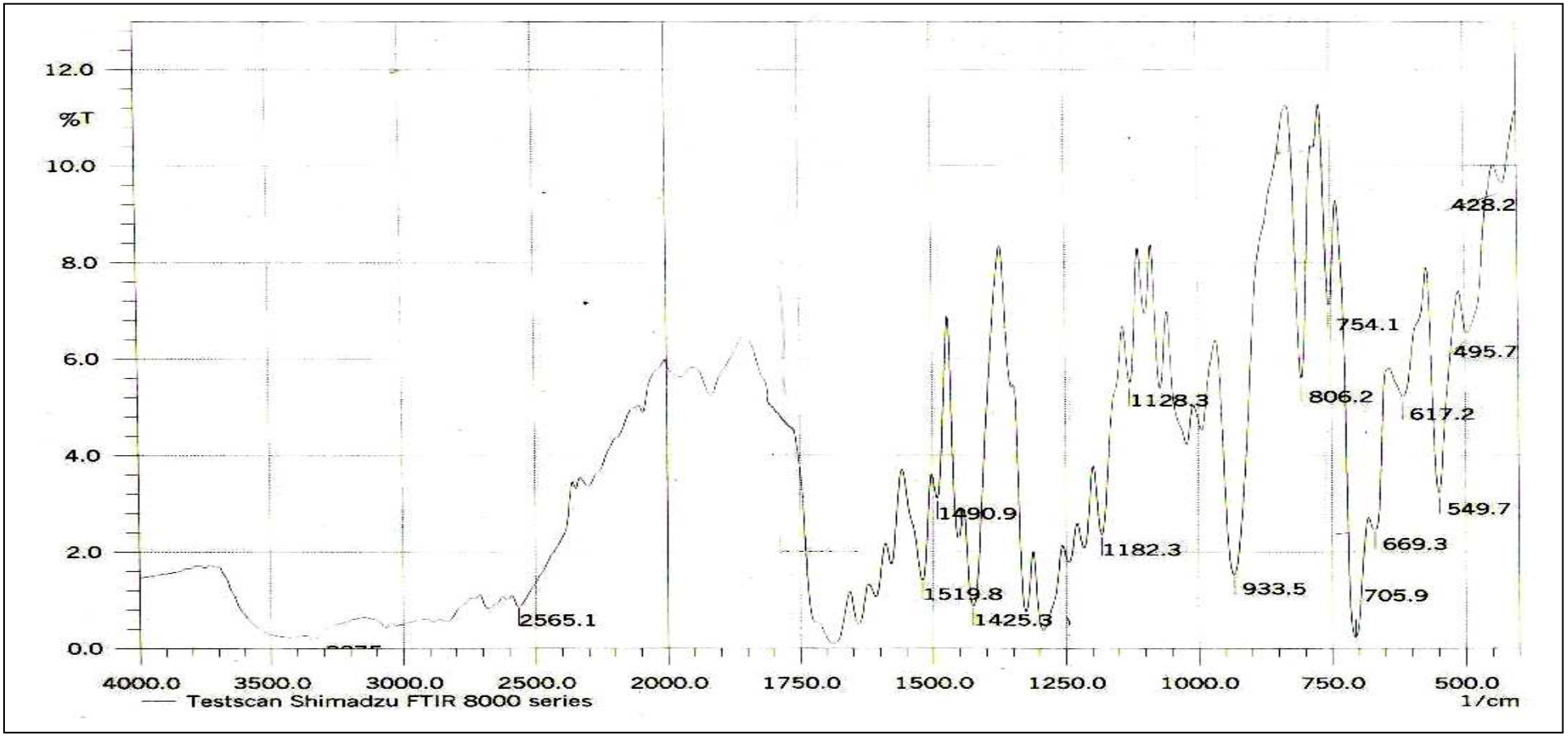
	Melting point (°C)	Characteristic bands (KBr, Cm^{-1})
	**266 – 268**	1. N-H stretch, 3363.6 2. Amide C=O stretch, 1629.7 3. Carboxylic C=O stretch, 1687.6 4. Asym. C-H stretch, 2966.3 5. Sym. C-H stretch, 2835.2

Figure (3.5) FT-IR spectrum of 2-benzamido-3-methyl-butanoic acid [3]



	Melting point (°C)	Characteristic bands (KBr, Cm^{-1})
	**94- 97**	1. N-H stretch, 3307.7 2. Amide C=O stretch, 1690 3. Carboxylic C=O stretch, 1640

Figure(3.7) FT-IR spectrum of 2-benzamido-4-methyl-pentanoic acid [4]



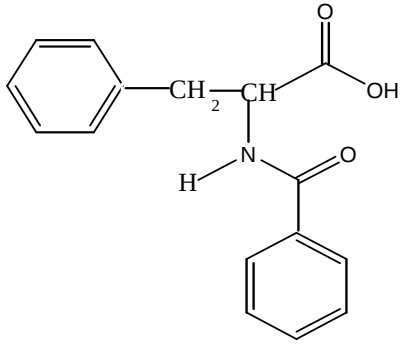
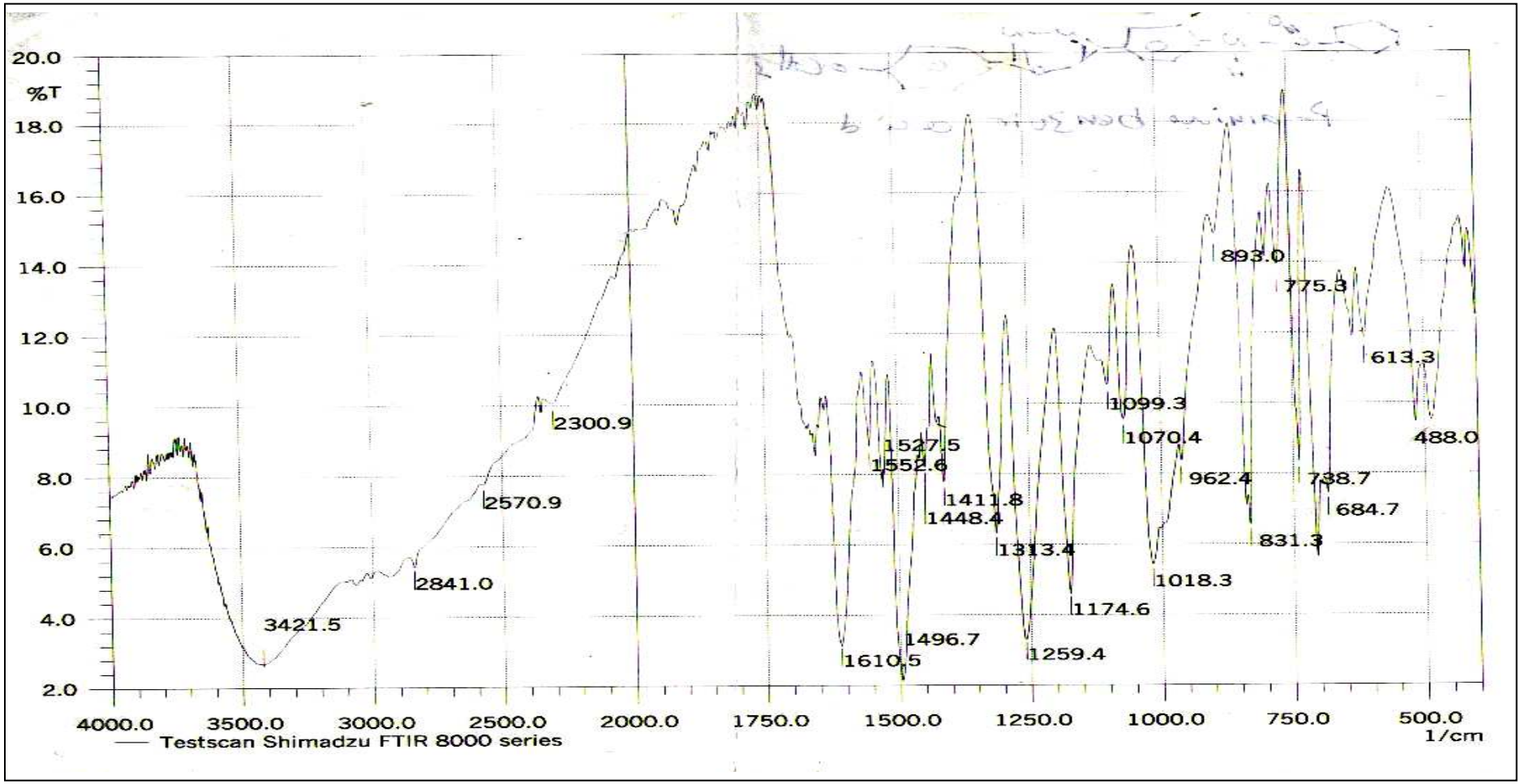
	Melting point (°C)	Characteristic bands (KBr, Cm^{-1})
	**260 – 262**	1. N-H stretch, 3375 2. Amide C=O stretch, 1640 3. Carboxylic C=O stretch, 1680

Figure (3.9) FT-IR spectrum of 2-benzamido-3-phenyl-propanoic acid [5]



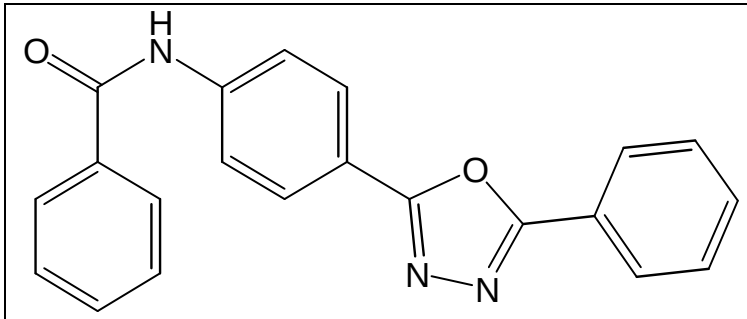
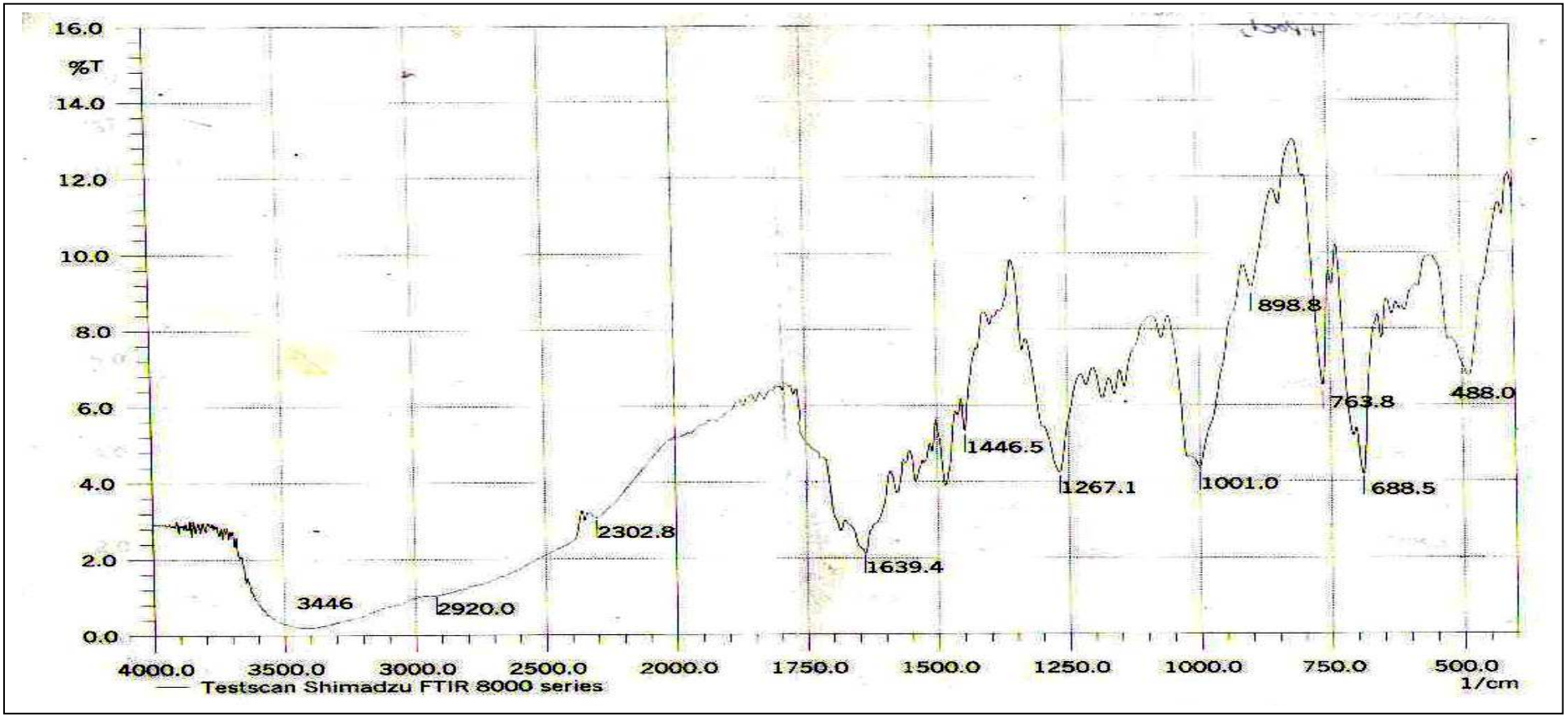
	Melting point (°C)	Characteristic bands (KBr, Cm^{-1})
	**259 - 260**	1. N-H stretch, 3421.5 2. Amide C=O stretch, 1640.5 3. C=N stretch, 1610.5 4. Asymmetric C-O-C stretch, 1259.4 5. Symmetric C-O-C stretch, 1070.4

Figure (3.2) FT-IR spectrum of 2-phenyl-5-[4-(benzamido)-phenyl]-1,3,4 -oxadiazole [6]



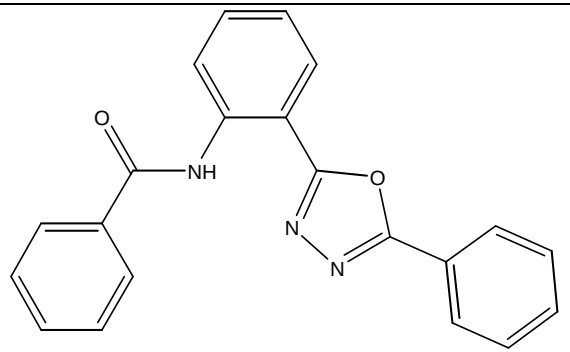
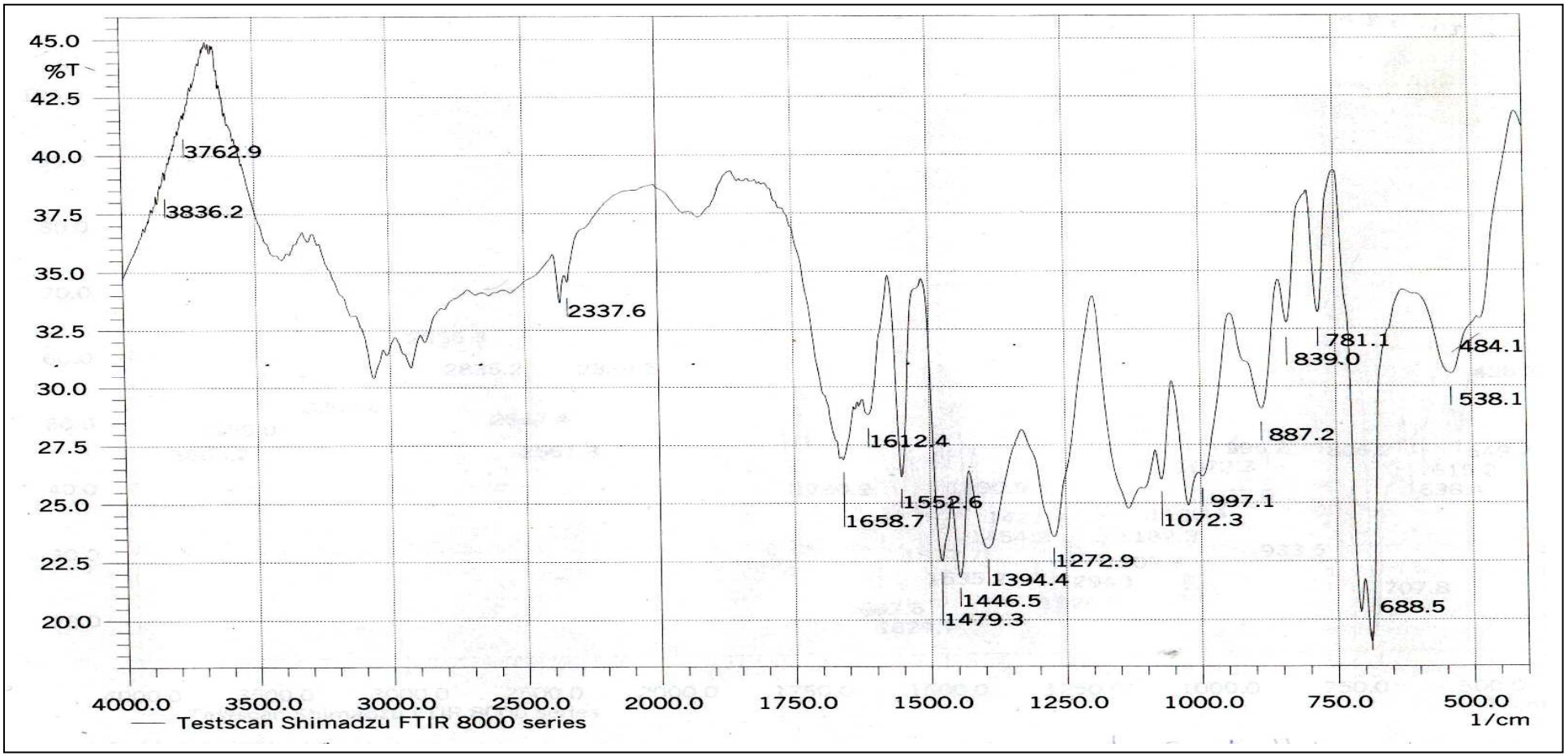
	Melting point (°C)	Characteristic bands (KBr, Cm^{-1})
	**275 - 277**	1. N-H stretch, 3446.0 2. Amide C=O stretch, 1677.7 3. C=N stretch, 1639.4 4. Asymmetric C-O-C stretch, 1267.1 5. Symmetric C-O-C stretch, 1001.0

Figure (3.4) FT-IR spectrum of 2-phenyl-5-[2-(benzamido)-phenyl]-1,3,4 - oxadiazole [7]



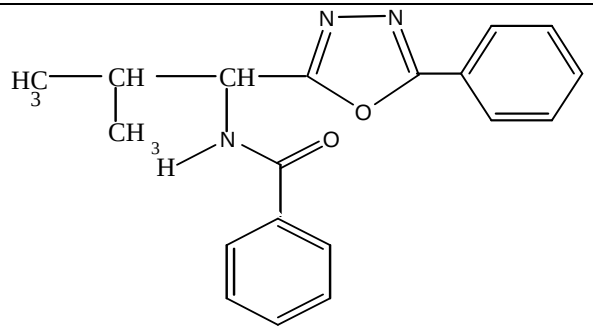
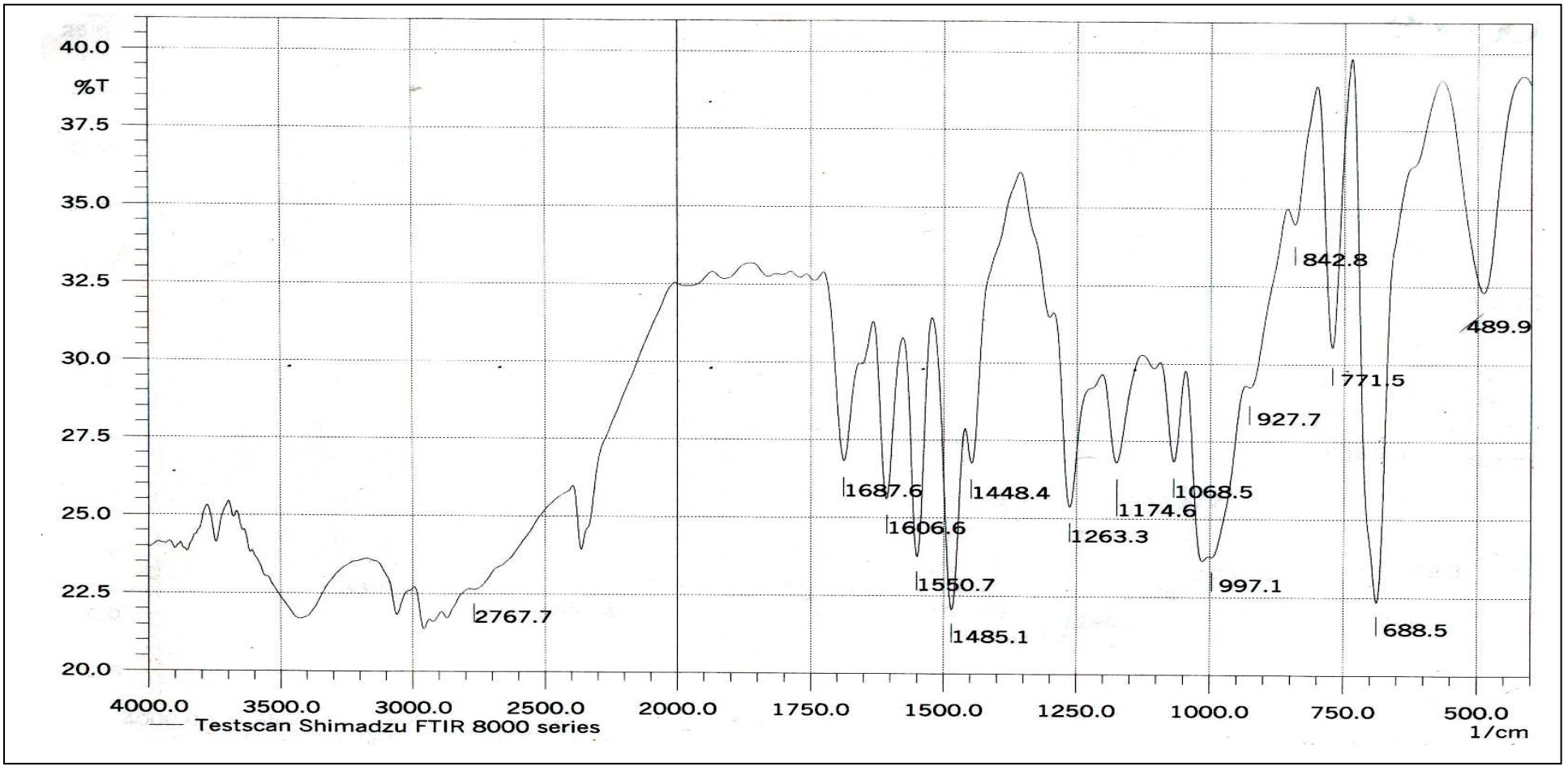
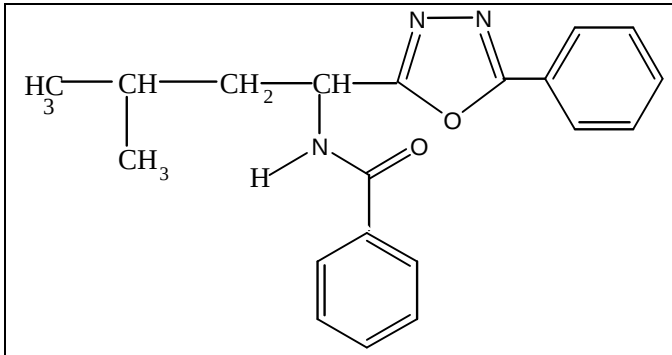
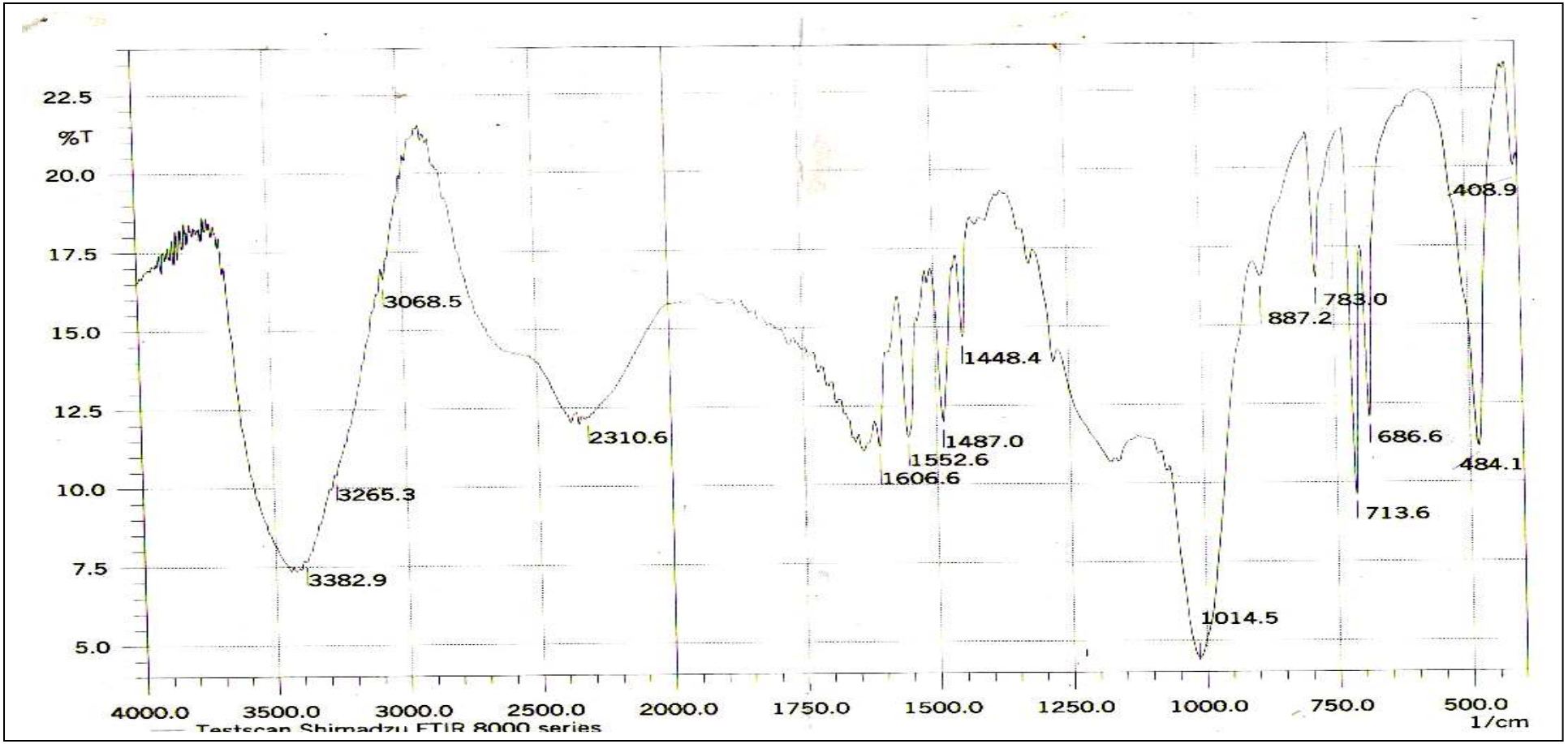
	Melting point (°C)	Characteristic bands (KBr, Cm^{-1})
	**109 - 111**	1. N-H stretch, 3380 2. Amide C=O stretch, 1658.7 3. C=N stretch,1612.4 4. A symmetric C-O-C stretch, 1272.9 5. Symmetric C-O-C stretch, 1072.3 6. A sym. C-H stretch, 2990 7. Sym. C-H stretch, 2830

Figure (3.6) FT-IR spectrum of [1-benzamido-1-(5-phenyl-1,3,4 -oxadiazole-2yl)-2methyl] propane [8]



	Melting point (°C)	Characteristic bands (KBr, Cm^{-1})
	**103 - 104**	1. N-H stretch, 3400 2. Amide C=O stretch, 1687.6 3. C=N stretch, 1606.6 4. A symmetric C- 0-C stretch, 1263.3 5. Symmetric C–O-C stretch, 1068.5

Figure(3.8) FT-IR spectrum of [1-benzamido-1-(5-phenyl-1,3,4-oxadiazole-2yl)-3-methyl]butane [9]



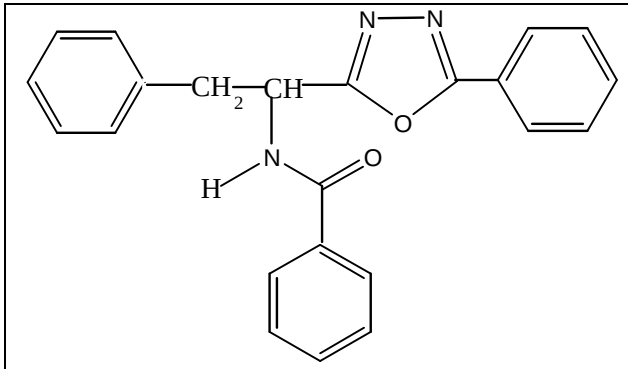
	Melting point (°C)	Characteristic bands (KBr, Cm^{-1})
	**106- 108**	1. N-H stretch, 3382.9 2. Amide C=O stretch, 1689.1 3. C=N stretch, 1606.6 4. Asymmetric C–O–C stretch, 1293.2 5. Symmetric C–O–C stretch, 1014.5

Figure (3.10) FT-IR spectrum of [1-benzamido-1-(5-phenyl-1,3,4-oxadiazole-2yl)-2phenyl]-ethan [10]