THE SYNTHESIS OF FIVE AND SIX-MEMBERED HETEROCYCLES CONTAINING OXYGEN, NITROGEN AND PHOSPHORUS

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THE SYNTHESIS OF FIVE AND SIX-MEMBERED HETEROCYCLES CONTAINING OXYGEN, NITROGEN AND PHOSPHORUS

by
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Approval of the Graduate School of Natural and Applied Sciences

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ABSTRACT

THE SYNTHESIS OF FIVE AND SIX-MEMBERED HETEROCYCLES CONTAINING OXYGEN, NITROGEN AND PHOSPHORUS

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The aim of this work is the synthesis of 2,4-disubstituted-2,3-dihydro-1,3,5,2-oxadiazaphosphole-2-oxides and 2,3-disubstituted-1,3,2-oxazaphospholidine-2-oxide , its thionated analog, heterocycles by the ring closure reactions of mono amidoximes with phenylphosphonyldichloride. Heterocyclic systems that include a phosphorus linked to an oxygen and nitrogen atom have been reported to have anti-tumor alkylating, anti-hypertensive , biocatalysts, catalyse the enantioselectiveaminolysis of lactones activities. For this purpose, first, amidoximes as starting compounds were synthesized according to the literature procedures. The amidoximes were then reacted with phenylphosphonyldichloride to give 2,4-disubstituted-2,3-dihydro-1,3,5,2-oxadiazaphosphole-2-oxide heterocycles and 2-anilinoethanol to give 2,3-disubstituted-1,3,2-oxazaphospholidine-2-oxide.

All of the compounds newly synthesized were identified by means of spectral measurements (IR, NMR, MS) and physical constants (e.g. melting points, Rf values) and in this regard, this work is an important contribution to the synthetic organic chemistry.

Keywords: Amidoxime, Phenylphosphonyldichloride, Ringclosure reaction, oxadiazaphosphole 2-oxide and oxazaphospholidine-2-oxide

ÖZET

BEŞ VE ALTI ÜYELİ OKSİJEN, AZOT VE FOSFOR İÇEREN HETERO HALKALI BİLEŞİKLERİN SENTEZİ

İvgen, Hakan
Yüksek Lisans Tezi , Kimya Bölümü
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Bu çalışmanın amacı yeni 2,4-disubstitue-1,3,5,2-oksadiazafosfol-2-oksitlerin, 2,3- disubstitue-1,3,2-oksazafosfolidine-2-oksitlerin ve bunun thio anoloklu heterohalkalarının bazı amidoksimlerle fenilfosfonildiklorat ile birlikte halka kapama reaksiyonları ile sentezlenmiştir. Bu amaçla, öncelikle literatürdeki yöntemlere göre amidoksimler sentezlenmiştir. Daha sonra, amidoksimler ve 2-anilinoetanol, 2,4-disubstitue-1,3,5,2-oksadiazafosfol-2-oksitler ve 2,3- disubstitue-1,3,2-oksazafosfolidine-2-oksit heterohalkalarının sentezi için fenilfosfonildiklorat ile reaksiyona sokulmuşlardır.

Yeni bileşiklerin yapıları spektroskopik ölçümler (IR, NMR, Kütle Spektrumları) ve fiziksel sabitler (erime noktası, Rf değerleri) yardımıyla aydınlatılmıştır.

Anahtar Kelimeler: Amidoksim, Fenilfosfonildiklorür, Halka Kapanma Reaksiyonları, oksadiazafosfol ve oksazafosfolidin.

TO MY PARENTS AND MY ELDER BROTHER

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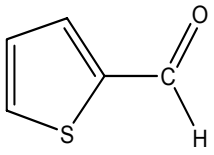
LIST OF SYMBOLS AND ABBREVIATIONS

$NH_2OH.HCl$	: Hydroxylamine hydrochloride
$NaCH_3COO.3H_2O$	: Sodium acetate trihydrate
KBr	: Potassium bromide
Na_2SO_4	: Sodium sulfate
Et_3N	: Triethyl amine
NCS	: *N*-Chlorosuccinimide
DMF	: *N,N*-Dimethylformamide
PB	: Petroleum Benzine
EtOAc	: Ethyl acetate
DCM	: Dichloromethane
NH_3	: Ammonia
TLC	: Thin Layer Chromatography
Δ	: Heat
GC-MS	: Gas Chromatography-Mass Spectroscopy
IR	: Infra Red
NMR	: Nuclear Magnetic Resonance
Rf	: Retention Factor
M.p.	: Melting Point

FORMULAE



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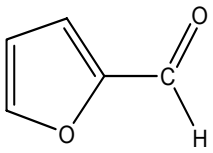

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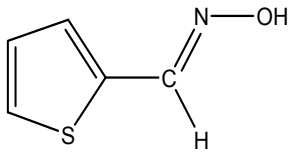

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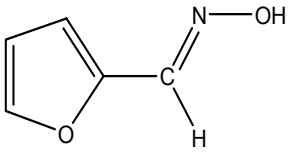

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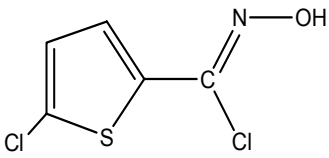

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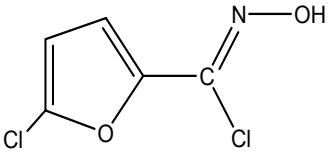

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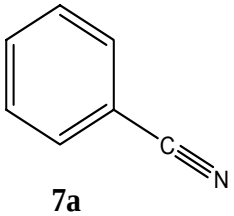

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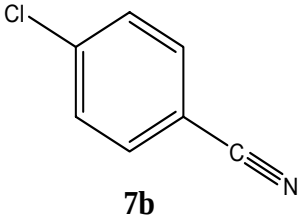

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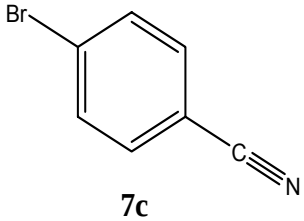

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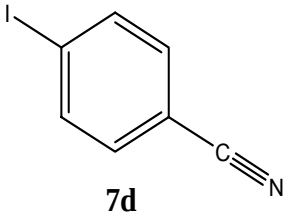

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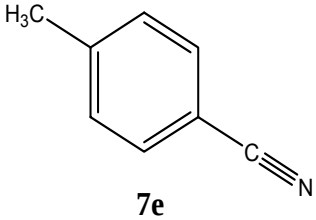

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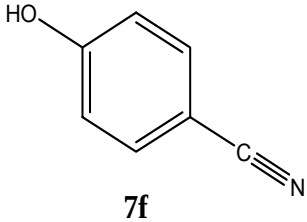

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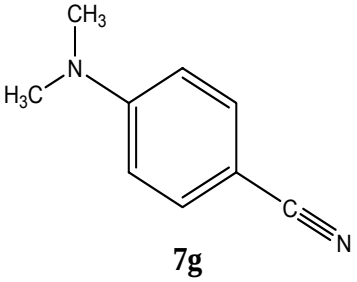

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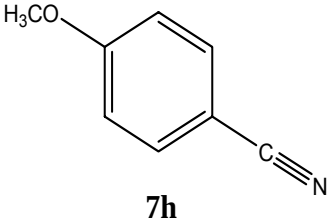

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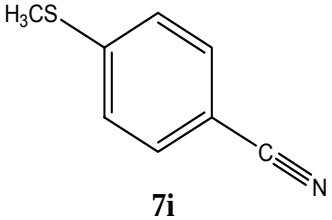

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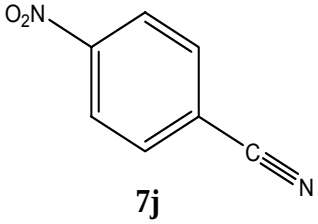

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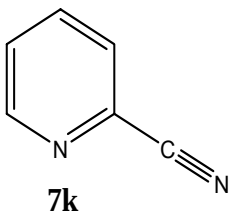

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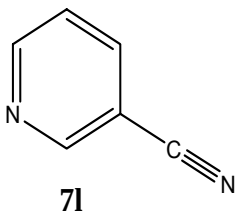

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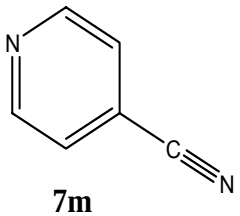

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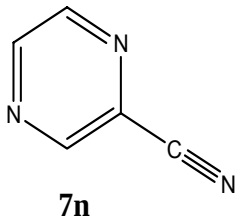

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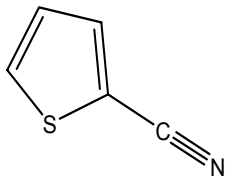

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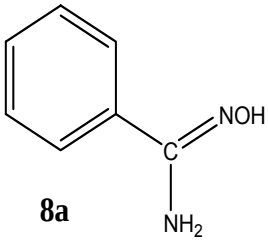

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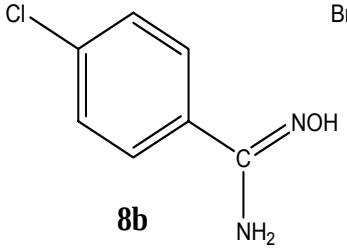

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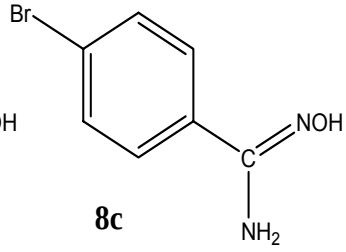

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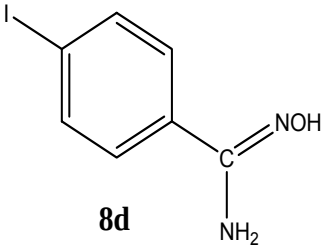

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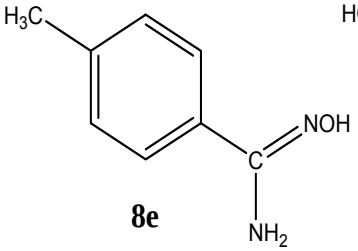

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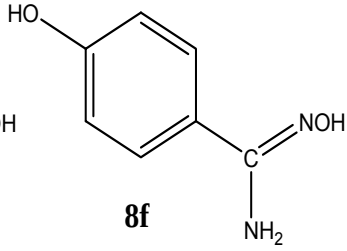

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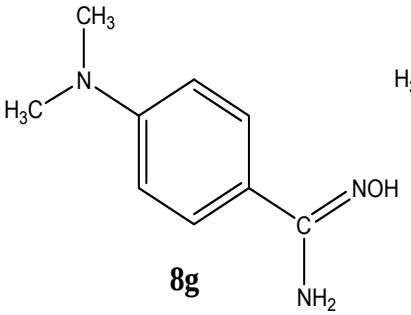

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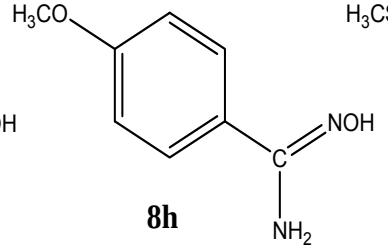

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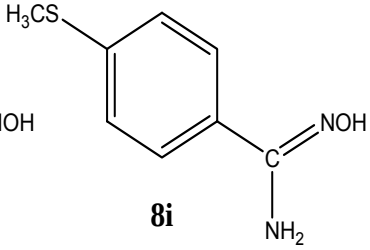

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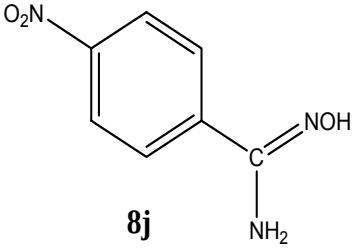

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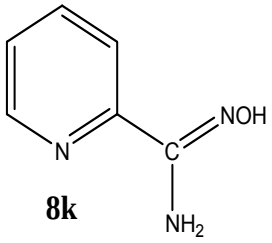

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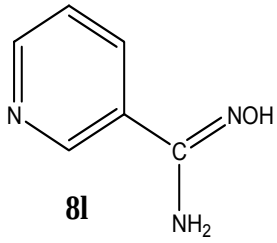

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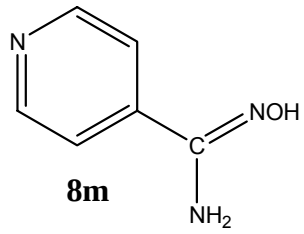

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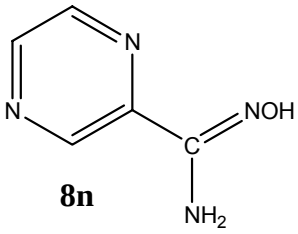

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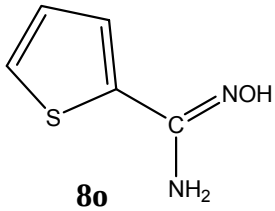

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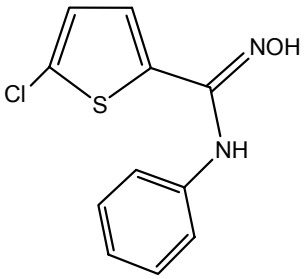

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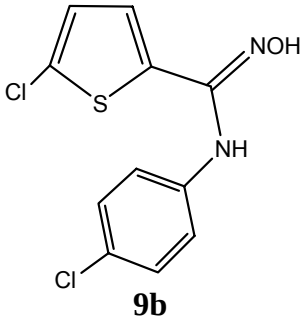

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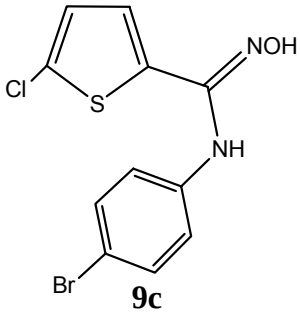

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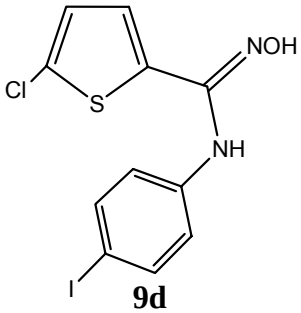

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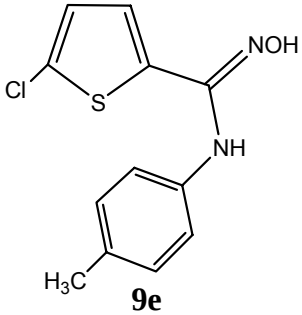

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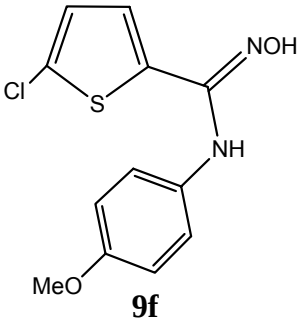

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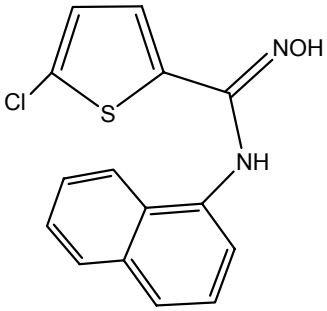

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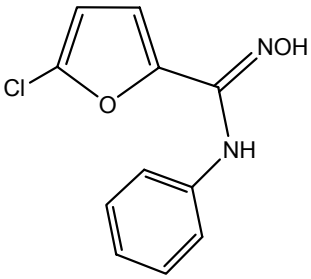

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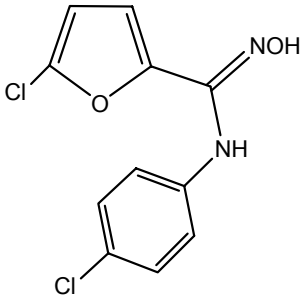

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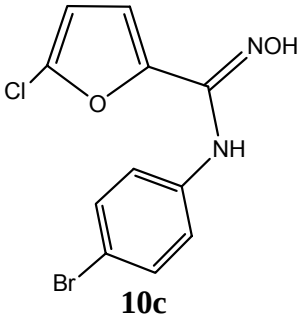

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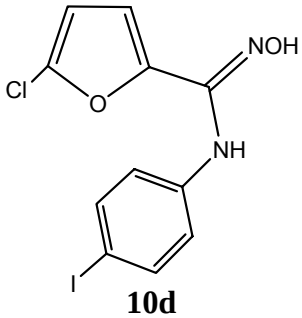

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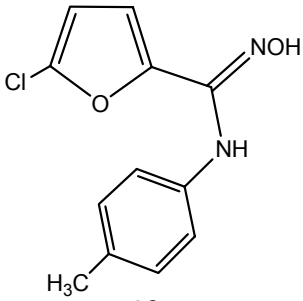

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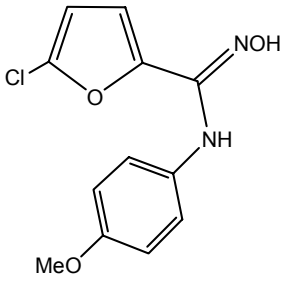

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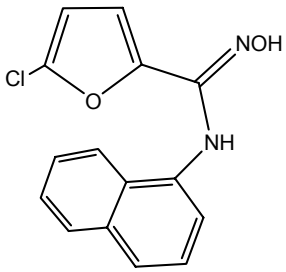

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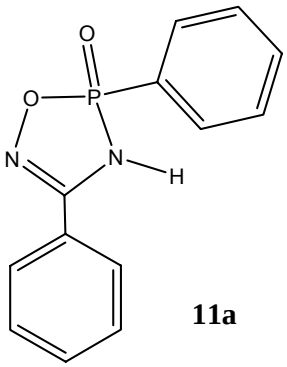

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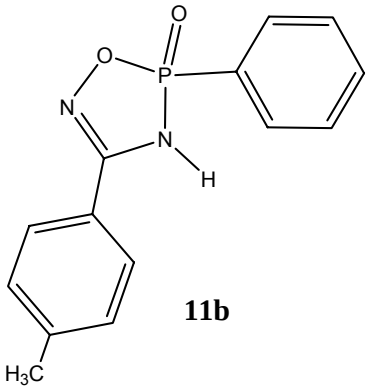

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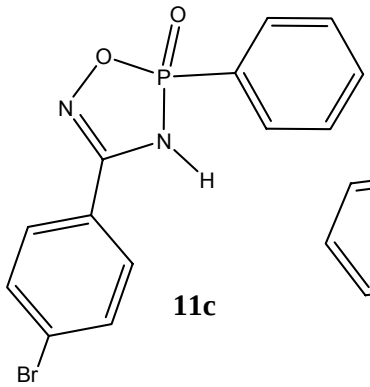

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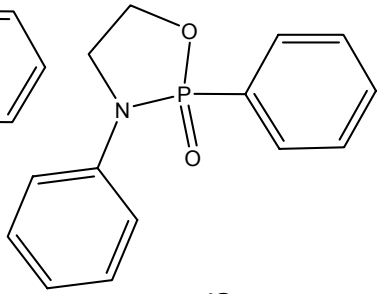

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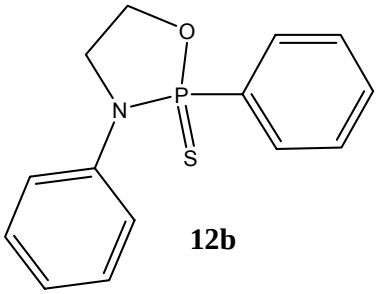

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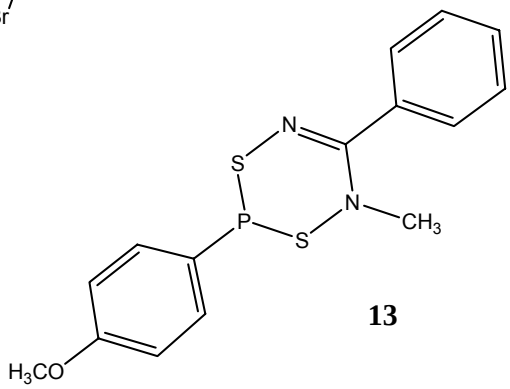

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CHAPTER I

INTRODUCTION

1.1. AMIDOXIMES

Amidoximes are the important class of compounds bearing both a hydroxyimino and an amino function at the same carbon atom and have been used for the synthesis of a variety of valuable compounds [1].

In 1873, Lossen and Schifferdecher [2] prepared the first amidoxime by reacting hydrogen cyanide with hydroxylamine. The compound is called as “isuretin” as shown below.

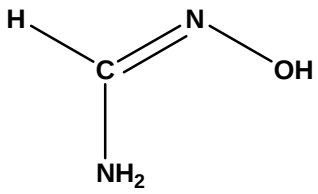


Figure 1 : Structure of isuretin

The name “amidoxime” was first used by Tiemann [3] who prepared two related compounds mandelamidoxime and benzamidoxime in 1884 by addition reaction of hydroxylamine to benzaldehyde cyanohydrin and to benzonitrile, respectively.

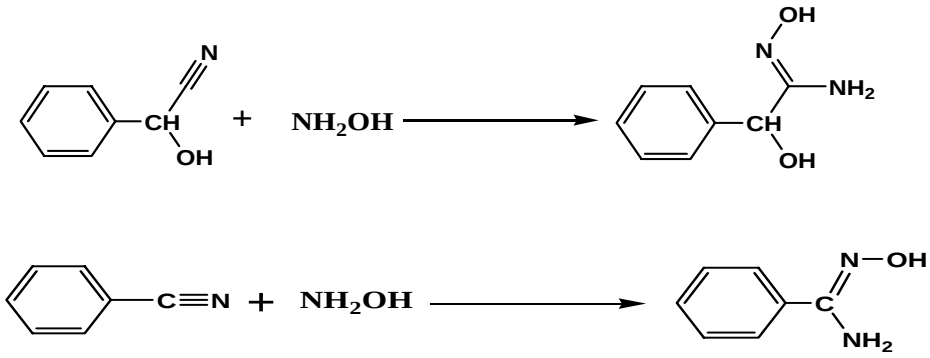


Figure 2: Mandelamidoxime and Benzamidoxime

During the last years more amidoximes have been tested for pharmacological properties and have been found to be bactericidal and fungicidal [4], local anaesthetics and fibrinogen receptor antagonists [5].

1.1.1. Molecular Structure

Eventhough the first amidoxime whose name is isuretin was synthesized in 1873 by Lossen and Schifferdecker [2], these authors did not establish the structure of this compound. Tiemann [3] assigned a structural formula to the novel functional group. Tiemann proved the structure of the amidoxime function by showing the simultaneous presence of NH_2 and NOH groups [7] : benzamidoxime forms salts with metals and with mineral acids just as would oximes and amines, respectively. The isonitroso group is identified by its acidic character and its reaction with nitrous acid with evolution of nitrous oxide.

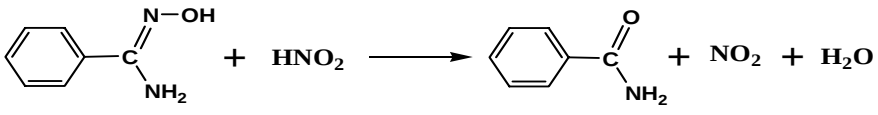
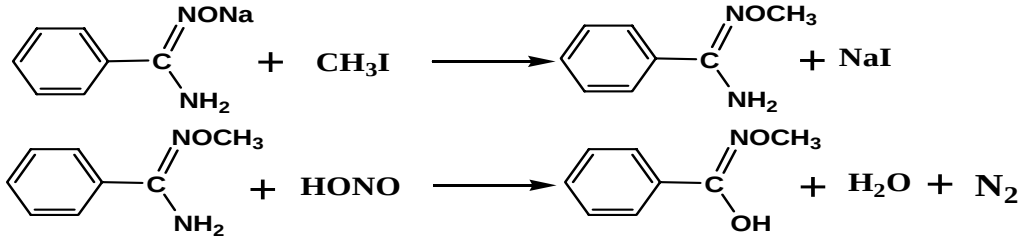
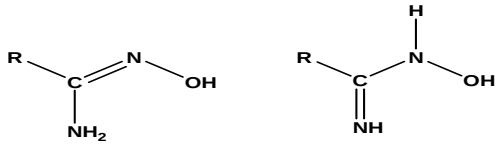


Figure 3

When the sodium salt of benzamidoxime is alkylated with methyl iodide the resulting compound reacts with nitrous acid to yield nitrogen, thus proving the presence of the amino group.



Tiemann recognized that amidoximes may be present in two tautomeric forms (a and b), with former is predominant.



-a- -b-

Figure 5 : Tautomeric form of amidoxime

1.1.2. Synthesis of Amidoximes

1.1.2.1. Action of Hydroxylamine on Nitriles

The preparation of amidoximes from nitriles by the action of hydroxylamine was first studied by Tiemann and Krüger [3].

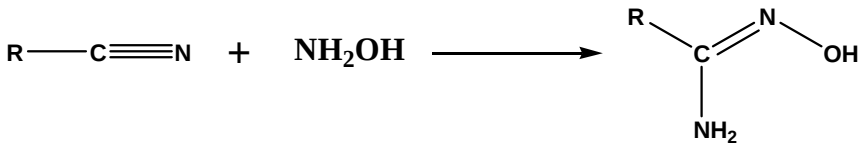


Figure 6: Action of hydroxylamine on nitriles

Addition of the equivalent amount of nitrile in enough alcohol, generally ethanol, to hydroxylaminehydrochloride whose hydrochloride part is liberated by strong base (generally; sodium carbonate, triethylamine, sodiumhydroxide, potssium hydroxide) yields amidoximes at 60-80 ^{0}C during

a few hours. This is the most used process for the preperation of monoamidoximes. **(*Method A1*)**

To avoid the seperation of amidoximes from sodium or potassium chloride salts some authors used a solutıon of free hydroxylamine in absolute methanol ot ethanol. **(*Method A2*)**

Amidoximes with highest yields were obtained when a 15% excess of a solution of hydroxylamine in butanol was used [8].

1.1.2.2. Action of Hydroxylamine on Amides or Thioamides

Hydroxylamine, as a rule, does not react with amides. This method has only been reported [9,10] for the preperation of two amidoximes as shown below.

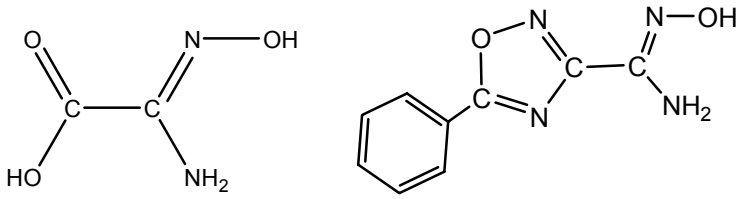


Figure 7

The procedure for the synthesis of amidoximes from thioamides is same as from nitriles. By this method some aromatic amidoximes have been prepared [11-14]. **(*Method B*)**

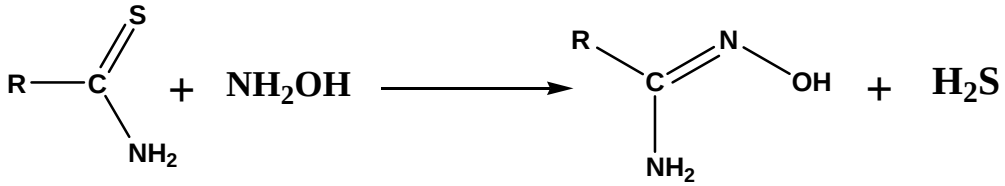


Figure 8: Action of hydroxylamine on thioamides

1.1.2.3. Reduction of Nitrosolic and Nitrolic Acids

The reduction of nitrosolic and nitrolic acids with hydrogen sulfide and hydrogen gases respectively gives amidoximes. Wieland and Bauer [16] prepared benzamidoxime by reducing benzonitrosolic acid with hydrogen sulfide. **(*Method C*)**

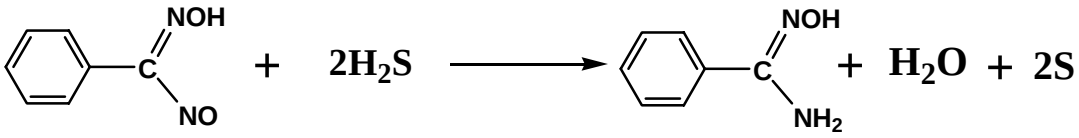


Figure 9 : Reduction of Nitrosolic Acids by Hydrogen Sulfide

1.1.2.4. Action of Amonia on Hydroximic Acid Chlorides

Chloroximes are formed by direct chlorination of aldoximes. These compounds reacts easily with ammonia to yield amidoximes.**(*Method D*)** This procedure was firstly used by Werner [17,18].

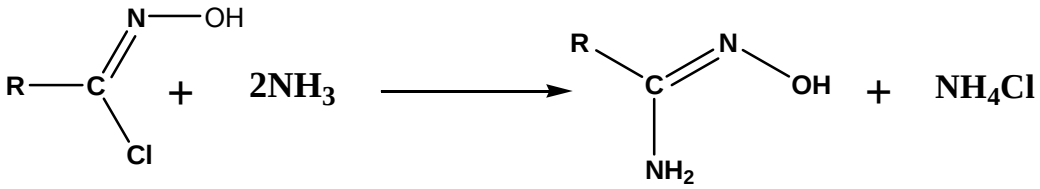


Figure 10 : Action of ammonia on chloroxime

1.1.2.5. Reduction of Oxyamidoximes

Ley and Ulrich [15] was prepared benzoxyamidoxime by reacting phenyl hydroxymoyl chloride with hydroxylamine **(*Method E*)**. The reduction of the product with sulfurdioxide yields benzamidoxime.

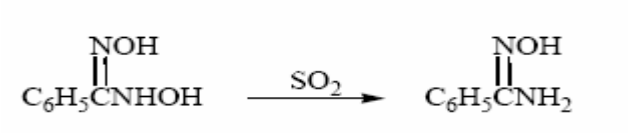


Figure 11 : Reduction of oxyamidoximes with sulfurdioxide

1.1.2.6. Action of Hydroxylamine on Iminoethers

This reaction was firstly reported by Pinner [19] and Lossen [20], who obtained benzamidoxime by treating ethyl iminobenzoate with hydroxylamine. (***Method F***)

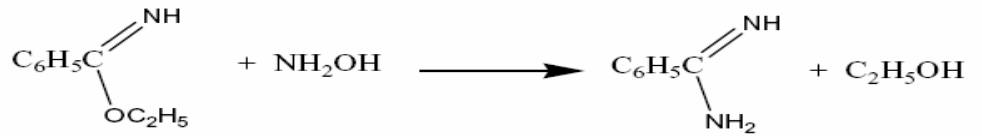


Figure 12 : Synthesis of Benzamidoxime

Since the benzonitrile is the starting material for the synthesis of the iminoether, this reaction is not practical method for the synthesis of amidoximes compering with method A.

1.1.2.7. Action of Hydroxylamine on Amidine Hydrochlorides

Pinner [19] prepared benzamidoxime by treating benzamidine hydrochloride with hydroxylamine (***Method G***). This reaction has no practical interest, since amidines generally are obtained from nitriles, thioamides, or iminoethers (compare with methods A, B, and F).

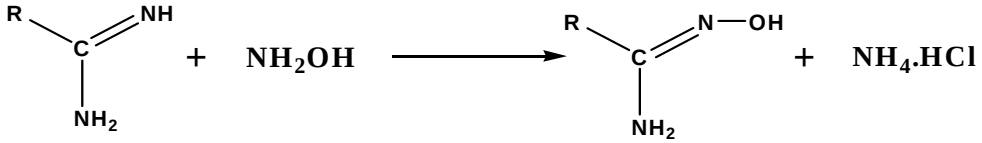


Figure 13

1.1.2.8. Action of Ammonia on Oximinoethers

When heated in a pressure bottle for 8 hrs. at 175^0 , an alcoholic solution of ammonia and ethyl benzhydroxamic acid yields benzamidoxime [21] . This reaction has not found general application. **(*Method H*)**

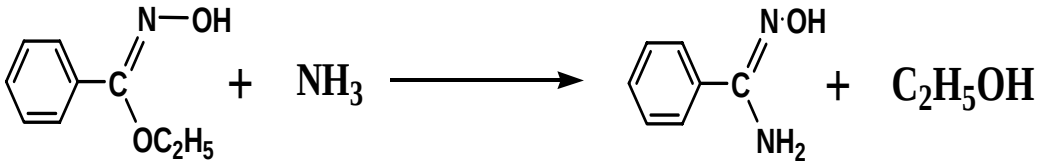


Figure 14

1.1.2.9. Action of Formamidoxime on Aromatic Aldehydes

According to Conduché [22] formamidoxime reacts with aromatic aldehydes, leading to an aldol condensation. **(*Method K*)**

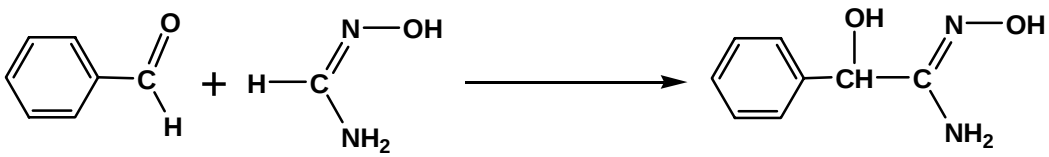


Figure 15

1.1.2.10. Action of Ammonia on Glyoxime Peroxides

Dehydrogenation of substituted glyoximes yields “oxides”. Depending on the relative configuration of the NOH groups *(syn, anti,* or *amphi)* and on the nature of the substituents, the “oxides” are considered as nitrile oxides, furazane oxides, or peroxides . **[6] (R’ = H)**

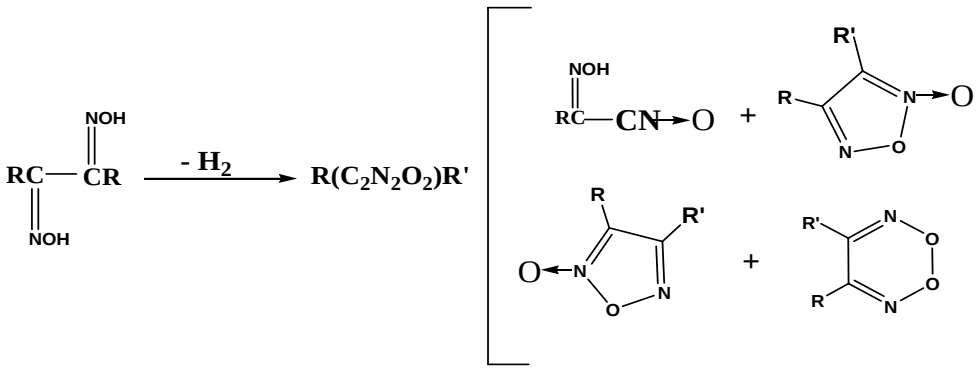


Figure 16

On treatment with ammonium hydroxide phenylglyoxime peroxide yields an oxime containing amidoxime [23-25].

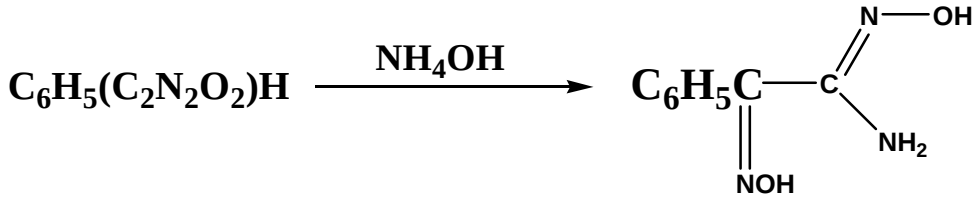


Figure 17

The reaction is analogous to that of the 0-benzoylated nitrile-oxide [30].

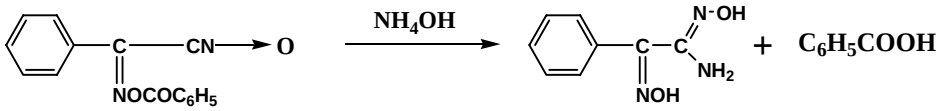


Figure 18

Another example is the reaction of dibenzoylglyoxime peroxide with ammonium hydroxide [31].

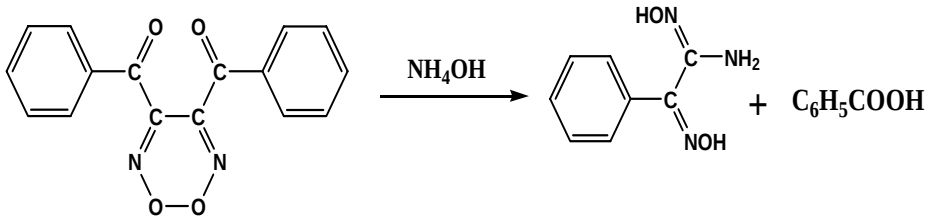


Figure 19

1.1.3 Properties and Reactions of Amidoximes

1.1.3.1 Physical Properties of Amidoximes

The amidoximes are colorless crystalline compounds which can be decomposed by heating over their melting points. Aryl amidoximes which are insoluble in water and soluble in alcohols and some organic solvents are more stable than aliphatic amidoximes. The first member of aliphatic series is soluble in water but their solubilities decrease with increasing molecular weight. The amidoximes are O−H acids, not N−H acids as is brought out by the appreciably higher pKa of *O*-methyl derivative of benzamidoxime whose pKa value is 26.0. The pKa value of benzamidoxime is 23.0 [32]. Tautomerism, conformation, and configuration are important characteristics associated with amidoximes. Considerable work has been done since 1960 in determining these properties for simple amidoximes such as benzamidoximes, formamidoxime, and *N*,*N*-dimethylacetamidoxime. These studies indicate that there is a major configurational difference between unsubstituted amidoximes or their *N*-alkyl anologues and the *N,N*-dialkyl derivatives.

Infrared and nuclear magnetic resonance spectroscopy established that amidoximes and their *O*-acyl derivatives exist in solutions in the amino oxime form [33]. The infrared spectra of amidoximes shows two well defined absorption bands: the first is a doublet at 3484-3412 cm^{-1} and 3378-3300 cm^{-1}, assigned to the two NH2 stretching modes; the second between 1680 and 1644 cm-1 to the C=N stretching. The OH stretching band of the NOH group is very broad and has its maximum at approximately 3125 cm^{-1}.

1.1.3.2 Chemical Properties and Reaction of Amidoximes

1.1.3.2.1 Salt Formation

The amidoximes are amphoteric substances, soluble in dilute mineral acids as well as in aqueous alkaline solutions [42].

The amino group in the molecule confers basic properties to the amidoximes. Salts of amidoximes with mineral or organic acids are known; they are crystalized easily and have well defined melting points. The hydrogen atom of the NOH group can be substituted by a metal. Many sodium and silver salts have been described [6].

Amidoximes form colored crystalline compounds with the salts of some metals. Werner [43] prepared a great number of such compounds with different amidoximes and proved that they are internal complexes in which the metal atom is linked to the oxime group as well as the amino group. These amidoximes have been used as analytical reagents for various cations [44,45]. Nicotinamidoxime can be used for thespectrophotometric determination of uranium [46].

1.1.3.2.2 Organic Complexes

Amidoximes form with chloral bimolecular complexes, which are insoluble in water and organic solvents. They have sharp melting points and may be used for the identification of amidoximes. [47-50]

1.1.3.2.3 Thermal Decomposition

Generally, amidoximes are decomposed when heated in the neighborhood of their melting point. Benzamidoxime is melting at 80 ^{0}C and stable up to 170 ^{0}C. At this temperature it decomposes, yielding several products which were identified [51] as nitrogen, nitrous oxide, ammonia, water, benzonitrile, benzamide, diphenyl 1,2,4-oxadiazole, diphenyl-1,2,4-triazole and triphenyl-1,3,5-triazine.

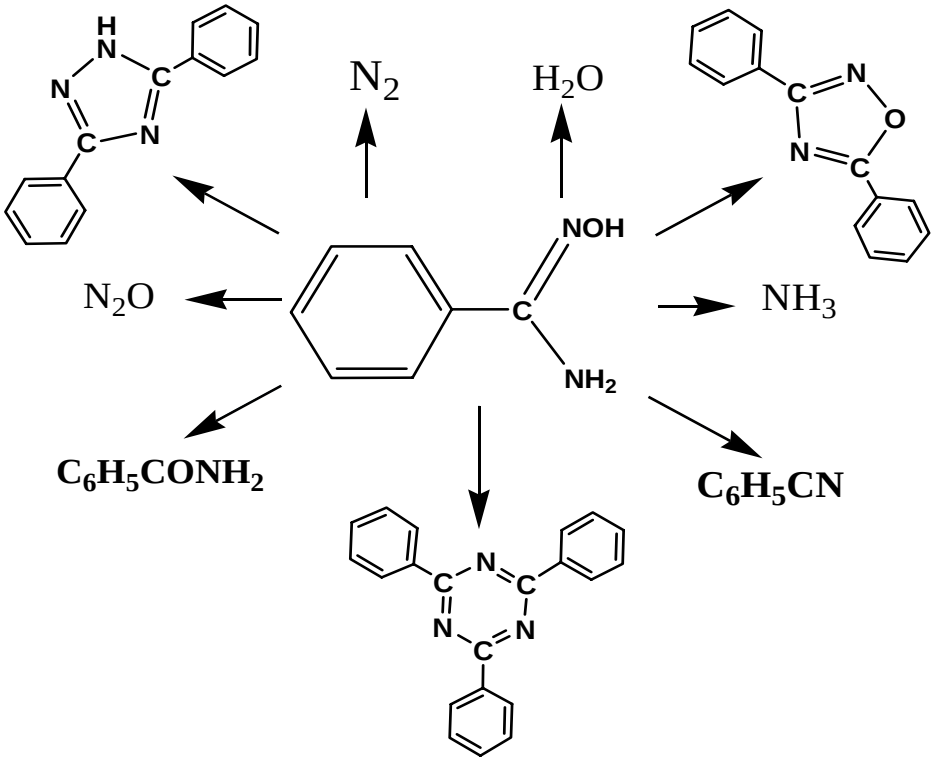


Figure 20: Decomposition of Benzamidoxime

1.1.3.2.4 Hydrolysis

Many amidoximes, which at room temperature form soluble salts with dilute mineral acids and alkalies, are hydrolyzed completely when heated in the same media [52]. Amides and hydroxylamine are formed, and under drastic conditions the amides are hydrolyzed into the corresponding acids;

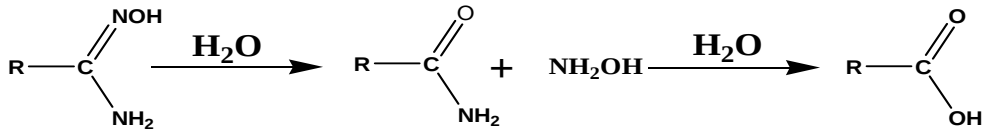


Figure 21 : Hydrolysis of Monoamidoximes

1.1.3.2.5 Oxidation

The oxidation of benzamidoxime with some oxidizing agents such as potassium ferricyanide, chlorine or bromine in acetic acid, and iodine in aqueous bicarbonate yield a product which corresponds to an aminodihydrooxadiazole. Iodine in sodium hydroxide yields benzonitrile with benzamidoxime. The oxidation of oxamidedioxime studied by Holleman [34] failed to yield any defined product.

To investigate deoxygenation of nitrosoazomethine derivatives as a method for the generation of azomethine nitrenes, a preparation of nitroso compounds by the oxidation and dehydrogenation of secondary amidoximes has been studied by Boyer and Frints [35] in 1968.

1.1.3.2.6 Reduction

The reduction of benzamidoxime with sodium amalgam [36,37] produces ammonia and benzaldoxime with a yield of only 10 to 12%; most of the amidoxime remains unchanged.

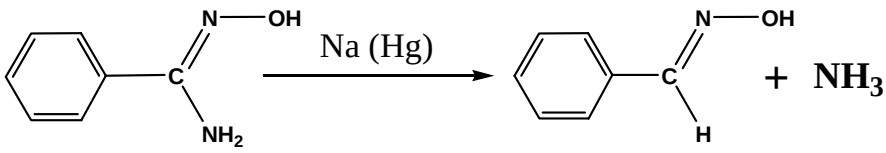


Figure 22: The reduction of benzamidoxime

Zinc and hydrochloric acid do not reduce amidoximes. Therefore this reagentreduces p-nitrobenzamidoxime to p-aminobenzamidoxime [38].

When *N*-substituted amidoximes are reduced on a palladium charcoal catalyst under 10 to 20 atm of hydrogen [39], only 3 moles of hydrogen are taken up; there is evidence that both nitrogen atoms are still present in the reaction product but the structure of these substances has not yet been established.

Amidines can be prepared by reduction of the corresponding amidoximes [40,41] in the presence of Raney nickel at 30 atm. and 60-80 ^{0}C.

1.1.3.2.7 O- Alkylation

When sodium salts of amidoximes which obtained from sodium alcoholate, treated with aliphatic halogen compounds, *O*-alkyl ethers are yield [6].

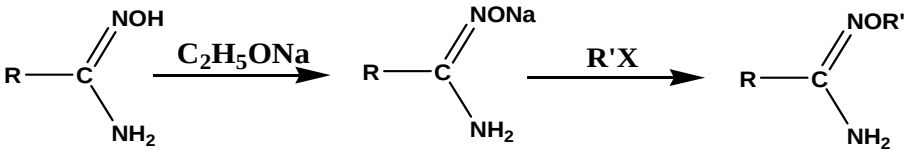


Figure 23: O- Alkylation of Amidoxime

Instead of sodium ethoxide, potassium or sodium hydroxide in aqueous alcoholic solution can be used [53].

1.1.3.2.8 Action of Nitrous Acid

The reaction of nitrous acid on benzamidoxime has been one of the methods which helped to elucidate the structure of the amidoxime group [6].

Tiemann and Krüger [42] identified the presence of the NOH group by the fact that benzamidoxime, as hydroxylamine itself, evolves nitrous oxide when treated with an equivalent amount of nitrous acid. Under these conditions, benzamidoxime is transformed into benzamide. Acetamidoxime react similarly yielding acetamide and nitrous oxide [54] .

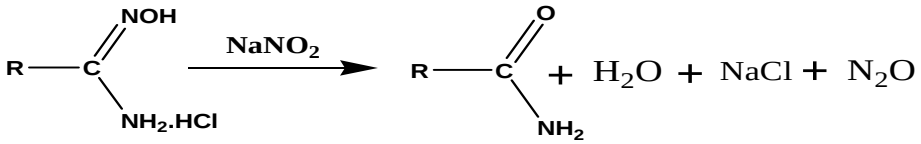


Figure 24

However, an O-alkylated benzamidoxime treated with nitrous acid evolves nitrogen, which proves that an amino group is present in the molecule. In this reaction the corresponding hydroximic acid is not isolated, but in the presence of an excess hydrochloric acid, the hydroximic acid chloride is formed in almost quantitative yields [54].

1.1.3.2.9 Acylation

Acylation of amidoximes can be achieved on both oxygen and the amino nitrogen atoms. In fact acylation always occurs on the oxygen, unless the hydroxyimino function is substituted. *O*-acylated amidoximes can be prepared by acid chlorides or anhydrides at room temperature [6].

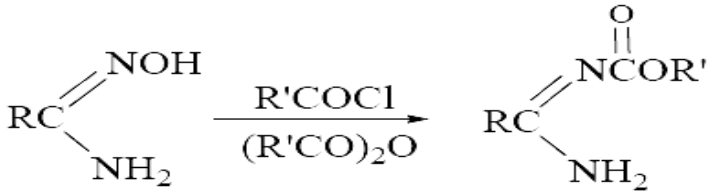


Figure 25 : Acylation of Amidoxime

Instead of acid anhydrides and chlorides, other reagents have been used, such as ketene, mixed carboxylic-carbonic anhydrides, carboxylic acid azides, and thioacetic acid [8].

N-Acylated amidoximes have been described by Ponzio and his collaborators who studied the acylation of two isomers α and β of 1-phenyl-2-aminoglyoxime corresponds to the structures I and II respectively. On acylation, the amidoxime group of the former is N-acylated, while the latter undergoes O-acylation. In order to prove this point, cyclization with aqueous alkali is performed, which leads to a furazan III in the first case and to an oxadiazole ring IV in the second [55,56].

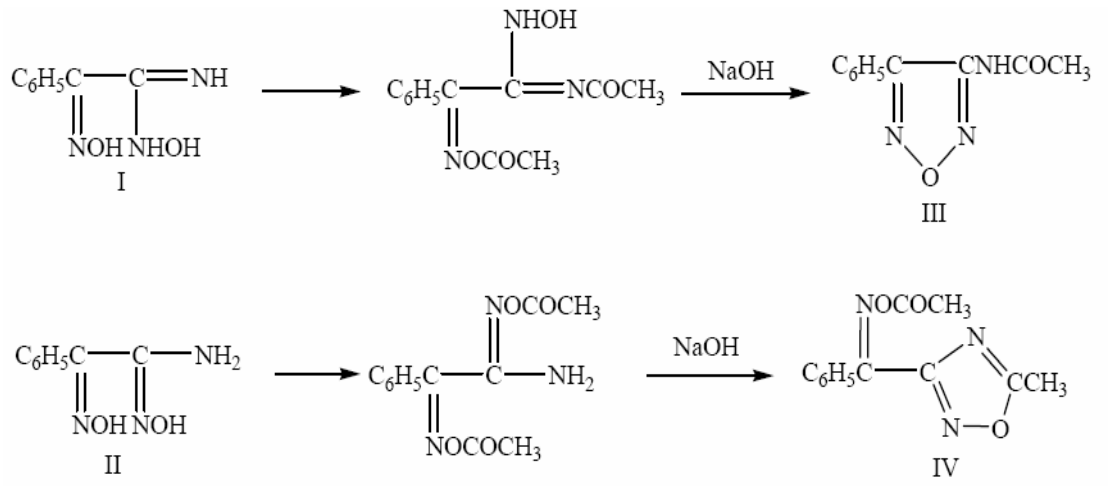


Figure 26: Cyclization with aqueous alkali

1.1.3.2.10 N-Substitution

1.1.3.2.10.1 Action of an Amine on Hydroximic Acid Halides

N-substituted amidoximes can be prepared by reaction of hydroximic acid chlorides with primary and secondary, aliphatic and aromatic amines. This is the usual way of preparing *N*-substituted amidoximes and the reaction

is carried out in absolute ethanol, chloroform or in ether at room temperature and an excess of amine is used to neutralize the hydroximic acid halide formed [6].

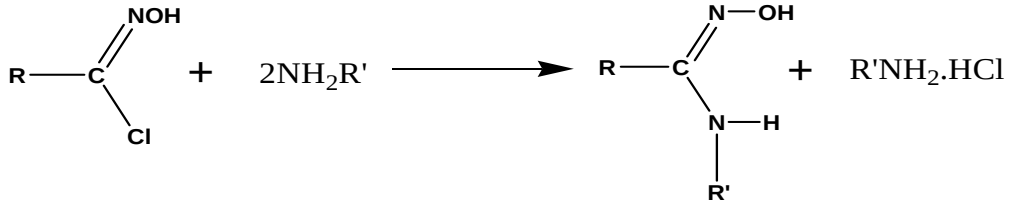


Figure 27: Action of an amine on hydroximic acid chloride

1.1.3.2.10.2 Action of Hydroxyl Amine on *N*-substituted Thioamides

The yields are less than in the case of unsubstituted thioamides [57-59].

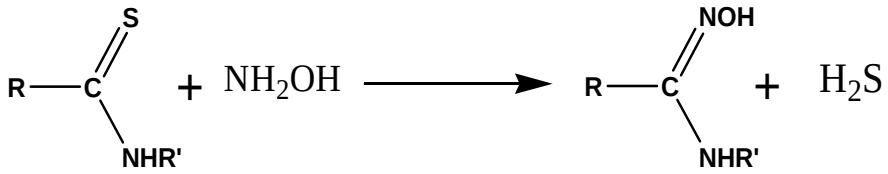


Figure 28: Action of hydroxylamine on *N*-Substituted thioamide

1.1.3.2.10.3 Action of Amines on Glyoxime Peroxides

N-substituted aminoglyoximes can be prepared by reacting amines with glyoxime peroxides [60-62].

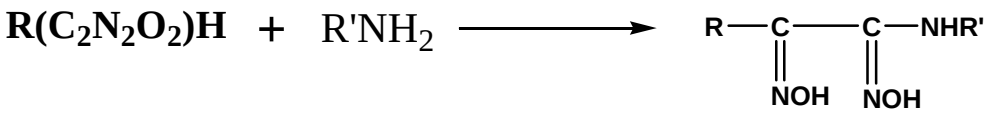


Figure 29: Action of amines on glyoxime peroxides

1.1.3.2.10.4 Action of Aniline on Amidoximes

The reaction of acetamidoxime and formamidoxime hydrochloride at 80-90 ^{0}C was resulted with the formation of the corresponding *N*-substituted amidoximes and the evolution of ammonia [63-64]

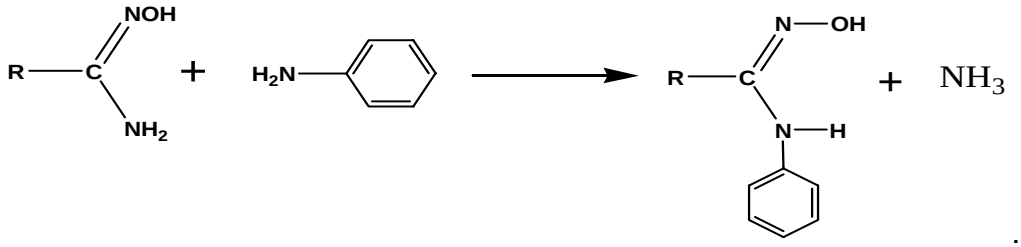


Figure 30: Action of aniline on amidoximes

1.1.3.2.10.5 Action of Isocyanates and Isothiocyanates

According to Tiemann [42] cyanic acid and phenyl isocyanate react with benzamidoxime to yield ureide or phenylureide oximes. In the case of *O*-alkyl amidoximes, isocyanates can evidently yield only ureide oximes [65-67].

Figure 31: Action of isocyanate

Benzanilidoxime hydrochloride is reported to react with potassium cyanate [57]. The formula proposed for the reaction product is that of a ureide oxime but the compound is completely insoluble in alkali and therefore it is more probable that the correct structure is that of a carbamate.

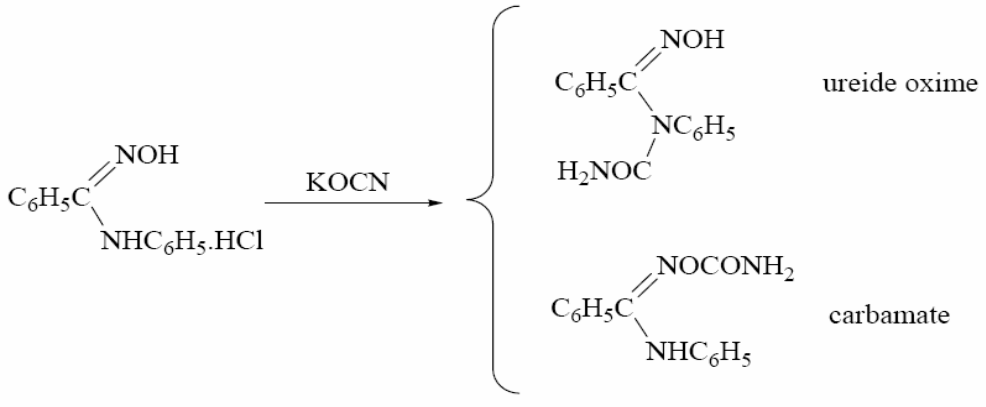


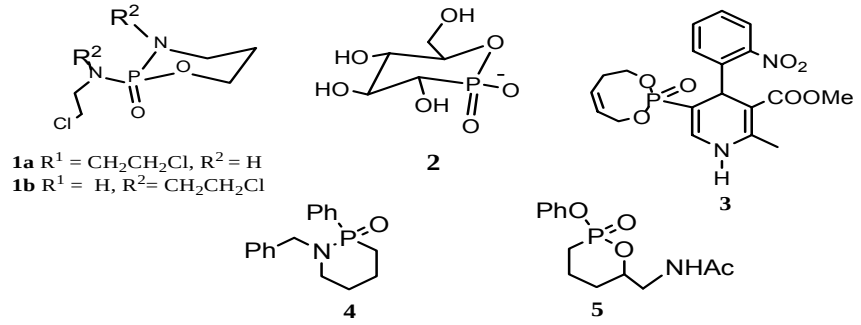
Figure 32: Action of potassium cyanate

When phenyl isothiocyanate and benzamidoxime react in equimolar amounts and the reaction is carried out at room temperature, benzoylphenylthiourea oxime is formed [68,69].

1.2 PHOSPHORUS CONTAINING HETEROCYCLES

Heterocyclic systems that include a phosphorus linked to an oxygen or nitrogen atom are common to a diverse array of important biological molecules [70], e.g. 1-5 (Scheme 1).

These include cyclophosphamide,**1a**, an anti-tumor alkylating agent which together with its structural isomer ifosfamide **1b** act as prodrugs relying on metabolism for their action [71]. In another group of compounds, cyclic phosphonates as exemplified by compound **2** are hexapyranose analogs modified at the anomeric carbon [72]. As a result, these analogs can regulate key steps in carbohydrate linked biological processes, e.g. cellular recognition [73]. 1,4- Dihydropyridine-5-cyclic phosphonate derivatives such as compound **3** are analogs of 1,4-dihydropyridine-3,5-dicarboxylate calcium antagonists and are therefore anti-hypertensive agents [74]. 1,2-Azaphosphorine such as compound **4** were developed in the search for biodegradable insecticides [75]. More recently, cyclic organophosphorus compounds have been employed for the generation of novel biocatalysts **[76].The** cyclic phosphonate **5** has been successfully used to generate antibodies that catalyse the enantioselectiveaminolysis of lactones [77].

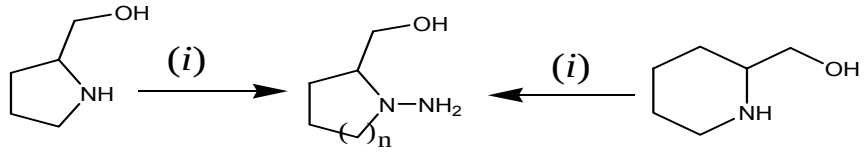


Scheme 1

1.2.1 Phosphonylhalides and Ring Closure Reactions

1.2.1.1 By using Hydrazino Alcohols

The hydrazino alcohols **8** and **9** required for the synthesis of the 1,3,4,2-oxadiazaphosphinane derivatives were prepared from the corresponding amino alcohols **6** or **7**, the *N*-nitroso derivatives of which were reduced with $LiAlH_4$ according to literature procedures [78-79]

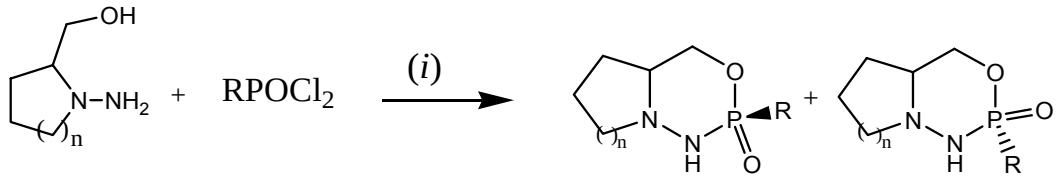


6 n=1 : **8** n=2 : **9** **7**

i= 1. $NaNO_2$, AcOH, H_2O, rt, 8 h, 2. $LiAlH_4$, THF, rt, 2 h, 52%.

Schame 2

The cyclizations of compounds **3** and **4** with phenylphosphonic dichloride, phenyl dichlorophosphate and bis-(2-chloroethyl)phosphoramidic dichloride were performed at ambient temperature by using a given procedure [80].

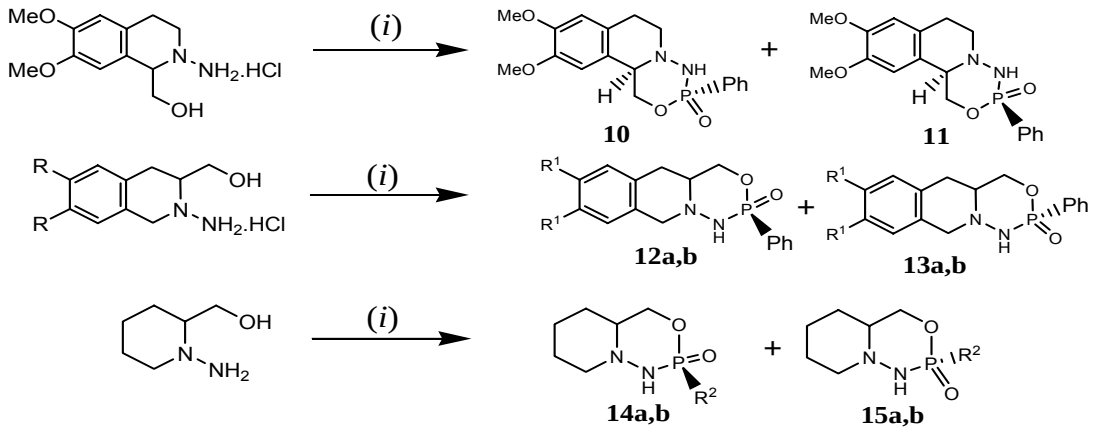


n=1 n=2 n=1 n=2 n=1 n=2

Reagents and conditions: *(i)* = Et_3N, THF, RT, 2 days then column chromatography
R= -Ph , -OPh or bis(2-chloroethyl)amine

Schame 3

In 2006, Zita Zalan [81] and his co-workers used hydrazino alcohol derivatives to synthesize 1,3,4,2-oxadiazaphosphinanes and also conformational analaysis of these kind of compounds was studied.



Compound	R^1	R^2	Diasteriomericr ration in the crude product
10:11	-	-	48 : 52
12a :13a	H	-	50 :50
12b :13b	OMe	-	~0 : ~100
14a :15a	-	Ph	21 : 79
14b : 15b	-	OPh	50 : 50

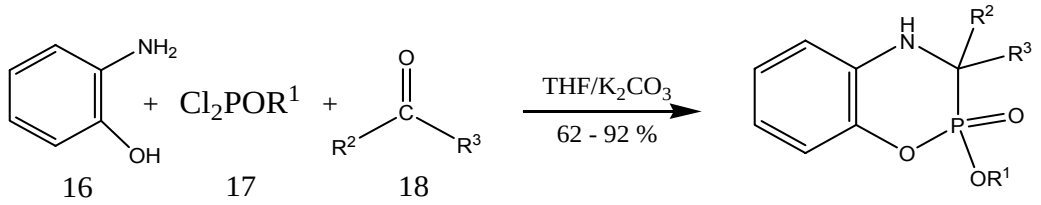
Reagents and conditions (*i*) = Cl_2POPh or $Cl_2PO(OPh)$ Et_3N, THF, 48 hr, 34-51%

Scheme 4

1.2.1.2 By Using Amino Alcohol (Aminophenol)

To the best of our knowledge, some papers deal with 1,4,2 oxaza-phosphinane structures. They all described the synthesis of this organophosphorus heterocycle starting with imines and different phosphines participate. However, in 2007, Bin Wang [82] and his co-workers synthesized α-carbon atom substituted 2-oxo-1,4,2-oxazaphosphinanes without using diimine as a starting substrate.

As shown in Scheme 5 , *o*-aminophenol **16** was allowed to react with alkyl dichlorophosphinite **17** and various substituted ketones or benzaldehyde **18** in anhydrous THF containing a small amount of potassium carbonate to give the aimed compounds in good yields.

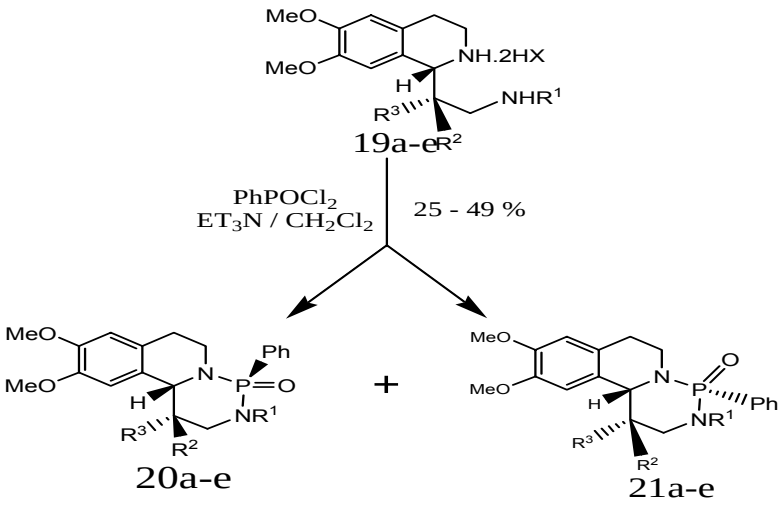


16 17 18

Scheme 5

1.2.1.3 By Using Diamines and Diimines

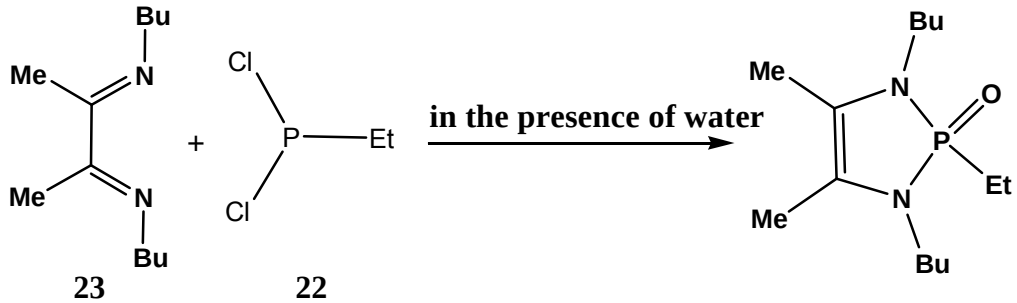
In 2003, Zita Zalan and his co-workers sysnthesized 1,3,2- diazaphosphorinanes and the nitrogen-bridged tricyclic system. 1-(2'-Aminoethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines 1a–e, the starting materials for the preparation of the target diazaphosphorinanes, were prepared in five steps, starting from the corresponding N-protected balanines and homoveratrylamine [83].



	R^1	R^2	R^3	Diastereomic ratio (20:21) in the crude product
a	H	H	H	56:44
b	Ph	H	H	29:71
c	Me	H	H	27:73
d	H	Me	H	~100:~0
e	H	H	Me	57:43

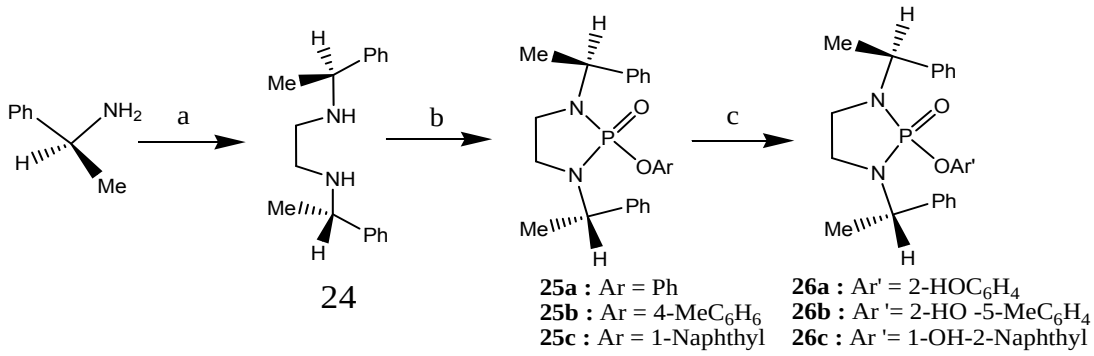
Scheme 6

The heterocyclic system arises in the reaction of ethyldichlorophosphine **22** with N,N'-dibutyl-2,3-butanediimine **23** in the peresence of water [84,85].



Scheme 7

In 2003, Zhuohong Yang [86] and his co-workers used optically active diamine **24** as a starting substrate to synthesize cyclic *o*-hydroxyl-arylphosphonodiamide **26**.

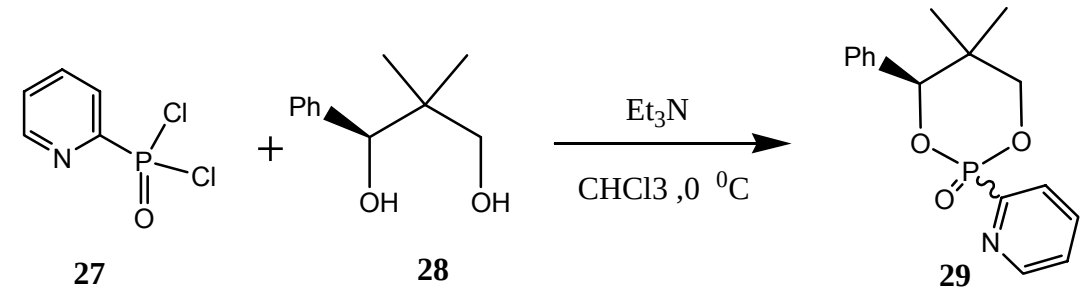


(a) $BrCH_2CH_2Br$, Et_3N, 110 ^0C ; **(b)** $ArOP(O)Cl_2$, Et_3N/CH_2Cl_2 , r.t. ; **(c)** n-BuLi/THF, -78 ^oC

Scheme 8

1.2.1.4 By Using Racemic Chiral Diols

Reaction of (2-pyridine)phosphonyldichloride **27** with enantiometrically pure 1-phenyl-2,2-dimethylpropane- 1,3-diol **28** leads to a mixture of two epimeric 2-oxo-2-(2-pyridinyl)-4-phenyl-5,5-dimethyl-l,3,2-dioxaphosp-horinanes **29**.

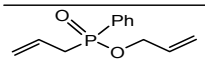
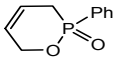
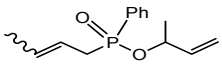
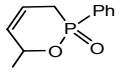
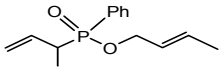
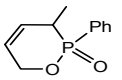
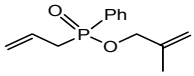
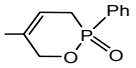
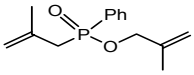
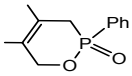
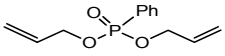
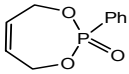
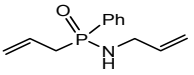
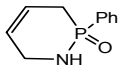
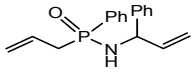
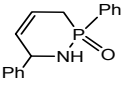
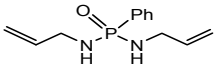
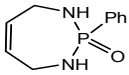
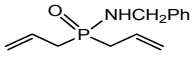
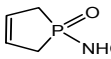
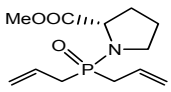
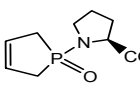


Scheme 9

The epimers were separated by cohmm chromatography and after crystallization **29a** and **29b** were obtained as white crystalline solids in 37% and 24% yields, respectively [87].

1.2.1.5 By Using Dienes Containing Phosphopus

In 2000, L. Hetherington [88] and his co-workers synthesized five, six and seven membered heterocycles containing phosphorus, starting from dienes containing phosphorus. And Ru-catalyst was used for the ring-closing metathesis reaction. RCM of dienes **31a-k** were carried out in dichloromethane in the presence of 2-16 % Ru-catalyst and at concentration of 0.02 M to give the corresponding cyclised product with moderate to exellent yields (Scheme 10).

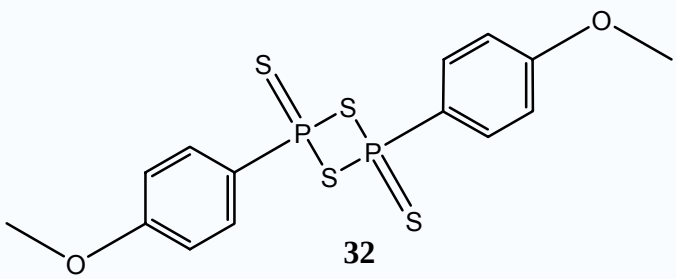
Substrate	Product	Condition	Yield[a]
 **30a**	 **31a**	4% **30**, 30 h	92 %
 **30b**	 **31b**	8% **30**, 21 h	84%[b]
 **30c**	 **31c**	8% **30**, 3 d	95%[b]
 **30d**	 **31d**	10% 30, 3d	31 %
 **30e**	 **31e**	6% **30**, 5d	no RCM[c]
 **30f**	 **31f**	16% **30**, 5d	34 %
 **30g**	 **31g**	3% **30**, 18 h	85 %
 **30h**	 **31h**	8% **30**, 24 h	63 %[b]
 **30i**	 **31i**	6% **30**, 3 d	36 %
 **30j**	 **31j**	6% **30**, 2 d	43 %
 **30k**	 **31k**	6% **30**, 2 d	80 %

[a]Isolated yields [b]Mixture of Disasteriomers [c]100% recovered starting material

Scheme 10

1.3 LAWESSON'S REAGENT AS A THIATION AGENT

Lawesson's reagent **(32)**, or LR, is a chemical compound used in organic synthesis as a thiation agent. It is made by the reaction of anisole **(33)** with phosphorus pentasulfide (P_4S_{10}).



32

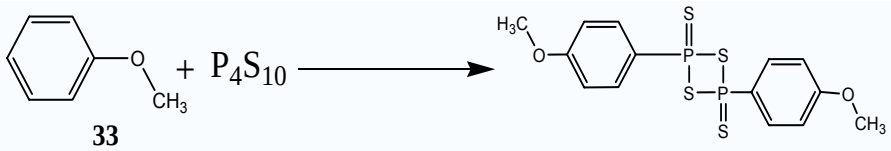
Figure 33 : Molecular Structure of Lawesson's Reagent

1.3.1 History

Lawesson's reagent was first made popular by Sven-Olov Lawesson, who did not, however, invent it. Lawesson's reagent was first made many years ago during a systematic study of the reactions of arenes with P_4S_{10} [89]. In later years a series of inorganic chemists have explored the general chemistry of Lawesson's reagent and related compounds.

1.3.2 Preperation

A mixture of anisole **(33)** (methoxybenzene) with phosphorus pentasulfide (P_4S_{10}) should be heated until the mixture is clear and no more hydrogen sulfide is formed [90]. Recrystallization from toluene or xylene will yield pure LR.



33

Figure 34: Preparation of Lawsson's Regent

As Lawesson's reagent has a strong and unpleasant smell, it is best to prepare the compound within a fume-hood and to treat all glassware used with a decontamination solution before taking the glassware outside the fume-hood. One common and effective method of destroying the foul smelling residues is to use an excess of sodium hypochlorite.

1.3.3 Mechanism of Action and Uses

Lawesson's reagent has a four membered ring of alternating sulfur and phosphorus atoms. With heating, the central phosphorus/sulfur four-membered ring can open to form two reactive dithiophosphine ylides ($R\text{-}PS_2$). Much of the chemistry of Lawessons's reagent is in fact the chemistry of these reactive intermediates.

A common use of LR is to convert a carbonyl into a thiocarbonyl. For instance, an amide can be converted into a thioamide using Lawesson's reagent. In addition LR has been used for the synthesis of thioesters and thioketones.

In one study [91] reaction of Maltol **(34)** with LR **(32)** results in a selective oxygen replacement in two positions (3-hydroxy-2-methyl-4H-thiopyran-4-thione) **(35)**.

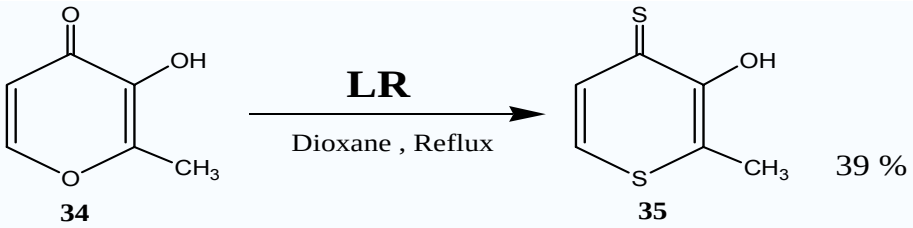
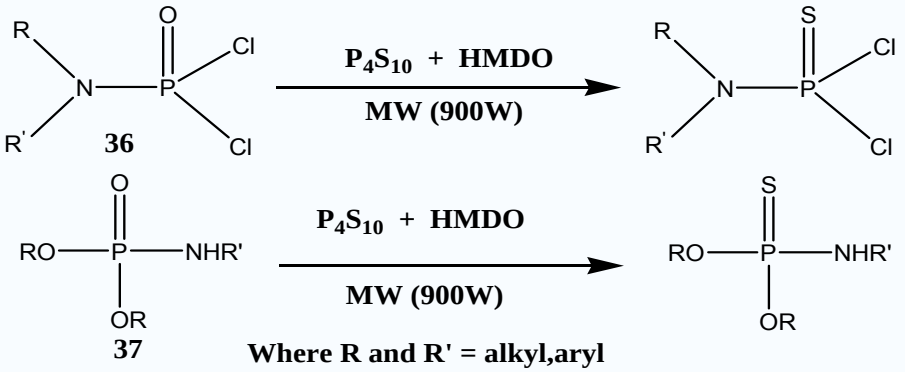


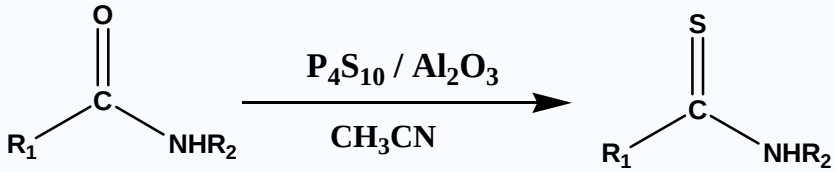
Figure 35: Reaction of maltol with LR

In one study [92] LR was used for thionation of phosphoramidodichloridates (**36)** and phosphoramidate diesters **(37)** using phosphorus pentasulfide and hexamethyldisiloxane under microwave irradiation.



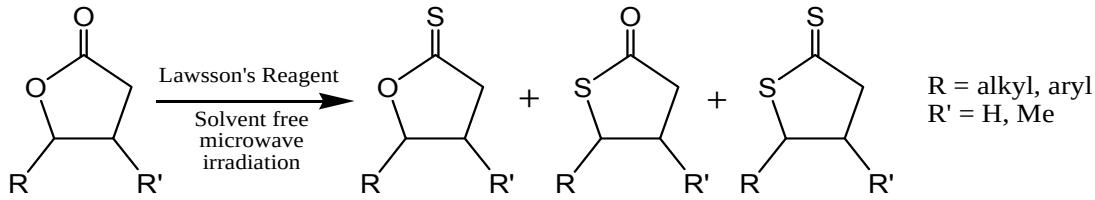
Scheme 11

In the other study [93] in 2006, alumina encapsulated phosphorus pentasulfide (P_4S_{10}/Al_2O_3) was found to be an efficient solid supported reagent for the thionation of long chain amides.



Scheme 12

In the other study [94] in 2006, solvent free thionation of □-lactones under microwave irradiation was done. Even though LR shows a remarkable selectivity under standard conditions (dry toluene/xylene, inert atmosphere, 0.5 molar equiv.), it is somewhat less selective under solvent-free and non-homogeneous conditions (heterogeneous phase, unstirred reaction mixture and non-focused microwave irradiation), and provides some of the dithioderivative **38d** and some of the thioderivative **38c** at trace levels (scheme 13).

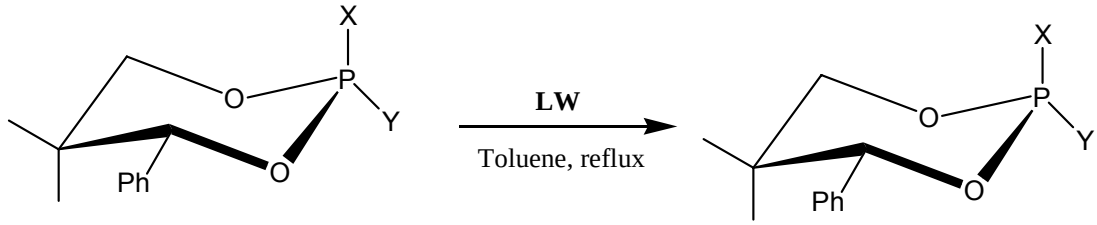


38a **38b** **38c** **38d**

65 - 95 %

Scheme 13: Synthesis of sulfurized □- lactones using Lawesson's reagent under microwave irradiation.

Finally, synthesis and conformations of cyclic pyridinyl-2-thiophosphonates **40a,b** were briefly examined (Scheme14) in 1998 by A. C. Dros [95] and his co-workers. Treatment of **39a** and **39b** with Lawesson's Reagent in boiling toluene.



39a X= 2-py Y= O
39b X= O Y= 2-py

40a X= 2-py Y= S
40b X= S Y= 2-py

Scheme 14

CHAPTER II

EXPERIMENTAL

Aldehydes, nitriles, *N*-chlorosuccinimide and primary amines were purchased from Merck and Fluka. Phenylphosphonyldichloride was purchased from Aldrich. ^{1}H , ^{13}C and ^{31} P NMR spectra were recorded on BRUKER spectrometer (400 MHz for ^{1}H; 100 MHz for ^{13}C and 162 MHz for ^{31}P). IR spectra were recorded on a SHIMADZU FTIR 8400-S instrument (KBr pellet). Mass spectra were run on Agilent GC 6890 instrument with MS 5975 mass detector. Melting points were determined on a Meltemp apparatus and uncorrected. Flash column chromatography was performed on Silica Gel (Merck, 230-400 Mesh ASTM). TLC was done using precoated plates with fluorescent indicator (Merck 5735). The stain solutions of permanganate, *p*-anisaldehyde and iodine were used for visualization of the TLC spots.

Thiophene-2-carboxaldehyde oxime (3):

To a solution of thiophene-2-carbaldehyde **(1)** (5.00 g, 45.0 mmol) in 30 ml of ethanol, a mixture of $NaCH_3COO.3H_2O$ (12.5 g, 90.0 mmol) and $NH_2OH.HCl$ (6.25 g, 90.0 mmol) prepared by dissolving separately in a minimum amount of water was added and the mixture was heated under reflux for 5h. Ethanol was evaporated under the reduced pressure, then crude product was filtered, and crystallized from 30% ethanol-water mixture as white needles.

Yield: 4.83 g, 85%

M.p. : 129 – 129.5 ^{0}C (Lit[1]: 130-132 ^{0}C)

Rf : 0.383 (Eluant: Hexane: Ethyl acetate; 1:1)

IR (KBr, v: cm^{-1}): 3126 and 2833 (broad, NOH, H-bonded), 1631 (C=N)

5-Chloro-thiophene-2-hydroximoyl chloride (5):

To a stirred solution of thiophene-2-carbaldehyde oxime **(3)** (5.25 g, 41.3 mmol, 1.0 eq.) in *N,N*-dimethyl formamide (DMF) (30 mL) at room temperature, *N*-chlorosuccinimide (11.58 g, 86.7 mmol, 2.1 eq.) was added in portions over 15 min. The reaction mixture was stirred for 2 d. The solution was poured into ice-water (60 mL) mixture and extracted with diethyl ether (3x50 mL), washed with brine and dried over anhydrous sodium sulphate, Na_2SO_4, and finally evaporated under reduced pressure to give the thiophene-2-hydroximoyl chloride **(5).** The product was used without further purification to obtain the *N*-substituted thiophene-2-carboxamidoximes.

Yield: 6.94 g, 92.4%

M.p. : 99-102 ^{0}C (Lit[1]: 99-102 ^{0}C)

Rf : 0.683 (Eluant: Hexane: Ethyl acetate; 1:1)

IR (KBr, v: cm^{-1}): 3197 and 2985 broad, (NOH), 1597 (C=N)

Furan-2-carbaldehyde oxime (4):

NaOH (9.16g, 229 mmol, 1.1 eq.) was dissolved in a min amount of water and and it was added to a furfural **(2)** (20g, 208 mmol, 1.0 eq.) in 80 mL ethanol (EtOH) . After that, $NH_2OH.HCl$ (15.9g, 229 mmol, 1.1 eq.) was

added slowly within 15 min. And the reaction was allowed to stand for 4 h at 0 ^{0}C and then 1 h at RT. Finally, ethanol was evaporated under the reduced pressure, then crude product was crystallized from 30% ethanol-water mixture as a white crystals.

Yield: 17.6 g, 76 %

M.p. : 85.5 - 87 ^{0}C (Lit[1]: 86-88 ^{0}C)

Rf : 0.50 (Eluant: Hexane: Ethyl acetate; 3:4)

IR (KBr, v: cm^{-1}): 3166 and 2862 (broad, NOH, H-bonded), 1645 (C=N)

5-Chloro-furan-2-hydroximoyl chloride (6):

To a stirred solution of furan-2-carbaldehyde oxime **(4)** (5.00 g, 45.012 mmol, 1.0 eq.) in *N,N*-dimethyl formamide (30 mL) at room temperature, *N*-chlorosuccinimide (12.92 g, 96.78 mmol, 2.15 eq.) was added in portions over 15 min. The reaction mixture was stirred for 2 d. The solution was poured into ice-water (80 mL) mixture and extracted with diethyl ether (3x50 mL), washed with brine and dried over anhydrous Na_2SO_4 and finally evaporated under reduced pressure to give the 5-chloro-furan-2-hydroximoyl chloride **(6).** The product was used without further purification to obtain the *N*-substituted furan-2-carboxamidoximes.

Yield: quantitative

M.p. : oily

Rf : 0.615 (Eluant: Hexane : Ethyl acetate; 3:4)

IR (KBr, v: cm^{-1}): 3236 and 3132 broad, (NOH), 1654 (C=N)

Benzamidoxime (8a):

To a solution of benzonitrile **(7a)** (3.82 g, 37.0 mmol) and triethylamine, Et_3N (101 g, 56.7 mmol) in 100 mL ethanol, $NH_2OH.HCl$ (4.05 g, 56.7 mmol) was added slowly by stirring until all $NH_2OH.HCl$ was dissolved. The mixture was stirred under reflux for 24 h. Solvent was evaporated under the reduced pressure and the crude product was extracted with ethyl acetate:water (25mL:25mL)x4. Combined organics was washed with brine solution and dried with anhydrous Na_2SO_4. Solvent was evaporated under the reduced pressure and the product was crystallized from benzene.

Yield: 3.015 g, 60 %

M.p. : 71.8 – 73.2 ^{0}C (Lit[1]: 72-74 ^{0}C)

Rf : 0.455 (Eluant: Hexane : Ethyl acetate; 2:3)

IR (KBr, v: cm^{-1}): 3454, 3362 (N−H), 1649 (C=N)

***p*-Chlorobenzamidoxime (8b) :**

To a solution of *p*-chlorobenzonitrile **(7b)** (6.5 g, 47.2 mmol, 1.0 eq.) and Et_3N (6.21 g, 61.4 mmol, 1.3 eq.) in 100 mL ethanol, $NH_2OH.HCl$ (3.87 g, 56.5 mmol, 1.2 eq.) was added slowly by stirring until all $NH_2OH.HCl$ was dissolved. The mixture was stirred under reflux for 5 h. Solvent was evaporated under the reduced pressure and the crude product was extracted with ethyl acetate:water (25mL:25mL)x4. Combined organics was washed with brine solution and dried with anhydrous Na_2SO_4. Solvent was evaporated under the reduced pressure and the crude product was crystallized from benzene.

Yield: 6.45 g, 80 %

M.p. : 130-132 ^{0}C (Lit[1]: 130-132 ^{0}C)

Rf : 0.60 (Eluant: Hexane : Ethyl acetate; 1:2)

Rf : 0.245 (Eluant: Hexane : Ethyl acetate; 2:1)

IR (KBr, v: cm^{-1}): 3451 (N−H), 1651 (C=N)

***p*-Bromobenzamidoxime (8c) :**

To a solution of *p*-bromobenzonitrile **(7c)** (4 g, 22 mmol, 1.0 eq.) and Et_3N (4.0 g, 39.5 mmol, 1.8 eq.) in 50 mL ethanol, $NH_2OH.HCl$ (2.26 g, 33.0 mmol, 1.5 eq.) was added slowly by stirring until all $NH_2OH.HCl$ was dissolved. The mixture was stirred under reflux for 5 h. Solvent was evaporated under the reduced pressure and the crude product was extracted with ethyl acetate : water (25mL:25mL)x4. Combined organics was washed with brine solution and dried with anhydrous Na_2SO_4. Solvent was evaporated under the reduced pressure and the crude product was crystallized from benzene.

Yield: 3.7 g, 85 %

M.p. : 132.5 – 134.6 ^{0}C (Lit[1]: 133-135 ^{0}C)

Rf : 0.605 (Eluant: Hexane : Ethyl acetate; 1:2)

***p*-Iodobenzamidoxime (8d):**

To a solution of *p*-iodobenzonitrile **(7d)** (2.5 g, 10.9 mmol, 1.0 eq.) and Et_3N (1.436 g, 14.2 mmol, 1.3 eq.) in 50 mL ethanol, $NH_2OH.HCl$ (0.36 g, 5.92 mmol, 1.2) was added slowly by stirring until all $NH_2OH.HCl$ was dissolved. The mixture was stirred at RT for 24 h. Solvent was evaporated under the reduced pressure and the crude product was extracted with ethyl

acetate : water (25mL:25mL)x4. Combined organics was washed with brine solution and dried with anhydrous Na_2SO_4. Solvent was evaporated under the reduced pressure and the crude product was crystallized from benzene.

Yield: 2.35 g, 82 %

M.p. : 148-150 ^{0}C (Lit[1]: 148-150 ^{0}C)

Rf : 0.512 (Eluant: Hexane : Ethyl acetate; 1:2)

IR (KBr, v: cm^{-1}): 3481 (N−H), 1660 (C=N)

***p*-Toluamidoxime (8e):**

To a solution of *p*-tolunitrile **(7e)** (4.0 g, 34 mmol, 1.0 eq.) and Et_3N (4.49 g, 44.3 mmol, 1.3 eq.) in 50 mL ethanol, $NH_2OH.HCl$ (2.80 g, 40 mmol, 1.2 eq.) was added slowly by stirring until all $NH_2OH.HCl$ was dissolved. The mixture was stirred at RT for 24 h. Solvent was evaporated under the reduced pressure and the crude product was extracted with ethyl acetate:water (25mL:25mL)x4. Combined organics was washed with brine solution and dried with anhydrous Na_2SO_4. Solvent was evaporated under the reduced pressure and the crude product was crystallized from benzene.

Yield: 4.2 g, 81 %

M.p. : 138.2 - 140 ^{0}C

Rf : 0.257 (Eluant: Hexane : Ethyl acetate; 1:2)

IR (KBr, v: cm^{-1}): 3500, 3369 (N−H), 1666 (C=N)

***p*-Hydroxybenzamidoxime (8f):**

To a solution of *p*-hydroxybenzonitrile **(7f)** (2.5 g, 21 mmol,) and Et_3N (2.5 g, 24.6 mmol,) in 50 mL ethanol, $NH_2OH.HCl$ (1.46 g, 21.4 mmol) was added slowly by stirring until all $NH_2OH.HCl$ was dissolved. The mixture was stirred at RT for 24 h. Solvent was evaporated under the reduced pressure and the crude product was extracted with ethyl acetate:water (25mL:25mL)x4. Combined organics was washed with brine solution and dried with anhydrous Na_2SO_4. Solvent was evaporated under the reduced pressure and the crude product was crystallized from benzene.

Yield: 1.48 g, 46 %

M.p. : 133.4 – 134.5 ^{0}C

Rf : 0.11 (Eluant: Hexane : Ethyl acetate; 1:2)

IR (KBr, v: cm^{-1}): 3481 (N−H), 1660 (C=N)

***p*-*N,N*-Dimethylaminobenzamidoxime (8g)**

To a solution of *p*-(*N,N*-dimethylamino)benzonitrile **(7g)** (3.0 g, 20.5 mmol, 1.0 eq.) and Et_3N (2.49g, 24.6 mmol, 1.2 eq.) in 50 mL ethanol, $NH_2OH.HCl$ (1.55g, 22.6 mmol, 1.1 eq.) was added slowly by stirring until all $NH_2OH.HCl$ was dissolved. The mixture was stirred under reflux for 4 h. Solvent was evaporated under the reduced pressure and the crude product was extracted with ethyl acetate : water (25mL:25mL)x4. Combined organics was washed with brine solution and dried with anhydrous Na_2SO_4. Solvent was evaporated under the reduced pressure and the crude product was crystallized from benzene.

Yield: 2,79g 75%

M.p. : 148 – 150 ^{0}C decompose (Lit[1]: 153-154 ^{0}C)

Rf : 0.15 (Eluant: Hexane : Ethyl acetate; 1:2)

IR (KBr, v: cm^{-1}): 3497 (N−H), 3234 (broad, NOH, H-bonded), 1655 (C=N)

_p_-Methoxybenzamidoxime (8h)

To a solution of *p*-methoxybenzonitrile **(7h)**(2.5 g, 18.8 mmol, 1.0 eq.) and Et_3N (3. 41g, 33.7mmol, 1.8 eq.) in 50 mL ethanol, $NH_2OH.HCl$ (1.93g, 28.2 mmol, 1.5 eq.) was added slowly by stirring until all $NH_2OH.HCl$ was dissolved. The mixture was stirred under reflux for 5 h. Solvent was evaporated under the reduced pressure and the crude product was extracted with ethyl acetate : water (25mL:25mL)x4. Combined organics was washed with brine solution and dried with anhydrous Na_2SO_4. Solvent was evaporated under the reduced pressure and the crude product was crystallized from benzene.

Yield: 2,45g 77%

M.p. : 122 – 123 ^{0}C

Rf : 0.15 (Eluant: Hexane : Ethyl acetate; 1:2)

IR (KBr, v: cm^{-1}): 3497 (N−H), 3234 (broad, NOH, H-bonded), 1655 (C=N)

_p_-Methylthio benzamidoxime (8i)

To a solution of *p*-methylthio benzonitrile **(7i)** (2.5 g, 16.8 mmol, 1.0 eq.) and Et_3N (2.55 g, 25.2mmol, 1.5 eq.) in 50 mL ethanol, $NH_2OH.HCl$ (1.5g, 21.8 mmol, 1.3 eq.) was added slowly by stirring until all $NH_2OH.HCl$ was dissolved. The mixture was stirred under reflux for 4 h. Solvent was

evaporated under the reduced pressure and the crude product was extracted with ethyl acetate:water (25mL:25mL)x4. Combined organics was washed with brine solution and dried with anhydrous Na_2SO_4. Solvent was evaporated under the reduced pressure and the crude product was crystallized from benzene.

Yield: 2,95g 97%

M.p. : 130 - 131 ^{0}C

Rf : 0.15 (Eluant: Hexane : Ethyl acetate; 1:2)

IR (KBr, v: cm^{-1}): 3497 (N−H), 3234 (broad, NOH, H-bonded), 1655 (C=N)

***p*-Nitrobenzamidoxime (8j) :**

To a solution of *p*-nitrobenzonitrile **(7j)** (5.0 g, 33.8 mmol, 1 eq.) and Et_3N (5.12 g, 48.9 mmol, 1.3 eq.) in 80 mL ethanol, $NH_2OH.HCl$ (2.77 g, 40.6 mmol, eq.) was added slowly by stirring until all $NH_2OH.HCl$ was dissolved. The mixture was stirred under reflux for 8 h. Solvent was evaporated under the reduced pressure and the crude product was extracted with ethyl acetate:water (25mL:25mL)x4. Combined organics was washed with brine solution and dried with anhydrous Na_2SO_4. Solvent was evaporated under the reduced pressure and the crude product was crystallized from benzene as a yellow powder.

Yield: 5.635 g, 91 %

M.p. : 180 – 180.2 ^{0}C (Lit[1]: 148-150 ^{0}C)

Rf : 0.70 (Eluant: Hexane : Ethyl acetate; 1:2)

IR (KBr, v: cm^{-1}): 3463 (N−H), 3184 (broad, NOH, H-bonded), 1661 (C=N)

Pyridine-2-carboxamidoxime (8k):

To a solution of pyridine-2-carbonitrile **(7k)** (1.126 g, 12.1 mmol, 1.0 eq.) and Et_3N (1.42 g, 14.3 mmol, 1.3 eq.) in 50 mL ethanol, $NH_2OH.HCl$ (0.89 g, 13 mmol, 1.2 eq.) was added slowly by stirring until all $NH_2OH.HCl$ was dissolved. The mixture was stirred under reflux for 24 h. Solvent was evaporated under the reduced pressure and the crude product was extracted with ethyl acetate:water (25mL:25mL)x4. Combined organics was washed with brine solution and dried with anhydrous Na_2SO_4. Solvent was evaporated under the reduced pressure and the crude product was crystallized from benzene.

Yield: 0.80 g, 48 %

M.p. : 114-116 ^{0}C (Lit[1]: 114-116 ^{0}C)

Rf : 0.34 (Eluant: Hexane : Ethyl acetate; 1:2)

IR (KBr, v: cm^{-1}): 3466 (N−H), 1647 (C=N)

Pyridine-3-carboxamidoxime (8l):

To a solution of pyridine-3-carbonitrile **(7l)** (4. g, 38.4 mmol, 1.0 eq.) and Et_3N (4.66 g, 46.1 mmol, 1.2 eq.) in 50 mL ethanol, $NH_2OH.HCl$ (2.89 g, 42.2 mmol) was added slowly by stirring until all $NH_2OH.HCl$ was dissolved. The mixture was stirred under reflux for 6 h. Solvent was evaporated under the reduced pressure and the crude product was extracted with ethyl acetate:water (25mL:25mL)x4. Combined organics was washed with brine solution and dried with anhydrous Na_2SO_4. Solvent was evaporated under the reduced pressure and the crude product was crystallized from benzene.

Yield: 1.71 g, 33 %

M.p. : 122.7 – 123.6 ^{0}C (Lit[1]: 127-128 ^{0}C)

Rf : 0.16 (Eluant: Hexane : Ethyl acetate; 1:2)

IR (KBr, v: cm^{-1}): 3420 (N−H), 1646 (C=N)

Pyridine-4-carboxamidoxime (8m):

To a solution of pyridine-3-carbonitrile **(7m)** (3.0 g, 28.8 mmol, 1.0 eq.) and Et_3N (3.79 g, 37.5 mmol, 1.3 eq.) in 50 mL ethanol, $NH_2OH.HCl$ (2.37 g, 34.6 mmol, 1.2 eq.) was added slowly by stirring until all $NH_2OH.HCl$ was dissolved. The mixture was stirred under reflux for 6 h. Solvent was evaporated under the reduced pressure and the crude product was extracted with ethyl acetate:water (25mL:25mL)x4. Combined organics was washed with brine solution and dried with anhydrous Na_2SO_4. Solvent was evaporated under the reduced pressure and the crude product was crystallized from benzene.

Yield: 1.78 g, 45 %

M.p. :198-199.5 ^{0}C (Lit[1]: 198-199.5 ^{0}C)

Rf : 0.08 (Eluant: Hexane : Ethyl acetate; 1:2)

IR (KBr, v: cm^{-1}): 3348 (N−H), 1647 (C=N)

Pyrazinecarboxamidoxime (8n):

To a solution of pyrazinecarbonitrile **(7n)** (4.0 g, 38.1 mmol, 1.0 eq.) and Et_3N (4.62 g, 45.7 mmol, 1.3 eq.) in 80 mL ethanol and 20 mL methanol, $NH_2OH.HCl$ (2.87 g, 41.9 mmol, 1.2 eq.) was added slowly by stirring until all $NH_2OH.HCl$ was dissolved. The mixture was stirred under reflux for 2 h.

Solvent was evaporated under the reduced pressure and the crude product was extracted with ethyl acetate:water (25mL:25mL)x4. Combined organics was washed with brine solution and dried with anhydrous Na_2SO_4. Solvent was evaporated under the reduced pressure and the crude product was washed with petroleum ether to remove unreacted pyrazinecarbonitrile.

Yield: 5.2 g, 99 %

M.p. :180.4 – 181.9 ^{0}C

Rf : 0.28 (Eluant: Hexane : Ethyl acetate; 1:2)

IR (KBr, v: cm^{-1}): 3348 (N−H), 1647 (C=N)

Thiophene-2-carbonitrile (7o) :

The mixture of thiophene-2-carboxaldehyde oxime **(3)** (2.12 g, 16.7 mmol) and phthalic anhydride (2.72 g, 18.4 mmol) in a beaker was heated in a sand bath at about 150 – 160 ^{0}C for ten min. After dehydration of all thiopehene-2-carboxaldehyde the crude product was dissolved in dichloromethane and 30 mL 5 % NH_3 solution was added. The mixture was extracted, washed with water and brine solution and dried with anhydrous Na_2SO_4. After evaporation of the solvent under the reduced pressure to give thiophene-2-carbonitrile. The product was used without further purification to obtain corresponding amidoxime.

Thiophene-2-carboxamidoxime (8o) :

To a solution of thiophene-2-carbonitrile **(7o)** (0.87 g, 8.0 mmol) and Et_3N (2.02 g, 20 mmol) in 30 mL ethanol, $NH_2OH.HCl$ (1.19 g, 17.4 mmol) was added slowly by stirring until all $NH_2OH.HCl$ was dissolved. The mixture

was stirred under reflux for 24 h. Solvent was evaporated under the reduced pressure and the crude product was extracted with ethyl acetate:water (25mL:25mL)x4. Combined organics was washed with brine solution and dried with anhydrous Na_2SO_4. Solvent was evaporated under the reduced pressure and the crude product was crystallized from benzene.

Yield: 5.2 g, 99 %

M.p. :94.7 – 95.3 ^{0}C

Rf : 0.28 (Eluant: Hexane : Ethyl acetate; 1:2)

IR (KBr, v: cm^{-1}): 3348 (N−H), 1647 (C=N)

5-Chloro-*N*-phenylthiophene-2-carboxamidoxime (9a):

To a solution of 5-chloro-thiophene-2-hydroximoyl chloride **(5)** (2.5 g, 12.8 mmol) in chloroform (25 mL) was added drop wise aniline (1.13 g, 27.5 mmol) in chloroform with constant stirring at room temperature. The reaction mixture was stirred for 2 d. The precipitate was filtered and the solution was evaporated under the reduced pressure. The residual solid was subjected to flash column chromatography (eluant: hexane : ethylacetate; 1:3) to give 5-chloro-*N*-phenylthiophene-2-carboxamidoxime **(11o)**.

Yield: 1.65 g, 51 %

M.p. : 135.3 - 136 ^{0}C (Lit[1]: 131-133 ^{0}C)

Rf : 0.30 (Eluant: Hexane : Ethyl acetate; 2:1)

IR (KBr, v: cm^{-1}): 3368 (N−H), 3204−3099 (broad, NOH), 1630 (C=N)

5-Chloro-*N*-(*p*-chlorophenyl)thiophene-2-carboxamidoxime (9b):

To a solution of thiophene-2-hydroximoyl chloride **(5)** (3.58 g, 18.4 mmol) in chloroform (30 mL) was added drop wise *p*-chloro aniline (5.27 g, 41.3 mmol) in chloroform with constant stirring at room temperature. The reaction mixture was stirred for 2 d. The precipitate was filtered and the solution was evaporated under the reduced pressure. The residual solid was subjected to flash column chromatography (eluant: hexane: ethyl acetate;1:3) to give 5-chloro-*N*-(*p*-Chlorophenyl)thiophene-2-carboxamidoxime **(9b)**.

Yield: 1.78 g, 35 %

M.p. : 143.4 – 144.6 ^{0}C

Rf : 0.50 (Eluant: Hexane : Ethyl acetate; 3: 2)

IR (KBr, v: cm^{-1}): 3382 (N−H), 3215 (broad, NOH), 1626 (C=N)

5-Chloro-*N*-(*p*-bromophenyl)thiophene-2-carboxamidoxime (9c):

To a solution of 5-chloro-thiophene-2-hydroximoyl chloride **(5)** (1.25 g, 6.4 mmol) in chloroform (30 mL) was added drop wise *p*-bromoaniline (2.31 g, 13.4 mmol) in chloroform with constant stirring at room temperature. The reaction mixture was stirred for 2 d. The precipitate was filtered and the solution was evaporated under the reduced pressure. The residual solid was subjected to flash column chromatography (eluant: hexane : ethyl acetate;1:3) to give 5-chloro-*N*-(*p*-Bromophenyl)thiophene-2-carboxamidoxime **(9c)**.

Yield: 1.00 g, 60 %

M.p. : 146.3-146.6 ^{0}C (Lit[1]: 143-145 ^{0}C)

Rf : 0.37 (Eluant: Hexane : Ethyl acetate; 2:1)

IR (KBr, v: cm^{-1}): 3387 (N−H), 3235 (broad, NOH), 1630 (C=N)

5-Chloro-*N*-(*p*-iodophenyl)thiophene-2-carboxamidoxime (9d):

To a solution of 5-chloro-thiophene-2-hydroximoyl chloride **(5)** (0.83 g, 4.26 mmol) in chloroform (20 mL) was added drop wise *p*-iodoaniline (1.75 g, 7.99 mmol) in chloroform with constant stirring at room temperature. The reaction mixture was stirred for 2 d. The precipitate was filtered and the solution was evaporated under the reduced pressure. The residual solid was subjected to flash column chromatography (eluant: hexane:ethyl acetate;1:3) to give 5-chloro-*N*-(*p*-Iodophenyl)thiophene-2-carboxamidoxime **(9d)**.

Yield: 0.65 g, 52 %

M.p. : 141-142.5 ^{0}C (Lit[1]: 141-144 ^{0}C)

Rf : 0.30 (Eluant: Hexane : Ethyl acetate; 2:1)

IR (KBr, v: cm^{-1}): 3394 (N−H), 3217 (broad, NOH), 1636 (C=N)

5-Chloro-*N*-(*p*-tolyl)thiophene-2-carboxamidoxime (9e):

To a solution of thiophene-2-hydroximoyl chloride **(5)** (2.0 g, 10.3 mmol) in chloroform (30 mL) was added drop wise *p*-toluidine (2.21 g, 20.6 mmol) in chloroform with constant stirring at room temperature. The reaction mixture was stirred for 2 d. The precipitate was filtered and the solution was evaporated under the reduced pressure. The residual solid was crystallized in hexane : EtOAc (3:1) to give *N*-*p*-Tolylthiophene-2-carboxamidoxime **(19e)**.

Yield: 1.15 g, 43 %

M.p. : 132.8 – 133.8 ^{0}C (Lit[1]: 154-156 ^{0}C)

Rf : 0.169 (Eluant: Hexane : Ethyl acetate; 3:4)

IR (KBr, v: cm^{-1}): 3360 (N−H), 3163−3101 (broad, NOH), 1629 (C=N)

5-Chloro-*N*-(*p*-methoxyphenyl)thiophene-2-carboxamidoxime (9f):

To a solution of 5-chloro-thiophene-2-hydroximoyl chloride **(5)** (3.3 g, 18.1 mmol) in chloroform (30 mL) was added drop wise *p*-methoxyaniline (4.69 g, 38.1 mmol) in chloroform with constant stirring at room temperature. The reaction mixture was stirred for 2 d. The precipitate was filtered and the solution was evaporated under the reduced pressure. The residual solid was subjected to flash column chromatography (eluant: hexane:ethyl acetate;1:3) to give 5-chloro-*N*-(*p*-methoxyphenyl)thiophene-2-carboxamidoxime **(9f)**.

Yield: 1.67 g, 35 %

M.p. : 146.1 – 146.8 ^{0}C (Lit[1]: 180-183 ^{0}C)

Rf : 0.375 (Eluant: Hexane : Ethyl acetate; 2:1)

IR (KBr, v: cm^{-1}): 3342 (N−H), 3200−3106 (broad, NOH), 1631 (C=N)

5-Chloro-*N*-(1-naphthyl)thiophene-2-carboxamidoxime (9g):

To a solution of 5-chloro-thiophene-2-hydroximoyl chloride **(5)** (1.00 g, 6.19 mmol) in chloroform (20 mL) was added drop wise 1-naphthylamine (1.77 g, 12.0 mmol) in chloroform with constant stirring at room temperature. The reaction mixture was stirred for 2 d. The precipitate was filtered and the solution was evaporated under the reduced pressure. The residual solid was recrystallized in hexane:EtOAc to give 5-Chloro-*N*-(1-naphthyl)thiophene-2-carboxamidoxime **(9g)**.

Yield: 0.780 g, 25 %

M.p. : 168-170 ^{0}C (Lit[1]: 168-170 ^{0}C)

Rf : 0.30 (Eluant: Hexane : Ethyl acetate; 2:1)

IR (KBr, v: cm^{-1}): 3381 (N−H), 3224-3103 (broad, NOH), 1632 (C=N)

5-Chloro-*N*-phenylfuran-2-carboxamidoxime (10a):

To a solution of 5-hloro-furan-2-hydroximoyl chloride **(6)** (2.0 g, 11.2 mmol) in chloroform (30 mL) was added drop wise aniline (2.17 g, 23.3 mmol) in chloroform with constant stirring at room temperature. The reaction mixture was stirred for 2 d. The precipitate was filtered and the solution was evaporated under the reduced pressure. The impure product was crystallized from hexane : ethyl acetate (3:1) to give *N*-phenylfuran-2-carboxamidoxime **(10a)**.

Yield: 0.75 g, 28 %

M.p. : 141 - 142 ^{0}C (Lit[1]: 147-149 ^{0}C)

Rf : 0.334 (Eluant: Hexane : Ethyl acetate; 2:1)

IR (KBr, v: cm^{-1}): 3384 (N−H), 3119-2945 (broad NOH), 1627 (C=N)

5-Chloro-*N*-(*p*-chlorophenyl)furan-2-carboxamidoxime (10b):

To a solution of 5-chloro-furan-2-hydroximoyl chloride **(6)** (1.83 g, 10.2 mmol) in chloroform (20 mL) was added drop wise *p*-chloroaniline (2.72 g, 21.4 mmol) in chloroform with constant stirring at room temperature. The reaction mixture was stirred for 2 d. The precipitate was filtered and the solution was evaporated under the reduced pressure. The impure product was crystallized from hexane:ethyl acetate (3:1) to give *N*-(*p*-chlorophenyl)furan-2-carboxamidoxime **(10b)**.

Yield: 0.58 g, 20 %

M.p. : 147-148 ^{0}C (Lit[1]: 142-144 ^{0}C)

Rf : 0.29 (Eluant: Hexane : Ethyl acetate; 3:1)

IR (KBr, v: cm^{-1}): 3382 (N−H), 3127-3094 (broad, NOH), 1622 (C=N)

5-Chloro-*N*-(*p*-bromophenyl)furan-2-carboxamidoxime (10c):

To a solution of 5-chloro-furan-2-hydroximoyl chloride **(8)** (1.425 g, 8.0 mmol) in chloroform (20 mL) was added drop wise *p*-bromoaniline (2.50 g, 14.5 mmol) in chloroform with constant stirring at room temperature. The reaction mixture was stirred for 2 d. The precipitate was filtered and the solution was evaporated under the reduced pressure. The impure product was crystallized from hexane:ethyl acetate (3:1) to give *N*-(*p*-bromophenyl)furan-2-carboxamidoxime **(10c)**.

Yield: 0.53 g, 21 %

M.p. : 156.6 – 157.4 ^{0}C (Lit[1]: 163-164 ^{0}C)

Rf : 0.14 (Eluant: Hexane:Ethyl acetate; 2 :1)

IR (KBr, v: cm^{-1}): 3382 (N−H), 3087-2970 (broad, NOH), 1625 (C=N)

5-Chloro-*N*-(*p*-iodophenyl)furan-2-carboxamidoxime (10d):

To a solution of 5-chloro-furan-2-hydroximoyl chloride **(6)** (0.60 g, 3.35 mmol) in chloroform (20 mL) was added drop wise *p*-iodoaniline (1.50g, 11.6 mmol) in chloroform with constant stirring at room temperature. The reaction mixture was stirred for 2 d. The precipitate was filtered and the solution was evaporated under the reduced pressure. The residual solid was subjected to flash column chromatography (eluant: hexane:ethyl acetate;1:3) to give *N*-(*p*-iodophenyl)furan-2-carboxamidoxime **(10d)**.

Yield: 0.77 g, 64 %

M.p. : 164.9 – 165.6 ^{0}C (Lit[1]: 165-167 ^{0}C)

Rf : 0.55 (Eluant: Hexane : Ethyl acetate; 1:2)

IR (KBr, v: cm^{-1}): 3385 (N−H), 3082-2962 (broad, NOH), 1627 (C=N)

5-Chloro-*N*-(*p*-tolyl)furan-2-carboxamidoxime (10e):

To a solution of 5-Chloro-furan-2-hydroximoyl chloride **(6)** (2.00 g, 11.11 mmol) in chloroform (20 mL) was added drop wise *p*-toluidine (2.50 g, 23.33 mmol) in chloroform with constant stirring at room temperature. The reaction mixture was stirred for 2 d. The precipitate was filtered and the solution was evaporated under the reduced pressure. The impure product was crystallized from hexane:ethyl acetate (3:1) to give *N*-*p*-Tolylfuran-2-carboxamidoxime **(10e)**.

Yield: 0.57 g, 21 %

M.p. : 143 - 145 ^{0}C (Lit[1]: 157-159 ^{0}C)

Rf : 0.32 (Eluant: Hexane : Ethyl acetate; 1:1)

IR (KBr, v: cm^{-1}): 3384 (N−H), 3089-2970 (broad, NOH), 1624 (C=N)

5-Chloro-*N*-(*p*-Methoxyphenyl)furan-2-carboxamidoxime (10f):

To a solution of 5-Chloro-furan-2-hydroximoyl chloride **(6)** (2.00 g, 11.2 mmol) in chloroform (20 mL) was added drop wise *p*-methoxyaniline (2.88 g, 23.4 mmol) in chloroform with constant stirring at room temperature. The reaction mixture was stirred for 2 d. The precipitate was filtered and the solution was evaporated under the reduced pressure. The impure product

was crystallized from hexane:ethyl acetate (3:1) to give *N*-(*p*-methoxyphenyl)furan-2-carboxamidoxime **(10f)**.

Yield: 1.56 g, 41 %

M.p. : 146.3 – 147.5 ^{0}C (Lit[1]: 141-143 ^{0}C)

Rf : 0.525 (Eluant: Hexane : Ethyl acetate; 1:2)

IR (KBr, v: cm^{-1}): 3363 (N−H), 3191−3155 (broad, NOH), 1641 (C=N)

5-Chloro-*N*-(1-Naphthyl)furan-2-carboxamidoxime (10g):

To a solution of 5-Chloro-furan-2-hydroximoyl chloride **(6)** (2.00 g, 11.2 mmol) in chloroform (30 mL) was added drop wise 1-naphthylamine (3.06 g, 121.4 mmol) in chloroform with constant stirring at room temperature. The reaction mixture was stirred for 2 d. The precipitate was filtered and the solution was evaporated under the reduced pressure. The impure product was crystallized from hexane:ethyl acetate (3:1) to give *N*-(1-naphthyl)furan-2-carboxamidoxime **(10g)**.

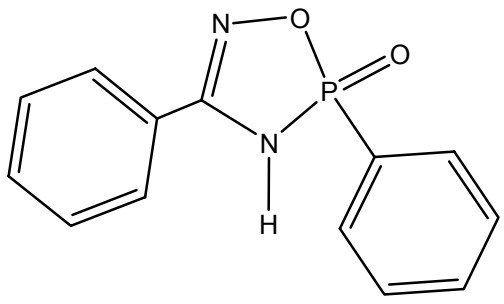
Yield: 0.96 g, 30%

M.p. : 112.8 – 113.7 ^{0}C (Lit[1]: 128-129 ^{0}C)

Rf : 0.68 (Eluant: Hexane : Ethyl acetate; 1:2)

IR (KBr, v: cm^{-1}): 3365 (N−H), 3143 (broad, NOH), 1636 (C=N)

2,4-Diphenyl-2,3-dihydro-1,3,5,2-oxadiazaphosphole 2-oxide (11a)



To a stirred solution of benzamidoxime **(8a)** (0.35 mg, 2.57 mmol) and Et_3N (1.12g, 11.05 mmol) in 30 mL dichloromethane, a solution of phenylphosphonyldichloride (0.50g, 2.57 mmol) in 10 mL of dichloromethane was added dropwise under inert atmosphere. The mixture was stirred at 0 ^{0}C for 2 hours and then 3 hours at room temperature under argon atmosphere. The reaction mixture was extracted with water and dried with Na_2SO_4.The solvent was evaporated under reduced pressure. The residual solid was subjected to flash column chromatography (eluant : EtOAc) to give 5-oxo-3,5-diphenyl-1,2,4,5-oxadiazaphosphole **(11a)**.

Yield: 0.40 g, 60%

M.p. : 148.4 – 148.6 ^{0}C

Rf : 0.354 (Eluant : Ethyl acetate)

IR (KBr, v: cm^{-1}): 3487,3446 (N−H), 1627 (C=N),1236 (P=O), 1130.32 (P−N)

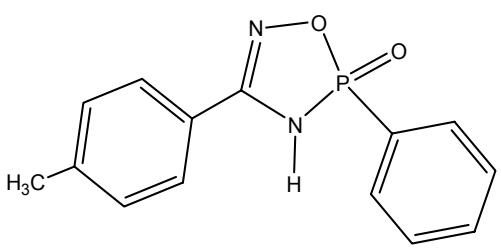
^{1}H NMR, δ_H ($CDCl_3$+DMSO-d_6, 400 MHz), 7.99-7.93 (m, 1H), 7.64-7.28 (m, 6H, 6.18(s, 2H).

^{13}C NMR, δ_C ($CDCl_3$+DMSO-d_6, 400 MHz):158, 132. 8, 132.7, 131.2, 130.6, 128.4, 128.1,128.0,126.0, 100.

^{31} P NMR, δ_P (DMSO-d_6, 161.96 MHz): 22.52.

MS (m/z %): 113 (100), 91 (72), 77 (31)

2-phenyl-4-(*p*-tolyl)-2,3-dihydro-1,3,5,2-oxadiazaphosphole 2-oxide (11b)



To a stirred solution of *p*-methylbenzamidoxime **(8e)** (0.35 mg, 2.21 mmol) and Et_3N (0.96g, 9.52 mmol) in 30 mL dichloromethane, a solution of phenylphosphonyldichloride (0.432g, 2.21 mmol) in 10 mL of dichloromethane was added drop wise under inert atmosphere. The mixture was stirred at 0 ^{0}C for 2 h and then 3 h at room temperature under argon atmosphere. The reaction mixture was taken into water (40 mL) and organic layers collected were dried with anhydrous Na_2SO_4.The solvent was evaporated under reduced pressure. The residual solid was subjected to flash column chromatography (eluant : EtOAc) to give **(11b)**.

Yield: 0.553 g, 92%

M.p. : 144.4 – 144.7 ^{0}C

Rf : 0.45 (Eluant : Ethyl acetate)

IR (KBr, v: cm^{-1}): 3487 (N−H), 1627 (C=N),1232 (P=O), 1132.25 (P−N).

^{1}H NMR , δ_H ($CDCl_3$+DMSO-d_6, 400 MHz): 7.95 (broad d, 2H), 7.48 (s, 4H), 7.10 (s, 2H), 2.29 (s, 3H).

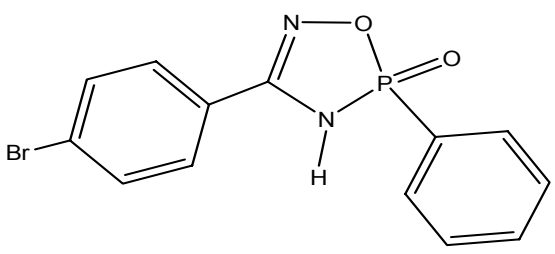
^{13}C NMR, δ_C ($CDCl_3$+DMSO-d_6, 400 MHz):158, 136, 135, 129, 126, 22.

^{31} P NMR, δ_P (DMSO-d_6, 161.96 MHz): 22.14.

MS (m/z %): 133 (100 %), 104 (39%), 91 (11%). (RT:10.24)

MS (m/z %): 201 (100), 166 (43), 117 (83), 94 (21). (RT:10.33)

2-Phenyl-4-(*p*-bromophenyl)-2,3-dihydro-1,3,5,2-oxadiazaphosphole-2-oxide (11c)



To a stirred solution of *p*-chloro benzamidoxime **(8c)** (0.40 mg, 1.86 mmol) and Et_3N (0.82g, 8.10 mmol) in 30 mL dichloromethane, a solution of phenylphosphonyldichloride (0.401g, 2.00 mmol) in 10 mL of dichloromethane was added drop wise under inert atmosphere. The mixture was stirred at 0 ^{0}C for 2 h and then 3 h at room temperature under argon atmosphere. The reaction mixture was extracted with water and dried with Na_2SO_4.The solvent was evaporated under reduced pressure. The residual solid was subjected to flash column chromatography (eluant:EtOAc) to give **(11c)**

Yield: 0.229 g, 36%

M.p. : 143.5 – 144.1 ^{0}C

Rf : 0.55 (Eluant : Ethyl acetate)

IR (KBr, v: cm^{-1}): 3487,3446 (N−H), 1629 (C=N), 1236 (P=O), 1130 (P−N).

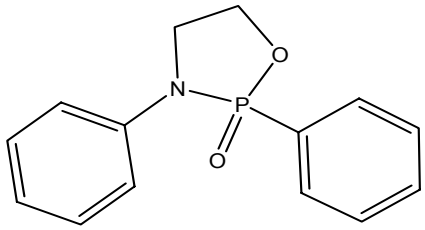
^{1}H NMR , δ_H ($CDCl_3$+DMSO-d_6, 400 MHz): 7.96-7.89 (m, 2H), 7.54 (d, 3H), J=9.5Hz), 7.46-7.41 (d and m 3H, J=8.5 Hz), 6.54 (s, 2H).

^{13}C NMR, δ_C ($CDCl_3$+DMSO-d_6, 400 MHz): 157.3, 132.7, 131.5, 130.5, 128.8, 128.2,124.5.

^{31} P NMR, δ_P (DMSO-d_6, 161.96 MHz): 22.22.

MS (m/z, %): 181 (100),102 (85), 75 (24), 50 (14).

2,3-Diphenyl-1,3,2-oxazaphospholidine 2-oxide (12a)



To a stirred solution of 2-anilinoethanol (1.0 g, 7.29 mmol) and Et_3N (0.82g, 31.4 mmol) in 50 mL dichloromethane, a solution of phenylphosphonyldichloride (1.42g, 7.29 mmol) in 20 mL of dichloromethane was added drop wise under inert atmosphere. The mixture was stirred at 0 ^{0}C for 2 hours and then 3 hours at room temperature under argon atmosphere. The reaction mixture was washed with 5% HCl solution (3x 80mL) and dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The residual solid was subjected to flash column chromatography (eluant:EtOAc) to give **(12a).**

Yield: 1.2 g, 64%

M.p. : 125.3 – 125.9 ^{0}C

Rf : 0.24 (Eluant: Ethyl acetate : Hexane; 1:1)

IR (KBr, v: cm^{-1}): 1498 (C−N), 1215 (P=O), 1130 (P−N) .

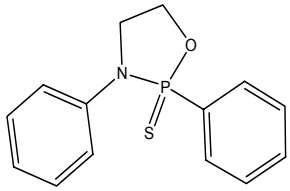
^{1}H NMR , δ_H ($CDCl_3$, 400 MHz): 7.83-7.78 (m, 2H), 7.55-7.51 (m, 1H), 7.46-7.410 (m, 2H), 7.24-7.20 (t, 2H), 7.10 (d, 2H, *J*=8.5 Hz), 6.93 (t, 1H), 4.75-4.70 (m, 1H), 4.59-4.50 (m, 1H), 4.02-3.94 (m, 2H).

^{13}C NMR, δ_C ($CDCl_3$, 400 MHz):140.5, 140.4, 132.8, 132.4, 132.3, 129.6, 129.3,128.8,128.6, 127.8, 121.7, 116.0, 115.9, 64.4, 46.8.

^{31} P NMR, δ_P ($CDCl_3$,161.96 MHz): 27.57.

MS (m/z, %): (M^+,259),240 (2.8), 217 (10), 182 (14),118 (15), 105 (22), 91 (15), 77 (27).

2,3-Diphenyl-1,3,2-oxazaphospholidine 2-sulfide (12b)



A mixture of 2-oxo-2,3-diphenyl-1,3,2-oxazaphospholidine **(12a)** (280 mg, 1.08 mmol) and Lawesson's reagent (LW) (330 mg,0.81 mmol) in toluene (20 mL) was refluxed under inert atmosphere with molecular sieves (4Å) for 3 hours. The reaction mixture was filtered and the solvents was evaporated under the reduced pressure. The product was subjected to flash column chromatography (eluant : hexane : ethyl acetate; 2:1) to give **(12b)** as oil.

Yield: 217 mg, 73%

Rf : 0.875 (Eluant: Ethyl acetate : Hexane; 1:1)

: 0.412 (Eluant: Ethyl acetate : Hexane; 2:1)

IR (KBr, v: cm^{-1}): 1597, 1500 (C=C), 1111 (P−N-C), 949 (P-O-C), 752, 734 (P=S)

^{1}H NMR , δ_H ($CDCl_3$, 400 MHz): 8.00-7.94 (m, 2H), 7.57-7.53 (m, 1H), 7.49-7.44 (m, 2H), 7.28-7.19 (m, 2H), 7.07 (d, 2H, *J*=8.5 Hz), 6.96 (t, 1H), 4.71-4.63 (m, 1H), 4.54-4.46 (m, 1H), 4.05-3.98 (m, 1H), 3.96-3.90 (m, 1H).

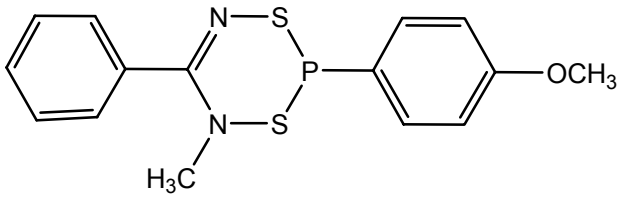
^{13}C NMR, δ_C ($CDCl_3$, 400 MHz):140.8, 140.7, 134.5, 133.7, 133.5, 133.2, 132.8, 131.8, 131.6, 129.1,128.9, 128.8, 128.6, 123.0, 121.6, 120.19, 120.14, 117.0, 116.9, 114.2, 114.0, 113.8, 65.56, 65.52, 47.25, 47.15.

^{31}P NMR, δ_P ($CDCl_3$, 161.96 MHz): 87.45, 80.06.

MS (m/z, %): 275 (M^+,259), 242 (9) , 195 (7) , 166 (12), 119 (41), 104 (30), 77 (29).

Reaction between *N*-methyl benzamidoxime and Lawesson's Reagent:

Synthesis of 6-(4-methoxyphenyl)-2-methyl-3-phenyl-2H-1,5,2,4,6-dithiadiazaphosphinine (13)



To a stirred solution of *N*-methyl benzamidoxime (150 mg, 1 mmol) in toluene (20 mL), Lawesson's reagent (204 mg, 0.5 mmol) was added in portions over 15 min. The reaction mixture was stirred under reflux with molecular sieves (4A) for 3h. After cooling the reaction mixture, Et_2O (10 mL) was added and solid particles were filtered off. The filtrate was evaporated under reduced pressure and crude product was crystallized from toluene: petroleum ether (1:1) mixture to give (**13**).

Yield: 65 mg, 20%

M.p. : 114 – 116.5 ^{0}C

Rf : 0.77 (Eluant: Ethyl acetate : Hexane; 1:1)

IR (KBr, v: cm^{-1}): 1595 (C=N), 1120 (P-S).

MS (m/z,%): 256 (100), 192 (28), 160(48), 128 (52), 96 (19), 64(96)

CHAPTER III

RESULTS AND DISCUSSION

The ring closure reactions of monoamidoximes with phenylphosphonodichloride gave 2,4-disubstituted-2,3-dihydro-1,3,5,2-oxadiazaphosphole 2-oxide compounds **11a-c** which are novel heterocycles containing oxygen, nitrogen and phosphorus on the same ring to our best knowledge of literature survey of the data bases Science Finder Scholar and Web of Knowledge (SCI-expanded). There are no examples related to the reactions between phenyl phosphonodichloride and amidoximes. For these reasons we are focused, in this study, to obtain oxadiazaphosphole-oxides starting from monoamidoximes.

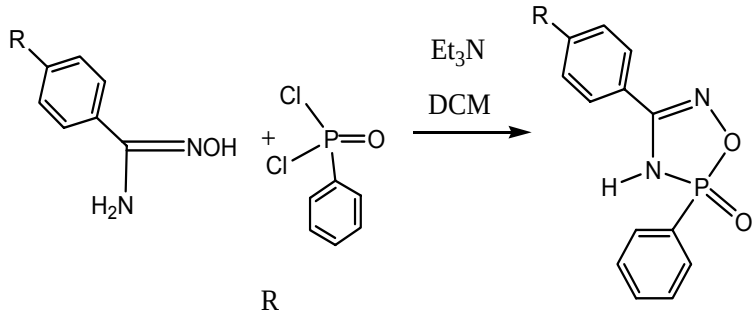
The present research work is basically consisted of three parts. In the first part monoamidoximes were prepared according to the literature Refs .They were purified by flash chromatography and recrystallized from appropriate solvents.

In the second part, the pure monoamidoximes were reacted with phenylphosphonodichloride in dry dichloromethane by cooling with ice then stand to room temperature to give corresponding oxadiazaphosphole oxides .

In the third part, we attempted to synthesize disubstituted-1,3,2-oxazaphospholidine-2-oxide , its thionated analog; disubstituted-1,3,2-oxazaphospholidine-2-sulphide. In addition, we also wanted to investigate the products which may arise from the reaction between *N*-substituted amidoximes and Lawesson's Reagent.

All the new nitrogen,oxygen,sulfur and phosphorus containing heterocyclic compounds were identified by means of physical (melting point determination, Rf values), spectroscopic methods (IR, ^{1}H NMR, ^{13} C NMR, ^{31} P NMR and Mass Spectra).

Scheme 15 indicates the reaction sequence for the preparation of oxadiazaphosphole oxides **(11a-c).**

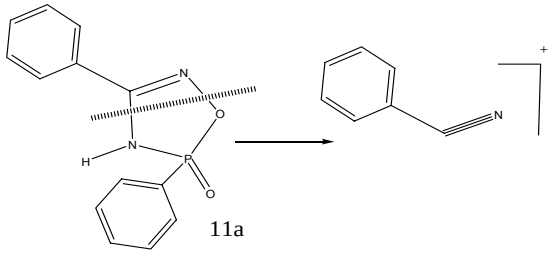


	R
11a	H
11 b	Me
11c	Br

11a-c

Scheme 15

The structural elucidation of the oxadiazaphosphole oxides were performed by IR, NMR (^{1}H, ^{13}C and ^{31}P)and Mass Spectra. In the IR spectra , the following absorption bands related were observed ; C=N streching vibrations at around 1625 cm $^{-1}$, P=O in the range of 1320-1305; P-O-C vibrations around 1230-1225 cm^{-1} . These values were found in accord with the previously reported literature ones [97]. The mass spectra of these heterocycles were somewhat different that was expected. We could not observe the molecular ion peak. Instead, a fragment which might be generated by the following cleaveage corresponding benzonitrilium ion peak was observed in **11a** and **11b**.



11a

Figure 36: The mass spectral fragmentations of the compound **11a**

But, however, in the case of *p*-methyl substituted oxadiazaphosphole 11b, we observed two peaks in the GC and their mass spectra were attributed to the following fragmentations:

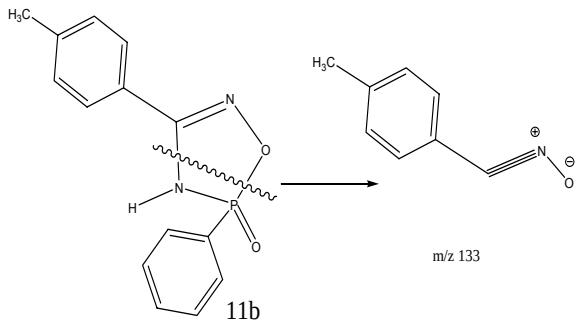
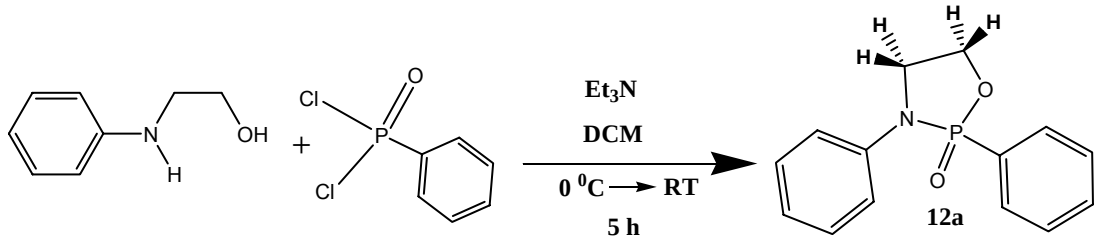


Figure 37: The mass spectral fragmentations of the compound **11b**

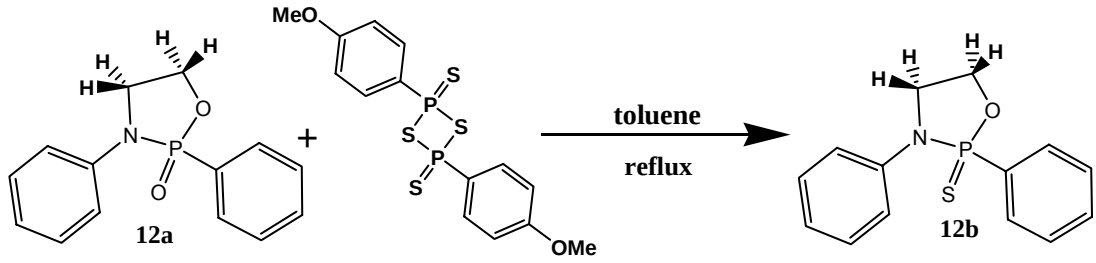
Phenyl phosphonodichloride were reacted with 2-anilinoethanol in the presence of triethylamine to give **12a** (Scheme 16)**.** OCH_2 (4.75 ppm) and NCH_2 (4 ppm) protons were splitted into multiplets instead of doublets or triplets ,These splittings could be accounted for the effect of phoshphorus atom nucleus.



Scheme 16

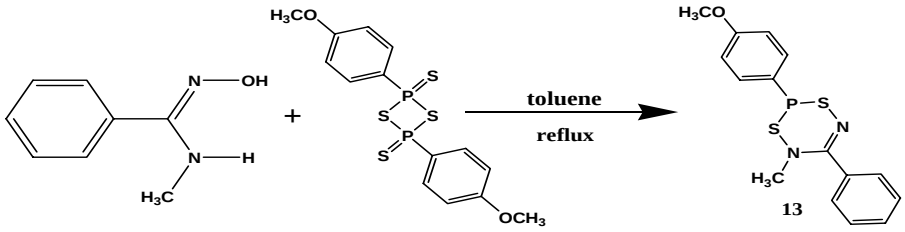
Phosphorus 31 NMR also was recorded and P=O phosphorus atom was found to resonate at 27.5 ppm which is in accord with the literature values given for P=O bonded phosphorus.

2,3-Diphenyl-1,3,2-oxazaphospholidine 2-oxide (**12a**) was converted into thio analog (**13)** by means of usage of Lawesson's reagent at reflux temperature of toluene and its structure was identified.



Scheme 17

In addition to the above synthetic applications, we attempted also the following transformation at which, this time an *N*-substituted amidoxime was reacted with the Lawesson's reagent and possible structure was assigned as **13** by investigating IR and especially its GC-MS spectra. GC showed one peak as the proof of the purity of the compound.



Scheme 18

The molecular ion peak in the mass spectrum m/z 256 can be deduced from the fragmentation pathway of the compound **13** via a S_2 extrusion and formation of diazaphosphete ring ion.

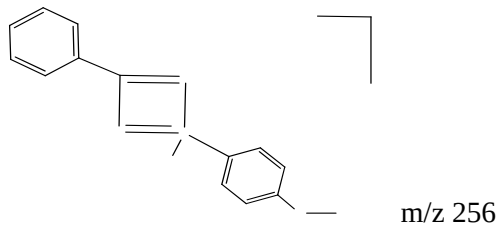


Figure 38: The mass spectral fragmentations of the compound **13**

CHAPTER IV

CONCLUSION

This work presents the synthetic applications of phenyl phosphonodichloride to obtain heterocycles involving oxygen,nitrogen and phosphorus. Five new compounds were added to the literature registry. In addition, amino alcohol and phenyl phosphonodichloride were used to obtain oxazaphospholidine and its thia analog . And finally, it was given an example of the the reaction between an *N*-substituted amidoxime and Lawesson's reagent.

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APPENDICES

APPENDIX

The IR spectra of aldoximes **(3-4)**, amidoximes **(8a-o, 9a-g, 10a-g),** 3,5-disubstituted-1,2,4,5-oxadiazaphospholes **(11a-c),** 2,3-disubstituted-1,3,2-oxazaphospholidine **(12a-b)** and 3,6-disubstituted-2H-1,5,2,4,6-dithiadiazaphosphinine **(13) .** ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR and mass spectra of 3,5-disubstituted-1,2,4,5-oxadiazaphospholes **(11a-c)** and 2,3-disubstituted-1,3,2-oxazaphospholidine **(12a-b)** and 3,6-disubstituted-2H-1,5,2,4,6-dithiadiazaphosphinine **(13).**

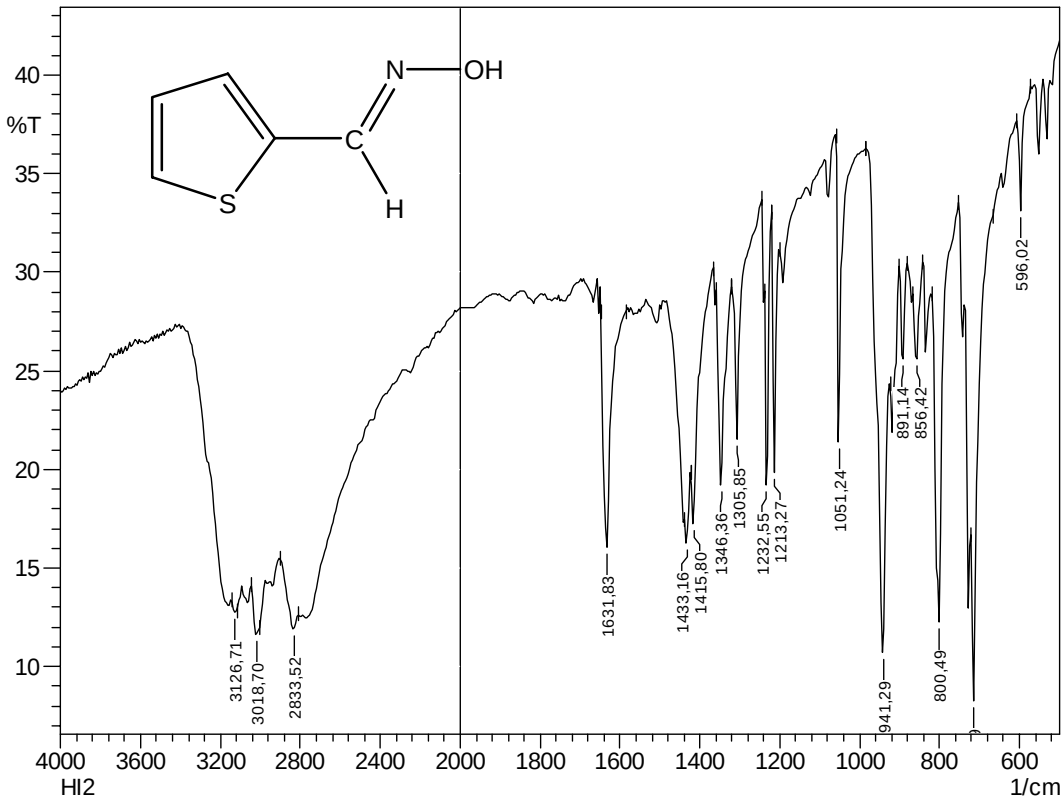

Figure 39: The IR spectrum of **3**

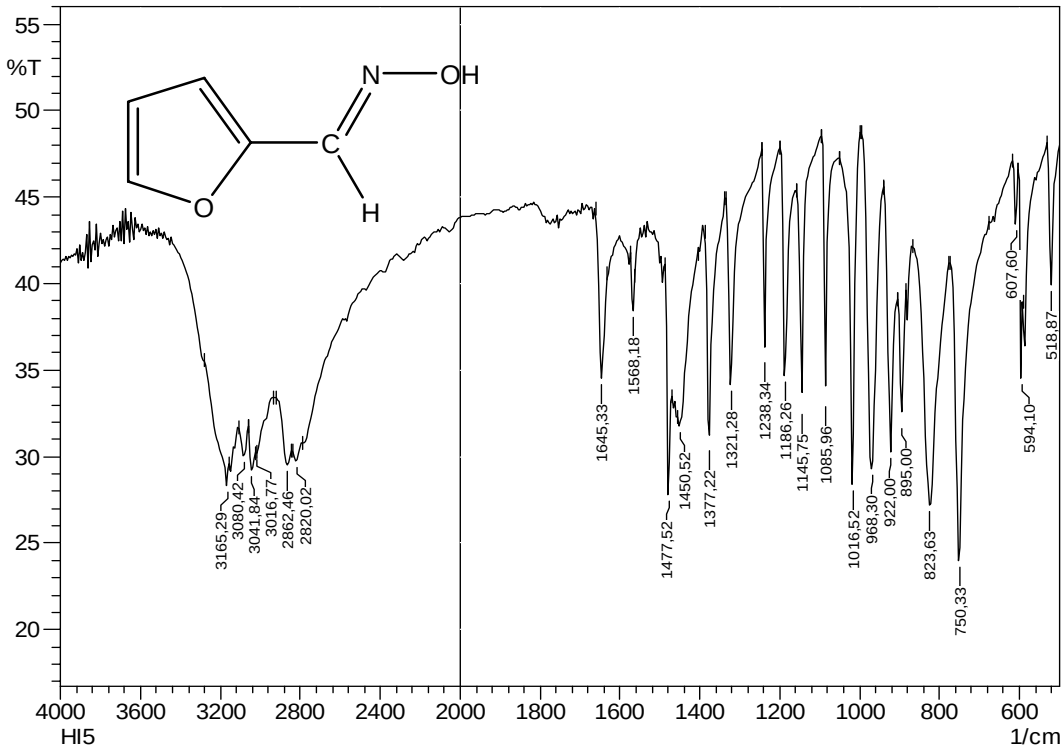

Figure 40: The IR spectrum of **4**

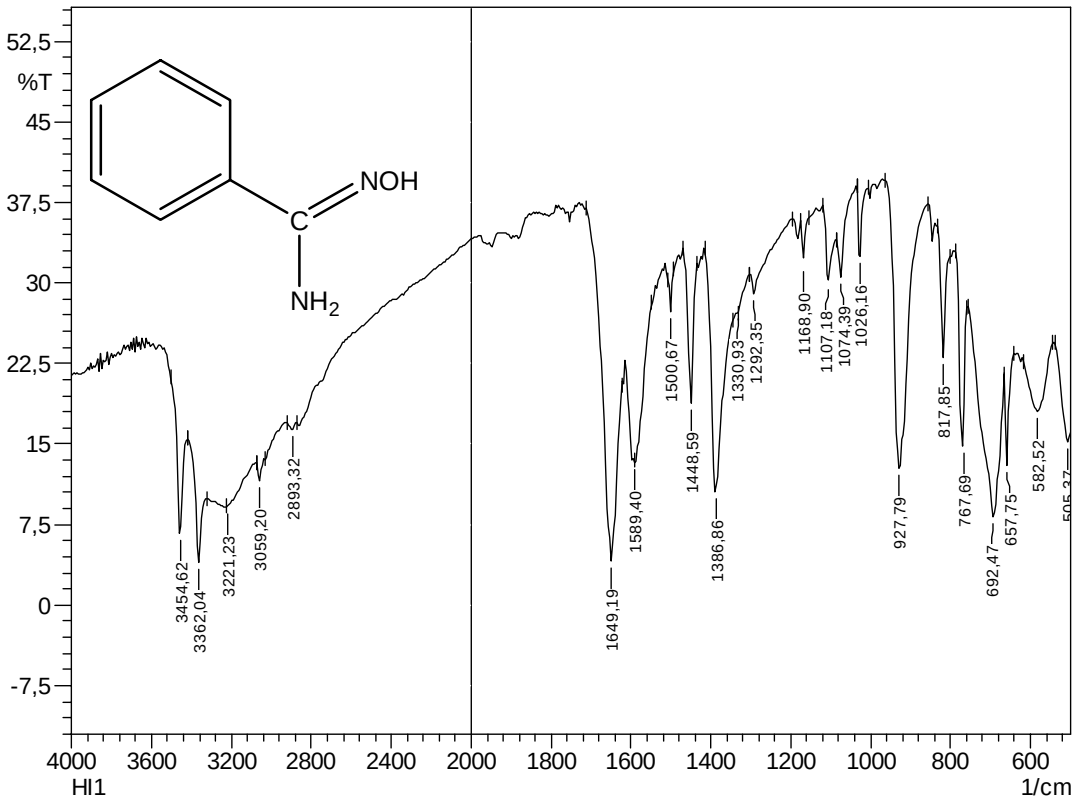

Figure 41: The IR spectrum of **8a**

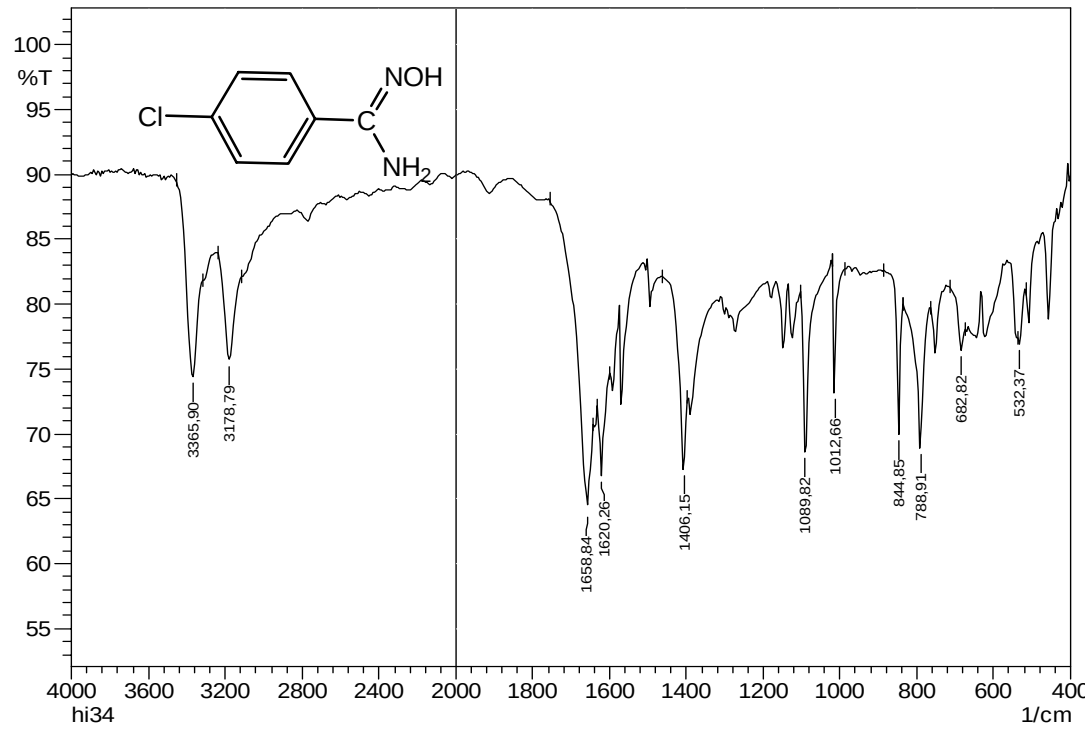

Figure 42: The IR spectrum of **8b**

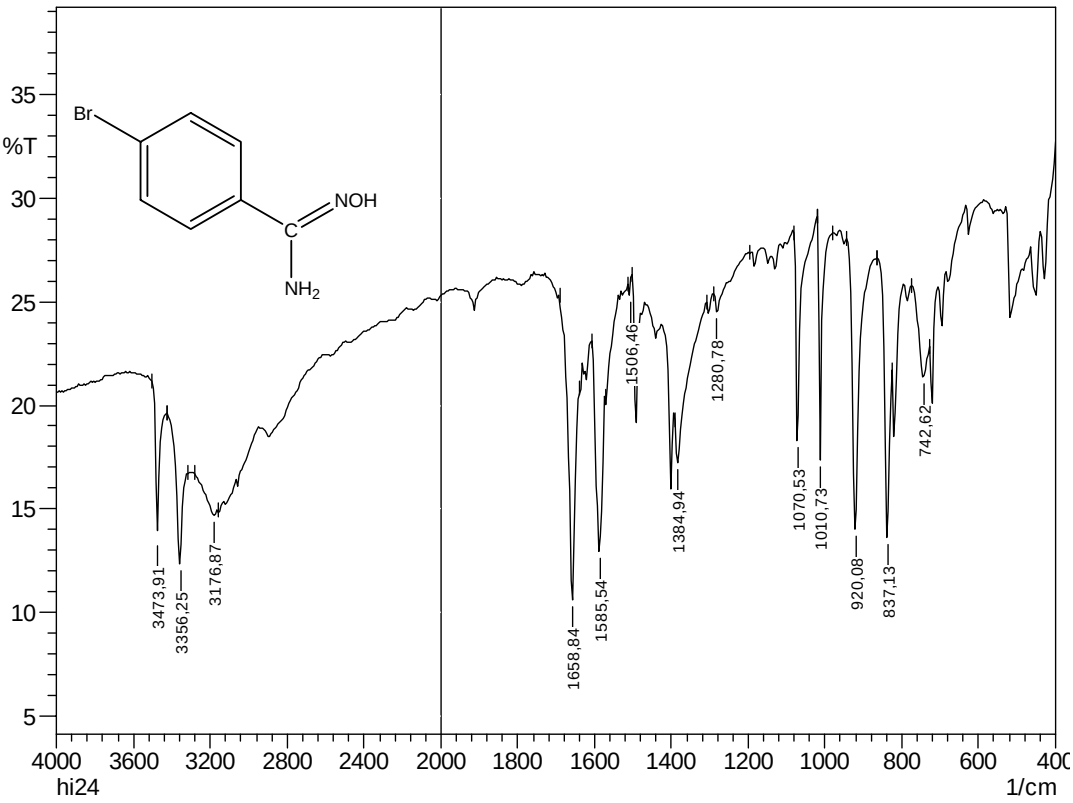

Figure 43: The IR spectrum of **8c**

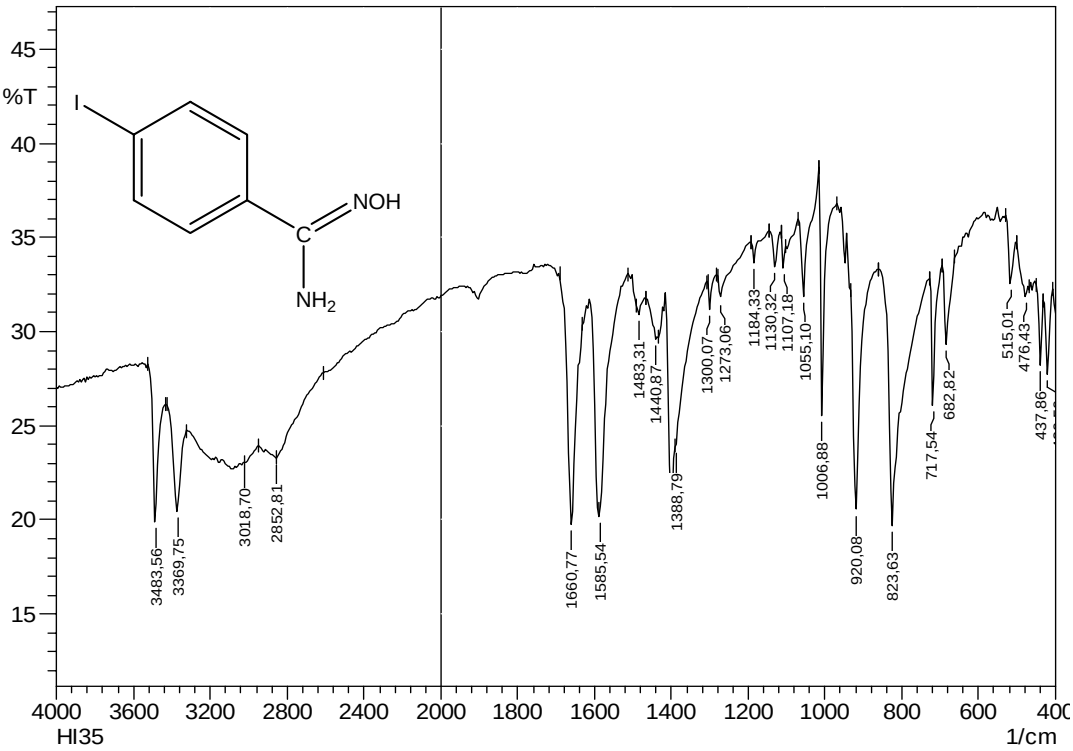

Figure 44: The IR spectrum of **8d**

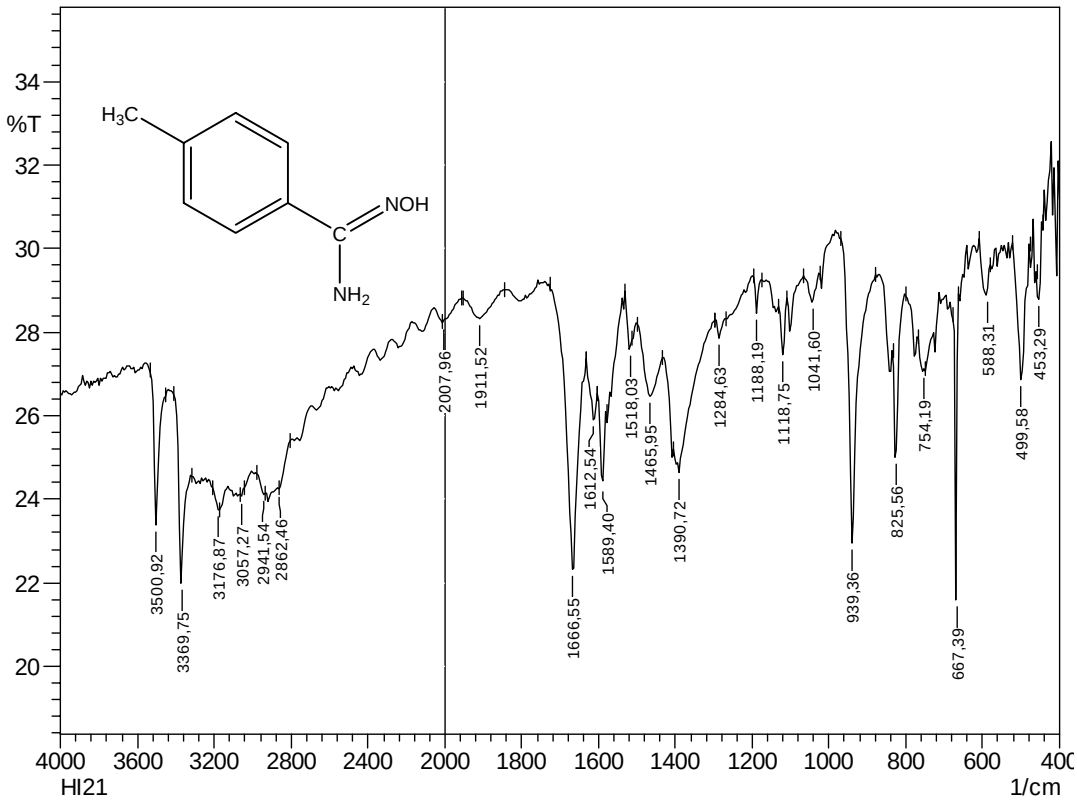

Figure 45: The IR spectrum of **8e**

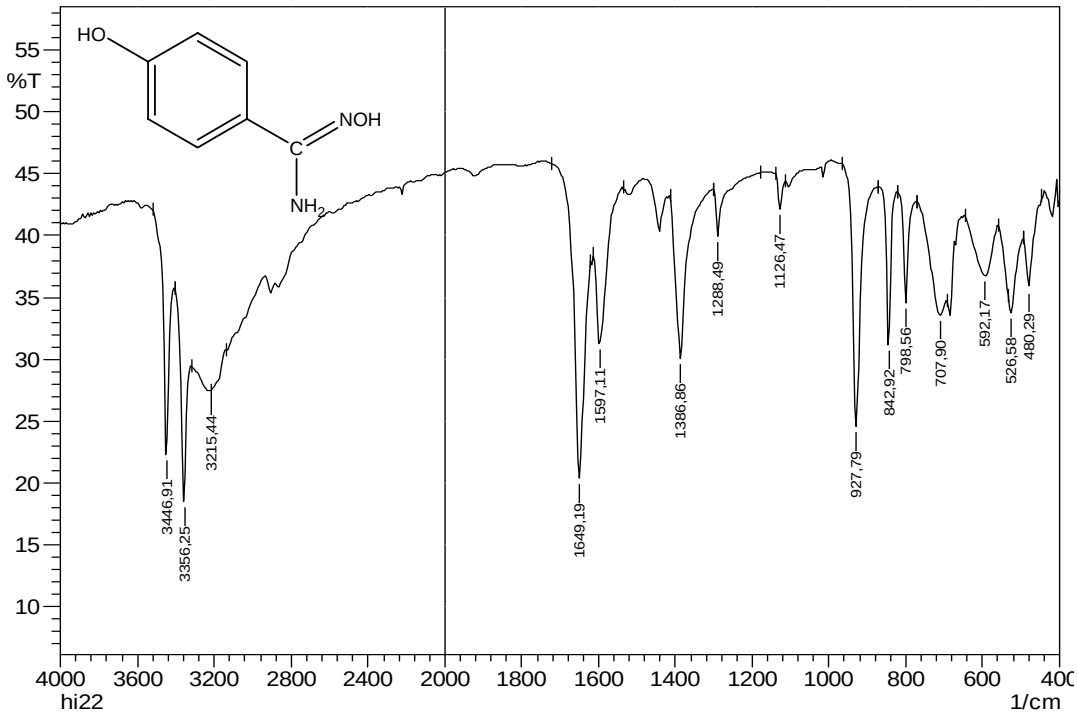

Figure 46: The IR spectrum of **8f**

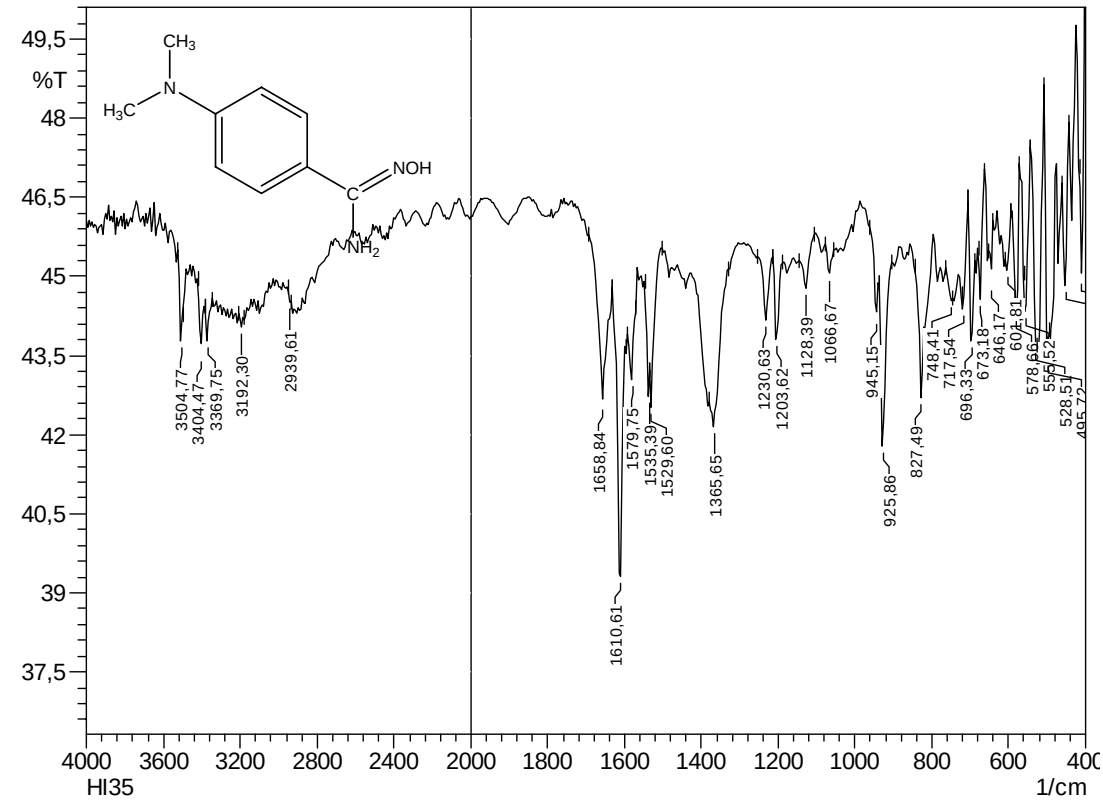

Figure 47: The IR spectrum of **8g**

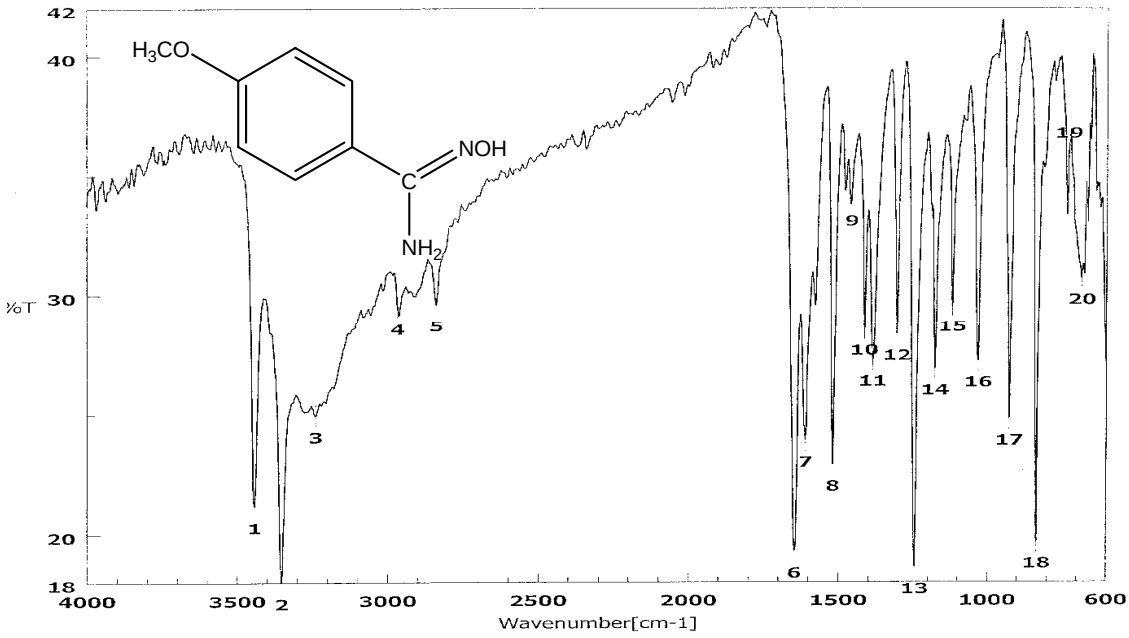

Figure 48: The IR spectrum of **8h**

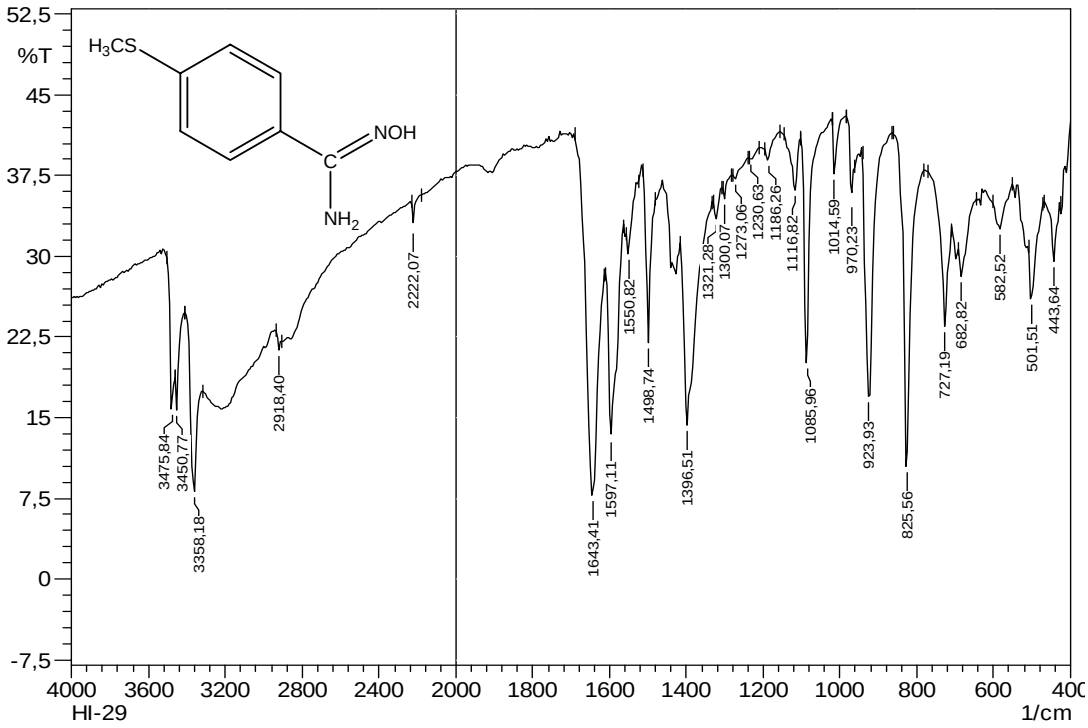

Figure 49: The IR spectrum of **8i**

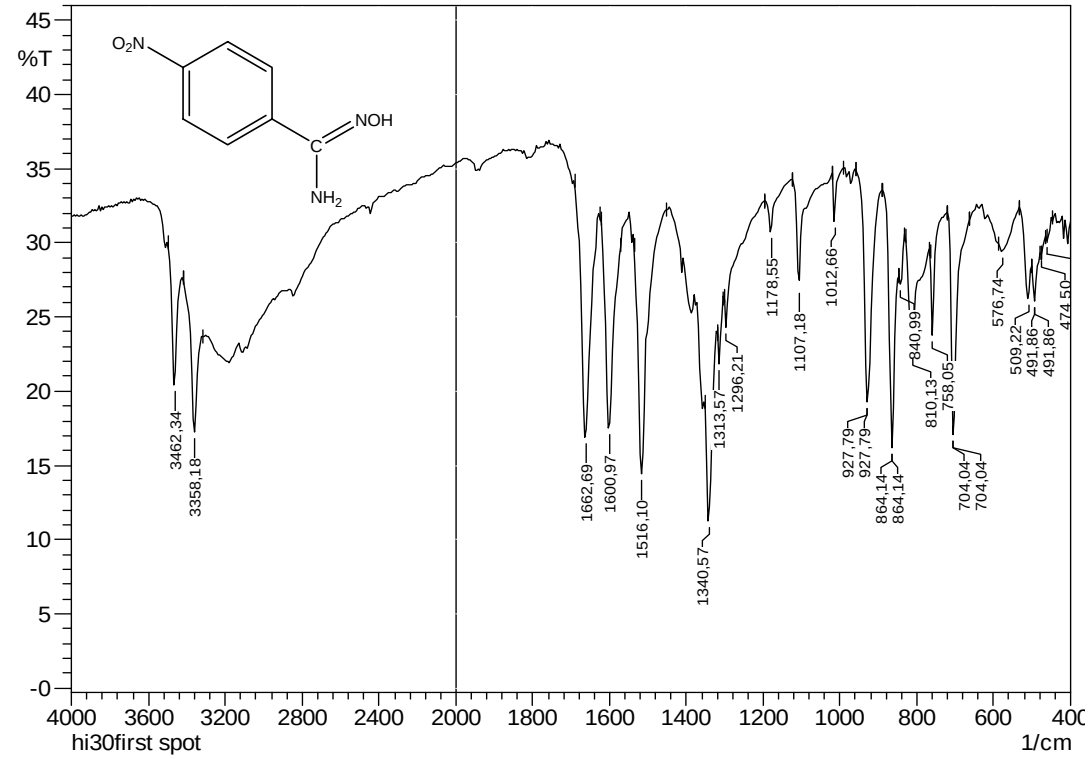

Figure 50: The IR spectrum of **8j**

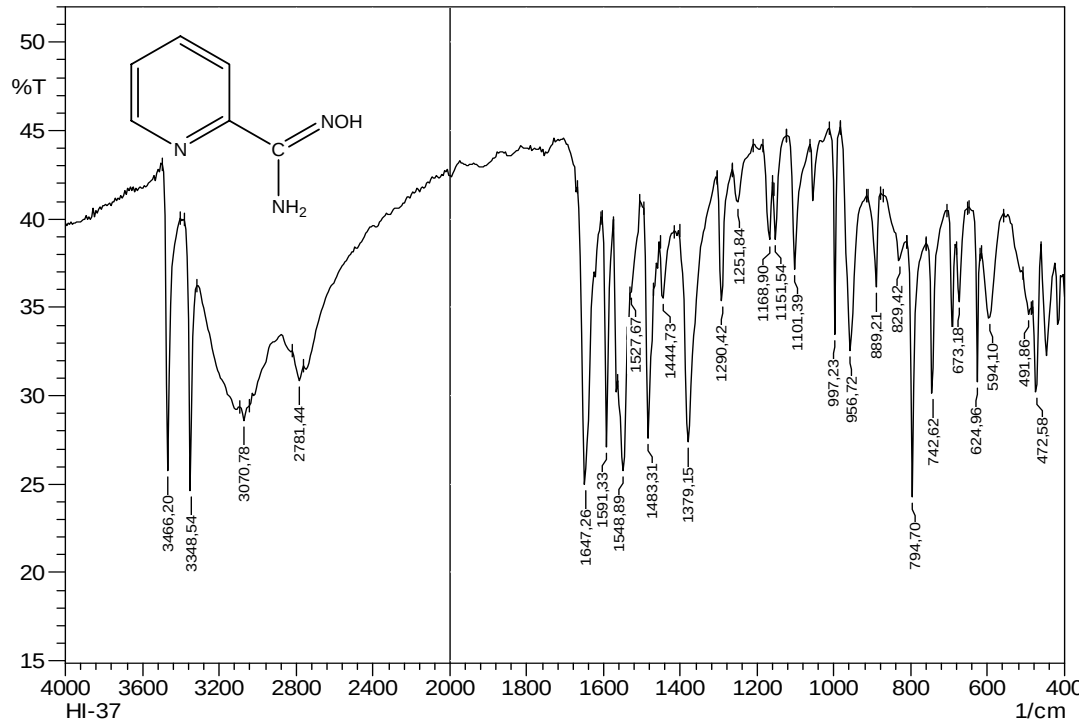

Figure 51: The IR spectrum of **8k**

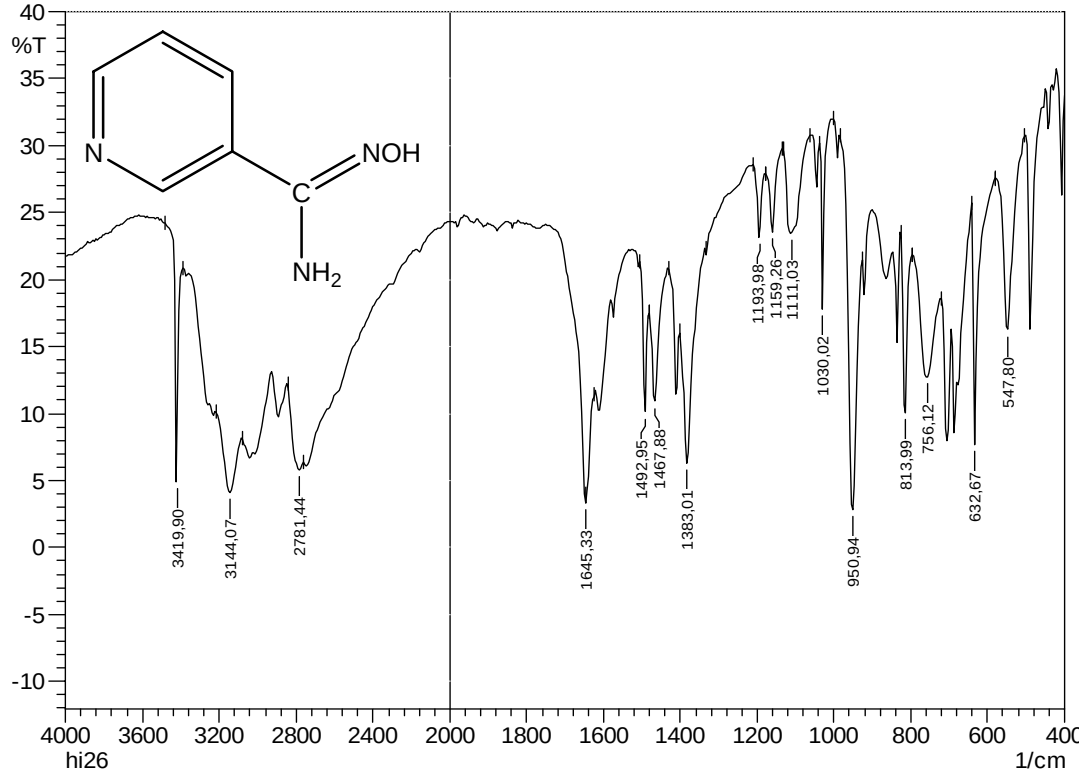

Figure 52: The IR spectrum of **8l**

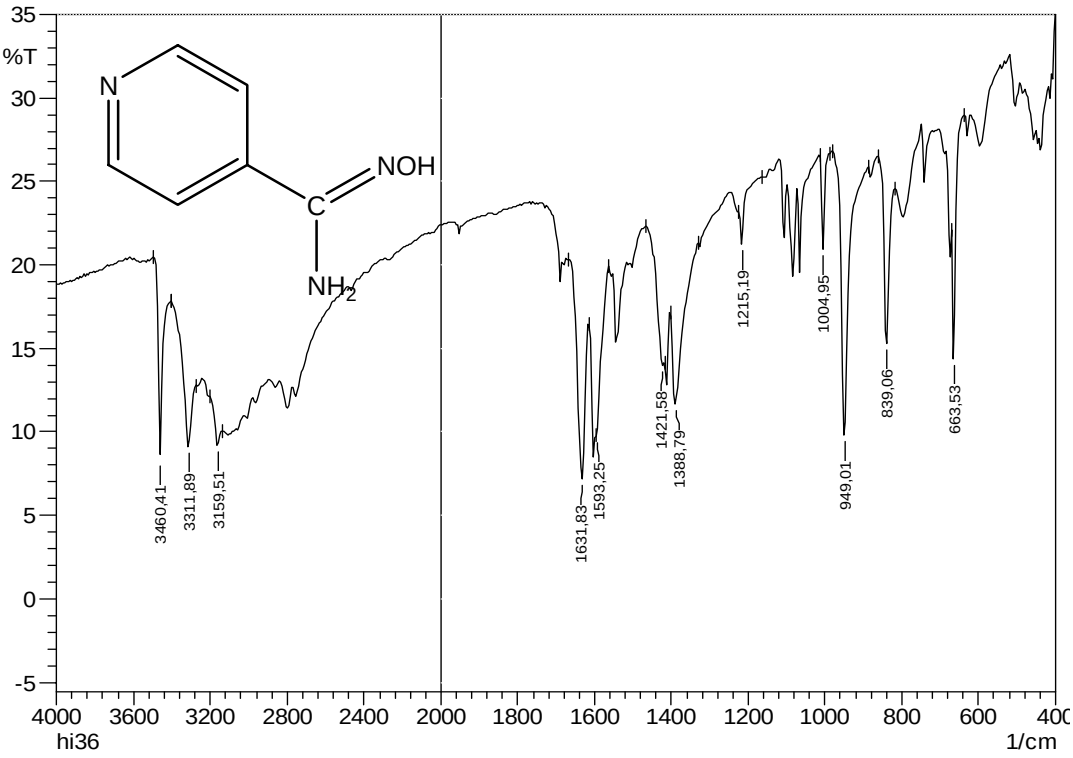

Figure 53: The IR spectrum of **8m**

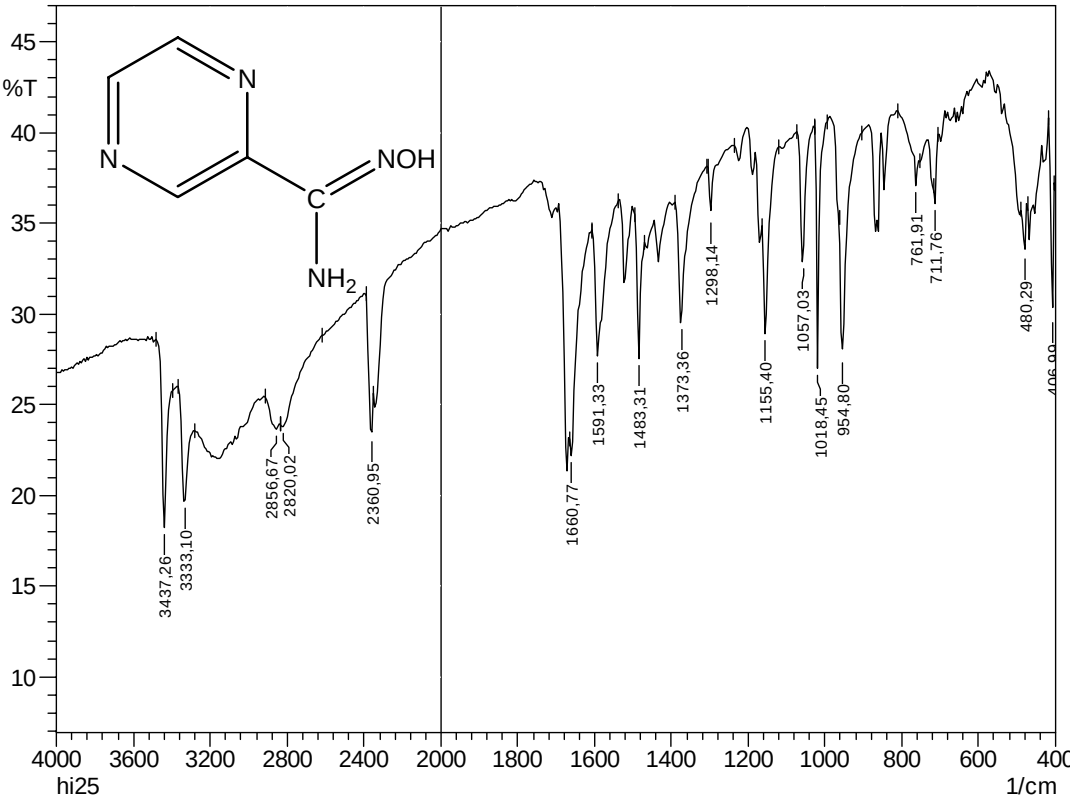

Figure 54: The IR spectrum of **8n**

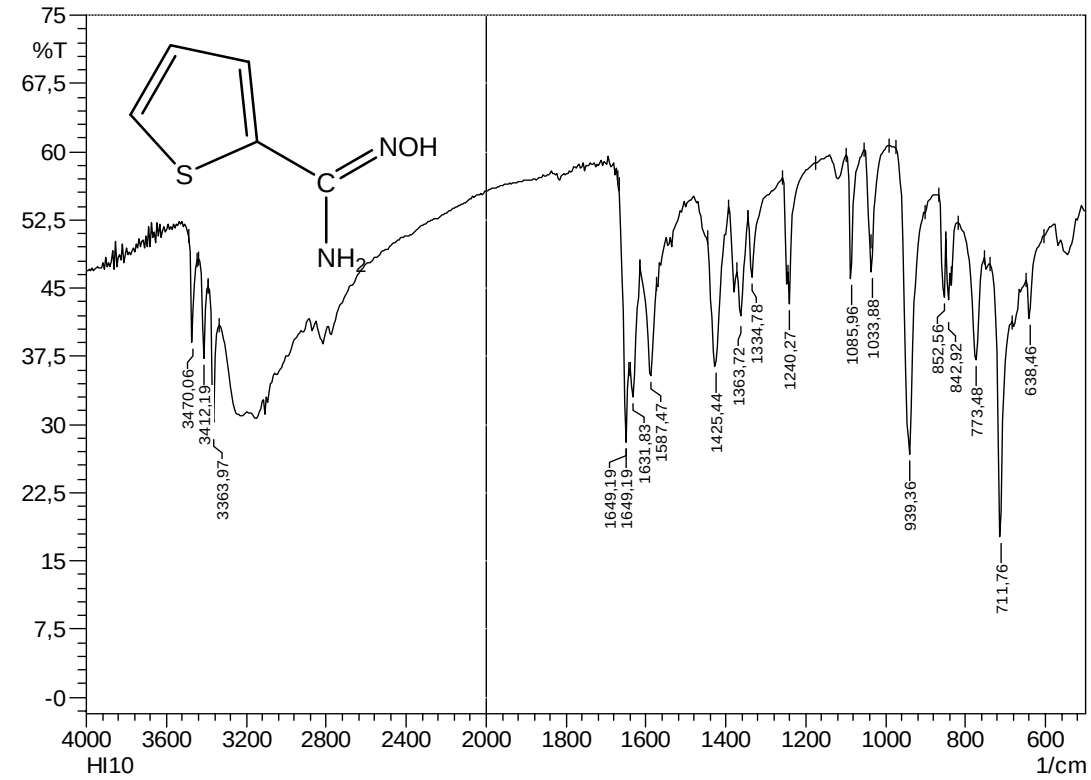

Figure 55: The IR spectrum of **8o**

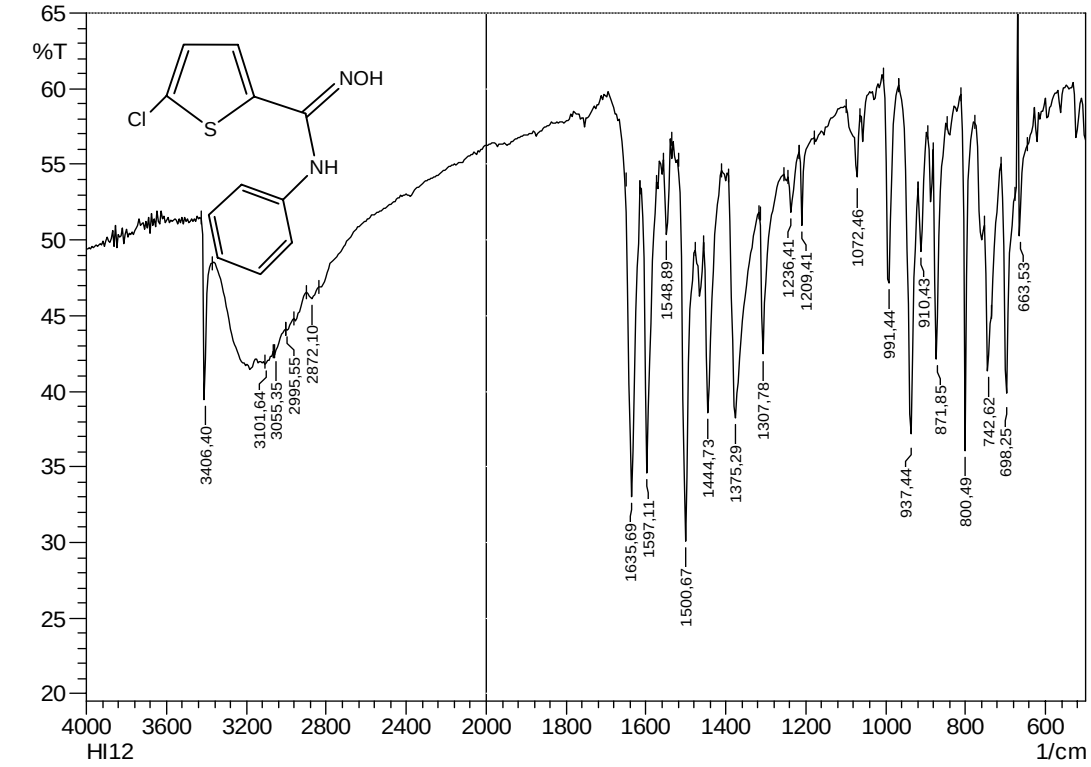

Figure 56: The IR spectrum of **9a**

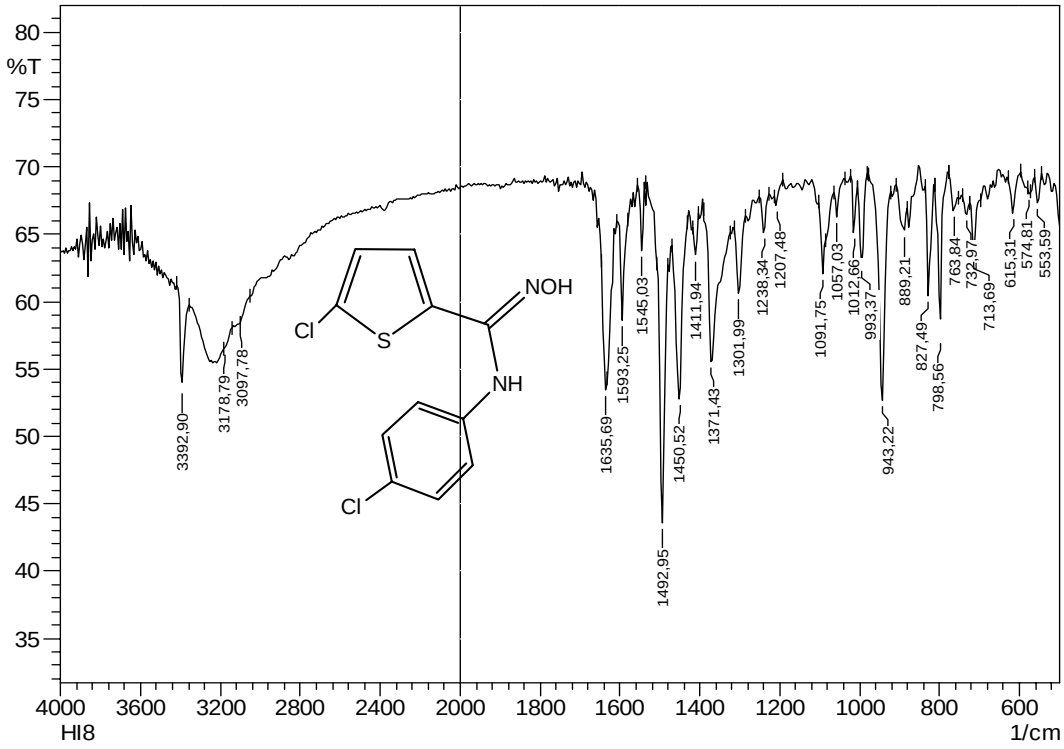

Figure 57: The IR spectrum of **9b**

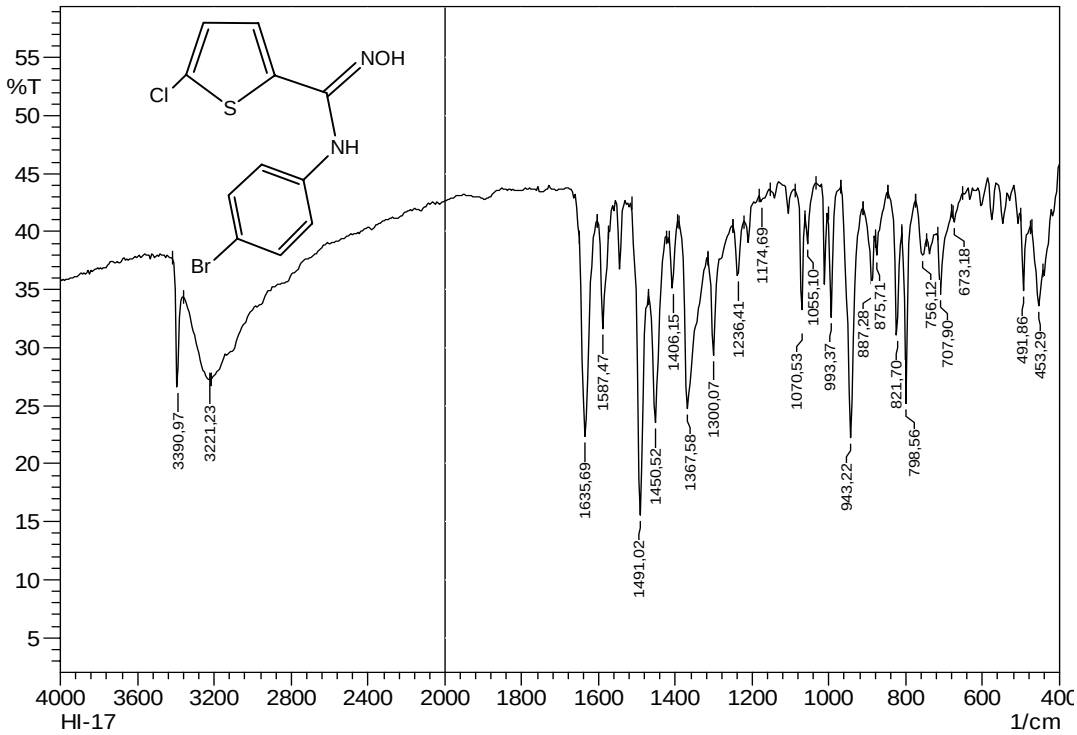

Figure 58: The IR spectrum of **9c**

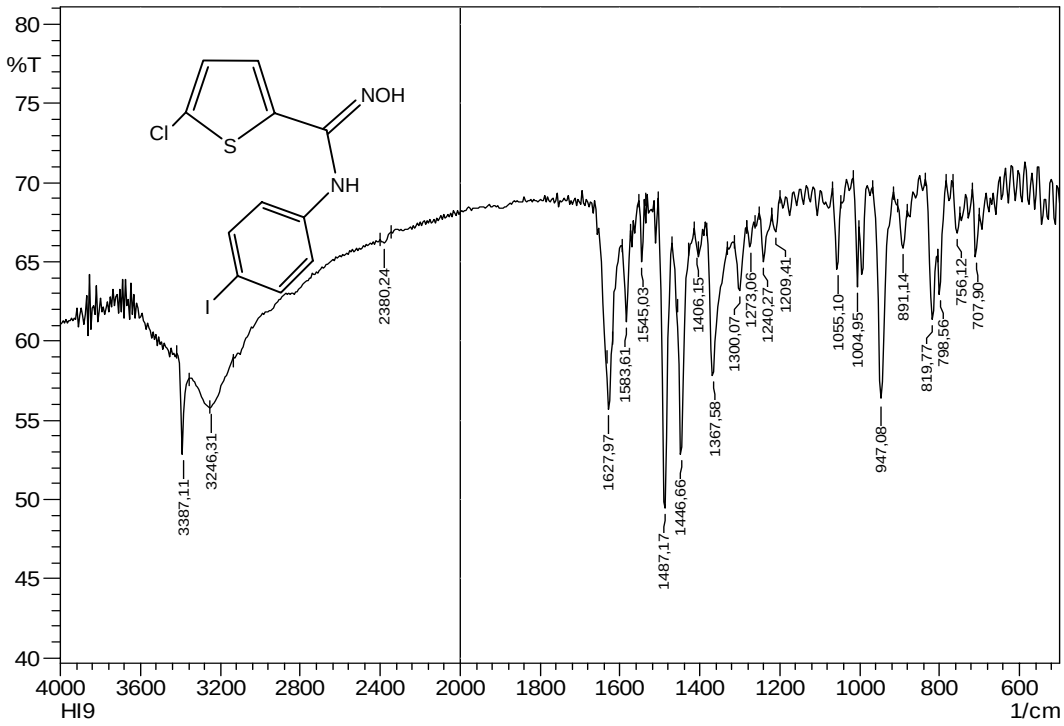

Figure 59: The IR spectrum of **9d**

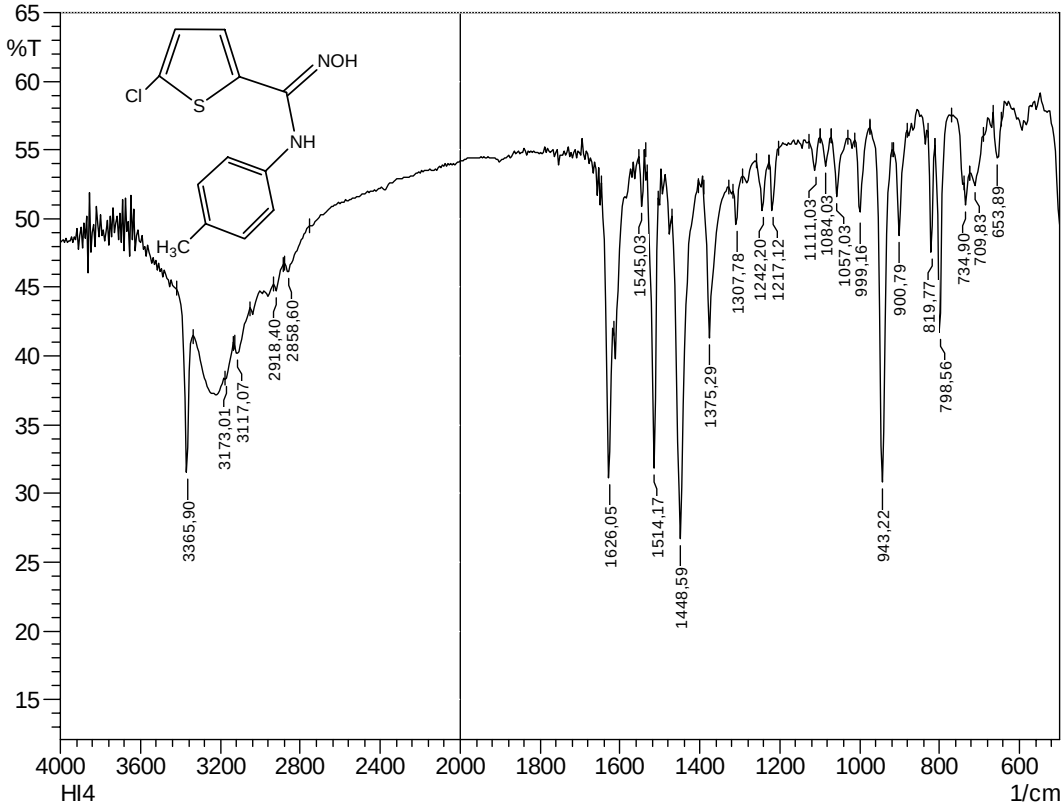

Figure 60: The IR spectrum of **9e**

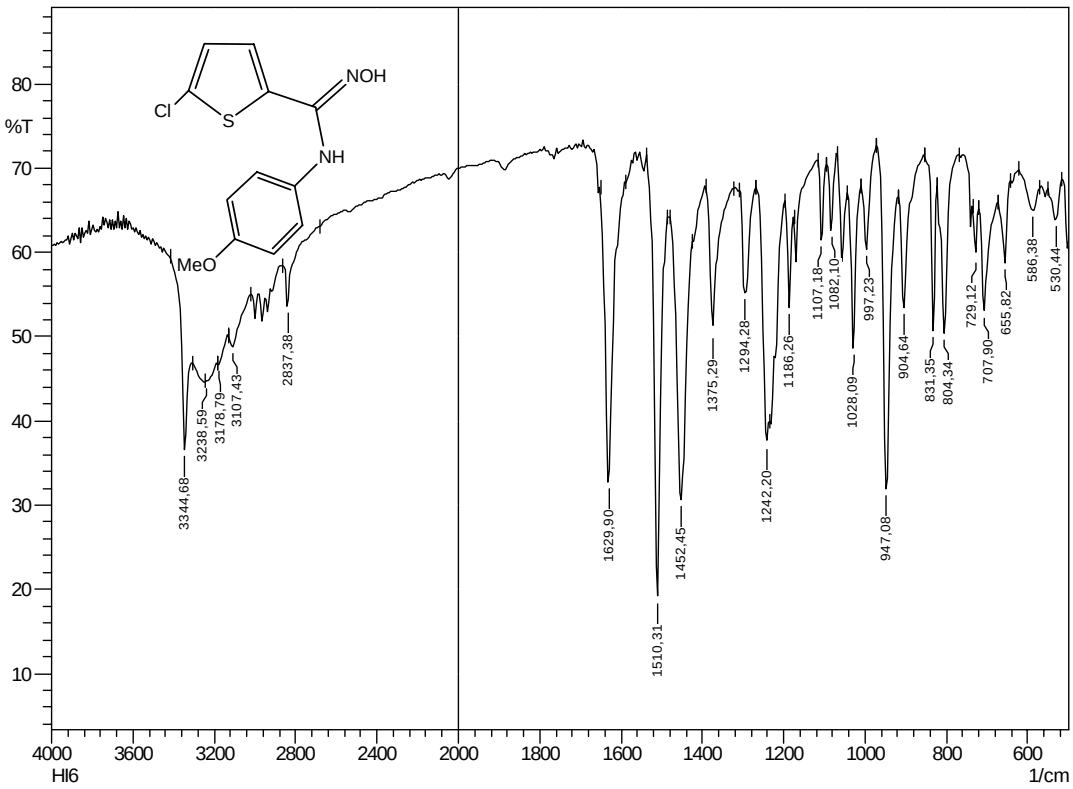

Figure 61: The IR spectrum of **9f**

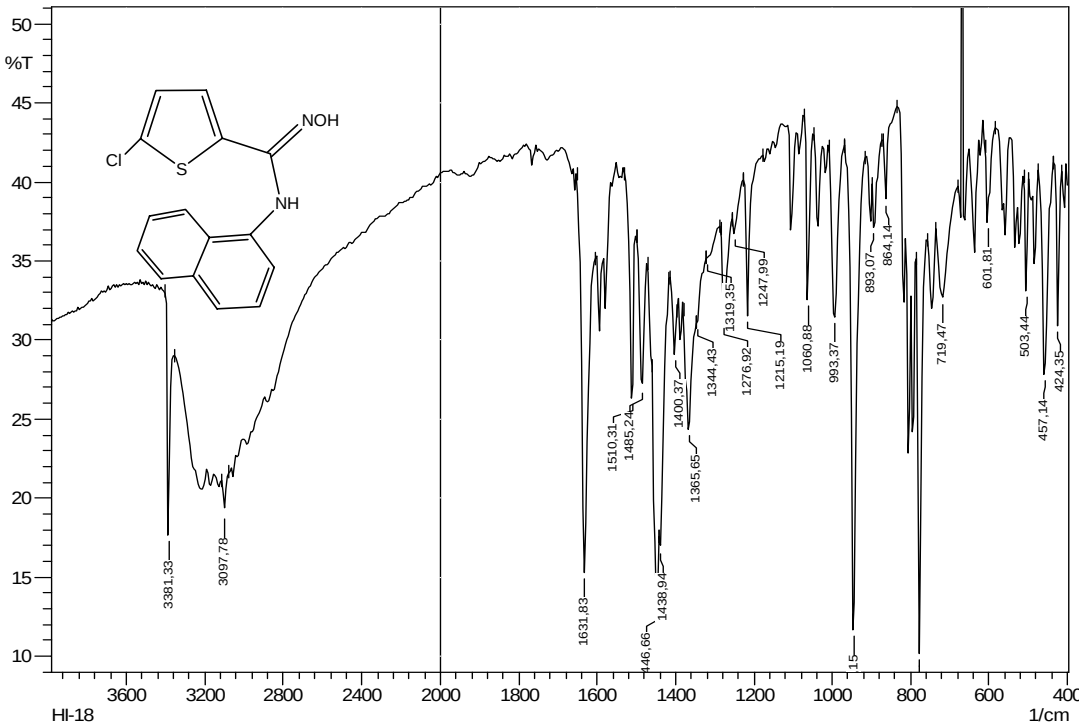

Figure 62: The IR spectrum of **9g**

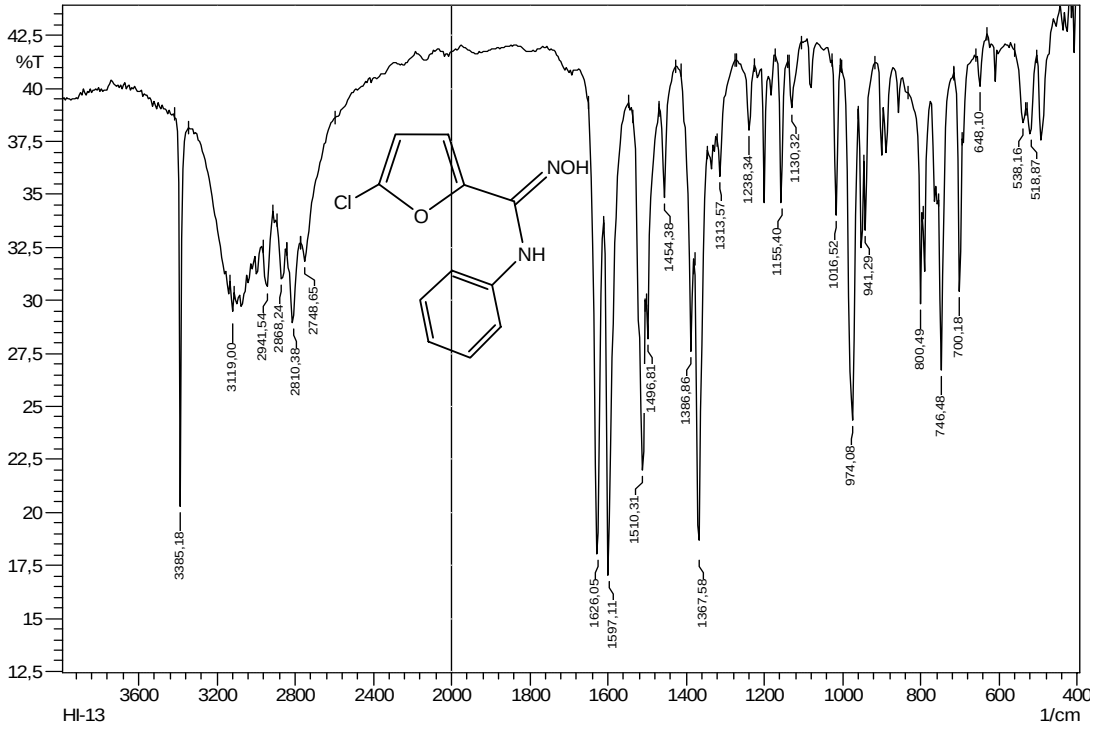

Figure 63: The IR spectrum of **10a**

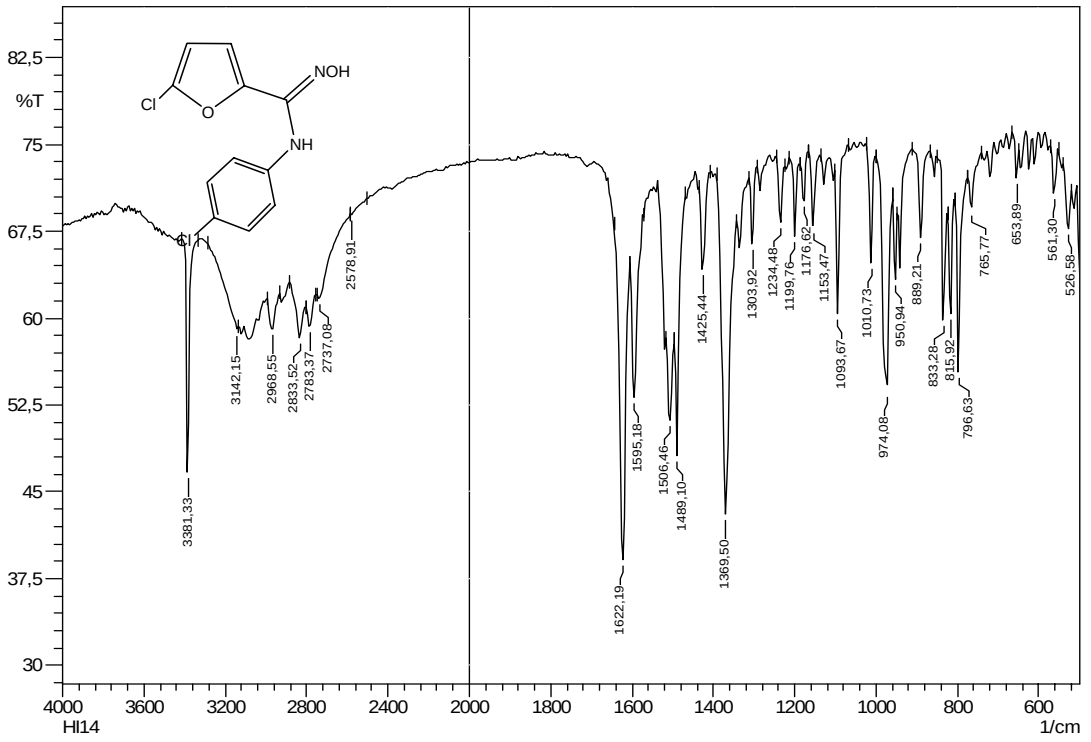

Figure 64: The IR spectrum of **10b**

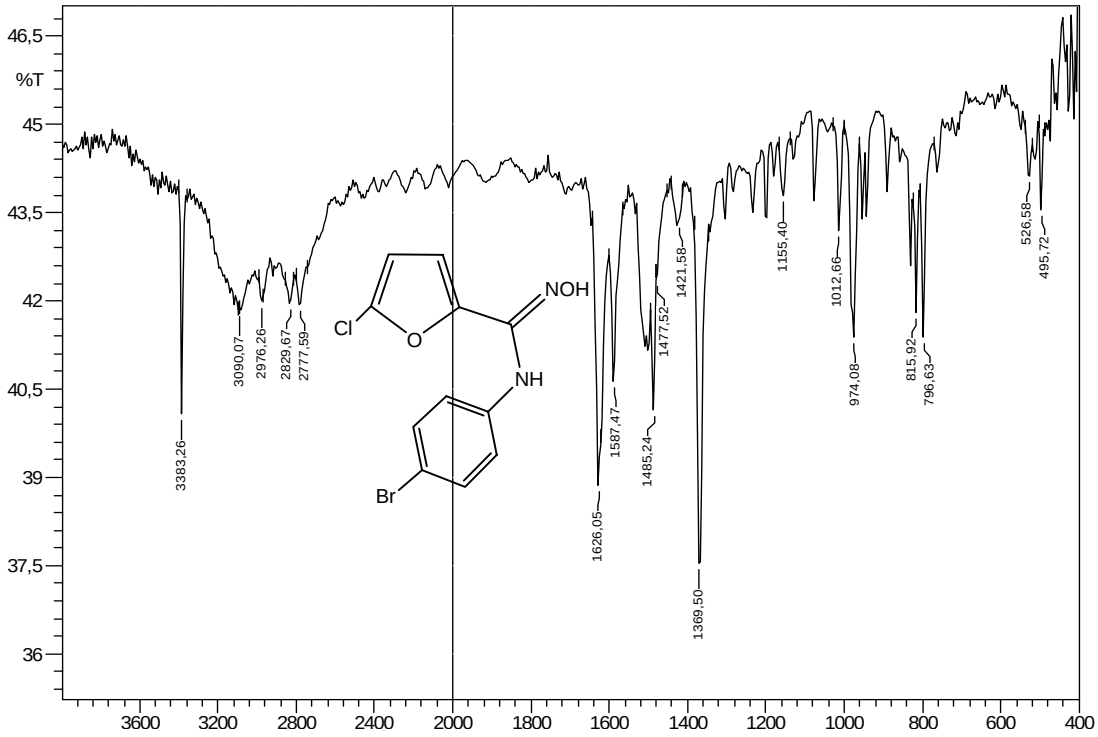

Figure 65: The IR spectrum of **10c**

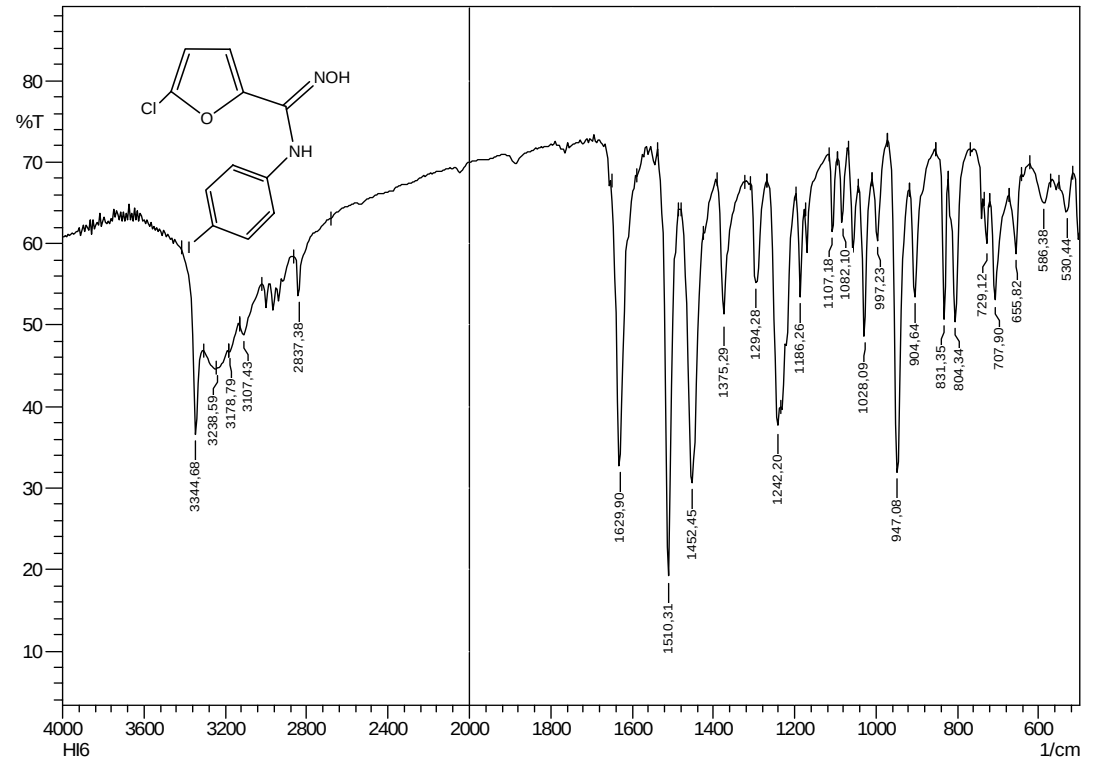

Figure 66: The IR spectrum of **10d**

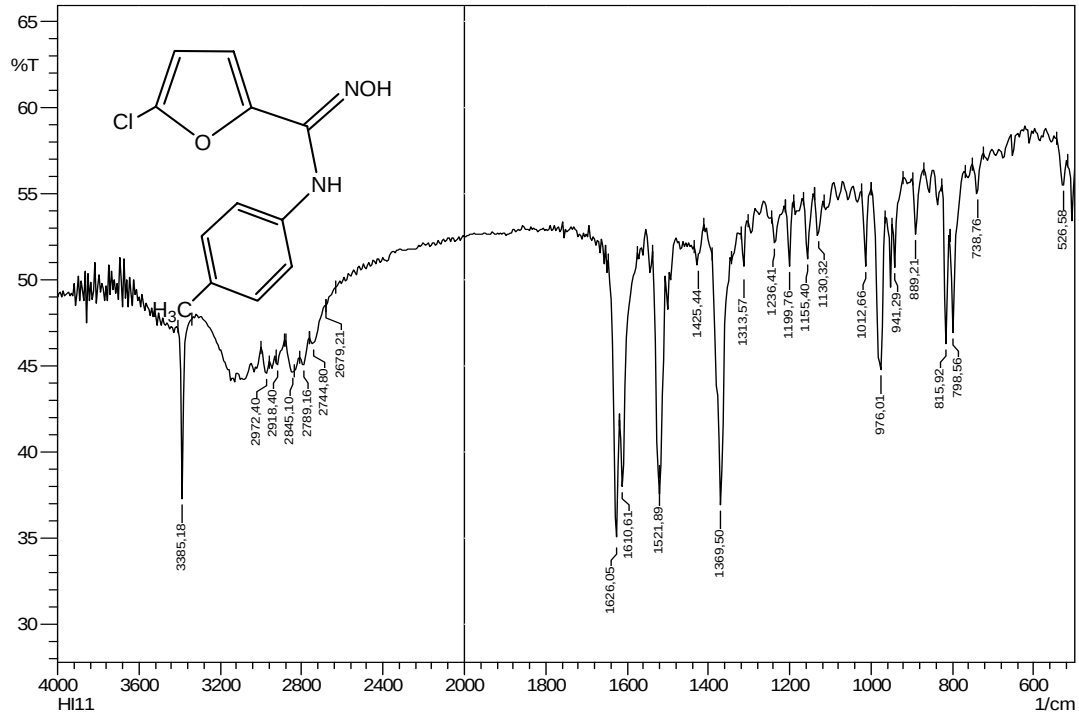

Figure 67: The IR spectrum of **10e**

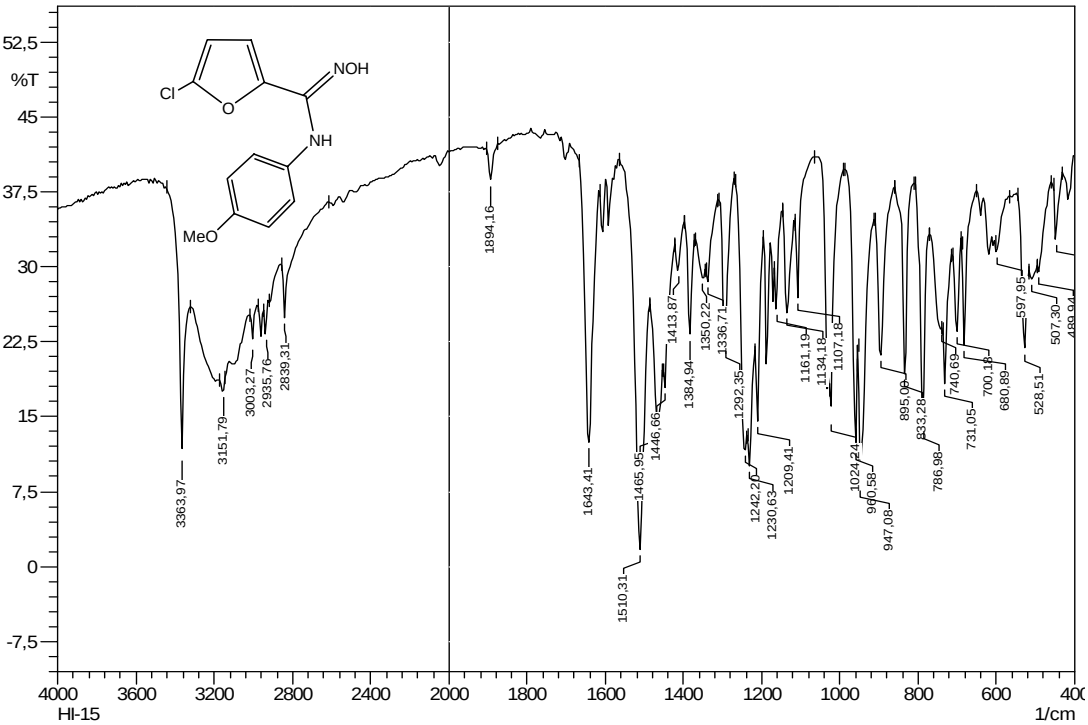

Figure 68: The IR spectrum of **10f**

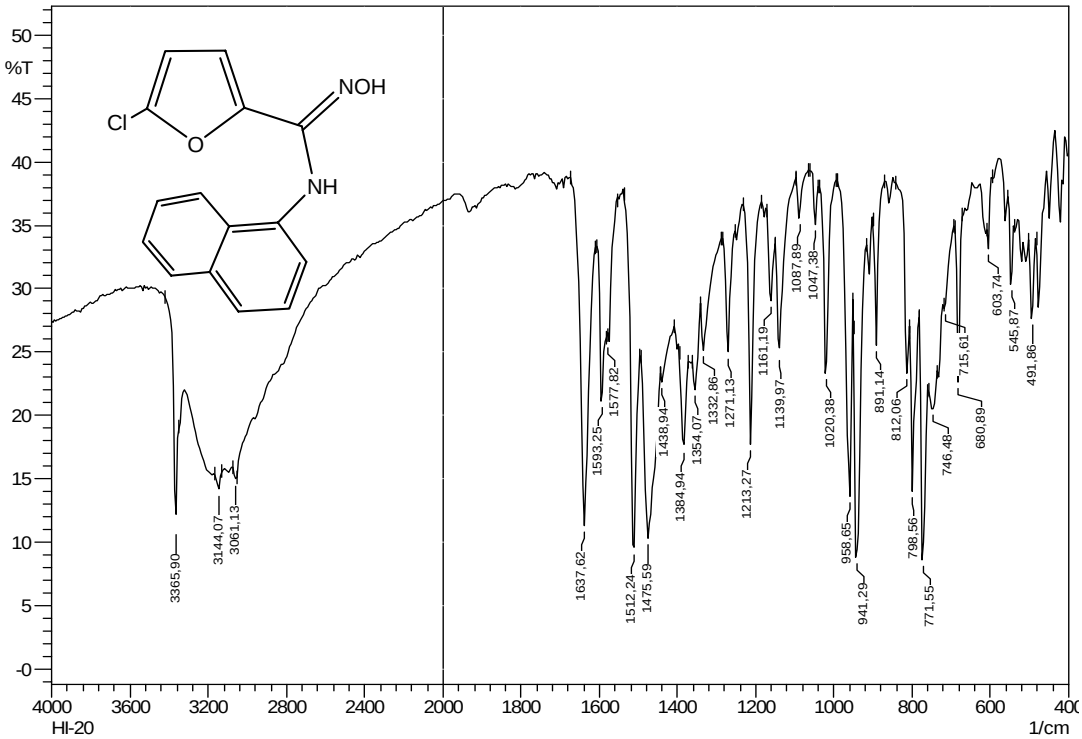

Figure 69: The IR spectrum of **10g**

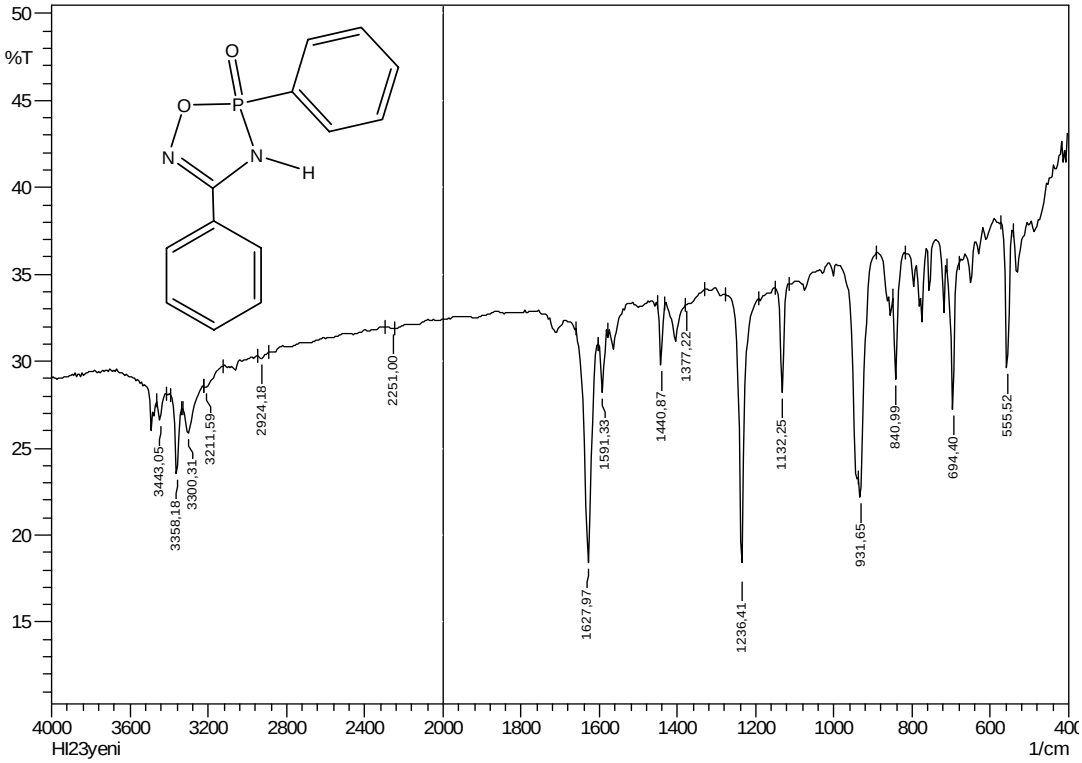

Figure 70: The IR spectrum of **11a**

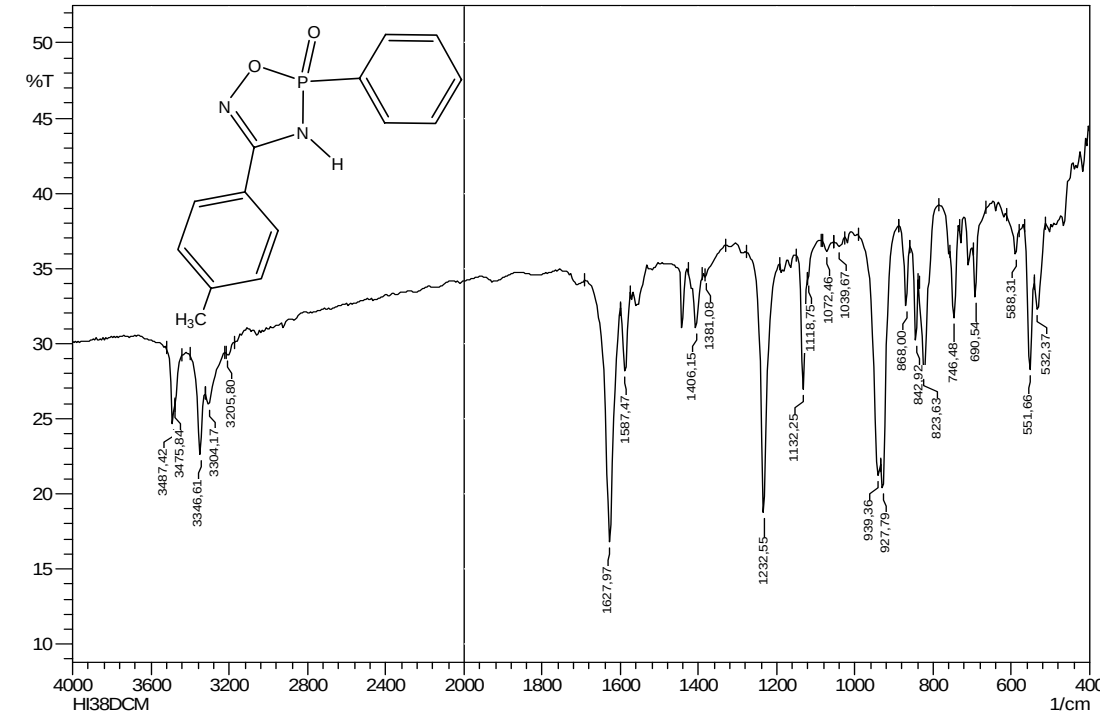

Figure 71: The IR spectrum of **11b**

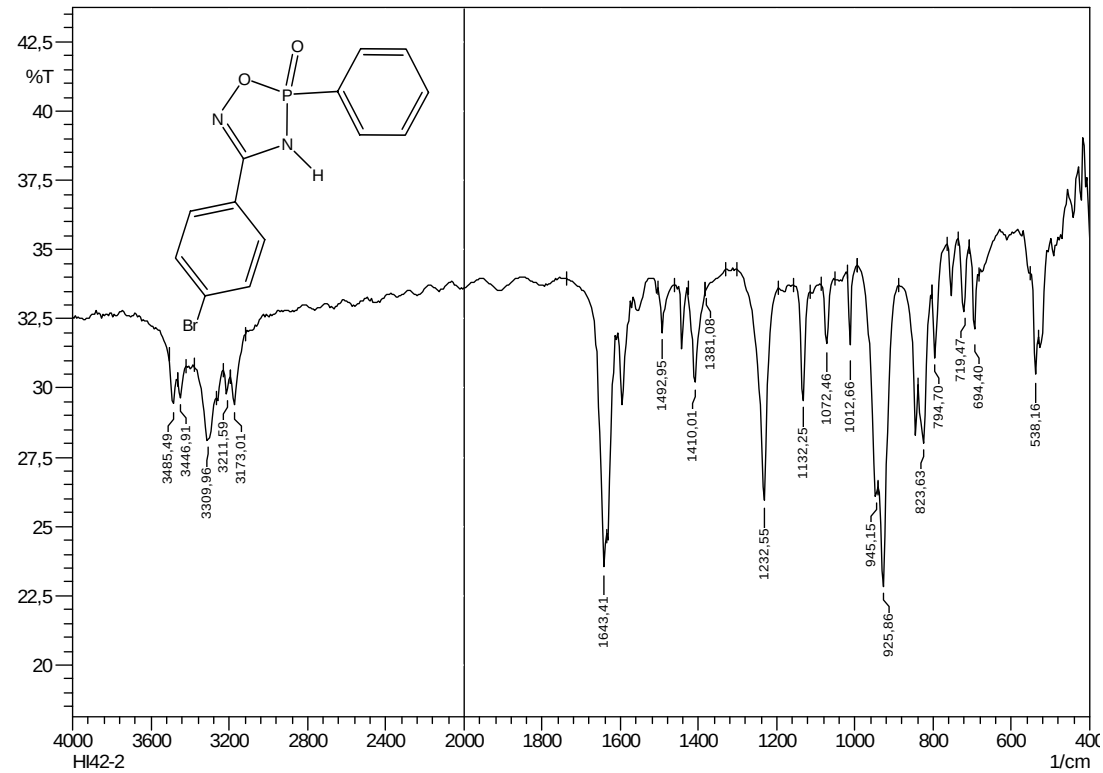

Figure 72: The IR spectrum of **11c**

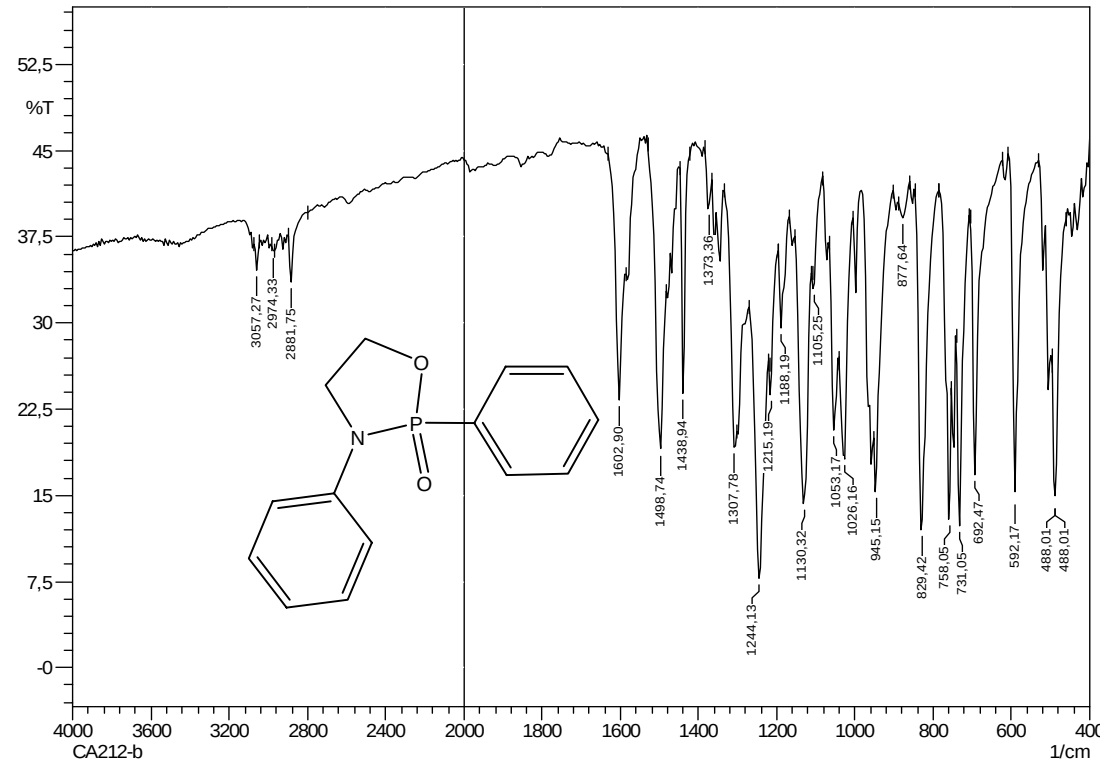

Figure 73: The IR spectrum of **12a**

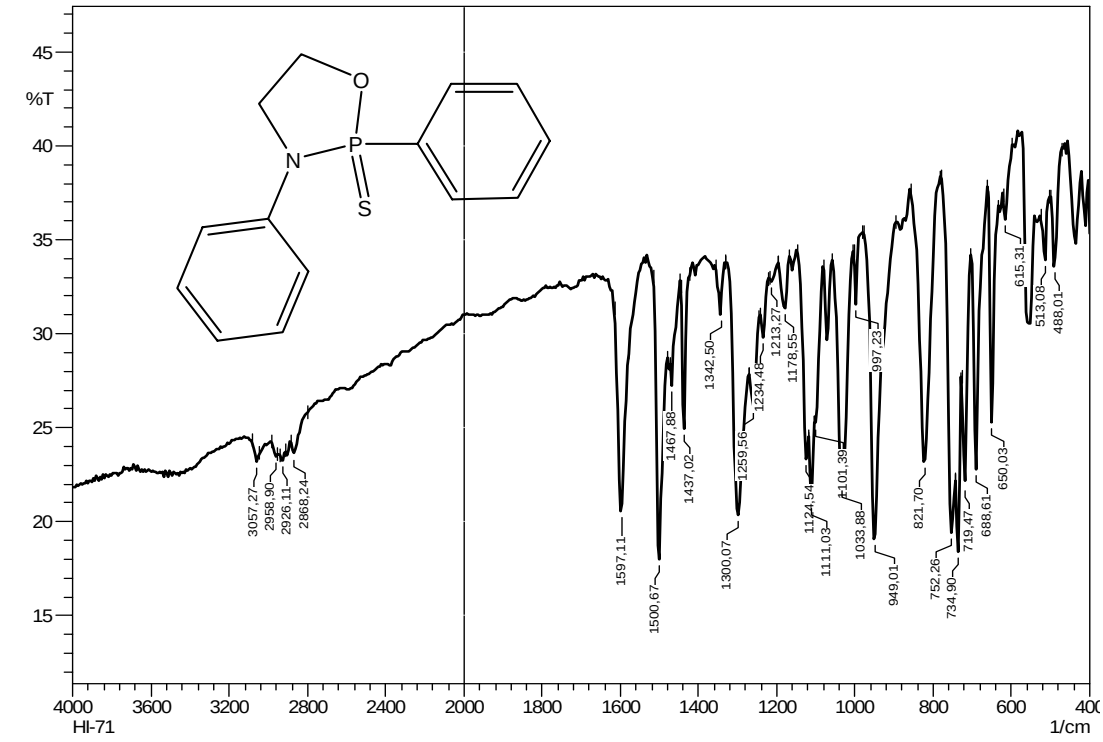

Figure 74: The IR spectrum of **12b**

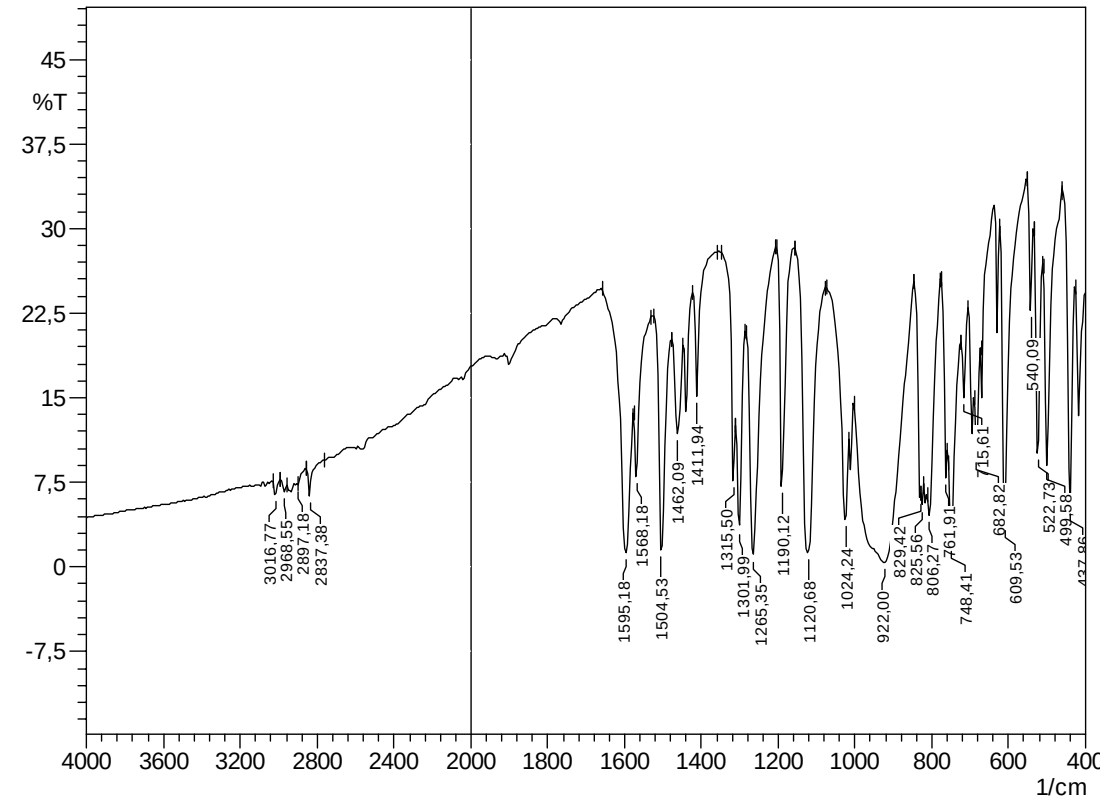

Figure 75A: The IR spectrum of **13**

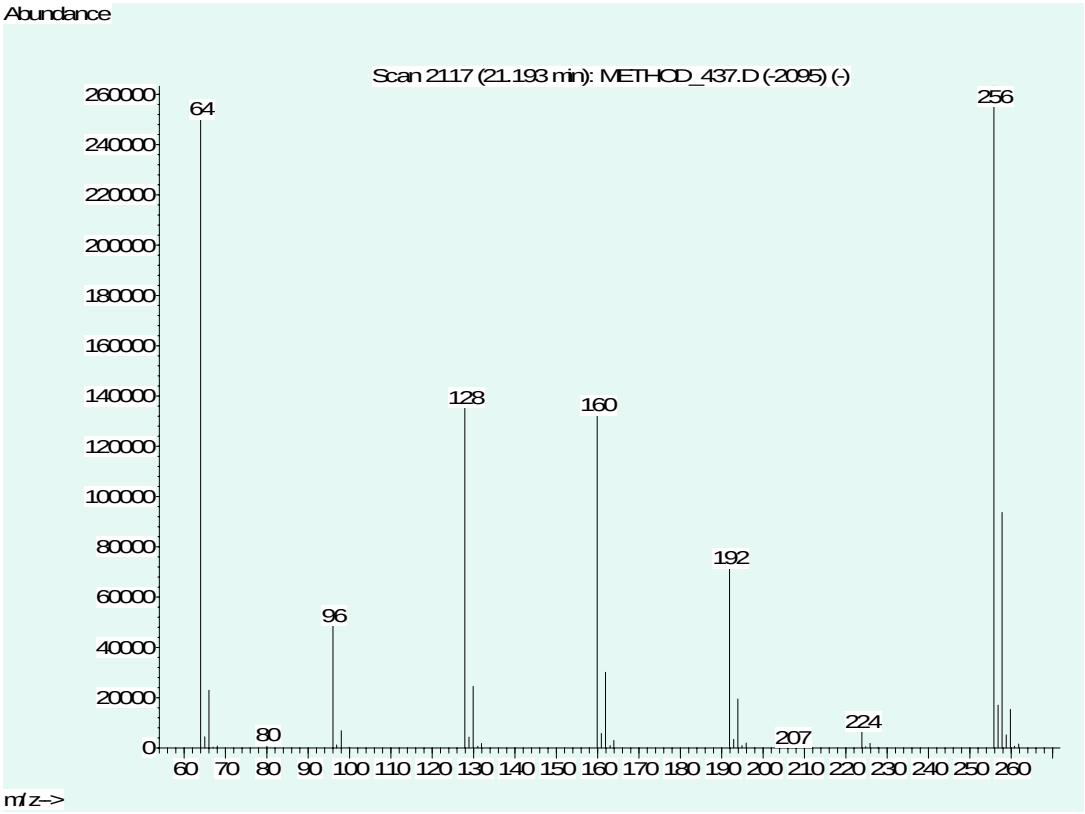

Figure 75B: The mass spectrum of **13**

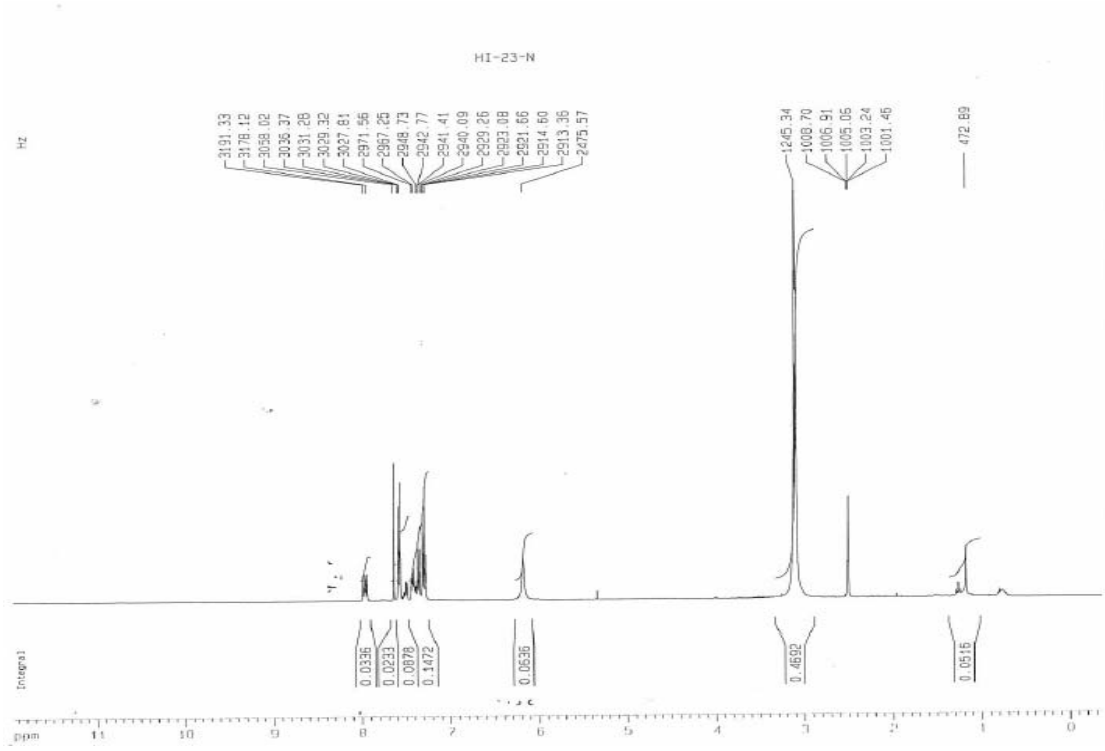

Figure 76A: The ^{1}H-NMR spectrum of **11a**

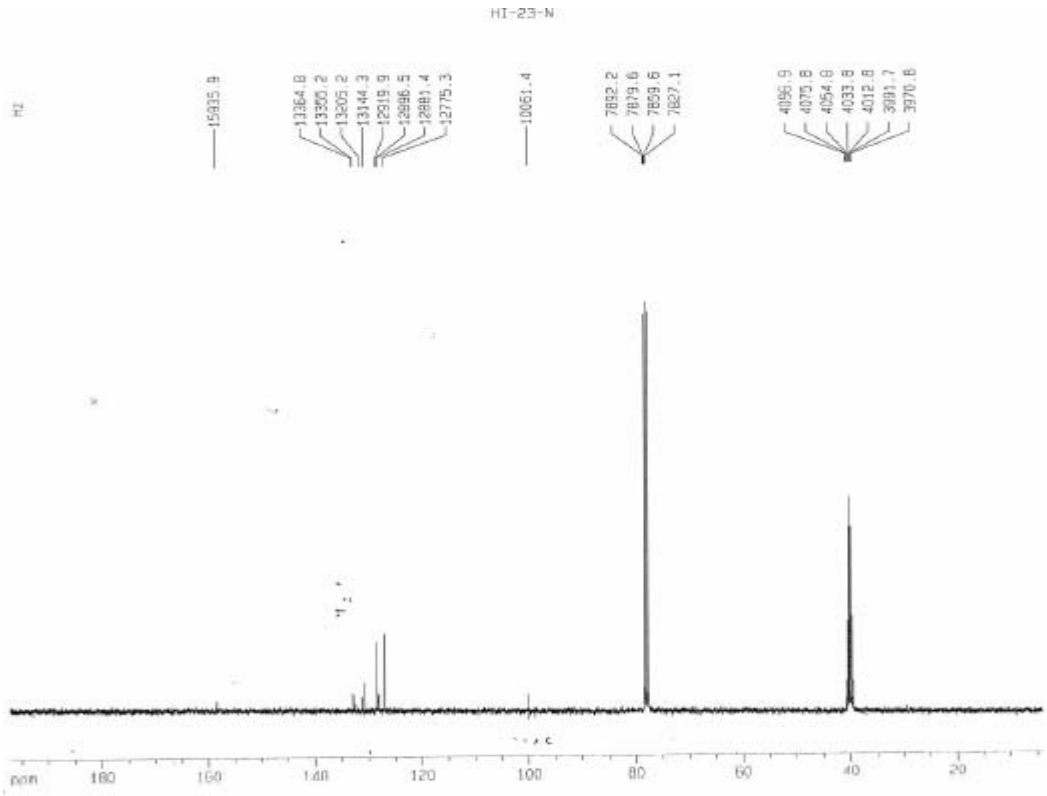

Figure 76B: The ^{13}C-NMR spectrum of **11a**

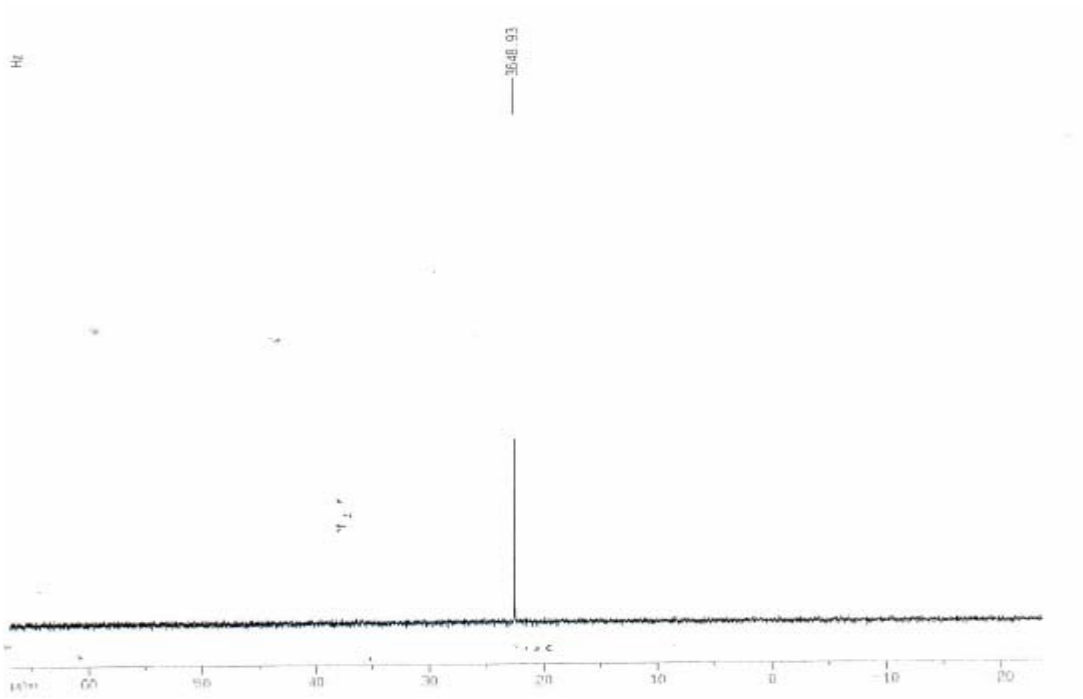

Figure 76C: The ^{31}P-NMR spectrum of **11a**

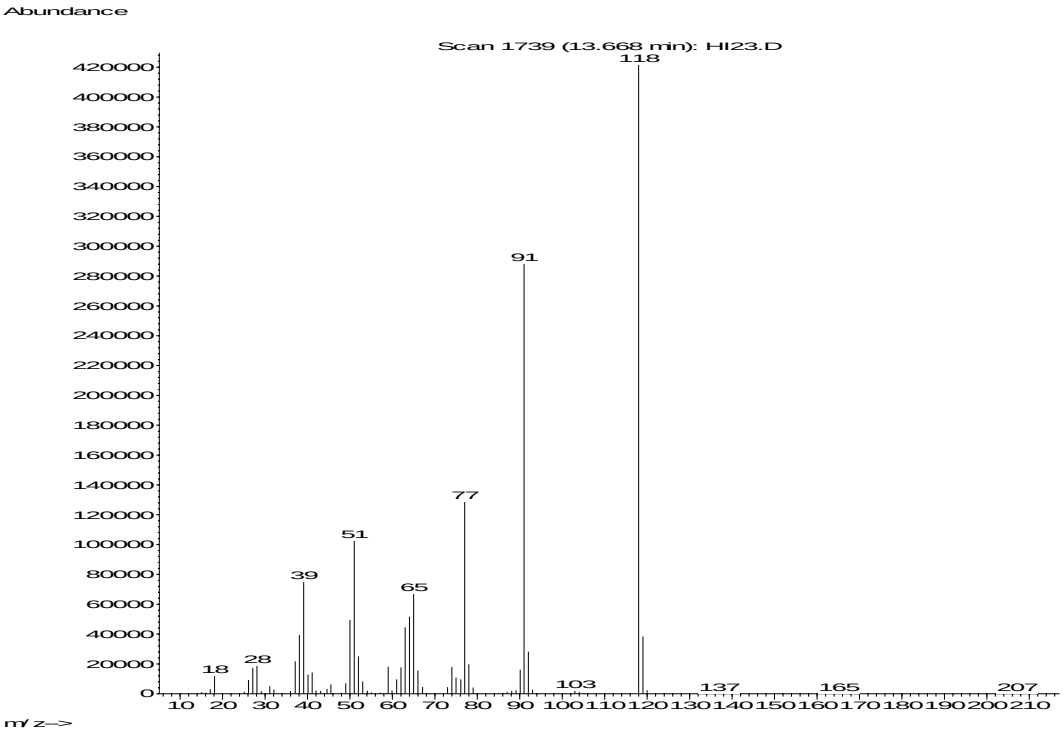

Figure 76D: The mass spectrum of **11a**

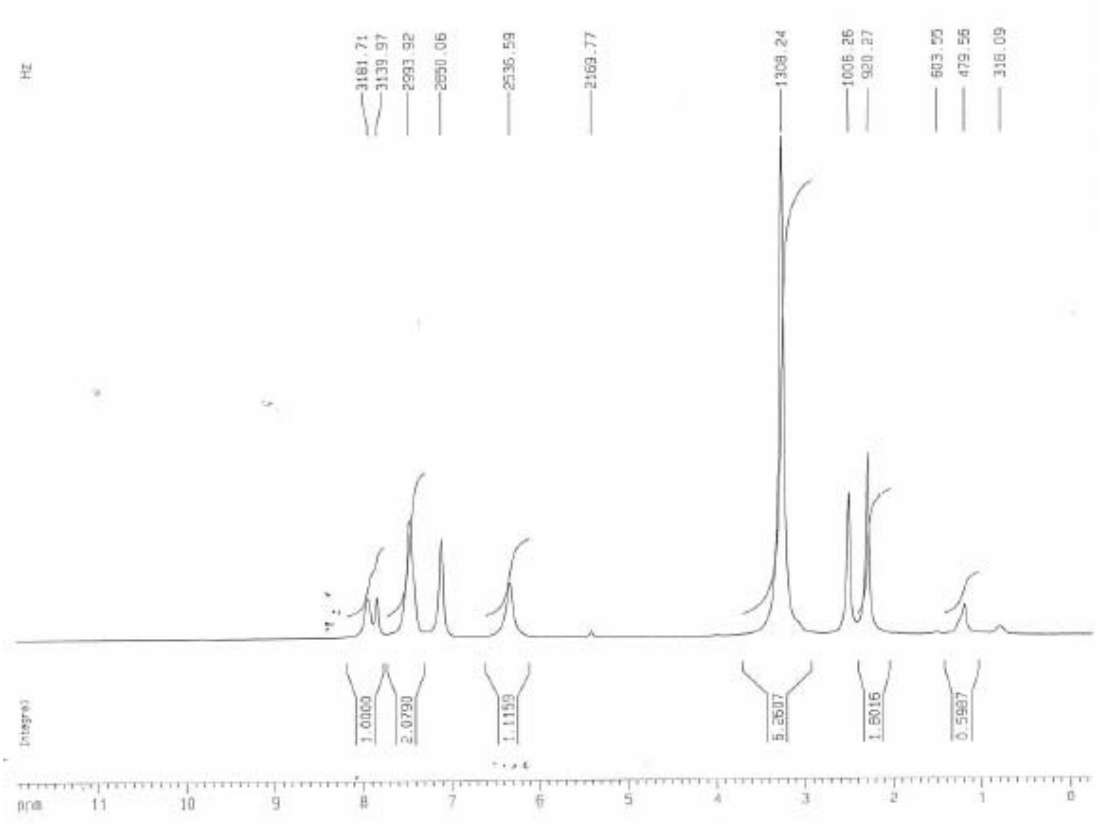

Figure 77A: The ^{1}H-NMR spectrum of **11b**

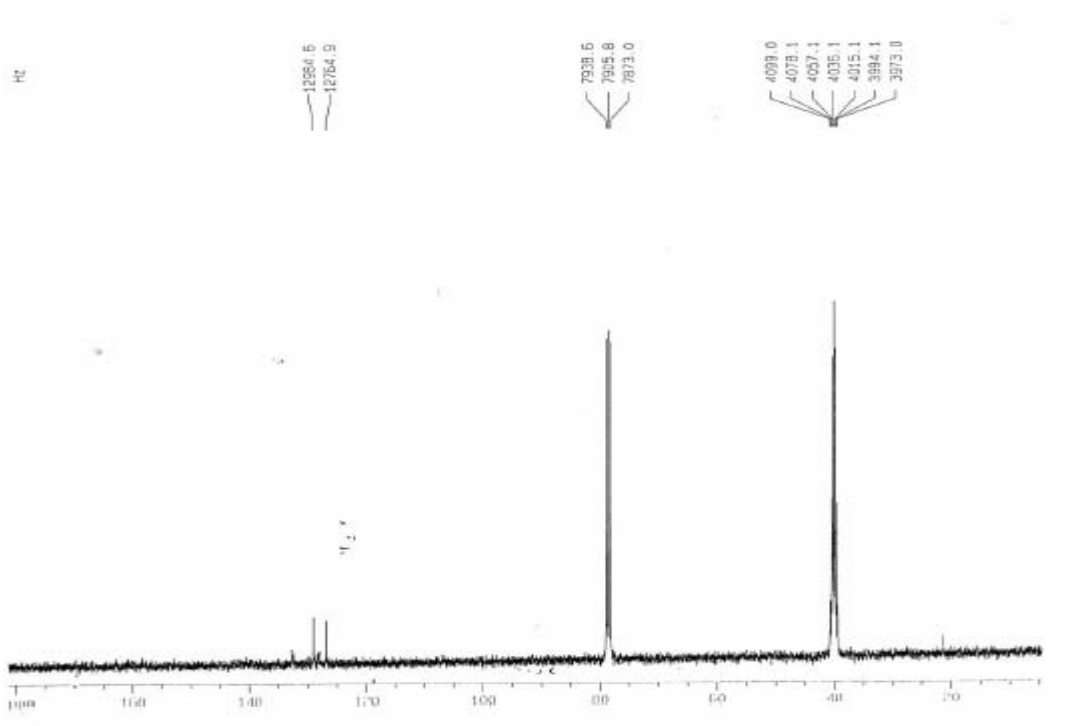

Figure 77B: The ^{13}C-NMR spectrum of **11b**

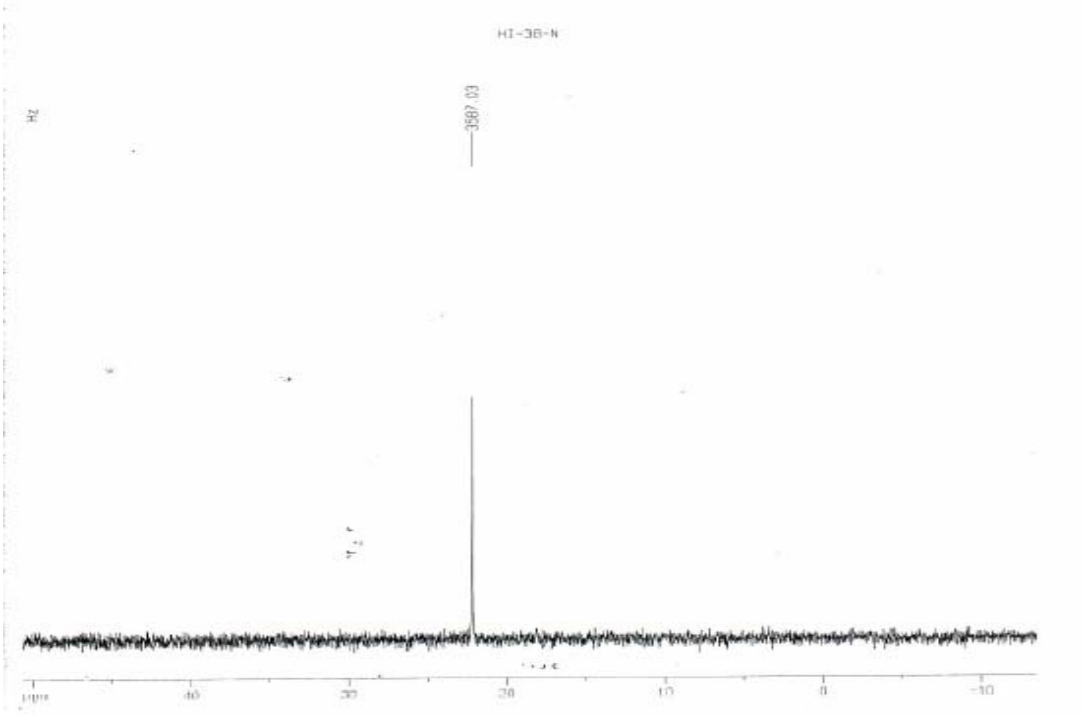

Figure 77C: The ^{31}P-NMR spectrum of **11b**

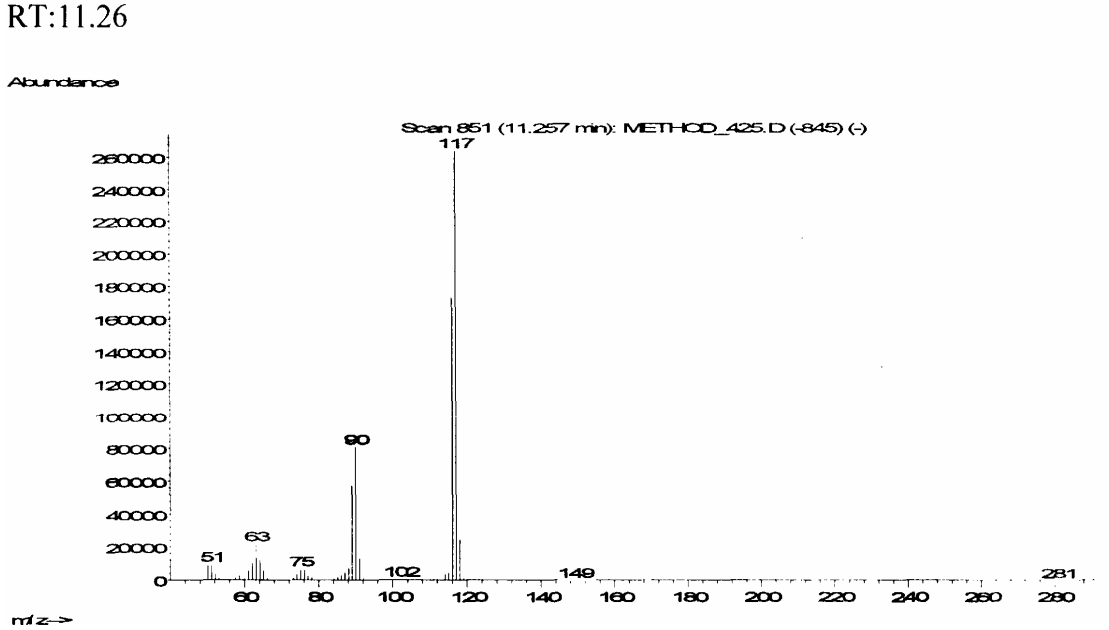

Figure 77D: The mass spectrum of **11b**

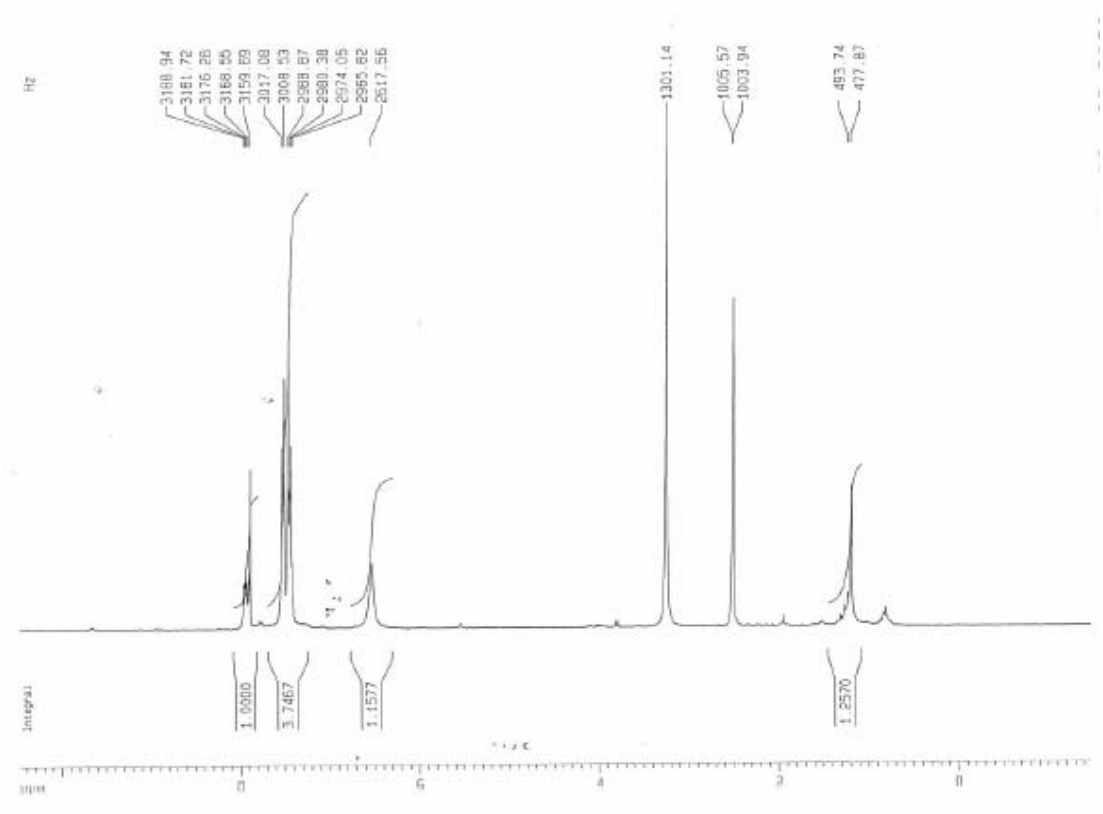

Figure 78A: The ^{1}H-NMR spectrum of **11c**

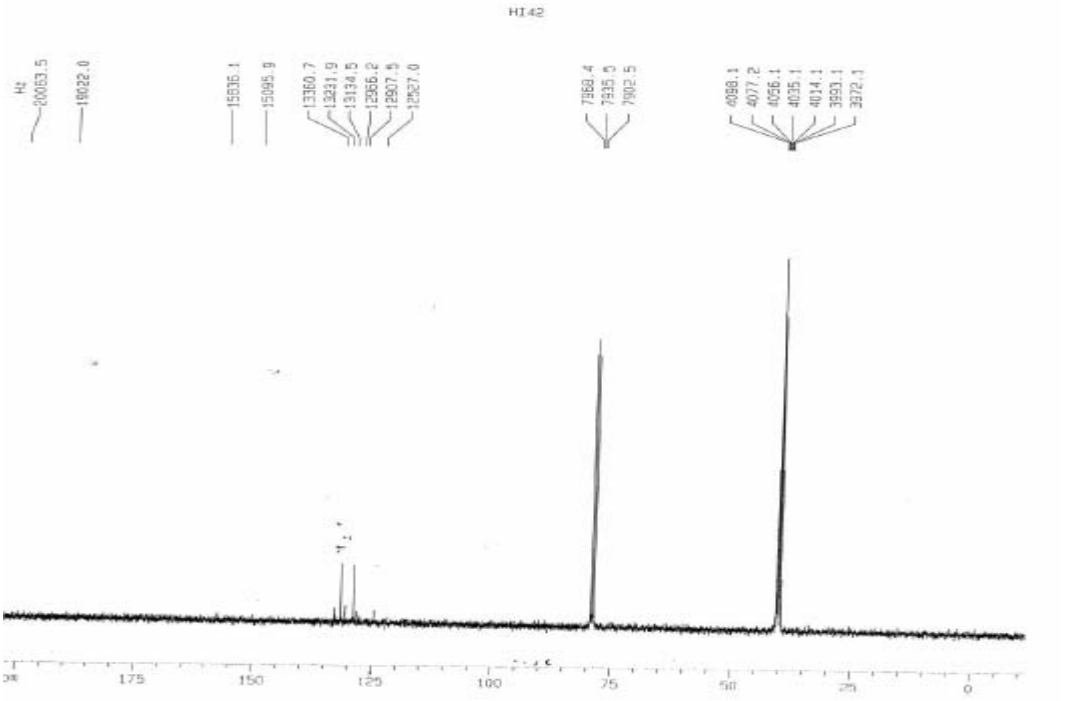

Figure 78B: The ^{13}C-NMR spectrum of **11c**

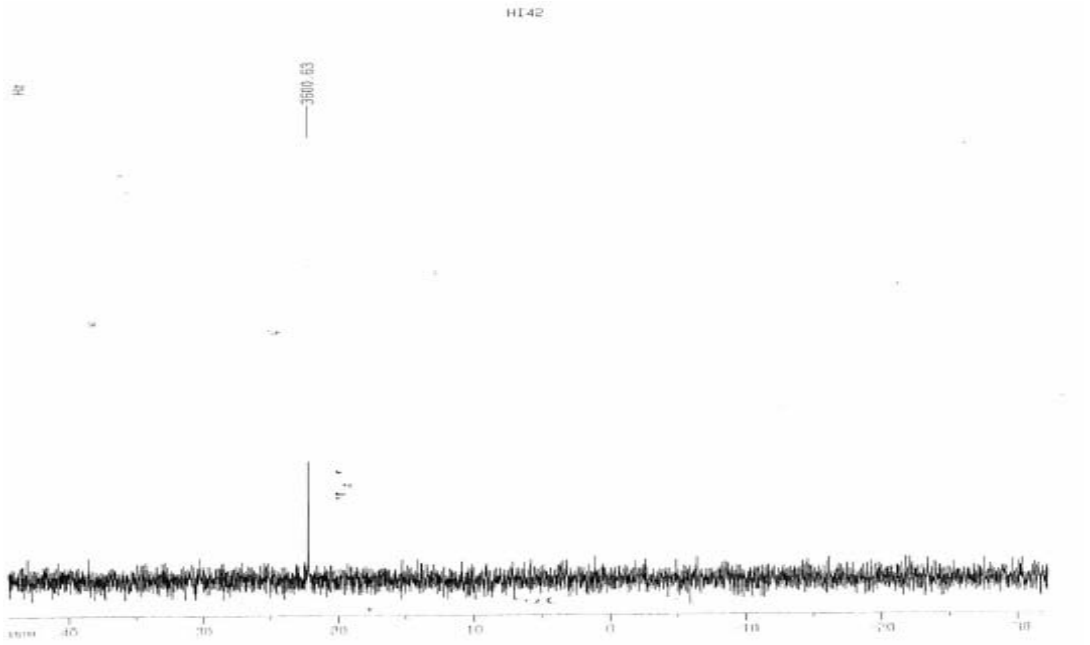

Figure 78C: The ^{31}P-NMR spectrum of **11c**

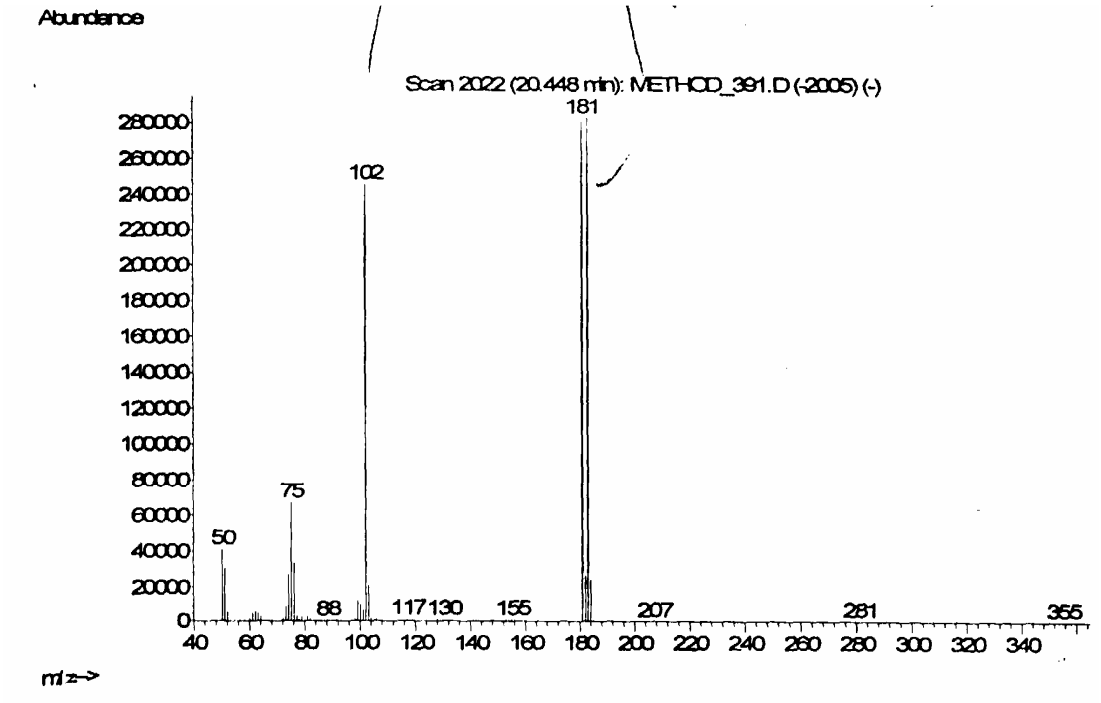

Figure 78D: The mass spectrum of **11c**

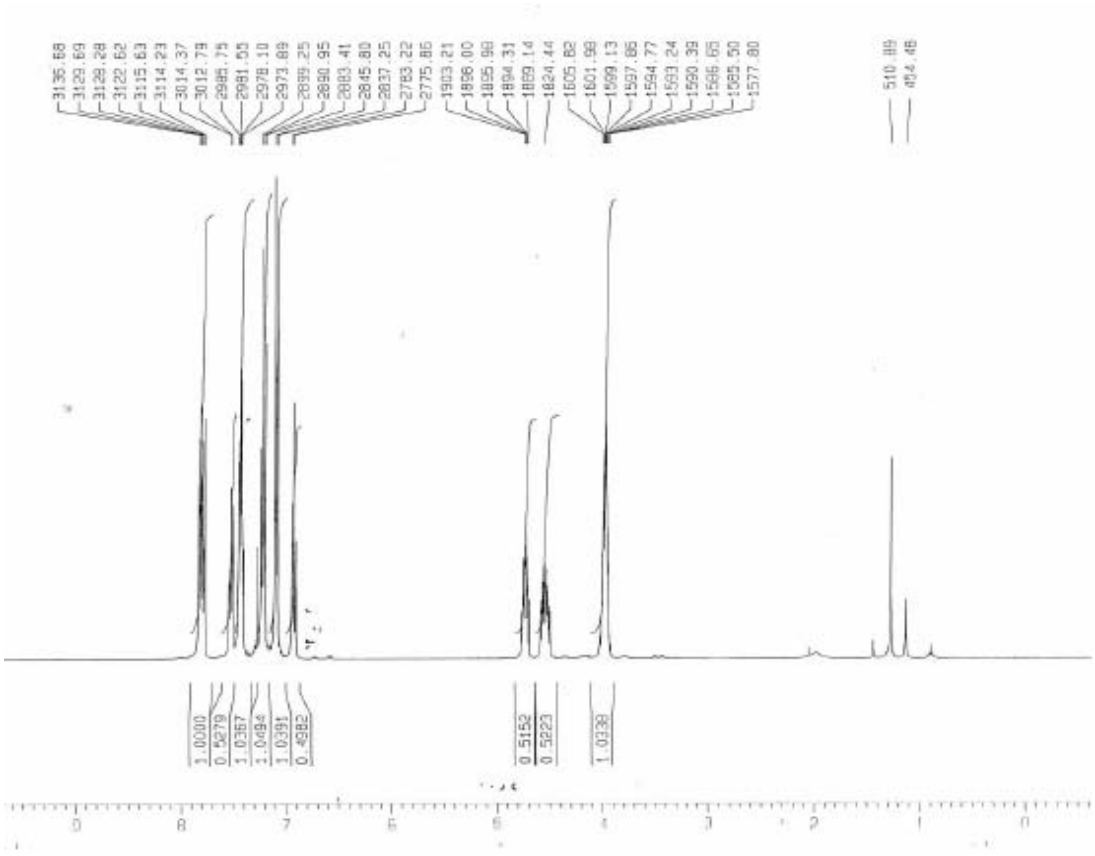

Figure 79A: The ^{1}H-NMR spectrum of **12a**

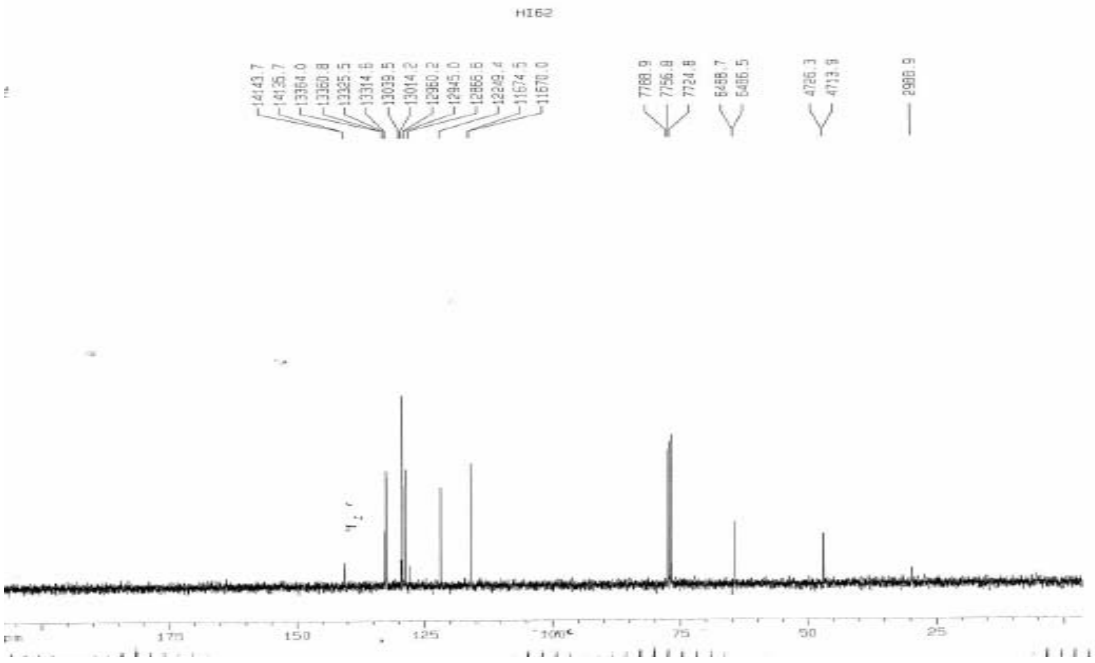

Figure 79B: The ^{13}C-NMR spectrum of **12a**

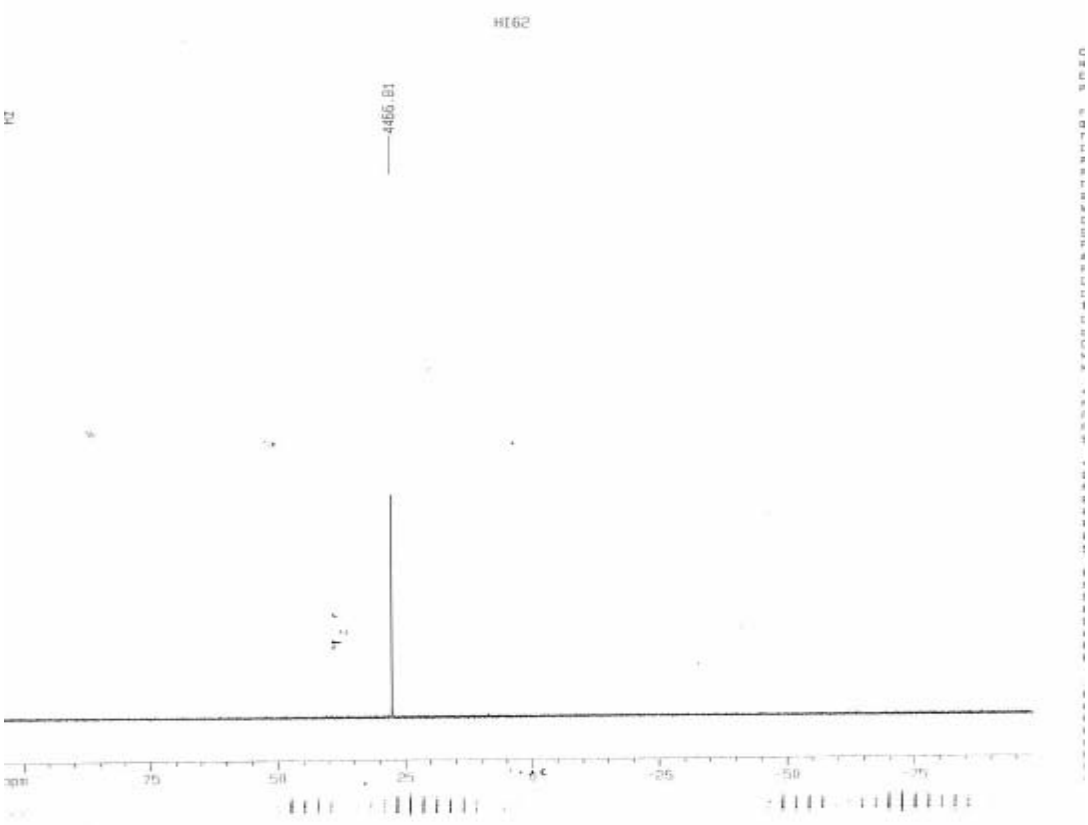

Figure 79C: The ^{31}P-NMR spectrum of **12a**

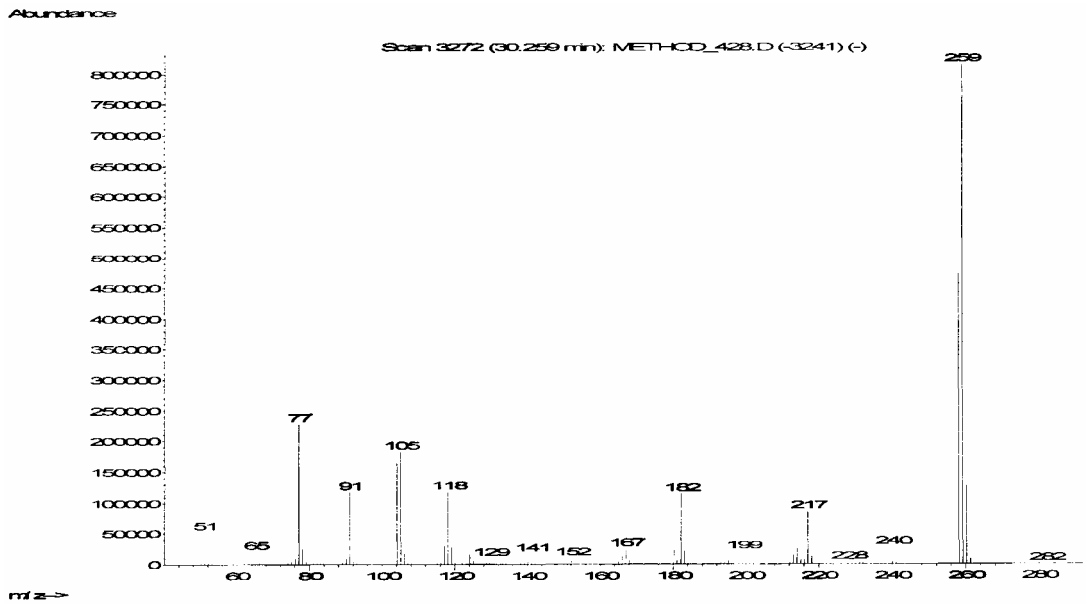

Figure 79D: The mass spectrum of **12a**

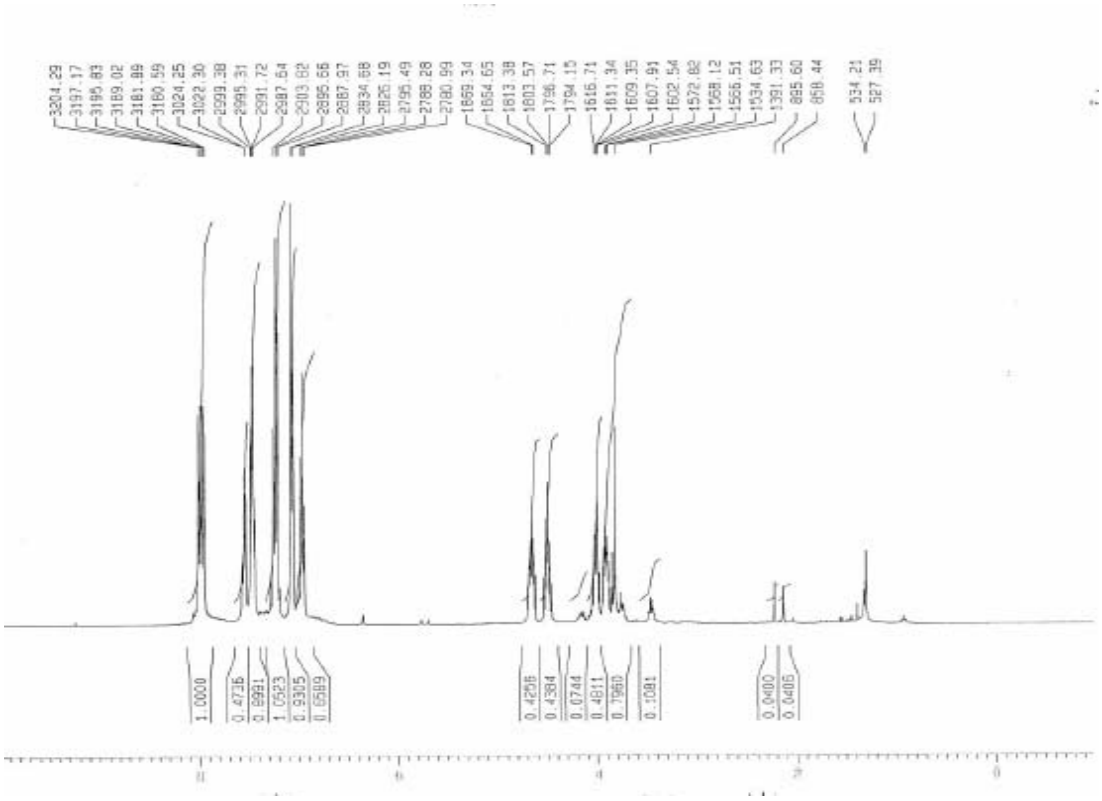

Figure 80A: The ^{1}H-NMR spectrum of **12b**

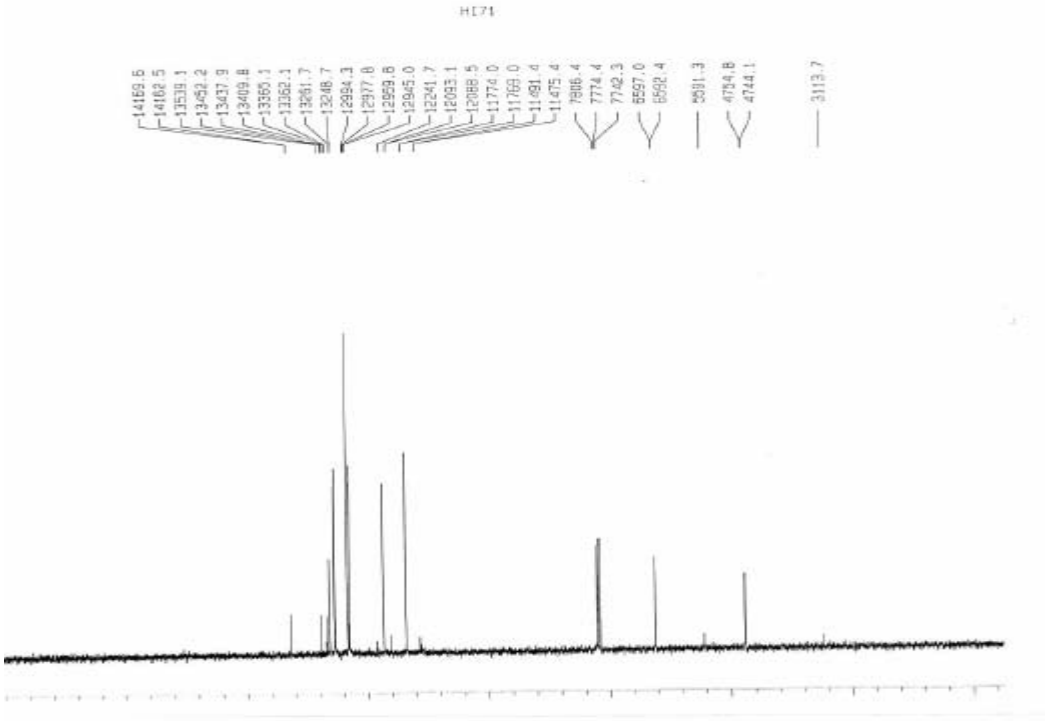

Figure 80B: The ^{13}C-NMR spectrum of **12b**

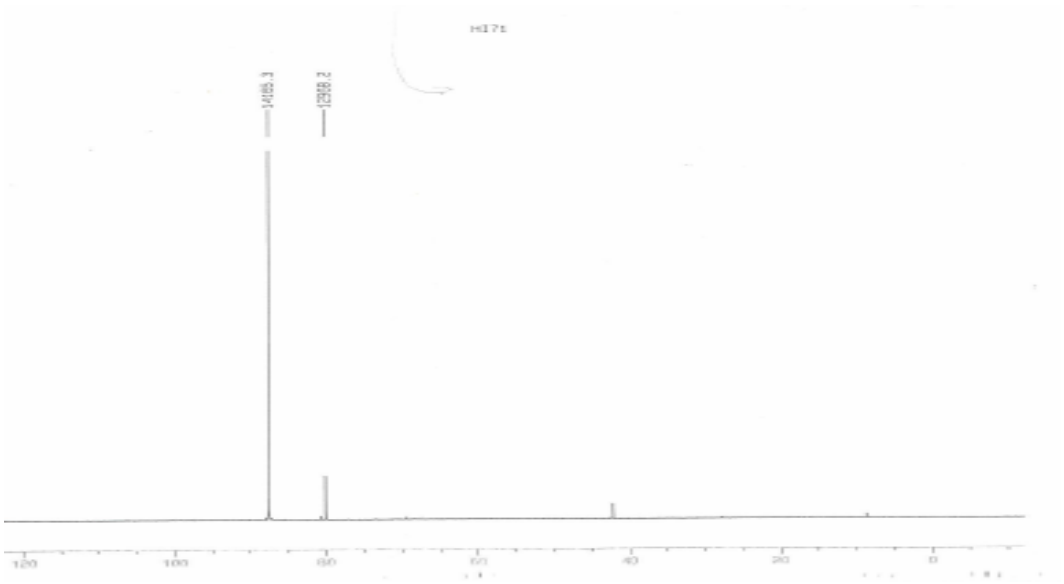

Figure 80C: The ^{31}P-NMR spectrum of **12b**

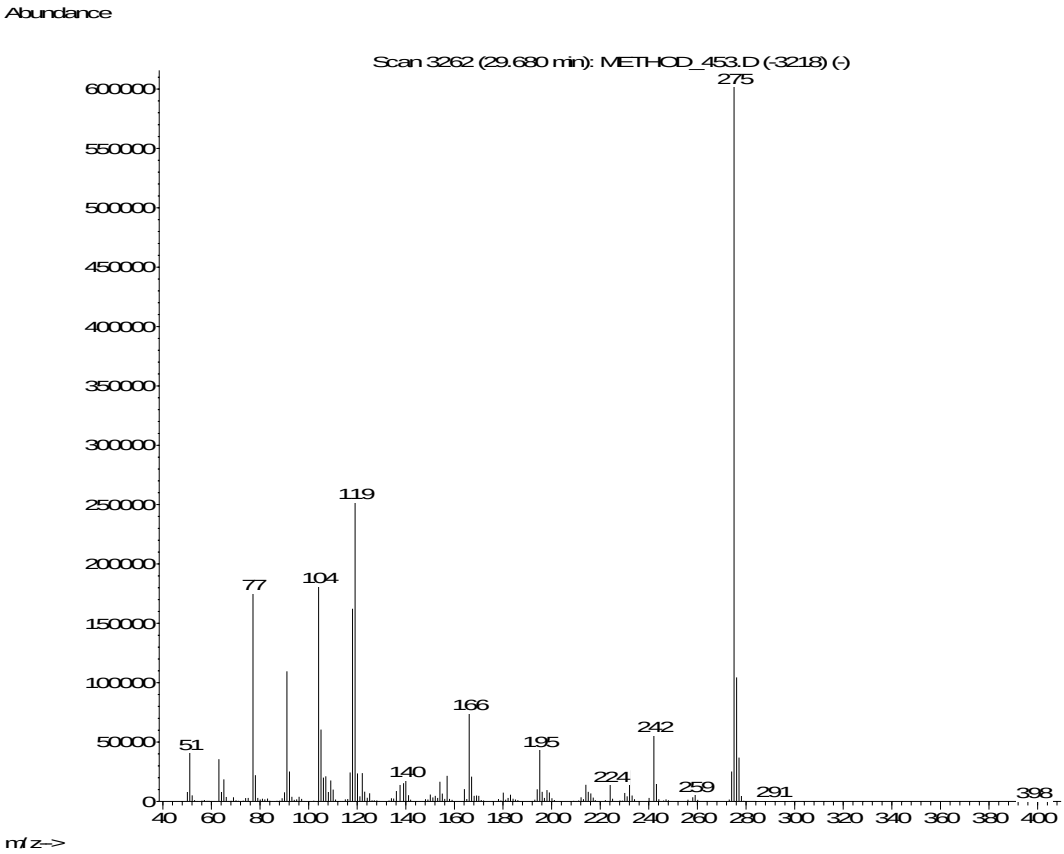

Figure 80D: The mass spectrum of **12b**