"SYNTHESIS AND EVALUATION OF SOME NOVEL ISOXAZOLES FOR PHARMACOLOGICAL ACTIVITY"

By

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Rajiv Gandhi University of Health Sciences, Karnataka, Bangalore

In partial fulfillment of the requirements for the

MASTER OF PHARMACY

In

PHARMACEUTICAL CHEMISTRY

Under the guidance of,

Dr. B. RAMESH

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I hereby declare that this dissertation entitled **"SYNTHESIS AND EVALUATION OF SOME NOVEL ISOXAZOLES FOR PHARMACOLOGICAL ACTIVITY"** is a bonafied and genuine research work carried out by me under the guidance of **Dr. B.RAMESH.**, Professor, Department of Pharmaceutical Chemistry, SAC College of Pharmacy. B.G. Nagara.

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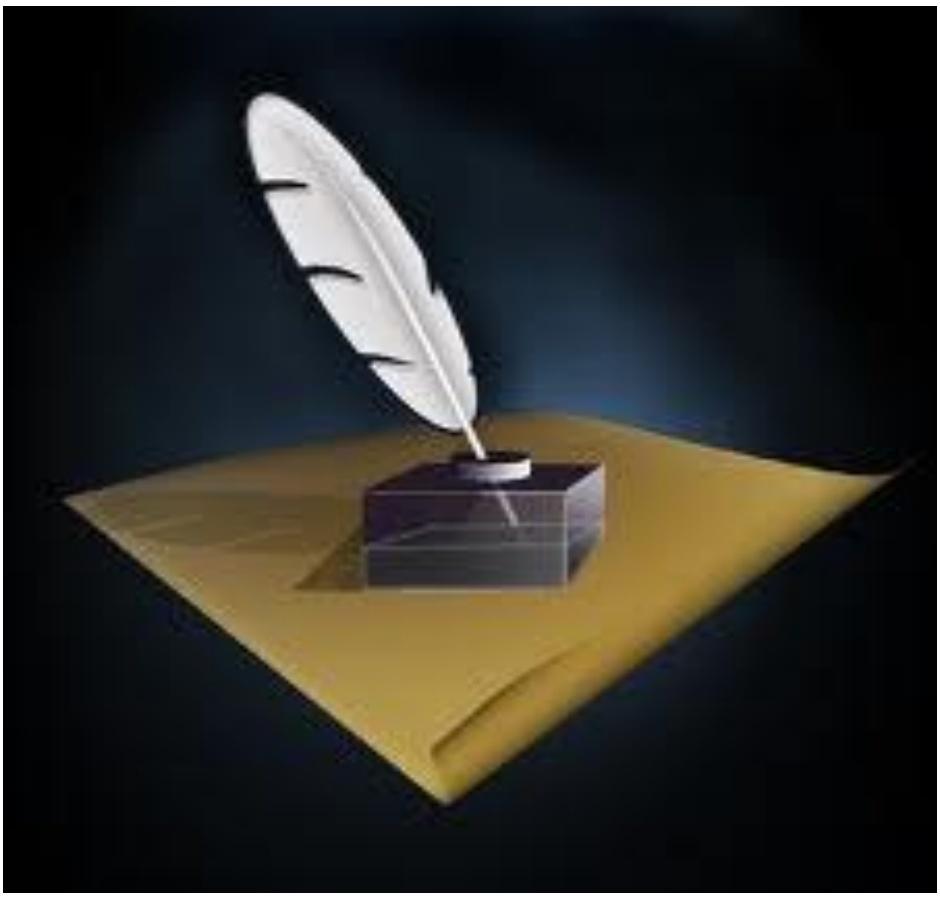

DEDICATED TO MY MOM SHOBHA & PAPA LAXMAN & FAMILY

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Many Thanks to Almighty ***Revansidha and jyotirling****, for it He who began this work in me and carried it to completion. It is He who has blesses me with the people whose names I feel privileged to mention here. The satisfaction that accompanies the successful completion of any task would be incomplete without mention of the people who made it possible with constant guidance, support and encouragement that crows all effort with success.*

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B.G. Nagara.

March2012 ***POL SAGAR LAXMAN***

LIST OF ABBREVIATIONS

Bu	:	Butyl
^{o}C	:	Degree Centigrade
COX	:	Cyclo-Oxygenase
DMSO	:	Dimethyl sulphoxide
D	:	doublet
e.g.	:	example
Et	:	Ethyl
et al.,	:	and others
FT-IR	:	Fourier Transform Infra Red
HIV	:	Human Immuno Deficiency Virus
^{1}H-NMR	:	Proton Nuclear Magnetic Resonance
hr.	:	hours
KBr	:	Potassium Bromide
KOH	:	Potassium Hydroxide
M	:	Mole
M	:	multiplet
Min	:	minutes
mL	:	milli Liter
Mol	:	molar
Nm	:	nano meter
NO	:	Nitric Oxide
NSAIDS	:	Non-Steroidal Anti-Inflammatory Drugs

PBS	:	Phosphate Buffered Saline
%	:	Percentage
Ppm	:	parts per million
S	:	singlet
SAR	:	Structure Activity Relationship
TLC	:	Thin Layer Chromatography
TMS	:	Tetra Methyl Silane
UV	:	Ultra Violet
AMP	:	Adenosin monophosphate

ABSTRACT

OBJECTIVE:

Isoxazole is five membered heterocyclic ring having a broad spectrum of pharmacological activities like anti-tubercular, anti-cancer, anti-bacterial, anti-fungal, anti-HIV, anti-inflammatory and anti-hypertensive activities.

In the present research work we reported the synthesis of some novel isoxazoles by using various different substituted chalcones and screened for their anti-inflammatory activity and anti-microbial activity.

METHODOLOGY:

Equimolar quantities of aromatic aldehydes and aromatic acetophenones were dissolved in 25 mL of alcohol. Sodium hydroxide solution (0.02 mol) was added slowly and the mixture stirred for 12 hr. until the entire mixture becomes very cloud. Then the mixture was poured slowly into 400 mL of water with a constant stirring and kept in refrigerator for 24 hr. Then precipitate obtained was filtered, washed and recrystallized from ethanol.

A mixture of chalcone hydroxylamine hydrochloride (0.02 mol) and sodium acetate (0.02 mol) in ethanol (25 mL) was refluxed for 6 hr. The mixture was concentrated by distilling out the solvent under reduced pressure and poured into ice water. The precipitate obtained was filtered, washed and recrystallized from acetone.

EXPERIMENTAL SECTION:

All the melting points were determined on Micro-controller based melting point apparatus CL 725/726 and were uncorrected. Chloro and nitro benzaldehydes were purchased from Techno chemicals, Bangalore. Other chemicals like hydroxyl amine hydrochloride & sodium acetate were purchased from S.D. Fine chemicals, Bangalore. Silica gel G plates (3x8cm) were used for TLC and spots were located by

UV or in iodine chamber. The IR spectra (KBr) were determined on FTIR 8400S, SHIMADZU Spectrometer and the values were expressed in cm^{-1} ^{1}H-NMR were recorded in either $CDCl_3$ or DMSO-d_6 solvents using TMS as an internal reference standard at IIT Chennai and IISc Bangalore.

BIOLOGICAL ACTIVITY:

All the synthesized compounds were screened for anti-inflammatory activity by using carrageenan induced rat edema paw method. The paw volumes were recorded by using plethysmograph and statistical data was calculated by using SPSS Software. Diclofenac sodium was taken as standard drug. The anti-bacterial activity was carried out using cup and plate method using the strains of *E-coli , S.Aureus, ps.Auruginosa, klebsiella,* at the concentration 100, 200, 400, 500 µg/ml. The few compound showed better activity against *E-coli, S-Aureus, Ps. Auruginosa , klebiseilla* strains of bacteria.

RESULTS AND DISCUSSION:

All the synthesized compounds were characterized by using FT-IR, ^{1}H-NMR, Mass spectral techniques. The synthesized molecules were screened for anti-inflammatory activity. Among the synthesized compounds **C_9, N_1, N_9** and **C_5** showed significant activity when compared to standard Diclofenac sodium. Compound **N_1** and **N_9**, selected for in-vivo anti-inflammatory activity by using carrageenan induced rat paw edema method. Showed significant activity when compared to standard diclofenac sodium. All the compounds were screened for anti-bacterial activity. Among the synthesized compounds**,** **N_1**, **N_4**, **N_9** and **C_1**, **C_9** showed significant activity when compared to standard ciprofloxacin.

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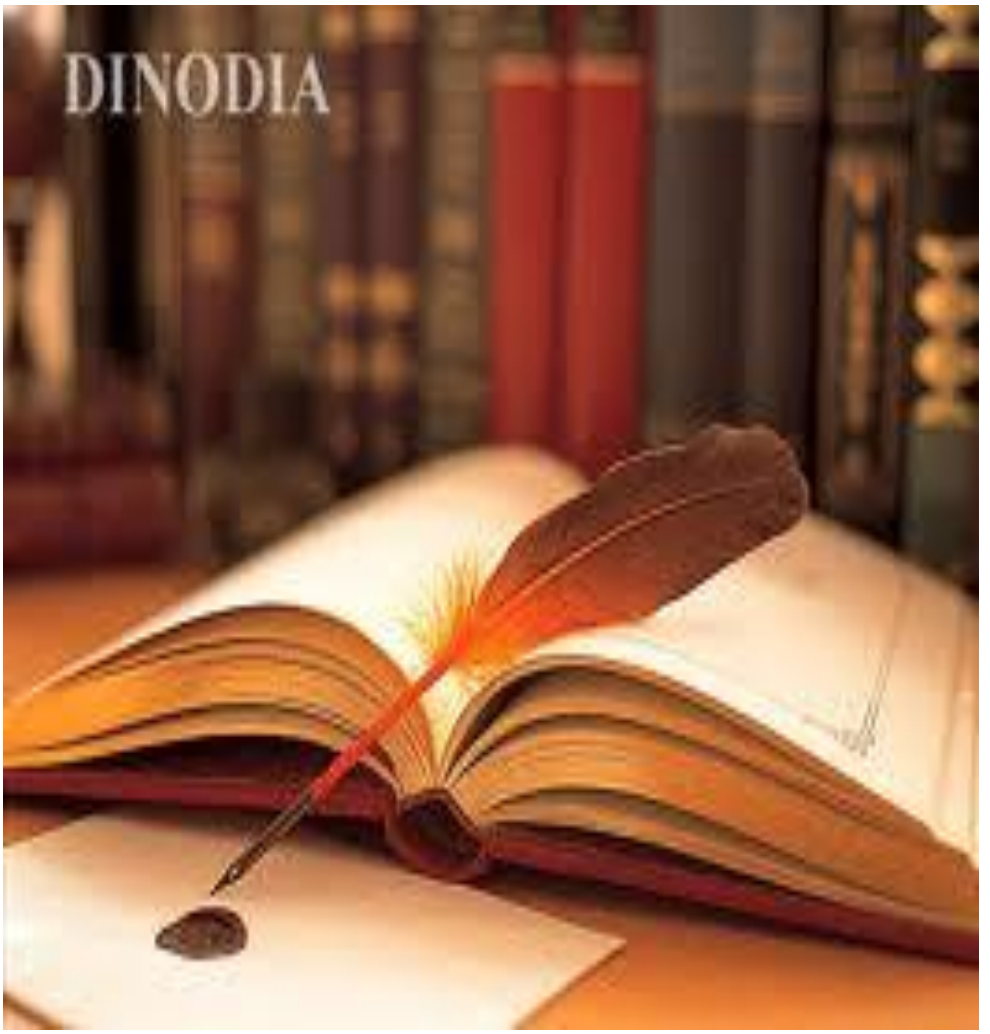
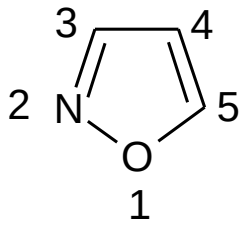


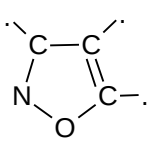
INTRODUCTION

ISOXAZOLE:

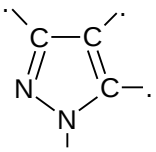
*I*soxazole is a five membered heterocyclic compound having two hetero atoms: oxygen at position 1 and nitrogen at position 2. Claisen first reported an isoxazole (I) for a product from the reaction of 1,3 diketone with hydroxylamine hydrochloride. Subsequently a solid foundation for the chemistry of isoxazole was laid down by Claisen and his students. It was shown to possess typical properties of an aromatic system but under certain reaction conditions. Particularly in reducing or basic media, it becomes very highly labile. [1]



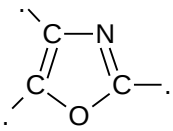
The next important contribution to the chemistry of isoxazoles was made by Quelico in 1945, when he began to study the formation of isoxazoles from nitrile N-oxide and unsaturated compounds. The chemistry of isoxazole is associated with name of ludwing claisen who recognized in the year 1888.The cyclic structure of the product (3-methyl-5-phenyl isoxazole) that ceresole had obtained in 1884 from the action of hydroxylamine on benzoyl acetone. He advanced hypothesis that it might contain the five membered ring C_3NO. (1), the oxygen analog of the C_3N_2 ring of pyrazole (2). Claisen suggested for it the name of monoazole which was eventually modified by Hantzch. To isoxazole from already known isomeric ring of oxazole.



(1)



(2)



(3)

More recently,the development of isoxazole chemistry has advanced from the discovery of the new synthetic methods. Most of these based on the capacity of substances containing the highly reactive group nitrile found in nitrile oxides to react with aliphatic triple and double bond forming respectively the isoxazole and isoxazoline ring.[1]

The nitrile oxide synthesis of isoxazoles has taken its origin from earlier investigation on the action of nitric acid on acetylene and other unsaturated compounds which

leads to isoxazole derivatives.

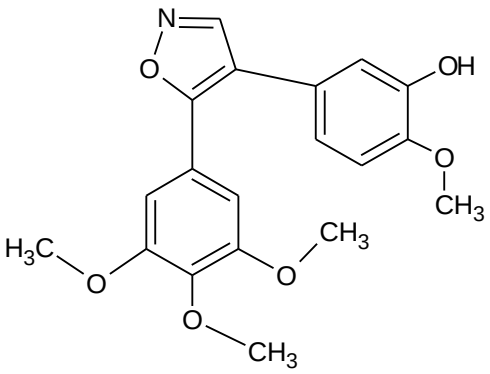
Isoxazoles are unique in their chemical behaviour not only among heterocyclic compounds in general, but also among related azoles. This is because isoxazole possesses the typical properties of the aromatic system, which are in fact rather pronounced in these derivatives, together with the high liability of the ring under certain conditions, particularly at the nitrogen-oxygen bond. From a purely formal point of view isoxazole can be considered as an analogue of pyridine just as furan is an analogue of benzene. Such a formal analogy is to some extent valid, isoxazole resembles pyridine more than other heterocyclic compounds as far as chemical properties are concerned. It differs from pyridine in undergoing more readily electrophilic substitution reactions and possessing a more liable ring; this relationship thus resembles that between furan and benzene.[2]

Isoxazole have played crucial role in the history of hetrocyclic chemistry and been extensively important pharmacophore and synthons in the field of organic chemistry owing to their versatile chemotherapeutic importance, a significant amount of research effort has been focused on these nuclei. The nitrogen containing heterocyclic such as pyrimidines and isoxazole is a promising structural moiety for drug designing. The development of methodologies useful for the assembly of molecules containing heterocyclic templates continues to attract the attention of both the academic and industrial communities.[3] Isoxazole is a five membered heterocyclic ring system containing oxygen and nitrogen atoms. In recent years, the synthesis of novel isoxazole derivatives remains a main focus of medicinal research. Isoxazoles have been reported to posses anthelmantic, antibacterial, antihyperglycemic, analgesic, anti-inflammatory, antipyretic, antiviral and antitumor properties.[4]

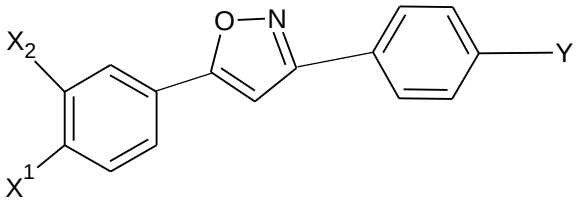
Although isoxazole derivatives have been known for more than 80 years, the investigation of their chemistry commended rather slowly. Earlier studies were mainly devoted to the development of synthetic methods. Recently the attention was focused on the investigation of chemical properties and in particular on the peculiarities of the behaviour of isoxazole derivatives and the elucidation of their physicochemical characteristics. This enabled new datas to be obtained that were considerable importance.

Julia Kaffy et al.[5] have been synthesized various five membered heterocycles with oxygen and nitrogen atoms. The 4,5-diarylisoxazole (IX) exhibited greater antitubulin activity, but modest antiproliferative activity. Kai Fan Cheng [40] have been synthesized 3-(4-hydroxyphenyl)-4,5-dihydro-5-aceticacidmethylester isoxazole, an inhibitor of the proinflammatory cytokine MIF, two critical modifications and chiral

resolution have significantly improved the potency of the inhibition. Compound (X) inhibits MIF tautomerase with an IC50 of 550 nm.



The required starting material chalcone was obtained by Claisen -Schmidt condensation which on further refluxed with hydroxylamine hydrochloride in the presence of rectified spirit and sodium acetate yielded substituted isoxazole derivatives.[6]



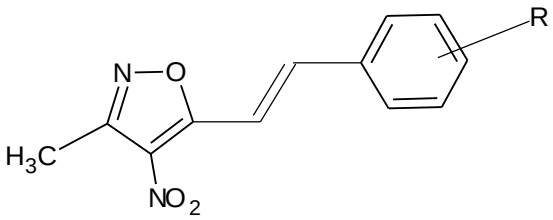
$Y=NH_2$

$X^1=OH$

$X_2=H$

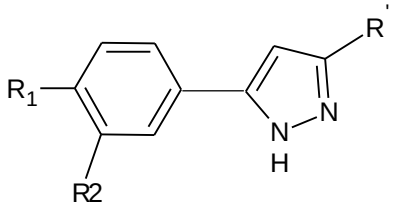
The starting material 3,5-dimethylisoxazole was prepared by the cyclization of acetylacetone with hydroxylamine hydrochloride in aqueous alcohol. Nitration of 3,5-

dimethylisoxazole has been carried out with fuming nitric acid and concentrated sulphuric acid at 0°C to give 3,5-dimethyl-4-nitroisoxazole. This compound was condensed with various substituted benzaldehydes in absolute alcohol in presence of catalytic amounts of piperidine. The reaction was carried out on hot water bath at reflux temperature for half an hour to four hours to yield respective 5-styrylisoxazole but not 3-styrylisoxazole.[7]



R=H, Cl, CH_3

Some novel heterocyclic derivatives such as thazines, oxazines, isoxazoles and pyrazoles (I_{a-d}, II_{a-d}, III_{a-d}) were synthesized from various chalcones. The synthesized compounds have been characterized by TLC, elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR and Mass Spectroscopy. These compounds were screened for their anti-inflammatory, anti-bacterial and anti- fungal activities.[8]

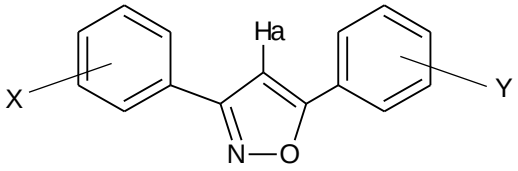


Id = R_1 = OCH_3, R_2=H,R'=C_6H_5

IId = R_1=H, R_2=Cl, R'=C_6H_5

IIId =R_1=H, R_2=NO_2, R' C_6H_5

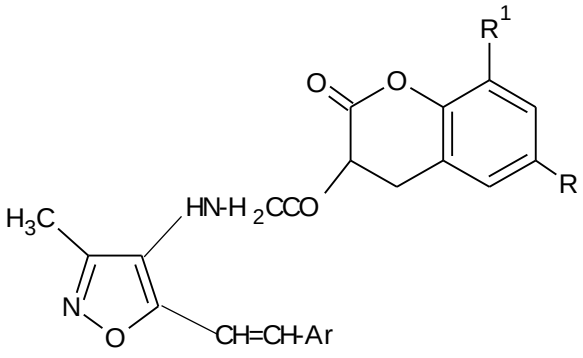
A series of 3,5 diarylisoxazole have been synthesized starting from substituted α,β unsaturated carbonyl compounds which undergo cyclization reaction with hydroxylamine hydrochloride in a search program towards an efficient antibacterial, antifungal and anti-inflammatory agents. The synthesized compound were characterized and confirmed on the basis of FT-IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data. Compound (3a-j) were screened their antibacterial and anti-inflammatory activities[9]



3(a-j)

X=(H, p-Br, p-Cl) Y=(H, p-Br,p-Cl,p-NO $_2$)

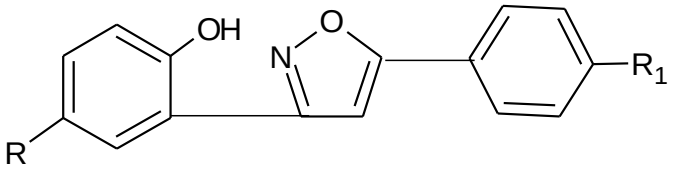
The reaction of substituted 4-amino-3-methyl-5-styrylisoxazoles obtained from the corresponding substituted 3-methyl-4-nitro-5-styrylisoxazoles, with 3-(2-bromoacetyl) coumarine in absolute ethanol led to the formation of 3-[2-(3- methyl-5-styryl-isoxazol-4-ylamino)acetyl] chormen -2- one in 60- 70 % yields.[10]



R^1=H,Br, OCH_3

R=H, Br

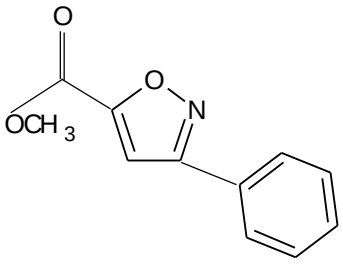
Reactions of 2-hydroxy chalcone dibromides 2_{a-I} with phenyl hydrazine and hydrazine hydrate afford pyrazoles 1_{a-I} and with hydroxylamine hydrochloride give isoxazoles 5_{a-f} in triethanolamine medium.[11]



R_1= OCH_3, Cl

R= CH_3

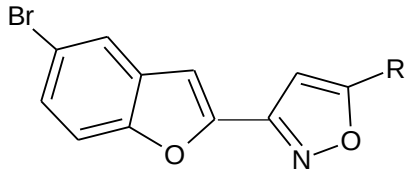
The regioselective synthesis of 3,5-disubstituted isoxazoles was achieved through the 1,3-dipolar cycloaddition of nitrile oxides with 1,1-disubstituted bromoalkenes. The substituted bromoalkenes function as alkyne synthons which were used to construct 5,5-disubstituted bromoisoxazoline intermediates that aromatize to the analogous isoxazoles through the loss of HBr.[12]



1-(5-bromo-1-bezofuran-2-yl)-3-(substituted phenyl)-prop-2-en-1ones were prepared by the reaction of 5-bromo-2-acetylbenzofuran **1** with different aromatic aldehydes in presence of alkali. Reaction with urea, thiourea and hydroxylamine hydrochloride to

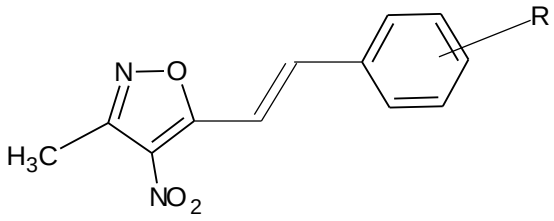
gave 4-(5-bromo-1-benzofuran-2-yl)-6-(substituted phenyl)-pyrimidine-2-ol4-(5-bromo-1-benzofuran-2-yl)-6-(substituted phenyl)-pyrimidine-2-thiol and 3-(5-bromo-1-benzofuran-2-yl)-5-(substituted phenyl)-4, 5 dihydroisoxazole respectively. The characterization of all synthesized compounds

was done by analytical and spectral studies.[13]



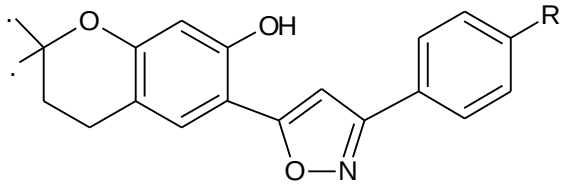
R=$C_6H_4N(CH_3)$

The starting material 3,5-dimethylisoxazole was prepared by the cyclization of acetylacetone with hydroxylamine hydrochloride in aqueous alcohol. Nitration of 3,5-dimethylisoxazole has been carried out with fuming nitric acid and concentrated sulphuric acid at 0°C to give 3,5-dimethyl-4-nitroisoxazole. This compound was condensed with various substituted benzaldehydes in absolute alcohol in presence of catalytic amounts of piperidine. The reaction was carried out on hot water bath at reflux temperature for half an hour to four hours to yield respective 5-styrylisoxazole but not 3-styrylisoxazole.[14]

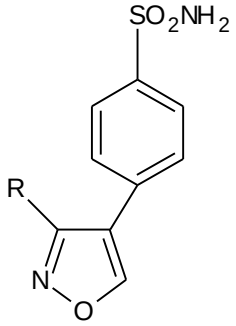


R=H, Cl, CH_3

Some new 2-isoxazole derivatives prepared from α,β-dibromochalcones showed mild antibacterial activity [12]. A group of 4,5-diphenyl isoxazoles, 3,4-diphenyl-5-trifluoro methyl isoxazoles and 4,5-diphenyl-3-methyl sulfonoamido isoxazole possessing a variety of substitutions (H, F, MeS, MeSO, MeSO2) at the para position of one of the phenyl rings were used as analgesic and selective COX-2 inhibitory, and anti-inflammatory agents. Isoxazolyl naphthoquinones act as potential trypanocidal and antibacterial agents[15]

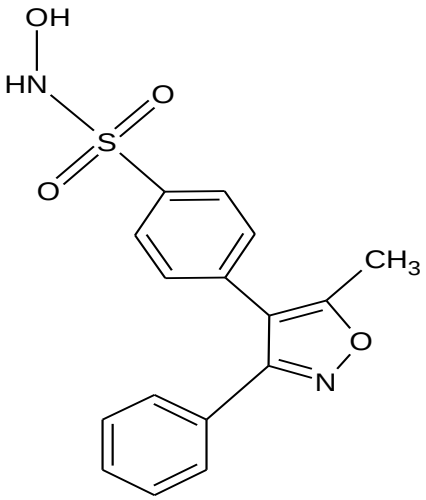


Novel 3,4-diarylisoxazole analogues of valdecoxib were synthesized and screened for anti-inflammatory activity. Among the synthesized compounds the a, b and c are showed good anti-inflammatory activity compared to the standard drug.[16]

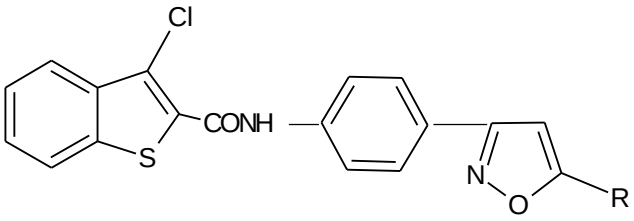


(a) R=phenyl, (b) R=5-chloro-2-furyl, (c) R=3-chloro-2,4,6-trimethoxyphenolN-hydroxy valdecoxib analogues were synthesized, in these compounds, N-hydroxy 4-[5-methyl-3-phenyl isoxazolol-4-yl]benzene sulfonamide primary metabolite of the highly selective COX-2 inhibitor showed potent anti-

inflammatory activity in carrageenan induced rat paw edema in chronic and acute pain models.[17]

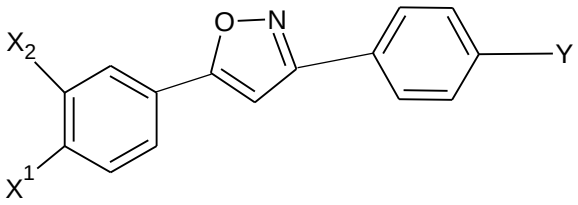


Compounds $1_{a\text{-}l}$ on cyclization with hydroxylamine hydrochloride in presence of sodium acetate furnished 1-[p-(3'-chloro-2'-benzo(b)thiophenoylamino)-phenyl]-5-aryl-isoxazoles.[18]



R=C_6H_5

The required starting material chalcone was obtained by Claisen -Schmidt condensation which on further refluxed with hydroxylamine hydrochloride in the presence of rectified spirit and sodium acetate yielded substituted isoxazole derivatives.[19]

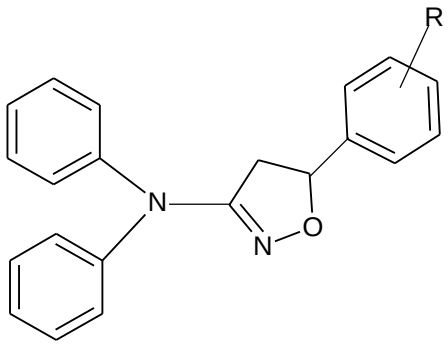


$Y=NH_2$

$X^1=OH$

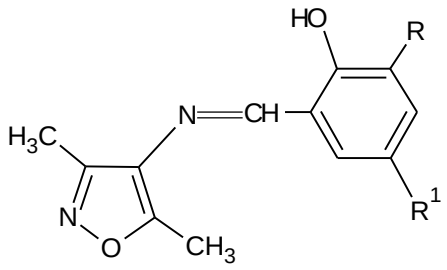
$X_2=H$

Diphenylamine taken as a starting material, was subjected to nucleophilic substitution in the presence of acetyl chloride to form corresponding acetamide. The total reaction proceeded at low temperature due to low boiling point of acetyl chloride and gave better yield as compared to the reported. Claisen-Schmidt condensation of corresponding acetamide with substituted benzaldehydes, gave the corresponding α,β-unsaturated carbonyl compounds, which on cyclization with hydroxylamine hydrochloride resulted in isoxazoline formation.[20]



R= OH, OCH_3

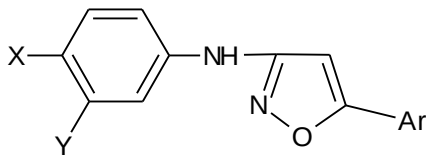
4-Amino-3,5-dimethylisoxazole was condensed with substituted salicylaldehydes by refluxing in ethanol to get the desired 2[(3,5- dimethyl - isoxazol-4- ylimino)-methyl]- phenols.[21]



R= H, R^1= Cl

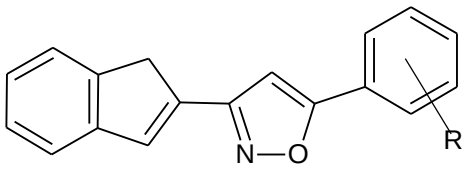
Some new 3-(4-substituted anilino)-5-(3', 4'-disubstituted aryl)-2-isoxazoles were synthesized by

microwave irradiation (560 w) of 3-phenyl or substituted phenyl -1- anilino or substituted anilino -2- propene -1- ones with hydroxylamine hydrochloride and sodium acetate. Thestructures of the compounds were proved by means of their IR, ^{1}H-NMR, Mass spectroscope.[22]



iiia-r X= H Y= C_6H_5

Synthesis of 3-(1-benzofuran-2-yl)-5-(substituted phenyl) isoxazole, **I_1-I_7** was evaluated for *in vitro* cytotoxic activity .HeLa cell lines at the minimum seven concentrations at two fold dilutions. Amongst all the compound **I_4** has shown good activity. While, Compound **I_5** has shown moderate activity.[23]



R= (NO_2 , NO_2 , OH)

INFLAMMATION:[24]

Inflammation is defined as the local response of living mammalian tissues to injury due to any agent. It is body defense reaction in order to eliminate or limit the spread of injurious agent as well as to remove the consequent dead cells and tissues.

The agents causing inflammation are:

- Physical agents like heat, cold, radiation, mechanical trauma.
- Chemical agents like organic and inorganic poisons.
- Infective agents like bacteria, viruses and their toxins.
- Immunological agents like cell mediated and antigen-antibody reactions.

SIGNS OF INFLAMMATION:

- Rubor (redness)
- Tumour (swelling)
- Calor (heat) and
- Dolar (pain).

To these, fifth sign functio laesa (loss of function) was later added by Virchow. The word inflammation means burning. This nomenclature had its

origin in old times but now we know that burning is only one of the signs of inflammation.

TYPES OF INFLAMMATION

Depending upon the defense capacity of the host and duration of response inflammation can be classified as acute and chronic.

ACUTE INFLAMMATION:

- Acute inflammation is of short duration and represents the early body reaction and is usually followed by repair.

The main features of inflammation are:

1. Accumulation of fluid and plasma at the affected site;
2. Intravascular activation of platelets; and
3. Polymorphonuclear neutrophils as inflammatory cells.

- Chronic inflammation is of longer duration and occurs either after the causative agents of acute inflammation, persists for a long time or, the stimulus is such that it induces chronic inflammation from the beginning.
- The characteristic feature of chronic inflammation is presence of chronic inflammatory cells such as lymphocytes, plasma and macrophages.

CHRONIC INFLAMMATION:

Chronic inflammation is defined as prolonged process in which tissue destruction and inflammation occur at the same time.

Chronic inflammation can be caused by 3 ways. They are:

1. Chronic inflammation following acute inflammation.
2. Recurrent attacks of acute inflammation.
3. Chronic inflammation starting *de novo.*

TYPES OF CHRONIC INFLAMMATION:

Chronic inflammation is of two types. They are specific and non-specific chronic inflammation.

- Specific chronic inflammation: It occurs when injurious agent causes a characteristic histological response.

  e.g.: Tuberculosis, syphilis, leprosy.

- Non- Specific chronic inflammation: This is non-specific in nature, caused when an irritant substance produces non-specific inflammatory reaction with formation of granulation tissue.

  e.g.: chronic osteomyleitis, chronic ulcer.

ANTI-INFLAMMATORY AGENTS :[25]

Non-steroidal anti-inflammatory drugs (NSAIDS) are widely used for the treatment of Inflammation. The anti-inflammatory drugs are classified as:

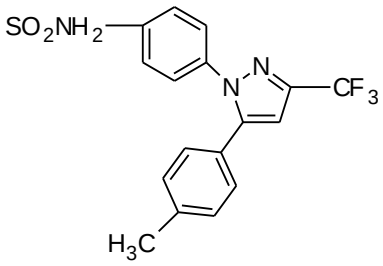
- Heteroaryl acetic acid analogues:
  - Indomethacin
  - Tolmetin sodium

- Zomepiac sodium

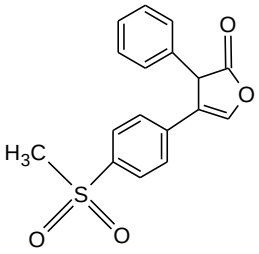
- Aryl acetic acid analogues:
  - Sulindac
  - Ibufenac
  - Diclofenac sodium
- Aryl propionic acid analogues:
  - Ibuprofen
  - Flubiprofen
  - Ketopofen
  - Napoxen
- Selective COX-2 inhibitors:
  - Celecoxib
  - Rofecoxib
  - Valdecoxib.

Mechanism of action:

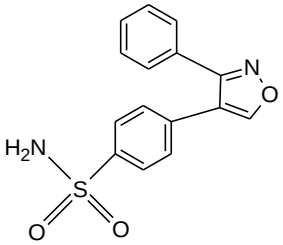
NSAIDs inhibit the Cyclooxygenases, the enzyme that catalyses the synthesis of cyclic endopeoxidases from the Arachidonic acid to form Prostaglandins. The two COX isoenzymes are COX-1 and COX-2. COX-2 is responsible for the production of prostaglandins at inflammation site. Selective COX-2 inhibitors may eliminate the side effects associated with NSAIDs due to COX-1 inhibition such as gastric and renal effect.



Celecoxib



Rofecoxib



Valdecoxib

CHAPTER 2

OBJECTIVES

OBJECTIVES

The isoxazole derivatives have played a crucial role in the history of heterocyclic chemistry and been used extensively important pharmacophores. In the field of organic chemistry Nitrogen containing hetrocycles such as isoxazole is a promising structural moiety for drug designing.

Isoxazole are an important class of heterocyclic compounds and have served as versatile building blocks in organic synthesis. Such isoxazole derivatives constitute a unique class of nitrogen and oxygen containing five member heterocycle and they are associated with wide spectrum of biological effects such as anti-inflammatory, anticancer, antibacterial. Compounds containing isoxazole nucleus find unique place in medicinal chemistry and place significant role as they are associated with immense biological activity.

Several isoxazolines exhibit important biological activities such as antibacterial, antinociceptive, antiviral, anti-inflammatory, anti-hypertensive and anti tubercular.

The development of methodologies useful for the assembly of molecules containing heterocyclic templates continues to attract the attention of both the academic and industrial communities. Isoxazole is a five membered heterocyclic ring system containing oxygen and nitrogen atoms. In recent years, the synthesis of novel isoxazole derivatives remains a main focus of medicinal research. Non-steroidal anti-inflammatory drugs are mainly used in the treatment of pain and inflammation related to variety of pathologies. Their anti-inflammatory effect are exerted by blocking the biosynthesis of prostaglandin, especially drugs act on cox-2 inhibitors.

In view of the wide range of therapeutic value of isoxazole ring system promoted to plan and their increasing importance in pharmaceutical and biological field and research on biologically active heterocycles.

THE MAIN OBJECTIVES OF THE PROPOSED WORK WAS

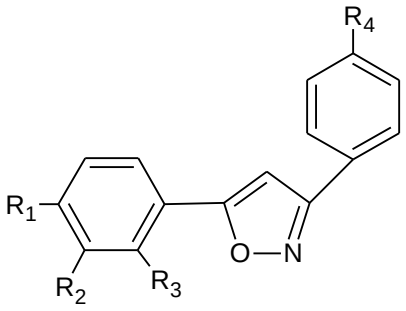
- Synthesis of some new Isoxazole derivatives
- Characterization of synthesized molecules by M.P, TLC, FT- IR, ^{1}H- NMR, ^{13}C-NMR, MASS spectroscopic techniques.
- To screen the newly synthesized analogues for their Anti-inflammatory activity using wister albino rats, and antibacterial activity using cup and plate method.

CHAPTER 3

REVIEW OF LITERATURE

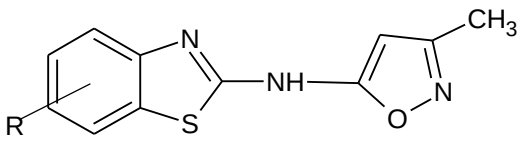
REVIEW OF LITERATURE

Sathish N.K. et al.,[26] have synthesized new isoxazoles from various unstable Chalcones and screened for their anti-inflammatory activity. Compounds **I_3, I_5, I_6** and **I_{11}** showed significant activity when compared to standard Diclofenac sodium.



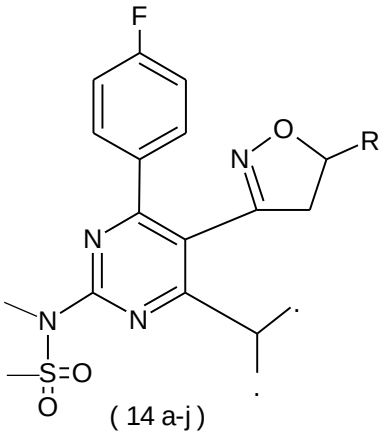
$R_{1=}$ (H) R_2= (NO_2 ,H) R_3= (H, OH)
R_4= (OH ,H)

Bhausaheb K.M. et al.,[27] reported Isoxazoles have been prepared by the reaction of various 3Carboxamido-(substitutedbenzothiazole-2yl)-propane-2-one an hydroxyl amine hydrochloride. substituted 2–amino benthiazoles were prepared from various substituted amines via substituted phenyl thiourea. antibacterial screening indicated that good activity was shown by compounds **3e,3f** against Staphylococcus aureus and compounds **3b,3c** showed good activity towards Pseudomonas areuginosa.



[R= H, 4 CH3, CH3, 4 Cl, 5 Cl, 6 Cl]

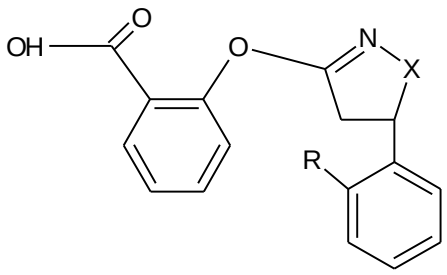
Rajgopal H. U. et al.,[28] reported analogues of Rosuvastatin compounds (**14aj**) synthesized by the cyclisation of allyl compounds with substituted pyrimidine oxime using chloromine-T in multiple steps. The synthesized compounds were evaluated for their ***in- vitro*** antmicrobial and anti-inflammatory activity. The compounds **14a, 14b,** **14c** and **14e** showed good activity, whereas the compounds **14d** and **14h** showed moderate activity.



(14 a-j)

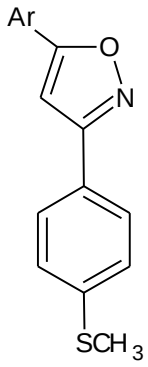
R = 13a, 14a = CN; 13b, 14b = CH2OH; 13c, 14c = CH2Cl
13d, 14d = CH2Br; 13e, 14e = COOCH3; 13f, 14f = COOC2H5
13g, 14g = C6H5; 13h,14h = 4-CH3-C6H5; 13i, 14i = 4-OCH3-C6H5
13j, 14j = 4-Cl-C6H5

Banerjee M. et al.,[29] have reported some novel 2-(5-phenyl-4, 5-dihydroisoxazol-3-yl) benzoic acids (2a-b) / 2-(5-phenyl-4, 5-dihydro-1*H*pyrazol-3-yl) benzoic acids (2c-d) and tested for their ***in-vitro*** protein denaturation activity.Compound **2d** was found to be promising and was more potent than the acetylsalicylic acid (NSAID) in the inhibition of bovine serum albumin denaturation.



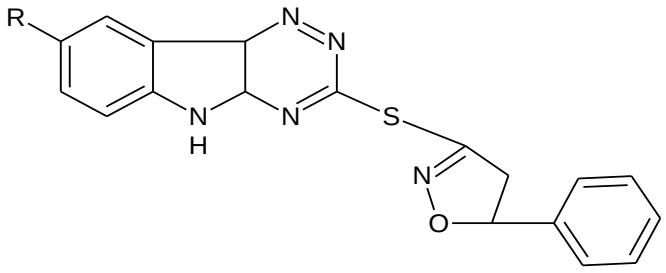
X= O & NH R = H & OH

Karabasanagouda T. et al.,[30] reported some new pyrazoline **3a-m** and isoxazole **4a-k** from 4-acetylthionisole , 1-with aryl aldehyde through α,β unsaturated ketones.The synthesized compounds have been screened their analgesic and anti-inflammatory activity. reveal that **3a ,3g,3i** and **3k** displayed slightly lower anti-inflammatory than standard diclofenac sodium.



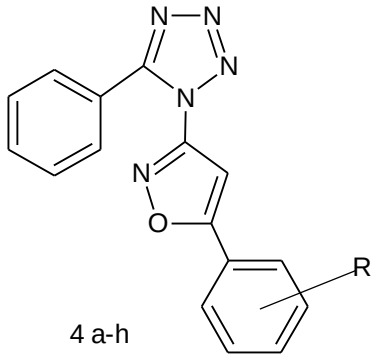
Ar = 4, 4 Biphenyl, 2-amino-3-pyridyl

Manju S.V. et al.,[31] reported series of (5' Phenyl isoxazolinyl thio) 8-substituted (1, 2, 4) triazino (5, 6 b) indole derivatives and evaluated for their anticonvulsant and anti inflammatory activities. The compounds **4e**, and **4b** showed significant protection from the tonic extensor phase and the compound **4c** possessed moderate anticonvulsant activity and rest of the compounds showed mild activity.



R=H =a Cl =d CH_3 = b Br =e F = c

Bhaskar V.H et al.,[32] reported different tetrazole derivatives containing isoxazole 5-phenyl tetrazoles **(1)** was cyclized using sodium azide and ammonium chloride and benzonitrile. The 5-phenyl tetrazoles on treatment with acetic anhydride formed 5-phenyl 1-acetyl tetrazole (2) which on reaction with different aromatic aldehydes forms chalcones (**3a-h**).The chalcones further undergo cyclisation with hydroxylamine hydrochloride in presence of KOH to form 5-phenyl-1-(5-substituted phenyl isoxazol-3-yl)-1*H*-tetrazole (4a-h). compounds have been selected and evaluated for their anticancer activity.

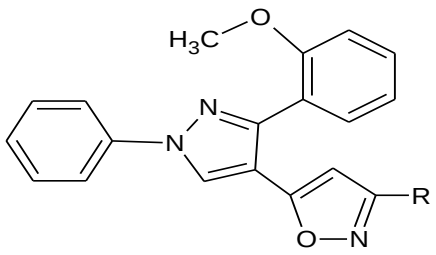


4 a-h

R=H; 2-Cl,4-Cl; 4-Br; 4-OCH3; 3-NO2;; 4-CH3; 4-N-(CH3)2

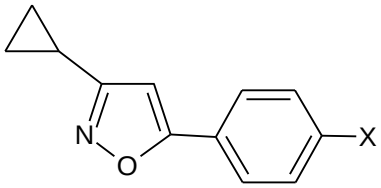
Parmar K.A. et al.,[33] reported cyanopyridone and isoxazole derivatives by condensation of chalcones (I) with acetate and hydroxylamine hydrochloride respectively. Antimicrobial activities of the synthesized compounds have been

determined qualitatively against different pathogenic bacteria. The compound **1_b,1_c,1_g,1_i,1_1** were shown significant activities.



R= C_6H_5 , 4-$NH_2C_6H_4$, 4-Cl-C_6H_4

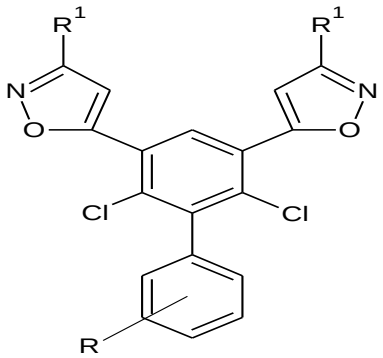
Nagwa M.M.H. et al.,[34] reported Chalcones by condensing ketones with aromatic aldehydes in the presence of suitable bases. They are very useful intermediates for the synthesis of five- [1,2], six- [1,3] and seven-membered [4] heterocyclic compounds. synthetic methods have been developed for the preparation of heterocycles starting from chalcone precursors that have been tested for their antimicrobial activities.



X= NO_2 ,OMe , H

Rajput A.P. et al.,[35] reported series of new isoxazoles **5a-f** by reaction of propenones **4** with hydroxylamine hydrochloride while the propenones **4a-f** were prepared by the condensation of 2, 6 – dichloro -1- (*N*-substituted phenyl)-1, 4 – dihydropyridine -3, 5 – dicarbaldehydes **3** with different aromatic ketones.

The newly synthesized title compounds have been screened for their in-*vitro* antimicrobial activities.

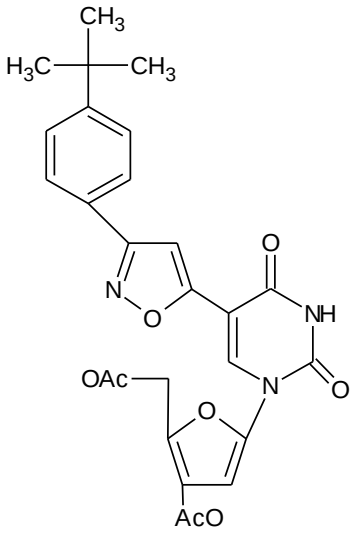


5 a f(i) (ii)

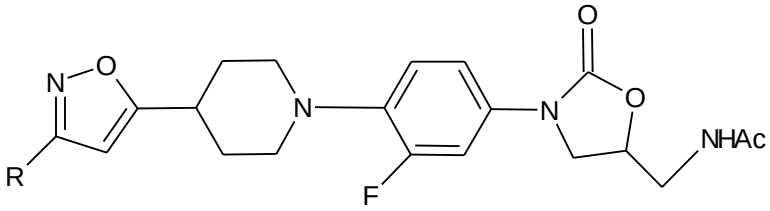
R
a = - H
b = - 4 CH_3
c = - 2 Cl
d = - 4 Cl
e = - 3 Cl
f = - 4 OCH_3

R', (i) = -Ph
(ii) = -4OH-Ph

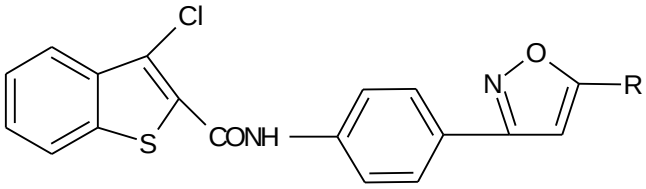
Yoon S. *et al.,*[36] synthesized 5- isoxazo-5-yl-2'-deoxyuridines from 5- iodo-2'-deoxyuridine and screened for anti-HSV activity. The isoxazole nucleosides exhibited anti-HSV activity.



Jae seoklee. *et al.,*[37] synthesized a series of isoxazolyl tetrahydropyridinyl isoxazolidinones and screened for anti-bacterial activity. Compounds having hydrophilic group at 3-position showed good anti-bacterial activity.

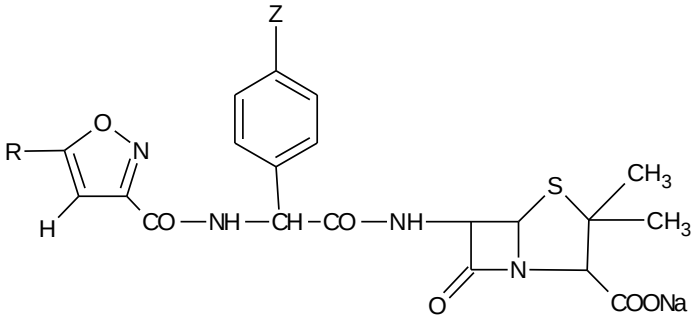


Kachhadia VV. *et al.,*[38] synthesized isoxazole derivatives by condensing the chalcones with hydroxyl amine hydrochloride and malono nitrile and screened for anti-microbial activity. Few synthesized compounds showed good anti-microbial activity.



(a) R = -3-Cl-C_6H_4, (b) R = -4- N $(CH_3)_2$-C_6H_5

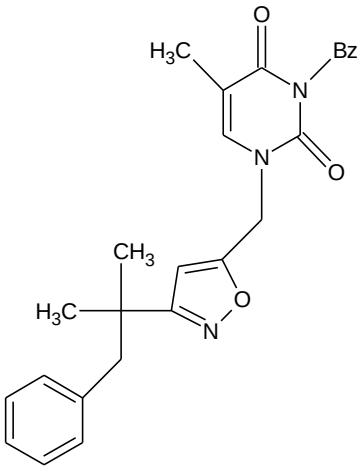
Naohiko Y. *et al.,*[39] synthesized antibacterial activity of new penicillin derivatives having 5-arylisoxazole 3-carboxamide group at the α position of benzyl penicillin/P-hydroxy benzyl penicillin and screened for anti-bacterial activity. Among the synthesized compounds **a** and **b** showed good anti-bacterial activity.



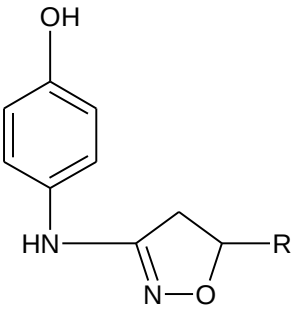
(a) R = -C_6H_6 Z = -H, (b) R = -CH_3, Z = -H

Yoon suklee. *et al.,*[40] designed and synthesized novel antiviral nucleoside analogues consisting of isoxazole rings and screened for anti-polio activity.

Following compound showed most potent anti-polio activity compared to standard drug.

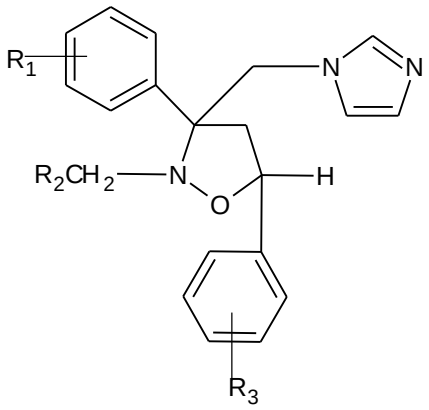


Sahu SK. *et al.*,[41] synthesized a series of novel 4-(5'-substituted-aryl-4',5'-dihydro-isoxazole-3'-yl-amino) phenols and screened for anti-bacterial activity. Following compounds showed significant anti-bacterial activity.



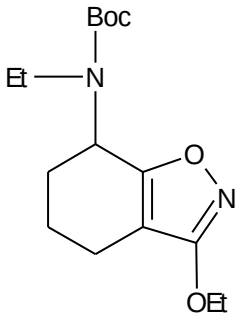
(a) R = -C_6H_5, (b) R = -4-NO_2-C_6H_4, (c) R = -4-OCH_3-C_6H_5

George BM. *et al.*,[42] studied anti-fungal activity of novel synthesized 3,5-diphenyl-3-[1H-imidazol-1-ylmethyl]-2-alkylisoxazolidine derivatives and screened for anti-fungal activity. Compounds **a, b, c** and **d** tested against Aspergillus fumigatus showed potent anti-fungal activity.

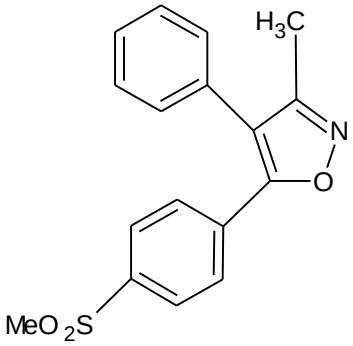


R_1, R_2, R_3 = -H, (b) R_1 = -4-Cl, R_2 = -H, R_3 = -H

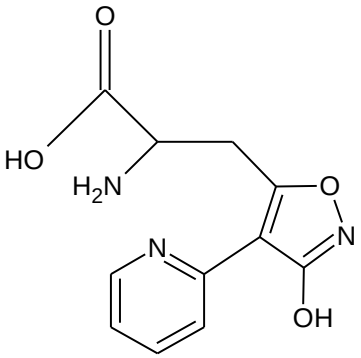
Erik F. *et al.*,[43] synthesized some novel enantiomers of 3-hydroxy-4 amino-4,5,6,7-tetrahydro-1,2-benzisoxazole and screened for anti-convulsant activity. In the series of compounds the following showed anti-convulsant activity.



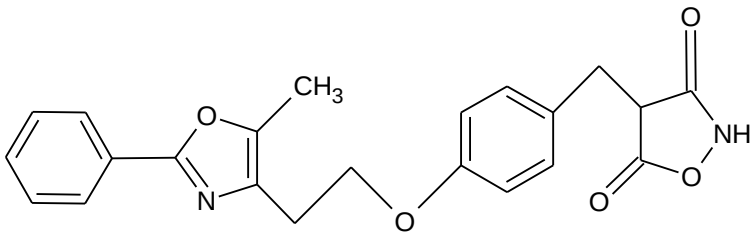
Amgad GH. *et al.*,[44] designed 4,5-diphenyl-5-(4-methylsulfonylphenyl)-4-phenyl-4-isoxazoline and screened for their anti-inflammatory activity. Following compound exhibited excellent anti-inflammatory activity in carrageenan induced rat edema paw method.



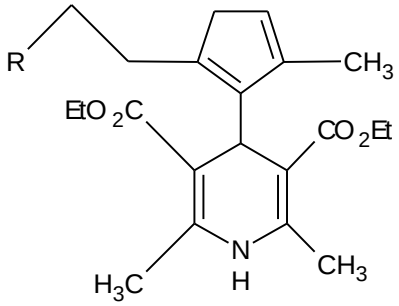
Hasse K. *et al.,*[45] synthesized 4-aryl-3-isoxazolol amino acids and screened for antagonistic at group-I metabotropic glutamate receptors. Following compound showed potent AMPA receptor antagonistic activity.



Hisashi S. *et al.,*[46] synthesized isoxazolidine-3, 5-dione as a hypoglycemic agent. Among the synthesized compounds the following compound showed potent activity.

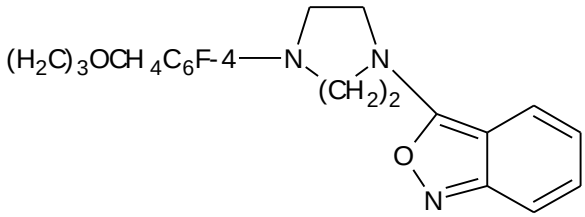


Nicholas RN. *et al.,*[47] synthesized 4-isoxazolyl-1,4 dihydropyridines bearing lipophilic side chains at C-5 position and screened for anti-inflammatory activity. Among the series of compounds **a, b** and **c** showed good anti-inflammatory activity by carrageenan induced rat paw edema method.

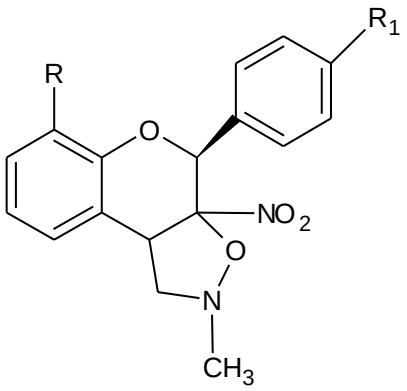


(a) R = -1-naphthyl, (b) R = -m-Br-phenyl, (c) R = -m-OCH_3-phenyl

Joseph PY. *et al.,*[48] synthesized (1,2-benzisoxazol-3-yl) piperazine derivatives as potential anti-psychotic agents. Following compound showed good anti-psychotic activity.

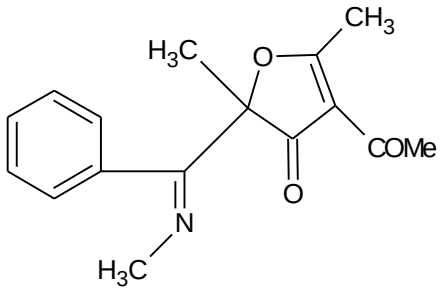


Hariharan S. *et al.,*[49] reported intermolecular 1,3-dipolar cycloaddition of *in situ* generated N-methylnitrone to 3-nitroflavenes which regiospecfically yielded the corresponding benzopyrano[4,3-d]isoxazoles in moderate yields.

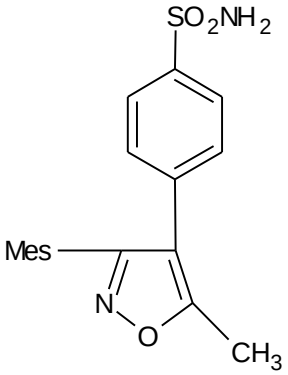


(a) R = -H, R_1 = -H, (b) R = -H, R_1 = -OCH_3, (C) R = -H, R_1 = -CH_3, (d) R = -H, R_1 = -Cl, (e) R = -OCH_3, R_1 = -H

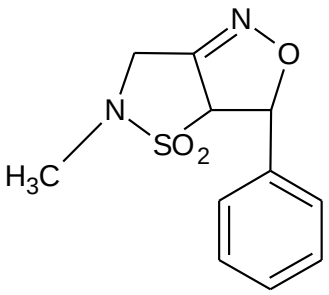
Donato D. *et al.*,[50] investigated photochemical behavior of some 5-alkylidene-2,5-dihydroisoxaozles. This reaction produced *cis*-4,5-dihydro furo azetidinones.



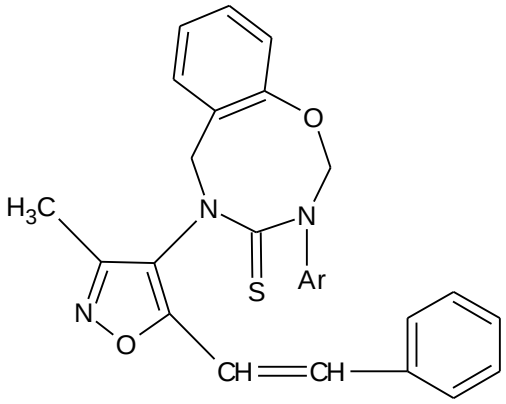
Jane EM. *et al.*,[51] reported [3+2] cyclo addition reaction of nitrile oxides and alkyl boronates provided direct access to a wide variety of isoxazole boronic esters. Specifically, this technique has been employed to generate tri-substituted isoxazole 4-boronates and di-substituted isoxazoles, where the boronic ester moiety can be installed at C-4 or C-5 with high levels of regiocontrol.



Chiacchio U. *et al.*,[52] functionalized isothiazoloisoxazole-4,4-dioxide, pyrazole isothiazole-1,1-dioxide, [1,2] thiazinoisoxazole-4,4-dioxide and benzo [1,2] thiazino isoxazole-4,4-dioxide systems obtained by intermolecular 1,3 dipolar cyclo addition starting from substituted α- and β-sulfonamides.

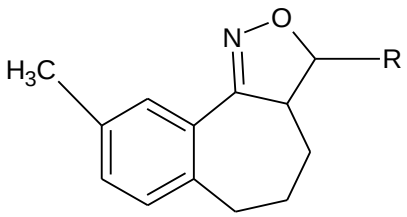


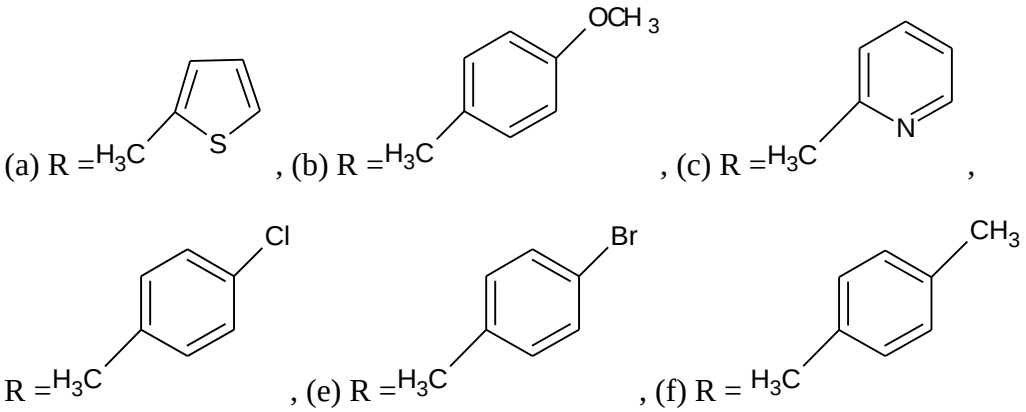
Rajanarendar E. *et al.,*[53] synthesized novel isoxazolyl 1,3,5-benzoxadiazocine-4-thiones accomplished by condensation of 4-amino-3-methyl-5-strylisoxazole with salicylaldehydes followed by reduction, treatment with aryl isothiocyanates and subsequent ring closure in presence of formaldehyde.



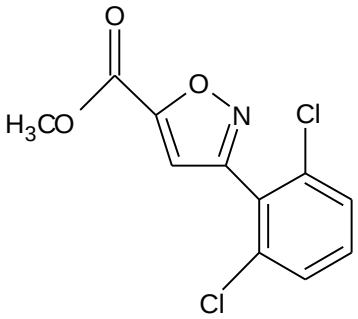
(a) Ar = -C_6H_5, (b) Ar = -4-Cl-C_6H_5, (c) Ar = -4-Br-C_6H_5, (d) Ar = -4-CH_3-C_6H_5

Venkateswarlu P. *et al.,*[54] reported 3-methyl benzocyclohepten-5-one with appropriate aromatic aldehydes on reaction with hydroxylamine hydrochloride in alkaline medium to give 9-methyl-3-phenyl-3a,4,5,6-tetrahydro-3H-benzo [6,7] cyclohepta derivatives.

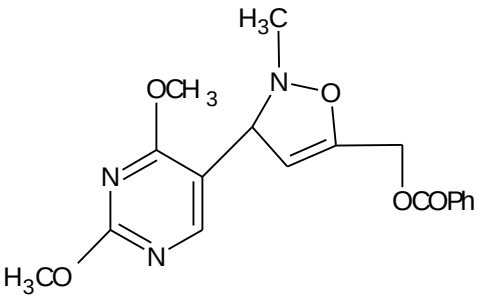




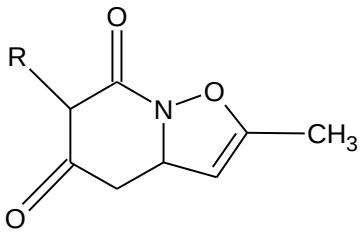
Suresh Babu D. *et al.*,[55] synthesized 3,5-disubstituted isoxazoles through the 1,3-dipolar cycloaddition of nitrile oxides with 1,1-disubstituted bromoalkenes. The substituted bromoalkenes function as alkyne, which were used to synthesize 5,5-di-substituted bromo isoxazoline intermediates that aromatize to the analogues of isoxazoles through the loss of HBr.



Evdoxia CA. *et al.*,[56] synthesized isoxazole, isoxazoline and isoxazolidine analogues of C-nucleosides related to pseudouridine by 1,3-dipolar cyclo addition reactions of nitrile oxides and nitrones derived from mono and disubstituted uracil-5-caraldehydes and heterocyclic ring instead of sugar moiety.

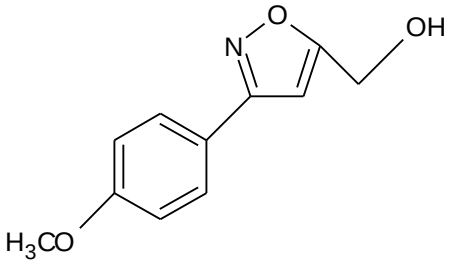


Ihsan A. *et al.*,[57] synthesized derivatives of two novel *meso*-ionic ring systems i.e., isoxazolo[2,3-a] pyrimidinedione and 1,3,4-oxadiazolo[3,2-a] pyrimidinedione, where both the ring systems were relatively an alkyl group n either ring system when the 6-position substituted by an alkyl group.



(a) R = -H, (b) R = -CH_3, (c) R = -CH_2-CH_3

Tornd VH. *et al.*,[58] synthesized 3,5 disubstituted isoxazoles obtained in good yields by a convenient one pot, three step procedure utilizing a regioselective copper (I)-catalyzed cycloaddition reaction between generated nitrile oxides and terminal acetylenes.



a) R = -4-(OCH_3)-C_6H_4

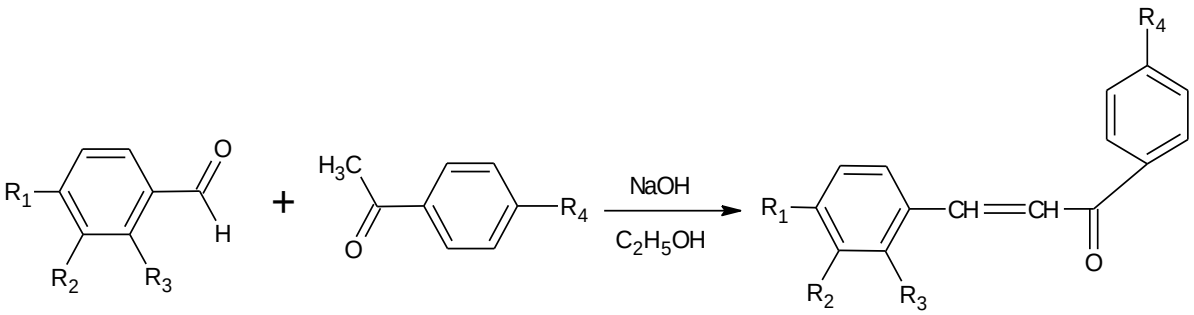
CHAPTER 4

METHODOLOGY

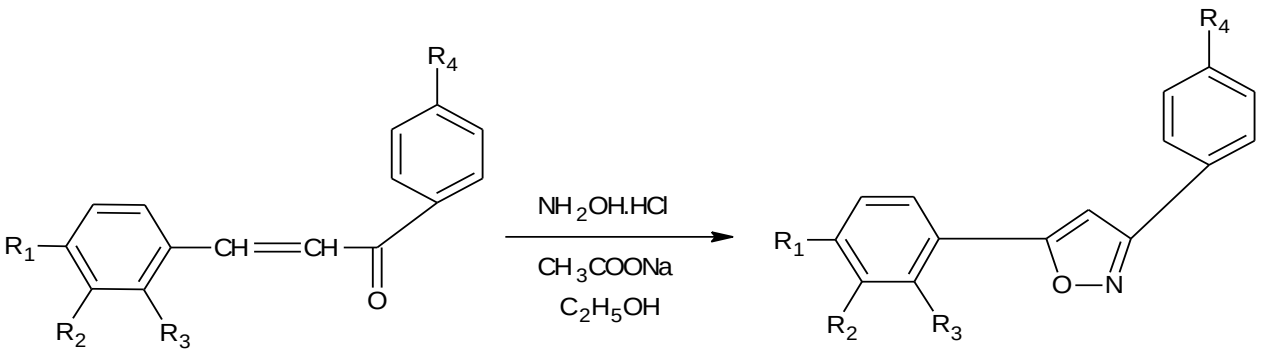
METHODOLOGY

SCHEME:

STEP-1:



STEP2:



R_4= (Different substituted acetophenone)

R_1,R_2,R_3= (Different substituted Aldehyde)

SUBSTITUTION:

COMPOUNDS	R_1	R_2	R_3	R_4
N_1	OCH_3	H	H	NO_2
N_2	NO_2	H	H	NO_2
N_3	H	NO_2	H	NO_2
N_4	Br	H	H	NO_2
N_5	Cl	H	H	NO_2
N_6	OH	H	H	NO_2
N_7	H	OH	H	NO_2
N_8	H	OCH_3	H	NO_2
N_9	$N(CH_3)_2$	H	H	NO_2
N_{10}	OCH_3	H	H	Cl
C_1	NO_2	H	H	Cl
C_2	H	NO_2	H	Cl
C_3	Br	H	H	Cl
C_4	Cl	H	H	Cl
C_5	OH	H	H	Cl
C_{16}	H	OH	H	Cl
C_{17}	H	OCH_3	H	Cl
C_{18}	$N(CH_3)_2$	H	H	Cl

SYNTHESIS:

Step 1:

GENERAL PROCEDURE FOR SYNTHESIS OF CHALCONES

Equimolar quantities of different substituted aromatic benzaldehyde (0.01mol) and substituted aromatic acetophenones (0.01mol) were dissolved in 25 mL of alcohol. Sodium hydroxide solution (0.02mol) was added slowly and the mixture stirred for 12 hr. until the entire mixture becomes very cloud. Then the mixture was poured slowly into 400 mL.of water with constant stirring and kept refrigerator for 24hr. Then precipitate obtained was filtered. Washed and recrystallised from ethanol.

Step 2:

GENERAL PROCEDURE FOR CYCLISATION OF CHALCONES

0.015 mol of chalcone, 0.015mol of hydroxyl ammonium hydrochloride and sodium acetate 0.015mol in 25 mL of ethanol was refluxed for 6hr. The mixture was concentrated by distilling out the solvent under reduced pressure and poured into ice cold water. The precipitate obtained was filtered ,washed and recrystllized from acetone.

TABLE-1: PHYSICAL CHARACTERISATION DATA OF COMPOUND N_1

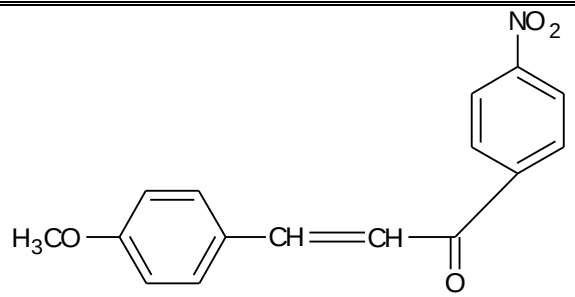
Structure	
Chemical name	1-(4-nitrophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one
Physical state	Yellow Colour crystals
Molecular Formula	$C_{16}H_{13}NO_4$
Molecular Weight	283.27
Melting point	155ºC
Percentage Yield	65%
TLC Solvent system used	Ethyl acetate: Petroleum ether (8:2)
R_f value	0.76

TABLE-2: PHYSICAL CHARACTERISATION DATA OF COMPOUND N_2

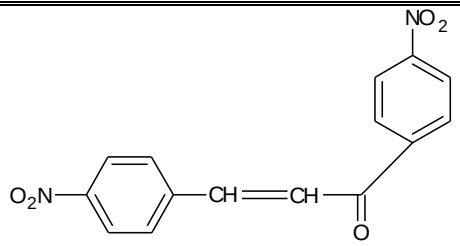
Structure	
Chemical name	1-(4-nitrophenyl)-3-(4nitrophenyl)prop-2-en-1-one
Physical state	Brown Colour crystals
Molecular Formula	$C_{15}H_{10}N_2O_5$
Molecular Weight	298
Melting point	185ºC
Percentage Yield	60%
TLC Solvent system used	Ethyl acetate: Petroleum ether (8:2)
R_f value	0.66

TABLE-3: PHYSICAL CHARACTERISATION DATA OF COMPOUND N_3

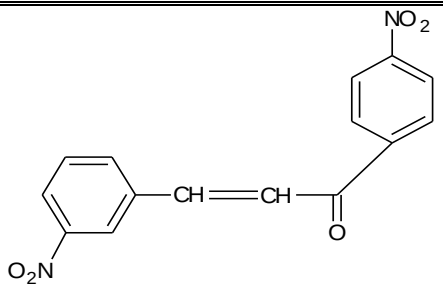
Structure	
Chemical name	1-(4-nitrophenyl)-3-(3-nitrophenyl)prop-2-en-1-one
Physical state	Yellow Colour crystals
Molecular Formula	$C_{15}H_{10}N_2O_5$
Molecular Weight	298
Melting point	155ºC
Percentage Yield	62%
TLC Solvent system used	Ethyl acetate: Petroleum ether (8:2)
R_f value	0.66

TABLE-4: PHYSICAL CHARACTERISATION DATA OF COMPOUND N_4

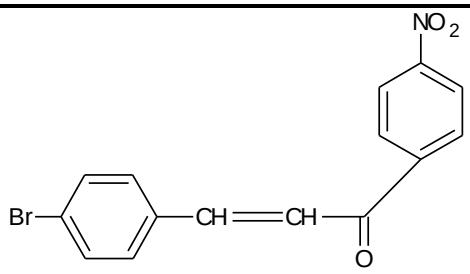
Structure	
Chemical name	1-(4-nitrophenyl)-3-(4-bromophenyl)prop-2-en-1-one
Physical state	Yellow Colour crystals
Molecular Formula	$C_{15}H_{10}BrNO_3$
Molecular Weight	332
Melting point	150ºC
Percentage Yield	65%
TLC Solvent system used	Ethyl acetate: Petroleum ether (8:2)
R_f value	0.80

TABLE-5: PHYSICAL CHARACTERISATION DATA OF COMPOUND N_5

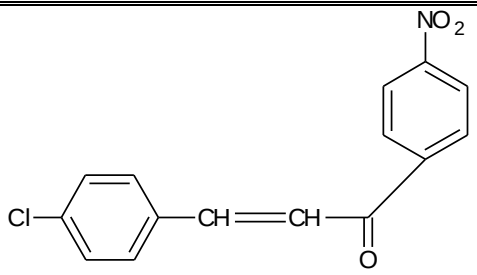
Structure	
Chemical name	1-(4-nitrophenyl)-3-(4-chlorophenyl)prop-2-en-1-one
Physical state	Brown Colour crystals
Molecular Formula	$C_{15}H_{10}ClNO_3$
Molecular Weight	287.69
Melting point	140ºC
Percentage Yield	55%
TLC Solvent system used	Ethyl acetate: Petroleum ether (8:2)
R_f value	0.77

TABLE-6: PHYSICAL CHARACTERISATION DATA OF COMPOUND N_6

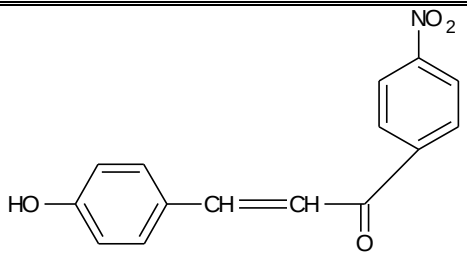
Structure	
Chemical name	1-(4-nitrophenyl)-1-(4-Phenol)prop-2-en-1-one
Physical state	Brown Colour crystals
Molecular Formula	$C_{15}H_{11}NO_4$
Molecular Weight	269.25
Melting point	168ºC
Percentage Yield	65%
TLC Solvent system used	Ethyl acetate: Petroleum ether (8:2)
R_f value	0.76

TABLE-7: PHYSICAL CHARACTERISATION DATA OF COMPOUND N_7

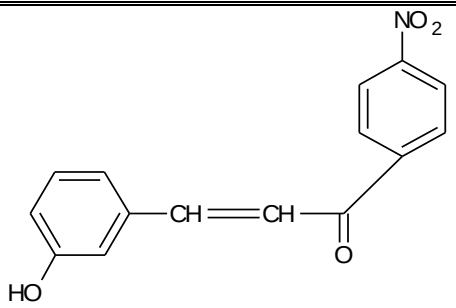
Structure	
Chemical name	1-(4-nitrophenyl)-3-(3-phenol)prop-2-en-1-one
Physical state	Yellowish brown Colour crystals
Molecular Formula	$C_{15}H_{11}NO_4$
Molecular Weight	269.25
Melting point	175ºC
Percentage Yield	55%
TLC Solvent system used	Ethyl acetate: Petroleum ether (8:2)
R_f value	0.72

TABLE-8: PHYSICAL CHARACTERISATION DATA OF COMPOUND N_8

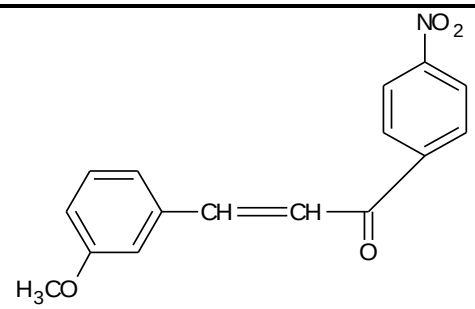
Structure	
Chemical name	1-(4-nitrophenyl)-3-(3-methoxyphenyl)prop-2-en-1-one
Physical state	Yellow Colour crystals
Molecular Formula	$C_{16}H_{13}NO_4$
Molecular Weight	283.27
Melting point	167ºC
Percentage Yield	65%
TLC Solvent system used	Ethyl acetate: Petroleum ether (8:2)
R_f value	0.76

TABLE-9: PHYSICAL CHARACTERISATION DATA OF COMPOUND N_9

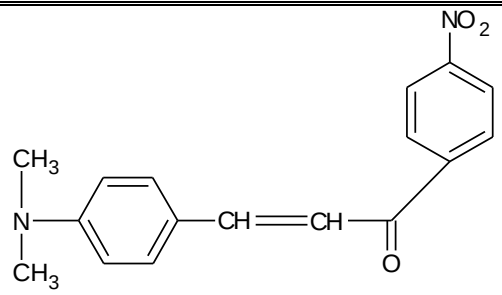
Structure	
Chemical name	1-(4-nitrophenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one
Physical state	Red Colour crystals
Molecular Formula	$C_{17}H_{16}N_2O_3$
Molecular Weight	296.32
Melting point	189ºC
Percentage Yield	65%
TLC Solvent system used	Ethyl acetate: Petroleum ether (8:2)
R_f value	0.70

TABLE-10: PHYSICAL CHARACTERISATION DATA OF COMPOUND C_1

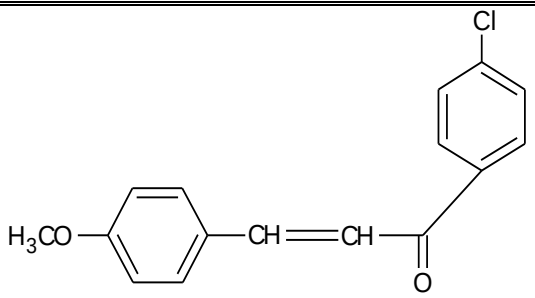
Structure	
Chemical name	1-(4-chlorophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one
Physical state	Yellow Colour crystals
Molecular Formula	$C_{16}H_{12}N_2O_4$
Molecular Weight	296
Melting point	155ºC
Percentage Yield	65%
TLC Solvent system used	Ethyl acetate: Petroleum ether (8:2)
R_f value	0.76

TABLE-11: PHYSICAL CHARACTERISATION DATA OF COMPOUND C_2

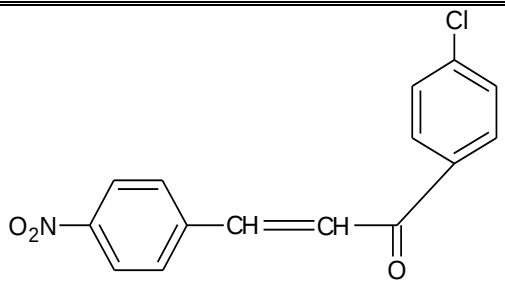
Structure	
Chemical name	1-(4-Chlorophenyl)-3-(4-nitrophenyl)prop-2-en-1-one
Physical state	Brown Colour crystals
Molecular Formula	$C_{15}H_{10}ClNO_3$
Molecular Weight	287.69
Melting point	100ºC
Percentage Yield	65%
TLC Solvent system used	Ethyl acetate: Petroleum ether (8:2)
R_f value	0.80

TABLE-12: PHYSICAL CHARACTERISATION DATA OF COMPOUND C_3

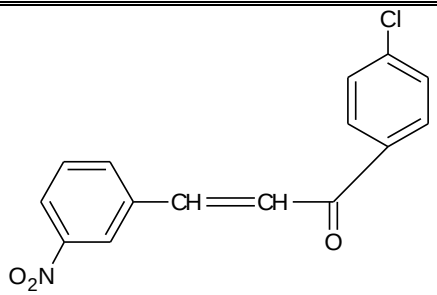
Structure	
Chemical name	1-(4-Chlorophenyl)-3-(3-nitrophenyl)prop-2-en-1-one
Physical state	Brown Colour crystals
Molecular Formula	$C_{15}H_{10}ClNO_3$
Molecular Weight	287.69
Melting point	110ºC
Percentage Yield	60%
TLC Solvent system used	Ethyl acetate: Petroleum ether (8:2)
R_f value	0.76

TABLE-13: PHYSICAL CHARACTERISATION DATA OF COMPOUND C_4

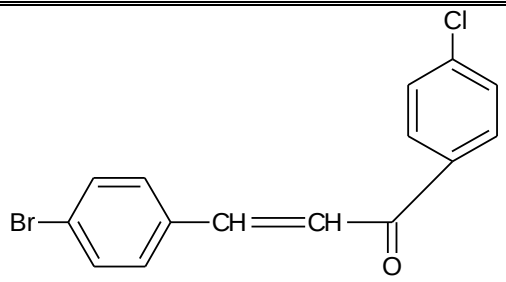
Structure	
Chemical name	1-(4-Chlorophenyl)-3-(4-bromophenyl)prop-2-en-1-one
Physical state	White Colour crystals
Molecular Formula	$C_{15}H_{10}BrClO$
Molecular Weight	321.59
Melting point	110ºC
Percentage Yield	55%
TLC Solvent system used	Ethyl acetate: Petroleum ether (8:2)
R_f value	0.82

TABLE-14: PHYSICAL CHARACTERISATION DATA OF COMPOUND C_5

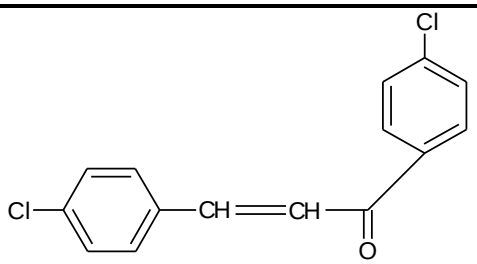
Structure	
Chemical name	1-(4-Chlorophenyl)-3-(4-chlorophenyl)prop-2-en-1-one
Physical state	White Colour crystals
Molecular Formula	$C_{15}H_{10}Cl_2O$
Molecular Weight	277.14
Melting point	115ºC
Percentage Yield	65%
TLC Solvent system used	Ethyl acetate: Petroleum ether (8:2)
R_f value	0.84

TABLE-15: PHYSICAL CHARACTERISATION DATA OF COMPOUND C_6

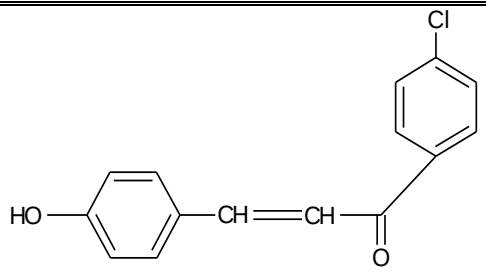
Structure	
Chemical name	1-(4-Chlorophenyl)-3-(4-phenol)prop-2-en-1-one
Physical state	Yellow Colour crystals
Molecular Formula	$C_{15}H_{11}ClO_2$
Molecular Weight	258.69
Melting point	130ºC
Percentage Yield	66%
TLC Solvent system used	Ethyl acetate: Petroleum ether (8:2)
R_f value	0.66

TABLE-16: PHYSICAL CHARACTERISATION DATA OF COMPOUND C_7

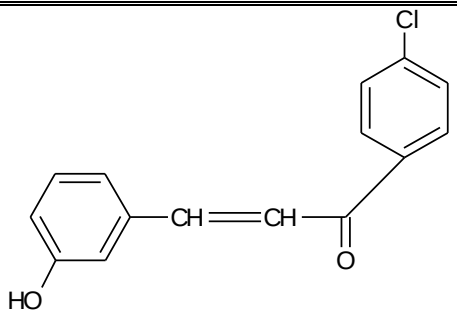
Structure	
Chemical name	1-(4-Chlorophenyl)-3-(3-phenol)prop-2-en-1-one
Physical state	Yellow Colour crystals
Molecular Formula	$C_{15}H_{11}ClO_2$
Molecular Weight	258.69
Melting point	123ºC
Percentage Yield	65%
TLC Solvent system used	Ethyl acetate: Petroleum ether (8:2)
R_f value	0.66

TABLE-17: PHYSICAL CHARACTERISATION DATA OF COMPOUND C_8

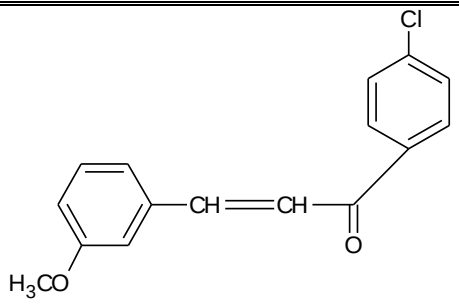
Structure	
Chemical name	1-(4-Chlorophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one
Physical state	Yellow Colour crystal
Molecular Formula	$C_{16}H_{13}ClO_2$
Molecular Weight	272.72
Melting point	135ºC
Percentage Yield	55%
TLC Solvent system used	Ethyl acetate: Petroleum ether (8:2)
R_f value	0.66

TABLE-18: PHYSICAL CHARACTERISATION DATA OF COMPOUND C_9

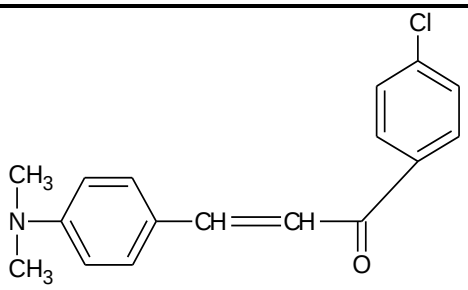
Structure	
Chemical name	1-(4-Chlorophenyl)-3-(4-(dimethylamino))prop-2-en-1-one
Physical state	Red Colour crystal
Molecular Formula	$C_{17}H_{16}ClNO$
Molecular Weight	285.76
Melting point	120ºC
Percentage Yield	65%
TLC Solvent system used	Ethyl acetate: Petroleum ether (8:2)
R_f value	0.84

TABLE-19: PHYSICAL CHARACTERISATION DATA OF COMPOUND N_1

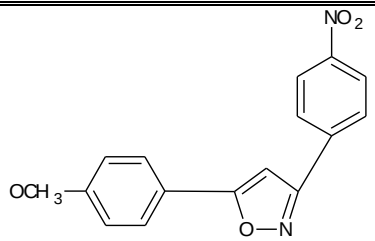
Structure	
Chemical name	3-(4-methoxyphenyl)-5-(4- nitrophenyl)isoxazole
Physical state	Yellow Colour crystal
Solubility	DMSO
Molecular Formula	$C_{16}H_{12}N_2O_4$
Molecular Weight	296
Melting point	155ºC
Percentage Yield	65%
TLC Solvent system used	Chloroform: methanol (9:1)
R_f value	0.76
Composition	C(64.86%) H(4.08%) N(9.45%) O(21.60%)

TABLE-20: PHYSICAL CHARACTERISATION DATA OF COMPOUND N_2

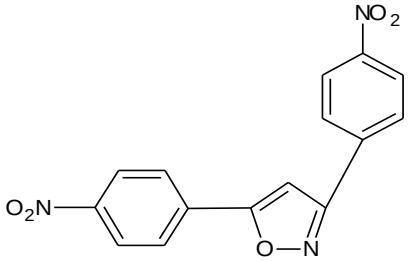
Structure	
Chemical name	3,5-bis(4-nitrophenyl)isoxazole
Physical state	Brown Colour crystal
Solubility	DMSO
Molecular Formula	$C_{15}H_9N_2O_5$
Molecular Weight	297
Melting point	165ºC
Percentage Yield	75%
TLC Solvent system used	Chloroform: methanol (9:1)
R_f value	0.75
Composition	C(57.88%) H(2.91%) N(13.50%) O(25.70%)

TABLE-21: PHYSICAL CHARACTERISATION DATA OF COMPOUND N_3

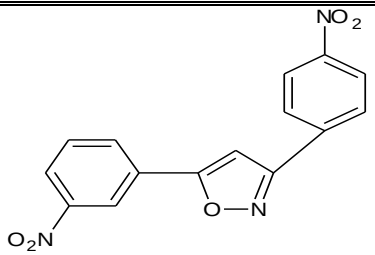
Structure	
Chemical name	5-(3-nitrophenyl)-3-(4-nitrophenyl)isoxazole
Physical state	Colourless crystal
Solubility	DMSO
Molecular Formula	$C_{15}H_9N_2O_5$
Molecular Weight	297
Percentage Yield	62%
Melting point	160ºC
TLC Solvent system	Chloroform: methanol(9:1)
R_f value	0.64
Composition	C(52.20%) H(2.63%) Br(23.15%) N(8.12%) O(13.91%)

TABLE-22: PHYSICAL CHARACTERISATION DATA OF COMPOUND N_4

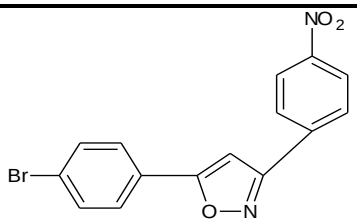
Structure	
Chemical name	5-(4-bromophenyl)-3-(4-nitrophenyl)isoxazole
Physical state	Pale Brown crystal
Solubility	DMSO
Molecular Formula	$C_{15}H_9N_2O_3Br$
Molecular Weight	345
Percentage Yield	50%
Melting point	169ºC
TLC Solvent system	Chloroform: methanol(9:1)
R_f value	0.77
Composition	C(52.20%) H(2.63%) Br(23.15%) N(8.12%) O(13.91%)

TABLE-24: PHYSICAL CHARACTERISATION DATA OF COMPOUND N_5

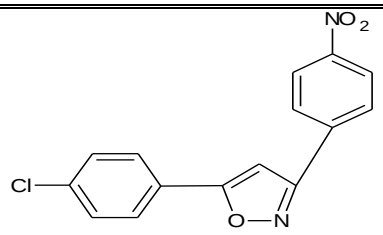
Structure	
Chemical name	5-(4-chlorophenyl)-3-(4-nitrophenyl)isoxazole
Physical state	Brown Colour crystal
Solubility	DMSO
Molecular Formula	$C_{15}H_9N_2O_3Cl$
Molecular Weight	310
Percentage Yield	60%
Melting point	156ºC
TLC Solvent system	Chloroform: methanol(9:1)
R_f value	0.66
Composition	C(59.91%) H(3.02%) Cl(11.79%) N(9.32%) O(15.96%)

TABLE-25: PHYSICAL CHARACTERISATION DATA OF COMPOUND N_6

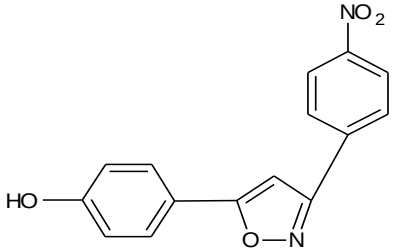
Structure	
Chemical name	4-[3-(4-nitrophenyl)isoxazol-5-yl]phenol
Physical state	Brown colour crystal
Solubility	DMSO
Molecular Formula	$C_{15}H_9N_2O_3$
Molecular Weight	266
Percentage Yield	62%
Melting point	155ºC
TLC Solvent system	Chloroform: methanol(9:1)
R_f value	0.58
Composition	C(63.83%) H(3.57%) N(9.92%) O(22.67%)

TABLE-26: PHYSICAL CHARACTERISATION DATA OF COMPOUND N_7

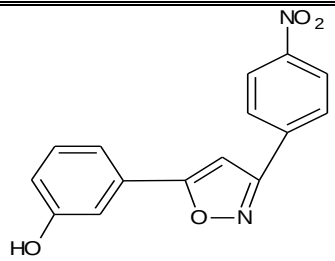
Structure	
Chemical name	3-[3-(4-nitrophenyl)isoxazol-5-yl]phenol
Physical state	Brown Colour crystal
Solubility	DMSO
Molecular Formula	$C_{15}H_{10}N_2O_3$
Molecular Weight	266
Percentage Yield	65%
Melting point	170ºC
TLC Solvent system	Chloroform: methanol(9:1)
R_f value	0.58
Composition	C(63.83%) H(3.57%) N(9.92%) O(22.67%)

TABLE-27: PHYSICAL CHARACTERISATION DATA OF COMPOUND N_8

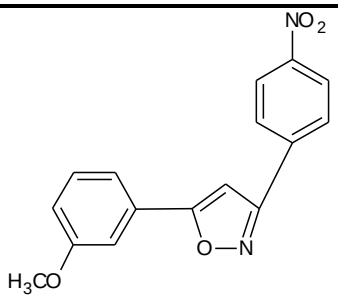
Structure	
Chemical name	5-(3-methoxyphenyl)-3-(4-nitrophenyl)isoxazole
Physical state	Yellow colour crystal
Solubility	DMSO
Molecular Formula	$C_{16}H_{12}N_2O_4$
Molecular Weight	309
Percentage Yield	62%
Melting point	160ºC
TLC Solvent system	Chloroform: methanol(9:1)
R_f value	0.65
Composition	C(64.86%) H(4.08%) N(9.45%) O(21.60%)

TABLE-28: PHYSICAL CHARACTERISATION DATA OF COMPOUND N_9

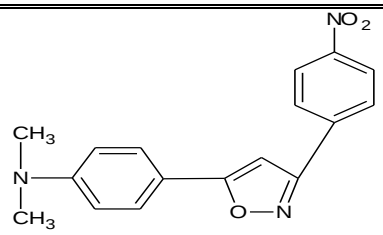
Structure	
Chemical name	4-[3-(4-chlorophenyl)isoxazol-5-yl]-*N*,*N*-dimethylaniline
Physical state	Brown Colour crystal
Solubility	DMSO
Molecular Formula	$C_{17}H_{15}N_3O_3$
Molecular Weight	309
Percentage Yield	72%
Melting point	178ºC
TLC Solvent system	Chloroform: methanol(9:1)
R_f value	0.73
Composition	C(68.34%) H(5.06%) Cl(11.87%) N(9.38%) O(5.36%)

TABLE-29: PHYSICAL CHARACTERISATION DATA OF COMPOUND C_1

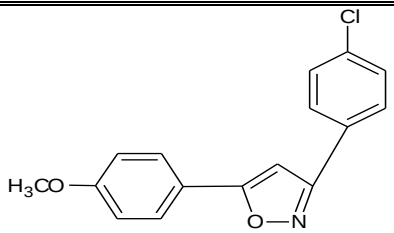
Structure	
Chemical name	3-(4-chlorophenyl)-5-(4-methoxyphenyl)isoxazole
Physical state	yellow colour crystal
Solubility	DMSO
Molecular Formula	$C_{16}H_{12}NO_2Cl$
Molecular Weight	285
Percentage Yield	50%
Melting point	110ºC
TLC Solvent system	Chloroform: methanol(9:1)
R_f value	0.74
Composition	C(67.26%) H(4.23%) Cl(12.41%) N(4.90%) O(11.20%

TABLE-30: PHYSICAL CHARACTERISATION DATA OF COMPOUND C_2

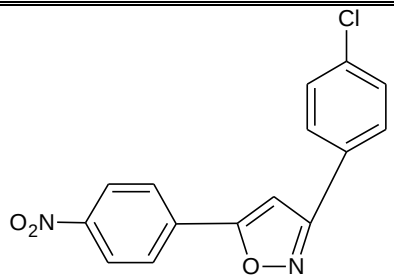
Structure	
Chemical name	3-(4-chlorophenyl)-5-(4-nitrophenyl)isoxazole
Physical state	Colourless crystals
Solubility	DMSO
Molecular Formula	$C_{15}H_9N_2O_5Cl$
Molecular Weight	300.69
Percentage Yield	60%
Melting point	90ºC
TLC Solvent system	Chloroform: methanol(9:1)
R_f value	0.52
Composition	C(59.91%) H(3.02%) Cl(11.79%) N(9.32%) O(15.96%)

TABLE-31: PHYSICAL CHARACTERISATION DATA OF COMPOUND C_3

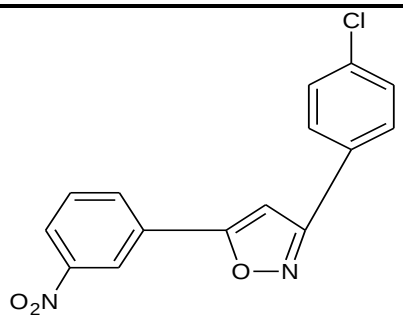
Structure	
Chemical name	3-(4-chlorophenyl)-5-(3-nitrophenyl)isoxazole
Physical state	Brown colour crystal
Solubility	DMSO
Molecular Formula	$C_{15}H_9N_2O_3Cl$
Molecular Weight	300.69
Percentage Yield	60.54%
Melting point	190ºC
TLC Solvent system	Chloroform: methanol(9:1)
R_f value	0.74
Composition	C(59.91%) H(3.02%) Cl(11.79%) N(9.32%) O(15.96%)

TABLE-32: PHYSICAL CHARACTERISATION DATA OF COMPOUND C_4

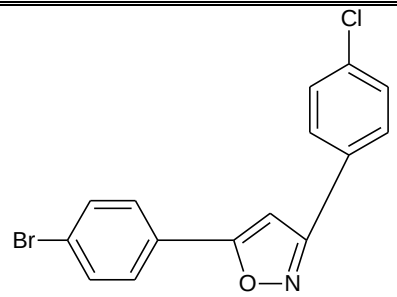
Structure	
Chemical name	5-(4-bromophenyl)-3-(4chlorophenyl)isoxazole
Physical state	White Colour crystal
Solubility	DMSO
Molecular Formula	$C_{15}H_9NOClBr$
Molecular Weight	334.59
Percentage Yield	60.54%
Melting point	210ºC
TLC Solvent system	Chloroform: methanol(9:1)
R_f value	0.80
Composition	C(53.84%) H(2.71%) Br(23.88%) Cl(10.60%) N(4.19%) O(4.78%)

TABLE-33: PHYSICAL CHARACTERISATION DATA OF COMPOUND C_5

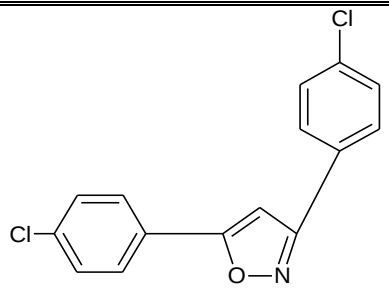
Structure	
Chemical name	3,5-bis(4-chlorophenyl)isoxazole
Physical state	Pale yellow crystal
Solubility	DMSO
Molecular Formula	$C_{15}H_9Cl_2NO$
Molecular Weight	290.14
Percentage Yield	65.54%
Melting point	220ºC
TLC Solvent system	Chloroform: methanol(9:1)
R_f value	0.62
Composition	C(62.09%) H(3.13%) Cl(24.44%) N(4.83%) O(5.51%)

TABLE-34: PHYSICAL CHARACTERISATION DATA OF COMPOUND C_6

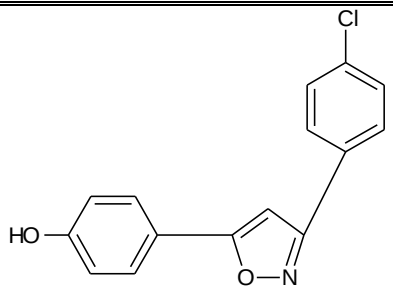
Structure	
Chemical name	4-[3-(4-chlorophenyl)isoxazol-5-yl]phenol
Physical state	Pale yellow crystal
Solubility	DMSO
Molecular Formula	$C_{15}H_{10}ClNO_2$
Molecular Weight	271.69
Percentage Yield	65.54%
Melting point	220ºC
TLC Solvent system	Chloroform: methanol(9:1)
R_f value	0.62
Composition	C(66.31%) H(3.71%) Cl(13.05%) N(5.16%) O(11.78%)

TABLE-35: PHYSICAL CHARACTERISATION DATA OF COMPOUND C_7

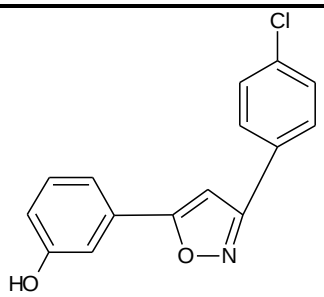
Structure	
Chemical name	3-[3-(4-chlorophenyl)isoxazol-5-yl]phenol
Physical state	Pale yellow crystal
Solubility	DMSO
Molecular Formula	$C_{15}H_{10}ClNO_2$
Molecular Weight	271.69
Percentage Yield	65.54%
Melting point	220ºC
TLC Solvent system	Chloroform: methanol(9:1)
R_f value	0.62
Composition	C(66.31%) H(3.71%) Cl(13.05%) N(5.16%) O(11.78%)

TABLE-36: PHYSICAL CHARACTERISATION DATA OF COMPOUND C_8

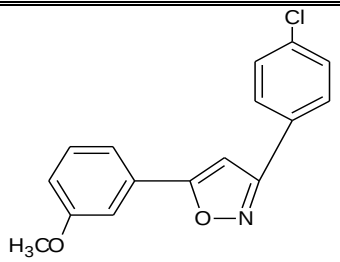
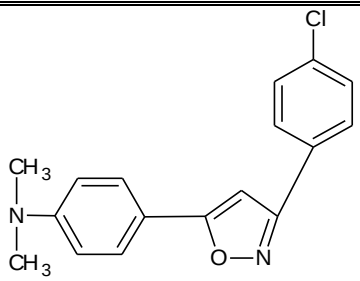
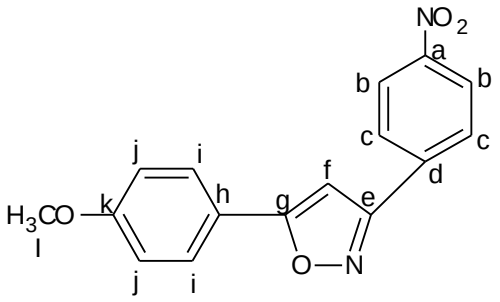
Structure	
Chemical name	3-(4-chlorophenyl)-5-(3-methoxyphenyl)isoxazole
Physical state	Pale yellow crystal
Solubility	DMSO
Molecular Formula	$C_{16}H_{12}ClNO_2$
Molecular Weight	285.72
Percentage Yield	65.54%
Melting point	220ºC
TLC Solvent system	Chloroform: methanol(9:1)
R_f value	0.62
Composition	C(67.26%) H(4.23%) Cl(12.41%) N(4.90%) O(11.20%)

TABLE-37: PHYSICAL CHARACTERISATION DATA OF COMPOUND C_9

Structure	
Chemical name	4-[3-(4-chlorophenyl)isoxazol-5-yl]-*N*,*N*-dimethylaniline
Physical state	Brown crystal
Solubility	DMSO
Molecular Formula	$C_{17}H_{15}ClN_2O$
Molecular Weight	298.76
Percentage Yield	65.54%
Melting point	120ºC
TLC Solvent system	Chloroform: methanol(9:1)
R_f value	0.78
Composition	C(62.09%) H(3.13%) Cl(24.44%) N(4.83%) O(5.51%)

CHEMICAL CHARACTERISATION DATA OF COMPOUND N_1



IR Spectra:

Functional group	**Frequency in cm^{-1}**
C=C stretching (for aromatic)	1657
C=N stretching	1573
C-H stretching	2855
C-O stretching	1031
R-NO_2	1440

^{1}H NMR Data:

Protons	**δ in ppm**
CH_3	s(3.8-4)
Ar-H, 8H and CH, 1H	m(6.7-8.3)

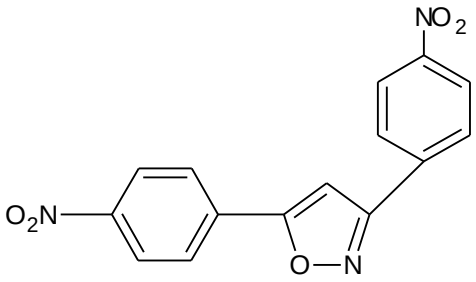
MASS Data:

Molecular Weight	**Fragmentation**
296.09	149, 165, 198, 236,267

^{13}C-NMR:

Ca-1	162.29
C_b-2	114.61
C_c-2	130.63
C_d-1	130.20
C_e-1	143.48
C_f -1	127.06
C_g-1	143.48
C_i-2	114.61
C_h-1	118.98
C_i-2	130.63
C_k-1	114.61
C_I-2	55.48

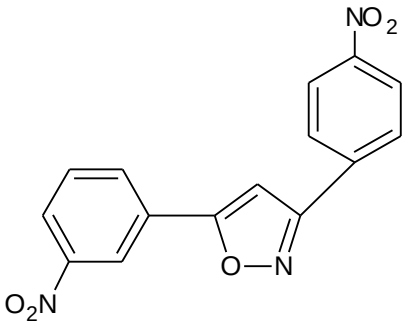
CHEMICAL CHARACTERISATION DATA OF COMPOUND N_2



IR Spectra:

Functional group	**Frequency in cm^{-1}**
C=C stretching	1595
C=N stretching	1597
C-O aromatic stretching	1711.33
R-NO_2 stretching	1456

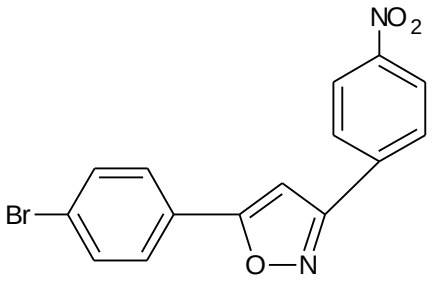
CHEMICAL CHARACTERISATION DATA OF COMPOUND N_3



IR Spectra:

Functional group	**Frequency in cm^{-1}**
C-H stretching (for aromatic)	2967
C=N stretching	1593
C=C aromatic stretching	1649
C-O stretching	1100
R-NO_2 stretching	1374

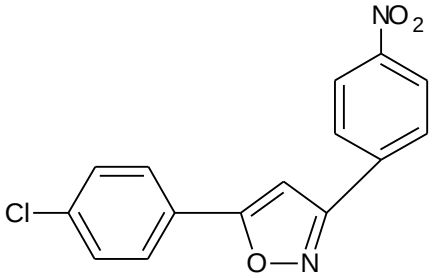
CHEMICAL CHARACTERISATION DATA OF COMPOUND N_4



IR Spectra:

Functional group	**Frequency in cm^{-1}**
Ar-C-H stretching	3191
C=N stretching	1527
Ar-C=C stretching	1597
C-O stretching	1101
C-Br stretching	692
R-NO_2 stretching	1494

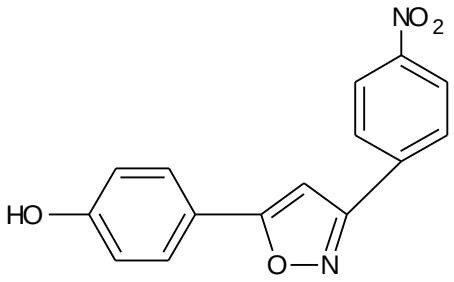
CHEMICAL CHARACTERISATION DATA OF COMPOUND N_5



IR Spectra:

Functional group	**Frequency in cm^{-1}**
Ar-C-H stretching	3150
C=C stretching	1518
C=N stretching	1622
C-O stretching	1015
C-Cl stretching	693
R-NO_2 stretching	1447

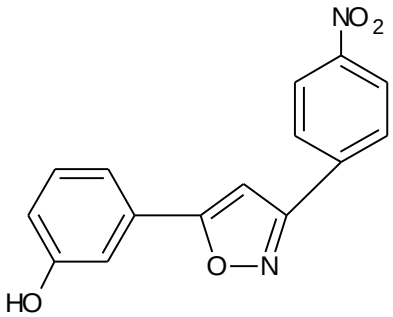
CHEMICAL CHARACTERISATION DATA OF COMPOUND N_6



IR Spectra:

Functional group	**Frequency in cm^{-1}**
Ar-C-H stretching	2954
C=N stretching	1688
Ar-C=C stretching	1515
C-O stretching	1009
C-OH stretching	3254

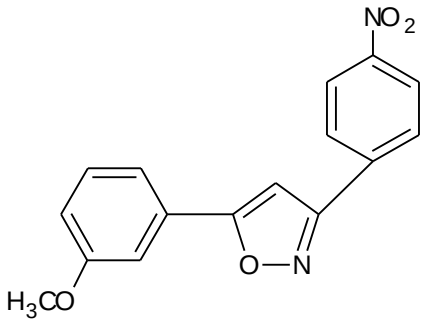
CHEMICAL CHARACTERISATION DATA OF COMPOUND N_7



IR Spectra:

Functional group	**Frequency in cm^{-1}**
Ar-C-H stretching	2927
C=N stretching	1602
C=C stretching	1578
C-O stretching	1100
C-OH stretching	3218
R-NO_2 stretching	1390

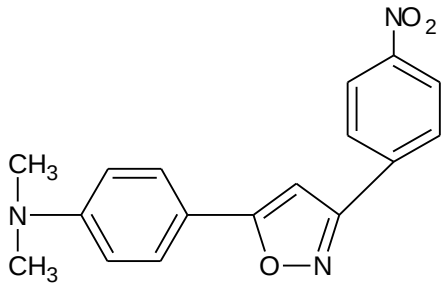
CHEMICAL CHARACTERISATION DATA OF COMPOUND N_8



IR Spectra:

Functional group	**Frequency in cm^{-1}**
C-H stretching	2959
C=C stretching	1494
C-O stretching	1036
R-NO_2 stretching	1397

CHEMICAL CHARACTERISATION DATA OF COMPOUND N_9



IR Spectra:

Functional group	**Frequency in cm^{-1}**
C=N stretching	1647
Ar-C=C stretching	1519
C-H stretching (for CH_3)	2911.19
C-O stretching	1066
R-NO_2 stretching	1519

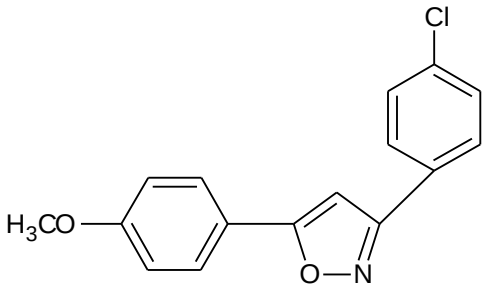
^{1}H NMR Data:

Protons	**δ in ppm**
Ar-H, CH, 1H	m(6.7-8.4)
CH_3	S(2.77)

MASS Data:

Molecular Weight	**Fragmentation**
309	117,138, 176, 213, 260,283

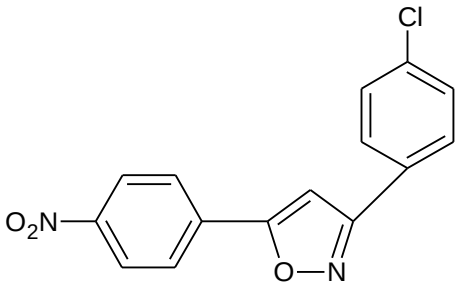
CHEMICAL CHARACTERISATION DATA OF COMPOUND C_1



IR Spectra:

Functional group	**Frequency in cm^{-1}**
C=N stretching	1654
C-H stretching	2965
C=C stretching	1509
C-O stretching	1029
C-Cl stretching	739

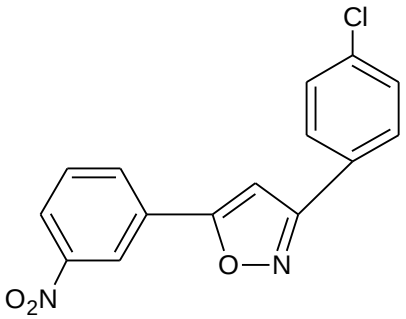
CHEMICAL CHARACTERISATION DATA OF COMPOUND C_2



IR Spectra:

Functional group	**Frequency in cm^{-1}**
Ar-C-H stretching	3295
C=N stretching	1667
C-O stretching	1012
C=C stretching	1519
C-Cl stretching	750

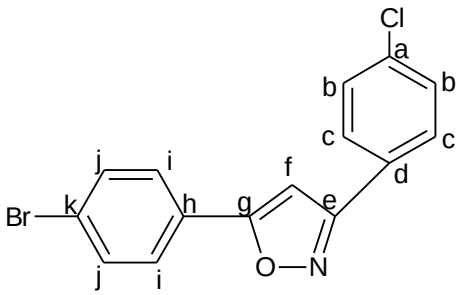
CHEMICAL CHARACTERISATION DATA OF COMPOUND C_3



IR Spectra:

Functional group	**Frequency in cm^{-1}**
Ar-C-H stretching	3250
C=N stretching	1654
Ar-C=C stretching	1549
C-O stretching	1032
R-NO_2 stretching	1408
C-Cl stretching	696

CHEMICAL CHARACTERISATION DATA OF COMPOUND C_4



IR Spectra:

Functional group	**Frequency in cm^{-1}**
C=C stretching	1483
C=N stretching	1655
C-O stretching	1004
C-Br stretching	663
C-Cl stretching	738

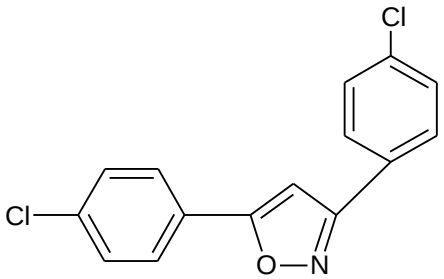
^{1}H NMR Data:

Protons	**δ in ppm**
Ar-H, CH,1H and 8H	M(6.4-8.1)

^{13}C-NMR:

C_a-1	154.7
C_b-2	117.1
C_c-2	130.4
C_d-d	131.6
C_e-1	136.6
C_{f-}1	127.3
C_g-1	134.2
C_{h-1}	122.2
C_i-2	131.6
C_j-2	117.7
C_k-2	100
C_i-1	29.38

CHEMICAL CHARACTERISATION DATA OF COMPOUND C_5



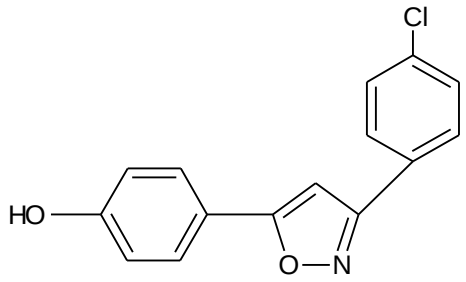
IR Spectra:

Functional group	**Frequency in cm^{-1}**
C=C stretching	1562
Ar-C-H stretching	2950
C=N stretching	1657
C-O stretching	1033
C-Cl stretching	664

^{1}H NMR Data:

Protons	**δ in ppm**
Ar-H, 8H, and CH,1H	m(7.04-7.69)

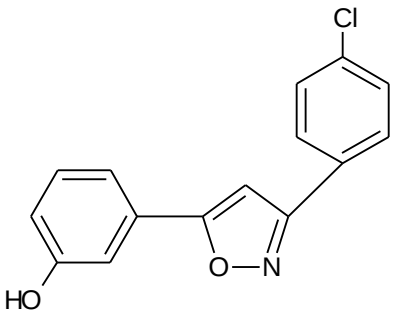
CHEMICAL CHARACTERISATION DATA OF COMPOUND C_6



IR Spectra:

Functional group	**Frequency in cm^{-1}**
C=C stretching	1469
C=N stretching	1684
O-H stretching	3143
C-O stretching	1015
C-Cl stretching	640

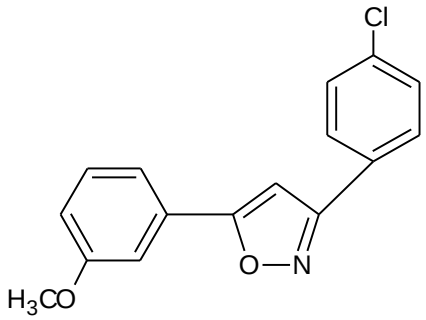
CHEMICAL CHARACTERISATION DATA OF COMPOUND C_7



IR Spectra:

Functional group	**Frequency in cm^{-1}**
C=C stretching	1582
Ar-C-H stretching	2800
O-H stretching	3397
C-O stretching	1108
C=N stretching	1582
C-Cl stretching	693

CHEMICAL CHARACTERISATION DATA OF COMPOUND C_8



IR Spectra:

Functional group	**Frequency in cm^{-1}**
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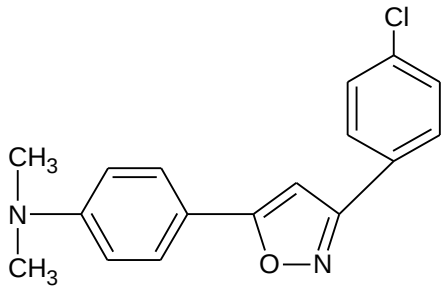
C-H stretching	2840
C=N stretching	1662
C-O stretching	1042
C-Cl stretching	683

CHEMICAL CHARACTERISATION DATA OF COMPOUND C_9



IR Spectra:

Functional group	**Frequency in cm^{-1}**
Ar-C=C stretching	1566
C=N stretching	1647
C-H stretching (for CH_3)	2911
C-O stretching	1039
C=N aromatic stretching	1313.20
C-Cl stretching	698

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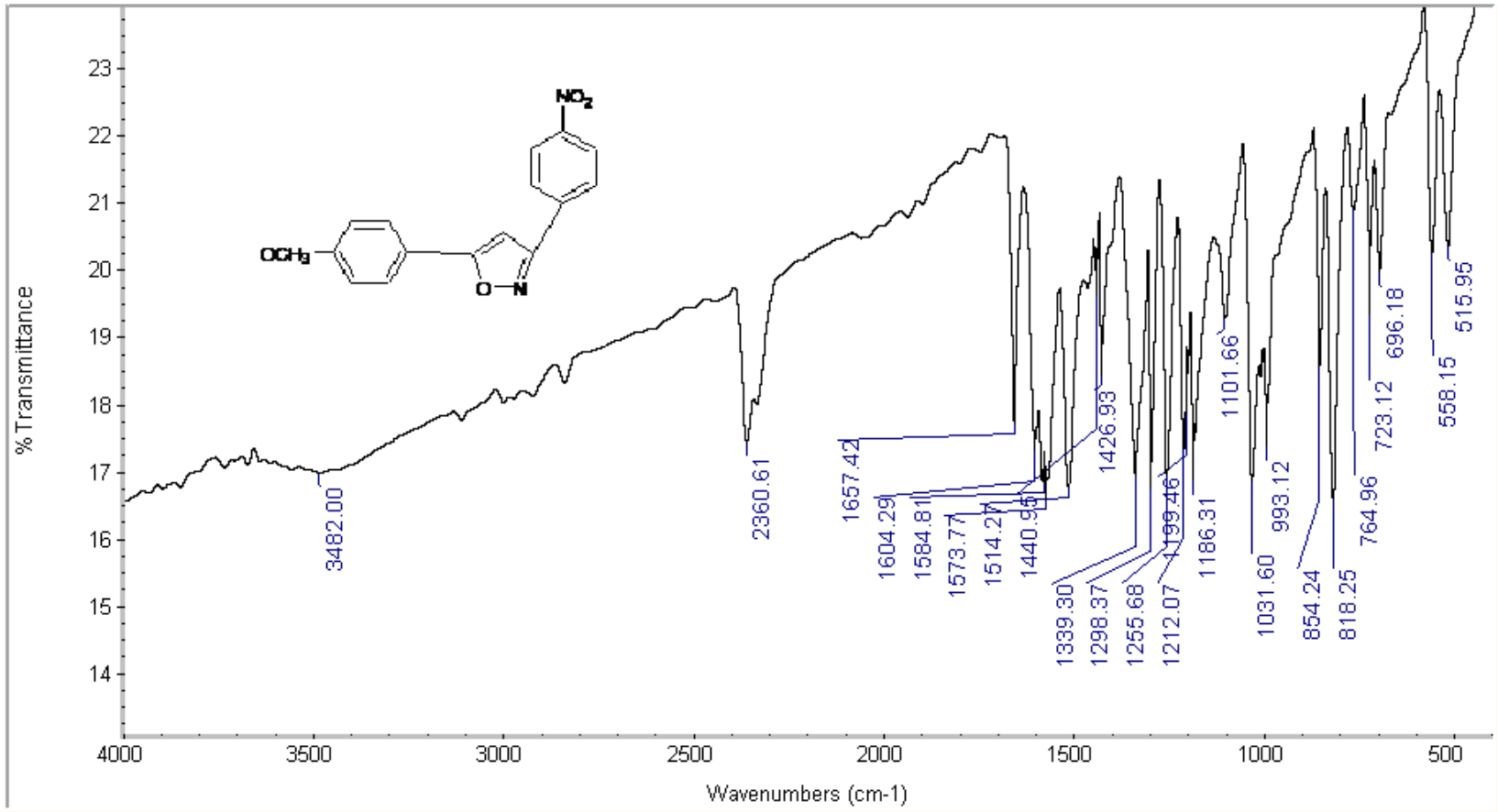
Fri Sep 16 16:50:29 2011 (G

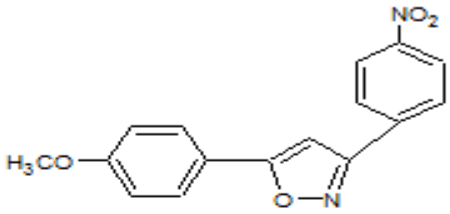


Detector: DTGS KBr
Beamsplitter: KBr
Source: IR

4-METHOXY DER

Performed By :

4-Methoxy der

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PROCNO                         1

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PULPROG                     zg30
TD                         32768
SOLVENT                    CDCl3
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RG                           203
DW                        48.400 usec
DE                         6.50 usec
TE                        298.3 K
D1                     1.00000000 sec
TD0                            1

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PL1                        0.00 dB
PL1W                23.53637505 W
SFO1                500.1330885 MHz

F2 - Processing parameters
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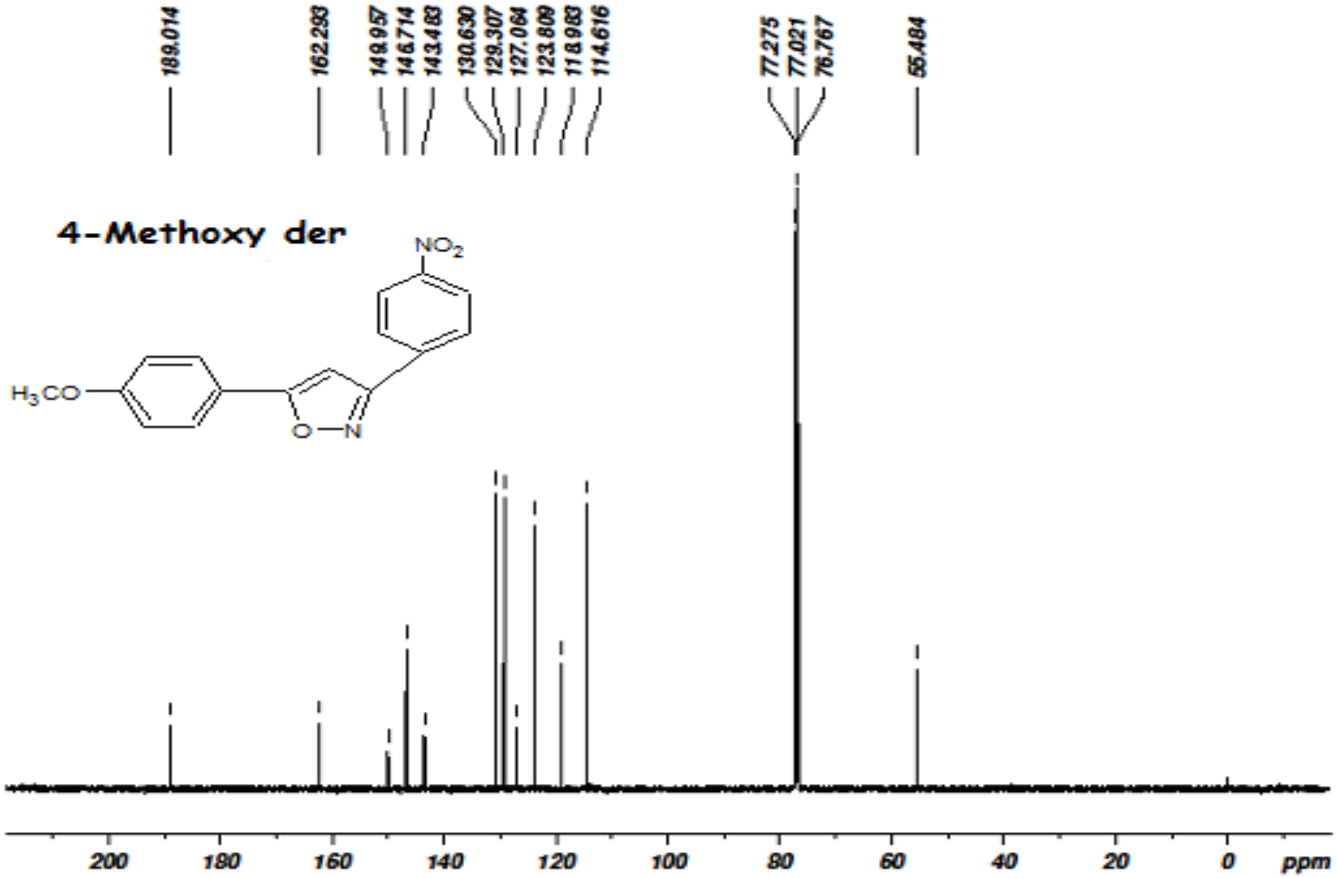


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RG                          203
DW                       16.800 usec
DE                        6.50 usec
TE                       300.1 K
D1                    2.00000000 sec
D11                   0.03000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                          7.80 usec
PL1                         0.00 dB
PL1W                70.83519745 W
SFO1               125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2                  waltz16
NUC2                         1H
PCPD2                      80.00 usec
PL2                         0.00 dB
PL12                       17.50 dB
PL13                       17.50 dB
PL2W                23.53637505 W
PL12W                0.41854253 W
PL13W                0.41854253 W
SFO2               500.1320005 MHz

F2 - Processing parameters
SI                        32768
SF                 125.7577890 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
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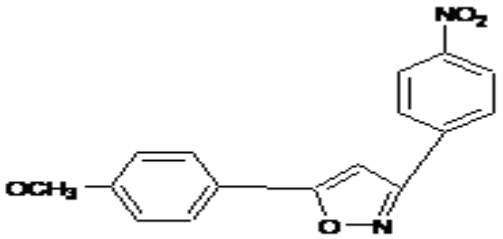
Oxygen Healthcare Research P. Ltd

35, Panchratna Ind. Estate,
Nr. IBP Laxminarayan petrol pump,
Sarkhej-Bawla Highway, Changodar
Ahmedabad-382 213.

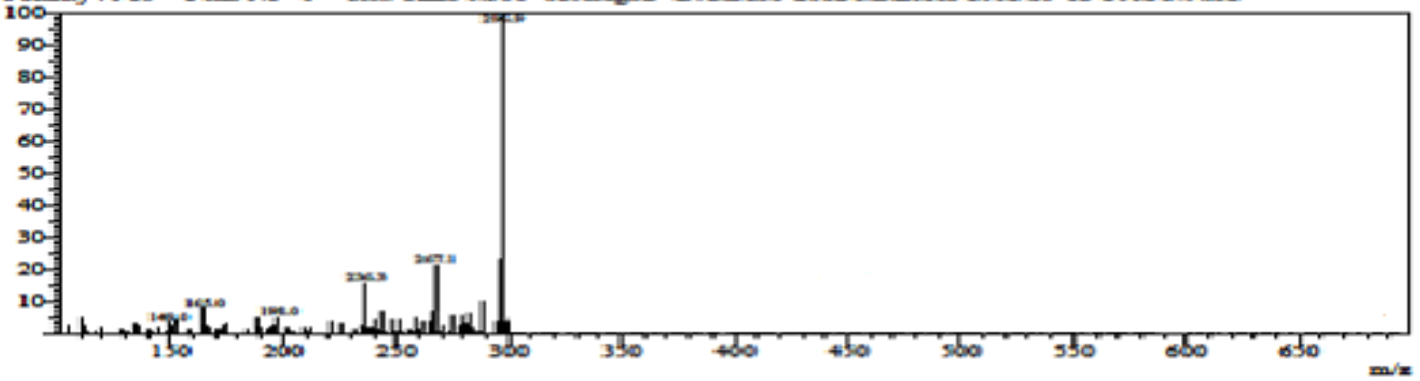
Sample : 4-Methoxy der



Date Acquired : 2:12:35 PM: 3/19/2012
Vial : 4
Injection Volume : 5
Data file : N9.lcd// ID-4 //2:12:35 PM
Method File : MASS-ESI.lcm
Data processed : 3/19/2012 2:14:19 PM

MS Spectrum Graph

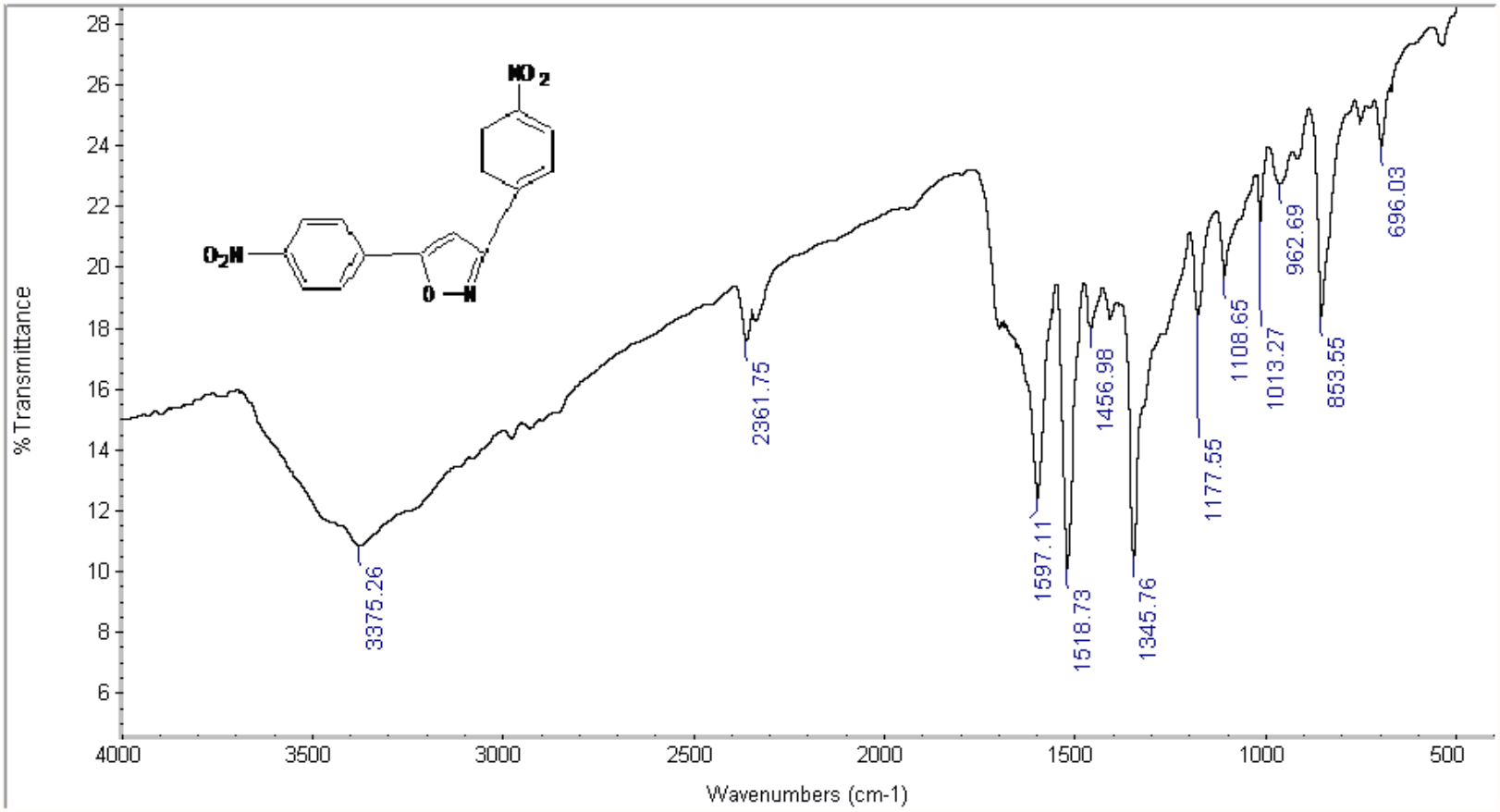
Polarity : Pos Peak No 1 Ret. Time 0.300 Averaged D:\MASS-2012\MARCH-2012\19-03-2012\N9.lcd



Sri Adichunchanagiri College of Pharmacy.,

Dept of Pharmacetuical Chemistry,
B.G. Nagara - 571448

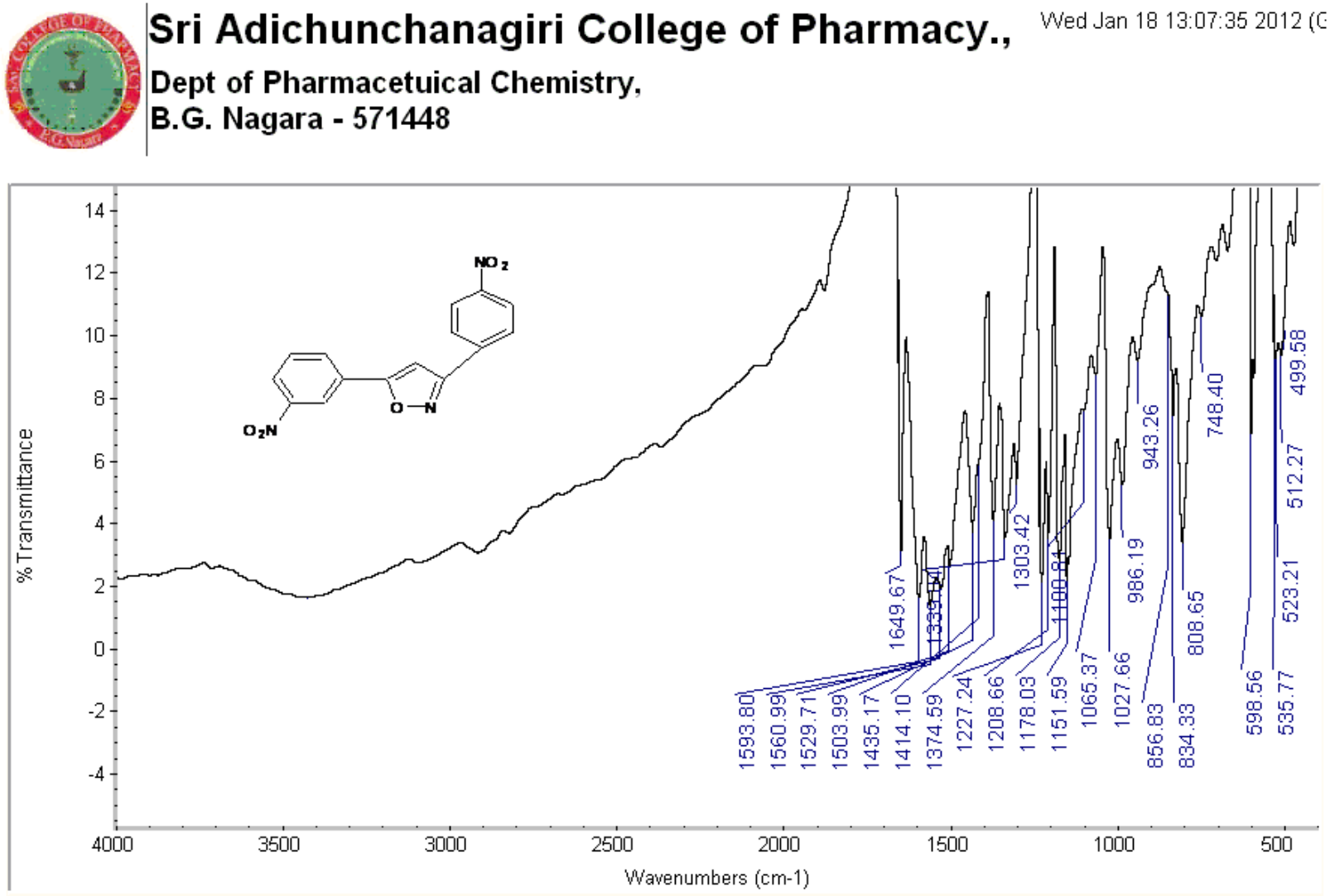
Mon Nov 28 15:46:08 2011 (



Detector: DTGS KBr
Beamsplitter: KBr
Source: IR

4-NITRODER

Performed By :


Sri Adichunchanagiri College of Pharmacy.,
Wed Jan 18 13:07:35 2012 (G
Dept of Pharmacetuical Chemistry,
B.G. Nagara - 571448
% Transmittance
Wavenumbers (cm-1)
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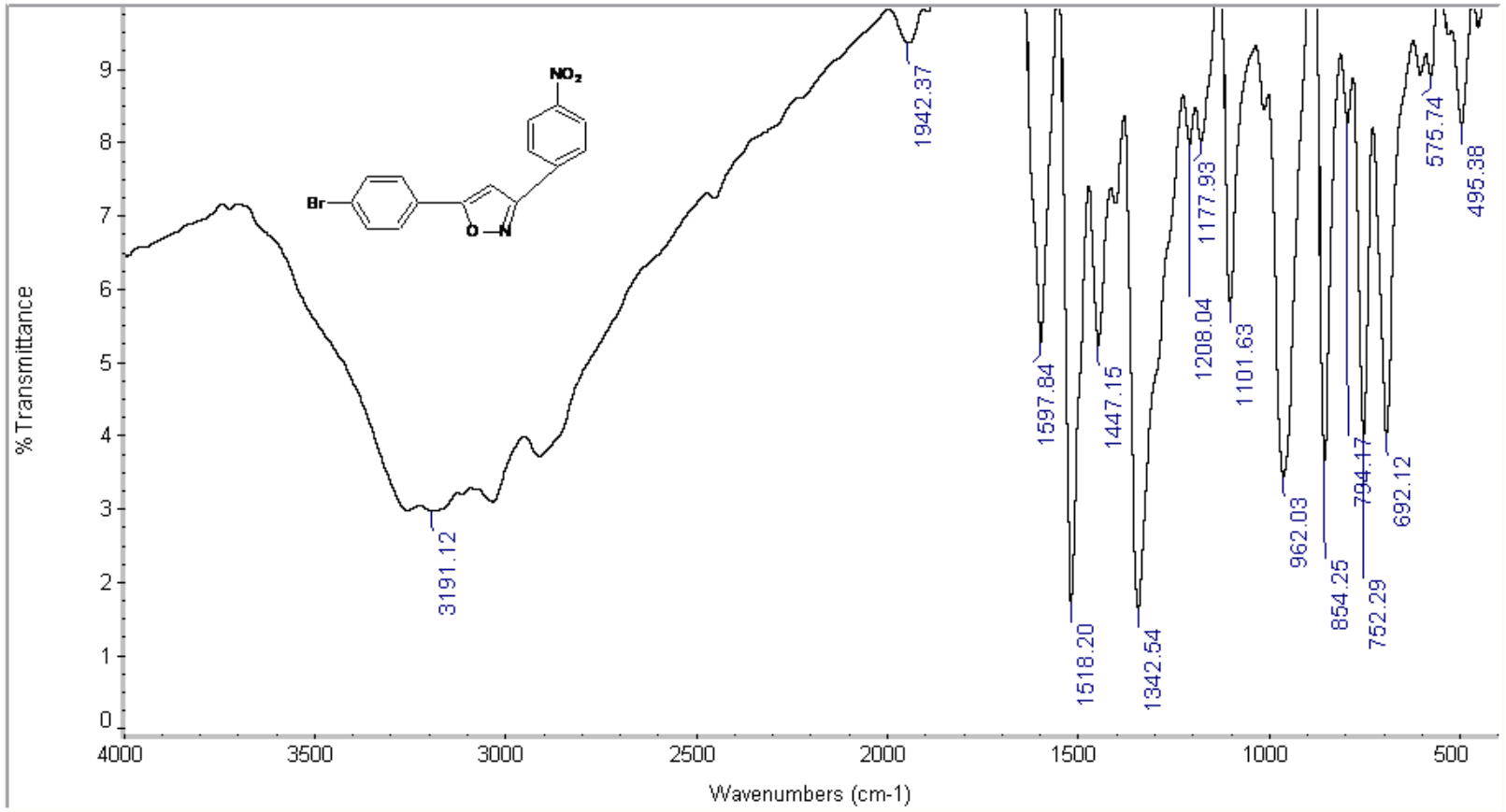
1560.99
1529.71
1503.99
1435.17
1414.10
1374.59
1227.24
1208.66
1178.03
1151.59
1065.37
1027.66
986.19
943.26
856.83
834.33
808.65
748.40
598.56
535.77
523.21
512.27
499.58
1303.42
Detector: DTGS KBr
Beamsplitter: KBr
Source: IR
3-NItro der
Performed By :

Sri Adichunchanagiri College of Pharmacy.,

Dept of Pharmacetuical Chemistry,
B.G. Nagara - 571448

Fri Jul 29 17:03:38 2011 (GM



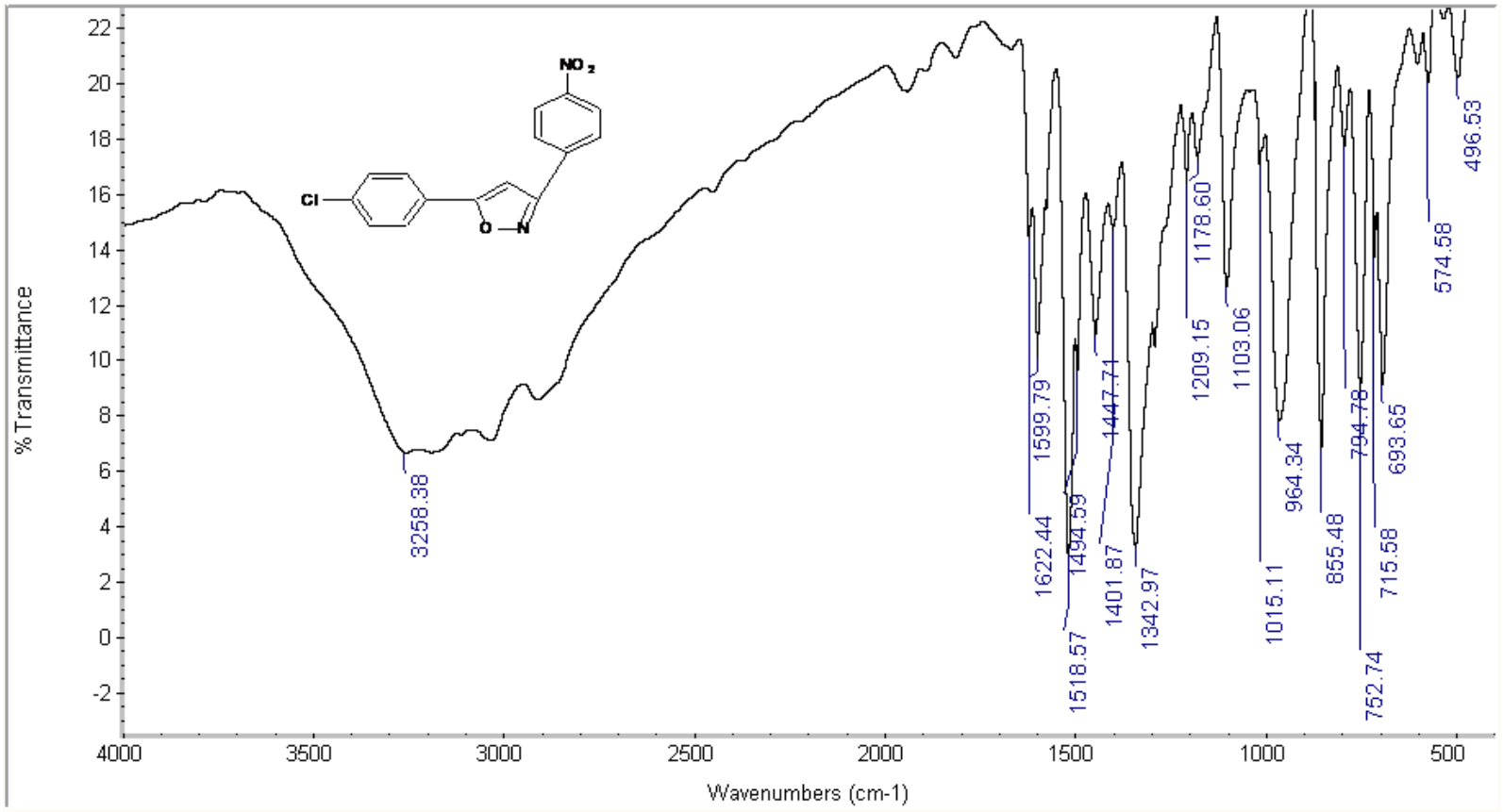
Detector: DTGS KBr
Beamsplitter: KBr **4-bromo der**
Source: IR

Performed By :

Sri Adichunchanagiri College of Pharmacy.,

Dept of Pharmacetuical Chemistry,
B.G. Nagara - 571448

Fri Jul 29 17:13:08 2011 (GM



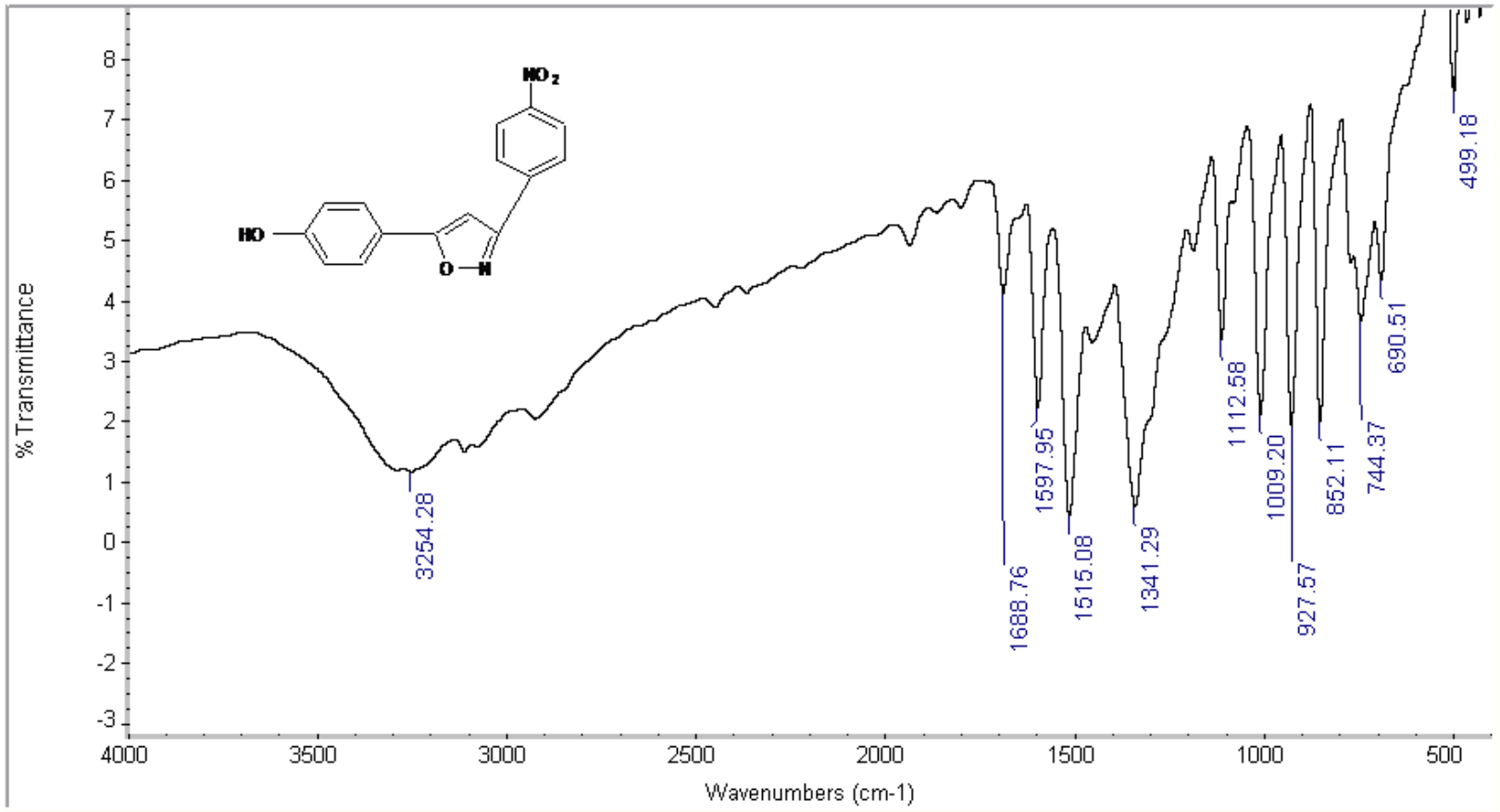
Detector: DTGS KBr
Beamsplitter: KBr
Source: IR

4-chloro der

Performed By :

Sri Adichunchanagiri College of Pharmacy.,
Dept of Pharmacetuical Chemistry,
B.G. Nagara - 571448

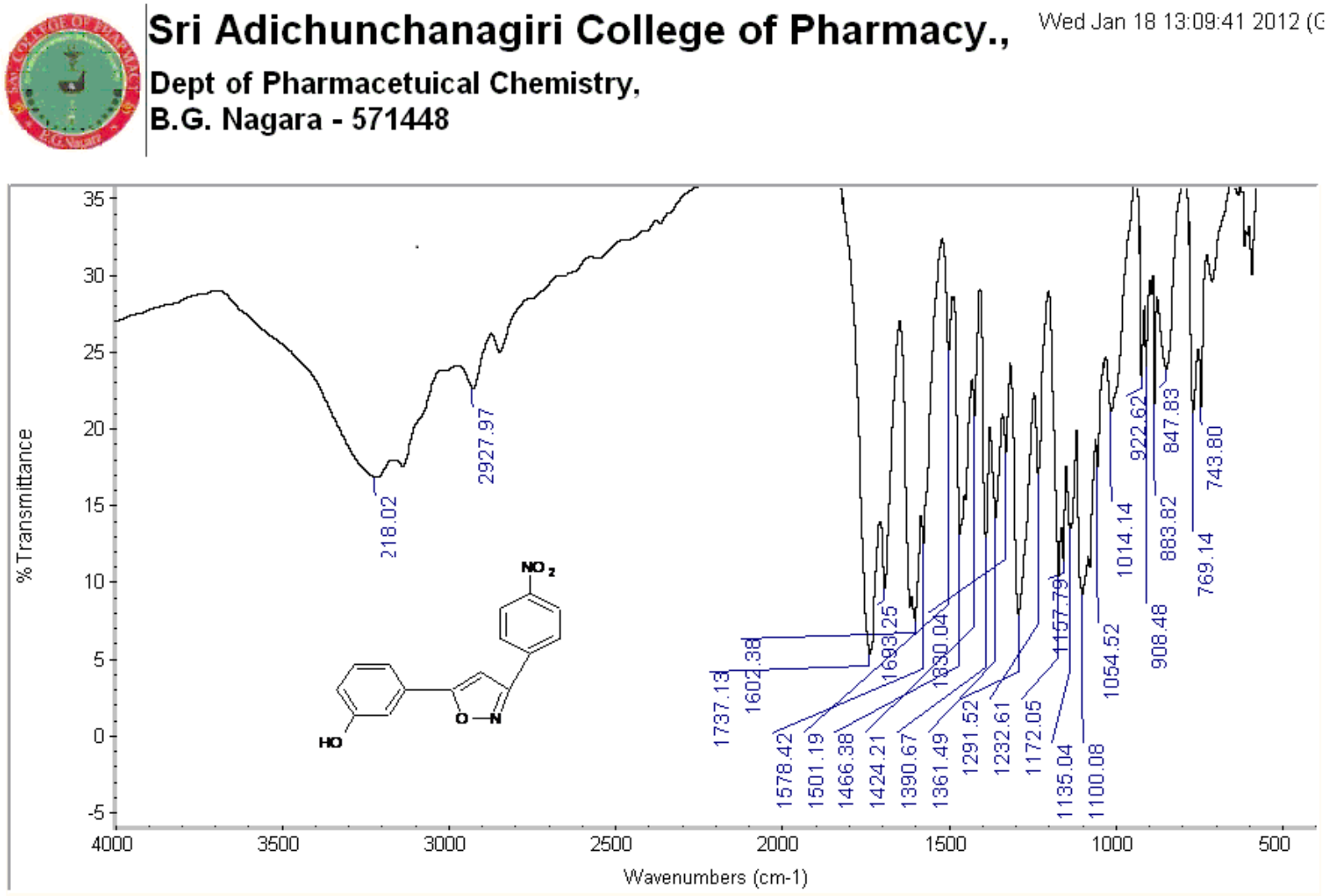
Wed Dec 14 18:09:27 2011 (



Detector: DTGS KBr
Beamsplitter: KBr
Source: IR

4-OH DER

Performed By :


Sri Adichunchanagiri College of Pharmacy.,
Dept of Pharmacetuical Chemistry,
B.G. Nagara - 571448
Wed Jan 18 13:09:41 2012 (G
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1014.14
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847.83
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NO2
HO
O
N
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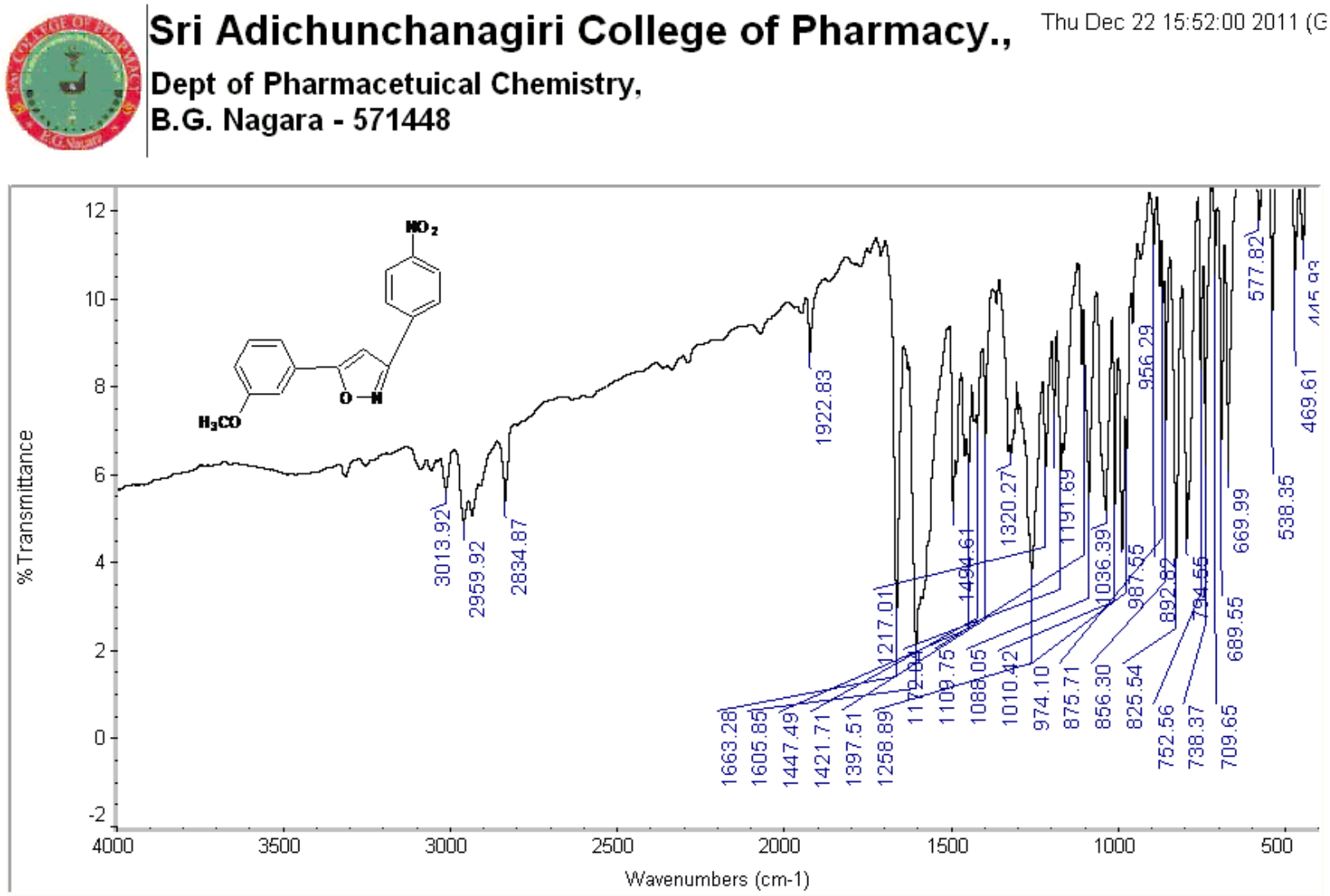
Beamsplitter: KBr
Source: IR
3-hydroxy der
Performed By :


Sri Adichunchanagiri College of Pharmacy.,
Dept of Pharmacetuical Chemistry,
B.G. Nagara - 571448
Thu Dec 22 15:52:00 2011 (G
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1191.69
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987.55
956.29
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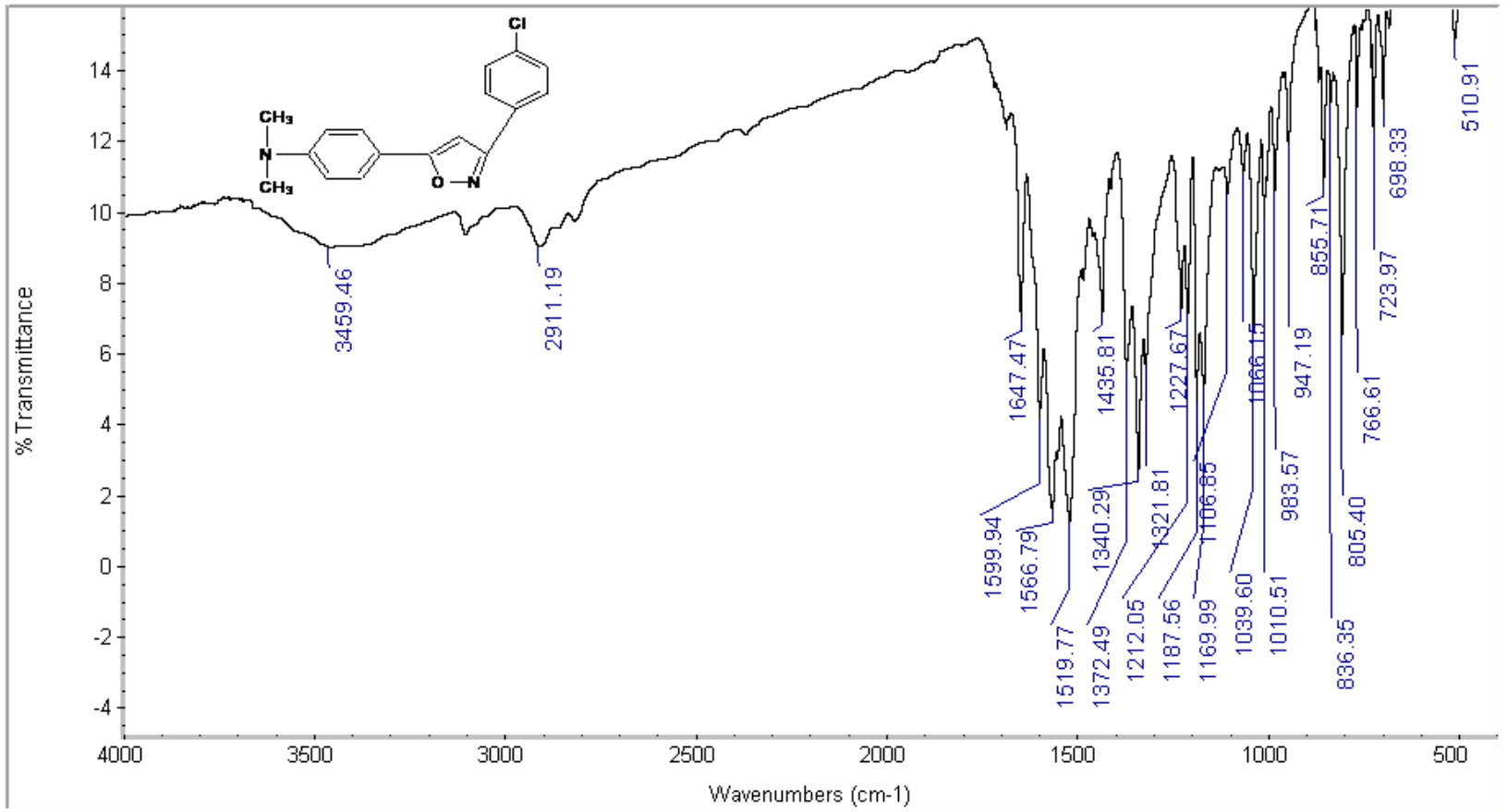
Detector: DTGS KBr
Beamsplitter: KBr
Source: IR
3-METHOXY DER
Performed By :

Sri Adichunchanagiri College of Pharmacy.,

Dept of Pharmacetuical Chemistry,
B.G. Nagara - 571448

Tue Nov 08 11:02:00 2011 (

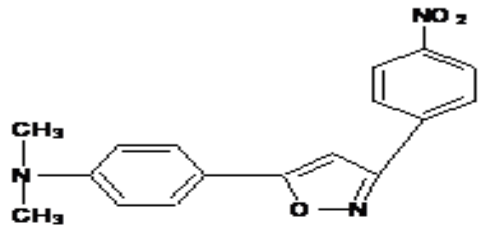


Detector: DTGS KBr
Beamsplitter: KBr
Source: IR

4-DIMETHYL AMINO DER

Performed By :

N-dimethyl amino der



BRUKER

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PROCNO	1	
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PULPROG	zg	
TD	28594	
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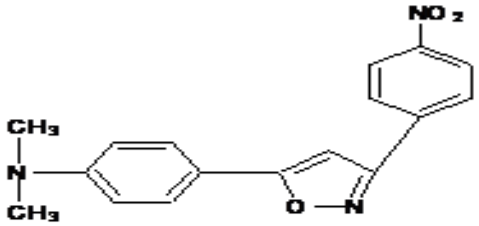
NS	32	
DS	2	
SWH	4832.474	Hz
FIDRES	0.166672	Hz
AQ	2.9999626	sec
RG	203	
DW	103.467	usec
DE	6.50	usec
TE	298.0	K
D1	2.00000000	sec
TD0	1	
========	CHANNEL f1	========
NUC1	1H	
P1	14.10	usec
PL1	-2.00	dB
PL1W	13.42244530	W
SFO1	400.2320296	MHz
SI	65536	
SF	400.2300133	MHz
WDW	EM	
SSB	0	
LB	0.30	Hz
GB	0	
PC	1.00	

Oxygen Healthcare Research P. Ltd

35, Panchratna Ind. Estate,
Nr. IBP Laxminarayan petrol pump,
Sarkhej-Bawla Highway, Changodar
Ahmedabad-382 213.

Sample : N-dimethyl amino der



Date Acquired : 2:09:39 PM: 3/19/2012
Vial : 3
Injection Volume : 5
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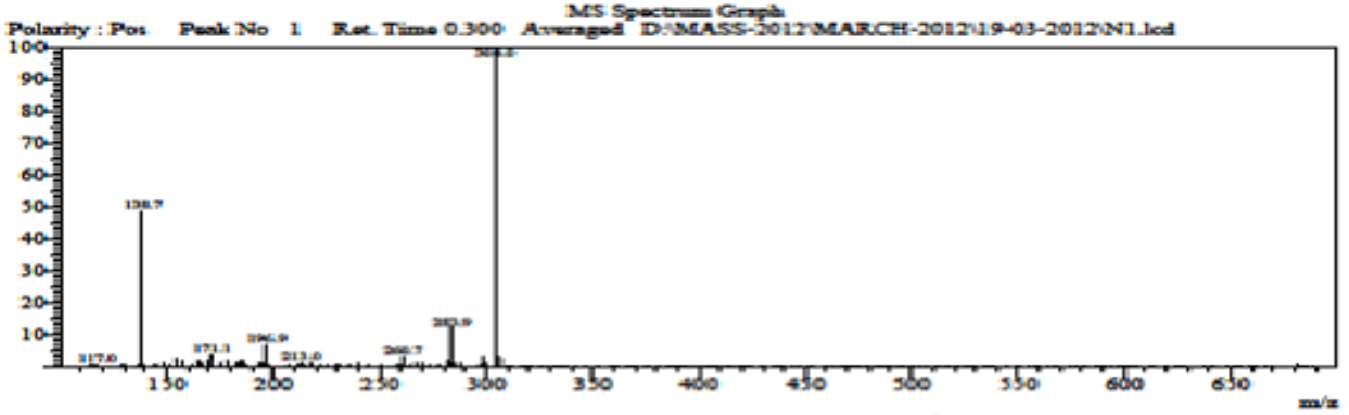

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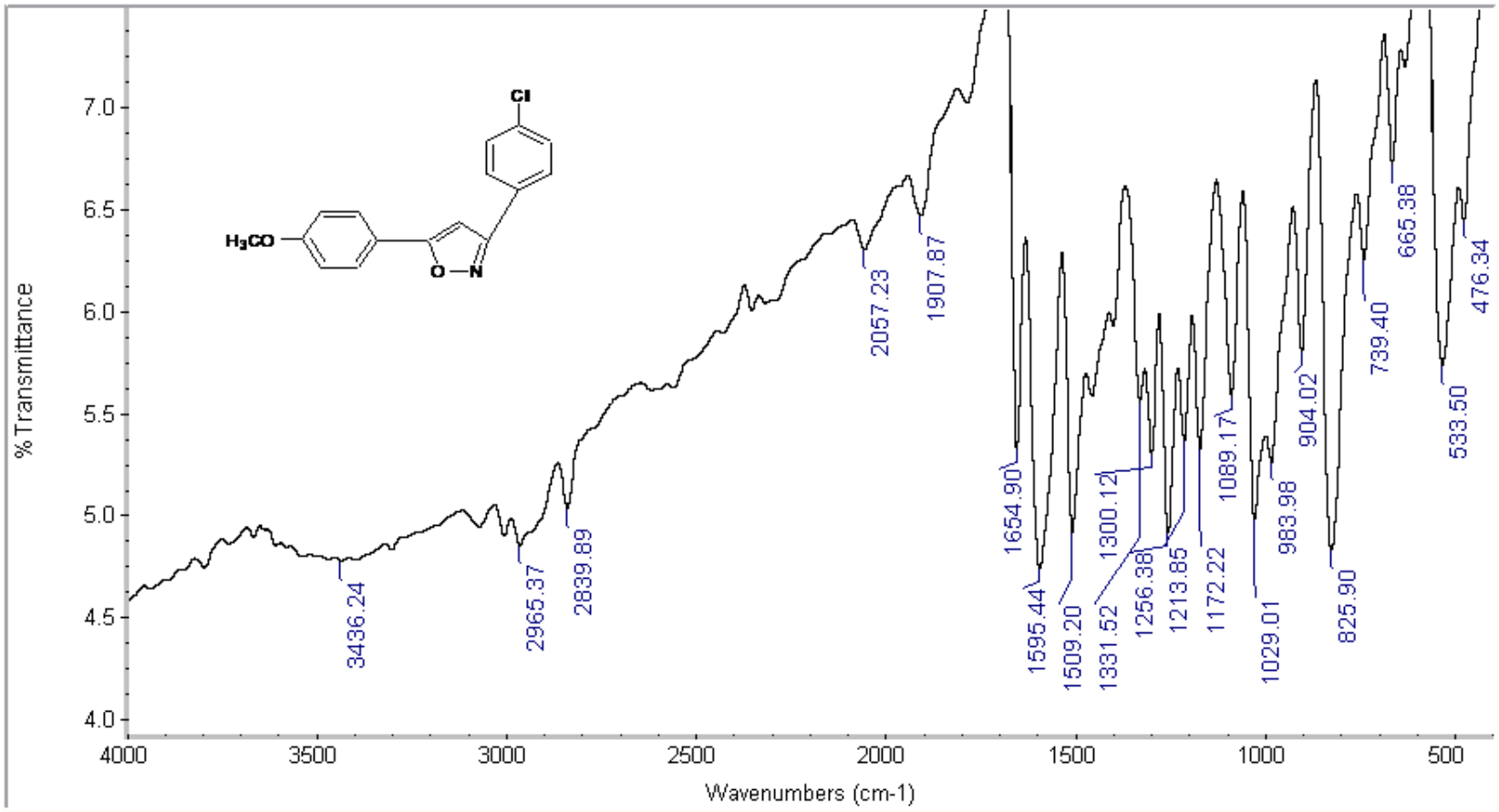

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Beamsplitter: KBr
Source: IR

4-METHOXY DER
CHLORO

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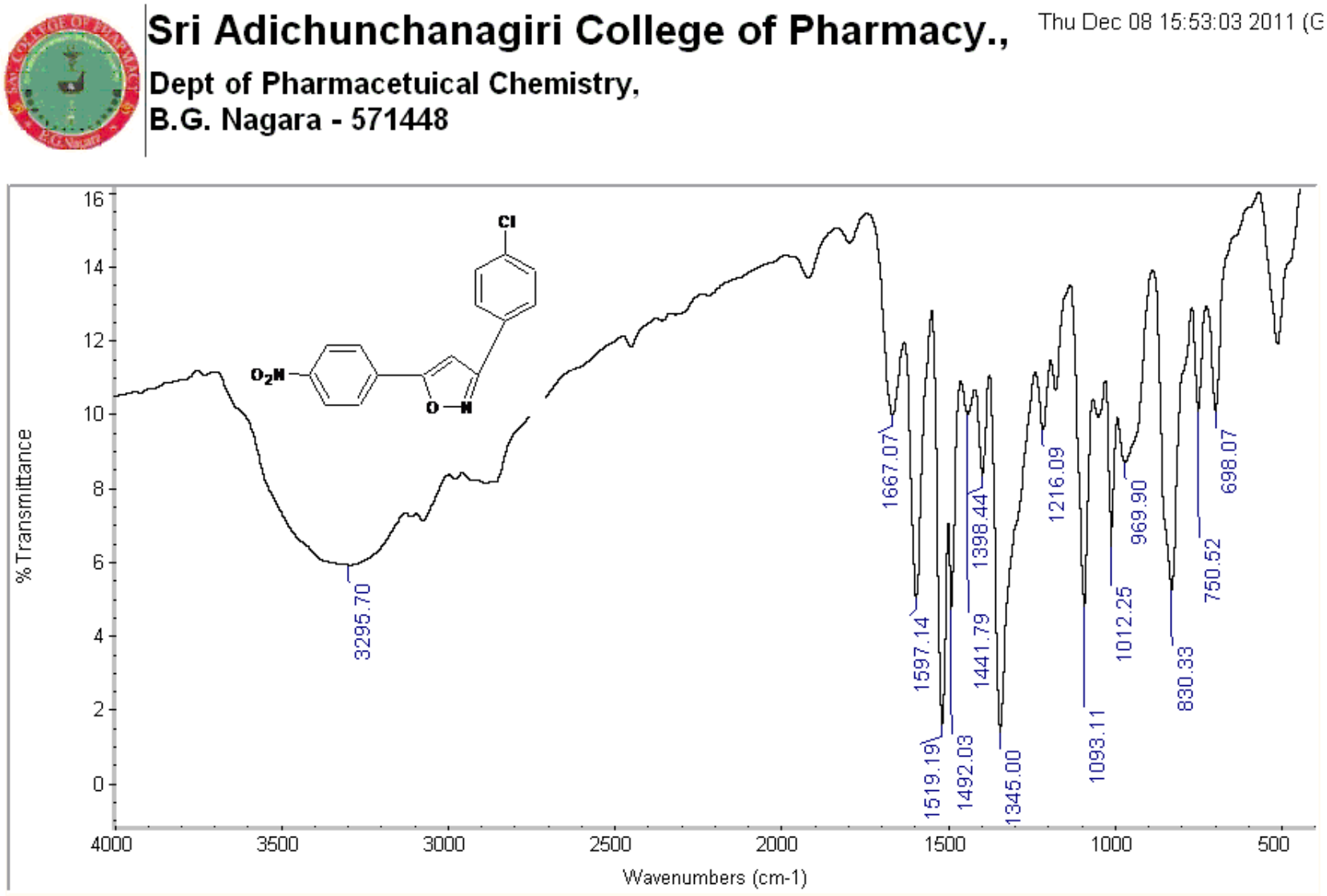
Sri Adichunchanagiri College of Pharmacy.,
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Thu Dec 08 15:53:03 2011 (G
Cl
O2N
O
H
% Transmittance
Wavenumbers (cm-1)
3295.70
1667.07
1597.14
1519.19
1492.03
1441.79
1398.44
1345.00
1216.09
1093.11
1012.25
969.90
830.33
750.52
698.07
Detector: DTGS KBr
Beamsplitter: KBr
Source: IR
4-NITRO DER
chloro
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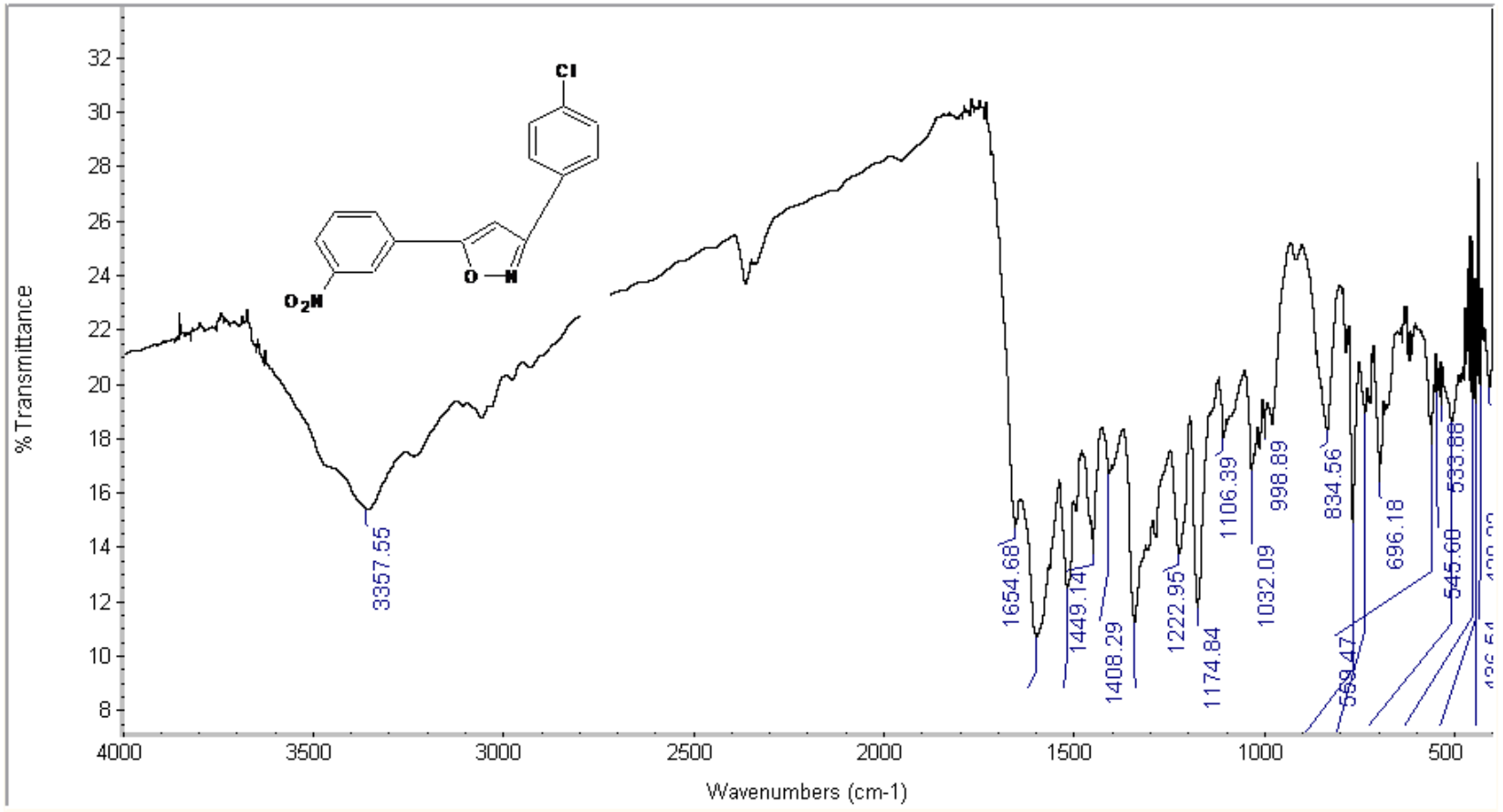

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3-NITRO DER
CHLORO

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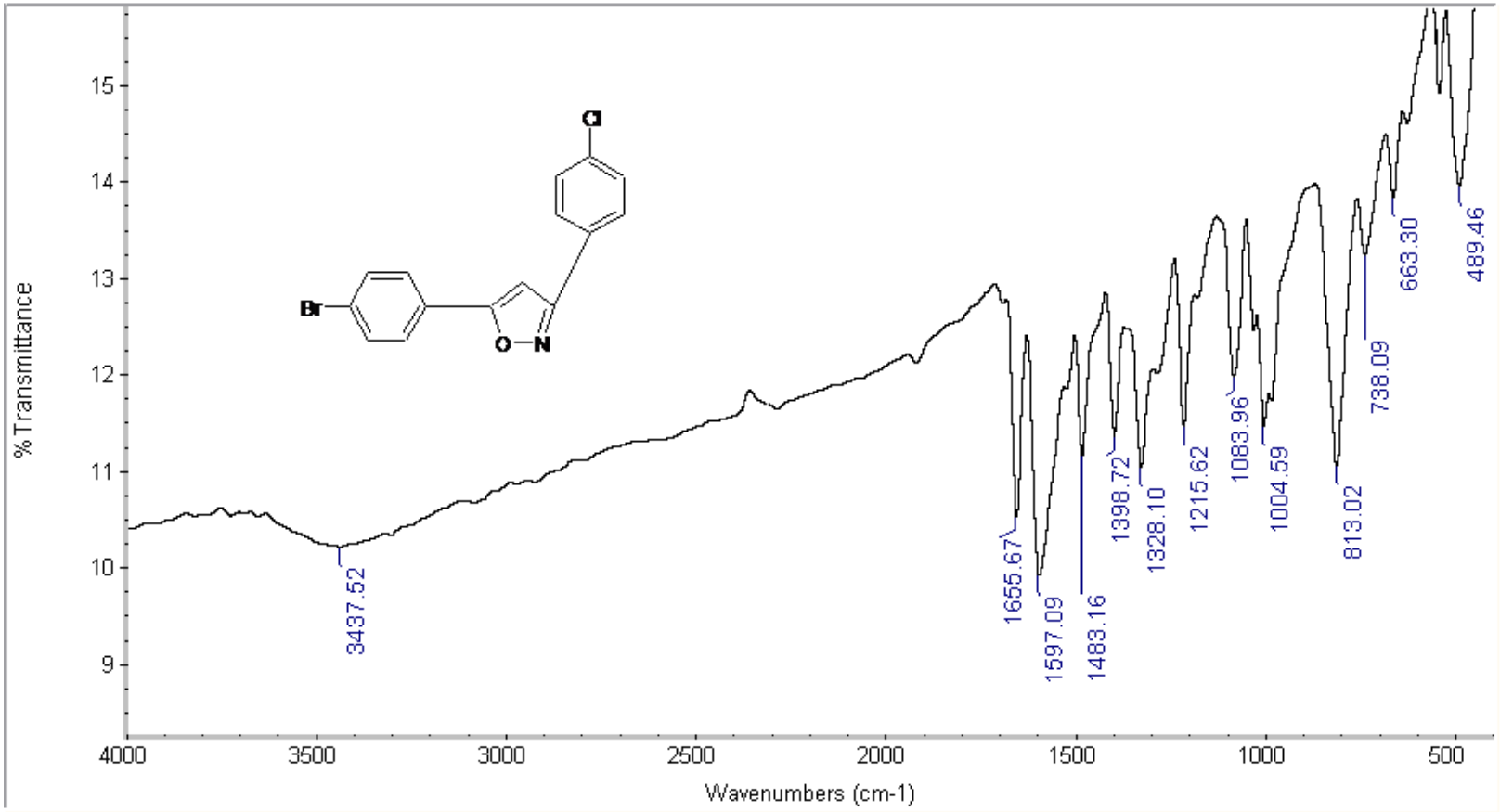

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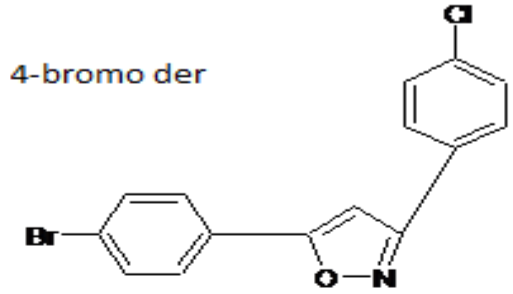

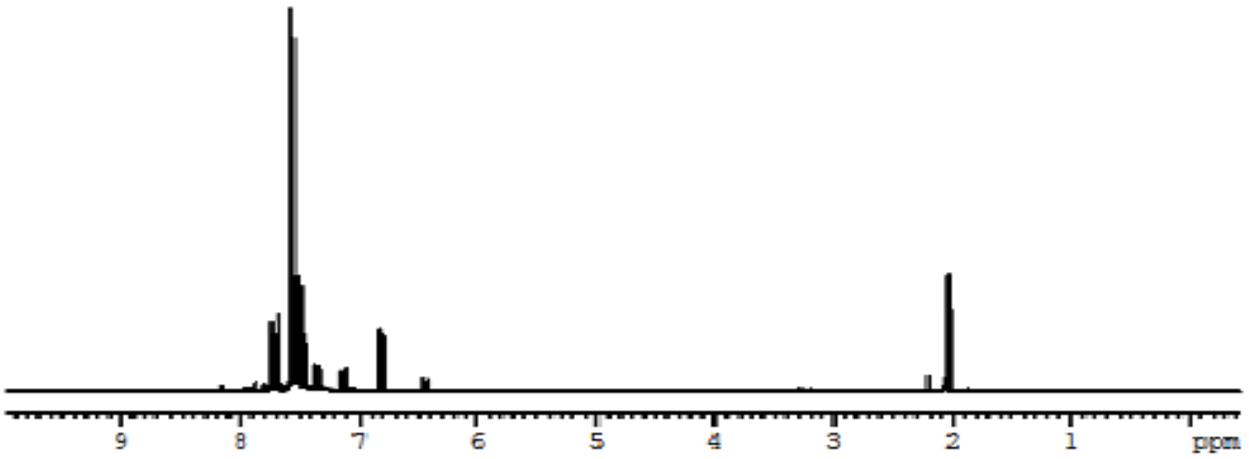

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PULPROG	zg	
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SOLVENT	Acetone	
NS	16	
DS	2	
SWH	4496.403	Hz
FIDRES	0.250022	Hz
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RG	203	
DW	111.200	usec
DE	6.50	usec
TE	298.0	K
D1	2.00000000	sec
TD0	1	
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PL1	-3.00	dB
PL1W	13.42244530	W
SFO1	400.2318965	MHz
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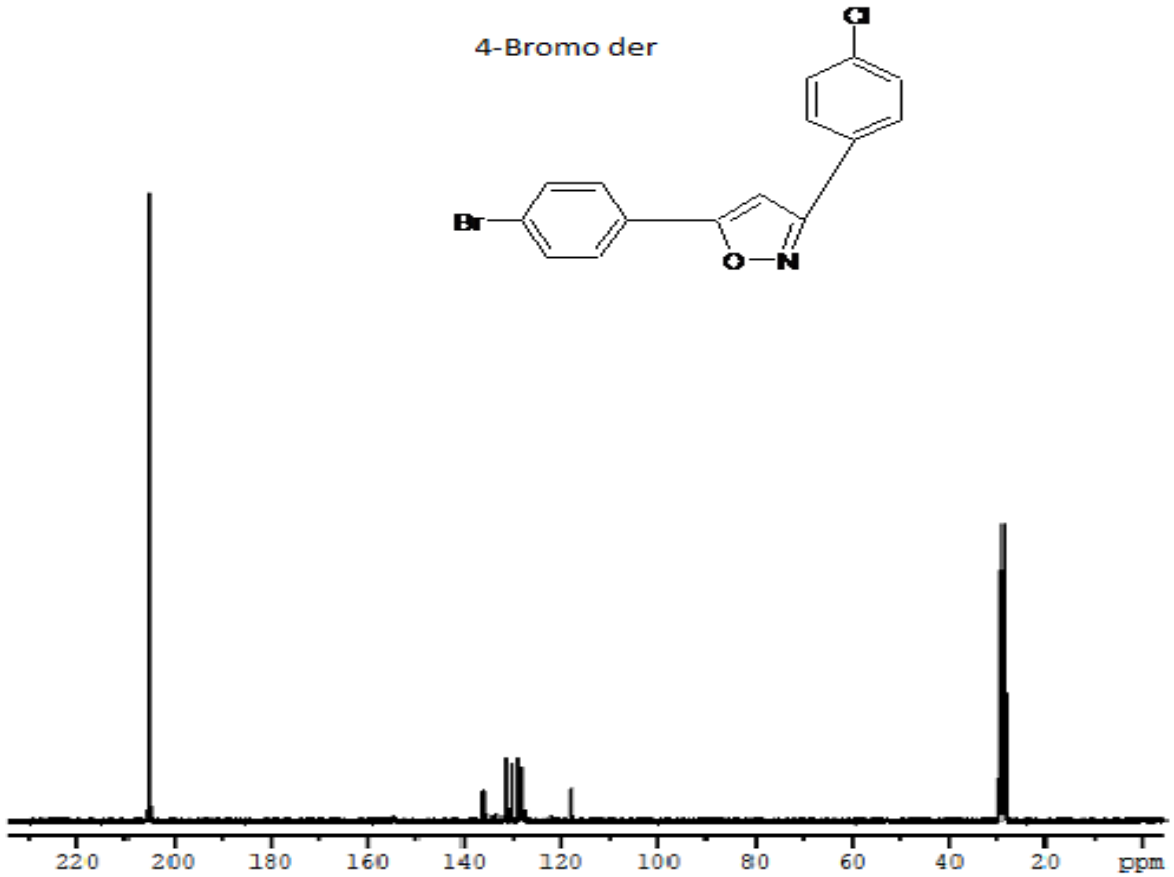

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TD0	1	
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PL12	13.10	dB
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SSB	0	
LB	3.00	Hz
GB	0	
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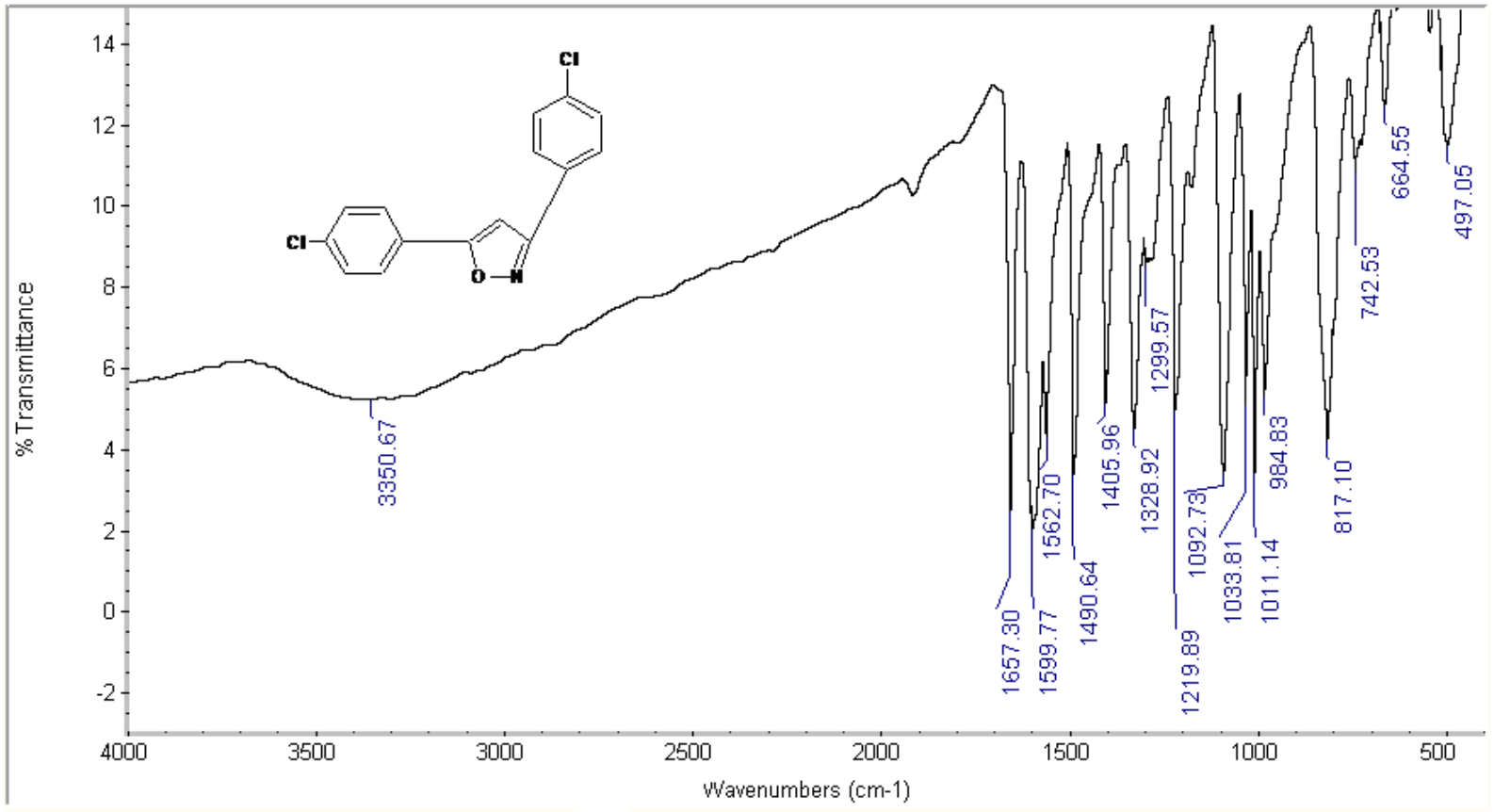
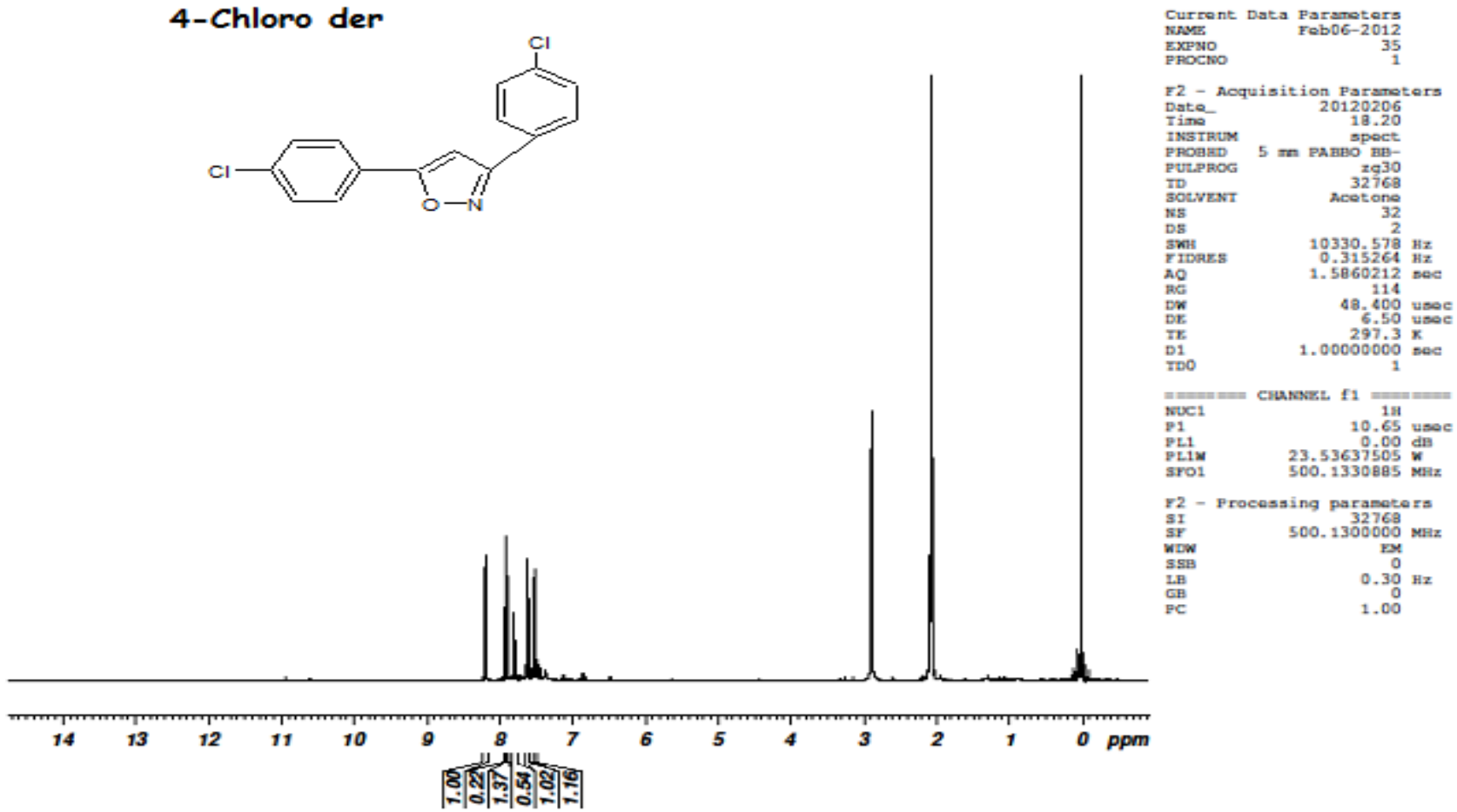


Detector: DTGS KBr
Beamsplitter: KBr
Source: IR

4-CHLORO DER

Performed By :

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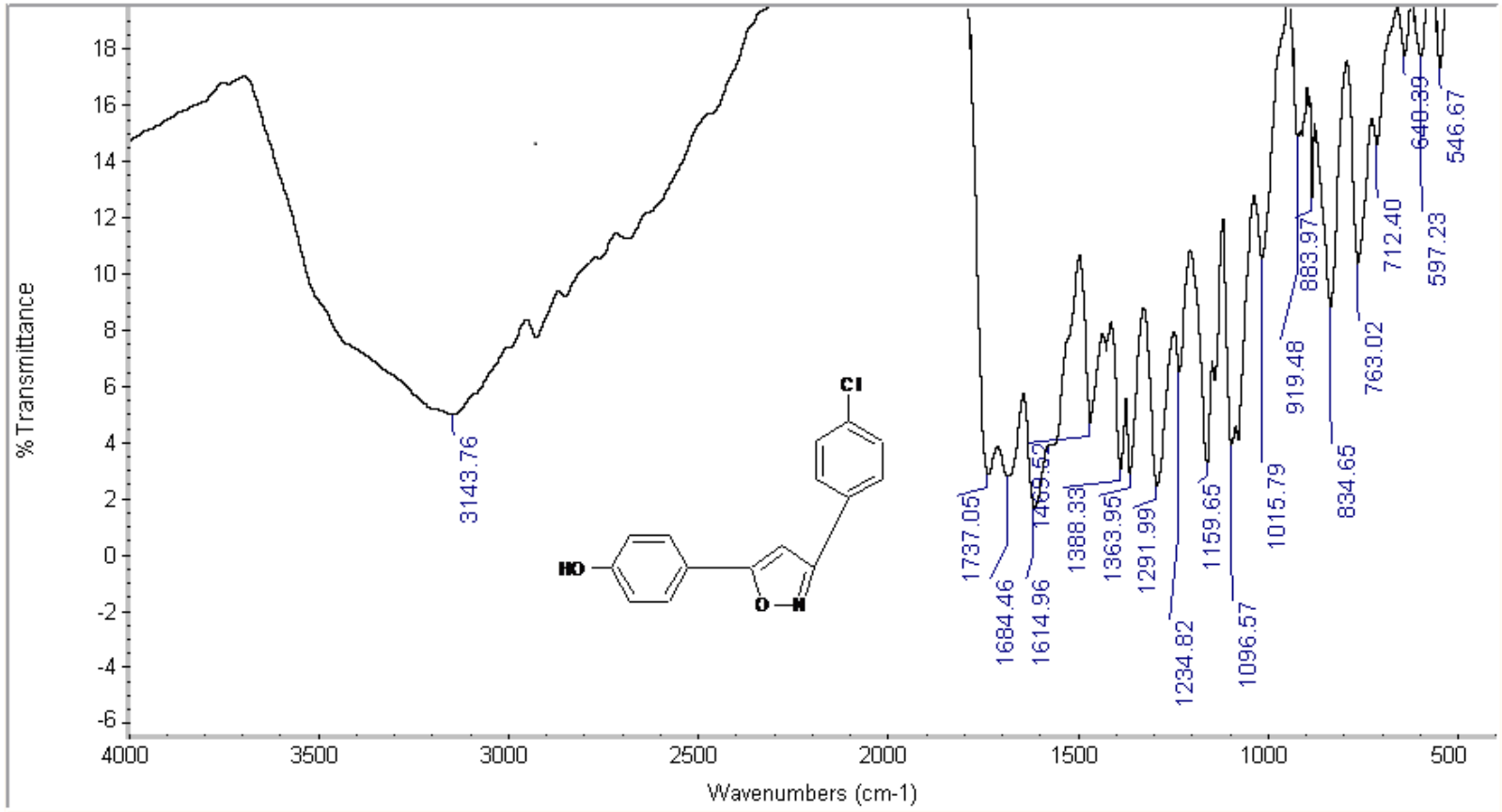

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Beamsplitter: KBr
Source: IR 4-OHder CL Performed By :

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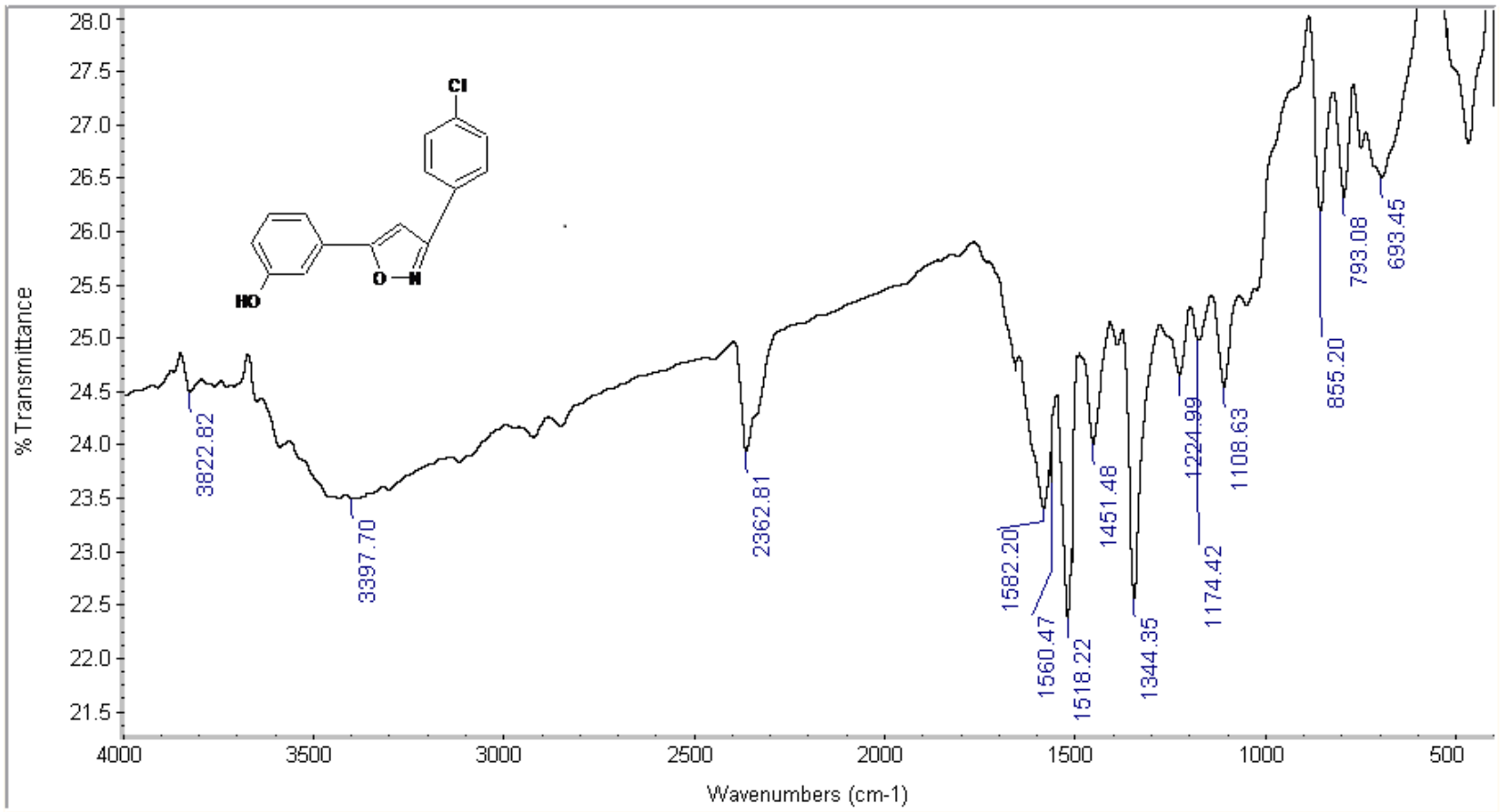

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Beamsplitter: KBr
Source: IR

3-OHDER

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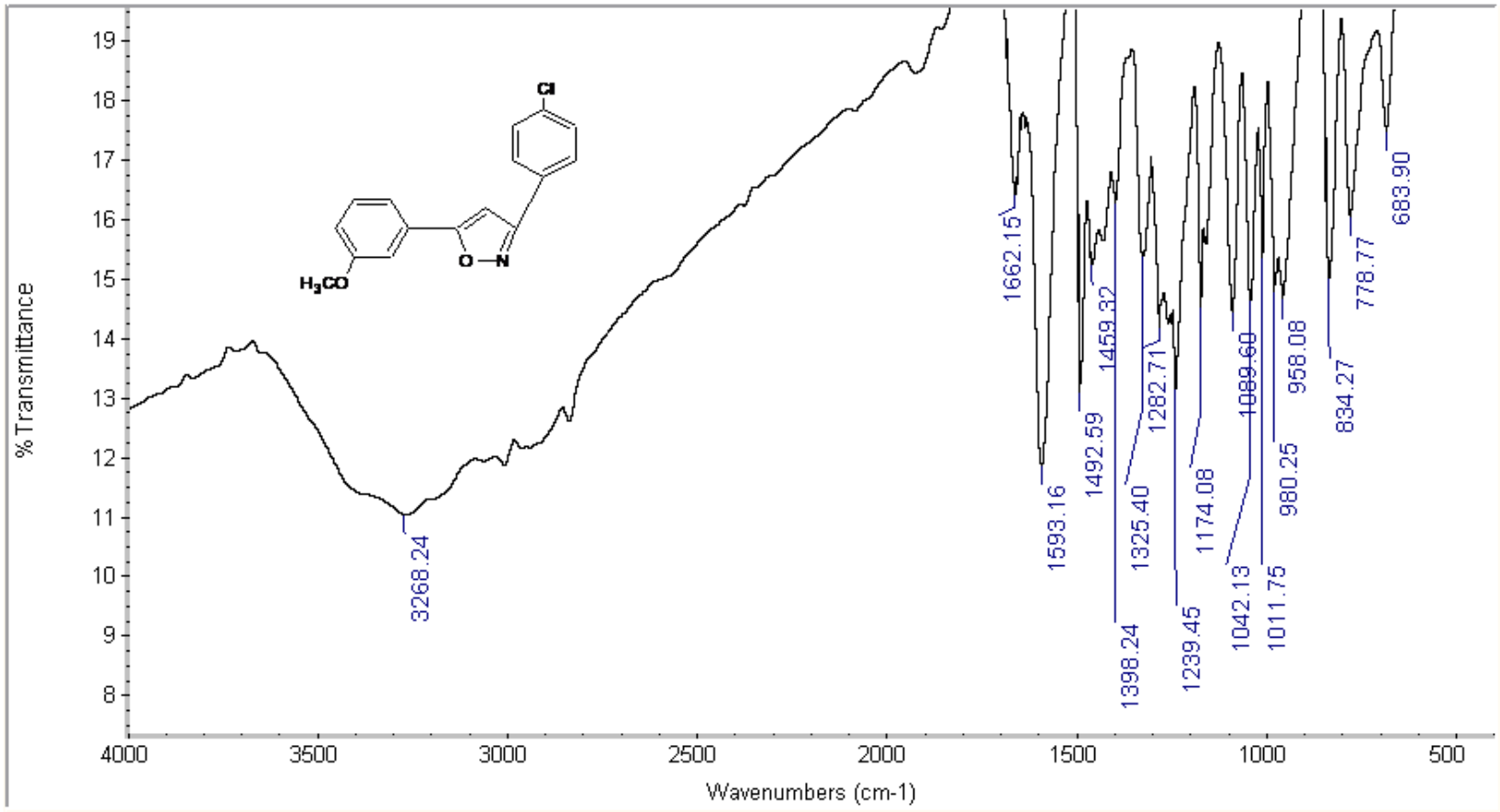

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Beamsplitter: KBr
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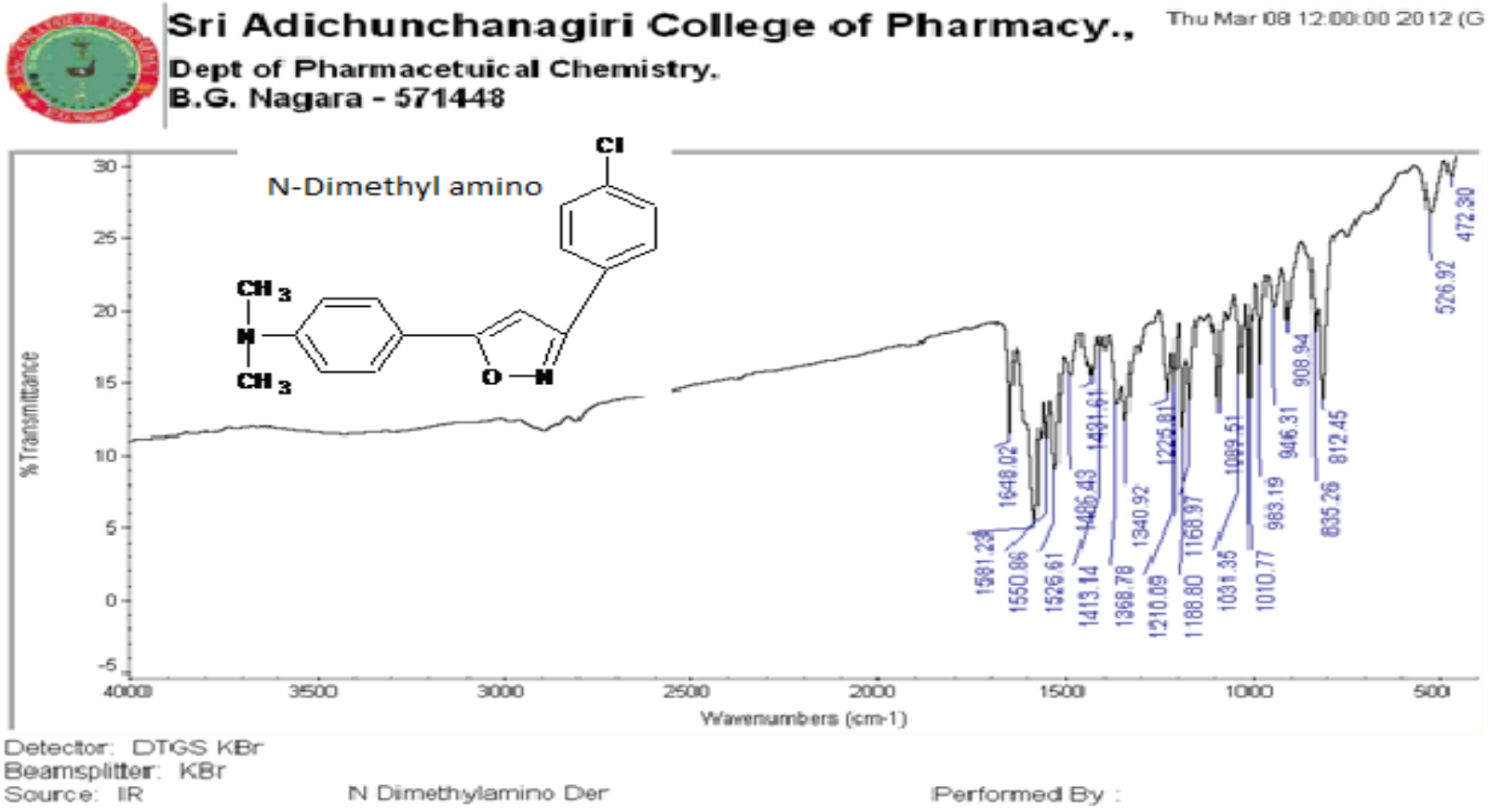
Sri Adichunchanagiri College of Pharmacy.,
Thu Mar 08 12:00:00 2012 (G
Dept of Pharmacetuical Chemistry.
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N-Dimethyl amino
Cl
CH3
N
CH3
O
H
% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
30
25
20
15
10
5
0
-5
1581.23
1550.86
1526.61
1413.14
1366.78
1210.09
1188.80
1031.35
1010.77
983.19
635.26
1648.02
1486.43
1491.61
1340.92
1225.81
1168.97
1089.51
946.31
908.94
812.45
526.92
472.30
Detector: DTGS KBr
Beamsplitter: KBr
Source: IR
N Dimethylamino Der
Performed By :

CHAPTER 5

BIOLOGICAL ACTIVITY

BIOLOGICAL ACTIVITY

Anti-Inflammatory activity[66-68]

IN-VITRO model : inhibition of albumin denaturation

Many *in-vitro* assays, each based on a specific biochemical or cellular mechanism have been developed for the initial screening of the anti-inflammatory compounds. Denaturation of proteins as one of the causes of inflammation well documented. A number of anti-inflammatory drugs are known to inhibit the denaturation of proteins as an *in vitro* screening model for anti-inflammatory compounds.

Materials and methods

Bovine serum albumin (Loba Chem), diclofenac sodium (standard) and all other chemicals used in the experiment were of analytical grade.

Procedure

The standard drug and test compounds were dissolved in minimum amount of DMF and diluted with phosphate buffer (0.2M, pH 7.4) in such a way that concentration of DMF in all solutions was less than 2.5%. Test solution (1 ml) containing different concentrations of drug was mixed with 1 ml of 1% albumin solution in phosphate buffer and incubated at $27^0 \pm 1^0$C in an incubator for 15 min. Denaturation was induced by keeping the reaction mixture at $60^0 \pm 1^0$ C in a water bath for 10 min. After cooling, the turbidity was measured at 660 nm. Percentage of inhibition of denaturation was calculated from control where no drug was added. Each experiment was done in triplicate and average is taken. The diclofenac was used as standard drug. The percentage of inhibition was calculated using the formula

$$\% \text{ Inhibition} = \frac{\text{Vc} - \text{Vt}}{\text{Vc}} \times 100$$

Where, V_t: Absorbance of test compounds V_C: Absorbance of Control

Table- 38 : In-vitro Anti-inflammatory activity of the compounds I_1-I_{18}

% inhibition of protein denaturation			
Sample	10µg/ml	50µg/ml	100µg/ml
N_1	54	61	69
N_2	50	52	60
N_3	37	41.55	66
N_4	45	51	56
N_5	16	30	39
N_6	38	41	54
N_7	27	36	42
N_8	30.98	44.49	48.60
N_9	54	60.15	69.16
C_1	38	59.79	66.50
C_2	41	54.47	56.24
C_3	25.11	26.87	30.98
C_4	50.07	54.47	60.35
C_5	40	45	51
C_6	12	17	28
C_7	45.66	50.07	56.24
C_8	45.66	50.07	56.24
C_9	53	56.24	60.35
Standard	**55.65**	**64.02**	**76.21**
control	**0.0681**		

***In-vivo* anti-inflammatory method: carragenan induced paw edema method[69-72]**

The albino wister rats weighing 150-200 gm were taken and kept under standard conditions in central animal house. Animals were housed in groups of five in PVC cages, under 12-h light/ 12-h dark cycle with hard food pellets and tap water. Animals were divided into four groups. Before the experimentation, rats were acclimated to the animal care facility for at least two days and fasted for 12 h but allowed free access to tap water. Carrageenan was purchased from Sigma Aldrich and 1% carrageenan suspension freshly prepared in physiological saline.

Procedure:

- Acute inflammation was produced by the subplantar administration of 50 µl of 1% carrageenan in normal saline in the right hind paw of each rat.
- The different groups were treated with dose (100 mg/kg, p.o.), the control vehicle (0.3% CMC), and the standard diclofenac (50 mg/kg, p.o.) are administered orally ½ h before the injection of carrageenan.
- The volume of the paw was measured at 0, 30, 60, 120, and 240 min after the injection of carrageenan. Edema was expressed as the increment in paw thickness due to carrageenan administration The thickness of the paw was measured before and 3 h after carrageenan injection using a plethysmometer (Model 7140, Ugo Basile).The rat having the paw edema volume increase more than 50 % normal paw volume were chosen into the experiments. The mean increase of paw volume each time interval was compared with that of control group treated with carrageenan, but without test compounds at the same time intervals.

- 24 albino rats of either sex were divided into 4 groups of 3 animals in each. The animals in all the groups were fasted overnight before the experiment.

  Group 1: Receives the solvent and serves as normal

  Group 2: Receives the standard (diclofenac sodium)

  Group 3: Receives the derivative-1 (100mg/kg)

  Group 4: Receives the derivative-2 (100mg/kg)

- A mark is made on the ankle joint of each rodent. Paw volume up to the ankle joint is measured in drug treated and untreated groups before and 3 hours after carrageenan challenge using a plethysmograph filled with mercury.

Table no.39: In-vivo Anti-inflammatory activity of Isoxazole derivatives N_1-N_9

Treatment	NO.of animals	Paw edema volume									
		After 30min		60min		120min		180min		240min	
		Mean± SEM	% ROV	Mean ± SEM	% ROV	Mean ± SEM	% ROV	Mean ± SEM	% ROV	Mean ± SEM	% ROV
Control (CMC)	6	0.46±0.027	-	0.73± 0.033	-	1.12 ±0.040	-	1.17 ±0.042	-	1.32 ±0.030	-
Standard (diclofenac sodium)	6	0.4±0.021	8.39	0.5±0.00	31.03	0.5± 0.00	55.22	0.4± 0.021	63.71	0.4± 0.021	67.85
N_1	6	0.40 ±0.00	12.41	0.72 ±0.05	1.15	0.63 ± 0.067	44.03	0.50 ± 0.00	57.14	0.40 ±0.00	69.62
N_9	6	0.42± 0.16	8.76	0.63 ±0.067	13.79	0.55 ±0.022	50.75	0.47 ±0.021	60	0.48 ±0.016	63.29

Antibacterial activity[72-75]

The successive isoxazole derivatives were tested for antibacterial activity systematically against four different strains of bacteria (gram-positive and gram negative) by the agar cup and plate method.

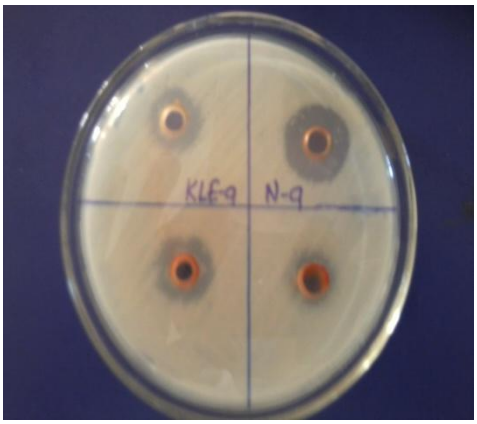
Generally, the antibacterial activity of a compound is expressed in terms of its ability to inhibit the growth of bacteria in nutrient broth or agar; the bacterial inhibition can be measured by two methods: one is the serial dilution method and the other is diffusion method. The serial dilution method is very much useful for the determination of the antibacterial activity. But it is not much useful for the qualitative detection tests and also for the evaluation of a large number of compounds. Therefore, in this investigation the latter is employed. Further, the contemplated agar diffusion method is of three types: (i) Cup-plate method (disc method), (ii) Filter paper strip method, and (iii) Gradient plate method.

The specific method adopted in the present investigation was cup-plate method involving discs of standard diameter, the nutrient agar medium and containing standard bacterial inoculum. The test compounds were introduced into the discs and the diameters of the zones of inhibition were measured. All the derivaties were evaluated for antibacterial activity against, *Eschrichia coli, Pseudomonas aeruginosa, Klebsiella, Staphyllococcus aureus* following the agar diffusion method.

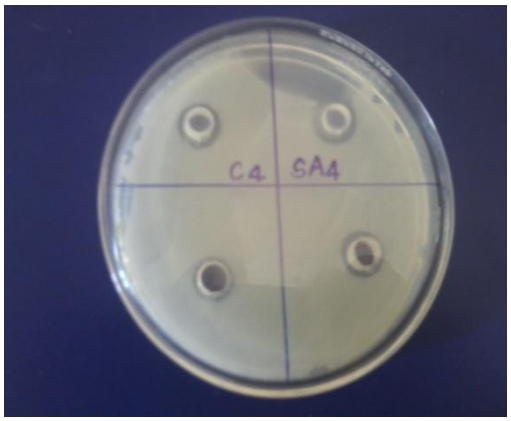
- The organisms were sub-cultured using nutrient agar medium. The tubes containing sterilized medium were inoculated with respective bacterial strain. Stock cultures were maintained. Bacterial inoculum was prepared by transferring a loop full of stock culture to nutrient broth (100 mL) in a clean sterilized conical flask (250 mL).

- The flasks were incubated at 37 ± 1 ^{o}C for 18 h before the experimentation. Solutions of the compounds were prepared by dissolving 10 mg of each in 1 mL DMSO.
- Reference standard for gram-positive and gram-negative bacteria were made by dissolving accurately weighed quantity of ciprofloxacin, respectively in DMSO solution, separately. The nutrient agar medium was sterilized by autoclaving at 121 ^{o}C (15 lb/sq. inch).
- The petri-plates, tubes and flasks plugged with cotton were sterilized in hot air-oven at 160 ^{o}C for an hour. Into each sterilized petri-plate (10cm diameter), about 30 ml each of molten nutrient bacteria (6 mL of inoculum to 300 mL of nutrient agar medium) was transferred, aseptically.
- The plates were left at room temperature to allow the solidification. In each plate, four wells of 6 mm diameter were made with a sterile borer. Then, 0.1 ml of the test solution was added to the discs, aseptically and labelled, accordingly. The plates were kept undisturbed for at least 2 h at room temperature to allow diffusion of the solution properly, into nutrient 2 h. at room temperature to allow diffusion of the solution properly, into nutrient agar medium.
- After incubation of the plates at 37 ± 1 ^{o}C for 24 h. the diameter of the zone of inhibition surrounding each of the discs was measured with the help of an ‘antibiotic zone reader. All the experiments were carried out in triplicate. Simultaneously, controls were maintained employing 0.1 ml of methanol to observe the solvent effects.

Mean zone of inhibition is including disc diameter: Disc diameter is 6 mm

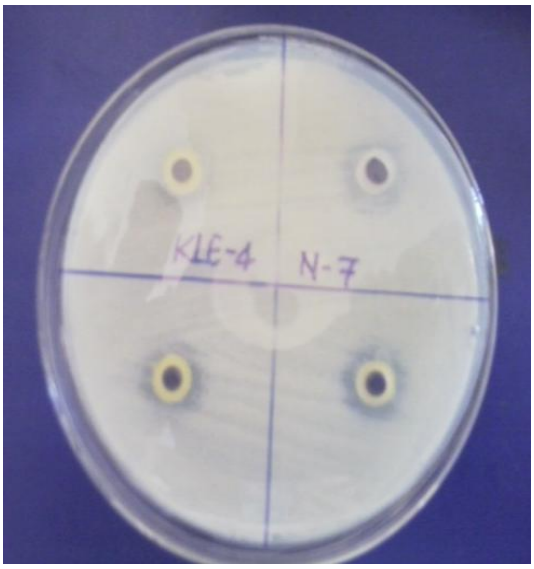


N_9 **Klebsiella Pneumoniae**



C_4 **Staphylococcus aureus**

N_5 **Staphylococcus aureus**



N_7 **Klebsiella Pneumoniae**

Antibacterial activity of Isoxazole derivatives

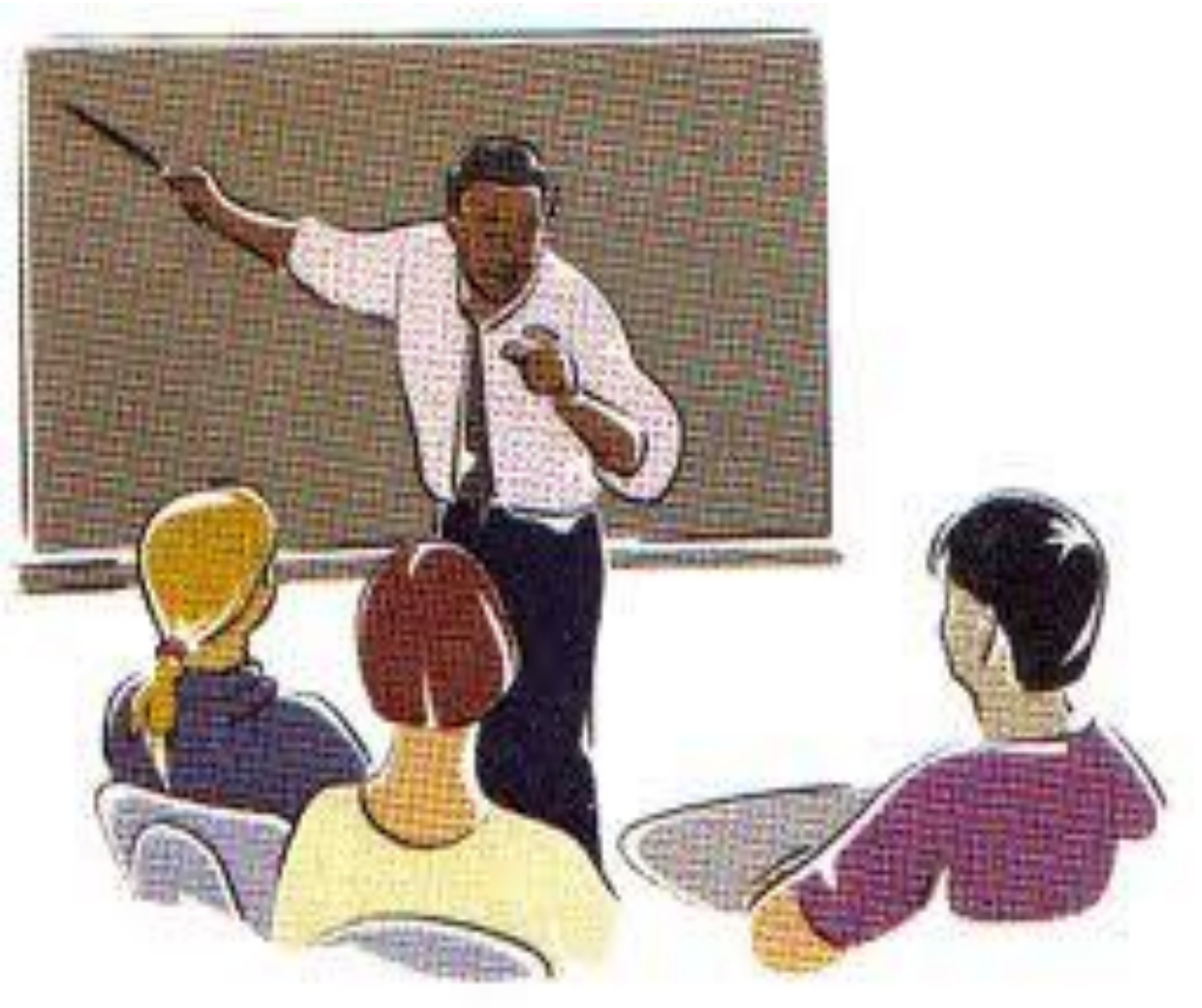
Table 40. : Antibacterial activity of Isoxazole derivatives at different concentration by well diffusion method (values in mm)

Compound code	Mean zone of inhibition (in mm)															
	S .Aureus				E. coli				P. Auruginosa			Klebsiella				
	100 µg/ml	200 µg/ml	400 µg/ml	500 µg/ml	100 µg/ml	200 µg/ml	400 µg/ml	500 µg/ml	100 µg/ml	200 µg/ml	400 µg/ml	500 µg/ml	100 µg/ml	200 µg/ml	400 µg/ml	500 µg/ml
Standard Ciprofloxacin	8	11	14	18	26	28	30	31	30	31	31	34	26	30	32	34
N_1	-	-	-	-	8	11	13	16	-	-	-	-	9	10	12	14
N_2	-	-	-	-	-	-	-	-	-	-	-	17	9	12	16	18
N_3	8	8	10	11	-	-	-	-	-	-	-	-	-	-	-	-
N_4	-	-	-	-	-	-	-	-	-	12	14	15	8	10	12	14
N_5	7	9	11	14	-	-	-	-	-	-	-	-	10	12	14	15
N_6	-	-	-	-	-	-	-	-	7	9	11	12	8	10	11	12
N_7	-	-	-	-	-	-	-	-	-	-	-	-	9	12	15	16
N_8	5	7	7	8	-	-	-	-	-	-	-	-	-	8	11	15
N_9	-	-	-	-	9	11	13	13	9	12	14	15	11	14	16	18
C_1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
C_2	8	10	13	16	-	-	-	-	7	9	10	14	-	-	-	-
C_3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
C_4	9	10	12	16	-	-	-	-	-	-	-	-	10	11	13	15
C_5	5	6	6	7	-	-	-	-	-	-	-	-	6.5	7	9	11
C_6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
C_7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
C_8	-	-	-	-	8	10	11	12	-	-	-	-	10	14	16	18

Table no.- Lipophilicity of isoxazole derivatives compounds 1-18

Sr.no.	Compound code	$logP_{10}$
1	N_1	4.27
2	N_2	3.91
3	N_3	3.89
4	N_4	4.83
5	N_5	5.04
6	N_6	3.86
7	N_7	3.84
8	N_8	4.24
9	N_9	4.31
10	C_1	5.37
11	C_2	5.04
12	C_3	5.06
13	C_4	5.69
14	C_5	5.83
15	C_6	4.76
16	C_7	4.75
17	C_8	5.35
18	C_9	4.92

CHAPTER 6



RESULTS AND DISCUSSION

RESULTS AND DISCUSSION

Isoxazole is a five membered heterocyclic ring system containing oxygen and nitrogen atoms. In recent years, the synthesis of novel isoxazole derivatives remains a main focus of medicinal research. Isoxazoles have been reported to posses anthelmantic, antibacterial, antihyperglycemic, analgesic, anti-inflammatory, antipyretic, antiviral and antitumor properties.

Isoxazoles derivatives were synthesized and screened for their antibacterial and anti-inflammatory activity.

The synthesis of the various isoxazoles derivatives was carried out in two step process where equimolar quantities of different substituted aromatic benzaldehyde and substituted aromatic acetophenones reacted in ideal condition to give chalcones where further reacted with hydroxyl ammonium hydrochloride and sodium acetate to give cyclised products.

All the compound were recrystalised with ethanol. The synthesized isoxazole compounds were characterised by IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectral data. The spectral data showed the presence of major functional groups in the compounds. The IR spectral data presented the expected absorption bands at the ranges of 2850 cm^{-1}, 1031 cm^{-1}, 1460 cm^{-1}, 1514 cm^{-1}, 1640 cm^{-1}, 690 cm^{-1} resembles the C-H, C-NO_2,C-O, C=C, C=N. ^{1}H-NMR spectra of the compounds showed a multiplet at about δ(6.8-8.3) ppm integrated for nine protons attributed to Ar-H protons, another singlet at about δ 3.8-4 ppm integrated for three protons attributed to CH_3 protons. These two multiplet and singlet protons are belonging to the aromatic ring and methoxy group. Other protons were seen at the expected chemical shifts. ^{13}C-NMR spectra of the compounds showed at about δ 114-130 ppm integrated for eight carbons attributed to

Ar-C carbons. Mass spectra of the compounds showed molecular ions in the form of 296.09, M^{+1}. The ions were usefulness for characterization of the derivatives.

The synthesized isoxazole derivatives were screened for antibacterial and anti-inflammatory activities. The anti-bacterial activity has done systematically against four different strains of bacteria against *Eschrichia coli, Pseudomonas aeruginosa, Klebsiella, Staphylococcus aureus* (gram-positive and gram negative) by the agar diffusion method. **N_1,N_4,N_9 and C_4,C_9** exhibited good activity against both gram-positive and gram-negative bacteria.

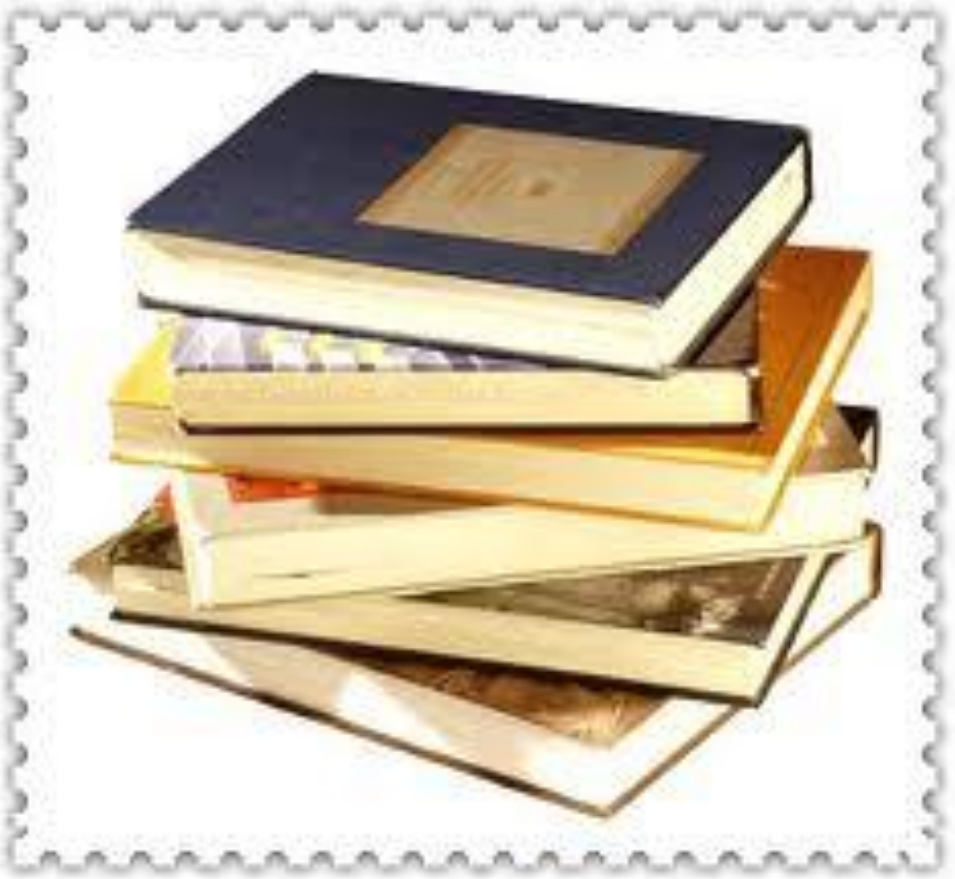
The *in-vitro* anti-inflammatory has done by % inhibition of protein denaturation method. And *in-vivo* anti-inflammatory activity done by carrageenan induced paw edema of Wister Albino rats and compared with diclofenac sodium, which is a standard drug. The paw volumes were recorded within 1 hr. interval time.

The study indicated that compounds **N_1, N_9, C_5, C_9** had exhibited highly potent *in-vitro* anti-inflammatory activity and compounds **N_1, N_9** were screened for in-vivo studies. Both showed significant anti-inflammatory activity when compared to standard diclofenac sodium. Other compounds exhibited less anti-inflammatory activity. Structural activity studies of the title compounds for anti-inflammatory activity reveals having $–OCH_3$, $-N(CH_3)$, -Cl,-Br groups showed more activity.

The compounds lipophilicity was determined using the software ALOGPS. The efficiency of a drug will depend in part on its ability to accumulate in cells. Lipophilicity of compounds plays a vital role in the effect of the compounds. The isoxazole derivatives are weak bases and able to exist in both charged (protonated) and uncharged (unprotonated) forms. The lipophilicity data of **1-18** varying from 3.86-5.69, expressed in **$LogP_{10}$**

The isoxazole nucleus with $–OCH_3$ at position R-1 and R-2 and $–NO_2$ at R-4 showed enhancement in the $LogP_{10}$ and also high activity. Analysis of the relationship between $logP_{10}$ values and various activity such as anti-inflammatory, anti-bacterial activity showed high correlation. The major outlier in this analysis was nucleus $N_{1,}$ $N_{5,}$ $N_{9,}C_{1,}$ $C_{5,}C_{9}$ are comparatively having higher $logP_{10}$ values. Therefore, the degree of lipophilicity of each drug would screen to be important, but it is not the sole determinant for various activity of isoxazole derivatives.

CHAPTER 7



SUMMARY AND CONCLUSION

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Isoxazole have played crucial role in the history of hetrocyclic chemistry and been extensively important pharmacophores and synthons in the field of organic chemistry owing to their versatile chemotherapeutic importance, a significant amount of research effort has been focused on these nuclei. Isoxazole is a five membered heterocyclic ring system containing oxygen and nitrogen atoms have been reported to posses anthelmintic, antibacterial, antihyperglycemic, analgesic, anti-inflammatory, antipyretic, antiviral and antitumor properties.

In present study we fused the two moieties (aromatic substituted ketone and aromatic substituted aldehyde) to isoxazole with the view to get good pharmacological activity and less toxicity.

As expected, isoxazole derivatives exhibited both anti-bacterial and anti-inflammatory activities in which some compounds are good and some are moderately active like standard employed for comparision. The antibacterial activity which has done on some gram-positive and gram negative showed that few compounds were exhibiting the antibacterial activity by observing zone of inhibition.

The anti-inflammatory activity testing showed that few compounds have promising anti-inflammatory activity when compared to standard drug, Diclofenac sodium.

Further the detailed structural activity relationship studies are required along with the molecular manipulation i.e. molecular modeling may give better drugs. Molecules prepared for the biological testing do not always turn out as potential new drugs, but may be intended to serve as models for evaluation of hypothesis.

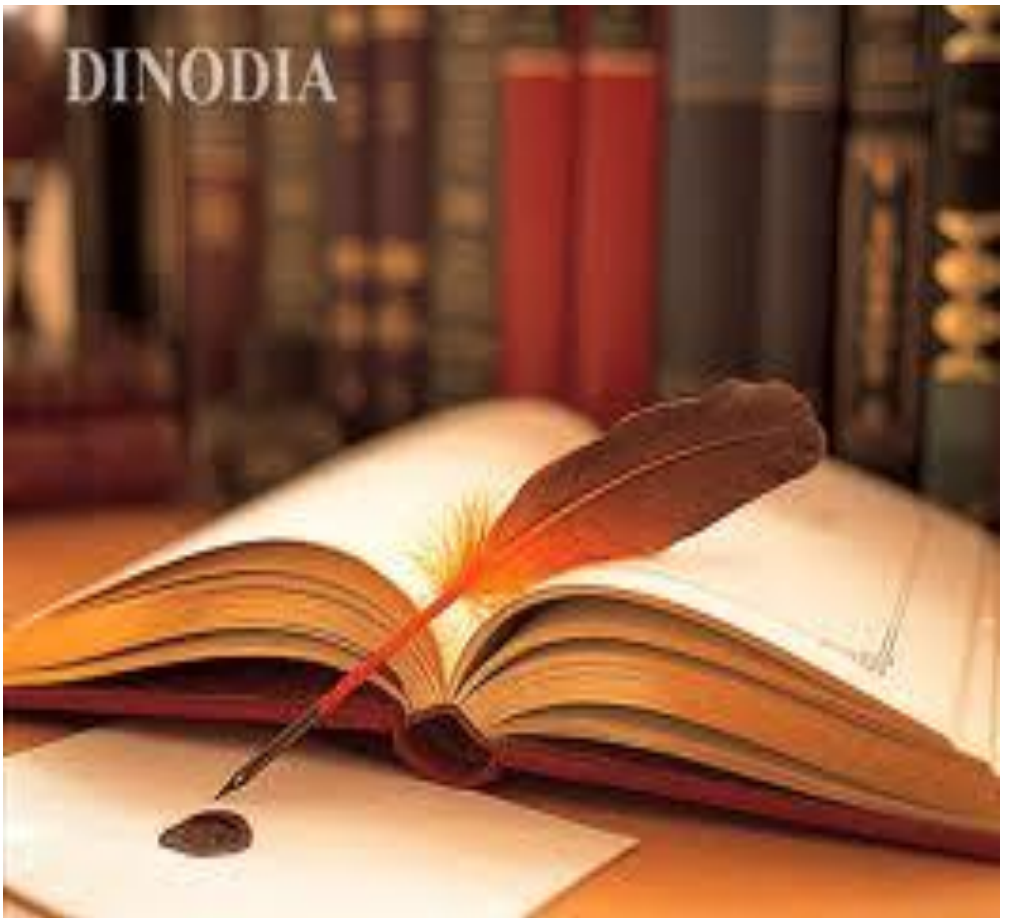
From the data of anti-inflammatory activity it is clearly concluded that the synthesized compounds are having good anti-inflammatory activity.

When these were screened for anti-inflammatory activity showed a very good result. The compound **N_1**,has isoxazole nucleus with groups **OCH_3** at position **R_1** and **NO_2** at **R_4** also showed enhancement in anti-inflammatory activity and anti-bacterial activity.

In the compound **N_9** substitution of **R_1**of dimethyl amino and **NO_2** at **R_4**position of the aromatic ring also resulted in a enhancement of anti-inflammatory and anti-bacterial activity. In the compound **C_4**, **C_9** substitution Br and $N(CH)_3$ at **R_1** position and **Cl** at **R_4**also showed significant anti-inflammatory activity and anti-bacterial activity.

Hence in the present study, the aromatic substituted ketone and aromatic substituted aldehydes when linked with isoxazole moiety showed highly potent, more specific anti-inflammatory and antibacterial activity.

CHAPTER 8



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